8 POLYCYSTIC OVARIAN DISEASE (PCO) AND INFERTILITY

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Introduction:

Polycystic ovarian Syndrome (PCOS) is commonly encountered in Infertility clinics in India where the syndrome is assuming epidemic proportions. The increasing prevalence of PCOS has paralleled with increase in obesity and metabolic syndrome amongst women in India.

Insulin resistance, hyperinsulinemia and chronic inflammation are considered as the most important etio-pathological underlying mechanism of PCOS. There are often other associated features of metabolic dysfunctions like dyslipidemia, dysglycemia and hypertension in these young women. It is thus imperative to screen women with PCOS for features of metabolic syndrome and underlying insulin resistance prior to and during addressing their fertility management.

Chronic anovulation is a hall mark of the diagnosis of PCOS besides clinical/biochemical hyperandrogenism and ultrasonic features of polycystic ovaries. Anovulation is the main causative feature for infertility in women with PCOS. Restoration/induction of ovulation is multimodal and rewarding for pregnancy outcome when a comprehensive management of these patients is extended beyond infertility treatment. If the underlying pathophysiology like pre-diabetes or pre-hypertension is neglected there are immediate and long-term adverse health consequences like gestational diabetes, pregnancy-induced hypertension, poor obstetric outcome, risks for cardiovascular diseases and endometrial proliferative diseases .

Management Of infertility in PCOS:

Diagnosis of PCOS demand ruling out of other endocrine causes which may have polycystic features on USG such as late-onset adrenal hyperplasia, primary hypothyroidism, Cushing's syndrome and establishing the diagnosis of PCOS as per Rotterdam criteria. Treatment modalities can be classified into four groups as follows: 1. Non-pharmacological Treatment, 2 Pharmacological Treatments, 3.Surgical Treatment, 4 Assisted Reproductive Technology (ART).

1. Non-pharmacological Treatment:

Life-style management modules consisting of nutrition, physical exercise, yoga, acupuncture and other stress management therapies. The life-style management treatment is imperative whether given as a standalone or as an addendum to other two modalities for their overall health-benefit that positively influences infertility treatment outcome. Weight loss achieved by hypo-caloric diet, increased physical activity, both diet and exercise or bariatric surgery has a positive impact on anthropometric, metabolic and reproductive markers in obese PCOS. Selective loss of intra-abdominal fat is associated with resumption of ovulation even when weight change may not be remarkable. An addition of metformin, an insulin sensitizer when combined with life-style modification may improve clinical, metabolic and endocrine variables in women with PCOS. Metformin has been widely utilized today for women with PCOS for multiple indications. In PCOS women seeking fertility, it may be used as first-line treatment or in combination with clomiphene citrate.

2. Pharmacological Treatments:

Insulin sensitizers have emerged as ovulation restoration agents. Insulin sensitizing agents like metformin with or without addition of ovulation inducing agents like clomiphene citrate, aromatase inhibitor like letrozole provide primary line of medical management. Gonadotropin-therapy (recombinant /urinary FSH alone &/or in combination with HMG) is offered to clomiphene-resitant and letrozole- failures.

In patients with PCOS, subfertility is common due to anovulation clomiphene citrate, remains as first line of medical management for ovulation- induction, even after more than 40years of its introduction. Though ovulation rate range between 75-80%, pregnancy occurs in a smaller percentage of patients. The stimulation is done in increasing doses depending upon ovarian response. We have found that both ovulation and occurrence of pregnancy improve in cases of failure or clomiphene-resistance, when adjuvant therapies such as dexamethasone or bromocryptine are added in cases of adrenal hyper androgenism or when hyper prolactinemia co-exists. Clomiphene citrate in combination with insulin- sensitizers like metformin is shown to improve ovulation and pregnancy rates in clomiphene- resistant & obese women with PCOS (videsupra). Individual patient may require additional correction of factors like improvement of cervical mucus or endometrum if anti-estrogenicity of CC persist at these targets in face of ovulation.

In clomiphene-resistant patients or those who ovulate but have target antiestrogenic effects are offered gonadotropin therapy. There are multiple regimens like step-up, low dose step-up and step-down ones. Low-dose gonadotropin regimens are preferred as it aims at mono-follicular response avoiding multiple gestation and ovarian hyperstimulation syndrome (OHSS). In a step-up protocol low dose of gonadotropin (37.5-50IU)is initially given while monitoring follicular growth under ultrasonographic control. Increase in dose by 50% is done after one week if there is a poor response.

