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Uterine disorders in reproductive life

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Abstract

The development of new medical diagnostic technologies and procedures and the drop in the birth rate observed in the last decades represent the main causes of increased incidence of uterine disorders. Endometriosis, adenomyosis and uterine fibroids are benign uterine disorders whose understanding have greatly increased and clinical management have improved in recent times. Molecular pathogenetic aspects, new imaging technologies (transvaginal ultrasound and magnetic resonance), biochemical markers, hormonal drugs, minimally invasive surgical technologies were studied for diagnosis and treatment of endometriosis, adenomyosis and uterine fibroids. Sex steroid hormones, inflammation and fibrosis are key pathogenetic mechanisms of uterine disorders.

Endometriosis is characterized by endometrial cells migrating outside the uterus and implanting in the pelvis, associated with inflammation, neuroangiogenesis and fibrosis causing dysmenorrhea, pelvic pain, dysuria and dyschezia. The painful symptoms may activate central sensitization and stress responses.

Adenomyosis is caused by the presence of endometrial cells within the myometrium, characterized by pelvic pain, abundant menstrual bleeding and infertility. Heavy menstrual bleeding can cause the reduction of iron reserves and consequently iron deficiency anemia.

Uterine fibroids are the most common benign tumors of the uterus in women of reproductive age. They can be asymptomatic, but they frequently manifest with abnormal uterine bleeding, pelvic discomfort, and challenges with fertility. Submucosal or intramural fibroids can hinder embryo implantation and potentially lead to pregnancy-related complications such as miscarriage, placenta previa, preterm labor, or postpartum hemorrhage.

The increased incidence of uterine disorders has a major clinical impact on women's health and a very poor quality of life is often reported. Therefore, prompt diagnosis and effective management are mandatory.

Keywords: endometriosis, adenomyosis, uterine fibroids, uterine disorders

Introduction

In the last decades two major changes occurred worldwide in the reproductive life of women: the birth rate significantly decreased, and the first pregnancy has been postponed over 30 years old. Both changes were determined by socio-economic reasons, however they determined a relevant impact on reproductive function of women. The reduction of pregnancy-related amenorrhea has caused the rise of the number of menstruations from a mean value of 150-200 to 450-500 during the fertile age[1,2]. This is a possible risk factor for uterine disorders development. All epidemiological studies agree that an increasing number of patients with endometriosis, adenomyosis or fibroids are diagnosed at adolescence and during the reproductive years. Nevertheless, this is also due to the increasing awareness about menstrual health and the improvement of diagnostic techniques. Since these disorders significantly decrease after menopause, they are defined sex steroid hormones-dependent diseases[3]. Abnormal uterine bleeding, pain and infertility are symptoms of endometriosis, adenomyosis and uterine fibroids, making more difficult a differential diagnosis, also because they

may occur concomitantly in the same patient[4]. The development of ultrasound (US) and magnetic resonance imaging (MRI) allowed to reduce the diagnostic delay and nowadays are fundamental tools. The therapeutic strategy is different for each of the uterine disorder, even thought there are some shared medical options.

1. Endometriosis

Endometriosis is a disease typical of the woman's reproductive age and is linked to the migration and implantation of endometrial cells outside the uterine cavity at the time of menstruation (Figure 1). It is an estrogen-dependent disease[5,6], and its prevalence is difficult to determine because the clinical presentation varies, because the increased inflammatory mechanisms which occur in the pathogenesis of the disease[7]. It is estimated to affect approximately 6-10% of women. However, the prevalence is higher (35-50%) in women who experience pain, infertility, or both (35-50%) and it is estimated 6 of 10 endometriosis cases are undiagnosed [8] [9].

