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MANAGEMENT OF INFERTILITY TODAY

Anatomical causes of female infertility and their management

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ABSTRACT

The main female anatomical causes of infertility include post-infectious tubal damage, endometriosis, and congenital/acquired uterine anomalies. Congenital (septate uterus) and acquired (myomas and synechiae) diseases of the uterus may lead to infertility, pregnancy loss, and other obstetric complications. Pelvic inflammatory disease represents the most common cause of tubal damage. Surgery still remains an important option for tubal factor infertility, with results in terms of reproductive outcome that compare favorably with those of in vitro fertilization. Endometriosis is a common gynecologic condition affecting women of reproductive age, which can cause pain and infertility. The cause of infertility associated with endometriosis remains elusive, suggesting a multifactorial mechanism involving immunologic, genetic, and environmental factors. Despite the high prevalence of endometriosis, the exact mechanisms of its pathogenesis are unknown. Specific combinations of medical, surgical, and psychological treatments can ameliorate the quality of life of women with endometriosis. In the majority of cases, surgical treatment of endometriosis has promoted significant increases in fertilization rates. There are obvious associations between endometriosis and the immune system, and future strategies to treat endometriosis might be based on immunologic concepts.

1. Anatomical anomalies: The most prevalent cause of female infertility?

Anatomical causes of female infertility include tuboperitoneal abnormalities, endometriosis, myomas distorting the uterine cavity, congenital uterine anomalies, and other, less frequent anomalies of the reproductive tract.

Between 25% and 35% of women presenting for infertility evaluation are found to have a tuboperitoneal involvement [1,2], and the most frequent cause of tubal damage is pelvic inflammatory disease (PID). Monitoring data suggest that in the United Kingdom and the United States, PID is diagnosed each year, respectively, in 1.7% and 8% of the women aged from 16 to 46 years; that PID will be diagnosed in 15% of all Swedish women in their lifetimes; and that more than 1 million women living in the United States are treated annually for PID. The prevalence of tubal infertility has been reported to be 12% after 1 episode, 23% after 2 episodes, and 54% after 3 episodes of PID. The authors of a recent review of 24 articles from the United States and several European countries concluded that up to 18% of women in these countries may become infertile after being symptomatic for PID from any cause [3]. In high-income countries, PID is caused mainly by Chlamydia trachomatis infection, which is sexually transmitted [4]. The infection often being asymptomatic, women are unaware of having tubal disease when their medical history is taken. Other identifiable causes of tubal damage include postsurgical adhesion formation or endometriosis (stage III or IV).

A gynecological condition affecting 5% to 15% of women of reproductive age, endometriosis can cause pain and infertility even though 20% to 25% of affected women are asymptomatic. The cause of infertility associated with endometriosis remains elusive, but it certainly involves a multifactorial mechanism that includes immunological, genetic, and environmental factors, with a mechanical factor dominance in the advanced stages of the disease.

Conditions that distort the uterine cavity can be congenital (e.g., a septate uterus) or acquired (e.g., myomas and synechiae), but they can all result in implantation failure, which is manifested by recurrent pregnancy loss or infertility [5]. Congenital uterine malformations may be associated with recurrent pregnancy loss, preterm labor, abnormal fetal presentation, and infertility. The most common malformation, a septate uterus, is associated with the poorest reproductive outcome, with pregnancy losses of more than 60%, and fetal survival rates reported to be as low as 6% to 28% [6,7].

Uterine myomas affect 20% to 50% of women of reproductive age. Submucous or intramural myomas adversely affect fertility, in both natural conception and in vitro fertilization (IVF) [8]. Intrauterine synechiae, or adhesions, may partially or completely obliterate the uterine cavity, resulting in hypomenorrhea or amenorrhea and subfertility. As

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much as 40% of the women presenting with synechiae report in their histories delayed removal of placental tissue or repeated curettage following spontaneous abortion [9]. In some instances, despite all possible effort to reach a diagnosis, the cause of infertility remains unknown.