3. Surgical Treatment:

Ovarian drilling or wedge resections of ovaries have been considered as a second line of treatment when primary treatment with clomiphene/ letrozole with or without metformin fails. Wedge resection of the ovaries has been majorly replaced by the ovarian drilling to restore ovulation in patients where medical management has failed. This second line surgical treatment is preferred over gondotropin stimulation protocol as PCOS cases are known to hyper respond resulting at times in life-threatenng complication of Ovarian Hyper Stimulation Syndrome (OHSS) and multiple gestations. The surgical modalities are more cost-effective as compared to gonadotropin stimulation therapy. Though the procedure has advantage of avoiding multiple gestation and OHSS, postoperative adhesions remain a concern.

4. Assisted Reproductive Technology (ART).

ART is increasingly applied in management of inferlity in PCOS patients after failures of medical and surgical treatments. Sometimes it may be a primary treatment for a PCO patient with other associated infertility factors like male factor, tubal and endometriosis. However, prevention of OHSS and multiple gestations in PCOS patients undergoing ART remain a great challenge. Careful choice of stimulation protocol, type and dosage of gonadotropin injections along with other management strategies can minimize the risk of these complications without compromising the pregnancy rate. Step- down dosage, coasting, use of dopamine agonist, elective cryopreservation of embryos and transfer in subsequent cycle, cycle cancellation and in vitro maturation technique to be considered as viable options. Use of metformin and /or weight loss prior to ART can reduce OHSS and also improve pregnancy rates and outcome. In the past gonadotropin stimulation along with GnRH agonist to prevent LH surge was commonly used protocol in PCOS patients undergoing ART cycle but currently number of studies have shown the antagonist protocol to be equally / more effective, safer and less expensive.

In vitro Maturation, IVM is being increasingly employed in ART in high risk patients for prevention of OHSS. IVM is also considered in poor responders to conventional IVF-ET, unexplained poor embryo qualities and in patients with PCOS. This modality of IVM in ART is currently under experiential domain and controlled randomized trials are awaited for evidence.

Conclusion:

Today the world is witnessing escalating prevalence of Polycystic Ovarian Syndrome amongst women of reproductive age group. They face higher risks of metabolic syndrome, infertility, compromised response to fertility treatment and pregnancy-related complications. However, availability and application of insulin sensitizing non-pharmacological and pharmacological therapeutic modalities along with refined ovulation-inducing strategies with multiple treatment options have made fertility treatment in these patients safer and rewarding. Research and development with globally sharing of expertise and infrastructure for ART in these PCOS patents have also made pregnancy relatively safer and a dream come true for childless couples.

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9 ENDOMETRIOSIS IN INFERTILITY

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Introduction

Endometriosis is defined as the presence of endometrium-like tissue outside the uterus, which induces a chronic, inflammatory reaction [1]. It commonly involves the ovary in the form of an implant or as an endometrioma. Other common sites are peritoneal surfaces like the pouch of Douglas, rectovaginal septum and rarely have been reported in the pleura, pericardium and brain. The pathogenesis is complex with various theories. While retrograde menstruation of endometrial fragments into the peritoneal cavity is the most accepted [2], endometriosis affects only a select group of women having retrograde menstruation. Perhaps an altered local immunologic, inflammatory and neoangiogenetic process is involved [3, 4, 5]. Peritoneal leptin levels have been shown to be significantly higher in infertile patients with endometriosis as compared to infertile patients without endometriosis[6]. As endometriosis is a chronic, relapsing disorder, clinicians should individualize treatment for each patient on the basis of her symptoms and goals for fertility and quality of life

Problem Statement

Globally the incidence of endometriosis is variedly reported as 5-10% in the reproductive agegroup [1]. It is more prevalent in women with infertility and chronic pelvic pain reaching figures ranging from 20 to 90% [1]. It does not discriminate by race and socio-economic status.

Mechanism Of Infertility In Endometriosis

There is an observed association between endometriosis and infertility, although a causal relation ship has not been proven. Monthly fecundity is lower in women with endometriosis than in fertile controls. There is a higher prevalence of endometriosis in infertile women than in fertile women undergoing tubal ligation. [7] The exact mechanism is still a matter of debate. Plausible mechanisms are [7]:

1) Distortion of the pelvic anatomy by adhesions, resulting in mechanical blockage of the fallopian tubes or impaired ovum release

2) Complex interplay of inflammation, immune response, and angiogenesis in a complex pathologic process leading to ovum, sperm and blastocyst scavenging (fig 1).

