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State of the art on HPV-related cervical lesions

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To the Editor,

cervical carcinoma is the third most common cancer by incidence and mortality in the female population, with over 600,000 new cases per year and

more than 340,000 deaths. There are over 200 strains of human papillomavirus (HPV), but most cervical neoplasia cases are attributable to persistent sexually transmitted infections caused by oncogenic strains, such as HPV-16, HPV-33, HPV-18, HPV-31,

HPV-45, HPV-52, HPV-58 [1]. This disease can manifest in a severe form, but is susceptible to highly effective treatment, especially when early detected through prevention strategies, early diagnosis and appropriate therapies. Currently, in comparison to other gynaecological malignancies, several prevention modalities are available for cervical carcinoma. First, abstention from smoking and the use of barrier contraception methods may contribute to the prevention of acquiring HPV infection. Moreover, available scientific evidence indicates that HPV vaccination, recommended during adolescence for both sexes, can limit the incidence of infection and reduce the occurrence of precancerous lesions and cervical carcinoma [2-4]. Screening methods, such as cervical cytology and human papillomavirus testing, and colposcopy allow the detection of cervical dysplasia and early-stage cervical carcinoma, guiding patients toward appropriate management modalities and follow-up. Finally, tertiary prevention focuses on the treatment of previously identified lesions through surgery and other therapeutic strategies. DTC (electrocoagulation diathermy) is a safe, widespread and effective therapeutic approach for the management of non-invasive lesions, instead, the therapeutic approach to cervical carcinoma varies depending on the diagnostic stage at the time of evaluation. In recent years, several studies have analysed the safety and efficacy of minimally invasive surgery (MIS), highlighting its benefits [5, 6]. The 2023 guidelines issued by the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP), supported the MIS as a potential option for low-risk tumours (with a diameter of less than 2 cm and negative margins after conization), considering it acceptable for lymph node staging [7]. However, to date, the selection of the most appropriate surgical approach for the treatment of cervical carcinoma remains a matter of debate. The LACC (Laparoscopic Approach to Carcinoma of the Cervix) study raised questions about the oncological outcomes of MIS, showing a four-fold higher recurrence rate and a six-fold higher all-cause mortality rate compared to laparotomy [8]. The risk of recurrence following surgery for cervical intraepithelial lesions of grade 2 (CIN 2) or grade 3 (CIN 3) cannot be underestimated, and therefore, several studies have performed an in-depth analysis to identify the main determinants of the risk of recurrence. Following prima-

ry conization, patients who retained the presence of the human papillomavirus six months after the procedure had a 7.46% probability of recurrence. However, the persistence of HPV at twelve months is strongly associated with a significantly increased risk of disease recurrence (risk of recurrence: 13.1%). The magnitude of the risk of CIN2⁺ recurrence increases proportionally to the duration of HPV persistence up to one year, whereas HPV persistence beyond the first year does not appear to be a significant risk factor [9, 10]. In addition, a retrospective survey conducted on a sample of 2,966 patients who underwent conjugation for high-grade cervical lesions showed that the presence of positive endocervical margins is one of the main risk determinants associated with a five-year probability of recurrence. Despite the inherent importance of surgical treatment of cervical intraepithelial lesions in preventing progression to cervical carcinoma, it may result in adverse outcomes for pregnant women, increasing the risk of preterm delivery, low birth weight and premature rupture of membranes before 37 weeks of gestation. Indeed, the postponement of treatment for cervical dysplastic lesions identified during pregnancy until the postpartum period is a safe and well-established practice for both maternal and neonatal health. The management of cervical carcinoma remains a subject of growing concern. As this disease can also affect young women who are seeking pregnancy, early diagnosis and implementation of highly personalized treatment approaches are of crucial importance.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

T.G.D., A.G.: Conceptualization, resources, software, project administration. I.C., A.E., A.D.: Data curation, writing – original draft. A.S.L., O.D.: Investigation, methodology. V.D.D., G.B., L.M.: Supervision, validation, writing – review & editing.

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REFERENCES

- Jaisamrarn U, Castellsagué X, Garland SM, Naud P, Palmroth J, Del Rosario-Raymundo MR, et al. Natural history of progression of HPV infection to cervical lesion or clearance: analysis of the control arm of the large, randomised PATRICIA study. *PLoS One*. 2013;8(11):e79260. doi: 10.1371/annotation/cea59317-929c-464a-b3f7-e095248f229a.
- Sankaranarayanan R, Joshi S, Muwonge R, Esmey PO, Basu P, Prabhu P, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. *Vaccine*. 2018;36(32 Pt A):4783-91. doi: 10.1016/j.vaccine.2018.02.087.
- Despot A, Fureš R, Despot AM, Mikuš M, Zlopaša G, D'Amato A, et al. Reactive oxygen species within the vaginal space: An additional promoter of cervical intraepithelial neoplasia and uterine cervical cancer development? *Open Med (Wars)*. 2023;18(1):20230826. doi: 10.1515/med-2023-0826.
- Bogani G, Sopracordevole F, Ciavattini A, Ghelardi A, Vizza E, Vercellini P, et al. HPV-related lesions after hysterectomy for high-grade cervical intraepithelial neoplasia and early-stage cervical cancer: A focus on the potential role of vaccination. *Tumori*. 2024;110(2):139-45. doi: 10.1177/03008916231208344.
- Di Donato V, Bogani G, Casarin J, Ghezzi F, Malzoni M, Falcone F, et al. Ten-year outcomes following laparoscopic and open abdominal radical hysterectomy for "low-risk" early-stage cervical cancer: A propensity-score based analysis. *Gynecol Oncol*. 2023;174:49-54. doi: 10.1016/j.ygyno.2023.04.030.
- Pecorino B, D'Agate MG, Scibilia G, Scollo P, Giannini A, Di Donna MC, et al. Evaluation of Surgical Outcomes of Abdominal Radical Hysterectomy and Total Laparoscopic Radical Hysterectomy for Cervical Cancer: A Retrospective Analysis of Data Collected before the LACC Trial. *Int J Environ Res Public Health*. 2022;19(20):13176. doi: 10.3390/ijerph192013176.
- Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, et al. ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer - Update 2023. *Int J Gynecol Cancer*. 2023;33(5):649-66. doi: 10.1136/ijgc-2023-004429.
- Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Engl J Med*. 2018;379(20):1895-904. doi: 10.1056/NEJMoa1806395.
- Bogani G, Sopracordevole F, Ciavattini A, Vizza E, Vercellini P, Giannini A, et al. Duration of human papillomavirus persistence and its relationship with recurrent cervical dysplasia. *Eur J Cancer Prev*. 2023;32(6):525-32. doi: 10.1097/CEJ.0000000000000822.
- Bogani G, Sopracordevole F, Ciavattini A, Vizza E, Vercellini P, Ghezzi F, et al. HPV persistence after cervical surgical excision of high-grade cervical lesions. *Cancer Cytopathol*. 2024;132(5):268-9. doi: 10.1002/cncy.22760.



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What does the cardiotocography say about SARS-CoV-2 infection? Cardiotocograph monitoring during the pandemic era: a narrative short review

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ABSTRACT

Although emerging data indicate an increased risk of preeclampsia, intra-uterine growth restriction, preterm birth, and stillbirth, several questions remain unsolved in the case of SARS-CoV-2 infection in pregnant women. Cardiotocography (CTG) is the main method for monitoring the foetal well-being during the intrapartum period and is now used worldwide for the early detection of foetal distress during labour and delivery. This literature review aims to assess different intrapartum CTG changes observed in SARS-CoV-2 positive mothers, to understand whether CTG should be specifically interpreted or correlated with the seropositivity of mother to improve their management.

We reviewed titles and abstracts of 44 records regarding CTG and SARS-CoV-2, in PubMed and SCOPUS, abstracting the full text for 10. Of these, 6 studies met the eligibility criteria and were included in this narrative short review. Maternal SARS-CoV-2 infection has been associated with changes observed in CTG, such as the increase in the baseline due to fever, inflammatory response and the “cytokine storm”. Moreover, the impact that SARS-CoV-2 had on the placenta has noticed to be still accountable for most of the alterations in CTG.

Despite the lack of specificity of CTG alterations in SARS-CoV-2 positive patients, obstetricians are encouraged not to neglect foetal monitoring because of the isolation of positive woman, owing the virus’s harmful effects on placentas and maternal health.

INTRODUCTION

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), known as the cause of the COVID-19 disease, was declared a pandemic by the World Health Organization in March 2020. It infected over 100 million individuals at an exponential accelerating rate, since its first identification in December 2019 [1]. Pregnant women and their foetuses are particularly exposed to ad-

verse outcomes, such as maternal mortality and morbidity, and perinatal death, when infected by coronaviruses, basing on past epidemics experiences [2]. SARS-CoV-2 has been associated with a more severe clinical presentation of COVID-19 disease during pregnancy, since pregnancy is a time of increased susceptibility to infection [2-4]. The most important pregnancy-related complications, include a higher risk of stillbirth, intrauterine growth restriction (IUGR), preeclampsia and

preterm birth [4-6]. The potential role of the placenta in the infectious process has been postulated basing on the presence of the angiotensin-converting enzyme 2 (ACE2) receptor on the cell membrane [7]. As well as being a potential site of virus entry, the receptor is part of the renin-angiotensin-aldosterone system, which plays a pivotal role in maternal hemodynamic adaptation during pregnancy [7, 8].

Cardiotocograph (CTG) is a worldwide used method to assess foetal well-being monitoring foetal heart rate (FHR) and detecting signs of intrapartum hypoxia and acidaemia [9]. Qualitative and quantitative descriptions of several parameters, including the baseline foetal heart rate, variability, accelerations and decelerations, are part of the interpretation of a CTG trace [9, 10]. These parameters give us information about the oxygenation of the foetal brain and heart, reflecting the activity of foetal somatic and autonomic nervous systems [10]. In case of utero-placental insufficiency, foetal metabolism shifts from aerobic to anaerobic as a result of the hypoxia, causing a reduction in the cardiac workload of the foetus [11]. This complex mechanism is displayed in the CTG trace as deceleration [11]. Moreover, baseline tachycardia and decelerations in the CTG trace may be indicative of foetal distress caused by maternal pyrexia or other inflammatory diseases [12]. In 2008, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the American College of Obstetricians and Gynaecologists, and the Society for Maternal-Fetal Medicine, revisited the nomenclature, the interpretation, and the recommendations for intrapartum electronic foetal heart rate monitoring [13] simplifying its categorization and interpretation into a 3-tier system, as shown in **Table 1** [14].

That said, since SARS-CoV-2 infection and the consequent COVID-19 disease trigger an important inflammatory process, negative consequences and unfavourable obstetric outcomes on women and fetuses are possible risks.

The purpose of this short review is to summarize the evidence related to the association between SARS-CoV-2 infection and detectable changes in the CTG trace. In addition, we reported possible patterns identified in relation to the severity of the disease, with the specific purpose of gaining knowledge in this area, to ensure better management of these cases under emergency conditions.

Table 1. 3-Tier foetal heart rate interpretation system [14].

| Category | Tracing | Description |
|----------|---------------|---|
| I | Normal | <ul style="list-style-type: none"> • Baseline rate: 110-160 beats/min • Moderate variability • Absence of any late or variable decelerations • Early decelerations may or may not be present • Accelerations may or may not be present |
| II | Indeterminate | <ul style="list-style-type: none"> • Baseline rate <ul style="list-style-type: none"> • Tachycardia • Bradycardia not accompanied by absent baseline variability • Baseline Foetal Heart Rate variability <ul style="list-style-type: none"> • Minimal baseline variability • Absent baseline variability not accompanied by recurrent decelerations • Marked baseline variability • Absence of induced accelerations after foetal stimulation (e.g., scalp stimulation, vibroacoustic stimulation, direct foetal scalp sampling, transabdominal halogen light) • Periodic or episodic decelerations <ul style="list-style-type: none"> • Recurrent variable decelerations accompanied by minimal or moderate baseline variability • Prolonged deceleration ≥ 2 min but < 10 min • Recurrent late decelerations with moderate baseline variability • Variable decelerations with other characteristics, such as slow return to baseline, "overshoots", or "shoulders" |
| III | Abnormal | <ul style="list-style-type: none"> • Absent baseline Foetal Heart Rate variability along with any of the following: <ul style="list-style-type: none"> • Recurrent late decelerations • Recurrent variable decelerations • Bradycardia • Sinusoidal pattern |

METHODS

An initial systematic search was conducted using the Medline, PubMed, and Scopus databases. Publications without a limit in the timeframe were selected. The following set of search terms were included: Cardiotocography OR Cardiotocograph OR CTG AND SARS-CoV-2 OR COVID-19 (Title/ Abstract). Forty-four articles resulted from the initial search. A preliminary screening of titles and abstracts according to the scope of the review, was carried out by the authors after eliminating duplicates (**Figure 1**). If it was not clear from the abstract whether the article might contain relevant data or not, the full article was assessed. Non-English articles were excluded. The first and the third

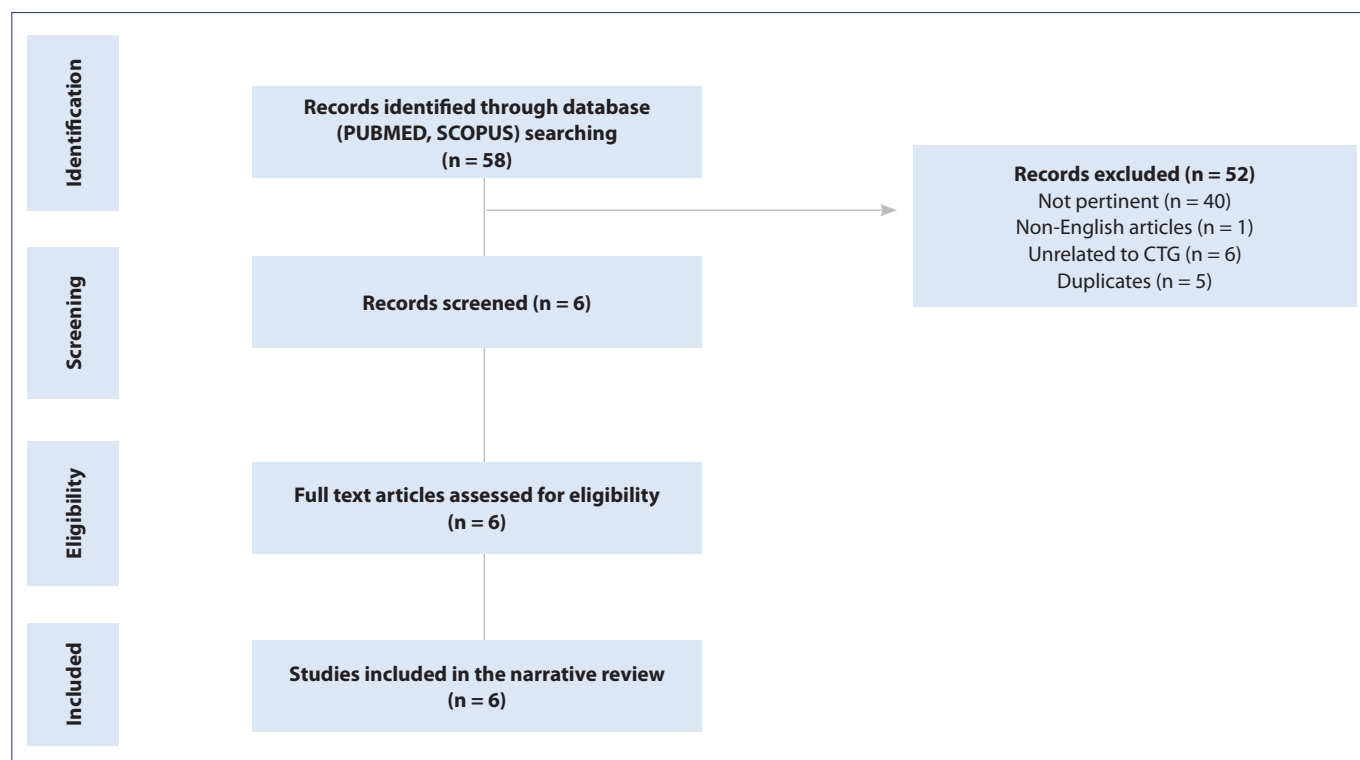


Figure 1. Flowchart of included studies.

Table 2. Included articles with main findings in the cardiotocographic pattern.

| Author/Date | Participants | Type of article | Gestational age (weeks) | Primary Objective(s) | Cardiotocographic patterns |
|-----------------------------------|---|--------------------------|---|---|--|
| Sinaci et al., 2022 | 224 COVID-19 positive women | Prospective cohort study | 37 (32-41) | Relation between CTG traces and the severity of COVID-19 | <ul style="list-style-type: none"> 25.0% minimal or absence of variability; <ul style="list-style-type: none"> 4.0% ZigZag pattern; 13.4% absence of acceleration; 25.0% presence of decelerations; <ul style="list-style-type: none"> 5.4% tachycardia; 1.3% bradycardia; 66.5% uterine contractility. |
| Farhan et al., 2022 | 30 COVID-19 positive women; 60 Controls | Case-control study | 36.73 ± 2.47 (cases) 38.38 ± 1.6 (Controls) | Verify intrapartum CTG changes and their impact on delivery mode and neonatal outcome | <ul style="list-style-type: none"> 60% of COVID-19 cases exhibited abnormal CTG changes versus 19.4% in controls; CS for abnormal foetal heart tracing occurred in 33.3% versus 15.6% (P-value = 0.015) for cases versus healthy controls. |
| Gracia-Perez-Bonfils et al., 2020 | 12 COVID-19 positive women | Retrospective analysis | 38+1 (28-40+6) | Determine the CTG changes in COVID-19 positive patients | <ul style="list-style-type: none"> Increased baseline FHR > 10% compared to the initial recording in all foetuses; Gross foetal tachycardia (>210 bpm) in one case; <ul style="list-style-type: none"> Absence of acceleration in all fetuses; 83.3% Late or prolonged decelerations; <ul style="list-style-type: none"> 58.3% absence of cycling; 33% ZigZag pattern. None sinusoidal pattern; 83.3% evidence of excessive uterine activity. <ul style="list-style-type: none"> CTG was interpreted as pathological. |
| Ivert et al., 2023 | 5 COVID-19 positive women | Case series | 28+5 (24-33+5) | SARS-CoV-2 effect on the placenta | <ul style="list-style-type: none"> CTG was interpreted as pathological. |
| Dumont et al., 2021 | 1 COVID-19 positive women | Case-report | 29+1 | SARS-CoV-2 Alpha variant effects on the placenta | <ul style="list-style-type: none"> Abnormal pattern with greatly reduced variability. |
| Suresh et al., 2020 | 1 COVID-19 positive women | Case-report | 34+1 | Highlights the challenges of modifying antepartum testing strategies during the COVID-19 pandemic | <ul style="list-style-type: none"> CTG was interpreted as pathological. |

FHR: foetal heart rate; CTG: cardiotocography, CS: caesarean section.

author, assessed independently, and subsequently discussed the quality of all eligible studies. The analytic process was then completed by reading and categorizing all articles and summarizing the findings. Six articles were included in this narrative review, responding to the author's purpose (Table 2). A narrative synthesis of the studies was conducted, integrating the material with theoretical notions selected from book chapters or other articles referenced in included studies.

EVIDENCE SYNTHESIS

A prospective cohort study [15], evaluated the CTG traces of 224 women, infected with SARS-CoV-2 (Table 2). The authors included 224 pregnant women of 32 weeks or more (mean 36.4 ± 3.44), including only singleton pregnancies. All women resulted positive for SARS-CoV-2 using quantitative RT-PCR (qRT-PCR) on samples from the respiratory tract. CTG traces were observed comparing the one performed during hospital admission with the one performed the third day of positivity. The rationale was that the SARS-CoV-2's viral replication reaches its higher replication rate on day 3 [16]. 84% of patients had a mild COVID-19 symptomatology. 96% didn't report a worsening in the disease during the observation, and 83.9% didn't require any medical treatment at all. The CTG category was I in 63% (163/224) of patients. The CTG classification didn't change in 82.1% of the cases (184/224) during the observation. On the other hand, twenty-five % (56/224) of patients had minimal or absence of variability, while 4.0% (9/224) had a ZigZag pattern (exaggerated variability). 13% (30/224) hadn't acceleration, and 25.0% (56/224) showed decelerations. 5% (12/224) of the patients had tachycardia, while 1.3% (3/224) had bradycardia. 66% (149/224) of patients showed uterine contraction at the trace, and a caesarean section (CS) was performed in 44.6% (100/224) of the cases. Along these observations, authors concluded that there was no statistically significant relationship between the COVID-19 severity and the CTG category.

A case-control study [17] analysed 90 pregnant women at term. Patients were categorized into two groups: COVID-19 positive (30/90), confirmed by real-time RT-PCR test, and healthy controls (60/90) who tested negative (Table 2). COVID-19 patients showed significantly higher maternal

pulse rate, temperature, and leukocyte counts. The CS rate was higher in the group of positive versus controls (70% vs 53.3%; $p = 0.45$). The CS indication was "abnormal foetal heart tracing" for 33.3% of patients in the COVID-19 positive group, while 15.6 % ($p = 0.015$) in the group of negative. 60% of cases in the group of positive patients had foetal tachycardia and reduced variabilities at the CTG trace. These features were registered in 19.4% of cases in the control group. In 23% of the positive patients, there variability was reduced and 3% had a foetal demise.

A retrospective analysis [18] evaluated 12 CTG traces in symptomatic COVID-19 infected pregnant women, over the 37th week of gestation (Table 2). The aim was to understand if there were correlation between the CTG trace, the maternal severity of COVID-19 infection and the perinatal outcomes. These latter were defined by APGAR Score < 7 at five minutes, umbilical cord arterial pH < 7.0 or admission to the neonatal unit that was not expected. According to the authors, all CTG where uterine contractions were registered (10 out of 12) showed excessive uterine activity. Moreover, late, or prolonged decelerations were recorded in 10 out of 12 traces (83.3%). Just a single case presented a gross foetal tachycardia (> 210 bpm). 58% of cases showed no cycling. An exaggerated or augmented variability > 25 bpm was recorded in 33% of the cases, confirming a ZigZag pattern.

Despite the abnormalities recorded, such as absence of accelerations, increased baseline of the foetal heart, and the presence of late or prolonged decelerations, there were no adverse perinatal outcome.

In a case series [19], five pregnant women with a mild SARS-CoV-2 infection, were admitted for reduced foetal movements between 24+0 and 33+5 weeks of gestation. None of the women received a vaccination for COVID-19 (Table 2). At the time of admission, an ultrasound scan showed reduced foetal movements and CTG category was recorded as III. A few hours later, four out of the five women underwent a CS. Even if none of the new-borns was positive for SARS-CoV-2, all placentas tested positive. The histopathologic analysis of these latter, showed a massive peri-villous fibrin deposition and histiocytic inter-villosities, related to the placental insufficiency and the hypoxia.

In a case report [20], a 37-year-old woman who resulted positive for SARS-CoV-2 Alpha variant, was admitted to a tertiary care hospital at 29+1 weeks of

gestation because of oligohydramnios and reduced foetal movements for 10 days (**Table 2**). At the time of admittance, CTG demonstrated a normal pattern while the following day, CTG demonstrated abnormal pattern with greatly reduced variability. With the purpose of the foetal neuroprotection, intravenous magnesium sulphate was administered. An urgent caesarean section was therefore performed. Due to its prematurity, the neonate was admitted to the NICU. Two nasopharyngeal swabs were obtained from the neonate on two occasions: both were negative for SARS-CoV-2. Moreover, the umbilical cord and neonatal blood analysis, showed no SARS-CoV-2 RNA.

In another case report [21], a 28-year-old gravida at 34 weeks of gestation was found positive for SARS-CoV-2 after reporting rhinorrhoea, anosmia, and mild cough (**Table 2**). She reported normal perception of the foetal movement and denied any contractions, vaginal bleeding, or leakage of amniotic fluid. Findings from the CTG showed baseline rate 140 beats/min, moderate variability, periodic decelerations, and irregular uterine contractions. The CTG was recorded as Category II. Since the category II tracing persisted, the clinicians decided to perform an urgent repeated caesarean section.

DISCUSSION

SARS-CoV-2 infection seems to cause an excessive release of pro inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 β (IL-1 β), tumour necrosis factor- α (TNF- α) and chemokines such as monocyte chemoattractant protein-1 (MCP-1/CCL2) [6, 22, 23]. Moreover, the infection leads to an hyperactivation of immune cells especially in the lungs, and an hypercytokinemia with an abnormal innate immune response in the mother [6, 22, 23]. The severity of COVID-19 depends on this event, known as “cytokine storm”, that could lead to an acute respiratory distress syndrome and in the worst of the cases to a multiorgan failure [24, 25]. On the other hand, the placental intervillous thrombosis is associated with the maternal hypoxia, the cytokine storm, and the hypercoagulability status [6, 26].

The changes in the CTG trace, in particular the FHR, is the result of a reactive response, more likely secondary to the maternal inflammatory status and the fever [27]. Plus, the foetal tachycardia (>210 bpm) is likely connected to the “cytokine

storm” [27]. This result in an augmented foetal sympathetic reactivity with a cardiac arrhythmia secondary to the incremented inflammatory response [27]. The ZigZag pattern is probably secondary to the autonomic instability [27] due, once again, to the maternal cytokine storm and pyrexia. The foetal bradycardia could be linked to the placental insufficiency and the thrombosis of the umbilical vein [27]. In addition, severe hypoxia of the mother can result as a sinusoidal pattern [27]. Absence of accelerations, late, or prolonged decelerations are most likely related to the depression of the foetal somatic nervous system [27]. The hypoxia status of the mother could lead to an increased placental oxygen consumption with the purpose of saving the foetal somatic muscle activity [15]. Plus, a depressive effect on the foetal brain for the loss of the normal active and quiet sleep phases, is recorded as an absence of cycling in the CTG trace [15].

Increased uterine contractility recorded on CTGs could depends on maternal fever or the maternal inflammatory status [28]. This result in a reduction of the utero-placental oxygen transfer and could lead to an irritation of the myometrium [28]. The remarkable involvement of placenta during SARS-CoV-2 infection is confirmed by a higher rate of decidual arteriopathy and other maternal impaired perfusion features, when SARS-CoV-2 positive placentas are compared to normal placentas [29]. The same phenomenon was confirmed in other studies, where placental deposition of fibrin has been retained responsible for the maternal-foetal gas exchange, increasing foetal distress and risk of emergency caesarean section [20, 30]. Demise of foetuses in the case of positivity of the mothers, can be related to the pregnancy-induced maternal hypercoagulability status, which is increased by the viral pro-thrombotic effect [17]. At the same time, the fever and inflammatory mediators of the mother, are retained responsible for the thrombosis of the placenta and the umbilical veins according to other authors [31, 33].

The authors of a study included in this review [18] suggested, before considering any intervention based on abnormal CTGs, to correct the maternal hypoxia, pyrexia and inflammatory response.

The studies included in this review are not devoid of limitations. These limitations could be extended to most of the studies facing with the COVID-19. The most important issue encountered, is related to the patients' selection: most of the studies

reviewed, described CTG patterns of SARS-CoV-2-infected women without comparing them with an uninfected group. Another concern is that not all studies describe the SARS-CoV-2 variants involved, and we cannot determine whether different variants – for example, Omicron *versus* Delta – induce different CTG alterations [34, 35]. Furthermore, not in all the studies, the COVID-19 symptomatology was sufficiently described, determined nor specified [36].

Nevertheless, numerous factors or circumstances may have influence on the characteristics of the CTG trace, including the time of the day, the position and activity of the mother, her use of medications and even the foetal movements.

Despite the analysed CTGs showed a high percentage of abnormalities such as decelerations, excessive uterine activity, or the absence of accelerations, it is not possible to state that correcting the maternal environment, the CTGs traces change. Another imposing limitation is that women included in the studies had different gestational ages, and probably different severity of COVID-19 symptomatology. Other limitations are the lack of information on the newborns umbilical cord pH and APGAR score.

Finally, not all the analysed studies report histopathological exams of the placentas: we cannot therefore establish whether an infected placenta itself or specific histologic alteration related to the infection of the mothers, can further modify the CTG patterns.

CONCLUSIONS

Abnormal patterns in CTGs traces have been reported in studies on mothers infected by SARS-CoV-2. These include an increase in the baseline due to the maternal pyrexia, maternal inflammatory response and the “cytokine storm”. Alternatively, the SARS-CoV-2 effect on the placentas is retained responsible for most of the changes in the CTG. CTG changes in SARS-CoV-2 positive patients seems to be non-specific but considering the negative effects of the virus on the placentas and on the maternal wellbeing, it is relevant to highlight the importance for obstetricians to implement foetal surveillance in these patients.

Further research is needed to understand the effect of SARS-CoV-2 on pregnancy and neonatal outcomes and in this regard, considering the lack

of knowledge on placentas and COVID-19, histological examination should always be considered for SARS-CoV-2 positive patients, to increase the knowledge on the virus’s effects on the placenta and the consequent effects on the foetus.

The authors self-evaluated the narrative review according to the Scale for the Assessment of Narrative Review Articles - SANRA [37] (justification of the article’s importance for the readership, statement of concrete aims or formulation of questions, description of the literature search, referencing, scientific reasoning, appropriate presentation of data) totalizing a score of 12/12.

The authors followed the EQUATOR Guidelines for reporting health research [38].

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.L.: Conceptualization. A.L., A.N., L.T.: Data curation, formal analysis. A.L., A.N., L.T., V.R.: Investigation, project administration, visualization. A.L., L.T.: Methodology. V.R.: Supervision, validation. A.L., A.N.: Writing – original draft. A.L., L.T., V.R.: Writing – review & editing.

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The authors declare that they have no conflict of interests.

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REFERENCES

- Davies NG, Jarvis CI, CMMID COVID-19 Working Group, Edmunds WJ, Jewell NP, Diaz-Ordaz K, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature*. 2021;593(7858):270-4. doi: 10.1038/s41586-021-03426-1.
- Patberg ET, Adams T, Rekawek P, Vahanian SA, Akerman M, Hernandez A, et al. Coronavirus disease 2019 infection and placental histopathology in women delivering at term. *Am J Obstet Gynecol*. 2021;224(4):382.e1-382.e18. doi: 10.1016/j.ajog.2020.10.020.
- Cosma S, Borella F, Carosso A, Sciarrone A, Cusato J, Corcione S, et al. The "scar" of a pandemic: Cumulative incidence of COVID-19 during the first trimester of pregnancy. *J Med Virol*. 2021;93(1):537-40. doi: 10.1002/jmv.26267.
- Verma S, Carter EB, Mysorekar IU. SARS-CoV2 and pregnancy: An invisible enemy? *Am J Reprod Immunol*. 2020;84(5):e13308. doi: 10.1111/aji.13308.
- Kumar D, Verma S, Mysorekar IU. COVID-19 and pregnancy: clinical outcomes; mechanisms, and vaccine efficacy. *Transl Res*. 2023;251:84-95. doi: 10.1016/j.trsl.2022.08.007.
- Rasmussen SA, Smulian JC, Lednický JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol*. 2020;222(5):415-26. doi: 10.1016/j.ajog.2020.02.017.
- Azinheira Nobrega Cruz N, Stoll D, Casarini DE, Bertagnolli M. Role of ACE2 in pregnancy and potential implications for COVID-19 susceptibility. *Clin Sci (Lond)*. 2021;135(15):1805-24. doi: 10.1042/CS20210284.
- Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci U S A*. 2020;117(21):11727-34. doi: 10.1073/pnas.2003138117.
- Bardakci M, Balci O, Acar A, Colakoglu MC. Comparison of modified biophysical profile and doppler ultrasound in predicting the perinatal outcome at or over 36 weeks of gestation. *Gynecol Obstet Invest*. 2010;69(4):245-50. doi: 10.1159/000274488.
- Aquino CI, Amadori R, Vaianella E, Bonassisa S, Libretti A, Surico D, et al. Cardiotocography pattern: not always a true friend. *Acta Biomed*. 2023;94(S1):e2023054. doi: 10.23750/abm.v94iS1.14011.
- Pinas A, Chandraharan E. Continuous cardiotocography during labour: Analysis, classification and management. *Best Pract Res Clin Obstet Gynaecol*. 2016;30:33-47. doi: 10.1016/j.bpobgyn.2015.03.022.
- Chandraharan E, Arulkumaran S. Prevention of birth asphyxia: responding appropriately to cardiotocograph (CTG) traces. *Best Pract Res Clin Obstet Gynaecol*. 2007;21(4):609-24. doi: 10.1016/j.bpobgyn.2007.02.008.
- Robinson B, Nelson L. A Review of the Proceedings from the 2008 NICHD Workshop on Standardized Nomenclature for Cardiotocography: Update on Definitions, Interpretative Systems With Management Strategies, and Research Priorities in Relation to Intrapartum Electronic Fetal Monitoring. *Rev Obstet Gynecol*. 2008;1(4):186-92.
- Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol*. 2008;112(3):661-6. doi: 10.1097/AOG.0b013e3181841395.
- Sinaci S, Ocal DF, Ozden Tokalioglu E, Halici Ozturk F, Aydin Senel S, Keskin LH, et al. Cardiotocographic features in COVID-19 infected pregnant women. *J Perinat Med*. 2022;50(1):46-55. doi: 10.1515/jpm-2021-0132.
- Cantini F, Goletti D, Petrone L, Najafi Fard S, Niccoli L, Foti R. Immune Therapy, or Antiviral Therapy, or Both for COVID-19: A Systematic Review. *Drugs*. 2020;80(18):1929-46. doi: 10.1007/s40265-020-01421-w.
- Farhan FS, Nori W, Al Kadir ITA, Hameed BH. Can Fetal Heart Lie? Intrapartum CTG Changes in COVID-19 Mothers. *J Obstet Gynaecol India*. 2022;72(6):479-84. doi: 10.1007/s13224-022-01663-6.
- Gracia-Perez-Bonfils A, Martinez-Perez O, Llurba E, Chandraharan E. Fetal heart rate changes on the cardiotocograph trace secondary to maternal COVID-19 infection. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:286-93. doi: 10.1016/j.ejogrb.2020.06.049.
- Ivert A, Lindblad Wollmann C, Pettersson K. A Case Series on Pregnant Patients with Mild Covid-19 Infection and Signs of Severe Placental Insufficiency. *Case Rep Obstet Gynecol*. 2023;2023:2018551. doi: 10.1155/2023/2018551.
- Dumont S, Balduyck J, Reynders M, Vanwallegem L, Lebbe B. Acute SARS-CoV-2 alpha

- variant infection leading to placental insufficiency and fetal distress. *J Med Virol.* 2022;94(3):1196-200. doi: 10.1002/jmv.27379.
21. Suresh SC, MacGregor CA, Ouyang DW. Urgent Cesarean Delivery Following Nonstress Test in a Patient with COVID-19 and Pregestational Diabetes. *Neoreviews.* 2020;21(9):e625-30. doi: 10.1542/neo.21-9-e625.
 22. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* 2020;130(5):2620-9. doi: 10.1172/JCI137244.
 23. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol.* 2017;39(5):517-28. doi: 10.1007/s00281-017-0639-8.
 24. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;395(10229):1033-4. doi: 10.1016/S0140-6736(20)30628-0.
 25. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect.* 2020 Jun;80(6):607-13. doi: 10.1016/j.jinf.2020.03.037.
 26. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet.* 2020;395(10226):809-15. doi: 10.1016/S0140-6736(20)30360-3
 27. Modanlou HD, Murata Y. Sinusoidal heart rate pattern: Reappraisal of its definition and clinical significance. *J Obstet Gynaecol Res.* 2004;30(3):169-80. doi: 10.1111/j.1447-0756.2004.00186.x.
 28. Ayres-de-Campos D, Spong CY, Chandraran E, FIGO Intrapartum Fetal Monitoring Expert Consensus Panel. FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography. *Int J Gynaecol Obstet.* 2015;131(1):13-24. doi: 10.1016/j.ijgo.2015.06.020.
 29. Prochaska E, Jang M, Burd I. COVID-19 in pregnancy: Placental and neonatal involvement. *Am J Reprod Immunol.* 2020;84(5):e13306. doi: 10.1111/aji.13306.
 30. Schoenmakers S, Snijder P, Verdijk RM, Kuiken T, Kamphuis SSM, Koopman LP, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Placental Infection and Inflammation Leading to Fetal Distress and Neonatal Multi-Organ Failure in an Asymptomatic Woman. *J Pediatric Infect Dis Soc.* 2021;10(5):556-61. doi: 10.1093/jpids/piaa153.
 31. Chen D, Yang H, Cao Y, Cheng W, Duan T, Fan C, et al. Expert consensus for managing pregnant women and neonates born to mothers with suspected or confirmed novel coronavirus (COVID-19) infection. *Int J Gynaecol Obstet.* 2020;149(2):130-6. doi: 10.1002/ijgo.13146.
 32. Nori W, Hameed BH, Thamir AR, Fadhil A. COVID-19 in Pregnancy: Implication on Platelets and Blood Indices. *Rev Bras Ginecol Obstet.* 2021;43(8):595-9. doi: 10.1055/s-0041-1733912.
 33. Nori W, Ali AI. Maternal alpha-1-antitrypsin as a novel marker for growth restriction in pre-eclampsia. *J Obstet Gynaecol Res.* 2021;47(12):4250-5. doi: 10.1111/jog.15043.
 34. Kammoun M, Jarraya A, Ellouze Y, Derbel M, Ben Hamad A, Chaaben K, Kolsi K. The impact of COVID-19 booster vaccination in the current pregnancy during the Omicron waves on maternal and perinatal outcomes: a multicentre observational study. *Ital J Gynaecol Obstet.* 2023;35(4):550-9. doi: 10.36129/jog.2023.100.
 35. Guida M, Carbone L, Ferrara C, Avino L, Buonfantino C, De Angelis MC, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection: a single centre experience. *Ital J Gynaecol Obstet.* 2023;35(2):252-62. doi: 10.36129/jog.2022.49.
 36. Libretti A, Troia L, Cappello AM, Casarotti C, D'Amato AT, Dallarda G, et al. Pregnancy and neonatal outcomes of SARS-CoV-2 infection discovered at the time of delivery: a tertiary center experience in North Italy. *J Perinat Med.* 2023;52(2):215-21. doi: 10.1515/jpm-2023-0280.
 37. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev.* 2019;26(1):4-5. doi: 10.1186/s41073.
 38. Simera I, Altman DG, Moher D, Schulz KF, Hoey J. Guidelines for reporting health research: the EQUATOR network's survey of guideline authors. *PLoS Med.* 2008;5(6):139. doi: 10.1371/journal.pmed.0050139.



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A case of early neonatal diagnosis of familial tuberous sclerosis

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ABSTRACT

Background. Tuberous Sclerosis Complex (TSC) is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance. It is characterized by hamartomas that affect multiple organs, in particular skin, central nervous system, heart, lungs and kidney.

Case presentation. Here we report a case of early post-natal diagnosis of familial TSC.

Conclusions. TSC is a quite rare genetic disease and early diagnosis is very uncommon, given few cases published in literature. In our patients, early diagnosis has been performed by using early postnatal ultrasound screening, without a prenatal diagnosis.

INTRODUCTION

Tuberous Sclerosis Complex (TSC) is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance. It is characterized by hamartomas that affect multiple organs, in particular skin, central nervous system (CNS), heart, lungs and kidney [1-4].

There are several genes involved in the aetiology of this disease in particular the tumour suppressor

genes TSC1 and TSC2 respectively located on chromosome 9 and 16 that codify for the proteins hamartin and tuberin [3, 5].

The role of this protein complex is to control cellular growth, by suppressing mTOR (mechanistic target of rapamycin) pathway, involved in the proliferation and inhibition of cellular apoptosis. Inactivating mutation or deletion leads to a permanent mTOR pathway activation and so to the development of hamartomas in multiple organs [6].

Skin manifestations (hypopigmented macule, “confetti lesions”, angiofibroma, cephalic plaque, shagreen patches, unguis fibroma) are the most common and overall, they affect 90% of patients [4, 5, 7, 8].

The main neurological manifestation is epilepsy (70-90%) that starts usually in the first three years of life; in addition, TSC patients have a high risk of neurocognitive impairment (autism, mental retardation, movement disturbance). Notably, neuroimaging shows cortical and subcortical tubers, subependymal nodules in the lateral ventricles, subependymal giant astrocytomas (SEGA) [4, 10, 11].

Whilst, cardiological manifestations are represented by rhabdomyomas, diagnosed in the foetus and new-born, usually in the ventricular wall. These are mostly asymptomatic, even though they can cause cardiomegaly, arrhythmias and even death [9].

Other manifestations are renal (80% of cases) as angiomyolipoma [10, 12], pulmonary (lymphangiomyomatosis) [10], ophthalmological (retinal hamartoma) and hepatic (angiomyolipoma) [7, 13].

Importantly first diagnostic criteria of 1998 have been reviewed in 2012 in the second International Tuberous Sclerosis Complex Consensus Conference, by including genetic tests. Based on the new criteria, a pathogenic mutation in TSC1 or TSC2, is sufficient to assess the diagnosis, regardless clinical manifestations [7]. Nevertheless, 10% to 25% of patients could not have a pathogenic mutation in conventional genetic testing. Therefore, a normal molecular test cannot exclude a diagnosis of TSC.

Clinical criteria are divided into major: hypopigmented macules (≥ 3 , with at least 5 mm diameter), angiofibroma (≥ 3) or fibrous cephalic plaque, unguis fibromas (≥ 2), shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis, angiomyolipoma (≥ 2); and minor: “confetti” lesion, enamel pits (> 3), intraoral fibroma (≥ 2), retinal hypopigmented macule, multiple renal cysts and nonrenal hamartomas. If two major criteria or one major and two minor criteria are all met diagnosis can be definitive. While it can be probable with one major criterion or two or more minor.

The diagnostic suspect comes usually from pre-natal individuation of cardiac rhabdomyomas; in the post-natal period, the identification of hypopigmented macules on the skin has been ob-

served; in childhood the seizures are the most common clinical manifestation followed by cognitive impairment.

Here we report a case of early post-natal diagnosis of familial TSC.

CASE PRESENTATION

A trigeminal pregnancy obtained through intracytoplasmic sperm injection technique delivered at 31+6 weeks of gestational age with an emergency C-section for preterm premature rupture of the membranes.

The mother had an history of epilepsy treated with Levetiracetam. She had a postoperative course uncomplicated, and she was discharged at day 3 after delivery.

The first twin was born without any complication and discharged day 3 after birth.

The second born, A., had an APGAR score of 2 and 7, at 1 and 5 minutes respectively; she received Cardio-Pulmonary Resuscitation and ventilated through endotracheal tube for severe cardiorespiratory depression. Neonatal birth weight was 1,458 grams (25-50° pct), length 40 cm (25-50° pct), cranial circumference 28.5 cm (25-50° pct). She received invasive respiratory assistance for 4 days, then she underwent non-invasive respiratory assistance until discharge. She received antibiotic therapy with Ampicillin and Gentamicin. Cultures were always negative. Echocardiography performed for neonatal screening showed multiple hyperechogenic formations considered as rhabdomyomas, furthermore a Patent Ductus Arteriosus with left-right shunt and thereby right hyperflux resistant to medical closure therapy. Therefore, she received surgical closure intervention with no complications. At physical examination, she also had a prominent skin lesion on the nape.

The third born, S., had an APGAR score of 2 and 7, at 1 and 5 minutes respectively; she received Cardio-Pulmonary Resuscitation and ventilated through endotracheal tube for severe cardiorespiratory depression. Neonatal birth weight was 1,393 grams (25° pct), length 38.5 cm (10-25° pct), cranial circumference 27.7 cm (10-25° pct). She received invasive respiratory assistance for the first 72 hours and administered endotracheal surfactant, then she received non-invasive respiratory assistance for 48 hours and underwent spontaneous breathing afterwards. Blood tests and cultures were al-

ways negative. She received a course of 24 hours phototherapy for neonatal hyperbilirubinemia. She received partial parenteral nutrition for 11 days and Minimal Enteral Feeding from first day of life, then completely full enteral feeding with good weight gain. At physical examination two prominent and rugous plaques on left forearm and left thigh were detected and suspected for skin fibromas. She started a diagnostic iter and performed complete ultrasound screening. Abdominal US showed a left renal hyperechogenic lesion with intralesional cysts compatible with renal angiomyolipoma. Echocardiography (**Figure 1**) showed multiple rounded endocardia hyperechogenic formations along Intra Atrial Septum and Intra Ventricular Septum considered as rhabdomyomas or hamartomas. Cerebral US showed right first grade Intra Ventricular Haemorrhage, bilateral rounded hyperechogenic > 1 cm nodules localized in the cortical-subcortical wall (**Figure 2**), considered as subependymal nodules. She was then transferred to the Pediatric Cardiology Unit and monitored. After discharge, she experienced seizures and was admitted to Neurology Unit where she performed Electroencephalogram consistent for right centro-temporal epileptiform abnormalities and brain

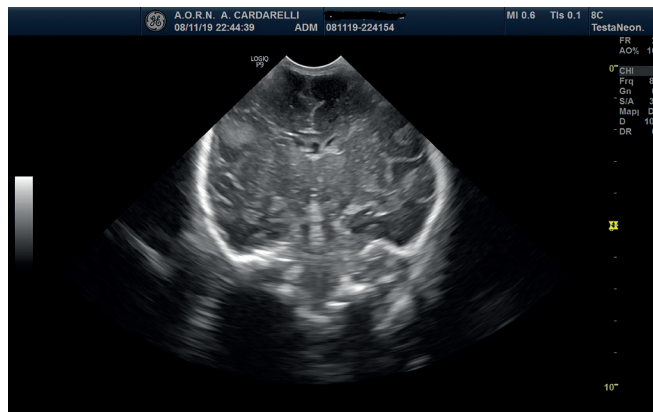


Figure 2. Cerebral ultrasound.

Magnetic Resonance Imaging with evidence of bilateral multiple cortical-subcortical and periventricular lesions consistent for hamartomas. She started antiepileptic therapy with phenobarbital and clonazepam, with good control. Based on 2012 Criteria of second International Tuberous Sclerosis Complex Consensus Conference, the second twin had cardiac rhabdomyoma (major criterion) and one skin fibroma, thus a diagnosis of TSC was probable. The third twin had a cardiac rhabdomyoma (major criterion), subependymal nodules (major criterion), one renal angiomyolipoma, and two skin fibromas so a definitive diagnosis of TSC has been made.

In suspicious of hypothesis of familial Tuberous Sclerosis, a genetic panel was performed, that resulted negative for all the three children and both parents.

DISCUSSION

TCS is a multisystemic neurocutaneous genetic condition with autosomal dominant inheritance. The first manifestation of TSC is a cardiac tumor assessed by using foetal ultrasound [14, 15]. With regards to clinical manifestation of TCS in the fetal period cardiac rhabdomyomas are often seen and these are, usually identified through US screening of second trimester. However, it remains challenging to detect these benign hamartomas in other organs such as the brain, the kidneys, the heart, and the skin. Notable, foetal magnetic resonance imaging (MRI) is useful in detecting extracardiac hamartomas but is difficult to use as a screening tool.

A family history of TSC is an important clue in the diagnosis of foetal TSC and it may require a target-

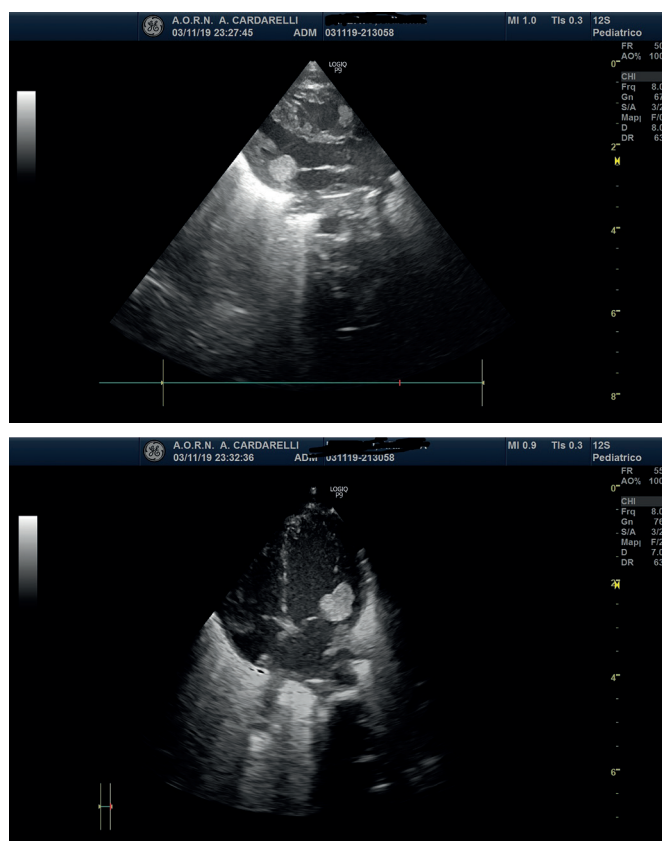


Figure 1. Heart ultrasound.

ed genomic sequencing of TSC1 and TSC2 genes, to improve the efficacy of prenatal detection of TSC and facilitate prognosis, counselling, and potential early intervention to improve the outcomes of these individuals [16].

In 2012, the Tuberous Sclerosis Consensus Conference updated diagnostic criteria and surveillance management of the disease [7]. In the recent years, relevant data on clinical and genetic came from the TOSCA (Tuberous Sclerosis registry to increase disease Awareness) study, a long registry of patients with TSC [10]. In this registry the median age of diagnosis of TSC was one year, with central nervous system (CNS) involvement (most of the time seizures) as the main postnatal characteristic (73.3%) while cardiac rhabdomyoma detected in 22.1% of patients antenatally. In addition, genetic testing was available in 53.5% of patients, while no mutation identified in 19.6% of patients.

In the case we described there was no family history of TSC, but the mother of the three twins had a not defined history of epilepsy even though without a clear diagnosis and with no evidence of cardiac or skin abnormalities.

The early diagnosis of TSC has been assessed by using echocardiography and cerebral ultrasound performed in the early days of life for prematurity screening. In our twins the genetic test for TSC1 and TSC2 genes was negative.

Our epileptic patient in the follow up was treated with antiepileptic therapy but new studies have been made on mTOR inhibitors as a molecular target for the treatment of TSC manifestation including epilepsy, behaviour, TSC-related subependymal giant cell astrocytomas (SEGA) and renal angiomyolipoma [17].

This treatment is also safe and efficacious in TSC patients under 2 years of age. However, no prediction on long term safety under maintenance therapy can be made and further multicentre studies and registers with larger cohorts and longer follow-up periods are awaited.

In the last few years, noninvasive prenatal diagnosis (NIPD) based on cell-free DNA (cfDNA) has been introduced into the clinical application for some monogenic disorders but not for tuberous sclerosis (TSC) yet, which is an autosomal dominant disease caused by various variations in TSC1 or TSC2 gene. However, recently, Yang *et al.* showed that NIPD based on cfDNA is feasible for TSC, but required to be confirmed with more samples [18].

CONCLUSIONS

In summary, TSC is a quite rare genetic disease and early diagnosis is very uncommon, given few cases published in literature. In our patients, early diagnosis has been performed by using early postnatal ultrasound screening, without a prenatal diagnosis. In the next future a better knowledge of this disease, leads to an early diagnosis and treatment without requiring a genetic positive test or family history.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors contributed equally to this work.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

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Data sharing

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REFERENCES

1. Rodrigues DA, Gomes CM, Costa IM. Tuberous sclerosis complex. *An Bras Dermatol.* 2012;87(2):184-96. doi: 10.1590/s0365-05962012000200001.
2. Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans TK; International Tuberous Sclerosis

- Consensus Group. Cardiovascular manifestations of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendations from the International Tuberous Sclerosis Consensus Group. *J Am Heart Assoc.* 2014;3(6):e001493. doi: 10.1161/JAHA.114.001493.
3. Sadowski K, Kotulska K, Schwartz RA, Józwiak S. Systemic effects of treatment with mTOR inhibitors in tuberous sclerosis complex: a comprehensive review. *J Eur Acad Dermatol Venerol.* 2016;30(4):586-94. doi: 10.1111/jdv.13356.
 4. DiMario FJ Jr, Sahin M, Ebrahimi-Fakhari D. Tuberous sclerosis complex. *Pediatr Clin North Am.* 2015;62(3):633-48. doi: 10.1016/j.pcl.2015.03.005.
 5. Jacks SK, Witman PM. Tuberous Sclerosis Complex: An Update for Dermatologists. *Pediatr Dermatol.* 2015;32(5):563-70. doi: 10.1111/pde.12567.
 6. MacKeigan JP, Krueger DA. Differentiating the mTOR inhibitors everolimus and sirolimus in the treatment of tuberous sclerosis complex. *Neuro Oncol.* 2015;17(12):1550-9. doi: 10.1093/neuonc/nov152.
 7. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49(4):243-54. doi: 10.1016/j.pediatrneurol.2013.08.001.
 8. Wheless JW, Almoazen H. A novel topical rapamycin cream for the treatment of facial angiofibromas in tuberous sclerosis complex. *J Child Neurol.* 2013;28(7):933-6. doi: 10.1177/0883073813488664.
 9. Ng KH, Ng SM, Parker A. Annual review of children with tuberous sclerosis. *Arch Dis Child Educ Pract Ed.* 2015;100(3):114-21. doi: 10.1136/archdischild-2013-304948.
 10. Kingswood JC, Bruzzi P, Curatolo P, de Vries PJ, Fladrowski C, Hertzberg C, et al. TOSCA - first international registry to address knowledge gaps in the natural history and management of tuberous sclerosis complex. *Orphanet J Rare Dis.* 2014;9:182. doi: 10.1186/s13023-014-0182-9.
 11. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol.* 2015;14(7):733-45. doi: 10.1016/S1474-4422(15)00069-1.
 12. Bhatt JR, Richard PO, Kim NS, Finelli A, Manickavachagam K, Legere L, et al. Natural History of Renal Angiomyolipoma (AML): Most Patients with Large AMLs >4cm Can Be Offered Active Surveillance as an Initial Management Strategy. *Eur Urol.* 2016;70(1):85-90. doi: 10.1016/j.eururo.2016.01.048.
 13. Jeong A. Tuberous Sclerosis Complex: A Roadmap for Future Research. *Pediatr Neurol Briefs.* 2016;30(7):32. doi: 10.15844/pedneurbriefs-30-7-1.
 14. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med.* 2006;355(13):1345-56. doi: 10.1056/NEJMr055323.
 15. Sampson JR, Yates JR, Pirrit LA, Fleury P, Winship I, Beighton P, et al. Evidence for genetic heterogeneity in tuberous sclerosis. *J Med Genet.* 1989;26(8):511-6. doi: 10.1136/jmg.26.8.511.
 16. Gu X, Han L, Chen J, Wang J, Hao X, Zhang Y, et al. Antenatal screening and diagnosis of tuberous sclerosis complex by fetal echocardiography and targeted genomic sequencing. *Medicine (Baltimore).* 2018;97(15):e0112. doi: 10.1097/MD.00000000000010112.
 17. Saffari A, Brösse I, Wiemer-Kruel A, Wilken B, Kreuzaler P, Hahn A, et al. Safety and efficacy of mTOR inhibitor treatment in patients with tuberous sclerosis complex under 2 years of age - a multicenter retrospective study. *Orphanet J Rare Dis.* 2019;14(1):96. doi: 10.1186/s13023-019-1077-6.
 18. Yang XY, Meng Y, Wang YY, Lu YP, Wang QH, You YQ, et al. Noninvasive prenatal diagnosis based on cell-free DNA for tuberous sclerosis: A pilot study. *Mol Genet Genomic Med.* 2022:e1952. doi: 10.1002/mgg3.1952.



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Relationship between fear of COVID-19 and mental health in pregnant women

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ABSTRACT

Objective. The impact of crises such as the COVID-19 epidemic on the health of pregnant mothers is much bigger than that of other people in the society which can lead to irreparable consequences. The present study was conducted with the aim of determining the relationship between fear of COVID-19 and mental health in pregnant women presenting to health centres in Mashhad.

Materials and Methods. This cross-sectional study was conducted in 2022 on 205 pregnant women who presented to health centres in Mashhad. The data were collected using a demographic profile questionnaire, a mental health scale, and a fear of COVID-19 scale, whose validity and reliability have been confirmed. Data analysis was performed using SPSS version 21 and descriptive statistics, independent samples t-test, ANOVA and Pearson correlation. Value level was considered significant at $p \leq 0.05$.

Results. the mean score of fear of COVID-19, psychological well-being and psychological distress was 17.80 ± 5.72 , 55.74 ± 8.51 and 34.68 ± 9.59 , respectively. There was a significant relationship between fear of COVID-19 and psychological well-being ($r = -0.19$, $p = 0.008$), fear of COVID-19 and psychological distress ($r = 0.22$, $p = 0.001$), psychological well-being and psychological distress ($r = -0.50$, $p < 0.001$).

Conclusions. The results of this study showed that the Corona catching induced anxiety was related to fear of COVID-19 and psychological distress in pregnant women. It is necessary to carry out interventions to improve the mental health of pregnant women and reduce the fear caused by COVID-19 during the Corona pandemic.

INTRODUCTION

Coronavirus in humans causes a range of disorders, from mild respiratory tract infections, such as the common cold to lethal infections, such as the severe acute respiratory syndrome (SARS), Middle East

respiratory syndrome (MERS) and Coronavirus disease 2019 (COVID-19). The COVID-19 pandemic caused thousands of deaths, along with physical and mental problems in the affected people [1-3]. As a result of the COVID-19 contagiousness and broken containment [4], many people suffered

much fear and stress in these conditions and believed that the disease threatened them, their neighbours, and their families [5]. Stress is a non-specific body response to a demand as a result of a reaction or stimulus [6]. Such factors as disease prolongation, increased hospitalizations, deaths, virus behaviour change and its increased contagion to all age groups even children, and the re-infection of patients created a kind of constant fear and stress among people [7, 8]. Such psychological reactions have had a major impact on mental health in recent decades. Furthermore, mental health disorders have been identified as one of the most common and important health problems, accounting for over one-third of disability and premature death [9, 10]. Mental health disorders can, in turn, affect physical or social health and other dimensions of health and significantly reduce the quality of life [10-12].

According to the National Burden of Disease Survey, women are more vulnerable than men which is one of the important causes of women's mortality due to pregnancy and childbirth. Meanwhile, pandemics have a greater effect on pregnant mothers' health than on other people in a society because pregnancy is one of the most sensitive periods of mothers' life which can lead to irreparable consequences. Injuries to the foetus during pregnancy can cause many physical and mental disorders in the following years of a person's life. Therefore, as mothers' health is highly important, dangerous signs during pregnancy which may significantly affect the pregnancy outcome should be detected. In addition, health promotion of pregnant mothers is one of the priorities in health programs of the Ministry of Health in Iran [13]. Considering the importance of the mental health of pregnant women, especially during the COVID-19 pandemic, the present study aimed to evaluate the relationship between fear of COVID-19 and mental health in pregnant women.

