Chapter 2
Pre-conception Risk Assessment: Gynaecological Problems

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Introduction

Infertility has increased in Western societies; one in six couples will encounter problems with fertility. Infertility is defined as failure to achieve a clinical pregnancy after regular intercourse for 12 months. Women are delaying childbearing due to life style changes like completing higher education, following a career and seeking for financial independence. Increasingly, infertile couples are using assisted reproductive technology (ART) in order to achieve a pregnancy. This chapter aims to cover gynaecological pathologies like fibroids, polyps, uterine anomalies, endometriosis, adenomyosis and hydrosalpinx which can adversely influence reproductive outcome. Furthermore, the pathology, effect on fertility and pregnancy and evidence based management of those gynaecological conditions are described here.

Fibroids

Uterine fibroids (leimyoma) are benign tumours of uterine smooth muscles and have an estimated prevalence of 20–40 % of women during their reproductive years [1]. Fibroids are classified according to their location in the uterus (submucous, intramural and subserous) and can be single or multiple. A relationship between uterine fibroids and infertility has been recognised. Women wishing to conceive are

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more likely to present with uterine fibroids due to the delay in childbearing. The effect of fibroids on fertility depends on the location of the uterine fibroid. Submucosal fibroids interfere with fertility and removal is recommended. Subserosal fibroids do not have an effect on fertility while the effect of intramural fibroids is controversial.

Most fibroids are asymptomatic, but they can also cause symptoms such as abnormal uterine bleeding, pelvic pressure and pain, infertility and miscarriage.

The diagnosis is made by ultrasound or magnetic resonance imaging (MRI). It is important to assess the number, size, location and any disruption of the junctional zone.

Effect on Fertility and Pregnancy

Submucous Fibroids

Submucous fibroids may contribute to miscarriage and infertility possibly by an effect on embryo implantation. The most common classification of submucous fibroids developed by the European Society of Gynaecological Endoscopy describes them according to the location to the uterine cavity. Type 0 fibroids are entirely in the uterine cavity, type 1 fibroids are ≥50 % and type 2 fibroids are ≤50 % located in the uterine cavity.

Improvement of reproductive outcomes has been shown after removal of submucous fibroids. A retrospective study observed a significant reduction in pregnancy loss and increase in live births after hysteroscopic myomectomy in women with infertility and recurrent pregnancy loss [2]. A prospective, randomised controlled study of hysteroscopic myomectomy versus hysteroscopy and biopsy in patients with unexplained primary infertility showed a statistically significant increase in spontaneous pregnancies in women following myomectomy (type 0: 57.9 % vs. 33.3 %, $p<0.001$; type 1: 35.7 % vs. 17.2 %, $p<0.001$) [3]. Women with submucosal fibroids undergoing IVF treatment have reduced pregnancy rates [4, 5] whereas hysteroscopic myomectomy improves pregnancy rates in women undergoing IVF treatment [6].

However, there is still controversy about the effect of intramural fibroids on reproductive outcomes. The exact mechanisms through which fibroids interfere with reproduction are not clear, but could include anatomical distortion, disruption of the uterine junctional zone, alteration of uterine contractility or endometrial blood supply or receptivity [7–9].

Intramural Fibroids

Some studies have shown a negative effect of intramural fibroids on IVF outcomes [10, 11] whereas other studies did not find an effect [12–15]. The first systematic review on fibroids and infertility did not show an effect of intramural

fibroids on infertility [16]. An updated systematic review demonstrated a possible negative effect of intramural fibroids on reproductive outcomes [17]. Nevertheless, removal of intramural fibroids did not seem to improve significantly reproductive outcome [16, 17]. Another systematic review looked into the effect of intramural fibroids without cavity distortion and found a negative impact on IVF outcomes in women with intramural fibroids when compared to women without fibroids [18]. The most recent systematic review and meta-analysis initially confirmed a negative impact of intramural fibroids on clinical pregnancy rates, but not on live birth or miscarriage rates [19]. However, there was no significant effect of intramural fibroids on reproductive outcomes when only high quality studies were included and removal of intramural fibroids did not significantly improve clinical pregnancy or miscarriage rates [19]. This highlights the need for more good quality studies regarding the effect of intramural fibroids on reproductive outcomes.

In the meantime, the management of women with intramural fibroids needs to be individualised and any involvement of the uterine cavity needs to be excluded. However, many clinicians consider removal of intramural fibroids larger than 4 cm.