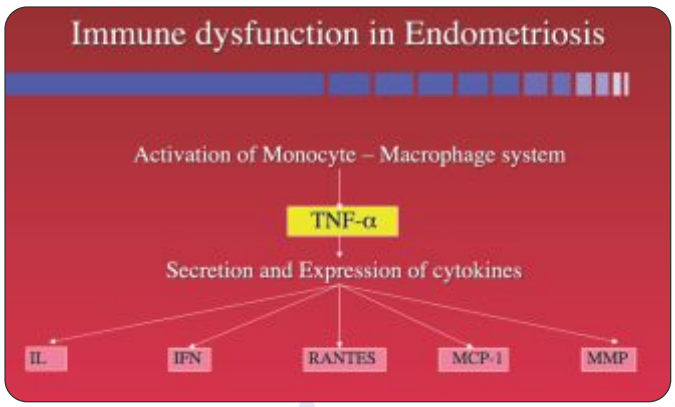

Fig 1: Immune dysregulation in endometriosis

Abbreviations in Fig.1:

TNF-á = Tumor necrosis factor-á; IL = Interleukin; IFN = Interferon; RANTES = Regulated upon activation: normal T cell expressed / secreted; MCP-1 = Monocyte Chemotactic protein-1; MMP = matrix metalloproteinase.

Management Of Infertility Caused By Endometriosis :

Surgical management:

Treatment of infertility caused by endometriosis consists of either surgical removal of endometriotic tissue by adhesiolysis in order to restore normal anatomy or assisted reproductive technology. Both laparoscopic and open approaches are equally efficacious. However laparoscopy reduces complication rates by close to 50% in the hands of an expert and has the added advantages of cosmesis and shorter hospitalization [8].

Indications For Laparoscopy

a) *Patients without pain and essentially normal pelvic examination*

Additional benefits of diagnostic laparoscopy with the concomitant treatment of minimal endometriosis is controversial in women with normal hysterosalpingography findings and normal semen analysis of the husband. One study noted only one additional pregnancy among every eight patients undergoing laparoscopic surgery [9].

b) *Positive findings on pelvic examination:*

Here surgery has the additional advantage of providing intervention for pain relief. Surgical excision of deep endometriotic lesions has been associated with improved fertility in one study .Surgical removal is often recommended for those with an endometrioma of diameter greater than 3 cm [9].

The goal of surgery is to remove endometriotic lesions as far as possible, restore normal anatomy with adhesiolysis especially the fimbrio-ovarian relation, with use of the principles of microsurgery (magnification, meticulous hemostasis, reduced cauterisation, avoidance of tissue dessication and use of fine sutures) which is better achieved by laparoscopy. Excision is preferred over fenestration, drainage, or ablation of the cyst lining for the treatment of ovarian endometrioma [9].

Recommended surgical practice is to use an instrument such as a grasper, via a secondary port, to mobilize the pelvic organs and to palpate lesions which can help determine their nodularity. It is also important to document in detail the type, location and extent of all lesions and adhesions in the operative notes and to map the findings as per the revised ASRM staging. There is no strong evidence to justify timing the laparoscopy at a specific time in the menstrual cycle, but it should not be performed during or within three months of hormonal treatment so as to avoid under-diagnosis. During laparoscopy, deeply infiltrating endometriosis may have the appearance of minimal disease, resulting in an underestimation of disease severity [9,10]

Medical management options:

Hughes et al. conducted a meta-analysis of all randomised controlled clinical trials (RCTs) of ovulation suppression in women with endometriosis and the effect on fertility [10]. The results suggested that suppressing ovarian function to improve fertility in minimal to mild endometriosis is not effective alone. There is no evidence of increased effectiveness of hormonal suppression before or after surgical treatment of endometriosis over that of surgery alone [10].

Intrauterine insemination together with controlled ovarian stimulation may be effective in improving fertility in patients with endometriosis and this appears to be predominantly due to the ovarian stimulation. Hormonal

suppression for pre-treatment may be of use in patients with endometriosis and infertility who undergo IVF. Sallam et al [11] reviewed 3 RCTs of 165 women treated with IVF for infertility related to endometriosis. The clinical pregnancy rate per woman was significantly higher in those receiving GnRH agonist downregulation for 3 to 6 months before IVF than in the control group (OR 4.28, 95% CI 2.0 to 9.15). This therapy also alleviates pain and thus oocyte retrieval becomes easier. Women over the age of 35 years should be referred for IVF.

Controversies and current evidence: A review:

Despite the above mentioned general principles, based on the available literature there is still no consensus on the treatment of ovarian endometriotic cysts in women with subfertility.

