Issue 2

Infertility and its management

From genetic mutation screening to minimally invasive IVF

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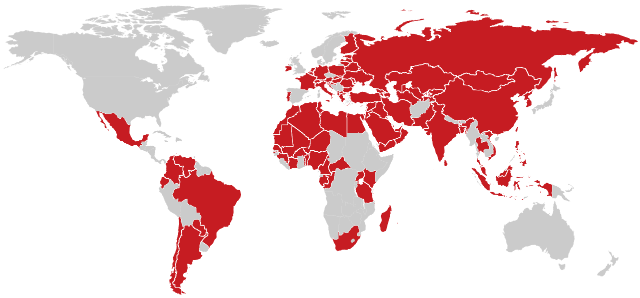

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Contraindications for the use of estrogens when used in combination with dydrogesterone. Warnings and Precautions: Before initiating dydrogesterone treatment for abnormal bleeding, the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. Pregnancy and Lactation: Pregnancy: It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Some progestogens have been reported in the literature to be associated with an increased risk of hypospadias. However due to confounding factors during pregnancy, no definitive conclusion can be drawn regarding the contribution of progestogens to hypospadias. Clinical studies, where a limited number of women were treated with dydrogesterone early in pregnancy, have not shown any increase in risk. No other epidemiological data are hitherto available. Effects in non-clinical embryo-fetal and post-natal development studies were in line with the pharmacological profile. Untoward effects occurred only at exposures which exceeded the maximum human exposure considerably, indicating little relevance to clinical use. Dydrogesterone can be used during pregnancy if clearly indicated. Breastfeeding. No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicates that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period. Fertility: There is no evidence that dydrogesterone decreases fertility at therapeutic dose. Adverse Reactions: The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness. Undesirable effects that are associated with an estrogen-progestogen treatment : Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer • Venous thromboembolism • Myocardial infarction, coronary artery disease, ischemic stroke. Issued on: 3/4/14. Source : Prepared based on full prescribing information (version 03) dated 13/03/2015.

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Preface

According to the World Health Organization in 2012, more than 80 million couples around the world are suffering from fertility problems. Couple infertility has become a social problem that results in isolation, domestic violence, low self-esteem, depression, polygamy, and divorce. Also, infertility is considered as a real disease recognizing its effects on people's health and well-being highlighting that 1 from 6 couples at the reproductive age suffers from infertility problem. Nowadays, the infertility is a big problem for human being, especially for men. The mobility of the sperm does not depend on the number of sperm present in the semen. To avoid infertility, the detection rate of the multi moving sperms is to measured. There are different algorithms utilized for the detection of sperms in the human semen, but their detection rate is not up to the mark.

This book covers some of the important upcoming topics in the area of infertility. The Y chromosome possesses unique characteristics in many aspects. Its role in sex determination and reproductive functions has been widely accepted. More details are provided in the first chapter. The second chapter talks about the importance of CFTR gene mutation and its role in infertility. The third chapter discusses about the place of minimally invasive IVF as an alternative treatment of option for infertility couples. The next chapter talks about the treatment modalities for antisperm antibodies-mediated immune infertility.

Important insights into infertility and how to manage it effectively is the main theme of this book. We hope to touch many lives and help in creating many more lives through this initiative.

Happy reading!

Contents

A novel approach for tracking sperm from human semen particles to avoid infertility

Sumant K. Mohapatra, Sushil K. Mahapatra, Sakuntala Mahapatra, Santosh K. Sahoo, Shubhashree Ray, Smruti R. Dash

Nowadays, infertility is a big problem for human being, especially for men. The mobility of the sperm does not depend on the number of sperm present in the semen. To avoid infertility, the detection rate of the multi moving sperms is to measured. Different algorithms are utilized for detection of sperms in the human semen, but their detection rate is not up to the mark. This article proposed a method to track and detect the human sperm with high detection rate as compared to existing approaches. The sperm candidates are tracked using Kalman filters and proposed algorithms.

Keywords: Sperm tracking, Detection rate, Background subtraction, Multi moving

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Introduction

In the emerging technological world, infertility raises rapidly and destroys life of about 15% human couples [1]. Wenzhong *et al.* [2] and Menkveld *et al.* [3] describes the semen parameter for proper monitoring. Different approaches are utilized to study about semen ability [4–7] to strengthen the human body. Nowadays, different methods are used to know the detection rate of sperms in the human semen to avoid infertility. The proposed method is very efficient for tracking multiple sperm in human semen.

In the paper, Sect. 2 describes the multiple sperm detection and tracking system; Sect. 3 describes the proposed algorithm; Section 4 describes experimental results and discussion and Section 5 describes the conclusion part, respectively.

Multiple Sperm Detection and Tracking

Block diagram of our proposed multiple sperm detection and tracking system is shown in Fig. 1. Background subtraction module is given to camera.

To compute the evidence of sperm presence for each pixel on the image, segmented foreground is used. By locating storage element, the detection of sperm is performed. After detection of sperm candidate, analytical models are computed for each of the candidates. To match sperms we have developed an efficient method. Each tracked sperm is represented by its analytical model and associated by Kalman filter. During matching process candidates are updated.

For background subtraction, a pixel p represents color f(p), represented in rgl space (normalized red, normalized green and light intensity) Each pixel P_i with models, is classified as:

$$\left| f_n(P_i) - m_k^c \right| > d_{th} V_k^c \tag{1}$$

where

d_{th} decision boundary threshold
V_k^c variance in channel c
m_k^c k-th Gaussian mean vector in channel c

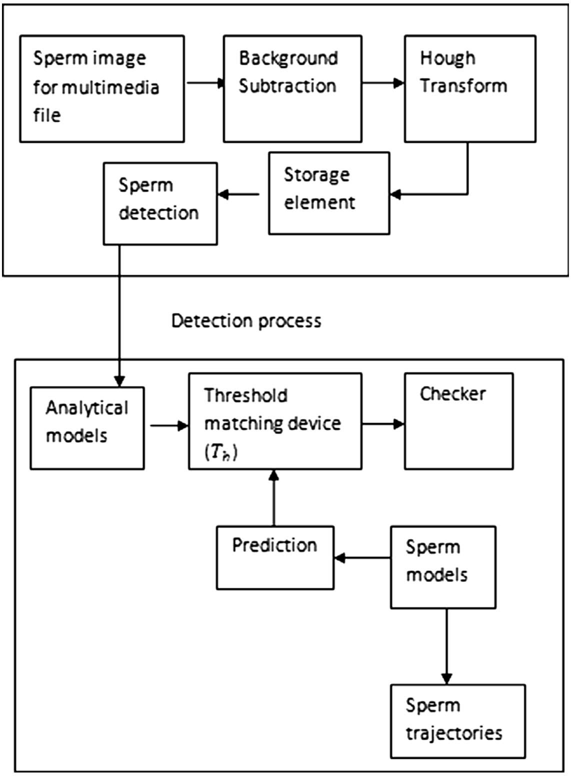

Fig. 1 The proposed sperm tracking system.

$(\mathrm{u} = P_i, \ldots P_n),\ T_h^{(min)},\ T_h^{(max)}$

Where $T_h^{(min)}$ *and* $T_h^{(max)}$ are the minimum and maximum thresholds.

Step 3: If x_i is foreground then $f_i \leftarrow f_i + 1$

Else $f_i \leftarrow f_i - 1$

end if

Step 4: $f_j = i - T_h^{(max.)} P_i$

If $f_j > 0\ T_h^{(max.)} \leftarrow [f_i - f_j]/P_i$

else

$$T_h^{(max.)} \leftarrow f_i/P_i$$

end if

Step 5: If $T_h \geq T_h^{(min)}$

Then $S(P_i) \leftarrow T_h$

Proposed Algorithm

Step 1: Load microscopic video of human sperm.
Step 2: The line segment compute the support by counting sperms contained

Table 1. Output for moving lyme disease tracking in rhesus macaques blood.

Microscopic video	Detection rate (D_r)	Trial time in sec.
Human Sperm Microscopic Video	98.12%	0.011

Where, $S(P_i)$ = Supporting element for $T_h^{(min)}$ and $T_h^{(max)}$ for sperm dimension determination.
Else

$$S(P_i) \leftarrow 0$$

End if, until the value is converged.

Experimental Results and Discussion

This paper used a specific algorithm to detect multi moving sperms in human semen for proper diagnosis. The calculations of detection rate as indicated in Eq. 2.

$$D_r = \frac{T_p}{T_p + F_N} \tag{2}$$

where

T_p detected pixel
F_N undetected pixel

Table 1 shows the output result of the proposed algorithm. From our knowledge, the detection rate of proposed method is higher than the previously used approaches. The detection rate from microscopic view of semen specimen with sperms was satisfactory and for real time implementation which is shown in Figs. 2, 3, 4, 5 and 6.

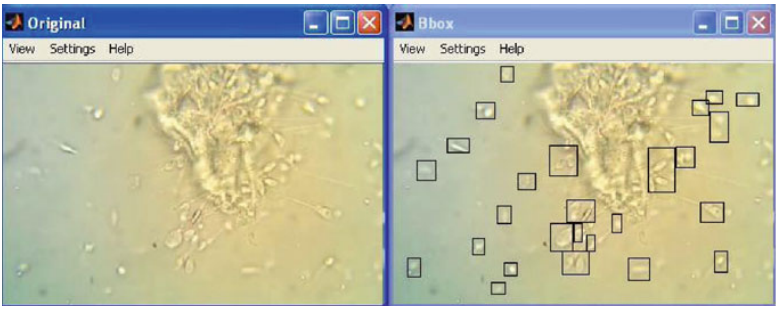

Fig. 2 The 40X detected video.

Fig. 3 The 100X detected video.

Fig. 4 The 350X detected video.

Fig. 5 The 400X detected video.

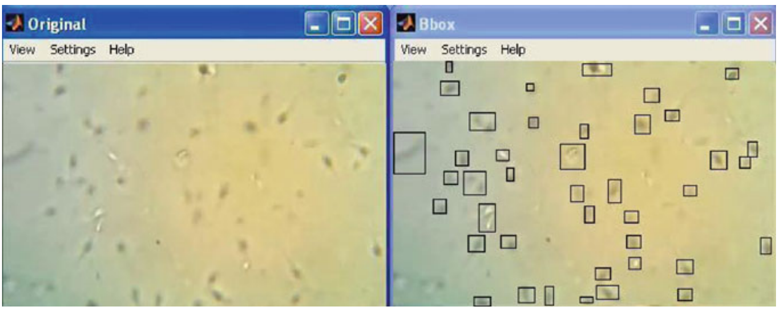

Fig. 6 The 450X detected video.

Conclusion

In this paper, a novel method for tracking sperm is proposed. The utilization of this method is able to track the sperms and detect with high detection rate. The detection rate is higher than the previously existing approaches. So this can be utilized for proper analysis of infertility in future.

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Source: Sumant K. Mohapatra, Sushil K. Mahapatra, Sakuntala Mahapatra, *et al*. A novel approach for tracking sperm from human semen particles to avoid infertility. In: H.S. Behera, D.P. Mohapatra (eds). Computational Intelligence in Data Mining: Proceedings of the International Conference on CIDM, 10-11 December 2016. 1st ed. Singapore: Springer; 2017, pp 415-420. DOI 10.1007/978-981-10-3874-7_38.

Treatment modalities for antisperm antibodies-mediated immune infertility

Rajesh K. Naz

Immune infertility due to antisperm antibodies is an important cause of infertility in humans. The incidence of ASA in infertile couples is 9–36 % depending on the reporting center. ASA directed against the fertilization-related antigens are more relevant to infertility than the immunoglobulin binding to sperm antigens that do not play a role in fertility. Several methods have been reported for the treatment of immune infertility. These include immunosuppressive therapies using corticosteroids or cyclosporine; assisted reproductive technologies such as intrauterine insemination, gamete intrafallopian transfer, in vitro fertilization, and intracytoplasmic sperm injection; and laboratory techniques such as sperm washing, immunomagnetic sperm separation, proteolytic enzyme treatment, and use of immunobeads. Some of these available techniques have side effects, and others are invasive and expensive, with low efficacy, and provide conflicting results. Presently, antisperm antibodies-mediated immune infertility is primarily treated in the clinics using the assisted reproductive technologies. Recent findings on delineating sperm antigens that have a role in fertilization/fertility may provide novel modalities for the treatment which will be less invasive and expensive.

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Introduction

Antisperm antibodies (ASA) can cause infertility. Incidents of antisperm immunity in infertile couples are 9–36 %, depending on the reporting center [7, 15, 40, 54]. ASA reactive with sperm antigens that are involved in fertilization and expressed on the surface for antibody binding are more relevant to infertility. Also, these antibodies have to be present in the genital tract secretions of a female partner or bound on the sperm surface in a male partner in sufficient amount to cause infertility effects. The kinetics, valency, and class/subclass of antibodies play an important role in defining the significance of ASA in infertility.

Although there are several articles written on various aspects of immune infertility, there are only a few, covering the therapeutic treatment modalities for male and female immune infertility. The aim of this chapter is to review the conventional treatment methods for immune infertility, discuss their relative merits and limitations, and describe the recent novel perspectives that are being investigated. The focus of the chapter is on antisperm antibodies-mediated immune infertility and not on pregnancy loss due to immune dysfunction. A PubMed search (1971–2015) was performed using keywords: "immune infertility," "antisperm antibodies," and "treatment of immune infertility." All of the articles were read, and also the articles referenced in these publications were thoroughly examined.

Discussion

Although the understanding of etiology of ASA has increased, the therapeutic measures have not made the same strides [46]. Various treatment methods available at present can be divided broadly into four categories: immunosuppressive therapies, assisted reproductive technologies (ART), laboratory techniques, and novel recent perspectives using defined sperm antigens.

Immunosuppressive Therapies

The method of immunosuppression that has been most commonly used is corticosteroid therapy. Pregnancy rates of 6–50 % have been reported after corticosteroid therapy [56]. However, almost all studies reported in the literature for the effect of steroid treatment on immunosuppression of ASA titers lack appropriate placebo controls, have employed different doses and regimens of various immunosuppressive drugs, and have used different laboratory techniques to monitor the ASA titers to examine the effect of drug treatment. These factors make it difficult to compare and conclude whether or not immunosuppression is indeed effective in the treatment of immune infertility.

Two of the clinical trials had appropriate placebo controls and are worth describing here. One study conducted a 6-month randomized trial using high dose of prednisolone given through cycle days 1–10 of the female partner, which was then tapered rapidly for the next 2 days [27]. The steroid treatment group resulted in a pregnancy rate of 31 % compared with 9 % in the placebo group. Another prospective, double-blind, placebo-controlled study included 43 men that had ASA bound to sperm [25]. Of these, 24 were given methylprednisolone and 19 received placebo for three cycles. There was a statistically significant decrease in sperm-associated IgG, but not IgA, in the steroid treatment group and not in the placebo group. However, in spite of decrease in the antibody titer, there was no statistically significant difference in pregnancy outcome between the two groups.

The efficacy of steroid treatment, if any, must be judged against the potential adverse side effects. The steroid therapy could cause several side effects [55]. The potential adverse effects and lack of effectiveness in many cases have decreased the enthusiasm for the use of steroids for the treatment of immunologic infertility. As an alternative, cyclosporine was tested in a cohort of men with ASA. After treatment, a pregnancy rate of 33 % was observed [9]. Since this study did not have placebo controls, no definite conclusions can be drawn.

Assisted Reproductive Technologies (ART)

Recently, ART have been used to treat ASA. Several studies have examined the use of intrauterine insemination (IUI), gamete intrafallopian transfer (GIFT), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) procedures for the treatment of immune infertility in men and women as discussed below.

IUI Procedure

IUI has been found to be useful for the treatment of ASA-positive infertile men and women. Theoretically, it should circumvent problems related to sperm transport in the female genital tract especially sperm passage through the cervical canal/mucus. However, in women having ASA in the cervical mucus, pregnancy rates after IUI, were identical to women who did not have ASA, if the male partner did not have ASA or male factor infertility [13]. In two other studies of female sperm immunity, IUI treatment did not increase the pregnancy rates per couple or per cycle [23, 37]. However, the pregnancy outcome significantly improved after including the ovarian hyperstimulation treatment along with IUI.