Subserosal Fibroids

Subserosal fibroids seem to interfere less with fertility unless they distort reproductive organs such as fallopian tubes. A prospective controlled study could not find a significant difference in pregnancy rates in women with removal of subserous fibroids compared to controls [20]. Other studies have also not demonstrated a negative effect of subserous fibroids on pregnancy rates following IVF [4, 5, 12]. Therefore, surgery for subserous fibroids in asymptomatic, infertile women is not recommended.

Management

Hormonal Treatment

Fibroids are hormone-sensitive tumours with sex steroid receptors [21]. Estrogens and progestogens enhance tumour growth. Medical treatment in the form of gonadotropin-releasing hormone analogue (GnRHa) can be given prior to myomectomy in order to reduce the size of the fibroid [22]. However, prolonged use can cause estrogen deficiency and a decrease in bone mineral density. Another medical treatment is the use of selective progesterone receptor modulators (SPRM) with mixed agonist/antagonist activity. Studies have confirmed the efficacy and safety of the SPRM ulipristal acetate (Esmya®) for the treatment of fibroids preoperatively [23–26]. However, the effect on subsequent fertility is as yet unknown.

Interventional Radiology

Uterine artery embolisation (UAE) occludes the uterine blood flow to the fibroid leading to necrosis and shrinkage [27]. Evidence suggests a 50–60 % reduction in fibroid size and 85–95 % symptom relief after UAE [28]. Complications include haematoma, thrombosis, pain, infection and vaginal discharge. The post-embolisation syndrome consists of pain, nausea, flu like symptoms, mild pyrexia and raised inflammatory markers.

UAE in women wishing to conceive is controversial. UAE has been associated with ovarian failure [29, 30] and the risk of infertility following the procedure is unknown. Pregnancies following UAE are at an increased risk of pre-term delivery, miscarriage, abnormal placentation and postpartum haemorrhage [31–34]. A randomised controlled trial looking into reproductive outcomes following UAE and myomectomy reported higher pregnancy and live birth rates and lower miscarriage rates in women following myomectomy [35]. Another study identified several atypical hysteroscopy findings 3–9 months following UAE including tissue necrosis, intracavitary fibroid protrusion and intrauterine adhesions [36].

A recent Cochrane review found low level evidence suggesting that myomectomy may be associated with better fertility outcomes than UAE [37]. Furthermore, women after UAE have an increased likelihood for further surgical intervention [37].

Magnetic resonance guided focused ultrasound surgery (MRgFUS) is a new method of thermal ablation for the treatment of fibroids beneath the anterior abdominal wall. However, only few patients are eligible for this new technique. Nevertheless, reproductive outcomes following this procedure are promising. A miscarriage rate of 26 % and a live birth rate of 41 % have been reported in women following this procedure [38].

Surgical Treatment

Hysteroscopic resection of a submucous fibroid is performed using a monopolar or bipolar resectoscopes. Complications include fluid overload that may lead to cerebral and pulmonary oedema, coagulopathy or death. Other complications are cervical laceration, bleeding, infection, uterine perforation (<1 %) and intrauterine adhesions. These risks are less with the use of bipolar technology.

Surgical treatment for intramural fibroids in the form of myomectomy can be performed abdominally or laparoscopically dependent on the position of the fibroid and the skills of the surgeon. Risks of myomectomy are intra-operative bleeding and formation of postoperative adhesions. The advantages of the laparoscopic procedure over an abdominal approach are reduction in postoperative pain, hospital stay and recovery [39]. However, laparoscopic myomectomy is technically challenging and time consuming. According to a systematic review there is no significant difference between those two approaches and fertility outcome [40].

Endometrial Polyps

Endometrial polyps are benign growths of the endometrium. Polyps can be single or multiple, sessile or pedunculated. Up to 25 % of women with unexplained infertility [41, 42] and 46.7 % of subfertile women with endometriosis [43] have endometrial polyps on hysteroscopy.

The relationship between endometrial polyps and subfertility is not entirely clear. However, endometrial polyps may affect fertility in many ways. They can interfere mechanically with sperm and embryo transport and implantation. Furthermore, polyps cause chronic inflammation and thereby make the endometrium unfavourable for implantation and interfere with the blood flow to the endometrium. A study suggested that endometrial polyps alter endometrial receptivity as reduced HOXA10 and HOXA11 mRNA levels, markers of endometrial receptivity, were found on endometrium with endometrial polyps [44]. In addition, the number, size or location may have an influence on reproductive outcome.

