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The Sperm DNA Fragmentation Study Group (SFRAG) Guideline and its relevance for practicing gynecologists

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ABSTRACT

This editorial highlights the key recommendations of the novel evidence-based *Sperm DNA Fragmentation Guideline* (SFRAG guideline) for gynecologists providing infertility care. Sperm DNA fragmentation is a biomarker of sperm's chromatin quality. Elevated sperm DNA fragmentation rates contribute to couple's infertility and negatively impact medically assisted reproduction outcomes. There are five main clinical scenarios in which gynecologists should consider sperm DNA fragmentation testing to guide their decision-making process. They include unexplained infertility, recurrent pregnancy loss, before (or after failed) medically assisted reproduction, and the presence of male infertility risk factors. The SFRAG guideline emphasizes the importance of corrective measures to decrease sperm DNA fragmentation rates and selection of the best medically assisted reproduction modality for the affected couples. The intended goal is to provide the foundation for standardizing care in this area while maintaining clinicians' autonomy.

SOMMARIO

Questo editoriale mette in evidenza le raccomandazioni chiave delle nuove *linee guida per la frammentazione del DNA dello sperma* basata sulle evidenze (linea guida SFRAG) per i ginecologi che forniscono cure per l'infertilità. La frammentazione del DNA dello sperma è un biomcatore della qualità della cromatina dello sperma. I tassi elevati di frammentazione del DNA dello sperma contribuiscono alla sterilità della coppia e hanno un impatto negativo sui risultati della riproduzione assistita. Esistono cinque scenari clinici principali in cui i ginecologi dovrebbero prendere in considerazione i test di frammentazione del DNA dello sperma per guidare il loro processo decisionale. Includono infertilità inspiegabile, interruzione della gravidanza ricorrente, prima (o dopo il fallimento) della riproduzione medicalmente assistita e la presenza di fattori di rischio di infertilità maschile. La linea guida SFRAG sottolinea l'importanza di misure correttive per diminuire i tassi di frammentazione del DNA dello sperma e la selezione della migliore modalità di riproduzione medicalmente assistita per le coppie affette. L'obiettivo prefissato è quello di fornire le basi per la standardizzazione dell'assistenza in quest'area mantenendo al contempo l'autonomia dei medici.

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Key words

Infertility; sperm DNA fragmentation; medically assisted reproduction; unexplained infertility; miscarriage.

INTRODUCTION

Sperm DNA integrity is essential for the birth of healthy progeny (1). Sperm DNA fragmentation (SDF), a marker of damaged chromatin, has an independent and critical role in male infertility diagnosis and reproductive success (2). The reasons relate to the often higher SDF levels in ejaculated sperm of infertile men (*vs* fertile counterparts) and the adverse impact of SDF on the sperm's ability to fertilize the egg and promote healthy embryo development (2, 3). Consequently, elevated SDF has been associated with longer time-to-pregnancy, increased risk of pregnancy loss, and decreased success in medically-assisted reproduction (MAR) (*e.g.*, intrauterine insemination [IUI] and in vitro fertilization/intracytoplasmic sperm injection [IVF/ICSI]) (4, 5). The adverse effect of SDF on reproductive success is modulated by the oocyte's DNA repair capacity, which is intrinsically related to female age (6). Sperm DNA damage exceeding the oocyte's repair capacity – or the oocyte's failure to repair DNA damage – negatively influences the embryo's development potential and offspring's health (7).

Routine semen analysis – the laboratory backbone of infertility investigation – has low diagnostic discriminatory power (unless at extremely lower levels) as there is considerable overlap between semen characteristics (*e.g.*, sperm count, motility, and morphology) of fertile and infertile men (8). The need for more robust male infertility diagnosis methods has been the driving force of the ongoing efforts to develop and implement SDF testing in clinical practice.

While it is not a replacement for the current tools for infertility diagnosis, SDF testing may add independent information about sperm quality at the molecular level, and its integration into practice may provide better counseling, diagnosis, and treatment planning. Despite that, SDF testing is not routinely recommended during the infertility evaluation by infertility societies. Insufficient clinical data, tests' technical limitations and lack of effective treatment options to overcome SDF related-infertility have been the common grounds for the reluctance to endorse the clinical application of SDF tests (9). However, evidence on these areas has increased steadily, justifying the development of clinical practice guidelines to refine efficiency in diagnosing and treating clinical conditions associated with SDF.

This editorial aims to highlight a recently published evidence-based guideline for the investigation and treatment of SDF – the SFRAG guideline (10). This consensus guideline provides a comprehensive evidence summary about the role of SDF on infertility and offers best practice advice on testing and care of infertile couples affected by SDF. The primary goals of the SFRAG guideline are to provide clinicians – gynecologists, reproductive endocrinologists, urologists, and andrologists – with clear advice on best practices in SDF. The SFRAG recommendations were developed based on the best available evidence, ranging from moderate to low quality. Like other guidelines (11), the SFRAG guideline may be used to help standardize care while securing physician autonomy, making it an invaluable resource for a broad range of professionals providing infertility care, including gynecologists.

In the first part, the SFRAG guideline outlines the SDF pathophysiology and explains the existing laboratory tests available to measure SDF. Several conditions, including varicocele, chronic illnesses, male accessory gland infections, advanced paternal age, inadequate lifestyle (*e.g.*, smoking, obesity), occupational and environmental factors, use of medication with potential gonadotoxic effect, and exposure to ionizing and non-ionizing radiation have been associated with high SDF levels. These conditions can promote abortive apoptosis or increase the generation of reactive oxygen species (ROS). Excessive ROS promote oxidative stress, representing a significant causative factor of SDF in live sperm. The SFRAG guideline highlights the four reliable tests to measure SDF, namely:

1. terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL assay);
2. sperm chromatin structure assay (SCSA);
3. sperm chromatin dispersion test (SCD);
4. the Comet assay.

Although the results provided by these tests do not necessarily line up, there is a good correlation between SDF rates reported by TUNEL, SCSA, SCD, and alkaline Comet. Under this section, the guideline provides 13 recommendations on how testing should be carried out and results analyzed. For example, it underlines the importance of using a standardized protocol with strict quality control for achieving reliable test results. Besides, it explains that a neat semen sample should be used for SDF testing, collected after ejaculatory abstinence of 2-5 days. Thresholds of about 20% by TUNEL, SCSA,

SCD, and alkaline Comet, assessed on neat semen should be used to discriminate fertile from infertile men. Additionally, thresholds of 20-30% evaluated by SCSA, alkaline Comet, and SCD are clinically useful for classifying infertile couples into a statistical probability of longer time to achieve natural pregnancy, decreased pregnancy by MAR, and increased miscarriage. Lastly, the SFRAG guideline emphasizes use of a fixed ejaculatory abstinence length for SDF testing, particularly when monitoring the effects of medical and surgical interventions aimed at decreasing SDF levels.

The second part describes seven clinical situations that may benefit from SDF testing, including i. Varicocele, ii. Unexplained/idiopathic infertility, iii. Recurrent pregnancy loss (RPL), iv. Intrauterine insemination (IUI), v. In vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), vi. Infertility risk factors and vii. Sperm cryopreservation. The guideline provides specific recommendations for each condition – 28 in total – and best practices for treatment. The recommendations with higher clinical implications for practicing gynecologists are summarized below.

Unexplained infertility

Among couples with unexplained infertility, elevated SDF rates are found in up to 20% of individuals. These couples should be informed that abnormal SDF levels may adversely impact their chances of achieving a live birth. It may be therefore prudent to offer SDF testing in couples with unexplained or idiopathic infertility, as an abnormal test result may indicate that damaged sperm chromatin might be the underlying infertility factor. An abnormal test result should prompt a complete male evaluation to help identify and possibly treat conditions associated with poor sperm DNA quality. A decrease in SDF may allow these couples to achieve natural conception or eventually optimize reproductive outcomes of MAR. ICSI can be considered if no correctable male factor is identified, or if abnormal SDF levels persist after treatment, an advice that is particularly useful for couples with a limited reproductive time window.

Recurrent pregnancy loss

A plausible female factor-independent relationship exist between RPL and SDF. Indeed, miscar-

riage rates are increased in couples whose male partners have elevated SDF. It has been hypothesized that DNA fragmentation not repaired by the oocyte may contribute to poor blastocyst development, implantation failure, and miscarriage – the proposed mechanism involves oxidative stress. SDF testing in couples with RPL may help identify the cases in which SDF contributes to the condition, thus helping in patient counseling and guiding clinical management. For instance, a couple with RPL found to have elevated SDF should have the male partner evaluated to rule out male factors possibly associated with oxidative stress and SDF. If no causative factor is identified, ICSI may be a reasonable alternative to overcome the problem.

Medically assisted reproduction

Infertile couples eligible for MAR treatment should be informed that abnormal SDF levels may adversely impact their chances of achieving a live birth. IUI and IVF/ICSI pregnancy rates decrease in these couples, whereas the risk of miscarriage increases in those who achieve pregnancy. On this basis, SDF testing may have value not only in couples experiencing unexpected MAR failures, but also those about to embark on this type of treatment. Likewise, the male partner should be evaluated to rule out and/or fix any underlying male factors possibly causing SDF. The guideline goes on by adding that among couples with ICSI failure and persistently elevated SDF (*i.e.*, despite correctable measures taken), sperm retrieved from the testis may be considered for sperm injection in subsequent treatment cycles due to the lower SDF rates in testicular *vs* epididymal/ejaculated sperm and higher ICSI success rates with use of testicular sperm than ejaculated sperm in men with abnormal SDF levels.

Risk factors

SDF testing is recommended in men with infertility risk factors (*e.g.*, tobacco smoking, obesity, metabolic syndrome, exposure to environmental or occupational toxicants, use of licit or illicit drugs with gonadotoxic effects, and advanced paternal age). An abnormal SDF test may be used for counseling, reinforcing the importance of lifestyle changes and avoiding exposure to toxins, and monitoring the effect of lifestyle changes. It should also prompt a urological/andrological evaluation to help identi-

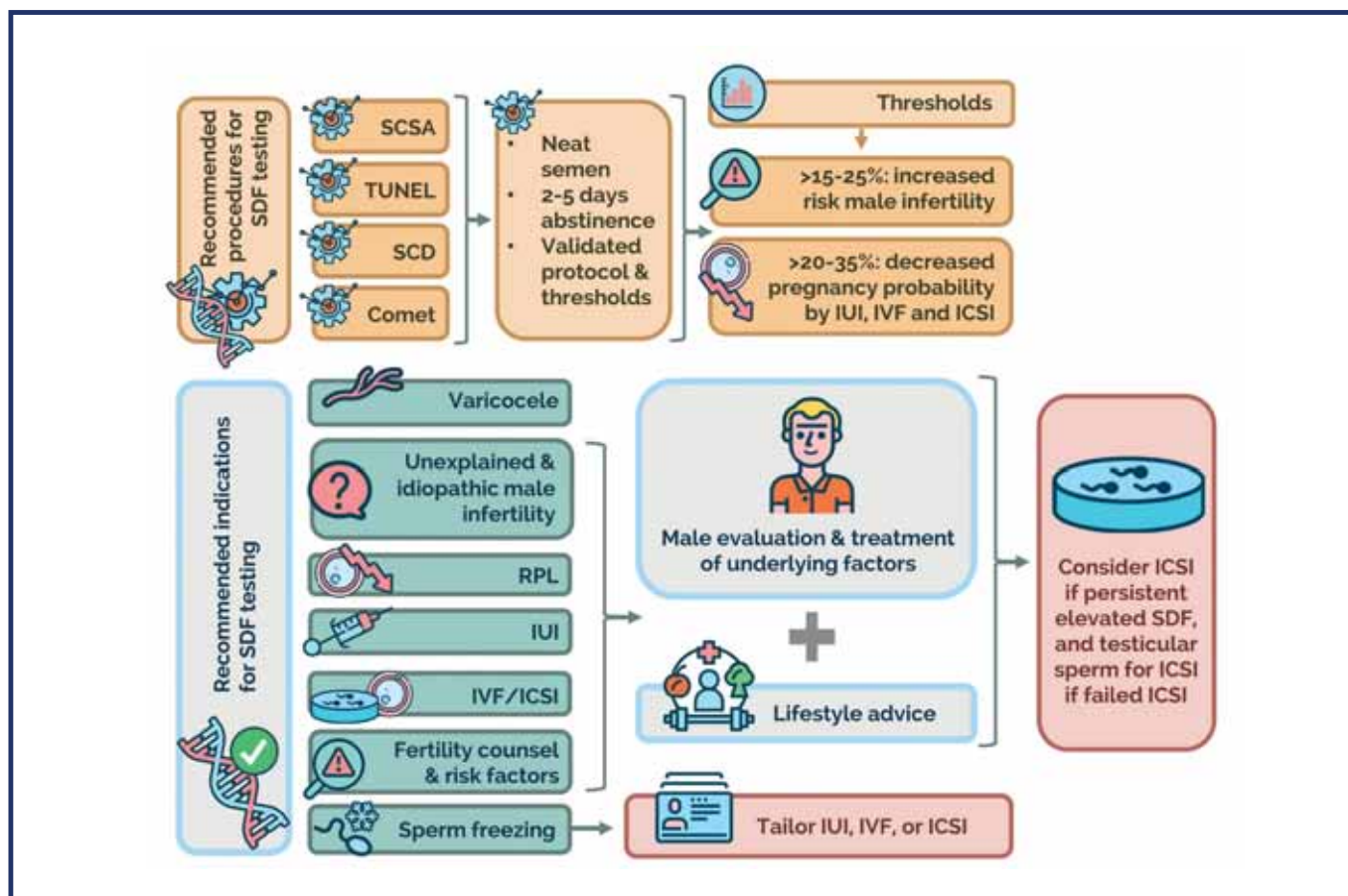


Figure 1. A pictorial summary of the recommendations for testing and management in infertile couples with high sperm DNA fragmentation (9).

IUI: intrauterine insemination; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; RPL: recurrent pregnancy loss.
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fy other hidden and potentially correctable conditions linked to SDF.

The SFRAG guideline has united reproductive urologists and gynecologists with clinical experience in diagnosing and treating male factor infertility. Moreover, the guideline working group included scientists pivotal in developing the main SDF assays, who deciphered each test and made it easy to interpret results and understand their limitations. For each recommendation, a strength rating based on both expert judgment and evidence levels is provided. The guideline emphasizes the central role of reproductive urologists/andrologists in the evaluation of the male partner and highlights the importance of corrective measures to improve the male reproductive health and SDF (figure 1). It also stresses the importance of selecting the adequate MAR modality for the affected couples. Lastly, the SFRAG guideline discusses the main gaps in knowledge and provides a series of recommendations for future research. We strongly believe gynecologists providing care to infertility patients should be fully

aware of the adverse impact of SDF on fertility and reproductive outcomes. The SFRAG guideline is an important document providing the foundation for standardizing care in this subject area while maintaining clinicians' autonomy.

CONFLICT OF INTERESTS

SCE is a member of the Sperm DNA fragmentation Group and leading author of the SFRAG guidelines, distributed as an open-access article under the Creative Commons Attribution License. The license permits unrestricted use, distribution, reproduction in any medium, remixing, transformation, and building upon the material for any purpose provided the original work is properly cited. The full version can be found at <https://onlinelibrary.wiley.com/doi/10.1111/and.13874>. The authors declare that they have no conflict of interests.

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Intestinal-type primary vaginal adenocarcinoma. Review of the literature with report of a case: from diagnosis to management

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ABSTRACT

Background. Intestinal-type primary vaginal adenocarcinoma is an extremely rare neoplasm, and very few cases are reported in the literature. The differential diagnosis of an intestinal-type adenocarcinoma at vaginal level (an organ almost free from glandular tissue) is particularly challenging given the anatomical complexity and different embryologic derivations of organs in this district. The main diagnostic issue consists in determining whether the vaginal neoplasm is primary, or it is a metastatic disease that extends to the vagina. A fundamental role in guiding diagnostic and therapeutic pathways is played by the pathologist.

Objective. This study is a systematic review of the literature in order to summarize and analyze different diagnostic and therapeutic approaches chosen for every single case of intestinal-type primary vaginal adenocarcinoma described. Moreover, we report the case diagnosed and managed at our center.

Methods. PubMed, ClinicalTrials.gov, Scopus, and Web of Science databases were systematically searched for records from January 1st, 1989, to December 1st, 2019.

Results. Overall, 23 cases of intestinal-type primary vaginal adenocarcinoma are reported in the literature. This tumor often presents with atypical vaginal discharge (64.7% of cases) and it affects mainly the posterior wall (54.5%) and the lower third (83.3%) of the vagina. The average age at its presentation is 53.6 years. Diagnostic workup looks at ruling out possible primary distant sources of the disease and colonoscopy is often performed. The immunohistochemical profile of the lesion has a major role, and the key markers investigated are CEA, CK20, CK7, and CDX2. Most patients are diagnosed with early-stage disease (85% of patients FIGO I) and the lesion average size is 3 cm. Of 18 patients with available data, a surgical approach was adopted in 8 cases. Ten patients underwent radiotherapy.

SOMMARIO

Contesto. L'adenocarcinoma vaginale primario di tipo intestinale è una neoplasia estremamente rara con pochissimi casi riportati in letteratura. La diagnosi differenziale per l'adenocarcinoma di tipo intestinale a livello vaginale (organo pressoché privo di tessuto ghiandolare) è particolarmente impegnativa data la complessità anatomica e le diverse derivazioni embriologiche degli organi di questo distretto. Il principale problema diagnostico consiste nel determinare se la neoplasia vaginale è primaria o è una malattia metastatica che si estende alla vagina, e a questo scopo, un ruolo fondamentale, nella guida dei percorsi diagnostici e terapeutici, è svolto dal patologo.

Obiettivo. Questo studio è una revisione sistematica della letteratura al fine di riassumere e analizzare i diversi approcci diagnostici e terapeutici scelti per ogni singolo caso descritto di adenocarcinoma vaginale primario di tipo intestinale. Segnaliamo inoltre un caso diagnosticato e gestito presso il nostro centro.

Metodi. Una ricerca sistematica della letteratura è stata condotta nei database PubMed, ClinicalTrials.gov, Scopus, e Web of Science dall'1 gennaio 1989 all'1 dicembre 2019.

Risultati. In letteratura sono riportati 23 casi di adenocarcinoma vaginale primario di tipo intestinale. Questo tumore si presenta spesso con perdite vaginali atipiche (64.7% dei casi) e colpisce principalmente la parete posteriore (54.5%) e il terzo inferiore (83.3%) della vagina. L'età media alla sua presentazione è di 53.6 anni. L'iter diagnostico parte esaminando le possibili fonti primarie della malattia e viene spesso eseguita la colonscopia. Il profilo immunostochimico della lesione ha un ruolo importante e gli indicatori chiave studiati sono CEA, CK20, CK7 e CDX2. Alla maggior parte dei pazienti viene diagnosticata una malattia allo stadio iniziale (85% dei pazienti FIGO I) e la dimensione media della lesione è di 3 cm. Dei 18 pazienti con dati

Patients managed surgically, compared with those who underwent radiotherapy, were younger and with a smaller mass at diagnosis, although differences were not statistically significant. Treatment options depended on clinical evaluation, patient's comorbidities, and patient's preferences.

Conclusions. Intestinal-type primary vaginal adenocarcinoma is a rare tumor, and no specific guidelines addressing this disease are available. Ruling out a metastatic disease at the vaginal level is fundamental, and the pathologist plays a major role in the differential diagnosis. A multidisciplinary approach to the disease is of fundamental importance and the treatment choice should be tailored considering the patient's comorbidities and the holistic evaluation of the case.

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INTRODUCTION

Primary vaginal carcinoma is a rare disease and accounts for about 3% of all female genital tract neoplasms (1, 2). Of note, 80% of all vaginal malignancies are secondary (3, 4).

HPV-related squamous cell carcinoma is the most common type of vaginal cancer and accounts for 83.4% of all primary vaginal malignancies (5).

Vaginal adenocarcinomas are sporadic, 9.3% of all vaginal tumors. A positive history of *in utero* exposure to diethylstilbestrol (DES) is a known risk factor for vaginal adenocarcinoma (6). There is also a group of primary vaginal adenocarcinomas not associated with *in utero* DES exposure. Given the complexity of embryologic vaginal origin, many theories have been postulated on the origin of this type of tumor in a tissue lacking glands (7). Among non-DES-related adenocarcinomas, there is also an extremely rare variant called "intestinal-type" for its histological characteristics (8).

When a vaginal adenocarcinoma is diagnosed, it is initially mandatory to rule out metastatic disease, and this is particularly true for intestinal-type adenocarcinomas. Primary adenocarcinoma of the gastrointestinal tract is, indeed, the second most common tumor with secondary involvement of the vagina (9).

disponibili, in 8 casi è stato adottato un approccio chirurgico. Dieci pazienti sono stati sottoposti a radioterapia. I pazienti gestiti chirurgicamente, rispetto a quelli sottoposti a radioterapia, erano più giovani e con una massa inferiore alla diagnosi, sebbene le differenze non fossero statisticamente significative. Le opzioni di trattamento dipendevano dalla valutazione clinica, dalle comorbidità del paziente e dalle preferenze del paziente.