The main risk factor for endometriosis is prolonged exposure to endogenous estrogen. Nulliparity, early age at menarche, late menopause, shorter menstrual cycles, and heavy menstrual bleeding are conditions that are characterized by a high proliferative stimulus on the endometrium and are associated with an increased risk of endometriosis. On the contrary, multiple pregnancies, prolonged lactation, and late menarche are protective against endometriosis[10]. Since women changed their reproductive rhythms by postponing the first pregnancy and reducing the number of pregnancie,s the incidence of endometriosis has increased. In addition, new chemical pollutants, endocrine disruptors (e.g., phthalates, dioxin and bisphenol A), have become part of diet and daily life, having estrogenic-like effects on the organs and reproductive function of women (and men) and can affect the development of diseases [11] [12] . Diet can significantly impact the progression of endometriosis by estrogen action or inflammatory processes. Polyphenols are an extensive group of biologically active compounds synthesized by plants. They have antioxidant, anti-inflammatory properties and, in addition, they can affect estrogen receptors. A reduced intake of these products and an increased use of inflammatory food has been shown in endometriosis patients [13].

Interestingly, the incidence of endometriosis in adolescents with genital tract anomalies has raised, especially in those associated with outflow tract obstruction. Endometriosis resolves after correction of the outflow tract abnormality, without other treatment [14]. Moreover, primary dysmenorrhea (PD) is associated with a higher risk of developing chronic pain state and shares some of the same pain pathways of endometriosis, such as prostaglandins overproduction, inflammation, peripheral sensitization, central sensitization, and abnormal stress responses. Women who suffer from

dysmenorrhea in adolescence have a higher risk of endometriosis in the future [15]. Women with endometriosis often experience increased stress levels, psychological and endocrine stress measures indicate that there is correlation with pain severity and disease extension[16,17]. Nevertheless, chronic stress might be a primary cause of endometriosis, and, consequently, avoiding or treating chronic stress might potentially reduce the risk of developing endometriosis.[18] Perinatal and early-life stressors have been implicated as potential risk factors for the future development of endometriosis: patients with endometriosis are often born preterm or from pregnancies complicated by preeclampsia and are more likely to have been Low Birth Weight (LBW) babies [19].

Finally, the first-degree relatives of affected women are at three- to ninefold higher risk of developing the disease. Genetic factors contribute about half of the variation in endometriosis risk, with an estimate of hereditability of 51%. A recent genome-wide association study meta-analysis has identified 42 genome-wide significant loci comprising 49 distinct association signals. Genetic correlations are more important for advanced disease and ovarian endometriosis [20].

Endometriosis has a great impact on the quality of life[21], it manifests by chronic pelvic pain and dysmenorrhea, but also dyschezia, dyspareunia, and dysuria might be present. Moreover, other less specific symptoms are often observed such as intestinal and urinary disorders. Endometriosis is also accompanied by infertility precisely because conception is often made difficult by inflammation in the pelvis, and because the uterus becomes inhospitable for the implantation of the embryo. In addition, a number of systemic comorbidities are often associated with the presence of endometriosis[22,23].

Endometrial cells can be localized at various levels and are distinguished superficial or peritoneal endometriosis (SUP), characterized by the presence of implants located on the surface of the peritoneum, ovarian (OMA), and deep endometriosis (DIE), which refers to lesions infiltrating deeper than 5 mm under the peritoneum [24]. Endometrial tissue can develop and proliferate on the pelvic (bladder, rectum, colon) and abdominal organs (diaphragm, liver) with very different symptoms depending on the location.

Endometriosis diagnosis is often delayed, with an average diagnostic lag of up to 12 years[25]. The prolonged delay contributes to disease progression over several years, resulting in increased treatment costs, extended adverse effects on quality of life, and augmented risks of surgical interventions and infertility. As initial screening method or complement to the patient clinical history diagnostic scoring questionnaires have been developed, these questionnaires are designed to systematically evaluate relevant symptoms and risk factors. The Florence Questionnaire [26] (Table 1) provides information on the most common risk factors, including genetic factors (family history), epigenetic factors (in utero

exposure to stressors), age of menarche, characteristics of menstruation during adolescence, developmental stressors (psychological or physical), and exposure to environmental disruptors (chemicals). Moreover, in order to estimate menstruation related distress MEDI-Q (menstrual distress questionnaire) has been validated [27,28]. In addition, using a Visual Analog Scale (VAS) score for dysmenorrhea, dyspareunia, dysuria or dyschezia is necessary to evaluate painful symptoms experienced by endometriosis patients and may be helpful in predicting pelvic organ involvement associated with deep infiltrating lesions [29]. Following the evaluation of family and clinical history, and the administration of questionnaires, the physical examination is deemed essential. Assessment of the pelvis in individuals suspected of having endometriosis should involve a comprehensive physical examination, including abdominal inspection and palpation, a digital vaginal examination, bimanual examination and speculum assessment.