2. Post-infectious tuboperitoneal causes: Current impact of infertility

Post-infectious tubal damage includes proximal tubal occlusion (PTO), periadnexal adhesions, and distal tubal occlusion (DTO) (Fig. 1). Assessing tubal patency before any fertility treatment is a gold standard intervention for infertile women [10,11]. Tubal patency in women with no history of PID can be evaluated by hysterosalpingography or, when appropriate expertise is available, by hysterosalpingo contrast sonography [11,12]. However, when findings are abnormal, diagnostic laparoscopy should be performed to prevent non-necessary IVF and embryo transfer [13]. On the other hand, laparoscopy is indicated as the primary approach for the evaluation of tubal factor infertility when there is evidence or strong suspicion of endometriosis, periadnexal adhesions, or tubal disease. Laparoscopy should also be seriously considered before applying aggressive empirical treatments involving significant costs and/or potential risks [11].

2.1. Proximal tubal occlusion

Proximal tubal occlusion occurs in 10% of 25% of women with tubal disease [12]. A lack of passage of the contrast medium at the level of the intramural-isthmic portion of the fallopian tube may be due to a true pathological occlusion resulting from post-infectious fibrosis; an obstruction due to technical artifacts, such as adequacy of cervical seal, level of intrauterine pressure achieved; a spasm of the uterine-tubal ostium; the thick endometrium acting as a valve; or plugs of amorphous material of unknown etiology, often appearing to form a cast of the tube [14]. It was reported that in 42% to 95% of cases, women diagnosed as having PTO actually do not have the condition [15,16].

In a retrospective study, Al-Jaroudi et al. [16] evaluated reproductive outcomes in women who underwent selective tubal catheterization following a diagnosis of bilateral PTO. Ninety-eight infertile women with hysterosalpingographic findings of bilateral PTO underwent a second hysterosalpingography before undergoing selective tubal catheterization. Tubal patency was bilateral in 14 and unilateral in 12 of the women, and PTO was bilateral in 72. Recanalization of both tubes was achieved in 25 (34.7%), and recanalization of at least 1 tube in 44 (61.1%), of the 72 women who underwent selective tubal catheterization. Of these, 23 conceived within 24 months of follow-up. The cumulative probability of conception was 28%, 59%, and 73% at 12, 18, and 24 months of follow-up, respectively. The few patients in whom tubal recanalization failed may have had a true occlusion from fibrotic scarring of the tubal lumen caused by salpingitis, endometriosis, or previous surgery. Microsurgical resection of the occluded tubal portion, followed by tubocornual anastomosis of the patent portion of the distal tube to the intramural portion of the tube, is regarded as the standard of care in these cases. Live birth rates of 27%, 47%, and 53% have been reported 1, 2, and 3 years after surgery [17].

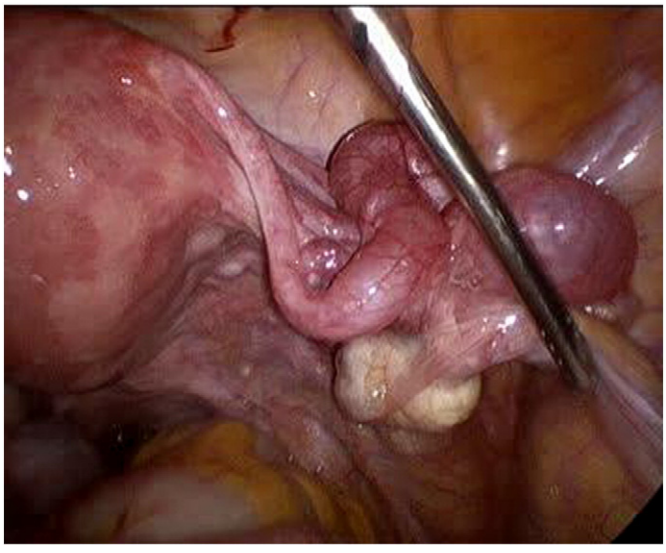

Fig. 1. Distal tubal occlusion of the right fallopian tube with mild periadnexal adhesions.

In a review of 9 case series including a total of 187 patients with PTO, Marana et al. [18] reported a 49% term pregnancy rate per patient, with a 4% risk of ectopic pregnancy after microsurgery by laparotomy. These results compare favorably with the results obtained from IVF [10,18].