Endometrial polyps can present with irregular bleeding. However, most of them are asymptomatic and are found coincidentally as part of routine investigations for subfertility. They can be diagnosed by ultrasound, hysterosonography, hysterosalpingogram and hysteroscopy. The gold standard for the diagnosis of endometrial polyps is hysteroscopy and treatment can be offered at the same time.

Effect on Fertility

Observational studies suggest a better reproductive outcome following removal of polyps by operative hysteroscopy [45, 46]. A randomised controlled trial looked at the effect of endometrial polyps on the pregnancy rate in women undergoing intrauterine insemination (IUI) procedure [47]. These patients had a hysteroscopy and polypectomy or hysteroscopy and biopsy of the polyp. The spontaneous pregnancy rate and the pregnancy rate following IUI treatment were significantly higher in the group of women with polypectomy when compared to the group of women with only polyp biopsy (68 % vs 23 %, $p < 0.001$) [47]. Another study looked at the location of the polyp and the effect on pregnancy and found that the removal of tubocornual polyps lead to higher pregnancy rates compared to the removal of polyps at other locations in the uterus [48].

A systematic review on the management of endometrial polyps in subfertile women included only 3 studies and found conflicting results with some evidence of an adverse effect of polyps on fertility [49]. Therefore, the review recommended removal of the polyp if detected prior to IVF treatment or an individualised approach when the polyp was detected during the IVF treatment cycle. The Cochrane review looked into hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities and concluded that polypectomy in women prior to IUI treatment might improve the pregnancy outcome and that more

good quality randomized controlled studies are necessary to assess the effectiveness of hysteroscopic polypectomy [50].

The effect of endometrial polyps on IVF remains unclear. Some studies suggest that endometrial polyps <2 cm in size have no impact on IVF outcome [51, 52]. Other studies could not confirm the effect of polyp size on fertility [47, 53, 54]. Stamatellos et al. demonstrated an increase in pregnancy rate following polypectomy independent of size or number of polyps [53]. Further studies are necessary to investigate the effect of large polyps, polyp location and number of polyps on IVF outcome.

Management

Polypectomy can be done by dilatation and curettage or hysteroscopy directed using scissors, loop electrode or morcellator. However, dilatation and curettage can remove endometrial polyps incompletely and is not recommended. Complication rates following hysteroscopic polypectomy are low with a polyp recurrence rate of 4.9 % [53].

If an endometrial polyp is detected during an IVF cycle treatment options include cycle cancellation and polypectomy or continuation of the cycle with cryopreservation and embryo transfer following polypectomy.

Overall, it is reasonable to remove an endometrial polyp prior to infertility treatment. This will provide a histological sample and also may improve reproductive outcome. Further studies on the effect of polyps on infertility and pregnancy are necessary.

Congenital Uterine Anomalies

Congenital uterine anomalies are mainly the result of a defect of development or fusion of the paired Mullerian ducts during embryogenesis. The most recent classification for uterine anomalies is the ESHRE/ESGE classification [55] (Table 2.1). The prevalence of uterine anomalies in the general population is between 1 and 3.5 %. Infertile women have a significantly higher incidence of Mullerian anomalies compared to fertile women [56].

Effect on Fertility and Pregnancy

The incidence of Mullerian anomalies in women with recurrent first trimester loss is estimated to be between 5–10 % and 25 % in recurrent second trimester loss [57]. Uterine anomalies are associated with infertility, miscarriage, malpresentations,

Table 2.1 Scheme of female genital tract anomalies according to the ESHRE/ESGE classification system

Uterine anomaly			Cervical/vaginal anomaly	
	Main class	Sub-class	Co-existant class	
U0	Normal uterus		C0	Normal cervix
U1	Dysmorphic uterus	(a) T-Shaped (b) Infantilis (c) Others	C1	Septate cervix
U2	Septate uterus	(a) Partial (b) Complete	C2	Double "normal" cervix
U3	Bicorporeal uterus	(a) Partial (b) Complete (c) Bicorporeal septate	C3	Unilateral cervical aplasia
U4	Hemi-uterus	(a) With rudimentary cavity (communicating or not horn) (b) Without rudimentary cavity (horn without cavity/no horn)	C4	Cervical aplasia
U5	Aplastic	(a) With rudimentary cavity (bi- or unilateral horn) (b) Without rudimentary cavity (bi- or unilateral uterine remnants/aplasia)	V0	Normal vagina
U6	Unclassified malformations		V1	Longitudinal non-obstructing vaginal septum
			V2	Longitudinal obstructing vaginal septum
			V3	Transverse vaginal septum
			V4	Vaginal aplasia