The increased use of 2D and 3D transvaginal ultrasound (TVUS) have played a significant role in the faster and less invasive diagnosis of endometriosis. This method is especially effective in identifying ovarian endometriomas and deep infiltrating endometriosis [30]. While it's useful to use magnetic resonance imaging (MRI) for the diagnosis of endometriosis in its less frequent and non-evident locations, especially those that are multifocal, deep and extrapelvic[31].

The therapeutic strategy must be tailored for each patient according to the symptoms, age and desire for pregnancy. It includes medical therapy, surgery and medically assisted reproduction[32]. Since endometriosis is a condition that is often identified in young people, who at the moment have no desire for pregnancy, the medical approach is the first-line choice. The most used are hormonal drugs that block ovulation by reducing ovarian estrogen secretion and/or inducing a pseudo-pregnancy state: progestins, analogues or antagonists of the gonadotropin-releasing hormone (GnRH-a). Surgery intervenes only when hormonal therapies and other antalgic approaches (anti-inflammatory, pain therapy) are not effective on painful symptoms [33 3 34].

2. Adenomyosis

Adenomyosis is a benign uterine disease and is caused by the presence of endometrial cells within the myometrium, characterized by pelvic pain, abundant menstrual bleeding and infertility[35,36]. The incidence of adenomyosis is not accurately established due to a lack of standard diagnosis criteria; epidemiological studies refer that 20-35% of women in reproductive life are affected by adenomyosis, with a prevalence in peri-menopausal women [37]. The main risk factors for adenomyosis are estrogen exposure[38] and parity: early menarche (≤10 years old), short menstrual cycles (≤24 days in length), oral contraceptive use, elevated body mass index (BMI), tamoxifen use, multiparity, and

pregnancy termination[39]. Adenomyosis is a disease that depends on estrogen and involves the abnormal thickening of the inner myometrium. During each menstrual cycle, the endometrium regenerates, and when this process is accompanied by altered angiogenesis, both adenomyosis and endometriosis may develop. Therefore, a common etiology for both conditions is suggested, which potentially involves the same pathways. However, recent studies have shown that adenomyosis is an independent disease from endometriosis, with specific pathogenic pathways such as sex steroid receptors, proliferation and fibrosis, inflammatory mediators, and neuroangiogenesis. These pathways are key pathogenic mediators of adenomyosis-related pain (dysmenorrhea, dyspareunia), abnormal uterine bleeding, and infertility [35 40 36].

Heavy menstrual bleeding (HMB) is associated with the reduction of iron reserves and the consequent iron deficiency anemia [41]. Patients report fatigue and need supplementation to restore haematological values in the normal range. In the patient with heavy menstrual bleeding and between menstruation it is necessary to make a differential diagnosis between adenomyosis, uterine fibromatosis and endometrial polyps [41], considering also that adenomyosis is often associated with endometriosis and uterine fibroids. In addition, adenomyosis is increasingly diagnosed in women with reproductive desires, they have reduced fertility, both for difficulty in conception but above all for recurrent miscarriages[42].

Adenomyosis is diagnosed based on clinical history, symptoms and the use of TVUS or MRI. TVUS is the first line of diagnosis for this disorder and should be performed very accurately. The asymmetrical thickening of uterine walls, intramyometrial cysts or hyperechoic islands (or both), fan-shaped shadowing of the myometrium, myometrial echogenic subendometrial lines and buds, translesional vascularity, and irregular or interrupted JZ are the criteria to be evaluated [43]. Magnetic resonance imaging is a second-level technique with greater specificity and sensitivity than transvaginal ultrasound [37].