MATERIALS AND METHODS

This cross-sectional study was conducted on all pregnant women referred to health centres of Mashhad, Iran, in 2022. The present research was approved by the Ethics Committee of Mashhad University of Medical Sciences (ethics code: IR.MUMS.NURSE.REC.1400.059) and it was registered in Mashhad University of Medical Sciences

with the code: 4000696. Prior to the study, written informed consent was obtained from all enrolled patients allowing data collection and analysis for research purposes. This manuscript conforms the Enhancing the QUALity and Transparency Of health Research (EQUATOR) network guidelines. The inclusion criteria were Iranian pregnant women (with any gestational age) living in Mashhad, having minimum basic literacy, and lack of the following criteria: having high-risk pregnancy, using psychotherapeutic drugs and narcotics, suffering from underlying and chronic diseases, and experiencing severely stressful events such as financial bankruptcy or death of first-degree relatives in the last six months. After the ethics committee at Mashhad University of Medical Sciences approved the study, the data collection was started using the stratified-cluster multi-stage method. All five healthcare centres in Mashhad were considered as classes, and the health centres in the five regions were considered as clusters. Then, one health centre was randomly selected from each class.

Using Poursardar and *et al's*. [14] and the following formula, and taking into account type 1 error of 0.05, power of 0.80, standard deviation of 10.53 and absolute error of 1.5, the sample size was obtained 189: $n = (z^2 \times s^2) / d^2 = (1.96^2 \times 10.53^2) / 1.5^2 \approx 189$. Considering 10% drop in the sample, the final sample size was considered equal to 200.

The data collection tool included a Personal, social and obstetric characteristic questionnaire, mental health and fear of COVID-19 scale. The mental health scale is a 28-item questionnaire consisting of two constructs: psychological well-being and psychological distress. The scale is scored based on a 5-point Likert scale from 1 (completely disagree) to 5 (completely agree). The reliability ranged from 0.89 to 0.94 using the internal consistency method and Cronbach's alpha coefficient calculation. A correlation coefficient of -0.87 and 0.88 was found between the subscales of the instrument and the general score of the general health questionnaire to confirm the concurrent validity of the tool [15, 16]. The validity and reliability of the fear of COVID-19 scale were confirmed by the factor analysis method and Cronbach's alpha coefficient (0.82), respectively, in the Iranian population [17]. According to the checklist of the research unit and considering the inclusion criteria, the researcher visited the health centres and selected all pregnant women who were seeking care during pregnancy. Then, the informed consent form, demographic and

midwifery questionnaire, fear of COVID-19 scale, and mental health scale were administered to the pregnant women which were completed in the self-report fashion.

The data were analysed using SPSS software version 21. Central and dispersion indices (mean \pm SD) and frequency distribution were used in order to describe the variables. Kolmogorov-Smirnov test was applied for assessing the normality of the data the results of which showed that the data distribution was normal. So, independent t-test, ANOVA and Pearson correlation were used to analyse the data. The significance level was 0.05 in all of the tests.

RESULTS

The mean score of pregnant women age, husband age and marriage years was 28.55 ± 6.04 , 33.09 ± 6.03 and 7.20 ± 4.84 , respectively. The average number of pregnancy, number of abortion, number of delivery, number of normal vaginal delivery (NVD), number of caesarean section (CS), number of children and gestational age was 2.02 ± 1.13 , 0.30 ± 0.55 , 0.77 ± 0.94 , 0.42 ± 0.77 , 0.35 ± 0.72 , 0.77 ± 0.94 and 22.77 ± 10.63 , respectively. The demographic information of pregnant women in the study is reported in **Table 1**. The results of the present study showed that the mean score of fear of COVID-19, psychological well-being and psychological distress was 17.80 ± 5.72 , 55.74 ± 8.51 and 34.68 ± 9.59 , respectively and there was a significant relationship between fear and psychological well-being ($r = -0.19$, $p = 0.008$), and fear and psychological distress ($r = 0.22$, $p = 0.001$) (**Table 2**).

The results of ANOVA showed that the pregnancy type was correlated with fear factor ($p = 0.027$) and psychological distress ($p = 0.016$) so that the mean of fear in wanted pregnancy, unplanned and unwanted pregnancy group was 94.07 ± 14.93 , 85.63 ± 16.89 and 94.07 ± 20.63 , respectively. Also, the mean of psychological distress in wanted pregnancy group was 33.47 ± 9.08 , in unplanned group was 33.67 ± 10.42 and in unwanted pregnancy group was 38.50 ± 10.16 .

Corona catching induced anxiety was related to fear of COVID-19 ($p < 0.001$) and psychological distress ($p = 0.041$) so that the mean score of fear of COVID-19 in the group with mild level of anxiety was 15.24 ± 4.60 , in the group with moderate level was 19.39 ± 4.55 and in the group with high level was 23.48 ± 5.98 . Also, the mean score of psycholog-

Table 1. Demographic and midwifery characteristic of pregnant women.

| Variable | Number (%) |
|---------------------------|------------|
| Education level | |
| Diploma and under diploma | 121 (59) |
| Higher than diploma | 83 (41) |
| Husband education | |
| Diploma and under diploma | 122 (60) |
| Higher than diploma | 83 (1) |
| Occupation | |
| Housewife | 157 (77) |
| Employed | 47 (23) |
| Husband occupation | |
| Worker | 148 (72) |
| Employee | 57 (28) |
| Family income | |
| Less than enough | 25 (12) |
| Sufficient or more | 180 (88) |
| Foetal sex | |
| Female | 66 (32) |
| Male | 71 (35) |
| Female and male (twin) | 4 (2) |
| Pregnancy planning | |
| Wanted pregnancy | 143 (70) |
| Unplanned pregnancy | 33 (116) |
| Unwanted pregnancy | 29 (14) |
| Desire for foetal sex | |
| Yes | 80 (46) |
| No | 12 (1) |
| No differences | 81 (53) |

Table 2. Relationship between fear of COVID-19, psychological distress and psychological well-being.

| | Fear of COVID-19 | Psychological well-being | Psychological distress |
|--------------------------|-------------------|--------------------------|------------------------|
| Fear of COVID-19 | 1 | - | - |
| Psychological well-being | -0.19 (0.008*) | 1 | - |
| Psychological distress | 0.22 (0.001*) | -0.50 ($< 0.001^*$) | 1 |

*Significance level of 0.05.

ical distress in the group with mild level was 33.34 ± 9.01 , in the group with moderate level was 33.30 ± 10.15 and in the group with high level was 38 ± 9.82 . The results of the independent t-test showed that if the women were infected with Corona during pregnancy, the mean score of psychological distress was 38.04 ± 9.20 and in the other group it was 34.25 ± 9.59 , the difference of which was statistically significant ($p = 0.049$). The information about Corona is reported in **Table 3**.

Table 3. Information about CORONA.

| Variable | Number (%) |
|--|------------|
| Corona catching induced anxiety | |
| Low | 111 (54) |
| Moderate | 61 (30) |
| High | 33 (16) |
| Corona infection before pregnancy | |
| Yes | 72 (35) |
| No | 133 (65) |
| Corona infection in pregnancy | |
| Yes | 23 (11) |
| No | 182 (89) |
| Corona infection in family or acquaintances | |
| Yes | 153 (75) |
| No | 52 (25) |
| Death duo to Corona in family or acquaintances | |
| Yes | 51 (25) |
| No | 154 (75) |

DISCUSSION

The COVID-19 pandemic has become a clinical threat, and the stress of getting infected has imposed a psychological threat to the general population worldwide. Moreover, the vague nature of the COVID-19 and the unknown course of the disease has also caused psychological disorders in different population groups. The fear and anxiety of expectant mothers when visiting midwifery service centres is one of the key factors contributing to the COVID-19 crisis [17]. The findings of this study showed that the Corona catching induced anxiety was related to the constructs of fear of the COVID-19 and psychological distress. Therefore, the average score of fear of COVID-19 and psychological distress in pregnant mothers with high anxiety was higher than that in the group with moderate anxiety. Psychological factors are the most dangerous factors when dealing with crises. The fear of death refers to the emotional response to perceived dangers, threats and signs of death [19], which can weaken the immune system, especially in patients [20]. Feelings or physical symptoms resulting from the fear of Corona during the outbreak of the COVID-19 were interpreted as "I am breathing faster than before, so I am infected by the COVID-19" [21, 22]. Therefore, excessive threat and risk assessment was associated with increased health anxiety [23, 24]. Lee *et al.* (2020) showed that the fear of COVID-19 had a significant relationship with

health anxiety [25]. In addition, Ahorso *et al.* (2020) reported a significant relationship between fear of COVID-19 and health anxiety [17].

The findings revealed that the average score of psychological distress in the group with a history of COVID-19 infection during pregnancy was higher. In addition to weakening the immune system, anxiety can damage mental health by harming people's moods [26]. Mental health is one of the variables that can affect disease anxiety [27]. The results indicated a significant relationship between the variables of fear of COVID-19 and psychological well-being, as well as fear of COVID-19 and psychological distress. The direct effect of the fear of COVID-19 on health anxiety is consistent with the studies of Lee *et al.* (2020) [25] and Ahorso *et al.* (2020) [17]. The studies conducted on past viral pandemics such as Ebola and bird flu showed that anxiety and health concerns during these pandemics are widespread [23]. This relationship can be explained by the fact that during the pandemic of the COVID-19, the media and environment stressed the challenges of the disease and observation of health precautions. Since the physical sensations and the person's interpretation can be affected by environmental events, increasing health concerns and fear of disease increases health anxiety [28].

Chen *et al.* (2020) studied nine pregnant women infected with the COVID-19 and showed that amniotic fluid, umbilical cord blood, throat swabs in infants, and breast milk samples infected with COVID-19 were negative in terms of virus contamination [30]. In Chen's study, three pairs of infected mothers were tested and reported negative for virus infection [30]. Zou *et al.* examined nine pregnant mothers with the COVID-19, based on which seven mothers gave birth by caesarean section, two mothers gave birth naturally with perfect health, and ten babies (a twin pregnancy) were reported to be negative for the COVID-19 infection [31]. In Liu's study in China, complications such as premature delivery, emergency caesarean section, acute respiratory syndrome, and long-term hospitalization in ICU were reported in 13 pregnant women infected with the COVID-19 [32]. The COVID-19 pandemic has created stress and anxiety for pregnant women in different regions of the world. Anxiety and stress during pregnancy were also associated with such complications as pre-eclampsia, depression, increased nausea and vomiting during pregnancy, premature birth, low birth weight, and low APGAR score [33].

The results of the present study showed that the bad history of midwifery was related to the fear of COVID-19. Therefore, the average score of fear of COVID-19 was higher in people with a bad history of midwifery.

The results of a systematic review by Kazemi *et al.* (2021) revealed that there is an increased risk of abortion in mothers with a positive test result of SARS-CoV-2. Reports related to abortion in pregnant women with COVID-19 showed that most miscarriages due to COVID-19 in the first trimester were due to placental insufficiency. Placental inflammation during the viral infection may result in foetal growth retardation and induce abortion [34]. Zahang *et al.* (2020) also reported that no significant difference was observed between the two groups regarding the type of delivery, gestational age, birth weight, premature delivery, meconium excretion, foetal position disturbance, and asphyxia. However, a significant difference was reported regarding the use of Carboprost protamine in mothers with COVID-19 compared to healthy mothers [35]. Tajbakhsh (2021) reported that women during the COVID-19 pandemic experienced a sense of insecurity in their financial, psychological, and social statuses [37], which could have affected their mental health [36].

The findings by Aziz-Ahari *et al.* (2021) showed an increased risk of preterm labor in the suspected mothers compared to that at the same time the year before the COVID-19 pandemic [38]. Higher rates of preterm delivery can also be considered as a consequence of maternal complications in the suspected mothers because there is the possibility of disease transmission from mother to foetus, which is unknown and requires more studies with a larger population [38, 39]. The findings of a study by Arakaki *et al.* (2020) showed an association between severe COVID-19 in pregnant women and gestational age ≥ 24 weeks and maternal age ≥ 32 . The rate of preterm delivery due to the infection was significantly higher in severe COVID-19 cases [40]. Meanwhile, as the COVID-19 pandemic could be the most challenging recent global threat, it is critical to meet the health needs of pregnant women, especially their mental health, by taking timely and appropriate measures to control and reduce the consequences of the COVID-19.

A limitation of the present study is that the participants were selected only from the volunteer pregnant women referred to health centres affiliated to Mashhad University of Medical Sciences in Kho-

rasan-e-Razavi Province, Iran, as mentioned earlier. The strength of this study is that the results can help reduce stress and increase the mental health of expectant mothers during the COVID-19 pandemic.

CONCLUSIONS

The results of this study showed that the Corona catching induced anxiety was related to the constructs of fear of COVID-19 and psychological distress, so that the average score of psychological distress in the group with a history of COVID-19 infection during pregnancy was higher. Also, the results indicated a significant relationship between the variables of fear of COVID-19 and psychological well-being, as well as fear of COVID-19 and psychological distress. Moreover, bad history of midwifery was related to the fear of COVID-19. Therefore, the average fear of COVID-19 score was higher in people with a bad history of midwifery. The global pandemic of COVID-19 presented one of the most critical situations for the health systems. The COVID-19 is still spreading in some countries, and the World Health Organization has not announced an end to this disease. Pregnant mothers are at higher risk of COVID-19 than other members of the society because of experiencing a polluted environment, facing an unpredictable environment, and the stressful nature of the pregnancy. Pregnant mothers should receive periodic information about the function of the virus due to the unknown nature of the disease. The stress caused by the COVID-19 can be reduced by holding resilience training courses, fostering empathy, and increasing communication between and among pregnant mothers by spending more time for communicating with the family. Besides, strengthening the safety culture, emphasizing compliance with health issues, preventing disease, reducing stress, and increasing mental health should be considered for pregnant mothers as priorities during the COVID-19 pandemic.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

H.Y., F.Z.K., E.J., M.A.: Conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing. H.Y., F.Z.K., E.J.: Investigation, writing – review & editing.

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Study registration

This research was registered in Mashhad University of Medical Sciences with code: 4000696.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This research was approved by the Ethics Committee of Mashhad University of Medical Sciences (ethics code: IR.MUMS.NURSE.REC.1400.059).

Informed consent

All participants were provided with necessary explanations about the objectives and each enrolled patient gave informed consent to allow data collection and analysis for research purposes prior to the start of the study.

Data sharing

The datasets used and analysed during the current study are available under reasonable request to the corresponding author.

REFERENCES

1. Clemente-Suárez VJ, Martínez-González MB, Benitez-Agudelo JC, Navarro-Jiménez E, Beltran-Velasco AI, et al. The Impact of the COVID-19 Pandemic on Mental Disorders. A Critical Review. *Int J Environ Res Public Health*. 2021;18(19):10041. doi: 10.3390/ijerph181910041.
2. Sadeghi Dousari A, Taati Moghadam M, Sartazadeh N. COVID-19 (Coronavirus Disease 2019): A New Coronavirus Disease. *Infect Drug Resist*. 2020;13:2819-28. doi: 10.2147/IDR.S259279.
3. Di Fazio N, Morena D, Delogu G, Volonnino G, Manetti F, Padovano M, et al. Mental Health Consequences of COVID-19 Pandemic Period in the European Population: An Institutional Challenge. *Int J Environ Res Public Health*. 2022;19(15):9347. doi: 10.3390/ijerph19159347.
4. Zangrillo A, Beretta L, Silvani P, Colombo S, Scandroglio AM, Dell'Acqua A, et al. Fast reshaping of intensive care unit facilities in a large metropolitan hospital in Milan, Italy: facing the COVID-19 pandemic emergency. *Crit Care Resusc*. 2020; 22(2):91-4. doi: 10.51893/2020.2.pov1. Online ahead of print.
5. Jafferany M, Patel A. Understanding psychocutaneous disease: psychosocial & psychoneuroimmunologic perspectives. *Int J Dermatol*. 2020;59(1):8-15. doi: 10.1111/ijd.14629.
6. Salleh MR. Life event, stress and illness. *Malays J Med Sci*. 2008;15(4):9-18.
7. Shahyad S, Mohammadi M T. Psychological Impacts of Covid-19 Outbreak on Mental Health Status of Society Individuals: A Narrative Review. *J Mil Med*. 2020;22(2):184-92. doi:10.30491/JMM.22.2.184.
8. Ghorbani V, Jandaghiyan M, Jokar S, Zanjani Z. The Prediction of Depression, Anxiety, and Stress during the COVID-19 Outbreak Based on Personality Traits in the Residents of Kashan City from March to April 2020: A Descriptive Study. *JRUMS*. 2021;20(5):503-18. doi: 10.52547/jrums.20.5.503.
9. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72(4):334-41. doi: 10.1001/jamapsychiatry.2014.2502.
10. Sayarifard A, Ghadirian L. Mental health literacy in iran: an urgent need for a remedy. *Int J Prev Med*. 2013;4(7):741-3.
11. Noroozi A, Khademolhosseini F, Lari H, Tahmasebi R. The Mediator Role of Mental Health Literacy in the Relationship Between Demographic Variables and Health-Promoting Behaviours. *Iran J Psychiatry Behav Sci*. 2018;12(2):e12603. doi: 10.5812/ijpbs.12603.
12. Grasaas E, Skarstein S, Mikkelsen HT, Småstuen MC, Rohde G, Helseth S, et al. The relationship between stress and health-related quality of life and the mediating role of self-efficacy in Norwegian adolescents: a cross-sectional study. *Health Qual Life Outcomes*. 2022 9;20(1):162. doi: 10.1186/s12955-022-02075-w.
13. Lupattelli A, Picinardi M, Einarson A, Nordeng H. Health literacy and its association with perception of teratogenic risks and health be-

- havior during pregnancy. *Patient Educ Couns*. 2014;96(2):171-8. doi: 10.1016/j.pec.2014.04.014.
14. Poursardar F, Abbaspour Z, Abdi Zarrin S, Sangari A. The impact of resilience on mental health and life satisfaction, a psychological model of well-being. *Sci Mag Yafte*, 2012;14(1):81-9. [Persian].
 15. Besharat M. Reliability and Validity of a short form of the Mental Health Inventory in an Iranian population. *Iran J Forensic Med*. 2009;15(2):87-91. [In Persian].
 16. Besharat M. Mental Health Inventory-28: Questionnaire, Instruction and Scoring. *Dev Psychol*. 2020;17(65):102-4. [In Persian].
 17. Ahorsu DK, Lin CY, Imani V, Saffari M, Griffiths MD, Pakpour AH. The Fear of COVID-19 Scale: Development and Initial Validation. *Int J Ment Health Addict*. 2022;20(3):1537-45. doi: 10.1007/s11469-020-00270-8.
 18. Mortazavi F, Ghardashi F. The lived experiences of pregnant women during COVID-19 pandemic: a descriptive phenomenological study. *BMC Pregnancy Childbirth*. 2021;21(1):193. doi: 10.1186/s12884-021-03691-y.
 19. Al Eid NA, Arnout BA. Crisis and disaster management in the light of the Islamic approach: COVID-19 pandemic crisis as a model (a qualitative study using the grounded theory). *J Public Aff*. 2020;20(4):e2217. doi: 10.1002/pa.2217.
 20. Sadeghi Yarandi M, Gholami A, Ghasemi M, Sadeghi Yarandi M, Ghasemi Koozekonan A, Soltanzadeh A. Investigating the Psychological Consequences of the COVID-19 Outbreak in the Occupational Society. *Journal Mil Med*. 2020;22(6):562-9. doi: 10.30491/JMM.22.6.562.
 21. Blakey SM, Abramowitz JS. Psychological Predictors of Health Anxiety in Response to the Zika Virus. *J Clin Psychol Med Settings*. 2017;24(3-4):270-8. doi: 10.1007/s10880-017-9514-y.
 22. Wytykowska A, Fajkowska M, Domaradzka E. BIS-dependent cognitive strategies mediate the relationship between BIS and positive, negative affect. *Personality and Individual Differences*. 2021;169:110241. doi: 10.1016/j.paid.2020.110241.
 23. Jalloh MF, Li W, Bunnell RE, Ethier KA, O'Leary A, Hageman KM, et al. Impact of Ebola experiences and risk perceptions on mental health in Sierra Leone, July 2015. *BMJ Glob Health*. 2018;3(2): e000471. doi: 10.1136/bmjgh-2017-000471.
 24. Bults M, Beaujean DJ, de Zwart O, Kok G, van Empelen P, van Steenberghe JE, et al. Perceived risk, anxiety, and behavioural responses of the general public during the early phase of the Influenza A (H1N1) pandemic in the Netherlands: results of three consecutive online surveys. *BMC Public Health*. 2011;11:2. doi: 10.1186/1471-2458-11-2.
 25. Lee SA, Jobe MC, Mathis AA, Gibbons JA. Incremental validity of coronaphobia: Coronavirus anxiety explains depression, generalized anxiety, and death anxiety. *J Anxiety Disord*. 2020;74:102268. doi: 10.1016/j.janxdis.2020.102268.
 26. Shomali Ahmadabadi M, Poorjanebollahi M, Behjat A, Barkhordari Ahmadabadi A. The Role of Experiential Avoidance and Professional Assistance Orientation in Predicting Covid Anxiety-19. *JCP*. 2021;9(36):67-78. [Persian].
 27. Fard SA, Saffarinia M. The prediction of mental health based on the anxiety and the social cohesion that caused by Coronavirus. *Soc Psychol Res Q*. 2020;9(36):129-41. [In Persian].
 28. Jungmann SM, Witthöft M. Health anxiety, cyberchondria, and coping in the current COVID-19 pandemic: Which factors are related to coronavirus anxiety? *J Anxiety Disord*. 2020;73:102239. doi: 10.1016/j.janxdis.2020.102239.
 29. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-15. doi: 10.1016/S0140-6736(20)30360-3.
 30. Chen S, Huang B, Luo DJ, Li X, Yang F, Zhao Y, et al. [Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases]. *Zhonghua Bing Li Xue Za Zhi*. 2020;49(5):418-23. Chinese. doi: 10.3760/cma.j.cn112151-20200225-00138.
 31. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;9(1):51-60. doi: 10.21037/tp.2020.02.06.
 32. Liu Y, Chen H, Tang K, Guo Y. Withdrawn: Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect*. 2020:S0163-4453(20)30109-2. doi: 10.1016/j.jinf.2020.02.028.

33. Rashidi Fakari F, Simbar M. Coronavirus Pandemic and Worries during Pregnancy; a Letter-to Editor. *Arch Acad Emerg Med.* 2020;8(1):e21.
34. Kazemi SN, Hajikhani B., Didar H., Hosseini SS, Haddadi S, Khalili F, et al. COVID-19 and cause of pregnancy loss during the pandemic: A systematic review. *PloS One.* 2021;16(8):e0255994. doi: 10.1371/journal.pone.0255994.
35. Zhang L, Jiang Y, Wei M, Cheng BH, Zhou XC, Li J, et al. [Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province]. *Zhonghua Fu Chan Ke Za Zhi.* 2020;55(3):166-71. Chinese. doi: 10.3760/cma.j.cn112141-20200218-00111.
36. Tajbakhsh G. A Grounded Theory of Insecurity Feeling in Women during the Corona Pandemic. *J Woman Fam Stud.* 2021;9(1):162-88. doi: 10.22051/JWFS.2021.34034.2579.
37. Aziz-Ahari S, Beigi B, Parsa E, Ghelichkhani F. Maternal and Neonatal Complications of COVID-19: A Case-series Study. *Iran J Ped.* 2021;31(4). doi: 10.5812/ijp.114479.
38. Ghanim SM, AlAasam AI, Alzubaidi AA, Shojaeian R. COVID 19 vertical transmission: A growing concern. *Iran J Pediatr.* 2020;30(4). doi: 10.5812/ijp.104465.
39. Saeedi M, Sangsari R, Mirnia K. COVID-19 in neonates: A review. *Iran J Pediatr.* 2020;31(1). doi: 10.5812/ijp.104423.
40. Arakaki T, Hasegawa J, Sekizawa A, Ikeda T, Ishiwata I, Kinoshita K. Risk factors for severe disease and impact of severity on pregnant women with COVID-19: a case-control study based on data from a nationwide survey of maternity services in Japan. *BMJ open.* 2022;12(12):e068575. doi: 10.1136/bmjopen-2022-068575.



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The impact of antenatal diagnosis of placenta accreta on reducing blood loss: a 57-case monocentre retrospective study

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ABSTRACT

Objective. The aim of our study was to investigate the impact of antenatal diagnosis of PA on blood loss, blood transfusions, and maternal and neonatal morbidity and mortality.

Materials and Methods. This is a monocentre retrospective study including all patients who had failed manual removal of the placenta or evidence of placental invasion at the surgery. The patients included were divided into 2 groups:

- Group 1: patients with an antenatal diagnosis according to the ultrasounds or magnetic resonance imaging data.
- Group 2: patients with unexpected placenta accreta.

Then, we compared blood loss estimated by Gross formula, transfusions, and maternal and neonatal morbidity in both groups.

Results. In our series, 57 cases of PA were included: 35 patients with antenatal diagnosis (group 1) and 22 with unexpected PA (group 2). The bleeding estimation was $1,610 \pm 908$ ml in group 1 versus $2,480 \pm 1,317$ ml in group 2, with $p = 0.007$. The need for transfusion was reduced from 95.4% to 17% when PA was diagnosed antenatally with $p = 0.001$. Unexpected PA was correlated with an increased risk of severe bleeding with OR 2.35, 95%CI 1.08-5.62 and transfusion requirements with OR 1.85, 95%CI 1.18-6.1. However, expected PA was correlated with a higher risk of prematurity with OR 2.04, 95%CI 1.05-4.8.

Conclusions. The antenatal diagnosis of placenta accreta allowed better maternal outcomes by reducing the blood loss and transfusions requirements. However, it increased the incidence of planned preterm birth.

INTRODUCTION

Placenta accreta is one of the most serious pregnancy complications in which the placenta is abnormally adherent and invades the uterine wall [1].

Its incidence is increasing all over the world following the trend of rising caesarean delivery and intrauterine interventions [2]. Placenta accreta can lead to a life-threatening severe and catastrophic haemorrhage, resulting in haemostatic hysterecto-

my, blood transfusion, and significant adverse maternal and neonatal outcomes [1].

Ultrasound is the primary tool in antenatal diagnosing placenta accreta, and magnetic resonance imaging is generally performed to help in the diagnosis [3, 4]. Furthermore, the antenatal diagnosis may allow better organization and some precautions that may improve maternal outcomes. The aim of this study was to investigate the role of antenatal diagnosis of placenta accreta and its impact on blood loss, transfusions, and maternal and neonatal morbidity and mortality.

MATERIALS AND METHODS

Study design

After obtaining patients' oral consent and the approval from the local ethics committee, we conducted a monocentre retrospective study by analysing the database of patients with confirmed placenta accreta to assess the impact of the antenatal diagnosis on maternal outcomes and particularly the blood loss and the need for transfusions and neonatal outcomes.

Study setting

The study was conducted in the maternity of the Hedi Chaker University Hospital in the region of Sfax in Tunisia. We studied a database of patients who were hospitalized for placenta accreta in the period lasting from January 2016 to March 2021.

Study population with selection criteria

We included patients aged from 18 to 45 years old with placenta accreta (where the chorionic villi attach directly to the surface of the myometrium), increta (where the chorionic villi penetrate deeply into the myometrium), and percreta (where chorionic villi penetrate through the uterine serosa). We considered placenta accreta all patients who experienced failed attempts to remove the placenta during the third stage of labour, evidence of placental invasion at surgery and failed manual removal of the placenta partly or totally.

We did not include patients aged less than 18 years, as well as individuals declining to consent or not being able to consent. We did not include patients with suspected placenta accreta, but not confirmed

during the delivery (complete placenta removal after delivery). Patients with confirmed placenta accreta who were operated on in other maternity hospitals and then referred to our tertiary centre were excluded from the study.

Data collection

We collected data about demographic parameters like age, weight, size, gestity, parity, and past history of caesarean delivery and intrauterine curettage. We also collected the clinical and biological features when admitted to the hospital like bleeding during the third trimester, transfusion during the current pregnancy (before delivery), the haemoglobin concentration, the prothrombin ratio, and platelet count.

The per-operative management including the mode of delivery, the anaesthesia technique, and the surgical technique was also assessed.

The surgical technique includes the radical treatment based on total surgical removal of the placenta (hysterectomy), or conservative treatment when the placenta was left *in situ* and the surgeon opted for haemostatic suture techniques, arterial ligation, and medical treatment using methotrexate.

The blood loss was calculated according to the Gross formula [5]:

$$\text{Blood loss} = \text{total blood volume of a pregnant woman} (80 \text{ ml/kg}) \times \text{weight (kg)} \times [(\text{Hb.i} - \text{Hb.d2})/((\text{Hb.i} + \text{Hb.d2})/2)] + 500 \text{ ml for every RBC unit transfused.}$$

Hb.i: haemoglobin concentration before delivery.

Hb.d2: haemoglobin concentration of the second day after delivery.

To assess the impact of antenatal diagnosis of placenta accreta, we compared the blood loss, the transfusions required, the need for catecholamines, and the anaesthesia and surgery-related complications. A massive transfusion was defined by the transfusion of more than 4 RBC units within the first hour or 10 RBC units within the first 24 hours after delivery. The duration of hospital stay was also compared. The neonatal outcomes including the term at delivery, the incidence of prematurity, the need for neonatal intensive care unit referral, and stillbirth were also assessed.

Study size

The sample size determination was based on data from the preliminary results of the 20 last patients enrolled in this study (10 with antenatal diagno-

sis and 10 without). The incidence of blood loss exceeding 2 L was 10% in the antenatal diagnosis group and 80% in the second group. So, we determined that a study sample of 14 patients in each group is required for a 95% confidence level and a 5% margin of error.

Bias

All patients had the same therapeutic protocol. All patients had an ultrasound examination in the third trimester of pregnancy. In the case of uncertain diagnosis of PA with ultrasounds, a MRI was done.

Patients with antenatal diagnosis of placenta accreta had elective caesarean section scheduled at the 35th or 36th gestational weeks. Special precautions were used. A multidisciplinary team, including 2 experimented obstetricians, an anaesthesiologist, an interventional radiologist, a neonatologist, and in some cases, an urologist, was involved in delivery. Two red blood cell (RBC) units were ready to use in the operation room. Patients with antenatal diagnosis were operated on under general anaesthesia. If placental removal failed, a caesarean hysterectomy or conservative treatment may be performed. In cases with extensive bladder involvement, when a caesarean hysterectomy was considered unsafe, a hysterectomy with bladder reconstruction and ureterostomy can be performed. The transfusion protocol was the same for both groups (the protocol was approved by the department and the institution). The thresholds of transfusion were 7 g/dL of haemoglobin, 50% of prothrombin ratio, and 20×10^6 /L of platelet count. As the blood loss clinical estimation (blood collection) was operator dependent, we used an objective method based on the variation of haemoglobin concentration in the first two days after delivery (Gross formula) to calculate the blood loss.

Groups definition

To assess the impact of the antenatal diagnosis on maternal outcomes (blood loss, transfusions, and maternal morbidity and mortality), the patients included were divided into two groups:

- Group 1: patients with antenatal diagnosis of placenta accreta according to the ultrasounds or the MRI data.
- Group 2: patients with an intrapartum diagnosis of placenta accreta (unexpected PA).

Statistical analysis

Statistical analyses were performed using the SPSS 23.0 (SPSS, Chicago, IL, USA) statistical package. Continuous variables were presented as means value \pm standard deviation. We distinguished two groups according to the antenatal diagnosis of placenta accreta. The comparison between groups was achieved by the Student's t-test and Chi² test for continuous variables and categorical variables, respectively. The Fisher exact test was used when the Chi² test was not applicable. The Mann-Whitney U test was used for non-parametric continuous variables. A binary logistic regression analysis was done to investigate the impact of antenatal diagnosis on maternal outcomes. Odds ratios (OR) and a confidence interval of 95% (95%CI) were reported. The significance threshold was set at $p < 0.05$.

Ethical approval

The approval of the Hedi Chaker University Hospital Local Ethics Committee was obtained before beginning the study.

RESULTS

In this study, we included 57 patients with placenta accreta over 44578 deliveries during the study period. Two patients who were initially taken in charge in other hospitals and secondly referred to our centre were excluded from the study. Placenta accreta was confirmed by anatomopathological examination in 53 cases (all cases treated by a hysterectomy). The incidence of placenta accreta was 0.13% (1/782 deliveries). All patients had obstetric ultrasounds examination but placenta accreta was suspected in only 35 patients (61.4%). Of these 35 suspected patients, only 15 patients had a MRI examination. The MRI confirmed the diagnosis of placenta accreta in all cases.

Then patients were divided into the antenatal diagnosis group (group 1, $n = 35$) and the unexpected PA group (group 2, $n = 22$).

The demographic parameters (age, weight, high) and historical characteristics (gravidity, parity, history of caesarean delivery or uterine surgery) of the women were comparable in both groups (**Table 1**). The current pregnancy characteristics and preoperative management were also comparable in both groups (**Table 2**).

Table 1. Demographic parameters.

| | Group 1 (n = 35) | Group (n = 22) | P-value |
|--|------------------|----------------|---------|
| Age (Years) | 36.47 ± 3.54 | 34.7 ± 3.39 | 0.112 |
| Weight (Kg) | 75.73 ± 6.69 | 76.37 ± 9.37 | 0.817 |
| Patients high (cm) | 162 ± 11 | 164 ± 12 | 0.800 |
| Gestivity (mean) | 4.73 ± 2.37 | 4.47 ± 1.67 | 0.61 |
| Patients with 1 gravidity | 0 (0%) | 0 (0%) | |
| Patients with 2 or more gravidities | 35 (100%) | 22 (100%) | |
| Parity (mean) | 3.73 ± 1.79 | 3.63 ± 0.99 | 0.873 |
| Patients with 1 parity | 0 (0%) | 0 (0%) | |
| Patients with 2 or more parities | 35 (100%) | 22 (100%) | |
| History of caesarean deliveries | | | 0.789 |
| Patients with 0 caesarean delivery | 0 (0%) | 1 (4.5%) | |
| Patients with 1 caesarean delivery | 6 (17%) | 5 (22.7%) | |
| Patients with 2 or more caesarean deliveries | 29 (82.5%) | 19 (86.3%) | |
| Patients with History of curettage | | | 0.745 |
| 0 | 30 (85.7%) | 17 (77.2%) | |
| 1 | 4 (11.4%) | 4 (18.1%) | |
| 2 or > 2 | 1 (2.8%) | 1 (4.5%) | |

Significant P-value ≤ 0.05.

Table 2. Current pregnancy characteristics and per operative management.

| | Group 1 (n = 35) | Group 2 (n = 22) | P-value |
|--|------------------|------------------|---------|
| Placenta previa in current pregnancy | 35 (100%) | 22 (100%) | 1 |
| Placenta accreta | 29 | 21 | |
| Placenta increta | 5 | 1 | 0.259 |
| Placenta percreta | 1 | 0 | |
| Preoperative haemoglobin concentration (g/dL) | 11.1 ± 1.67 | 11.18 ± 1.28 | 0.848 |
| Prothrombin ration (%) | 94.3 ± 2.8 | 95.1 ± 3.1 | 0.745 |
| Platelet level 10 ⁶ /mL | 174 ± 31 | 186 ± 22 | 0.215 |
| Bleeding during 3 rd trimester of pregnancy | 17 (48.5%) | 11 (50%) | 0.892 |
| Transfusion during pregnancy | 0 | 0 | - |
| Mode of delivery | | | 0.911 |
| Caesarean section | 35 (100%) | 21 (95.4%) | |
| Vaginal delivery | 0 (0%) | 1 (4.5%) | |
| Anaesthesia | | | 0.908 |
| General anaesthesia | 34 (97.1%) | 21 (95.4%) | |
| Loco regional anaesthesia | 1 (2.8%) | 1 (4.5%) | |
| Hysterectomy | 35 (100%) | 18 (81.8%) | 0.558 |
| Conservative treatment | 0 (0%) | 4 (18.1%) | |
| Uterine artery embolization | 0 (0%) | 0 (0%) | |

Significant P-value ≤ 0.05.

The antenatal diagnosis of placenta accreta reduced significantly the blood loss from 2,480 ± 1,317 ml in group 2 to 1,610 ± 908 ml in group 1 with p = 0.007.

Severe bleeding (blood loss superior to 2 L) was more frequent in patients without antenatal diagnosis of placenta accreta (81.8% versus 5.7% when diagnosed prenatally with p = 0.001 and OR 2.35,

95%CI 1.08-5.62). The antenatal diagnosis of PA reduced the need for transfusion. In group 1, only 10 patients needed transfusion (28.5%) versus 21 patients (95.4%) in group 2; $p = 0.001$. The risk of transfusion was higher when the placenta accreta was not diagnosed prenatally with OR 1.85, 95%CI 1.18-6.1. The transfusion details are summarized in **Table 3**.

Massive transfusion was higher in the unexpected PA group, but this difference was not statistically significant (**Table 3**). In our study, we noted 3 cases of haemorrhagic shock that needed the administra-

tion of catecholamines per-operatively. All of them were unexpected PA. Surgical and anaesthesia complications were comparable between both groups. Per- and post-operative maternal complications were also comparable between both groups (**Table 4**). For neonatal outcomes, preterm birth was more frequent when the PA was diagnosed antenatally (**Table 4**). Expected PA was correlated with a higher risk of prematurity with OR 2.04, 95%CI 1.05-4.8. However, the birth weight and the incidence of referral to the NICU were comparable in both groups. Any case of stillbirth was noted in our study.

Table 3. Blood loss and the need of transfusion.

| | Group 1 (n = 35) | Group 2 (n = 22) | P-value and OR [95%CI] |
|---|------------------|------------------|-----------------------------------|
| Blood loss (ml) | 1,610 ± 908 | 2,480 ± 1317 | 0.007 |
| Blood loss > 2 L | 2 (5.7%) | 18 (81.8%) | 0.001 and 2.35 [1.08-5.62] |
| Red cell unit transfused per patient | 0.93 ± 1.33 | 1.87 ± 1.57 | 0.045 |
| Patients needed RBC | 10 (28.5%) | 21 (95.4%) | 0.001 and 1.85 [1.18-6.1] |
| Patients needed massive transfusion (> 4 RBC/1hour) | 1 (2.8%) | 5 (22.7%) | 0.055 |
| FFP transfused per patient | 0.80 ± 2.24 | 1.40 ± 3.15 | 0.515 |
| Patients needed FFP | 1 (2.8%) | 7 (31.8%) | 0.066 |
| Platelets transfused per patient | 0 | 1.13 ± 3.09 | 0.165 |
| Patients needed Platelets transfusion | 0 (0%) | 3 (13.6%) | 0.084 |

OR: odds ratio; CI: confidence interval; RBC: red blood cells; FFP: fresh frozen plasma; significant P-value ≤ 0.05 in bold.

Table 4. Maternal and neonatal morbidity.

| | Group 1 (n = 35) | Group 2 (n = 22) | P-value and OR [95%CI] |
|---|------------------|------------------|----------------------------------|
| Maternal outcomes | | | |
| Haemorrhagic chock (need for catecholamine) | 0 (0%) | 3 (13.6%) | 0.24 |
| Surgical complication | 3 (8.5%) | 3 (13.6%) | 0.652 |
| Urinary tract injury | 2 | 2 | - |
| Digestive tract injury | 0 | 0 | - |
| Postoperative infections | 1 | 1 | - |
| Late bleeding or haematoma | 0 | 0 | - |
| Anaesthesia complication | 0 (0%) | 0 (0%) | - |
| Transfusion complication | 0 (0%) | 1 (4.5%) | - |
| Duration of hospitalization (days) | 5.13 ± 1.5 | 6 ± 3.59 | 0.379 |
| Neonatal outcomes | | | |
| Term at delivery | 35.4 ± 5.1 | 37.3 ± 3.8 | 0.089 |
| Preterm delivery ≤ 37 WG | 31 (88.5%) | 4 (18.1%) | 0.001 and 2.04 [1.05-4.8] |
| Birth weight (g) | 2,851 ± 345 | 3,010 ± 285 | 0.095 |
| Referral to the NICU | 32 (91.4%) | 21 (95.4%) | 0.845 |
| Stillbirth | 0 | 0 | - |

OR: odds ratio; CI: confidence interval; WG: weeks of gestation; NICU: neonatal intensive care unit; significant P-value ≤ 0.05 in bold.

DISCUSSION

In this study, we showed that the antenatal diagnosis of placenta accreta using ultrasounds technique and MRI allowed a significantly reduced blood loss and lower rates of transfusions requirements as a consequence. We showed also that the absence of this antenatal diagnosis was correlated with an increased risk of severe bleeding (blood loss superior to 2 L) and RBC transfusion.

So, this study emphasizes the role of the antenatal diagnosis that allows planned and organized management by a multidisciplinary team and thus can reduce haemorrhagic morbidity, compared with unexpected placenta accreta [6]. Our study has a clinical implication as it emphasizes the role of prenatal ultrasound and MRI as promising diagnostic tools for PA in the third trimester, in reducing the maternal blood loss and maternal morbidity as a consequence. As a low-income country, access to healthcare structures can be difficult at times, and high-level maternity hospitals with multidisciplinary teams are not available in all regions of our country [7]. So, we still have an important group of patients who did not have a correct antenatal screening of the placenta accreta. Furthermore, patients can sometimes neglect the utility of prepartum consultations, particularly multiparous ones. This study shows that gynaecologists as well as patients should be aware of the higher risk of postpartum complications due to the absence of an antenatal diagnosis of the placenta accreta [8].

The placenta accreta spectrum in our study was comparable with the literature data. The incidence was 1/782 which is near 1/1,000 of recent publications [9, 10]. The main risk factors including placenta previa, previous caesarean section, uterine surgeries, *in vitro* fertilization, and advanced maternal age were identified in our cases [6, 11]. Understanding placenta accreta spectrum risk factors may facilitate patient identification and may help in prenatal diagnosis. We suggest particular caution for patients at risk of abnormal placentation and we think that using advanced techniques like MRI for prenatal diagnosis seems to be reasonable [12]. MicroRNAs (miRNAs) are small non-coding RNA molecules (~22 nucleotides long) that suppress gene expression by binding to the 3' end of the untranslated region (3'-UTR) of target mRNAs [13]. It has been reported that miR-34a, miR-29a/b/c, and miR-125a are significantly down-regulated in placenta accreta but the mecha-

nisms by which miRNAs might contribute to PAS pathogenesis have yet to be determined [14]. Nevertheless, these biomarkers demonstrated modest screening efficiency [15].

The ultrasounds remain the primary tool in diagnosing placenta accreta [9]. Although the increasing role of MRI in placenta accrete diagnosis is evident, it requires experienced readers [16]. The literature reveals several disparate but conceptually overlapping MRI signs. Identifying and differentiating between placenta increta and percreta on imaging may be quite challenging even with MRI and sometimes even on final pathology [12, 16].

In our study ultrasound was performed in all patients, but diagnosed placenta accreta in only 61.4% of cases which is lower than literature [17]. However, in a recent meta-analysis including 3,209 pregnancies [17], ultrasounds had 90.6% of sensitivity and 97.1% of specificity for placenta accreta diagnosis. This may be explained by the operator dependence of this examination as well as his experience in managing such rare and unusual situations.

Other studies showed that prenatal MRI has an excellent diagnostic accuracy in identifying the depth and the topography of placental invasion [18], in spite of an interobserver variability [19]. This meta-analysis [18] including 20 studies with 1,080 pregnancies showed a high sensibility of the MRI in diagnosing accreta (94.4%), increta (100%), percreta (86.5%) and high specificity. The corresponding values for specificity were 98.8%, 97.3% and 96.8%. These results are comparable with those of our study in which MRI diagnosed antenatally the placenta accreta in 100% of cases.

Antenatal diagnosis allows safe delivery planning and better team organization like the referral to specialized centres for placenta accreta management, which may improve the maternal and neonatal outcomes [20]. This multidisciplinary organization can lead to reduced blood loss and reduced transfusion rates and so reduced maternal morbidity [21-23]. Recent studies showed that the maternal morbidity was also correlated to other factors like the invasion topography of the placenta [24]. Another study including 29 parturients with placenta accreta showed that MRI features may predict massive haemorrhage and may be helpful for pre-operative preparation of placenta accreta patients [25]. However, MRI features were not significant for predicting adverse neonatal events including preterm delivery, low birth weight, and 5-minute APGAR score [26].

In our study we noted a higher rate of preterm birth in expected placenta accreta patients. This may be due to the delivery planning from 35 to 36 WG to reduce the risk of severe haemorrhage. Similar results were found in previous studies [27, 28]. The main limitation of this study is the bias in the management protocol. Indeed, blood loss and transfusions may depend on the surgical procedure and particularly the rapid bleeding control [29], as well as the surgical expertise [30], which can't be the same in both groups. Our sample size was calculated on the basis of severe bleeding which resulted in a small number of patients that can't allow the comparison of maternal complications whose incidence is lower [31, 32]. It was reported that during caesarean hysterectomy, the risk for urinary tract injury is less than 15% [33]. On the other hand, leaving the placenta *in situ* exposes women to other serious complications, such as infection, and severe bleeding [34, 35]. This is why the majority of our patients had a caesarean hysterectomy. This may be due to the advanced age and multiparity of our patients but also to the unavailability of multidisciplinary innovative approaches using Balloon catheter occlusion or arterial embolization that may reduce blood flow and potentially prevent life-threatening haemorrhage complicating conservative treatments [36, 37].

CONCLUSIONS

The antenatal diagnosis of placenta accreta allows improved maternal outcomes. It can lead to reduced blood loss and lower rates of transfusions. Unexpected placenta accreta was correlated with an additional risk of severe bleeding and transfusion requirement. This may be due to the pre-operative cautions resulting in a safe delivery planning and better team organization. However, we noted a higher incidence of planned preterm birth in patients with antenatal diagnosis of placenta accreta.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.K.: Writing – original draft. A.J.: Conceptualization, investigation, methodology, writing – review & editing. J.H.: Formal analysis, investigation. Y.E.: Data curation, formal analysis, investigation. M.D.:

Data curation, investigation. K.C., K.K: Supervision, validation, visualization.

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Ethical approval

It was obtained from the HCUH (local Ethics Committee).

Informed consent

It was obtained from all patients included in the study.

Data sharing

Data are available under reasonable request to the corresponding author due to privacy/ethical restrictions.

REFERENCES

1. Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. *BJOG*. 2014;121(1):62-70. doi: 10.1111/1471-0528.12405.
2. Morlando M, Collins S. Placenta Accreta Spectrum Disorders: Challenges, Risks, and Management Strategies. *Int J Womens Health*. 2020;12:1033-45. doi: 10.2147/IJWH.S224191.
3. Di Mascio D, Cali G, D'antonio F. Updates on the management of placenta accreta spectrum. *Minerva Ginecol*. 2019;71(2):113-20. doi: 10.23736/S0026-4784.18.04333-2.
4. Satija B, Kumar S, Wadhwa L, Gupta T, Kohli S, Chandoke R, et al. Utility of ultrasound and magnetic resonance imaging in prenatal diag-

- nosis of placenta accreta: A prospective study. *Indian J Radiol Imaging*. 2015;25(4):464-70. doi: 10.4103/0971-3026.169456.
5. Jaramillo S, Montane-Muntane M, Capitan D, Aguilar F, Vilaseca A, Blasi A, et al. Agreement of surgical blood loss estimation methods. *Transfusion*. 2019;59(2):508-15. doi: 10.1111/trf.15052.
 6. Erfani H, Fox KA, Clark SL, Rac M, Rocky Hui SK, Rezaei A, et al. Maternal outcomes in unexpected placenta accreta spectrum disorders: single-center experience with a multidisciplinary team. *Am J Obstet Gynecol*. 2019;221(4):337.e1-337.e5. doi: 10.1016/j.ajog.2019.05.035.
 7. Ghardallou M, Limam M, Khelifi A, Khairi O, Khairi H, Mtiraoui A, et al. Obstetric referrals to a tertiary care maternity: a descriptive study. *Pan Afr Med J*. 2019;33:306. doi: 10.11604/pamj.2019.33.306.16906.
 8. Limam M, Hachani F, El Ghardallou M, Bachraoui M, Mellouli M, Mtiraoui A, et al. Availability, utilization and quality of emergency obstetric care services in Sousse, Tunisia. *Pan African Med J*. 2021;38:272. doi: 10.11604/pamj.2021.38.272.17758.
 9. Alves ÁLL, Silva LBD, Costa FDS, Rezende GC. Management of placenta accreta spectrum. *Rev Bras Ginecol Obstet*. 2021;43(9):713-23. doi: 10.1055/s-0041-1736371.
 10. Carusi DA. The Placenta Accreta Spectrum: Epidemiology and Risk Factors. *Clin Obstet Gynecol*. 2018;61(4):733-42. doi: 10.1097/GRF.0000000000000391.
 11. Jenabi E, Salimi Z, Salehi AM, Khazaei S. The environmental risk factors prior to conception associated with placenta accreta spectrum: An umbrella review. *J Gynecol Obstet Hum Reprod*. 2022;51(7):102406. doi: 10.1016/j.joghoh.2022.102406.
 12. Kapoor H, Hanaoka M, Dawkins A, Khurana A. Review of MRI imaging for placenta accreta spectrum: Pathophysiologic insights, imaging signs, and recent developments. *Placenta*. 2021;104:31-9. doi: 10.1016/j.placenta.2020.11.004.
 13. Chiofalo B, Laganà AS, Vaiarelli A, La Rosa VL, Rossetti D, Palmara V, et al. Do miRNAs Play a Role in Fetal Growth Restriction? A Fresh Look to a Busy Corner. *Biomed Res Int*. 2017;2017:6073167. doi: 10.1155/2017/6073167.
 14. Yang T, Li N, Hou R, Qiao C, Liu C. Development and validation of a four-microRNA signature for placenta accreta spectrum: an integrated competing endogenous RNA network analysis. *Ann Transl Med*. 2020;8(15):919. doi: 10.21037/atm-20-1150.
 15. Chen S, Pang D, Li Y, Zhou J, Liu Y, Yang S, et al. Serum miRNA biomarker discovery for placenta accreta spectrum. *Placenta*. 2020;101:215-20. doi: 10.1016/j.placenta.2020.09.068.
 16. Zawaideh JP, Freeman S, Smith J, Bruining A, Sadler TJ, Carmisciano L, et al. Placental MRI: Identification of radiological features to predict placental attachment disease regardless of reader expertise. *Eur J Radiol*. 2022;149:110203. doi: 10.1016/j.ejrad.2022.110203.
 17. Pagani G, Cali G, Acharya G, Trisch IT, Palacios-Jaraquemada J, Familiari A, et al. Diagnostic accuracy of ultrasound in detecting the severity of abnormally invasive placentation: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2018;97(1):25-37. doi: 10.1111/aogs.13238.
 18. Familiari A, Liberati M, Lim P, Pagani G, Cali G, Buca D, et al. Diagnostic accuracy of magnetic resonance imaging in detecting the severity of abnormal invasive placenta: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2018;97(5):507-20. doi: 10.1111/aogs.13258.
 19. Finazzo F, D'antonio F, Masselli G, Forlani F, Palacios-Jaraquemada J, Minneci G, et al. Interobserver agreement in MRI assessment of severity of placenta accreta spectrum disorders. *Ultrasound Obstet Gynecol*. 2020;55(4):467-73. doi: 10.1002/uog.20381.
 20. Ornaghi S, Maraschini A, Donati S; Regional Obstetric Surveillance System Working Group. Characteristics and outcomes of pregnant women with placenta accreta spectrum in Italy: A prospective population-based cohort study. *PLoS One*. 2021;16(6):e0252654. doi: 10.1371/journal.pone.0252654.
 21. Tikkanen M, Paavonen J, Loukovaara M, Stefanovic V. Antenatal diagnosis of placenta accreta leads to reduced blood loss. *Acta Obstet Gynecol Scand*. 2011;90(10):1140-6. doi: 10.1111/j.1600-0412.2011.01147.x.
 22. Jarraya A, Kammoun M, Bouzid K, Ellouze Y, Chaabene K, Kolsi K. The impact of fresh frozen plasma versus fibrinogen concentrates on maternal outcomes in a severe postpartum hemorrhage requiring massive transfusion. *Critical Care Shock*. 2022;25(6):301-8.
 23. Jarraya A, Zghal J, Abidi S, Smaoui M, Kolsi K. Subarachnoid morphine versus TAP blocks

- for enhanced recovery after caesarean section delivery: A randomized controlled trial. *Anaesth Crit Care Pain Med*. 2016;35(6):391-3. doi: 10.1016/j.accpm.2015.10.012.
24. Chen X, Shan R, Song Q, Wei X, Liu W, Wang G. Placenta percreta evaluated by MRI: correlation with maternal morbidity. *Arch Gynecol Obstet*. 2020;301(3):851-7. doi: 10.1007/s00404-019-05420-5.
 25. Zhang J, Xu H, Xin Y, Zhang C, Liu Z, Han X, et al. Assessment of the massive hemorrhage in placenta accreta spectrum with magnetic resonance imaging. *Exp Ther Med*. 2020;19(3):2367-76. doi: 10.3892/etm.2020.8457.
 26. Bourgioti C, Zafeiropoulou K, Fotopoulos S, Nikolaidou ME, Theodora M, Daskalakis G, et al. MRI prognosticators for adverse maternal and neonatal clinical outcome in patients at high risk for placenta accreta spectrum (PAS) disorders. *J Magn Reson Imaging*. 2019;50(2):602-18. doi: 10.1002/jmri.26592.
 27. Golbasi H, Bayraktar B, Golbasi C, Omeroglu I, Sever B, Adiyaman D, et al. Expected Versus Unexpected Delivery for Placenta Accreta Spectrum (PAS) Disorders with Same Team in Single Tertiary Center. *Z Geburtshilfe Neonatol*. 2022;226(6):391-8. doi: 10.1055/a-1915-5832.
 28. Bluth A, Schindelhauer A, Nitzsche K, Wimmerberger P, Birdir C. Placenta accreta spectrum disorders-experience of management in a German tertiary perinatal centre. *Arch Gynecol Obstet*. 2021;303(6):1451-60. doi: 10.1007/s00404-020-05875-x.
 29. Jarraya A, Khaled T, Kammoun M, Ameer K, Kolsi K. Golden hour for fibrinogen concentrate infusion to improve post partum hemorrhage. *Egypt J Anaesth*. 2018;34(2):73-4. doi: 10.1016/j.egja.2018.03.002.
 30. Doumouchtsis SK, Arulkumaran S. The morbidly adherent placenta: an overview of management options. *Acta Obstet Gynecol Scand*. 2010;89(9):1126-33. doi: 10.3109/00016349.2010.503869.
 31. Anderson DJ, Liu H, Kumar D, Patel M, Kim S. Placenta Percreta Complications. *Cureus*. 2021;13(10):e18842. doi: 10.7759/cureus.18842.
 32. Grace Tan SE, Jobling TW, Wallace EM, McNeilage LJ, Manolitsas T, Hodges RJ. Surgical management of placenta accreta: a 10-year experience. *Acta Obstet Gynecol Scand*. 2013;92(4):445-50. doi: 10.1111/aogs.12075.
 33. Hoffman MS, Karlinski RA, Mangar D, Whiteman VE, Zweibel BR, Lockhart JL, et al. Morbidity associated with nonemergent hysterectomy for placenta accreta. *Am J Obstet Gynecol*. 2010;202:628.e1-5. doi: 10.1016/j.ajog.2010.03.021.
 34. Eller AG, Porter TF, Soisson P, Silver RM. Optimal management strategies for placenta accreta. *BJOG*. 2009;116(5):648-54. doi: 10.1111/j.1471-0528.2008.02037.x.
 35. Herzberg S, Ezra Y, Haj Yahya R, Weiniger CF, Hochler H, Kabiri D. Long-term gynecological complications after conservative treatment of placenta accreta spectrum. *Front Med (Lausanne)*. 2022;9:992215. doi: 10.3389/fmed.2022.992215.
 36. Nieto-Calvache AJ, López-Girón MC, Quintero-Santacruz M, Bryon AM, Burgos-Luna JM, Echavarría-David MP, et al. A systematic multidisciplinary initiative may reduce the need for blood products in patients with abnormally invasive placenta. *J Matern Fetal Neonatal Med*. 2022;35(4):738-44. doi: 10.1080/14767058.2020.1731460.
 37. Sichertiu J, El-Tani Z, Mathevet P, Desseauve D. Conservative Surgical Management of Placenta Accreta Spectrum: A Pragmatic Approach. *J Invest Surg*. 2021;34(2):172-80. doi: 10.1080/08941939.2019.1623956.



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The dual danger of pyometra and endometrial carcinoma: a case report

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ABSTRACT

Background. Pyometra, a collection of purulent material within the endometrial cavity, is a relatively uncommon gynaecological condition. Spontaneous perforation of the uterus is an infrequent complication of pyometra, most often the result of malignant conditions in the uterus.

Case presentation. We report the case of an elderly woman who had acute abdominal pain due to a ruptured uterus secondary to pyometra resulting from an infected endometrial mass diagnosed on computed tomography. She underwent an urgent exploratory laparotomy, and a total hysterectomy and bilateral salpingo-oophorectomy were performed. Her CA-125 level was raised (102.3 U/ml) and the histopathological examination (HPE) of the endometrial mass confirmed an endometrial carcinoma. The rest of the HPE shows necrotic and inflamed perforated uterus and pyometra. No organism growth was detected in both endometrial or peritoneal pus cultures. Post-operatively, she received intravenous antibiotics and gradually recovered and discharge well.

Conclusions. When an elderly post-menopausal patient presented with an acute abdomen, the possibility of a ruptured uterine perforation secondary to pyometra needs to be considered and the cause of this condition needs to be further investigated.

INTRODUCTION

Pyometra is a condition in which purulent material accumulates in the endometrial cavity, commonly secondary to bacterial infection due to insufficient drainage of endometrial secretions via the cervix [1]. It is a relatively uncommon gynaecological entity but can lead to serious complications, including spontaneous perforation of the uterus.

Pyometra should always be considered in post-menopausal patients with fever, abdominal pain and vaginal discharge [2]. An additional finding of an enlarged uterus raises suspicion of associated malignancy, most commonly cervical cancer. Other malignancy associated with this condition includes sigmoid or rectal cancer, uterine leiomyosarcoma and endometrial cancer [3, 4].

This case report describes the clinical presentation, diagnostic findings, and outcome of an elderly

woman with endometrial malignancy and pyometra complicated with uterine perforation. This patient had multiple underlying medical conditions, including diabetes mellitus and stroke, which limits her physical activity, both predisposing factors for the development of pyometra [5]. Despite being a rare occurrence, this case highlights the importance of considering pyometra in the differential diagnosis of an acute abdominopelvic emergency, particularly in elderly post-menopausal women [6]. In addition, the coexistence of endometrial carcinoma in this case underscores the need for prompt and thorough evaluation and management of the acute gynaecological condition. This case report aims to increase awareness of this uncommon but potentially life-threatening condition among healthcare providers and emphasize the importance of early diagnosis and intervention.

CASE PRESENTATION

A 67-year-old woman who had been residing in a nursing home was brought to the Emergency Department for abdominal pain. She has underlying Diabetes Mellitus and stroke 10 years ago with residual right hemiplegia. She had been bedridden due to her hemiplegic state and muscle atrophy. On examination, she looked acutely ill. Her temperature was 37.9 °C, pulse rate was 98 beats per minute and blood pressure was 110/70 mmHg.