IUI also has been found to enhance pregnancy rates in some cases of ASA positive infertile men. A 56 % pregnancy rate has been reported after IUI procedure in ASA-positive infertile men, who had a poor postcoital test, compared with an 83% pregnancy rate in ASA-negative infertile men, who also had a poor postcoital test [12]. In another study, after IUI, the pregnancy outcomes in 19 couples having male immune infertility were compared with 86 couples having other diagnoses. No pregnancy was seen in 110 IUIs in the ASA-positive group (0 %) versus a 26 % pregnancy rate per couple and 5.6 % cycle fecundity in the control group [21]. From the Cleveland Clinic Foundation, Agarwal compared 42 ASA-positive couples with 117 ASA-negative infertile couples who were treated with sperm washing and IUI over a 2-year period [5]. There were 15 pregnancies in the ASA-positive group compared with 37 for the entire group.

Another study compared IUI with oral steroid therapy [34]. This study included 46 couples in which the male partner had ASA. The immune infertile men either received 20 mg/day of prednisolone for days 1–10 followed by 5 mg/day for days 11 and 12, respectively, of the cycle and timed intercourse or underwent IUI with no steroid treatment for three cycles. The couple was switched to the other group, if not pregnant. The pregnancy rate before switching for the IUI group was 16.7 % and for the steroid group was 0 %. After switching, one more pregnancy occurred in the IUI group and one in the steroid group. This study concluded that IUI is better than low dose steroid therapy for treating male immune infertility.

It is not clear, theoretically speaking, how IUI can circumvent male immune infertility. Washing the sperm in the incubation medium should not elute the antibodies bound to the sperm surface proteins, unless: (a) these antibodies are directed against the adsorbed seminal plasma proteins that are shed-off during capacitation/acrosome reaction, (b) the antibodies are of low binding affinity, which does not seem to be the case in immune infertility, and/or (c) the swim-up sperm used for IUI are not coated with antibodies like non-swim-up sperm, which also seems highly unlikely.

There are mixed reports on simple sperm washing on ASA elution from various laboratories. Adeghe [2] found that washing decreased IgG bound on the sperm surface. Another group [58] did not find the similar positive effects, nor did Haas and associates [26], even after subjecting the sperm to multiple washings. Antibodies were also not reduced by passing sperm through percoll gradient [6].

GIFT Procedure

In GIFT procedure, sperm and eggs are mixed *in vitro* and then transferred to the fallopian tubes for fertilization. Theoretically speaking, there is not a strong rationale to how it will help either the ASA-positive infertile men or women. Nevertheless, in one study, GIFT was performed in 16 immune infertile couples. This group achieved pregnancy rates of 43 % per couple and 24 % per cycle [57]. This study did not include any control group, and the pregnancy rates are comparable to those that are reported after GIFT in patients having other etiologies.

IVF Procedure

Several studies have shown decreased rates of oocyte fertilization in IVF in immune infertile patients [30]. An inverse relationship between ASA, titers and fertilization rates has been reported [19]. In a study, 33 ASA-positive infertile couples were subjected to 47 IVF cycles [32]. The couples with high ASA titers had lower fertilization rates than those with lower ASA titers. In contrast, there are also studies that found fertilization to be identical in ASA-positive and ASA-negative population [17]. Interestingly, there are also studies reporting increased rates of IVF outcome including implantation and pregnancy rates in ASA-positive infertile women compared to women with tubal factor infertility [16]. In IVF procedure, generally albumin instead of female partner's serum is used as a protein source in the insemination medium that circumvents the antibodies if present in the female partner. Thus, theoretically speaking, IVF can take care of female but not male immune infertility. Indeed, fertilization and pregnancies have been achieved using oocytes from ASA-positive infertile women where the men had normal semen analysis and were free of ASA [1, 62]. In ASA-positive infertile men, both the class/subclass specificity and subcellular localization of the antibodies on sperm have been correlated with various degrees of fertilization failure rates in IVF [54]. ASA that bind to the sperm head, may decrease fertilization more than ASA bound to mid piece or tail regions of the sperm cell. In the IVF procedures involving 21 immune infertile couples, it was found that the couples who had ASA bound to the head region of the sperm cell, showed more fertilization failure than those having ASA bound to the tail region [62]. Yeh and associates [59] reported that IgA significantly reduces fertilization rates in IVF procedure only when it was associated with IgM and was present on the sperm head. Equality of embryo obtained after IVF using sperm from ASA-positive men is generally poor compared to sperm from ASA-negative men [33, 36].

ICSI Procedure

IVF with ICSI have become a routine and widely acceptable procedure in the clinics. In ICSI procedure, a single sperm is injected into the cytoplasm of the oocyte. ICSI has been tried using sperm of ASA-positive infertile men. Two of these studies are worth mentioning here. One study subjected 29 infertile ASA-positive couples to ICSI; 22 of them were tested before in IVF procedure and had poor fertilization rate (6 %) [33]. After ICSI, the fertilization (79 %) and cleavage (89 %) rates in the ASA-positive group were similar to those (68 % and 93 %, respectively) in the ASA-negative group. Surprisingly, 46 % of the pregnancies in the ASA-positive group ended in spontaneous pregnancy loss compared with none in the ASA-negative group. In contrast, another study did not demonstrate any difference in pregnancy rates (30 %) between the ASA-positive and ASA-negative group undergoing the ICSI procedure [42].

Recently, meta-analysis was performed to obtain an odds ratio (OR) for the effect of ASA on pregnancy rates using IVF or ICSI [61]. This study analyzed 16 studies (10 IVF and 6 ICSI). The meta-analysis revealed that the combined OR for failure to achieve a pregnancy using IVF or ICSI in the presence of positive semen ASA was 1.22 (95 % Cl: 0.84, 1.77) and 1.00 (95 % Cl: 0.72, 1.38), respectively. The overall (IVF and ICSI) combined OR was 1.08 (95 % Cl: 0.85, 1.38). The meta-analysis indicated that semen ASA are not related to pregnancy rates after IVF or ICSI. However, all these studies ASA were sperm-reactive immunoglobulins, rather than fertility antigens-related antibodies [14, 53].

Postfertilization Effects of ASA

Some antisperm antibodies can have deleterious postfertilization effects on developing preimplantation embryos [3, 4, 38, 44]. ASA can affect early embryonic development if: (a) an oocyte is fertilized with a sperm cell, which carries these specific antibodies into the ooplasm, and/or (b) these antibodies are cross-reactive with the antigens present on the developing embryos. Some of these antigens and antibodies have been characterized, and the cDNA encoding for a few of these antigens has also been cloned and sequenced [29]. Using the ICSI procedure in immunoinfertile men, one can achieve higher fertilization rates than using the IVF procedure; however, the fertilized zygotes show higher degeneration and mortality and decreased embryonic development.

Laboratory Techniques

Several innovative laboratory techniques have been investigated and can broadly be classified into two categories: (1) methods that prevent binding of ASA to sperm or elute the bound ASA from sperm surface and (2) methods that separate ASA-free sperm from ASA-coated sperm. Although these methods have been explored extensively, due to conflicting findings, these techniques have not been accepted as methods for the treatment in the clinics. Some of these reports and their findings are discussed below.

It was erroneously thought that ASA bind to sperm during and/or just after ejaculation and the antibodies are mostly present in the secretions of prostate and seminal vesicles. Based upon this notion, the antibodies and the sperm are present and ejaculated in different fractions of the semen. To avoid binding of antibodies to sperm, splitting the semen into various fractions during ejaculation was attempted in various laboratories. However, it has been proven ineffective in decreasing ASA binding to sperm [35]. Collection of semen into insemination medium containing high concentrations of fetal cord/maternal serum has also been investigated to examine if it would decrease the antibody binding to sperm. Two studies [11, 18] observed that semen collection into serum-supplemented medium results in increased fertilization rates in IVF procedure, and one of these studies also showed an increase in pregnancy rates. We conducted a study to investigate at which site of the male genital tract the antibodies percolate from serum to bind to sperm [49]. I^{125} labelled antibodies to sperm-specific FA-1 antigen were injected, intravenously, into male mice. The results indicate that the antibodies, preferentially, transude into epididymis (especially corpus or caudal regions) and vas deferens to bind to sperm cells and not into testes. These findings indicate that in men ASA bind to sperm before ejaculation via transudation through epididymis, vas deferens, and probably rete-testis.

The immunomagnetic separation technique has been tried to separate the antibodies bound on the sperm surface [20]. The sperm with antibodies are tagged with anti-immunoglobulin antibodies coupled to magnetic microspheres, and then the magnetic field is applied. However, limited success in isolating sufficient number of ASA-free sperm of good motility makes this procedure theoretically interesting but, clinically, an unacceptable procedure.

Bronson suggested that protease treatment may be utilized to destroy antibodies on the sperm surface [10]. Kutteh and associates reported that IgA1 protease treatment was effective in reducing IgA on sperm [31]. In another study, incubation of sperm with chymotrypsin before IUI resulted in a 25 % cycle fecundity versus 3 % in controls [8]. However, this needs to be examined whether or not the treatment with proteolytic enzymes affect proteins especially the oocyte binding receptors present on the sperm surface [28].

The use of immunobeads has been suggested as a treatment to remove the sperm-bound antibodies. It has been reported that simple incubation of ASA-positive sperm from immune infertile men with immunobeads results in a time-dependent decrease in antibody concentration on sperm surface [22] and even enhanced pregnancies [24]. The explanation that the antibodies are removed from the sperm surface after incubation with immunobeads is not widely accepted, and it is generally believed that the immunobeads just select ASA-positive sperm, leaving ASA-free sperm. Theoretically, there is not a strong rationale why and how incubation with immunobeads should elute antibodies from sperm surface.

Novel Recent Perspectives Using Defined Sperm Antigens

Several sperm antigens have been defined from various laboratories that may be involved in fertilization and fertility [45]. Our laboratory showed that one of these, namely, fertilization antigen-1 (FA-1), is an exciting molecule because it is involved in human immune infertility, and thus, will be discussed here.

Immunoelution of Antibodies with FA-1 Antigen

FA-1 antigen is a well-defined novel sperm-specific surface molecule that is evolutionarily conserved on sperm of various mammalian species including humans [50]. Antibodies to FA-1 antigen inhibit human sperm-zona interaction and also block human sperm capacitation/acrosome reaction by inhibiting tyrosine phosphorylation [47, 52]. The cDNA encoding for mouse FA-1 and human FA-1 have been cloned and sequenced [49, 60], and vaccination of female mice with recombinant FA-1 antigen causes a long-term reversible contraception by raising sperm-specific immune response [48].

FA-1 antigen is involved in human immune infertility in both, men and women. The antibodies are found in sera as circulating antibodies and also, locally in genital tract secretions, such as seminal plasma of men and cervical mucus and vaginal secretions of women [39, 43]. The lymphocytes from immunoinfertile but not fertile men and women are sensitized against FA-1 antigen and proliferate on incubation with the antigen *in vitro* [51]. The presence of these antibodies inhibits fertilization in IVF procedure. The involvement of FA-1 antigen in human involuntary immune infertility has been confirmed in several laboratories by leading investigators working in the field of antisperm antibodies. Based upon these findings, a clinical trial was conducted at the University of Michigan Medical School to determine whether immunoadsorption with the human sperm FA-1 antigen would remove autoantibodies from the surface of sperm cells of immunoinfertile men, and thus, increasing their fertilizing capacity [41]. Adsorption with FA-1 antigen increased immunobead-free swimming sperm on an average of 50 % and 76 % for IgA and IgG antisperm antibodies, respectively. The acrosome reaction rates increased significantly and showed improvement in 78 % of the sperm samples after FA-1 adsorption. The IUI of FA-1treated antibody-free sperm resulted in normal pregnancies and healthy babies, indicating that the antigen treatment does not have a deleterious effect on implantation, and embryonic and fetal development. This study needs to be extended to a larger number of ASA-positive infertile men and constitutes an exciting therapeutic modality using well-defined sperm antigens.

Conclusion

In conclusion, although various methods have been tried, none have provided a satisfactory means of treating immune infertility. Almost all methods have yielded contradictory results, with the findings of one clinic, reporting a positive outcome and another contradicting it. This may be due to how immune infertility was defined in one clinic versus another. As discussed earlier, any immunoglobulin that binds to sperm should not be defined as "antisperm" antibody unless it has a functional significance. This, along with the kinetics, valency, titer, class/subclass, and circulating/local nature of the immunoglobulins, plays an important role in defining the significance of antisperm antibodies in the immune infertility. The antisperm antibodies present in a female partner may be bypassed by assisted reproductive technologies such as IVF/ICSI procedures. However, embryos obtained after IVF are of poor quality, and there are more spontaneous abortions/miscarriages after ICSI using sperm from ASA-positive men in several studies. The sperm-bound antibodies present in a male partner are difficult to remove even by using invasive and expensive reproductive technologies. The antibodies have to be of low affinity to elute them from the sperm surface by simple washing techniques. The developing knowledge of local immunity and sperm antigens that have a role in fertility will help to better define immune infertility and develop better methods for the treatment. The animal models immunized with defined sperm antigens will help in elucidating the mechanisms involved in physiology and pathophysiology of immune infertility and may assist to solve the controversy and confusion regarding the significance of antisperm antibodies in infertility and in the development of novel treatment modalities.

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Hysteroscopic management of intrauterine disorders: polypectomy, myomectomy, endometrial ablation, adhesiolysis, and removal of uterine septum

Michelle G. Park, Keith B. Isaacson

Introduction

Hysteroscopy is a minimally invasive and highly accurate means of diagnosing and treating a multitude of intrauterine pathologies. During hysteroscopy, a telescope is inserted, transvaginally, through the cervix and into the uterine cavity. A distention media is used to expand the uterine cavity in order to visualize the endometrium and tubal ostia. Pathology can then be detected and treated with direct visualization.

As the technology has advanced, hysteroscopy has become more accessible to gynecologists both, in the office as well as in the operating room. It has become an indispensable tool for treating fibroids, polyps, synechiae, and congenital uterine anomalies and for performing endometrial ablation procedures.

Many hysteroscopic procedures that were, historically, only performed in the operation theater are now performed in an office-based setting, often without the need for local or systemic anesthesia and often without the use of a vaginal speculum. These vaginoscopic procedures are well-tolerated by the patients and allows for the most rapid return to normal activities.

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Clinical Case

Mrs. F is a 29-year-old with regular cycles that are very heavy in flow who presents two spontaneous miscarriages and persistent bleeding since her third D&C following the last pregnancy 12 weeks ago. She reported no problem conceiving when trying. On her initial visit, a 3-D ultrasound was obtained which showed a uterine septum extending 2/3 down from the fundus to the cervix. The right horn demonstrated a thickened endometrial echo consistent with retained products of conception and on the left there was noted to be a type III 2 cm submucous myoma.

A 5.5-mm continuous flow hysteroscope was the instrument of choice in the office on the initial visit. Normal saline for distention was used to insert the scope vaginoscopically (without the need for a speculum or tenaculum). The hysteroscope was guided. This case demonstrates the value of combined U/S and hysteroscopic approach in an office setting. The patient likely had retained POCs by doing a D&C in the wrong uterine horn. Her early miscarriages could be due to the uterine septum, the myoma, or other unknown causes. Since she is young, it is reasonable to encourage her to conceive spontaneously after 8 weeks post septum repair. Should another miscarriage occur, she will consider a myomectomy.

Indications

The most common indications for the evaluation of the uterine cavity are abnormal uterine bleeding and infertility. Although hysterosalpingography (HSG) and modern ultrasonography are relatively sensitive in detecting intrauterine anomalies, diagnostic hysteroscopy remains the gold standard tool to visualize the cervical canal and uterine cavity. Today, there remains two schools of thought regarding the initial evaluation of the uterine cavity. Many clinicians utilize HSG, transvaginal ultrasonography, and sonohysterography for the initial evaluation. However, gynecologists can proceed directly to diagnostic hysteroscopy in the office or outpatient setting with little or no anesthesia for this purpose. Operative office hysteroscopy allows for a visually directed biopsy of focal lesions and treatment of intrauterine lesions, including endometrial polyps, intracavitary leiomyomas, uterine septa, and uterine synechiae.