The hormonal drugs that are used to improve the symptoms related to adenomyosis are like those used for endometriosis: progestins, both oral and intrauterine, and GnRH analogues or antagonists. There are also conservative surgical options through both endoscopic and laparoscopic techniques, although they are less used [44].

3. Uterine fibroids

Uterine fibroids (or leiomyomas) are the most common benign tumors (leiomyoma) of the uterus in women of reproductive age. They are often asymptomatic, but are frequently associated with abnormal uterine bleeding, pelvic pain, and infertility [45], causing menstrual distress and reduced

quality of life[46]. They can be located near the endometrium (submucosal), in the wall thickness of the myometrium (intramural) and more externally, below the peritoneal serosa (subserous) (Figure 2) [47]. The presence of submucosal or intramural fibroids can reduce the ability to implant the embryo and can also be associated with complications of pregnancy (abortion, placenta previa, premature birth or postpartum bleeding).

The major risk factors for this condition are age and ethnicity. In addition, aspects of lifestyle such as physical activity, diet, smoking and caffeine consumption affect the incidence of uterine fibroids. Sex steroid hormones (estrogens, progesterone) play a key role in the pathogenesis of uterine leiomyoma: estrogen and progesterone receptors have been found to be decisive in the development of fibroids [48]. US and MRI are diagnostic procedures used for diagnosis, allow differential diagnosis with adenomyosis or with malignant myometrial pathology [43 49].

Various therapeutic options exist for managing uterine fibroids, including surgery, hormonal drugs, uterine artery embolization, and high-intensity focused ultrasound (HIFU). The selection of the most suitable treatment depends on factors such as the patient's age, symptoms, desire for pregnancy, the number, size, and location of fibroids, as well as the presence of medical or surgical contraindications. Medical treatments encompass GnRH analogs or antagonists and selective progesterone receptor modulators (SPRM). These medications aim to alleviate symptoms, improve patients' quality of life, and circumvent the risks associated with surgical interventions. Nonetheless, in many cases surgery remains the predominant therapeutic approach. Hysterectomy is typically recommended as a definitive management option for symptomatic patients who do not desire future pregnancies or wish to retain their uterus. In younger patients or those desiring pregnancy, myomectomy is performed. Submucosal myomas can be excised via hysteroscopy, while laparoscopic or open surgery is employed for intramural and subserous fibroids. However, the latter is not a definitive treatment, and recurrence rates and the need for reintervention are high[50].

Repetitive surgery can pose challenges due to iatrogenic adhesions, sometimes necessitating hysterectomy. Recent advancements include interventional radiological procedures like uterine artery embolization and physical techniques such as HIFU or radiofrequency myolysis, showing promising results. Nevertheless, these procedures carry the risk of recurrence, attributed to the reappearance of both new lesions and associated symptoms [51].

Conclusions

Uterine disorders affect a large part of women during reproductive life, they share some pathogenetic features (estrogen dependent, dysfunctional progesterone receptors), some clinical symptoms

(dysmenorrhea, infertility), the diagnostic procedures (TVUS, MRI) and the therapeutical management (hormonal drugs, surgery, ART). The quality of life of these patients is very poor, impacting physical and psychological wellbeing, and as a consequence their social life. A delayed diagnosis is often observed, and in several cases uterine disorders may occur in the same patients concomitantly. More studies on pathogenesis, diagnosis (gene testing or circulating markers) and on therapeutical approaches (new drugs and minimally invasive surgery) are warranted.

Declarations

Conflict of Interest

The Author declares that there is no conflict of interest.

