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Early solitary splenic metastasis of endometrial cancer: a case report and review of literature

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ABSTRACT

Spleen involvement in the patients affected by endometrial cancer is an extremely rare event. The aim of this study is to report a case of early splenic metastasis of endometrial cancer and a systematic literature review to standardize management.
We describe the case of a 59-year-old patient affected by endometrial cancer FIGO stage IA G3 (N0). She developed an isolated splenic recurrence of clear cell adenocarcinoma and underwent to splenectomy and second line chemotherapy. After 55 months the patient is alive without disease.
The literature review highlights an asymptomatic onset and a 24-month recurrence presentation interval. In most cases the FIGO stage at diagnosis is the I and histotype is endometrioid. Treatment is surgery in all cases, followed by chemotherapy in 50% of cases.

INTRODUCTION

Endometrial cancer is the fifth most common cancer in women [1]. It occurs more frequently in postmenopausal women and the main risk factor is exposure to endogenous or exogenous estrogens in association with hypertension, obesity, diabetes, early menarche and late menopause, nulliparity and taking tamoxifen [2].
Most cases (75%) of endometrial cancer are diagnosed at early stage (FIGO I and II), with a 5-year survival ranging from 74 to 91% [3].
The recurrence of endometrial carcinoma mainly affects the pelvic/para-aortic lymph nodes (46%), upper vagina (42%), the peritoneum (28%) and the lungs (24%); the involvement of the spleen, pancreas, rectum, muscle tissue and brain is described in less than 5% of cases [4].
The aim of this study is to report a rare case of early splenic metastasis of endometrial cancer and a systematic review literature concerning splenic localization of endometrial cancer.

MATERIALS AND METHODS

Data of case report were extracted from clinical record, electronic database, instrumental imaging

and follow-up examinations. Systematic research on PubMed Central with MeSH (Medical Subject Headings): "Endometrial cancer AND splenic metastasis" was performed; information regarding age at the first diagnosis of endometrial cancer, the FIGO stage, grading and histotype, primary surgery and any adjuvant treatment, the interval of presentation of recurrence, treatment of recurrence and follow-up were obtained. The median age at the first diagnosis and the interval of presentation of splenic metastasis was calculated. The above-mentioned variables are summarized in **Table 1**.

RESULTS

The case report concerns a 59-year-old patient, multiparous, with a negative family history for cancer and a negative personal history. In May 2013, following pelvic pain and spotting, she underwent operative hysteroscopy with endometrial biopsy. The histological diagnosis was endometrioid adenocarcinoma. In August 2013 she underwent surgery by longitudinal laparotomy, with total hysterectomy, bilateral salpingo-oophorectomy and systematic pelvic lymphadenectomy. The histological diagnosis was "poorly differentiated adenocarcinoma of the endometrium with mixed aspects: serous, endometrioid and clear cell; myometrial infiltration less than 50%, free cervical canal, salpinxes, ovaries and the lymph nodes (0/15)". In September 2013, in consideration of surgery and histological diagnosis with evidence of high-grade mixed (endometrioid, serous and clear cell) carcinoma (FIGO stage IA G3, special histotype), adjuvant treatment with platinum-based chemotherapy was recommended. Pre-treatment staging chest-abdomen CT was negative. The patient underwent chemotherapy with Carboplatin + Paclitaxel schedule every 21 days for 6 cycles until January 2014, treatment was well tolerated and without side effects. Then the patient was included in a follow-up program with visits after 2, 5 and 8 months from the end of chemotherapy and abdomen ultrasound at 5 months. The ultrasound performed in July 2014 showed a small hypoechoic splenic area of 19 mm. The PET examination revealed accumulation of tracer in a small hypodense area at the splenic hilum. In November 2014, the patient underwent surgery by longitudinal xiphoid-pubic laparotomy with splenectomy, total omentectomy and aortic lymphadenectomy. The histological examination reported splenic metastasis of clear cell adenocarcinoma, free omentum and lymph nodes (0/12). In consideration of surgery, the diagnosis of isolated splenic recurrence of clear cell adenocarcinoma after first surgery and first line chemotherapy based on Carboplatin + Paclitaxel (8 months of platinum free interval), multidisciplinary team decision was second line chemotherapy. The patient underwent chemotherapy with Pegylated Liposomal Doxorubicin 40 mg/m^2 every 21 days for 5 cycles (6th cycle not performed due to toxicity), concluded in April 2015. After 55 months, the patient is alive, free of disease.

The details of the 19 case reports (including the case described in this paper) are summarized in **Table 1** [5-22]. Because of the unavailability of article's full text in Polish, the remaining 18 studies were considered for the study. Median age at diagnosis was 58 years (range 43-72). Primary surgery in all of the described cases was abdominal hysterectomy with bilateral salpingo-oophorectomy (except 1 case underwent to radical hysterectomy), including 5 cases with systematic pelvic lymphadenectomy.

FIGO stage at first diagnosis was: I in 10 (55%) cases; II in 3 (16%) cases; III in 2 (11%) cases; IV in 1 (5%) cases; unknown in 2 (11%) cases. All the described cases (excluding our case) had an endometrioid histotype. Grading was G2 in 6 patients, G3 in 5 cases, unknown in the remaining 7. The adjuvant treatment for surgery was: external beam radiotherapy in 8 cases, 2 of which with brachytherapy; chemotherapy in 2 cases; follow-up in 4 cases; chemo-radio therapy in 2 cases; hormone therapy in1 case; 1 unknown case. In all cases the diagnosis of splenic metastasis was metachronous to endometrial adenocarcinoma, except for 1 case in which the splenic localization was synchronous with the primary tumor. The median time interval of splenic metastasis was 24 months (range 0-120). Recurrence occurred asymptomatically in 8 (44%) patients, with left hypochondrial pain in 6 (33%), 2 (11%) cases of vaginal bleeding (1 for synchronous vaginal recurrence with splenic recurrence, 1 case for synchronous splenic localization to endometrial cancer), 1 (5%) case with palpable splenomegaly. The imaging method used to diagnose splenic metastasis was the abdomen ultrasound in 6 patients (33%), alone or in association with CT (3 cases) and PET (1 case); CT (6, 33%) was used alone or in association with PET (1 case) and MRI (1 case); the remaining cases were diagnosed with PET-CT (1 case) and MRI in association with PET (1 case); 4 case reports did not report the imaging method used.

Table 1. *Published case report of splenic metastasis by endometrial adenocarcinoma.*

Author, year	Age at first diagnosis (years)	FIGO stage, hystotype	Treatment primary tumor	Symptoms	Imaging	Time of recurrence (months)	Treatment of relapse	Follow-up
Pecorino, 2021 (this case)	59	IA G3, serous-endometrioid-clear cell	TAH+BSO+PL CHT (Carboplatin+Paclitaxel	Asymptomatic	US, PET	8	SPLENECTOMY CHT (Doxorubicin)	55 months NED
Pissarra, 2019 (synchronous)	70	IA G3, endometrioid	TAH+BSO CHT (Carboplatin+Paclitaxel)	Vaginal bleeding (synchronous)	MR, PET	0	SPLENECTOMY CHT (Carboplatin+Paclitaxel)	14 months NED
Gallotta, 2017	53	IB G2, endometrioid	TAH+BSO+PL FOLLOW-UP	Asymptomatic	PET-TC	37	ROBOTIC SPLENECTOMY CHT (Carboplatin + Doxorubicin)	2 months NED
Arif, 2013	50	IA G2, endometrioid	TAH+BSO FOLLOW-UP	Left hypochondrial pain	US, TC	50	SPLENECTOMY CHT (not specified)	Not available
Andrei, 2011 (full text not available)	Unknown	Unknown	Unknown	Unknown	Unknown	20	SPLENECTOMY CHT (not specified)	Unknown
Kara, 2011	56	IIIA, endometrioid	TAH+BSO+PL	Asymptomatic	TC, PET	26	Unknown	Unknown
Wei, 2009	54	IVA G3, unknown	TAH+BSO CH-RT (CYS+PTX)	Asymptomatic	US, TC	22	SPLENECTOMY CHT (not specified)	Unknown
Piura, 2009	58	IIB, endometrioid	TAH+BSO+PL EBRT+BRT	Asymptomatic	CT, PET	18	SPLENECTOMY CHT (Paclitaxel)	6 months NED
Gogas, 2004	52	IB G2, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	Unknown	30	SPLENECTOMY CHT (unknown)	46 months NED
Hadjileontis, 2004	53	endometrioid	TAH+BSO HT	Splenomegaly	Unknown	120	SPLENECTOMY HT	NED (time not recorded)
Takahashi, 2003	60	II, endometrioid	TAH+BSO EBRT	Asymptomatic	CT, MR	18	LAPAROSCOPIC SPLENECTOMY	18 months, NED
Aga-Mohammadi, 2001	62	IIB G2, unknown	RAH+PL FOLLOW-UP	Left hypochondrial pain	CT	82	SPLENECTOMY	Unknown
Giuliani, 1999	58	I G2, endometrioid	TAH+BSO+PL FOLLOW-UP	Vaginal bleeding (synchronous vaginal recurrence)	CT	28	SPLENECTOMY CHT	12 months, NED
Hamy, 1995	47	III, endometrioid	TH+BSO CHT (Adriamycin+Endoxan+Cysplatin) EBRT (30 Gy)	Asymptomatic	US, CT	82	SPLENECTOMY	36 months NED
Arend, 1992	62	IB, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	Unknown	12	SPLENECTOMY EBRT HT (Oral Progestin)	6 months AWD
Blake Gilks, 1989	72	IB G3, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	CT	33	SPLENECTOMY	6 months DOD
Nannestad Jorgensen, 1988	59	IA G3, endometrioid	TAH+BSO EBRT	Left hypochondrial pain	US	7	SPLENECTOMY HT (Oral progestin)	10 months DOD
Klein, 1987	66	IA G2, endometrioid	TAH+BSO EBRT+BRT	Asymptomatic	US	20	SPLENECTOMIY EBRT	27 months DOD
Kopacz, 1970 (full text not available)								

TAH: Total Abdominal Hysterectomy; RAH: Radical Abdominal Hysterectomy; PL: pelvic lymphadenectomy; US: ultrasound; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance; CHT: Chemotherapy; CH-RT: Chemo-radiation therapy; EBRT: External beam radiotherapy; BRT: Brachytherapy; HT: Hormone therapy; NED: No evidence disease; AWD: Alive with disease; DOD: Dead of disease.

Splenic recurrence was isolated in 16 (88%) patients, while in 2 cases (12%) it occurred synchronously with recurrence of the vaginal cuff (1 case) and lung localization (1 case). The treatment of splenic metastasis was splenectomy in all cases, one of which laparoscopic and one robotic; after surgery 9 patients (50%) underwent chemotherapy; 2 cases (11%) radiation therapy; 2 patients (11%) oral progestogen therapy; 3 cases (16%) sent for follow-up; 1 case (5%) unknown.

DISCUSSION

The spleen is a rare target of endometrial cancer and it is a rare event for all malignant neoplasms. About half of the cases of splenic metastasis originate from female genital tract tumors, more frequently the ovary and less frequently endometrium, cervix and tuba [23].
Some authors argue that the incidence of splenic metastases is underestimated because this event is asymptomatic often [24] and detectable only by imaging methods such as CT and MRI. In the present case, the splenic lesion was asymptomatic and diagnosed only by abdominal ultrasound and PET. The analysis of published cases showed that 44% of splenic metastasis of endometrial cancer was completely asymptomatic.
In consideration of the cases published before 2000, abdominal ultrasound alone is enough to diagnose recurrence. A particularity of the case described concerns the PET examination. The first and only work in the literature in this regard [12] highlights the validity of PET to identify early recurrences in the first follow-up year.
The median time of recurrence for all localizations is 13 months after the first surgery, with 65% of recurrences diagnosed within the second year [7]. ESMO Guidelines [6] for follow-up in patients affected by endometrial cancer suggests examinations every 3-4 months for the first two years and the execution of imaging methods in case of suspicious relapse. PET seems to be more sensitive and specific in these patients than CT and ultrasound.
Spleen involvement can be the consequence of hematogenous or lymphatic metastases, intraperitoneal dissemination or it can develop due to contiguity from adjacent organs [25]. Almost invariably splenic involvement is characterized by a single parenchymal metastasis and is an indicator of poor prognosis [10]. Splenic metastasis exhibits 3 macroscopic patterns of localization: macronodular, micronodular and diffuse [26]; the lesions infiltrate the upper or lower pole and the hilus, the capsule less frequently [27].
When the splenic lesion is solitary and circumscribed, it does not cause any functional alteration of the organ and does not give any symptoms, as occurred in our case and in the literature. When present, the symptoms and signs are asthenia, weight loss, abdominal pain, anemia and thrombocytopenia [10]. Even more rare is the possibility that the diagnosis of metastasis is made after emergency surgery for atraumatic splenic rupture.
The first endometrial carcinoma was FIGO IA stage, poorly differentiated. To date, the literature has not yet established any association between the time of presentation of the splenic metastasis and the starting stage of the endometrial tumor. Adnan's review of 2013 analyzed 13 cases with an average time of recurrence of about 35 months (range 11-120 months) [10], similar to the one reported in this review (24 months, range 0-120).

CONCLUSIONS

There is unanimous consensus (100% of cases) about the treatment of the splenic localization of endometrial carcinoma, which is based on splenectomy. In most cases the treatment was chemotherapy (9 cases out of 18) but the data concerning the protocols were reported only in a small number of patients. There is unanimous consensus regarding the most suitable treatment for this type of recurrence, consisting of splenectomy, possibly laparoscopic, followed by chemotherapy or less according to PFI (platinum free interval). In the present case, in consideration of the early relapse, a second line chemotherapy treatment based on pegylated liposomal doxorubicin was chosen.
In conclusion, the splenic metastasis of endometrial cancer represents a rare event, the diagnosis is often instrumental, and the treatment of choice is based on splenectomy followed by chemotherapy.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

B.P.: Writing – original draft. G.S., M.F.: Writing – review & editing. A.D.S. Writing – original draft. P.S.: Conceptualization and supervision.

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Data are available under reasonable request to the corresponding author.

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Accuracy of three-dimensional multislice view Doppler in diagnosis of placenta accreta spectrum

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ABSTRACT

Objective. To evaluate the accuracy of three-dimensional multislice view Doppler as a diagnostic tool in the diagnosis of placenta accreta spectrum.
Materials and Methods. Seventy eight pregnant women with persistent placenta previa totalis (after 28 weeks' gestation) were prospectively enrolled into this study. Gray-scale transabdominal ultrasound examination was performed to detect loss of the subendometrial echolucent zone and other abnormalities suggestive of placental invasion. Three-dimensional multislice view Doppler was used to scan the whole placenta to detect any vessels invading the uterine serosa-bladder interface or presence of abnormal lacunae. Ultrasound findings were analyzed with reference to histopathological results.
Results. Placenta accreta and its variants (increta and percreta) were confirmed in 39 women by pathological results. Diagnostic value of three-dimensional multislice view Doppler using 2 or more criteria of placental invasion showed a sensitivity of 87%, specificity of 96%, and accuracy of 91% (area under ROC curve [AUC] = 0.961). Disruption of the uterine serosa-bladder interface was the best single criterion for the diagnosis of placenta accreta (sensitivity = 95% and specificity = 96%).
Conclusions. Three-dimensional multislice view Doppler can be used as an accurate test for diagnosis of placenta accreta spectrum.

INTRODUCTION

Placenta accreta spectrum (PAS) has become a life-threatening issue, its incidence is increasing significantly with marked morbidity and mortality. The markedly increased rate of caesarean section and increased maternal age explain this upsetting increase in PAS [1]. PAS refers to different degrees of invasion of the uterine wall and/or its surrounding (placenta accreta, increta and percreta) [2]. Accurate antenatal diagnosis of PAS allows proper assessment and management by experienced multidisciplinary teams in tertiary referral centers, thus improving maternal outcome [3].
Current prenatal diagnosis depends on the interpretation of ultrasound findings using two-dimensional

(2D) grey-scale and color Doppler imaging. Many signs are reported in literature with varying degrees of sensitivity and specificity [4]. Several consensus statements have been published by experts aiming to standardize the description and allow appropriate comparison of imaging signs for diagnosis of PAS [5, 6]. Magnetic resonance imaging (MRI), although has proved a beneficial role in the diagnosis of PAS, yet did not show significant improvement in pregnancy outcome or management [7]. MRI is expensive and unavailable in most low and medium-income countries, hence it is only recommended as adjunct to ultrasound in certain cases [8].

This study investigates the value of three-dimensional multislice view (3D MSV) Doppler as a single adiagnostic tool in the diagnosis of PAS and compare its diagnostic performance based on receiver–operating characteristics (ROC) curve analysis.

MATERIALS AND METHODS

This prospective observational study was conducted at Ain Shams University Hospital, Cairo, Egypt, during the period from December 2019 to September 2021. Approval of the Obstetrics and Gynecology Department's Ethical Committee was obtained before commencement of the study (N = FWA000017585). 78 pregnant women diagnosed after 28 weeks' gestation with persistent low lying anterior placenta covering the scar of previous caesarean section were enrolled in the study. Placenta previa was diagnosed using 2-dimentional (2D) ultrasound (SAMSUNG MEDISON CO, LTD, Korea MODEL WS80A) with 4-7 MHz convex probe. An informed written consent was obtained from all women before enrollment in the study after explaining the aim and risks of the study.