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placental abruption, intrauterine growth restriction, preterm labour, retained placenta and fetal mortality [56, 58]. This may be due to diminished muscle mass, abnormal uterine blood flow and cervical insufficiency. One study looked at IVF outcomes in women with untreated uterine malformations and found significantly lower implantation and pregnancy rates when compared to the general population [59]. A correct diagnosis of the malformation is important for correct treatment. Mullerian anomalies are often associated with kidney and skeletal malformations.

Septate Uterus

The septate uterus is the most common structural uterine anomaly [56] and is caused by an incomplete resorption of the partition between the fused Mullerian ducts. The diagnosis can be made by HSG with accuracy between 20–60 % and together with an ultrasound examination the diagnostic accuracy improves to 90 % [60]. It is difficult to distinguish between bicornuate uterus and septate uterus by HSG alone as the uterine fundus is not visualised. Transvaginal ultrasound has a sensitivity of

100 % and specificity of 80 % in the diagnosis of the septate uterus [61]. Three-dimensional (3D) ultrasound (92 % sensitivity) [62] and magnetic resonance imaging (MRI) (100 % sensitivity) can also be used as a diagnostic tool [61]. However, the gold standard is hysteroscopy and laparoscopy.

Among the different types of uterine anomalies, the septate uterus is associated with the poorest reproductive outcome. The septate uterus maybe associated with pregnancy loss [63] and infertility [64].

Management

Hysteroscopic metroplasty is performed with scissors, electrosurgery or laser under ultrasonographic or laparoscopic control. This improves pregnancy outcome in women with recurrent miscarriage and 80 % term live birth rate has been reported following the procedure compared to 3 % before the procedure [63]. Most studies of metroplasty have looked into women with recurrent miscarriage. There is controversy whether metroplasty is helpful in infertile patients. However, a prospective controlled study looked into women with a septate uterus and unexplained infertility who underwent metroplasty versus women where metroplasty was not performed found a significantly higher live birth rate following metroplasty (34.1 % vs. 18.9 %) [65]. Another study reported a 29.5 % live birth rate after hysteroscopic metroplasty in women with otherwise unexplained infertility [64]. Furthermore, IVF is more successful in women following metroplasty [59].

Unicornuate Uterus

Unicornuate uterus results from a fusion defect of the Mullerian ducts with one cavity being normal with a fallopian tube and cervix, whereas disrupted development is seen in the other horn. The other horn can be completely absent or rudimentary with or without a cavity that may connect to the primary horn. 40 % of women with a unicornuate uterus have an associated urinary tract anomaly [66].

Unicornuate uteri are more common in women with infertility and miscarriage than the general population. Furthermore, they are associated with poor obstetric outcome with a live birth rate of only 29.2 %, prematurity rate of 44 %, miscarriage rate of 29 %, and ectopic pregnancy of 4 % [67]. Another review of 151 women with a unicornuate uterus had 260 pregnancies and a mean miscarriage rate of 37.1 %, mean preterm delivery rate of 16.4 % and the mean term delivery rate of 45.3 % [68]. However, different types of unicornuate uterus are associated with different reproductive outcomes depending on the vascular supply, muscular mass of the myometrium and degree of cervical competence.

The rudimentary horn can contain functional endometrium which can lead to endometriosis, haematometra, pelvic pain and pregnancy with a risk of uterine rupture. Therefore, removal of the uterine horn containing endometrium by laparoscopy or laparotomy is recommended. However, there is no evidence that removal of the rudimentary horn improves reproductive outcome.

Bicornuate Uterus

The bicornuate uterus results from an incomplete fusion of the two Mullerian ducts and is a common uterine anomaly (46.3 %) [57].