Figure 1

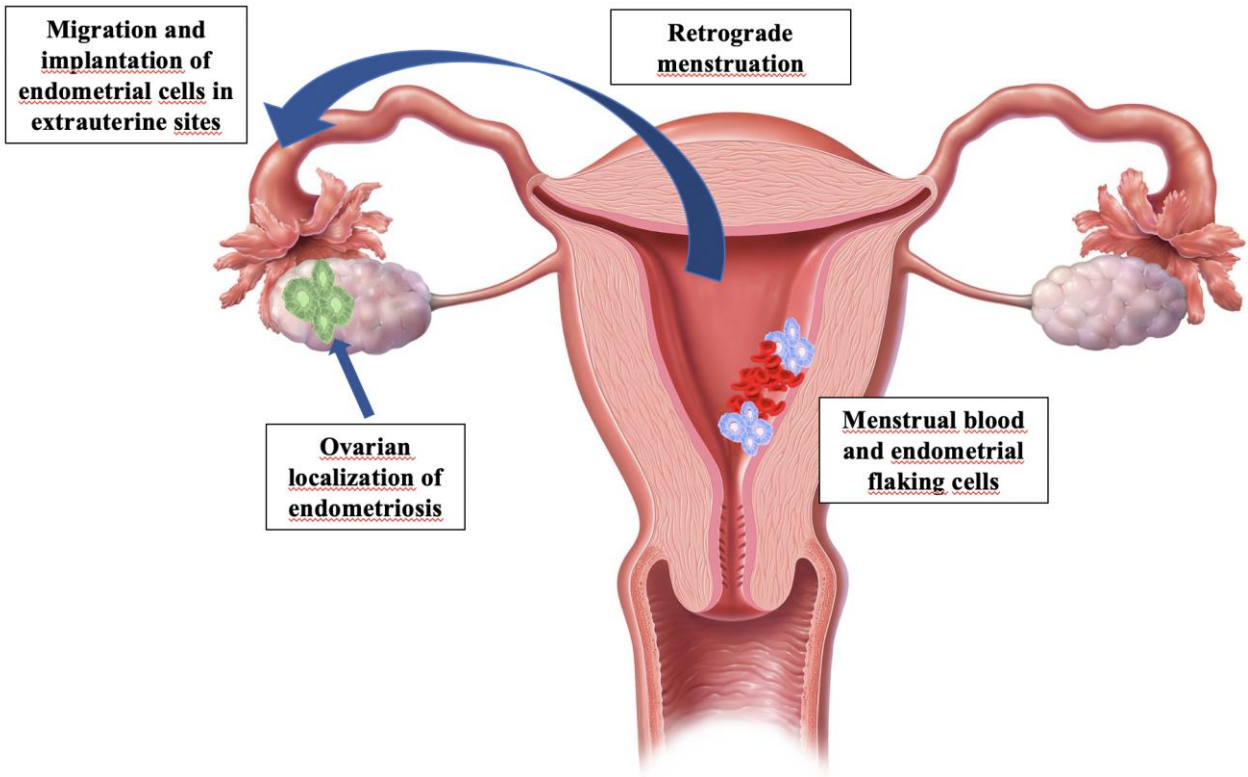

Figure 2

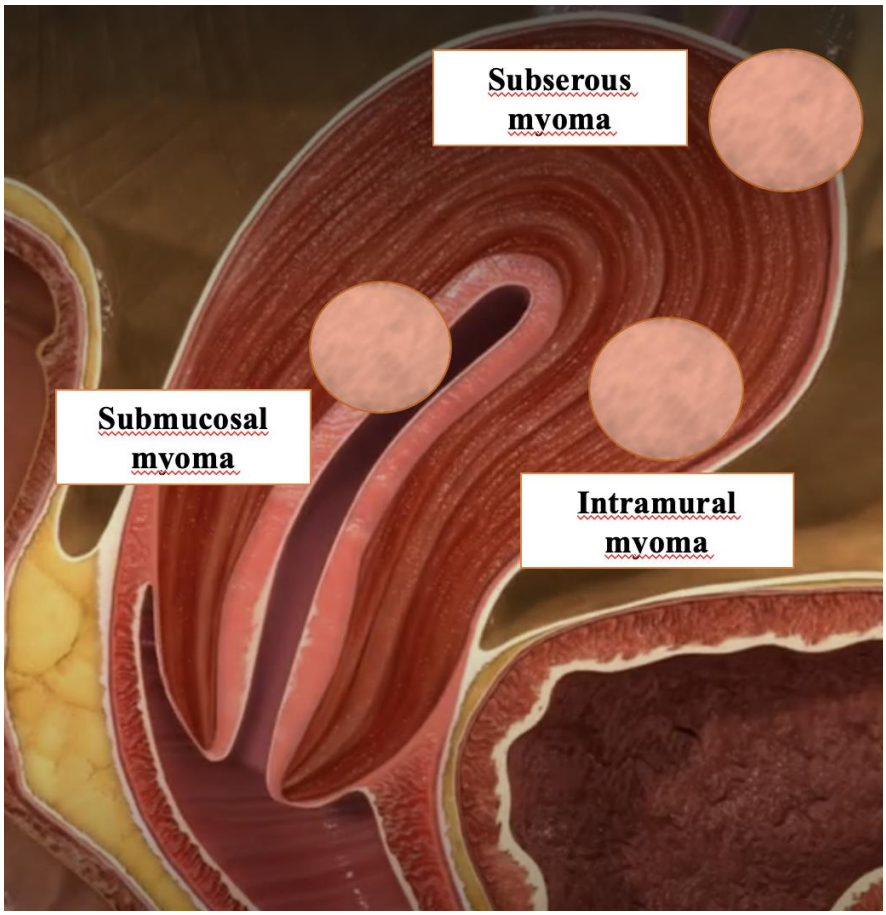

Table 1 - Florence Questionnaire

Family History
- First-degree relative with endometriosis

In Utero Exposure
- Premature birth
- Preeclampsia
- Exposure to dietylstilbestrol

Early Life Factors
- Low Birth Weight (small for gestational age/fetal growth restriction)
- Formula-fed infant

Adolescent History
- Physical, psychological and sexual abuse or violance
- Severe primary dysmenorrhea with negative effects on life activities
- Genital tract abnormalities (e.g. obstructive Müllerian anomalies)

Gynecologic Factors
- Early menarche
- Severe dysmenorrhea
- Short menstrual cycle length
- Heavy Menstrual Bleeding
- Vulvodynia

Comorbidities related Risk Factors
- Headache, migraine and the chronic pain syndrome
- Autoimmune diseases (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis).
- Gastrointestinal disorders (e.g., ulcerative colitis, Crohn's disease, IBS, celiac disease)

Environmental and Stress Related Risk Factors
- Psychological stress and sexual abuse
- Endocrine disruptors and diet
- High intensity physical activity and low BMI

Previous Obstetrical History
- Adverse pregnancy and perinatal outcomes
- Miscarriage(s)
- Previous History of Pelvic Surgery