2D gray-scale ultrasound and 3DMSV Doppler were performed for all women with sufficient urinary bladder volume to clearly visualize the serosa–bladder interface, and the angle of insonation was kept as low as possible. Criteria used to diagnose morbidly adherent placenta using the 2D gray-scale ultrasound were; Loss of the retro placental sonolucent zone (interruption of interface between the posterior bladder wall and the uterus) (**Figure 1**), irregular retro-placental sonolucent zone, thinning or disruption of hyperechoic serosa-bladder interface, presence of focal exophytic masses invading the urinary bladder (mass with same echogenicity as the placenta beyond the uterine serosa), and abnormal placental lacunae (irregular vascular spaces in the placental parenchyma) (**Figure 1**) [9].

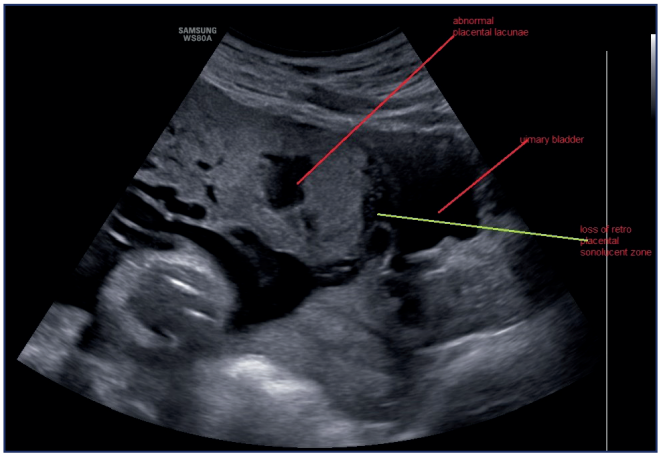

Figure 1. *2D gray-scale ultrasound showing loss of retro-placental sonolucent zone and abnormal placental lacunae.*

3D power Doppler examination was targeted to the region of the lower uterine segment and the placenta. Three to five 3D volumes were obtained in automatic sweeps using a motorized curved array transducer while the women held their breath. In order to interpret the data consistently, the settings of power were adjusted at 100% and pulse repetition frequency at 0.9 kHz for all examinations. Offline image analysis was performed using either the ultrasound platform or a PC-based program. Ultrasound examination was performed using a 3DMSV ultrasound system equipped with a 4-8 MHz transabdominal transducer (the WS80A with Elite features with Crystal Clear Cycle). During the 3DMSV Doppler technique, the 3D volume transducer was mechanically and systematically moved over the defined region of interest (ROI) to obtain volume data in three planes (sagittal, coronal, and axial). Sampling was performed between 95 and 255 consecutive slices per volume. The volume data were stored on the machine's hard drive. Slices were generated either from the initial plane or any other reconstructed ROI. The most informative image among the multiple slices was displayed with the use of Medison Dynamic MR, a post-processing tool that allowed one to reduce speckle artifacts, leading to sharper depiction of the tissue margins. Image processing was performed through the use of off-line software (Medison XI Viewer, version v1.1.0.723). Immediately after image acquisition was completed, the volume images were displayed on the monitor in a multislice view either for sagittal or coronal or axial planes. In addition, the volumes of a defined cube were manipulated to bring out a particular scan plane or reconstructed to a volume rendered image, and the general morphologic condition of

the vascular network within a ROI was obtained in power mode. The presence of at least one of the following criteria by 3DMSV doppler indicated placenta accreta (including its variants, placenta increta and placenta percreta): abnormal placental lacunae (**Figure 2**), disruption of the uterine serosa-bladder interface, numerous vessels invading the uterine serosa-bladder interface, or crowded vessels over the peripheral sub-placental zone (**Figures 3, 4**) [10].

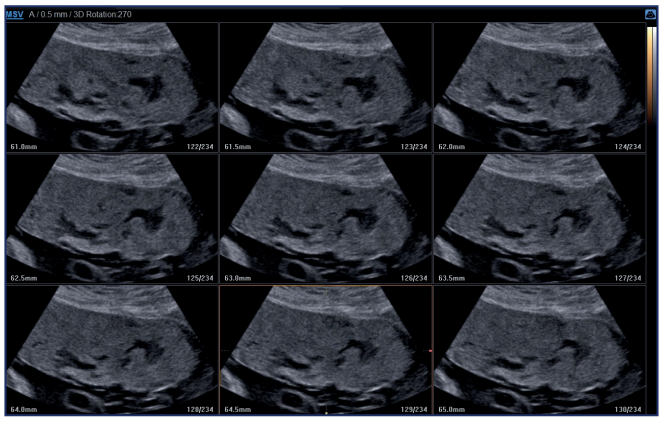

Figure 2. *3DMSV showing abnormal placental lacunae.*

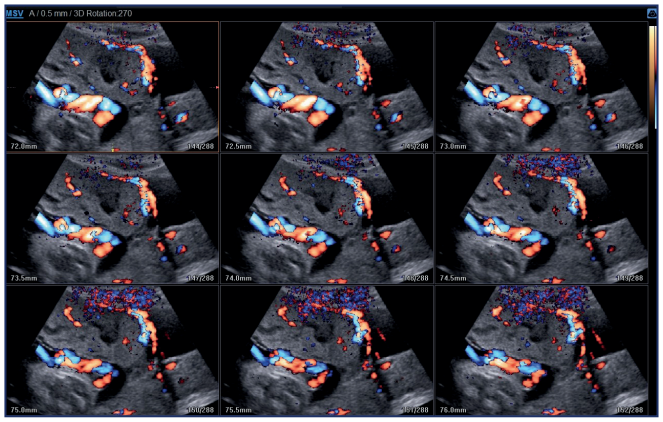

Figure 3. *Placenta accreta with 3DMSV showing abnormal placental lacunae, disruption of the uterine serosa-bladder interface, numerous vessels invading the uterine serosa-bladder interface, and crowded vessels over the peripheral sub-placental zone.*

According to the institutional protocol of management, women were delivered at completed 36 weeks, following adminstration of corticosteroids for fetal lung enhancement, or emergency cesarean section was performed if significant bleeding developed before the time of the planned delivery. Operative findings including difficulty of placental separation, and different degrees of placental invasion were recorded. Histopathological examination of the uterus was performed in cases managed by hysterectomy, while in those managed conservatively without hysterectomy, resection of part of the lower segment or curettage of the placental bed was done for histopathological examination when possible. Histopathology confirmed the diagnosis of PAS when placental villi where found anchored directly on, or invading into or through, the myometrium, without an intervening decidual plate. The placenta is characterized as accreta, increta, or percreta, depending on the greatest depth of myometrial invasion (superficial, deep, or penetrating the entire uterine wall). Histopathologic findings were compared with preoperative sonography findings to detect the accuracy of the 3DMSV Doppler to diagnose PAS .

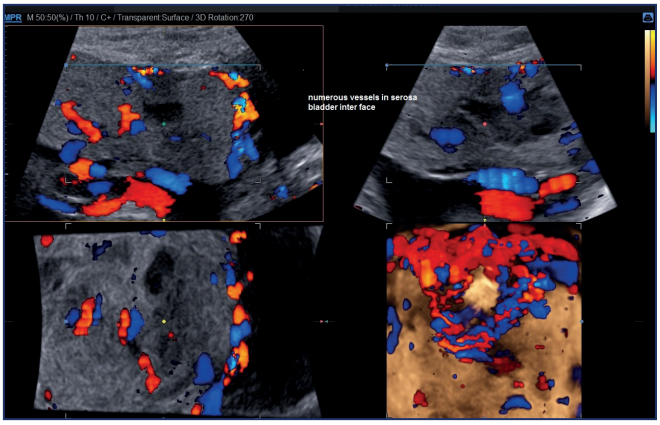

Figure 4. *3D power Doppler showing abnormal placental lacunae, disruption of the uterine serosa-bladder interface, numerous vessels invading the uterine serosa-bladder interface.*

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY). Categorical variables were presented as counts or proportions and percentages. Diagnostic accuracy for individual sonographic criteria was assessed using cross-tabulation of each criterion versus histopathologic diagnosis as the gold-standard and calculating the true positive (TP), false positive (FP), true negative (TN), and false-negative (FN) rates. The following diagnostic indices were then calculated: sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and correct classification and misclassification rates. Receiver-operating characteristic (ROC) curve analysis is used to identify the best cutoff number of sonographic criteria for diagnosis of placental invasion. The area under the ROC curve (AUC) is interpreted as follows:

- < 0.6 = fail;
- 0.6 to 0.69 = poor;
- 0.7 to 0.79 = fair;
- 0.8 to 0.89 = good;
- ≥ 0.9 = excellent.

RESULTS

During the 2 years period of the study, a total of 78 women diagnosed with low lying placenta were enrolled, base line charectiristics are shown in **Table 1**. Only 24 (30.8%) women were managed by cesarean hysterectomy, while 54 women were managed conservatively without hysterectomy. Histopathology was done only for 65 cases, where curreting of the placental bed was performed in 30 (38.5%) and part of the lower uterine segment was removed in 11 (14.1%) women while specimen were not obtained from 13 (16.7%) cases as the placenta was separated spontaneously without any signs of invasion. The histopathology proved the presence of PAS in 39/65 (60%) women and no placental invasion in the remaining 26/65 (40%) specimens. 2D gray scale ultrasound diagnosed diagnosed 38/78 (48.7%) women with at least on criteria suggesting PAS, while 3DMSV Doppler diagnosed 51/65 (65.4%) women (**Table 2**).

Receiver-operating characteristic (ROC) Curve for diagnosis of placental invasion using number of 2D gray scale US Criteria showed a poor diagnostic value (area under ROC curve [AUC] = 0.671) with best cutoff value is 2 or more criteria (sensitivity = 46%; specificity = 88%; J-index = 0.346; accuracy = 63%) (**Figure 5**). The presence of abnormal placental lacunae was the best single criterion for prediction of PAS (**Table 3**). Receiver-operating characteristic (ROC) Curve for diagnosis of placental invasion using number of 3DMSV Doppler criteria showed an excellent diagnostic value with area under ROC curve [AUC] = 0.961. Best cutoff is 2 or more criteria (sensitivity = 87%; specificity = 96%; J-index = 0.833; accuracy = 91%) (**Figure 6**). Disruption of the serosa bladder interface, visualized in the basal view of 3DMSV Doppler was the best single criterion for the diagnosis of PAS, with sensitivity of 95% and specificity of 96% (**Table 4**).

Table 1. *Base line characteristics of the women enrolled in the study.*

Characteristic		Mean ± SD or n (%)
Age (years)		29.6 ± 4.75
Parity	P_1	15 (19.2%)
	P_2	22 (28.2%)
	P_3	17 (21.8%)
	P_4	12 (15.4%)
	≥ P_5	12 (15.4%)
BMI (kg/m^2)		26.37 ± 4.93
Previous cesarean section (CS)	1 CS	19 (24.4%)
	2 CS	24 (30.8%)
	3 CS	20 (25.65)
	4 CS	8 (10.3%)
	5 CS	7 (9%)
Previous uterine curettage (D&C)	No	27 (34.6%)
	1 D&C	34 (43.6%)
	2 D&C	14 (17.9%)
	≥ 3 D&C	3 (3.9%)
Previous PAS		11 (14.1%)

Table 2. *Preoperative 2D gray scale ultrasound and 3DMSV Doppler diagnosis of PAS.*

2D gray scale ultrasound		
Characteristic		**N (%)**
Number of criteria for PAS	No	40/78 (51.3%)
	1 criteria	11/78 (14.1%)
	2 criterias	16/78 (20.5%)
	3 criterias	7/78 (9.0%)
	4 criterias	4/78 (5.1%)
Type of criteria for PAS	Abnormal placental lacunae	26/78 (33.3%)
	Disruption of serosa-bladder interface	20/78 (25.6%)
	Focal exophytic mass invading bladder	19/78 (24.4%)
	Loss of retro-placental sonolucent zone	15/78 (19.2%)
3DMSV Doppler		
Characteristic		**N (%)**
Number of criteria for PAS	No	27/78 (34.6%)
	1 criteria	10/78 (12.8%)
	2 criterias	9 /78 (11.5%)
	3 criterias	12/78 (15.4%)
	4 criterias	20/78 (25.6%)
Type of criteria for PAS	Abnormal placental lacunae	34/78 (43.6%)
	Disruption of serosa-bladder interface	44/78 (56.4%)
	Numerous coherent vessels invading serosa-bladder interface	32/78 (41.0%)
	Crowded vessels over peripheral sub-placental zone	34/78 (43.6%)

DISCUSSION

Antenatal diagnosis nof PAS can help to prevent several maternal mortalities and morbidities oweing to proper preoperative preparations [10], proper counseling for possible cesarean hysterectomy and other morbidities, referral to a well equipped tertiary center with available adequate blood products or cell-salvage technology, pre- and intra-operative preparations including anesthesia consul-

Table 3. *Diagnostic value of abnormal placental lacunae by 2D gray scale ultrasound.*

	Histopatholgy		
2D GSUS	**Histopathology (+ ve)**	**Histopathology (- ve)**	**Total**
Criterion (+ ve)	17	3	20
Criterion (- ve)	22	23	45
Total	39	26	65
Statistics	**Value**	**Lower bound (95%)**	**Upper bound (95%)**
Correct classification	62%	50%	73%
Misclassification	38%	27%	50%
Sensitivity	44%	29%	59%
Specificity	88%	70%	97%
False positive rate	12%	0%	23%
False negative rate	56%	42%	71%
Prevalence	60%	48%	72%
Positive predictive value	85%	69%	100%
Negative predictive value	51%	37%	66%
Positive likelihood ratio	3.78	1.23	11.61
Negative likelihood ratio	0.64	0.47	0.87
Relative risk	1.74	1.23	2.45
Odds ratio	5.92	1.64	21.41

Table 4. *Diagnostic value of disruption of serosa-bladder interface by 3DMSV Doppler.*

	Histopatholgy		
3DMSV Doppler	**Histopathology (+ ve)**	**Histopathology (- ve)**	**Total**
Criterion (+ ve)	37	1	38
Criterion (- ve)	2	25	27
Total	39	26	65
Statistics	**Value**	**Lower bound (95%)**	**Upper bound (95%)**
Correct classification	95%	90%	100%
Misclassification	5%	0%	10%
Sensitivity	95%	82%	99%
Specificity	96%	79%	100%
False positive rate	4%	0%	11%
False negative rate	5%	0%	12%
Prevalence	60%	48%	72%
Positive predictive value	97%	92%	100%
Negative predictive value	93%	83%	100%
Positive likelihood ratio	24.67	3.60	168.80
Negative likelihood ratio	0.05	0.01	0.21
Relative risk	13.14	4.03	42.91
Odds ratio	462.50	57.44	3723.67

tation, ureteric stenting, and balloon occlusion of hypogastric vessels might be beneficial [11, 12]. The surgical outcome and degree of hemorrhage in PAS is mainly dependent on the degree of placental invasion, uteroplacental vascularity, and placental invasion of adjacent structures as urinary bladder [13]. Thus, proper antenatal diagnosis enabeling proper preparation and timing of intervention, is crucial in the management of PAS.

Second and third trimester 2D gray scale ultrasound has been used for long as the main diagnostic tool for PAS mainly due to its availability, 2D Doppler have been used also in conjunction though has not proved to increase the diagnostic accuracy substantially [14]. Several signs were suggested and studied for the diagnosis of PAS with variable degrees of sensitivity and specificity, the most widely accepted are the loss or irregularity of the retro placental sonolucent zone, thinning or disruption of hyperechoic serosa-bladder interface, presence of focal exophytic masses invading the urinary bladder, and presence of abnormal pla-

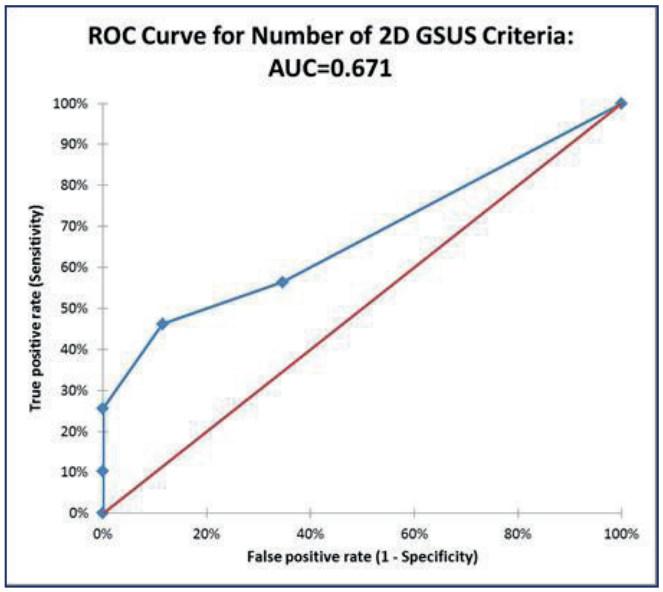

Figure 5. *Receiver-operating characteristic (ROC) Curve for diagnosis of placental invasion using number of 2D gray scale US Criteria.*

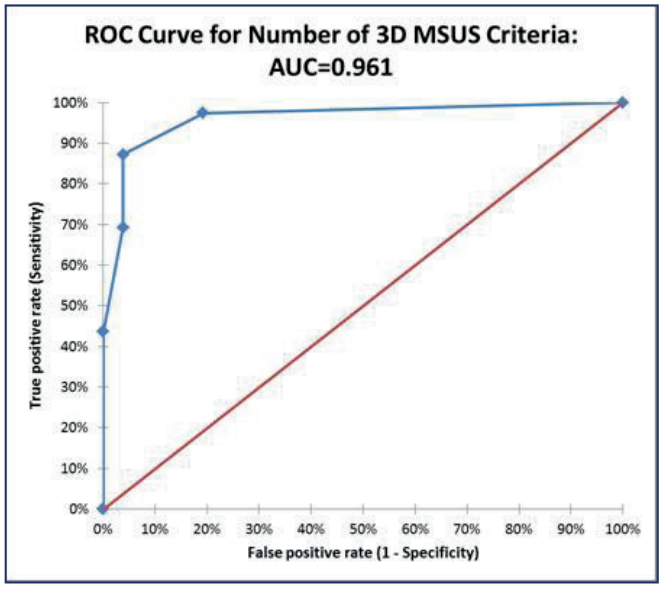

Figure 6. *Receiver-operating characteristic (ROC) Curve for diagnosis of placental invasion using number of 3DMSV Doppler criteria.*

cental lacunae [9]. Still, this study has found low diagnostic accuracy for the use of these criteria, sensitivity 46% and specificity 88% of a cutoff value of 2 or more criteria with the best diagnostic accuracy of presence of abnormal placental lacunae (sensitivity 44% and specificity 88%). Other studies showed better specificity for these signs but still with less than desirable sensitivity [10, 15, 16].