Bicornuate uteri are more common in women with infertility and miscarriage than the general population. Women with a bicornuate uterus are at increased risk of second trimester miscarriage and preterm birth. They usually do not need any surgical intervention. The mildest form of the bicornuate uterus is the arcuate uterus and does not necessitate surgery. A systematic review showed an increased rate of second trimester miscarriage and fetal malpresentations at delivery in women with an arcuate uterus [69].

Uterus Didelphys

Complete failure of fusion of the two Mullerian ducts results in the uterus didelphys with a duplication of uterus and cervix and sometimes bladder, urethra, vagina and anus [70]. The uterus didelphys is more common in infertile women and women with a miscarriage than the general population. There is an increased risk of preterm birth and fetal malpresentations [68].

Intrauterine Adhesions

The main reasons for the formation of intrauterine adhesions are previous intrauterine surgical procedures such as curettage and hysteroecopic resection of fibroids or a uterine septum. It may also follow uterine infections [71]. Taskin et al. reported the presence of intrauterine adhesions in 6.7 % (1/15) of women after resection of septa, 31.3 % (10/32) after hysteroscopic resection of a solitary fibroid and 45.5 % (9/20) after resection of multiple fibroids [72]. These intrauterine adhesions are also known as Asherman Syndrome.

The patients can be assessed with transvaginal ultrasonography, saline infusion sonohysterography, hysterosalpingography (HSG) or hysteroscopy. Intrauterine adhesions appear as filling defects on HSG. HSG has a sensitivity of 75 % and a positive predictive value of 50 % in the detection of intrauterine adhesions [73]. On ultrasound, adhesions appear as dense echoes within the cavity with irregular thickness of the endometrium. Sometimes, there are echo lucent areas interrupting the endometrium which represent collected blood. However, ultrasound has a low sensitivity (52 %) in the diagnosis of intrauterine adhesions [74].

There is no clear consensus regarding the optimum classification of intrauterine adhesions. The widely used American Fertility Society classification includes the extent and type of the adhesions found on hysterosalpingography or hysteroscopy and the menstrual pattern (Table 2.2) [75]. The European Society of Gynaecological Endoscopy (ESGE) formulated a classification of intrauterine adhesions depending on the extent of intrauterine adhesions from findings at hysteroscopy and hysterography (Table 2.3).

Table 2.2 American Fertility Society classification of intrauterine adhesions 1988

Classification	Condition		
Cavity involved	<1/3	1/3-2/3	>2/3
	1	2	3
Type of adhesions	Filmy	Filmy and dense	Dense
	1	2	3
Menstrual pattern	Normal	Hypomenorrhoea	Amenorrhoea
	0	2	4
Prognostic classification		HSG score	Hysteroscopy score
Stage I (mild)	1–4		
Stage II (moderate)	5–8		
Stage III (severe)	9–12		

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Table 2.3 European Society of Gynecological Endoscopy (ESGE) classification of intrauterine adhesions (IUA) (1995)

Grade	Extent of intrauterine adhesions
I	Thin or filmsy Easily ruptured by hysteroscope sheath alone, corneal areas normal
II	Singular dense adhesion Connecting separate areas of the uterine cavity Visualization of both tubal ostia possible Cannot be ruptured by hysteroscope sheath alone
IIa	Occluding adhesions only in the region of the internal cervical os Upper uterine cavity normal
III	Multiple dense adhesions Connecting separate areas of the uterine cavity Unilateral obliteration of ostial areas of the tubes
IV	Extensive dense adhesions with (partial) occlusion of the uterine cavity Both tubal ostial areas (partially) occluded
Va	Extensive endometrial scarring and fibrosis in combination with grade I or grade II adhesions with amenorrhea or pronounced hypomenorrhea
Vb	Extensive endometrial scarring and fibrosis in combination with grade III or grade IV adhesions with amenorrhea

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Effect on Fertility and Pregnancy

The volume of menstrual bleeding can indicate the reproductive prognosis as it tells how much healthy endometrial tissue is present. Women with this condition can present with amenorrhoea, hypomenorrhoea, dysmenorrhoea, recurrent pregnancy loss and infertility [76, 77]. Poor implantation following ART and abnormal placentation has been reported in women with intrauterine adhesions [76].