References

1. Critchley, H. O. D. *et al.* Menstruation: science and society. *American Journal of Obstetrics and Gynecology* **223**, 624–664 (2020).
2. Critchley, H. O. D., Maybin, J. A., Armstrong, G. M. & Williams, A. R. W. Physiology of the Endometrium and Regulation of Menstruation. *Physiological Reviews* **100**, 1149–1179 (2020).
3. Vannuccini, S., Clemenza, S., Rossi, M. & Petraglia, F. Hormonal treatments for endometriosis: The endocrine background. *Reviews in Endocrine and Metabolic Disorders* **23**, 333–355 (2021).
4. Capezzuoli, T. *et al.* Ultrasound findings in infertile women with endometriosis: evidence of concomitant uterine disorders. *Gynecological Endocrinology* **36**, 808–812 (2020).
5. Clemenza, S., Vannuccini, S., Ruotolo, A., Capezzuoli, T. & Petraglia, F. Advances in targeting estrogen synthesis and receptors in patients with endometriosis. *Expert Opinion on Investigational Drugs* **31**, 1227–1238 (2022).
6. Rossi, M. *et al.* Epigenetics, endometriosis and sex steroid receptors: An update on the epigenetic regulatory mechanisms of estrogen and progesterone receptors in patients with endometriosis. in *Vitamins and Hormones* vol. 122 171–191 (Elsevier, 2023).
7. Reis, F. M., Petraglia, F. & Taylor, R. N. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. *Human Reproduction Update* **19**, 406–418 (2013).
8. *Female Reproductive Dysfunction*. (Springer International Publishing, Cham, 2020). doi:10.1007/978-3-030-14782-2.
9. Agarwal, S. K. *et al.* Clinical diagnosis of endometriosis: a call to action. *American Journal of Obstetrics and Gynecology* **220**, 354.e1-354.e12 (2019).
10. Vercellini, P., Viganò, P., Somigliana, E. & Fedele, L. Endometriosis: pathogenesis and treatment. *Nature Reviews Endocrinology* **10**, 261–275 (2013).
11. Smarr, M. M., Kannan, K. & Buck Louis, G. M. Endocrine disrupting chemicals and endometriosis. *Fertility and Sterility* **106**, 959–966 (2016).
12. Cobellis, L. High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. *Human Reproduction* **18**, 1512–1515 (2003).
13. Markowska, A., Antoszczak, M., Markowska, J. & Huczyński, A. The Role of Selected Dietary Factors in the Development and Course of Endometriosis. *Nutrients* **15**, 2773 (2023).
14. Brosens, I., Puttemans, P. & Benagiano, G. Endometriosis: a life cycle approach? *American Journal of Obstetrics and Gynecology* **209**, 307–316 (2013).
15. Clemenza, S. *et al.* Is primary dysmenorrhea a precursor of future endometriosis development? *Gynecological Endocrinology* **37**, 287–293 (2021).
16. Lazzeri, L. *et al.* Endometriosis and Perceived Stress: Impact of Surgical and Medical Treatment. *Gynecol Obstet Invest* **79**, 229–233 (2015).
17. Lazzeri, L. *et al.* Surgical treatment affects perceived stress differently in women with endometriosis: correlation with severity of pain. *Fertility and Sterility* **103**, 433–438 (2015).
18. Reis, F. M., Coutinho, L. M., Vannuccini, S., Luisi, S. & Petraglia, F. Is Stress a Cause or a Consequence of Endometriosis? *Reproductive Sciences* **27**, 39–45 (2020).
19. Vannuccini, S. *et al.* Potential influence of in utero and early neonatal exposures on the later development of endometriosis. *Fertility and Sterility* **105**, 997–1002 (2016).
20. Rahmioglu, N. *et al.* The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions. *Nat Genet* **55**, 423–436 (2023).
21. Vannuccini, S. *et al.* Surgical treatment of endometriosis: prognostic factors for better quality of life. *Gynecological Endocrinology* **35**, 1010–1014 (2019).