Basic Hysteroscopic Hardware

Types of Hysteroscopes

Until recently, all hysteroscopes incorporated an optical system that includes mechanisms to deliver light into the uterine cavity and return the reflective image to an eyepiece or a camera. The most commonly used system is the rigid hysteroscope with an objective lens at the tip offset by 0, 12, 25, or 30 degrees from the horizontal plane. Other systems include the fiber-optic diagnostic single channel flexible hysteroscopes and digital flexible dual-channel hysteroscopes. All hysteroscopes include at least one channel for the inflow of distention media. Continuous flow hysteroscopes incorporate a second channel for the return of distention media and the placement of operative instruments. Since CCD and CMOS camera chips have been miniaturized and less expensive, new hysteroscopes have incorporated the "chip on a stick" and LED light design. This eliminates the need for a light source, and allows the image to be projected directly through an USB port for visualization and image capture.

Resectoscopes are all continuous flow systems that allow the attachment of operative instruments, including monopolar and bipolar electrodes in a variety of shapes. These are 7 to10-mm systems and are more typically utilized in the operating room setting. All resectoscopes incorporate a rod lens system for light delivery and image return.

Since the publication of the last edition of this text, intrauterine tissue shavers have become available in small sizes (6.5 mm O.D.) appropriate for hysteroscopic polypectomies and more larger robust designs for hysteroscopic myomectomies. One of the shavers combines bipolar and mechanical energy but most are purely mechanical. In general, this technology is far more expensive than resectoscopic RF systems but this may change with time. The other drawback for myomas is their inability to easily remove the intramural portion of submucous myomas.

Distention Media

The uterine cavity is a potential space that must be distended with either gas or fluid media in order to visualize the endometrium and intrauterine pathology in three dimensions. Each distention media has its own advantages and disadvantages.

Low-Viscosity Fluids

Low-viscosity fluids are the most common distention media used today because they are suitable for both diagnostic and operative hysteroscopy, are relatively inexpensive, and are relatively low-risk to use. The two groups of low-viscosity fluids are isotonic electrolyte-containing fluids and nonelectrolyte media that may be hypotonic or isotonic.

Isotonic electrolyte-containing fluids can be used for all operative procedures except those that require monopolar electrosurgery. Two commonly used fluids are 0.9% sodium chloride and acetated lactated Ringer's solution. Nonelectrolyte media is required for monopolar electrosurgery (i.e., resectoscopic) procedures.

When electrolyte-containing solutions are used (e.g., saline), the procedure should be discontinued when a fluid deficit of 2500 mL is reached. The patient may require a diuretic, if this fluid deficit is higher.

Hypotonic nonelectrolyte-containing fluids are required when the monopolar resectoscope is used, and several types are available. The most common fluids used are 5% mannitol, 3% sorbitol, and 1.5% glycine. The theoretical advantage of 5% mannitol is that it is isotonic, which, in theory, may reduce the risk of cerebral edema with excessive absorption [1]. Excessive absorption of all electrolyte-free media can lead to hyponatremia and its potentially life-threatening complications. Sodium levels fall 10 mEq/mL for every 1 L of electrolyte-free media absorbed.

When a fluid deficit of 1000 cm^3 of nonelectrolyte solution is identified, electrolytes should be drawn and the case should be terminated. Consideration should be given to administer diuretics with close monitoring of electrolytes following surgery. Injection of 3–4 mL of dilute vasopressin (10 units in 200 mL saline) into the cervix prior to the distention of the cavity can decrease both, intraoperative bleeding and intravasation for at least 20–30 min [2].

Carbon Dioxide

Carbon dioxide is less commonly used today and is only appropriate for diagnostic procedures.

Dextran 70

One of the first fluid-distention media used was high-viscosity hypertonic dextran 70. A 32% solution of dextran 70 in 10% dextrose in water is a nonelectrolytic, nonconductive fluid with syrup-like consistency that can be used for both, diagnostic and operative hysteroscopy. It is rarely used today as hysteroscopic distention media because of higher rates of allergic reactions and hypertonic-associated problems, including pulmonary edema [3].

Diagnostic Hysteroscopy

Diagnostic hysteroscopy is used to examine the intrauterine cavity. Patients should be on suppressive hormones or have the procedure timed to occur during the proliferative phase of their menstrual cycle in order to improve visualization. Diagnostic hysteroscopy can be performed in the office setting or the operating room, depending on the level of discomfort the patient experiences during the procedure.

Usually, diagnostic hysteroscopy can be performed in the office setting without the need of any analgesia or anesthesia. Narrow, rigid, and flexible hysteroscopes generally have diameters <4 mm that can be inserted with minimal discomfort to the patient. If the patient experiences discomfort, oral analgesics may be required, and if cervical dilation is necessary, a paracervical block may also be placed.

It is important to insert the hysteroscope slowly and under direct visualization of the canal so that a false channel is not created and uterine perforation can be avoided. In order to allow for controlled insertion of the hysteroscope, some patients may require cervical softening prior to hysteroscopy. Misoprostol is most commonly used for cervical softening. Vaginal misoprostol (200–400 mcg) can be given 8–12 h before surgery, or oral misoprostol (400 mcg) can be given 12 and 24 h before surgery. This should only be used if cervical stenosis is documented since routine use can lead to a cervix that is too soft and cannot maintain distention. If a patient is menopausal, the misoprostol is only effective after vaginal estrogen has been administered.

Once the uterine cavity is entered, visualization of landmarks is critical. A panoramic inspection of the endocervix, lower uterine segment, endometrial cavity, and tubal ostia should be performed as the hysteroscope is inserted. A careful, thorough survey is necessary so that pathology is not missed. Myomas of the endocervix and lower uterine segment can easily be missed with too rapid insertion of the hysteroscope.

Operative Hysteroscopy

For operative procedures, larger hysteroscopes and resectoscopes are used that require cervical dilation prior to insertion and, are therefore, used primarily in an operating room under sedation or with general or regional anesthesia.

Complications

The overall complication rate associated with hysteroscopy is reported to be 2.7% [4]. The operative complications of hysteroscopy include uterine perforation, excessive hemorrhage, air embolus, pulmonary edema, pelvic organ injury secondary to thermal damage if electrode surgical systems are used, excessive fluid absorption, major vessel injury, intrauterine scar formation, and infection [5]. The different procedures described below carry all these risks to varying degrees, depending on the pathology being treated and the equipment being used. These complications are, more or less, likely depending on the procedure being performed. For example, perforation is more likely during adhesiolysis of severe Asherman's syndrome, and fluid overload is more likely in procedures that require incisions deep into the myometrium, exposing the uterine venous sinuses, as in hysteroscopic myomectomy.

Office Hysteroscopy

Office hysteroscopy is the gold standard tool for the evaluation of intrauterine pathology. While it has been available for over 20 years, it has recently become more commonplace due to the improved technology, improved reimbursements, and patients' desire to avoid general anesthesia and the operating room setting. Also, there have been advances in office-based hysteroscopic procedures such as tubal occlusion for sterilization that increased awareness of this valuable tool for providers and patients.

Patients are able to undergo the procedure with minimal discomfort, most often with no or minimal oral and local analgesia.

When performing any procedure in the office setting, the clinician must be especially cognizant of possible complications of hysteroscopy given the limited resources available to manage any complications that may be encountered.

Office hysteroscopy is an effective and well-tolerated alternative to day-surgery hysteroscopy. One study randomized 40 women requiring polypectomy into either office hysteroscopy or day surgery hysteroscopy. The results demonstrated that the office hysteroscopy subjects experienced minimal pain during the procedure and had faster recovery times and lower postoperative analgesia requirements than the subjects who underwent day-surgery hysteroscopy. Ninety-five percent of women who underwent office hysteroscopy stated they would repeat outpatient hysteroscopy if their polyps recurred. Eighty-two percent of women who underwent day-surgery hysteroscopy stated that they would like to try office hysteroscopy if their polyps recurred [6]. Several studies, such as these, have demonstrated the safety and significantly lower cost of office hysteroscopy when compared to day surgery [6, 7]. Additionally, it seems that patients are well able to tolerate these hysteroscopic procedures in the office and they have the added benefit of avoiding general anesthesia. Given all of these benefits, clinicians should give serious thought to develop facilities for office hysteroscopy if they are lacking and promoting office hysteroscopy to their patients when appropriate.

Equipment

The two categories of hysteroscopes used in the office setting are rigid and flexible. Generally, the hysteroscopes used for office hysteroscopy range from 3 to 5 mm in diameter. Larger operative hysteroscopes that are 8–10 mm in diameter are generally reserved for the operating room because they require significant cervical dilation, which can be very uncomfortable for the patient. When diagnostic hysteroscopy is performed, the hysteroscopes are introduced without the operative sheaths so as to decrease the diameter of the hysteroscope and minimize trauma to the cervical canal. Rigid hysteroscopes may be used, which are 2.7–5 mm in outer diameter. Zero-, 15-, or 30-degree hysteroscopic lens are appropriate for diagnostic hysteroscopy. If the cervical canal is tortuous or the uterus is especially anteflexed or retroflexed, flexible hysteroscopes are generally superior to rigid hysteroscopes. They have the added advantage of having a tip that can deflect from 0° to 110° and curve with the natural course of the endometrial canal.

If operative procedures are planned in the office, operative sheaths must be used, which increase the diameter of the hysteroscope system to approximately 4–5 mm. These outer sheaths are needed to accommodate the instruments and provide an outflow of fluid, making the hysteroscope a continuous flow system with both, an inflow and outflow channel. The inflow channel is essential for appropriate distention of the uterine cavity, and the outflow channel is used to flush out any blood and debris that may accumulate, thereby, improving visibility.

The standard operative tools available in the office setting include cold scissors, biopsy cups, and graspers. Recent technologic advances have also made bipolar electrodes available for use in the office. These 5-Fr electrodes are small enough to pass through any standard operative port of the 5-mm office hysteroscope. Additionally, because they are bipolar electrodes, physiologic electrolyte-containing distention media can be used without dissipating the energy generated at the end of the electrode.

Technique

The traditional approach to office hysteroscopy involves the use of a speculum to visualize the cervix and a tenaculum to grasp the cervix and provide traction to straighten the cervical canal. Although this approach may be necessary for some patients when a difficult entry is encountered, in a vast majority of patients, the clinician may dispense with the speculum and tenaculum by traversing the vagina via vaginoscopy. Bettocchi *et al.* have shown that hysteroscopy can be performed very successfully with this technique, while decreasing the amount of pain experienced by the patient [8].

With this technique, the hysteroscope is placed just inside the vaginal canal and the distention media is instilled. The vaginal walls distend, allowing the clinician to advance the hysteroscope through the vaginal canal under direct visualization and without causing trauma to the walls.

The hysteroscope is directed along the posterior wall of the vagina until the posterior fornix is reached. It is then pulled back slightly and angled upward until the cervical os is visualized. The hysteroscope can then be introduced into the cervical os, which then distends the endocervical canal. With the inflow distention media on low flow, the hysteroscope is guided through the canal under direct visualization so that the clinician may follow the natural course of the canal with minimal trauma to the surrounding tissue. Unless cervical stenosis is encountered, this procedure can be performed with minimal discomfort to the patient. In many cases, no analgesia or anesthesia is required.

Pain Management

With appropriate pain management, office hysteroscopy is successful in 90–95% of cases [9, 10]. Many patients are able to tolerate hysteroscopy without any analgesics or anesthetics, especially when the vaginoscopic technique is used. However, if the patient experiences significant discomfort, the clinician should be armed with tools to manage the patient's pain so that the hysteroscopy can be completed successfully.

NSAIDs and Anxiolytics

Patients can be pretreated with nonsteroidal antiinflammatory drugs (NSAID) so that prophylactic pain management can be initiated before the procedure has even begun. Patients should be told to take NSAIDs 1–2 h prior to their procedure. The patient may take this orally before arriving at the office, or it may be administered at the office in the form of IM ketorolac once they arrive. Anxiolytics may also be administered to calm the patient; lorazepam is usually the drug of choice.

Topical Analgesia

Lignocaine spray of 30, 50, or 100 mg to the cervix and cervical canal was shown to decrease pain at the time of insertion of the hysteroscopy, and it was also shown to decrease vasovagal reactions [11]; 25 mg of lignocaine cream with 25 mg of prilocaine, administered to the cervix, was shown to have the same benefits. There have not been many studies in support of this method of analgesia. However, given the current data, topical analgesia is a reasonable option to reduce patient discomfort.

Paracervical Block

If cervical dilation is required, a paracervical block may be performed to minimize patient discomfort. In most studies, paracervical block was performed by placing 10 mL of mepivacaine or lidocaine via a 22-gauge spinal needle at 3, 5, 7, and 9 o'clock positions, paracervically. The studies are conflicted regarding the efficacy of the paracervical block. Some studies showed no significant difference in pain scores between groups, while an equal number of other studies showed a statistically significant decrease in pain overall [12]. In one study, patients were randomized into injections of lidocaine or saline. There was an improvement in pain at insertion of the hysteroscope in the group with lidocaine, but patients commented that the injections were as painful as the hysteroscopic procedure. Transcervical and intracervical blocks have not been shown to be effective [12]. It is imperative that the surgeon placing the paracervical block be aware of the maximum dose of the local anesthetic based on the patient's weight as well as signs of allergy. Protocols should be in place to prevent, recognize, and treat these events, should they occur.

Conscious Sedation

Conscious sedation is characterized by decreasing the patient's consciousness while allowing them to maintain their own airway. They are usually still able to respond to physical and verbal stimuli. Because the effects of the narcotics may be unpredictable, the patient's vital signs must be continuously monitored. Typical agents used for conscious sedation are fentanyl, propofol, and midazolam. Antiemetics may also be infused to counteract the gastrointestinal upset caused by the narcotics.

There are several requirements, outlined by the American Congress of Obstetricians and Gynecologists, which an office must fulfil in order to safely perform conscious sedation in the office setting [13]. The patient's oxygenation must be monitored continuously; this is most commonly done using pulse oximetry. If deeper sedation is administered, the patient's ventilatory function should also be monitored by direct observation, auscultation, or capnography. The patient's circulatory function should be monitored with a continuously displayed electrocardiogram, blood pressure and heart rate measurements every 5 min, and pulse plethysmography. Anesthesiologists or nurse anesthetists must be present to monitor the patient during conscious sedation. Gynecologists may administer conscious sedation after undergoing certification. However, they must keep in mind that an additional health-care professional must be present whose sole responsibility is that of monitoring and attending to the patient. The clinician must also be certified in ACLS, PALS, or BLS and must be sufficiently free after the procedure is performed to monitor the patient until stable for discharge.

Respiratory suppression is a significant concern when administering conscious sedation. The office must have all the equipment necessary to manage complications from the respiratory suppression. An oxygen source must be present, as well as suction, resuscitation equipments including a defibrillator, and emergency medications. This equipment must be maintained and tested according to manufacturer's specifications. If any of these requirements are lacking, conscious sedation is not recommended.

Patient Selection

Several factors must be considered when determining if a patient is a reasonable candidate for office hysteroscopy. First and foremost, a thorough history must be taken of the patient. The patient should be screened for significant comorbid conditions compromising her ability to tolerate the stresses of hysteroscopy. If a history of severe anxiety for example, the patient should be considered for day-surgery hysteroscopy [14].

In terms of the pathology that can safely be treated in the office setting, clinicians should consider what the patient will be able to tolerate and be wary of what complications can, potentially, be encountered. Appropriate procedures include diagnostic hysteroscopy, endometrial biopsies, lysis of adhesions, small polyps, tubal occlusion, and global endometrial ablation. These procedures are appropriate because they are relatively short, so that the patients will be able to tolerate them, and they have very low-risk of complications.

Any procedure requiring lengthy operative time (>15 min) is not suggested for an office-based procedure. The operating room is more appropriate in order for the patient to remain comfortable. Myomas or polyps larger than the internal os of the cervix (>1 cm) as well as extensive lysis of adhesion and large septum resections are more appropriately and safely done in the operating room.

Complications

Fluid Intravasation

Complications may be encountered regardless of the type of distention media used. A complication that may be seen, regardless of the type of distention media, is fluid overload, which occurs in approximately 0.2% of cases [15]. This is seen when there is a significant intravasation of the distention media. To prevent this from occurring, intrauterine pressure should be maintained at the lowest possible pressure while still maintaining adequate intracavitary visibility. Ancillary staff should be available to aid the clinician with the procedure and monitor the fluid deficit closely. If there is an evidence of rapid intravasation of distention media, the procedure should be terminated. Clinicians should be especially cautious when performing lysis of adhesions, myomectomies, resection of septums, or any other procedures that may open vascular channels and potentiate intravasation.