Magnetic resonance imaging (MRI) was introduced as a diagnostic modality for detection of PAS, still, due to its cost and unavailability, MRI use is mainly reserved when sonographic findings are inconclusive [17], some even failed to find a significant difference in its diagnostic accuracy, sensitivity, and specificity compared to sonography [18]. Owing to the importance and clinical significance of antenatal diagnosis of PAS, the search continues for a more accurate and feasible diagnostic modality. In the recent years, 3D ultrasound and Doppler have been studied as a useful diagnostic modality for many obstetric conditions one of which is PAS. In recent years, a new technique, 3DMSV was introduced for the diagnosis of some uterine and fetal anomalies but its value in the diagnosis of PAS was not well studied [19-21]. 3DMSV comprises both an oblique view mode and a multislice view mode, it allows sequential slice scans of a scanned 3D volume with an adjustable slice interval according to the volume size and ROI to obtain the best plane for analysis [21]. Similar to MRI and computed tomography, it allows to display several slices on one screen, thus, a slice-by-slice approach obtains a better choice of the most informative image to attain an accurate diagnosis. Thus, instead of depending on the operator skill who performs this process mentally during 2D ultrasound, 3DMSV provides a more subjective diagnostic tool [19].

The study used the same diagnostic criteria decribed by the ordinary 3D power Doppler for the evaluation of 3DMSV Doppler [10]. The current study suggests that 3DMSV Doppler might become a very valuable tool for the antenatal diagnosis of PAS, the best criterion suggested was the disruption of the hyperechoic serosa-bladder interface with sensitivity 95%, specificity 96%, and positive predictive value 97%. This technique has the advantage of being less operator dependent than ordinary 2D or 3D ultrasound, and the multislice images can be revised by other operators. Another case control study suggested that 3DMSV Doppler had a better diagnostic accuracy compared to 2D gray scale ultrasound and 3D power Doppler for the prediction of difficult placental separation and considerable intraoperative blood loss with the presence of crowded vessels over the peripheral sub-placental zone showing best sensitivity (82.6%) [22]. The current study compares the ultrasound findings to the postoperative histopathological findings rather than observational intraoperative findings. Still, this study being a diagnostic accuracy test, more trials are needed to validate the usefulness of this modality and its impact on clinical practice and obstetric outcome.

CONCLUSIONS

This study suggest that 3D MSVDoppler is a valuable diagnostic modality for PAS.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.E.G.: Clinical participation, collection of data, writing the manuscript, funding. W.M.A.A.: Study design, clinical participation, supervision of study, funding. K.H.S.: Study design, supervision of study, funding. E.A.N.: Clinical participation, collection of data, writing the manuscript, funding. A.E.: Study design, clinical participation, collection of data, funding.

Funding

None.

Study registration

The study was not registered as it is not a clinical trial.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Approval of the Obstetrics and Gynecology Department's Ehical Committee was obtained before commencement of the study (N = FWA000017585).

Informed consent

An informed written consent was obtained from all women before enrollment in the study after explaining the aim and risks of the study.

Data sharing

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary material. The data that support the findings of this study are available on request from the corresponding author.

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The failure rate and related factors of vaginal delivery after caesarean section

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ABSTRACT

Objective. In women with a previous caesarean section, whichever choice of mode of delivery -Elective Repeat Caesarean Section (ERCS) or Trial of Labour After Caesarean (TOLAC) - there is not an option free from risks for both the woman and the foetus. The main focus of this study was the successful rate of VBAC.
Patients and Methods. We conducted a retrospective cohort study of pregnant women from 2015 to 2019 who had a previous caesarean delivery. In the selected timeframe, 199 women with a previous caesarean gave birth. The criteria of inclusion were to have had only one previous caesarean section and no previous vaginal deliveries. The subjects were initially divided into TOLAC or ERCS. Then, the patients from the first group were further divided into successful group and failure group.
Results. Comparing the outcomes of women admitted to trial of labour and those of women who planned a repeat caesarean, we found that maternal age over 35 years was the most important factor influencing the choice of not admitting a woman to trial of labour (OR = 0.38; CI 95%: 0.21-0.69). Moreover, 81.5% of women giving birth at term had a TOLAC *vs* the 18.5% of women in the elective repeat caesarean section group (OR = 4.83; CI 95%: 2.36-9.84).
Conclusions. There were no significant differences between the successful VBAC group and the failure group (who underwent a caesarean section during trial of labour) in regard to nationality, marital status, level of education, maternal age, gestational age at delivery and birth weight.

INTRODUCTION

Trial of labour in a woman who had a previous caesarean section is an option available to most patients. The three most common mistakes obstetricians make in the management of a woman with a previous caesarean section are: underestimate the viability of a vaginal delivery, overestimate foetal risks, and underestimate the risks linked to a repeat caesarean section. The medical advice of the consultant obstetrician is very relevant: the more they consider vaginal birth as the main objective to pursue, the more they will be invested in facilitating and advising a trial of labour to the woman [1]. Whichever choice of mode of delivery - Elective Repeat Caesarean Section (ERCS) or Trial of Labour

After Caesarean (TOLAC) - there is not an option free from risks for the woman and the foetus. 80% of women with one previous caesarean section and no previous vaginal delivery can go through labour; 75% of them (60% of the total) will achieve a vaginal birth after caesarean section (VBAC). 85-90% of all women with a previous caesarean section and at least one previous vaginal delivery will achieve a successful VBAC [2].

The ability to identify women who have greater chances to achieve a vaginal birth after caesarean section could potentially reduce maternal and foetal morbidity, which is higher in the group of women who undergo an unplanned caesarean during trial of labour. For this very reason some studies have proposed scores based on indicators of success, but their clinical usefulness is not satisfactory [3]. A review of vaginal birth after caesarean section [4] highlighted as prognostic factors for a greater chance of achieving VBAC: at least one previous vaginal birth, spontaneous onset of labour and breech presentation as the indication of the previous caesarean section. In contrast, advanced age, high body mass index (BMI) and birth weight above 4000 gr are associated with greater rates of failed trial of labour and increased risk of adverse events. However, these studies consider the newborn's birth weight rather than estimated foetal weight before birth, therefore limiting the clinical usefulness of this data item. In fact, Chauhan reported that only 62% of the ultrasonographic estimates were within 10% of the actual birth weight [5]. Although some studies highlighted a lower chance of successful VBAC if the pregnancy goes beyond 40 weeks, this factor alone shouldn't prevent a TOLAC [6]. Finally, an important role in the likelihood of successful VBAC is the woman's motivation. There is evidence that prediction tools and decision aids may decrease anxiety and reduce uncertainty in decision making among patients [7]. Beside the motivation, a woman should be given the chance to know the statistical data from the hospital in which she has chosen to give birth. In Italy there are great disparities among regions: the rate of successful VBAC goes from 39.4% in the Provincia Autonoma di Bolzano to 2.3% in Basilicata [8]. The wide difference among regions in the rate of repeat caesarean in women with a previous caesarean section confirms the need for significant organizational and clinical improvements within the different hospitals.

The aim of our study is to analyse the failure rate (and related factors) of vaginal delivery after caesarean section among women who delivered in our hospital over the past five years.

MATERIALS AND METHODS

We conducted this retrospective cohort study of pregnant women from 2015 to 2019 who had a prior caesarean delivery. All of these women gave birth at the Sacra Famiglia FBF Hospital in Erba, a small urban non-teaching hospital in North Italy. The data has been collected analysing the birth register certificates from the relevant years. In the timeframe 2015-2019, 199 women with a previous caesarean section gave birth. These women's obstetric history included only one previous caesarean section and no previous vaginal delivery. In order to be admitted to TOLAC, when considered eligible, all women had to sign a consent form. The confidentiality of all participants was maintained during the data collection. In the timeframe 2015-2019 at the Sacra Famiglia FBF Hospital there have been 3424 births and the prevalence of women with previous caesarean section and no previous vaginal birth has been 5.8% (199/3424).

The data have been recorded by midwives immediately after delivery; then, the required data were gathered and entered a checklist with three different sections, including demographic characteristics, past and current obstetric history, mode of delivery and neonatal outcome.

By high level of education, we mean high school diploma or degree, by low level of education we mean middle or primary school completion or no level of education at all.

The focus of this study was the rate of successful VBAC. Therefore, the patients were divided into two groups: trial of labour (TOLAC) or planned repeat caesarean. Then, the patients form the first group were divided into successful group (if they achieved a spontaneous or instrumental vaginal delivery) and failure group (if they did not achieve a vaginal delivery and had to undergo an emergency caesarean section during trial of labour).

Statistical analysis

Chi-square test was used to compare the two groups regarding the rate of elective repeat caesarean section *vs* trial of labour, and the successful vaginal birth after caesarean section rate *vs* unplanned

repeat caesarean section rate. A P-value of less than 0.05 was considered significant in all analyses.

RESULTS

Out of the 199 women with one previous caesarean section and no previous vaginal delivery, 88 (44.2%) had a spontaneous or instrumental vaginal birth, 29 (14.6%) had an unplanned caesarean section during trial of labour, and 82 (41.2%) chose an elective repeat caesarean section. Out of the 117 women admitted to trial of labour, 75.2% achieved a vaginal birth. **Figure 1** shows the percentage of women with a previous caesarean section and those admitted to trial of labour over the five years. There are no significant changes over the years. The average of women with a previous caesarean section, over the five years, is 5.8% (+ 0.34%, - 0.46%). The average of women admitted to trial of labour is 3.4% (+ 0.32%, - 0.38%).
Breech presentation was the indication for elective caesarean section in 6 women, equal to 3% of the women with one previous caesarean section. 6% of the patients (12/199) received an induction of labour. In 2017, a woman admitted to TOLAC had one uterine rupture (0.5%), which didn't require a hysterectomy. The newborn baby was flat and acidotic at birth (pH 6.95), but he subsequently had a normal postnatal period. The same patient gave birth again via elective caesarean section at 37+ weeks in 2020. Five newborns required resuscitation at birth, all of them have had normal follow-ups so far.
Table 1 shows the outcomes of women admitted to trial of labour (TOLAC) and of women who planned a repeat caesarean section in the study cases. Chi-square test showed that maternal age over 35 years was the most important factor influencing the choice of not admitting a woman to trial of labour (OR = 0.38; CI 95%: 0.21-0.69). Moreover, 81.5% of the women giving birth at term (≥ 40 week) had a TOLAC, compared to 18.5% of women in the repeat elective caesarean section group (OR = 4.83; CI 95%: 2.36-9.84).
Table 2 shows the outcomes of successful VBAC and the rate of caesarean section during trial of labour. There were no significant differences regarding nationality (p = 0.277), marital status (p = 0.193), level of education (p = 0.478), maternal age (p = 0.777), gestational age at delivery (p = 0.358) and birth weight (p = 0.752).

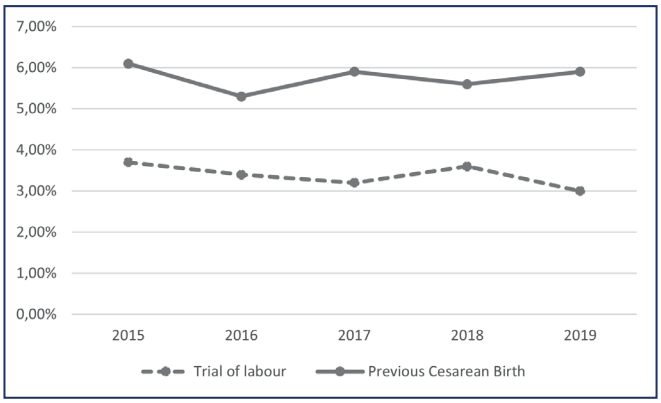

Figure 1. *Rate of women with one prior caesarean and women with trial of labour.*

DISCUSSION

The prevalence of women with one previous caesarean section and no previous vaginal delivery in our hospital is low in comparison with the 12.7%

Table 1. *Characteristics of women with trial of labor after cesarean by successful vaginal birth after cesarean.*

	VBAC	Unplanned Repeat Cesarean	TOT	P-value*	OR (CI 95% OR)
Italian born	64 (78.0%)	18 (22.0%)	82 (100%)		
Foreign born	24 (31.4%)	11 (31.4%)	35 (100%)	0.277	1.63 (0.67-3.94)
Married	62 (72.1%)	24 (27.9%)	86 (100%)		
Unmarried	26 (83.9%)	5 (16.1%)	31 (100%)	0.193	0.49 (0.17-1.44)
High school grade		17 (22.7%)	75 (100%)		
Lower school grade	30 (71.4%)	12 (28.6%)	42 (100%)	0.478	1.36 (0.57-3.22)
Maternal age < 35 y	52 (74.3%)	18 (25.7%)	70 (100%)		
Maternal age ≥ 35 y	36 (76.6%)	11 (23.4%)	47 (100%)	0.777	0.88 (0.37-2.09)
Gestational age at delivery < 40 w	46 (71.9%)	18 (28.1%)	64 (100%)		
Gestational age at delivery ≥ 40 w	42 (79.2%)	11 (20.8%)	53 (100%)	0.358	0.66 (0.28-1.58)
Birth weight < 3500 g	61 (74.4%)	21 (25.6%)	82 (100%)		
Birth weight ≥ 3500 g	27 (77.1%)	8 (22.9%)	35 (100%)	0.752	0.86 (0.33-2.18)

CI: Confidence interval; OR: Odds Ratio; VBAC: vaginal birth after cesarean section; *based Chi-square test.

prevalence of Robson's group V across Regione Lombardia in 2017 [9]. This is due to the meticulous care given to physiological labour in Robson's groups I and III at our hospital [10]. In fact, over the timeframe 2010-2019, the prevalence of caesarean section in Robson's groups I and III has been respectively 4.3% and 1.8% [11]. Breech presentation was the indication for a repeat caesarean section in 3% of the cases. From the analysis of the birth register certificates of our hospital, the overall prevalence of breech presentation at term is 3.2%. This shows that an external cephalic version in breech presentation at 37 weeks is practiced as well on women with a previous caesarean section. In fact, an external cephalic version trial can be attempted on women who wish to trial vaginal birth after previous caesarean section as highlighted by a recent review [12]. Induction of labour for nulliparous women at our hospital in the timeframe 2015-2019 has been 9.8%, a greater prevalence than the one in the population of women with a previous caesarean section (6%). This demonstrates a poor attitude towards using this procedure for women with a previous caesarean section. Although induction and augmentation of labour are not contraindicated in women with a previous caesarean section, there remains considerable disagreement among clinicians on their use. Induction of labour (particularly in women with an unfavourable cervix or by prostaglandins) and augmentation of TOLAC are associated with a 2 to 3-fold increased risk of uterine rupture and around 1.5-fold increased risk of emergency caesarean section, when compared to spontaneous TOLAC [2].

Considering women aged 35 and above, we noted a higher rate of elective caesarean section before labour (OR = 0.38; CI 95%: 0.21-0.69) (**Table 1**). Even Laura B. Attanasio and Mary T. Paterno [13] proved that women aged over 34 face an elective repeat caesarean section in 77.8% of cases, *vs* 22.2% of women admitted to trial of labour. In fact, maternal age of 40 years or above is an independent risk factor for stillbirth and unsuccessful VBAC. Published evidence suggests consideration of delivery of women aged 40 years or more by 39-40 weeks of gestation to reduce the risk of adverse perinatal outcome (particularly stillbirth) [2]. In our study, on the one hand we admitted to trial of labour a greater number of women aged 35 or above compared to the study by Laura B. Attanasio and Mary T. Paterno (47.5% *vs* 22.2%), but on the other hand in many cases we performed an elective repeat caesarean section much earlier than what recommended: 56% below 39 weeks. The Royal College of Obstetricians and Gynaecologists recommends that an elective repeat caesarean section is performed at 39 weeks of gestation, since there is a small increase in neonatal respiratory morbidity if done earlier [2].