Conclusioni. L'adenocarcinoma vaginale primitivo di tipo intestinale è un tumore raro e non sono disponibili linee guida specifiche per affrontare questa malattia. È fondamentale escludere una malattia metastatica a livello vaginale e il patologo svolge un ruolo importante nella diagnosi differenziale. Un approccio multidisciplinare alla malattia è di fondamentale importanza e la scelta del trattamento deve essere adattata alle comorbidità del paziente e ad una valutazione olistica del caso.

Key words

Primary vaginal adenocarcinoma; immunohistochemistry; Skene glands; intestinal type; systematic review.

Obviously, a correct diagnosis at the primary instance has dramatic importance on the therapeutic approach and, consequently, on prognosis. A primary vaginal tumor is mainly treated with radiochemotherapy, and the surgical approach is applied only in selected cases (10, 11). On the other hand, the management of a metastatic tumor follows the guidelines of the primary disease.

The diagnosis of an intestinal-type primary adenocarcinoma requires a multidisciplinary approach where the pathologist plays a key role (1). Despite the involvement of a dedicated pathologist, the diagnosis of this histological subtype is still challenging.

Herein we report a case of primary intestinal-type adenocarcinoma of the vagina diagnosed at our Gynaecology Oncology department. Given the complexity of the case, we also systematically reviewed the available literature.

Clinical case

A 62-year-old woman was referred to the Gynecologic Oncology Unit of the AOUI of Verona after an incidental finding of a 49 × 36 mm hyperechoic pelvic mass at abdominal ultrasound. The patient was affected by renal failure for stage V chronic

kidney disease, and she had a right pelvic kidney transplanted ten years earlier.

At the gynecological examination, the lesion involved the upper third of the anterior vaginal wall, with a strong suspicion of bladder trigone involvement. At the pelvic magnetic resonance, a clear cleavage plane between the vaginal mass and the bladder was not identified. Cervix and vulva were free of disease. The patient also underwent a positron emission tomography-computed tomography (PET-CT) scan, which excluded disease at sites other than the vagina.

During the cystoscopy, the urethra appeared regular, and the bladder showed bullous edema at the trigone. Biopsies of the bladder epithelium were negative for malignancy.

A vaginal biopsy was performed. In the specimen, small neoplastic emboli of carcinoma immunohistochemically positive for CDX2 and CK20 were found, ruling out a neoplasm of intestinal origin. The main clinical suspicion was of an intestinal-type primary vaginal tumor (figure 1 a).

Considering the patients' comorbidities and the risk linked to pelvic radio therapy due to the presence of the pelvic kidney, the patient was deemed eligible for surgical treatment.

She underwent anterior pelvic exenteration with type C2 radical hysterectomy (Querleu-Morrow classification), bilateral salpingo-oophorectomy, radical cystectomy, infralevatory vaginectomy, iliac and obturator lymphadenectomy, ileo-ureter-neocystostomy with the creation of a vaginal flap.

The gross examination showed a lesion with a maximum diameter of 6.5 cm fully infiltrating the

vaginal and urethral wall, involving the external urethral meatus with free margins less than 1 mm. The lesion infiltrated the bladder wall reaching the muscular layer but not the epithelium. The left parametrium was infiltrated as well. Ureters were free from lesions. The tumor was pathologically staged as FIGO III. Histologically, the tumor was an undifferentiated adenocarcinoma with extensive necrosis (figure 1 b). The immunophenotypic profile confirmed the intestinal differentiation and excluded the urothelial or neuroendocrine carcinoma (table I, figure 1 c, d), and a possible origin from Skene glands was finally considered.

The woman underwent a PET-CT scan one month postoperatively, showing the progression of the disease. After collegial discussion, the multidisciplinary oncologic group decided on palliative care only. A month later, the patient died.

METHODS

This review was performed according to the PRISMA statement and was registered in the PROSPERO register. A reference librarian with expertise in electronic search strategies for systematic reviews conducted the literature search under a senior gynecologist (SU). PubMed, ClinicalTrials.gov, Scopus, and Web of Science databases were systematically searched for records from January 1st, 1989, to December 1st, 2019. The following MESH search terms were used: vaginal, primary, adenocarcinoma, intestinal, female, urethral, Skene, Skene gland, immunohistochemistry, immunohistochemical. The electronic search was followed up with a secondary hand search of the references of the identified articles. Every article identified was evaluated independently by two researchers (PCZ, MB). Disagreements were resolved by reexamining the article in question discussing it with the senior

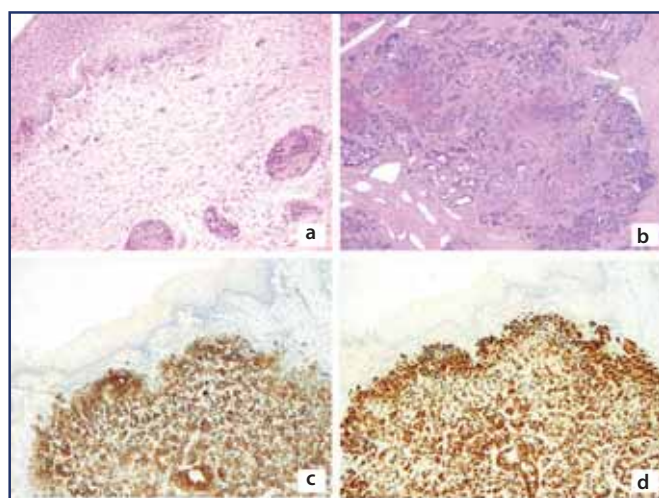


Figure 1. The vaginal biopsy revealed small neoplastic emboli of carcinoma (a). After the resection, an undifferentiated adenocarcinoma with extensive necrosis was observed (b), immunohistochemically positive for cytokeratin 20 (c) and CDX2 (d).

Table I. Patient immunohistochemical profile.

	POS	NEG
Biopsy	CK20; CDX2	CK7; PSA; GATA3; p40 poli; PAX8 (BC12); ER; Synaptophysin clone 27g12.
Definitive	CK20; CDX2; AMACR	CK7; PSA; CK 5 (XM26); Chromogranin A (DAK-A3); DeltaN-p63 (p40); PSAP; GATA3; PAX8; AR; ER; S100P

CK: cytokeratin; ER: estrogen receptor; AR: androgen receptor; PSA: prostate specific antigen; PSAP: prostatic specific acid phosphatase.

authors (MF, SU). We included studies in English, French, and Spanish. The exclusion criteria were primary vaginal cancers other than intestinal-type phenotype, metastatic vaginal cancer, benign intestinal-type vaginal lesions, DES-related cases.

From each case, we evaluated the following aspects:

- clinical presentation;
- diagnostic work-up;
- histologic diagnosis/himmunophenotypic profile;
- stage of the disease;
- treatment;
- surgical margins;
- survival.

Main review outcomes:

- to summarize the available evidence on intestinal-type primary vaginal cancer;
- to identify a diagnostic tool to guide the diagnostic process;
- to evaluate the therapeutic approach adopted in each case given the lack of guidelines;
- to understand if this specific variant, regardless of the stage, has a worse or better prognosis than the classic variants.

Data are presented as absolute numbers (percentage). The Mann-Whitney nonparametric test was applied to compare the differences between the two groups. The significance level was set at $\alpha = 0.05$, and the test was 2-tailed. No institutional review board approval was required because the present study deals with already existing data. The legally entitled person to give the consent provided consent for the anonymized publication of the case data and images. All authors participated in the search strategy design and in that of the inclusion and exclusion criteria.

RESULTS

The search strategy provided a total of 342 citations. Of them, 266 were discarded because after reviewing the abstract, it appeared evident that these papers did not meet the criteria. The 76 remaining citations were screened for eligibility, and, the full text of 50 citations was examined in more detail (**figure 2**). After a full-text search, only 13 studies describing a total of 23 cases of intestinal-type primitive vaginal cancer were identified for inclusion in the review. Studies and patients' characteristics are summarized in **table II**.

Clinical presentation

The average age at symptoms onset was 53.6 years (range 32-86). Atypical vaginal discharge was the most common clinical presentation, observed in 64.7% (11/17) of cases. Nine patients presented with vaginal bleeding (52.9%), while the other 2 cases reported foul-smelling vaginal discharge. In 11.8% (2/17) of cases, the onset symptom was hematuria (12). Only one patient was diagnosed incidentally during a routine gynaecological examination. At diagnosis, the lesion mean size was 3 cm (range 0.8-7 cm). In 54.5% of patients (12/22), the lesion developed from the posterior vaginal wall, in 36.4% from the anterior wall (8/22), while in only 2 cases, the lesion was identified on the lateral wall. The lower third of the vagina was involved in 83.3% of cases (in 15 out of 18 patients), representing the most frequently involved site. No cases of tumor extending to the vulva at the time of diagnosis were reported.

Diagnostic workup

In 56.5% (13/23) of reports, the authors did not report complete information regarding preoperative investigations. All the patients underwent a transvaginal ultrasound scan and biopsy of the lesion. Given the intestinal phenotype, 80% of patients underwent colonoscopy (8 out of 10). Other diagnostic studies included: computed tomography (CT) scan in 5 patients, magnetic resonance imaging (MRI) in 4 cases, cystoscopy in 4 cases, chest radiography, PET, and transrectal ultrasound in 2 cases, barium enema, mammography, and abdominal ultrasound in 1 case each.

Immunophenotype

The most frequently evaluated immunohistochemical markers were CEA (in 9 patients), CK20, CK7 (each one assessed in 8 patients), and CDX2 (in 4 patients). **Table III** summarizes the immunohistochemical profile of the cases.

Staging

Primary vaginal carcinoma is staged according to the 2009 FIGO staging. An early-stage tumor (stage I and II) is confined to the pelvis, while advanced disease (stage III and IV) goes beyond the pelvic wall (10). The majority of patients were diagnosed with an early-stage tumor (FIGO I stage in 17 of the patients). A

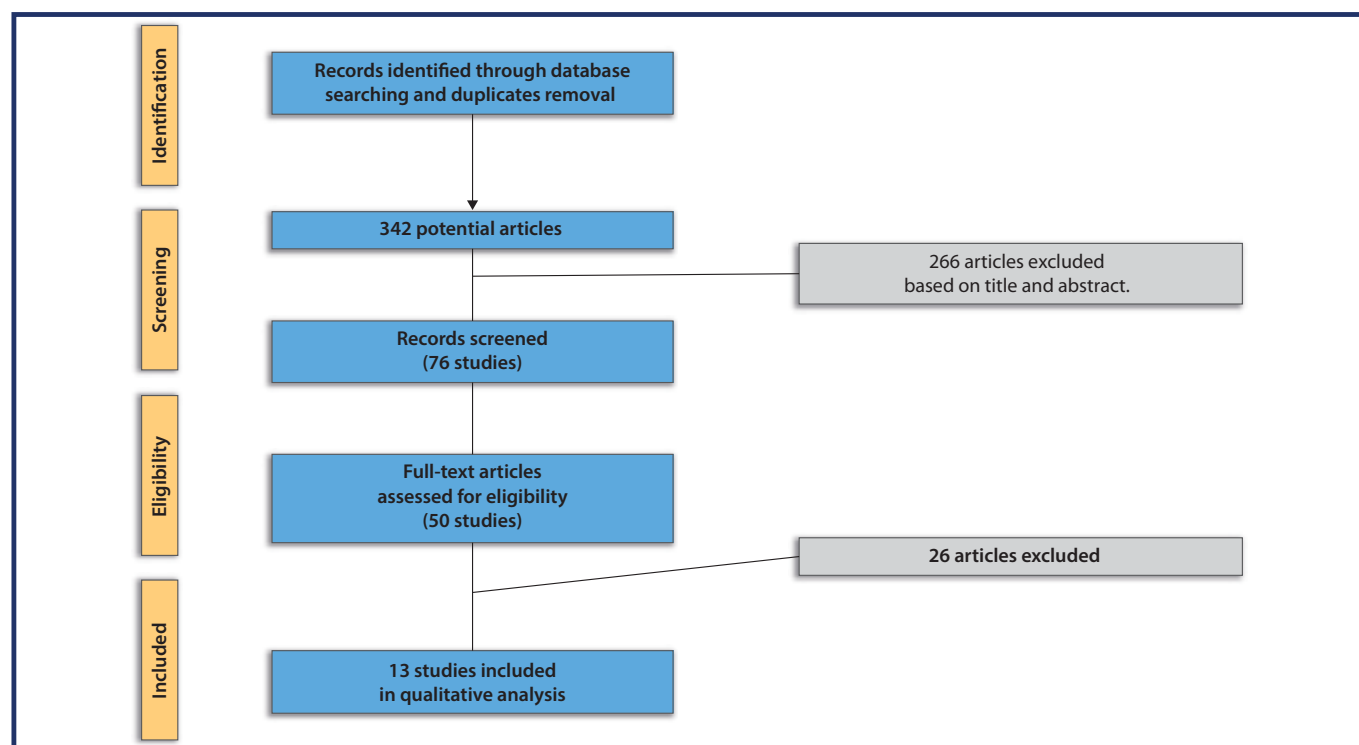


Figure 2. Flow-chart of the Literature search.

FIGO II tumor was encountered only in one patient, and only two patients staged FIGO III at diagnosis. No FIGO IV stage was found. Only two patients presented with metastatic disease, both of them at the nodal level. In one case, para-aortic nodes were involved, while in the other case, a bilateral inguinal node spread was found. Concerning surgical margins, data are available only for 5 of the 23 patients. Negative margins are described in 4 cases (7, 13-15) and positive margins in only 1 case (16). There has been no case of up-staging after surgery.

Management

Patients management was surgical in 8 cases, while 10 patients underwent radiotherapy. Information regarding the type of management lacks in 5 reports. The average age of patients was 50.2 years among those managed surgically and 53.7 years among patients managed with radiotherapy ($p = 0.6$). Exclusive radiotherapy was the management of choice in 9 cases. One patient underwent concomitant radiochemotherapy (17). Tumor size in patients managed surgically was smaller (2.4 cm on average) than in patients who underwent radiotherapy (4.1 cm on average). This difference is not statistically significant ($p = 0.12$). A total vaginal removal along with hysterectomy + adnexectomy was reported in 2 patients after

radiotherapy (15, 18). In one case, a residual mass was found, and the excision of the mass was chosen (17). Driss *et al.* (19) report a case managed with primary radiotherapy consisting of external beam radiation associated with interstitial radiotherapy. After three months, this patient was deemed eligible for anterior exenteration because of a peri-urethral recurrence, but she refused.

In 2 cases, the surgical approach consisted of a vaginectomy. In both cases, total vaginectomy and hysterectomy were performed, being impossible a total vaginectomy without concomitant hysterectomy; only in one case bilateral adnexectomy was additionally performed (18). In the other 2 cases, local excision of the lesion was chosen (associated with adnexectomy and omentectomy in one case (7, 18)). One case (stage FIGO II), underwent infra-levatorial total exenteration (11) while a second case, staged FIGO I, underwent anterior exenteration (14). Both these radical surgical approaches were decided only after a thorough discussion with the patient. Two patients were managed with an anterior exenteration (in one of these, the disease was staged as FIGO I, in the other, staging data are lacking). Only one case had an incidental diagnosis of vaginal mass encountered during a diagnostic work-up for postmenopausal vaginal bleeding. The approach, in this case, was a local wide resection followed by adjuvant radiotherapy and chemo-

Table II. Characteristics of identified studies and patients.

Author/year	Country	Age (y)	Symptoms	Site	Size (cm)	Diagnostic tools	Primary treatment	Staging	FU (m)
Fukushima (1986)	Japan	32		Lateral wall	lower		Radiationtx		Relapse
Fox (1988)	UK	35		Anterior wall	5		Surgery	Anterior Exenteration	NED
Yaghseizian (1992)	USA	52		Posterior wall	lower		Radiationtx	FIGO I	Relapse
Nagar (1999)	Dublin	36	VB	Anterior wall	upper	Colonoscopy; MRI	Surgery	Anterior Exenteration	FIGO I
Heller (2000)	USA	55	VB	Anterior wall	lower	Colonoscopy; cystoscopy	Radiationtx + Chtx	FIGO I	
Heller (2000)	USA	52	VL	Anterior wall	lower	Colonoscopy; cystoscopy; CT	Radiationtx	FIGO I	NED
Mudhar (2001)	UK	56	VB	Posterior wall	lower	Colonoscopy	Surgery	Local excision; SOB; Omentectomy	FIGO I
Saitoh (2005)	Japan	44	mass	Anterior wall	lower	CT; MRI	Radiationtx	FIGO I	12
Tjalma (2006)	Belgium	55	VB	Posterior wall	middle	Colonoscopy; US; MRI	Surgery	Total infralevatory exenteration	FIGO II
Ditto (2007)	Italy	53	no	Posterior wall	lower	Colonoscopy; CT; PET	Surgery	Wedge resection	FIGO I
Driss (2007)	Tunisia	70	hematuria	Anterior wall	lower	Colonoscopy; cystoscopy; US	Radiationtx		Relapse
Laalim (2013)	Marocco	46	VL	Posterior wall	lower	Colonoscopy; US; CT; MRI	Radiationtx	FIGO III	Relapse
Staats (2014)	Canada	36	VB	Posterior wall			Surgery	TA; Vaginectomy	FIGO I
Staats (2014)	Canada	52	VB	Anterior wall					FIGO I
Staats (2014)	Canada	51	mass	Lateral wall	middle			FIGO III	NED
Staats (2014)	Canada	78	mass	Posterior wall	lower			FIGO I	
Staats (2014)	Canada	86	hematuria	Posterior wall	lower		Radiationtx	FIGO I	
Staats (2014)	Canada	71		Posterior wall	lower			FIGO I	
Staats (2014)	Canada	51		Posterior wall	lower		Surgery	Local excision	FIGO I
Staats (2014)	Canada	80	VB	Posterior wall	lower		Surgery	Vaginectomy	FIGO I
Staats (2014)	Canada	60		Anterior wall			Radiationtx	FIGO I	
Staats (2014)	Canada	43	VB					FIGO I	DOD
Aloy (2019)	Nigeria	40	VB	Posterior wall	lower	CT	Radiationtx	FIGO I	NED
Franchi (Current case)	Italy	62	mass	Anterior wall	upper	Cystoscopy; CT; PET	Surgery	Anterior Exenteration	FIGOIII

VB: vaginal bleeding; VL: vaginal loss; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; Tx: therapy; SOB: Salpingo-oophorectomy; TA: total abdominal hysterectomy; missed: not available; NED: no evidence of disease; DOD: death of disease; y: years; m: months.

Table III. Immunohistochemical profile of the cases.

	CK20	CK7	CDX2	CEA	ER	PR	PSA	PSAP	AMACR	CA125	CA153	p53	p16	villin	mucin	GATA3	PAX8
Heller (2000)				pos			neg	neg									
Heller (2000)				pos			neg	neg									
Mudhar (2001)	pos	neg		pos											pos		
Saitoh (2005)				neg								neg					
Tjalma (2006)	pos	pos		pos	neg	neg					pos	pos					
Ditto (2007)	pos	neg	pos														
Driss (2007)	pos	neg		pos													
Laalim (2013)	pos	neg															
Staats (2014)	30%	neg	pos	pos	neg					neg			5%	neg			
Staats (2014)	70%	30%	pos	pos	neg								5%				
Staats (2014)	pos	30%	pos	pos	neg					10%							
Franchi (Current Case)	pos	neg	pos	neg	neg	neg		neg	pos							neg	neg

PSAP: prostatic specific acid phosphatase; PSA: prostate specific antigen; AMACR: Alpha methylacyl CoA racemase.

therapy (16). This is the only case where the patient underwent adjuvant therapy because of positive surgical margins.

In a second case, adjuvant chemotherapy was added because of the evidence of bulky lymph nodes at diagnosis (15). This despite a tumor staged as pT-0N0M0 at definitive pathologic specimen analysis.

Follow-up

Data on follow-up are not reported in many cases (10 out of 23 cases), and when available, they are not standardized. The median follow-up was 12 months (range 1.5-84 months). In 5 out of 13 (38.4%) cases followed up, a recurrence was documented at different times (range 3-24 months). Eight patients were declared free from the disease on the occasion of the last follow-up visit. Since the incompleteness of the data, we did not perform an analysis of follow-up data.

DISCUSSION

Intestinal-type primary vaginal adenocarcinoma is an extremely rare neoplasm, and very few cases are

reported in the literature. Symptoms are not specific. The most common clinical presentation is vaginal bleeding (52.9%), which is the most frequently encountered sign at the diagnosis of a gynecological neoplasm. This tumor may develop from both the anterior and posterior vaginal walls, but more regularly is identified in the lower third of the vagina (83.3%) without extending to the vulva and surrounding organs at the time of diagnosis.