2.2. Periadnexal adhesions

Operative laparoscopy is today the gold standard for salpingo-ovariolysis. The intrauterine pregnancy rate after laparoscopic salpingo-ovariolysis in non-selected patients was reported to range from 51% to 62%, and the ectopic pregnancy rate to range from 5% to 8% [10]. Recent prospective studies have demonstrated that the status of the tubal mucosa as evaluated by salpingoscopy (i.e., the direct evaluation of the tubal mucosa by a dedicated, small-caliber endoscope during laparoscopy) is the most important prognostic factor of reproductive outcome after salpingo-ovariolysis. [19–23].

Reports from Brosens et al. [20] and Marana et al. [21–23] indicate that about 80% of patients with periadnexal adhesions have a normal tubal mucosa, that 70% of these patients will have a term pregnancy after laparoscopic salpingo-ovariolysis, and that most of the pregnancies will occur within 1 year of surgery. Since in most patients with periadnexal adhesions the tubal mucosa is preserved, there is generally no need for salpingectomy, unless there is an associated hydrosalpinx with severe tubal damage.

2.3. Distal tubal occlusion

In a review of 10 studies including 1128 patients, Marana et al. [24] reported a cumulative pregnancy rate per patient of 33% for laparotomic salpingoneostomy performed using microsurgical techniques. Of the pregnancies, 77% were intrauterine, 61% were at term, 23% were ectopic, and 15% resulted in spontaneous abortions.

A meta-analysis evaluated 5 nonrandomized controlled studies that compared the results of laparotomic microsurgical tubal surgery and laparoscopic surgery for the treatment of DTO [25]. An intrauterine pregnancy occurred in 138 (28.9%) of the 478 women who underwent the laparotomic procedure and in 104 (30.9%) of the 336 who underwent the laparoscopic procedure. No significant difference was observed in the rate of intrauterine pregnancy occurred between these 2 groups. Moreover, in 3 of the studies, sufficient information was given to compare surgical techniques used at different stages of tubal disease. In the mild tubal disease subgroups, an intrauterine pregnancy occurred in 83 (32.8%) of 253 women who underwent laparotomy and in 96 (39.5%) of the 243 women who underwent laparoscopy. Again, there was no significant difference in the rates of intrauterine pregnancy.

In a report from the Practice Committee of the American Society for Reproductive Medicine [26], live birth rates range from 39% to 59% after surgical DTO treatment for mild tubal disease (which accounts for 25% of the total cases of DTO), with ectopic pregnancy rates of 4% to 10%. The rates of ectopic pregnancy are similar following reconstructive surgery and following IVF (4%–10% vs 1%–13%) [26].

In 2 separate articles, Schippert et al. [27,28] reported on pregnancy rates among women with mild or moderate acquired tubal disease who were treated surgically. The rates for pregnancy at term were 65%, 70%, and 80%, respectively, for those who underwent salpingoneostomy,

adhesiolysis, and reversal of tubal sterilization. The ectopic pregnancy rate ranged from 1% to 10% depending on the tubal disease, and it was less than 10% among women who underwent reversal of tubal sterilization. Following IVF, the rate ranged from 2.1% to 11%.

Moreover, in women undergoing salpingoneostomy or salpingoovariolysis, the status of the tubal mucosa on salpingoscopy is the most important prognostic factor for reproductive outcome after surgery. Studies by Brosens [20] and Marana et al. [21–23] indicate that the percentages of women with DTO who have a normal tubal mucosa range from 35% to 45%, and that 65% of these women will have a term pregnancy after laparoscopic salpingoneostomy. When the tubal mucosa is severely damaged, however, salpingectomy may be a better option. Recently, the authors of the present review have reported on a new, simplified technique for salpingoscopy that they have used in women with DTO, in which a small-caliber hysteroscope is introduced through an accessory trocar at the time of laparoscopy [29].