Table 2 shows no differences for the variables considered in terms of vaginal birth or caesarean section during trial of labour. This could be due to the small number of women included in our study or to a population mainly without other risk factors (obesity, pregnancy related hypertensive disorders, diabetes, induction of labour). In fact, reviews and meta-analysis with over 200,000 cases reach different conclusions [13, 14].

Our protocol establishes that in women with a previous caesarean section (and no vaginal delivery) the second period will not last more than 2 hours. After 1 hour of expulsive period the woman is visited by a trained obstetrician who will evaluate maternal and foetal well-being and the possibility to start with oxytocine perfusion. Gitas *et al*. [15] do not use an absolute maximum length of time

Table 2. *Characteristics of women with one prior cesarean by trial of labor after cesarean or planned repeat cesarean.*

	ERCS	TOLAC	TOT	P-value*	OR (CI 95% OR)
Italian born	63 (43.4%)	82 (56.6%)	145 (100%)		
Foreign born	19 (35.2%)	35 (64.8%)	54 (100%)	0.292	1.41 (0.74-2.70)
Married	64 (42.7%)	86 (57.3%)	150 (100%)		
Unmarried	18 (36.7%)	31 (63.3%)	49 (100%)	0.464	1.28 (0.65-2.49)
High school grade	58 (43.6%)	75 (56.4%)	133 (100%)		
Lower school grade	24 (36.4%)	42 (63.6%)	66 (100%)	0.320	1.35 (0.73-2.48)
Maternal age < 35 y	30 (30%)	70 (70%)	100 (100%)		
Maternal age ≥ 35 y	52 (52.5%)	47 (47.5%)	99 (100%)	0.001	0.38 (0.21-0.69)
Gestational age at delivery < 40 w	70 (52.2%)	64 (47.8%)	134 (100%)		
Gestational age at delivery ≥ 40 w	12 (18.5%)	53 (81.5%)	65 (100%)	< 0.001	4.83 (2.36-9.84)
Birth weight < 3500 g	57 (41%)	82 (59%)	139 (100%)		
Birth weight ≥ 3500 g	25 (41.7%)	35 (58.3%)	60 (100%)	0.93	0.97 (0.52-1.79)

CI: Confidence interval; OR: Odds Ratio; ERCS: elective repeat cesarean section; TOLAC: trial of labor after cesarean; *based Chi-square test.

for the second stage of labour, and they reported a median expulsive period of 79. 3 minutes (± 61.9) and VBAC's success rate of 55.6% in contrast to 75.2% of our study. Above all, Gitas *et al*. defined the expulsive period as the period from complete dilatation of the cervix to the delivery of the infant. In our study we defined it as the time the woman feels pushing.

Keeping in mind the standard of our hospital, apart from merely statistic considerations, the conclusions we can draw from our study are: first of all, our reality is shared by the majority of Italian hospitals (63.1% of birth centres counts less than 1000 births per year) [8]. Secondly, the importance of counselling during pregnancy, and of assessing the previous personal experience and the indication for the previous caesarean section; the importance of discussing benefits and risks of planned repeat caesarean section *vs* trial of labour, also based on the statistics of one's own hospital and considering the availability of analgesia in labour. A final decision for mode of delivery should be clearly documented in the notes. Thirdly, the focus to understand that planned trial of labour is a clinically safe choice for the majority of women with a single previous lower segment caesarean delivery. Such strategy is also supported by health economic modelling and would at least limit any escalation of caesarean sections rate and maternal morbidity associated with multiple caesarean deliveries [2]. Although it is hard to prove a causal link, the risk of morbidity generally increases with the number of caesarean deliveries. The greatest risk following repeated caesarean sections is that of placenta accrete spectrum and the complications linked to it, especially major post-partum haemorrhage. Other morbidities associated with repeated caesarean sections are foetal growth restriction, preterm birth and possibly stillbirth. Chronic maternal morbidities associated with multiple caesarean deliveries include pelvic pain, adhesions, decreased fertility, increased risk of spontaneous abortion and ectopic pregnancy [16]. It is well reported that, even after two caesarean sections, VBAC does not increase maternal or neonatal morbidity [17]. However, in Italy just few centres perform TOLAC after two caesarean sections, and most of them are Academic Hospital. Finally, our aim is to put in place strategies to reduce the primary caesarean sections rate, especially in the primiparous woman at term with a singleton foetus in cephalic presentation. This can be achieved by preserving the physiology of childbirth, using 6 cm as the cut off for active labour, allowing adequate time for second stage of labour and encouraging operative vaginal delivery [18].

CONCLUSIONS

TOLAC is an appropriate option that should be offered to all precesarized pregnant women with single pregnancy, cephalic fetus and previous caesarean section with transverse incision at the level of the lower uterine segment, with or without a history of previous vaginal delivery, provided that there are no specific contraindications.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

Each author gave a substantial contribution or the preparation of the manuscript.

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None.

Study registration

This study was not registered in an international database repository.

Disclosure of interests

The authors declare that they have no conflict of intersts.

Ethical approval

Ethical approval was not required since the study was classified as a hospital audit of current clinical practice. The confidentiality of all participants was maintained during the data collection.

Informed consent

The authors declare that they have no conflict of interests.

Data sharing

N/A

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Predisposing factors of unresolved gestational hydronephrosis among pregnant women

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ABSTRACT

Background. Gestational hydronephrosis is due to compression of upper urinary tracts resulting from uterine enlargement. Recognition of the predisposing factors would help to reduce the burden of the issue.
Objective. In this study, the various factors of maternal hydronephrosis among pregnant women were assessed.
Materials and Methods. In this prospective cohort, 105 consecutive pregnant women were assessed in an 18-month period of time for occurrence and severity of hydronephrosis and contributing factors were determined.
Results. In this study, 83.8% had gestational hydronephrosis that was alleviated in 76.1% in postpartum phase. Myoma, gestational diabetes mellitus, and twin pregnancies were related to both more occurrence and less improvement of hydronephrosis; however, high gravid was only related to less improvement of gestational hydronephrosis ($p < 0.05$).
Conclusions. Approximately, 4/5 of pregnant women experience gestational hydronephrosis that is alleviated in 3/4 of the cases in the postpartum phase. It is multifactorial and in high-risk women such as those with high gravid, twin pregnancy, gestational diabetes mellitus, and myoma, further screenings and cautions are required.

INTRODUCTION

Gestational hydronephrosis is an aggravated physiological phenomenon that often occurred in pregnancy from 6th to 10th weeks, and is usually due to compression of the upper urinary tracts by an enlarged uterine [1, 2]. It is more common in the right kidney of pregnant women. Although, gestational hydronephrosis is usually asymptomatic, it may be bothersome in some high-risk pregnant women. The symptoms of this phenomenon vary from mild flank pain to severe [3, 4]. Also, there is an increased risk of kidney scar in patients without improvement [5]. It may be asymptomatic or with flank, abdominal, or inguinal pain [6, 7]. Dysuria, urinary retention, and incontinence are less common symptoms, as well as, fever, nausea, vomiting, and hematuria, depending on the cause and severity of urinary obstruction [7, 8]. Multiple causes are proposed for gestational hydrone-

phrosis but enlarged uterine and pressure on the ureters may reduce the urinary flow that may be also aggravated by organ prolapse and increased progesterone secretion and muscle relaxation, totally leading to urinary retention with mild, moderate, and severe grades [9, 10]. Treatment of the main underlying cause is crucial, however, if only the pregnancy is contributing factor, no further interventions are required, and it would be resolved spontaneously after pregnancy termination. But drainage of retained urine by catheters would decrease the injury [11, 12]. Determination of the contributing factors would be useful for the prevention of hydronephrosis and consequent problems [13-20]. Hence, in this study, the predisposing factors of gestational hydronephrosis were assessed.

MATERIALS AND METHODS

In this prospective cohort, 105 consecutive pregnant women attending the hospitals with which the authors are affiliated, in 2018 and 2019, were enrolled. The exclusion criteria were history of renal disease, stone, urinary infection and hydronephrosis. Data were collected by checklists with interview and observation. Moreover, the hydronephrosis and severity were assessed by ultrasound across the study by a single expert radiologist.
The study was approved by the ethical committee of the authors' institution with Code IR.IUMS.Rec1396.8923496033. The patients signed informed consent for participating in the study. The study was performed in accordance with the ethical standards described in an appropriate version of the 1964 Declaration of Helsinki, as revised in 2013. No additional costs were imposed on the patients. Ultrasonography was carried out in each trimester to determine the ureter length and diameters. Additionally, six weeks after labour, it was repeated to monitor the resolution of hydronephrosis. In unresolved cases, serial ultrasound assessments were done.

Statistical analysis

Data analysis was done by SPSS version 22.0 software. The utilized tests were Independent-Sample-T, Mann-Whitney, Chi-Square, Fisher, Spearman, and Pearson. The P values less than 0.05 was considered significant.

RESULTS

Totally 105 women were assessed. The mean age was 31 ± 5 ranging from 19 to 42 years. Ultrasonography was carried out in the second and third trimester to evaluate the ureteral length and diameters. Moreover, six weeks after labour, follow up sonography was done to monitor the resolution of hydronephrosis. In unresolved cases, serial ultrasound evaluations were performed. Totally, 88 women developed gestational hydronephrosis (83.8%).
In the second trimester assessment, 39 women were normal; however, 29, 10, and 27 women had right, left, and bilateral hydronephrosis, respectively.
In the third trimester, 17 pregnant women were normal, though, 29, 4, and 55 had right, left, and bilateral hydronephrosis, respectively. Among 88 cases with gestational hydronephrosis in the third trimester, 67 patients were completely resolved after labour; anyhow, it was remained in right, left, and both sides in 12, 6, and 3 cases (**Figure 1**).

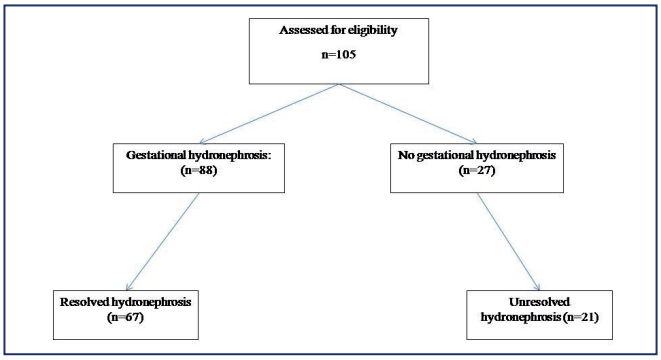

Figure 1. *Flow chart of the study.*

After multivariate analysis, the primigravidity was related to unresolved maternal hydronephrosis ($p = 0.001$), however, the parity was not related ($p > 0.05$).
In mothers with myoma, the hydronephrosis was related to myoma and right-side APD was significantly higher in the third trimester ($p = 0.004$). All myoma cases had no resolution in hydronephrosis on the right side ($p = 0.0001$).
In the postpartum phase, there was a significant association between gestational diabetes mellitus (GDM) and unresolved right-side hydronephrosis ($p = 0.036$), however, it was not related to unresolved left side hydronephrosis ($p = 0.07$).
Gestational hypertension was only seen in four mothers and comparison may not be comprehensive.

The mean amniotic fluid index (AFI) was 142.2 ± 23.8 and 135.1 ± 34.4 in the second and third trimesters, respectively. The mean AFI was not different in unresolved and resolved cases ($p = 0.024$). Mean fetal weight was 746.5 ± 176.8 and 2850.7 ± 363.8 in the second and third trimesters, respectively. In the second trimester, APD was related to fetal weight in second trimester ($p = 0.013$). The fetal weight was not significantly different between the unresolved and resolved group ($p = 0.15$).
The maternal weight in third trimester on the left side had a significant association with severe hydronephrosis ($p = 0.027$) and in both sides in third trimester was significantly higher ($p < 0.05$), though it was not related to unresolved hydronephrosis.
There were 5 women with twin pregnancy that all had hydronephrosis that had increased severity in all cases in the third trimester; however, surprisingly, all were resolved in the postpartum phase.

DISCUSSION

In this study, the severity and prevalence of gestational hydronephrosis were assessed and nearly 84% had hydronephrosis that was alleviated in 76.1% in the post-partum phase. Primigravity, myoma, GDM, fetal and maternal weight and also twin pregnancy is related to increased gestational hydronephrosis incidence. However, only Primigravidity, myoma and GDM were related to unresolved maternal hydronephrosis. Schulman and Herlinger reported that hydronephrosis was seen since mid-term to full-term pregnancy, but it was rare before mid-term. Also, 75% had right-side and 33.3% had left side hydronephrosis. It was right and left-sided in 10% and 86%, respectively. They concluded that hydronephrosis was not related to fetal position, gravidity, and urinary tract infection. The study by Rajaei *et al*. [3] among 59 cases showed that nearly 70% had unilateral or bilateral hydronephrosis. They found no significant association between gestational age and fetal presentation. But they reported higher rates in the first pregnancy and on the right side. However, in current assessments, the gravidity was related to hydronephrosis, and it was less significant in women without previous pregnancy.
The study by Fried *et al*. [10] among 20 asymptomatic women showed that 41.5% had hydronephrosis and dilatation and it was more common on the right side and was improved till six weeks after labour. In our study, the rate was higher (84%) and was disappeared in the majority of cases (76%). However, the remaining cases had also lower intensity. But as shown by Babu et al [13] the prognosis would be better in unilateral cases [13]. Sarhan *et al*. reported a rate of 70% for spontaneous improvement of gestational hydronephrosis. It was relatively higher in our study. Oyinloye and Okoyomo [2] assessed 135 pregnant and 43 non-pregnant women by ultrasound for hydronephrosis and among them, 93.4% and 84.4% had right-side and left-side hydronephrosis. The mean ureteral diameter was significantly higher in them in comparison with non-pregnant cases without urinary disorders and hydronephrosis with a significant difference for the right side. In our study, the prevalence of hydronephrosis was higher and with more severity in comparison with the left side. Macedo *et al*. [21] have evaluated different diagnosis with potentially changed renal function such as Preeclampsia. In their meta-analysis, they found that socioeconomic variables have a great role in the risk of preeclampsia. Laganà *et al*. [22] have studied on the biochemical pattern in serum to predict preeclampsia and reviewed the available information about early markers [23].
Some authors such as Buttice et al discuss other etiology of gestational hydronephrosis, such as pelvic ureteral endometriosis and ureteral stones [24] which should be considered in unresolved cases of the disease. Woo *et al*. [6] assessed 56 asymptomatic pregnant women and found that 89% had minimal ureteral dilatation and it was severe in six cases. The dilatation was seen in all of them in the second trimester and usually the return in the first five weeks is not common. The medium to severe dilatation is low in women with mild dilatation in second trimester. Similarly, in our study, there was no significant association between hydronephrosis in second and third trimesters.
Totally, it is concluded that nearly 84% of pregnant women have gestational hydronephrosis and some altering factors such as myoma, gestational diabetes mellitus, and weight increase may raise the possibility of gestational hydronephrosis and less improvement. Hence programming for these factors would be beneficial. But also, there are some non-changeable factors such as twin pregnancy, gravidity, and parity that would necessitate further cares. In this study, all twin mothers had severe hydronephrosis in the last pregnancy month that was usually bilateral and regarding a low number of these mothers, the association with other factors was not determined. Also, the role of sex may be masked due to the interaction effects of other variables. However, further

studies with a larger sample size are required to develop more definite results and finding other predisposing factors, especially in twin pregnancies.

CONCLUSIONS

Approximately 4/5 of pregnant women experience gestational hydronephrosis that is alleviated in 3/4 of cases in the postpartum phase. It is multifactorial and in high-risk women such as those with primigravidity, gestational diabetes mellitus, and myoma, further screenings and cautions are required for unresolved hydronephrosis.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contributions

M.A.G.: concept, design. E.K, A.S..: data collection or processing. M.R., A.S.: analysis or interpretation. M.R., A.S.: literature search. M.A.G., E.K., A.S.: drafting the work. All authors: final approval of the version to be published. All authors: agreement to be accountable for all aspects of the work.

Fundings

None.

Discolsure of interests

The authors declare thet they have no conflict of interests.

Ethical approval

The study was approved by ethical committee in Iran University of Medical Sciences with the code: IR.IUMS.Rec1396.8923496033.

Informed consent

The patients signed informed consent for participating in the study.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Repercussions of the COVID-19 pandemic in the emergency department of Gynecology and Obstetrics at a referral hospital in Portugal

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ABSTRACT

Objective. COVID-19 has spread worldwide and Portugal decreed the State of Emergency on March 18th, 2020. During this period, the population was encouraged to stay at home. Still, there were no restrictions on access to health care. Therefore, we aimed to compare the major causes for attending the Obstetrics and Gynaecology Emergency Department (ED) from a referral centre (Maternidade Dr. Alfredo da Costa, in Lisbon).
Materials and Methods. Several variables were collected and compared between two periods of time: from 19th March to 2nd April 2020 and the same period of 2019.
Results. During the COVID-19 pandemic period, 49.4% fewer patients visited the ED. We observed a higher number of urgent patients and hospitalization rate than previous year.
Conclusions. We experienced a reduction number of admissions to the Obstetrics and Gynaecology ED, but apparently the severity of cases that visited the ED increased.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since December 2019 it has spread worldwide when a number of patients with pneumonia of unknown aetiology emerged in Wuhan City, Hubei Province, Central China. Consequently, on March 11th, 2020, it was declared as a pandemic by the World Health Organization [1]. In Portugal, the first case was reported on 2nd March and the National Government decreed a State of Emergency on March 18th, 2020. On April 2nd, the State of Emergency was renewed and ended on May 2nd. During this period, the population was encouraged to stay at home; however, there were no restrictions on access to health care [2]. Nevertheless, most non-urgent activities were suspended during this period and different services had to be reorganized to shift some personnel to departments in need, even in the ED, in order to receive COVID patients.