In this review, most of the included cases were at an early stage (85% of patients had FIGO stage I tumors), and only two cases had lymph node metastasis at diagnosis (15, 18). Two cases presented with urinary symptoms (hematuria), while no presentation with gastrointestinal symptoms was reported. The mean age at diagnosis was 53.6 years, so it seems that this tumor presents at a younger age compared to vaginal squamous cell carcinoma, the most common histologic type of vaginal cancer, which usually peaks around 60 years, although the disease is seen occasionally in women in their 20s and 30s (20, 21). The main diagnostic issue consists of determining whether the vaginal neoplasm is primary or a metastatic disease that extends to the vagina. Different diagnostic tools have been used by various authors, such as CT, MRI, PET, and colonoscopy.

The latter, used in 80% of cases, appeared to be the most conclusive.

Radiation therapy is the treatment of choice for most patients with vaginal cancer, even in early-stage tumors (4). Surgery may be an alternative approach for tumors of the posterior wall involving the upper third of the vagina, or in particular conditions such as patients with particular anatomical conditions, advanced stages, fistulas, or relapses.

Eight (44.4%) out of 18 patients with available data underwent surgery. Patients treated with a surgical approach tend to be younger (average age 52 versus 58 years in the radiotherapy group) and tumors surgically treated appear generally smaller (1.4 cm versus 3.2 cm). These differences are not statistically significant. In 6 out of the 8 surgically managed cases, the tumor was on the posterior vaginal wall with an average size of 1.9 cm.

Considering patients with advanced disease (3/20, 15%), a total infralevator exenteration with vulvectomy was performed in a patient with stage II disease (13), and one of the two patients staged FIGO III (bilateral involvement of the inguinal lymph nodes) underwent radiochemotherapy followed by vulvectomy with vaginectomy and inguinal lymphadenectomy (15). No data are available about treatment for the second case, staged FIGO III.

Looking at patients managed with ultra-radical surgery (5/18, 27.7%), this approach was adopted in one case of extrvaginal disease (FIGO II) (13) and in 3 cases of disease staged FIGO I (14, 18). An ultra-radical approach has allowed not to use of adjuvant therapy. Women treated with ultra-radical surgery had lesions with size > 2 cm (mean size 3.5 cm, range 1.5-5 cm).

We cannot draw conclusions about the prognosis because the follow-up data are incomplete and not systematically collected. However, during follow-up, no evidence of disease was reported in 5 (62.5%) out of the 8 patients surgically managed, while recurrence was detected in 4 (40%) out of the 10 patients treated with radiotherapy. Data are not available for 3 patients of the surgery group and 2 patients of the radiotherapy group. Data from the literature show that this type of primary vaginal tumor has a poor prognosis with an increased risk of local and distant metastases (10). A review of 26 women with non-DES-related vaginal cancer at the MD Anderson Cancer Center found an overall five-year survival of 34% (22).

Immunohistochemical analysis in this rare tumor plays an essential role since it helps to identify the

origin of the tumoral cells. Cytokeratin 20 (CK20) is a low-molecular-weight cytokeratin expressed in several tumors, including colorectal carcinomas and urothelial carcinoma. CDX2 is a nuclear transcription factor expressed in intestinal-type adenocarcinoma that is more specific than CK20 (13).

Cytokeratin 7 (CK7) is a type II keratin of simple nonkeratinizing epithelia. It is expressed in the simple, pseudostratified, and ductal epithelium, mesothelium, and urothelium and generally is observed (with some variation) in the adenocarcinoma of lung, breast, thyroid, endometrium, cervix, ovary, salivary gland, upper GI tract, and urothelial carcinoma. At the same time, it is generally negative in colorectal carcinoma. A CK7⁺ and CK20⁺ profile is often found in urothelial-derived carcinoma (23). Instead, CK7⁺ but CK20⁻ usually favors a carcinoma from endometrium, lung, ovary, breast, thyroid, and salivary glands. The co-expression of both CK20 and CDX2, in the absence of CK7, instead indicates a carcinoma with intestinal differentiation, mainly colon cancer (24).

Markers such as progesterone receptor (PR), estrogen receptor (ER), and PAX8 are often used to evaluate the possibility of neoplasia of gynecological origin (25).

Prostate-specific antigen (PSA) search is performed to investigate cancers originating from the Skene glands. These glands are historically considered the female analog of the prostate in males (for similar structure and PSA production) (26). From more recent works, however, it emerged that positive PSA is not necessary to confirm that a tumor originates from Skene glands (27).

Along with PSA expression, an alpha-methyl acyl CoA racemase (AMACR) stain was performed. This cytoplasmic immunohistochemical staining is positive in prostatic adenocarcinoma, and it is sensitive (82-100%) and relatively specific (70-100%) in distinguishing prostate carcinoma from benign prostate (28). Based on the available literature, this marker is reported to be used to identify a Skene gland adenocarcinoma with intestinal differentiation (25).

In our case, the immunohistochemical investigations on the biopsy confirmed the "intestinal" profile (CK20⁺, CK7⁻, CDX2⁺) and allowed us to exclude the urothelial nature (CK7⁻, GATA3⁻).

Pathological results from the final specimen revealed a neoplastic cell immunophenotype negative for CK7, PAX8, GATA3, ER and PR, S100, and PSA. The specimen stained positively for CDX2, CK20, and AMACR. Along with pathological re-

sults, only clinical aspects rose a diagnostic suspect of adenocarcinoma from the Skene glands.

In the specific clinical condition of an intestinal-type primary vaginal adenocarcinoma, the pathologists play a fundamental role in guiding diagnostic and therapeutic pathways.

This is particularly evident if considering that some aspects of tumor invasion in our case emerged only after the pathologic study of the final specimen and that imaging and clinical analysis were not able to rule out an invasion of the adjacent organs unequivocally.

Moreover, thanks to the immunohistochemical profile, the possibility of ruling out vaginal secondaries is of great importance for the gynecologic surgeon when deciding the best therapeutic approach.

An immunohistochemical finding of a tumor of urothelial origin along with urethra and bladder free from lesions (macroscopically and at biopsy) would make it mandatory to look for a primary disease arising from other urothelial sites (*i.e.*, the ureter or the kidney).

Similarly, an immunohistochemical finding of a vaginal lesion of gynecological origin usually indicates an endometrial or cervical disease with caudal spread. Also, primary colorectal cancers can spread to the vagina. Stage IV disease should be diagnosed, and the patient should not be eligible for surgery.

All these considerations should be taken into account when facing a malignant glandular lesion of the vagina.

CONCLUSIONS

We here described the clinical management of a fragile patient with a rare intestinal-type primary vaginal adenocarcinoma and a transplanted kidney for renal failure with no indication for surgery at initial evaluation. We also reviewed the literature to outline the clinical management for these

patients, but we had to acknowledge the paucity of cases and incompleteness of data available. This is likely due to the very low prevalence of the disease (only 24 cases described in total).

Clinical aspects and preoperative evaluation must be actively integrated with a detailed pathological analysis. The presumptive diagnosis comes from clinical evaluation and imaging findings, and the pathologist confirms the diagnosis. The differential diagnosis of an intestinal-type adenocarcinoma at the vaginal level (an organ almost free from glandular tissue) is particularly challenging given the anatomical complexity and different embryologic derivations of organs in this district.

In our specific case, the initial clinical evaluation (a vaginal lesion presenting with vaginal bleeding, a urethra free from lesions and negative bladder biopsies) was associated with the immunohistochemical findings of an intestinal-type adenocarcinoma oriented the gynecologist toward a primary vaginal adenocarcinoma. After the pathologic analysis on the final surgical specimen, it was possible to appreciate a full-wall urethral invasion at its distal third. Given that Skene glands are at this urethral level and given the tumor positivity for potential specific markers (AMACR), the pathologist raised the possibility of a tumor from these glands.

A multidisciplinary approach to the disease is of fundamental importance where clinical, imaging, and laboratory evaluation meets pathologic analysis to obtain an adequate diagnosis. Due to the lack of specific guidelines addressing these rare diseases, the treatment of choice should be tailored considering the stage of the disease, the patient's comorbidities, and the multidisciplinary holistic evaluation of the case.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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Gestational trophoblastic disease: an update on pathology, diagnosis and state-of-the-art management

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ABSTRACT

Gestational trophoblastic disease (GTD) is a spectrum of disorders originating from the placenta, including premalignant forms, such as complete and partial hydatidiform mole, and the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. The incidence of GTD varies between countries and the prevalence depends on maternal age, previous GTD history, socioeconomic factors. Histology and molecular genetic studies can help in the diagnostic pathway. Diagnosis of GTD is based on a multifactorial approach consisting of clinical features, serial human chorionic gonadotropin titers, and imaging findings. GTD can result in significant morbidity and mortality if left untreated; early diagnosis of GTD is essential for prompt and successful management while preserving fertility.

SOMMARIO

La malattia trofoblastica gestazionale (GTD) rappresenta uno spettro di patologie derivanti dalla placenta, che include forme premaligne, come mola idatidiforme completa e parziale, e forme maligne quali mola invasiva, coriocarcinoma, tumore trofoblastico del sito placentare e tumore trofoblastico epitelioidale. L'incidenza di GTD varia, la prevalenza dipende dall'età materna, dalla precedente storia di GTD e dai fattori socio-economici. Istologia e genetica molecolare possono aiutare nel percorso diagnostico. La diagnosi di GTD si basa su un approccio multifattoriale costituito dalla clinica, valutazioni di gonadotropina corionica umana e di diagnostica per immagini. GTD se non trattata può provocare morbilità e mortalità significative; la diagnosi precoce di GTD è essenziale per una gestione ottimale che preservi la fertilità.

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Key words

Gestational trophoblastic disease; epidemiology; diagnosis; management; review.

INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a spectrum of tumors with a wide range of biologic behavior and potential for distant metastases, all arising from abnormal placenta (1). GTD includes the pre-malignant conditions of complete (CHM) and partial (PHM) hydatidiform mole and the malignant invasive mole, choriocarcinoma (CC) and the very rare placental site trophoblastic tumor and epithelioid trophoblastic tumor (PSTT/ETT) (2). The last four are referred to as gestational trophoblastic neoplasia (GTN) that often arises after molar pregnancy but can occur after any gestation including miscarriages and term pregnancies (3).

Epidemiology

The most common form of GTD is hydatidiform mole, which accounts for 80% of all cases, while invasive mole accounts for 15% and CC for 5%. PSTT represents only 0.2% of GTD cases within UK (4, 5). The prevalence of GTD varies depending on geography, maternal age, previous GTD history, socioeconomic factors, dietary factors, and possibly blood grouping (6, 7). A wide global variation in the prevalence of molar pregnancy has been reported (8). GTD arises more frequently in Asia than in North America or Europe. Hydatidiform mole occurs in 0.5-1 over 1000 pregnancies in North America and Europe, 1.5-6 over 1000 pregnancies in South America and 12 over 1000 pregnancies in Southeast Asia (8, 9). The incidence of choriocarcinoma is 1 in 40000 pregnancies in North America and Europe, 9.2 in 40000 pregnancies in Southeast Asia and 3.3 in 40000 pregnancies in Japan (10). Geographic differences in prevalence may be due to discrepancies between hospital-based and population-based data or in availability of central pathology review (11). Molar pregnancies are more frequent at the extremes of maternal age, *i.e.*, under 16 years old and over 45 years old. In these age ranges, gametogenesis and fertilization abnormalities are more frequent (12, 13). Furthermore, the risk of PHM and CHM increases by 1-2% after a molar pregnancy, and by 15-20% after two molar gestations. The risk does not decrease with a change of partner (14-16). Dietary deficiency of beta-carotene and animal fat has been advocated as a risk factor for CHM (17). Moreover, there may be an increased risk of choriocarcinoma in women who have used long-term oral contraceptives and with blood group A (18-20).

Pathophysiology and genetics

GTD identifies a group of tumors of gestational origin. Soon after implantation, placental trophoblasts differentiate into cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. While CHM, PHM and CC originate from cytotrophoblasts and syncytiotrophoblasts, PSTT and ETT arise from intermediate trophoblasts. In 90% of cases, CHM develops when an empty ovum that lost its maternal chromosomes is fertilized by one sperm, which then duplicates its DNA, resulting in a 46, XX karyotype with a complete paternally-derived set of chromosomes. About 10% of CHMs have a 46, XY karyotype, resulting from dispermic fertilization (21, 22). A rare form of CHM can result from a recurrent autosomal recessive disorder. In this case, CHM is diploid but of biparental origin. This condition is associated with mutations of two genes: NLRP7 and, rarely, KHDC3L (23-25). PHMs are almost always triploid, resulting from fertilization of a healthy ovum by two sperms or by one sperm that duplicates itself, resulting in the genotypes 69, XXX, 69, XXY, or 69, XYY. Rarely, PHMs can be tetraploid with a 92, XXXY genotype. Diploid PHM is unlikely, most reported cases representing misdiagnosed complete moles or twin pregnancies (21, 22). The malignant invasive mole and CC follow CHM in 15%-20% of cases and PHM in less than 5% of cases. Invasive mole is the most common form of GTN and always occurs after CHM. Therefore, it usually has a diploid karyotype that is completely paternal in origin (26). It is a clinical rather than pathological diagnosis based on persistent human chorionic gonadotropin (hCG) elevation after molar evacuation (3).

Pathology

Complete and Partial Hydatidiform mole

CHM and PHM have distinctive morphological characteristics. CHM is characterized by the absence of fetal parts, abnormal villous structure, trophoblast hyperplasia, stromal hypercellularity, stromal karyorrhectic debris and collapsed villous blood vessels. In contrast, PHMs have less pronounced histopathologic features, with irregular and scalloped villi as prophile showing trophoblast inclusions and less pronounced hyperplasia. Also, in PHM fetal tissue might be present, like nucleated red blood cells and fetal membranes (1). Morphological distinction between PHM and CHM can in some cases be difficult. Immunos-

taining with p57^{KIP2}, ploidy analysis with in-situ hybridization/flow cytometry, or molecular genotyping may be useful to rule out difficult cases (27-28-29). p57^{KIP2} gene is localized on chromosome 11p15.5 and it encodes an inhibitor of G1 cyclin/Cdk complexes. It acts as a negative regulator of cell proliferation. This gene is paternally imprinted and maternally expressed, thus its protein is a surrogate marker for the nuclear maternal genome (30). PHMs and non-molar normal and abnormal gestations with maternal genome display a strong nuclear p57 staining, while CHM is almost always p57-negative (28, 29). Rare types of CHM carrying a maternal copy of chromosome 11 are p57-positive (30). However, p57 cannot differentiate PHM from non-molar gestation (30).

Choriocarcinoma

CC may manifest after a hydatidiform mole, a normal pregnancy, or an abortion. Histologically, CC shows absence of chorionic villi and presence of abnormal intermediate trophoblast and cytotrophoblast, surrounded by syncytiotrophoblasts. CC has numerous and large areas of necrosis of haemorrhagic type; viable tumor can be scant. CC is characterized by numerous atypical mitoses and by an high Ki-67 Index. Moreover, it is characterized by the production of high levels of b-hCG (2).

Placental Site Trophoblastic tumor and Epithelioid Trophoblastic tumor

PSTT and ETT are tumors that typically occur after non-molar gestations and may manifest many years after a full-term delivery. They usually produce lower levels of b-hCG compared to other forms of GTN. Histologically, PSTT take origine from intermediate trophoblast of inplantation side, organized in small cords with indertwining stroma, with absence of villar structures and with a low mitotic count in contrast to CC. PSTT is characterized by the absence of chorionic villi and low mitotic count. Tumor cells diffusely express hPL, MUC-4, HSD3B1, HLA-G and CD-146. Ki-67 is expressed in 10% to 30% of cells. ETT is composed by islands of intermediate trophoblastic cells that are surrounded by extensive necrosis and hyaline matrix (31). CC can be differentiated from PSTT and ETT also by SALL4 positivity. SALL4 is a zinc finger transcription factor involved in embryonal development. Its expression in CC could reflect the low level of differentiation of CC compared to PSTT and ETT and cannot be observed in CHM (32).

Clinical presentation

Complete and Partial Hydatidiform mole

Patients with molar pregnancies most commonly present with vaginal bleeding and markedly elevated β -hCG values in the first or early second trimester (33). Vaginal bleeding is attributed to the rapid growth of trophoblastic tissue that separates blood vessels from the decidual bed damaging their wall. Due to routine use of ultrasonography in first-trimester examination and in the investigation of vaginal bleeding, diagnosis usually occurs before the classic clinical presentation can arise (34). Previously reported clinical signs and symptoms such as hyperemesis, excessive uterine enlargement for gestational age, pre-eclampsia, anemia, respiratory distress and hyperthyroidism, are now rare (35). Such symptoms were generally related to CHM, whereas in PHM they were less evident (36). Depending on the age of the woman, clinical presentation can be different. Symptoms tend to be more pronounced in older women, where clinical features are often misinterpreted, leading to a delay in correct diagnosis and a higher incidence of disease-related complications (37). However, despite the earlier diagnoses and the consequent reduction in the frequency of major clinical symptoms, the rate of progression to GTN reported in literature has not changed over time (38).

Gestational trophoblastic neoplasia

Clinical presentation of GTN can vary and depends on the condition determining its onset, the extent of the disease and histopathology. GTN can happen after a molar pregnancy: in these cases, diagnosis is clinical and is defined by plateaued or rising levels of β -hCG during follow-up. Furthermore, there are diagnostic criteria that are not always recognized such as: β -hCG > 20000 U/L to one year; histology of choriocarcinoma; positive β -hCG for 4-6 months. The most frequent symptom of postmolar GTN is irregular bleeding after uterine evacuation; less frequently, it develops without symptoms. Occasionally, a metastatic vaginal lesion may cause uncontrolled bleeding (39). CC after a non-molar gestation (spontaneous abortion, ectopic pregnancy or term pregnancy) is characterized by a heterogeneous clinical presentation which is related to invasion of tumor in the uterus or at metastatic sites such as lung, liver, spleen or brain (3). Symptoms related to bleeding from metastatic sites may occur, resulting in abdominal pain, hemoptysis, dyspnea,

cough, chest pain, melena, or symptoms related to increased intracranial pressure from intracerebral hemorrhage. In 1/3 of cases CC can present without gynecological symptoms. In all cases of metastatic disease of unknown origin in a woman of childbearing age with a positive history of pregnancy CC diagnosis must be considered (39).

PSTT and ETT generally occur with irregular uterine bleeding long after the non-molar pregnancy from which they originate. They often present with relatively low levels of serum β -hCG despite the volume of disease seen at imaging (40, 41).

Diagnosis

Partial and Complete Hydatidiform mole

Ultrasonography is a critical exam in posing the an early clinical suspicion of GTD. Ultrasound (US) morphological features allow differential diagnosis between PHM and CHM. However, PHM presents subtler US features so that its diagnosis is less common than CHM during first trimester. Early PHMs are characterized by cystic changes and increased echogenicity of the decidua and placenta in presence of embryonic tissue that can be identified as amorphous echoes (42, 43). In those few cases that proceed above 11 weeks (late PHMs), US features are characterized by enlarged and irregular molar placenta with focal villous edema and an abnormal triploid fetus carrying severe abnormalities (ventriculomegaly, hydrocephalus, holoprosencephaly, increased nuchal translucency, renal defects). CHMs are characterized by trophoblastic hyperplasia displayed as diffuse cystic spaces within the placenta ("snowstorm") in the absence of a fetus or embryonic tissue (1). The high levels of β -hCG can lead to excessive stimulation of the ovaries with theca lutein cysts, however this occurs in less than 20% of cases (44).

When US features are suspicious for HM, β -hCG levels, a blood group and screen/save must be determined. Histological examination after suction curettage is essential for diagnosis (3).

Gestational trophoblastic neoplasia (GTN)

Invasive mole

Postmolar GTN is usually diagnosed by hCG follow-up after histological diagnosis of HM. Invasive trophoblast can be identified at US by the presence of heterogeneous myometrial nodules or masses, which can be echogenic or hypoechoic, usually hypervascular (45). US findings of vascularized myometrial

nodules after uterine evacuation can correlate with a high risk of malignant evolution (46). Arteriovenous shunts are also common due to neoangiogenesis phenomena occurring within the tumor (43).

Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT)

The diagnosis of PSTT and ETT, which are the rarest forms of GTN, requires histopathologic examination. Their rarity makes diagnosis particularly challenging. US features are similar to other forms of GTN, *i.e.*, the presence of myometrial nodules with a heterogeneous structure consisting of cystic cavities and solid masses (43). At US, they show different patterns of myometrial invasion: while ETT expands with sharp borders, PSTT penetrates between myometrium muscle fibers (47).

Management

Hydatidiform mole

Treatment of hydatidiform mole consists of uterine evacuation by suction and curettage. US control is recommended to ensure a thorough evacuation and to minimize the risk of uterine perforation (48). When gestational age is higher than 16 weeks and the uterus is particularly enlarged, the procedure carries a significant risk of bleeding and embolization of molar tissue to the lungs but the treatment must always be done (3). Ergometrine or other sustained uterotonic must be started at the onset of suction curettage and continued postoperatively to enhance uterine contractility (48). In women with no childbearing desire, hysterectomy is a valid alternative to uterine curettage, but it requires careful hCG surveillance because these women could still develop GTN (49). Diagnosis should always be confirmed by histology and, whenever possible, genetic testing for karyotype determination. Rh-negative patients should be given anti-D prophylaxis. Repeated uterine curettages did not prove to be effective in reducing the need for subsequent chemotherapy or the risk of relapse (50). If mole diagnosis is confirmed, hCG follow-up should be started 3 to 4 weeks after evacuation with a frequency of once a week and continued until at least 2 consecutive negative tests. Subsequently, a single confirmatory hCG measurement is recommended for a PHM over 1 month, and monthly measurements are recommended for a CHM for 6 months. Oral contraceptives may be useful in this timeframe to avoid interferences with hCG measurements due to a new pregnancy or elevated

levels of luteinizing hormone (LH) (48). **Figure 1** reports the diagnostic pathway for HM.