For isotonic electrolyte-containing solutions, the maximum deficit in an office setting should not exceed 1000–1500 mL. If these deficits are surpassed, the patient should be monitored and the procedure terminated. There is no place to use electrolyte-free media in an office-based setting.

However, in most cases, procedures done in the office should be relatively quick, and fluid deficits should not be approaching maximum levels. Hysteroscopic procedures should be discontinued at lower fluid deficits than the thresholds described above, given that there is a limited acute care available in the outpatient setting [14]. Therefore, if a long operative time is anticipated for a procedure, it may be better to schedule it for the operating room where the patient can be monitored closely as the fluid deficit increases.

Perforation

The most frequently reported complication of hysteroscopy is uterine perforation, which occurs at a rate of 14.2/1000 procedures according to a survey conducted by the American Association of Gynecologic Laparoscopists in 1993 [15]. These perforations commonly occur during the dilation of the cervix, as well as during the hysteroscopic portion of the procedure. Perforations of the lower uterine segment and fundus of the uterus may be seen. In most cases, no treatment is required. However, if there are signs of intra-abdominal bleeding, such as when there is a lateral perforation through major vessels, the patient should be transferred immediately for laparoscopic exploration with possible repair of the defect. Management of perforation with an activated electrosurgical device also warrants emergent surgical evaluation. These thermal injuries usually occur when clinicians are activating the electrodes while moving them away rather than towards themselves. Additionally, certain procedures such as lysis of adhesions and resection of septums have much higher rates of perforation than other hysteroscopic procedures [16, 17]. Therefore, clinicians should be especially cautious when performing these procedures in the office.

Vasovagal Reaction

A vasovagal reaction is not uncommon in office hysteroscopy. One study reported a rate of 0.72% in patients undergoing hysteroscopy without analgesia [18]. Smaller hysteroscopes and improved pain control were shown to decrease the rates of vasovagal reaction [19]. A vasovagal episode is generally preceded by a feeling of light-headedness, nausea, diaphoresis, bradycardia, and/or pallor. If these symptoms are encountered, the procedure should be immediately terminated and patient should be placed in Trendelenburg position or with her legs raised. Her vital signs should be monitored closely, and an intravenous fluid bolus may be necessary. In most cases, patients recuperate quickly with these interventions. If a patient has known history of vagal reactions, one can pretreat with 0.4 mg of atropine IM prior to the procedure.

Bleeding

Most bleeding encountered during hysteroscopy is self-limiting. However, persistent bleeding may be encountered. This can be seen when the cervical canal is lacerated during dilation, after uterine perforation, or when vessels in the myometrium are transected, such as when clinicians are performing myomectomies or septum resections. If persistent bleeding is seen, electrocautery is most often ineffective. The primary treatment should be a Foley catheter placed into the cavity to tamponade the bleeding [20]. The Foley catheter is placed into the cavity and inflated with 15–30 mL of water until the bleeding stops [21]. If persistent bleeding is encountered despite these measures, more aggressive exploration in the operating room may be warranted.

Hysteroscopic Polypectomy

Symptomatic polyps are generally characterized by abnormal bleeding, postcoital staining, chronic vaginal discharge, or dysmenorrhea. Abnormal bleeding symptoms include intermenstrual spotting or heavier menstrual flow. There is a good evidence that polyps can decrease fertility and that their removal will improve the chances of pregnancy [22].

It is obvious that symptomatic endometrial polyps should be removed. However, it is also important to remove asymptomatic polyps, particularly in postmenopausal women [23]. Although the vast majority of polyps are benign, endometrial cancer and hyperplasia will be found in approximately 2% of endometrial polyps and are associated with coexisting malignancies elsewhere in the endometrium. In one study of over 1400 polyps, endometrial cancer was found in 27 polyps (1.8%) [23]. All, but one of these women, were postmenopausal, and only 26% were asymptomatic.

Technique

Polyps can generally be removed with hysteroscopic scissors and pulled through the cervical canal intact. Larger polyps, with thick stalks, require resection with morcellation, most often with a resectoscope so that the tissue can be removed piecemeal. More recently, mechanical hysteroscopic morcellators have been increasingly used to manage both polyps and fibroids. A variety of morcellators are available, and each utilizes an electromechanical drive system to power a cutting blade inserted into a metallic cylinder. A vacuum is created that suctions the polyp into the cylinder, and the tissue is collected via the outflow tract.

Of the various methods described above for removing polyps, none have been shown to be more safe or effective than another, though there is a significant increase in the cost of the procedure if disposable devices are used. The choice of equipment should be based on the surgeon's preference when cost, safety, and efficacy are taken into account.

Hysteroscopic Myomectomy

Patients with symptomatic myomas generally present with abnormal uterine bleeding (i.e., menorrhagia), infertility, pelvic pain, or pressure. When determining the optimal surgical approach for their removal, it is important to determine the fibroid location in relation to the endometrial cavity. Fibroids can be described using the European Society of Hysteroscopy classification system, which groups fibroids into types based on the degree to which the myomas intrude into the endometrium and myometrium (Table 1).

Classification

Type 0 myomas are pedunculated, with the myoma lying completely within the endometrial cavity (Fig. 1). Type I myomas are described as "sessile" with <50% intramural extension (Fig. 2). Type II myomas are submucosal in location, with >50% intramural extension. These include transmural myomas, which extend from the submucosal to serosal edge.

Table 1. Hysteroscopic and sonohysterographic classification system for myomas encroaching upon the endometrial cavity.

Hysteroscopic type [24]	Sonohysterographic class [25]	Description
Type 0	Class 1	Pedunculated myomas, where 100% of the myoma lies within the endometrial cavity with no intramural extension
Type I	Class 2	Sessile myomas, with <50% intramural extension
Type II	Class 3	Submucous myomas, with >50% intramural extension

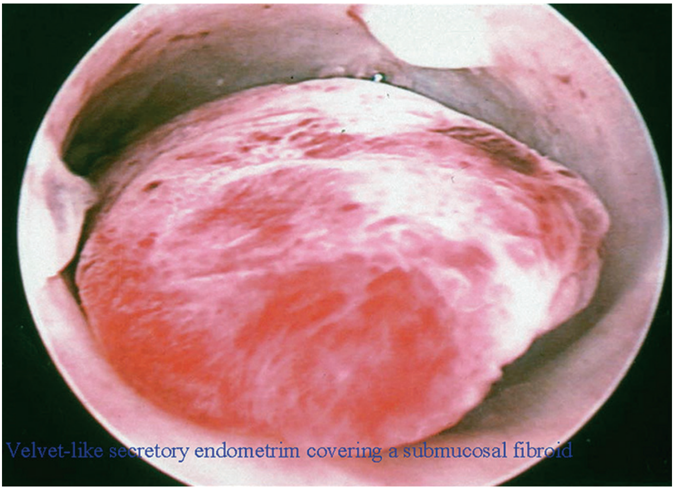

Fig. 1 Hysteroscopic view of a type 0 myoma. It is pedunculated, and the total myoma lies within 100% of the endometrial cavity (reproduced with permission from Bradley LD. In: Hurd WW, Falcone T, eds. Clinical reproductive medicine and surgery. St. Louis, MO: Mosby/Elsevier; 2007).

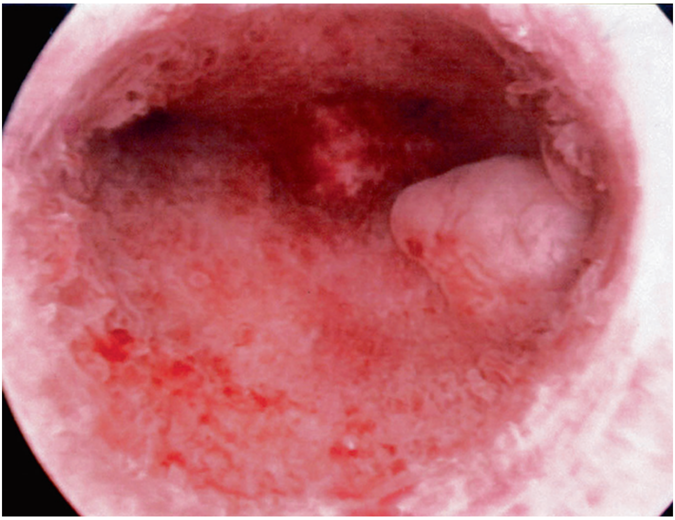

Fig. 2: Hysteroscopic view of a type I myoma that involves less than 50% of the myometrium (reproduced with permission from Bradley LD. In: Hurd WW, Falcone T, eds. Clinical reproductive medicine and surgery. St. Louis, MO: Mosby/Elsevier; 2007).

When viewed hysteroscopically, type II myomas form a bulge that can be seen in the endometrial cavity.

This system was originally designed to classify myomas exclusively on hysteroscopic appearance. However, this approach has significant limitations. During hysteroscopy, myomas can be compressed and recede into the myometrium as a result of the pressure of the distention media, thereby, preventing full visualization of the myoma. For this reason, preoperative evaluation with ultrasonography is required to accurately determine how many myomas are present and how deeply the myomas penetrate the myometrium. Magnetic resonance imaging (MRI) can also be used for this purpose.

Surgical Approach According to Stage

For a successful surgical outcome, it is important to preoperatively identify the size, number, location, and intramural extension of uterine myomas. These characteristics predict the surgeon's ability to completely resect the fibroids during one surgical procedure. Most often, when there is a large type II myoma, the procedure has to be terminated prior to the completion due to excessive fluid absorption [26].

The degree of surgical difficulty and, thus, the risk to the patient are related to the depth of penetration and size of the myomas. Pedunculated hysteroscopic type 0 (class 1) myomas up to 3 cm in diameter can usually be easily removed hysteroscopically. Larger hysteroscopic type 0 myomas (>3 cm) and hysteroscopic type I (class 2) myomas can also be approached hysteroscopically. However, the risk of fluid intravasation increases as a result of increased surgical time and the opening of myometrial venous channels during resection. Additionally, there is poorer visibility with larger myomas given the more limited space within the uterus, inability to distend the cavity well, and the large amount of myoma "chips" that accumulate within the cavity. Often, incomplete removal of larger myomas requires two or more separate operative procedures. Only the most experienced hysteroscopist would attempt a hysteroscopic resection of an intracavitary myoma 5 cm or larger.

Likewise, hysteroscopic resection of type II (class 3) myomas should only be approached by high volume hysteroscopists. They are more commonly approached, abdominally, by laparoscopy or laparotomy.

Hysteroscopic removal of type II myomas is also associated with a greater risk of fluid intravasation and uterine perforation and commonly requires two or more procedures for complete removal.

When patients have multiple intracavitary fibroids throughout the endometrial cavity, they would benefit from a "two-staged" operative hysteroscopic myomectomy, in which myomas are removed from only one uterine wall at a time. This is to decrease the risk of apposition of the uterine walls and the development of postoperative intrauterine synechiae.

Technique

There are various techniques for removing pedunculated and submucosal myomas, including avulsion, scissors, wire-loop resection with bipolar or monopolar equipment, morcellation, and laser vaporization. However, hysteroscopic wire-loop resection still remains the most popular method of removing myomas and will be the technique discussed in this section.

When monopolar energy is used for wire-loop resection, the current setting should be 60–80 W cutting current and requires an appropriately sized grounding pad. Higher settings may be necessary with very fibrous, dense, or calcified myomas. When the bipolar generator is used, it automatically adjusts the power to default settings.

Once the submucosal myoma is identified, the wire-loop electrode is advanced in clear view and retracted towards the surgeon behind the myoma. As the wire loop is drawn towards the surgeon, small, crescent-shaped "chips" or fragments of myoma are created. The whorled fibrous appearance of the myoma is clearly different from the fascicles of soft underlying myometrium. The fibrous tissue should be methodically resected until the border of the underlying myometrium is reached. However, increased bleeding from the myometrial bed and fluid intravasation may be encountered if the myometrium is breached. The resecting loop should stay within the pseudocapsule of the myoma and not cut this myometrium. If the hysteroscopist stays within the pseudocapsule, the likelihood of an uterine perforation will nearly be zero.

Myoma chips can remain free-floating until they interfere with visualization and are then removed with polyp forceps, Corson graspers, suction curette, or with the loop itself under direct visualization. All free-floating tissue fragments should be removed and sent for histologic examination.

Removing all free-floating tissue also prevents delayed vaginal extrusion of this tissue material, malodorous discharge, adhesions, and infection.

Intermittently throughout the procedure, the intrauterine pressure should be lowered to 30 mmHg or the least amount of pressure that is possible while still maintaining visualization. This rapid reduction in intrauterine pressure will aid in enucleation of the myoma via a decompression mechanism that releases the encapsulated myoma from its myometrial bed. The myoma may appear to increase in size. In fact, more myoma protrudes into the endometrial cavity allowing a more complete resection without having to resect myometrium. False-negative views can occur during hysteroscopy because of the high intrauterine pressures. The "disappearing phenomena" refers to the flattening of endometrial polyps or fibroids, resulting in a falsely negative hysteroscopic study. This disappearing phenomenon can be avoided by decreasing the intrauterine pressure at the end of the procedure and re-inspecting the endometrial cavity. As a general rule, the distention pressure within the uterine cavity should be the lowest pressure that gives the surgeon adequate flow and visualization. This will allow the myoma to protrude within the cavity and minimize unwanted fluid absorption.

Intraoperative Ultrasonography

Intraoperative ultrasonography guidance during operative hysteroscopy is useful for the resection of myomas that are hard to define. Ultrasound guidance allows constant visualization of the uterine walls, as well as the hysteroscopic instruments. Therefore, the hysteroscopist may know when they are in danger of perforating the uterine wall. This added imaging allows for resection beyond the limit conventionally defined by hysteroscopy [27].

Fertility Preservation

If the patient desires fertility, overzealous resection of the myometrium must be avoided. Asherman's syndrome may occur when large portions of overlying endometrial tissue are resected with a sessile myoma. Patients who desire fertility and have multiple intracavitary myomas, especially those with myomas on opposite walls, may require resection in two separate occasions to minimize chances of intrauterine synechiae developing postoperatively.

Complications

Complications of hysteroscopic myomectomies include uterine perforation, bleeding, infection, and fluid intravasation. Uterine perforation most often occurs with cervical dilation with a blunt dilator. These patients can be observed in the recovery room and sent home when stable.

Major bleeding after a hysteroscopic myomectomy is rare. When excessive bleeding is encountered, it is generally secondary to myometrial bleeding. When the bleeding is excessive, it can be controlled with a 25-cm^3 catheter balloon left in place for 4–12 h.

Endometrial Ablation

Endometrial ablation was developed as a minor surgical procedure to treat women with intractable heavy menses unresponsive to medical management, who no longer desire fertility. Each year approximately 200,000 women undergo an endometrial ablation. Compared to hysterectomy, endometrial ablation offers the advantages of avoiding the morbidity and prolonged recovery associated with major surgery when patients fail medical management. However, the disadvantages include recurrence of bleeding over time. Up to 35% of women who receive an endometrial ablation will receive a hysterectomy within 5 years of the procedure. Endometrial ablation should only be offered to women who are willing to accept eumenorrhea, hypomenorrhea, or cyclical bleeding rather than amenorrhea as a final clinical result. Only 40% of women having an ablation will be amenorrheic.

Endometrial Ablation Techniques

There are several methods for endometrial ablation. The three “first-generation” hysteroscopic techniques include electrosurgical laser ablation, endomyometrial resection, and electrosurgical roller ball ablation.

Second-generation techniques, also referred to as "global" methods, differ in that they do not require the use of the resectoscope to perform the ablation. Hysteroscopy is an integral part of only one of these systems.

First-Generation

Hysteroscopic Endometrial Ablation

Mimicking the physiologic effect of Asherman's syndrome, the ultimate goals of endometrial ablation were to create severe endometrial scarification and secondary amenorrhea.