The main purpose of this study was to compare major causes of presentation to the Obstetrics and Gynaecology ED. Also, we compared the number and demographic characteristics of patients attending it, between March 19th and April 2nd, 2020, with the same period of 2019.

MATERIALS AND METHODS

This is an observational, retrospective and single-centre study focusing on the use of the Obstetrics and Gynaecology ED at Maternidade Dr. Alfredo da Costa during the COVID-19 pandemic. Maternidade Dr. Alfredo da Costa is the maternity of the Central Lisbon Hospital Centre (CHULC), placed in Lisbon, Portugal, and considered a referential centre with a differentiated perinatal support, where Obstetrics and Gynaecology ED is located. The maternity was identified as one of the COVID-19 referral centres for pregnant women with creation of new COVID dedicated medical wards. Our study was approved by the institutional ethics committee.
Data were collected from institutional clinical software of ED from March 19th to April 2nd, 2020 and also from the same period of the previous year. Clinical severity under the Manchester triage system (MTS), age, parity, complaints that motivated the visit to the ED and need for hospitalization were the considered variables. Patients were allocated in one of two groups: pregnant *vs* non-pregnant.
International ethical standards were used on the elaboration of this study.

Statistical analysis

Statistical analysis, including descriptive and bivariate analyses, was performed using IBM SPSS® 23.0 version. Normal distribution was checked using Shapiro-Wilk or Skewness and Kurtosis. Concerning bivariate analysis, Chi-Square statistic and independent- samples T-test were used. All reported P-values are two-tailed, with a P-value of 0.05 indicating statistical significance. Categorical variables were presented as frequencies and percentages and continuous variables as means and standard deviations.

RESULTS

A total of 1413 patients were admitted to our department on the aforementioned dates, respectively 938 in 2019 and 475 in 2020, which means that during the COVID-19 pandemic period, 49.4% fewer patients visited the Obstetrics and Gynaecology ED, compared with the same period of the previous year. The mean age of total patients in 2019 was 32.40 ± 9.75 years *vs* 31.65 ± 7.64 in 2020, without statistical significance ($p = 0.116$). Considering clinical severity grade under the MTS, when we compare the urgent patient group (identified with orange and yellow bracelets) with non-urgent group (identified with green and blue bracelets) in the two periods (25.40% and 74.60% in 2019 *vs* 27.80% and 72.80% in 2020, respectively), a statistically significant difference was found ($p = 0.037$). Regarding the hospitalization rate, it was higher during the COVID-19 pandemic than in homologous period of 2019 (16.3% *vs* 5.7%; $p < 0.001$).
Pregnant women were the more frequent group on Obstetrics and Gynaecology ED (76.50% in 2019 *vs* 83.2% in 2020; $p = 0.004$). In the pregnant group, the mean gestational age was 24.26 ± 13.26 in 2019 *vs* 26,55 ± 13.47 in 2020 ($p = 0.007$) and more than 50% were nulliparous women in both analysed periods ($p = 1.000$), as mentioned in **Table 1**. Pregnant women addressed more to the ED in the third trimester of pregnancy in both years (50.4% *vs* 58.7%). During COVID-19 time there was a significant increase compared to the year before ($p = 0.008$).
The main cause of presentation to the ED in the pregnant group is shown in **Table 2**. Painful contractions were the most common reason of ED admission in 2020 ($n = 95$; 24.1% *vs* $n = 136$; 18.9% in 2019) with statistical significance ($p = 0.05$) and vaginal bleeding was the main reason in the 2019 period time ($n = 152$; 21.2% *vs* $n = 74$; 18.7%; $p > 0.05$). Pelvic pain (not related to contractions) had a lower incidence during the COVID-19 pandemic (9.1% *vs* 15.3%, $p = 0.003$). On the contrary, suspicion of amniotic fluid leak had a higher incidence in current year (13.7% *vs* 8.1% in 2019, $p = 0.004$). The rate of hospitalized women in the obstetric group was 21.2% ($n = 152$) in 2019 and 30.6% ($n = 121$) in 2020 ($p = 0.001$). Patients hospitalized in labour area totalized 74.3% in 2019 and 76.9% in 2020 ($p = 0.673$). One of the hospitalized pregnant-woman had a diagnosis of preterm premature rupture of membranes at 30 weeks' gestation and she was infected with SARS-CoV-2. In this case, the patient was hospitalized in the new COVID medical ward for specialized care and precautions.
Moreover, a minority of patients attended the emergency service having gynaecological or postpartum complaints (non-pregnant group). In this group, vaginal bleeding and pelvic pain were the most common pre-

Table 1. *Characteristics of ED visits.*

Pregnant group			
	2019 (n = 718)	**2020 (n = 395)**	**P-value[a]**
Age (years)	31.09 ± 6.470	30.85 ± 6.448	0.543
Gestational age of pregnant women (weeks)	24.25 ± 13.26	26,58 ± 13.47	0.007
1st trimester (≤ 14 weeks) – n (%)	227 (31.6)	113 (20.6)	0.308
2nd trimester (14-26 weeks) – n (%)	129 (18.0)	50 (12.7)	0.021
3rd trimester (> 26 weeks) – n (%)	368 (50.4)	232 (58.7)	0.008
Parity			
Nulliparous – n (%)	372 (51.8)	205 (51.9)	1.000
Primiparous – n (%)	207 (28.8)	128 (32.4)	0.220
Multiparous – n (%)	139 (19.4)	62 (15.7)	0.143
Manchester triage system			
Urgent group – n (%)	197 (27.4)	134 (33.9)	0.028
Hospitalization – n (%)	152 (21.2)	121 (30.6)	0.001
Hospitalized patient destination			
Labor area – n (%)	113 (74.3)	93 (76.0)	0.673
Maternal-fetal ward – n (%)	38 (25.0)	26 (21.5)	0.566
Gynecological ward – n (%)	1 (0.7)	2 (1.7)	0.586

[a]Independent-samples T-Test for continuous variables; Pearson chi-squared test for categorical variables.

sentation symptoms in the ED during the two analysed periods (n = 77; 35% in 2019 *vs* n = 24; 30% in 2020; p > 0.05 and n = 38; 17.3% in 2019 *vs* n = 13; 16.3% in 2020; p > 0.05, respectively). During the COVID-19 pandemic, the incidence of amenorrhea (without diagnosis of pregnancy) was higher than in the same period of 2019 (n = 6; 7.5% *vs* n = 2; 0.9%; p = 0.005). The remaining complaints are described in **Table 3**. In non-pregnant group, the number of hospitalized patients was similar (0.5% in 2019 and 1.3% in 2020; p > 0.05).

DISCUSSION

Recommendations from the national Government alerted people to remain at home during the presumably worst time of the COVID-19 pandemic [2]. This contributed to a significant decrease in the health care services, specifically Obstetrics and Gynaecology ED, as shown in our study. Recent studies regarding the COVID-19 pandemic and other specialties also support our results concerning their ED [3].

Based on literature, studies elucidate that women frequently use the ED during pregnancy, including visits for non-urgent indications [4]. Moreover, Portugal's Obstetrics and Gynaecology ED health system offers free access for pregnant women [5] which contributes to an increasing number of admissions. We consider that this is one of the reasons that explains why there is a significantly different percentage of pregnant *vs* non-pregnant women in our service. Maternal anxiety, specially related to uncertainty during the COVID-19 pandemic, could also be an important part of this reality. Surprisingly, given the services reorganization and suspension of non-urgent activities, in order to reduce the virus circulation among the population [6], we demonstrate a reduction of admitted patients with gynaecological complaints that could have their health care postponed. It should be noted that there were surgical emergencies, in particular ovarian torsion or ectopic pregnancy, that could not be delayed. Thereby, a COVID-19 testing and risk assessment were advised depending on the degree of the urgency [6].

On the other hand, and based on the Manchester triage system, we demonstrate a larger and significant affluence to the ED of urgent patients (orange and yellow bracelets) and an increase of the hospitalization rate during the COVID period occured, including in the pregnant group. We consider that the populations' reluctance to address the ED during this contingency period contributed to a reduction in the ED attendance for mild symptoms and a search for specialized help only with more severe symptoms at later stages of disease.

Pregnant women used more often the ED during the third trimester, which is also described by other authors [7]. It probably occurs because during the last weeks of pregnancy women experience some symptoms that can be related with starting of labour and all patients came to the ED at least once, to deliver. Experiencing other pregnancies could change the

Table 2. *Causes of presentation to the ED.*

Pregnant group			
	2019 n (%)	2020 n (%)	P-value[a]
Vaginal bleeding	152 (21.2)	74 (18.7)	0.351
Pelvic pain	110 (15.3)	36 (9.1)	0.003
Painful contraction	136 (18.9)	95 (24.1)	0.053
Suspected of amniotic fluid leak	58 (8.1)	54 (13.7)	0.004
Decreased fetal movements	28 (3.9)	12 (3.0)	0.565
High blood pressure	28 (3.9)	13 (3.3)	0.740
Vulvar pain	0 (0)	2 (0.5)	0.126
Vaginal discharge	21 (2.9)	4 (1.0)	0.003
Routine antenatal control	56 (7.8)	33 (8.4)	0.731
Gastrointestinal symptoms	19 (2.6)	12 (3.0)	0.707
Genitourinary symptoms	23 (3.2)	12 (4.0)	1.000
Amenorrhea	32 (4.5)	19 (4.8)	0.767
Others	55 (7.7)	28 (7.1)	0.812
Total	718 (100)	395 (100)	

[a]Pearson chi-squared test.

Table 3. *Causes of presentation to the ED.*

Non-pregnant group			
	2019 n (%)	2020 n (%)	P-value[a]
Vaginal bleeding	77 (35.0)	24 (30.0)	0.490
Pelvic pain	38 (17.3)	13 (16.3)	1.000
Vulvar pain	17 (7.7)	3 (3.0)	0.299
Vaginal discharge	26 (11.8)	10 (12.5)	0.843
Genitourinary symptoms	19 (8.6)	7 (8.8)	1.000
Amenorrhea	2 (0.9)	6 (7.5)	0.005
Mastalgia	11 (5)	8 (10)	0.177
High blood pressure (postpartum)	2 (0.9)	0 (0)	1.000
Routine postpartum control	6 (2.7)	5 (6.3)	0.170
Others	22 (10)	4 (5)	0.246
Total	220 (100)	80 (100)	

[a]Pearson chi-squared test.

pattern of coming to the ED, so we presume that multiparas would understand better the complaints that occur during pregnancy. In our study, a lower inflow of multiparas to the ED was observed, without statistical significance, though. Possibly the sample size has not been large enough to find these differences.

Regarding the causes for attendance at the ED among the pregnant group, we demonstrate that there was a big number of patients with important complaints, such as painful contractions and suspicion of amniotic fluid loss, during the COVID period. Furthermore, we found a significant reduction in other complains of pregnant women, such as vaginal discharge, considered less serious [8]. Fewer pregnant women accessed the ED with pelvic pain during the COVID period time. This nonspecific symptom can occur throughout pregnancy, with several causes and severity differences, so it cannot be undervalued. We didn't observe a significant difference in the remaining complaints.

In non-pregnant group, another non-urgent indication [7], amenorrhea (without pregnancy diagnosis), was a more frequent symptom during 2020 than in 2019. This could be related to the confinement at home, so it could be easier to access to the ED for the pregnancy detection and reassurance of women, instead of buying themselves a pregnancy test.

The authors of this study recognize an important limitation related to its retrospective nature and to the fact that only the first two weeks of the state of emergency in Portugal have been studied. We decided to analyse this period of time, given the current relevance of the topic and as it was an adaptation period with important changes in hospital services. The world countries dealt with the pandemic in different ways due to its novelty and to

the lack of unanimous consent on the best health-care management strategies.

CONCLUSIONS

The pandemic COVID-19 caught the world and especially the health care off guard and it was necessary to restructure health services, including the ED, to create new dedicated COVID-19 areas. It was supposed that urgent situations continued to be done, contrarily to different non-urgent care that was postponed. Even so, the number of admissions to the Obstetrics and Gynaecology ED decreased. On the contrary, it seems that the severity of the cases that recurred increased. The consequences of COVID-19 are yet to be determined and it would be interesting additional research to prolong observations, including a longer interval.

COMPLIANCE WITH ETHICAL STANDARD

Authors contribution

All authors contributed equally to the work.

Fundings

None.

Study registration

N/A

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

This study obtained ethical approval by Ethics Committee from Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal (protocol number 919/2020 - 02/26/2021).

Informed consent

Exemption from informed consent were requested, with the justification that the study was important and had be carried out in a short period of time, with an exclusively investigative purpose. Only pseudonymized data were used. As this was an exceptional situation, the general rule of obligatoriness to obtain informed consent, which is also legally provided in article 06, n° 1 d) of law n° 21/2014 of April 16, it becomed necessary to justify that request.

Data sharing

Data are available under reasonable request to the corresponding author.

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The effect of intravenous (IV) tranexamic acid plus buccal misoprostol on blood loss during and after cesarean delivery: a randomized double-blind study

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ABSTRACT

Objective. To investigate the efficacy and safety of tranexamic acid (TA) plus buccal misoprostol *versus* intravenous oxytocin in reducing bleeding during and after cesarean delivery in women with risk factors for postpartum hemorrhage.
Patients and methods. A randomized clinical trial (NCT03505333) conducted on 400 pregnant women at term (37-40 weeks) gestation, scheduled for elective cesarean delivery, who were assigned to either 1 gm intravenous (IV) tranexamic acid plus buccal misoprostol 400 mcg or intravenous infusion of 20 units of oxytocin after delivery of the neonate. The main outcome measures were blood loss at cesarean section and 6 hours after cesarean delivery, the need for any additional oxytocic drugs, and drug-related side effects.
Results. The overall mean blood loss was significantly lower in the misoprostol group compared to the oxytocin group (863.48 ± 194.95 mL *vs* 1047.10 ± 290.96 mL; p = 0.0001). There was a need for additional oxytocic therapy in 27% and 57% after the use of misoprostol and oxytocin, respectively (p = 0.0001). The incidence of side effects such as shivering and the metallic taste was significantly higher in the misoprostol group compared to the oxytocin group (p = 0.0001).
Conclusions. IV TA plus buccal misoprostol is more effective than an intravenous infusion of oxytocin in reducing total blood loss during and after cesarean delivery.

INTRODUCTION

Postpartum hemorrhage (PPH) is the main etiology of maternal death in both developed and developing countries [1]. Because it is a leading etiology of mortality and morbidity to the parturient women, and most maternal mortality is due to substandard care, prioritize the prevention and treatment of PPH in low-resource countries should be a priority in the development of national care guidelines [2].
The risk of PPH is much higher for women undergoing cesarean delivery, so the methods used to decrease blood loss during cesarean delivery have a great benefit to decrease postoperative morbidity and decrease the risks associated with blood transfusions [3].
Although many hospitals use oxytocin as the first line to prevent uterine inertia during cesarean delivery, it may not be the ideal agent for the prevention of PPH, especially in compromised patients with preeclampsia, cardiac disease, or prolonged labor [5]. Oxytocin only has a half-life of 4-10 min [4]; therefore, at cesarean section oxytocin must be administered as a continuous intravenous infusion to attain sustained uterotonic activity throughout the surgical procedure and the immediate postpartum period.
Misoprostol is a thermostable compound that is effective when given orally, buccal, sublingually,

vaginally, or rectally, raised the exciting possibility that it might be used especially in developing countries as it is cheap, where women are at most risk from the rapidly fatal effects of severe PPH [6]. Buccal misoprostol requires less skill to administer and is cheaper than oxytocin infusion. It is also probably more suitable for the lady as it relieves the restriction imposed by an infusion line. This is in addition to the superior heat stability and longer shelf life of misoprostol compared with oxytocin [6].

TA is an inexpensive, widely available medicine that has been shown to reduce bleeding in surgery and reduce the risk of death in bleeding trauma patients [7]. It is therefore unsurprising that there is interest in its role in the prevention of postpartum hemorrhage.

TA given at the time of delivery could prevent severe postpartum bleeding. Plasma t-PA (the main fibrinolytic activator) doubles within an hour of delivery, probably due to the trauma of childbirth [8]. In our previous study, prophylactic utilization of 1000 mg oral TA in addition to 600 μg buccal misoprostol during vaginal delivery effectively reduces the postpartum blood loss, blood transfusion needs as well as lower the incidence of PPH than misoprostol alone [9].

The current study compares the efficacy of TA plus buccal misoprostol to intravenous oxytocin in the prevention of blood loss following cesarean delivery in women with risk factors for postpartum hemorrhage.

MATERIALS AND METHODS

It was a clinically registered randomized, double-blind, clinical trial (ClinicalTrials.gov: NCT03710304) conducted in a tertiary university hospital. The ethical review board approved the study by a grant number of (Aswu/273/7/18). The study participants were women who attended the outpatient obstetric clinic, seeking antenatal care and they were scheduled for elective cesarean delivery (CD) and had risk factors for postpartum hemorrhage from 1st of January 2019 to 30th of June 2020. Women who met the selection criteria of the study were invited to participate after signing informed consent. This trial was conducted and reported according to the CONSORT updated guidelines for reporting parallel group randomized trials [10], and according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting randomized clinical trials.