Coexisting normal pregnancy with mole (CHM coexisting with a Healthy Fetus)

A multiple pregnancy consisting of a complete hydatidiform mole with a coexisting fetus (CHMCF) is very rare, complicating 1 per 20000 to 100000 pregnancies. This condition is normally diagnosed at the end of the second trimester (between 15 and 18 weeks) of pregnancy. Its US features are characterized by a complex cystic pattern adjacent to a normal placenta and a structurally normal fetus (43). In early first trimester, misdiagnosis with subchorionic hematoma is frequent (51). A recent meta-analysis including 244 cases reported that the incidence of antenatal maternal complications is around 80%, including vaginal bleeding (70%), hyperthyroidism (23%), and pre-eclampsia (14%). Live birth rate was 50% in ongoing pregnancies, with 78% pre-term births. Evolution into GTN happened in 34% of the patients whether pregnancy is stopped or continued. Therefore, these pregnancies should receive adequate counselling and be managed in a GTD center (52).

Gestational Trophoblastic Neoplasia

Prophylactic chemotherapy after HM diagnosis is not advisable (53). Indications for chemotherapy

after a molar pregnancy (see **table I**) include an hCG rise for at least 3 consecutive measurements for a period of at least 2 weeks or a plateau for at least 4 consecutive measurements over a period of at least 3 weeks (2). Chemotherapy is also indicated in case of hCG level greater than 20000 IU/L more than 4 weeks after uterine evacuation (54). Elevated but falling hCG values 6 months after evacuation are no longer treated by chemotherapy, since in most cases a spontaneous normalization occurs (55). Postpartum GTN can be diagnosed by histological examination or by evidence of multiple metastases in a woman of childbearing age with elevated hCG values (3). Histological diagnosis of CC is no longer considered an absolute indication to start chemotherapy, since spontaneous regression with falling hCG levels has been reported (56, 57).

Staging

GTN should be staged by transvaginal US, chest X-ray and body CT scan (48). These exams allow the definition of FIGO 2000 staging and scoring system (see **tables II** and **III**).

Only metastases detected by X-ray are included in the FIGO 2000 score, as micro-metastases are not associated with a worse prognosis (58). However, lung micrometastases are associated with a higher incidence of chemo-resistance (59). If lung metasta-

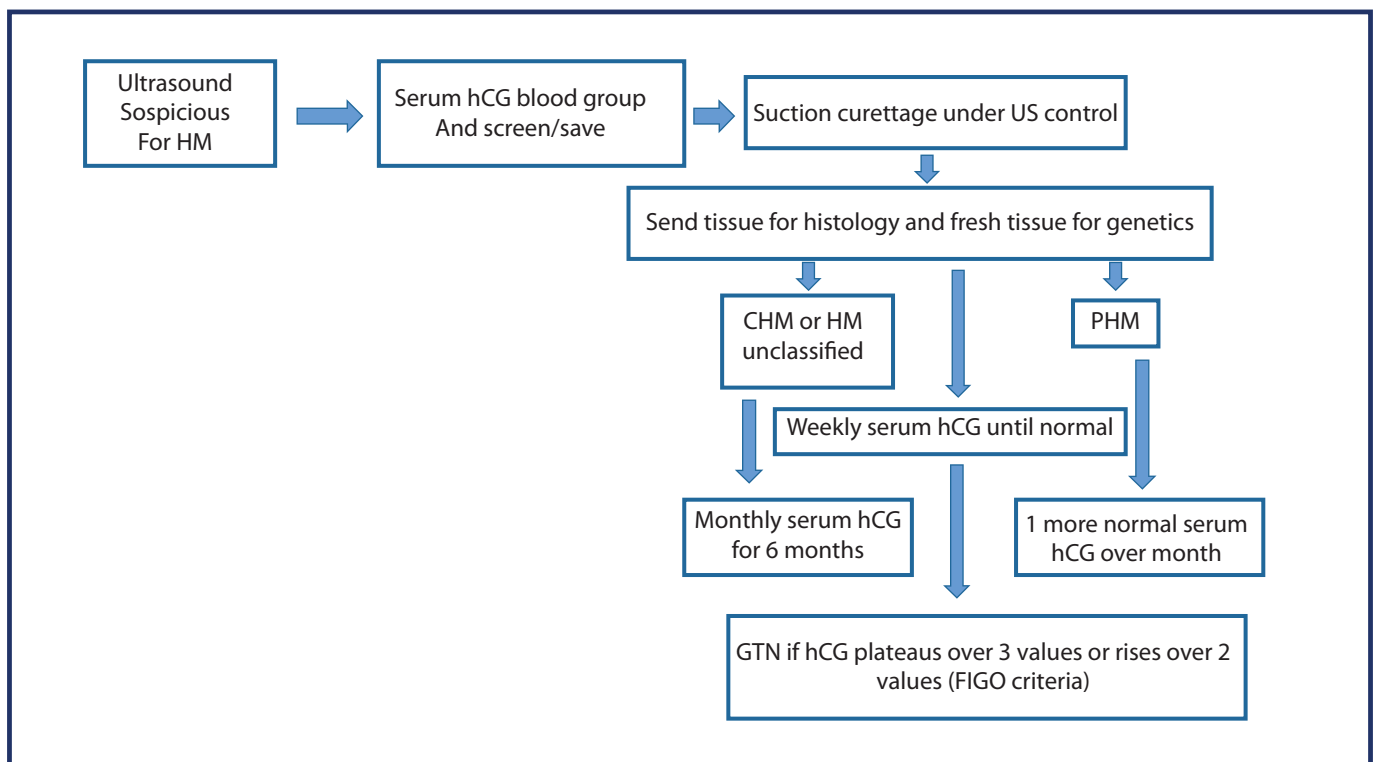


Figure 1. Diagnostic pathway for HM to GTN.

Table I. Indications for chemotherapy after a molar pregnancy.

Weekly hCG rising for at least 3 consecutive measurement for a period of at least 2 week (day 0-7-14)
Weekly hCG plateauing for at least 4 consecutive measurements for a period of at least 3 week (day 0-7-14-21)
Persistence of hCG more than 6 months after evacuation
Histological diagnosis of choriocarcinoma*
Serum hCG level greater than 20000 IU/L more than 4 weeks after evacuation*

*Criteria non absolute.

ses are present, brain MRI is also recommended (3). In staging, PET cannot replace conventional imaging and does not show any information in addition to that shown by conventional imaging. However, it could have an additional value in patients with high-risk disease to identify unconventional metastatic locations (60). Scoring system by prognostic factors is necessary to identify patients at risk to develop chemoresistant disease. Patients scoring below 6 are considered at low risk and can be treated by monotherapy, while patients scoring 7 or higher are at high risk of developing resistance to single-drug regimens and therefore should receive combination-agent chemotherapy as first line treatment (1). FIGO scoring system is less predictive of resistance for intermediate risk patients. Over 50% of patients who score 5-6 develop chemoresistance and need to switch to multiagent regimens, but almost all are eventually cured (11). Other factors have been advocated to be prognostic of drug resistance in this group of patients, such as uterine artery pulsatility index measured by Doppler ultrasonography (43). At diagnosis, all patients should at least be discussed with a GTD referral center. High-risk patients must be referred at a GTD center (48).

Low-risk GTN

Low-risk GTN can be treated either with methotrexate (MTX) or actinomycin-D (act-D) (see **table IV**). Act-D is probably the most effective treatment, being associated with higher primary response rates than MTX (61, 62). Nevertheless, in most centers MTX is preferred over act-D as first-line treatment because of the lower toxicity profile (no hair loss, less nausea and myelosuppression) (63) and cost-effectiveness (64). It is estimated that approximately 70% of low-risk patients will develop chemoresistance, but these patients will respond to salvage treatment with multiagent chemotherapy and will eventually be cured (3). Many different treatment schedules exist. The most widely used protocol consists of a 8-day regimen where MTX is administered on days 1, 3, 5, 7 alternated with a folinic acid (FA) rescue (generally 7.5 to 15 mg) on days 2, 4, 6, 8, repeated every 14 days. Some centers prefer to adjust MTX dose by body weight, although this is probably unnecessary (4). MTX can be also administered intravenously at the dose of 0.4 mg/kg for 5 days every 2 weeks. Act-D can be administered intravenously at the dose of 0.5 mg for 5 days, repeated every 14 days (1). Patients

Table II. FIGO 2000 scoring system for GTN.

Prognostic factors	0	1	2	4
Age, years	< 40	≥ 40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval from antecedent pregnancy	< 4	4-6	7-12	> 12
hCG (IU/L)	< 10 ³	10 ³ -10 ⁴	10 ⁴ -10 ⁵	> 10 ⁵
No of metastases	0	1-4	5-8	> 8
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Largest tumor mass	< 3	3-5 cm	> 5 cm	
Prior chemotherapy			Single drug	≥ 2 drugs

Table III. FIGO staging for GTN.

Stage I	Disease confined to the uterus
Stage II	Disease extending into the pelvis and/or vagina
Stage III	Disease spread to lungs and/or vagina
Stage IV	All other metastatic sites

with disease confined to the uterus not wishing to maintain fertility can be treated by hysterectomy; however, this does not eliminate the need for subsequent chemotherapy (49). Serum hCG measurements should be repeated at least every 2 weeks to monitor response to treatment. In case of resistance, re-imaging and a therapy switch should be considered. Primary resistance occurs if hCG rises after 2 courses or plateaus (< 10% change between measurements) after 3 courses. Acquired resistance is defined by a plateau over 2 courses (4 weeks) or rise over at least 2 weeks (48). In case of MTX resistance, if hCG \leq 1000 IU/L patient should receive act-D, if hCG > 1000 IU/L a multiagent regimen is recommended (48). The overall cure rate for low-risk disease patients is close to 100% (1). After normalization of bhCG levels, 3 consolidation treatments will decrease the chance of recurrence (65).

Table IV. Treatment of low-risk GTN.

8-day regimen: MTX (50 mg total dose intramuscular) day 1-3-5-7 with FA (15 mg) day 2-4-6-8; repeated every 14 day termed MTX/FA regimen*
Act-D 0.5 mg for 5 days repeated every 14 days

*First choice treatment.

High-risk GTN

High-risk patients with a FIGO score comprised between 7 and 12 should receive multiagent chemotherapy (see **table V**). The most used regimen is a combination of etoposide 100 mg/mq, MTX 300 mg/mq and ActD 0.5 mg (EMA) with repeated doses of etoposide and Act-D on day 2, alternated weekly to cyclophosphamide 600 mg/mq and vincristine 0.8 mg/mq (CO). This schedule requires a folinic acid rescue 24 hours after MTX administration 12 hourly for 4 doses (3). Chemotherapy should be administered weekly until hCG normalization and for 6-8 weeks of consolidation (48). EMA/CO-resistant disease can be salvaged with alternative platinum-based regimens: EMA (omitting the second day to reduce myelotoxicity) alternating weekly with etoposide and cisplatin (EP); paclitaxel and etoposide (TE) alternating every 2 weeks with paclitaxel and cisplatin (TP); etoposide, ifosfamide and cisplatin every 3 weeks; bleomycin, etoposide, and cisplatin every 3 weeks. In a study including over 400 patients, survival after treatment with these regimens was 94% in high-risk patients and 99% in the resistant low-risk group, with a median follow-up time of 4 years (66).

Table V. Treatment of High-risk GTN.

<p>EMA-CO</p> <p>Day 1:</p> <ul style="list-style-type: none"> o Actinomycin-D 0.5 mg iv. o Etoposide 100 mg/m² iv. o Methotrexate 300 mg/m² iv. <p>Day 2:</p> <ul style="list-style-type: none"> o Actinomycin-D 0.5 mg iv. o Etoposide 100 mg/m² iv. o Folinic acid 15 mg postoperatively 12 hourly x 4 doses Starting 24 hours after methotrexate. <p>Day 8:</p> <ul style="list-style-type: none"> o Vincristine 0.8 mg/m² (maximum, 2 mg). o Cyclophosphamide 600 mg/m².
<p>EP/EMA</p> <p>Day 1:</p> <ul style="list-style-type: none"> o Actinomycin-D 0.5 mg iv. o Etoposide 100 mg/m² iv. o Methotrexate 300 mg/m² iv. <p>Day 2</p> <ul style="list-style-type: none"> o folinic acid 15 - 30 mg po 12 hourly x 4 doses Starting 24 h after methotrexate week 2. <p>Day 8</p> <ul style="list-style-type: none"> o Etoposide 150 mg iv. o Cisplatin 75 mg/m² iv.
<p>TP/TE schedule for relapsed GTN</p> <p>Day 1</p> <ul style="list-style-type: none"> o Paclitaxel 135 mg/m². o Cisplatin 60 mg/m². <p>Day 15</p> <ul style="list-style-type: none"> o Paclitaxel 135 mg/m². o Etoposide 150 mg/m².

Table VI. Treatment of Ultra-High risk GTN.

<p>1. INDUCTION THERAPY on days 1 and 2 weekly for 1-3 cycles</p> <ul style="list-style-type: none"> · etoposide 100 mg/m²; · cisplatin 20 mg/m².
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Ultra-high risk GTN

Patients scoring 13 or higher should immediately be referred to a GTD center. The presence of liver and/or brain metastases is considered a risk factor for poor prognosis (11). Early deaths due to respiratory compromise and hemorrhage secondary to rapid tumor destruction with full-dose chemotherapy used to be frequent before the introduction of low-dose induction etoposide-cisplatin (EP) in patients with a high burden of disease at presentation (66). Induction therapy consists of the administration of etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2 weekly for 1-3 cycles. After induction, patients should be treated with EMA/EP or EMA/CO (see **table VI**). In case of brain metastatic disease, the MTX dose in the EMA should be increased to 1 g/m² alternating weekly with CO. Intra-theal MTX can be considered with CO. Patients with liver metastases should receive EMA/EP. With liver and brain involvement, the second day of etopo-

side and actinomycin D in EMA should be omitted. Treatment delays should be avoided by using G-CSF (granulocyte colony stimulating factor) support each week (48). Stereotactic radiotherapy or gamma-knife treatment at the end of chemotherapy could be used to treat residual lesions that are unsuitable for resection. Drug-resistant disease in a single site can be surgically removed (67, 68).

High-Dose chemotherapy and Immunotherapy as salvage treatment

Patients failing multiple lines of chemotherapy with unresectable disease could be salvaged by high-dose chemotherapy with peripheral blood stem cell support (69). Due to positive outcomes in selected patients with drug-resistant GTN, the use of pembrolizumab is a promising approach as salvage treatment (70). Genotyping of trophoblastic tumors with unusual presentations or atypical responses to therapy is recommended, to rule out non-gestational origin (67). Also, PSTT/ETT diagnosis should be suspected in case of chemoresistant disease.

Follow up after remission

After consolidation therapy is completed, weekly hCG measurements should be continued for at least 6 weeks, then monthly for at least 12 months. Follow-up should be continued for a few years; the recurrence risk drops off steeply after 3 years and no recurrences have been reported after 7 years (71). Since most relapses occur in the first 12 months, pregnancy seeking should be delayed for at least 1 year by the end of treatment.

Placental site trophoblastic tumor (PSTT) and Epithelioid trophoblastic tumor (ETT)

FIGO scoring does not apply to PSTT and ETT for treatment determination. The only recognized prognostic factors for these rare tumors are the interval from index pregnancy and presence of metastatic disease (72, 73). A stage-adapted, personalized approach is recommended for PSTT and ETT. In all cases, surgery remains the cornerstone of treatment. An interval ≥ 48 months from antecedent pregnancy is the most significant independent predictor of poor outcome and requires an intensification of treatment, generally with adjuvant platinum-based chemotherapy (*i.e.*, EMA/EP) (73).

Fertility after chemotherapy

After a CHM, the risk of another CHM is 1 in 100; after one or two consecutive CHMs the risk of a further CHM is 1 in 4. Women with a PHM have only a small increase in risk for further molar pregnancies (74). In a recent meta-analysis, the pregnancy rate among women treated with chemotherapy for GTN was 86% (75). Adverse pregnancy outcomes were similar to those of general population (75). The cumulative risk of early menopause after EMA-CO reaches 13% by age 40 years and 36% by age 45 years (76). Except for this risk of premature ovarian failure, which rarely happens in younger women and is only associated with multiagent regimens, both single-agent and multiagent chemotherapy do not compromise pregnancy rates and outcomes among women wishing to conceive. In our series, high-risk patients showed worse reproductive outcomes only because the rate of salvage hysterectomies was higher in their cohort compared to low-risk patients (77).

CONCLUSIONS

Gestational trophoblastic disease (GTD) is a rare and heterogeneous group of disorders characterised by abnormal proliferation of trophoblastic tissue. Outcomes for most women with GTD are excellent but 2% of them die from the disease, because of late presentation and diagnosis or drug resistance. Indeed, early diagnosis and effective therapeutic strategies with reduced toxicity are essential. Morbidity and mortality for GTD can be reduced by referring patients in specialised centres with multidisciplinary teams, that participate in clinical trials and national registrations to evaluate quality of care. Guideline development is an on-going process, therefore it is important to provide a basis for standardisation of definitions, treatment and follow-up protocols. These specialised centres are needed to avoid inappropriate treatment strategies.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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Hysteroscopy “As one stop approach” in the management of intrauterine pathology. Focus on patient’s satisfaction

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ABSTRACT

Objective. This study has been done to assess the effectiveness of hysteroscopy to the one stop approach in the management of intrauterine pathology and to review the patient’s satisfaction with this approach.

Materials and methods. This is a retrospective analysis conducted at a tertiary care hospital from March 2018 to March 2020. All the women who were admitted for hysteroscopy for one stop, diagnostic and therapeutic approach, were included in the study. All hysteroscopy were performed by the same surgeon. Data pertaining to clinical findings, diagnosis, hysteroscopic findings, complications, and histopathology report were obtained from patient’s record sheets. We conducted a telephonic survey with simple questionnaire to assess the patient’s satisfaction with this approach.

Results. Among the 150 women analyzed, AUB was the indication of hysteroscopy in 36% and infertility in 48%. 80% of women had abnormal hysteroscopy. Intrauterine adhesion was the most common lesion detected in infertile women whereas endometrial polyp was seen more frequently in AUB. Hysteroscopy was found to be 100% accurate in diagnosing endometrial cancer in PMB. 101 procedures were performed in the same sitting. 89 women responded to our telephonic survey. 88.7% women experienced significant improvement in the symptoms, 94% women accepted it as cost and time effective procedure and 88% women said that they would recommend this procedure to a friend.

Conclusions. Hysteroscopy has been indispensable in evaluating intrauterine pathology. The one stop approach which include diagnosis and treatment at the same sitting is minimally invasive, low risk, well tolerated, cost and time effective procedure and is being highly preferred by the patients.

SOMMARIO

Obiettivo. Questo studio è stato condotto per valutare l’efficacia dell’isteroscopia rispetto all’approccio one-stop nella gestione della patologia intrauterina e per esaminare la soddisfazione della paziente.

Materiali e metodi. Si tratta di un’analisi retrospettiva condotta presso un ospedale di cure terziarie da marzo 2018 a marzo 2020. Sono state incluse nello studio tutte le donne ricoverate per isteroscopia per approccio diagnostico e terapeutico one-stop. Tutte le isteroscopie sono state eseguite dallo stesso chirurgo. I dati relativi ai reperti clinici, alle diagnosi, ai reperti isteroscopici, alle complicanze e al referto istopatologico sono stati ottenuti dai fogli di registrazione delle pazienti. Abbiamo condotto un sondaggio telefonico con un semplice questionario per valutare la soddisfazione delle pazienti con questo approccio.

Risultati. Tra le 150 donne analizzate, AUB è stata l’indicazione di isteroscopia nel 36% e infertilità nel 48%. L’80% delle donne ha avuto un’isteroscopia anormale. L’adesione intrauterina è stata la lesione più comune rilevata nelle donne infertili, mentre il polipo endometriale è stato osservato più frequentemente nell’AUB. L’isteroscopia è risultata accurata al 100% nella diagnosi del cancro dell’endometrio nella PMB. 101 procedure sono state eseguite nella stessa seduta. 89 donne hanno risposto al nostro sondaggio telefonico. L’88,7% delle donne ha sperimentato un miglioramento significativo dei sintomi, il 94% delle donne l’ha definita come una procedura efficace in termini di costi e tempi e l’88% delle donne ha affermato che consiglierebbe questa procedura ad un’amica.