Her abdomen was distended and guarded, and a pelvis mass was palpable.

The results of the laboratory studies on admission were as follows: white blood cell count: $40.78 \times 10^3/\mu\text{L}$, haemoglobin: 7.9 g/dl, albumin: 23 g/dl and C-reactive protein level of 209 mg/dl. Her urine dipstick test detects positive protein, blood and nitrates.

Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis (**Figure 1**) revealed an enlarged uterus with expansion of endometrial and cervical cavity with complex fluid raising suspicion of pyometra complicated with uterine fundal wall rupture, rim enhancing pelvic collections, complex ascites and peritonitis. An irregular lobulated endometrial soft tissue attenuation was seen at the posterior uterine neck-cervical junction with parametrial and serosal invasion compatible with a neoplasm. No pneumoperitoneum.

An urgent exploratory laparotomy was done, and a total hysterectomy and bilateral salpingo-oophorectomy were carried out. About 2,800 ml of pus was found in the peritoneal cavity. The uterus was distended, fragile, entirely necrotic and with a wall defect at the anterior surface of the fundus measuring 2.4 cm in diameter. Pus was draining from the perforated uterine wall into the peritoneal cavity.

Her CA-125 level was raised (102.3 U/ml) and the histopathological examination (HPE) of the endometrial mass confirmed an endometrial carcinoma.

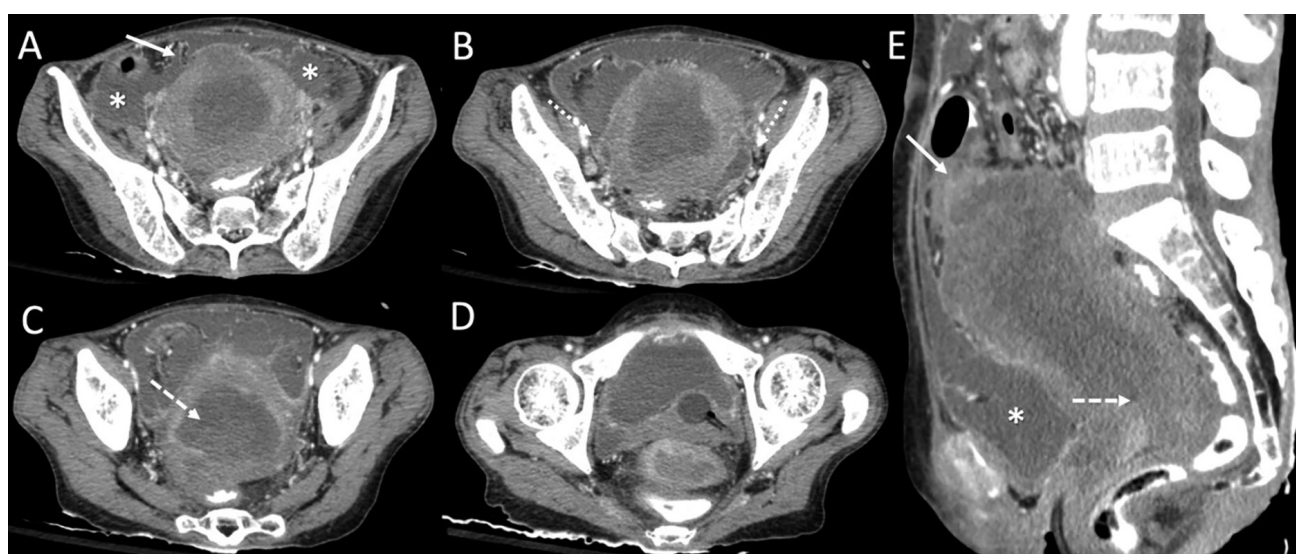


Figure 1. Contrast-enhanced computed tomography (CECT) pelvis in axial projections craniocaudally (A-D) and sagittal reformatted projection (E) showing gross ascites (*) and an enlarged uterus with heterogenous fluid-filled expansion of the endometrial cavity and cervical canal indicative of pyometra.

(A, E) Perforation at the uterine fundus (solid arrow); (B) Pelvic lymphadenopathy with rim-enhancing pelvic collections (dotted arrow) and enhancing peritoneal lining suggestive of peritonitis; (C, E) Endometrial soft tissue mass (dashed arrow) with myometrial and serosal extension to the right posterior wall of uterine neck-cervical junction; (D) Fluid-filled and expanded cervical canal.

The rest of the HPE shows necrotic and inflamed perforated uterus and pyometra. No organism growth was detected in both endometrial or peritoneal pus cultures. Postoperatively, the patient received intravenous antibiotics and supportive treatment. She gradually recovered and was discharged on postoperative day 62.

DISCUSSION

Between 0.01% and 0.5% of all gynaecological admissions and 13.6% of geriatric gynaecologic outpatients were diagnosed with pyometra [5, 6]. Patients with spontaneous uterine perforation resulting from pyometra have a mortality rate as high as 40% [1, 5, 6].

A variety of pathologies, such as malignant or benign gynaecological tumours, radiation cervicitis, atrophic cervicitis, congenital anomalies, puerperal infections, cervical occlusion after surgery, and postmenopausal cervical stenosis, can obstruct the cervical canal causing impaired endometrial drainage and with concurrent bacterial infection resulting in pyometra [5, 6].

The majority of the literature and case series reported cervical carcinoma as the most common malignancy complicated with pyometra and uterine rupture [1, 3, 5, 6]. Ikeda *et al.* conducted a literature review on spontaneous rupture of pyometra and found that out of 54 patients, 18 (34%) had malignant tumours. Among them, 12 patients (67%) had cervical cancer, 5 patients (28%) had sigmoid colon cancer, and 1 patient (5%) had endometrial cancer [3]. In contrast, Kerimoglu *et al.* reported a different outcome in their study. Among 12 patients, 5 (41.6%) were diagnosed with endometrial cancer, 3 (25%) with cervical cancer, and 1 (8.3%) with uterine leiomyosarcoma [4]. In our case, the pyometra developed due to cervical canal obstruction by an endometrial mass at the uterine neck-cervical junction.

The incidence of pyometra increases significantly with advancing age, declining physical activity, incontinence, and diabetes [7]. Suspect pathological factors include age-related uterine involution, senile cervicitis, and poor hygiene. The majority of elderly patients in nursing homes are immobile or bedridden and have an increased risk of infection due to poor medical conditions and/or poor hygiene, making them more susceptible to this condition [8].

The classic symptoms of these patients are the triad of fever, abdominal pain and purulent vaginal discharge [7, 8]. Non-specific symptoms include vomiting, constipation, uterine enlargement or genital bleeding. Furthermore, more than 50% of women with non-perforated pyometra are asymptomatic [3]. In our case, the patient's main complaint was abdominal pain. Fever was only detected during vital signs examination. Due to her advanced age and apparent cognitive decline, the patient was unable to describe any symptoms associated with the enlargement of her uterus, which mirrored a pelvic mass or vaginal discharge. In addition, she was unable to offer a comprehensive history of her symptoms, and her caretakers lacked relevant information.

Preoperative diagnosis of a perforated pyometra can be challenging in view of non-specific symptoms, lack of patients' awareness of underlying gynaecological condition and clinical examination mimicking other acute abdomen pathologies. The literature review by Ikeda *et al.* reported gastrointestinal (GI) perforation, generalized peritonitis, pneumoperitoneum, ileus and acute appendicitis as pre-operative diagnoses [3]. Gastrointestinal perforation is the most prevalent preoperative diagnosis, and this is likely attributed due to the presence of pneumoperitoneum in half the cases [1, 3, 9]. Only 19% of cases were preoperatively diagnosed accurately and most are identified by laparotomy [1].

YingYing *et al.* highlighted 5 CT characteristics to improve the diagnostic accuracy of spontaneous uterine perforation which include fluid within the endometrial cavity, fluid collection in the cul-de-sac, intra or peri-uterine free air and uterine wall defects [8]. There are only 3 features which are seen in our case, excluding the presence of intra or peri-uterine free air. Intra-uterine free air is commonly generated secondary to gas-forming bacterial infection within the uterus and when there is perforation, the air locules escape through the uterine wall defect and are mostly situated in the peri-uterine region.

According to Ikeda *et al.*, the most common bacterial cultures of peritoneal fluid or pus were *Escherichia coli* (51%) and anaerobes such as *Bacteroides* and *Peptococcus* species (41%) [3]. *Streptococcus*, *Staphylococcus*, *Klebsiella*, *Enterococcus*, *Proteus*, and *Porphyromonas* species comprised the remaining bacteria. No bacteria were isolated from the cultures in 8% of cases, similar to our culture.

Hysterectomy is the gold standard treatment, particularly in the case of uterine perforation, which requires immediate surgical intervention followed by intensive antibiotic therapy [3, 10, 11]. Conservative treatment for a uterine rupture with an intraperitoneal collection is not recommended and is associated with high comorbidity. However, it may be considered for patients at high surgical risk. In these instances, the alternate treatment is typically pus drainage and peritoneal lavage [3].

Bogani *et al.* started a study on radiomics and molecular classification in endometrial cancer (the ROME study) which discusses the potential of radiomic profiling, a method for extracting data from radiological images, to supplement molecular/genomic profiling in predicting the prognosis of endometrial cancer patients [12]. The study aims to evaluate newly diagnosed endometrial cancer patients through ultrasonographic evaluation and radiomic analysis to correlate with molecular/genomic profiling in order to identify various classes of risk for endometrial cancer, classify prognosis and tailor treatment accordingly. Radiomic profiling in this study has two pitfalls which include radiomic features variability which is affected by constitutional variables, and operator factor as ultrasound imaging is operator dependent, which might provide inconsistent readings. It is important to note, however, that the results of this study are currently unknown as it is still ongoing. It is worth noting that due to the expense associated with radiomic, genomic, and molecular profiling, these techniques are not currently employed at our centre.

The Modified Frailty Index is the most common instrument for assessing the frailty of gynecologic oncology patients [13]. Eleven variables were evaluated: diabetes, functional status index of 2 or higher, chronic obstructive pulmonary disease or pneumonia, congestive heart failure, myocardial infarction, percutaneous coronary intervention and/or stenting or angina, hypertension requiring medication, peripheral vascular disease or ischemic rest pain, impaired sensorium, transient ischemic attack or cerebrovascular accident, and cerebrovascular accident with deficit. The modified fragility index (mFI) > 3 is a significant predictor of overall and severe complications in endometrial cancer patients. This index should be included in the standard examination of patients, and it can be utilised to facilitate joint decision-making for individualised therapeutic options and perioperative treatment.

CONCLUSIONS

In light of the high morbidity and mortality that can occur as a result of a ruptured uterus linked to pyometra, it is crucial that emergency medical practitioners, radiologists, and gynaecologists work closely together to enable prompt and correct diagnosis. The possibility of this diagnosis should be taken into account when evaluating postmenopausal women who presented with acute abdomen and generalised peritonitis.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

D.C.F.: Conceptualization, writing – original draft. M.A.H.S.: Writing – review & editing. Z.A.S.: Resources. A.R.T.: Data curation. C.C.: Visualization.

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Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

The authors certify that they have obtained the patient's consent form. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Shapey IM, Nasser T, Dickens P, Haldar M, Solkar MH. Spontaneously perforated pyometra: an unusual cause of acute abdomen and pneumoperitoneum. *Ann R Coll Surg Engl.* 2012;94(8):e246-8. doi: 10.1308/003588412X13373405387410.
2. Kutuk MS, Ozgun MT, Tas M, Uludag S. Spontaneous uterine perforation due to pyometra. *J Obstet Gynaecol.* 2013;33(3):322-23. doi: 10.3109/01443615.2012.754415.
3. Ikeda M, Takahashi T, Kurachi H. Spontaneous perforation of pyometra: a report of seven cases and review of the literature. *Gynecol Obstet Invest.* 2013;75(4):243-9. doi: 10.1159/000349981.
4. Kerimoglu OS, Pekin A, Yilmaz SA, Bakbak BB, Celik C. Pyometra in elderly post-menopausal women: a sign of malignancy. *Eur J Gynaecol Oncol.* 2015;36(1):59-61.
5. Iwase F, Shimizu H, Koike H, Yasutomi T. Spontaneously perforated pyometra presenting as diffuse peritonitis in older females at nursing homes. *J Am Geriatr Soc.* 2001;49(1):95-6. doi: 10.1046/j.1532-5415.2001.49017.
6. Izumi J, Hirano H, Yoshioka H, Takisawa J. Computed tomography findings of spontaneous perforation of pyometra. *Jpn J Radiol.* 2010;28(3):247-9. doi: 10.1007/s11604-009-0413-5.
7. Ou YC, Lan KC, Lin H, Tsai CC, ChangChien CC. Clinical characteristics of perforated pyometra and impending perforation: specific issues in gynecological emergency. *J Obstet Gynaecol Res.* 2010;36(3):661-6. doi: 10.1111/j.1447-0756.2010.01184.
8. Yingying H, Chaoran L, Fang L, Zhigang S, Yangzong C, Jing L, et al. Five abdominal computer tomography characteristics facilitate diagnosis of spontaneous perforation of pyometra in women with acute abdomen: a case control study. *Clin Exp Obstet Gynecol.* 2021;48(6):1324-9. doi: 10.31083/j.ceog4806210.
9. Chan KS, Tan CK, Mak CW, Chia CC, Kuo CY, Yu WL. Computed tomography features of spontaneously perforated pyometra: a case report. *Acta Radiol.* 2006;47(2):226-7. doi: 10.1080/02841850500480634.
10. Uno K, Tano S, Yoshihara M, Mayama M, Ukai M, Kishigami Y, et al. A Case Report and Literature Review of Spontaneous Perforation of Pyometra. *J Emerg Med.* 2016;50(5):e231-6. doi: 10.1016/j.jemermed.2016.01.024.
11. Sawabe M, Takubo K, Esaki Y, Hatano N, Noro T, Nokubi M. Spontaneous uterine perforation as a serious complication of pyometra in elderly females. *Aust N Z J Obstet Gynaecol.* 1995;35(1):87-91. doi: 10.1111/j.1479-828x.1995.tb01840.x.
12. Bogani G, Chiappa V, Lopez S, Salvatore C, Interlenghi M, D'Oria O, et al. Radiomics and Molecular Classification in Endometrial Cancer (The ROME Study): A Step Forward to a Simplified Precision Medicine. *Healthcare (Basel).* 2022;10(12):2464. doi: 10.3390/healthcare10122464.
13. Giannini A, Di Donato V, Schiavi MC, May J, Panici PB, Congiu MA. Predictors of postoperative overall and severe complications after surgical treatment for endometrial cancer: The role of the fragility index. *Int J Gynaecol Obstet.* 2020;148(2):174-80. doi: 10.1002/ijgo.13020.



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Pudendal nerve block *versus* usual lidocaine infiltration for pain relief in episiotomy repair: a comparative prospective study

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ABSTRACT

Objective. We aimed to compare the anaesthetic and analgesic effect of the pudendal nerve block (PNB) and of the local lidocaine infiltration during episiotomy repair and in the following 24 hours.

Patients and Methods. 70 parturients undergoing natural birth requiring episiotomy and presenting contraindication or refusal of epidural analgesia were randomized to receive pudendal nerve block with ropivacaine or local lidocaine infiltration. The main endpoint was the evaluation of obstetric analgesia by visual analogical scale. The secondary judgment criteria were: haemodynamic parameters, suture duration, onset time of sensory block, time to first analgesic request, rehabilitation parameters, parturient and obstetrician satisfaction and pain intensifying factors.

Results. Mean VAS pain score was significantly lower in pudendal group *versus* infiltration group at T10 min (10 minutes after local anaesthetic injection) (7.20 ± 8.56 *vs* 20.43 ± 18.25 , $p < 0.01$), T 15 min (5.43 ± 8.17 *vs* 17.71 ± 16.42 , $p < 0.01$), T 20 min (repair starting) (29.63 ± 23.59 *vs* 44.06 ± 28.16 , $p = 0.023$), T 1h (13.14 ± 19.18 *vs* 32.20 ± 21.25 , $p < 0.01$), T 1h 30 min (10.57 ± 14.74 *vs* 27.34 ± 16.74 , $p < 0.01$) and T 2h (9.57 ± 15.69 *vs* 25.34 ± 16.32 , $p < 0.01$), T 6h (13.57 ± 14.07 *vs* 41.43 ± 23.24 , $p < 0.01$), T 12h (22.60 ± 20.41 *vs* 36.49 ± 23.35 , $p = 0.010$) and T 18h (12.23 ± 11.84 *vs* 27.94 ± 23.40 , $p < 0.01$). Significantly shorter average suture time and better obstetrician's satisfaction were observed in pudendal group. Nevertheless, parturient satisfaction did not reveal significant difference in our study, as well as time to first analgesic request.

Conclusions. Nerve stimulator guided PNB proved to be more effective for pain management in episiotomy repair than the classical lidocaine infiltration.

INTRODUCTION

Episiotomy is a surgical incision of the vagina and the perineum made during childbirth [1] used since the 19th century [2]. It is associated with a

higher risk of acute and chronic pain and threatens the mother's quality of life and the bonding with her baby [3-5].

Episiotomy pain is underestimated [4]. Despite being the gold standard for pain relief in natural

childbirth, epidural analgesia is used only on 4% of the parturients in the world [6-8].

Local anaesthetic infiltration is commonly used for episiotomy repair [9], an easy and effective technique which can be performed by the obstetrician. The pudendal nerve block (PNB) has demonstrated its efficiency in pain management for perineal procedures, particularly for episiotomy [10, 11].

The aim of this study is to compare the anaesthetic and analgesic effect, during suture and the following 24 hours, of the PNB to that of the local lidocaine infiltration in the episiotomy repair.

MATERIALS AND METHODS

This is a prospective, randomized study performed by the team of the Anaesthesia Department and the Gynecology-Obstetrics Department of a Tunisian University Hospital. The study period was from February to May 2022.

The study was approved by CPP SUD (Le Comité de Protection des Personnes SUD) under the reference CPP SUD N°0390/2022, and informed consent was taken prior to patient enrolment. Parturients undergoing natural birth requiring episiotomy were included if they had 20 years old or more, an ASA (American Society of Anesthesiologists) physical status I or II, BMI < 30 and presenting contraindication or refusal of epidural analgesia.

Parturient women who presented any contraindications to standard epidural analgesia could succeed to be included in our study if they responded to our inclusion criteria.

Non included parturient women weren't eligible for the trial from the beginning. Non-inclusion criteria were chronic pain, long-term use of analgesics, inability to use a visual analog scale (VAS), forceps delivery, allergy to local anaesthetics, tissue infection of the perineum, sepsis, diabetes, haemostasis disorders and neurological disorders. Excluded parturient women went through the trial procedure and were excluded if they presented one or more exclusion criteria which were block failure, eclampsia and the use of another type of anaesthesia.

Randomization

For each group (R or X), we accorded the same number of sealed envelopes.

After delivery and the consent of the parturient, and before episiotomy repair, an operator took

aleatory an envelope and prepared the syringe according to it. 70 participants were randomized into two groups.

- Group R (n = 35): unilateral PNB was performed on the episiotomy side with a nerve stimulator, 15 ml of ropivacaine 0.75% (Fresenius, Kabi) were injected.
- Group X (n = 35): the wound line was infiltrated with 10 ml of lidocaine 2% (Lidocaine, Aguetant).

The practitioner in charge of performing the technique and the assisting nurse were the only unblinded persons. A second anaesthetist, responsible for the documentation of outcomes, had access to the labour room after the injection. The parturient wasn't able to distinguish between the two techniques.

Pudendal nerve block

Ten minutes after episiotomy, the women still in lithotomy position, transperineal PNB was performed in a sterile fashion, guided by nerve stimulator (Stimuplex® HNS12), using a 100 mm short bevel insulated needle (Locoplex®, VYGON, France). The puncture site is located at the intersection of a vertical line passing inside the ischial tuberosity and a perpendicular line passing through the upper edge of the anus.

The contraction of the constrictor vulvae muscle or the bulbospongiosus muscle or the clitoral hood under 0.5 milliamperere of stimulation imposes local anaesthetic (LA) injection after repeated aspiration tests (with doses commonly used [12]).

Local lidocaine infiltration

Under the same conditions of timing, position and sterile preparation, and after negative aspirations, both edges of the wound were infiltrated while slowly withdrawing and redirecting the needle in order to infiltrate the maximum possible structures and layers (the dose used should be inferior than 200 mg [13]).

For both techniques, episiotomy repair started 20 minutes after the injection, all parturients were admitted for 2 hours after delivery in the labour room and for a minimum of 24 hours in the postpartum unit. Additional analgesia was ensured with paracetamol 1 g (4 × a day), and ketoprofen 50 mg (a maximum of 3 × a day).

Outcome measures

Demographic characteristics such as age, weight, height, medical and surgical history (including perineal injuries), gestational age, parity, and previous types of deliveries were collected. The pudendal nerve depth (for group R) was collected. Onset time of sensory block was measured using the cold test. The inability to proceed suturing without switching to another type of anaesthesia defined the block failure. The intensity of pain was evaluated according to the visual analogue scale (VAS). Non-invasive blood pressure, heart and respiratory rates and VAS were monitored every 5 minutes for 40 minutes starting from the incision, then every 30 minutes for 2 hours and then every 6 hours. T 10 min = episiotomy, T 0 min = LA injection, T 20 min = first knot for the suture. The main judgment criteria in this study is the quality of analgesia based on VAS pain score during repair and the following 24 hours. In the postpartum unit, static VAS (when resting) and dynamic VAS (when moving) were noted. Secondary outcomes included variations in blood pressure, heart and respiratory rates, time of the first request for rescue analgesics, suture duration, onset time of sensory block, rehabilitation after episiotomy (time of the first ambulation, first micturition and first defecation), parturient and obstetrician satisfaction and potential complications related to LA toxicity. Pain intensifying factors were studied too.

Statistical methods

Ten parturients (five in each group) were studied to determine the required sample size. Assuming a margin error of 0.05, a power of 0.80 and a possible drop out of about 10% of the participants, the results of this pre-study are reported in **Table 1**. Statistical analysis was performed using IBM SPSS (Statistical Package for Social Sciences) 28.0 for Windows. Continuous variables were expressed as means \pm standard deviations and categorical

variables were expressed as percentages. Normal distribution of data was assessed using Kolmogorov-Smirnov test. To compare two continuous variables, Student's t-test was used after normality verification, otherwise, Mann-Whitney U test was used. To compare multiple continuous variables (> 2), one-way ANOVA was used. Pearson's Chi-square test was used to compare categorical variables if expected frequencies > 5 , Fisher's exact test was used otherwise. A P-value < 0.05 was considered significant for all statistical tests.

RESULTS

The study included 70 randomized parturients (35 in pudendal group R and 35 in infiltration group X). All eligible patients accepted to participate and were enrolled in the study.

As shown on **Table 2**, no difference was detected between groups at baseline.

In the labour room, VAS scores in each group were summarized in **Figure 1**. Significant difference was observed at T 10 min (7.20 ± 8.56 vs 20.43 ± 18.25 , $p < 0.01$), T 15 min (5.43 ± 8.17 vs 17.71 ± 16.42 , $p < 0.01$), T 20 min (29.63 ± 23.59 vs 44.06 ± 28.16 , $p = 0.023$), T 1h (13.14 ± 19.18 vs 32.20 ± 21.25 , $p < 0.01$), T 1h 30 min (10.57 ± 14.74 vs 27.34 ± 16.74 , $p < 0.01$) and T 2h (9.57 ± 15.69 vs 25.34 ± 16.32 , $p < 0.01$) in the pudendal and infiltration groups, respectively.

Static and dynamic VAS scores in the post-partum unit are summarized respectively in **Figures 2,3**. The mean VAS was higher in the infiltration group with a significant difference at T 6h (static: 13.57 ± 14.07 vs 41.43 ± 23.24 , $p < 0.01$; dynamic: 30.29 ± 22.57 vs 59.46 ± 26.65 , $p < 0.01$), T12h (static: 22.60 ± 20.41 vs 36.49 ± 23.35 , $p = 0.010$; dynamic: 43.34 ± 20.53 vs 55.69 ± 23.65 , $p = 0.023$) and T 18h (static: 12.23 ± 11.84 vs 27.94 ± 23.40 , $p < 0.01$) in the pudendal and infiltration groups, respectively (**Table 3**).

Variations in heart rate, systolic and diastolic blood pressure and respiratory rate were similar between

Table 1. Required sample size.

| | Group R | Group X | Required sample size |
|----------|-------------|-------------|----------------------|
| T 20 min | 19 \pm 19 | 50 \pm 29 | 22 |
| T 30 min | 41 \pm 22 | 56 \pm 20 | 70 |
| T 6h | 34 \pm 26 | 52 \pm 22 | 62 |
| T 18h | 50 \pm 22 | 69 \pm 10 | 28 |

Group R: pudendal group; Group X: infiltration group; T 20 min: 20 minutes after injection; T 30 min: 30 minutes after injection; T 6h: 6 hours after injection; T 18h: 18 hours after injection.

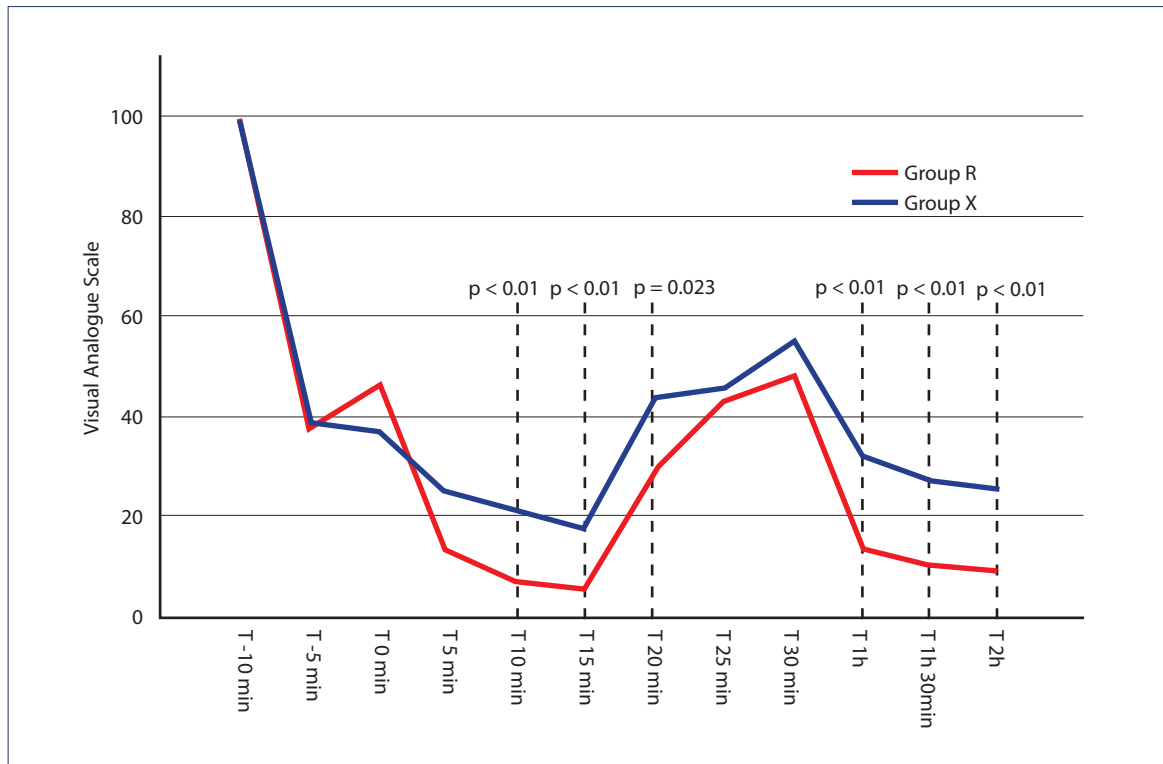


Figure 1. VAS in the labour room.

Table 2. Demographic characteristics.

| | Group R (n = 35) | Group X (n = 35) | P-value |
|---------------------------|-----------------------------------|---------------------------|---------|
| Age (years) | 27.43 ± 4.71 | 27.89 ± 3.81 | 0.657 |
| ASA 1 | 35 (100%) | 35 (100%) | 1 |
| Weight (kg) | 64.63 ± 10.85 | 62.77 ± 8.36 | 0.425 |
| Height (cm) | 162.74 ± 6.25 | 162.43 ± 5.32 | 0.821 |
| BMI (kg/m ²) | 24.27 ± 2.85 | 23.75 ± 2.59 | 0.433 |
| Parity (1/2/3/4/5) | 18(51%)/7(20%)/6(17%)/2(6%)/2(6%) | 18(51%)/9(26%)/8(23%)/0/0 | 0.338 |
| History of perineal tears | 3 (9%) | 5 (14%) | 0.452 |

Group R: pudendal group; Group X: infiltration group; ASA: American Society of Anesthesiologists; BMI: Body mass index; p < 0.05 shows significant difference between groups.

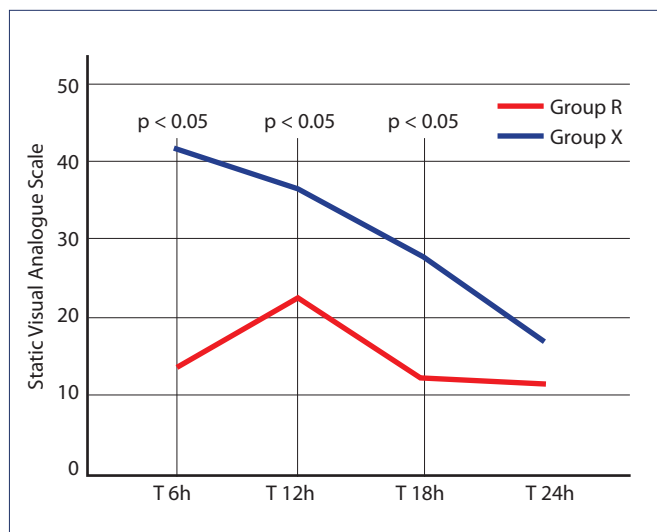


Figure 2. Static VAS in the postpartum unit.

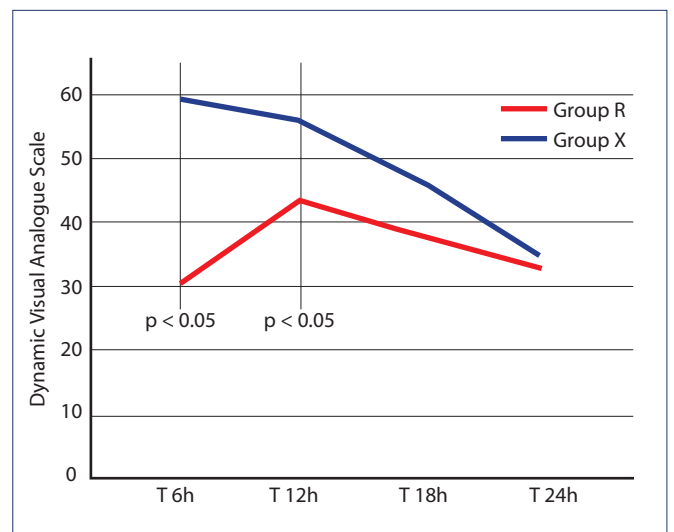


Figure 3. Dynamic VAS in the postpartum unit.

Table 3. VAS in the labor room and in the postpartum unit.

| Time | Group R | Group X | P-value |
|---------------|---------------|---------------|---------------------------------|
| T 10 min | 7.20 ± 8.56 | 20.43 ± 18.25 | p < 0.01 OR = 2.8 [1.2-2.8] |
| T 15 min | 5.43 ± 8.17 | 17.71 ± 16.42 | p < 0.01 OR = 3.2 [1.4-3.4] |
| T 20 min | 29.63 ± 23.59 | 44.06 ± 28.16 | p = 0.023 OR = 2.9 [1.1-2.9] |
| T 1h | 13.14 ± 19.18 | 32.20 ± 21.25 | p < 0.01 OR = 2.2 [1.3-4] |
| T 1h 30 min | 10.57 ± 14.74 | 27.34 ± 16.74 | p < 0.01 OR = 2.7 [1.1-3] |
| T 2h | 9.57 ± 15.69 | 25.34 ± 16.32 | p < 0.01 OR = 2.2 [1.2-1.9] |
| T 6h static | 13.57 ± 14.07 | 41.43 ± 23.24 | p < 0.01 OR = 3 [1.2-2.2] |
| T 6h dynamic | 30.29 ± 22.57 | 59.46 ± 26.65 | p < 0.01 OR = 2.8 [1.4-2.2] |
| T 12h static | 22.60 ± 20.41 | 36.49 ± 23.35 | p = 0.010 OR = 2 [1.1-2.8] |
| T 12h dynamic | 43.34 ± 20.53 | 55.69 ± 23.65 | p = 0.023 OR = 1.8 [1.6-2.1] |
| T 18h static | 12.23 ± 11.84 | 27.94 ± 23.40 | p < 0.01 OR = 2.5 [1.2-1.9] |
| T 18h dynamic | 38.1 ± 20.3 | 42.3 ± 21.23 | p = 0.02 OR = 2.6 [1.2-2.1] |

Group R: pudendal group; Group X: infiltration group; P-value < 0.05 shows significant difference between groups.

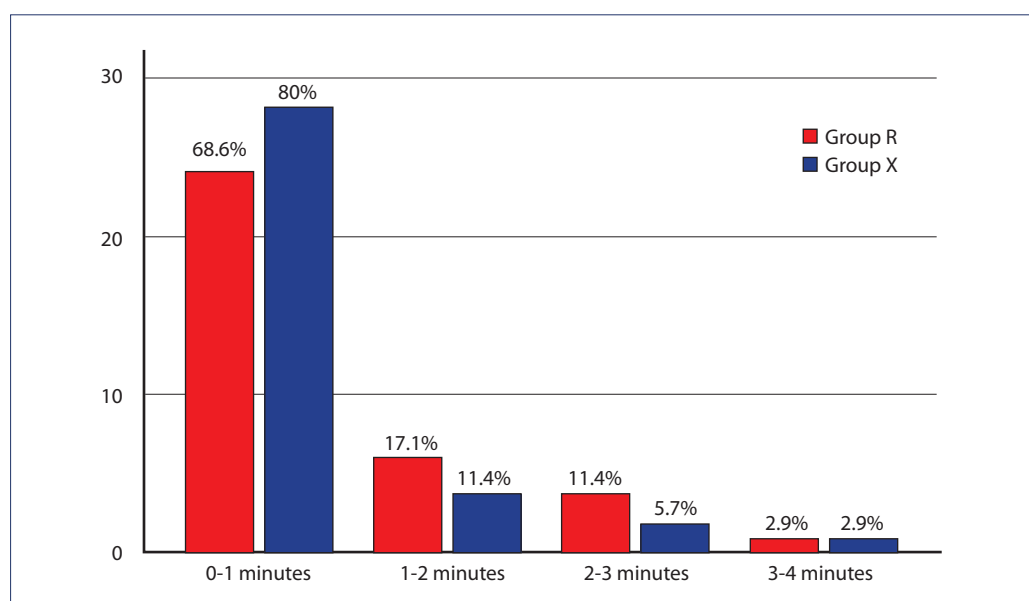


Figure 4. Onset time of sensory block.

the two groups. The average suture time was significantly shorter in pudendal group (17.5 ± 6.2 minutes vs 24 ± 7.5 minutes, p < 0.01).

Onset time of sensory block was longer in the pudendal group as shown in **Figure 4**, but the difference did not reach statistical significance (p = 0.712). 60% of parturients in group X and 54.3% in group R required additional analgesia (p = 0.629), time of

the first request for rescue analgesics was 9.68 ± 5.7 hours in group R against 8 ± 5.54 hours in group X (p = 0.35).

The rehabilitation data after episiotomy are summarized in **Table 4**.

As shown in **Table 5**, the evaluation of obstetrician’s comfort during suturing revealed statistically significant results in favour of pudendal group, maternal

Table 4. Rehabilitation after episiotomy.

| | Group R | Group X | P-value |
|---|-------------|-------------|---------------------------|
| Time to first ambulation | 4.10 ± 1.64 | 4.79 ± 2.04 | 0.125 |
| Time to first micturition | 8.70 ± 5.39 | 8.41 ± 4.55 | 0.811 |
| First defecation in the first 24h | 13 (37.1%) | 7 (20%) | 0.112 |
| Delayed transit recovery > 24 h due to pain | 4 (18.2%) | 9 (32.1%) | 0.264 |
| Time of first defecation if < 24h | 8.62 ± 1.79 | 14 ± 4.03 | < 0.001 OR = 2.5[1.2-2.1] |

Group R: pudendal group; Group X: infiltration group; p < 0.05 shows significant difference between groups.

Table 5. Parturient and obstetrician satisfaction.

| | | Group R | Group X | P-value |
|--|--------------------|------------|------------|-----------------------------|
| Maternal satisfaction | Dissatisfied | 4 (11.4%) | 4 (11.4%) | 0.463 |
| | Neutral | 11 (31.4%) | 16 (45.7%) | |
| | Satisfied | 13 (37.1%) | 12 (34.3%) | |
| | Strongly satisfied | 7 (20%) | 3 (8.6%) | |
| Obstetrician's comfort during suturing | Dissatisfied | 0 | 3 (8.6%) | < 0.001 OR = 3 [1.2-1.9] |
| | Neutral | 8 (22.9%) | 26 (74.3%) | |
| | Satisfied | 15 (42.9%) | 3 (8.6%) | |
| | Strongly satisfied | 12 (34.3%) | 3 (8.6%) | |

Group R: pudendal group; Group X: infiltration group; p < 0.05 shows significant difference between groups.

satisfaction was better too but the difference did not reach statistical significance.

During the study period, no adverse events related to LA toxicity were recorded in both groups.

In the study of pain intensifying factors, parturients under 30 years old and parturients with a BMI below 25 kg/m² experienced significantly more pain only at T 24h (at rest and during exercise) with p = 0.045. The intensity of pain was inversely proportional to parity with a significant difference at T 30min (ANOVA = 0.007), T 6h during exercise (ANOVA = 0.032), T 12h during exercise (ANOVA = 0.015), T 18h at rest (ANOVA < 0.001) and T 18h during exercise (ANOVA = 0.029). More pain was experienced by parturients with a history of perineal injury with a significant difference at T 12h during exercise (p = 0.033), T 18h at rest (p = 0.014) and T 18h during exercise (p = 0.07).

The mean depth of the pudendal nerve with the approach used in our study is 71.37 ± 7.58 mm with a median of 70 mm and a range of 55-85 mm.

DISCUSSION

Episiotomy is practiced in 60% to 70% of natural births in the general population. It is a protective practice in eutocic deliveries [14]. In fact, episiotomy can significantly reduce the number of genital

lacerations and delivery-related perineal trauma [15, 16]. It limits in some cases the duration of the second stage of labour and avoid extended perineal tears such like the disengagement of the deeply impacted foetal head [17]. But if the patient has extensive adenomyosis and a high risk of uterine rupture, she may require close follow up and eventual delivery assistance [18]. Besides, prelabour uterine rupture risk can be evaluated by a simple ultrasound examination [19].

LA perineal infiltration is the most commonly used technique for pain management during episiotomy repair [9, 20] due to its effectiveness, safety and ease of use, however intra wound multiple injections remains a painful and unaccepted procedure suggesting to think about alternative techniques. PNB is performed with a single puncture of intact skin [12] ensuring anaesthesia of an entire nerve territory. Despite being used only on 4% of parturients worldwide, epidural analgesia is the gold standard for labour pain management [21-23]. Yet the PNB still has a place even in the presence of epidural catheter, thanks to its ability to reduce LA doses and minimize side effects. In this study, PNB was done after delivery to avoid LA foetal toxicity as reported in literature [24].

For a long time, PNB has been used with the aid of a nerve stimulator to ensure optimal nerve location. During the 21st century, the use of ultrasonog-

raphy to guide invasive procedures in medicine including regional anaesthesia has decreased side effects such as vascular punctures and nerve injury. Ultrasound guided PNB is performed in the lateral position with a puncture in the gluteal region, which can make obtaining informed consent from women in labour difficult in our country.

Lidocaine is the only LA that can be intravenously administered, plenty of studies have proven its fast onset, short duration, low cost and safety [25-27]. Lidocaine perineal infiltration in the presence or not of epidural catheter is the most widely adopted protocol for pain management in episiotomy repair [26]. We tried to compare it like it is to a current technique with a recommended LA and used by the majority of authors, ropivacaine. It is characterized by a longer duration of action and a lower cardiotoxicity than other long-acting local anaesthetics [28] and point to a potential superiority in the context of multimodal analgesia.

The difference in analgesic effectiveness may be due to the injection technique, to the local anaesthetic or both. Arslan *et al.* reported significantly lower pain during the suture in pudendal group (mean VAS = 2.70 ± 2.50) than in infiltration group (mean VAS = 4.76 ± 1.97) using the same dose of prilocaine in each group [9]. In 2021, a meta-analysis showed similar analgesic effects of lidocaine and ropivacaine during episiotomy repair after performing a local anaesthetic infiltration [26]. Those trials concluded to the superiority of the PNB compared to local wound infiltration in term of analgesic efficacy at suturing regardless of the used LA which was comparable to the findings of our study.

In the study of Arslan *et al.*, PNB provided more effective analgesia than local infiltration 30 minutes after suturing [9]. Gutton *et al.* described a significantly greater analgesic effect of ropivacaine than lidocaine 2, 24, and 48 hours after repair under the same technique of local anaesthesia [13]. Deshpande and Saundattikar found similar results 2 and 4 hours after repair [29]. Schinkel *et al.* performed a local infiltration and did not find significant difference between both local anaesthetics during the first 24 hours [30].

51.4% of the included parturients in our study are primiparous. It is known that episiotomy concerns preferentially primiparous women [31, 32]. As was the case for our findings, Olayemi *et al.* [33] and Green [34] concluded that primiparous experienced more pain than multiparous women,

Eshkevari *et al.* [20] affirms that postpartum pain which is caused by the uterus' return to its original size is felt more intensely by multiparous women. Those studies did not separate episiotomy-related pain to postpartum pain. Parturients younger than 30 years of age and those with a BMI less than 25 felt significantly more pain only 24 hours after LA injection. The correlation between young age, lower weight and primiparity may explain this difference keeping in mind that the study of pain as a function of parity gave more conclusive results during different times. Perineal trauma and haemorrhoids are associated with an increased pain intensity after childbirth [20, 35], which concur with our results. Also, chronic pelvic pain due to some diseases such as endometriosis can cause more elevated level of pain [36, 37]. Other factors that may influence the severity of pain were not investigated in our study, such as information quality, psychological status [20], instrumental delivery [38], repair technique, suture type [39], ethnicity and education level [33].

Maternal and obstetrician satisfaction indicate the good management of the pre-, per-, and post-interventional periods. In our study, obstetricians were significantly more satisfied during repair in the pudendal group, coinciding with a shorter suture time in the same group and proving a higher anaesthetic efficacy of PNB. A higher rate of strongly satisfied mothers was found in group R. This difference did not reach statistical significance, which can be explained by the sample size, the inclusion of parturients who did not receive epidural analgesia, and the injection of LA after episiotomy. A new study by Xu *et al.* revealed a significantly higher rate of maternal satisfaction in the pudendal group *versus* placebo in the presence of epidural analgesia [40]. Gil-Wey *et al.* have identified other factors that may affect maternal satisfaction such as high-risk pregnancy, difficult delivery, overall negative experience, delay, poor care coordination and the presence of potential complications [41].

That's why our study offers an interesting alternative for parturients women who unfortunately can't have epidural analgesia (in case of contraindication or refusal). The use of neurostimulation in PNB offers more precision in the treatment of episiotomy's repair. This pain is known to be very intensive and causes a major discomfort even in the long term.

Several other modalities are used for episiotomy pain relief in addition to oral analgesics (parac-

etamol, nonsteroidal anti-inflammatory drug) such as epidural analgesia, prenatal perineal massage during the last 4 weeks of pregnancy [42], topical anaesthetics [43] and paracervical block [37]. Even Vocal Distraction proves to be a powerful weapon against fear and pain in women [38].

Points of strengths

Admittedly, our study has a potential contribution to improve analgesia protocols in obstetrics. Our results showed a statistically significant reduction of the pain during episiotomy repair. These results deserve to be further exploited in a large number of parturients. This study had some other limitations. There is a possibility that patients were not completely blinded. Besides, there was no long-term follow-up to detect eventual side-effects and complications of PND.

CONCLUSIONS

Episiotomy or tearing of perineal tissues during childbirth is associated with significant pain. Nerve stimulator guided PNB proved to be more effective for pain management in episiotomy repair than the classical lidocaine infiltration. Both techniques appear to be safe and unharmed, but PNB provided superior analgesia with less need for supplemental analgesia even in the postpartum period. High-quality and large-sized studies must be done to verify the safety of this procedure.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors contributed equally to this work.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The study was approved by CPP SUD (Le Comité de Protection des Personnes SUD) under the reference CPP SUD N°0390/2022.

Informed consent

A signed written consent from included patients was acquired.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Sultan AH, Thakar R, Ismail KM, Kalis V, Laine K, Räisänen SH, et al. The role of mediolateral episiotomy during operative vaginal delivery. *Eur J Obstet Gynecol Reprod Biol.* 2019;240:192-6. doi: 10.1016/j.ejogrb.2019.07.005.
2. Cleary-Goldman J, Robinson JN. The role of episiotomy in current obstetric practice. *Semin Perinatol.* 2003;27(1):3-12. doi: 10.1053/sper.2003.50000.
3. Glazener CM. Sexual function after childbirth: women's experiences, persistent morbidity and lack of professional recognition. *Br J Obstet Gynaecol.* 1997;104(3):330-5. doi: 10.1111/j.1471-0528.1997.tb11463.x.
4. Aissaoui Y, Bruyère R, Mustapha H, Bry D, Kamili ND, Miller C. A randomized controlled trial of pudendal nerve block for pain relief after episiotomy. *Anesth Analg.* 2008;107(2):625-9. doi: 10.1213/ane.0b013e31817ee48f.
5. Jiang DH, Fan YJ, Huang CJ, Zhang Y, Pan YL. Clinical effects of different anesthesia methods in lateral episiotomy. *Ann Ital Chir.* 2021;92:190-5.
6. Luo S, Chen Z, Wang X, Zhu C, Su S. Labor epidural analgesia versus without labor epidural analgesia for multiparous women: a retrospective case control study. *BMC Anesthesiol.* 2021;21(1):133. doi: 10.1186/s12871-021-01355-0.
7. Souza MA, Cecatti JG, Guida JP, Souza JP, Gulmezoglu AM, Betran AP, et al. Analgesia for vaginal birth: Secondary analysis from the WHO Multicountry Survey on Maternal and Newborn Health. *Int J Gynaecol Obstet.* 2021;152(3):401-8. doi: 10.1002/ijgo.13424.

8. Okojie NQ, Isah EC. Perception Of Epidural Analgesia For Labour Among Pregnant Women In A Nigerian Tertiary Hospital Setting. *J West Afr Coll Surg.* 2014;4(4):142-62.
9. Arslan M, Yazici G, Dilek U. Pudendal nerve block for pain relief in episiotomy repair. *Int J Gynaecol Obstet.* 2004;87(2):151-2. doi: 10.1016/j.ijgo.2004.06.020.
10. Fadel MG, Peltola L, Pellino G, Frunza G, Kontovounisios C. The Role of Pudendal Nerve Block in Colorectal Surgery: A Systematic Review. *J Invest Surg.* 2021;34(11):1238-45. doi: 10.1080/08941939.2020.1786611.
11. Rouholamin S, Jabalameli M, Mostafa A. The effect of preemptive pudendal nerve block on pain after anterior and posterior vaginal repair. *Adv Biomed Res.* 2015;4:153. doi: 10.4103/2277-9175.161580.
12. Nohuz E, Triki A, Albaut M, Fattouh M, Vitale E, El Drayi B. Comment je fais...un bloc du nerf pudendal à l'aide d'un neurostimulateur électronique [How I do...a nerve stimulator-guided pudendal nerve block]. *Gynecol Obstet Fertil.* 2015;43(3):253-5. French. doi: 10.1016/j.gyobfe.2015.01.011.
13. Gutton C, Bellefleur JP, Puppo S, Brunet J, Antonini F, Leone M, et al. Lidocaine versus ropivacaine for perineal infiltration post-episiotomy. *Int J Gynaecol Obstet.* 2013;122(1):33-6. doi: 10.1016/j.ijgo.2013.01.028.
14. Bianchedi D, Lemme E, De Matti A, Zurlo M, Testa G, Borrazzo C, et al. Pregnancy and returning to high-level sports: a retrospective study of Olympic athletes from Italian teams. *Ital J Gynaecol Obstet.* 2022;34(4):324-38. doi: 10.36129/jog.2022.79.
15. Franchi M, Parissonne F, Lazzari C, Garzon S, Laganà AS, Raffaelli R, et al. Selective use of episiotomy: what is the impact on perineal trauma? Results from a retrospective cohort study. *Arch Gynecol Obstet.* 2020;301(2):427-35. doi: 10.1007/s00404-019-05404-5.
16. Laganà AS, Terzic M, Dotlic J, Sturlese E, Palmara V, Retto G, et al. The role of episiotomy in prevention of genital lacerations during vaginal deliveries--results from two European centers. *Ginekolog Pol.* 2015;86(3):168-75. doi: 10.17772/gp/2058.
17. Visconti F, Quaresima P, Rania E, Palumbo AR, Micieli M, Zullo F, et al. Difficult caesarean section: A literature review. *Eur J Obstet Gynecol Reprod Biol.* 2020;246:72-8. doi: 10.1016/j.ejogrb.2019.12.026.
18. Vimercati A, Dellino M, Suma C, Damiani GR, Malvasi A, Cazzato G, et al. Spontaneous Uterine Rupture and Adenomyosis, a Rare but Possible Correlation: Case Report and Literature Review. *Diagnostics (Basel).* 2022;12(7):1574. doi: 10.3390/diagnostics12071574.
19. Vimercati A, Dellino M, Crupano FM, Gargano G, Cicinelli E. Ultrasonic assessment of cesarean section scar to vesicovaginal fold distance: an instrument to estimate pre-labor uterine rupture risk. *J Matern Fetal Neonatal Med.* 2022;35(22):4370-4. doi: 10.1080/14767058.2020.1849121.
20. Eshkevari L, Trout KK, Damore J. Management of postpartum pain. *J Midwifery Womens Health.* 2013;58(6):622-31. doi: 10.1111/jmwh.12129.
21. Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. *Cochrane Database Syst Rev.* 2011;(12):CD000331. doi: 10.1002/14651858.CD000331.pub3.
22. Chau A, Tsen LC. Update on Modalities and Techniques for Labor Epidural Analgesia and Anesthesia. *Adv Anesth.* 2018;36(1):139-62. doi: 10.1016/j.aan.2018.07.006.
23. Wang Q, Zheng SX, Ni YF, Lu YY, Zhang B, Lian QQ, et al. The effect of labor epidural analgesia on maternal-fetal outcomes: a retrospective cohort study. *Arch Gynecol Obstet.* 2018;298(1):89-96. doi: 10.1007/s00404-018-4777-6.
24. Pagès H, de la Gastine B, Quedru-Aboane J, Guillemain MG, Lelong-Boulouard V, Guillois B. Intoxication néonatale à la lidocaïne après analgésie par bloc des nerfs honteux: à propos de trois observations [Lidocaine intoxication in newborn following maternal pudendal anesthesia: report of three cases]. *J Gynecol Obstet Biol Reprod (Paris).* 2008;37(4):415-8. French. doi: 10.1016/j.jgyn.2008.01.010.
25. Yang X, Wei X, Mu Y, Li Q, Liu J. A review of the mechanism of the central analgesic effect of lidocaine. *Medicine (Baltimore).* 2020;99(17):e19898. doi: 10.1097/MD.00000000000019898.
26. Abu-Zaid A, Alomar O, Abuzaid M, Baradwan S, Kadah KA, Magzoub D, et al. Ropivacaine versus lidocaine infiltration for postpartum perineal pain: A systematic review and meta-analysis. *J Gynecol Obstet Hum Reprod.* 2021;50(8):102074. doi: 10.1016/j.jogoh.2021.102074.
27. Ford JM, Owen DJ, Coughlin LB, Byrd LM. A critique of current practice of transvaginal pudendal nerve blocks: a prospective audit of understanding and clinical practice. *J Obstet Gynaecol.* 2013;33(5):463-5. doi: 10.3109/01443615.2013.771155.

28. Mazoit JX, Decaux A, Bouaziz H, Edouard A. Comparative ventricular electrophysiologic effect of racemic bupivacaine, levobupivacaine, and ropivacaine on the isolated rabbit heart. *Anesthesiology*. 2000;93(3):784-92. doi: 10.1097/00000542-200009000-00028.
29. Deshpande JP, Saundattikar GY. Lignocaine Versus Ropivacaine Infiltration for Postpartum Perineal Pain. *Anesth Essays Res*. 2017;11(2):300-3. doi: 10.4103/0259-1162.177191.
30. Schinkel N, Colbus L, Soltner C, Parot-Schinkel E, Naar L, Fournié A, et al. Perineal infiltration with lidocaine 1%, ropivacaine 0.75%, or placebo for episiotomy repair in parturients who received epidural labor analgesia: a double-blind randomized study. *Int J Obstet Anesth*. 2010;19(3):293-7. doi: 10.1016/j.ijoa.2009.11.005.
31. Kartal B, Kızılrnak A, Calpbınici P, Demir G. Retrospective analysis of episiotomy prevalence. *J Turk Ger Gynecol Assoc*. 2017;18(4):190-4. doi: 10.4274/jtgga.2016.0238.
32. Räisänen S, Vehviläinen-Julkunen K, Gisler M, Heinonen S. A population-based register study to determine indications for episiotomy in Finland. *Int J Gynaecol Obstet*. 2011;115(1):26-30. doi: 10.1016/j.ijgo.2011.05.008.
33. Olayemi O, Morhason-Bello IO, Adedokun BO, Ojengbede OA. The role of ethnicity on pain perception in labor among parturients at the University College Hospital Ibadan. *J Obstet Gynaecol Res*. 2009;35(2):277-81. doi: 10.1111/j.1447-0756.2008.00937.x.
34. Green JM. Expectations and experiences of pain in labor: findings from a large prospective study. *Birth*. 1993;20(2):65-72. doi: 10.1111/j.1523-536x.1993.tb00419.x.
35. Macarthur AJ, Macarthur C. Incidence, severity, and determinants of perineal pain after vaginal delivery: a prospective cohort study. *Am J Obstet Gynecol*. 2004;191(4):1199-204. doi: 10.1016/j.ajog.2004.02.064.
36. D'Alterio MN, Saponara S, D'Ancona G, Russo M, Laganà AS, Sorrentino F, et al. Role of surgical treatment in endometriosis. *Minerva Obstet Gynecol*. 2021;73(3):317-32. doi: 10.23736/S2724-606X.21.04737-7.
37. Raffaelli R, Garzon S, Baggio S, Genna M, Pomini P, Laganà AS, et al. Mesenteric vascular and nerve sparing surgery in laparoscopic segmental intestinal resection for deep infiltrating endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2018;231:214-9. doi: 10.1016/j.ejogrb.2018.10.057.
38. Nikpoor P, Bain E. Analgesia for forceps delivery. *Cochrane Database Syst Rev*. 2013;9(9):CD008878. doi: 10.1002/14651858.CD008878.pub2.
39. Bhatia U, Soni P, Khilji U, Trivedi YN. Clonidine as an Adjuvant to Lignocaine Infiltration for Prolongation of Analgesia after Episiotomy. *Anesth Essays Res*. 2017;11(3):651-5. doi: 10.4103/0259-1162.204204.
40. Xu J, Zhou R, Su W, Wang S, Xia Y, Papadimos T, et al. Ultrasound-guided bilateral pudendal nerve blocks of nulliparous women with epidural labour analgesia in the second stage of labour: a randomised, double-blind, controlled trial. *BMJ Open*. 2020;10(8):e035887. doi: 10.1136/bmjopen-2019-035887.
41. Gil-Wey B, Savoldelli GL, Kern C, Haller G. Satisfaction maternelle de la prise en charge anesthésique durant l'accouchement: une étude de cohorte rétrospective [Risk factors associated with maternal satisfaction during childbirth: a retrospective cohort study]. *Can J Anaesth*. 2011;58(10):936-43. French. doi: 10.1007/s12630-011-9550-2.
42. Beckmann MM, Stock OM. Antenatal perineal massage for reducing perineal trauma. *Cochrane Database Syst Rev*. 2013;(4):CD005123. doi: 10.1002/14651858.CD005123.pub3.
43. Abbas AM, Mohamed AA, Mattar OM, El Shamy T, James C, Namous LO, et al. Lidocaine-prilocaine cream versus local infiltration anesthesia in pain relief during repair of perineal trauma after vaginal delivery: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2020;33(6):1064-71. doi: 10.1080/14767058.2018.1512576.
44. Novikova N, Cluver C. Local anaesthetic nerve block for pain management in labour. *Cochrane Database Syst Rev*. 2012;2012(4):CD009200. doi: 10.1002/14651858.CD009200.pub2.
45. Palermo P, Serva A, D'Alfonso A, Colagrande I, Necozone S, Cofini V, et al. Role of vocal distraction analgesia on pain management in the office hysteroscopy procedure: a randomized controlled study. *Ital J Gynaecol Obstet*. 2022;34(4):302-9. doi: 10.36129/jog.2022.24.



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Neonatal outcome-based performance of the recent International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) definition of foetal growth restriction: retrospective study

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ABSTRACT

Objective. To evaluate the performance of ISUOG definition for placenta-mediated foetal growth restriction (FGR) in predicting foetuses at risk of adverse neonatal outcomes. The definition is based on a combination of measures of foetal size percentile and Doppler abnormalities.

Materials and Methods. This retrospective study included medical records of 55 singleton pregnancies with FGR who were admitted in Ain Shams University Maternity Hospital. FGR was defined as EFW and/or AC below the 10th percentile using Hadlock's foetal growth standard. These criteria were reevaluated in accordance with the ISUOG definition for placenta-mediated foetal growth restriction in predicting adverse outcomes. Our primary outcome was to assess the accuracy of the ISUOG definition in predicting the composite adverse neonatal outcome (ANO) including one or more of the following parameters: neonatal intensive care unit (NICU) admission, 5-min APGAR score < 7, respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), necrotizing enterocolitis, periventricular leukomalacia, neonatal anaemia, pulmonary hypertension, seizures and/or death.

Results. Of the 245 pregnancies that were evaluated, only 55 records fulfilled the parameters needed to evaluate the performance of the ISUOG definition. The current study revealed that the ISUOG criteria for the diagnosis of FGR identified all pregnancies that were significantly at risk for composite adverse neonatal outcome.

Conclusions. According to the current study, the ISUOG criteria for foetal growth restriction can accurately identify foetuses at risk of adverse perinatal outcomes.