Management

Hysteroscopy is the gold standard for diagnosis and treatment of intrauterine adhesions. Hysteroscopic adhesiolysis with scissors, electrosurgery or laser can restore the size of the uterine cavity. Severe intrauterine adhesions may require multiple operations. The division of adhesions can be performed under ultrasound or laparoscopic guidance to prevent perforation of the uterus. Other complications of the procedure include haemorrhage and infection. The reformation of adhesions seems to be related to the severity of the adhesions. There are a number of surgical and hormonal approaches in order to prevent postoperative adhesion formation. Estrogen is used to help with endometrial proliferation following the procedure [78]. An intrauterine placement of a device helps with the mechanical separation of the endometrial walls. This can be in the form of an intrauterine copper coil or an intrauterine triangular balloon [78, 79]. Furthermore, adhesion barriers such as hyaluronic acid seem to be promising. A systematic review looked at the effect of anti adhesion barrier gels following operative hysteroscopy and could find a reduction in adhesions at second look hysteroscopy 3 months later [80]. The postoperative assessment of the uterine cavity after adhesiolysis is recommended 1–2 months following the initial surgery and can be in the form of a midcycle ultrasound to measure the endometrial thickness, HSG and hysteroscopy [81]. Early recognition of recurrence of adhesions is important to achieve the best outcome and reduce obstetric risks [78].

An overall pregnancy rate from 40 to 63 % has been reported following adhesiolysis [77, 82–84]. More recently, intrauterine adhesion treatment with resectoscope or versapoint with subsequent hormone therapy and intrauterine copper coil placement showed to have an overall live birth rate of 41 % [83].

The reproductive outcome is dependent on the menstrual pattern, the severity of the adhesions and recurrence following treatment [85]. Nevertheless, pregnancies following treatment of intrauterine adhesions are at high risk of spontaneous miscarriage, preterm delivery, intrauterine growth restriction, abnormal placentation or uterine rupture and require careful monitoring [76].

Endometriosis

Endometriosis is a condition whereby endometrial like cells are found outside the uterus. It is an estrogen dependent chronic inflammatory condition in women of reproductive age. Endometriosis can lead to dysmenorrhoea, deep dyspareunia, chronic pelvic pain, cyclical pain and infertility [86]. However, some women do not have any symptoms. The prevalence of endometriosis depends on diagnostic methods, but ranges between 25–40 % of infertile women and 0.5–5 % of fertile women [87]. The pathogenesis is still not clear and several explanations exist. One theory for the development of endometriosis is retrograde menstruation [88]. However, most women have retrograde menstruation and only a few develop endometriosis. Another explanation

is implantation of endometrial cells and coelemic metaplasia [89]. There is some evidence that there is a genetic component to the condition together with some environmental factors [90, 91]. Endometriosis may be a heterogeneous disease.

Common sites of endometriosis are pelvic peritoneum, ovaries and rectovaginal septum [92, 93]. An endometrioma is formed following the invagination of endometriotic deposits on the ovarian cortex, eventually forming what is commonly described as 'chocolate' cysts [93]. Ovarian endometriomas are found in 17–44 % of women with endometriosis [94, 95]. The gold standard to diagnose endometriosis is by laparoscopy and histological examination of the lesions. The extent of the disease has been classified in 4 stages (I–IV or minimal – severe) using the American Fertility (rAFS) System based on the laparoscopy findings. There is no correlation between the classification system and symptoms.

Effect on Fertility

Endometriosis is a chronic inflammatory condition. Moderate to severe endometriosis can lead to anatomical changes and thereby impair fertility. However, it is less clear how minimal to mild endometriosis interferes with fertility.

It has been suggested that ovulation, oocyte pick up by the fallopian tubes, fertilisation, embryo transport and implantation maybe disrupted in women with endometriosis [96].

Management

Hormonal medical treatment with progestins, oral contraceptives and gonadotropin releasing hormone agonists suppresses ovulation and menstruation and is not suitable for women seeking fertility. A Cochrane review showed that hormonal treatment in women diagnosed with minimal-mild endometriosis does not improve spontaneous conception [97, 98]. However, surgical treatment of minimal-mild endometriosis increases spontaneous conception rates compared to diagnostic laparoscopy (OR 1.64, 95 % CI 1.05–2.57) [99, 100]. Surgical treatment of infertile women with moderate to severe endometriosis also increases spontaneous pregnancy rates when compared to expectant management [101]. Surgery for deep infiltrating endometriosis is mainly performed to alleviate pain, but carries risk of major complications like ureteral and rectal injuries [102]. Furthermore, it may not greatly improve reproductive outcome [103]. Surgical treatment of endometriosis aims to remove visible endometriosis and restore the anatomy.