2.4. Tubal reconstructive surgery vs IVF

Although tubal reconstructive surgery is still performed widely, the treatment of tubal infertility has shifted toward IVF in recent years. However, many couples refuse IVF for ethical, religious, and/or financial reasons. It is important to point out that IVF does not eliminate tubal damage but bypasses it, whereas surgery is curative in women with normal tubal mucosa. These women are then able to conceive naturally and more than once without further treatment, and to experience pregnancy and delivery just like women who never had tubal infertility, without the risks of ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, premature birth, and congenital malformations associated with IVF. The risks associated with tubal surgery are very low and related only to the possible complications of anesthesia and surgery [30], whereas IVF is associated with specific complications, particularly OHSS. This syndrome is a potentially life-threatening effect of ovulation induction. The intravascular depletion associated with OHSS can lead to dehydration, hypovolemia, electrolyte disturbances, and thrombosis due to hemoconcentration. In IVF cycles, the rate of OHSS varies from 1% to 10%, with severe cases occurring in 0.25% to 2% of IVF cycles [31].

In a summary of the procedures and outcomes of assisted reproductive technologies since 2001 and published in 2007 [32], the American Society for Reproductive Medicine registry reports a live birth rate of 27.2% per cycle. Moreover, data published in Europe in 2010 indicate a clinical pregnancy rate of 29.0% per retrieval [33]. The European report has incomplete data for the calculation of a live birth rate per cycle, but a range of 21.0% to 22.5% can be extrapolated. The latest results in Italy [34] indicate a live birth rate of 16.8% per cycle. The proportions of singleton, twin, and triplet deliveries after IVF are 64.1%, 32.0%, and 3.7% in the United States and 79.2%, 19.9%, and 0.9% in Europe. Therefore, compared with natural conception, the major problem associated with IVF worldwide is still the wide occurrence of multiple pregnancies, with rates of premature birth and cesarean delivery higher than normal, in addition to other adverse outcomes [14,35].

With regard to the cumulative pregnancy rates after IVF reported by Sharma et al. [36] (66% following 4 cycles of IVF), it has to be considered that the dropout rates were very high during their study, 74% after the first, 61% after the second, and 69% after the third unsuccessful attempt. Disappointment and psychological stress are the main factors influencing the decision to discontinue treatment after an increasing number of attempts [37].

In recent years, evidence has been accumulated on adverse outcomes of pregnancies conceived via IVF, even of singleton pregnancies [38]. It has been reported that the rates of perinatal mortality, low birth weight, and preterm birth were twice those of pregnancies naturally conceived, and that the risk of birth defects were 30% to 40% greater [38–49]. A Danish study [50] published in 2010 analyzed information about 20 166 singleton pregnancies. After adjusting for maternal age, body mass index, level of education, smoking habits, and alcohol and/or coffee intake during pregnancy, it found the risk of stillbirth to be more than 4 times greater among the women who underwent IVF procedures than among those who conceived naturally.

In conclusion, in spite of the improving outcomes of IVF, tubal reconstructive surgery remains an important option for many couples. Moreover, surgery should be the first-line approach for a correct diagnosis and treatment of tubal infertility. The success of surgical treatment depends on careful patient selection using appropriate diagnostic techniques.

3. Endometriosis in the 21st century

Endometriosis is characterized by the presence of endometrial glands and stroma outside the uterine cavity [51]. It is estimated that 5% to 15% of women of reproductive age have endometriosis. Dysmenorrhea, deep dyspareunia, chronic pelvic pain, abnormal uterine bleeding, intestinal disorders, and infertility are the main symptoms associated with endometriosis [51]. The prevalence of endometriosis is higher among women with chronic pelvic pain or infertility than among women without these symptoms (40%–60% vs 20%–30%) [52]. The gold standard for diagnosis is direct visualization of endometriosis by laparoscopy, which can be confirmed by histologic analysis [53].

Three theories have attempted to explain the etiology of endometriosis, one considering endometriosis to be of embryonic origin [54]; another considering endometriosis to stem from coelomic metaplasia [55]; and the widely accepted theory of retrograde menstruation first presented by Sampson [56], which considers that endometrial fragments are displaced and grow into the peritoneal cavity. Although the pathogenesis of endometriosis and associated pain and infertility remain incompletely understood, treatments aimed at correcting progesterone resistance (e.g., treatments with selective progesterone-receptor modulators) and systemic immune dysfunction have been proposed, as well as treatments targeting angiogenesis, inflammation, neurotropism, and pain transmission, including neuropathic pain [57].