Conclusioni. L’isteroscopia è stata indispensabile nella valutazione della patologia intrauterina. L’approccio one-stop che include diagnosi e trattamento nella stessa seduta è una procedura minimamente invasiva, a basso rischio, ben tollerata, efficace in termini di costi e tempi ed è altamente preferita dalle pazienti.

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Key words

Intrauterine pathology; hysteroscopy; abnormal uterine bleeding; infertility.

Abbreviations

AUB: Abnormal Uterine Bleeding

IUA: Intrauterine Adhesion

USG: Ultrasonography

HSG : Hysterosalpingography

OT: Operation Theatre

INTRODUCTION

Intrauterine pathology can present with spectrum of symptoms ranging from asymptomatic to abnormal uterine bleeding and infertility. Though the uterine factor can be found only in 2-3% of infertile women, intrauterine pathology is much more prevalent in this setting (40-50%) (1). Observational studies have suggested increased pregnancy rate after Hysteroscopic removal of these lesion (1). Abnormal uterine bleeding (AUB) is a common gynecological problem and impacts women's life at every stage from adolescence, through reproductive periods to menopause and postmenopausal time period. Role of hysteroscopy is indispensable in the work-up of AUB and infertility. In addition it provides opportunity to treat certain pathology at the same sitting, thereby reduces multiple visits and increases patient compliance. Transvaginal sonography being non-invasive has been utilized as first modality in the evaluation of infertility and AUB though it has poor sensitivity in detecting intrauterine pathology like endometrial polyp, submucosal fibroid, intrauterine adhesion and septum (2). Though the WHO recommends hysteroscopy only when clinical or complementary (USG, HSG) exam is suggestive of intrauterine pathology, but many specialists feel that hysteroscopy as least invasive and more accurate in diagnosing intrauterine pathology (2, 3). Hysteroscopy is considered as gold standard in assessment of endometrial pathology as it eliminates the limitation of blind dilatation and curettage by allowing direct visualization of endometrial cavity and performance of targeted biopsy from suspected area. Miniaturization of hysteroscope has further reduced the need of anesthesia and made it more acceptable by the patients. In addition, vaginoscopic

approach of performing hysteroscopy allows detection of vaginal pathology besides reducing the discomfort due to cervical holding. Advent of newer techniques and miniature hysteroscope has opened up the new horizon for diagnosing and treating the intrauterine pathology at the same sitting. This study has been done with the objective to assess the effectiveness and patient's satisfaction of hysteroscopy to the one stop approach in the management of intrauterine pathology. Secondly to discuss the prevalence of various endometrial pathologies in AUB and infertility.

MATERIALS AND METHODS

After obtaining clearance from institute ethical committee, this retrospective cohort study was conducted from March 2018 to March 2020 in the department of obstetrics and gynecology at our institute. All patients who underwent hysteroscopy for evaluation of abnormal uterine bleeding, infertility or other uterine pathology during specified period were included in the study. Data including demographic details, pre-operative diagnosis, anesthesia used, operative procedures and complications were obtained from clinical record sheet of the patients. All patients after full clinical evaluation and pre-anesthetic check-up, underwent hysteroscopy. The procedure to pursue, choice of instrument and need of anesthesia was decided on the preclinical information. When the sonographic findings were suggestive of minor pathology like single polyp, endometrial thickness less than 12 mm or retained intrauterine CuT, hysteroscopy was performed without use of anesthesia. In case of major pathology type of anesthesia (conscious sedation, short

general or spinal) was decided according to expected duration of procedure and clinical characteristics of the patients inside the OT. All hysteroscopy were performed following vaginoscopic approach by single surgeon SJ using 2.9 mm hysteroscope. Uterine distension was provided with normal saline by using the continuous flow and pressure-controlled pump system. Hysteroscopy was performed with standard sequence, inspection of cervix, endocervical canal, uterine cavity, tubal ostia and endometrium. Procedures like septal resection, adhesiolysis, foreign body removal, polypectomy and myoma resections were performed using appropriate techniques at the same sitting when required. Endometrial biopsy had been taken in suspected cases. Operative findings were documented in the record sheets. A telephonic survey had been conducted by S.K pertaining to patient's satisfaction in terms of periprocedural experience and improvement in symptoms using simple questionnaire. We tried to contact all patients who underwent hysteroscopic procedure during the specified time period. Statistical analysis was done using Fischer exact t-test and P value < 0.05 was considered as statistically significant. Statistical analysis was done using online facility available at website www.medcalc.org.

RESULTS

A total of 150 patients with various complaints underwent hysteroscopy over a span of two years. Out of 150 patients, ninety eight did not require

anesthesia however 52 did. Mean age of presentation was 34.3 years (range 17-65 years). Abnormal uterine bleeding was the indication for hysteroscopy in 36% (54/150) and infertility in 48% (72/150). Data regarding age and indication of hysteroscopy have been summarized in the **table I**.

Hysteroscopy was abnormal in 80% (120/150). **Table II** compares the prevalence of normal and abnormal hysteroscopy in various diagnoses among the studied population. 83.4% (45/54) of women with AUB had abnormal pathology compared to 75% (54/72) in infertile women. Among 6 women with PMB, 2 were diagnosed with thin endometrium, one with endometrial carcinoma, 2 with endometrial polyp and 1 with endocervical polyp. Biopsies in these women confirmed the Hysteroscopic diagnosis. Two patients who presented with post tuberculous secondary amenorrhea, one had severe intrauterine adhesion and another one had cervical stenosis.

Various intrauterine pathology detected on hysteroscopy are enlisted in **table III**. Endometrial polyp was the commonest abnormality detected accounting for 22% of the pathology followed by intrauterine adhesion in 20%. **Table IV** is showing sub-group analysis among two major entity AUB and infertility. Incidence of endocervical and endometrial polyp was higher in AUB group (42.3% vs 26.3% at p-value 0.123) but the difference was not statistically significant.

Total 101 procedures were performed (**table IV**). Sixty five patients did not require anesthesia whereas 36 patients needed anesthesia. We removed all

Table I. Age distribution and indication of hysteroscopy in the studied population.

Age group (years)	Frequency (n = 150)	Percentage
15-20	4	2.6%
21-30	64	42.6%
31-40	52	34.6%
41-50	22	14.6%
50-60	2	1.3%
> 60	6	4%
Indication of Hysteroscopy		
AUB	54	36%
Primary infertility	50	33.3%
Secondary infertility	22	14.6%
Post-menopausal bleeding	6	4%
Missing thread	4	2.6%
AUB with primary infertility	8	5.3%
AUB with secondary infertility	4	2.6%
Secondary amenorrhea	2	1.3%

AUB: Abnormal Uterine Bleeding.

Table II. Incidence of abnormal Hysteroscopy in various pathology.

Diagnosis	Normal findings	Abnormal findings
AUB (n = 54)	9 (16.6%)	45 (83.4%)
PMB (n = 6)	0	6 (100%)
Primary infertility (n = 50)	13 (26%)	37 (74%)
Secondary infertility (22)	5 (32%)	17(68%)
AUB with primary infertility (n = 8)	2 (22.7%)	6 (77.3%)
AUB with secondary infertility (n = 4)	1 (25%)	3 (75%)
Secondary amenorrhea (n = 2)	0	2 (100%)

AUB: Abnormal Uterine Bleeding; PMB: Postmenopausal Bleeding.

Table III. Hysteroscopic findings.

Hysteroscopic finding	Frequency (n = 150)	Percentage
Endocervical polyp	14	9.3%
Endometrial Polyp	33	22%
IUA mild	30	20%
IUA moderate	3	2%
IUA severe	2	1.3%
Bony chip	6	4%
CuT	4	2.6%
Submucosal myoma	12	8%
Hyperplastic endometrium	6	4%
Endocervical carcinoma	1	0.6%
Endometrial carcinoma	2	2.6%
Septum	4	2.6%
Unicornuate uterus	3	2%
Normal	30	20%

IUA: Intrauterine Adhesion; CuT: Copper T.

Table IV. Hysteroscopic findings and procedures performed among AUB and infertility patients.

Hysteroscopic findings	Menstrual irregularity (n = 54)	Infertility (n = 72)	P-value
Endocervical polyp	7 (12.9%)	4 (5.5%)	0.14
Endometrial polyp	16 (29.6%)	12 (16.6%)	0.123
IUA	5 (9.2%)	23 (32%)	0.002
Bony chip	2	3	0.89
Submucosal myoma	9 (16.6%)	2 (2.7%)	0.008
Hyperplastic endometrium	4 (7.4%)	2 (2.7%)	0.4
Endocervical carcinoma	1 (1.8%)	0	0.41
Endometrial carcinoma	1 (1.8%)	0	0.18
Septum	0	4 (5.5%)	0.031
Unicornuate uterus	0	4 (5.5%)	0.031
Normal	9 (16.6%)	18 (25%)	0.282
Procedure performed			
Polypectomy	23	16	
Adhesiolysis	4	21	
Myomectomy	4	2	
Septal resection	0	4	
Bony chip removal	2	3	

IUA: Intrauterine device.

diagnosed polyp ranging from 0.5 to 3.5 cm. Out of 35 diagnosed intrauterine adhesion, adhesiolysis could be completed in 33 patients. Among them, 26 patients did not require anesthesia but 9 did. We could perform only 7 myomectomies from the 12 diagnosed myoma as 3 patients denied myomectomy and 2 patients had myoma > 3 cm size. Mean operating time for polypectomy and myomectomy were 13.4 minutes and 28.8 minutes respectively. Mean pain score (VAS) was 2.9 in the group who did not require anesthesia. We tried to contact all but only 89 patients responded to our telephonic survey (table V). Among this 38 had been treated for AUB and 51 for infertility. In the AUB group, 86.8% experienced significant improvement in the symptoms. In two patients heavy bleeding persisted even after treatment and they were counselled for LNG-IUS insertion. Three patients had to undergo hysterectomy. 92.1% said that they would recommend this procedure to friends. In infertility group, symptomatic improvement occurred in 90.1% but only 27.8% conceived after treatment but 84.3% said they would recommend this procedure to friends.

DISCUSSION

We found abnormal hysteroscopy in 74% of primary infertility and 68% of secondary infertility cases. This observation is in accordance with Sahu *et al.*

Table V. Likert scale analysis of patient's satisfaction.

Questionnaire	Very good	Good	Bad	Worst
How was your perioperative experience in terms of pre-operative preparation, post-operative pain and timing of discharge	61.2%	33.2%	5.6%	-
Grade your ease with one stop approach i.e. undergoing diagnosis and treatment at same sitting	58%	36.6%	4.4%	1%
Grade the cost effectivity of this procedure	57.8%	30%	11.2%	1%
How will you grade your symptom improvements following treatment	69%	19.7%	9%	2.3%
	Yes	No		
Did you conceive following the treatment	14 27.4%	37 72.6%		
Would you recommend this procedure to your friend	78 87.6%	11 12.4%		

(4) who reported comparable incidence of 33% and 39% in primary and secondary infertility respectively. Previous studies have reported wide variation in the incidence range of 7.2-64%. This variation may be attributed to demographic difference, inter-observer variation, preoperative tool used for patient selection and type of infertility (5, 6).

Intrauterine adhesion usually develops following trauma or infection causing damage to the endometrial basalis which heals by fibrosis resulting in obliteration of uterine cavity. The common risk factor in Indian population are genital infection and uterine surgeries. IUA was detected in 29% (35/120) of the studied women. Adhesiolysis was performed in all the patients with sharp scissors except in two patients. In one patient with severe adhesion, dissection couldn't be completed, in another patient uterine perforation had occurred during adhesiolysis, (this patient had history of uterine perforation during previous dilatation and curettage which she had disclosed after the procedure). Among them, 74% women did not require anesthesia. Most of them had presented with complaints of hypo menorrhea and dysmenorrhea. Menstrual pattern has improved following adhesiolysis in > 90% of women. Though assessing the effect of adhesiolysis on fertility outcome is beyond the scope of this study, few studies have evaluated the reproductive outcome after adhesiolysis and have reported overall pregnancy rate ranging from 25 and 76% (7).

Polyps were diagnosed in 21% of infertility patients in present study. The reported prevalence in the literature is as high as 32% in infertile women (8). Causal relationship of polyps and infertility is not yet well established but the putative mechanism may be mechanical interference with sperm transportation and implantation or due to defec-

tive implantation as glands and stroma of polyp is unresponsive to progesterone. Thus removal of endometrial polyp is justified to improve pregnancy rate. A systemic review analysis on outcome of hysteroscopy in treating infertility associated with uterine pathology suggests that 63% of women (95% CI 50% to 76%) will achieve a clinical pregnancy after the hysteroscopic removal of the endometrial polyps (1). Polyp was detected in 40% of AUB patients in this study. Reported incidence of this disease in AUB is around 50% (9). In addition to abnormal uterine bleeding, atypical hyperplasia and endometrial cancer may arise in up to 6.7% and 2.2% of endometrial polyps, respectively (10). Hysteroscopic removal is the recommended optimum treatment for endometrial polyp, small and pedunculated polyp can easily be removed using scissors, electrosurgical loop may be the best option to excise sessile ones (11). Surgical resection of polyp results in significant reduction in bleeding as well as avail tissue for histological examination to exclude malignancy. A study by Garuti *et al.* has reported that polyps could be resected in 81% of the cases but in present series we could resect all detected polyps (47/120) (12). All were confirmed as benign on histology. The mean operating time for polypectomy was 14.5 minutes in this study. 87% women had regression of symptoms on follow-up which demonstrated high efficacy of hysteroscopy in treating intrauterine lesion thereby increasing patient's satisfaction.

Submucosal fibroid was seen more frequently in abnormal uterine bleeding compared to infertility (16.6% vs 2.7%). Submucosal fibroid can cause infertility by interfering with egg and sperm transportation and their implantation, thus warrants its removal. Causal relationship of submucosal fibroid with heavy bleeding is well established. Removal

of the cause of AUB can substantially reduce the need of hysterectomy. We performed 4 myomectomy in AUB and 2 in infertility group. 3 patients in AUB group chose hysterectomy over myomectomy. The mean operating time for myomectomy was 24.8 minutes which is comparable to the mean operating time reported in the literature (13). We could perform myomectomy in 50% of diagnosed cases which suggests one stop approach a feasible option for its diagnosis and treatment.

Septate uterus was noted in 5.5% (4/72) and unicornuate uterus in 4% (3/72) in this series. Concurrent laparoscopy can increase the detection of other uterine anomalies. Among the septate uterus, 2 were complete and two were incomplete. Resection of septum was done in all of them, three patients required anesthesia whereas one did not. Reproductive outcome had been excellent following surgery as 3 patients conceived within one year, two delivered at term but one ended in first trimester abortion. This demonstrated high efficacy of Hysteroscopic septal resection and improved patient's satisfaction with the one stop approach. Wang *et al.* have reported 71.43% of pregnancy rate after septal resection in 12 months of follow-up period (14).

Besides, major pathologies, retained bony chip and left out CuT had been detected in 8.6% of studied population with comparable incidence among infertility and AUB cases. Foreign body in the uterine cavity has been associated with reduced infertility as well as abnormal uterine bleeding. Its removal resulted in spontaneous correction of symptomatology. Besides being an easily treatable cause it relieves the patient's anxiety as well.

Carcinoma was detected in 3.2%, it included both endometrial and endocervical carcinoma. One woman among them presented with postmenopausal bleeding and two as heavy menstrual bleeding. All of them were > 60 years old. Hysteroscopic diagnosis was confirmed on histopathology and were referred to oncological unit for further management. In line with our result, the study by Antunes had reported 1.2% incidence of endometrial carcinoma with 100% accuracy in diagnosing carcinoma and its precursor with combined approach of hysteroscopy and biopsy (15). Endometrial hyperplasia was noted in 4%, which returned as simple hyperplasia on histology and were managed medically. As thorough investigation is mandatory to rule out malignancy, one stop approach is best suited in this age group.

Despite all its advantage, hysteroscopy is not widely used in the developing countries. Main hindrances are use of anesthesia, pain and cost of the procedure. Pain during hysteroscopy is mainly caused by tenaculum application and cervical dilatation. Small diameter scope and employment of vaginoscopic entrance through the cervix reduces the pain and requirement of anesthesia thereby increasing the acceptance of the technique. In this series out of hundred one patients who underwent Hysteroscopic surgery, sixty five did not require anesthesia. The rates of severe pain have been reported to range from 2 to 14% in parallel with the diameter of the hysteroscope (16). The mean pain score (VAS) in our series was 2.9. We did not apply vaginal speculum or tenaculum to hold cervix as these tool might cause anxiety and pain. Employment of vaginoscopic approach, avoiding holding cervix, using small diameter scope reduced the need of anesthesia thereby reducing hospital stay but simultaneously allowing performance of almost all planned procedures resulted in high patient's satisfaction with this approach in this series. We did telephonic survey regarding patient satisfaction with this approach, 89 women responded to the questionnaire. 89% women experienced symptomatic improvement and 87% women found it cost effective. 11 women had not had good experience and reasons stated by them were- uterine perforation during adhesiolysis, incomplete adhesiolysis and persistence of amenorrhea, requirement of additional treatment and inability to conceive following treatment. However, significant number of women (over 90%) had agreed that it is safe, effective and worthwhile procedure. Filiz *et al.* reported that 89.3% patients found office hysteroscopy comfortable which is comparable to our study (17).

We could diagnose pathology in 120 cases and performed 101 procedures at the same sitting that indicate that 86% pathology had been treated, making this 'one stop approach' an effective option in management of intrauterine pathology. The reported complication rate during hysteroscopy in literature is 1-3% (18), but in our series it was minimal with only one case of uterine perforation during adhesiolysis. These data demonstrate that hysteroscopy is extremely safe in the hand of experienced surgeon. Advent of high definition mini hysteroscope has facilitated performance of these procedures in the office setting obviating the need of anesthesia and without compromising optical

performance. But the limiting factor for the newer techniques is the cost especially in developing countries. This study clearly demonstrate that hysteroscopy offers high diagnostic accuracy, allows concurrent accomplishment of surgical treatment of visualized pathology, avoids complication, allows quicker recovery time and is well preferred by the women.

Despite certain limitations in this studies due to inherent retrospective nature and small sample size, our findings strongly supports the utilizations of hysteroscopy in management of intrauterine pathology.

CONCLUSIONS

Hysteroscopy in the present era has acquired first place in the management of endometrial pathology as it guarantees accurate diagnosis of intrauterine pathology. In addition to diagnosis, it also allows skilled gynecologist to perform various therapeutic procedures simultaneously. The data from this se-

ries clearly demonstrate that hysteroscopy as 'one stop approach' that is diagnose and treat the pathology simultaneously, is simple, safe, effective and well accepted by most women in the management of intrauterine pathology. It will also reduce the hysterectomy burden on the hospitals. So the author recommends that hysteroscopy should be included in the initial work-up of infertility and AUB.

ETHICS

Ethical approval and consent to participate- Study had been approved by institute ethical committee (AIIMS/Pat/IEC/2020/514). Verbal consent had been obtained from the study participants. Ethical committee approved this procedure.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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Post-partum hemorrhage: can it be prevented by assisting the natural physiological process?

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ABSTRACT

Background. Anteversion of the uterus is essential for the abdominal pregnant uterus growth and for the uterine contraction during labor and post-partum period. The role of the round ligaments is not yet completely understood, but certainly do have a coherent synergistic role with that of the neo-myometrium. The uterine contraction depends not only by the uterine muscle fibers, but also by the integrated pelvic myofascial system, connecting the uterine body to the round ligaments, to the ileo-psoas muscles and to the abdominal wall. In view of these functional anatomy reflections, it is possible to understand the procedures used in our management of postpartum hemorrhage and in our study.

Materials and methods. We have a retrospective observational study of a population of 5927 women who delivered by Cesarean Section or vaginal labor between 2014 and 2018, after the 34th gestational week. Of these, 173 women with risk factors for postpartum hemorrhage (PPH) or with mild PPH were treated with a non-invasive method consisting of an abdominal band for uterine compression/ anteversion, in combination with standard drug or surgical therapy.

Results. We had only one peripartum hysterectomy on 5927 birth 0.016/1000 (Italy-ItOSS 1.08/1000, Regno Unit UKOSS-NethOSS-Nord Europa NOSS 0.3-0.4/1000). Five women received 4 or more blood transfusions on 5927 delivers (0.85/1000).

Conclusions. The non-invasive uterine compression technique reduced the incidence of PPH in high-risk women and prevented maternal morbidity and mortality.

SOMMARIO

Background. L'antiversione uterina è essenziale per l'espansione dell'utero gravidico nell'addome e per le contrazioni durante il travaglio e nel post-partum. Il ruolo dei legamenti rotondi non è ancora del tutto compreso, ma sicuramente ha un ruolo coerente e sinergico con quello del neo-miometrio. La contrazione uterina dipende non solo dalle fibre muscolari uterine, ma dal sistema integrato miofasciale pelvico, che collega il corpo uterino ai legamenti rotondi, ai muscoli ileo-psoas e ai muscoli della parete addominale. In considerazione di queste riflessioni anatomico-funzionali, è possibile comprendere le procedure che abbiamo utilizzato nella gestione dell'emorragia postpartum e nel nostro studio.