Endomyometrial resection utilizing a resectoscope was first reported by DeCherney and Polan in 1983 [28]. This technique utilizes unipolar electrocautery and is performed with hypotonic nonelectrolyte-containing distention media. This technique was the forerunner of hysteroscopic *roller ball endometrial ablation*, which has become the "gold standard" to which all emerging endometrial ablation technology is compared. Each of these devices destroys the basalis layer of the endometrium and is designed to result in hypomenorrhea or amenorrhea.

Technique: First-Generation Hysteroscopic Endometrial Ablation

The general concept of hysteroscopic endometrial ablation involves thorough destruction of the basalis layer of the cornua and lower uterine segment. For this reason, the patient should ideally be scheduled during the early proliferative phase. Otherwise, hormonal suppression of the endometrium is required to thin the endometrium and increase the chances of success of the ablation. Hormonal suppression also increases visualization by ridding the cavity of excess blood and tissue. Hormonal options for endometrial suppression include the use of depot leuprolide acetate, danacrine, oral contraceptive pills, or progesterone-only pills 4–8 weeks prior to surgery. Surgical preparation with suction or sharp curettage immediately prior to ablation has also been used with reported success.

Vasopressin

Vasopressin is used to decrease the risk of fluid absorption, fluid overload, and intraoperative bleeding [29]. A dilute solution of vasopressin (10 units in 50 mL saline) is injected as 5-mL aliquots into the stroma of the cervix at 12, 3, 6, and 9 o'clock positions. This causes intense arterial and myometrial wall contractions for 20–45 min. Vasopressin is not approved by the FDA for this purpose and should not be used in patients who are hypertensive.

Technique: Rollerball and Endomyometrial Resection

Several varieties and shapes of electrodes are available to perform hysteroscopic endometrial ablation, including ball, barrel, ellipsoid, and large-caliber loops. Most surgeons perform rollerball endometrial desiccation with a 3-mm rollerball probe, with the goal of systematically destroying the entire endometrium to the lower uterine segment and cornual region. The technique of endomyometrial resection is also a popular method for endometrial ablation and is performed with a 90-degree wire-loop electrode. Following a systematic surgical plan ensures optimal clinical outcomes. Excellent visualization of the entire uterine cavity and endocervix is imperative. All intrauterine landmarks are clearly delineated, hysteroscopically, before initiating the procedure. Once a panoramic view of the endometrium is accomplished, the surgeon should determine if there is any previously unrecognized pathology. If a subtle lesion is discovered, then a directed biopsy with a wire-loop electrode is performed and the specimen labelled and submitted separately.

Once the surgeon visualizes all of the landmarks, the lower uterine segment is cauterized circumferentially to mark the endpoint and lowest level of endometrial ablation therapy. Ablation of the endocervix is avoided to minimize the risk of cervical stenosis. Cervical stenosis can result in cyclic pain, dysmenorrhea, and, in severe cases, hematometra.

After the lower uterine segment is identified and coagulated circumferentially, the cornua and fundal region are treated initially. With the rollerball, the electrode is advanced to the fundus and then directed at the cornua utilizing a "touch technique" to desiccate the cornua. It must be remembered that the thinnest region of the uterus is at the cornua.

Extra care must be taken to avoid forward pressure, which could cause perforation. The most challenging part is the fundus, since the rollerball cannot truly be rolled against the fundus. The fundus should be addressed as the first step. The posterior wall should be resected next, followed by the lateral walls and anterior walls. Traditional technique utilizes direct tissue contact, such that one half of the roller ball is buried in the endomyometrial juncture. The rollerball should only be activated when the electrode is moving toward the surgeon to avoid perforation. Perforation with the rollerball has the added risk of inflicting burns to the pelvic viscera beyond the uterine wall. Intermittently, the rollerball may need to be cleaned and debris evacuated to provide optimal visualization.

The endomyometrial resection with a wire loop follows the same principles. This loop is generally 3–4 mm deep. The loop should be buried into the endometrium just below the superficial level of the myometrium. The cut is performed using 60–80 W of cutting current. The loop is then advanced under direct view from the fundus to the lower uterine segment. Thus, the endomyometrial junction is shaved-off, creating "crescent-shaped" tissue fragments.

At the conclusion of the endometrial ablation procedure, the intrauterine pressure is reduced in order to identify bleeding areas which may be treated with coagulation current.

Outcomes

The majority of patients who undergo endometrial ablation are satisfied with their clinical outcome, and at least 90% will notice symptomatic improvement. However, 5–10% of patients may ultimately be required to undergo additional interventions, such as repeat ablation or hysterectomy [30].

Hysteroscopic endometrial ablation is an outpatient procedure associated with a rapid return to work, minimal complications, and high patient satisfaction. Approximately, 20–60% of patients undergoing endometrial ablation with rollerball techniques will achieve amenorrhea, 65–70% will become hypomenorrhic, and 5–10% will fail. Approximately, 35% of patients treated by endometrial ablation will require a subsequent operation [30]. Women receiving appropriate preoperative counselling may find this attractive in treating menstrual disorders.

Second-Generation Endometrial Ablation Devices

Second-generation or "global" endometrial ablation refers to the destruction of the entire endometrium with devices that require little or no hysteroscopic skills. Currently, FDA-approved second-generation devices available in the USA utilize intrauterine balloons, hot saline irrigation, cryosurgery, bipolar radio frequency, and microwave energy.

Second-generation technology offers the advantage of shorter procedure times while retaining the acceptable outcome rates similar to traditional rollerball ablation. However, these second-generation devices have limited or no ability to treat intracavitary pathology. For this reason, it is important for clinicians who routinely use these ablation devices to be skilled in operative hysteroscopy so that they will be equipped to treat any intracavitary pathology that they may encounter prior to performing the ablation procedures.

Complications of Endometrial Ablation

When energy using heat is used, the most concerning complication is perforation of the uterus with concurrent thermal damage to the surrounding viscera. Perforations of this kind require immediate laparoscopy to determine whether or not thermal injury to the pelvic organs has occurred. Thermal injury to the bowel that is not repaired may result in breakdown of the intestinal wall with spillage of bowel contents into the abdomen. When this occurs, it generally results in massive pelvic infections that may progress to disseminated intravascular coagulopathy. Other complications include skin burns with circulating hot saline, direct coupling vaginal burns from monopolar energy, and unwanted bladder or bowel thermal injuries from cryotherapy.

Hysteroscopic Resection of Adhesions

Most commonly, intrauterine adhesions form in the postpartum or postabortion period. Unfortunately, there is usually no way to avoid this complication during these critical periods, such as when a patient presents with postpartum hemorrhage and requires intrauterine procedures (i.e., D + C) for hemostasis. Early detection of intrauterine synechiae is a key preventative feature following intrauterine surgery, curettage, or spontaneous abortion. This is because early detection allows for the identification of adhesions while they are still filmy, thin, and easily resected with prompt adhesiolysis [24, 31–34].

The incidence of Asherman's syndrome in a select group of women, especially after curettage for missed or incomplete abortion, is reported in the range of 17%, but rates as high as 30% are reported in the literature, the majority of which are mild in severity [35–38]. Furthermore, in at risk women, such as those who undergo curettage postpartum, the rate is speculated to be even higher [5, 39].

Pathophysiology

Any intervention that destroys the endometrium may generate adhesions of the myometrium in the opposing uterine walls. The key predictive factor to intrauterine adhesions is the gravid uterus. The gestational changes noted with a gravid uterus soften the uterine wall, resulting in greater denudation of the basalis layer during surgical interventions. The basalis layer is crucial because it is the regenerative layer of the endometrium [40].

Classification of Intrauterine Adhesions

March Classification

Intrauterine adhesions can be characterized based on the extent of uterine involvement [25]. Minimal adhesions are defined as adhesions that involve less than one-fourth of the uterine cavity and are thin and filmy. The fundal and ostia areas are minimally involved or devoid of any adhesions. Moderate adhesions involve one-fourth to three-fourths of the uterine cavity but no agglutination of the uterine wall is seen. The tubal ostia and fundus are only partially occluded. Severe adhesions involve greater than three-fourths of the uterine cavity with agglutination of the uterine walls or thick bands with occlusion of the tubal ostia and upper uterine cavity. The March classification system is simple and easy to apply, but it is not prognostic [25] (Table 2).

American Society for Reproductive Medicine Classification

According to the 1988 ASRM (formerly the American Fertility Society) classification system, synechiae are classified in three stages, with stage III being complete obliteration of the uterine cavity (Table 2) [41].

Table 2. Classification system for intrauterine adhesions[a].

Grade	Finding
Minimal	Less than 1/4 of the uterine cavity is involved
	Thin, filmy adhesions
	Fundus and ostia are clear of adhesions
Moderate	1/4–3/4 of the uterine cavity is involved
	No agglutination of uterine walls; only adhesions are present
	Upper uterine cavity and ostial areas are only partially occluded
Severe	More than 3/4 of the uterine cavity is involved
	Agglutination of uterine walls or thick adhesion bands
	Upper uterine cavity and ostial areas are totally occluded

[a]Adapted from [25]

Table 3. American Fertility Society intrauterine adhesions classification system[a].

Extent of cavity involved	<1/3	1/3–2/3	>2/3
	1	2	4
Type of adhesions	Filmy	Filmy and dense	Dense
	1	2	4
Menstrual pattern	Normal	Hypomenorrhea	Amenorrhea
	0	2	4
Prognostic classification		HSG[b] score	Hysteroscopy score
Stage I (mild)	1–4	–	–
Stage II (moderate)	5–8	–	–
Stage III (severe)	9–12	–	–

[a]Reproduced from American Fertility Society. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies, and intrauterine adhesions (Fertil Steril 1988; 49:944–55, with permission from Elsevier the American Society for Reproductive Medicine)
[b]All adhesions should be considered dense

The ASRM classification system provides both, an indirect and direct grading of intrauterine adhesions with HSG and hysteroscopy, respectively. The location of the adhesions is presumed to be prognostic for reproductive outcome given that most implantation occurs in the top fundal portion of the uterine cavity and cornual adhesions may cause tubal obstruction. In addition, unlike the March classification system, the significance of endometrial sclerosis or atrophy is included in the ASRM system by ascertaining the menstrual pattern (Table 3).

Clinical Manifestations

The most common presentation of intrauterine adhesions is menstrual disturbance and/or reproductive disturbance (infertility and recurrent pregnancy loss). If conception occurs, it may be complicated by preterm labor or abnormal placentation such as placenta previa or placenta accreta. Menstrual disturbances are most often categorized by amenorrhea or hypo or oligomenorrhea but can also be seen in eumenorrheic women.

The most common single presentation is infertility, representing 43% of reported cases. The second most common is amenorrhea, which is seen in 37% of cases [42]. The rate of abnormal placentation, although elevated in women with intrauterine adhesions, is the least common presentation reported in women with intrauterine adhesions

Diagnosis

Sonohysterogram

A sonohysterogram is performed with transvaginal sonography (TVS) and can enhance the detection of intrauterine adhesions. Saline serves as a homogenous, echo-free contrast medium enabling better visualization of the uterine cavity than transvaginal ultrasonography alone. Alborzi *et al.* [43] published the largest series to evaluate the diagnostic accuracy of sonohysterogram compared to laparoscopy and hysteroscopy, which are the gold standards for diagnosis. The prospective study reviewed 86 women with infertility. In this study, sonohysterogram had a high diagnostic accuracy for the detection of Asherman's syndrome. Sonohysterogram accuracy in diagnosis was greater than that for hysterosalpingogram, with a sensitivity of 76.8%, a specificity of 100%, a PPV of 100%, and an NPV of 97.7%.

Transvaginal ultrasound should be performed in the late follicular or early luteal phase of the cycle, as the endometrium is thick enough to appear more echogenic than the myometrium and not too thick to obscure the midline echo. The classic appearance of the three-layer endometrium enables better imaging of uterine defects than the postmenstrual endometrium, which is thin, <3 mm. The typical appearance of uterine synechiae is focal, hyper-echoic, irregular, cord-like structures seen within the echo-free space between the basalis layers, which interrupt the continuity of the endometrial cavity. These structures can vary in size (2–6 mm) and/or in location within the cavity [44].

Hysteroscopy

Diagnostic hysteroscopy is the gold standard for the diagnosis of intrauterine adhesions, with demonstrated superiority to sonohysterogram and hysterosalpingogram, specifically in false-positive rates. Both radiologic techniques have high false-positive rates. Hysteroscopy has the added advantage of being able to assess intrauterine adhesions and classify them by location, shape, size, and nature.

Surgical Treatment

Hysteroscopic Surgery

Hysteroscopy has become not only an accurate tool for the diagnosis of adhesions but also the main method for their treatment. Hysteroscopic lysis of adhesions is indicated when the extent of adhesions is moderate to severe or access to tubal ostia is blocked. The significance of mild adhesions is still controversial, yet surgical treatment may be considered if all other causes of infertility or recurrent pregnancy loss have been excluded and/or successfully corrected and the patient still experiences persistent reproductive failure.

The basic technique involves resection of the intrauterine adhesions either by sharp and/or blunt dissection. Successful hysteroscopic resection can be accomplished by the use of sharp dissection using semirigid scissors, electrosurgery, and/or fiber-optic laser. Electrocautery is used by some clinicians. However, the disadvantage of its use in this context is possible thermal damage to the endometrium.

Adhesiolysis begins inferiorly and is carried out cephalad until a panoramic view of the endometrial cavity can be obtained and the tubal ostia are seen. The initiation of the adhesiolysis is from the internal os. The maintenance of adequate distention is the key to the successful resection of intrauterine adhesions; distention provides traction to the scar tissue so that they may be more effectively resected with hysteroscopic scissors. In cases of severe disease, transabdominal ultrasound guidance with a full bladder is very helpful in preventing the creation of a false passage or uterine perforation.

Postoperative Adjunctive Therapy

Despite advances in the development of techniques for adhesiolysis, the two basic problems associated with poor outcome with these procedures still exist: the inability to treat extensive or severe adhesions and the lack of methods to prevent recurrence of the adhesions postoperatively. The use of Foley catheters, antibiotics, and high-dose estrogen postoperatively to prevent recurrence of adhesions is still widely debated, and no consensus exists [40]. A typical regimen is conjugated estrogen, 0.625–1.25 mg twice daily, or estradiol, 2 mg twice daily for 25 days, followed by 12 days of progesterone (10 mg is prescribed).

Another approach is to place a postoperative intrauterine stent. Either a pediatric catheter inflated with 15–20 cm^3 or a balloon uterine stent specifically designed for this purpose (Cook OB/GYN, Spencer, Indiana) may be inserted for 7–10 days to prevent the juxtaposition of the uterine walls.

A final approach is to perform office hysteroscopy within the first 7–14 days following extensive myomectomy to evaluate the endometrium for synechiae. If detected early, the adhesions are filmy and easily lysed with the distal tip of the hysteroscope. In some circumstances, hysteroscopic visualization every 7–10 days may be required until regeneration of the endometrium is confirmed and filmy adhesions treated. When performed too late, dense fibrous adhesions may be encountered, requiring repeat operative hysteroscopic adhesiolysis.

Complications

Complications after hysteroscopic adhesiolysis include all the standard risks seen with any operative hysteroscopy. The perforation risk is highest during hysteroscopic adhesiolysis [45]. The risk of postoperative infection after hysteroscopy in general is 1.42%, but the risk of early onset endometritis is highest after lysis of synechiae compared to other hysteroscopic procedures including uterine septa [45].

Outcome

The success of surgery can be assessed by repeat hysteroscopy or imaging or simply by the presence of withdrawal bleeding, suggestive of adequate regeneration of the endometrium. Successful pregnancy outcome is also a parameter or measure of success in women trying to conceive and seems to be correlated with the severity of the intrauterine adhesions.

A number of series have been published reporting the outcome of hysteroscopic treatment of intrauterine adhesions. However, randomized clinical trials are lacking. A report of 40 consecutive women with recurrent pregnancy loss (24 women) or infertility (16 women) resulting from intrauterine adhesions showed excellent surgical results with mild or moderate disease [46]. Of the 40 women, 10 had mild adhesions, 20 had moderate and 10 had severe adhesions, according to the March classification system. Hysteroscopic adhesiolysis was performed with hysteroscopic scissors or monopolar electrosurgery. Prophylactic antibiotics were used, and, postoperatively, a pediatric Foley was placed and estrogen was administered. All women with recurrent pregnancy loss conceived after adhesiolysis; 71% were term or preterm with a viable pregnancy. Among the women with infertility, 62% conceived, resulting in a 37.5% live birth rate. Adhesion re-formation was absent or rare in women with mild or moderate adhesions, reported as 0–10%. However, adhesion reformation was seen in 60% of women with severe intrauterine adhesions, and none of the patients with severe adhesions conceived. Only one perforation was reported in a patient with severe adhesions.