INTRODUCTION

Foetal growth restriction (FGR) is one of the main determinants of perinatal morbidity, neurological and cognitive impairment. It is highly associated with academic and social performance decrements [1]. FGR is a term used to describe the foetus failing to reach its genetically predetermined growth

potential, however, this term remains inconsistent and therefore confusing [2, 3].

FGR is thought to affect approximately 10% of pregnancies, with its prenatal recognition being a major factor tackled by different preventive strategies aiming to prevent stillbirth. However, the proposed estimates remain imprecise in the absence of a gold standard diagnostic criteria [3].

According to Quaresima *et al.*, FGR was the most common pregnancy related risk factor associated with stillbirth, occurring in 56.6% of stillbirth cases occurred from 2012 to 2020 in a single tertiary obstetric care unit in Italy [4].

The traditional widely used definition of FGR based on biometric measures of foetal weight and /or AC below the 10th percentile may misdiagnose many of the healthy constitutionally small foetuses as having growth restriction [5].

The diagnosis of FGR is a challenging process due to variability in the used definitions, such as those of The American Congress of Obstetricians and Gynecologists (ACOG) [6] and Royal College of Obstetricians and Gynecologists (RCOG) [7] which use the cutoff value of 10th percentile as a predictor for increased risk of perinatal morbidity and mortality. This definition was adopted by the recent SMFM guidelines in 2020 [8]. On the other hand, The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [3] and FIGO [9] adopted the Delphi consensus criteria for the diagnosis of FGR that incorporated sequential ultrasound measurements focusing on declining/crossing growth centiles along with functional parameters such as Doppler waveform analysis and the biometric measurements in order to achieve better identification of the foetuses at risk and to reduce the misdiagnosis of physiological smallness as FGR to avoid unnecessary monitoring and interventions [10].

Despite adopting the recent definition, FIGO reported that the implementation of this definition is limited by the lack of recommendations on which growth chart should be used to define the 10th and 3rd percentiles for EFW and foetal abdominal circumference. Moreover, further research is needed to correlate this definition with adverse perinatal outcomes [8].

Objectives

The purpose of this study was to evaluate the accuracy of ISUOG definition for FGR using biometric measures and Doppler parameters to identify foetuses at risk of adverse perinatal outcomes.

MATERIALS AND METHODS

Study design and participants

This was a descriptive retrospective study included medical records of 245 pregnancies complicat-

ed by FGR (AC/EFW < 10th percentile) who were admitted in Ain Shams University Maternity Hospital during the period from January 2017 till December 2021. The records were reviewed for strict exclusion criteria to include only placental mediated FGR (early or late onset FGR). We excluded cases with foetal structural malformations or chromosomal abnormalities as detected by neonatal examination and anomaly scan during pregnancy. Infectious causes detected during pregnancy or immediately by postnatal examination and multiple pregnancies were also excluded. The records that missed important antenatal or perinatal outcome data, or records in which the gestational age (GA) could not accurately be obtained or with significant discrepancy between GA determined by LMP and that determined by ultrasound (defined as a difference of > 5 days up to 9 weeks' gestation, > 7 days up to 16 weeks, > 10 days up to 22 weeks and > 14 days up to 27 weeks) were excluded.

Ethical considerations

The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, Faculty of Medicine Ain Shams University Ethical Research Committee (FMASU ERC) (FMASU MS 254/2021) on 17/4/2021 and Ethical Committee of the Council of Obstetrics and Gynecology Department. The study was conducted and reported in accordance with STROBE guidelines for reporting observational studies.

Baseline data of the enrolled subjects were collected, including maternal age, parity, mode of conception, inter-pregnancy interval, past maternal medical disorders, any pregnancy induced disorder such as gestational HTN or preeclampsia, previous pregnancies outcomes especially placental mediated disorders such as previous FGR, preeclampsia or stillbirth, index pregnancy information including gestational age calculation, medications received during pregnancy, sonographic findings including biometric measurements, amniotic fluid volume and Doppler velocimetry, data regarding the mode and indication of pregnancy termination, urgency of delivery, birth weight, and sex as well.

The required data to evaluate the performance of ISUOG definition was available in only 55 medical records. For the analysis, the studied population which consist of 55 cases diagnosed to be FGR

using the current biometric definition (EFW or AC < 10th percentile) were subdivided into 2 groups according to the ISUOG definition (group A that fulfilled the ISUOG new criteria, and group B that did not fulfil ISUOG criteria).

The ISUOG definition of FGR has been proposed by a Delphi procedure and includes either EFW or AC < 3rd percentile or EFW or AC < 10th percentile combined with abnormal Doppler findings or a decrease in growth centiles, depending on gestational age at FGR diagnosis. Abnormal Doppler criteria was either abnormal uterine artery pulsatility index (PI) a value > 95th percentile, and/or abnormal umbilical artery PI as a value > 95th percentile in early onset FGR and abnormal umbilical artery PI as a value > 95th percentile and/or abnormal cerebroplacental ratio as a value < 5th percentile in late onset FGR.

The primary outcome was to assess the accuracy of the ISUOG definition for predicting composite adverse neonatal outcome (ANO) including one or more of neonatal intensive care unit (NICU) admission, 5-min APGAR score < 7, respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), necrotizing enterocolitis, periventricular leukomalacia, neonatal anaemia, pulmonary hypertension, seizures and death.

Statistical methods

Sample size was calculated using PASS 11 program, setting power at 80% and x-error at 0.05. Result from previous study by Rizzo *et al.* [11] showed that the expected incidence of adverse perinatal outcomes was 32.5%, area under ROC curve for consensus for prediction of adverse outcomes 0.74, so sample size needed is at least 55 women that had pregnancies with FGR (EFW < 10th percentile).

Data were collected, tabulated and subjected to the proper statistical analysis using SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA).

Categorical variables were presented as number and percentage and inter-group differences were compared using the Pearson chi-squared test or Fisher's exact test as appropriate. Ordinal data were compared using the chi-squared test for trend. Continuous numerical variables were presented as mean and SD. P-values < 0.05 were considered statistically significant.

Multivariable binary logistic regression analysis was used to examine the relation between EFW, and composite ANO as adjusted for possible confounding factors.

Table 1. Baseline demographic and clinical criteria.

| Variable | FIGO definition | | P-value |
|--------------------------------------|------------------|-----------------|----------|
| | FGR (n = 40) | No FGR (n = 15) | |
| Maternal age | 28.42 ± 5.77 | 29.6 ± 7.57 | 0.54 |
| Parity | | | 0.452 |
| Primiparous | 15 (27.3%) | 4 (7.3%) | |
| Multiparous | 25 (45.5%) | 11 (20.0%) | |
| Birth weight | 1927.62 ± 603.15 | 2552.0 ± 287.77 | < 0.001* |
| Birth weight z score | -3.71 ± 2.25 | -1.44 ± 0.636 | < 0.001* |
| Pregnancy induced disorders | | | |
| No | 21 (38.2%) | 8 (14.5) | |
| Preeclampsia with severe features | 15 (27.3%) | 6 (10.9%) | |
| Preeclampsia with no severe features | 1 (1.8%) | 1 (1.8%) | 0.645 |
| Gestational HTN | 3 (5.5%) | 0 (0) | |
| Past medical disorders | | | |
| No | 33 (60.0%) | 11 (20.0%) | |
| Apas | 2 (3.6%) | 0 (0) | |
| Chronic HTN | 1 (1.8%) | 2 (3.6%) | |
| Pregestational DM | 1 (1.8%) | 1 (1.8%) | 0.275 |
| Epilepsy | 2 (3.6%) | 0 (0) | |
| Asthma | 0 | 1 (1.8%) | |
| Hbv | 1 (1.8%) | 0 (0) | |

*Statistically significant; APAS: antiphospholipid syndrome; HTN: hypertension; DM: diabetes mellitus; HBV: hepatitis B viral infection.

Table 2. Different sonographic parameters in the studied cases.

| Variables | FGR | | no FGR | | P-value | 95%CI | |
|------------------|----------|--------|----------|---------|---------|---------|---------|
| | Mean | SD | Mean | SD | | Lower | Upper |
| HC | 295.05 | 29.52 | 322.40 | 10.26 | 0.001* | -43.07 | -11.62 |
| HC percentile | 14.33 | 17.72 | 35.66 | 19.21 | 0.000* | -32.38 | -10.27 |
| AC | 268.179 | 32.57 | 304.6 | 12.87 | 0.000* | -53.88 | -18.95 |
| AC percentile | 4.231 | 5.5034 | 12.867 | 7.9988 | 0.000* | -12.46 | -4.811 |
| FL | 63.949 | 7.2799 | 69.467 | 3.3138 | 0.007* | -9.4542 | -1.5817 |
| FL percentile | 23.263 | 24.885 | 39.067 | 27.295 | 0.048* | -31.45 | -0.1504 |
| EFW | 1,955.25 | 549.89 | 2,594.13 | 254.043 | 0.000* | -936.10 | -341.65 |
| EFW percentile | 1.575 | 1.6154 | 5.267 | 2.0862 | 0.000* | -4.7557 | -2.6276 |
| UAPI | 1.1385 | 0.3924 | 0.8967 | 0.08950 | 0.022* | .03550 | .44816 |
| UPI percentile | 75.18 | 28.63 | 58.73 | 17.742 | 0.043* | 0.53 | 32.35 |
| UA RI | 0.67 | 0.146 | 0.60 | 0.068 | 0.174 | -0.032 | 0.173 |
| MCA PI | 1.4493 | 0.2642 | 1.5533 | 0.12952 | 0.266 | -29087 | 0.08278 |
| MCAPI percentile | 23.536 | 22.473 | 35.000 | 8.8176 | 0.147 | -27.165 | 4.2368 |

*Statistically significant; HC: head circumference; AC: abdominal circumference; FL: femur length; EFW: estimated foetal weight; UAPI: umbilical artery pulsatility index; UA RI: umbilical artery resistance index; MCA PI: middle cerebral artery pulsatility index.

Receiver-operating characteristic (ROC) curve analysis was used to examine the predictive value of different ultrasound parameters in predicting composite ANO.

RESULTS

A total of 55 singleton pregnancies complicated by foetal growth restriction identified according to our current definition (AC or EFW < 10th

centile) were enrolled. Of the cohort, only 40 cases (72.7%) fulfilled the recent ISUOG criteria; therefore, the cohort was divided into two groups: FGR and non FGR group.

There was no significant difference between both groups in the baseline demographic and clinical criteria (Table 1) while, birth weight differed significantly between both groups.

There was a significant difference between both groups regarding all biometric measurements and the umbilical artery pulsatility index as shown in Table 2.

As noted in Table 3, composite ANO occurred in 21 (38.2%) of the 55 included pregnancies (all were in FGR group according ISUOG definition). The new ISUOG definition of FGR significantly succeeded in predicting composite ANO (p < 0.0001) including principally RDS (p = 0.001) and NICU admission (p < 0.001).

Figure 1 shows that EFW had poor predictive value with an area under the ROC curve (AUC) of 0.689 (95%CI 0.550-0.807, P-value = 0.0017). The best cut-off criterion is < 3rd centile which had a sensitivity of 85.7% and specificity of 52.9%.

AC had good predictive value with an area under the ROC curve (AUC) of 0.807 (95%CI 0.676-0.901, P-value < 0.0001). The best cut-off criterion is < 3rd centile which had a sensitivity of 66.6% and specificity of 90.9% as shown in Figure 2. UAPI had fair predictive value with an area under the ROC curve (AUC) of 0.747 (95%CI 0.612-

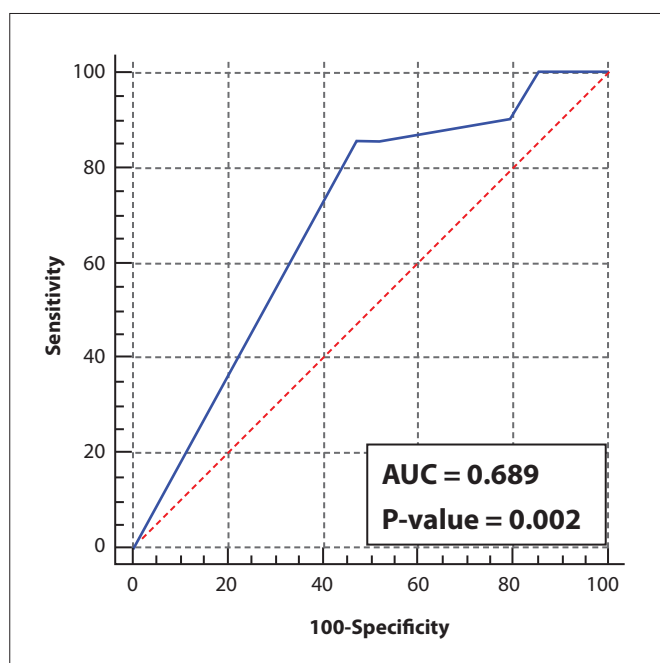


Figure 1. ROC curve for prediction of ANO using EFW centile'.

Table 3. The relationship between FGR using new definition and neonatal outcomes.

| Neonatal outcome | According to new definition | | P-value |
|-------------------------------|-----------------------------|------------|-----------|
| | FGR | No FGR | |
| Composite adverse outcome | | | < 0.0001* |
| Yes | 21 (38.2%) | 0 (0) | |
| No | 19 (34.5%) | 15 (27.3%) | |
| Respiratory distress syndrome | | | 0.001 |
| Yes | 20 (36.4%) | 0 (0) | |
| No | 20 (36.4%) | 15 (27.3%) | |
| Neonatal death | | | 0.112 |
| Yes | 6 (10.9%) | 0 (0) | |
| No | 34 (61.8%) | 15 (27.3%) | |
| Neonatal ICU admission | | | < 0.001* |
| Yes | 21 (38.2%) | 0 (0) | |
| No | 19 (34.5%) | 15 (27.3%) | |
| SGA neonate | | | 0.01* |
| Yes | 38 (69.1%) | 8 (14.5%) | |
| No | 2 (3.6%) | 7 (12.7%) | |

% within total sample used for validation; *statistically significant.

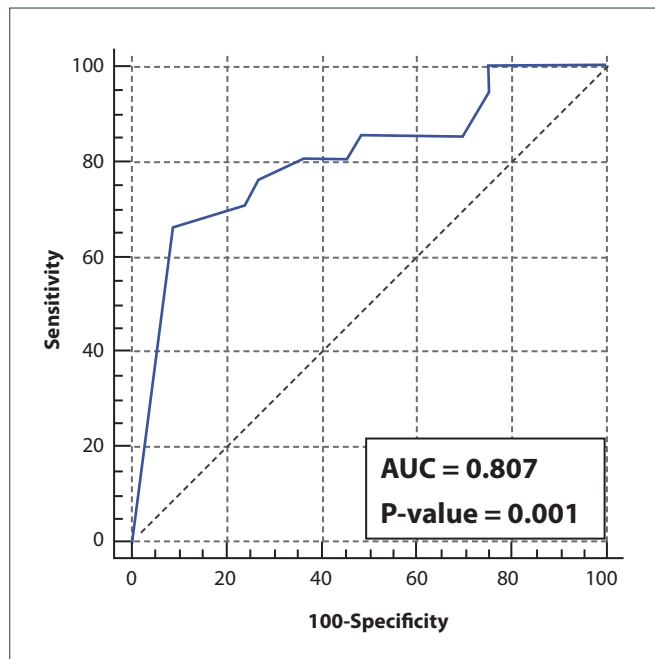


Figure 2. ROC curve for prediction of ANO using AC centile'.

0.855, P-value 0.0014). The best cut-off criterion is > 95th centile which had a sensitivity of 71.4% and specificity of 79.4% (Figure 3).

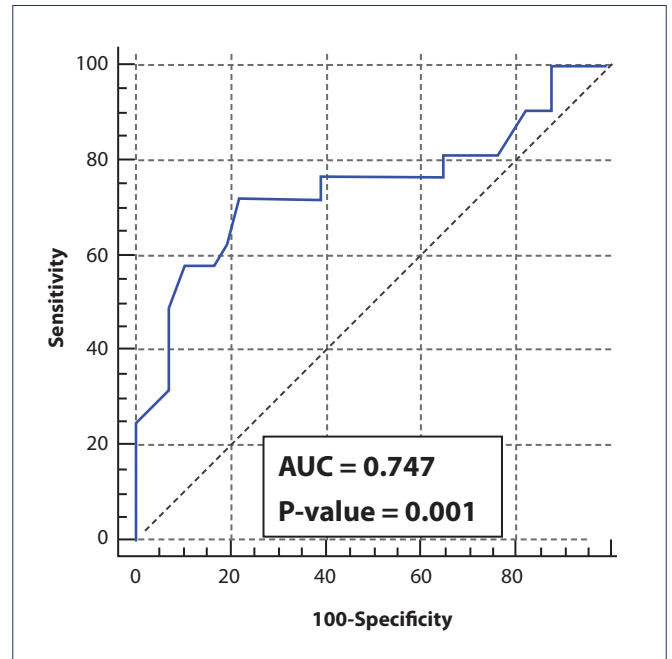


Figure 3. ROC curve for prediction of ANO using umbilical artery PI percentiles.

DISCUSSION

Defining FGR by the presence of aberrations in biometric measures of foetal weight and/or abdominal circumference < 10th centile usually misdiagnoses healthy but constitutionally small foetuses as FGR. Thus, provoking unnecessary parental anxiety and precludes the allocation of resources to caring for the foetuses that are actually at risk for adverse outcomes [12].

The current study showed that the recent ISUOG criteria identified all pregnancies that were complicated by composite adverse neonatal outcome and SGA neonates when compared to the traditional definition (p < 0.0001 and p = 0.01, respectively).

According to Roeckner *et al.* [13] and Schreiber *et al.* [14] the traditional definition (using biometric measurements only) had higher detection rates of SGA neonates. In their studies, both the definition based on biometric and Doppler parameters and that used only the biometric measurements performed poorly in predicting adverse neonatal outcomes.

Molina *et al.* [12] reported that the definition encompassing biometric and Doppler parameters identified more pregnancies that were significantly at risk for composite ANO when compared to the traditional definition. However, the definition encompassing biometric and Doppler parameters

identified fewer SGA neonates than did the traditional definition.

The admission to the NICU mainly due to RDS is one of the most significant contributors to estimating FGR related adverse neonatal outcomes. The current study showed that ISUOG definition could accurately detect all foetal growth restricted cases that developed RDS or needed NICU admission. On the contrary, Roeckner *et al.* [13] found that neither the traditional definition nor the new definition was able to predict RDS, while the new definition was associated with increased odds of NICU admission (OR 2.3, 95%CI 1.19-4.55).

Of the individual components of the ISUOG criteria, EFW < 3rd percentile was the most prevalent component in our sample. It was recorded in 85% of those identified as FGR according to ISUOG criteria. Moreover, we found that AC had good predictive value for ANO with best cut-off criterion is < 3rd centile with a sensitivity of 66.6% and specificity of 90.9%. The EFW had poor predictive value with the best cut-off criterion is < 3rd centile had a sensitivity of 85.7% and specificity of 52.9%.

In their meta-analysis Blue *et al.* [15] found that after 24 weeks gestation AC and EFW < 10th percentile had similar ability to predict SGA. Instead, Baschat and Weiner found that AC percentile had the highest sensitivity (98.1%) for the diagnosis of FGR when compared with either estimated foetal weight (85.7%) or UA S/D ratio (67.3%) [16].

According to Marchand *et al.* [17], AC was proved to be the most suitable sonographic parameter in predicting FGR, especially in advanced weeks of gestation, as it reflects the size of the liver, which is affected early in the process of growth retardation due to glycogen depletion. It correlates with the degree of foetal malnutrition. Thus, it has the highest sensitivity for diagnosing FGR.

Abdominal circumference less than 3rd percentile rather than the 10th percentile was a good predictor of composite ANO according to Lees *et al.* [18].

Unterscheider and his colleagues [19] found that all foetuses with an EFW less than 3rd centile were at increased risk for either adverse perinatal outcome or NICU admission. In the same line, a large retrospective cohort study, found that the risk of stillbirth was inversely proportional to the percentile of birthweight for gestational age. The risk for stillbirth in those < 3rd percentile was as high as 58 per 10,000 at-risk foetuses, and 26.3 for < 10th percentile compared to 5.1 for non-SGA gestations [20].

In the era of molecular medicine, different biomarkers were investigated for predicting pre-eclampsia, FGR and stillbirth such as microRNAs, endothelial progenitor cells (EPCs) and natural killer (NK) cells with promising results [21, 22]. These advances can be used for future verification of ISUOG criteria for FGR identification.

The main limitation of our study was the relatively small sample size, and the use composite adverse neonatal outcomes instead of individual components as outcomes such as IVH, neonatal anaemia, NEC, neonatal seizures or stillbirth because they were rare or absent. Moreover, NICU admission policies as regard the age of viability were major obstacles in studying early-onset FGR.

A main strength of this study is that ISUOG adopted a definition obtained through a Delphi procedure that is usually useful in topics that cannot be answered by clinical research through a series of sequential rounds of questions to reach consensus between a panel of experts, yet. It might introduce new definition parameters based on opinions into clinical practice. So, this study was an attempt to provide evidence to support ISUOG definition.

CONCLUSIONS

As evident from the current study, ISUOG definition for foetal growth restriction can accurately identify foetuses at risk of adverse perinatal outcomes.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.H.: Data curation, formal analysis, investigation. G.E.: Conceptualization, formal analysis, methodology. M.S., R.A.: Conceptualization, methodology, resources, supervision, validation, visualization. M.S., M.H., G.E.: Writing – review & editing. R.A.: Writing – original draft.

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Study registration

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The authors declare that they have no conflict of interests.

Ethical approval

The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, Faculty of Medicine Ain Shams University Ethical Research Committee (FMASU ERC) (FMASU MS 254/2021) on 17/4/2021 and Ethical Committee of the Council of Obstetrics and Gynecology Department and an informed consent was obtained from all subjects involved in the study.

Informed consent

Informed consent for data collection for research purposes was obtained from all subjects involved in the study.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Calagna G, Picciotto F, Guiglia RA, Messina L, Bisanti A, Schiattarella A, et al. Early-onset fetal growth restriction with severe preeclampsia: our experience of a challenging topic. *Ital J Gynaecol Obstet.* 2022;34(4):310-6. doi: 10.36129/jog.2022.46.
2. Gordijn SJ, Beune IM, Ganzevoort W. Building consensus and standards in fetal growth restriction studies. *Best Pract Res Clin Obstet Gynaecol.* 2018;49:117-26. doi: 10.1016/j.bpobgyn.2018.02.002.
3. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol.* 2020;56(2):298-312. doi: 10.1002/uog.22134.
4. Quaresima P, Saccone G, Morelli M, Interlandi F, Votino C, Zuccalà V, et al. Stillbirth, potentially preventable cases: an Italian retrospective study. *Ital J Gynaecol Obstet.* 2022;34(2):89-102. doi: 10.36129/jog.2022.20.
5. Abuhamad A, Martins JG, and Biggio JR. Diagnosis and management of fetal growth restriction: the SMFM guideline and comparison with the ISUOG guideline. *Ultrasound Obstet Gynecol.* 2021;57:880-3. doi: 10.1002/uog.23663.
6. VV.AA. Fetal Growth Restriction: ACOG Practice Bulletin, Number 227. *Obstet Gynecol.* 2021;137(2):e16-e28. doi: 10.1097/AOG.0000000000004251.
7. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small-for-Gestational-Age Fetus. Green-top guideline No. 31. RCOG. 2014.
8. Society for Maternal-Fetal Medicine (SMFM). Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). *Am J Obstet Gynecol.* 2020;223(4):B2-B17. doi: 10.1016/j.ajog.2020.05.010.
9. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet.* 2021;152(Suppl 1):3-57. doi: 10.1002/ijgo.13522.
10. Gordijn SJ, Beune IM, Thilaganathan B, Papa-georghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol.* 2016;48(3):333-9. doi: 10.1002/uog.15884.
11. Rizzo G, Mappa I, Bitsadze V, Słodki M, Khizroeva J, Makatsariya A, et al. Role of Doppler ultrasound at time of diagnosis of late-onset fetal growth restriction in predicting adverse perinatal outcome: prospective cohort study. *Ultrasound Obstet Gynecol.* 2020;55(6):793-8. doi: 10.1002/uog.20406.
12. Molina LCG, Odibo L, Zientara S, Običan SG, Rodriguez A, Stout M, et al. Validation of Delphi procedure consensus criteria for defining fetal growth restriction. *Ultrasound Obstet Gynecol.* 2020;56(1):61-6. doi: 10.1002/uog.20854.
13. Roeckner JT, Pressman K, Odibo L, Duncan JR, Odibo AO. Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction. *Ultrasound Obstet Gynecol.* 2021;57(6):925-30. doi: 10.1002/uog.23638.
14. Schreiber V, Hurst C, da Silva Costa F, Stoke R, Turner J, Kumar S. Definitions matter: detection rates and perinatal outcome for infants

- classified prenatally as having late fetal growth restriction using SMFM biometric vs ISUOG/Delphi consensus criteria. *Ultrasound Obstet Gynecol.* 2023;61(3):377-85. doi: 10.1002/uog.26035.
15. Blue NR, Yordan JMP, Holbrook BD, Nirgudkar PA, Mozurkewich EL. Abdominal Circumference Alone versus Estimated Fetal Weight after 24 Weeks to Predict Small or Large for Gestational Age at Birth: A Meta-Analysis. *Am J Perinatol.* 2017;34(11):1115-24. doi: 10.1055/s-0037-1604059.
 16. Baschat AA, Weiner CP. Umbilical artery doppler screening for detection of the small fetus in need of antepartum surveillance. *Am J Obstet Gynecol.* 2000;182(1 Pt 1):154-8. doi: 10.1016/s0002-9378(00)70505-9.
 17. Marchand C, Köppe J, Köster HA, Oelmeier K, Schmitz R, Steinhard J, et al. Fetal Growth Restriction: Comparison of Biometric Parameters. *J Pers Med.* 2022;11;12(7):1125. doi: 10.3390/jpm12071125.
 18. Lees C, Stampalija T, Hecher K. Diagnosis and management of fetal growth restriction: the ISUOG guideline and comparison with the SMFM guideline. *Ultrasound Obstet Gynecol.* 2021;57(6):884-7. doi: 10.1002/uog.23664.
 19. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. *Am J Obstet Gynecol.* 2013;208(4):290.e1-6. doi: 10.1016/j.ajog.2013.02.007.
 20. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol.* 2012;207(4):318.e1-6. doi: 10.1016/j.ajog.2012.06.039.
 21. Chiofalo B, Laganà AS, Vaiarelli A, La Rosa VL, Rossetti D, Palmara V, et al. Do miRNAs Play a Role in Fetal Growth Restriction? A Fresh Look to a Busy Corner. *Biomed Res Int.* 2017;2017:6073167. doi: 10.1155/2017/6073167.
 22. Laganà AS, Giordano D, Loddo S, Zoccali G, Vitale SG, Santamaria A, et al. Decreased Endothelial Progenitor Cells (EPCs) and increased Natural Killer (NK) cells in peripheral blood as possible early markers of preeclampsia: a case-control analysis. *Arch Gynecol Obstet.* 2017;295(4):867-72. doi: 10.1007/s00404-017-4296-x.



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Spontaneous hemoperitoneum in pregnancy due to rupture of uterine vessels in woman with endometriosis: a case report

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ABSTRACT

Background. Spontaneous rupture of uterine vessels is a rare and life-threatening event than can rarely occur during spontaneous and low-risk pregnancies. The definitive association between adverse obstetrical events and pelvic endometriosis is still under evaluation. We report a severe case of spontaneous hemoperitoneum in pregnancy (SHiP) due to a rupture of the uterine vessels related to decidualized endometriosis.

Case presentation. A 38-year-old primigravida woman at 33 weeks of pregnancy with an uncomplicated pregnancy and a history of endometriosis was admitted to the emergency room of our Institution, due to a spontaneous rupture of the right uterine vessels. An alive and vital baby was delivered by hysterotomy. In order to achieve haemostasis, a total hysterectomy with bilateral salpingectomy was performed.

Conclusions. In case of spontaneous rupture of uterine vessels and resulting hemoperitoneum, prompt diagnosis and treatment are the crucial points in order to minimize maternal and foetal/neonatal complications. Further studies are necessary in order to identify endometriosis as a possible cause of spontaneous rupture of uterine vessels in pregnancy.

INTRODUCTION

Spontaneous hemoperitoneum in pregnancy (SHiP) is a rare and dramatic complication correlated with a high rate of maternal and foetal/neonatal mortality. Approximately only 100 cases have been reported in the literature, and since 1950 the maternal mortality rate has been 49.3% [1, 2]. However, nowadays, thanks to medical advances, the mortality rate dropped to 3.6% [3, 4]. Although the aetiology of SHiP remains unclear, haemodynamics and hormonal factors have been involved in the pathogenesis [1]. Endome-

triosis represents a benign chronic disease characterized by the presence of functional endometrial tissue out-side of the uterus. In this sense, the endometriotic lesions undergoing the process of decidualization generate a subsequent inflammatory microenvironment. For all these reasons, endometriosis has been suggested to be involved in the mechanisms of spontaneous rupture of uterine vessels during pregnancy [5]. Because of the increased number of patients with severe endometriosis with the desire for fertility, physicians would need to consider endometriosis-related SHiP among possible causes of hypotension and

acute abdomen during the third trimester of pregnancy. Here, we describe a case of spontaneous hemoperitoneum in a healthy woman at 33 weeks of her first spontaneous pregnancy.

CASE PRESENTATION

A 38-year-old primigravida woman was admitted to the emergency room of our Institution for abdominal pain at week 33 of pregnancy. There was no history of vaginal bleeding, rupture of membranes, abdominal trauma, previous abdominal surgeries, or drug assumptions. The patient had a medical history of deep infiltrating endometriosis treated with progestin-only drugs with good response. The pregnancy was spontaneous, and the antenatal course was uneventful until the admission. On admission, the patient was hypotensive with a blood pressure of 80/50 mmHg, heart rate was 120 beats per minute, respiratory rate was 14 breaths per minute, and body temperature of 36.3 °C. The physical examination detected a gravid abdomen, tender at the superior quadrants. No dysuria, vomiting or diarrhoea was reported. The ultrasound assessment confirmed the presence of a singleton cephalic foetus with a normal biophysical profile, a regular placenta, and normal amniotic fluid volume. Moderate maternal abdominal free liquid was detected. Cervical length was 25 mm, and tocography revealed no uterine contractions. Her laboratory tests resulted in a haemoglobin level of 9.0 g/dL and $18.20 \times 10^3/\mu\text{L}$ leukocytes. Metabolic hepatic panel and urinalysis were negative. Intramuscular steroid therapy was submitted in order to induce foetal lung maturation.

After 6 hours, the value of haemoglobin level dropped to 7.9 g/dL, and the free abdomen liquid detected at the ultrasound assessment was significantly increased. Moreover, the patient presented an exacerbation of abdominal pain, despite analgesic infusion.

Ten hours after the arrival at the emergency room, considering the worsening of clinical features and the suspicious diagnosis of hemoperitoneum, the patient underwent urgent laparotomy. About 1.5 L of free blood was aspirated from the abdominal cavity. The surgical exploration revealed a haematoma in the posterior and right uterine walls and active bleeding from the right uterine vessels (**Figure 1**). Moreover, there were several endometriotic foci in the pelvic peritoneum and severe pelvic ad-

hesions. There was no sign of uterine anomalies, such as arteriovenous malformation and uterine rupture. The surgery proceeded with a low-segment caesarean section and extraction of a male foetus, alive and vital, weighed 1.400 kg and with APGAR scores of 8 and 9 at the first and fifth minute, respectively. After uterine closure, persistent bleeding appeared from decidualized endometrial lesions on the posterior surface of the uterus and the right parametrium. Because of the difficulty in achieving safe haemostasis without possible damage to the parametrial structures, we decided to proceed with a total hysterectomy. After intraoperative patient's oral consensus, a total hysterectomy with bilateral salpingectomy and ovarian preservation was performed. Successful haemostasis was finally achieved, and the abdominal wall was closed. Estimated blood loss during the hysterectomy was 700 mL and no intraoperative transfusions were performed. No intraoperative and postoperative blood transfusions were performed. No complications were reported, and the patient was discharged after 6 days. The infant had an uneventful course and was discharged after few weeks in good condition. On histopathology examination, uterine, tubal, and right parametrial specimens have reported elements suggestive of endometriotic foci, such as haemorrhagic infarction, fibrosis and prominent deciduid changes.

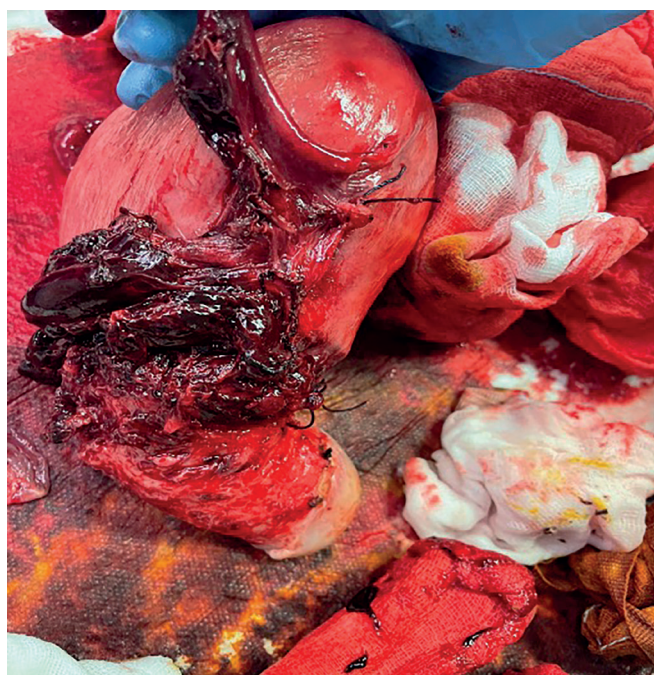


Figure 1. The right parametrium and the posterior surface of the uterus are covered by blood clots as site of active bleeding.

DISCUSSION

The current study represents a clear case of spontaneous hemoperitoneum in pregnancy (SHiP) as direct consequence of spontaneous rupture of uterine vessels due to endometriotic lesions in an otherwise uncomplicated pregnancy.

Endometriosis has increased in recent decades and is frequently associated with infertility, pelvic pain, and dysmenorrhoea. Endometriosis is a very complex condition that could impact sexuality, quality of life and psychology of affected woman. Although these aspects could not be correlated to the severity of disease, they have an important role on psychological wellbeing and interpersonal relationships [6, 7]. Endometriosis can be correlated with pregnancy complications, such as severe preeclampsia, placental abruption, placental abnormalities, premature rupture of membranes, preterm birth, and retained placenta [8, 9].

SHiP is a rare and potentially life-threatening condition that occurs in pregnant women out-of-labour in 61% of cases, of which 39% happened between 33-37 weeks of gestation [10, 11]. According to the International Network of Obstetric Survey Systems (INOSS), SHiP is defined as a non-traumatic intraperitoneal haemorrhage during pregnancy up to 42 days postpartum, excluding ectopic pregnancy, uterine rupture and caesarean section-associated bleeding [12].

In literature, trends regarding parity, age, and length of gestation in patients with SHiP have not been documented [1].

In a review of 25 cases of SHiP, endometriosis has been recognized as the major risk factor and the spontaneous rupture of uterine vessels or direct bleeding of endometriotic lesions were the most common findings [1].

Moreover, in a recent systematic review by Lier *et al.*, the authors reported that the SHiP was associated with rupturing utero-ovarian vessels in 57% of cases, endometriotic implants in 23% of cases, haemorrhagic nodules in 2% of cases, and a combination of these events in 20% of cases [13].

Furthermore, in almost half of the patients reported in the literature, the diagnosis of endometriosis was misunderstood until the laparotomic visualization of endometriotic lesions and the histological confirmation [10]. Conversely, in our case, the diagnosis of endometriosis was already known at the time of clinical presentation, and the histopathologic examination of the samples confirmed the presence of decidualized ectopic endometrial tissue.

It is well known that the phenomenon of decidualization during the first trimester of pregnancy consists of the loss of pigmentation and fibrosis of endometriotic implants [10]. Recently, it has been supposed that the SHiP is linked to an involution of the decidualization process due to the decrease of progesterone levels and a supposed progesterone resistance. This mechanism causes the production of chemokine, proinflammatory cytokine, metalloproteinases, apoptotic factors, cell death, and bleeding [10].

The incidence of SHiP may be influenced by the use of assisted reproductive techniques (ART), as women with endometriosis could overcome subfertility/infertility problems [14]. The use of ART is linked to a high dosage of progesterone, which can facilitate the process of decidualization. In a recent review of 362 pregnancies reported from 2010 to 2018, Benaglia *et al.* documented that the frequency of SHiP in women with endometriosis submitted *in vitro* fertilization is 0.3% [15]. However, in our case, the patient had a spontaneous pregnancy. Besides endometriosis and ART as risk factors, a recent prospective population-based study reported some additional factors associated with SHiP, such as multiple pregnancies, ≥ 35 years of age in mothers, and previous abdominal surgery [11].

Although the recent evidence, the etiopathogenesis of this condition remains unclear. Increased venous pressure in utero-ovarian circulation due to pregnancy status or muscular activity such as defecation and coughing could be possibly implicated in the pathophysiology of SHiP [16].

In the literature, three factors have been described as explanations for spontaneous rupture of uterine vessels: vessels leakage caused by endometriosis-linked chronic inflammation, adhesions between vessels with relative tensions, decidualization of endometrial foci [5, 17, 18]. Our patient had either a diagnosis of deep infiltrating endometriosis or pelvic adhesions. Indeed, during the surgery, adhesiolysis was performed. Moreover, in a few cases, the origin of the bleeding remains unknown, even during laparotomy. During the surgery of our patient, arteries and superficial veins of the posterior surface of the uterus and right parametria have been involved in the bleeding. The surgical visualization of the endometriotic implants' bleeding and the medical history of our patient suggest that the phenomenon of decidualization of endometriotic foci lead to massive and sudden hemoperitoneum in our patient.

In all cases of spontaneous hemoperitoneum in pregnancy, the onset symptoms were acute or subacute abdominal pain, free abdominal fluid, hypovolemic shock, and decreasing values of haemoglobin [10]. A prompt differential diagnosis is a crucial requirement. Placental abruption, uterine rupture, placenta percreta, appendix, hepatic, and splenic ruptures are the most common preoperative misdiagnosis. Vascular sources of hemoperitoneum in pregnancy should be considered as a result of the rupture of a visceral abdominal artery aneurysm such as splenic artery [1].

Our patient's symptoms were similar to clinical presentation described in the literature. Lier *et al.* reported the most common signs of presentation of SHiP: subacute abdominal pain (94.9%), a decreased level of haemoglobin (62.7%), imaging showing free peritoneal fluid (62.7%) [13]. The sensibility of contrast enhanced computed tomography in the identification of bleeding is documented, but maternal and foetal potential risks from ionizing radiation have to be considered. Ultrasonography could be helpful for the detection and monitoring of abdominal free fluid, but the real diagnosis is often obtained only by laparotomic exploration. In a preterm pregnancy, the decision making should be balanced between risks related to prematurity, delayed diagnosis, and maternal complications. In our case, the worsening symptoms and the haemoglobin drop level guided our decision on laparotomy.

Several questions remain unknown about the management of endometriosis in pregnancy: whether any medical or surgical treatment of endometriosis in the preconception period would add any benefit and prevent pregnancy complications such as SHiP; whether adopting any particular management in pregnancies with a previous diagnosis of endometriosis (in terms of follow-up and mode of delivery); whether to choose any specific flowchart in case of a pregnant woman with acute abdomen and free blood abdominal liquid. Yet, endometriotic lesions should be considered a possible cause of hemoperitoneum during the third trimester of pregnancy [5]. Rapid diagnosis and prompt intervention are essential to correctly manage such complicated cases.

CONCLUSIONS

In conclusion, our case represents a rare case of SHiP related to endometriosis confirmed by histo-

logic examination. Moreover, a prompt diagnosis of SHiP was crucial in managing this unique clinical scenario without either maternal or fetal complications. Exploring the association between the diffusion of endometriosis and the severity of SHiP could be a new challenge.

In consideration of the risk of spontaneous rupture of uterine vessels and SHiP, physicians should be aware that prompt diagnosis and interventions are crucial to minimize maternal and foetal/neonatal morbidity and mortality. More attention to SHiP, with a particular focus on endometriosis as a cause, would help prevent maternal and foetal adverse events.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.M., F.F.: Conceptualization. G.Z.: Writing – original draft. A.M., F.F.: Writing – review & editing. A.M., G.Z., G.P., A.M., F.F.: Data curation, validation.

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Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Hardin N, Delozier A, Alireza Torabi A, Laks S. Spontaneous Rupture of the Uterine Artery in an Otherwise Normal Pregnancy. *J Radiol Case Rep.* 2017;11(7):7-13. doi: 10.3941/jrcr.v11i1.2946.
2. Hodgkinson CP, Christensen RC. Hemorrhage from ruptured utero-ovarian veins during pregnancy; report of 3 cases and review of the literature. *Am J Obstet Gynecol.* 1950;59(5):112-7. doi: 10.1016/s0002-9378(16)39178-5.
3. Jang JH, Kyeong KS, Lee S, Hong SH, Ji I, Jeong EH. A case of spontaneous hemoperitoneum by uterine vessel rupture in pregnancy. *Obstet Gynecol Sci.* 2016;59(6):530-4. doi: 10.5468/ogs.2016.59.6.530.
4. Simonetto C, Garzon S, Laganà AS, Raffaelli R, Cromi A, Uccella S, et al. Maternal sepsis: a comprehensive review from definition to treatment. *Ital J Gynaecol Obstet.* 2020;32(3):166-81. doi: 10.36129/jog.32.03.03
5. Cozzolino M, Corioni S, Maggio L, Sorbi F, Guaschino S, Fambrini M. Endometriosis-Related Hemoperitoneum in Pregnancy: A Diagnosis to Keep in Mind. *Ochsner J.* 2015;15(3):262-4.
6. La Rosa VL, De Franciscis P, Barra F, Schiattarella A, Török P, Shah M, et al. Quality of life in women with endometriosis: a narrative overview. *Minerva Med.* 2020;111(1):68-78. doi: 10.23736/S0026-4806.19.06298-0.
7. La Rosa VL, De Franciscis P, Barra F, Schiattarella A, Tropea A, Tesarik J, et al. Sexuality in women with endometriosis: a critical narrative review. *Minerva Med.* 2020;111(1):79-89. doi: 10.23736/S0026-4806.19.06299-2.
8. Gruber TM, Ortlieb L, Henrich W, Mechsner S. Deep Infiltrating Endometriosis and Adenomyosis: Implications on Pregnancy and Outcome. *J Clin Med.* 2021;11(1):157. doi: 10.3390/jcm11010157.
9. Vannuccini S, La Torre F, Gallucci E, Toscano F, Ruotolo A, Capezzuoli T, et al. Previous surgery for endometriosis: a further risk for obstetric complications? *Ital J Gynaecol Obstet.* 2023;35(Suppl 1):81. doi: 10.36129/jog.2022.S80.
10. Brosens IA, Fusi L, Brosens JJ. Endometriosis is a risk factor for spontaneous hemoperitoneum during pregnancy. *Fertil Steril.* 2009;92(4):1243-5. doi: 10.1016/j.fertnstert.2009.03.091.
11. Mazzocco MI, Donati S, Maraschini A, Corsi E, Colciago E, Guelfi F, et al. Spontaneous hemoperitoneum in pregnancy: Italian prospective population-based cohort study. *Acta Obstet Gynecol Scand.* 2022;101(11):1220-6. doi: 10.1111/aogs.14431.
12. Say L, Souza JP, Pattinson RC; WHO working group on Maternal Mortality and Morbidity classifications. Maternal near miss--towards a standard tool for monitoring quality of maternal health care. *Best Pract Res Clin Obstet Gynaecol.* 2009;23(3):287-96. doi: 10.1016/j.bpobgyn.2009.01.007.
13. Lier MCI, Malik RF, Ket JCF, Lambalk CB, Brosens IA, Mijatovic V. Spontaneous hemoperitoneum in pregnancy (SHiP) and endometriosis - A systematic review of the recent literature. *Eur J Obstet Gynecol Reprod Biol.* 2017;219:57-65. doi: 10.1016/j.ejogrb.2017.10.012.
14. Gao FM, Liu GL. Four Case Reports of Endometriosis-Related Hemoperitoneum in Pregnancy. *Chin Med J (Engl).* 2018;131(4):502-4. doi: 10.4103/0366-6999.225048.
15. Benaglia L, Reschini M, La Vecchia I, Candotti G, Somigliana E, Vercellini P. Endometriosis and spontaneous hemoperitoneum in pregnancy: evaluation of the magnitude of the risk in women becoming pregnant via in vitro fertilization. *Fertil Steril.* 2021;115(4):1023-8. doi: 10.1016/j.fertnstert.2020.10.030.
16. Katorza E, Soriano D, Stockheim D, Mashach R, Zolti M, Seidman DS, Schiff E, Goldenberg M. Severe intraabdominal bleeding caused by endometriotic lesions during the third trimester of pregnancy. *Am J Obstet Gynecol.* 2007;197(5):501.e1-4. doi: 10.1016/j.ajog.2007.04.030.
17. Inoue T, Moriwaki T, Niki I. Endometriosis and spontaneous rupture of utero-ovarian vessels during pregnancy. *Lancet.* 1992;340(8813):240-1. doi: 10.1016/0140-6736(92)90506-x.
18. Passos F, Calhaz-Jorge C, Graça LM. Endometriosis is a possible risk factor for spontaneous hemoperitoneum in the third trimester of pregnancy. *Fertil Steril.* 2008;89(1):251-2. doi: 10.1016/j.fertnstert.2007.02.009.



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The role of salpingoscopy and fallopscopy in current clinical practice: a review

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Key words

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ABSTRACT

Objective. Tubal pathology accounts for a third of infertility cases of which about 80% affects the ampulla and distal tube and 10-25% the proximal tube. Infertile patients with tubal pathology have two options for treatment, *in vitro* fertilization or tubal reconstructive microsurgery. The present study aims to perform a literature review to give a comprehensive knowledge of the role of salpingoscopy / fallopscopy in the assessment of tubal pathology in infertile couples and its impact on clinical practice.

Materials and Methods. A review of various articles on the technique of salpingoscopy / fallopscopy and its clinical use in infertile patients was undertaken by searching databases like PubMed, Scopus, Medline, Cochrane database, Embase, Web of science, Science direct, *etc.* The studies describing the methods and clinical scope of salpingoscopy and fallopscopy were included in the present study.

Results. The method of salpingoscopy / fallopscopy and its role in the management of infertile patients has been studied in various aspects. The technique, the assessment and classification of tubal pathology, and the clinical impact on the management of the infertile couple has been reported as per actual literature data.

Conclusions. Salpingoscopy and fallopscopy are two important methods to assess the tubal mucosal surface. The conventional methods of examining the tubes by laparoscopy and HSG are inadequate for the study of tubal pathology. An endoscopic examination of the fallopian tubes along with HSG and laparoscopic evaluation of the pelvis will give complete information about the fallopian tubes.

INTRODUCTION AND BACKGROUND

Tubal disease accounts for 25 to 40% of female factor infertility [1, 2]. The outer fallopian tube is most commonly affected about 80%, usually a hydrosalpinx, and the proximal tube is affected in 10 to 25% of cases [1]. The current trend in infertility treatment is to refer patients with tubal disease for

in vitro fertilization (IVF) treatment. The success rate in IVF is about 30% live birth rate per cycle in women across all ages with tubal factor infertility. Estimated live birth rates can range from 9% to 69% in cases of tubal disease after correction by reconstructive microsurgery [1]. Although surgery has perioperative events it can yield good results in properly selected cases of tubal disease. Fur-

thermore, it affects a long-term cure where several pregnancies can be attempted. However appropriate selection is the mainstay to offer the procedure to patients of tubal infertility. At present the main methods of assessing tubal disease are laparoscopy and hysterosalpingography (HSG). Both methods examine the gross pathology and the external disease of the fallopian tube. They do not examine the inner mucosal surface of the tube. Without examining the inner mucosa, it is not possible to give an objective assessment of tubal pathology [3, 4]. The important techniques of examining directly the inner mucosal layer of the fallopian tubes are salpingoscopy and falloposcopy. The aim of the current study is a comprehensive non-systemic review of the literature to assess the feasibility and application of these procedures in infertility investigations and their impact on clinical decision-making. More objective information regarding the fallopian tubes is important to the clinician and the patient before making a decision for tubal microsurgery or IVF.

AIMS AND OBJECTIVE

1. To review the literature on salpingoscopy and falloposcopy.
2. Current place of these procedures in tubal and unexplained infertility.

MATERIALS AND METHODS

A non-systemic review of various articles on salpingoscopy and falloposcopy, the methods, and clinical application of these procedures in infertility treatment was undertaken by searching the databases such as PubMed, Cochrane database, Embase, Science direct, Google Scholar, etc. Studies describing the techniques, scoring systems, application in management, and prognosis in tubal and unexplained infertility were included. We searched various publications and studies till January 2023. The keywords used were falloposcopy, salpingoscopy, tubal surgery, tubal infertility, and unexplained infertility.

DISCUSSION

Fallopian tube disease accounts for 25 to 40% of female factor infertility [1, 2]. Salpingoscopy is an

endoscopic technique to visualize the tubal mucosa of the distal tubal segment of the fallopian tubes during laparoscopy. Salpingoscopy can be done in conjunction with laparoscopy or laparotomy under general anaesthesia and requires hospitalization. It can also be done as an office procedure performed in conjunction with a transvaginal hydro-laparoscopy [5].

Falloposcopy is a technique by which microendoscopy of the lumen of the fallopian tube from the utero-tubal ostia to the fimbria is performed by a non-incisional transvaginal approach.

Methods and techniques of salpingoscopy and falloposcopy

Salpingoscopy as an inpatient procedure under general anaesthesia [4]

During a laparoscopic assessment of an infertile patient, a salpingoscopy can also be done to assess and evaluate the tubal mucosal morphology in greater detail. The colpomicrohysteroscope (Richard Wolf, Knittlingen, Germany) is used for the procedure. The tubal ostia are localized by means of two atraumatic forceps. The salpingoscope without its sheath is introduced through a second suprapubic incision. It is inserted through the ostium and advanced along the tubal lumen until the isthmus ampullary junction is reached. The tubal lumen is distended by saline injection through the cervix of the uterus via Ruben's cannula. If the patient has a proximal tubal block, then the salpingoscope is introduced with its sheath, and saline is injected through its sheath. The procedure is monitored laparoscopically via the umbilical incision. Complications that are rare during the procedure include injury to the tubal epithelium, perforation, and bleeding [4].

Transvaginal salpingoscopy as an office procedure under local anaesthesia [5]

The patient is put in the horizontal decubitus procedure. The central part of the posterior fornix is infiltrated with Alphacaine. The posterior lip of the cervix is lifted and the Veress needle which is part of a specially designed dilating trocar system is introduced approximately 1.5 cm below the cervix and tested by deeper insertion for intraperitoneal location. About 100 ml of saline solution at 37 degrees C (diluted in 1% lidocaine) is instilled in the pouch of Douglas. The Veress needle is removed and a rigid endoscope of diameter 2.7 mm with an

optical angle of 30 degrees and flow channel is introduced through the trocar sheath approximately 1 cm into the pouch of Douglas. A digital video camera is attached to it. By manipulation of the scope, the posterior wall of the uterus is inspected and the tuboovarian structures are identified. Saline irrigation is continued. The tubal ostia are identified, and the scope is introduced into the ampulla of the tube. The microanatomical structure of the ampullary folds is inspected. No instruments are used to stabilize the ampulla. The success rate of the procedure is approximately 47%. Bleeding from the mucosal or serosal surface did not occur. The anterior pelvis however cannot be visualized in this method. The patient is conscious and can follow the procedure on the monitor [5].

Transvaginal falloposcopy under hysteroscopic guidance under general anaesthesia [6]

A hysteroscope is gently introduced through the cervical canal into the uterine cavity without cervical dilation. The uterine cavity is irrigated with Lactated Ringer’s solution. Under video monitoring, the distal tip of the hysteroscope is directed to within 3 mm of one of the tubal ostia so a direct longitudinal view of the intramural tubal lumen can be seen. The coaxial technique involved passage of a small floppy, steerable stainless steel tapered guide wire into the fallopian tube under video hysteroscope monitoring [6]. When the wire passed the point of resistance or beyond the utero tubal ostium, a flexible teflon cannula was introduced over the guide wire and through the tubal ostium under direct hysteroscopic vision to the fimbrial segment of the fallopian tube. The guidewire is then withdrawn while the teflon cannula is kept in place and the falloposcope is introduced through the teflon cannula. Fluid irrigation is done through the cannula lifting the endothelium off the lens of the falloposcope so it can be advanced under direct vision. In all cases, a better inspection of the tubal epithelium is obtained by the retrograde withdrawal of the falloposcope from the fimbria towards the uterine ostia. Dual monitoring is used for both hysteroscopic and falloposcopic recordings [6]. Falloposcopy failed in 11% of cases. No complications such as bleeding, trauma, or perforation were noted from within the tube or around the external tube.

Falloposcopy by a linear everting catheter system [7]

The linear everting catheter system consists of an inner and outer catheter which are joined cir-

cumferentially at their distal tips by a flexible membrane. This membrane is flexible enough to conform to the anatomy of the fallopian tube and at the same time firm enough to open the internal lumen under pressure. The balloon pressure is controlled via a fluid-filled syringe fitted to the inflation port. The controlled pressure results in the eversion of the balloon membrane as it advances through the fallopian tube. The falloposcope can be introduced into this space and then advanced along the length of the everted balloon. Irrigation is delivered through the lumen. The linear everting catheter is introduced transcervically. The procedure is monitored through a video system [7].

Various scoring systems for fallopian tube pathology

American Fertility Society Classification of distal tubal occlusion [8]

The American Fertility Society (AFS) classification of distal tubal occlusion includes parameters such as distal ampullary diameter, tubal wall thickness, mucosal folds at the neostomy site, extent of adhesions, and type of adhesions. All the parameters are given a score, and the tubal damage is assessed as mild (1-8), moderate (9-10) and severe (> 10).

Tubal disease staging by Winston Margara [9, 10]

Table 1 depicts the classification of tubal disease by Winston Margara.

Table 1. *Winston Margara classification of tubal disease.*

| Stage | Details |
|-------|--|
| I | Hydrosalpinx (thin-walled) with or without minimal fibrosis Mucosa: no flattened areas and thrown into folds Flimsy adhesions limited to ampulla and ovary Ovary: found and mostly free |
| II | Hydrosalpinx (thick-walled) with normal mucosa Mucosal fold: flattened areas or few folds along with thin-walled areas Adhesions: thick and fibrous on tube and ovary Ovary: found and mostly free |
| III | Thick-walled hydrosalpinx along with extensive mucosal damage Thick fibrous adhesions Clean hydrosalpinx having thin wall along with patent isthmus showing nodularity Ovary: absent on that side or incarcerated against sidewalls of pelvis |
| IV | Tube-ovarian mass/fibrous, Adherent hydrosalpinx Incarcerated ovary ± Ischemic damage |

Tubal disease classification by Hull and Rutherford [11] Table 2 depicts the classification of tubal disease by Hull and Rutherford.

Table 2. Hull and Rutherford classification of tubal disease.

| Grade of the disease | Severity | Details |
|----------------------|----------------------|---|
| I | Minor disease | On occlusion (proximal) absent tubal fibrosis On distal tubal occlusion: absent tubal distension Mucosa: favourable Adhesions on tube and ovary: flimsy |
| II | Intermediate disease | Tubal damage: Unilateral and severe ± Contralateral affected tube Adhesions on tube and ovary: limited and dense |
| III | Severe disease | Tubal damage: bilateral severe Fibrosis of the tube: extensive Tubal distension > 1.5 cm Mucosa: abnormal looking Bipolar occlusion Adhesions: extensive and dense |

New evaluation score that uses salpingoscopy to reflect fallopian tube pathology [12]

Nakagawa *et al.* [12] devised a scoring system using the results of salpingoscopy. Six findings were noted during the salpingoscopy:

1. Adhesions.
2. Loss of mucosal folds.
3. Rounded edges of mucosal folds.
4. Debris.
5. Foreign bodies.
6. Abnormal vessels.

One abnormal finding was given an F score of 1 point. The maximum F score is 12 points.

Classification of tubal pathology by falloposcopy

Kerin *et al.* [13] devised a classification where they looked at the following parameters during falloposcopy, patency of the tubes, abnormal vascular pattern, degree of adhesion formation, amount of dilation, and abnormal intrauterine contents. Scoring for each of the 4 segments of the left and right tubes is done. According to scoring fallopian tube disease was classified as mild < 20, moderate 20-30 and severe > 30.

REVIEW OF LITERATURE

One of the early descriptions of salpingoscopy for the evaluation of the fallopian tube was in 1988

[14]. 10 patients undergoing laparoscopy and 7 patients undergoing a laparotomy had a salpingoscopy performed with the same procedure. The tube was visualized from the fimbrial end to a point just distal to the ampullary-isthmic junction. No complications were observed. A discordance of 23.5% was noted overall between the fimbrial appearance at surgery and the salpinoscopic examination. They concluded patients with significant endosalpingeal damage have a poor prognosis following tuboplasty and should be given the option of IVF. There is a discordance rate of 23% between salpingoscopy and conventional methods *i.e.*, laparoscopy and HSG [14]. Marconi *et al.* [15] evaluated 42 infertile patients using salpingoscopy as an adjunct to laparoscopy. Alteration in major and minor folds of the mucosa of the fallopian tubes and their vascularization, presence of micro adhesions, and cellular nuclei dyed with methylene blue in the lumen were evaluated. 50% of the patients with no previous history of tubal disease presented with endosalpingeal alteration and in 37% of normal laparoscopies the salpinx had unilateral or bilateral salpingoscopic abnormalities. They concluded salpingoscopy should be carried out in all cases being evaluated for infertility during laparoscopy not only ones with pathology.

Nakagawa *et al.* [12] proposed a scoring system using the results of salpingoscopy which evaluated the relationship between scores and the outcome of pregnancy in 104 patients with unexplained infertility. They assessed six factors: adhesions, loss of mucosal folds, rounded edges of mucosal folds, debris, foreign bodies, and abnormal vessels. 1 F point was given for each factor. Patients with an F score of 0 and 1 had 30.6 % and 20% pregnancies respectively. Pregnancy with an F score of 0 was significantly higher than with high F scores. IUI and timed intercourse were advised in low F scores and patients with severe tubal damage were referred for IVF. Another method of salpingoscopy is a transvaginal office salpingoscopy. Gordts *et al.* in 1998 [5] assessed transvaginal salpingoscopy as an office procedure for infertility investigation. They examined 70 women with primary symptoms of infertility with no history of pelvic disease or pelvic surgery, normal gynaecological exam, and vaginal sonogram. Salpingoscopy was successful in 47% of the attempted tubes. Hydrolaparoscopy and transuterine dye hydrotubation can be performed in the same sitting [5]. Abdominal ostia can be cannulated with minimal or no manip-

ulation. There is greater success in the pre-ovulatory or early post-ovulatory period with 64% success in the attempted tubes *vs* 31% in the follicular and late luteal phase. The overall success rate was 47% in the attempted tubes. The advantage of transvaginal salpingoscopy is that the normal position of the ampulla lies in the axis of the scope, and adhesions are better visualized under fluid than by laparoscopy. However tubal cannulation is difficult if there are adhesions, or the tubes are in an abnormal position. In the absence of a panoramic view, therapeutic manipulation at transvaginal hydrolaparoscopy is limited [5]. The major advantage of transvaginal salpingoscopy over falloposcopy is the visualization of both adnexal and mucosal adhesions. Kerin *et al.* [6] described a microendoscopic technique of visual exploration of the fallopian tube. 44 women were examined by falloposcopy of which 36 had tubal damage and 8 served as controls. 38 underwent concurrent laparoscopy. Technical failure the inability to negotiate the tubal lumen in the absence of obstructive tubal disease was 11%. There were 63 successful procedures. The tubal lumen was falloposcopically normal in 44% (n = 28) of cases. Defects from partial to total obstruction were seen in the remaining 35 tubes (56%).