Materiali e metodi. Si tratta di uno studio retrospettivo osservazionale su una popolazione di 5927 donne che hanno partorito con taglio cesareo o per via vaginale in un periodo compreso tra il 2014 e il 2018, dopo la 34esima settimana gestazionale. Di queste, 173 donne con fattori di rischio per emorragia postpartum (EPP) o con lieve EPP sono state trattate con un metodo non invasivo costituito da una fascia addominale per la compressione/ antiversione uterina, in combinazione con farmaci standard o terapia chirurgica.

Risultati. Abbiamo avuto solo un'isterectomia peripartum su 5927 nascite. 0.016/1000 (Italia-ItOSS 1,08/1000, Unità Regno UKOSS-NethOSS-Nord Europa NOSS 0,3-0,4/1000). Cinque donne hanno ricevuto 4 o più trasfusioni di sangue su 5927 parti (0,85/1000).

Conclusioni. La tecnica di compressione uterina non invasiva ha ridotto l'incidenza dell'EPP nelle donne ad alto rischio e ha evitato morbilità e mortalità materna.

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Key words

Postpartum hemorrhage; cesarean section; operative delivery; device; uterine position; myofascial system; round ligaments.

INTRODUCTION

Did bipedal posture change only the pelvis?

The literature is rich of data on the pelvic changes related to human upright posture. The biological compromise was imposed on humans by two opposing biological pressures developing standing posture during our evolutionary process. It was called, in 1960, "obstetric dilemma" by the American bio-anthropologist Sherwood L. Washburn.

From an anthropological point of view, the reduction in the size of the birth canal in the human pelvis followed the adoption of bipedal posture. In addition, in nature there has been growth of large fetal skulls, in parallel to the growth of the neocortex volume. Anthropology and comparative anatomy show a bias linked to greater attention to the hard parts of the organism, which have been better preserved than soft tissues. Little attention has been taken, instead, with other important biological modifications imposed by the standing posture. The uterus arises in the most evolved primates from fusion of two horns, as present in the majority of the mammals. In fact, the Muellerian ducts are fused to give rise to bi-corneal uterus. In the more primitive mammals, however, there are two separate uteri and a double uterus occurs in the Marsupials, in many Rodent species and in bats (1).

Uterine malformations (septate uterus, uterus didelphis, etc.) derive from the same embryological origin. The presence of a single-space uterus has often been linked to the developmental needs of a single fetus, an advantageous way of having a single pregnancy from an evolutionary point of view. This observation is not consistent with many comparative anatomical studies. The mare, for example, which is a uniparous quadruped animal with a modified bipartite uterus, has an incidence of twin pregnancies between 1% and 16% and a very high number of poor outcomes (2).

Changing the position from quadruped to biped, on the contrary, required biological modifications also of the pelvic viscera. The erect position required postural uterine modifications which is very mobile, being able to assume all positions. Uterine orientation is conditioned by the women position, by the filling degree of bladder, rectum and intestinal loops, in harmonic physiological conditions (3). The wide uterine mobility is linked to the uterine muscle characteristics. Uterus is a unitary smooth muscle, like the bladder, differing from the multi-unit smooth muscle, because the contractions are synchronized by communicating junctions, allowing to coordinate the cells contraction (4). The smooth muscle, despite having a myosin content of about 20% and a consumption of ATP 100 times lower than the skeletal muscle, can develop the same strength for transverse section area. It happens either for much slower rhythmical contractions, or for an architecture of the smooth muscle cell and the unitary organization of smooth muscle, structured in a syncytium (4, 5). A uterine muscle behaves like a viscous mass and it is also characterized by a tension variability exerted at any given extent, and there is either no relationship between extent and tension, nor between extent and a length of rest (6). Thanks to this plasticity, a strip of visceral smooth muscle, when stretched, first exerts a certain tension, but if the stretch is maintained, the tension gradually decreases and can go down to the initial or even lower level of tension (7).

The uterine tone is a persistent state of partial contraction, showing continuous irregular contractions independent from the innervation and the membrane potential is unstable, with no real resting value. A uterine muscle can, therefore, be considered as a "viscous mass" that needs to be oriented in extension and during contraction, with the lasting crucial role of the neo-myometrium and of the round ligaments (7). At the time of the fusion of the Muellerian ducts, the neo-myometrium,

peripheral layer of the uterus appears and develops mostly for functional reasons (8). It is known that the physiological uterine posture is usually in anteversion and this posture becomes necessary, for the purpose of maintenance of the species, especially at the end of the first trimester, to allow the uterus to develop outside the pelvis, avoiding rare cases of “uterine incarceration”.

The need arises to anteriorize the uterus for its abdominal development during pregnancy which would otherwise be suffocated in the pelvis or could crush the large vessels, to place the cervix in the posterior fornix during coitus, but also because a uterus lying backwards after delivery does not contract well (6, 7, 9,10).

Round Ligaments these strangers: are they useful in pregnant physiology?

The role of round ligaments is poorly understood. They were credited for pulling the uterus forward during coitus, thus facilitating the entry of the semen into the cervical canal (11). Based on these assumptions, many uterine suspension surgeries during years 1950-1960 were performed. The role of round ligaments as a support structure for the non-pregnant uterus has become less convincing in recent decades. Nevertheless, the round ligament role in pregnancy and its function in labor tend to remain unchanged in obstetric textbooks (12).

From a phylogenetic point of view, it is in women that the round ligament reaches its greatest development and it is not an ancient vestige (13). The development of the round ligaments and the neo-myometrium is associated with the erect posture and the new reproductive needs and strategies connected to them (8, 14).

The round ligaments are improperly anatomically linked to the pelvic suspension system, because they are real muscles, as they can bear a load of up to 600 to 900 grams. Moreover, the round ligaments are the essential element that determines the orientation of the body of the uterus “like a horse held by the reins” (15). During pregnancy, the round ligaments become 3 to 4 times thicker and the resistance they offer to traction increases up to 40 kg. Always during pregnancy, is more anatomically evident (15) that they move away from the uterine fundus and the “Calza’s Bundle” (central longitudinal band that in primates constitutes the neo-myometrium of the uterus, not more bicorned as in the quadrupeds) where they depart. It

is probably due to the horn asymmetrical development, where the implant took place (7).

The round ligaments are formed by fibers and smooth muscle and, after the passage in the inguinal canals, by striated muscles from the transversus and oblique abdominal muscles, in analogy to the cremasteric muscles.

The round ligaments connect *fundus* of the uterus to *labia majora* and to the mons pubis and, even in sexual activity the stimulation of these areas leads to the uterine contractions of the orgasm (16). They are also present in quadrupeds, although they are poorly represented, since they obviously have a belly down and gravity favors the anterior position of the uterus. This biological finding shows that round ligaments have more a role of muscle nerve terminal than support (13) for connecting the external *genitalia* and the uterine horns (17).

Round ligaments orient uterine contraction also in labor, where there are different types of uterine contraction (18) with different receptors (or different sensitivity) for each muscular layer (neo-myometrium, paleo-myometrium and arch-myometrium) (6, 7, 9).

The Braxton Hicks contractions therefore serve to orient the uterus in the abdominal cavity during pregnancy and they also work in the latent phase of labor, to adapt the fetal head to birth canal. They are postural contractions related to round ligaments and the neo-myometrium, they cannot be the same muscle fibers that contract in the active phase of labor (19, 20).

The round ligaments and the neo-myometrial complex could orient the uterus, adapting to its content and playing an important role during pregnancy and labor (10).

The asymmetric position of the pregnant uterus at term, with a frequent dextro-position, is linked to the unequal contraction of the two round ligaments. The so called “ligament round pain”, poorly diagnosed in Italy, is better known and investigated by Osteopaths, than by the Obstetrician.

Therefore, the evolutionary meaning of the neo-myometrium and the “new” round ligaments is not only to unify the two horns, but also to become the helm of the uterus (8, 11).

The gestational sac is usually located eccentrically in the uterine cavity because implantation occurs in one of the two horns even in a simple uterus (21, 22). Physiologically it cannot implant in the central part of the uterine cavity at the level of the neo-myometrium. The ultrasound report of gesta-

tional chamber in the center of uterine cavity might indicate an ectopic pregnancy (23).

Moreover, the numerous morphological variants of the placenta often have little clinical relevance, but they tell us the history of the migration of the trophoblast and the endometrial receptivity for embryo implantation (24). They are not physiologically possible in all areas of the uterine cavity, because the small contractions, useful for uterine posture, of the round ligaments and the neo-myometrium, in pregnancy would reduce the placental blood flow.

Mahran and Ghaleb (1964) have reported that strips of the human round ligament in its muscular portion contract spontaneously both in the non-pregnant and pregnant state and that they respond to electrical stimulation. They observed that during pregnancy spontaneous contractions of these strips were of low frequency and high tension, while during labor the contractions increased both in frequency and in amplitude and start asymmetrically from one of the two horns.

Synthetic oxytocin stimulates indistinctly and irregularly uterine contractions, but not always the round ligaments or, at least, not at the same time. Hence, synthetic oxytocin cannot help the uterine position (10, 19).

Today it is known that there is also a local (uterine) production of oxytocin demonstrated by the presence of oxytocin mRNA, at least in rats, and this could mean that for postural contractions (Braxton Hicks?) pituitary oxytocin is not needed. Furthermore, in the last expulsive phase of labor, during the disengagement of the fetal ("coronal") head, this presses, during vaginal distension, on the labia majora (also these more developed in women) (25) and on the terminal fibers of the ligaments rounds that contract and position the uterus contracted anteriorly (detrusorial contraction). The innervation of the so-called Geigel reflex, a less studied female count part of cremasteric reflex, is provided by the sensory and motor fibers of genital-femoral nerve originating from the L1-L2 spinal nerve nuclei, and whose genital branch reaches the inguinal canal and the round ligaments.

The hypothesis of integrated pelvic myofascial system and the "Tension network"

At the end of the first trimester, anteversion of the uterus, necessary for the abdominal expansion of the pregnancy, coincides with the accentuation of

the lumbar lordosis, which is the spine adjusting to realign the center of gravity, in a non-casual harmony. It is linked to the relaxation of the ileo-psoas muscle, which is the main protagonist in determining the position of the pelvis and lumbar tract and consequently of the whole posture (26).

So far, most studies have been done on cadavers and the uterus and its ligaments have been studied sectorally *in vitro*. Today, by new imaging and radiological techniques and by the contribution offered by sports medicine, osteopathy and psycho-neuro-endocrine-immunology, it is possible to frame uterine contraction in a more global and more complex process (27).

The uterine contraction, in the expulsion phase of labor is "detrusor type", like the bladder, and the volume of the uterus decreases as its cavity is emptied. The uterine muscle, being in three layers, has the neo-myometrium (on the fundus) that continues with the fibers of the round ligaments (like a Bolivian wool cap). But this is still a partial view of complex pelvic supporting visceral system (28). Uterine muscle is a complex system working by contraction, myofascial system and round ligaments, which constitute the link between the uterine muscle and the myofascial system.

Hence the hypothesis that the uterine contraction could depend not only by uterine muscle fibers, but by a complex integrated pelvic myofascial system, connecting the uterine muscle to the round ligaments, to the Ileo-Psoas muscles (via the genital femoral nerve) and to the muscles of the anterior and posterior abdominal wall.

The "axial fascia" or "deep fascia" (29) wraps and connects the uterine muscle, its ligaments, the postural muscles in a single interconnected system, that, after delivery, progressively returns to the "*status quo ante*". The term "fascia" refers to the collagen-fibrous tissues that are part of a broad system of transmission of tension forces in the human body (30-31). The "fascia" appears as an interconnected "tension network" consisting of the dense and loose connective tissue, from the surface to the depth. The ligaments are local densifications of this network. There is an extended continuity of the fibrous tissue, and the collagen tissue expresses a gradual transition. So, it is impossible to make a clear distinction between the ligament and the loose part of the intra-abdominal and pelvic fascia (32, 34).

Therefore, within the human body, the fascial body represents a wide anatomical structure with structural and functional network functions, consisting

of bags, ropes (local densifications), thousands of cavities inside other cavities, all connected by robust or soft septa (30, 33, 34).

The “visceral fascia” consists of collagen and elastic fibers and covers the body cavities (35). The bands wrapping the organs are called pleura, peritoneum, sheath, but they remain visceral bands (30-32, 34).

Currently, rethinking to obstetric daily experience in delivery room, it must, therefore, consider a re-arrangement of the whole myofascial system, favoring directly the abdominal viscera descent behind the uterus during labor and indirectly the intra-abdominal pressure increase. In the human body architecture, the myofascial system is the anatomical structure which connects the anatomical districts and the human organs in the body (29).

In the postpartum uterine contraction, the uterine body is “guided” by the round ligaments, which contracts down and forward (35), and the lower uterine segment (LUS) contracts towards the pubic symphysis.

All the studies on uterine contraction focused on the characteristics of the muscle fiber and on the electrical potential of the membrane, rather than on the uterine muscle, structured in a syncytium. Very interesting is the significant increase in the risk of “*postpartum* hemorrhage” PPH in Ehlers Danlos syndrome, characterized by severe connective tissue disorders. In fact, pregnant women with Ehlers Danlos syndrome experienced *postpartum* hemorrhage (19% vs 7%) more often than the unaffected women (36).

In light of these reflections, it is now possible to frame the procedures used in our management of postpartum hemorrhage and in the observational study, of which we will discuss, experience from which research on this rational functional anatomy emerged. The simplification and the progression of procedures (from simplex to complex) is necessary in complex tasks and is a necessity of medicine which is a procedural knowledge.



Figure 1. During Caesarians it can be verified that the thrust of the exteriorized uterus actually directs the LUS against the pubic symphysis. With the limit of the abdominal wall that prevents a complete anteriorization (in the cesarean section the abdomen is open), the bandage produces this movement.

MATERIALS AND METHODS

In the obstetric department of Canosa and subsequently in the obstetric department of Barletta, for over twenty years in the postpartum, we have used an external uterine compression technique in all conditions at high risk for PPH as an aid in medical and surgical therapy (also after Bakri Balloon where necessary) of PPH. The aim was to help uterine contraction, preventing the “ascent” of the uterus and replacing manual massage. The compression band was positioned around the waist, above the contracted uterus after massaging it. It was more or less tight depending on individual needs. In severe cases, it also tightened to compress blood vessels and reduce arterial flow. The logic of our use of the compression band was to mimic the natural physiological process of post-partum hemorrhage which is mainly mechanical contraction which happens immediately after the delivery and continues throughout the uterine involution. The Balloon is certainly helpful and we used it in our delivery rooms but it works exactly against the physiological way of hemostasis.

The technique therefore:

1. prevents the distension of the puerperal uterus;
2. also pushes the intestinal mass behind the uterine body;
3. assisting the anterior position of the uterus by pushing the lower uterine segment towards the symphysis as in bimanual compression.

In the case of mild *postpartum* hemorrhage or in the case of select risk factors our management has been:

- the first step was to do a noninvasive uterine compression, after manual massage;
- the first- and second-line drug therapy;
- the alarm;
- the exclusion of lacerations and rupture of the uterus or retention of placental material;
- the use of the intrauterine Bakri balloon;

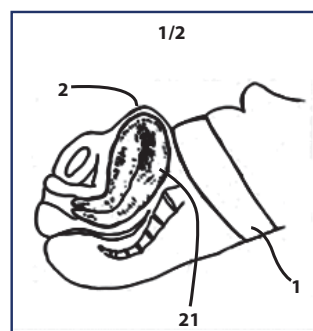


Figure 2. 1) position of application of the bandage, 2) external shape of the “safety globe”, 21) contracted uterus.

- in case of postpartum hemorrhage during cesarean section or in case of placenta previa, the first step was the use of intrauterine balloon and then exertion of noninvasive uterine compression, after the closure of the abdominal wall, to obtain a double internal and external compression of the uterine muscle.

Application procedure

The application procedure includes the following steps:

1. manually and gently massage the uterus from the outside, in order to stimulate its contraction;
2. applying the bandage that compresses, in a circumferentially uniform manner, the abdominal area of the patient in at least a part of the region between the rib arch and the "safety globe", formed by the uterine contraction, leaving instead not compressed all the underlying abdominal region.

Safety globe is caused by the contraction of the uterine muscle and has the function of interrupting the bleeding resulting from childbirth. It is an easily identifiable anatomical part and, therefore, easily usable as a reference for the application of the fascia.

The area subject to compression is therefore entirely supra-umbilical, and as already explained it does not include the abdominal part under the navel which, indeed, must necessarily be left uncompressed for the execution of the method.

RESULTS

In the period between 2014 and 2018 we recorded 5927 deliveries. The rate of primary cesarean section (CS) in nullipara singleton vertex term (NSVT) pregnant women ranged between 14 and 24%. This range is an indicator of the physiology propensity of the Operative Unit.

173 women, with risk factors or with initial hemorrhage from atony of the postpartum, have been treated with a non-invasive uterine compression technique. The orthopedic bandage for compressive wrapping was used. Nine pregnant women with placenta previa or with bleeding due to suspected placental accretism, were treated with the simultaneous use of bandage and an intrauterine Balloon, to perform a double compression, internal and external.

Only one postpartum Hysterectomy among 5927 birth was necessary (0.016/1000) and only five women received 4 or more transfusions of blood on 5927 parts (0.85/1000).

All data are showed in **table I**.

DISCUSSION

Revising our results, the incidence of peripartum hysterectomies was significantly lower than in Italy (ItOSS 1.09/1000) and in Europe (UKOSS-NethOSS-Northern Europe NOSS 0.3-0.4/1000). The incidence of severe PPH was also lower than in Italy (1.12/1000) and in European average (0.3-1.2/1000) (37, 38). It is a retrospective observational study which could give an explanation and an anatomical functional rationale to an ancient method of uterine compression, the origins of which, with different tools such as bandages or belts, are lost in the mist of time and which today, in the light of new knowledge, can find a new dignity. Other trials are needed (39, 40). The purpose of this study is to demonstrate the need to learn the functional anatomy to respect physiology and help it with too hastily abandoned methods, which can be effective in light of current knowledge. There is a "global range" that, during pregnancy, is subject to mechanical tensions gradually increasing both from the growing fetus and from the pressures of the uterus (41). The abdominal diaphragm has a sort of dome turned upside down, the pelvic diaphragm is a dome upwards and these two muscle groups are located at the upper and lower extremities of the peritoneal cavity which, like a balloon, encloses the abdominal organs (42). The transmission of pressure takes place inside (intra-abdominal) and outside (abdominal and trunk muscles) of this balloon and it is transmitted to all the abdominal organs, by an integrated pelvic myofascial system (43). The contraction of the uterus in its natural position and of the round ligaments occur in this fundamental context (44).

The non-invasive uterine compression technique, used by us, helps the natural physiological processes that are sometimes altered, especially in the obese, in caesarean sections and in patients with obstetric complications like polyhydramnios and fetal macrosomia (45). The rationale integrates that of the old bimanual compression with the new role of the myofascial system.

Table I. NSVT (Nulliparous, singleton, vertex, term) is used as an indicator of physiological management; 153 applications of tensoplast (abdominal bandage) prophylactic or therapeutic; all 9 cases of placenta previa treated with balloon and and tensoplast abdominal bandage; 1 Peripartum Hysterectomy/5927 birth (0.016/1000); 5 cases of severe bleeding treated with 4 or > pockets of red blood cells.

YEAR	2014	2015	2016	2017	2018	Total
N° Births	1184	1203	1248	1196	1096	5927
Caesarean rate NSVT	20.60%	24%	13.80%	17%	23%	
n. compressions	26	33	40	39	35	173
Atony with haemorrhage	16	13	18	17	13	77
MODE OF DELIVERY						
Caesarean section	12	11	16	13	17	69
Vaginal birth	17	13	21	18	16	85
VBAC			1			
Induction of birth	2	3	7	3	4	19
Risk Factors						
Placenta praevia	0	0	1	3	5	9
Twin pregnancy	2	11	11	11	6	41
Manual placenta removal	3	1	1	0	0	5
Previous caesarean section	1	1	3	3	3	11
Primigravida	15	8	11	11	5	50
Parous	5	6	13	11	10	45
Preeclampsia	2	2	4	2	2	12
THERAPY						
Prophylactic compression	6	13	15	17	9	60
Therapeutic compression	12	13	14	14	16	69
Blood transfusions < 4 bags	3	6	6	6	5	26
Blood transfusions ≥ 4 bags	4*	0	3	1	1	9
BAKRI BALLOON	1	1	2	1	4	9
Hysterectomy peripartum	1					1
Admission in Intensive Care	1	0	1	0	0	2
Vagistop	1	2	2	0	0	5
Puerperium complications						
Puerperal Genitals Hematomas			1			1
Uterine Cavity Revisions			3			3

* Less than four pockets of red blood cells with fresh frozen plasma.