Valle and Sciarra [16] reviewed 81 infertile women and reported a term pregnancy rate of 81%, 66%, and 15%, respectively, in women with mild, moderate, and severe disease. Among these women with recurrent pregnancy loss, the term pregnancy rate was 94%, 89%, and 65% in women who had mild, moderate, and severe adhesions, respectively. The literature is unified and quite clear that for women with severe intrauterine adhesions, the reproductive outcome remains poor even after hysteroscopic adhesiolysis [16, 46]. The recurrence rate of severe adhesions was 48.9% and decreased to 35% after repeat adhesiolysis [16].

The overall live delivery rate following adhesiolysis in women was 43.5% during a mean follow-up period of 39.2 month (± 4.5 months). The live delivery rate based on the stage of adhesions was 33.3%, 44.4%, and 46.7% for stages I, II, and III, respectively. The live birth rate among women who tried naturally was 61.9% vs. 28% after in vitro fertilization. Similar pregnancy rates were noted in women who conceived naturally whether the resectoscope or the coaxial bipolar system was used. The mean time for the conception in these women was 12.2 months, and all pregnancies were achieved within 2 years post-adhesiolysis.

Increase in pregnancy complication rate was noted. Preterm rate was 50%, and hysterectomy for abnormal placentation (placenta accreta) was seen in 2 of the 20 patients (10%). In addition, Zikopoulos *et al.* [47] reviewed the literature of existing studies examining delivery rates in women undergoing hysteroscopic adhesiolysis. A large array of techniques were used in these studies. He identified seven published studies in the last decade. A total of 126 women were reported with an overall delivery rate of 38.1% (48/126) among all the studies analyzed.

Pabuccu *et al.* [46] reported the highest success rate among women with recurrent abortion, with a delivery rate of 70.8% vs. women with infertility with a 37.5% delivery rate. The overall delivery rate was similar to that reported by Siegler and Valle [48] in 1988. They reviewed a series of studies that encompassed 775 subjects, of which 302 (38.9%) achieved a term delivery.

The mainstay of diagnosis and treatment of intrauterine adhesions remains hysteroscopy. However, one cannot stress enough the need to exert due diligence and avoid forced or extensive interventions on the post-gravid uterus to minimize the development of intrauterine adhesions. Mild and moderate adhesions are associated with improved reproductive outcome post adhesiolysis, but severe intrauterine adhesions carry a very poor prognosis.

Uterine Septa

Etiology

Uterine septa are created when there is a failure of resorption of the midline septum between the Müllerian ducts. The etiology of a septate uterus remains to be elucidated. Sporadic case reports on family pedigrees suggest familial aggregation exists, but no clear genetic cause has been linked to the development of a septate uterus [28, 49]. In general, 92% of women with congenital uterine anomalies have a normal karyotype, 46 XX, and approximately, 8% of women have an abnormal karyotype [50]. In rare cases, early in utero exposure to radiation, infection, such as rubella, and teratogens (diethylstilbestrol, thalidomide) has been implicated as the causal factor of the uterine anomaly.

Classification

A number of classification systems have been reported for Müllerian anomalies. However, the classification system proposed by the ASRM in 1988 is most commonly used to describe or define Müllerian defects. The classification system organizes uterine anomalies into six major uterine anatomic types or categories. In this classification system, a septate uterus is a class V anomaly. It is among the vertical fusion defects described by the ASRM classification system. Va is a complete septate uterus, and Vb is a partial septate uterus.

A septate uterus is characterized by a smooth external fundal contour with two uterine cavities. The extent of the septum or the degree of septation can vary from a small midline septum to total failure of resorption, resulting in a complete septate uterus with a longitudinal vaginal septum.

Incidence

The reported incidence of Müllerian or uterine anomalies is between 0.5 and 6% of reproductive age women and highest among women with poor reproductive outcome. The overall incidence of Müllerian defects reported in a series by Acien [51] was 5% among women with normal reproductive history, 3% among infertile women, and 5–10% among women with first-trimester recurrent miscarriage and greater than 25% in women with late first or early second-trimester loss or preterm delivery. The most frequent to least frequent anomaly is bicornuate uterus, arcuate uterus, incomplete uterine septum, uterus didelphys, complete uterine septum, and a unicornuate uterus [51]. In this combined series of women, bicornuate uteri and complete or partial septums represented 74% of the uterine anomalies.

In women with recurrent pregnancy loss, the relative frequency of a septate vs. bicornuate uterus is less clear. This is often attributed to old surgical data that often did not definitely differentiate a septate from a bicornuate uterus. In one of the largest studies of patients with recurrent pregnancy loss that were evaluated with either laparoscopy or sonohysterogram, the septate uterus was more prevalent in women with recurrent pregnancy loss than the controls [52]. A septate uterus is the most likely anomaly in patients with recurrent pregnancy loss.

Pathophysiology of Pregnancy Complications

The key presentation in women with a septate uterus is difficulty in maintaining a pregnancy and not a decreased ability to conceive (infertility). Additionally, a septate uterus is thought to impair normal reproductive performance by increasing the risk or incidence of early and late abortion, preterm delivery, and the rate of obstetrical complications [53].

The pathogenesis of pregnancy complications in women with a septate uterus has not been completely elucidated. The most widely accepted causal theory includes the inadequate vascularization of the fibroelastic septum and altered relations between the myometrial and endometrial vessels, thus, exerting negative effects on fetal placentation.

The septum is primarily composed of avascular, fibromuscular tissue. Hence, it has been proposed that in the endometrium lining, the septum responds poorly to estrogen, resulting in irregular differentiation and estrogenic maturation [54]. Implantation on this poorly vascularized, fibrous septum leads to abnormal implantation, defective embryonic development, and subsequent abortion [55–57].

Diagnosis

Uterine imaging techniques used as a method of detection of uterine anomalies include HSG; TVS, with or without three- and four-dimensional technology; saline infusion sonohysterography (SHG); and MRI.

Hysterosalpingogram

HSG is an useful screening test and should be the first step in the evaluation of the uterine cavity. HSG is a simple, safe, relatively noninvasive radiological procedure performed under fluoroscopic guidance that enables visualization of the uterine cavity, but it is limited in differentiating between a septate and bicornuate uterus. Consequently, the limitations of HSG require additional evaluation.

Ultrasonography

Two-dimensional ultrasound and SHG can also be used to diagnose women suspected of Müllerian anomalies. The diagnostic accuracy of two dimensional TVS and SHG compared to HSG is shown in Table 4 [58]. However, the presence of a uterine septum is best diagnosed

Table 4. Diagnostic accuracy of HSG, TVS, and SHG for uterine malformations[a,b].

Examination	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
HSG	75.0 (21.9–98.7)	95.1 (85.4–98.7)	50.0 (13.9–86.1)	98.3 (89.7–99.9)
TVS	0.0 (0.0–69.0)	95.2 (85.6–98.7)	0.0 (0.0–69.0)	95.2 (85.6–98.7)
SHG	75.0 (21.9–98.7)	93.4 (83.3–97.9)	42.9 (11.8–79.8)	98.3 (89.5–99.9)

HSG hysterosalpingogram, *SHG* sonohysterography, *TVS* transvaginal sonography, *PPV* positive predictive value, *NPV* negative predictive value

[a]Reprinted from Fertility and Sterility, 73/2, Soares SR, dos Reis MMBB, Camargos AF, Diagnostic accuracy of sonohysterography, transvaginal sonography, and hysterosalpingography in patients with uterine diseases, 406–11, Copyright 2000, with permission from Elsevier

[b]The numbers in parentheses are the limits of the 95% confidence interval

with a three-dimensional ultrasound scan. One study examined 61 patients with a history of recurrent miscarriage or infertility. Subjects underwent a hysterosalpingogram, two-dimensional TVS, and three-dimensional TVS. The study demonstrated that three-dimensional ultrasonography was superior in the detection of arcuate uteri and major congenital anomalies. It facilitated visualization of the uterine cavity and myometrium, allowing easier diagnosis of septate uteri [59].

Magnetic Resonance Imaging

MRI can accurately predict the presence of uterine anomalies and has become the imaging method of choice to confirm inconclusive results from other methods. The clear advantages of an MRI include the ability to distinguish between myometrial and endometrium tissue, image the uterus in several planes, and define uterine contour [47, 60–62]. Because MRI can delineate the uterine contour, a septate uterus can be distinguished from a bicornuate uterus, unlike with other radiographic imaging modalities. Furthermore, the uterine septum can be further characterized by the absence of myometrial tissue and vascularization in the septum. Instead, a uterine septum is seen to have a fibrous consistency throughout its entire length. In a review of 23 cases of Müllerian anomalies, the correct diagnosis was made in 96% of cases with MRI, compared to 85% for TVS [63].

Another advantage of MRI is its ability to detect the associated anomalies in other organ systems typically seen with Müllerian anomalies such as renal or the urinary tract anomalies. The major disadvantage includes the lack of portability and higher costs compared with other imaging modalities.

After initial imaging has been performed with either HSG, TVS, or SHG, an MRI may be used to determine the contour of the uterine fundus to distinguish between a septate uterus and bicornuate uterus. There must be a less than 1 cm indentation at the fundus to qualify as a septate uterus. If there is any ambiguity in terms of the diagnosis, the gold standard for the accurate and proper classification for the diagnosis of a uterine anomaly is laparoscopy and hysteroscopy.

Surgical Treatment

Indication

The most common and accepted indication for the surgical resection of an uterine septum is recurrent pregnancy loss in either the first or early second trimester. The goal of surgical repair of a uterine septum is restoration of a normal uterine cavity. However, normal surgical restoration of the uterine cavity does not necessarily imply good reproductive prognosis, as uterine vascularization may also be impaired.

Most studies would support the observation that primary infertility in the presence of a septate uterus is not an indication for hysteroscopic metroplasty. This procedure should only be considered after a comprehensive infertility evaluation. If no other etiologies are discovered, and the patient's infertility persists, this procedure may be undertaken. On the other hand, the simplicity and low morbidity of the hysteroscopic metroplasty has led many experts to recommend immediate removal prior to more comprehensive evaluation, especially in women with advanced age, given that uterine septums increase the rate of miscarriage.

Hysteroscopic metroplasty is the method of choice, with benefits that include lower morbidity, faster recovery, and lower-risk of infection, hemorrhage, and adhesions than with metroplasty via laparotomy or laparoscopy. Additionally, by avoiding large incisions into the myometrium, hysteroscopic metroplasty does not result in the recommendation for cesarean delivery in future pregnancies.

Hysteroscopic Technique

Operative hysteroscopy is usually performed under general anesthesia using either an operative hysteroscope or resectoscope. The basic technique usually involves simple incision of the septum rather than removal or resection. However some large, broad-based septums are sometimes excised partially.

Micro-scissors are the method of choice for surgical resection of the septum. However, one limitation of the scissors is increased difficulty in dissecting and cutting broad-based septums. In these instances, electrocautery with the wire loop can be used. Generally, electrocautery is avoided secondary to theoretical concern that the use of electrocautery will cause thermal damage on the endometrium and myometrium, with potential risk of uterine rupture with a subsequent pregnancy.

Hysteroscopic metroplasty is performed ideally in the early follicular phase of the menstrual cycle when the endometrium is thin, hence, not requiring any preparation of the endometrium. Classical teaching has described the use of a laparoscope to visualize the uterine fundus while it is transilluminated with the hysteroscope. This allows for the assessment of myometrial thickness, which is important to optimally resect the septum while avoiding uterine perforation. However, this is not necessary in most cases. More recent data suggest that a transabdominal intraoperative ultrasound can be used both safely and adequately to prevent perforation.

Resection or horizontal incision of the septum is carried out from the lower margin of the septum and continued cephalad toward the tubal ostia, always staying in the midline and horizontal plane of the septum. Incision into the myometrium should be minimized. One can safely assume that the base of the septum has been reached if increased bleeding is noted.

The surgical technique used for the complete uterine septum includes placement of a plastic uterine dilator, balloon hysterosalpingogram catheter, or Foley balloon through the contralateral cervix to indent the septum wall. It also functions to prevent the loss of distention medium through the second cervical opening. The hysteroscope is then inserted into the opposite cervix, and resection is initiated over the indented septum wall, enabling a safe resection. It is important to identify the point above the cervix at which the resection can be initiated. Once the passage is created, resection is then completed as described above, while sparing the cervical tissue. Limited studies exist, but the recommendation is to spare the cervical portion and preserve the septum below the internal os in order to minimize the risk of cervical incompetence in subsequent pregnancies [4, 64, 65].

The endpoint of resection can be characterized by a number of parameters. Visualization of pink, vascular myometrium, distinct from the white, avascular tissue of the septum, is important. It is also important to examine the relationship of the resection to the tubal ostia and the proximity of the resection to the uterine serosa, which can be assessed via the laparoscope or ultrasound. A successful resection of the septum is defined when the tubal ostia are seen together with no separation in between, an enlargement of the uterine cavity is demonstrated, and an improvement in the uterine shape is accomplished.

Abdominal Metroplasty

Abdominal metroplasty is, at times, performed if the uterine septum cannot be resected hysteroscopically. This entails either a wedge resection at the fundus that removes the septum, as in the Jones procedures, or opening the uterus in the midline and removing the septum, as in the Tompkins metroplasty technique. Abdominal metroplasty is rarely performed and should only be undertaken by skilled surgeons.

Postoperative Care

Postoperative estrogens or intrauterine contraceptive devices have been used. However, randomized studies in women undergoing hysteroscopic resection of their uterine septums have noted no difference in the postoperative intrauterine adhesion rates, when followed-up with HSG or hysteroscopy, despite the use of either agent [66, 67]. Studies have also not shown any added value with use of prophylactic antibiotics.

Complications

The complications associated with the hysteroscopic metroplasty can be viewed in two major categories: those intrinsic to operative hysteroscopy and those related to the technique and instruments used for the septum resection The major concern with the use of the electrosurgical systems is uterine rupture at the actual site of the septum with a later pregnancy secondary to weakening of the uterine wall from thermal damage. However, vaginal delivery is still recommended unless extensive damage has occurred through thermal injury or a fundal perforation has occurred. The rate of uterine perforation is lower with resection of an uterine septum than it is for intrauterine adhesiolysis. It is reported to be less than 1%.

Outcome

Many studies exist that report both, presurgical and postsurgical outcomes in women with hysteroscopic metroplasty. However, to date, there are no published randomized clinical trials that compare pregnancy outcomes in treated vs. untreated groups of symptomatic women. Hence, surgical outcomes after the treatment of septate uteri are based on retrospective studies evaluating the reproductive outcome of women, often using patients as their own control. The overall reported rate of successful pregnancy after hysteroscopic metroplasty is 85–90% [48, 68–70].

Hickok *et al.* wrote a small retrospective series of 40 women with uterine septums. Preoperatively, they observed a miscarriage rate of 77.4%, delivery rate of 22.6%, and uncomplicated delivery rate of 6.5%. After hysteroscopic metroplasty, the miscarriage rate was seen to be 18.2%, delivery rate was 81.8%, and uncomplicated delivery rate was 77.3% [71]. Kupesic reviewed the reproductive outcome from 13 studies in women with untreated septate uterus and reported on 1,304 pregnancies. They observed a miscarriage rate of 81.9% and a preterm delivery rate of 9.6% [72]. But the authors caution that the group of women reviewed may represent a biased group of women; women with a septate uterus and normal reproductive outcome may have been excluded. Kupesic also reported a review of the existing literature with regard to the reproductive outcome before and after hysteroscopic metroplasty for the septate uterus. In 388 patients, 1,059 pregnancies were achieved before metroplasty and 362 pregnancies after the surgery. The miscarriage rate and preterm and term delivery rates before and after were 87.8%, 9.0%, and 3.2% vs. 14.6%, 5.2%, and 80.1%, respectively [72]. These and other studies demonstrated an improvement in fertility after metroplasty. The chance of pregnancy was not affected by maternal age, number of previous pregnancy losses, and method of septal resection (micro-scissors, resectoscope, or laser) nor the type of septum present, partial or complete [58, 73].