1) The presence of an endometriotic cyst in women undergoing IUI or IVF supposedly has a negative influence on the results of these treatments, although the literature is inconsistent [12]. The advantage of surgically treating a cyst before IVF or IUI is the acquisition of a histological diagnosis. A disadvantage is the loss of ovarian reserve.

2) Type of surgical treatment for ovarian endometriosis viz. fenestration and drainage, fenestration, drainage and coagulation of the cystic wall, or cystectomy is also a raging debate [12,13]. Fenestration and drainage does not seem to be sufficient, although no randomised study is available [13]. Cystectomy is probably the better option.

3) Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF [14].

4) Ovulation induction: whether or not and which?

   In patients with unexplained infertility including minimal/mild or surgically treated endometriosis logistic regression analysis of a metaanalysis of 13 trials showed that the likelihood of conception was significantly increased by each of the interventions i.e. selective estrogen receptor modulators (SERMs) e.g. clomifene treatment, hMG treatment and IUI, independently by roughly 2 fold [15].

Future directions:

Of all the newer drugs like selective estrogen receptor modulators (SERMs), aromatase inhibitors and immunomodulators, the latter especially anti-neoangiogenesis agents hold out most promise in endometriosis associated with infertility [16].

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10 FIBROID UTERUS AND INFERTILITY

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Introduction

Uterine fibroids occur in up to 30% of reproductive age women (Verkauf, 1992). Fortunately, despite this impressive epidemiological burden, the vast majority of fibroids are asymptomatic and do not require treatment. A critical and still unsolved question in this field is the relationship between fibroids and infertility.

This issue is assuming increasing relevance considering that, in the developed world, there is the tendency to start a family at an age when natural female fertility is in decline and the incidence of fibroids is increasing. It is essential to clarify whether these tumours affect fertility and, if so, which kind of lesions deserves treatment. Although most women affected with fibroids are fertile, fibroids may interfere with fertility with the effect being dictated largely by the location and size of the fibroid (Ubaldi *et al*., 1995; Rackow and Arici, 2005).

Classification of Fibroid

Submucous fibroids are those that distort the uterine cavity and are further divided into three subtypes: pedunculated (type 0), sessile with intramural extension of fibroid <50% (type I) and sessile with intramural extension 50% (type II). Intramural fibroids are those which do not distort the cavity and with <50% of the tumour protruding into the serosal surface of the uterus. Fibroids protruding 50% out of the serosal surface are considered subserosal. They are further divided into sessile or pedunculated (Bajekal and Li, 2000).

Fibroids and fertility

Reviews *focusing on the relationship between fibroids and infertility reported that these lesions might be responsible for only 23% of infertility cases (Donnez and Jadoul, 2002; Practice Committee of the ASRM, 2006).*

Mechanisms by which fibroids may reduce fertility have been proposed.

It is generally believed that fibroids may interfere with sperm migration, ovum transport and embryo implantation. Detrimental effects on these phenomena may be mediated by alteration of the uterine cavity contour causing mechanical pressure or by the occurrence of abnormal uterine contractility. In addition, local inflammation associated with the presence of submucosal fibroids may result in a hostile endometrial environment that impairs sperm transport and embryo implantation. An inadequate blood supply to the endometrium has also been advocated to explain reduced embryo implantation. If fibroids are localized near the cervix or near the tubal ostia, the anatomical distortion may reduce access to the tubes by ejaculated sperm, whereas large corneal lesions might impair ovum retrieval by the tubes. A higher frequency of uterine peristalsis during the mid-luteal phase might be one of the causes of infertility associated with intramural-type fibroids. (Yoshino et al., 2010)

A decreased risk of fibroids in parous women when compared with nulliparous women has been repeatedly reported. Parity may be a protective factor or, alternatively, fertility may be partly compromised in women with fibroids.

Fibroids and IVF treatment outcome

With regards to *in vitro* fertilization (IVF) treatment, submucosal and intramural fibroids that protrude into the endometrial cavity have been associated with decreased pregnancy rates (PRs) and implantation rates (IRs) (Bernard *et al*., 2000). Studies have shown that IVF outcome is markedly improved in women with cavity-distorting submucosal fibroids following myomectomy (Surrey *et al*., 2005). However, the effect of fibroids not distorting the uterine cavity on the outcome of IVF treatment remains poorly understood with studies yielding conflicting results. Conclusions regarding intramural lesions have been conflicting. The two initial meta-analyses failed to document a harmful effect (Donnez and Jadoul, 2002,Practice Committee of ASRM (2006). On the contrary, results from the meta-analysis of Benecke *et al.* (2005) show a lower pregnancy rate in women with intramural fibroids.