Assisted reproductive technology (ART) can be offered to infertile women with endometriosis. Stimulated IUI treatment in women with minimal to mild endometriosis maybe considered as it increases live birth rates compared to expectant management [104]. However, the most recent NICE guideline on fertility does not

recommend routine IUI treatment in women with mild endometriosis [105]. They recommend IVF treatment after a total of 2 years without conception. IVF treatment is offered to women with endometriosis as it overcomes anatomical distortion and the abnormal peritoneal environment. Nevertheless, the pregnancy rates are lower compared to women with tubal factor infertility and women with severe endometriosis have even lower pregnancy rates than women with mild endometriosis [106]. A systematic review looked at the effect of endometriosis on IVF outcome and reported reduced fertilisation rates in women with stage I/II endometriosis (RR = 0.93, 95%CI 0.87–0.99) [107]. Women with stage III/IV endometriosis had low implantation (RR = 0.79, 95%CI 0.67–0.93) and clinical pregnancy rates (RR 0.79, 95%CI 0.69–0.91) [108]. Nonetheless, prolonged down-regulation with GnRH agonist 3–6 months prior to IVF improves clinical pregnancy rates as confirmed by a meta-analysis of three randomized trials [108].

The management of endometriomas depends on factors like size and previous ovarian surgery. Conservative treatment of endometrioma maybe considered with a small size (<3 cm). Surgical excision of endometrioma may lead to damage of healthy ovarian tissue and can reduce the ovarian reserve [109, 110]. Therefore, surgery should be avoided in women with previous ovarian surgery. Surgical treatment may be considered in women with large endometriomas (>3 cm) to improve endometriosis-associated pain or accessibility during egg collection for IVF treatment [111]. Laparoscopic excision of endometrioma is the preferred treatment as it has a lower recurrence and higher spontaneous pregnancy rate compared to drainage or coagulation of the endometrioma [112]. Furthermore, cystectomy gives a histological diagnosis. When the endometrioma is very large a two step procedure (surgery followed by 3 months GnRH agonist treatment and repeat surgery) may be considered. Medical management in the form of GnRH analogue can reduce the size of the endometrioma. A study showed that the presence of endometrioma affected the number of oocytes collected for IVF treatment, but oocyte quality or clinical pregnancy rate was not affected when compared to women without endometrioma [113]. Studies have demonstrated that there is no cumulative recurrence risk of endometriosis following assisted reproductive technology (ART) [114–116].

Overall it is important to take into account the benefits and risks of surgery, medical treatment and ART when managing couples with endometriosis associated infertility.

Adenomyosis

Adenomyosis is a condition whereby ectopic endometrial islands are found in the myometrium and causes dysmenorrhoea, abnormal uterine bleeding and infertility. A recent meta-analysis confirmed a reduced clinical pregnancy rate and an increased miscarriage rate after IVF/ICSI treatment in women with adenomyosis [117]. There are several possible explanations for this detrimental effect, including a chronic

inflammatory condition [118], increased local estrogen production [119], uterine dysperistalsis leading to impaired utero-tubal sperm transport [120] and lower uterine receptivity suggested by the presence of implantation marker defects [121] and abnormal levels of intrauterine free radicals [122]. Adenomyosis is most commonly localised in the posterior uterine wall and can be diffuse or with focal nodules, also called adenomyoma. Adenomyosis is frequently encountered with other pathologies like endometriosis, polyps or fibroids. The diagnosis can be made with 2D/3D transvaginal ultrasound and MRI. 2D ultrasound criteria are globular uterus, asymmetry of uterine walls, poorly defined junctional zone and myometrial cysts [123]. An MRI is recommended if the uterus is enlarged or associated with a fibroid.

Pathogenesis

Multiple factors could be contributing to the pathogenesis of adenomyosis. One theory is that the basal layer of the endometrium invaginates between smooth muscle cell bundles or along lymphatic vessels into the myometrium [124]. Another theory is that adenomyosis may develop de novo through metaplasia of Mullerian remnants [125]. The relationship between adenomyosis and fertility is not exactly clear. On one hand adenomyosis is found in multiparous women and on the other hand it is seen in women with infertility and miscarriages [126].