However, other studies demonstrate that there is no improvement in outcome in women with recurrent pregnancy loss after metroplasty. Kirk *et al.*, in a series of 146 women, showed no increase in the number of living children after metroplasty [74]. However, there was also no negative effect of hysteroscopic metroplasty on fertility potential in women with recurrent pregnancy loss.

The possible adverse effect of the presence of a septate uterus on the outcome of assisted reproductive technology is still debated. The existing studies do not demonstrate any impairment on ovarian response to stimulation nor implantation rates in the presence of Müllerian anomalies to include a septate uterus. However, the studies do report a higher rate of abortion and preterm delivery if the septum is uncorrected [72, 75]. Although the hysteroscopic metroplasty is not intended to enhance fertility, it may be indicated for the improvement of their pregnancy outcome, especially after multiple treatment failed assisted reproductive cycles.

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The robotic-assisted treatment of endometriosis: a colorectal surgical perspective

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Background

Endometriosis is a common benign gynecologic condition defined as the presence of uterine lining, or endometrium, outside of the uterine cavity. Specifically, pathologic diagnosis is based on the presence of ectopic endometrial glands and stroma [1]. Implants of endometriosis are hormone responsive, expressing both estrogen and progesterone receptors. A pro-inflammatory environment is present secondary to the production of cytokines, prostaglandins, and metalloproteinases. The inflammation present in endometriosis lesions leads to scar tissue formation and adhesions between pelvic organs. In addition, endometriotic implants release angiogenic and neurogenic growth factors leading to the expression of nerve fibers, lymphatic vessels, and blood vessels in the tissue surrounding the implants as well as the implants themselves [2]. The most common anatomical locations affected by endometriosis are the pelvic peritoneum and the ovaries, but endometriosis can involve almost any organ including the pericardium, pleura, and the brain [3]. Common symptoms of endo-

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metriosis include painful menses, chronic pelvic pain, pain with intercourse, and infertility. Symptoms also vary by anatomic involvement, such as significant dysuria with bladder involvement, flank pain with ureteric involvement, and dyschezia with bowel involvement [4].

Pathophysiology

The exact etiology of endometriosis is unknown, but a number of hypotheses have been described. The most well-accepted is the transplantation theory, which suggests that retrograde menstruation through the fallopian tubes allows for the implantation of ectopic endometrial glands on the pelvic peritoneum [5]. This hypothesis is supported by the increased incidence of endometriosis in women and girls with Müllerian anomalies that lead to the obstruction of menstrual outflow through the vagina [6]. In addition, it is suggested that the cause of endometriosis of surgical incisions, such as in episiotomy and cesarean section incisions, is similarly caused by the transplantation of endometrial tissue during delivery or surgery [7]. The second hypothesis is that of lymphatic or hematogenous spread [8], which is supported by reports of endometriosis in distant sites, such as the lungs [9] and the brain [10]. The third theory is that of coelomic metaplasia. This theory proposes that undifferentiated mesothelial cells of the coelomic (peritoneal) cavity have the potential to differentiate into endometrial cells. This hypothesis is supported by embryologic studies suggesting that all pelvic organs, including the endometrium, originate from cells lining the coelomic cavity [11]. In addition to these three theories, studies suggest that exposure to toxins, altered immunity, and genetic predisposition influence susceptibility to endometriosis [12].

Epidemiology

Though endometriosis is estimated to affect 6–11 % of reproductive age women, up to a third of women do not have symptoms of the disease [13]. In subgroups of women manifesting symptoms of endometriosis, prevalence rates are markedly increased. For example, women with chronic pelvic pain have an estimated prevalence of 25 % [14], and women with infertility have an estimated prevalence of 25–40 % [15].

Disease Classification

Upon surgical exploration, endometriosis can present in a spectrum from mild disease involving only superficial peritoneum of the pelvis, to severe disease causing dense adhesions that fix pelvic structures completely.

Disease severity has been historically described using the American Society of Reproductive Medicine (ASRM) endometriosis staging system (Fig. 1), which was originally designed in 1979 and was most recently revised in 1997 [16]. The ASRM endometriosis staging system considers factors such as lesion appearance, size, depth of invasion, and location. Depending on these factors, points are assigned and endometriosis is classified as stage I (mild), stage II (minimal), stage III (moderate), and stage IV (severe), respectively.

Several limitations exist with this system including lack of reproducibility [17] and poor correlation of symptoms with stage of disease [18, 19]. In 2005, the ENZIAN [20] system was proposed as an adjunct to the ASRM staging of endometriosis to describe deeply infiltrative disease in further detail. More recently, the endometriosis fertility index (EFI) was developed and validated for the prediction of spontaneous pregnancy in women with endometriosis [21, 22]. This system considers patient characteristics such as age, duration of infertility, ASRM score, and the extent of disease involving the ovaries and fallopian tubes. Though both the ENZIAN and EFI systems have recognized clinical utility, neither has been widely adopted for the staging of endometriosis.

From a clinical standpoint, endometriosis is distinguished by three distinct manifestations: (1) superficial endometriosis, (2) ovarian endometriomas, and (3) deeply infiltrating endometriosis (DIE) [23, 24]. Though they can present simultaneously, these three types of endometriosis vary in severity, symptoms, and management.

DIE is of the most clinical importance from a colorectal surgical perspective. This is the most advanced form of endometriosis and is relatively rare, estimated to affect 1–3 % of all reproductive age women [25]. These lesions invade beyond the superficial peritoneum and can involve sites such as the rectovaginal space, the bowel, appendix, bladder, ureter, lung, liver, umbilicus, as well as other locations (Fig. 2). When DIE involves the rectosigmoid, such as with transmural infiltration leading to stenosis or

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name ______ Date ______
Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total ______

Laparoscopy ______ Laparotomy ______ Photography ______
Recommended Treatment ______
Prognosis ______

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial		Complete
		4		40
	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Additional Endometriosis: ______

Associated Pathology: ______

To Be Used with Normal Tubes and Ovaries

To Be Used with Abnormal Tubes and/or Ovaries

Fig. 1: Revised American Society for Reproductive Medicine classification of endometriosis.

obstruction, a preoperative colorectal surgical consultation and multidisciplinary surgical approach are often necessary.

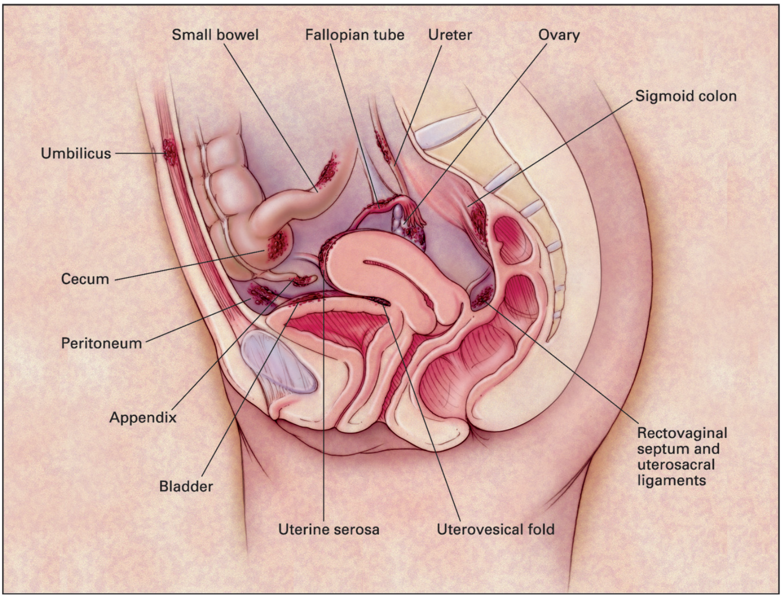

Fig. 2: Common locations of endometriotic lesions.

Symptoms

Symptoms of endometriosis can be debilitating, affecting work productivity and quality of life [26]. Severe dysmenorrhea and chronic pelvic pain are the most common symptoms of women diagnosed with endometriosis. In a study of 1,000 women with endometriosis, 79 % reported having dysmenorrhea and 69 % reported chronic pelvic pain [27]. Dyspareunia, another common symptom, is reported in 45 % of women with endometriosis [27] and is associated with rectovaginal and uterosacral involvement [28]. Dysuria, dyschezia, constipation, and diarrhea [29] may also be present and can be suggestive of DIE involving the bladder and bowel, respectively. However, these symptoms may also be present without deeply infiltrative disease [25, 26]. In cases of DIE of the rectosigmoid, cyclic hematochezia may be reported [30], and in rare cases of transmural infiltration of lesions, stenosis and even occlusion of the intestinal lumen can occur [31, 32].

Another common manifestation of endometriosis is infertility. Up to 50 % of women with endometriosis suffer from infertility and even higher rates can be seen with worsened disease severity. In some cases, infertility is the only symptom suggesting the presence of endometriosis [15].

Other symptoms seen with endometriosis include myofascial pain syndromes, painful bladder syndrome, irritable bowel type symptoms, depression, and anxiety.

Diagnosis

Historically, the formal diagnosis of endometriosis involving the abdominal cavity has been through laparoscopy, with or without biopsy for histologic evaluation [3]. However, the presence of endometriosis can be suggested clinically with the assistance of a good history, exam, and appropriate imaging. Thus, it is commonly suggested that surgery should be reserved for therapeutic purposes rather than diagnosis.

A history suggestive of endometriosis would include the symptoms discussed earlier (i.e., a long history of disabling dysmenorrhea, chronic pelvic pain, dyspareunia, infertility, irritable bowel type symptoms, fatigue, depression, and anxiety). Depending on the severity of disease, the physical examination may vary. In the case of superficial endometriosis, lesions cannot be palpated on bimanual exam. Endometriomas may be palpable on bimanual or abdominal examination depending on the size. Adnexal tenderness may also be present. Deeply infiltrating nodules of endometriosis are often palpable on bimanual and rectovaginal examination as uterosacral nodularity, retroflexion of the uterus, and fixation of the posterior cul-de-sac. When concomitant myofascial or painful bladder syndrome symptoms are present, levator ani pain and bladder pain may also be present.

Transvaginal ultrasonography is the initial imaging study of choice and when possible, should be performed in the late secretory phase of the menstrual cycle given that this is when the disease is most active. Superficial lesions are often not visible on transvaginal ultrasonography but endometriomas can be reliably diagnosed with this imaging modality [33]. For cases of DIE, transvaginal and transrectal ultrasonography can be useful for the identification of lesions involving the rectovaginal septum, parametrium, and uterosacral ligaments [34]. However, ultrasonography is highly operator-dependent and it can lack sensitivity for smaller nodules of DIE [33]. In addition, many facilities lack the option to provide transrectal sonographic imaging.

T1 and T2-weighted magnetic resonance imaging (MRI) with and without fat suppression can reliably diagnose small nodules when DIE is suspected but transvaginal ultrasound is equivocal. MRI should be performed with and without gadolinium. When bladder involvement is suspected, ensuring a full bladder during MRI may enhance the ability to recognize nodules. When rectal involvement is suspected, a bowel prep followed by an antispasmodic agent to reduce artifact from peristalsis may also enhance the sensitivity of MRI [35].

In cases where bladder and/or ureteric endometriosis are suspected, renal ultrasonography and intravenous urography can assist with diagnosis. In addition, rectosigmoidoscopy should be performed, ideally during menses, if rectal infiltration is suspected [12].

Treatment of Endometriosis

Medical Therapy

Treatment algorithms are dependent on patient symptomatology, location of lesions, and desire to conserve the option for future child-bearing. In patients presenting with mild to moderate pain and without the desire for immediate conception, empiric medical therapy is appropriate. First-line regimens include combined oral contraceptives (COCs) and progestins. There is abundant observational data to support the use of combined oral contraceptives (COCs) for the relief of endometriosis-related pain. COCs act to cause an inactivation of implants through a process of decidualization [36]. Regimens for oral contraceptives may be cyclic but extended cycle and continuous regimens are often used for women with disabling dysmenorrhea. COCs have a good side effect profile and are generally well-tolerated by patients. For women on extended cycle and continuous regimens, break through bleeding is the most common side effect [37]. For women who are not candidates for estrogen containing therapy, progestins alone are utilized. These agents inactivate endometrial implants by antagonizing the effects of estrogen. One randomized trial examined the effectiveness of medroxyprogesterone acetate against placebo to cause regression of endometriotic implants. Women who received medroxyprogesterone acetate had significant reduction of lesions after 6 months on second-look laparoscopy when compared to women who received placebo. Symptoms were improved in the medroxyprogesterone acetate group as well [38]. Other progestins have also been shown to improve symptoms related to endometriosis, such as norethindrone acetate and the levonorgestrel intrauterine device [39, 40]. Side effects of progestins can include weight gain, edema, acne, and irregular bleeding which may limit their acceptability by the patients.

For women with symptoms refractory to COCs and progestins, second-line agents include gonadotropin releasing hormone (GNRH) agonists, such as leuprolide acetate. There is a strong evidence supporting the efficacy of GNRH agonists to reduce pain related to endometriosis. However, GNRH agonists also lead to a hypoestrogenic state simulating menopause and side effects can be poorly-tolerated. These include significant loss of bone mineral density and vasomotor symptoms (hot flashes) [41]. Combining GNRH agonists with low dose "add-back" hormone therapy significantly reduces the hypoestrogenic effects and makes the regimen more tolerable for patients. Aromatase inhibitors have been more recently introduced as a potential treatment for endometriosis-related pain. Several studies have shown that these agents reduce pain symptoms in women with endometriosis. When used alone, they share a similar side effect profile to GNRH agonists that make them difficult to tolerate. However, recent study of aromatase inhibitors with combined oral contraceptives showed significant pain relief with an improved acceptability. This option remains promising for otherwise refractory cases but is not yet widely utilized. Androgens, such as danazol, have also been shown to significantly reduce the size of endometriotic lesions and improve the pain symptoms, but have significant androgenic effects making them generally not well-accepted by patients [2].

Surgical Therapy

When symptoms are refractory to medical therapy, or in circumstances that preclude the use of medical treatments, surgery is the next approach to treatment. For superficial disease, studies comparing surgical treatment through excision or ablation of endometriotic lesions show a significant improvement in pain (63 % versus 23 %) when compared to expectant management. Studies comparing ablative techniques, such as laser ablation versus electrosurgical ablation, have not found a difference in symptom relief [42]. In addition, studies assessing excisional removal versus ablative removal of superficial endometriotic lesions did not show a significant difference in symptoms [42].

In the case of endometrioma, moderate level data supports excisional surgery for the relief of pain symptoms. Women with small endometriomas that are asymptomatic present a challenge, as there is little data to suggest that excisional therapy has benefits over medical management [43].

For the management of deeply infiltrative endometriosis associated with moderate to severe pain, excisional surgery is the current standard of care. However, surgery for DIE is technically challenging and up to 35 % of women need a bowel resection as part of their management [44]. Thus, surgical expertise and a multidisciplinary approach involving colorectal surgery are necessary to safely complete this type of surgery.

A number of studies have demonstrated relief of pain with excisional surgical treatment for DIE. In 2014, Fritzer and colleagues, performed a systematic review of three studies that included a total of 128 patients. The authors assessed surgical intervention for the management of refractory pain in women with deeply infiltrative endometriosis. Significant reductions in overall pain and sexual function were seen [45]. The authors noted that though pain was improved and complications were rare, the surgeries required were often radical, thus, putting patients at risk for related complications. The most commonly reported complications were hemorrhage requiring transfusion and formation of rectovaginal fistula. A prospective cohort study of 83 patients with rectovaginal endometriosis evaluated long-term outcomes after radical excisional surgery. Though the majority of patients had improvement in symptoms, about 40 % of these patients required bowel resection. In addition, the study showed a 30 % rate of recurrence over time [46]. Complications included bladder denervation with associated atony, and hemorrhage requiring transfusion.