Dechaud *et al.* [16] evaluated routine falloposcopy in infertile patients undergoing basic infertility investigations. Based on HSG and laparoscopy 75 infertile women were classified into tubal or unexplained infertility. All patients underwent falloposcopic examination under GA with a linear everting catheter. Based on the falloposcopic findings they were reclassified as falloposcopic tubal or falloscopic unexplained infertility. The tubal catheterization rate was 94.5%. The mean duration was 19 minutes per tube. Based on a standard scoring system spontaneous pregnancy rates were 26.6% for a score of < 20, 11.5% for a score of 21-30, and 0% for a score of > 30. The complication rate was 5.1% and there was pinpoint perforation. 3 tubal infertility patients were reclassified as unexplained and 2 unexplained infertility patients were reclassified as tubal lesions by falloposcopic evaluation. Cox’s statistical model was used to examine certain parameters such as age, duration of infertility, aetiology of infertility by HSG or laparoscopy, and aetiology of infertility by falloposcopy to predict the likelihood of pregnancy. None of the factors were statistically significant in predicting pregnancy. However, the only predictive factor nearing

statistical significance was infertility defined by falloposcopic criteria. HSG and laparoscopy were not predictive. The pregnancy rate was directly correlated with the state of the tubal mucosa. Rimbach *et al.* [17] reported a large prospective international multicentric study that investigated the feasibility of falloposcopy as a routine investigation in infertility patients. 367 patients with 639 tubes were recorded in 18 centres. Falloposcopy was performed by hysteroscopic guidance and coaxial tubal cannulation. The procedure was successful in 69.6% of tubes. The number of patients who received a complete falloposcopic examination was 57%. Another 23.7% of patients had unilateral evaluation depending on the indication. Failures occurred in hysteroscopy (6.1%), cannulation step (10.6%), and visualization (16.4%). Intracavitary pathology or thick endometrium interfered with hysteroscopic access [18, 19]. However technical insufficiencies resulting in catheter damage or vision-disturbing light reflections were the cause of most cannulation. They concluded that the procedure is limited by technical difficulties and indicated in selected cases rather than routine application.

The principal goal of surgical treatment is to restore the normal anatomy of the tubes and their functional integrity. The main surgical procedures include adhesiolysis, salpingoovariolysis, fimbrioplasty, and neosalpingostomy (summarised listed below in **Table 3**). Reconstructive microsurgery can be done both by laparoscopy and laparotomy. A meta-analysis of 5 non-randomized controlled trials revealed a pooled intrauterine pregnancy rate of 28.9% under laparoscopic operation and 30.9% after open surgery [1]. The difference was not statistically significant. The crucial element of reproductive surgery is to prevent secondary adhesions.

Table 3. Surgical treatment options.

| Options for surgical treatment |
|--------------------------------|
| Adhesiolysis |
| Salpingoovariolysis |
| Fimbrioplasty |
| Neosalpingostomy |

The success of the surgery depends on the severity of tubal disease and the condition of the endosalpinx. Many studies show that about 80% of women with peri adnexal adhesions have healthy endosal-

pinx and within 1 year of adhesiolysis about 70% were pregnant and have a term delivery [20-23]. Fimbrioplasty has high success rates. In a case series of 273 patients, Tran reports a live birth rate of 71.5% after this procedure [24]. Rates after neosalpingostomy in a meta-analysis of 22 observational studies (1972-2014) showed a pooled live birth of 25% [25]. Reproductive rates are good in well-selected patients. Good prognosis cases are limited to flimsy adhesions and mildly dilated tubes < 3 cm pliable walls and lush normal folded mucosa. However tubal surgery not only results in increased intrauterine pregnancies but also ectopic pregnancy. The patient should be counselled regarding this.

The inner part of the fallopian tube is a cause of tubal obstruction in 15-20% of cases. Allahbadia *et al.* [26] reviewed minimal invasive transuterine tubal catheterization for both diagnostic and therapeutic indications. Endoscopic techniques falloposcopic/hysteroscopic/laparoscopic tubal aqua dissection, guidewire cannulation with dilatation, and direct balloon tubuloplasty may be used to break down intraluminal adhesions or dilate a stenosed but relatively healthy tube. High patency and pregnancy rates have been reported [27, 28].

Abnormal findings were detected in the fallopian tubes of 40% of patients with unexplained infertility who underwent salpingoscopy in this study. HSG, vaginal ultrasound, and laparoscopy cannot detect these abnormalities. Patients who were positive for chlamydia antibodies had a high incidence of tubal mucosal abnormalities. Women with infertility are more likely to have chronic endometritis (CE). Bacterial interaction with the endometrial milieu leads to changes in the leukocyte population, cytokine production, and growth factors, all of which lead to detrimental effects on the receptivity of the endometrium. In women with unexplained recurrent pregnancy loss (RPL), effective antibiotic treatment of CE appears to enhance the pregnancy and live birth rates. In addition to conventional histology, immunohistochemistry is advised to improve detection accuracy [29].

Vitagliano *et al.* in their study showed that the negative effects of CE on negative IVF outcome may be restricted to severe disease, whereas mild CE may have no influence on IVF success rate [30].

Salpingoscopy is the only method available for the assessment of the inside of the oviducts. It is capable of producing *in vivo* images of the actual site of human fertilization. This can direct decisions

toward tubal reconstructive microsurgery or artificial reproductive technique (ART).

Salpingoscopy is an important component of the examination of the tubes and should be incorporated into the routine investigation of the infertile couple for the following reasons:

- It can be safely incorporated as a step during laparoscopy or pelvic hydrolaparoscopy.
- Complicated equipment is not required. The abdominal salpingoscopy can be done with a rigid hysteroscope, a colpomicrohysteroscope which is introduced through a second suprapubic incision [4]. A more simplified technique using a standard 2.9 mm diagnostic hysteroscope with a single flow diagnostic sheath is introduced through an accessory port. This adds an extra 15 mins to the surgical procedure [31].
- The learning curve is less as compared with falloposcopy and the time taken to examine each tube is less. Furthermore, the rate of success is approximately 97% in abdominal salpingoscopy whereas it is only 70% in transuterine falloposcopy [17] with several failures due to technical issues.
- Almost 75-80% of tubal pathology involves the outer 2/3rds of the fallopian tubes *i.e.*, from the fimbria and ampulla to the ampullary isthmic junction [1]. Therefore, a routine examination of these organs during the fertility workup is important. This should not be restricted to abnormal findings but also to normal laparoscopic findings as diseased tubal mucosa is found in 37% of normal laparoscopies [15].

Successful pregnancies vary from 80% in salpingo-adhesiolysis to 25% in complicated neosalpingostomies [1]. These rates are encouraging. Furthermore, the pregnancy rates are almost similar following laparoscopy or laparotomy [1].

Recanalization is contraindicated in florid infection and long tubal obstruction. Falloposcopic intervention has good outcomes in well-selected patients of proximal tubal occlusion (PTO).

Schmidt *et al.* used a linear everting catheter system on 62 patients and reported a pregnancy rate of 52% overall in patients with normal endosalpinx and 80% following insemination. There were no ectopic pregnancies [32].

Falloposcopy is technically a more difficult procedure than salpingoscopy. The method requires complex instrumentation using a hysteroscope with a coaxial catheter or everting catheter system falloposcope [33]. Both these methods have a long learning

curve and high failure rates. Success rates amount to between 47% to 70% [5, 17]. Therefore falloposcopic examination should be restricted to selected cases. Proximal tubal block in HSG reports, abnormal laparoscopy dye test, high chlamydia antibodies, and history of tuberculosis should alert the clinician to the possibility of proximal tubal block. The aim of assessing the inner mucosal surface of the fallopian tube which requires an extra procedure is to select the patient appropriately for tubal microsurgery.

Fallopian tube recanalization can be performed with catheters, flexible guidewires or balloon systems under falloposcopic guidance. Falloposcopy provides a unique possibility to accurately image the fallopian tube and identify endotubal disease and classify proximal tubal obstruction. Non-hysteroscopic transcervical falloposcopy with a linear eversion catheter is an outpatient technique with good predictive value [34].

When compared to parous women, women with recurrent pregnancy loss had considerably higher levels of AGR3 and S100P immunostaining in the ciliated cells of the luminal epithelium, indicating that these conditions may have an abnormal subcellular location-associated pathogenesis [35].

In the peritoneal milieu, CTLA4-based autoimmunity contributes to chronic inflammation, and there is preliminary indication that anti-CTLA antibodies could provide a novel target therapy for endometriosis. CTLA4 gene studies, however, do not support the hypothesis that CTLA4-linked autoimmunity is a major factor in the etiology of endometriosis. These results support the function of intricate connections among the immune checkpoint molecule family concerned [36].

With accuracy comparable to HSG, sonohysterosalpingography (HyCoSy) is a non-invasive method. A number of research have been conducted on various contrast agents that might be utilized during this procedure, and more recent studies have looked at the hysterosalpingo-foam sonography (HyFoSy) process as a new method for examining the function of the tubes in infertile women. HyFoSy is a technique that is frequently employed to check for tubal patency nowadays, although its effectiveness in terms of pregnancy outcomes is not entirely known [37].

CONCLUSIONS

Many patients of unexplained infertility are reclassified as tubal infertility after full evaluation

which includes examination of the inner mucosal layer of the uterine tubes. The conventional methods of examining tubes by laparoscopy and HSG are inadequate for the study of tubal pathology. Without a study of the inner mucosa of the tube, an assessment of the fallopian tube is incomplete. Salpingoscopy and falloposcopy are two important methods to assess the tubal mucosal surface and clinical assessment is incomplete without these methods. Salpingoscopy assesses the outer 2/3 of the tube whereas falloposcopy can examine the whole length of the tube from the uterine cornu to the peritoneal surface. The primary importance of falloposcopy is that it can examine the inner 1/3 of the uterine tubes and check for the proximal tubal block. Following an appropriate assessment of the fallopian tubes aided by salpingoscopy and falloposcopy the decision to proceed with natural pregnancy or tubal surgery or ART must be made after discussing with the patient her needs and prognosis.

A falloposcopic examination combined with a conventional examination of HSG/laparoscopy dye test will give a complete assessment of the tubes and guide the clinician as to whether the best line of treatment would be spontaneous birth, ART, or tubal reconstructive microsurgery. Discussion and involvement of the affected couple are important to decide the course of action. Furthermore, low-resource setup may not be able to offer expensive and complex IVF treatments.

Tubal reconstructive microsurgery has an advantage over IVF in that it improves the patient's fertility so that she has the chance to conceive several times over several cycles whereas IVF only allows conception over one or two cycles and the patient remains infertile. The prognosis of tubal microsurgery is good in well-selected cases, and this means not only the results are encouraging but it can be done in a low-resource setting and where there are financial constraints. Surgeons can be trained without expensive endoscopic equipment.

However, without endoscopic examination of the tubal mucosa, good results will not be evident. Tubal surgery not only improves pregnancy rates but also increases ectopic rates. This should be discussed with the patient. It is therefore imperative to assess all tubal factors before attempting tubal reconstructive microsurgery and reconsider patients who would otherwise be referred for IVF treatment or labelled as infertile.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

S.P.: Writing – original draft. A.D., L.L.: Writing – review & editing. R.M.: Supervision. P.T.: Validation, writing – review & editing.

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The authors declare that they have no conflict of interests.

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REFERENCES

- Obrzut B, Obrzut M. Is There Still a Place for Reconstructive Surgery in Distal Tubal Disease? *J Clin Med*. 2022;11(12):3278. doi: 10.3390/jcm11123278.
- Practice Committee of the American Society for Reproductive Medicine. Role of tubal surgery in the era of assisted reproductive technology: a committee opinion. *Fertil Steril*. 2021;115(5):1143-50. doi: 10.1016/j.fertnstert.2021.01.051.
- Dechaud H, Daures JP, Hedon B. Prospective evaluation of falloposcopy. *Hum Reprod*. 1998;13(7):1815-8. doi: 10.1093/humrep/13.7.1815.
- Marconi G, Auge L, Sojo E, Young E, Quintana R. Salpingoscopy: systematic use in diagnostic laparoscopy. *Fertil Steril*. 1992;57(4):742-6. doi: 10.1016/s0015-0282(16)54952-8.
- Gordts S, Campo R, Rombauts L, Brosens I. Transvaginal salpingoscopy: an office procedure for infertility investigation. *Fertil Steril*. 1998;70(3):523-6. doi: 10.1016/s0015-0282(98)00186-1.
- Kerin J, Daykhovsky L, Segalowitz J, Surrey E, Anderson R, Stein A, et al. Falloposcopy: a microendoscopic technique for visual exploration of the human fallopian tube from the uterotubal ostium to the fimbria using a transvaginal approach. *Fertil Steril*. 1990;54(3):390-400. doi: 10.1016/s0015-0282(16)53750-9.
- Pearlstone AC, Surrey ES, Kerin JF. The linear everting catheter: a nonhysteroscopic, transvaginal technique for access and microendoscopy of the fallopian tube. *Fertil Steril*. 1992;58(4):854-7. doi: 10.1016/s0015-0282(16)55345-x.
- The American Fertility Society. Classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, müllerian anomalies and intrauterine adhesions. *Fertil Steril*. 1988;49(6):944-55. doi: 10.1016/s0015-0282(16)59942-7.
- Winston RM, Margara RA. Microsurgical salpingostomy is not an obsolete procedure. *Br J Obstet Gynaecol*. 1991;98(7):637-42. doi: 10.1111/j.1471-0528.1991.tb13448.x.
- Boer-Meisel ME, te Velde ER, Habbema JD, Kardaun JW. Predicting the pregnancy outcome in patients treated for hydrosalpinx: a prospective study. *Fertil Steril*. 1986;45(1):23-9. doi: 10.1016/s0015-0282(16)49091-6.
- Rutherford AJ, Jenkins JM. Hull and Rutherford classification of infertility. *Hum Fertil (Camb)*. 2002;5(1 Suppl):S41-5. doi: 10.1080/1464727022000199911.
- Nakagawa K, Inoue M, Nishi Y, Sugiyama R, Motoyama K, Kuribayashi Y et al. A new evaluation score that uses salpingoscopy to reflect fallopian tube function in infertile women. *Fertil Steril*. 2010;94(7):2753-7. doi: 10.1016/j.fertnstert.2010.03.012.
- Kerin JF, Williams DB, San Roman GA, Pearlstone AC, Grundfest WS, Surrey ES. Falloposcopic classification and treatment of fallopian tube lumen disease. *Fertil Steril*. 1992;57(4):731-41. doi: 10.1016/s0015-0282(16)54951-6.
- Shapiro BS, Diamond MP, DeCherney AH. Salpingoscopy: an adjunctive technique for evaluation of the fallopian tube. *Fertil Steril*. 1988;49(6):1076-9. doi: 10.1016/s0015-0282(16)59964-6.

15. Marconi G, Auge L, Sojo E, Young E, Quintana R. Salpingoscopy: systematic use in diagnostic laparoscopy. *Fertil Steril*. 1992;57(4):742-6. doi: 10.1016/s0015-0282(16)54952-8.
16. Dechaud H, Daures JP, Hedon B. Prospective evaluation of falloposcopy. *Hum Reprod*. 1998;13(7):1815-8. doi: 10.1093/humrep/13.7.1815.
17. Rimbach S, Bastert G, Wallwiener D. Technical results of falloposcopy for infertility diagnosis in a large multicentre study. *Hum Reprod*. 2001;16(5):925-30. doi: 10.1093/humrep/16.5.925.
18. Manchanda R, Yadav T, Dave A. Management of thin endometrium by hysteroscopic instillation of platelet rich plasma: a narrative review. *Ital J Gynaecol Obstet*. 2023;35(1):81-5. doi: 10.36129/jog.2022.55.
19. Jha S, Surabhi K. Hysteroscopy "As one stop approach" in the management of intrauterine pathology. Focus on patient's satisfaction. *Ital J Gynaecol Obstet*. 2021;33(2):102-9. doi: 10.36129/jog.33.02.04.
20. Heylen SM, Brosens IA, Puttemans PJ. Clinical value and cumulative pregnancy rates following rigid salpingoscopy during laparoscopy for infertility. *Hum Reprod*. 1995;10(11):2913-6. doi: 10.1093/oxfordjournals.humrep.a135818.
21. Marana R, Rizzi M, Muzii L, Catalano GF, Caruana P, Mancuso S. Correlation between the American Fertility Society classifications of adnexal adhesions and distal tubal occlusion, salpingoscopy, and reproductive outcome in tubal surgery. *Fertil Steril*. 1995;64(5):924-9. doi: 10.1016/s0015-0282(16)57903-5.
22. Marana R, Catalano GF, Muzii L, Caruana P, Margutti F, Mancuso S. The prognostic role of salpingoscopy in laparoscopic tubal surgery. *Hum Reprod*. 1999;14(12):2991-5. doi: 10.1093/humrep/14.12.2991.
23. Marana R, Catalano GF, Muzii L. Salpingoscopy. *Curr Opin Obstet Gynecol*. 2003;15(4):333-6. doi: 10.1097/01.gco.0000084245.09900.dd.
24. Tran DK. Can open tubal microsurgery still be helpful in tubal infertility treatment? *Gynecol Surg*. 2010;7:385-400. doi: 10.1007/s10397-010-0556-5.
25. Chu J, Harb HM, Gallos ID, Dhillon R, Al-Rshoud FM, Robinson L, et al. Salpingostomy in the treatment of hydrosalpinx: a systematic review and meta-analysis. *Hum Reprod*. 2015;30(8):1882-95. doi: 10.1093/humrep/dev135.
26. Allahbadia GN, Merchant R. Fallopian tube recanalization: lessons learnt and future challenges. *Womens Health (Lond)*. 2010;6(4):531-48, quiz 548-9. doi: 10.2217/whe.10.34.
27. Kuzmin A, Linde V. Diagnostic and remedial capability of transcervical falloposcopy in conjunction with laparoscopy. *Gynecol Endocrinol*. 2014;30 Suppl 1:17-9. doi: 10.3109/09513590.2014.945771.
28. Sueoka K, Asada H, Tsuchiya S, Kobayashi N, Kuroshima M, Yoshimura Y. Falloposcopic tuboplasty for bilateral tubal occlusion. A novel infertility treatment as an alternative for in-vitro fertilization? *Hum Reprod*. 1998;13(1):71-4. doi: 10.1093/humrep/13.1.71.
29. Puente E, Alonso L, Laganà AS, Ghezzi F, Casarin J, Carugno J. Chronic Endometritis: Old Problem, Novel Insights and Future Challenges. *Int J Fertil Steril*. 2020;13(4):250-6. doi: 10.22074/ijfs.2020.5779.
30. Vitagliano A, Laganà AS, De Ziegler D, Cicinelli R, Santarsiero CM, Buzzaccarini G, et al. Chronic Endometritis in Infertile Women: Impact of Untreated Disease, Plasma Cell Count and Antibiotic Therapy on IVF Outcome-A Systematic Review and Meta-Analysis. *Diagnostics (Basel)*. 2022;12(9):2250. doi: 10.3390/diagnostics12092250.
31. Muzii L, Angioli R, Tambone V, Zullo MA, Marana R, Panici PB. Salpingoscopy during laparoscopy using a small-caliber hysteroscope introduced through an accessory trocar. *J Laparoendosc Adv Surg Tech A*. 2010;20(7):619-21. doi: 10.1089/lap.2010.0051.
32. Schmidt S, Weidner A, Sierra F, Krebs D. Prognostische Wertigkeit der Falloposkopie [Prognostic value of Fallopian tube endoscopy]. *Zentralbl Gynakol*. 2000;122(9):489-94. German. doi: 10.1055/s-2000-10610.
33. Bauer O, Diedrich K, Bacich S, Knight C, Lowery G, van der Ven H, Werner A, Krebs D. Transcervical access and intra-luminal imaging of the fallopian tube in the non-anaesthetized patient; preliminary results using a new technique for fallopian access. *Hum Reprod*. 1992;7 Suppl 1:7-11. doi: 10.1093/humrep/7.suppl_1.7.
34. Venezia R, Zangara C, Knight C, Cittadini E. Initial experience of a new linear everting falloposcopy system in comparison with hysterosalpingography. *Fertil Steril*. 1993;60(5):771-5. doi: 10.1016/s0015-0282(16)56274-8.
35. Laganà AS, Uccella S, Chiantera V, Garzon S. Molecular Biology of Human Fertil-

- ity: Stepping towards a Tailored Approach. *Int J Mol Sci.* 2022;23(14):7517. doi: 10.3390/ijms23147517.
36. Mikuš M, Goldštajn MŠ, Brlečić I, Dumančić S, Laganà AS, Chiantera V, et al. CTLA4-Linked Autoimmunity in the Pathogenesis of Endometriosis and Related Infertility: A Systematic Review. *Int J Mol Sci.* 2022;23(18):10902. doi: 10.3390/ijms231810902.
37. Piccioni MG, Tabacco S, Merlino L, Del Negro V, Mazzeo A, Logoteta A, et al. Does hysterosalpingo-foam sonography have any therapeutic effect? A systematic review. *Minerva Ginecol.* 2020;72(1):55-8. doi: 10.23736/S0026-4784.20.04514-1.



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Comparative study between the effect of carbetocin *versus* oxytocin plus sublingual misoprostol and oxytocin in the management of postpartum blood loss > 500 ml after vaginal delivery: a randomized controlled trial

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ABSTRACT

Objective. In comparison to oxytocin alone, researchers wanted to examine how carbetocin and oxytocin plus sublingual misoprostol influenced the estimated and measured amount of blood loss following vaginal birth in women who had blood loss > 500 ml.

Patients and Methods. 135 women with blood loss greater than 500 ml after vaginal delivery were recruited in the current randomized open-label clinical trial at a tertiary university hospital between April 2019 and December 2022 (NCT03870503), after receiving standard treatments for managing the third stage of labour and signing an informant consent. They were separated into three groups: group 1 received 100 µg of carbetocin (Pabal Ferring, UK), group 2 received 400 µg of sublingual misoprostol with 20 IU of oxytocin (Syntocinon, Novartis, Switzerland), and group 3 received just 20 IU of oxytocin. Blood loss of 500 millilitres or less following postpartum haemorrhage therapy was the main goal.

Results. When compared to the carbetocin and oxytocin plus misoprostol groups, the oxytocin group had a substantial drop in haemoglobin concentration and a significant increase in estimated blood loss ($p = 0.0001$; 0.0001 , respectively). The estimated blood loss in the oxytocin plus misoprostol group was significantly lower than in the carbetocin group ($p = 0.004$). When comparing the carbetocin (13.3%) to the oxytocin plus misoprostol group (11.1%) and the oxytocin (24.4%), the incidence of postpartum blood loss > 1,000 ml was higher in the oxytocin group ($p = 0.0001$).

Conclusions. Oxytocin plus misoprostol is more effective than oxytocin and carbetocin in the management of post-partum blood loss > 500 ml after vaginal delivery.

INTRODUCTION

Postpartum haemorrhage (PPH) is defined as bleeding lasting quite 500 millilitres after vaginal delivery, but the American College of Obstetrics and Gynecology (ACOG) revised the definition in 2017, and therefore the current definition is cumulative blood loss

greater than 1,000 millilitres with signs and symptoms of hypovolemia within 24 hours, no matter delivery method [1, 2]. While this adjustment was made with the understanding that blood loss at the time of birth is usually underestimated, blood loss of quite 500 ml during vaginal delivery should be considered abnormal and should require medical attention [3].

The failure of the uterus to contract and retract after childbirth has been recognized because the most dramatic explanation for PPH for millennia, and it complicates up to 10% of pregnancies worldwide. PPH is liable for one maternal fatality every seven minutes in the underdeveloped world [4].

By stimulating uterine contractions and avoiding uterine atony, active treatment of the third stage of labour aims to assist placenta delivery and prevent primary postpartum haemorrhage (PPH). After the placenta is delivered, the customary elements include, if necessary, the administration of uterotonic drugs, controlled cord traction, and uterine massage [5].

Oxytocin must be kept and transported at 2-8 °C. In low-resource countries, the cold chain isn't commonly available. A heat-stable uterotonic medication would be highly helpful since it might not only reduce storage and shipping costs and logistical problems but might also prevent atonic PPH deaths caused by denatured and useless oxytocin [6]. Carbetocin has the potential to be a newer long-acting oxytocin analogue [7].

Continuous contractions last 11 minutes and rhythmic contractions last 120 minutes after carbetocin is run into the uterus [8]. A heat-stable carbetocin is currently available [9]. The World Health Organization (WHO) authorized carbetocin for the prevention of PPH altogether births in December 2018 when the value was like other effective uterotonics [3].

The main disadvantage of carbetocin is that it's significantly more costly than oxytocin and isn't widely available, particularly in low-resource countries [8]. Misoprostol is especially useful in these conditions since it's inexpensive, temperature-resistant, and readily available in resource-poor countries [10]. The exciting possibility that misoprostol might be employed by traditional birth attendants, or self-administered, for births occurring far away from health services and health personnel, where women are most in danger of the rapidly fatal effects of severe PPH, raised the likelihood that it might be employed by traditional birth attendants, or self-administered [11]. When oxytocin is unavailable or the standard of oxytocin can't be guaranteed, another injectable oxytocic (carbetocin) or oral misoprostol should be used instead.

Despite the utilization of a uterotonic drug as a preventative measure, PPH remains a frequent complication, accounting for one-quarter of all maternal fatalities worldwide. When prophylaxis fails and PPH develops, it's advised that uterotonic

medicines be used as "first line" therapy. However, it's unclear whether a uterotonic drug is best for treating PPH as a "first line" therapy [10].

Oxytocin, carbetocin, ergometrine, misoprostol, injectable prostaglandins, and combinations of those medications are among the uterotonic therapies available, with varying degrees of efficacy and adverse effects.

The purpose of this study is to evaluate the efficacy of oxytocin plus sublingual misoprostol against carbetocin and oxytocin alone within the treatment of blood loss greater than 500 ml following standard active third-stage labour management.

MATERIALS AND METHODS

Study type, setting, and duration

From April 1, 2019, to December 30, 2022, we performed an open label randomized controlled study on 135 pregnant women attending the labour wards at Aswan University Hospital in Aswan, Egypt. After the research protocol was approved by the institutional review board (Aswu/280/7/18), we prospectively filed it at clinicaltrials.gov (NCT03870503). We offered each participant a thorough description of the study's purpose and methods. Before the trial began, eligible patients who were invited to participate in the study in case they develop PPH gave written informed consent. This manuscript conforms to the enhancement, quality, and transparency of health research (EQUATOR) network guidelines.

Study participants

Only women who signed informed consent papers were included in the research. In all the cases, PPH was defined as vaginal haemorrhage > 500 ml following vaginal delivery and uterine atony confirmed by abdominal palpation. Women who met the following criteria were not permitted to participate: < 37 weeks of pregnancy, genital tract injuries, coagulation deficit, hypertension, preeclampsia, cardiac, renal, or hepatic disease, epilepsy, and carbetocin or oxytocin hypersensitivity are all risk factors.

Randomization and allocation

135 women with atonic PPH were divided into three equal groups using computer-generated random numbers. An independent individual created the

allocation sequence, and all medicines were tagged, packed, and stored in the labour ward before recruitment. By using opaque sealed packets with sequentially numbered medication codes, the allocation was hidden. Each lady was issued an order, and the medication was provided to her with a code that linked to her envelope number. In addition to normal treatment, we randomly allocated women to receive oxytocin alone, oxytocin with misoprostol, or carbetocin.

Intervention

All women underwent routine active management of the third stage of labour with standard uterotonics, controlled cord traction after the delivery of the baby, and gentle uterine massage after the delivery of the placenta. At the delivery of the anterior shoulder of the baby, one of two uterotonic regimens was administered: intravenous 10 IU of oxytocin given either intramuscularly or intravenously. Immediately after the delivery of the baby, blood loss was collected by placing a clean fracture bedpan directly under the woman's buttocks for a minimum of one hour [1, 3].

Markings were written onto the bedpan to show when 500 ml had been reached. Women losing less than 500 ml were not entered into the trial.

Women losing 500 ml, or more were enrolled in the trial, and a clean bedpan was placed underneath their buttocks to collect blood lost after PPH diagnosis. A fresh, large perineal pad with plastic backing was positioned just below the bedpan to capture any spattering blood. Once the delivery attendant considered active bleeding to have stopped, the blood was transferred to a calibrated jar for measurement. Two 14-gauge cannulas were placed, and a crystalloid intravenous (i.v.) infusion was begun when atonic PPH occurred. An oxygen concentration of 10 L/min was given through a face mask. A Foley catheter was placed, and a fluid balance chart was recorded after the fundus was massaged. Every 15 minutes, the patient's pulse and blood pressure were recorded, and venipuncture was performed for cross-matching four units of blood, a full blood count, a coagulation screen, and urea and electrolytes testing.

To rule out retained products of conception and genital tract damage, an ultrasound scan and examination of the genital tract were performed.

Eligible participants were assigned to one of three study groups after diagnosis of blood loss of more

than 500 ml due to uterine atony: group I (carbetocin group) (45 patients received 100 µg carbetocin (Pabal Ferring, UK)), group II (oxytocin plus misoprostol group) (45 patients received 400 µg sublingual misoprostol (Cytotec Pfizer, New York, USA) plus 20 unit of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h (Syntocinon, Novartis, Switzerland), group III oxytocin group) (45 patients received 20 unit of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h) [1, 3].

The uterine tone and quantity of bleeding were evaluated 5 minutes after the medication was given, and the necessity for more uterotonic drugs and blood transfusion was decided.

The amount of blood lost was calculated by weighing the swabs and utilizing graphical charts. The haemoglobin level in the blood was measured 24 hours after birth: oxytocin (Syntocinon, Novartis, Switzerland) infusion 40 IU in 500 ml lactated ringer's solution 125 ml/h, misoprostol (Cytotec Pfizer, New York, USA) 600 µg rectally, insertion of an intrauterine Bakri balloon, laparotomy, and B lynch stitch, bilateral uterine artery ligation, hysterectomy.

Nausea, vomiting, tachycardia, diarrhoea, fever, and tachycardia were all noted as potential consequences.

Study outcomes

The primary endpoint was measured as excessive bleeding blood loss ≥ 500 mills after PPH treatment; secondary outcomes included change in haemoglobin, side effects, need for additional interventions including blood transfusion, additional uterotonics, balloon tamponade, hysterectomy, and mean blood loss $> 1,000$ ml.

Sample size

The primary outcome measure was used to calculate the sample size. To detect a 100-ml difference in additional average blood loss after enrolment at a 5% significance level with 80 percent power (assuming mean additional blood loss of 400 ml in the carbetocin group and 300 ml in the oxytocin plus sublingual misoprostol, and a standard deviation of 200 ml in both groups), 45 women per group were needed. Epi-Info 6.0 was used to double-enter, verify, and clean data, and Stata 7.0 was used to analyse it (Stata, Texas, USA).

Statistical analysis

The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 16 was used to enter data and perform statistical analysis. Numbers and percentages were used to describe qualitative data. The Chi-square test and the Monte Carlo test were employed to compare groups when needed. Quantitative data were expressed as means (SD) or medians, depending on the situation. The Kolmogorov-Smirnov test was used to determine their normalcy. A one-way ANOVA test with LSD *post-hoc* multiple comparisons were performed for comparison between groups in the normally distributed variables, if applicable. The Mann Whitney test and the Kruskal-Wallis test were employed to compare groups in non-normally distributed data, where applicable. We estimated odds ratios and their 95% confidence intervals. The statistical significance of P-value 0.05 was established.

RESULTS

A total of 5,349 women were approached about taking part in the study. A total of 5,214 women were removed from the study: 39 women were found to be ineligible, 213 women declined to participate, and 4,962 women did not develop postpartum haemorrhage. The remaining 135 women were divided into three research groups at random (Figure 1). There were no significant differences in age, weight, height, BMI, parity, gestational age, first haemoglobin, blood pressure, or temperature between the three groups (Table 1).

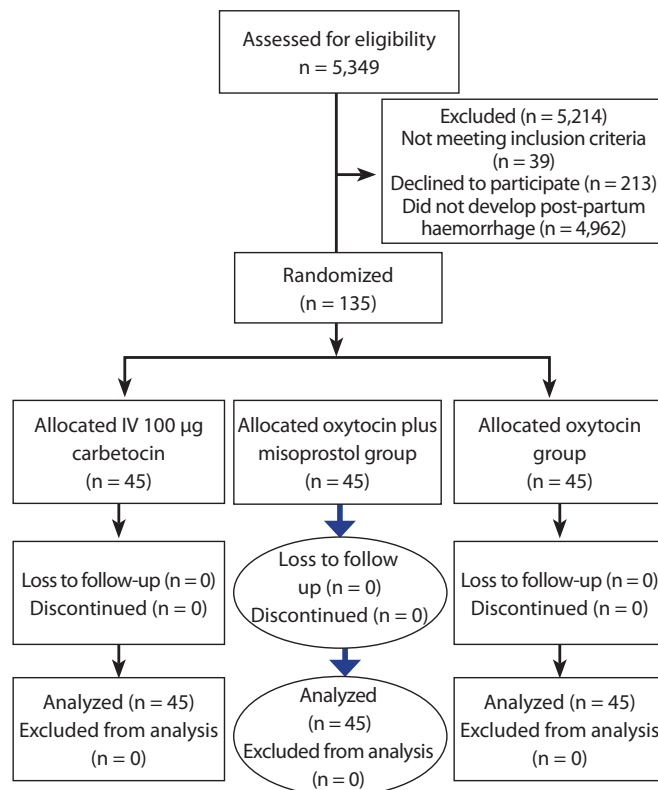


Figure 1. Consort flowchart showing enrolment of participants.

The oxytocin group had a statistically significant higher post-delivery pulse rate than the carbetocin group (p = 0.0001, 95%CI 2.68-7.86) and the oxytocin plus the misoprostol group (p = 0.0001, 95%CI 3.80-8.99). In addition, there was no significant difference in post-delivery pulse rate between the oxytocin plus misoprostol and carbetocin groups (p = 0.692, 95%CI -1.47 to 3.72). The oxytocin group had a statistically significant lower post-delivery SBP and DBP than the carbetocin group.

Table 1. Baseline characteristics of pregnant women in the study groups.

| Parameters | Group I (n = 45) | Group II (n = 45) | Group III (n = 45) | P-value |
|-----------------------------------|------------------|-------------------|--------------------|---------|
| Age (year) | 29.5 ± 2.42 | 29.6 ± 2.68 | 29.83 ± 2.85 | 0.854 |
| Weight (kg) | 69.25 ± 7.76 | 69.43 ± 7.18 | 69.4 ± 7.77 | 0.994 |
| Height (cm) | 162.45 ± 4.19 | 163.58 ± 4.38 | 163.52 ± 4.6 | 0.436 |
| BMI (kg/m ²) | 26.2 ± 2.55 | 25.96 ± 2.74 | 25.94 ± 2.71 | 0.888 |
| Parity (median) (minimum-maximum) | 3 (0-4) | 2 (0-5) | 3 (0-5) | 0.866 |
| Gestational age (weeks) | 38.4 ± 1.45 | 38.55 ± 1.34 | 37.5 ± 1.22 | 0.878 |
| Initial haemoglobin | 10.97 ± 0.624 | 10.98 ± 0.623 | 10.83 ± 0.622 | 0.905 |
| Duration of first stage (h) | 9.78 ± 2.91 | 9.81 ± 2.06 | 9.92 ± 1.06 | |
| Duration of second stage (mins) | 64.72 ± 16.12 | 63.72 ± 17.13 | 63.72 ± 13.16 | |
| Duration of third stage (mins) | 4.42 ± 1.2 | 4.73 ± 2.3 | 4.23 ± 1.3 | 0.965 |
| Birth weight (g) | 3,176 ± 376.64 | 3,182 ± 35.21 | 3,182 ± 35.25 | |

BMI: Body Mass Index; CS: caesarean section; CPD: cephalopelvic disproportion; variables are presented as mean and standard deviation, median (minimum-maximum) and number (percentage).

Table 2. Post-delivery variables in the three groups.

| Blood loss | Group I (n = 45) | Group II (n = 45) | Group III (n = 45) | P-value |
|-----------------------------------|------------------|-------------------|--------------------|----------------------------------|
| Amount of bleeding (ml) | 811 ± 525.66 | 722 ± 312.77 | 910 ± 389.17 | 0.007* 0.03*/0.04*/0.0001* |
| PPH > 1,000 ml (%) | 6 (13.3 %) | 5 (11.1%) | 11 (24.4 %) | 0.0001* 0.326/0.0001*/0.0001* |
| Temperature | 36.91 ± 0.07 | 37.45 ± 0.64 | 36.95 ± 0.43 | 0.0001* 0.0001*/0.12/0.0001* |
| Pulse (30 minutes after delivery) | 94.46 ± 7.5 | 93.99 ± 9.7 | 96.99 ± 9.7 | 0.692 0.721/0.692/0.126 |
| Hb 24 h after delivery(g/dl) | 9.98 ± 2.71 | 8.98 ± 4.21 | 9.93 ± 3.27 | 0.0001* 0.0001*/0.221/0.0001* |
| SBP (30 minutes after delivery) | 119.09 ± 3.67 | 116.04 ± 7.23 | 103.04 ± 6.12 | 0.0001* 0.193/0.0001*/0.0001* |
| DBP (30 minutes after delivery) | 86.32 ± 3.36 | 81.41 ± 5.15 | 73.41 ± 4.48 | 0.0001* 0.026*/0.026*/0.0001 |

*Statistically significant difference (Group I versus Group II/Group I versus Group III/Group II versus Group III); variables are presented as mean and standard deviation, and number (percentage).

cin group (p = 0.0001, 95%CI -7.88 to -4.69) and the oxytocin plus misoprostol group (p = 0.0001, 95%CI -7.89 to -4.70).

When compared to both the oxytocin and carbetocin groups the oxytocin plus the misoprostol group, had a substantial rise in post-delivery temperature (p = 0.0001).

When compared to the carbetocin and oxytocin plus the misoprostol groups, the oxytocin group had a statistically significant lower haemoglobin level and greater blood loss (p = 0.0001). The TA + oxytocin group had a statistically significant higher haemoglobin level and less blood loss than the carbetocin group (p = 0.004 and 0.043, respectively) (Table 2).

PPH was more common in the oxytocin group (9.1%) than in the carbetocin group (2.5%) or the oxytocin plus the misoprostol group (0.83%) (p = 0.0001).

There was no significant difference in the incidence of PPH between the carbetocin group and the oxytocin plus misoprostol group (p = 0.298), therefore the oxytocin group used more extra uterotonics than the other two groups. Only 14 (10.8%) women in the oxytocin group required blood transfusion.

The oxytocin + misoprostol group had a higher rate of diarrhoea and increase temperature (6.6%) than the carbetocin group (0%) or the oxytocin group (0%). There were no significant differences in the incidence of nausea, vomiting, or diarrhoea across the three groups (Table 3).

Table 3. Adjuvant interventions and side effect measurements.

| Variables | Group I (n = 45) | Group II (n = 45) | Group III (n = 45) | P-value |
|-----------------------------|------------------|-------------------|--------------------|-------------------------------------|
| Additional uterotonics (%) | 7 (15.5) | 6 (13.3 %) | 12 (26.6) | 0.0001* 0.261 / 0.0001*/ 0.0001* |
| Bakri balloon (%) | 1 (2.2) | 1 (2.2) | 3 (6.6) | 0.132 |
| B lynch stitch (%) | 1 (2.2) | 1 (2.2) | 2 (2.2) | 0.536 |
| Uterine artery ligation (%) | / | / | 1 (7.5) | / |
| Hysterectomy (%) | / | / | / | / |
| Need Blood Transfusion (%) | 8 (50) | 7 (12.5) | 13 (7.5) | 0.0001* 0.214 / 0.0001*/ 0.0001* |
| Tachycardia (> 100 b/min) | 9 (20) | 10 (22.2) | 15(33.3) | 0.0001* 0.672 / 0.0001*/ 0.0001* |
| Fever (%) | / | 3 (6.6) | / | / |
| Nausea (%) | 2 (4.4) | 3 (6.6) | 3(6.6) | 0.906 |
| Vomiting (%) | 1 (2.2) | 1 (2.2) | 2 (4.4) | 1.000 |
| Diarrhoea (%) | 1 (2.2) | 1 (2.2) | 3 (6.6) | 0.620 |

*Statistically significant difference (Group I versus Group II/Group I versus Group III/Group II versus Group III); variables are presented as mean and standard deviation and number (percentage).

DISCUSSION

This research was designed to compare the efficacy of intravenous 100 µg carbetocin against 20 units of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h with 400 µg sublingual misoprostol, as well as 20 units of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h alone, in reducing blood loss in pregnant women who are having a vaginal birth and experience blood loss > 500 ml. Our research found that using oxytocin in combination with sublingual misoprostol or i.v. carbetocin reduces determined blood loss, the incidence of PPH, and hence the requirement for further uterotonics, compared to oxytocin alone.

In comparison to oxytocin, carbetocin dramatically reduced postpartum blood loss and reduced the need for extra uterotonics in women with atonic PPH, with no notable adverse effects or hemodynamic abnormalities. This is often thanks to carbetocin's longer half-life, which causes a greater uterine response in terms of frequency and amplitude of uterine contractions [10]. These findings were also the results of several studies published within the literature [12-15].

Our findings matched those of Samimi *et al.*, who gave carbetocin or syntometrine to 200 women undergoing childbirth to avoid PPH. The need for extra uterotonics was observed to be considerably reduced within the carbetocin group. Carbetocin was shown to be more efficient than syntometrine in preventing PPH [13].

Our findings matched those of one study, which randomly assigned 200 women who delivered vaginally and had at least two risk factors for atonic PPH to receive either 100 µg i.m. carbetocin or 5 IU i.m. oxytocin. The quantity of bleeding, the prevalence of PPH, and therefore the requirement for extra uterotonics were all shown to be considerably reduced within the carbetocin group. They concluded that carbetocin is a better alternative to conventional oxytocin for preventing PPH in women with at least two PPH variables, with fewer hemodynamic abnormalities and adverse effects [14].

Another study randomly assigned 100 women who delivered vaginally and had experienced atonic PPH to receive either 100 mcg i.m. carbetocin or 10 IU i.m. oxytocin. The quantity of bleeding and the requirement for additional uterotonics were all shown to be considerably reduced in the carbetocin group [15].

Boucher *et al.* recently published research in which they found that the carbetocin group needed substantially less uterine massage and other uterotonics,

which matched our findings. They administered carbetocin 100 µg i.m. or oxytocin 10 IU i.v. oxytocin infusion over 2 hours to 160 women with at least one risk factor for PPH who delivered delivery vaginally [16]. Carbetocin 100 g has all the earmarks of being as effective as oxytocin in decreasing PPH, according to Boucher *et al.* [16], Elboholy *et al.* [17], Widmer *et al.* [18] and Fenix *et al.* [19]. Similarly, adding sublingual misoprostol to oxytocin improves the efficacy of oxytocin as compared to i.v. carbetocin in terms of determined blood loss in our study.

Evidence suggests that prior oxytocin exposure appears to desensitize oxytocin receptors, leading to poor oxytocin-induced uterine contractility [20].

In 2010, Winikoff *et al.* published the results of a single trial that compared the effectiveness of misoprostol *vs* traditional uterotonics in the absence of oxytocin prophylaxis [21]. In this study, 978 women were treated for PPH at four hospitals in Ecuador, Egypt, and Vietnam. Participants were randomly assigned to receive either 800-g sublingual misoprostol (n = 488) or 40 IU intravenous oxytocin (n = 490). Misoprostol, while being less effective than oxytocin, was able to stop active bleeding in 90% of women. As a result, the researchers concluded that it was effective enough to be utilized as a first-line treatment for PPH in the absence of oxytocin.

Blum *et al.* evaluated the effects of misoprostol and conventional uterotonics after delivery of 10 IU oxytocin prophylaxis in one of two studies [22]. PPH was treated in a total of 807 women. Participants were given either 800 g sublingual misoprostol (n = 407) or 40 IU intravenous oxytocin (n = 402) at random. When used for the management of PPH owing to uterine atony, the authors found that misoprostol is clinically comparable to oxytocin in women who had received oxytocin prophylaxis during the third stage of labour. Lokugamage *et al.* presented the results of research looking at the effects of misoprostol after oxytocin prophylaxis in 2001. When given to 64 women with PPH, they found that 800 g rectal misoprostol had a substantial benefit over a combination of syntometrine i.m. plus syntocinon i.v. for PPH therapy [23]. In favour of misoprostol, there was a 28.1% difference in the rate of bleeding cessation within 20 minutes (p = 0.01).

Despite continuing efforts, less competent health personnel attend births in low-resource countries, which can lower maternal mortality; as a result, the maternal death rate in developing countries remains high [1]. Preventing and treating PPH is particularly difficult in areas where most deliveries take place at pa-

tients' homes or in tiny clinics, and when obstetric care is limited [3]. Without skilled delivery attendants, sublingual misoprostol with oxytocin might be a one-of-a-kind combo, and it could potentially be the only medical option for treating PPH after births [17]. Misoprostol does not need to be kept at a certain temperature; thus, it can be used in the absence of skilled labour and delivery personnel or when injectable oxytocin is unavailable [10].

The findings of this trial, in agreement with other trials [23-27], add to the body of data on the safety of misoprostol for PPH therapy. In this trial, no serious side effects or safety issues were observed among women who used misoprostol for treatment as well as prevention.

There were several limitations to the study. First, the generalizability of our findings may be restricted since this was a single-centre study with a small number of women with PPH.

The comprehensive data collection that took place over a two-and-a-half-year period to document the use of carbetocin *versus* oxytocin plus misoprostol and oxytocin alone for the treatment of PPH is a significant strength of this study.

The randomized trial was sufficiently powered to evaluate the effects of intravenous TA with oral misoprostol *vs* intravenous carbetocin on the amount of blood loss, which was one of the study's merits.

The simplicity with which sublingual misoprostol and i.v. TA can reduce postpartum blood loss by a clinically significant amount is another highlight of the research.

Clinical implications

This study demonstrates that utilizing oxytocin in conjunction with sublingual misoprostol and i.v. carbetocin alone lowers the occurrence of severe PPH and the need for further uterotonics when compared to using oxytocin alone. Compared to carbetocin, adjuvant sublingual misoprostol improves oxytocin's effectiveness. Misoprostol appeared to reduce blood loss more successfully when used in conjunction with oxytocin as secondary prophylaxis of postpartum haemorrhage.

CONCLUSIONS

Oxytocin plus misoprostol is more effective than oxytocin and carbetocin in the management of

post-partum blood loss > 500 ml after vaginal delivery. Adjuvant sublingual misoprostol increases oxytocin's efficiency in comparison to carbetocin. When administered in conjunction with oxytocin as a supplementary prophylactic for postpartum haemorrhage, misoprostol seems to increase the efficacy of oxytocin to lessen blood loss more successfully.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors contributed equally to this work.

Funding

None.

Study registration

It was a clinically registered randomized, double-blind, clinical trial (ClinicalTrials.gov: NCT03870503).

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The ethical review board approved the study by a grant number of (Aswu/280/7/18).

Informed consent

Informed consent was received from the patient for the publication of this case report.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 183: Postpartum Hemor-

- rhage. *Obstet Gynecol.* 2017;130(4):e168-86. doi: 10.1097/AOG.0000000000002351.
2. Pertile R, Tenaglia F, Piffer S. Monitoring of postpartum haemorrhage through current information flows in Trentino Region, Italy. *Ital J Gynaecol Obstet.* 2022;34(3):189-201. doi: 10.36129/jog.2021.06.
 3. Anger H, Durocher J, Dabash R, Winikoff B. How well do postpartum blood loss and common definitions of postpartum hemorrhage correlate with postpartum anemia and fall in hemoglobin? *PLoS One.* 2019;14(8):e0221216. doi: 10.1371/journal.pone.0221216.
 4. Tunçalp O, Souza JP, Gülmezoglu M; World Health Organization. New WHO recommendations on prevention and treatment of postpartum hemorrhage. *Int J Gynaecol Obstet.* 2013;123(3):254-6. doi: 10.1016/j.ijgo.2013.06.024.
 5. Belpiede A, Tinelli A, Crescini C, Stark M, Losito A, Cassetta R, et al. Post-partum hemorrhage: can it be prevented by assisting the natural physiological process. *Ital J Gynaecol Obstet* 2021;33(2):110-9. doi: 10.36129/jog.33.02.05.
 6. Torloni MR, Gomes Freitas C, Kartoglu UH, Metin Gülmezoglu A, Widmer M. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. *BJOG.* 2016;123(13):2076-86. doi: 10.1111/1471-0528.13998.
 7. Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, Assempour N, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res.* 2018;46(D1):D1074-82. doi: 10.1093/nar/gkx1037.
 8. Arrowsmith S, Wray S, Quenby S. Maternal obesity and labour complications following induction of labour in prolonged pregnancy. *BJOG.* 2011;118(5):578-88. doi: 10.1111/j.1471-0528.2010.02889.x.
 9. Malm M, Madsen I, Kjellström J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. *J Pept Sci.* 2018;24(6):e3082. doi: 10.1002/psc.3082.
 10. Parry Smith WR, Papadopoulou A, Thomas E, Tobias A, Price MJ, Meher S, et al. Uterotonic agents for first-line treatment of postpartum haemorrhage: a network meta-analysis. *Cochrane Database Syst Rev.* 2020;11(11):CD012754. doi: 10.1002/14651858.CD012754.pub2.
 11. Meher S, Cuthbert A, Kirkham JJ, Williamson P, Abalos E, Aflaifel N, et al. Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study. *BJOG.* 2019;126(1):83-93. doi: 10.1111/1471-0528.15335.
 12. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, et al. WHO CHAMPION Trial Group. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. *N Engl J Med.* 2018;379(8):743-52. doi: 10.1056/NEJMoa1805489.
 13. Samimi M, Imani-Harsini A, Abedzadeh-Kalahroudi M. Carbetocin vs. Syntometrine in Prevention of Postpartum Hemorrhage: A Double Blind Randomized Control Trial. *Iran Red Crescent Med J.* 2013;15(9):817-22. doi: 10.5812/ircmj.7881.
 14. Maged AM, Hassan AM, Shehata NA. Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high-risk women. *J Matern Fetal Neonatal Med.* 2016;29(4):532-6. doi: 10.3109/14767058.2015.1011121.
 15. Maged AM, Hassan AM, Shehata NA. Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) after vaginal delivery: a randomised controlled trial. *Arch Gynecol Obstet.* 2016;293(5):993-9. doi: 10.1007/s00404-015-3911-y.
 16. Boucher M, Nimrod CA, Tawagi GF, Meeker TA, Rennicks White RE, Varin J. Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery: a double-blind randomized trial. *J Obstet Gynaecol Can.* 2004;26(5):481-8. doi: 10.1016/s1701-2163(16)30659-4.
 17. Elboholy AE, Mohammed WE, Sweed M, Bahaa Eldin AM, Nabhan A, Abd-El-Maeboud KH. Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following an elective cesarean delivery. *Int J Gynaecol Obstet.* 2016;134(3):324-8. doi: 10.1016/j.ijgo.2016.01.025.
 18. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, et al. WHO CHAMPION Trial Group. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. *N Engl J Med.* 2018;379(8):743-52. doi: 10.1056/NEJMoa1805489.

19. Fenix AM. Double-blind randomized controlled trial comparing the effect of carbetocin with oxytocin for the prevention of postpartum hemorrhage among high-risk women following vaginal delivery. *Int J Gynaecol Obstet.* 2012;119:S347-48. doi: 10.1016/S0020-7292(12)60677-8.
20. Robinson C, Schumann R, Zhang P, Young RC. Oxytocin-induced desensitization of the oxytocin receptor. *Am J Obstet Gynecol.* 2003;188(2):497-502. doi: 10.1067/mob.2003.22.
21. Winikoff B, Dabash R, Durocher J, Darwish E, Nguyen TN, León W, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet.* 2010;375(9710):210-6. doi: 10.1016/S0140-6736(09)61924-3.
22. Blum J, Winikoff B, Raghavan S, Dabash R, Ramadan MC, Dilbaz B, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet.* 2010;375(9710):217-23. doi: 10.1016/S0140-6736(09)61923-1.
23. Lokugamage AU, Sullivan KR, Niculescu I, Tigere P, Onyangunga F, El Refaey H, et al. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand.* 2001;80(9):835-9. doi: 10.1034/j.1600-0412.2001.080009835.x.
24. Raghavan S, Geller S, Miller S, Goudar SS, Anger H, Yadavannavar MC, et al. Misoprostol for primary versus secondary prevention of postpartum haemorrhage: a cluster-randomised non-inferiority community trial. *BJOG.* 2016;123(1):120-7. doi: 10.1111/1471-0528.13540.
25. Abbas DF, Jehan N, Diop A, Durocher J, Byrne ME, Zuberi N, et al. Using misoprostol to treat postpartum hemorrhage in home deliveries attended by traditional birth attendants. *Int J Gynaecol Obstet.* 2019;144(3):290-6. doi: 10.1002/ijgo.12756.
26. Borovac-Pinheiro A, Priyadarshani P, Burke TF. A review of postpartum hemorrhage in low-income countries and implications for strengthening health systems. *Int J Gynaecol Obstet.* 2021;154(3):393-9. doi: 10.1002/ijgo.13618.
27. Chatterjee S, Sarkar A, Rao KD. Using Misoprostol for Primary versus Secondary Prevention of Postpartum Haemorrhage - Do Costs Matter? *PLoS One.* 2016;11(10):e0164718. doi: 10.1371/journal.pone.0164718.



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Ureteral injuries management in gynaecologic surgery: the role of the conservative approach

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ABSTRACT

Objective. Ureter is one of the most important landmarks to be taken into consideration during gynaecological surgery. Today, mini-invasive techniques are available to treat ureteral injuries in a more conservative way. This study aims to propose a progressive operative model to manage ureteral injuries by comparing conservative and open approaches.

Materials and Methods. This retrospective study analysed 27 injuries in 24 patients admitted for ureteral injuries following gynaecological surgery (in 3 cases, ureteral injuries were bilateral). We obtained data from 16 lacerations, 5 stenosis and 6 fistulas. Patients in the study were treated with three different techniques for ureteral injuries: cystoscopy with retrograde ureteral stenting, interventional radiology and ureterocystoneostomy.

Results. In a retrospective analysis for ureteral lacerations, success rates of the various techniques were: 100% ureterocystoneostomy, 67% rendezvous, 58% percutaneous nephrostomy plus ureteral stenting, 33% percutaneous nephrostomy and 33% cystoscopy with ureteral stenting. Considering ureteral stenosis, success rates were: ureterocystoneostomy 100%, percutaneous nephrostomy plus ureteral stent 33%, rendezvous, percutaneous nephrostomy and cystoscopy with ureteral stent 0%. For ureteral fistula, success rates were ureterocystoneostomy 100%, rendezvous 100%, percutaneous nephrostomy plus ureteral stent 100%, cystoscopy with ureteral stent 33%, percutaneous nephrostomy 0%.

Conclusions. According to the obtained results, conservative radiologic procedures represent a valid alternative to open surgery. We propose a progressive operative model: interventional radiology represents an effective approach that could postpone or avoid invasive procedures. Ureterocystoneostomy is the procedure with higher success rates.

INTRODUCTION

Ureter is one of the most important landmarks to be taken into consideration during gynaecological surgery, as it is one of the organs most involved in complications during this type of surgery. Ureteral injury incidence is 0.1-1.5% for benign surgery (myomectomy, hysterectomy, *etc.*) and 5% for oncologic surgery (radical hysterectomy, cytoreduction *etc.*, if we consider surgery for endometriosis, incidence increases to 21% [1-6]. A separate note appears to be important for cancer patients who may present an increase in perioperative morbidity and frailty, scores have been created for this type of patient to prevent and reduce these complications [6-11].

Cystoscopy may help in the identification of ureteral injury and insertion of ureteral stents could help in the diagnosis and its reparation [12, 13]. Regarding treatment, ureteral stenosis is generally treated with the insertion of a ureteral stent or with ureteral reimplantation surgery. If stent insertion is complicated, contemporary laparoscopy may be useful to completely diagnose the type of ureteral injury and to avoid ureteral perforation [3, 14]. A simple suture is generally avoided because it can cause subsequent stenosis, so the ureteral reimplantation must be considered [15]. Recently, other techniques are available to treat ureteral injuries in mini-invasive ways, like interventional radiology. In this category, various procedures may be used, like percutaneous nephrostomy with or without the insertion of a ureteral stent and the endoscopic-radiologic procedure also known as rendezvous. This procedure has higher success rates, until 88% and is a valid alternative to laparoscopic or laparotomy ureteral reimplantation [16]. After the procedure, if patients are asymptomatic and/or creatinine levels are stable, nephrostomy may be removed, and the stent is substituted or removed after 6 months or less [17, 18]. The study aims to propose a progressive operative model to manage ureteral injuries by comparing conservative and open approaches; we also propose a therapeutic algorithm to reduce invasiveness.

MATERIALS AND METHODS

This is a retrospective study conducted in the Department of Gynecology, Campus Bio-Medico University Hospital Foundation Rome on 24 patients admitted for 27 ureteral injuries caused by gynaecological surgical procedures between 15th January

2016 and 6th September 2021. After consultation with our local Ethical Committee, our study was defined as exempt from IRB since the study was observational and not interventional (no randomization was made), due to the type of retrospective study design. This study was conducted following the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996). The clinical management of patients included in the study was identical to that routinely proposed in the same period according to our internal protocols. For this reason, all eligible patients were adequately informed of the nature and objectives of the study, and written signed consent was obtained, following the Italian Privacy Law (675/96). A database containing all data from these patients was recorded in a Microsoft Excel sheet. We recorded data regarding primary pathology, type of surgery, laparoscopic or laparotomy technique, ureteral injury, location, clinical manifestations, imaging and laboratory diagnosis, the treatment used and follow-up.

Ureteral injuries included in our study were lacerations, stenosis, and ureterovaginal fistulas:

- Stenosis is defined a reduction of ureteral lumen, and it may be a consequence of coagulation, trauma, kinking or ligation. In our database, we divided stenosis into complete stenosis (ligation) and partial stenosis (stricture).
- A laceration is a partial opening of the ureteral wall.
- Fistula is pathologic communication between ureter and vagina. We distinguished two types of fistulas: ureterovaginal and ureteral-peritoneal-vaginal fistulas, according to the type of fistular link.