Management

Medical and surgical treatments are available. Medical treatment is in the form of NSAIDs, progestogens and GnRH agonists. Women undergoing IVF treatment benefit from long agonist stimulation protocols with GnRH agonists [127]. However, women with adenomyosis had a lower clinical pregnancy rate on the antagonist cycle compared to women without adenomyosis (OR 0.4, 95%CI 0.18–0.92) [128]. A systematic review about adenomyosis and IVF outcome showed a 28 % reduction in the likelihood of a clinical pregnancy following IVF/ICSI [117].

Hydrosalpinx

Hydrosalpinges are found in 10–30 % of couples with tubal factor infertility and can be diagnosed by ultrasound or hysterosalpingogram.

Hydrosalpinx is a fluid collection in the fallopian tube due to distal tubal occlusion. The most common cause is pelvic inflammatory disease from Chlamydia trachomatis or Neisseria gonorrhoeae. A hydrosalpinx can also be a result of tubal tuberculosis, endometriosis, appendicitis or following abdomino-pelvic surgery.

Effect on Fertility and Pregnancy

It has been shown that implantation, pregnancy, and live birth rates are reduced by 50 % in women with hydrosalpinx [129–131]. Furthermore, miscarriage rates are doubled [130]. The presence of hydrosalpinx fluid in the uterine cavity is embryotoxic and alters the embryo endometrium receptivity as well as the tubo-uterine flow dynamics [132, 133].

Management

The management of hydrosalpinges involves the disruption of the tubo-uterine communication. A randomised controlled trial found that women following laparoscopic salpingectomy for hydrosalpinx prior to IVF doubled their live birth rates compared to women without surgery [134]. This interrupts the communication between the fallopian tube and the uterine cavity. A systematic review confirmed a doubling of clinical pregnancy rates following surgical treatment of hydrosalpinges (OR 2.14, 95 % CI 1.23–3.73) [135]. However, salpingectomy can reduce the blood supply to the ovary and thereby reduce the ovarian reserve. Studies looking into the ovarian response during IVF treatment did not show a significant difference in women who had a previous salpingectomy [136, 137]. If the surgical skills are present the tubal mucosa could be assessed and if found to be healthy a salpingostomy could be attempted. These patients need to be informed about the risk of an ectopic pregnancy. Laparoscopic tubal occlusion is possible if there are severe pelvic adhesions present. A systematic review confirmed a significant increase of pregnancy rates following this approach [135]. Laparoscopic tubal occlusion is as effective as laparoscopic salpingectomy in improving clinical pregnancy rates (RR 1.1, 95%CI 0.85–1.6) [138].

Hysteroscopic occlusion of the tube with the help of Essure® (Bayer, Whippany, NJ, USA) can be considered in women when laparoscopy is contraindicated. Essure® is a 4 cm long microinsert with polyethylene terephthalate fibres that induce a tissue reaction resulting in tubal occlusion. It is used for hysteroscopic tubal sterilisation. Initially there were concerns about the possible effect of the coils from the Essure® device protruding into the uterine cavity on implantation and pregnancy [139]. However, a study assessed the pregnancy outcome of 50 pregnancies following Essure® insertion and concluded that the device is unlikely to interfere with implantation and pregnancy [140]. A systematic review looked into the efficacy of Essure in the management of hydrosalpinx before IVF and found a 27.9 % live birth rate per embryo transfer (95 % CI 21.7–36.6 %) [141]. It appears that Essure ® is an effective treatment option for women with hydrosalpinges before IVF when the laparoscopic approach is contraindicated.

If a hydrosalpinx is detected during the IVF cycle freezing of all embryos can be considered followed by treatment of the hydrosalpinx. Transvaginal aspiration of the fluid after egg collection and embryo transfer showed a trend in increasing the

clinical pregnancy rate compared to no treatment, but this was statistically not significant (RR 1.7, 95 % CI 0.69–4.0) [142]. Further research is needed to assess the value of aspiration of hydrosalpinges.

In summary, laparoscopic surgical treatment should be considered for all women with hydrosalpinx before IVF. When laparoscopy is not recommended, hysteroscopic tubal occlusion seems the most effective option for the management of hydrosalpinx before IVF.

Conclusion

Gynaecological pathologies are frequently found in infertile women. The correct diagnosis is essential in order to counsel the couple on risks and benefits of treatment alternatives to allow informed choices. Medical and/or surgical and/or ART are available to increase the chances for a healthy pregnancy and live birth.

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