With regards to the surgical treatment of endometriosis for infertility, well-designed trials are lacking. A randomized control trial comparing diagnostic laparoscopy with excisional or ablative removal of mild endometriosis showed a statistically significant, but clinically modest, improvement in cumulative pregnancy rates in women with surgical removal. A subsequent smaller trial showed no difference in pregnancy rates in women who had a diagnostic surgery versus a therapeutic surgery [47]. In women with endometrioma, surgical removal of endometriomas increases the likelihood of conception in infertile women but also has the effect of diminishing ovarian reserve. In women with deeply infiltrative disease, one prospective cohort study assessing women with rectovaginal endometriosis evaluated pregnancy rates between those who underwent surgery and those who had expectant management. Pregnancy rates were equivalent in the surgical and expectant management groups [48].

Thus, the general approach to the treatment of endometriosis is medical therapy for mild pain symptoms with surgery reserved for moderate to severe symptoms refractory to medical therapy or for circumstances precluding the use of hormonal therapy. The potentially radical nature of surgery and the associated risk of complications necessitates appropriate patient counselling prior to the decision to move forward with surgery. Women should be counseled that surgery may temporarily alleviate pain, but that recurrence is common. Women with infertility and significant pain are not hormonal therapy candidates and, thus, should be offered surgery. However, these patients should be counseled that pregnancy rates have not been shown to improve substantially after surgery and that assistive reproductive technology should be considered. Women with infertility who plan undergoing in vitro fertilization but significant anatomic distortion may also require surgery for anatomic restoration to facilitate safe oocyte retrieval.

Preoperative Assessment

The initial step in assessing a patient with suspected deep infiltrating endometriosis of the rectum involves taking a thorough history. Of particular importance is ascertaining whether or not the patient is experiencing any pain. This includes obtaining a detailed history on multiple components of pain including the location, severity, timing, and whether the pain is associated with any rectal bleeding. Pain associated with rectal bleeding is particularly concerning as it may be due to full thickness erosion of the rectum secondary to the endometriosis. Temporal relationship of pain with menses should be investigated as this may signal endometriosis, particularly DIE [49]. Dyspareunia and dyschezia are other symptoms that are frequently present in rectal endometriosis.

The next step in the assessment includes obtaining a thorough surgical history. The purpose of this is two-folds. First, it prepares the surgeon for adhesive disease from prior surgery, though DIE often presents as dense adhesions involving the colon, uterus, ovaries, fallopian tubes, and ureters. Second, and more importantly, it determines whether a minimally invasive surgical approach (MIS) is realistic. The presence of adhesions makes an MIS approach more difficult, and many surgeons will opt for an open approach if there is a significant history of surgeries. However, it should be noted that this practice varies from surgeon to surgeon based on preference and surgical expertise. As with taking any other surgical history, it is important to document the date of the surgery, the primary surgeon, and to note whether there were any complications in the surgery.

As part of the history, it is imperative to inquire about any family inheritance of colorectal conditions including, but not limited to, colon and rectal cancer, inflammatory bowel disease, and hemorrhoids. Any family history of cancer should also be fully explored in depth, whether the cancer is of a colorectal nature or not. Further questioning should also attempt to deduce whether the patient is suffering from any fecal incontinence (FI). Though FI is not particularly associated with endometriosis, it is an important consideration as low anterior resections (LAR) are associated with exacerbation of FI due to loss of the rectal reservoir.

After a thorough history has been obtained, the next step is an in-depth physical examination. In particular, the presence of any abdominal incisions should be noted, specifically checking around the umbilicus and for the presence of any smaller scars for past incisions. Tenderness to palpation or the presence of any palpable masses increases the suspicion for endometriosis. The most important aspect of the physical exam in these patients, however, is the digital rectal exam (DRE). This will yield a great deal of information about the patient. On this part of the exam, the surgeon may be able to palpate areas of endometriosis in addition to assessing the strength of the anal sphincter. The strength of the anal sphincter can be determined by having a patient bear down while the surgeon is performing the DRE. A bimanual examination will yield even further information, possibly revealing the presence of endometriosis in the rectovaginal septum or thickened uterosacral ligaments upon palpation. Lastly, a proctoscopy performed outpatient may allow the surgeon to visualize deeply infiltrating endometriosis, and how proximal it is relative to the anal sphincters. This ultimately will allow the surgeon to gage how low any future anastomosis will need to be.

Whether or not endometriosis is suggested based on physical examination, it is important to obtain imaging to further elucidate the extent of disease. As noted in the "Diagnosis" section earlier, transvaginal ultrasound (TVUS) is still the preferred starting diagnostic imaging study with a relatively high sensitivity [30, 50]. If transrectal ultrasonography is readily available, it should be offered [34], but more than likely MRI is the initial next step if DIE of the rectum is suspected [35]. Additionally, further imaging with the use of a colonoscopy should be obtained prior to any surgical intervention to rule out full thickness erosion or any other colonic pathology such as colon cancer or bowel stenosis.

If surgery is agreed upon, consent is obtained from the patient, and the surgeon should discuss shaving as well as LAR with a possible loop ileostomy [30, 51, 52]. If an ileostomy is considered likely based on the preoperative assessment, the patient should be counseled as such, and preoperative the ostomy site should be determined prior to surgery. Extensive counselling about shaving lesions, discoid resection, low anterior resection, and possible loop ileostomy should be discussed prior to the surgery.

Surgical Technique

The goal of surgical management of endometriosis is to destroy or remove all visible lesions of endometriosis and to restore normal anatomy. For superficial lesions, either ablative or excisional procedures may be utilized. Ablative techniques include electrocautery or Argon Neutral Plasma Energy. Excisional techniques include sharp dissection of lesions and the involved peritoneum as well as respective procedures of the bowel, bladder, vagina, uterosacral ligaments, and ureters when invasive disease is present. Laparoscopic management of endometriomas and superficial endometriosis is considered the standard of care [42]. In addition, there are increasing reports of laparoscopic management of DIE, even in cases where bowel resection is necessary [53]. More recently, the benefits of a robotic surgical approach for the surgical management of endometriosis have been examined. Thus far, limited data suggests comparable outcomes between conventional laparoscopy and robotic-assisted laparoscopy, but a longer operating time [54]. Proponents of robotic surgery suggest that the design advantages of the robotic platform, such as stereoscopic three-dimensional visualization, increased range of movement, and enhanced surgeon comfort, enable surgeons to complete complex dissections necessary for the surgical management of endometriosis. In cases of rectal involvement, robotic assistance has been shown to be feasible and safe with comparable outcomes to laparotomy [55].

Gynecologic Approach to Robotic-Assisted Surgical Treatment of Endometriosis

For a robotic approach, ideal patient positioning is in low lithotomy with arms tucked at the side. A foley catheter is placed to gravity drainage and a uterine manipulator placed to allow for appropriate retraction of the uterus during the surgery. In cases with severe rectovaginal involvement, the ureters are often displaced medially by adhesive disease.

Urology is, thus, typically consulted for the placement of lighted ureteral stents to allow for the identification of the ureters throughout the surgery. Several docking techniques have been reported. Both side docking and central docking are feasible. A Veress needle is used to achieve pneumoperitoneum and a 12-mm optical midline port, usually at the umbilicus, is placed under visualization. The ports utilized for robotic arms one and two are placed about 8 cm laterally and slightly caudad on either side of the port accommodating the robotic laparoscope. Arm 3 is set 8 cm to the left of the port for robotic arm 2. When necessary, a 5- or 12-mm assistant port placed in the left upper quadrant.

Once the docking is complete, a monopolar scissor is placed in robotic arm 1, and a bipolar forceps is placed in arm 2. A grasping instrument is placed in arm 3. A careful exploration is undertaken to ensure all endometriotic lesions are visualized. Retroperitoneal dissection is often initiated lateral to the infundibulopelvic ligament with a cephalad to caudad approach. Careful traction and counter traction is utilized to incise the peritoneum. The incision is extended parallel to the infundibulopelvic ligament and the ureter is identified medially and dissected laterally, allowing for safe resection of the pelvic peritoneum involved with endometriosis. Similarly, a lateral to midline approach is utilized to create a plane between the ovaries, uterus, and rectum. If present, excision of uterosacral nodules and/or rectovaginal nodules is then completed. If rectal involvement is present colorectal is often consulted for management. One of three approaches may be utilized including shaving, discoid resection, and segmental bowel resection.

Colorectal Approach to Robotic-Assisted Surgical Treatment of Endometriosis

The discussion of optimal port placement and docking generally takes place prior to the surgery as the gynecologic surgeons are often initiating the case. A two-operative arm approach is utilized in most cases, but rarely, an extra left-sided upper abdominal part can be placed to utilize all three arms.

The initial step in the surgery is the identification of both ureters. A complete dissection and lateralization of the ureters is typically necessary for the gynecologic portion of the surgery and is performed by the gynecologic surgeon. Lighted ureteral stents placed by the urological service prior to the initiation of the case can also facilitate identification of the ureters.

Based on degree of rectal involvement, a multitude of approaches can then be taken. If the endometriosis is occluding less than 30 % lumen diameter, the surgeon can try to shave-off the areas of endometriosis. It is important that cautery is not used for shaving, and instead a surgical knife is utilized. Once shaven, the thin areas can then be oversewn to prevent tears from forming. An on-table colonoscopy can then be performed to look for leaks and thin areas under transillumination. If there is an involvement of greater than 30 % of the lumen, a formal lower anterior resection should be performed. Additionally, if the anastomosis is less than 6 cm from the anal verge, a divergence with a proximal loop ileostomy should be performed.

DIE generally obliterates the planes laterally and anteriorly along the rectum and, thus, a posterior approach is used initially to avoid dense adhesions. Dissection beneath the upper rectum, just adjacent to the rectal mesentery to avoid inadvertent injury to nerve fibers emanating from the sacral promontory, allows access to the presacral space. Throughout the dissection, the left ureter, which has typically been dissected by the gynecologic surgeon, is traced medially as it traverses under the sigmoid and into the pelvis to avoid injury. With care to preserve the inferior mesenteric artery, the total mesorectal plane is completely dissected posteriorly beyond the coccyx. The lateral dissections are then completed until the rectum is released, circumferentially. The final dissection is anteriorly as this is the area typically involved with endometriosis. Once the adhesions between the uterus ovaries are released, and the anterior rectum is visible, an assessment can be made as to whether a "shaving" technique of DIE is safe and feasible, or whether a formal resection is indicated. In our practice, the lesion is shaved if less than 30 % of the anterior wall of the rectum is involved. Visual haptics can facilitate the identification of the borders of the nodule of DIE. DIE is often fibrous and dense, creating a hard nodule, while the borders of the normal rectum are much softer in appearance. If a shaving approach is feasible, a sharp dissection is completed with a robotic scissor and interrupted 2-0 polyglactin 910 stitches are placed to imbricate the thinned area of rectum. If the endometriosis is invasive to the point where a full thickness excision is needed, but <30 % of the lumen is involved, a discoid resection is completed and interrupted 2-0 polyglactin 910 stitches are placed to close the defect. An intraoperative sigmoidoscopy is subsequently completed for both the shaving and discoid resection approaches to ensure an airtight repair.

If the endometriosis is deemed infiltrative and involves >30% of the lumen, a resection procedure is completed. Dissection is completed both proximally and distally such that resection can be completed with margins uninvolved by endometriosis. Subsequently, the mesentery of the rectum is dissected distally and ligated with the robotic vessel sealer. The sigmoid and left colon are mobilized sufficiently to exteriorize the colon through a widened left lower quadrant port. The proximal transection is then completed through the abdominal incision with care to ensure margins are clear from endometriosis. A purse string stitch is placed around the circumference of the lumen. Intravenous indocyanine green 3 cc/10 mg is injected and the robotic Firefly system is utilized to ensure sufficient perfusion to the descending colon. A 29 EEA anvil is then placed into the descending colon and the purse string is tied down. An intracorporeal anastomosis is, subsequently, completed with a 29 EEA stapler. The anastomosis is checked using a sigmoidoscope and an air leak test is completed with the anastomosis under irrigation fluid. A diverting loop ileostomy is placed if the anastomosis is less than 6 cm from the anal verge.

Postoperative Care

Postoperatively, patients who undergo any colorectal procedure (shaving, discoid resection, or segmental resection) are admitted for close monitoring as they are at high-risk for postoperative complications. In one cohort, 20 % of patients who underwent bowel resection for DIE experienced at least one major complication [48]. Among the most common is rectovaginal fistula. Patients are also at risk for pelvic infection and the need for reoperation should be counseled as such. Close follow-up by both the gynecologic and colorectal services postoperatively is imperative for optimal outcomes. With appropriate patient selection as well as coordinated and standardized care, a multidisciplinary approach to the management of DIE can optimize surgical outcomes and potentially lead to sustained remission of symptoms.

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Notes:

RANZCOG: The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. FOGSI: Federation of Obstetric and Gynecological Societies of India.

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* Data On file.

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Abbreviated Prescribing Information. Dydrogesterone Tablets IP. Duphaston® Composition: Each white film-coated tablet contains: Dydrogesterone IP 10 mg. Excipients q.s. Colour: Titanium dioxide IP. Indications: Progesterone deficiencies, Treatment of progesterone deficiencies such as: • Treatment of dysmenorrhoea • Treatment of endometriosis • Treatment of secondary amenorrhoea • Treatment of irregular cycles • Treatment of dysfunctional uterine bleeding • Treatment of pre-menstrual syndrome • Treatment of threatened and habitual abortion • Treatment of infertility due to luteal insufficiency. Hormone replacement therapy - To counteract the effects of unopposed oestrogen on the endometrium in hormone replacement therapy for women with disorders due to natural or surgical induced menopause with an intact uterus. Dosage and Administration: Dosages, treatment schedule and duration of treatment may be adapted to the severity of the dysfunction and the clinical response. Dysmenorrhoea: 10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. Endometriosis: 10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously. Dysfunctional uterine bleeding: When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days. For continuous treatment, 10 or 20 mg dydrogesterone per day should be given during the Second half of the menstrual cycle. The starting day and the number of treatment days will depend on the individual cycle length. Withdrawal bleeding occurs if the endometrium has been adequately primed with either endogenous or exogenous estrogen. Secondary amenorrhoea: 10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen. Pre-menstrual syndrome: 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Irregular cycles: 10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Threatened abortion: An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30mg per day until symptoms remit. Habitual abortion: 10 mg dydrogesterone twice daily until the twentieth week of pregnancy. Infertility due to luteal insufficiency: 10 or 20 mg dydrogesterone daily starting with the Second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles. Hormone replacement therapy: Continuous sequential therapy: An estrogen is dosed continuously and one tablet of 10 mg dydrogesterone is added for the last 14 days of every 28 day cycle, in a sequential manner. Cyclic therapy: When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12-14 days of estrogen therapy depending on the clinical response, the dosage can subsequently be adjusted to 20 mg dydrogesterone per day There is no relevant use of dydrogesterone before menarche. The safety and efficacy of dydrogesterone in adolescents aged 12-18 years has not been established. Currently available data are described in section 4.8 and 5.1, but no recommendation on a posology can be made. Contraindications: Known hypersensitivity to the active substance or to any of the excipients. Known or suspected progestogen dependent neoplasms. Undiagnosed vaginal bleeding. Contraindications for the use of estrogens when used in combination with dydrogesterone. Warnings and Precautions: Before initiating dydrogesterone treatment for abnormal bleeding, the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. Pregnancy and Lactation: Pregnancy: It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Some progestogens have been reported in the literature to be associated with an increased risk of hypospadias. However due to confounding factors during pregnancy, no definitive conclusion can be drawn regarding the contribution of progestogens to hypospadias. Clinical studies, where a limited number of women were treated with dydrogesterone early in pregnancy, have not shown any increase in risk. No other epidemiological data are hitherto available. Effects in non-clinical embryo-fetal and post-natal development studies were in line with the pharmacological profile. Untoward effects occurred only at exposures which exceeded the maximum human exposure considerably, indicating little relevance to clinical use. Dydrogesterone can be used during pregnancy if clearly indicated. Breastfeeding. No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicates that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period. Fertility: There is no evidence that dydrogesterone decreases fertility at therapeutic dose. Adverse Reactions: The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness. Undesirable effects that are associated with an estrogen-progestogen treatment : Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer • Venous thromboembolism • Myocardial infarction, coronary artery disease, ischemic stroke. Issued on: 3/4/14. Source : Prepared based on full prescribing information (version 03) dated 13/03/2015.