Several authors have attempted to clarify the role of the immune system in women with endometriosis [58,59]. Number and activation of peritoneal macrophages, decrease in cytotoxicity of T and NK cells, increase in the levels of several pro-inflammatory cytokines and growth factors, and changes in cellular immunity facilitate the deployment and growth of ectopic endometrial cells. In turn, these cells promote proliferation, inflammation, and angiogenesis [60–63]. Recent studies have reported the presence of endometrial stem cells in the adult uterus, the menstrual fluid, and endometrial implants outside the uterus. These stem cells could be implicated in the pathogenesis of endometriosis [64].

Endometriosis can be peritoneal, ovarian, or deeply infiltrating [65,66]. In the latter case, endometriosis can infiltrate the rectovaginal septum, retrocervical region, sigmoid, rectum, ureters, and bladder, and the lesions can be greater than 5 mm in depth [67]. The American Society for Reproductive Medicine [68] categorizes the disease as minimal (stage 1), mild (stage 2), moderate (stage 3), and severe (stage 4).

Among tumor markers, cancer antigen 125, which is derived from human epithelial carcinoma, is the most extensively studied. Although it is used as serum marker of endometriosis, it has limited utility in diagnosing endometriosis [69,70]. The main diagnostic developments have occurred in the imaging field, and transvaginal ultrasound is now considered the best imaging method for endometriosis [71–73].

Far from being curative, current therapeutic approaches focus on managing the clinical symptoms of the disease. Combinations of medical, surgical, and psychological treatments can ameliorate the quality of life of women with endometriosis. A variety of medications have been shown to reduce pain, including nonsteroidal anti-inflammatory drugs, oral contraceptives, gonadotropin-releasing hormone agonists, danazol, and progestins [74].

The cause of infertility associated with endometriosis remains elusive. Many possibilities have been investigated, including altered folliculogenesis, ovulatory dysfunction, reduced preovulatory

steroidogenesis of granulosa cells, sperm phagocytosis, impaired fertilization, toxicity against early embryonic development, defective implantation, and alterations within the oocyte [63]. Other abnormalities associated or not with endometriosis, but related to the cervix (cervical stenosis), uterus (acquired and congenital abnormalities), fallopian tubes (PTO and DTO), and pelvis (perifimbrial and peritubal adhesions) should also be taken into account, as they could play a role in a patient's infertility [75].

It is noteworthy that about 50% of the problems related to conception are either caused entirely by the male partner or by both partners. A large of array of examinations are available for diagnosing male infertility, but semen analysis is the most important [76].

The treatment of infertility associated with endometriosis is still a complex clinical issue. Although pain associated with endometriosis can be treated temporarily, medically treating the disease does not seem to treat infertility. Randomized clinical trials and meta-analyses have demonstrated no evidence of effectiveness of medical treatment alone, and no superiority of medical treatment in combination with surgical treatment over surgical treatment alone [77,78]. As to expectant management, there are no randomized clinical trials comparing the results of not treating with those of surgical treatment. However, the very low rates of spontaneous conception in the absence of treatment reported by several studies contraindicate this approach [78]. Surgery, on the other hand, may be efficacious in the management of endometriosis-associated infertility. A recent meta-analysis reported that in cases of infertility associated with milder forms of endometriosis (stages 1 and 2), the conception rates were significantly higher following surgery than following mere diagnostic laparoscopy [79]. In cases of more advanced disease, surgery should be preferred to expectant management even in the absence or randomized clinical trials because it may yield postoperative pregnancy rates as high as 50% to 67% (Fig. 2) [80,81].

Owing to the difficulty of performing randomized studies in this field, there is no consensus about the benefits of surgery compared with those of using reproductive technology to treat infertile women with deep endometriosis. The only randomized study, by Bianchi et al. [82], shows better results after surgery than after IVF with no previous surgery. Further studies are necessary to clarify both the role of deep endometriosis in women with infertility-associated endometriosis and the options for its management. Recently, Darai et al. [83] found that spontaneous pregnancy was more frequent after laparoscopy than after laparotomy for the treatment of severe colorectal endometriosis.

4. Congenital and acquired uterine causes

Congenital uterine anomalies are the most common malformations of the female reproductive tract. Such anomalies, which result from an incomplete fusion of the müllerian ducts, are present in 4% of fertile women [7]. The most common are septate uterus, bicornuate uterus, and arcuate uterus [7]. Unicornuate uterus and didelphys uterus are less frequent.