Eligible participants

Study inclusion criteria were women who were scheduled for elective CD and had risk factors for postpartum hemorrhage. Exclusion criteria were:

1. patients with any medical or metabolic disorders or take medications that can interact with the drugs in the study, for example cardiac, preeclampsia, renal, hepatic, severe anemia, thromboembolic disease or diabetes miletus;
2. patients with placenta previa;
3. patients had an allergy to tranexamic acid, oxytocin, or misoprostol;
4. patients with any pelvic pathology need extra surgical interference, for example severe endometriosis, uterine leiomyoma, severe pelvic adhesion, *etc*.;
5. patients having any contraindications for spinal anesthesia.

450 patients were asked to participate, 50 patients were excluded, 35 patients did not meet inclusion criteria and 15 patients refused to participate. Therefore the remaining 400 patients were included in the study. All participants underwent detailed history, general, and obstetric examinations, body weight, and Hight were calculated and preoperative hemoglobin was done for all participants after that an abdominal ultrasound examination was undertaken. The participants who fulfilled the eligibility criteria were explained about the study with the beneficial and possible adverse effects of misoprostol and tranexamic acid. Informed consent was obtained from them after that participants were randomized to 2 groups (the oxytocin group (group 1) and the TA plus buccal misoprostol group (group 2)) (**Figure 1**).

Randomization

Patients were randomized to two groups, each composed of 200 patients according to a two-blocked randomization list which was coded (I or II) at a 1:1 ratio. The two parallel groups were prepared using a computer-generated randomization system. The allocated groups were concealed in serially numbered sealed opaque envelopes that were only opened after recruitment. Patient allocation was performed before the induction of spinal anesthesia by an independent person, who was not otherwise involved in this study. The trial was appropriately blinded; the participants, outcome assessors, and the surgeon performing the procedure were blinded to the used medication type.

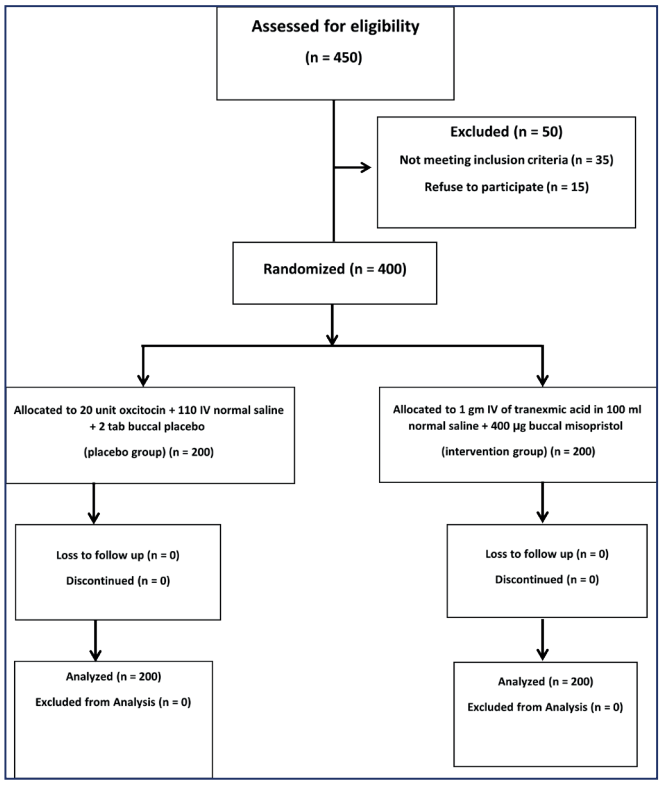

Figure 1. *Flow chart of the study.*

Intervention

Eligible participants were allocated to one of the two groups after induction of spinal anesthesia and immediately after delivery of the neonate.

The oxytocin group (group 1) received 20 IU oxytocin dissolved in 500 mL of lactated Ringer's and infused at the rate of 75 mL/h, immediately after delivery of the neonate, plus placebo to buccal misoprostol in form of 2 tablets buccal (ranitidine) plus placebo to TA (110 normal salines) by slow intravenous injection at an approximate rate of 1 mL per min.

The TA plus buccal misoprostol group (group 2) received 1 gm TA plus 400 µg of sublingual misoprostol. It received 400 µg buccal misoprostol (2 tablets of 200 µg) plus 1-gram tranexamic acid (10 mL) in 100 mL saline infusion by slow intravenous injection at an approximate rate of 1 mL per min plus placebo to oxytocin infusion (500 mL of lactated Ringer's and infused at the rate of 75 mL/h). The uterine tone was assessed according to a 5-point Likert scale (0 floppy, 4 rock hard) by the operating obstetrician immediately after delivery of the placenta and then every 5 min until abdominal closure began.

Additional oxytocic therapy was given if the uterine tone was inadequate or the cesarean section become hemorrhagic. The available options were ergonovine and 15-methyl prostaglandin $F_{2\alpha}$.

Blood loss estimation

Intraoperative blood loss was measured by adding the volume of the contents of the suction bottle after delivery of the baby and placenta and the difference in weight (in grams) between the dry and the soaked operation sheets and towels (1 gram = 1 mL). Post-operative blood loss was measured through vaginal blood loss during the first 24 hours post-operative by calculating the difference in weight (in grams) between the dry and the soaked vaginal pads (1 gram = 1 mL). Then the estimated total blood loss was calculated by the addition of intraoperative and postoperative blood loss.

Study outcome

The primary outcome was the estimation of blood loss during and after cesarean delivery following administration of TA plus buccal misoprostol or intravenous oxytocin.

The secondary outcome measures included the need for any additional oxytocic drugs, postoperative Hemoglobin concentration, the incidence of postpartum hemorrhage, operative time, and incidence of side effects (unpleasant taste, fever, shivering, nausea, vomiting, and diarrhea).

Sample size

The sample size was calculated based on the primary outcome (blood loss in women after cesarean delivery), taking mean blood loss with the use of oxytocin as 974 mL with a standard deviation of 285 mL [11]. Assuming that TA plus buccal misoprostol is more effective than oxytocin in reducing blood loss by 125 mL, 200 participants in each group will have > 85% power at 5% significance to detect such a difference (Epi-info: Centers for Disease Control and Prevention, Atlanta, GA, USA).

Statistical analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. A Chi-square test was used for comparison between groups. Quantitative data were described as means (SD) or medians, as appropriate. They were tested for normality by the Kolmogorov-Smirnov test. In the normally distributed variables, independent

samples t-test was used for comparison between groups. In the non-normally distributed variables, the Mann-Whitney test was used for comparison between groups. Odds ratios and their 95% confidence interval were calculated. P-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Our study started with 450 patients who were asked to participate, 50 patients were excluded, 35 patients did not meet inclusion criteria and 15 patients refused to participate. Therefore, the remaining 400 patients were randomized into 2 groups each group comprised 200 patients.

Group I: received 110 gm IV normal saline + 2 tablets placebo buccal (ranitidine) just before skin incision + 20 unit oxytocin in 500 mL of IV saline infusion over 15 min after delivery of the baby.

Group II: received 400 μg buccal misoprostol (2 tablets of 200 μg) + 1 gm tranexamic acid in 100 mL normal saline over 30-60 seconds before skin incision + 500 mL normal saline IV over 15 min after delivery of the baby).

There was no significant difference between the two groups concerning their age, weight, height, body mass index (BMI), parity, gestational age, initial hemoglobin, and an indication of CS (**Table 1**).

Group II showed a significant reduction in intraoperative blood loss compared with Group I, (p = 0.0001), but no significant difference between the two groups in postoperative blood loss (p = 0.624), however the overall estimated blood loss in group II showed a highly significant reduction compared with group I (p = 0.0001) (**Table 2**).

Table 1. *Preoperative characteristics of pregnant women in the study groups.*

Parameters	Group I (n = 200)	Group II (n = 200)	Significance
Age (year)	29.02 ± 4.32	29.05 ± 4.04	0.943
Weight (kg)	69.32 ± 6.87	69.29 ± 6.21	0.970
Height (cm)	162.94 ± 4.18	163.44 ± 4.28	0.248
BMI	26.07 ± 2.06	25.94 ± 2.11	0.536
Parity (median) (minimum-maximum)	2 (0-6)	2 (0-5)	0.525
Gestational age (weeks)	38.27 ± 0.84	38.33 ± 0.87	0.521
Initial hemoglobin	10.624 ± 0.74	10.616 ± 0.79	0.917
indication of CS (%)			
repeated cs	108 (54)	110 (55)	0.978
breech	37 (18.5)	34 (17)	
macrosomia	25 (12.5)	24 (12)	
twin	24 (12)	24 (12)	
patient request	6 (3)	8 (4)	

BMI: body mass index; CS: cesarean Section; variables are presented as mean and standard deviation, median (minimum-maximum) and number (percentage).

Table 2. *Primary outcome in the study groups.*

Blood loss	Group I (n = 200)	Group II (n = 200)	Significance
Intraoperative	879.25 ± 280.57	694.70 ± 186.15	0.0001*
Postoperative	167.85 ± 39.03	169.78 ± 39.48	0.624
Total blood loss	1047.10 ± 290.96	863.48 ± 194.95	0.0001*
Additional uterotonics (%)	114 (57)	54 (27)	0.0001*

*Statistically significant difference; variables are presented as mean and standard deviation and number (percentage).

The incidence of the need for additional uterotonics was a significant decrease in group II, 54 (27%) patients compared to group I, 114 (57%) patients (p = 0.0001). Also, the incidence of postpartum hemorrhage was a significant decrease in group II, 23 (11.5%) patients compared to group I, 68 (34%) patients (p = 0.0001). Patients who needed extra surgical intervention also had a significant decrease in group II, 21 (10.5%) compared to 66 (33%) patients in group I (p = 0.0001). Also, the incidence of blood transfusion was decreased in group II, 19 (9.5%) patients compared with 51 (25.5%) patients in group I, (p = 0.0001). However, no significant difference between the two groups concerning post-operative hemoglobin (p = 0.089).

There was a significant decrease in operative time in group II compared with group I (p = 0.0001). But no significant difference between the two groups concerning the duration of in-hospital stay (p = 0.474).

Finally, we found that the drugs complications in form of unpleasant taste, fever, and shivering were significant increase in group II [18 (9%), 22 (11%), and 26 (13%)] patients compared to [2 (1%), 8 (4%), and 5 (2.5%)] patients in group I (p = 0.0001, 0.008, and 0.0001), respectively. However, no significant difference concerning nausea, vomiting and diarrhea between the two groups (p = 0.111, 0.065, and 0.066 respectively) (**Table 3**).

DISCUSSION

This study is the first double-blind randomized placebo-controlled trial comparing the effectiveness of intravenous TA plus buccal misoprostol *versus* intravenous oxytocin for diminishing blood loss for pregnant ladies who are experiencing CD. The outcomes demonstrated that the intravenous

Table 3. *Secondary outcome in the study groups.*

Variables	Group I (n = 200)	Group II (n = 200)	Significance
Post hemoglobin	9.74 ± 0.61	9.85 ± 0.68	0.089
Operative time	72.96 ± 16.32	67.17 ± 12.35	0.0001*
Hospital stay	4.22 ± 0.58	4.18 ± 0.54	0.474
Post-partum hemorrhage (%)	68 (34)	23 (11.5)	0.0001*
Need Blood Transfusion (%)	51 (25.5)	19 (9.5)	0.0001*
Extra surgical intervention (%)	66 (33)	21 (10.5)	0.0001*
	2 (1)	18 (9)	0.0001*
Unpleasant taste shivering	5 (2.5)	26 (13)	0.0001*
Fever (%)	8 (4)	22 (11)	0.008*
Nausea (%)	13 (6.5)	22 (11)	0.111
Vomiting (%)	4 (2)	11 (5.5)	0.065
Diarrhea (%)	6 (3)	14 (7)	0.066

*Statistically significant difference; variables are presented as mean and standard deviation and number (percentage).

TA plus buccal misoprostol could essentially decrease the intraoperative and total blood loss, blood transfusion after CD, the incidence of postpartum hemorrhage, and the need for extra additional uterotonics. Also, no cases with deep venous thrombosis as well as respiratory embolism were recognized.

To the best of our knowledge for the utilization of TA plus buccal misoprostol in reducing blood loss during CD, no studies were recognized. Past principal research had detailed that the degrees of plasminogen activators expanded 30 minutes after the initiation of surgery [8]. Thus, the hypothetical basis could clarify an expected efficiency of TA for decreasing loss for surgical procedures with special concern with CD and can use as adjunctive to misoprostol in reducing blood loss during CD especially in situations oxytocin is not available. TA offers an alternative way to support hemostasis by inhibiting the enzymatic action of plasmin on fibrin. Given that tranexamic acid reduces surgical bleeding, it had the potential to improve outcomes for women with postpartum hemorrhage.

Our study showed that there was a significant increase in estimated blood loss in the oxytocin group compared with TA plus misoprostol group ($p = 0.0001$). These results were also following findings from Osman *et al*. [12], Vlassoff *et al*. [13], Nielsen *et al*. [14], Owonikoko *et al*. [15] have reported that the hemoglobin concentration tends to be less in the misoprostol group than other groups.

Our study was also following findings from Ugwu *et al*. [10], Okonofua *et al*. [16], Blum *et al*. [17], and Eftekhari *et al*. [18] who found that oral/sublingual misoprostol 400 μg appears to be as effective in minimizing blood loss in the third stage of labor as oxytocin.

Mousa *et al*. conducted a meta-analysis to evaluate the role of misoprostol in postpartum hemorrhage and they concluded that oxytocin infusion is more effective and causes fewer side effects when used as first-line therapy for the treatment of primary postpartum hemorrhage. The review suggests that among women who received oxytocin for the treatment of primary postpartum hemorrhage, the adjunctive use of misoprostol confers no added benefit [19].

A systematic review and meta-analysis was finished by Conde-Agudelo to assess the utilization of misoprostol during CD and found no factually significant differences among misoprostol and oxytocin in diminishing intraoperative and postoperative blood loss at CD [20]. There were no huge contrasts in the intraoperative and postoperative drain when misoprostol was contrasted with oxytocin. However, these findings were based on a few trials with methodological constraints. Seventeen studies (3174 ladies) were incorporated of which 7 assessed misoprostol *vs* oxytocin and 8 assessed misoprostol plus oxytocin *vs* oxytocin alone. Overall, there were no significant differences in intraoperative and postoperative blood loss between sublingual or oral misoprostol and oxytocin.

Our study supports the hypothesis that intravenous TA plus buccal misoprostol is more effective than oxytocin in reducing postpartum blood loss and that more patients in the oxytocin group required additional oxytocic drugs with statistical significance. The long life outside the refrigerator and oral administration of misoprostol make it attractive for use in the prevention and management of postpartum hemorrhage especially in low-resource areas due to ease of storage and distribution. It also has no effect on blood pressure or causes Bronchoconstriction, and so can be safely used in women with asthma [3].

During delivery, when the placenta separates from the uterine wall, sequential physiologic and hemostatic changes occur and reduce bleeding, including strong myometrial contractions, increased platelet activity, and a massive release of coagulant factors; however, at the same time, fibrinolytic activity increases [21]. While misoprostol administration enhances the first mechanism, TA administration might be able to counter the latter and thus

facilitate the hemostatic process. Finally, the close relation observed between reduced fibrinogen levels and outcome in cases of PPH further suggests that TA might be effective in PPH [22].
The incidence of side effects such as shivering and an unpleasant taste in women receiving misoprostol was significantly higher than that in the oxytocin group. These findings are similar to the results of other studies [11, 12, 16, 17].
Chunbo Li *et al*. conduct a systematic review and meta-analysis to assess the efficacy and safety of tranexamic acid (TA) in reducing blood loss and lowering transfusion needs for patients undergoing cesarean section (CS) or vaginal delivery (VD). They conclude that intravenous TA for patients undergoing CS was effective and safe. Although prophylactic TA administration is associated with reduced PPH [23].
Faraoni *et al*. [24] conducted a meta-analysis with ten studies that demonstrate the efficacy of TA administration in reducing blood loss for women undergoing CS or VD. They concluded that TA administration significantly reduced blood loss and lowered the occurrence rate of PPH regardless of the mode of delivery.
Simonazzi *et al*. conducted a meta-analysis on the prophylactic administration of TXA at the time of the cesarean section [25]. Results show significant decreases in surgical blood loss, rates of postpartum hemorrhage, postoperative drops in hemoglobin, and risk of requiring a blood transfusion. In these studies, there were no reported adverse events of statistical significance such as deep-vein thrombosis (DVT), pulmonary embolism, stroke, or seizure.
A recent Cochrane review showed that timely administration of TA in patients with postpartum hemorrhage following delivery by any route resulted in not only reduced total blood loss but also decreased maternal mortality due to hemorrhage (relative risk RR 0.81; 95% CI: 0.65-1.00) [8]. These results were also following findings of the world maternal antifibrinolytic trial [26, 27].
The study had its limitations. First, was a single-center study and we have not used the alkaline hematin method which is a validated method for accurate measurement of blood loss but uses instate a gravimetric method to measure the amount of blood loss. However, Marcel *et al*. 2004 in veterinary surgery compare gravimetric and colorimetric methods of quantifying surgical blood loss and conclude that Estimation of blood loss using a gravimetric method is an accurate and objective tool to evaluate intraoperative blood loss [26].
Additionally, blood loss can also be related to proper surgical complications that are not considered in our study. Moreover, between 37 and 40 weeks there is a difference in the susceptibility of the uterine receptors to oxytocin, however, there is no statistically significant difference between the study groups regarding gestation age at CD.
One of the strengths of our investigation was that a double-blind randomized examination was adequately powered to compare the effect of intravenous TA plus buccal misoprostol versus intravenous oxytocin on the amount of perioperative blood loss. Another quality of the investigation lies in its simplicity of use of buccal misoprostol and intravenous TA can bring about a clinically significant decrease in intraoperative blood loss.