CONCLUSIONS

Our experience using orthopedic bendage in PPH prevention has allowed us to simplify the procedure therapy of PPH, to reduce the risks and improve the results. We used the balloon exclusively during CS in the case of placenta previa and/or suspected placental accretism and in combination with the same non-invasive external compression technique. Basing on our experience, we could propose to use the bandage also in several PPH in association with the Balloon to diminish the need for surgical procedures such as compressive surgical sutures and peripartum hysterectomies. The bandage use could replace other surgical uterine compression techniques, with a technique similar to bimanual compression, but without its discomfort. The validity of the observational studies compared to a controlled trials is demonstrated by the weight of the clinical

results, as already described by Sackett, “inventor” of the EBM which gives the clinical experience the same weight as the statistical evaluation. Evidence based medicine is not restricted to randomized trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions, without which they become “statistical games”. And if no randomized trial has been carried out for our patient’s predicament, we must follow the trail to the next best external evidence and work from there (46).

In a randomized study aimed at evaluating the effectiveness of these compression maneuvers, the control group would be formed by women who would present postpartum hemorrhage without receiving the same type of risk-free assistance. This would entail posed a significant ethical problem. Anyway, this proposal is a project at an initial step and needs to be improved with a large prospective trial.

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CONFLICT OF INTERESTS

At the moment the authors declare that they have no conflict of interests.

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A study of postpartum depression and its risk factors in a Tertiary Hospital in India

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ABSTRACT

Background. To determine the proportion of postpartum depression in women attending a Tertiary Hospital and to determine and study the risk factors associated with postpartum depression.

Methods. The present study was a Hospital based Cross-sectional study in which 561 women were assessed on the 3rd postnatal day and at 6 weeks postpartum for depression and significant risk factors associated with it.

Results. Total number of 600 postnatal women participated in the study. 39 women were lost to follow up at 6 weeks. Final sample size for analysis 561. Out of the total 561 postnatal women, 135 of them had a score of > 13 on the EPDS on the 3rd postpartum day, indicating 24.1% of the postnatal women with "Postpartum Blues". The proportion of postpartum depression was 7.7%.

Conclusions. The present study found factors like Age of the woman, low level of education, low socio-economic status, age at marriage, primiparity, obstetric complications, previous miscarriage, preference for a male child, neonatal complications, psychiatric disorder, living in joint families, marital conflict, lack of family support and alcohol abuse by the husband were the risk factors for Postpartum depression. There was no association between postpartum depression and factors like age at first pregnancy, whether the pregnancy was planned or unplanned, infertility treatment, mode of delivery (vaginal or caesarean, medical comorbidities and adverse life event during pregnancy).

SOMMARIO

Contesto. Determinare la percentuale di depressione postpartum nelle donne che frequentano un ospedale terziario e studiare i fattori di rischio associati alla depressione postpartum.

Metodi. Il presente studio era uno studio trasversale basato sull'ospedale in cui 561 donne sono state valutate per la depressione ed i fattori di rischio significativi ad essa associati, il terzo giorno dopo il parto ed a 6 settimane.

Risultati. 600 donne hanno partecipato allo studio a seguito del parto. 39 donne sono state perse al follow-up a 6 settimane. La dimensione del campione finale per l'analisi è pari a 561. Sul totale di 561 donne postnatali, 135 di loro avevano un punteggio > 13 sull'EPDS il terzo giorno dopo il parto, indicando una percentuale pari al 24,1% delle donne postnatali con "sindrome del terzo giorno". La percentuale di depressione postpartum era del 7,7%.

Conclusioni. Il presente studio ha trovato che i fattori di rischio per depressione postpartum sono: età della donna, basso livello di istruzione, basso stato socio-economico, età al matrimonio, primiparità, complicazioni ostetriche, precedente aborto spontaneo, preferenza per un figlio maschio, complicazioni neonatali, disturbo psichiatrico, convivenza in famiglie comuni, conflitti coniugali, mancanza di sostegno familiare e abuso di alcol del coniuge. Non c'era alcuna associazione tra depressione postpartum e fattori come l'età alla prima gravidanza, se la gravidanza era pianificata o non pianificata, trattamento dell'infertilità, modalità di parto (vaginale o cesareo, comorbidità mediche ed eventi avversi della vita durante la gravidanza).

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Key words

Postpartum; depression; risk factors; Tertiary Hospital; India.

INTRODUCTION

Depression is an important cause of morbidity worldwide especially in developing countries (1). The rate of depression in women is found to be twice as that in men. Pregnancy, childbirth and motherhood are very crucial phases in a woman's lifetime. Mothers are highly prone to develop psychiatric disorders in the postnatal period. The term "Postpartum Depression" (PPD) is an umbrella which includes many mood disturbances that occur following delivery. Postpartum depression (PPD) is found to affect 10-15% of postnatal women, but is as much as 35% in a few populations (2). PPD is frequently underdiagnosed and continues to be one of the most commonly occurring complications of childbirth and the most commonly found psychiatric disturbance in the postpartum period, in which women are found to be at a maximum risk within their first postpartum year. The causes why PPD remains undiagnosed are due to limitations like time and the acceptability of screening methods by the society. The social stigma and fear of being referred to as an 'unhappy mother' is one of the major causes why PPD cases remain undiagnosed (3). Upon formal screening, most of the women who are prone to develop PPD completely admit to feeling depressed, realizing that the feelings are neither transient nor minor. However they refuse to accept the term "postpartum depression" because it implies that the depressive thoughts maybe due to their newborns (4). For such mothers, it is the stigma associated with the disorder of depression which is the cause for shame, worry, embarrassment and feelings of guilt (5). These women as a result, suffer worrying about the various factors leading to this disorder, a condition that can actually be treated and even prevented. When left untreated, postpartum depression can result in several adverse effects affecting the woman and her baby. For the woman, it may lead to recurrent episodes of depression. For the child, it can cause serious impairment of cognitive, intellectual

and emotional development. Despite the serious negative outcomes that it can lead to, less than half of mothers suffering from depression are diagnosed and treated. It is thus essential to determine the factors that contribute to the development of PPD so that the women at risk can be identified which can help in early diagnosis and treatment if necessary.

It is very important to differentiate between the several types of psychiatric disorders that follow childbirth, as each one of them may differ in their modalities of treatment or might not need any treatment at all. These disorders may have many similar overlapping symptoms, but have many unique, distinguishing features (6).

AIMS AND OBJECTIVES

To determine the proportion of postpartum depression in women attending a Tertiary Hospital; to determine and study the risk factors associated with postpartum depression; to identify the women at risk for postpartum depression for early follow-up and intervention.

MATERIALS AND METHODS

The present study was a Hospital based Cross-sectional study, conducted in teaching hospitals belonging to Kasturba Medical College, Mangalore-Government Lady Goschen Hospital and KMC Hospital, Attavar, Mangalore, Karnataka, India. Period of the study was from October 2014 to July 2016. 561 postnatal women following delivery by vaginal route or caesarean section on 3rd postnatal day and at 6 weeks postpartum were selected as subjects. Subjects were selected as per the inclusion criteria. All subjects were enrolled in the study after having been informed and subscribed a written consent. Detailed clinical history was taken along with other details on a detailed proforma.

Formula used to calculate sample size

$$N = Z^2 P Q / d^2$$

Z = SNV at 95% confidence level = 1.96, P = estimated prevalence of PPD, Q = 100-P, d = relative precision.

It was calculated taking 95% confidence level and 80% power with prevalence of postpartum depression as 15.8% based on previous study (8). Taking 3.2 as relative precision the sample size was calculated to be 504. Adding 10% as non-response error, the final sample size to be studied was 560.

Inclusion criteria

Postnatal women following delivery by vaginal route or caesarean section on 3rd postnatal day and at 6 weeks postpartum.

Exclusion criteria

Those who did not give consent.

The study was started after obtaining approval from Institutional Ethics Committee (IEC) of Kasturba Medical College, Mangalore. The Edinburgh Post Natal Depression Scale (EPDS) is a 10-item self-report measure designed to screen women for symptoms of emotional distress during pregnancy and the postnatal period. A total score of 13 and above on this scale requires further assessment and appropriate management as the likelihood of depression is high. The original EPDS scale was used to create translated version of the scale in Kannada and Malayalam. Each of the study subjects was given the validated Kannada/Malayalam version of the questionnaire to fill up and was guided in case of any queries. All the participants were briefed about the objectives of the study in their vernacular language and written informed consent was taken from those who agreed to participate in the study. The questionnaires were distributed to those participants who were able to read, and interview was conducted for those participants who were not able to read. The data was collected using a pre-tested, semi-structured questionnaire consisting of various sections based on the risk factors associated with postnatal depression like socio-economic status, level of education, marital and obstetric factors such as relationship with husband or in-laws, number of pregnancies, planned/unplanned pregnancy, gender of the infant.

Data analysis

Data was entered in Microsoft Office Excel worksheet and analysed using statistical software SPSS version 17.0. The results were analysed using the Chi square test and the Fisher's Exact test, $p < 0.05$ was considered evidence of a statistically significant difference between predictive and outcome variables. Multivariate Logistic Regression Analysis was used to determine the most important risk factors.

RESULTS

Total number of 600 postnatal women participated in the study. 39 women were lost to follow up at 6 weeks. Final sample size for analysis 561. Out of the total 561 postnatal women, 135 of them had a score of > 13 on the EPDS on the 3rd postpartum day, indicating 24.1% of the postnatal women with "Postpartum Blues" (figure 1).

43 postnatal women out of them continued to have depressive symptoms with a score of > 13 on the EPDS at 6 weeks postpartum, thus the prevalence of Postpartum Depression in this study was found to be 7.7% (figure 2).

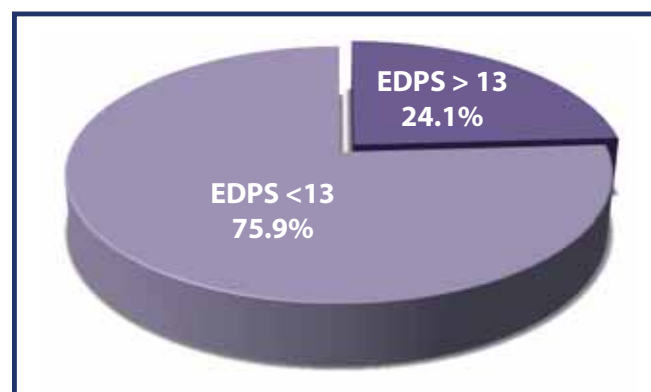


Figure 1. Postpartum Blues.

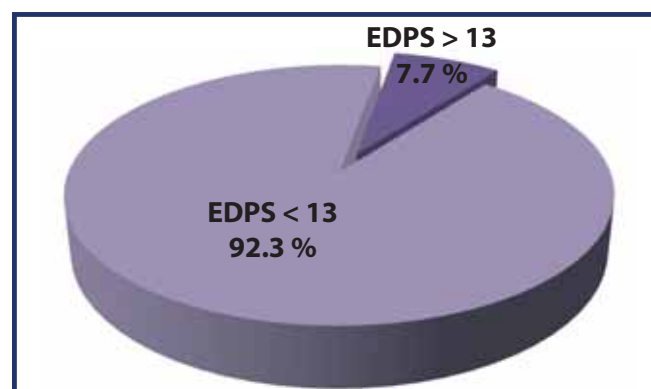


Figure 2. Postpartum depression

Risk factors

1. Age (**table I**): women between the ages of 26 and 30 years were more at risk for postpartum depression.

Table I. Age.

Age (years)	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Under 20	0 (0)	48 (9.3)
21-25	6 (14)	180 (34.7)
26-30	32 (74.4)	220 (42.5)
31-35	5 (11.6)	62 (12)
> 35	0 (0)	8 (1.5)

p Value – 0.001.

2. Level of education (**table II**): women with an educational status of less than Class 10 had a higher risk of developing postpartum depression.

Table II. Level of education.

Level of education	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
< Class 10	32 (74.4)	210 (40.5)
Class 10-12	11 (25.6)	239 (46.1)
Graduation	0 (0)	69 (13.3)

p Value – 0.000.

3. Socio-economic status (**table III**): women belonging to Low Socio-economic status were at a higher risk for postpartum depression.

Table III. Socioeconomic status.

Socio-economic status	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Lower	34 (79.1)	443 (85.5)
Upper lower	9 (20.9)	43 (8.3)
Lower middle	0 (0)	27 (5.2)
Upper middle	0 (0)	5 (1)

p Value – 0.035.

4. Age at marriage (**table IV**): women with an age at marriage between 26 and 28 years were at risk for postpartum depression.

Table IV. Age at marriage.

Age at marriage	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Under 20	9 (20.9)	150 (29)
21-22	4 (9.3)	61 (11.8)
23-25	9 (20.9)	166 (32)
26-28	15 (34.9)	101 (19.4)
> 28	6 (14)	40 (7.8)

p Value – 0.031.

5. Parity (**table V**): primiparae were found to be more at risk for the development of postpartum depression in comparison with Multiparae.

Table V. Parity.

Number of children	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
0	4 (9.3)	1 (0.2)
1	22 (51.2)	365 (70.5)
2	3 (7)	122 (23.6)
3	8 (18.6)	27 (5.2)
> 4	6 (14)	3 (0.6)

p Value – 0.000.

6. Obstetric complications (**table VI**): women with Obstetric complications were more at risk for postpartum depression than those without.

Table VI. Obstetric complications.

Obstetric complications	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	8 (18.6)	33 (6.4)
No	35 (81.4)	485 (93.6)

p Value – 0.000.

7. Previous miscarriage (**table VII**): women with a history of previous Miscarriage were more at risk for postpartum depression.

Table VII. Previous miscarriage.

Previous miscarriage	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	10 (23.3)	28 (5.4)
No	33 (76.7)	490 (94.6)

p Value – 0.000.

8. Gender of the baby (**table VIII**): preference for a male baby while a female baby was born was found to be a significant risk factor for postpartum depression.

Table VIII. Gender of the baby.

Gender preference of the baby	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Wanted male delivered female	27 (62.8)	130 (25.1)
Wanted male delivered male	1 (2.32)	145 (28)
Wanted female delivered male	2 (4.6)	24 (4.63)
Wanted female delivered female	13 (30.2)	219 (42.2)

p Value – 0.000.

9. Neonatal complications (**table IX**): mothers whose newborns had complications were found to be at a higher risk for postpartum depression.

Table IX. Neonatal complications.

Neonatal complications	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	6 (14)	29 (5.6)
No	37 (86)	489 (94.4)

p Value – 0.000.

10. Psychiatric disorder (**table X**): history of psychiatric disorder was significantly associated with the risk of developing postpartum depression.

Table X. Psychiatric disorder.

Psychiatric disorder	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	8 (18.6)	3 (0.6)
No	35 (81.4)	515 (99.4)

p Value – 0.000.

11. Type of family (**table XI**): women living in Joint families were more at risk for postpartum depression than those living in nuclear families.

Table XI. Type of family.

Type of family	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Joint	33 (76.7)	197 (38)
Nuclear	10 (23.3)	321 (62)

p Value – 0.000.

12. Marital conflict (**table XII**): postnatal women with history of marital conflict were at risk for postpartum depression.

Table XII. Marital conflict.

Marital conflict	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	13 (30.2)	10 (1.9)
No	30 (69.8)	508 (98.1)

p Value – 0.000.

13. Family support (**table XIII**): risk of developing Postpartum Depression was more in women who had inadequate support from the family.

Table XIII. Family support.

Family support	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	11 (25.6)	474 (91.5)
No	32 (74.4)	44 (8.5)

p Value – 0.000.

14. Alcohol abuse by the husband (**table XIV**): women who gave history of Alcohol Abuse by the husband were more at risk for postpartum depression.

Table XIV. Alcohol abuse by the husband

Husband's alcohol abuse	EPDS > 13 n = 43 (%)	EPDS < 13 n = 518 (%)
Yes	9 (20.9)	11 (2.1)
No	34 (79.1)	507 (27.9)

p Value – 0.000.

There was no association between postpartum depression and the following factors:

1. age at first pregnancy;
2. planned or unplanned pregnancy;
3. H/o infertility treatment;
4. Mode of delivery – vaginal or caesarean;
5. presence of medical comorbidities;
6. adverse life event during pregnancy.

The results were subjected to Multivariate Logistic Regression and the following were found to be the most significant risk factors:

1. **Age:** women in the age group of 26-30 years had 1.97 times more chances of developing PPD when compared to rest of them (p value – 0.001, OR – 1.97).
2. **Socio-economic status:** women belonging to low socio-economic status carried a 1.8 times higher risk than others for developing PPD (p value – 0.03, OR – 1.8).
3. **Previous miscarriage:** women with a previous history of miscarriage were 22 times more at risk for developing PPD when compared to those without miscarriages in the past (p value – 0.04, OR – 22.8).
4. **Family support:** women who had inadequate support from the family had 4.8 times more chances of developing PPD (p value – 0.06, OR – 4.8).
5. **Gender preference of the baby:** women who had a preference for a male baby but delivered a female baby had 4.8 times more chances of developing PPD than the others (p value – 0.005, OR – 4.8).

DISCUSSION

The objectives of the present study were to determine the proportion of postpartum depression and to identify the various risk factors that were signif-

icant in contributing towards the development of postpartum depression in a Tertiary Care Hospital. According to this study, 7.7% of the postnatal women were found to be at an increased risk for developing PPD. The risk factors that were significantly associated with PPD were low level of Education, low socio-economic status, age at marriage, parity, obstetric complications, previous miscarriage, preference for a male baby, neonatal complications, history of psychiatric disorder, living in joint families, lack of family support and history of marital conflict and alcohol abuse by the husband. In a previous study conducted by Gupta Swapan *et al.* (7) in 2013 among North Indian women, 15.8% of them were diagnosed to have postpartum depression. The PRIME MD Today questionnaire was used for assessment. The significant risk factors that were found in this study were low educational level, low socio-economic status, delivered a female baby when there was preference for a male baby, history of psychiatric disorder in the past and lack of support from the family. History of adverse life event and alcohol abuse by the husband were also considered as significant risk factors according to this study. However, there was no association seen between obstetric risks and the development of PPD, unlike in the present study where women with obstetric complications were found to have symptoms of depression postnatally. The North Indian study highlights the impact of cultural practices prevalent in countries like India that can aggravate the symptoms of depression. According to a study in Gujarat, by Desai Nimisha *et al.* (8), postpartum depression was detected in 12.5% of the mothers. A Semi structured proforma that included the DSM-IV TR criteria for diagnosis of depression and a predictive index of postnatal depression was used by the Gujarat study. The predictors of PPD according to this study were found to be factors such as Multiparity, previous miscarriage, delivery of a girl child and poor relationship with the partner. A study by Vikram Patel *et al.* (9) in Goa, found 23% of the women to have postnatal depression. The participants were recruited through the General Health Questionnaire with a semi-structured interview. Assessment was done during the last trimester of pregnancy antenatally, at 6 weeks and 6 months postpartum with the help of Edinburgh Postnatal Depression Scale. In this study, the significance of factors like poor marital relations, history of marital violence, antenatal history of psychiatric illness and preference for male baby and financial

difficulty is well established. In addition, a planned pregnancy was considered to be a significant risk factor for PPD in this study but the present study showed no significance when comparing planned and unplanned pregnancies. The Goan study attributes the presence of psychiatric illness antenatally as a significant contributor towards PPD.

In a study in Tamil Nadu by Chandran. M. *et al.* (10), 11% of the women were found to have postpartum depression. The study was conducted through a structured interview, the revised Clinical Interview Schedule. Poor relationships with family members, adverse events during pregnancy, preference for male baby were the factors associated with the risk of PPD. Low level of education was not found to be significant in this study unlike in the present study, where women with low educational attainment were more at risk for the development of PPD.

The prevalence rates of PPD vary within and across different countries. In a study conducted among Bahraini women, a prevalence rate of postpartum depression of 37.1% was obtained (11). The Arabic version of the Edinburgh Postnatal Depression Scale was used for screening the postnatal women. Unlike in the present study where the age of the mother, her age at marriage and her level of education, presence of neonatal complications had a significant role in the development of PPD, there was no significant association found with these factors in the Bahrain study. There was however, significant association seen with a past history of depression and lack of support from the family according to the study as in the present study.

In another similar study conducted in Iran (12), the prevalence of PPD was found to be 34.8%, which was found to be slightly higher than that in other national and international studies which could be attributed to the differences in culture and socio-economic status.

It is evident that the prevalence of postpartum depression varies when the above discussed studies were compared with the present study. This could be a consequence of differences in screening tools used, the various cut-off points chosen in the tools, the point of time when the screening was conducted, antenatal or postnatal and also the various socio-cultural aspects assessed in the study.

The present study aims at focussing on the major health issue of postpartum depression and the risk factors associated with it so that measures can be taken for its prevention or early treatment if necessary. The limitation of this study was the lack of

awareness and the loss of patients to follow up at 6 weeks postpartum. Practical constraints prevented assessment of personality and other variables that might be risk factors for post-partum depression, such as sexual abuse and marital violence. There is a need for further research in this direction to incorporate more accurate instruments into the maternal and child health programs to help detect the problem of postpartum depression and to elucidate appropriate treatment modalities as early as possible.

CONCLUSIONS

The present study found factors like age of the woman, low level of education, socio-economic status, age at marriage, parity, obstetric and neonatal complications, history of a psychiatric disorder, previous miscarriage, preference for a male child, living in joint families, marital conflict, lack of family support and alcohol abuse by the husband as predictors for postpartum depression.