Regarding the clinic, for each patient we recorded data about fever, abdominal pain, vaginal discharges, stranguria and polyuria. For laboratory data, we registered changes in inflammatory factors (VES, PCR, WBC count) or data about renal function (creatinine). We also registered the post-operative day in which clinical manifestations appeared. Treatment approaches were divided into three main procedures: cystoscopy with retrograde stent insertion (CpS), interventional radiology and laparotomy ureteral reimplantation. Another analysis was then conducted dividing radiological procedures in simple percutaneous nephrostomy (PN), percutaneous nephrostomy plus ureteral stent (NpS) with anterograde insertion and combined radiologic-endoscopic procedure, rendezvous (RV).

Cystoscopy and stent positioning

Bladder filling is carried out at low pressure, with cannulation of the ureter with a guide for ureteral stent in its soft portion. Double J stent is placed on the soft guide and location inside the bladder is controlled with cystoscopy.

Rendezvous (RV)

This procedure consists of two phases: the first one is represented by nephrostomy. The second phase is the RV. It can be divided into an anterograde and a retrograde approach. In the anterograde approach, a guidewire is advanced through the nephrostomy catheter reaching the ureter. Then, in the retrograde approach, a guidewire, thanks to a cystoscope, is advanced through the ureteral orifice till the ureter. At this point, a device (Gooseneck) takes the guidewire introduced through the bladder. Subsequently, a double J stent is inserted to maintain the alignment and to help the reparation of ureteral injury.

Laparotomy/laparoscopy ureteral reimplantation/ureterocystoneostomy

The technique allows the creation of a new ureteral orifice on the bladder wall in the portion of the trigone. It crosses one or both ureters depending on whether one or both ureters are replanted.

Regarding follow-up, we registered eventual complications after the failure of the abovementioned procedures or the simple removal of ureteral stents when patients needed no other procedures. We excluded from the study patients that received the positioning of a prophylactic ureteral stent, patients with non-iatrogenic ureteral injuries and patients lost at follow-up.

Data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

RESULTS

Retrospectively analysing our database for ureteral injuries in patients undergoing gynaecologic surgical procedures between 15th January 2014 and 6th September 2021, we identified 33 ureteral injuries in 30 patients, of which 6 did not meet the inclusion criteria: 4 were lost at follow-up and 2 because of prophylactic ureteral stent. In this paper, we analysed 27 ureteral

Table 1. Characteristics of the patients and their ureteral damage.

| | Ureteral lesion (n = 27) |
|---|--------------------------|
| Age, year (mean ± SD) | 54.20 ± 9.95 |
| Pathology | |
| Uterine fibromatosis, n (%) | 3 (11.1) |
| Endometrial cancer, n (%) | 3 (11.1) |
| Cervical cancer, n (%) | 8 (29.6) |
| Ovarian cancer, n (%) | 4 (14.8) |
| Endometrial hyperplasia, n (%) | 4 (14.8) |
| Endometriosis, n (%) | 2 (7.4) |
| Ovarian Cysts, n (%) | 1 (3.7) |
| Leiomyosarcoma, n (%) | 2 (7.4) |
| Type of surgery | |
| Laparotomic hysterectomy ± bilateral adnexectomy, n (%) | 15 (55.6) |
| Laparoscopy hysterectomy ± bilateral adnexectomy, n (%) | 7 (25.9) |
| Laparotomic radical hysterectomy ± bilateral adnexectomy, n (%) | 3 (11.1) |
| Laparoscopy ovarian cyst removal, n (%) | 2 (7.4) |
| Type of lesion | |
| Laceration, n (%) | 16 (59.3) |
| Stenosis, n (%) | 5 (18.5) |
| Ligation, n (%) | 4 (14.8) |
| Stricture, n (%) | 1 (3.7) |
| Fistulas, n (%) | 6 (22.2) |
| Ureterovaginal fistulas, n (%) | 2 (7.4) |
| Ureteral-peritoneal-vaginal fistulas, n (%) | 4 (14.8) |
| Clinical manifestation, days (mean ± SD) | 13.29 ± 12.72 |
| Clinical manifestation | |
| Fever, n (%) | 9 (33.3) |
| Abdominal pain, n (%) | 15 (55.6) |
| Vaginal discharges, n (%) | 7 (25.9) |
| Dysuria, anuria, n (%) | 3 (11.1) |

SD: standard deviation; n: number.

injuries in 24 patients: 3 patients had bilateral ureteral injuries. More specifically, we obtained data from 16 lacerations, 5 stenosis (4 ligations and 1 stricture) and 6 fistulas. Two of these fistulas were ureterovaginal and four of them were ureteral-peritoneal-vaginal. The characteristics of the patients and their ureteral damage are reported in **Table 1**. The procedures leading to ureteral damage were laparotomic in 67% of cases and laparoscopic in 33%. Injuries' diagnosis was intraoperative in 2 cases (7%) and postoperative in 25 cases (93%). Diagnosis was based on clinical suspicion, laboratory exams and imaging. Abdominal pain and abdominal distension were found in 15 patients, fever (T > 38 °C) in 9 patients, vaginal discharges in 7 patients and urinary symptoms in

3 patients. These clinical manifestations appeared in different intervals from surgery, all in a maximal lapse of 45 days. Around 58% of laboratory data were considered to clinically diagnose injuries. TC was the gold standard for the diagnosis of ureteral injuries. Ureteral stents were removed after 6 months in patients that received successful treatment.

Results analysed according to the approach

Three main approaches were used for the management of ureteral injuries: cystoscopy with retrograde ureteral stent (CpS), interventional radiology (RI) and ureterocystoneostomy (UCN). Data showed that 44% of ureteral injuries were solved with a single approach, meanwhile 56% of cases were solved using additional or multiple procedures.

Two of the 27 injuries were diagnosed intraoperatively and managed at first instance with ureterocystoneostomy (UCN) with a success rate of 100%. Five of the 27 injuries were treated with CpS as first approach, with only one case solved at first glance (success rate 20%) with subsequent failure of the other 4 injuries (Figure 1a). In one of the 4 injuries in which CpS failed, a RV was attempted, with a success rate of 100%. In the other 3 cases, treatment was NpS as second approach; one case was solved uneventfully, in the other 3 cases, RV approach was tempted, but unfortunately failed with a subsequent need for ureteral reimplantation (fourth approach) that was resolute in all the cases.

Interventional radiology (NpS, PN and RV) was used in the first instance in 20 of the 27 injuries with a resolution of 9/20 ureteral injuries (global success rate of 45%) (Figure 1b). In 11/20 injuries NpS was used in the first instance with the resolution of 7 injuries (success rate of 64%); in the other 4 cases attempt failed and a second approach was used. In 6/20 injuries PN was used in the first instance: in all cases, the approach failed, and a second procedure was used. In 3/20 injuries RV was used in the first instance, with the resolution of 2 cases (success rate of 67%), and failure in 1 case (failure rate of 33%) and a second approach was attempted. Interventional radiology was not resolute as the first approach in 11 of the 20 ureteral injuries and in these 11 injuries a second procedure was used. Four of the 11 cases were treated with UCN with resolution in all cases (success 100%). 2/11 ureteral injuries were treated with NpS as second approach with the resolution of 1 injury (success of 50%). RV was used in 1/11 injury as the second approach with success (success rate 100%). The second radiological procedure brought to resolution in 6/11 injuries (global success if 67%). 5/11 were treated with CpS as second approach which was not decisive in any case. 5/11 injuries were not resolved with a second procedure and continued with a third approach. 3/5 underwent laparotomy ureteral reimplantation with a 100% success rate. 1/5 of injuries resolved with CpS as third approach and 1/5 of injuries

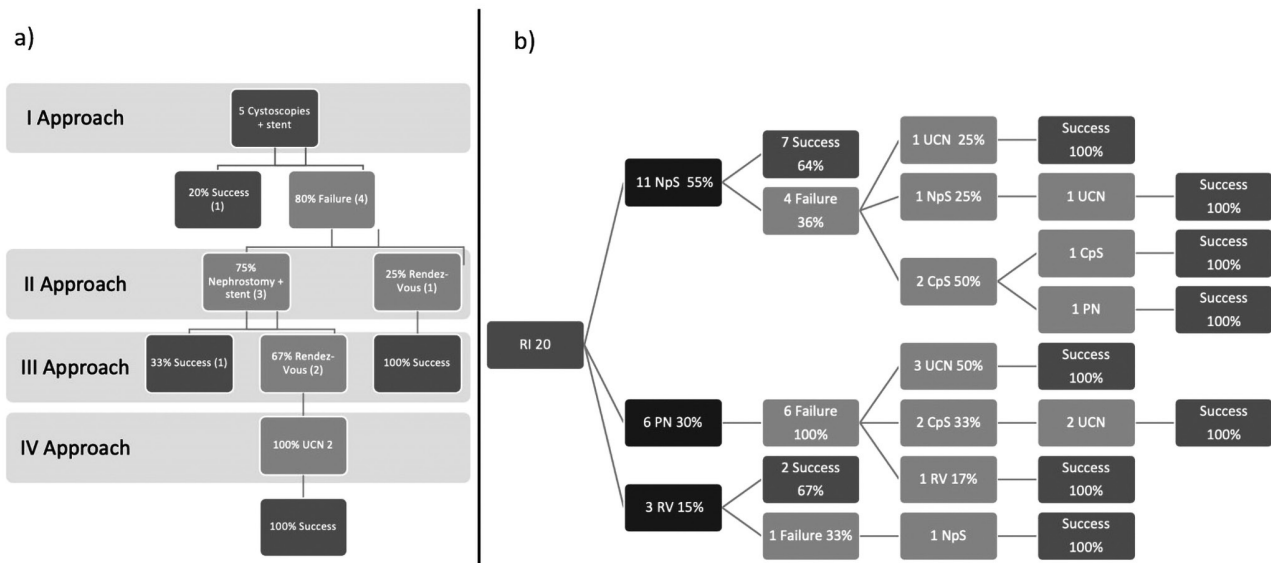


Figure 1. (a) Patient treated in first instance with retrograde positioning of ureteral stent; (b) Patient treated in first instance with interventional radiology. UCN: ureterocystoneostomy; CpS: cystoscopy + stent; NpS: percutaneous nephrostomy + stent; RV: Rendezvous; NP: simple percutaneous nephrostomy; IR: interventional radiology.

resolved with PN as third approach. 7/20 injuries treated in the first instance with IR in the end underwent UCN with subsequent resolution (success rate 100%). All these last approaches solved the problem (Figure 1b). The combined radiologic-endoscopic approach of RV had a success rate of 67% at the first attempt with only one injury that required stent apposition with nephrostomy, with resolution at the second intervention.

Sub-analysis showed global success rates of the different methods used. These data were obtained from the success and failure rates of each approach used. In this way, we found a success rate of 25% for CpS, 100% for ureteral reimplantation and 58% for all interventional radiology procedures. The success rate for each radiological procedure was 14% for simple PN, 57% for RV and 56% for NpS.

Results analysed for injury

A further analysis was done on the result for injury classification (stenosis, lacerations and fistulas) concerning the different techniques used for the treatment.

The 5 stenotic injuries were treated as follows (Figure 2a): in two of the 5, ligations CpS was used, in two of the 5, ligation PN was used, and in one of the 5, strictures NpS was used. CpS as first approach had a negative outcome in bilateral ureteral ligation and required other 3 interventions (NpS, RV and UCN) before definitive resolution. Globally, PN as first approach showed a failure rate of 100%: injuries were treated with laparotomic ureteral reimplantation, and half of them first received cystoscopy with a negative outcome. In this type of ureteral damage, conservative techniques did not conduce

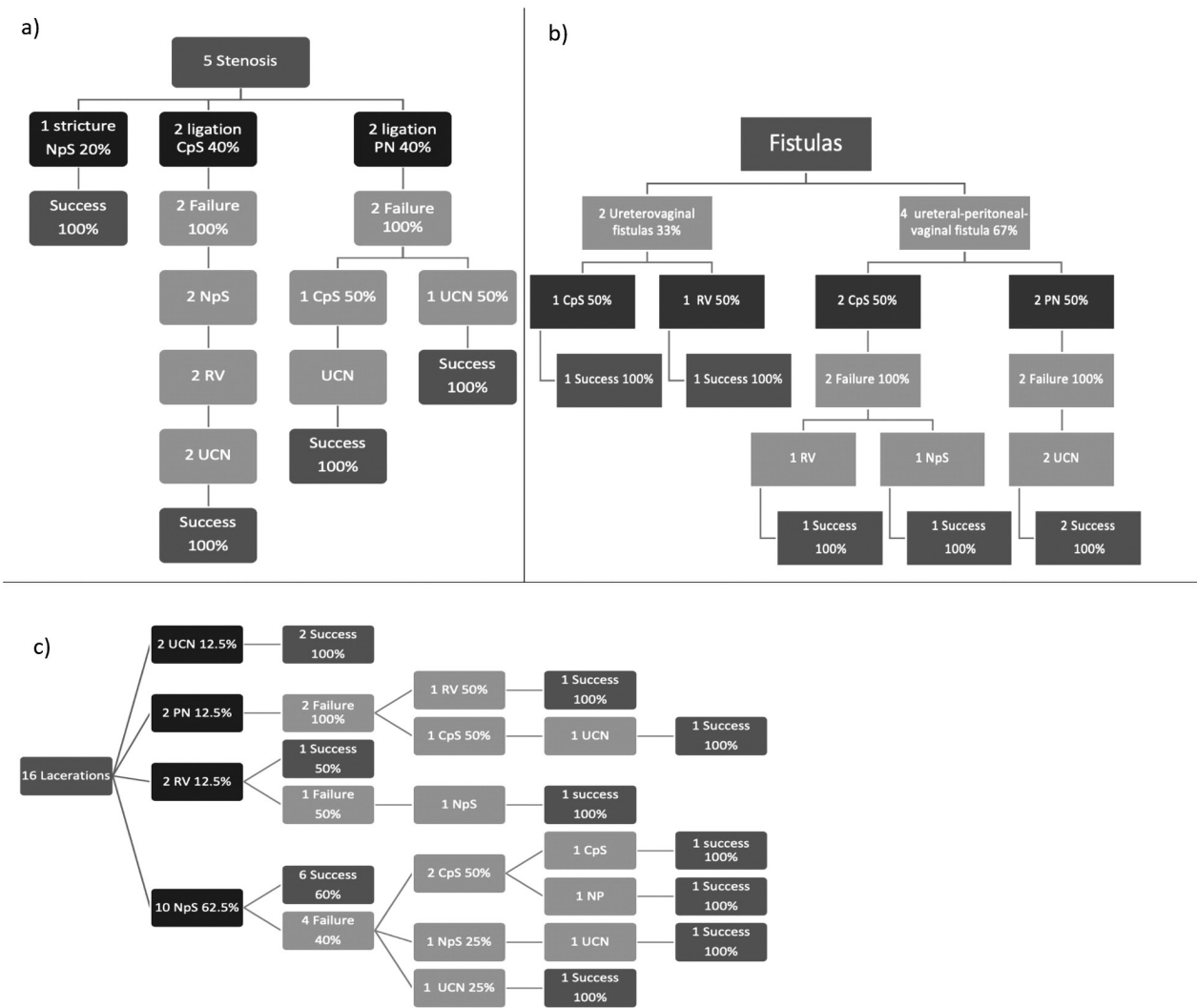


Figure 2. (a) Stenosis treatment; (b) Fistula treatment; (c) Laceration treatment.

UCN: ureterocystoneostomy; CpS: cystoscopy + stent; NpS: percutaneous nephrostomy + stent; RV: Rendezvous; NP: simple percutaneous nephrostomy; IR: interventional radiology.

to resolution and, in 80% of cases, patients received laparotomy: CpS, RV and PN never solved ureteral damage, while NpS positioning had a success rate of 33% (Figure 3).

The 16 lacerations were treated (Figure 2c) with UCN in 2 of the 16 ureteral injuries, RV in 2 of the 16 injuries, PN in 2 of the 16 injuries and NpS in the other 10 cases. The combined anterograde and retrograde approach had direct success in 50% of cases; in the other 50% of cases, NpS was necessary. PN in the first instance had negative results in all cases and injuries required RV in half cases and ureteral reimplantation in other cases. In the end, NpS positioning had a 60% success rate in the first instance. The Conservative procedure mainly used in lacerations was RV with a 67% success rate, followed by NpS (58% success rate). PN and CpS had good results with a rate of 33%. Ureteral reimplantation was effective in 5 lacerations with a success rate of 100% (Figure 3).

The 6 fistulas comprised 2 ureterovaginal fistulas and 4 ureteral-peritoneal-vaginal fistulas (Figure 2b). Ureterovaginal fistulas are solved, 1 with RV and 1 with CpS for a 100% success rate, respectively. The 4 ureteral-peritoneal-vaginal fistulas had a negative outcome in all the procedures first attempted: 2/4 CpS failed and also 2/4 PN. After radiologic failure, in 2 cases laparotomic ureteral reimplantation was used with a 100% success rate. In the other 2 cases with the previous failure of CpS, one was solved using RV and the other one with NpS (Figure 2b). For this type of injury, UCN was effective in 2 of the 6 ureteral injuries. In the other 4 cases, IR conservative approaches had good outcomes: RV was used in two cases with a 100% success rate, and also for NpS 1/6 and CpS had a 33% resolution rate

when applied in three cases. PN failed in both of the cases in which it was used (Figure 3).

Subsequently, a global rate for IR was calculated. We reported a success rate for lacerations (67%) and fistulas (60%). IR procedures for stenosis showed a lower success rate (25%).

DISCUSSION

Ureteral injuries are associated with high morbidity rates because the ureter is near to vascular structures and pelvic organs. Around 75% of ureteral injuries are iatrogenic: in particular, the third tract of the ureter has a higher risk because it is the most accessible during gynaecological surgery [19]. Incidence varies according to surgery complexity: 0.03-2% for abdominal hysterectomy, 0.02-0.5% for vaginal hysterectomy, 0.2-5% for LAVH, 1.7-3% for urogynaecological procedures [20].

Although ureteral repair is historically an open technique, we believe that the recent technological advancements in the field of minimally invasive surgery lead to the possibility of evaluating, as first option, a more conservative management: laparoscopic reimplantation or IR techniques. The advent of interventional radiology with the RV technique in addition to the classic techniques can allow the restoration of ureteral integrity, especially in the case of lacerations or ureteral transections [21].

The recent evidence in literature supports the use of a minimally invasive approach by IR (e.g., RV or NpS) as a first step in the case of ureteral injuries, as it presents a low risk of perioperative complications, shorter hospital stays and good success rate [22, 23]. In this paper, we analysed 27 ureteral injuries from 24 patients (three patients had bilateral injuries). The diagnosis was made during surgery in 2 cases (7%) and postoperative in 25 cases (93%). These data concerning post-operative diagnoses is in line with the literature, as the injuries are often not immediately visible. A large number of post-operative diagnoses it is also relatable to the type of surgery that is performed in our hospital, which is a referral centre for complex benign surgery, deep endometriosis and oncological surgery. The 2 injuries that were diagnosed during surgery were treated with UCN.

Laparotomic UCN is the gold standard treatment first described by Boari and modified over the years. This surgical procedure has a high success rate, which in the last decades has been revisited with a minimally invasive laparoscopic and robotic approach with

Ureteral injuries - global success rates according to techniques

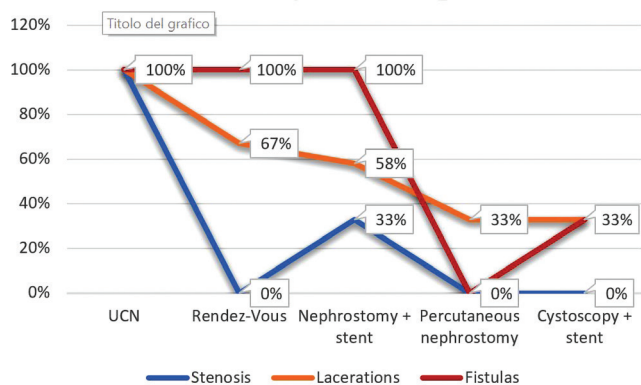


Figure 3. Ureteral injuries - global success rates according to techniques. UCN: ureterocystoneostomy.

similar success rates [24, 25]. Currently, the psoas hitch is a useful technique for injuries involving the lower third of the ureter. The success rate, regardless of the method, is very high among different studies. The minimally invasive approach for laparoscopic ureteral reimplantation is associated with a success rate of 95.8% (including psoas hitch, psoas hitch plus Boari flap, and extravesical ureteral reimplantation) [26]. In cases of failure, the persistence of ureteral obstruction, presenting as a long-term complication, is caused by ureteral ischemia, tension on the anastomosis, or kinking and often requires surgical management. Ureteral kinking may occur if the ureter is replaced in the lateral bladder wall, which is more mobile. A ureteral fistula may be related to ischemia, tension, and a lack of water-tight anastomosis. In case of failure of the bladder flap procedure, the UCN with psoas hitch is indicated.

In the other cases, treatment was CpS positioning or IR.

CpS had a global rate of success of 25%, but when used in the first instance in 5 ureteral injuries it had good results in 1 of 5 cases (20%). Failures are all due to endoprosthesis positioning: surgeon experience, distal location of injury and damage entity are the factors that mainly influenced the results of this procedure. Other causes of CpS failure in ureteral injuries are related to several factors, such as the impossibility of assessing the size of the lacerations, the impossibility of overcoming the strictures, and the possible risk of enlargement of small injuries. Complete stenosis and ureters-peritoneal-vaginal fistulas made difficult stent positioning. There are no good quality randomized or prospective studies in the literature that indicate the role of CpS and its outcome in the various types of injuries. The role of CpS in pelvic surgery has a recognized role only in minor ureteral injuries, ureteral decompressions and its use in the prevention of ureteral injury in patients where ureteral recognition is difficult [27, 28]. IR was used as the first approach in 20 injuries. The global success rate was 58% for all the approaches. Despite few data are disposable about the comparison between open surgery and minimally invasive techniques, these data are similar to those obtained in other studies: Ku *et al.* obtained a success rate of 64% for the conservative approach [29].

PN was used in the first instance in 6 cases and only once as subsequent approaches. 6 failures in the first instance out of a total of 7 PN procedures were due to complications during the procedure (stenosis and leakage), clinical complications (renal failure, hy-

dronephrosis) or in most of the cases to impossible stent positioning in cases of total stenosis and ureteral-peritoneal-vaginal procedures. So, failure derived from PN was expected because the stent was not positioned, and did not offer support to the ureteral wall, making healing difficult in case of large lacerations or fistulas. Literature agrees that in the case of ureteral damage stent positioning is better than simple PN [30, 31]. This technique was used because of contraindications to other techniques: these aspects can explain its apparent failure in a group of radiological successful procedures.

NpS would seem to be useful for small lacerations and incomplete stenoses. The advantage over PN is the presence of the stent, which increases the repair capacity of the ureteral tissue. Ureteral stenting promotes the healing process because it allows the realignment of the two stumps, excluding the damaged site from the passage of urine into the bladder, and maintains an adequate lumen, which prevents scar stenosis by reaction of the fibroblasts [32]. The possible success linked also in non-tightened stenosis (stricture) is probably linked to the passage of the guide and therefore of the stent, safeguarding renal function.

RV turns out to be an innovative technique introduced in the last two decades with a combined percutaneous antegrade and cystoscopic retrograde approach. From our results, this approach is effective in the resolution of lacerations and fistulas with a good success rate. There are several studies in literature reporting numerous successes. Yates *et al.* report the resolution of 8 strictures with a rendezvous success rate of 100%. Similar data are also reported by Macrì *et al.* with a success rate ranging between 78-88% on strictures [21, 22]. Regarding lacerations, we found in this paper a high success rate, in line with the literature. Liu *et al.*, using the RV technique, resolved 8 ureteral transections with a mean ureteral injury length of 19 mm (range 15-30 mm) with a success rate of 100% [33].

Regarding lacerations, the global success rate of IR procedures was 67%. The conservative procedure with a higher success rate was RV, with a 67% success rate, followed by NpS (58% success rate). PN and CpS had good success rates (both 33%). UCN had success in 5 injuries (100% success rate). So, there is a high success rate considering all radiological procedures together, but these rates reduce when we consider each single specific technique: NpS and RV demonstrated to be otherwise valid techniques and good alternatives to surgery in the

first instance. Despite the higher success rate of laparotomy reimplantation, IR is a valid alternative to surgery. Open surgery is associated with higher infective rate, haemorrhage, mortality and morbidity. Failures obtained with these two techniques are due to complications raised after the procedures themselves: stenosis, fistulas and leakage. A probable cause was the excessive tissue damage due to the injury entity, the number of attempts trying to solve it and difficult diagnostic interpretation. In the case of laceration, a combined radiological-endoscopic procedure is a valid alternative to the gold standard as the first step. If NpS is used as the first approach without success, it is better to use RV because the success rate is higher. CpS and PN should be avoided. We found in our study a similar success rate, considering each radiological procedure: success rates were 58% for NpS positioning and 67% for RV similar to Ku *et al.* [29].

Regarding iatrogenic stenosis, CpS had a 0% success rate, IR 14% with only a case of NpS that was solved in the first instance. This injury was the unique partial stenosis while the others were complete stenosis: all solved thanks to UCN. In this case, it was possible to observe a reduced success rate for IR, especially in cases of serrated stenosis. It is fundamental to analyse the grade of stenosis: in case of stricture, nephrostomy with stent positioning may be considered, but in case of ligation it is necessary to undergo open surgery. CpS should be avoided in stenosis. There are studies in literature about this topic, but they mainly concern stenosis following renal transplantation and they propose still open techniques, even if minimally invasive [34]. Despite the classic open/minimally invasive approach, some studies show good results of the endoscopic approach with laser endopyelotomy and balloon dilation especially on non-ischemic stenosis, not from malignant pathology and less than 2 cm in length [35]. These two techniques have a variable success rate based on the site of the injury, the residual vascularity, and the length of the stenosis which are 52-83% with laser endopyelotomy and from 33-100% with balloon dilation (in the case of stenosis greater than 2 cm long 0-17%) [35, 36]. In our study in the case of stenosis, it was possible to observe a reduced success rate for IR, disagreeing with success rates reported by the abovementioned studies, especially in serrated stenosis. In case of stricture, NpS positioning may be considered, but in the case of ligation is necessary UCN [37]. Therefore, either from the literature or in our study, in the case of ureteral stenosis, it is possi-

ble to try a minimally invasive approach with interventional radiology, but the definitive and standard treatment is the classic technique.

Regarding fistulas, CpS had a global success rate of 33% while IR reached 60%: PN failed in both cases it was used while RV and NpS had a 100% success rate. In 2 of the 6 fistulas, injuries were treated with ureteral reimplantation. Considering two types of fistulas, we observed that both radiological and urological conservative approaches were effective for ureterovaginal fistulas. For ureteral-peritoneal-vaginal fistulas, other approaches (50% surgical and 50% conservatives) were necessary before the final resolution. We can conclude that conservative approaches are more effective in case of ureterovaginal fistula. On the other side, a conservative approach should be avoided in ureteral-peritoneal-vaginal fistulas because of a more difficult stent positioning: in this case, ureteral reimplantation should be preferred. In literature, there are no randomized studies about the minimally invasive approach in the management of iatrogenic ureteral fistulas. In case of ureteral fistula, the vesicovaginal fistula must always be investigated as the two conditions can be associated [38]. In the study conducted by Angioli *et al.* on the management of vesicovaginal fistulas, even if associated with ureteral ones, an attempt at conservative management for 4-6 weeks is foreseen [39]. We believe that the CpS approach is justified in the first instance. In our study, CpS had a global success rate of 33%, higher than that of simple waiting with an intravesical foley (15-20%), but above all with a mini-invasive approach RV and NpS had a 100% success rate. Considering two types of fistulas, we observed that for ureterovaginal fistulas both radiological and urological conservative approaches were effective. On the other side, a conservative approach should be avoided in ureteral-peritoneal-vaginal fistulas because of a more difficult stent positioning: in this case, UCN should be preferred.

Limitations

The limitations of this study are the small number of ureteral injuries and the fact that it is a retrospective study based on the experience of a single centre.

CONCLUSIONS

According to the obtained results, conservative IR procedures are valid alternatives to open surgery.

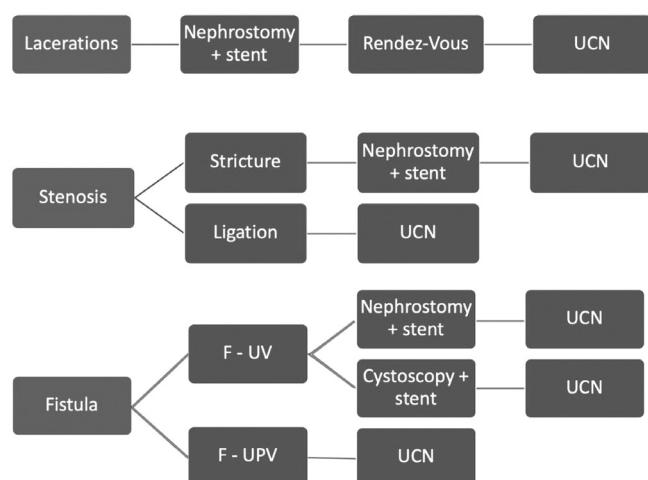


Figure 4. Flow chart for the treatment of ureteral injuries.

UCN: ureterocystoneostomy; CpS: cystoscopy + stent; NpS: percutaneous nephrostomy + stent; RV: Rendezvous; NP: simple percutaneous nephrostomy.

UCN is otherwise the procedure with higher success rates, despite it presents various limits of applications, especially in older patients with other pathologies. Interventional radiology represents an effective approach that could postpone or avoid the use of invasive procedures. Other studies are needed to have more data and validate various conservative treatment strategies.

We propose the following flow chart for the treatment of ureteral injuries (**Figure 4**).

For ureteral lacerations, the first approach that should be used is NpS or RV and only subsequently UCN.

In case of ureteral stenosis, NpS should be used for strictures first and then UCN. In case of ligation stenosis, the intended approach is directly UCN.

In case of fistula, we distinguish the ureterovaginal fistulas and the ureteral-peritoneal-vaginal. In case of ureterovaginal fistulas, CpS or NpS should be used as the first approach, and in case of failure, UCN is the best approach.

For ureteral-peritoneal-vaginal fistulas, the best approach is to perform a UCN.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

C.D.C.N., F.F., L.F., C.D.L., F.P., R.M., D.L., G.L., R.M., R.A., C.T.: Conceptualization, investigation, methodology, resources, software, visualization. C.D.C.N., F.F., L.F.: Data curation. C.D.C.N., F.F.: Formal analysis. C.D.C.N., F.F., C.T.: Project admin-

istration, supervision, validation, writing – original draft, writing – review & editing.

Funding

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Considering the retrospective nature of the study (observational and not interventional, no randomization was made) not approval by our IRB was requested. Approval was granted by the University “Campus Bio-Medico” of Rome. This study was conducted following the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1946).

Informed consent

The enrolled patients gave their informed consent to the study.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

- Schonman R, De Cicco C, Corona R, Soriano D, Koninckx PR. Accident analysis: factors contributing to a ureteric injury during deep endometriosis surgery. *BJOG*. 2008;115(13):1611-5. doi: 10.1111/j.1471-0528.2008.01941.x
- Plotti F, Ficarola F, Messina G, Terranova C, Montera R, Guzzo F, et al. Tailoring parametrectomy for early cervical cancer (Stage IA-IIA FIGO): a review on surgical, oncologic outcome and sexual function. *Minerva Obstet Gynecol*. 2021;73(2):149-59. doi: 10.23736/S2724-606X.20.04683-3.

3. Lim MC, Lee BY, Lee DO, Joung JY, Kang S, Seo SS, et al. Lower urinary tract injuries diagnosed after hysterectomy: seven-year experience at a cancer hospital. *J Obstet Gynaecol Res.* 2010;36(2):318-25. doi: 10.1111/j.1447-0756.2009.01153.x.
4. Bogani G, Di Donato V, Scambia G, Raspagliesi F, Chiantera V, Sozzi G, et al. Radical Hysterectomy for Early Stage Cervical Cancer. *Int J Environ Res Public Health.* 2022;19(18):11641. doi: 10.3390/ijerph191811641.
5. Bogani G, Donato VD, Scambia G, Landoni F, Ghezzi F, Muzii L, et al. Practice patterns and 90-day treatment-related morbidity in early-stage cervical cancer. *Gynecol Oncol.* 2022;166(3):561-6. doi: 10.1016/j.ygyno.2022.07.022.
6. Montera R, Ficarola F, Plotti F, Terranova C, De Cicco Nardone C, Guzzo F, et al. The use of sealing hemostat patch (HEMOPATCH®) in laparotomic myomectomy: a prospective case-control study. *Arch Gynecol Obstet.* 2023;307(5):1521-8. doi: 10.1007/s00404-023-06957-2.
7. D'Oria O, Golia D'Auge T, Baiocco E, Vincenzoni C, Mancini E, Bruno V, et al. The role of preoperative frailty assessment in patients affected by gynecological cancer: a narrative review. *Ital J Gynaecol Obstet.* 2022;34(2):76-83 doi: 10.36129/jog.2022.34.
8. Di Donato V, Di Pinto A, Giannini A, Caruso G, D'Oria O, Tomao F, et al. Modified fragility index and surgical complexity score are able to predict postoperative morbidity and mortality after cytoreductive surgery for advanced ovarian cancer. *Gynecol Oncol.* 2021;161(1):4-10. doi: 10.1016/j.ygyno.2020.08.022.
9. Giannini A, Di Donato V, Schiavi MC, May J, Panici PB, Congiu MA. Predictors of postoperative overall and severe complications after surgical treatment for endometrial cancer: The role of the fragility index. *Int J Gynaecol Obstet.* 2020;148(2):174-80. doi: 10.1002/ijgo.13020.
10. Di Donato V, Caruso G, Bogani G, Giannini A, D'Oria O, Perniola G, et al. Preoperative frailty assessment in patients undergoing gynecologic oncology surgery: A systematic review. *Gynecol Oncol.* 2021;161(1):11-9. doi: 10.1016/j.ygyno.2020.12.030.
11. Di Donato V, D'Oria O, Giannini A, Bogani G, Fischetti M, Santangelo G, et al. Age-Adjusted Charlson Comorbidity Index Predicts Survival in Endometrial Cancer Patients. *Gynecol Obstet Invest.* 2022;87(3-4):191-9. doi: 10.1159/000525405.
12. Gilmour DT, Dwyer PL, Carey MP. Lower urinary tract injury during gynecologic surgery and its detection by intraoperative cystoscopy. *Obstet Gynecol.* 1999;94(5 Pt 2):883-889. doi: 10.1016/s0029-7844(99)00456-1.
13. Rigatti P, Pompa P. La patologia dell'uretere ginecologico [Pathology of the gynecologic ureter]. *Arch Ital Urol Androl.* 2002;74(1):21-2.
14. Burks FN, Santucci RA. Management of iatrogenic ureteral injury. *Ther Adv Urol.* 2014;6(3):115-24. doi: 10.1177/1756287214526767.
15. De Cicco C, Ret Dávalos ML, Van Cleynenbreugel B, Verguts J, Koninckx PR. Iatrogenic ureteral lesions and repair: a review for gynecologists. *J Minim Invasive Gynecol.* 2007;14(4):428-35. doi: 10.1016/j.jmig.2007.01.003.
16. Pastore AL, Palleschi G, Silvestri L, Leto A, Autieri D, Ripoli A, et al. Endoscopic rendezvous procedure for ureteral iatrogenic detachment: report of a case series with long-term outcomes. *J Endourol.* 2015;29(4):415-20. doi: 10.1089/end.2014.0474.
17. Trombatore C, Giordano G, Magnano San Lio V. Interventional radiology in iatrogenic ureteral leaks: case series and literature review. *Radiol Med.* 2017;122(9):696-704. doi: 10.1007/s11547-017-0774-2.
18. De Cicco C, Schonman R, Craessaerts M, Van Cleynenbreugel B, Ussia A, Koninckx PR. Laparoscopic management of ureteral lesions in gynecology. *Fertil Steril.* 2009;92(4):1424-7. doi: 10.1016/j.fertnstert.2008.08.021.
19. Esparaz AM, Pearl JA, Herts BR, LeBlanc J, Kapoor B. Iatrogenic urinary tract injuries: etiology, diagnosis, and management. *Semin Intervent Radiol.* 2015;32(2):195-208. doi: 10.1055/s-0035-1549378.
20. De Cicco C, Ussia A, Koninckx PR. Laparoscopic ureteral repair in gynaecological surgery. *Curr Opin Obstet Gynecol.* 2011;23(4):296-300. doi: 10.1097/GCO.0b013e328348a29a.
21. Yates DR, Mehta SS, Spencer PA, Parys BT. Combined antegrade and retrograde endoscopic retroperitoneal bypass of ureteric strictures: a modification of the 'rendezvous' procedure. *BJU Int.* 2010;105(7):992-7. doi: 10.1111/j.1464-410X.2009.08807.x.
22. Macrì A, Magno C, Certo A, Basile A, Scuderi G, Crescenti F, et al. Combined antegrade and retrograde ureteral stenting: the rendezvous technique. *Clin Radiol.* 2005;60(2):257-60. doi: 10.1016/j.crad.2004.06.008.

23. Raimondo D, Alboni C, Orsini B, Aru AC, Farulla A, Maletta M, et al. Comparison of perioperative outcomes between standard laparoscopic and robot-assisted approach in patients with rectosigmoid endometriosis. *Acta Obstet Gynecol Scand.* 2021;100(9):1740-6. doi: 10.1111/aogs.14170.
24. Passoni N, Peters CA. Robotic Ureteral Reimplantation. *J Endourol.* 2020;34(S1):S31-4. doi: 10.1089/end.2019.0619.
25. Rassweiler JJ, Gözen AS, Erdogru T, Sugiono M, Teber D. Ureteral reimplantation for management of ureteral strictures: a retrospective comparison of laparoscopic and open techniques. *Eur Urol.* 2007;51(2):512-23. doi: 10.1016/j.eururo.2006.08.004.
26. Gözen AS, Cresswell J, Canda AE, Ganta S, Rassweiler J, Teber D. Laparoscopic ureteral reimplantation: prospective evaluation of medium-term results and current developments. *World J Urol.* 2010;28(2):221-26. doi: 10.1007/s00345-009-0443-8.
27. Linder BJ, Occhino JA. Cystoscopic ureteral stent placement: techniques and tips. *Int Urogynecol J.* 2019;30(1):163-5. doi: 10.1007/s00192-018-3762-8.
28. A Al-Kandari AM, Al-Shaiji TF, Shaaban H, Ibrahim HM, Elshebiny YH, Shokeir AA. Effects of proximal and distal ends of double-J ureteral stent position on postprocedural symptoms and quality of life: a randomized clinical trial. *J Endourol.* 2007;21(7):698-702. doi: 10.1089/end.2007.9949.
29. Ku JH, Kim ME, Jeon YS, Lee NK, Park YH. Minimally invasive management of ureteral injuries recognized late after obstetric and gynaecologic surgery. *Injury.* 2003;34(7):480-3. doi: 10.1016/s0020-1383(02)00412-6.
30. Hesselman S, Högborg U, Jonsson M. Effect of remote cesarean delivery on complications during hysterectomy: a cohort study. *Am J Obstet Gynecol.* 2017;217(5):564.e1-564.e8. doi: 10.1016/j.ajog.2017.07.021.
31. Vorobev V, Beloborodov V, Golub I, Frolov A, Kelchevskaya E, Tsoktoev D, et al. Urinary System Iatrogenic Injuries: Problem Review. *Urol Int.* 2021;105(5-6):460-9. doi: 10.1159/000512882.
32. Lang EK. Antegrade ureteral stenting for dehiscence, strictures, and fistulae. *AJR Am J Roentgenol.* 1984;143(4):795-801. doi: 10.2214/ajr.143.4.795.
33. Liu C, Zhang X, Xue D, Liu Y, Wang P. Endoscopic realignment in the management of complete transected ureter. *Int Urol Nephrol.* 2014;46(2):335-40. doi: 10.1007/s11255-013-0535-7.
34. Engel O, Rink M, Fisch M. Management of iatrogenic ureteral injury and techniques for ureteral reconstruction. *Curr Opin Urol.* 2015;25(4):331-5. doi: 10.1097/MOU.0000000000000175.
35. Lucas JW, Ghiraldi E, Ellis J, Friedlander JI. Endoscopic Management of Ureteral Strictures: an Update. *Curr Urol Rep.* 2018;19(4):24. doi: 10.1007/s11934-018-0773-4.
36. Richter F, Irwin RJ, Watson RA, Lang EK. Endourologic management of benign ureteral strictures with and without compromised vascular supply. *Urology.* 2000;55(5):652-7. doi: 10.1016/s0090-4295(00)00484-2.
37. Bilotta A, Wiegand LR, Heinsimer KR. Ureteral reconstruction for complex strictures: a review of the current literature. *Int Urol Nephrol.* 2021;53(11):2211-9. doi: 10.1007/s11255-021-02985-6.
38. Goodwin WE, Scardino PT. Vesicovaginal and ureterovaginal fistulas: a summary of 25 years of experience. *J Urol.* 1980;123(3):370-4. doi: 10.1016/s0022-5347(17)55941-8.
39. Angioli R, Penalver M, Muzii L, Mendez L, Mirhashemi R, Bellati F, et al. Guidelines of how to manage vesicovaginal fistula. *Crit Rev Oncol Hematol.* 2003;48(3):295-304. doi: 10.1016/s1040-8428(03)00123-9.



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Single-port laparoscopy *versus* conventional laparoscopy for management of benign adnexal masses during pregnancy: a comparative study

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ABSTRACT

Objective. Single-port laparoscopic surgery (SPL) is a newly developed surgical technique which was evolved from conventional laparoscopic surgery (CL). Sufficient evaluation of roles and benefits of SPL surgery for excision of adnexal masses discovered during pregnancy was not done.

Aim of the study was to compare between SPL and CL surgeries in management of benign adnexal masses during pregnancy regarding benefits, advantages, disadvantages and operative outcomes.

Patients and Methods. This retrospective cohort study included 100 patients who underwent laparoscopic adnexal surgeries during pregnancy. We divided included patients into 2 groups the first group included 50 and underwent single-port laparoscopic surgery (SPL) and the second group included 50 patients and underwent conventional laparoscopic surgery (CL).

Results. There was a statistically significant difference between both groups of patients as regard cosmetic scar satisfaction which was more in the SPL group ($p \leq 0.001$).

Operative time was longer in the SPL group of patients than in the CL group of patients with statistically significant differences ($p < 0.001$).

Conclusions. We showed that SPL was considered a feasible and safe approach for laparoscopic excision of adnexal masses during pregnancy.

INTRODUCTION

Single-port laparoscopic surgery (SPL) is a newly developed surgical technique which was evolved from conventional laparoscopic surgery (CL) [1]. SPL surgery needs a single incision in the skin, so it has a better cosmetic appearance in comparison to CL surgery. SPL surgical procedures were primarily applied for tubal sterilization that were applied in digestive, urologic and gynaecological surgeries [2]. SPL surgery was assessed in removing benign adnexal masses in comparison with CL surgery

[3], but sufficient evaluation of roles and benefits of SPL surgery for excision of adnexal masses discovered during pregnancy was not done [4].

There were previously reported studies in this topic [5-7], but still concerns were found for evaluating roles of SPL surgery in management of benign adnexal masses during pregnancy [8].

When diagnosis of an adnexal mass occurred during third trimester of pregnancy, clinical management needs a multidisciplinary team to compare between malignancy risks, mass size and the health of foetus [9].

The aim of the study was to compare between SPL and CL surgeries in management of benign adnexal masses during pregnancy regarding benefits, advantages, disadvantages and operative outcomes.

PATIENTS AND METHODS

This retrospective cohort study included 100 patients who underwent laparoscopic adnexal surgeries during pregnancy at the Department of Gynecology and Obstetrics Zagazig University Hospitals in the period between October 2016 and January 2022.

We divided included patients into 2 groups the first group included 50 and underwent single-port laparoscopic surgery (SPL) and the second group included 50 patients and underwent conventional laparoscopic surgery (CL).

Inclusion criteria for the study

Pregnant patients with clinically and radiologically benign adnexal masses with a large mass (> 6-10 cm), symptomatic patients, patients with high risks of torsion or rupture of the cysts, or obstructed labour, patients with normal preoperative laboratory tests as normal complete blood count, normal electrolytes, chemistry, and coagulation profile, absence of any pregnancy or non-pregnancy-related complications were included.

Exclusion criteria

Patients with clinical or radiological evidence of malignant ovarian tumours were excluded from the study.

We acquired written informed consents from all participants written informed consent before starting the study.

Perioperative outcomes

We collected and evaluated perioperative outcomes of included patients as operative time, intra-operative blood loss, haemoglobin level changes after surgery, costs and duration of hospital stay, intraoperative and postoperative complications.

After discharging patients from the hospital, we followed them up for a period of time ranged from 6 to 12 months after the operation by telephone, to assess rate of scar satisfaction and cosmetic results.

We asked patients to rate their overall satisfaction from the scar using a 10-points scale: 10 indicated very satisfied and 1 indicated very unsatisfied. Moreover, we evaluated pregnancy results and neonatal outcomes.

Surgical techniques

After general anaesthesia administration, all patients were placed in dorsal lithotomy position with supporting both legs in stirrups.

We performed a 2.5 cm umbilical incision for inserting wound retractor inner ring for fascial incision stretching, then we rolled wound retractor outer ring to connect the sealing member. Except for ports number of ports, SPL port retractor include four access ports, the surgical procedures in both SPL and CL were similar. In the SPL group, we employed an extracorporeal surgical approach as previously showed by [10].

We performed adnexal cystectomy in both included groups of patients and used endobag technique for spillage prevention [11].

In SPL for umbilical incision closure, we sutured the peritoneum, fascia then skin separately.

We continuously monitored maternal vital signs during the operations as oxygen saturation, and carbon dioxide pressure. Moreover, we performed continuous foetal sonographic monitoring for assessment of foetal heart rate pre-operative and just after the operation.

Statistical analyses

We presented data as mean, SD or by number (percentage). We analysed differences between-group of normally distributed quantitative data by using Student's t-test. We analysed quantitative data without normal distribution by using Wilcoxon rank sum test. We analysed differences between groups in qualitative data by using Fisher's exact test.

We performed all analyses using SPSS software, version 20.0 (IBM, Armonk, NY, USA) and considered a P-value < 0.05 as statistically significance value.

RESULTS

We included 100 pregnant females underwent laparoscopic surgeries for excision of benign adnexal masses. 50 patients underwent SPL (50%) and 50 patients underwent CL (50%).

We found no differences between both groups of patients as regard patient age, parity, high risk pregnancy, multiple gestation or history of caesarean section (Table 1).

There are no statistically significant differences between both groups as regard histopathological sub-types of the adnexal cysts that was, teratoma (29% of cysts), endometriotic cyst (20%), and serous cystadenoma (16%).

There was a statistically significant difference between both groups of patients as regard cosmetic scar satisfaction, which was more in the SPL group ($p \leq 0.001$) (Table 2).

We found neither complication, infection in the surgical wound nor umbilical hernia in both included groups of patients.

Table 1. Baseline data of the studied patients.

| | n = 100 | % |
|--|--------------|---------|
| Parity | | |
| P0 | 5 | 5% |
| P1 | 20 | 20% |
| P2 | 20 | 20% |
| P3 | 30 | 30% |
| P4-7 | 25 | 25% |
| Mode of delivery | | |
| NVD | 40 | 40% |
| CS | 60 | 60% |
| Previous abdominal surgery | 40 | 40% |
| Previous pelvis surgery | 40 | 40% |
| SPL | 50 | 50% |
| CLS | 50 | 50% |
| Mass | | |
| Cystic | 29 | 29% |
| Solid | 38 | 38% |
| Mixed | 33 | 33% |
| Histopathology | | |
| Endometriosis | 19 | 19% |
| Functional cyst | 8 | 8% |
| Mucinous cyst | 26 | 26% |
| Serous cyst | 26 | 26% |
| Teratoma | 21 | 21% |
| Surgery | | |
| Ovarian cystectomy | 74 | 74% |
| Oophorectomy | 10 | 10% |
| Salpingectomy | 16 | 16% |
| | Mean ± SD | Range |
| Age (year) | 34.29 ± 5.67 | 22-48 |
| BMI (kg/m ²) | 21.51 ± 1.83 | 17-25.5 |
| Ovarian volume (cm ³) | 6.71 ± 1.69 | 4-11 |
| Operative time (min) | 13.36 ± 2.75 | 9-20 |
| Intraoperative bleeding (ml) | 18.65 ± 3.35 | 10-28 |
| Return of bowel function (h) | 14.09 ± 2.98 | 9-20 |
| Ambulation time (h) | 13.51 ± 3.88 | 8-19 |
| Postoperative 12-hour VAS cosmetic score | 8.65 ± 1.76 | 5-11 |
| Postoperative analgesic use (ampoule) | 5.44 ± 1.65 | 3-9 |

Table 2. Comparison between surgical approach and the studied parameters.

| | Approach | | χ ² | P-value |
|--|--------------|--------------|--------------------|-----------|
| | CLS | SPL | | |
| Parity | | | | |
| P0 | 3 (6%) | 2 (4%) | 0.683 ^s | 0.409 |
| P1 | 11 (22%) | 9 (18%) | | |
| P2 | 10 (20%) | 10 (20%) | | |
| P3 | 15 (30%) | 15 (30%) | | |
| P4-7 | 11 (22%) | 14 (28%) | | |
| Mode of delivery | | | | |
| NVD | 17 (37%) | 17 (35.4%) | 0.024 | 0.877 |
| CS | 29 (63%) | 31 (64.6%) | | |
| Previous abdominal surgery | 20 (40%) | 20 (40%) | 0 | > 0.999 |
| Previous pelvis surgery | 22 (44%) | 18 (36) | 0.667 | 0.414 |
| Mass | | | | |
| Cystic | 16 (32%) | 13 (26%) | 1.173 | 0.556 |
| Solid | 20 (40%) | 18 (36%) | | |
| Mixed | 14 (28%) | 19 (38%) | | |
| Histopathology | | | | |
| Endometriosis | 8 (16%) | 11 (22%) | 1.175 | 0.882 |
| Functional cyst | 5 (10%) | 3 (6%) | | |
| Mucinous cyst | 13 (26%) | 13 (26%) | | |
| Serous cyst | 14 (28%) | 12 (24%) | | |
| Teratoma | 10 (20%) | 11 (22%) | | |
| Surgery | | | | |
| Ovarian cystectomy | 40 (80%) | 34 (68%) | 2.736 | 0.255 |
| Oophorectomy | 5 (10%) | 5 (10%) | | |
| Salpingectomy | 5 (10%) | 11 (22%) | | |
| | Mean ± SD | Mean ± SD | t | P-value |
| Age (year) | 33.86 ± 4.53 | 33.16 ± 5.81 | 0.672 | 0.503 |
| BMI (kg/m ²) | 23.18 ± 2.74 | 24.98 ± 7.08 | -1.676 | 0.098 |
| Ovarian volume (cm ³) | 7.49 ± 1.66 | 5.93 ± 1.34 | 5.179 | < 0.001** |
| Operative time (min) | 12.66 ± 3.06 | 15.06 ± 1.57 | 5.344 | < 0.001** |
| Intraoperative bleeding (ml) | 19.62 ± 2.86 | 17.68 ± 3.54 | 3.015 | 0.003* |
| Postoperative 12-hour VAS cosmetic score | 7.22 ± 1.2 | 10.08 ± 0.8 | -13.999 | < 0.001** |
| | Median (IQR) | Median (IQR) | Z | P-value |
| Postoperative analgesic use (ampoule) | 7 (5-8) | 4 (4-5) | 9.844 | < 0.001** |

^sChi square for trend test; χ²: Chi square test; t: independent sample t test; * P-value < 0.05 is statistically significant; **P-value ≤ 0.001 is statistically highly significant; IQR: interquartile range; Z: Mann Whitney test.

Operative time was longer in the SPL group of patients than in the CL group of patients with statistically significant differences ($p < 0.001$).

There are no statistically significant differences between both groups of patients regard blood loss, haemoglobin level or duration of hospital stay.

There are no patients in both included groups required blood fusion or conversion from laparoscopy to laparotomy.

Table 3. Partial correlation between postoperative analgesic use and studied parameters.

| | r | P-value |
|--------------------------------|--------|---------|
| Operative time | 0.117 | 0.249 |
| Ovarian volume | -0.091 | 0.369 |
| Intraoperative bleeding | -0.008 | 0.934 |
| Ambulation time | -0.003 | 0.978 |
| Time to return to bowel habits | 0.086 | 0.397 |

r: Spearman rank correlation coefficient; P-value < 0.05 is statistically significant;
**P-value ≤ 0.001 is statistically highly significant.

Included patients in both groups had a full-term delivery with no statistically significant differences in neonatal outcomes as regard APGAR scores and average birth weight.

There are no statistically significant differences between both groups of patients regard the rate of neonatal complications as jaundice, arrhythmia, hypoglycaemia, small for gestational age and respiratory distress syndrome.

After controlling approach used, there is statistically non-significant correlation between number of postoperative analgesic ampoules used and all of ovarian time, intraoperative bleeding, ovarian volume, time to return of bowel habits and ambulation time (Table 3).

DISCUSSION

In the present study we compared SPL and CL adnexal masses excision in pregnant females as regard operative, peri-operative outcomes, patient satisfaction, maternal and foetal outcomes. Results showed that patients who underwent SPL surgery have better cosmetic satisfaction without increased risks of adverse maternal or foetal outcomes.

Chen *et al.* [4] compared both SPL and CL in management of adnexal cystic masses in pregnant patients. They reported similar results to ours: patients who underwent adnexal surgery via SPL have better cosmetic satisfaction in comparison with patients who underwent CL approach; moreover, they showed adnexectomy via SPL makes few adverse peri-operative events and less economic burden with no increase in the adverse maternal or neonatal complications.

Similar results were demonstrated by previous studies which included non-pregnant patients and showed that SPL surgery has better cosmetic appearance and more patient satisfaction in comparison with CL surgery [12, 13].

These findings might be due to reduced abdominal incisions number that led to better patients' cosmetic requirements.

We showed that SPL surgery was associated with less postoperative pain, shorter hospital stays, and lower anxiety that was similar to results of previous studies [7, 11-14].

Due to increased connective tissue laxity and abdominal stress with progression of pregnancy [15], it was hypothesized that enlarged umbilical incision in SPL surgery might lead to increased incidence of postoperative hernia formation during pregnancy.

Closure of fascia and prolonged surgical time were associated with postoperative pain and the need for consumption of opioids. Surgical training to decrease surgical time could decrease postoperative pain and opioids [16].

Posterior colpotomy can be considered a feasible option for surgical specimens retrieval after performing laparoscopic surgeries [17].

Laparoscopic surgeries during pregnancy are safe and associated with good oncological and obstetrical outcomes [18].

In our study we do similar to Chen *et al.*'s study [4]: umbilical skin incision in patients who underwent SPL surgery were closed with simple continuous suture of the peritoneum, fascia and a separate subcuticular suture of the skin, and we reported no umbilical hernia or any complications in the umbilical incision.

Points of strength of our study

Our study was a comparative and prospective study to overcome limitations of previous retrospective studies.

Additionally, we collect data regarding postoperative pain, cosmetic and economic satisfaction.

CONCLUSIONS

In the present study we compared between SPL and CL for excision of adnexal masses in pregnancy and showed that SPL surgery provide better cosmetic satisfaction without increasing perioperative complications, or adverse maternal and neonatal outcomes.

Moreover, we showed that SPL was considered a feasible and safe approach for laparoscopic excision of adnexal masses during pregnancy.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.E.: Conceptualization. A.A-A.A.: Formal analysis. M.A.E.: Writing - original draft. O.A.H., A-R.E.A-R.: Writing - review & editing.

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Study registration

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Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Acquired from the local institutional review board of Faculty of Medicine, Zagazig University.

Informed consent

Obtained from all included patients.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Wheelless CR Jr. Elimination of second incision in laparoscopic sterilization. *Obstet Gynecol.* 1972;39(1):134-6.
2. Daykan Y, Bogin R, Sharvit M, Klein Z, Josephy D, Pomeranz M, et al. Adnexal Torsion during Pregnancy: Outcomes after Surgical Intervention-A Retrospective Case-Control Study. *J Minim Invasive Gynecol.* 2019;26(1):117-21. doi: 10.1016/j.jmig.2018.04.015.
3. Schmitt A, Crochet P, Knight S, Tourette C, Loundou A, Agostini A. Single-Port Laparoscopy vs Conventional Laparoscopy in Benign Adnexal Diseases: A Systematic Review and Meta-Analysis. *J Minim Invasive Gynecol.* 2017;24(7):1083-95. doi: 10.1016/j.jmig.2017.07.001.
4. Chen S, Zhang G, Hua K, Ding J. Single-port laparoscopy versus conventional laparoscopy of benign adnexal masses during pregnancy: a retrospective case-control study. *J Int Med Res.* 2022;50(10):3000605221128153. doi: 10.1177/03000605221128153.
5. Takeda A, Imoto S, Nakamura H. Gasless laparoendoscopic single-site surgery for management of adnexal masses during pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2014;180:28-34. doi: 10.1016/j.ejogrb.2014.06.019.
6. Xiao J, Fu K, Duan K, Wang J, Sunkara S, Guan X. Pregnancy-preserving Laparoendoscopic Single-site Surgery for Gynecologic Disease: A Case Series. *J Minim Invasive Gynecol.* 2020;27(7):1588-97. doi: 10.1016/j.jmig.2020.02.009.
7. Jiang D, Yang Y, Zhang X, He F, Wu Y, Niu J, et al. Laparoendoscopic single-site compared with conventional laparoscopic surgery for gynaecological acute abdomen in pregnant women. *J Int Med Res.* 2021;49(10):3000605211053985. doi: 10.1177/03000605211053985.
8. Han L, Wan Q, Chen Y, Zheng A. Single-Port Laparoscopic Surgery for Adnexal Mass Removal During Pregnancy: The Initial Experience of a Single Institute. *Front Med (Lausanne).* 2022;8:800180. doi: 10.3389/fmed.2021.800180.
9. Cacciottola L, Eugenio C, Giuseppe S, Giuseppe T, Trojano M, Vignali V. Management of adnexal masses during the third trimester of pregnancy: a case report in twin-pregnancy and review of the literature. *Ital J Gynaecol Obstet.* 2016;28(2):36-40. doi: 10.14660/2385-0868-40.
10. Kim WC, Kwon YS. Laparoendoscopic single-site surgery for exteriorization and cystectomy of an ovarian tumor during pregnancy. *J Minim Invasive Gynecol.* 2010;17(3):386-9. doi: 10.1016/j.jmig.2009.12.024.
11. Köchli OR, Schnegg MP, Müller DJ, Surbek DV. Endobag extractor to remove masses during laparoscopy. *Obstet Gynecol.* 2000;95(2):304-5. doi: 10.1016/s0029-7844(99)00516-5.
12. Lee D, Kim SK, Kim K, Lee JR, Suh CS, Kim SH. Advantages of Single-Port Laparoscopic Myomectomy Compared with Conventional Laparoscopic Myomectomy: A Randomized Controlled Study. *J Minim Invasive Gynecol.* 2018;25(1):124-32. doi: 10.1016/j.jmig.2017.08.651.