22. Vannuccini, S. *et al.* Mental health, pain symptoms and systemic comorbidities in women with endometriosis: a cross-sectional study. *Journal of Psychosomatic Obstetrics & Gynecology* **39**, 315–320 (2018).
23. Chen, H. *et al.* Comorbidities and Quality of Life in Women Undergoing First Surgery for Endometriosis: Differences Between Chinese and Italian Population. *Reprod. Sci.* **28**, 2359–2366 (2021).
24. Chapron, C., Marcellin, L., Borghese, B. & Santulli, P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol* **15**, 666–682 (2019).
25. Pino, I. *et al.* "Better late than never but never late is better", especially in young women. A multicenter Italian study on diagnostic delay for symptomatic endometriosis. *The European Journal of Contraception & Reproductive Health Care* **28**, 10–16 (2023).
26. Petraglia, F. *et al.* The modern non-invasive diagnosis of endometriosis. *Journal of Reproductive Medicine and Embryology* **0**, 0–0 (2024).
27. Vannuccini, S. *et al.* Menstrual Distress Questionnaire (MEDI-Q): a new tool to assess menstruation-related distress. *Reproductive BioMedicine Online* **43**, 1107–1116 (2021).
28. Cassioli, E. *et al.* The menstrual distress questionnaire (MEDI-Q): reliability and validity of the English version. *Gynecological Endocrinology* **39**, 2227275 (2023).
29. Chapron, C. *et al.* A new validated screening method for endometriosis diagnosis based on patient questionnaires. *eClinicalMedicine* **44**, 101263 (2022).
30. Guerriero, S. *et al.* Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. *Ultrasound Obstet Gynecol* **48**, 318–332 (2016).
31. Bazot, M. & Daraï, E. Diagnosis of deep endometriosis: clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. *Fertility and Sterility* **108**, 886–894 (2017).
32. Petraglia, F., Vannuccini, S., Santulli, P., Marcellin, L. & Chapron, C. An update for endometriosis management: a position statement. *Journal of Endometriosis and Uterine Disorders* **6**, 100062 (2024).
33. Capezzuoli, T., Rossi, M., La Torre, F., Vannuccini, S. & Petraglia, F. Hormonal drugs for the treatment of endometriosis. *Current Opinion in Pharmacology* **67**, 102311 (2022).
34. De Ziegler, D., Borghese, B. & Chapron, C. Endometriosis and infertility: pathophysiology and management. *The Lancet* **376**, 730–738 (2010).
35. Vannuccini, S. *et al.* Pathogenesis of adenomyosis: an update on molecular mechanisms. *Reproductive BioMedicine Online* **35**, 592–601 (2017).
36. Zhai, J., Vannuccini, S., Petraglia, F. & Giudice, L. C. Adenomyosis: Mechanisms and Pathogenesis. *Semin Reprod Med* **38**, 129–143 (2020).
37. Chapron, C. *et al.* Diagnosing adenomyosis: an integrated clinical and imaging approach. *Human Reproduction Update* **26**, 392–411 (2020).
38. Vannuccini, S. & Petraglia, F. Adenomyosis: is an endocrine-related uterine dysfunction? *Gynecological Endocrinology* **38**, 1017–1018 (2022).
39. Struble, J., Reid, S. & Bedaiwy, M. A. Adenomyosis: A Clinical Review of a Challenging Gynecologic Condition. *Journal of Minimally Invasive Gynecology* **23**, 164–185 (2016).
40. Bulun, S. E., Yildiz, S., Adli, M. & Wei, J.-J. Adenomyosis pathogenesis: insights from next-generation sequencing. *Human Reproduction Update* **27**, 1086–1097 (2021).
41. Vannuccini, S., Jain, V., Critchley, H. & Petraglia, F. From menarche to menopause, heavy menstrual bleeding is the underrated compass in reproductive health. *Fertility and Sterility* **118**, 625–636 (2022).
42. Vannuccini, S. & Petraglia, F. Recent advances in understanding and managing adenomyosis. *F1000Res* **8**, 283 (2019).
43. Van Den Bosch, T. *et al.* Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. *Ultrasound Obstet Gynecol* **46**, 284–298 (2015).
44. Vannuccini, S., Luisi, S., Tosti, C., Sorbi, F. & Petraglia, F. Role of medical therapy in the management of uterine adenomyosis. *Fertility and Sterility* **109**, 398–405 (2018).
45. Petraglia, F. Uterine fibroid: from pathogenesis to clinical management. *Best Practice & Research Clinical Obstetrics & Gynaecology* **34**, 1–2 (2016).

46. Vannuccini, S. *et al.* Uterine Fibroids, Perceived Stress, and Menstrual Distress: a Key Role of Heavy Menstrual Bleeding. *Reprod. Sci.* **30**, 1608–1615 (2023).
47. Munro, M. G., Critchley, H. O. D., Fraser, I. S., & the FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Intl J Gynecology & Obste* **143**, 393–408 (2018).
48. Pavone, D., Clemenza, S., Sorbi, F., Fambrini, M. & Petraglia, F. Epidemiology and Risk Factors of Uterine Fibroids. *Best Practice & Research Clinical Obstetrics & Gynaecology* **46**, 3–11 (2018).
49. *Uterine Fibroids: A Clinical Casebook*. (Springer International Publishing : Imprint : Springer, Cham, 2018).
50. Capezzuoli, T. *et al.* Recurrence of Uterine Fibroids After Conservative Surgery or Radiological Procedures: a Narrative Review. *Reprod. Sci.* (2023) doi:10.1007/s43032-023-01418-2.
51. Donnez, J. & Dolmans, M.-M. Uterine fibroid management: from the present to the future. *Hum. Reprod. Update* **22**, 665–686 (2016).