Uterine malformations may be associated with recurrent pregnancy loss, preterm labor, abnormal fetal presentation, and infertility [6,7]. Although anatomically the less complex, the most common malformation, septate uterus, is associated with the poorest reproductive outcome, with pregnancy losses of more than 60% and fetal survival rates as low as 6% to 28% [6].

The feature common to the most frequent uterine malformations is the presence of a partial doubling (incomplete septum, arcuate uterus, bicornuate uterus), or of a complete doubling (complete septum, didelphys uterus), of the uterine cavity. Whereas the inner contour of a double uterine cavity can be perceived on hysterosalpingography or hysteroscopy, differentiating between the different anomalies can only be made by evaluating the outer contour of the uterine fundus. The latter will be single if the uterus is septate or arcuate, and double if it is bicornuate or didelphys. Traditionally, the outer contour of the uterus has been evaluated by laparoscopy performed concomitantly with hysteroscopy. Less invasive diagnostic techniques, such as magnetic resonance imaging and 3-dimensional ultrasound, have now obviated the need to perform laparoscopy for the diagnosis of uterine malformations. Recently, intraoperative 3-dimentional ultrasound has also been proposed as an adjunctive tool to reduce the risk of incompletely removing the uterine septum during hysteroscopy [84].

Traditionally, the surgical correction of a uterine malformation was indicated after 2 or more spontaneous abortions. As surgery has become less invasive, surgical correction has been performed prophylactically, when no spontaneous abortion has occurred, particularly in women with a septate uterus; and since an association between some uterine malformations and infertility has been demonstrated, surgical correction has also become performed in infertile women. The septate and arcuate uterus can be treated by means of operative hysteroscopy. Hysteroscopic correction of the malformation can be performed with cold scissors or electrosurgery, either monopolar or bipolar, with similar results. Term delivery rates after removal of the septum are reported to be approximately 75% [7]. More complex anomalies, which are generally associated with better reproductive outcome if left untreated, are not treatable by hysteroscopic surgery. If surgery was needed, it would be via laparotomy.

Uterine myomas are the most common benign tumors among women of reproductive age, affecting 20% to 50% of this population [85]. The myomas are classified as submucosal if they distort the uterine

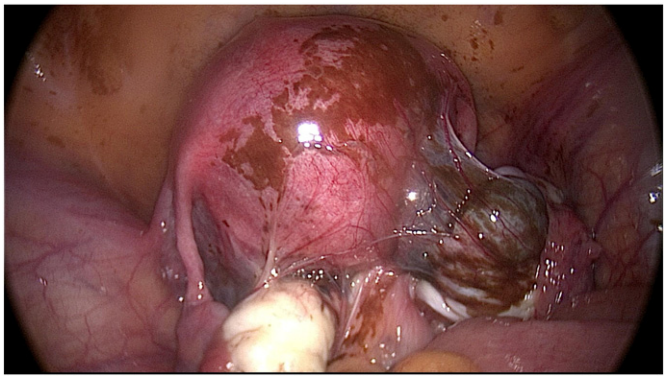

Fig. 2. Severe case of endometriosis, with bilateral ovarian-endometriomal adhesions and obliteration of the cul-de-sac.

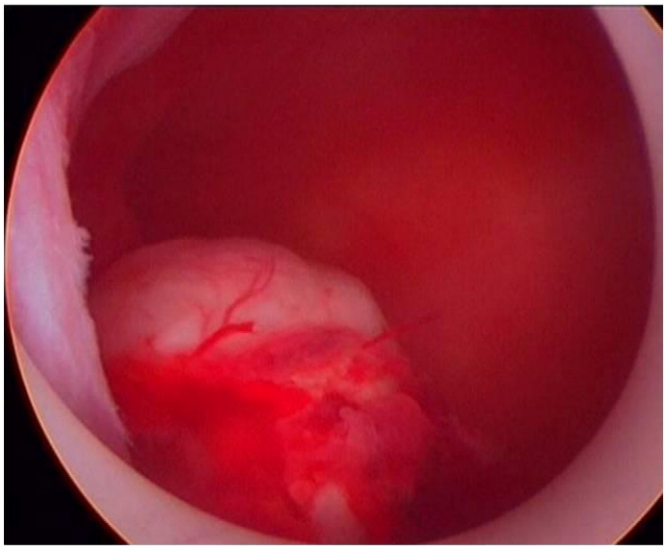

Fig. 3. Submucosal myoma with bleeding visualized during hysteroscopy.