CONCLUSIONS

IV TA plus buccal misoprostol is more effective than an intravenous infusion of oxytocin in reducing blood loss during and after CD. Adding tranexamic acid may increase the efficacy of buccal misoprostol to decrease blood loss during and after CD. In settings in which oxytocin is not available or its provision is not feasible, alternative buccal misoprostol plus tranexamic may be considered for use.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

N.S.: design, literature review, manuscript preparation. H.S.: conception and design, literature review, manuscript preparation. H.S.: manuscript preparation.

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None.

Study registration

ClinicalTrials.gov. Identifier: NCT03505333.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The study protocol was approved by the Ethics Committee of Aswan University Faculty of Medicine (ASWU/273/7/18). The study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Data sharing

The data are available under reasonable request to the corresponding author.

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Endoscopic inguinal sentinel node biopsy using indocyanine green in early-stage vulvar cancer: an innovative technique

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ABSTRACT

Background. Minimally invasive lymphadenectomy is progressively emerging as an appealing strategy in patients with vulvar cancer, and at the same time, sentinel node biopsy is currently recognized as standard of care in patients with early-stage disease.
Case presentation. The integration of minimally- invasive approaches and sentinel node biopsy appears as an intriguing horizon, and we present here the first endoscopic sentinel node biopsy using indocyanine green performed in a patient with early-stage vulvar cancer.
Twenty-five mg of indocyanine green powder was diluted in 20 ml of injectable solution, and two ml of the solution were injected next to the vulvar lesion. After 10 minutes, the sentinel node was detected using a camera with Karl Storz near infrared system and removed using two ancillary 3 mm trocars. The sentinel node biopsy procedure duration was 25 minutes. Ipsilateral complete endoscopic inguino-femoral lymphadenectomy was then performed. The patient was discharged on post-operative day 1. At frozen section, and final histology one sentinel node was detected, and resulted negative for metastasis. No lymph-nodal metastases were detected in non-sentinel nodes. No surgical complications were observed, and 15 months after surgery the patient was free from disease.
Conclusions. We present the first successful endoscopic inguinal sentinel node biopsy using Indocyanine green. Further studies are needed to clarify the feasibility and safeness of the procedure.

INTRODUCTION

Vulvar cancer is a rare condition affecting older women and accounts for 3-5% of all gynecological cancers, and primary treatment is radical vulvectomy with inguinal nodal staging [1, 2]. However, radical lymphadenectomy is associated with significant morbidities, and in the last decade, a growing attention has been dedicated to the development of sentinel node biopsy (SNB) in women with gynaecological cancer [3-8]. In this context, indocyanine green (ICG) has progressively emerged as the most effec-

tive tracer in both endometrial, and cervical cancer given its quick lymphatic diffusion, and favourable economic profile compared to standard radiotracers such as technetium-99 [4-10]. On the other hand, the procedure of SNB has been recently introduced in the clinical practice also in women with early-stage vulvar cancer [11]. At the same time, several reports have demonstrated the feasibility of minimally invasive inguinal lymphadenectomy with significant benefits in term of post-operative complications [12-14]. For these reasons, the combination of inguinal SNB and endoscopic approach appears a promising strategy, giving the opportunity to perform a scarless procedure with a clear clinical advantage for the patients. However, a surgical description of this challenging surgical technique has never been provided.

CASE PRESENTATION

The presented paper provides a step-by-step description of an endoscopic inguinal SNB using indocyanine green in early-stage vulvar cancer. The procedure has been performed at the Department of Gynecologic Oncology of the University of Palermo. Formal ethical approval was not required for this technical demonstration. Written informed consent to be enrolled, and for personal data to be published in the present article was obtained.
The patient was an eighty-two years old woman with 3 cm vulvar squamous cell carcinoma (**Figure 1**). Computed Tomography scan and physical exam revealed absence of inguinal lymphadenopathies.

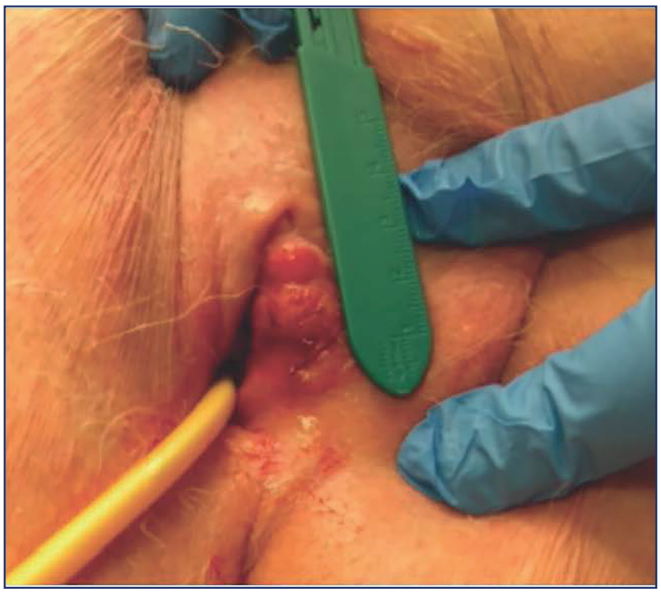

Figure 1. *Vulvar lesion.*

We briefly describe here the surgical steps required to complete the procedure.

First step

As first step, we drew on the patient's leg the femoral triangle, also identifying the femoral artery (**Figure 2**).

Second step

A 10-mm trocar for endoscope was placed around 10 cm below the inguinal ligament, furthermore two additional 3-mm trocars were placed externally to the femoral triangle in order to have a direct access to the groin (**Figure 3**).

Third step

The definition of the surgical field is the further step of the procedure consisting of a careful dissection

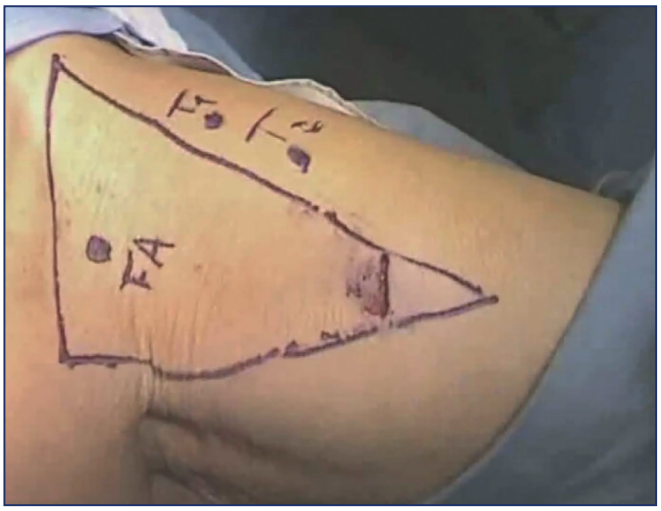

Figure 2. *Transcutaneous identification of the femoral triangle and of the femoral artery.*

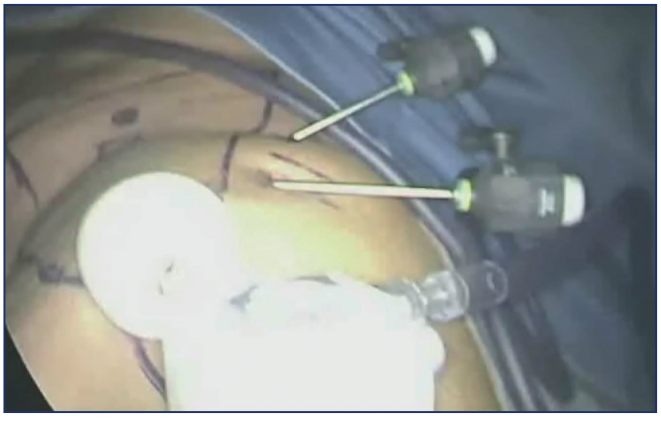

Figure 3. *Trocar placement.*

of subcutaneous fatty tissue avoiding as much as possible sealing and cutting thus preserving lymphatic vessels (**Figure 4**). At the end of this part of the surgery, we were able to identify the two major surgical landmarks: the inguinal ligament ventrally, and the great saphenous vein in the dorsal part of the field (**Figure 5**).

Fourth step

Then, 25 mg of ICG powder was diluted in 20 ml of water, and 2 ml of the solution were injected next to the vulvar lesion (**Figure 6**).

Fifth step

After 10 minutes the camera was introduced through the 10-mm trocar, and the sentinel node was detected in the area of superficial inguinal lymph nodes using the endoscopic Karl Storz near infrared system (**Figure 7**).

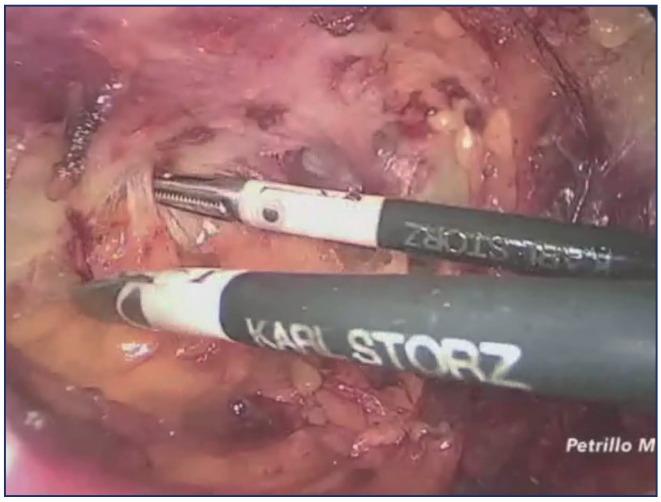

Figure 4. *Definition of the surgical field.*

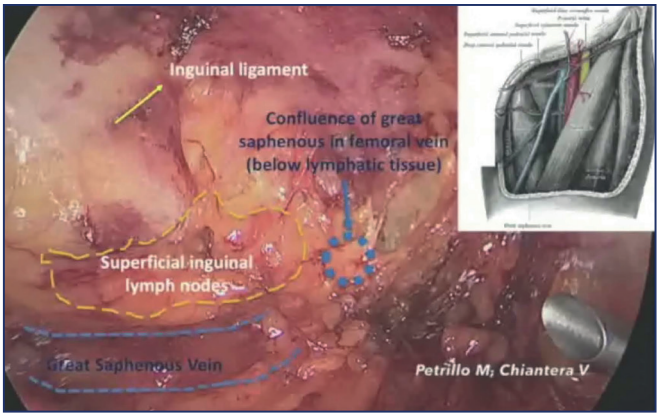

Figure 5. *Identification of the principal anatomical landmarks.*

Sixth step

Then a careful dissection of the great saphenous vein was performed, which confirmed the ICG uptake only in the detected sentinel node.

Seventh step

Finally, the sentinel node was removed in endobag end submitted to histological examination (**Figure 8**).

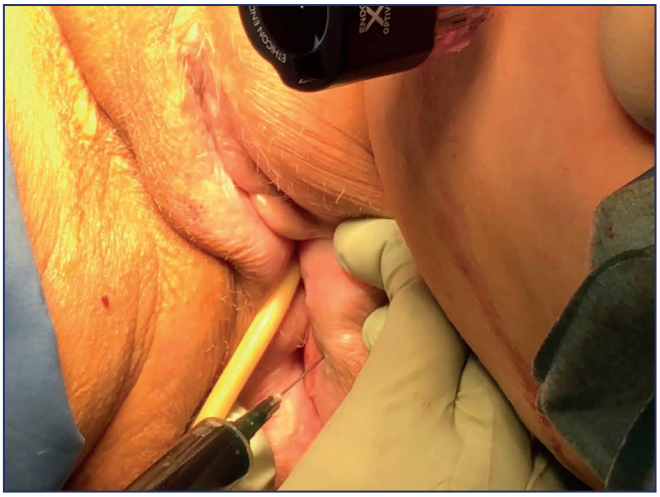

Figure 6. *ICG peri-lesional injection.*

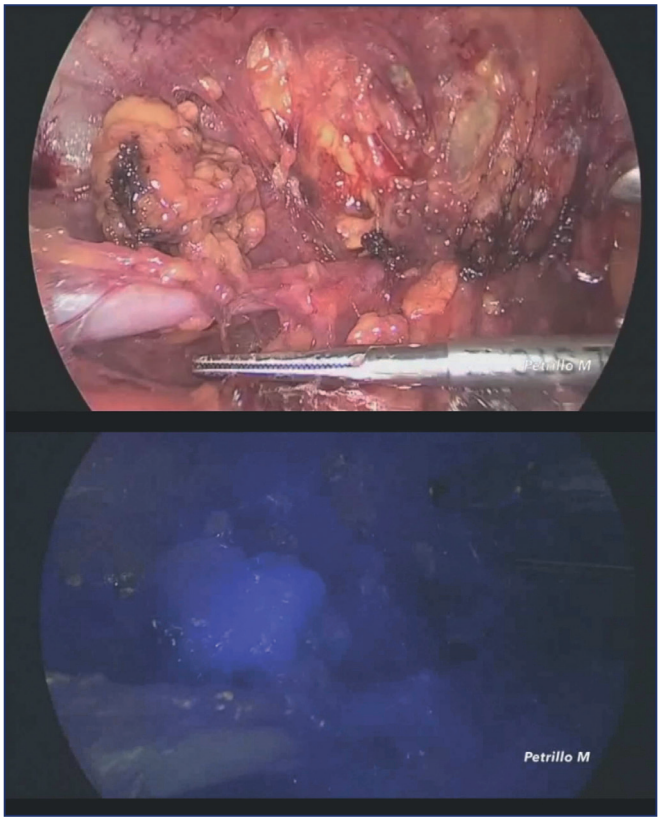

Figure 7. *Detection of the sentinel node.*

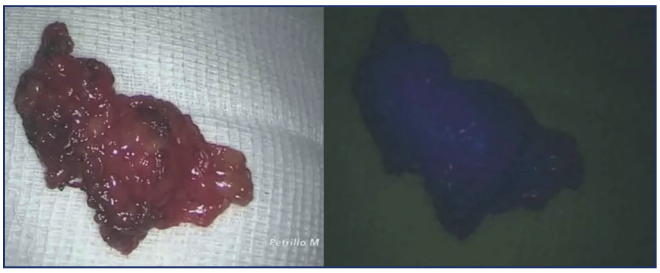

Figure 8. *Removal of the sentinel node.*

Because of the innovativeness of the procedure, that needs to be validated yet, completion ipsilateral inguino-femoral radical lymphadenectomy was performed as previously described [12-15]. Finally, left radical hemi vulvectomy was performed to complete the surgical procedure.

RESULTS

The SNB procedure duration was 25 minutes, and no significant haematic blood loss were recorded. The patient discharged on post-operative day 1. At frozen section analysis, and at final histology one sentinel node was detected, and resulted negative for metastasis. No lymph-nodal metastases were detected in non-sentinel nodes. No early or late surgical complications were observed and a scarless result was obtained (**Figure 9**). Fifteen months after surgery the patient was free from disease.

CONCLUSIONS

We present the first case of successful endoscopic inguinal SNB using ICG, a very innovating surgical technique, that could represent a further alternative option for the management of early-stage vulvar cancer. However, our successful demonstration does not support the routine application of the described technique, and further studies are needed to confirm our promising results. The validation of our technique could give the opportunity to perform this minimally invasive technique avoiding a radical lymphadenectomy as suggested by the principal guidelines [8].

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.P.: conceptualization, data curation, methodology, writing – original draft, writing – review & editing. G.So.: conceptualization, data curation, methodology, writing – original draft, writing – review & editing. G.P.: methodology and data curation. M.D.: methodology and data curation. G.Sc.: conceptualization, supervision, validation, writing – original draft, writing – review & editing. V.C.: conceptualization, supervision, validation, writing – original draft, writing – review & editing.

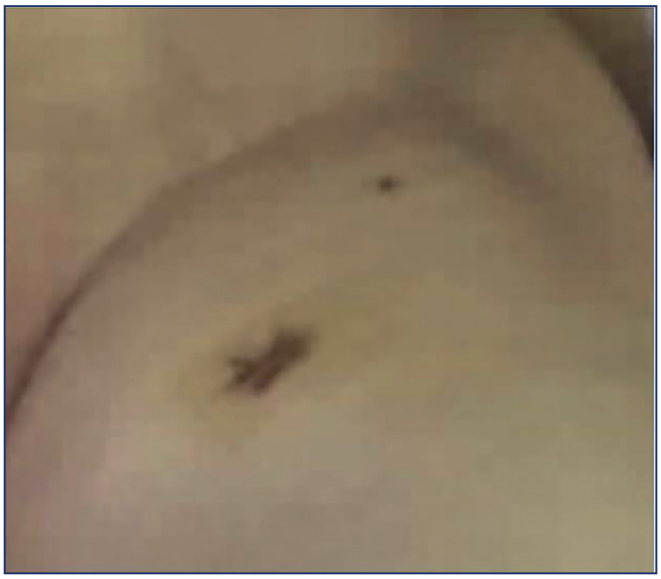

Figure 9. *Aesthetic result at two weeks after surgery.*

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None.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Formal ethical approval was not required for this technical demonstration.