13. Phillips MS, Marks JM, Roberts K, Tacchino R, Onders R, DeNoto G, et al. Intermediate results of a prospective randomized controlled trial of traditional four-port laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy. *Surg Endosc.* 2012;26(5):1296-303. doi: 10.1007/s00464-011-2028-z.
14. Chen YJ, Wang PH, Ocampo EJ, Twu NF, Yen MS, Chao KC. Single-port compared with conventional laparoscopic-assisted vaginal hysterectomy: a randomized controlled trial. *Obstet Gynecol.* 2011;117(4):906-12. doi: 10.1097/AOG.0b013e31820c666a.
15. Nussbaum R, Benedetto AV. Cosmetic aspects of pregnancy. *Clin Dermatol.* 2006;24(2):133-41. doi: 10.1016/j.clindermatol.2005.10.007.
16. Buzzaccarini G, Török P, Vitagliano A, Petousis S, Noventa M, Hortu I, et al. Predictors of Pain Development after Laparoscopic Adnexectomy: A Still Open Challenge. *J Invest Surg.* 2022;35(6):1392-3. doi: 10.1080/08941939.2022.2056274.
17. Laganà AS, Casarin J, Uccella S, Garzon S, Cromi A, Guerrisi R, et al. Outcomes of In-bag Transvaginal Extraction in a Series of 692 Laparoscopic Myomectomies: Results from a Large Retrospective Analysis. *J Minim Invasive Gynecol.* 2022;29(12):1331-8. doi: 10.1016/j.jmig.2022.09.009.
18. Vercellino GF, Koehler C, Erdemoglu E, Mangler M, Lanowska M, Malak AH, et al. Laparoscopic pelvic lymphadenectomy in 32 pregnant patients with cervical cancer: rationale, description of the technique, and outcome. *Int J Gynecol Cancer.* 2014;24(2):364-71. doi: 10.1097/IGC.000000000000064.



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Iron deficiency in pregnancy: an Italian survey

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ABSTRACT

Objective. Iron deficiency with (IDA) or without anaemia (IDWA) represents a global health issue. The present paper aims to evaluate several skills concerning the prevention of IDWA and the appropriate management of IDA, in pregnancy and in the postpartum, testing a heterogeneous group of Italian obstetricians.

Materials and Methods. On April 2022, a group of obstetricians of Lazio region (GOAL Working Group) promoted an online survey among its mem-

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Key words*Iron deficiency; iron deficiency anaemia; pregnancy; iron treatment.*

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INTRODUCTION

Worldwide approximately one-third of the population is anaemic. In hospitalized patients, the prevalence of anaemia is approximately 25-50% percent, depending on comorbidities and demographic factors (*e.g.*, age, gender), and increases within the processes of care (*e.g.*, procedural blood loss and phlebotomies) [1]. Anaemia has been recognized as an independent risk factor for adverse outcome including higher risk of hospitalization or readmission, prolonged hospital stay, morbidity and mortality [2, 3], as well as additional costs to the health care system [4]. The most common of anaemia is represented by iron lack. During pregnancy and the postpartum, iron deficiency anaemia (IDA) and iron deficiency without anaemia (IDWA) represent global health issues thus involving over 40% of women [5], leading to an increased risk of adverse maternal and/or perinatal outcomes (*e.g.*, reduced physical activity, cognitive performance status and immune function as well as tiredness and increased depressive episodes, for the mother; preterm birth, foetal growth restriction, intrauterine foetal death, low APGAR scores and neonatal infection, for the baby). Such risks arise from the pivotal role of iron to several biologic functions (*e.g.*, respiration, energy production, DNA synthesis and cell proliferation) [6-8]. The human body is able to store iron thanks to different pathways, including the recycling of martial storages after the breakdown of red cells and the retention of iron in the absence of an excretion mechanism. IDWA refers to the reduction of iron stores precedes overt IDA or persists without progression; symptoms of IDWA are basically

based on 27 questions dealing with IDA and IDWA in pregnancy and in the postpartum; aspects related to the Patient Blood Management (PBM) have also been investigated.

Results. About 30% of the GOAL members answered the questionnaire. The prevalence of IDWA is thought to be around 41%, leading to a higher risk of adverse pregnancy outcomes. 54.1% of responders evaluate iron storage at the first visit in pregnancy thus proposing a diet rich in iron to all women they follow (67.2%). Although iron administration is more often needed to correct haemoglobin levels before starting labour, the prevalence of blood transfusion in the postpartum is thought to be around 2-5% (50.8%). Only the half of responders knows the PBM approach.

Conclusions. It is desired to define how clinicians who care for pregnant perceive, frame and treat IDA and IDWA, which are too often not promptly diagnosed and managed, in order to improve antenatal care.

the same found in patients with IDA. The diagnostic approach includes the evaluation of blood cell count, serum ferritin, serum iron, transferrin (or total iron binding capacity) and transferrin saturation (or saturated iron binding capacity) (TSAT). The appropriate diagnosis is crucial for an adequate therapeutic approach: when a pathological cause is identified, iron supplementation should be combined to the treatment of the underlying cause. Iron replacement should be done orally as the first choice; subjects who need a rapid correction of anaemia as well as those with intolerance or refractoriness to oral therapy, or defective intestinal absorption, benefit from intravenous iron administration; on the contrary, the increase of iron intake through the diet alone is not sufficient to treat documented cases of iron deficiency. Transfusion is recommended when clinically indicated. For this reason, the World Health Organization (WHO) promoted an approach called Patient Blood Management (PBM), which is defined as “the timely application of evidence-based medical and surgical concepts designed to maintain haemoglobin concentration, optimize haemostasis and minimize blood loss in an effort to improve patient outcome” by the Society for the Advancement of Blood Management (SABM) (available at: <http://www.sabm.org/>). However, questions are raised about the development of knowledge on iron metabolism and available therapies. Being the appropriate management of IDA and IDWA desired for both maternal and newborn health, the present paper aims at evaluating several clinical skills concerning the management of such conditions during pregnancy and the postpartum, testing a heterogeneous group of Italian obstetricians.

MATERIALS AND METHODS

On April 2022, an Italian group of obstetricians of Lazio region (the so-called GOAL Working Group) promoted an online survey among its members (about 200) based on a smart list of 27 questions dealing with the importance of iron stores and iron deficiency, the management of IDA and IDWA, as well as on the use of the Patient Blood Management (PBM), during pregnancy and the postpartum.

The survey design involved the following steps:

1. The creation of a working group dedicated to carrying out the survey.
2. The review of the available literature.
3. The drafting of the survey.
4. The collection of an informed consent.

5. The submission of the survey to the GOAL Working Group members.

6. A reminder 15 days after the submission.

The list of the questions is reported in **Table 1**; the first two investigate clinicians' experience (years of clinical practice and number of annual births in the hospitals where they work) while the other ones deal with several clinical skills about IDA and IDWA (e.g., prevention, diagnosis, management, outcome and follow-up). The results of the online survey, based on the independent opinions and personal experiences of the members who answered the questionnaire, have been reported in this manuscript in order to provide an overview on the perception of IDA and IDWA, during pregnancy and the postpartum, among clinicians who care for pregnant.

Table 1. The questionnaire sent to the GOAL Working Group members, and its results (expressed as percentage of responders).

| | A | B | C | D | E |
|--|-----|-----|------|-----|-----|
| 1 How many years have you been practicing? A. Less than 5 years; B. 5-10 years; C. 10-15 years; D.15-20 years; E. More than 20 years | 10% | 10% | 8% | 15% | 57% |
| 2 How many births are carried out every year in the hospital where you work? A. Less than 1,000; B. 1,000-2,000; C. 2,000-3,000; D.3,000-3,500; E. More than 3,500 | 37% | 30% | 3% | 3% | 27% |
| 3 In your experience, how many women present at delivery in accordance with the haemoglobin threshold set by the WHO? A. Less than 10%; B. 10-30%; C. 30-50%; D.50-70%; E. More than 70% | 4% | 20% | 28% | 30% | 18% |
| 4 In your experience, which is the rate of women affected by iron deficiency without anaemia (IDWA) in pregnancy? A. Less than 10%; B. 10-30%; C. 30-50%; D.50-70%; E. More than 70% | 6% | 33% | 41% | 15% | 5% |
| 5 In your experience, what is the most common cause of anaemia? In what percentage? A. Vitamin B12 deficiency; B. Folic acid deficiency; C. Iron deficiency; D. Renal insufficiency; E. Other causes | - | - | 100% | - | - |
| 6 In your experience, what complications do you think may be related to iron deficiency in pregnancy? A. Postpartum anaemia; B. Increase length of hospital stay; C. Increase infective risk; D. Increase risk of blood transfusion; E. All | 15% | 1% | - | 5% | 79% |
| 7 What is the average amount of iron needed throughout pregnancy? A. 100-200; B. 200-500 mg; C. 500-700 mg; D. 700-1000 mg; E. More than 1000 mg | 12% | 20% | 9% | 26% | 33% |
| 8 In general, which blood tests do you need for the diagnosis of iron deficiency anaemia? A. Blood count and serum iron levels; B. Blood count, serum iron levels and ferritin; C. Blood count, serum iron levels, ferritin and transferrin; D. Haematocrit; E. Other | 10% | 36% | 54% | - | - |
| 9 In the first trimester, or at the first visit in pregnancy, do you carry out an in-depth study on iron metabolism? If so, in what percentage of cases? A. Yes; B. No; C. Only in specific cases | 54% | 44% | 2% | - | - |
| 10 Diet rich in iron: in which cases is it proposed? A. To all women at the beginning of pregnancy or, in any case, at the first visit; B. In women with haemoglobin level less than 11 g/dL; C. In cases of known food intolerances; D. In vegetarian/vegan women; E. Other cases | 67% | 28% | 2% | 2% | 1% |
| 11 Dietary correction: what recommendations? A. Verbal recommendations; B. Personalized written diet; C. Evaluation of food and drug interactions; D. Information brochure; E. Evaluation of drug interactions | 62% | 6% | 7% | 25% | - |
| 12 What are, in your experience/opinion, the objectives to be pursued when administering martial therapy? In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. Start labour with adequate haemoglobin values; B. Correct haemoglobin levels and iron stores (serum ferritin); C. Prevent avoidable transfusion; D. Provide adequate iron support to the mother and her foetus; E. Reduce the risk of blood transfusion | 46% | 18% | - | 26% | 10% |
| 13 Oral iron in pregnancy: A. To all women, as a prophylaxis; B. The most tolerated, in my experience; C. In low doses, in order to reduce the side effects; D. As a drug, only in the presence of anaemia; E. Every other day | 13% | 15% | 9% | 59% | 4% |



| | A | B | C | D | E |
|---|-----|-----|-----|-----|-----|
| 14 In your opinion, which is the main limitation of oral iron therapy? A. Prolonged therapy over time; B. Slow increase of haemoglobin levels; C. Gastrointestinal side effects that reduce compliance; D. Insufficient to support iron demand in late pregnancy; E. Cost to be paid by the patient | 10% | 16% | 57% | 10% | 7% |
| 15 You must choose oral iron therapy in an anaemic woman: A. Supplement, to then get to the drug; B. Drug with a possible subsequent change; C. A proper diet is usually sufficient; D. A multivitamin is usually sufficient; E. Other | 34% | 57% | 9% | - | - |
| 16 How do you check the effectiveness of oral iron therapy? A. Blood count and iron profile after 15 days; B. Blood count and iron profile after 30 days; C. Haemoglobin and serum ferritin levels; D. I change the therapy in case of further drop in haemoglobin values; E. There is no re-evaluation in pre-established times | 13% | 74% | 7% | 3% | 3% |
| 17 In your clinical practice, which are the most frequent causes of discontinuation of oral iron therapy? A. Hive disorders; B. Lack of clinical efficacy; C. Failure to resolve the symptoms of anaemia; D. Poor patient compliance; E. Therapy costs | 37% | 5% | 3% | 53% | 2% |
| 18 In which trimester of pregnancy do you administer intravenous iron therapy? A. Postpartum; B. Second trimester; C. Third trimester; D. Second and third trimesters; E. Never | 5% | - | 39% | 39% | 17% |
| 19 If you administering intravenous iron therapy, how do you determine the amount of iron to be given? A. Minimum effective dosage; B. By calculation with the Ganzoni formula; C. According to the clinical experience; D. Based on the severity of the symptoms; E. Based on the length of hospital stay | 30% | 30% | 16% | 18% | 6% |
| 20 Which are, in your opinion, the main limitations of intravenous iron therapy? In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. Logistics; B. Costs; C. Risks linked to intravenous injection; D. Lack in Evidence Based Medicine; E. All | 43% | 9% | 38% | 6% | 4% |
| 21 In your experience, which are the causes that most frequently induced a transfusion of red blood cells? A. Low haemoglobin levels few weeks before delivery; B. Peripartum complications; C. Risk factors; D. Arrival of an anaemic woman few days before giving birth; E. Failure or ineffective management of anaemia during pregnancy | 17% | 55% | 2% | 6% | 20% |
| 22 When do you ask for a consultation (to the transfusion centre or to the haematologist)? In case of multiple answers, indicate the degree of priority (1,2,3,4) A. Low haemoglobin levels; B. Haemoglobinopathies; C. Persistent symptoms; D. Failure to respond to a well-conducted oral iron therapy | 12% | 46% | 15% | 27% | - |
| 23 Postpartum: in which cases do you evaluate a therapeutic support with oral iron therapy? In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. Haemoglobin levels < 10 g/dL 24-48 hours postpartum; B. Haemoglobin levels < 11 g/dL one week postpartum; C. Haemoglobin levels < 12 g/dL 8 weeks postpartum; D. Always; E. In case of high blood losses (> 500 ml) | 85% | - | - | - | 15% |
| 24 Postpartum: in which cases do you evaluate therapeutic support with intravenous iron therapy? In case of multiple answers, indicate the degree of priority (1,2,3,4,5) A. In case of prepartum known IDA; B. Caesarean section; C. IDWA diagnosis; D. Blood loss greater than 300 ml; E. Acute blood loss during delivery | 15% | - | - | - | 85% |
| 25 In your experience, what is the percentage of women transfused in the postpartum? A. < 1%; B. 2-5%; C. 5-7%; D. 7-10% | 30% | 51% | 17% | 1% | 1% |
| 26 Do you know the Patient Blood Management? A. Yes; B. No | 58% | 42% | - | - | - |
| 27 Patient Blood Management should be implemented: A. In cases with haemoglobin levels less than 9 g/dL; B. In cases with coagulation disorders; C. Before a planned surgical intervention; D. In consideration of religious belief (Jehovah's Witnesses) or refusal to transfusion; E. Always | 32% | 5% | 7% | 12% | 44% |

RESULTS

About 30% (60/200) of the GOAL members answered the questionnaire. The clinical experience of the respondents is detailed in **Table 2**: 57% of them have been working for more than 20 years and 15% of the GOAL members have a clinical experience of 15-20 years.

Table 2. Clinical experience of the respondents.

| Characteristic | Frequency (n = 60) |
|-----------------------------|--------------------|
| Clinical experience (years) | |
| < 5 | 6 (10%) |
| 5/10 | 6 (10%) |
| 10/15 | 5 (8%) |
| 15/20 | 9 (15%) |
| > 20 | 34 (57%) |
| > 45 | - |

The results of the survey are reported in **Table 1**. According to physicians' opinions and personal experiences, the prevalence of women who start pregnancy with IDWA is thought to be around 41% while the percentage of those entering labour with an adequate Hb level is one third of the total. Iron deficiency is considered the most common cause of anaemia in pregnancy, in more than the half of cases. Several adverse events (*e.g.*, postpartum anaemia, length of hospital stay, infective risk, risk of blood transfusion) are thought to be associated with IDWA in 78.3% of responders. The iron supplementation needed throughout pregnancy is thought to be greater than 1,000 mg, in more than one third of clinicians (32.8%). Blood count, serum iron levels, ferritin and transferrin are included in the diagnostic approach in 54.1% of responders. Iron storage is assessed by more than the half of clinicians (54.1%) at the first visit in pregnancy; 67.2% of them proposed a diet rich in iron to all women they follow at the beginning of pregnancy, by means of verbal recommendations (62.3%). Iron therapy is thought to be principally needed to correct Hb levels before starting labour (45.9%); other reasons of martial supplementation are providing adequate iron support to the mother and her foetus (26.2%), and correcting Hb levels and iron stores (18%). The majority of responders (59%) considers oral iron therapy only in pregnant affected by IDA, changing the drug if not well tolerated (57.4%). The main limitation of oral iron therapy is represented by gastrointestinal side effects that negatively impact on patient's compliance (55.7%). 78.4% of responders check the effectiveness of oral iron therapy testing blood count and iron profile 30 days after iron supplementation. The most frequent causes of oral iron therapy discontinuation are poor patient's compliance and hive disorders, in 53.2% and 37.1% of clinicians, respectively. Intravenous iron is more frequently administered during the second and the third trimesters of pregnancy (28.8%). The amount of iron needed is calculated by means of Ganzoni's formula (30.4%); 28.6% of clinicians administer the minimum effective dosage. The main limitations of intravenous iron are represented by logistic problems and risks linked to intravenous injection, in 43.1% and 37.9% of responders, respectively. Red blood cells transfusion is generally required in women who experienced peripartum complications (55%); blood transfusion is

thought to be due to the failure or the ineffective management of IDA throughout gestation in 20% of clinicians. In the majority of cases, they ask for a consultation (to the transfusion centre or to a haematologist) in patients affected by haemoglobinopathies (45.5%) or in cases who not respond to a well-conducted oral iron therapy (27.1%). Focusing on the postpartum, cases for whom clinicians prescribe oral iron therapy are those with Hb levels lower than 10 g/dL 24-48 hours after delivery; intravenous iron administration is more frequently considered in patients who experienced an acute blood loss during delivery. The prevalence of blood transfusion in the postpartum is thought to be around 2-5% in the half of responders (50.8%). The 57.4% of clinicians know the PBM approach while 42.6% do not. Such approach should be implemented, in routine practice or in cases with Hb levels lower than 9 g/dL for 43.9% and 31.6% of clinicians, respectively.

DISCUSSION

Iron content in a woman's body is normally maintained at about 40 mg/kg, balancing iron absorption by enterocytes in the duodenum, and iron mobilization from liver parenchyma and macrophages. Such processes are regulated by hepcidin, produced by the liver, which binds to a cellular iron export protein called ferroportin, causing its internalization. When hepcidin levels are increased, iron is retained in enterocytes or macrophages while when is decreased, stored iron is mobilized into the circulation [9]. A singleton pregnancy carried to term requires a transfer of 500-800 mg of maternal iron. IDWA represents a global health issue leading to an increased risk of adverse pregnancy outcomes (*e.g.*, premature delivery, low birth weight, and infant death) and impaired cognitive development in early childhood [9, 10]. Although the impact cited above, iron deficiency is often under-recognized by health system leaders and clinicians, independently from their clinical experienced [11, 12]. First of all, the definition of a normal haemoglobin (Hb) concentration throughout gestation is controversial and lacks consistency across studies. Ideally, the cut-off values should be derived from studies focused on healthy iron-replete (as well as folate- and vitamin B12-replete) women who had normal singleton gestation and delivery. The WHO (2011)

defines anaemia in pregnancy as Hb levels less than 11 g/dL and classifies such condition as mild (Hb 10-10.9 g/dL), moderate (Hb 7-9.9 g/dL) and severe (Hb levels less than 7 g/dL), according with Hb levels. There are no WHO recommendations on the use of different cut-off points for each trimester, but it is recognized that during the second trimester of gestation, Hb concentration decreases by approximately 0.5 g/dL. Both the American College of Obstetricians and Gynecologists (ACOG) and the UK guidelines recommend screening for anaemia as a surrogate for detecting IDWA. The successful management of IDWA and IDA depends on oral preparations, parenteral infusion, and blood transfusion. Treatment of iron deficiency anaemia generally begins with oral supplementation which can lead to gastrointestinal side effects. When the serum ferritin level is higher than 70 $\mu\text{g/L}$, iron stores are adequate to support pregnancy and no supplementation is given; on the contrary, when serum ferritin is less than 30 $\mu\text{g/L}$, the patient is treated with 80-100 mg elemental iron/day orally. Iron intravenous administration is indicated when oral iron fails because of compliance/tolerance issues, in subjects affected by comorbidities which may affect iron absorption or ongoing iron losses that exceed absorptive capacity [13, 14]. In the last years, several activities (*e.g.*, hospital meetings, internal discussions and congresses) dealing with anaemia in pregnancy were conducted in the maternal-foetal medicine units. Being the appropriate management of iron deficiency beneficial and desired for both maternal and newborn health, a key point is to understand how obstetricians manage iron deficiency in their routine practice. Furthermore, to avoid inappropriate practices, the WHO promoted the PBM approach which is a systematic and multidisciplinary approach able to optimize haemostasis, manage anaemia, minimize iatrogenic blood loss, and improve tolerance to anaemia and outcomes, in both surgical and nonsurgical patients. In Italy, the implementation of the PBM approach is mandatory by law and so, the Lazio region adopted it in both public and private hospitals.

CONCLUSIONS

During pregnancy and the postpartum, IDA and IDWA represent global health issues as well as

nutrition and lifestyle [15]. IDA and IDWA involve over 40% of women [5], leading to an increased risk of adverse maternal and/or perinatal outcomes. For example, in clinical routine practice gynaecologists deal with postpartum haemorrhage management which requires iron/red blood cells administration combined or not with other procedures in order to reduce maternal morbidity and mortality [16]. The present survey summarizes how a heterogeneous group of Italian obstetricians perceives, frames and treats iron anaemia in order to improve clinical care.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

G.P.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – review & editing. L.A., F.B., F.A.B., Mi.Bo., Ma.Bo., R.B., F.C., B.C., A.C., M.C., G.D.M., D.D.V., M.D., A.D.C., R.D.I., S.F., A.L., F.L., P.M., F.M., M.M., E.M., R.M., V.N., G.N., M.O., P.P., C.P., A.R., P.S., G.S., G.S., F.S., V.S., H.V.: Conceptualization, supervision, validation, investigation. A.L.: Conceptualization, supervision, validation, data curation, methodology, project administration.

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N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

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N/A.

Informed consent

N/A.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

- Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: insights into etiology, consequences, and management. *Am J Respir Crit Care Med*. 2012;185(10):1049-57. doi: 10.1164/rccm.201110-1915CI.
- Migone De Amicis M, Poggiali E, Motta I, Minonzio F, Fabio G, Hu C, et al. Anemia in elderly hospitalized patients: prevalence and clinical impact. *Intern Emerg Med*. 2015 Aug;10(5):581-586. doi: 10.1007/s11739-015-1197-5.
- Caughey MC, Avery CL, Ni H, Solomon SD, Matsushita K, Wruck LM, et al. Outcomes of patients with anemia and acute decompensated heart failure with preserved versus reduced ejection fraction (from the ARIC study community surveillance). *Am J Cardiol*. 2014;114(12):1850-4. doi: 10.1016/j.amjcard.2014.09.024.
- Nissenson AR, Wade S, Goodnough T, Knight K, Dubois RW. Economic burden of anemia in an insured population. *J Manag Care Pharm*. 2005;11(7):565-74. doi: 10.18553/jmcp.2005.11.7.565.
- Sweet MG, Schmidt-Dalton TA, Weiss PM, Madsen KP. Evaluation and management of abnormal uterine bleeding in premenopausal women. *Am Fam Physician*. 2012;85(1):35-43.
- Hentze MW, Muckenthaler MU, Galy B, Camaschella C. Two to tango: regulation of mammalian iron metabolism. *Cell*. 2010;142(1):24-38. doi: 10.1016/j.cell.2010.06.028.
- Ferreira C, Bucchini D, Martin ME, Levi S, Arosio P, Grandchamp B, Beaumont C. Early embryonic lethality of H ferritin gene deletion in mice. *J Biol Chem*. 2000;275(5):3021-4. doi: 10.1074/jbc.275.5.3021.
- Cooperman SS, Meyron-Holtz EG, Olivier-Wilson H, Ghosh MC, McConnell JP, Rouault TA. Microcytic anemia, erythropoietic protoporphyria, and neurodegeneration in mice with targeted deletion of iron-regulatory protein 2. *Blood*. 2005;106(3):1084-91. doi: 10.1182/blood-2004-12-4703.
- Means RT. Iron Deficiency and Iron Deficiency Anemia: Implications and Impact in Pregnancy, Fetal Development, and Early Childhood Parameters. *Nutrients*. 2020;12(2):447. doi: 10.3390/nu12020447.
- Igbinosa I, Berube C, Lyell DJ. Iron deficiency anemia in pregnancy. *Curr Opin Obstet Gynecol*. 2022 34(2):69-76. doi: 10.1097/GCO.0000000000000772.
- Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2014;123(5):615-24. doi: 10.1182/blood-2013-06-508325.
- Muñoz M, Gómez-Ramírez S, Kozek-Langenecker S, Shander A, Richards T, Pavía J, et al. 'Fit to fly': overcoming barriers to preoperative haemoglobin optimization in surgical patients. *Br J Anaesth*. 2015;115(1):15-24. doi: 10.1111/anae.13304.
- Percy L, Mansour D, Fraser I. Iron deficiency and iron deficiency anaemia in women. *Best Pract Res Clin Obstet Gynaecol*. 2017;40:55-67. doi: 10.1016/j.bpobgyn.2016.09.007.
- Elmore C, Ellis J. Screening, Treatment, and Monitoring of Iron Deficiency Anemia in Pregnancy and Postpartum. *J Midwifery Womens Health*. 2022;67(3):321-31. DOI: 10.1111/jmwh.13370
- Cetin I, Passoni D, Laoreti A. Nutritional challenges during pregnancy. *Ital J Gynaecol Obstet*. 2022;34(3):202-15. doi: 10.36129/jog.2021.08.
- Belpiede A, Tinelli A, Crescini C, Stark M, Losito A, Cassetta R, et al. Post-partum hemorrhage: can it be prevented by assisting the natural physiological process? *Ital J Gynaecol Obstet*. 2021;33(2):110-9. doi: 10.36129/jog.33.02.05.



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The relationship of perceived social support with sexual satisfaction and marital commitment in Iranian married women

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ABSTRACT

Objective. Perceived social support is another effective factor in sexual satisfaction and marital commitment. This study aimed to determine the relationship of perceived social support with sexual satisfaction and marital commitment in Iranian married women in 2022.

Materials and Methods. This cross-sectional study was conducted on 330 women who attended the Women's Healthcare Clinic in Iran from June to December 2022. The questionnaires were Larsson sexual satisfaction and marital commitment Adams and Sarason's Perceived Social Support were assessed. Data were analysed using Pearson, independent t, one-way ANOVA tests, and descriptive statistics.

Results. The mean age of women was 27.45 ± 5.77 years. There was a significant correlation of perceived social support with sexual satisfaction and marital commitment ($p < 0.01$, $r = 0.678$). An adjusted general linear model showed a significant statistical relationship of perceived social support with sexual satisfaction (B: 0.7; 95%CI 0.6-0.8; $p < 0.001$), and marital commitment (B: 0.3; 95%CI 0.2-0.4; $p < 0.001$).

Conclusions. Women with more perceived social support levels had higher sexual satisfaction and marital commitment. Therefore, health planners should adopt strategies to increase perceived social support, sexual satisfaction and marital commitment in married women.

INTRODUCTION

Marital commitment is strongest and the vast majority stable foreseeing component from claiming personal satisfaction and soundness of a marriage [1]. When couples require whole deal perspectives also, they settle on sacrifices with the individual relationship. They settle on every attempt ought to stay with likewise strengthen their bonds also they

remain wedded in reality setting of this purpose when fizzles [2]. There might be a join between higher levels of matrimonial commitment, extra need expression, higher flexible and reliability to matrimonial relationship, better issue comprehending abilities, in addition to matrimonial commitment. Additionally, more levels matrimonial guarantee are joined with matrimonial exhaustion. Furthermore, as commitment levels increase in marriage,

there is no risk of marital exhaustion. It seems like the commitment of both partners and additional guarantees will strengthen the relationship and potentially lead to a successful partnership [3]. Despite several investigations, compelling reason has been guided to Iranian amount to be illustrated. This research might be supportive to distinguish a few factors influencing sexual satisfaction. Moving forward, this consciousness might convince social insurance suppliers to create context-based, project to tend to conjugal satisfaction; thereby, higher conjugal fulfilment might lead with crew dependability. Perceived social support is another effective factor in sexual satisfaction and marital commitment [4]. It can be defined as the presence or availability of reliable friends. Those who let us know they care about, envalue and love us [6]. Perceived social support emphasizes the availability and quality of relationship with people who provides us with supportive necessary resources. It consists of emotional, instrumental and informational support [7]. Its existence helps individuals maintain physical health, improves the adjusting and treating of illness, and reduces psychiatric symptoms. It also helps an individual to deal with the anxiety and loneliness following the death of a family member [2]. Couples can reduce stressful events in life or prevent them through perceived social support. It creates positive reinforcement and a sense of belonging and enhances satisfaction in marriage and life. This support acts as a shield or buffer against environmental stresses such as marital issues and loss. Those receiving perceived social support in their marriage are less prone to physical and psychological issues and experience more marital commitment [8, 9]. The quality of sexual relations, the satisfaction level in such relations, and marital commitment are crucial factors in the family and society's health. We found no previous study on the relationship between perceived social support with sexual satisfaction and marital commitment. This study aimed to determine the relationship between perceived social support and both sexual satisfaction and marital commitment in married females referring to health centres in Iran.

MATERIALS AND METHODS

This is a descriptive-analytical cross-sectional study on 330 married women of reproductive referring to health centres in Iran in 2022.

Inclusion criteria

- Married women of 15-49 years.
- Having a tendency to participate in the study.
- Being Iranian.

Exclusion criteria

- Women during breastfeeding.
- Menopausal women.
- Pregnant women.
- Consumption of hormonal drugs.

Ethical approval (IR.TRJUMS.REC.1402.006) for this study was gained from the research Ethics Committee at Iran. Before the enrolment, an informed consent was obtained from all the participants.

The sample size was calculated based on study on perceived social support for women of reproductive age [20]. According to the formula, the sample size was 300, and, by adding 10% for dropouts, the sample size was increased to 330:

$$n = [(Z1 - \alpha/2)^2 \times (P \times q)] / d^2 = 0.895/0.003 = 298.33 \sim 330$$

where:

$$Z1 = 1.96$$

$$\alpha = 0.05$$

$$P = 0.63$$

$$q = 0.37$$

$$d = 0.1 \times P$$

This cross-sectional study was conducted using a convenience sampling method on 330 women. In each selected centre, the appropriate number of samples was calculated as a fraction of the total sample size according to the centre's demographics (number of married female clients of the centre between 15 and 49 years old). The researcher contacted people using their filled contact numbers and gave them a brief explanation of the reasons of the research, the workflow, and the methods. Individuals were evaluated by inclusion and exclusion criteria in the same call. The eligible ones were asked to attend the corresponding health centre on a certain date and time to fill out the questionnaires. The visiting people were provided with comprehensive information regarding the research necessity, benefits, results, workflow, and confidentiality of information. They were then asked to fill out a consent form. Finally, data were collected through study questionnaires via interviews with participants. The instruments for this study are: the socio-demographic character-

istics questionnaire, the Marital Commitment Adams Questionnaire, Marital Commitment Adams scale and The Larsson sexual satisfaction scale.

This consists of questions about age, duration of the marriage, education level, women's job, husband's job, the adequacy of household income, place of residence, marital commitment, and the number of children.

Marital commitment Adams (1997) standard questionnaire was applied. This questionnaire covers three aspects of personal commitment (questions 4, 8, 10, 11, 14, 16, 18, 21, 24, 25, 27, 28, 31, 32, 35, 36, 38, 44), moral commitment (questions 6, 9, 13, 20, 22, 23, 26, 29, 30, 34, 37, 41) and structural commitment (questions 5, 7, 12, 15, 17, 19, 33, 39, 40, 42, 43) and consists of 44 questions. 5-level Likert spectrum is used to answer the questions, with 1 being very little and 5 being very much. Most of the items of the questionnaire are scored directly, but questions 11, 12, 16, 23, 28, 29, 30, 32, 34, 35, 36, 38 are scored in reverse order. The general scoring range is between 1 and 172, and the higher scores show higher levels of marital commitment. The instrument's Cronbach's alpha and Interclass Correlation Coefficient (ICC) were 0.84 and 0.9, respectively [20].

The questionnaire contains 25 questions with quintuple-choice answers based on a Likert scale of 1-5 scores. Scores of 25-50, 51-75, 76-100, and 101-125 denote zero, low, intermediate, and high sexual satisfaction levels, respectively. The Cronbach's alphas for perceived social support, sexual satisfaction, and marital commitment were 0.82, 0.92, and 0.95, respectively.

Data collected by questionnaires were entered into SPSS ver. 22. Quantitative and qualitative variables were reported using mean (SD: standard deviation), and frequency (percentage) indices, respectively. The normality of the data was measured using kurtosis and skewness. All the data were normally distributed. Pearson correlation test was used for the univariate analysis of the relationships between perceived social support, and both marital commitment and sexual satisfaction, and a general linear model adjusted by socio-demographic information was used for the multivariate analysis. The socio-demographic variables that had a relationship with marital commitment or sexual satisfaction were entered into the model as possible confounders ($p < 0.2$). A P-value less than 0.05 was considered statistically significant.

RESULTS

The mean (SD) of participants' age and marriage durations were 36.1 (10.7) and 14.3 (9.5). A little more than half of them (50.7%) were high school graduates and most of their husbands were either college graduates (48.3%) or high school graduates (43.2%). The reported occupation of about half of their husbands was self-employment (48.3%) and the reported household income was somewhat sufficient (70.2%). Nearly half of them (44.5%) had two or more children and were somewhat satisfied with their marriage (62.3%).

There was a significant correlation between sexual satisfaction with age ($p = 0.659$) and marriage duration ($p = 0.830$). According to one-way ANOVA results, mean sexual satisfaction and marital commitment scores were significantly associated with the woman's and husband's education ($p < 0.05$), husband's occupation, household income and place of residence ($p < 0.001$) (B: 0.4; 95%CI 0.2-0.4; $p < 0.001$) (Table 1). The mean (SD) of scores for perceived social support, sexual satisfaction, and marital commitment was 100 (18.8), 50.2 (18.5), and 145.9 (11.8), respectively. The score ranges for the same variables were 25-175, 0-100, and 40-160, respectively. Perceived social support had an average positive correlation with marital commitment ($p < 0.001$; $r = 0.57$) and a good positive correlation with sexual satisfaction ($p < 0.001$; $r = 0.83$) (B: 0.4; 95%CI 0.2-0.4; $p < 0.001$) (Table 2).

In order to determine the relationship between perceived social support and marital commitment based on the general linear model with the adjustment of basic characteristics, the variables of the woman's education, husband's education and occupation, family income, and place of residence were entered into the model. Perceived social support and marital commitment were significantly related after this adjustment ($p < 0.001$). An increase in the perceived social support score would increase the marital commitment score (B: 0.4; 95%CI 0.2-0.4; $p < 0.001$) (Table 3). The variables including the woman's age and education, marriage duration, husband's education and occupation, household income, and place of residence entered into the model in order to determine the relationship between perceived social support and sexual satisfaction based on the general linear model. There was a significant relationship between sexual satisfaction and perceived social support ($p < 0.001$). An increase in the perceived social support score

Table 1. Demographic characteristics of women and their relationship perceived social support with sexual satisfaction and marital commitment in Iranian women.

| Characteristics | Number (Percent) or Mean (SD) | Sexual satisfaction Mean (SD) | P-value | Marital commitment Mean (SD) | P-value |
|---|-------------------------------|-------------------------------|----------------------|------------------------------|----------------------|
| Age (years) | 35.1 (10.7) ^a | 0.03 ^a | 0.659 ^b | 0.08 ^a | 0.254 ^b |
| Marriage age (month) | 11.3 (9.5) ^a | 0.01 ^a | 0.830 ^b | 0.05 ^a | 0.282 ^b |
| Women's educational level | | | 0.014 ^c | | 0.003 ^c |
| Illiterate and Primary | 14 (4.24) | 36.4 (16.2) | | 133.0 (6.6) | |
| Secondary school | 12 (6.68) | 43.6 (17.5) | | 129.8 (6.7) | |
| High school | 30 (9.09) | 48.0 (21.8) | | 9.9))130.0 | |
| Diploma | 167 (50.6) | 53.2 (19.2) | | 135.5 (12.0) | |
| University | 97 (29.39) | 54.5 (18.9) | | 138.9 (11.9) | |
| Husband's education level | | | 0.004 ^c | | 0.025 ^c |
| Primary and Secondary school | 7 (2.4) | 34.9 (14.9) | | 135.7 (12.4) | |
| High school | 18 (6.2) | 55.7 (19.8) | | 134.2 (10.1) | |
| Diploma | 126 (43.2) | 49.0 (19.8) | | 133.8 (11.7) | |
| University | 179 (54.24) | 55.4 (18.5) | | 135.9 (11.8) | |
| Women's occupation | | | 0.111 ^d | | 0.114 ^d |
| Housewife | 197 (59.69) | 50.5 (18.9) | | 135.1 (11.5) | |
| Employed | 133 (45.5) | 54.2 (19.9) | | 136.8 (12.1) | |
| Husband's occupation | | | < 0.001 ^c | | < 0.001 ^c |
| Unemployed | 28 (9.6) | 41.2 (16.4) | | 130.7 (8.7) | |
| Employee | 93 (31.8) | 54.6 (19.9) | | 138.9 (11.6) | |
| Worker | 30 (10.3) | 42.6 (18.6) | | 128.3 (9.3) | |
| Self-employment | 179 (54.24) | 54.7 (18.6) | | 136.5 (12.0) | |
| Sufficiency of income for family expenses | | | < 0.001 ^c | | < 0.001 ^c |
| Sufficient | 23 (7.9) | 62.8 (13.6) | | 143.4 (9.3) | |
| Somewhat sufficient | 205 (70.2) | 55.7 (18.4) | | 137.3 (11.9) | |
| Insufficient | 102(30.90) | 36.9 (16.5) | | 128.4 (8.6) | |
| Place of residence | | | < 0.001 ^c | | < 0.001 ^c |
| Private house | 91 (31.2) | 58.2 (16.0) | | 140.4 (12.3) | |
| Rented house | 120 (41.1) | 51.8 (19.5) | | 135.4 (11.3) | |
| The house of the woman's parents | 87 (26.36) | 44.6 (21.8) | | 132.0 (9.4) | |
| The house of the husband's parents | 32 (11) | 47.7 (20.4) | | 130.7 (11.4) | |
| Satisfaction with married life | | | < 0.001 ^c | | < 0.001 ^c |
| Completely satisfied | 18 (6.2) | 66.6 (10.0) | | 145.7 (10.0) | |
| Somewhat satisfied | 220 (66.66) | 60.15 (15.6) | | 139.3 (10.6) | |
| Dissatisfied | 92 (31.5) | 33.5 (13.6) | | 127.2 (9.2) | |
| The number of children | | | 0.898 ^c | | 0.393 ^c |
| 1 | 100 (34.2) | 52.42(19.9) | | 136.6 (10.7) | |
| 2 | 168 (50.9) | 52.43(20.0) | | 134.9 (12.5) | |
| 3 ≤ | 62 (21.2) | 51.1(18.0) | | 136.6 (12.1) | |

^aMean (SD); ^bcorrelation coefficient; ^cPearson correlation test; ^done-way ANOVA; ^eindependent t-test.

Table 2. Correlation of perceived social support with marital commitment and sexual satisfaction.

| Variable | Mean (SD) | Obtained score range | Obtainable score range | Correlation with perceived social support ^a r (^b P-value) |
|--------------------------|--------------|----------------------|------------------------|--|
| Perceived social support | 100.0 (18.8) | 57 to 141 | 25 to 175 | - |
| Sexual satisfaction | 50.2 (18.5) | 4 to 89 | 0 to 100 | 0.78 (< 0.001) |
| Marital commitment | 145.9 (12.8) | 101 to 166 | 40 to 160 | 0.59 (< 0.001) |

^aCorrelation coefficient; ^bPearson correlation test.

would increase the sexual satisfaction score (B: 0.7; 95%CI 0.6-0.8; $p < 0.001$) (Table 4).

Table 3. Relationship of perceived social support with marital commitment based on the general linear model.

| Variable | β (95%CI) | P-value* |
|--------------------------|------------------|----------|
| Perceived social support | 0.4 (0.2 to 0.4) | < 0.001 |

*Statistically significant < 0.001.

Table 4. Relationship of perceived social support with sexual satisfaction based on the general linear model.

| Variable | β (95%CI) | P-value* |
|--------------------------|------------------|----------|
| Perceived social support | 0.8 (0.6 to 0.8) | < 0.001 |

*Statistically significant < 0.001.

DISCUSSION

This study aimed to determine the relationship between perceived social support and both marital commitment and sexual satisfaction in married women referring to health centres in Iran. The results indicates that the mean perceived social support and marital commitment scores of participants are high, and sexual satisfaction is average. The positive correlation is moderate between perceived social support and marital commitment, and good between perceived social support and sexual satisfaction. An adjusted general linear model showed a significant relationship between perceived social support and both sexual satisfaction and marital commitment.

The study demonstrated a significant statistical correlation between perceived social support and marital commitment. Theoretical models of perceived social support emphasize the priority of support received from spouses to improve marital performance [25]. Such support acts as a psychological distress alleviation tool in couples' relationships. It is correlated negatively with depression and anxiety and positively with marital adjustment [19]. Supportive measures initiate several cognitive and emotional development in couples. These developments enhance the marital relationship and prevent marital conflict, distress, and deterioration [26]. Our findings are consistent with Rafiee *et al.*'s [27] results, showing that lifestyle and perceived social support predict marital commitment in the elderly. Khodabakhshi *et al.* [28] results also indicated a positive significant correlation between family, friends, and other people's perceived social support components

and sexual satisfaction [28]. Abbasi *et al.* [19] observed a significant correlation between perceived social support and marital commitment in nurses. Marital commitment also increases with the husband's support, as the most significant source, in mothers suffering breast cancer (Baheiraei *et al.*'s [20] study).

Our study also showed a positive correlation between sexual satisfaction and marital commitment. Marital commitment components are personal (such as affection expression by the spouses toward each other), environmental (such as equative decision-making and financial income management and sharing tasks and issues) [25]. According to existing studies, the couples' ability to express sexual desire is one of the most effective factors in sexual function and marital commitment [29]. Peixoto and Lopes [30] confirmed that lower sexual satisfaction can cause marital despair. It is mostly due to the more frequent sexual relations of women who share their sexual desires and feelings with their husbands and have high sexual intimacy with them. This leads to improved marital commitment [15]. According to Lee *et al.* [31], lack of sexual satisfaction in female university students was a predictive factor for not being maritally satisfied. Woerner and Abbey [32] observed that couples' sexual satisfaction could predict sexual pleasure. This is associated with positive emotions in marital relationships. Dehghani Champiri and Dehghani [5] in a cross-sectional study also indicated a positive correlation between marital commitment and sexual satisfaction in married women and men. In Shampour *et al.*'s [33] interventional study, providing sexual counselling increased sexual satisfaction, which in turn improved the couples' marital commitment.

Healthy sexual relations and desires positively affect marital commitment. This enhances mental health and creates healthy families. Extensively, promoting sexual satisfaction education, particularly in societies where women generally suffer low sexual satisfaction and patriarchal gender stereotypes prevail – including many Asian countries such as Iran – seems essential [33, 34].

Accumulating evidence suggests that postpartum period and psychology are strongly associated with female sexual dysfunction (FSD). Also, pregnancy and the postpartum period are associated with sexual dysfunction in women. Both the health professionals (nurses/midwives) who su-

pervise the stages of pregnancy as well as health institutions should play their part in promoting this care [35, 36].

The experience of gynaecologic cancer and treatment with surgery, chemotherapy and/or radiation affects the sexual function and psychological well-being of patients [37, 38].

Women with provoked vestibulodynia (PVD) suffer from experiencing high levels of sexual dysfunction and associated distress, including difficulties with desire, arousal, orgasm and satisfaction [39].

One of the strengths of this study was that women of reproductive ages that were not pregnant, cancer, menopause, provoked vestibulodynia or lactating period were examined, because these situations could have different effects on sexual function. Therefore, it is suggested that effects of stress on sexual function in the mentioned groups can be studied.

This study was conducted only on women referred to public health clinics in Iran, so the results may not represent the entire population. Besides, because of the cultural and religious limitations in our society, people may not be able to speak easily about their sexual issues, so the potential insecurity of some people in expressing explicitly their issues was a limitation. Provoked vestibulodynia investigation is not done and was limitation of study.

CONCLUSIONS

This study showed a moderate positive correlation between perceived social support and marital commitment in married women referring to health centres. It also indicated a good positive correlation between perceived social supported sexual satisfactions in the same group.

Considering the importance of sexual satisfaction in the family and the impacts on marital commitment and satisfaction of couples, health policy makers and family counsellors should provide women with training strategies, so that they can take a step forward towards safe fertility.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

S.P. and Z.J. entirely contributed to this work.

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None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

All procedures performed on human samples were conducted following the relevant guidelines and regulations of the Helsinki Declaration. The study protocol was approved by the Research Ethics Committee in Iran.

Informed consent

Written informed consent was obtained from the participants for the publication of this research.

Data sharing

Data are available under reasonable request to the corresponding author.

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REFERENCES

1. Halajian Z, Babakhani V, Pooyamanesh J, Jafari A. Comparison of the effectiveness of couple therapy based on acceptance and commitment and couple therapy based on guttman method on marital commitment. *J Psychol Sci.* 2022;21(115):1485-501. doi: 10.52547/JPS.21.115.1485.
2. Gharlipour Z. Relationship of sexual satisfaction with spiritual health and demographic characteristics in women referring to health centers in

- Qom. *Health Spiritual Med Ethics*. 2020;7(4):1-7. doi: 10.52547/jhsme.7.4.1.
3. Ghorbani B, Shahnazari M, Hosseindoust SS, Sehat Z. Predicting Home Violence, According to Perceived Social Support and Marital Satisfaction for Infertility Women in Tehran, Iran. *JSBCH*. 2022;6(2):920-31. doi: 10.18502/jsbch.v6i2.11143.
 4. Esfandiyari Baghbemidi F, Hajjalizadeh K, Amirfakhraei A. The Relationship between Family Function, Marital Function and Perceived Social Support of Mothers with their Child Abuse Mediated by Anxiety. *Iran Evol Psychol J*. 2022;4(1):84-91. doi: 10.52547/ieepj.4.1.84.
 5. Dehghani Champiri F, Dehghani A. Predicting sexual satisfaction in Iranian women by marital satisfaction components. *Sex Relation Ther*. 2020;38(7):1-15. doi: 10.1080/14681994.2020.1736279.
 6. Otero MC, Wells JL, Chen KH, Brown CL, Connelly DE, Levenson RW, Fredrickson BL. Behavioral indices of positivity resonance associated with long-term marital satisfaction. *Emotion*. 2020;20(7):1225-33. doi: 10.1037/emo0000634.
 7. Seyyedzadeh-Aghdam N, Chizari M, Vakilian K, Ranjbarvar M. Prognostic factors of sexual dysfunction in women in Tehran. *J Mazandaran Univ Med Sci*. 2016;26(144):361-57.
 8. Asadi E, Mansour L, Khodabakhshi A, Fathabadi J. The relationship between couple burnout, sexual satisfaction, and sexual dysfunctional beliefs in women with diabetic husbands and comparing them with women with non-diabetic husbands. *J Fam Res*. 2013;9(3):311-24.
 9. Hatfield EC, Luckhurst C, Rapson RL. Sexual motives: The impact of gender, personality and sexual motives on sexual behavior-especially risky sexual behavior. *Interpersona*. 2011;5(2):95-133. doi: 10.5964/ijpr.v5i2.60.
 10. Santos-Iglesias P, Sierra JC, Vallejo-Medina P. Predictors of sexual satisfaction: The role of sexual desire, Attitudes and partner abuse. *Arch Sex Behav*. 2013;42(6):1043-52. doi: 10.1007/s10508-012-9998-3.
 11. Zhang H, Xie L, Lo SST, Fan S, Yip P. Female sexual assertiveness and sexual satisfaction among Chinese couples in Hong Kong: A dyadic approach. *The J Sex Res*. 2022;59(2):203-11. doi: 10.1080/00224499.2021.1875187.
 12. Seyedzadeh-Aghdam N, Chizari M, Vakilian K, Ranjbaran M. Predictors of female sexual self-disclosure in Tehran. *J Mazandaran Univ Med Sci*. 2017;26(144):357-61.
 13. Mallory AB. Dimensions of couples' sexual communication, relationship satisfaction, and sexual satisfaction: A meta-analysis. *J Fam Psychol*. 2021;36(3):358-71. doi: 10.1037/fam0000946.
 14. Rahnema P, Hidarnia A, Shokravi FA, Kazemnejad A, Oakley D, Montazeri A. Why Iranian married women use withdrawal instead of oral contraceptives? A qualitative study from Iran. *BMC Public Health*. 2010;10:289. doi: 10.1186/1471-2458-10-289.
 15. Hurlbert DF. The role of assertiveness in female sexuality: A comparative study between sexually assertive and sexually nonassertive women. *J Sex Marital Ther*. 1991;7(3):183-90. doi: 10.1080/00926239108404342.
 16. Sarason IG, Levine HM, Basham RB, Sarason BR. Assessing perceived social support: The perceived social support questionnaire. *J Pers Soc Psychol*. 1983;44(1):127-39. doi: 10.1037/0022-3514.44.1.127.
 17. Peterson SJ, Bredow TS. *Middel Range Theoris Application to Nursing Research*. Lippincott, Williams. 2004.
 18. Kazim SM, Rafique R. Predictors of marital commitment in individualistic and collectivist cultures: a mini review. *J Res Psychol*. 2021;3(1):55-67. doi: 10.31580/jrp.v3i1.1958.
 19. Abbasi G, Montazar A. The relationship between appreciation, sense of humor and perceived social support with marital commitment in nurses. *J Health Care*. 2019;21(1):34-43. doi: 10.29252/jhc.21.1.34.
 20. Baheiraei A, Mirghafourvand M, Mohammadi E, Charandabi SM, Nedjat S. Perceived social support for women of reproductive age and its predictors: a population-based study. *BMC Womens Health*. 2012;12(1):1-7. doi: 10.1186/1472-6874-12-30.
 21. Weinert C, Brandt P. Measuring perceived social support with the PRQ. *West J Nurs*. 1987;9:589-602.
 22. Yousefi N, Farsani K, Shakiba A, Hemmati S, Nabavi Hesar J. Halbert Index of Sexual Desire (HISD) Questionnaire Validation. *Clin Psychol Personal*. 2014;2:107-18. doi: 20.1001.1.23452188.1392.11.2.12.0.
 23. Olson DH. Prepare/Enrich. *Encyclopedia of Couple and Family Therapy*. 2019;2305-9. doi: 10.1007/978-3-319-49425-8_402.
 24. Bafrani MA, Nourizadeh R, Hakimi S, Mortazavi SA, Mehrabi E, Vahed N. The Effect of Psychological Interventions on Sexual and Mar-

- ital Satisfaction: A Systematic Review and Meta-Analysis. *Iran J Public Health*. 2023;52(1):49-63. doi: 10.18502/ijph.v52i1.11666.
25. Dehle C, Landers JE. You can't always get what you want, but can you get what you need? Personality traits and perceived social support in marriage. *J Soc Clin Psychol*. 2005;24(7):1051. doi: 10.1521/jscp.2005.24.7.1051.
 26. Okoh E, Edu E, Elizabeth O. Relationship between spousal support and marital commitment among married bank female workers in consolidated banks in Warri metropolis. *J Emerg Trends Ed Res Pol Stud*. 2015;6(6):432-38.
 27. Rafiee S, Toozandehjani H, Ahooei MR. Relationship of lifestyle and perceived social support with marital commitment of elderly. *Iranian J Ageing*. 2016;11(2):226-33. doi: 10.21859/sija-1102226.
 28. Khodabakhshi-Koolaei A, Mirafzal NS. Relationship between humor and perceived social support with sex satisfaction in elderly married women. *J Gerontol*. 2017;2(2):1-10. doi: 10.29252/joge.2.1.1.
 29. Saadat M, Ansari-Lari M, Farhud DD. Consanguineous marriage in Iran. *Ann Hum Biol*. 2004;31(2):263-9. doi: 10.1080/03014460310001652211.
 30. Peixoto MM, Lopes J. Solitary and dyadic sexual desire and sexual satisfaction in women with and without sexual concerns. *J Sex Marital Ther*. 2023;49(1):77-87. doi: 10.1080/0092623X.2022.2077271.
 31. Lee JY. Predictors of female college students' relationship satisfaction: attachment and sexual satisfaction. *Psychol Stud*. 2017;62(1):70-4. doi:10.1007/s12646-017-0389-7.
 32. Woerner J, Abbey A. Positive feelings after casual sex: The role of gender and traditional gender-role beliefs. *J Sex Res*. 2017;54(6):717-27. doi: 10.1080/00224499.2016.1208801.
 33. Shampour S, Heidari H, Zanganeh F, Davoodi H. The effectiveness of integrated couple therapy training on commitment, intimacy, individual and interpersonal forgiveness in couples with marital boredom. *JPPW*. 2022;6(1):1273-80.
 34. Jalambadani Z. Education based on the Trans-Theoretical Model on sexual function of married women in Iran. *Ital J Gynaecol Obstet*. 2022;34(4):254-61. doi: 10.36129/jog.2022.23.
 35. Hidalgo-Lopezosa P, Pérez-Marín S, Jiménez-Ruz A, López-Carrasco JC, Cubero-Luna AM, García-Fernández R, et al. Factors associated with postpartum sexual dysfunction in Spanish women: A cross-sectional study. *J Personalized Med*. 2022;12(6):926. doi: 10.3390/jpm12060926.
 36. Laganà AS, Burgio MA, Ciancimino L, Sicilia A, Pizzo A, Magno C, et al. Evaluation of recovery and quality of sexual activity in women during postpartum in relation to the different mode of delivery: a retrospective analysis. *Minerva Ginecol*. 2015;67(4):315-20.
 37. Vitale SG, La Rosa VL, Rapisarda AMC, Laganà AS. Fertility preservation in women with gynaecologic cancer: the impact on quality of life and psychological well-being. *Hum Fertil (Camb)*. 2018;21(1):35-8. doi: 10.1080/14647273.2017.1339365.
 38. D'Oria O, D'Auge TG, Baiocco E, Vincenzoni C, Mancini E, Bruno V, et al. The role of preoperative frailty assessment in patients affected by gynecological cancer: A narrative review. *Ital J Gynaecol. Obstet*. 2022;34(2):76-83. doi: 10.36129/jog.2022.34.
 39. De Seta F, Stabile G, Antoci G, Zito G, Nappi RE. Provoked Vestibulodynia and Topical Treatment: A New Option. *Healthcare (Basel)*. 2022;10(5):830. doi: 10.3390/healthcare10050830.



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Assessment of the long Pentraxin 3 level in polycystic ovarian syndrome-related infertility

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ABSTRACT

Objective. To evaluate the role of Pentraxin 3 level in polycystic ovarian syndrome (PCOS)-related infertility and its correlation with the disease's hormonal profile.

Patients and Methods. A case-control study involves a total of 90 women for one year, 30 women diagnosed with PCOS who are fertile, 30 women diagnosed with PCOS who are infertile, and 30 healthy controls; all women in the early follicular phase were sent for baseline investigations: FSH, LH, AMH, fasting blood sugar, insulin, testosterone, TSH, and Pentraxin 3 that were measured by sandwich electrochemiluminescence immunoassay.

Results. There were statistically significant variations in LH, LH/FSH ratio, testosterone levels, and AMH across the groups. The mean of Pentraxin for the fertile PCOS group (4.14 ± 1.97) ng/mL was significantly higher than for the infertile PCOS group (1.39 ± 1.10 ng/MI) and control (1.99 ± 1.66 ng/mL). For the infertile PCOS group, the correlation of Pentraxin was significantly positive with age and negative with AMH. ROC Curve analysis showed a cutoff value of 1.05 ng/ml with a sensitivity of 46.67% and specificity of 83.33% for the infertile group.

Conclusions. Pentraxin 3 level is significantly higher in fertile PCOS patients and lower in the infertile PCOS group in comparison to the control group suggesting its possible role in PCOS-related infertility.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is among the common endocrinopathies seen in females and is manifested with hyperandrogenism, oligo-ovulation, and polycystic ovaries on ultrasound examination with established long-term metabolic disorders [1]. The main underlying pathology is not fully understood for which the researchers postulated many possible theories underlying its aetiology as the microcystic ovarian inflammation theory, the ovarian congestion theory, and the ovarian dystrophy theory, with possible morphological

changes expressed as thick ovarian struma that is reflected in its endocrine function [2].

The ovarian folliculogenesis is disrupted with consequent abnormal recruitment of the follicles resulting from inadequate follicle stimulating hormone production and local action with excessive Antimullerian hormone and other factors mediating follicular growth a fact that differentiates PCOS from other pathologies leading to ovarian dysfunction [3].

A meta-analysis described four phenotypes of this syndrome depending on the presenting complaints as phenotype A: the full PCOS picture in-

cluding hyperandrogenism, oligo-ovulation, and polycystic ovarian ultrasound morphology; phenotype B: hyperandrogenism and oligo-ovulation; phenotype C: hyperandrogenism and polycystic ovarian ultrasound morphology; phenotype D: oligo-anovulation and polycystic ovarian ultrasound morphology [4].

Investigating its pathogenesis is paramount, which may help in the treatment, as the available treatment till now is directed towards the symptomatology rather than the disease process itself. Among the inflammatory markers studied in PCOS, the long Pentraxin 3 (PTX3) was chosen to be evaluated in the current study, as it is a multifunctional glycoprotein implicated in innate immunity response, regulation of inflammation, angiogenesis and formation and remodelling of the extracellular matrix [5].

The PTX3 is released by white blood cells and myeloid dendritic cells following stimulation with pro-inflammatory cytokines (Interleukin-1 and Tumour necrosis factor- α), agonists of toll like receptors, or microbial components [6]. The production is also stimulated in myeloid cells by the anti-inflammatory cytokine interleukin-10, which is essential for suppressing inflammation and minimizing tissue damage. Human neutrophils store PTX3 in lactoferrin-positive granules and rapidly release them at the inflammatory site. Additionally, it is produced in many body cells, such as muscles, fibrous tissues, fatty tissues, cartilage, and ovarian tissue, due to its potential role in modulating the inflammatory reaction by binding elements of the complement cascade and regulating complement activation [7]. PTX3 is specifically expressed by the cumulus cells in the ovary, following the Luteinizing hormone or human chorionic gonadotropin stimulation of pre-ovulatory follicles [8].