cavity (Fig. 3), intramural if they reside predominantly within the myometrial wall, and subserosal if they protrude out of the uterine surface [86]. The mechanisms by which myomas may affect fertility are the following: displacement of the cervix, enlargement or deformity of the uterine cavity, obstruction of the proximal fallopian tubes, altered tubo-ovarian anatomy, increased or disordered uterine contractility, distortion or disruption of the endometrium and consequently of implantation, impaired endometrial blood flow, endometrial inflammation, and abnormal secretion of vasoactive substances [8,87].

The main factors likely to favor the growth of uterine myomas were identified within the tumors themselves. Estrogen and progesterone receptors, aromatase P450, and estrogen synthetase concentrations vary according to the phase of the menstrual cycle, but are in higher concentrations within myomas than in the surrounding myometrium [88,89].

In most women, uterine myomas are asymptomatic. When symptoms are present, they include abnormal uterine bleeding, dysmenorrhea, pelvic pressure, pain, increasing abdominal girth, urinary or rectal symptoms, and reproductive failure [87]. Transvaginal ultrasound characterizes the size, number, and location of myomas, and the procedure can be useful to determine whether the myoma may be treated hysteroscopically or by the abdominal route [8,87]. Submucous myomas, i.e., myomas growing inside the endometrial cavity, are best treated by operative hysteroscopy. Retrospective and case-control studies have shown that submucosal and intramural myomas that protrude into the endometrial cavity are associated with lesser pregnancy and implantation rates, but that their removal heightens pregnancy rates [90–92].

For larger submucous myomas, treatment with gonadotropin-releasing hormone analogues administered before hysteroscopy may improve the outcome of surgery [93]. Intramural, subserous, and pedunculated myomas are treated by the abdominal route, whether by laparoscopy (when the number and size of the myomas allow an endoscopic approach) or by laparotomy. When fertility is not an issue, and the patient accepts a non-conservative treatment, hysterectomy may be performed instead of myomectomy.

Intrauterine synechiae, i.e., adhesions inside the uterus, may partially or completely obliterate the uterine cavity. The prevalence of this condition in infertile women is about 1.5% [94]. The most common symptoms are menstrual disturbances (hypomenorrhea and amenorrhea) or infertility [9,95]. Repeated curettage following abortions and the delayed removal of placental tissue may be responsible for up 40% of the development of synechiae [96]. The gold standard for determining the presence, extent, and nature of intrauterine synechiae is diagnostic hysteroscopy [97].

The surgical treatment consists in adhesiolysis under hysteroscopic vision. The restoration of normal anatomy, restoration of menstruation, and subsequent pregnancy outcome depend on the initial severity of the adhesions [95,97]. Rates of 3% to 23% have been reported for adhesion recurrence, and the rates are even higher for severe adhesions (20%–62%) [95]. Adjunctive treatments are frequently used, both pharmacological and physical. These are stimulation of the endometrium by estrogen administration; insertion, following surgery, of an intrauterine contraceptive device; insertion of a Foley catheter in the uterine cavity; or newer synthetic barriers that physically separate the walls of the endometrial cavity [9,95,98–100].

5. Perspectives

Congenital and acquired diseases of the uterus may lead to infertility and pregnancy loss. Improvements in diagnostic and therapeutic techniques have prompted better care for women who have a uterine factor of infertility. In women with tuboperitoneal conditions, a better selection of candidates for reconstructive tubal surgery may yield intrauterine pregnancy rates of 65%–70%. Endometriosis is a very complex disease with a great impact on infertility management. Surgical treatment has been associated with significant increases in fertilization rates. Despite the high prevalence of endometriosis and its enormous physical, psychological, and economic burden, the exact mechanisms of its pathogenesis are still not understood. There are obvious associations between endometriosis and the immune system, and future strategies to treat endometriosis might be based on immunological concepts and methods.

Conflict of interest

The authors have no conflicts of interest.

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