Informed consent

Written informed consent to be enrolled, and for personal data to be published in the present article was obtained.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Relationship between prelabour uterine rupture and previous placenta previa diagnosis: case reports and review of literature

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ABSTRACT

Background. The number of Caesarean sections is growing worldwide, intensifying the risk of complications in subsequent pregnancies and leading to increased maternal and fetal morbidity and mortality. In particular, the literature shows a higher risk of uterine rupture in subsequent pregnancy with trial of labor after caesarean section. Furthermore, there are few data about pre-labor uterine rupture in scarred uteri.
Objective. Since the key factor for management is timing, the aim of this cases report was to describe the accuracy of prenatal ultrasound of scars in the early determining of pre-labor UR risk in two cases with a previous Caesarean sections during their subsequent pregnancy.
Case presentation. We reported two cases of uterine rupture occurring outside of labour in patients with a history of caesarean section due to placenta previa. In the current cases was reported how a higher hysterotomy, combined with some risk factors, could increase the prevalence of UR in the subsequent pregnancy.
Conclusions. In these cases, a higher uterine incision due to placenta previa or isthmic myoma seems to be correlated with a major risk of UR. Therefore, although in a limit experience, we report that the periconceptional prenatal ultrasound examination of previous cesarian section level could represented a useful predictive factor of pre-labor uterine rupture in subsequent pregnancies.

INTRODUCTION

Uterine rupture (UR) is a discontinuous area inside the uterine wall, including its serosa (overlying peritoneum) and possibly involving the bladder and wide ligament [1]. Uterine dehiscence often precedes UR, but it does not involve the serosa or the gestational sac.
Thus keeping the umbilical cord, placenta and fetus inside the uterus, leading to a lower rate of maternal-fetal complications [2]. UR is an obstetric emergency that can be related to adverse neonatal (intrapartum death, ischemic-hypoxic encephalopathy, *etc.*) and maternal outcomes, (severe haemorrhage, requiring blood transfusion, repeated laparotomy, hysterectomy) [3]. In the last few years, the incidence of UR has significantly increased both in women without a previous hysterotomy (due to labour management, especially when medically induced) and in those with a previous caesarean sec-

tion (CS), mostly when combined with risk factors [4]. Indeed, despite conflicting opinions, the literature reports specific risk factors for UR [5]. Because of the increasing rate of CS in recent years and its complications, it is clear why the incidence of UR among women with a previous CS enhanced from 0.22 to 0.5% in developed countries [6].
We report two cases of spontaneous UR out of labour in women with a history of CS performed for placenta previa and hysterotomy performed more cranially from the low uterine segment (LUS).
We informed both patients about the use of their personal data for scientific purposes, under the protection of the Privacy Act, and they accepted and signed a related informed consent.

CASE PRESENTATIONS

Case 1

A 35-year-old patient with no relevant medical history, para 0/1/0/1 had a previous pregnancy terminated with an emergency CS due to a central placenta previa abruption at 32 weeks of gestational age; a placental flap was extending anteriorly over the LUS for 3 cm and a transverse hysterotomy was performed more cranially than usual.
After 2 years, the woman was pregnant again and at 32 gestational weeks, she presented to our obstetric emergency unit because of a severe abdominopelvic pain: she was conscious, pale and asthenic with BP: 100/60 mmHg, HR: 100 bpm, rhythmic pulse and obstetric shock index (OSI): 0.9 (normal value < 1). There was evidence of generalised tenderness, but no vaginal bleeding or amniotic fluid leakage was observed; because examination of the vaginal fornices was very painful, it was not possible to complete the obstetric digital examination. Both a transvaginal and a transabdominal scan were performed and thus reported: cervical length was 3 cm, single pregnancy, normal heart beat, fetal movements were detected, amniotic fluid index was normal, placenta was normally implanted on the anterior uterine wall. We observed fluid into the Morison's pouch and heterogeneous material both into the Douglas and the recto-uterine pouch. We could not determine the origin of the haemoperitoneum, as well as we could not exclude an extra-pelvic aetiology. Therefore, an emergency CS was performed with lower midline incision approximately 1000 ml of blood were drained. The gestational sac was outside the uterus, bulging through a dehiscent hysterotomic breach with sclerotic edges, which was partially removed and sent for histological examination (**Figure 1 A, B**). After removing the gestational sac and placenta, which was almost totally detached from the uterine wall, the breach was sutured with interrupted stitches and a good haemostasis was obtained, thus a conservative approach was feasible. The haemoglobin decreased from 9.6 gr/dL before surgery to 8.5 gr/dL on the day of surgery and 7.8 gr/dL on the first post-operative day: two units of packed red blood cells (pRBC) were transfused. The woman was discharged on day five with antibiotics, antithrombotics, iron and uterotonics. The histological examination confirmed the presence of scar tissue over the breach edges. The fetus reported no abnormalities and the growth was found to be consistent with the gestational age. The placenta was normal as well.

Case 2

A 34 years old woman with no relevant medical history, para 1/0/1/1, had an elective CS at 39 weeks of gestational age due to an anterior placenta previa that required a transverse hysterotomy above the LUS.
After two years she was pregnant again and an ultrasound at 7 gestational weeks showed the higher CS scar location (**Figure 2**). At 36 gestational weeks the patient presented to our obstetric emergency unit because of severe and abdominopelvic pain which was worsening in the last three hours. She presented conscious, nervous, asthenic and pale. Blood pressure was 95/50 mmHg, heart rate was 85 bpm, rhythmic pulse and OSI: 0.8.
A superficial and deep abdominal palpation revealed a generalised tenderness and the digital examination of the vaginal fornices was painful, especially when exploring the area close to the pouch of Douglas; the cervix was not dilated and vaginal bleeding / amniotic fluid leakage was not observed. A CTG examination pointed out fetal bradycardia (80 bpm for 8 minutes) and no uterine contractions; a transabdominal scan confirm fetal bradycardia, but did not provide any further information. An emergency CS with a Pfannenstiel laparotomy over the previous scar. After draining 1500 ml of blood, the fetus was found outside of the uterus. After removing the placenta, almost totally detached from the uterine wall and bulging into the abdomen, a large breach over the middle third of the anterior wall was noted and sutured with interrupted stitches. Because the haemostasis

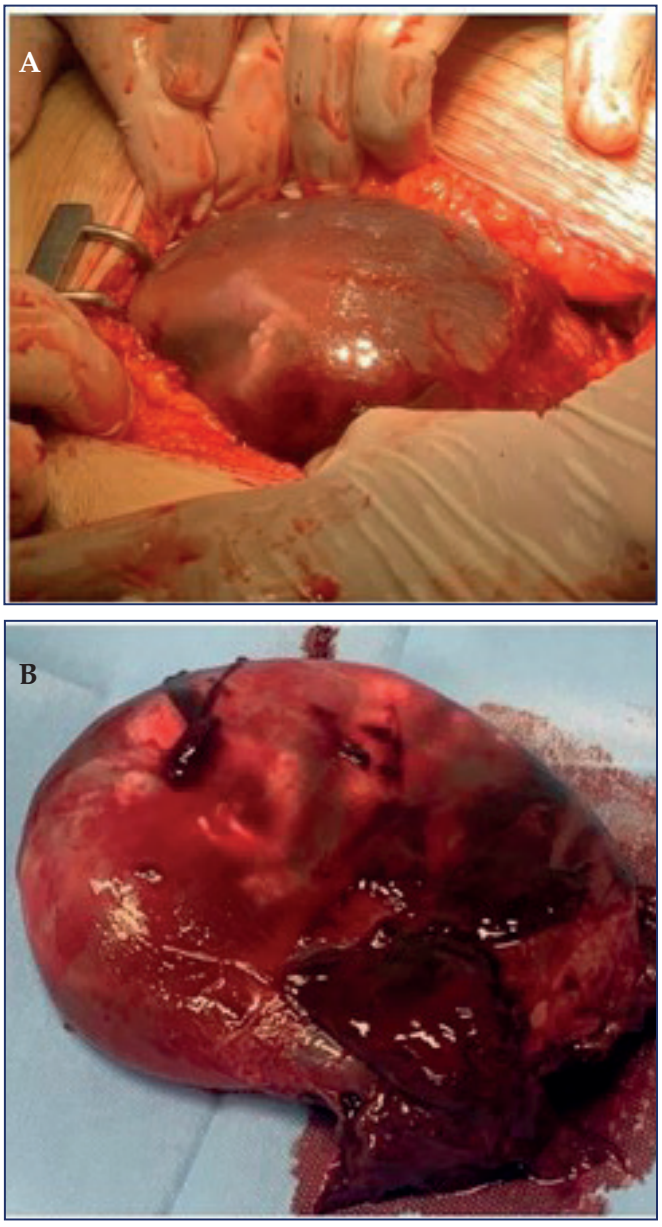

Figure 1. ***CASE 1. (A)*** *Gestational sac expelled through the dehiscent hysterotomic breach and immediately visible when opening the abdomen.* ***(B)*** *Gestational sac outside the uterus.*

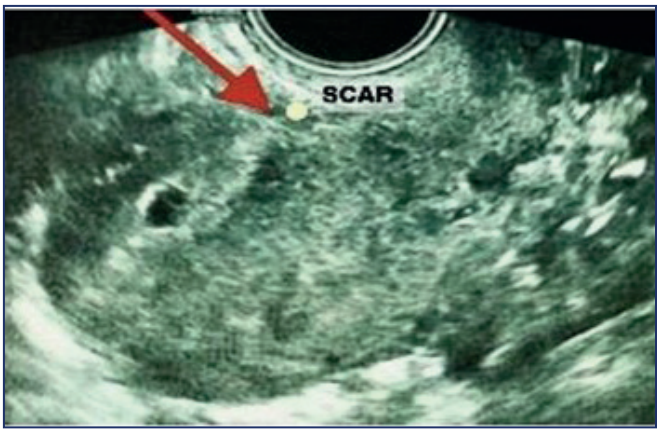

Figure 2. ***CASE 2.*** *Ultrasound assessment (gestational age: 7 weeks) shows the previous CS-scar located above the lower uterine segment.*

was good, we opted for a conservative approach. Three units of pRBC and two units of plasma were infused during the CS because of the huge amount of blood collected into the abdomen and the low haemoglobin level (8.5 gr/dL). Soon after the CS, the haemoglobin was stable (9.5 g/dL) but the following day it decreased to 7.8 gr/dL, so another administration of pRBC was required. The patient was discharged on day four with antibiotics, antithrombotic and iron. Regarding fetal outcome. The new-born was a male, 2500 g, Apgar score 3 at 1 minute and 5 at 5 minutes, umbilical artery. PH was 6.8 - Lactate 12.8 mmol/L - BE 20mmol/L. He was immediately transferred to Neonatal Intensive Care Unit. Magnetic resonance performed 30 days after birth diagnosed a hypoxic-ischemic encephalopathy with severe neurological sequelae.

DISCUSSION

UR usually occurs during the late gestational age and commonly involves the LUS area (scarred uterus 92.1% - unscarred uterus 63.63%), less resistant than the uterine corpus and fundus [7].
In this manuscript, there are reported two cases with uterine rupture in both cases out of labor, in women underwent cesarean section in previous pregnancy with an incision performed more cranially of usual and far from the lower uterine segment for the presence of a placenta previa.
In these situations, we suppose that a different mechanism of scarring is involved and consequently it could be considered a risk factor in order to prevent UR complications.
Indeed, in most cases, UR is an intraoperative diagnosed pregnancy complication; it may be suspected by performing a detailed gynaecological and ultrasound examination, but only a surgical evaluation can confirm the diagnosis [8].
Moreover, the clinical onset is often nonspecific, only later becoming more typical with abdominal pain, haemorrhagic shock and absence of fetal heart activity [9].
The first case presented with a nonspecific clinical pattern and the ultrasound examination was not supportive either. The prompt surgery reduced the risk of maternal complications but the fetal outcome was sealed by the early gestational age (19 weeks).
For our second case, clinical evaluation was delayed by about three hours. Despite the unclear preoperative diagnosis, clinicians wisely decided to carry out a surgi-

cal treatment in a short time. Nevertheless, the patient's late presentation finally resulted in a worse maternal and fetal outcome (intraoperative blood transfusion and hypoxic-ischemic fetal encephalopathy).

According to our experience and other Authors' opinion, in order to improve the maternal-fetal outcome, high-risk patients (previous CS, abdominal pain, sickness, signs of peritoneal irritation and pelvic effusion) should be promptly identified and referred to adequate obstetric emergency units for urgent surgical treatment [10].

Moreover, Literature reports that in case of myomectomy, is more frequent the uterine rupture during pregnancy course and not during labor, compare to uterine rupture after cesarean section in which the uterine rupture is more frequent during labor [11].

Actually, the relative weight of every risk factor is not defined, but in case of fetal surgery it is 14% for both uterine dehiscence and UR [12]. A previous T or J uterine incision moves the risk of UR from 4% to 9%, double that of a previous vertical incision over the LUS and five times that of a transverse one. Actually, a "low" transverse uterine incision over the LUS is related to a low risk (0.4-0.7%), while the consequences of a "high" transverse incision over the LUS are not well detailed. Some Authors give it no relevance, while others state that every incision of the uterine contractile tissue increases the risk of UR [13]. Therefore, the importance of detailing the height of a CS scar in the patient's discharge letter becomes clearly evident, necessary to plan a proper management of the next pregnancy. This is the case with both our patients, with a previous CS due to placenta previa and a hysterotomy performed more cranially than usual, involving the uterine contractile tissue and possibly increasing the risk of UR [14]. Moreover, ultrasound measurement of the distance between the CS scar and the internal uterine orifice may screen patients with a high risk of UR, both during preconception counselling and early pregnancy.

Actually, the role of ultrasound in the prediction of uterine rupture is not demonstrate yet, and it is necessary caution in the interpretation of data.

However, all the possible risk factors for UR should be investigated when counselling these patients. Regarding our cases:

- the first patient had a CS at 32 weeks due to placenta previa abruption, thus statistically increasing the risk of UR, even in the case of LUS hysterotomy (1.8% pre-term Vs 0.4% term-pregnancy) [15];
- the second patient had an elective CS at 39 weeks that should be taken in account as well; also in these cases the risk of UR is increased, related to a suboptimal scar healing [16].

The last statement has two possible explanations: firstly, an incision over a less developed LUS can be related to a deeper myometrial damage; secondly, without a cervical dilatation and a full uterine drainage, there is a higher risk of post-partum infection, phlogosis, abnormal scar healing and UR [5]. The amount of time from the last CS is another important risk factor; in our cases, it was of 16 and 21 months respectively. By reviewing the current literature, the importance of this detail is clear, but a standard "safe" range of time is not reported. Some studies suggest a 6 to 19 month period, while other Authors prefer an interval of 12 or 18 months. An observational study focuses on 1500 women and, removing all the biases (type of stitches, oxytocin induction, and epidural anaesthesia) but still preserving an odds ratio for UR of 2.65 (95% CI 1.08-6.46), suggests a period of 24 months as optimal [17]. Finally, the literature confirms the higher risk of UR for patients with a recent CS, and a period of 18-24 months appears to be the safest one [18]. This evidence points out another risk factor for our patients, probably contributing to the final outcome and confirming again the importance of detailed pre and post-delivery counselling.

CONCLUSIONS

When counselling patients with a previous CS, detailed information about the short and long-term related risks factors should be investigated and collected, including the length of time (less than 18-24 months) since the last CS and the type of hysterotomy performed. Ultrasounds can measure the distance between the CS scar and the internal uterine orifice or the vesicovaginal pouch, useful for patients who had an incision higher than usual: this parameter is not yet standardized but it could detect the height of the CS scar to assess the risk of UR [19]. Ongoing pregnancies should be investigated for all the possible anamnestic risk factors: reason for CS, type of hysterotomy, other uterine surgeries, gestational age at the time of CS, emergency or planned surgery, range of time from the last pregnancy, and height of the incision (also assessable by ultrasounds). Through this approach, we can perform a proper risk assessment and schedule serial follow-ups to early detect and treat a possible UR. This could reduce the time between diagnosis and surgery, thus

having more time to manage safely the emergency (expert clinician, promptly available blood products, and well-equipped facilities) [10]. Therefore, the early screening of potentially at-risk pregnancies would allow to plan a periodic follow-up of these patients and the rapid detection of UR symptomatology. This could be extremally important, since a preventive diagnosis and early intervention may significantly improve maternal and fetal outcome.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

M.D.: Writing – original draft. F.M.C.: Data acquisition.A.C.R: Writing – review & editing. H.X.: Formal Analysis. R.T: Analysis tools. E.C, A.V.: Analysis design.

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Study registration

N/A

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

All procedures performed in this study were in accordance with the Helsinki Declaration. In addition, the patient was also informed that the data collected for this study are protected by the Privacy Act.

Informed consent

The data were collected and used after written subscription of further informed consent aimed at obtaining the written authorization from each patient to the use of personal data for scientific purposes only.

Data sharing

For any information related to the data you can refer to the corresponding author who presents the raw.

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