The presence of PTX3 in the cumulus matrix and in the follicular fluids aspirated from *in vitro* fertilization cases suggest its role in human female fertility [9].

The study aims to evaluate the role of PTX3 level in PCOS-related infertility and to determine its correlation with the disease's hormonal profile.

MATERIALS AND METHODS

This is a case-control study conducted at the Department of Obstetrics and Gynaecology of Al-Yarmouk Teaching Hospital; the study was

conducted for one year, for January 2022 to December 2022.

Inclusion criteria

Of the total women involved in the study (Iraqi women accessed to AL Yarmouk teaching hospital in Baghdad), ninety were assigned as:

- Fertile PCOS group: thirty women diagnosed with polycystic ovary syndrome according to Rotterdam's criteria [4] who are fertile corresponding to phenotype C [10].
- Infertile PCOS group: thirty women diagnosed with polycystic ovary syndrome according to Rotterdam's criteria [4] who are Infertile corresponding to phenotype B [10].
- Control group: thirty healthy women who are ovulating with normal ovarian morphology, matched for the age (mean age 27-28 years) and Body mass index (BMI) with PCOS groups.

After obtaining informed consent from all participants, a physical examination was performed, including general weight and height estimation, to calculate BMI and features of androgen excess.

All women in the early follicular phase of their menstrual cycle were subjected to blood sampling of three milliliters of venous blood in the morning between 8:00 and 9:00 am after overnight fasting state and had been sent for baseline investigations, including: luteinizing hormone (LH), follicle stimulating hormone (FSH), insulin, fasting blood sugar (FBS), Antimullerian hormone (AMH), testosterone, prolactin, thyroid stimulating hormone (TSH), and the long Pentraxin 3. These parameters were analysed using sandwich electrochemiluminescence immunoassay "ECLIA".

Exclusion criteria

Pregnancy, endocrine disorders, chronic diseases, drugs, smoking, alcohol intake, and other causes of infertility such as tubal and male factors were considered as exclusion criteria.

Study registration, ethical and methodological standards

The protocol was approved by the Mustansiriyah Scientific Council of Obstetrics and Gynaecology / Iraq MOG-107 in DEC 2021; written informed consent was taken from all participants following the Declaration of Helsinki and local guidelines.

Statistical analysis

Analysis of data was explained using descriptive statistics: mean, standard deviation, standard error of the mean, median, minimum, and maximum. ANOVA Test was used to determine the difference in means among the groups. T-test was used to compare paired groups.

To assess the quality of the correlation using Pearson's method, small effect sizes were defined as correlation coefficients (r) between 0.10 and 0.29, moderate effect sizes as coefficients between 0.30 and 0.49, and large effect sizes as coefficients above 0.50.

ROC curve comparison of Pentraxin, AMH, and LH/FSH ratio as they differentiate between the study groups, the P-value was significant if less than 0.05.

RESULTS

The demographic, biochemical, and hormonal characteristics of the study groups are clarified in **Table 1**.

Age and BMI showed no statistically significant variations as the groups were matched for these

Table 1. Summary statistics table for demographic, biochemical, and hormonal variables by groups.

| Variable | Groups (number) | Mean | SD | SEM | Median | Min | Max | P-value |
|--------------------------|---------------------|--------|-------|------|--------|--------|--------|---------|
| Age (years) | Control (30) | 27.20 | 5.05 | 0.37 | 23.45 | 18.70 | 27.4 | 0.14 |
| | Fertile PCOS (30) | 28.21 | 4.83 | 0.91 | 28.00 | 19.00 | 38.00 | |
| | Infertile PCOS (30) | 27.97 | 5.06 | 0.92 | 27.00 | 18.00 | 42.00 | |
| BMI (Kg/m ²) | Control (30) | 27.30 | 5.42 | 0.99 | 27.00 | 18.00 | 41.00 | 0.65 |
| | Fertile PCOS (30) | 28.61 | 6.09 | 1.15 | 27.50 | 18.00 | 41.00 | |
| | Infertile PCOS (30) | 27.50 | 5.6 | 1.02 | 26.50 | 20.00 | 39.00 | |
| LH (mIU/L) | Control (30) | 7.22 | 2.92 | 0.54 | 6.50 | 2.50 | 12.00 | < 0.001 |
| | Fertile PCOS (30) | 9.31 | 5.08 | 0.96 | 7.96 | 0.62 | 20.80 | |
| | Infertile PCOS (30) | 3.48 | 1.63 | 0.29 | 2.85 | 2.12 | 8.10 | |
| FSH (mIU/L) | Control (30) | 7.49 | 1.72 | 0.31 | 7.55 | 4.90 | 10.80 | < 0.001 |
| | Fertile PCOS (30) | 6.98 | 1.93 | 0.37 | 6.94 | 4.00 | 12.90 | |
| | Infertile PCOS (30) | 4.79 | 0.95 | 0.17 | 4.87 | 2.80 | 6.22 | |
| LH/FSH ratio | Control (30) | 1.05 | 0.56 | 0.11 | 0.86 | 0.32 | 2.24 | < 0.001 |
| | Fertile PCOS (30) | 1.37 | 0.72 | 0.14 | 1.30 | 0.11 | 2.76 | |
| | Infertile PCOS (30) | 0.74 | 0.31 | 0.06 | 0.62 | 0.38 | 1.48n | |
| Insulin(mIU/L) | Control (30) | 8.05 | 2.92 | 0.53 | 8.08 | 1.50 | 13.40 | 0.001 |
| | Fertile PCOS (30) | 25.49 | 24.78 | 4.68 | 18.00 | 6.16 | 104.80 | |
| | Infertile PCOS (30) | 22.78 | 22.35 | 4.08 | 15.71 | 3.71 | 121.10 | |
| FBS (mg/dl) | Control (30) | 101.40 | 12.82 | 2.34 | 98.00 | 82.00 | 120.00 | < 0.001 |
| | Fertile PCOS (30) | 113.43 | 12.36 | 2.33 | 115.50 | 90.00 | 142.00 | |
| | Infertile PCOS (30) | 114.23 | 6.13 | 1.12 | 114.50 | 102.00 | 129.00 | |
| AMH (ng/ml) | Control (30) | 5.90 | 1.35 | 0.25 | 5.70 | 4.10 | 9.20 | 0.080 |
| | Fertile PCOS (30) | 8.21 | 1.62 | 0.30 | 8.28 | 5.55 | 11.90 | |
| | Infertile PCOS (30) | 8.97 | 1.82 | 0.33 | 9.08 | 5.77 | 12.07 | |
| Testosterone (mIU/L) | Control (30) | 0.39 | 0.27 | 0.05 | 0.39 | 0.07 | 0.82 | < 0.001 |
| | Fertile PCOS (30) | 0.62 | 0.23 | 0.04 | 0.56 | 0.33 | 0.98 | |
| | Infertile PCOS (30) | 0.69 | 0.18 | 0.03 | 0.67 | 0.40 | 0.99 | |
| Prolactin (ng/ml) | Control (30) | 16.98 | 6.28 | 1.15 | 17.45 | 6.88 | 27.70 | < 0.001 |
| | Fertile PCOS (30) | 17.95 | 6.22 | 1.18 | 17.75 | 6.88 | 30.00 | |
| | Infertile PCOS (30) | 9.34 | 3.28 | 0.60 | 7.80 | 6.00 | 19.00 | |
| TSH (mIU/L) | Control (30) | 2.91 | 1.13 | 0.20 | 2.75 | 0.89 | 5.00 | 0.008 |
| | Fertile PCOS (30) | 2.94 | 1.02 | 0.19 | 2.95 | 1.60 | 5.00 | |
| | Infertile PCOS (30) | 2.23 | 0.69 | 0.13 | 1.92 | 1.20 | 4.00 | |

Results for testing the mean differences by groups using F-Tests; SD: Standard deviation; SEM: Standard error of the mean; Min and Max: Minimum and maximum respectively.

two variables to minimize their influence on the study results.

Concerning LH level, compared to the infertile group (3.48 ± 1.61 mIU/L), the control (7.22 ± 2.93 mIU/L) and the fertile group (9.31 ± 5.07 mIU/L) had significantly higher mean LH levels $p < 0.001$. While the mean FSH for infertile PCOS (4.79 ± 0.95 mIU/L) was lower than that of the control group (7.49 ± 1.71 mIU/L), the mean FSH for fertile PCOS (6.98 ± 1.95 mIU/L) was higher than that of the non-fertile PCOS group ($p < 0.01$).

LH/FSH ratio for the infertile PCOS group had an average of 0.74 ± 0.32 which is lower than the control group (1.05 ± 0.58) and for the fertile PCOS group (1.37 ± 0.74).

Insulin and FBS were significantly lower in the control group than in both PCOS groups.

The mean of AMH for the control (5.90 ± 1.36 ng/mL) was significantly lower than for the fertile PCOS group (8.21 ± 1.61 ng/mL) and for the infertile PCOS group (8.97 ± 1.83 ng/mL), as $p < 0.001$. Likewise, for testosterone, control subjects had a significantly lower mean (0.39 ± 0.25 ng/mL) than those in the fertile PCOS group (0.62 ± 0.20 ; $p = 0.001$ ng/mL) and then those infertile PCOS group (0.69 ± 0.16 ng/mL) ($p = 0.001$ for both comparisons).

Prolactin and TSH showed significant variations among the groups as P-value < 0.05 ; however, none exceeds the normal reference values.

Pentraxin levels were different among the groups (ANOVA; $p = 0.001$). Using the t-test, a pairwise comparison between groups was done. The mean of Pentraxin for the fertile PCOS group (4.14 ± 1.97 ng/mL) was significantly higher than both control (1.99 ± 1.66 ng/mL) ($p = 0.001$), and infertile PCOS group (1.39 ± 1.10 ng/mL) ($p = 0.001$). Infertile PCOS showed a non-significant lower value than

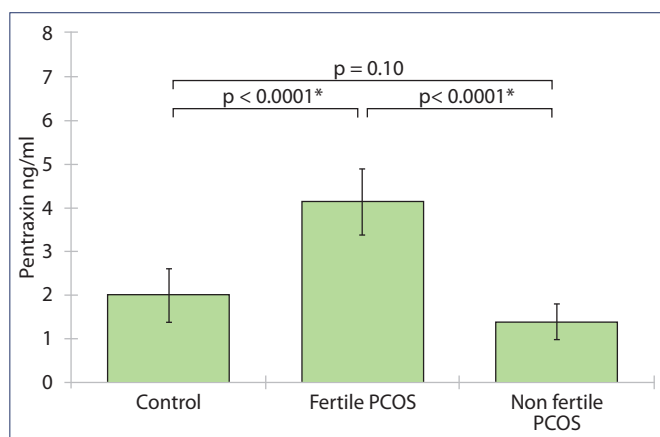


Figure 1. Means and confidence interval of Pentraxin for PCOS patients and control.

Table 2. Pearson correlation results of pentraxin 3 with age, BMI, LH, FSH, LH/FSH ratio, TSH, PRL, testosterone, AMH, FBS, and insulin in the infertile group.

| Variables | Pentraxin 3 n = 30 | | |
|--------------|-----------------------|-----------------------|--------------|
| | r | 95%CI | P-value |
| Age | 0.44 | 0.10-0.69 | 0.014 |
| BMI | -0.15 | -0.49-0.22 | 0.420 |
| LH | -0.08 | -0.42-0.29 | 0.689 |
| FSH | -0.02 | -0.38-0.34 | 0.917 |
| LH/FSH ratio | -0.08 | -0.43-0.29 | 0.676 |
| TSH | 0.30 | -0.07-0.60 | 0.107 |
| PRL | -0.13 | -0.47-0.24 | 0.485 |
| Testosterone | -0.01 | -0.37-0.35 | 0.949 |
| AMH | -0.39 | -0.66 to -0.04 | 0.031 |
| FBS | -0.01 | -0.37-0.35 | 0.953 |
| Insulin | -0.25 | -0.56-0.12 | 0.183 |

r: correlation confidence; CI: confidence interval.

the control group. The Pentraxin levels for PCOS patients and controls are shown in **Figure 1**.

Correlation analysis of the infertile PCOS group

An examination of the relationship between Pentraxin and the other factors in the infertile PCOS group was performed. Pentraxin was shown to have a moderately positive correlation with age ($r = 0.44$, $p = 0.014$, 95%CI 0.10-0.69). The correlation between Pentraxin and advancing age is strong enough here to support the conclusion that Pentraxin tends to decrease with advancing age. The inverse relationship between Pentraxin and AMH was statistically significant ($r = -0.39$, $p = 0.031$, 95%CI -0.66 to -0.04), with a moderate effect size.

Accordingly, as Pentraxin levels rise, AMH levels fall; this data is shown in **Table 2**.

ROC curve comparison of Pentraxin, AMH, and LH/FSH ratio as they differentiate the infertile PCOS group from the control group showed a good specificity of PTX3 with a high sensitivity of both AMH and LH/FSH ratio as clarified in **Figure 2** and **Table 3**.

DISCUSSION

Main findings

The hormonal investigations showed that there were significant variations in LH, FSH, and their

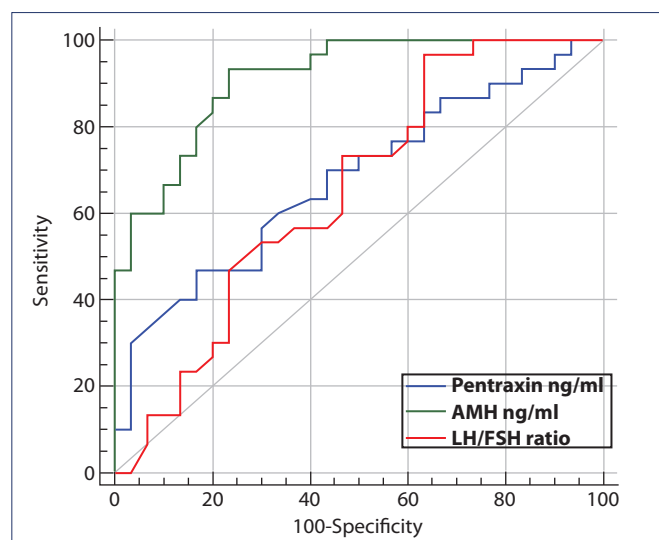


Figure 2. ROC curve comparison of Pentraxin 3, AMH, and LH/FSH ratio.

ratio in infertile PCOS patients compared with control groups and the fertile PCOS.

The core result of this study is the significantly lower PTX3 in non-fertile *versus* fertile PCOS suggests its potential role in ovarian dysfunction and PCOS-related infertility.

The correlation of biochemical and hormonal variables of the infertile study group with Pentraxin and AMH that was statistically significant with a moderate effect size.

ROC curve analysis revealed a cutoff value of PTX3 (≤ 1.05) that shows low sensitivity but good specificity, suggesting its possible diagnostic role in PCOS infertility. The application of the ROC curve for AMH and LH/FSH ratio shows higher sensitivity than PTX3, but lower specificity as coincides with another study [34], and this suggests the beneficial application of combined parameters in the diagnosis of PCOS-related infertility.

Strengths and limitations

The strength of the study is the evaluation of patients with PCOS according to phenotypes and fertility issues to determine the role of markers in different disease categories.

The limitation has been the enrolment of phenotypes B and C only to achieve a statistically significant sample study size.

Interpretation and comparison with other literature

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in young age women [11]. It presents with hyperinsulinemia, ovarian dysfunction, and metabolic syndrome. Pentraxin is released in response to inflammation, and many studies suggest its usefulness as an inflammatory marker released from peripheral blood leukocytes and myeloid dendritic cells following stimulation with pro-inflammatory cytokines. PTX3 had been evaluated in cases with PCOS with conflicting results regarding obesity, insulin resistance, and infertility, suggesting its role in ovarian function disturbances [12].

Age and BMI variation are common presenting features in PCOS. The current study design considered matching of these variables to minimize their biased effect on the results as accumulating evidence suggests that one of the most important mechanisms of PCOS pathogenesis is the insulin-resistance. For this reason, the use of insulin sensitizers, such as inositol isoforms, gained increasing attention due to their safety profile and effectiveness [13], and other studies showed that there are positive genetic correlations between PCOS and adult BMI [14], but the inverse correlation between PTX 3 and obesity in other studies [15].

Table 3. ROC curve comparison between different markers showing ROC criteria in the classification of infertility from control.

| Variable | AUC | SE | 95% CI | Cutoff | Sen | Spe | +PV | -PV | P-value |
|--------------|------|------|-----------|-------------|-------|-------|------|------|---------|
| Pentraxin 3 | 0.68 | 0.07 | 0.55-0.79 | ≤ 1.05 | 46.67 | 83.33 | 73.7 | 61.0 | < 0.001 |
| AMH | 0.91 | 0.03 | 0.81-0.97 | > 6.5 | 93.33 | 76.67 | 80.0 | 92.0 | < 0.001 |
| LH/FSH ratio | 0.65 | 0.07 | 0.52-0.77 | ≤ 1.33 | 96.67 | 36.67 | 60.4 | 91.7 | < 0.037 |

AUC: area under the curve; SE: standard error; CI: confident interval; Sen: sensitivity; Spe: specificity; PV: predictive value.

The hormonal investigations showed that there were significant variations in LH, FSH, and their ratio in infertile PCOS patients compared with control groups and the fertile PCOS. LH was significantly lower in the infertile group than in controls, but it is higher in the fertile PCOS compared to the control, while other comparative studies revealed higher values in the infertile group *versus* the fertile group [16]. On the other aspect, the FSH values were significantly lower in the non-fertile PCOS group than in the control and fertile PCOS groups, and this is against another study which showed an insignificant difference between the PCOS group and the control [17], and this related to the study sample size, population, and study design.

LH/FSH ratio in literature presents controversial conclusions. Banaszewska *et al.* did not find significant differences between LH/FSH ratio means between women with and without PCOS [18]. In our study, we found it to be significantly lower in infertile PCOS than fertile PCOS group and control; a comparative study disagrees with our results regarding the non-fertile group only and states that LH and LH/FSH ratio showed insignificant results in the PCOS group [19, 20], this discrepancy in LH and the ratio possibly can be justified by the BMI of the participants as the means of our sample were in the overweight range for all groups and this tends to lower the LH value in the current study [21].

Insulin is highly elevated in PCOS patients, and hyperinsulinemia is among the main pathophysiological mechanisms of this syndrome [22] and this increased secretion of insulin is a consequence of insulin resistance that is commonly apparent in women with PCOS and could be due to defects in the expression and/or activity of insulin receptor even after matching the BMI [23].

The value of AMH in PCOS patients was higher than in control, and this is compatible with a study that found a significant relationship between AMH levels and inflammatory markers in PCOS due to a greater release of inflammatory factors into the systemic circulation, thus affecting AMH production in the ovaries [24]. The raised number of ovarian follicles and follicular arrest underlies the elevated AMH in PCOS with adverse effects on fertility outcomes [25]. These results are in concordance with a study that showed higher intra-follicular AMH levels in women with PCOS compared to controls [26]. In addition, the study demonstrated a Strong correlation between circulating AMH levels and antral follicle count on ultrasound in PCOS [27].

Testosterone serum levels were elevated in fertile and non-fertile PCOS compared with the control group; this finding resembles the findings of previous studies [27, 28]; the pathogenesis of the disease state could explain this.

Hyperandrogenism is an important clinical feature in patients with PCOS and it is overt in non-fertile PCOS *versus* both fertile and control in concordance with another previous study [20].

The prolactin and TSH levels showed a significant decrement in the infertile PCOS group compared with the control and the fertile group but still within normal range values, and this is against the study by Jin *et al.* [29] that revealed a higher prolactin level in the PCOS group, possibly due to the sample size and population studied.

Accumulating evidence suggests that several vitamin disbalances, as well as nutraceutical supplementation to counteract them, may play a significant role in women's health and modulate molecular and endocrine as well as metabolic pathways [13, 30].

The infertile PCOS group had significantly lower PTX3 values than the fertile PCOS group, while its value was higher in fertile PCOS *versus* control. Variable findings were found in PCOS in different studies; for example, PTX3 was found to be low in Tosi *et al.* [31], in which the sample was entirely constituted of Caucasian women; additionally, the study design was a cohort of PCOS patients mostly consisted of women with the "classic" phenotype. While in our study, we evaluated different ethnic groups with sub-classification according to fertility issues. While another study [32] showed high PTX3 levels in PCOS, which we agree is considered fertile PCOS to be compared with healthy control.

Another study showed the circulating PTX3 level was elevated in PCOS women and significantly associated with the presence of hyperandrogenism [29], which our study agrees definitely.

The core result of this study is the significantly lower PTX3 in non-fertile *versus* fertile PCOS, suggesting its potential role in ovarian dysfunction and PCOS-related infertility.

The correlation of biochemical and hormonal variables of the infertile study group with Pentraxin showed an inverse relationship between Pentraxin and AMH that was statistically significant with a moderate effect size. In contrast, other studies showed that other parameters (Body Mass Index, blood sugar, lipids, and total testosterone) had

also significant correlations [33], as the study was a cohort study involving all cases with PCOS regardless of phenotypes.

ROC curve analysis revealed a cutoff value of PTX3 (≤ 1.05) that shows low sensitivity but good specificity, suggesting its possible diagnostic role in PCOS infertility, and a few studies discuss the possible fertility effect of PTX3; these studies demonstrate that PTX3 plays important roles in cumulus cell-oocyte interaction in the peri-ovulatory period as a downstream protein in the dominant follicle signal transduction cascade [34].

The application of the ROC curve for AMH and LH/FSH ratio shows higher sensitivity than PTX3 but lower specificity, as coincides with another study [35], and this suggests the beneficial application of combined parameters in the diagnosis of PCOS-related infertility.

CONCLUSIONS

Pentraxin 3 level is significantly higher in fertile PCOS patients and lower in the infertile PCOS group in comparison to the control group suggesting its possible role in PCOS-related infertility.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

N.E.: Data collection, formal analysis, investigations, methodology, validation, visualization, writing – original draft. B.H.: Conceptualization, formal analysis, methodology, project administration, software, supervision, validation, visualization, writing – review & editing.

Funding

None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The protocol was approved by the Mustansiriyah Scientific Council of Obstetrics and Gynaecology / Iraq MOG-107 in DEC 2021.

Informed consent

Written informed consent was taken from all participants following the Declaration of Helsinki and local guidelines.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Strauss J, Barbieri R, Gargiulo A. Yen & Jaffe's Reproductive Endocrinology: Physiology Pathophysiology and Clinical Management, 8th edn. 2018. Elsevier, Netherlands, pp 322.
2. Gautam A, Merchant R. Manual of Ovulation Induction and Ovarian Stimulation Protocols. 3rd edn. 2016. Jaypee Brothers Medical, India, pp 380.
3. Azziz R. PCOS in 2015: New insights into the genetics of polycystic ovary syndrome. *Nat Rev Endocrinol.* 2016;12(3):183. doi: 10.1038/nrendo.
4. Bozdog G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod.* 2016;31(12):2841-55. doi: 10.1093/humrep/dew218.
5. Kurek Eken M, Sahin Ersoy G, Yayla Abide C, Sanverdi İ, Devranoglu B, Kutlu T, et al. Association between circulating neuregulin 4 levels and metabolic, atherogenic, and AMH profile of polycystic ovary syndrome. *J Obstet Gynaecol.* 2019;39(7):975-80. doi: 10.1080/01443615.2019.1581754.
6. Chen ZJ, Zhao H, He L, Shi Y, Qin Y, Shi Y, et al. Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. *Nat Genet.* 2011;43(1):55-9. doi: 10.1038/ng.732.
7. Baranova NS, Foulcer SJ, Briggs DC, Tilakaratna V, Enghild JJ, Milner CM, et al. Inter- α -inhibitor impairs TSG-6-induced hyaluronan cross-link-

- ing. *J Biol Chem.* 2013;11;288(41):29642-53. doi: 10.1074/jbc.M113.477422.
8. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulinaemic clamp. *Hum Reprod.* 2013;28(3):777-84. doi: 10.1093/humrep/des463.
 9. Goodarzi MO, Quiñones MJ, Azziz R, Rotter JI, Hsueh WA, Yang H. Polycystic ovary syndrome in Mexican-Americans: prevalence and association with the severity of insulin resistance. *Fertil Steril.* 2005;84(3):766-9. doi: 10.1016/j.fertnstert.2005.03.051.
 10. Balen A. Polycystic Ovary Syndrome and Secondary Amenorrhoea. Keith E, Lees C, Bourne T. Dewhurst's Textbook of Obstetrics & Gynaecology, 9th edn. 2018. Wiley-Blackwell United States, pp 637.
 11. Akram W, Nori W, Zghair MAG. Area under the curve of carotid artery Doppler as a sensitive marker of insulin sensitivity among Iraqi women with polycystic ovarian syndrome: a cross-sectional study. *Ital J Gynaecol Obstet.* 2023;35(4):453-62. doi: 10.36129/jog.2022.86.
 12. Luciano M, Ganong W. Neuroendocrinology. Volume 1 2013. Elsevier Science, Netherlands, Academic Press 2013.
 13. Paul C, Laganà AS, Maniglio P, Triolo O, Brady DM. Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: state-of-the-art and future perspectives. *Gynecol Endocrinol.* 2016;32(6):431-8. doi: 10.3109/09513590.2016.1144741.
 14. Liu Q, Tang B, Zhu Z, Kraft P, Deng Q, Stener-Victorin E, et al. A genome-wide cross-trait analysis identifies shared loci and causal relationships of type 2 diabetes and glycaemic traits with polycystic ovary syndrome. *Diabetologia.* 2022;65(9):1483-94. doi: 10.1007/s00125-022-05746-x.
 15. Jin C, Zou K, Xu Y, Yang H, Pan J. Elevated plasma pentraxin-3 in polycystic ovary syndrome is associated with hyperandrogenism: a case-control study. *BMC Endocr Disord.* 2021;21(1):240. doi: 10.1186/s12902-021-00886-4.
 16. Shanmugham D, Vidhyalakshmi R, Shivamurthy H. The effect of baseline serum luteinizing hormone levels on follicular development, ovulation, conception and pregnancy outcome in infertile patients with polycystic ovarian syndrome. *Int J Reprod Contracept Obstet Gynecol.* 2017;7:318. doi: 10.18203/2320-1770.ijrcog20175869.
 17. Desforgues-Bullet V, Gallo C, Lefebvre C, Pigny P, Dewailly D, Catteau-Jonard S. Increased anti-Müllerian hormone and decreased FSH levels in follicular fluid obtained in women with polycystic ovaries at the time of follicle puncture for in vitro fertilization. *Fertil Steril.* 2010;94(1):198-204. doi: 10.1016/j.fertnstert.2009.03.004.
 18. Banaszewska B, Spaczyński RZ, Pelesz M, Pawelczyk L. Incidence of elevated LH/FSH ratio in polycystic ovary syndrome women with normo- and hyperinsulinemia. *Rocz Akad Med Białymst.* 2003;48:131-4.
 19. Khattak M, Sultana N, Usman R, Khattak U, Zafar U, Salman H. Luteinizing Hormone To Follicle Stimulating Hormone Ratio In Patients With Polycystic Ovary Syndrome. *J Ayub Med Coll Abbottabad.* 2020;32(2):255-8.
 20. Khmil M, Khmil S, Marushchak M. Hormone Imbalance in Women with Infertility Caused by Polycystic Ovary Syndrome: Is There a Connection with Body Mass Index? *Open Access Maced J Med Sci.* 2020;20;8(B):731-7. doi: 10.3889/oamjms.2020.4569.
 21. Winters S, Huhtaniemi I. Male Hypogonadism: Basic, Clinical and Therapeutic Principles. 2nd edn. 2017 springer, Berlin, pp 147.
 22. Laganà AS, Rossetti P, Buscema M, La Vignera S, Condorelli RA, Gullo G, et al. Metabolism and Ovarian Function in PCOS Women: A Therapeutic Approach with Inositols. *Int J Endocrinol.* 2016;2016:6306410. doi: 10.1155/2016/6306410.
 23. Stracquadanio M, Ciotta L, Palumbo MA. Relationship between serum anti-Müllerian hormone and intrafollicular AMH levels in PCOS women. *Gynecol Endocrinol.* 2018;34(3):223-8. doi: 10.1080/09513590.2017.1381838.
 24. Sopa N, Larsen EC, Nyboe Andersen A. Low dose HP-hMG in an antagonist protocol for IVF in ovulatory and anovulatory patients with high AMH. *Gynecol Endocrinol.* 2018;34(7):623-6. doi: 10.1080/09513590.2018.1428302.
 25. Soufizadeh N, Farhadifar F, Seyedoshohadaei F, Rezaei M, Rasouli MA, et al. The effect of inofolic supplementation on women with polycystic ovarian syndrome (PCOS): a Randomized Clinical Trial study. *Ital J Gynaecol Obstet.* 2021;33(4):256-62. doi: 10.36129/jog.33.04.05 256-262.
 26. Christiansen SC, Eilertsen TB, Vanky E, Carlsen SM. Does AMH Reflect Follicle Number Similarly in Women with and without PCOS? *PLoS*

- One. 2016;11(1):e0146739. doi: 10.1371/journal.pone.0146739.
27. Liu Q, Xie YJ, Qu LH, Zhang MX, Mo ZC. Dyslipidemia involvement in the development of polycystic ovary syndrome. *Taiwan J Obstet Gynecol.* 2019;58(4):447-53. doi: 10.1016/j.tjog.2019.05.003.
 28. Saei Ghare Naz M, Mousavi M, Mahboobifard F, Niknam A, Ramezani Tehrani F. A Meta-Analysis of Observational Studies on Prolactin Levels in Women with Polycystic Ovary Syndrome. *Diagnostics (Basel).* 2022;12(12):2924. doi: 10.3390/diagnostics12122924.
 29. Jin C, Zou K, Xu Y, Yang H, Pan J. Elevated plasma pentraxin-3 in polycystic ovary syndrome is associated with hyperandrogenism: a case-control study. *BMC Endocr Disord.* 2021;21(1):240. doi: 10.1186/s12902-021-00886-4.
 30. Chiaffarino F, Parazzini F, Surace M, Benzi G, Chiantera V, La Vecchia C. Diet and risk of seromucinous benign ovarian cysts. *Eur J Obstet Gynecol Reprod Biol.* 2003;110(2):196-200. doi: 10.1016/s0301-2115(03)00115-5.
 31. Tosi F, Di Sarra D, Bonin C, Zambotti F, Dall'Alida M, Fiers T, et al. Plasma levels of pentraxin-3, an inflammatory protein involved in fertility, are reduced in women with polycystic ovary syndrome. *Eur J Endocrinol.* 2014;170(3):401-9. doi: 10.1530/EJE-13-0761.
 32. Wyskida K, Franik G, Pohl N, Markuszewski L, Owczarek A, Madej P, et al. Pentraxin 3 as a marker of endothelial dysfunction in young women with polycystic ovary syndrome (PCOS). *Scand J Clin Lab Invest.* 2019;79(6):419-23. doi: 10.1080/00365513.2019.1637535.
 33. Sahin FK, Sahin SB, Balik G, Ural UM, Tekin YB, Cure MC, et al. Does low pentraxin-3 levels associate with polycystic ovary syndrome and obesity? *Int J Clin Exp Med.* 2014;7(10):3512-9.
 34. Varani S, Elvin JA, Yan C, DeMayo J, DeMayo FJ, Horton HF, et al. Knockout of pentraxin 3, a downstream target of growth differentiation factor-9, causes female subfertility. *Mol Endocrinol.* 2002;16(6):1154-67. doi: 10.1210/mend.16.6.0859.
 35. Deveer M, Deveer R, Basaran O, Turkcu UO, Akbaba E, Cullu N, et al. Serum Copeptin, Pentraxin 3, Anti-Mullerian Hormone Levels With Echocardiography and Carotid Artery Intima-Media Thickness in Adolescents With Polycystic Ovary Syndrome. *J Clin Med Res.* 2015;7(12):989-94. doi: 10.14740/jocmr2375w.



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Impact of granulocyte colony stimulating factor infusion on the implantation rate in women with unexplained previous intracytoplasmic sperm injection failure: a case control study

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ABSTRACT

Objective. We studied the granulocyte colony stimulating factor (G-CSF)'s effect on women with unexplained infertility and previous intracytoplasmic sperm injection (ICSI) failure. Unexplained infertility is a condition when couples are not able to conceive despite normal semen analysis and absence of female infertility factor(s). Cytokines, transcription factors and signaling pathways are essential for complex interactions of decidualization. G-CSF is a glycoprotein with growth factor and cytokine functions, which are produced in many tissues.

Patients and Methods. The study was done on a total of 200 women with only 196 women who ended the study (99 women as a study group, 96 women as a control group). All women were complaining of unexplained infertility with previous history of failed ICSI. All cases proceed through ICSI procedure while study group only undergone G-CSF infusion intrauterine at time of ovum pickup.

Results. We found that intrauterine G-CSF injection at time of ovum pickup in the study group, in comparison with control group, did not improve neither implantation rate (16.68% vs 19.66%, $p = 0.243$) nor the chemical (54.5% vs 67%, $p = 0.074$), clinical pregnancy (51.5% vs 62.9%, $p = 0.108$) rates as well as live birth rates (31.0% vs 39.8%, $p = 0.227$).

Conclusions. Intrauterine infusion of G-CSF may not improve implantation rate in women with unexplained previous intracytoplasmic sperm injection (ICSI) failure. Further studies are needed to conclude if the dose, route and timing of the drug administration can give better results.

INTRODUCTION

Unexplained infertility is a condition in which couples are unable to conceive despite normal semen analysis and the absence of any female infertility factors. While the results of intracytoplasmic sperm injection (ICSI) procedures have generally been positive, there is a new challenge that couples

face: recurrent implantation failure (RIF). Roughly 10% of women seeking ICSI experience RIF [1]. This can leave couples feeling confused and frustrated. Coughlan and colleagues have proposed a definition of RIF, which states that it is the inability to achieve a clinical pregnancy after three fresh or frozen cycles with four Class A embryos transferred in a woman under the age of 40 [2, 3].

While there is now an international consensus on the definition of RIF, managing it requires a multi-disciplinary approach beyond just evaluating the quality of embryos and endometrium. Other outcome parameters related to ICSI must also be considered to effectively manage RIF [3].

Sperm fragmentation [4], oocyte quality, chromosomal structure, immunologic and thrombophilic factors, endometrial sonographic parameters [5] and even living conditions can affect the success rate of the ICSI procedure [6]. While numerous ICSI "add-ons" have been developed and are widely believed to be safe and effective, the scientific evidence supporting these techniques is either strongly contradictory or, at best, unclear. From these innovations, aiming not to reach RIF, are endometrial scratching, assisted hatching, embryo glue and elective freeze all cycles [7].

In recent times, there has been an increasing recognition of the importance of immunological factors in embryo implantation. However, the effectiveness of immunological treatments for women with RIF remains a topic of debate as conflicting results have been reported in studies up to the present day [8]. Additional research is necessary to explore the clinical significance of emerging immunotherapy approach [9], cytokines, transcription factors and signalling pathways are essential for complex interactions of decidualization. A proper immune reaction is essential for embryo attachment and invasion [10]. Granulocyte Colony Stimulating Factor (G-CSF), also known as filgrastim, is a type of haematopoietic cytokine that is produced by bone marrow cells, macrophages, stromal cells, and fibroblasts. The phagocytosis and oxidative reactions induced by G-CSF are believed to play a crucial role in the process of implantation [11]. The G-CSF receptor has been detected in non-haematopoietic cell types such as trophoblastic, endothelial, placental, and granulosa lutein cells [8]. G-CSF appears to play a significant role in the regulation of endometrial gene expression, vascular remodeling, cellular adhesion mechanisms, and local immune modulation, all of which are crucial to the process of implantation [11]. Studies have shown that systemic administration of G-CSF can have an impact on embryonic development and trophoblastic growth [12]. However, local administration of G-CSF is believed to be crucial for endometrial remodelling and receptivity, particularly when administered intra-uterine [13]. G-CSF supplementation has emerged as a potential new therapy in the

field of reproductive medicine, and is currently an area of active investigation [6].

Aim of the study

The objective of this study is to investigate the impact of intrauterine injection of G-CSF into the uterine cavity of women with unexplained infertility who have experienced previous ICSI failure. Specifically, the study aims to examine the effects of G-CSF on implantation rate, miscarriage rate, chemical and clinical pregnancy rates, as well as live birth rate.

PATIENTS AND METHODS

This prospective randomized controlled study was conducted at the Bedaya IVF centre, a private IVF centre, in collaboration with the infertility clinic of the National Research Center over the course of a year. The study was carried out after obtaining approval from the Ethical Committee. This study involved a total of 200 women with unexplained infertility who had previously undergone a failed cycle of intracytoplasmic sperm injection (ICSI). The women were randomly divided into two groups: the G-CSF group and the control group, with 100 women in each group. Standard antagonist long protocol was used for ovarian stimulation in both groups. Once at least two follicles had reached a diameter of 18 mm, human chorionic gonadotropin (hCG) (Choriomon 10000 IU, IBSA Institute, Switzerland) was administered to induce final oocyte maturation. Transvaginal oocyte retrieval was carried out 36 hours after hCG injection, and the retrieved oocytes were fertilized using the intracytoplasmic sperm injection method.

Group I (G-CSF group) (n = 100)

At the day of ovum pickup and after oocytes collection, 300 µg in 1 mL G-CSF (300 µg/mL rHu G-CSF, Neukine; Intas Pharmaceuticals Ltd., India) will be administered by slow transcervical intra-uterine infusion with IUI catheter [12].

Group II (control group) (n = 100)

Normal saline of 1 mL was infused into the endometrial cavity of patients in the control group at the day of ovum pickup.

Vaginal micronized progesterone was administered on the day of oocyte retrieval to provide luteal phase support. At least three good quality embryos (as per the Society for Assisted Reproductive Technology embryo grading system, 2010) were transferred into all patients using an embryo transfer catheter (Cook USA) five days after oocyte retrieval.

A positive serum β hCG test 14 days after embryo transfer was considered indicative of a chemical pregnancy, while the observation of a gestational sac on transvaginal ultrasound examination three weeks after a positive serum β hCG result was considered indicative of a clinical pregnancy. Implantation rate was calculated by dividing the number of gestational sacs by the number of transferred embryos in each group [14]. The ongoing pregnancy rate was defined as the presence of foetal heart activity on ultrasonography after 12 weeks of pregnancy. Miscarriage rate was assessed by dividing the number of miscarriages before 20 weeks gestation by the number of women with a positive β hCG test.

The women who were included in this study were between 18 and 40 years of age and had a complaint of primary or secondary infertility for more than one year. To be eligible, women had to have unexplained infertility, with no abnormalities in the uterine cavity, normal Fallopian tubes, normal ovulation, and normal semen analysis results according to WHO 2010 criteria for the male partner. They must also have had a previous failed ICSI procedure with an embryo transfer of at least 3 good quality embryos on day 5 (either fresh or frozen embryos). In terms of laboratory findings, women had to have an Anti-Müllerian hormone level of ≥ 1 ng/mL and/or follicle stimulating hormone levels of ≤ 13 IU/L in the early follicular phase. They should have had a regular cycle of 25-35 days, positive ovulation tests, and/or midluteal progesterone levels of ≥ 25 nmol/L in an unstimulated cycle. Women who were excluded from the study were below 18 or over 40 years of age, had a body mass index (BMI) of ≥ 35 kg/m², or had any contraindications for G-CSF (such as active infections, kidney disease, sickle cell anaemia, malignancies, or chronic neutropenia).

All women who participated in the study underwent a review of their medical records and assessment sheets, with a specific focus on their personal history, including age, residence, schooling level, socioeconomic status, fertility problems, obstetric history (including the number of pregnancies and

living children), and ultrasound for any uterine or tubal anomalies, as well as antral follicle count and measurement of the dominant follicle. A simple, computer-generated randomization was carried out with the assistance of an impartial statistician at a 1:1 ratio. Written informed consent was obtained from each participant, and the women were blinded to which group they were assigned to, while the medical practitioner was not blinded.

The data were described statistically in terms of mean (standard deviation (SD)), median and range, or frequencies (number of cases) and percentages as appropriate. Numerical data were assessed for normality using the Kolmogorov-Smirnov test. A Student's t-test for independent samples was used to compare numerical variables between the study groups, while a chi-square (χ^2) test was used to compare categorical data. In cases where the expected frequency was less than 5, an exact test was used instead. P-values less than 0.05 were considered statistically significant, and all statistical calculations were performed using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS

In total of 200 women, only 196 women with unexplained infertility who experienced previous ICSI failure were included in this study, with 99 patients (50.5%) in the G-CSF group and 97 patients (49.5%) in the control group. Four women discontinued the study upon their request either due to failure of fertilization or cancelation of embryo transfer (Figure 1).

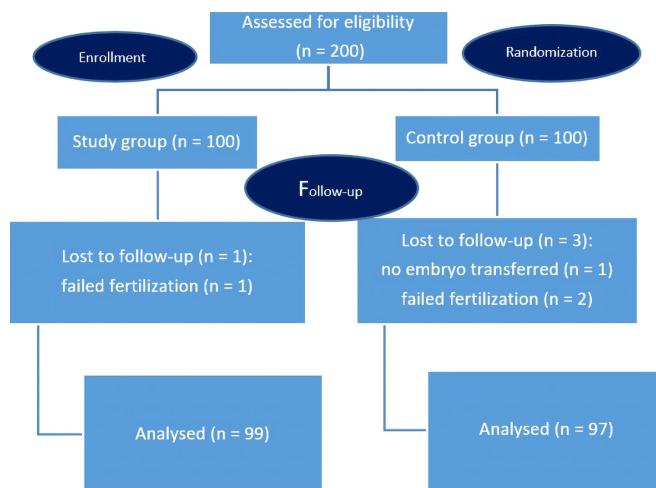


Figure 1. Consort flow diagram.

Table 1. Demographic characteristics of the research groups.

| | Control | Case | P-value |
|-------------------------|----------------|----------------|---------|
| Age | 28.87 ± 4.482 | 29.87 ± 4.12 | 0.518 |
| Duration of infertility | 6.14 ± 4.913 | 5.87 ± 4.265 | 0.683 |
| FSH | 6.251 ± 1.242 | 6.018 ± 1.309 | 0.633 |
| AMH | 4.095 ± 1.8108 | 3.560 ± 2.1953 | 0.064 |
| AFC | 24.42 ± 9.086 | 25.13 ± 10.939 | 0.623 |
| Endometrial thickness | 9.41 ± 1.881 | 9.42 ± 1.467 | 0.977 |
| Previous IVF | 1.59 ± 0.910 | 1.40 ± 1.106 | 0.206 |
| Previous pregnancy | 0.92 ± 1.891 | 0.75 ± 0.993 | 0.430 |

All data are expressed by mean ± standard deviation; P-value significant < 0.05.

Table 1 shows the demographic data and baseline characteristics of patients enrolled in the study. No differences were found in both groups regarding the women's age, duration of infertility, number of previous pregnancies, number of previous IVF failures, antral follicle count and endometrial thickness. For the biochemical parameters, the mean follicle stimulating hormone (FSH) level was 7.22 ± 2.14 (G-CSF 6.242 ± 2.1833 and control 7.206 ± 2.0036) and the Antimullerian hormone was 3.824 ± 2.0269 (G-CSF 3.560 ± 2.1953 and control 4.095 ± 1.8108). The mean of endometrial thickness at the day of hCG trigger was 9.42 ± 1.680 mm (G-CSF 9.42 ± 1.467 , control 9.41 ± 1.881 and P-value 0.977).

Table 2 shows no significance difference regarding induction of ovulation criteria. The mean gonadotropin (GN) duration was 10.51 ± 1.025 days (G-CSF 10.47 ± 1.043 days and control 10.55 ± 1.011 days) and the gonadotropin dose was 252.70 ± 83.104 IU (G-CSF 255.30 ± 85.660 IU and control 250.05 ± 80.769 IU). For the oocyte quality parameters, the mean number of retrieved oocytes $22.95 \pm$

11.474 (G-CSF 22.18 ± 10.797 , control 23.73 ± 12.133 and P-value 0.346), the mean number of metaphase 2 oocytes (M2) was 14.67 ± 8.716 (G-CSF 13.61 ± 9.344 , control 15.75 ± 7.928 and P-value 0.085), the mean number of injected oocytes (including metaphase 1 oocytes) was 15.18 ± 8.477 (G-CSF 14.43 ± 9.076 , control 15.94 ± 7.793 and P-value 0.215) and the mean number of fertilized oocytes was 12.21 ± 7.302 (G-CSF 11.95 ± 7.715 , control 12.47 ± 6.886 and P-value 0.616).

As shown on **Table 3**, sixty-five women (67%) had a chemical pregnancy (positive β hCG titer) after embryo transfer in G-CSF group while 54 women (54.5%) was positive in control group. Only sixty-one women established clinical pregnancy in G-CSF group 62.9% (61 out of 99) and in control group 51.5% (51 out of 97 patients). The difference of chemical pregnancy as well as clinical pregnancy was not significant with a P-value 0.074 and 0.108 respectively. The live birth babies in G-CSF group to control group was 39.8% to 31% in order with a P-value 0.227.

From 588 embryos were transferred, the implantation rate was 16.68% in G-CSF group and 19.66% in control group. Referring to **Table 2**, the implantation rate was not statistically different for G-CSF regarding control group ($p = 0.243$). There were

Table 2. Induction of ovulation criteria.

| | Control | Case | P-value |
|-------------------------------|-----------------|-----------------|---------|
| Gonadotropins duration | 10.55 ± 1.011 | 10.47 ± 1.043 | 0.626 |
| Gonadotropins dose | 250.05 ± 80.769 | 255.30 ± 85.660 | 0.659 |
| Number of retrieved oocytes | 23.73 ± 12.133 | 22.18 ± 10.797 | 0.346 |
| Number of Metaphase 2 oocytes | 15.75 ± 7.928 | 13.61 ± 9.344 | 0.085 |
| Number of injected oocytes | 15.94 ± 7.793 | 14.43 ± 9.076 | 0.215 |
| Number of fertilized oocytes | 12.47 ± 6.886 | 11.95 ± 7.715 | 0.616 |
| No of ET | 3.59 ± 1.058 | 3.62 ± 1.057 | 0.850 |
| No of sacs | 0.67 ± 0.473 | 0.55 ± 0.500 | 0.075 |
| Implantation rate | 19.66 ± 16.232 | 16.68 ± 19.142 | 0.243 |

All data are expressed by mean ± standard deviation; P-value significant < 0.05.

Table 3. Pregnancy outcome parameters.

| | Control | Case | P-value |
|--------------------|---------|-------|---------|
| Chemical pregnancy | 67% | 54.5% | 0.074 |
| Clinical pregnancy | 62.9% | 51.5% | 0.108 |
| Live birth rate | 39.8% | 31.0% | 0.227 |
| Miscarriage rate | 16.5% | 9.1% | 0.120 |

Data expressed by percent of positive cases in each group; P-value significant < 0.05.

sixteen cases (16.5%) miscarriages in G-CSF group and nine cases (9.1%) in control group ($p = 0.120$).

DISCUSSION

The results of our study showed that intrauterine G-CSF injection did not lead to a significant improvement in pregnancy outcome parameters. However, a systematic review published in 2018 concluded that G-CSF may have a positive effect on improving endometrial receptivity and pregnancy rates in women with thin endometrium. Nonetheless, the review recommended conducting more controlled randomized studies, as previous studies on this topic have produced conflicting results [15]. Another study investigated the impact of subcutaneous injection of G-CSF on women with repeated IVF failure and concluded that it resulted in better implantation rates and pregnancy rates [16]. Additionally, Zeyneloglu and colleagues found that a dual method of administration of G-CSF (both subcutaneous and systemic) was significantly more effective than the subcutaneous only method [17]. It is believed that subcutaneous injection of G-CSF just before embryo transfer could elicit a systemic immunological response that enhances the local effect of the drug.

In a study conducted by Eftekhar and colleagues, they investigated cases of recurrent implantation failure despite normal endometrial thickness and found that intra-uterine infusion of G-CSF did not increase endometrial thickness or significantly improve pregnancy rates [18]. Barad and colleagues showed the same results as well [19]. While Eftekhar and other researchers were unable to demonstrate that G-CSF improves endometrial thickness, they did find that it may result in better chemical and clinical pregnancy rates in women with thin endometrium after a frozen-thawed embryo transfer cycle [20]. The observed differences in results may be attributed to differences in the timing and route of administration, endometrial thickness, and sample size. Administering G-CSF at the time of ovum pick-up may provide a stable environment for the attached embryos at the early stage of implantation.

A recent meta-analysis by Kamath *et al.* suggested that G-CSF may induce an unknown immunological process that allows embryo implantation without showing endometrial regeneration [21]. However, a Turkish research group found no sta-

tistically significant difference in endometrial thickness, implantation, and pregnancy rates with the use of G-CSF. They excluded women with thin endometrium by freezing embryos in cases where the endometrium was less than 7 mm in thickness [6]. Similarly, our study found that intrauterine injection of G-CSF did not play a role in the implantation process in women with normal endometrium. Studies have shown that different routes of G-CSF administration can yield varying results. Those using the systemic subcutaneous route have reported an increase in pregnancy rates [6, 22, 23]. However, studies using endometrial infusion, including our study, as well as those conducted by Kalem *et al.* and Eftekhar *et al.*, found no significant difference in implantation and pregnancy rates between the study and control groups [6, 20]. Singal and colleagues claimed in 2020 that both intrauterine and subcutaneous routes can improve endometrial thickness, with intrauterine infusion being more beneficial for assisted reproductive techniques [24]. In 2021, Jindal *et al.* compared subcutaneous and intrauterine infusion of G-CSF starting on day 14 of the cycle. Although they found a difference in clinical pregnancy rates between the two groups in favour of the intrauterine group, it was not statistically significant [25]. In 2022, the same research group focused on intrauterine infusion of G-CSF on the day of trigger in women with thin endometrium. Although they found a significant increase in endometrial thickness and implantation and clinical pregnancy rates, they recommend more multicentre trials to assess its potential for improving implantation rates [26].

In studies comparing subcutaneous and local uterine application of G-CSF, ovulation parameters tend to be better in the subcutaneous route [21]. This may explain why our study did not show a change in pregnancy rates, as we administered G-CSF locally and did not benefit from the claimed systemic effects of G-CSF.

Our randomized case control study showed no statistical significance in clinical pregnancy as well as live birth rates. Most of the studies did not comment on live birth rates and this is why we consider our study to be more accurate as we are concerned with the "To Go Home Baby" which is considered the main aim of all infertility related studies. Long-term follow-up of children born after ICSI is an important issue that should be addressed in future research, as the available data on this topic is still limited [27]. We also selected cases of unexplained

infertility with previous ICSI failure to examine the immunomodulatory part of G-CSF. We considered the patient selection and standardization of the ICSI protocols is the main limitation for the study. Also, the economic inflation was a big limitation due to lack of cases as most of infertility procedures is not covered by insurance in our country.

CONCLUSIONS

In conclusion, we have doubts about the effectiveness of G-CSF in cases of unexplained infertility. However, future studies are needed to investigate the effects of different doses and routes of administration of G-CSF that may have a beneficial effect. Uterine perfusion of G-CSF could be a promising new tool for addressing the intractable problem of unexplained ICSI failure in women.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.M.: Conceptualization, methodology, supervision. E.S.: Data curation, formal analysis, validation, writing – original draft, writing – review & editing. A.O.: Data curation, formal analysis, investigation, methodology, validation.

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Study registration

None.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Ethical approval has been obtained from the Research Ethics Committee of Faculty of Medicine, Cairo University. The research involved human participants. The research data that support the findings of this study are available upon request. We declare that this manuscript adheres to the En-

hancing the QUALity and Transparency Of health Research (EQUATOR) network guidelines.

Informed consent

Written informed consent was obtained from each patient before being enrolled in the present study.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Ray A, Shah A, Gudi A, Homburg R. Unexplained infertility: an update and review of practice. *Reprod Biomed Online*. 2012;24(6):591-602. doi: 10.1016/j.rbmo.2012.02.021.
2. Bashiri A, Halper KI, Orvieto R. Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions. *Reprod Biol Endocrinol*. 2018;16(1):121. doi: 10.1186/s12958-018-0414-2.
3. Coughlan C, Ledger W, Wang Q, Liu F, Demiroglu A, Gurgan T, et al. Recurrent implantation failure: definition and management. *Reprod Biomed Online*. 2014;28(1):14-38. doi: 10.1016/j.rbmo.2013.08.011.
4. Esteves SC, Conforti A, Alviggi C. The Sperm DNA Fragmentation Study Group (SFRAG) Guideline and its relevance for practicing gynecologists. *Ital J Gynaecol Obstet*. 2021;33(2):74-8. doi: 10.36129/jog.33.02.01.
5. Ibrahim MA-M, Hamed BM, Elasy AN. Endometrial sonographic parameters in prediction of intracytoplasmic sperm injection outcome following fresh embryo transfer in normal responders: a cohort study. *Ital J Gynaecol Obstet*. 2023;35(4):493-502. doi: 10.36129/jog.2022.91
6. Kalem Z, Namli Kalem M, Bakirarar B, Kent E, Makrigiannakis A, Gurgan T. Intrauterine G-CSF Administration in Recurrent Implantation Failure (RIF). *An Rct Sci Rep*. 2020;10(1):5139. doi: 10.1038/s41598-020-61955-7.
7. Glatthorn HN, Decherney A. The efficacy of add-ons: selected IVF “add-on” procedures and future directions. *J Assist Reprod Genet*. 2022;(3):581-9. doi: 10.1007/s10815-022-02410-6.
8. Mekinian A, Cohen J, Alijotas-Reig J, Carbillon L, Nicaise-Roland P, Kayem G, et al. Unexplained Recurrent Miscarriage and Recurrent Implan-

- tion Failure: Is There a Place for Immunomodulation? *Am J Reprod Immunol.* 2016;76(1):8-28. doi: 10.1111/aji.12493.
9. Mikuš M, Goldštajn MŠ, Brlečić I, Dumančić S, Lagana AS, Chiantera V, et al. CTLA4-Linked Autoimmunity in the Pathogenesis of Endometriosis and Related Infertility: A Systematic Review. *Int J Mol Sci.* 2022;23(18):10902. doi: 10.3390/ijms231810902.
 10. Rocha MNC, Florêncio RS, Alves RRF. The role played by granulocyte colony stimulating factor (G-CSF) on women submitted to in vitro fertilization associated with thin endometrium: systematic review. *JBRA Assist Reprod.* 2020;24(3):278-82. doi: 10.5935/1518-0557.20200025.
 11. Weissman A, Horowitz E, Ravhon A, Nahum H, Golan A, Levran D. Pregnancies and live births following ICSI with testicular spermatozoa after repeated implantation failure using ejaculated spermatozoa. *Reprod Biomed Online.* 2008;17(5):605-9. doi: 10.1016/s1472-6483(10)60306-9.
 12. Würfel W. Treatment with granulocyte colony-stimulating factor in patients with repetitive implantation failures and/or recurrent spontaneous abortions. *J Reprod Immunol.* 2015;108:123-35. doi: 10.1016/j.jri.2015.01.010.
 13. Rahmati M, Petitbarat M, Dubanchet S, Bensussan A, Chaouat G, Ledee N. Granulocyte-Colony Stimulating Factor related pathways tested on an endometrial ex-vivo model. *PLoS One.* 2014;9(9):e102286. doi: 10.1371/journal.pone.0102286.
 14. Griesinger G. Beware of the 'implantation rate'! Why the outcome parameter 'implantation rate' should be abandoned from infertility research. *Hum Reprod.* 2016;31(2):249-51. doi: 10.1093/humrep/dev322.
 15. Okada H, Tsuzuki T, Murata H. Decidualization of the human endometrium. *Reprod Med Biol.* 2018;17(3):220-7. doi: 10.1002/rmb2.12088.
 16. Aleyasin A, Abediasl Z, Nazari A, Sheikh M. Granulocyte colony-stimulating factor in repeated IVF failure, a randomized trial. *Reproduction.* 2016;151(6):637-42. doi: 10.1530/REP-16-0046.
 17. Zeyneloglu HB, Tohma YA, Onalan G, Moran U. Granulocyte colony-stimulating factor for intracytoplasmic sperm injection patients with repeated implantation failure: which route is best? *J Obstet Gynaecol.* 2020;40(4):526-30. doi: 10.1080/01443615.2019.1631772.
 18. Eftekhar M, Hosseinisadat R, Baradaran R, Naghshineh E. Correction to "Effect of granulocyte colony stimulating factor (G-CSF) on IVF outcomes in infertile women: An RCT" *Int J Reprod BioMed* 2016;(14):341-6. *Int J Reprod Biomed.* 2022;20(1):68. doi: 10.18502/ijrm.v20i1.10411.
 19. Barad DH, Yu Y, Kushnir VA, Shohat-Tal A, Lazaroni E, Lee HJ, et al. A randomized clinical trial of endometrial perfusion with granulocyte colony-stimulating factor in in vitro fertilization cycles: impact on endometrial thickness and clinical pregnancy rates. *Fertil Steril.* 2014;101(3):710-5. doi: 10.1016/j.fertnstert.2013.12.016.
 20. Eftekhar M, Sayadi M, Arabjahvani F. Transvaginal perfusion of G-CSF for infertile women with thin endometrium in frozen ET program: A non-randomized clinical trial. *Iran J Reprod Med.* 2014;12(10):661-6.
 21. Kamath MS, Kirubakaran R, Sunkara SK. Granulocyte-colony stimulating factor administration for subfertile women undergoing assisted reproduction. *Cochrane Database Syst Rev.* 2020;1(1):CD013226. doi: 10.1002/14651858.CD013226.pub2.
 22. Scarpellini F, Sbracia M. G-CSF treatment in the implantation failure with a fixed dose of 60mcg/day: preliminary data of a controlled trial. In *Human Reproduction.* 2013;(28):145-6. Great Clarendon St, Oxford Ox2 6dp, England: Oxford Univ Press.
 23. Scarpellini F, Sbracia M. The use of G-CSF for implantation failure in IVF: a clinical trial. *Fertil Steril.* 2011;96(3):S93. doi: 10.1016/j.fertnstert.2011.07.359.
 24. Singal S, Sharma RK, Ahuja N. GCSF in patients with thin endometrium— subcutaneous or intrauterine? *Fertil Sci Res.* 2020;7(1):43. doi: 10.4103/2394-4285.288714.
 25. Jindal PC, Singh M. P-347 A comparative RCT of Intrauterine-GCSF versus Subcutaneous-GCSF in Thin Endometrium in IVF-ICSI Cycles. *Human Reproduction.* 2021;36(Supplement_1):deab130-346.
 26. Jindal PC, Singh R, Singh M. O-026 RCT of INTRA-Uterine administration of granulocyte colony-stimulating factor (G-CSF) before embryo-transfer in resistant thin endometrium in IVF-ICSI cycles. *Human Reproduction.* 2022;37(Supplement_1):deac104-026.
 27. Gullo G, Scaglione M, Cucinella G, Perino A, Chiantera V, D'Anna R, et al. Impact of assisted reproduction techniques on the neuro-psycho-motor outcome of newborns: a critical appraisal. *J Obstet Gynaecol.* 2022;42(7):2583-7. doi: 10.1080/01443615.2022.2109953.