There was no association found between the development of PPD and factors like age at pregnancy, whether the pregnancy was a planned or an unplanned one, history of taking infertility treatment, mode of delivery – whether vaginal or caesarean, presence of medical co morbidities and history of adverse events during pregnancy.

When the results were subjected to Multivariate Logistic Regression analysis, age of the woman, low socio-economic status, previous miscarriage,

lack of family support and preference for a male baby were the most significant risk factors for postpartum depression.

This study correlates with most of the results obtained from previous studies. The associated risk factors provide significant information about the role played by socio-cultural environment and practices especially in developing countries. These risk factors can be identified during routine Antenatal visits and hence these issues must be addressed by the Health care providers and the women themselves must be made aware too so that women at risk are identified early for further follow up and intervention. This can be further achieved by the incorporation of Mental health care programs into the Maternal Health Care system. Further studies in this direction will help to improve the quality of care and reduce maternal morbidity as a result of depression and neglect.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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A painful vulvar mass: Bartholin gland cyst or aggressive angiomyxoma of the vulva?

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ABSTRACT

Aggressive angiomyxoma (AAM) is a rare invasive mesenchymal tumor of the pelvis and vulvar region, frequently occurring in women. We present a report in a 44 years old woman with a persistent vulvar mass on the right *labium majus* misdiagnosed as a Bartholin gland cyst.

SOMMARIO

L'angiomixoma aggressivo (AAM) è un raro tumore mesenchimale invasivo del bacino e della regione vulvare, che si verifica frequentemente nelle donne. Presentiamo il caso di una donna di 44 anni con una massa vulvare persistente sul *labium majus* destro diagnosticata erroneamente come una cisti della ghiandola di Bartolini.

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Key words

Aggressive angiomyxoma; Bartholin cyst; mesenchymal tumor; vulvar mass; tumors of uncertain differentiation.

INTRODUCTION

Aggressive angiomyxoma (AAM) is a rare type of soft tissue benign neoplasia, typically arising on the perineal region, which was first described in 1983 by Steeper and Rosai (1).

The term aggressive is used to emphasize the locally aggressive behaviour and the high frequency (40%) of local recurrence (2-4), although it does not reflect a high probability for metastasis, as only 2 cases with metastatic disease have been reported (5, 6). The name angiomyxoma derives from its analogy with myxoma and its vascular component. The etiopathogenesis is unclear, molecular mechanism is unknown. In some cases of AAM chromosomal abnormalities has been reported. The most involved chromosome is 12. Several analyses have shown how abnormalities of chromosomal 12 are associated with rearrangement of HMGIC gene, which is already implicated in the pathogenesis of others mesenchymal tumors (breast fibroadenomas, cutaneous lipomas, endometrial polyps and uterine leiomyoma) (7).

The AAM is commonly immunoreactive for desmine, smooth muscle actin, muscle specific actin, vimentin, estrogen and progesterone receptor, and hyaluronate receptor CD44. AAM generally reveals negativity for S100 protein, MUC4 and CD34. This tumor is distinguished from other mesodermal lesions by these histopathological features (8). The growth is slow and asymptomatic, and it can often be mistaken for a Bartholin Cyst, thus early diagnosis is rarely achieved (9). Most symptoms (feeling of local pressure, pain, dyspareunia) occur when the mass reaches dimensions higher than 8-10 cm (3, 10, 11).

Case report

We hereby present the case of a nulliparous, 44-year-old South-American woman, with no specific medical history, referring to our Emergency Room (ER) because of a painful mass in vulvar region. The patient reported a progressive and asymptomatic enlargement of the vulvar mass during the last 6 years, which has worsened in the last few days causing intolerable pain, difficult deambulation and dyspareunia.

Physical examination showed a bulky subcutaneous nodular lesion, of around 8 cm in diameter, painful at palpation involving the right labium majus. Overlying skin was normal, with no sign of in-

flammation and no bulky inguinal node. Intra-vaginal ultrasonography proved unremarkable. Pain relievers were administered unsuccessfully.

Diagnosis of a Bartholin cyst was then made. In a few hours, the patient underwent surgical excision because of the symptoms.

After surgical incision of the skin, a tubular, cul-de-sac cavity, was evident, macroscopically similar to intestinal serosa (**figure 1**). Thus, a herniated Meckel's diverticulum was suspected, surgical conversion to laparotomy was decided and general surgeon was involved.

Through bi-manual intra- and extra-abdominal palpation, hernias were excluded. The mass appeared completely independent from adjacent tissues and was then excised (**figure 2**).

Histology showed a 13 × 8 cm cystic mass, with smooth and translucent surface. The mass was capsulated and comprised lardaceous, translucent, homogenous tissue. Immunohistochemistry was positive for desmine, ER/PGR receptors and actin-MS, and the final diagnosis of aggressive angi-



Figure 1 Approximately 10 cm mass macroscopically similar to intestinal serosa.



Figure 2 The mass appeared completely independent from adjacent tissues after the wide excision.

omyxoma was reported. The patient was referred to a tertiary care center and she is currently in good clinical condition with no sign of recurrence.

DISCUSSION

AAM is a rare mesenchymal tumor arising from connective tissue of the pelvis and the perineal region, and is typical of women about 95%, usually in the reproductive age with a female to male ratio of 6:1 (1).

The peak incidence of AAM is at 35-40 years of age like our case.

Steeper and Rosai (1) first described the histological aspects and highlighted its tendency to local infiltration and recurrence in 1983. Around one hundred and fifty cases have been reported in the world medical literature since then (12).

The cases described in literature were characterized by typical features including slow growth, gelatinous appearance and locally infiltrative, but non-metastasizing nature without evidence of nuclear atypia or mitosis; distant metastasis (to the lung) has been reported in only two cases (3, 5, 6). It is classified under "Tumors of uncertain differentiation" in the latest WHO classification.

Diagnosis is frequently difficult, because it is often asymptomatic until it become a bulky mass.

For this reason it is frequently misdiagnosed as a Bartholin's gland cyst, hydroadenoma, angiomyofibroblastoma, leiomyoma, inguinal hernias, vaginal prolapse and vulvar abscess. (9).

The presentation size is extremely variable ranging from 1 up to 60 cm, but most of them are > 10 cm (3). Only histology evaluation and specific immunohistochemistry allows definitive diagnosis. Magnetic Resonance Imaging (MRI) can be useful in order to evaluate the relationship with surrounding tissues and to plan surgical excision (13). In our case no biopsy or imaging of the lesion were performed as a diagnostic study because of the clinical conditions of the patient requiring prompt surgery.

Chemo- or radiotherapy have not proven efficient, but hormone therapy might be used as adjuvant treatment, because of the frequent expression of ER/PGT receptors by the AAM tissue (8). Hormonal therapy (GnRH, SERM or combinations of them) may be used as neoadjuvant therapy in case of enlarged masses, relapse or when surgery is contraindicated (14).

Treatment of choice is still a wide surgical excision with tumor free margins (1). However, retrospective studies have demonstrated that positive resection margins after surgery are not associated with higher rate recurrence (3), confirming the benign nature of the neoplasia, which is associated with very good prognosis.

Notwithstanding, patients should be informed that recurrence is not rare, even after decades after first surgical excision, thus, a long clinical follow-up is strongly recommended.

CONTRIBUTIONS

VM and SE did the project development. BC, BV, ZPL and PR did data collection and manuscript writing. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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Congenital spastic paraplegia with neobladder: pregnancy and caesarean section

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ABSTRACT

Spinal cord injury (SCI) in women requires a multidisciplinary approach to monitor their health. Although rare, pregnancies among women with SCI are on. Hereditary spastic paraplegias represent a set of rare neurodegenerative diseases on a genetic basis characterized by progressive spasticity and hyperreflexia of the lower limbs. Hypertonic urinary disorders, deep sensitivity of the lower limbs and, occasionally, joint proprioception are also often associated. The most frequent complications during pregnancy are urinary tract infections (pyelonephritis), venous thrombosis/pulmonary embolism, preterm rupture of membranes, and preterm/obstructed labour.

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SOMMARIO

La lesione del midollo spinale (LM) nelle donne richiede un approccio multidisciplinare per monitorare la salute. Anche se rare, le gravidanze tra le donne con LM sono possibili. Le paraplegie spastiche ereditarie rappresentano un insieme di malattie neurodegenerative rare su base genetica caratterizzate da spasticità progressiva e iperreflessia degli arti inferiori. Molto spesso sono associati disturbi urinari ipertonici, sensibilità profonda degli arti inferiori e, occasionalmente, propriocezione articolare. Le complicanze più frequenti durante la gravidanza sono le infezioni del tratto urinario (pielonefrite), trombosi venosa/embolia polmonare, rottura pretermine delle membrane e travaglio pretermine/ostacolato.

Key words

Spastic paraplegia; neobladder; pregnancy; spinal cord injury; pre-natal diagnosis.

Abbreviations

SCI: Spinal Cord Injury
IVF: *In Vitro* Fertilization
MR: Magnetic Resonance
AH: Autonomic Hyperreflexia
IUGR: Intrauterine Growth Restriction
PI-UA: Pulsatility Index-Umbilical Artery

INTRODUCTION

Spinal cord injury (SCI) in women requires a multidisciplinary approach to monitor their health and for the necessary care related to pregnancy and childbirth (1, 2). SCI does not necessarily decrease a woman's desire for pregnancy (3, 4). Although rare, pregnancies among women with SCI are on the rise and generally have favorable outcomes. However, various factors should be considered during pregnancy and childbirth: urological complications, the risk of thromboembolism and of autonomic dysfunction. The most frequent complications during pregnancy are urinary tract infections (pyelonephritis), venous thrombosis/pulmonary embolism, preterm rupture of membranes, and preterm/obstructed labour (5). Hereditary spastic paraplegias (HSP) represent a set of rare neurodegenerative diseases on a genetic basis characterized by progressive spasticity and hyperreflexia of the lower limbs (6). From a clinical point of view, there are two forms: "pure" and "complicated". Pure forms, which progress slowly, are characterized by spasticity and weakness in the lower limbs. Hypertonic urinary disorders, deep sensitivity of the lower limbs and, occasionally, joint proprioception are also often associated. Complicated forms also present neurological and non-neurological diseases. Spastic paraplegias can be inherited as an autosomal dominant, autosomal recessive or X-linked recessive trait, and there are multiple dominant and recessive variants. Treatment is symptomatic (muscle-relaxant drugs, functional rehabilitation). In some studies, in order to reduce spasticity, therapy by intramuscular injection of botulinum toxin into the muscles of adults and children affected by spasticity has been described (7, 8).

Case presentation

We present the case of a 38-year-old woman with congenital spastic paraplegia of uncertain etiology. The patient was born from elective caesarean section for previous maternal caesarean section, with neonatal weight of 2.600 kg. The mother reports the physiological course of pregnancy and denies taking drugs. From birth there was a strong motor impairment of the lower limbs which appeared to be hypotonic. No special checks were carried out until the age of 14, when an MRI was performed which showed a medullary cord reduced in thickness at the level of D12-L1 with marked reduction

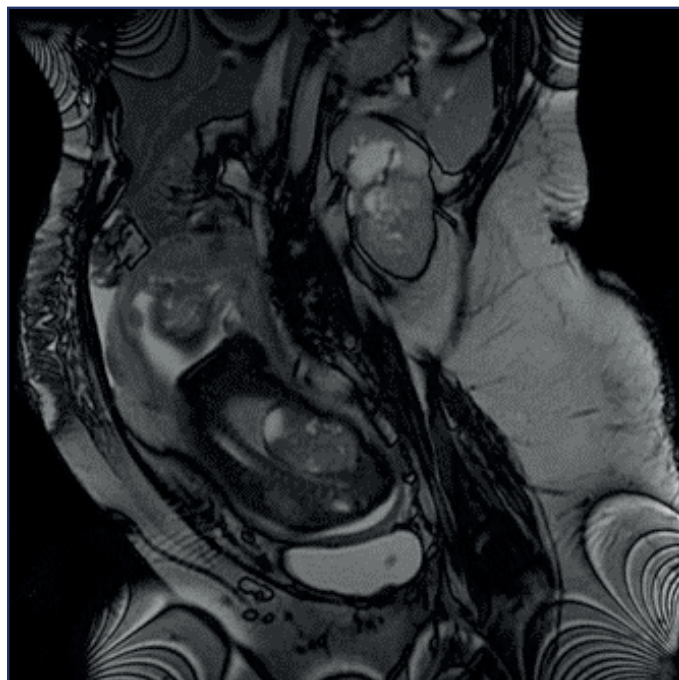
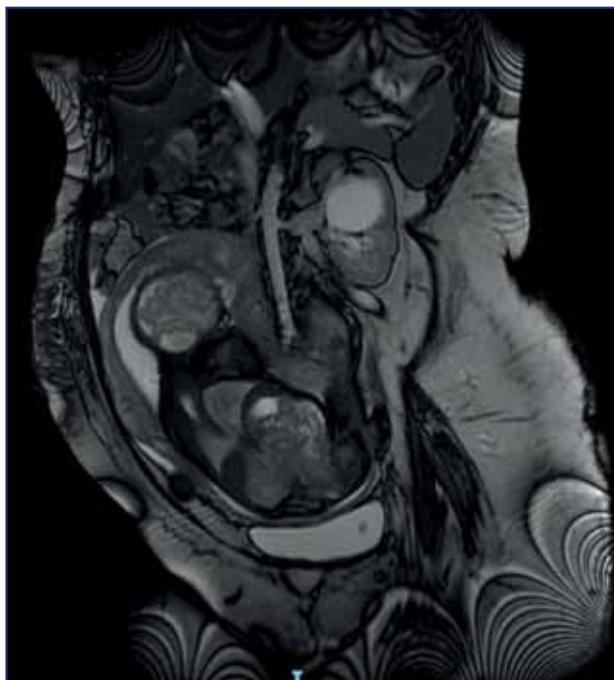
of the surrounding liquor spaces. The patient also showed a severe neurogenic bladder dysfunction (neuropathic bladder with detrusor hyperreflexia and detrusor-sphincter dysynergy) with complete urinary incontinence. Continent urinary diversion was scheduled. The enlargement cystoplasty, bladder neck closure and cutaneous appendectomy according to Mitrofanoff were performed at the age of 17. In 2007 and again in 2009, due to the formation of bladder stones (vesical calculi), the patient underwent endoscopic crushing and removal surgery. All stone fragments were removed. The patient regularly performed bladder self-catheterization. A genetic investigation has never been carried out in the diagnostic process, so it cannot be excluded the case of an hereditary form.

At the age of 30, chronic hypertension was diagnosed and treated with drug therapy with perindopril + Indapamide 2.5 mg one tablet a day, until the patient undertook IVF, for which the drug was replaced by Methyldopa 500 mg.

The patient II gravida 0 para (1 previous spontaneous abortion, pregnancy obtained by IVF), comes to our observation during her second pregnancy, obtained by medically assisted homologous procreation (ICSI). Her partner was also paraplegic because of an accident at work. During pregnancy several episodes of urinary infection (at least 3 episodes) have been reported and treated with antibiotic therapy. Due to immobility, 6000 IU heparin therapy was performed throughout the pregnancy to reduce venous thrombosis/pulmonary embolism.

At the 34th week of pregnancy, an upper and lower abdomen MRI was performed in order to see the course of vesicostomy and to study the relationship between the bladder and uterus for the planning of surgical access. From the Magnetic Resonance (MR) of the upper and lower abdomen, it was shown that the neo bladder was located in the middle of the pelvic excavation. In the bladder lumen the end of the catheter previously positioned via the umbilical way was recognizable. The catheter was followed throughout its course in the subfascial area up to the paraumbilical site, where its path became horizontal for about 5 cm reaching the navel from which it emerged (figures 1, 2).

Pregnancy was complicated by pre-eclampsia (arterial hypertension refractory to drug therapy, rise in uric acid and changes in coagulation factors). In addition, there is also IUGR with increase in PI-UA and brain sparing. For this reason a caesarean section at the 35th week of pregnancy, after disodium



Figures 1, 2. MRI at the 34th week of pregnancy. Neo-bladder with catheter previously positioned was located in the middle of the pelvic excavation. It is clear dorsal and lumbar scoliosis.

betamethasone phosphate cycle, was performed. The female infant weighed 1675 g at birth, 42 cm in length, Apgar 8'-9'.

A longitudinal umbilical pubic incision and a J hysterotomy were made during caesarean section; a myomectomy of a pedunculated myoma was also performed.

The conditions of the baby at birth were optimal. The patient was discharged without maternal complications 72 hours after delivery.

DISCUSSION

We presented a quite complex case in the pre-conception, prenatal and perinatal period for maternal comorbidities and disability of both parents, congenital for the mother, acquired for the father with infertility. Maternal and neonatal outcome, however, was positive.

About 2000-3000 women in childbearing age suffer spinal cord injury each year, especially following trauma (9, 10). By itself, the fertility is not compromised in women with spinal cord injury: menstrual irregularities in the first 3-9 months and subsequent return to the situation pre damage with a maximum of 36% post trauma pregnancy (11-13). In our case the etiology of spastic paraplegia seems to be unknown, even if genetic investigations have not been performed. Only prenatal data available is ma-

ternal alloimmunization, so our little patient underwent phototherapy for neonatal jaundice: perinatal suffering has not been documented and there are no studies correlating neonatal hemolysis to paraplegia. In preconceptional management, in addition to information on present and potential problems, it is also necessary to consider the need for drugs, such as anticonvulsants, possible to take during pregnancy to avoid crisis.

Ghidini *et al.* (10) observed that 90% of women with SCI had not received the right information about pregnancy during the rehabilitation period. Patients with paraplegia and pregnancy should be informed about the importance of caring for their skin, their gastrointestinal and genitourinary systems.

The known maternal-fetal complications in SCI patients are: recurrent urinary tract infections, kidney stones, constipation, pressure ulcers, preeclampsia on chronic hypertension, venous thrombosis, gestational diabetes and premature birth.

According to the literature, patients with acquired SCI don't have an increased risk of congenital malformations or intrauterine fetal death (14). In our case, a genetic evaluation was not made during pregnancy, but second level ultrasound series.

Scientific studies have shown that 100% of self-catheterized pregnancies suffer from recurrent urinary tract infections in pregnancy and in the postpartum (2) and that paraplegia brings 25% more complications than women without disabilities (13).

For the prevention of premature births, it is necessary to investigate and treat any urinary, intestinal and vaginosis infections, check objective ultrasound parameters such as cervix length considering the poor perception of abdominal pain and the consequent cervical incontinence. There are known cases of precipitous birth without painful contractions (15).

Hypertension continues to be a major problem for SCI patients, but the possible medication taken during pregnancy are many, such as nifedipine or alpha methyl dopa.

In our case, chronic hypertension complicated by preeclampsia, recurrent urinary tract infections, kidney stones before pregnancy were found; there was no onset of gestational diabetes. Intermittent self-catheterization at the level of the umbilical stoma every 4 hours with a hydrophilic catheter has improved the recurrence of urinary infections in pregnancy, without episodes of renal colic. No Botox injections were necessary.

Autonomic hyperreflexia (AH), feared complication in paraplegic patients, was not found in our case, despite the stress factors such as contractions and pressure rise. It is important to discriminate between AH and preeclampsia, since inadequate treatment leads to an inadequate response. AH is characterized by excessive sweating, headache, patchy rash, pilo-motor erection, facial flushing, nasal congestion, convulsions and, consequently, placental uterine vasoconstriction, hypoxemia and fetal bradycardia (14).

About the mode of delivery and the type of anesthesia data are a bit contrasting: vaginal delivery is not contraindicated and anesthesia is often not necessary. It prefers epidural anesthesia especially in the onset of AH (16).

The caesarean section (up to 49% of cases) is often carried out for the onset of maternal complications such as hypertension or related fetal complications such as prematurity, intrauterine growth restriction (IUGR) or fetal wrong position (10% of cases) (9).

In our case, caesarean section under general anesthesia was performed for maternal preeclampsia with IUGR and severe dorsal/lumbar scoliosis;

surgical procedure was complicated by the anomalous neo bladder, for which the execution of MRI before the surgical intervention and the collaboration with the urologists during the intervention was fundamental.

It is preferred to use metal clips for suturing the skin because of documented occurrence of infections or altered metabolism of the suture. The denervated area does not absorb the thread well with consequent sterile abscesses or suture dehiscence (17).

Therefore, an evaluation by a multidisciplinary team of experts, such as the gynecologist-obstetric surgeon, the anesthesiologist and the urologist, is necessary, as well as the neonatologist with neonatal intensive care in a tertiary center.

CONCLUSIONS

Although SCI is common today, pregnant women with paraplegia are rare compared to cases in the past. It gives witness literature, full of examples until last decade.

It is important to know to manage pregnancies with this type of problem, because the situation could become very difficult. Often paraplegia pregnant arouses anxiety in caregivers because of lack of knowledge and the rarity of cases (18).

Above all, it is necessary to intervene in the pre-conceptional phase trying to prevent anything that could complicate this type of pregnancy, which disabled girls can still deal with due support.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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