Somigliana et al (2007) published a meta-analysis of 17 studies investigating the influence of fibroids located at different sites in IVF cycles. Overall, their results showed that myomas negatively affect pregnancy rates. Although based on a small number of studies, submucous fibroids appeared to strongly interfere with the chance of pregnancy: OR (95% CI) for conception and delivery being 0.3 (0.1-0.7) and 0.3 (0.1-0.8) respectively. The impact of intramural fibroids was less dramatic although still statistically significant: OR (95% CI) for conception and delivery being 0.8 (0.6-0.9) and 0.7 (0.5-0.8) respectively. In general, these effects appeared to be more relevant when considering the delivery rate compared to the clinical pregnancy rate. Conversely, subserosal fibroids did not seem to affect pregnancy rates.

Two limitations of studies focusing on IVF should be considered. First, they can do no more than evaluate the impact of fibroids on embryo implantation. Possible detrimental effects on tubal transport of oocytes and/or embryos are overcome by the technique. Second, recent findings suggest that the size of the fibroids is positively related to implantation failure, in particular when the diameter of the lesion exceeds 4 cm (Oliveira *et al.*, 2004). The mean or median diameter of the fibroids included in studies on IVF and fibroids is rarely above 3 cm. Indeed, the policy of the units reporting on the influence of fibroids on IVF outcome is generally to recommend surgery for lesions exceeding 5 cm in diameter.

A recent updated systematic review by Pritts et al (2009) evaluated the effects on fertility by location of fibroids. Their results were consistent in showing that women actively attempting to conceive and with submucous fibroids, compared to women without fibroids, demonstrated a significantly lower clinical pregnancy rate (RR 0.36; 95% CI 0.17-0.73), implantation rate (RR 0.28; 95% CI 0.12-0.64), and ongoing pregnancy/ live birth rate (RR 0.31; 95% CI 0.11-0.85) and a significantly higher spontaneous abortion rate (RR 1.67; 95% CI 1.37-2.05). Women with intramural fibroids also produced significantly lower implantation rate (RR 0.79; 95% CI 0.69-0.90) and ongoing pregnancy/ live birth rate (RR 0.78; 95% CI 0.69-0.88) and a significantly higher spontaneous abortion rate (RR 1.89; 95% CI 1.47-2.42). When women with subserous fibroids were compared with women without fibroids, no difference was observed for any outcome measure.

There is controversy on the impact of intramural fibroids that do not distort the uterine cavity on IVF treatment outcome. This was addressed in a recent systematic review Sunkara et al (2010) that looked at 19 observational studies comprising a total of 6087 IVF cycles. Meta-analysis of these studies showed a significant decrease in live birth rate by 21% and the clinical PR by 15% per IVF cycle in women with non-cavity distorting intramural fibroids compared to those without fibroids, following IVF treatment. The relatively lower chance of achieving a live birth compared with clinical pregnancy probably reflects the adverse influence of intramural fibroids on the course of pregnancy.).

The inverse relationship between IVF outcome and the presence of non-cavity distorting intramural fibroid may be explained by altered uterine vascular perfusion, myometrial contractility, endometrial function or myometrial/endometrial gene expression.

Demonstration of reduction in IVF live births in women with non-cavity-distorting intramural fibroids does not necessarily mean that removal of such fibroids will restore the live birth rates to the levels expected in women without fibroids. Therefore this evidence does not justify advocating routine myomectomy for these women, as a favourable risk benefit analysis of this surgical intervention or any other interventions, in this clinical context is currently lacking.

Fertility after Myomectomy

Several reviews of literature on pregnancy rates following myomectomy have been published. One of the early reviews focussing on studies published between 1933 and 1980 by Buttram and Reiter (1981) reported a 40% pregnancy rate following abdominal myomectomy (480 out of 1202 cases). This rate was 54% when patients with other causes of infertility were excluded. Another review by Vercellini et al (1998) confirmed this rate of success following myomectomy. They reported a post surgical pregnancy rate of 57% across prospective studies. When including women with unexplained infertility, this rate was 61%. The advent of endoscopic surgery did not seem to modify this result. In a review by Donnez and Jadoul (2002) the pregnancy rate among women undergoing hysteroscopic and laparoscopic myomectomy was reported as 45% and 49% respectively. These findings have further been confirmed by more recent and larger studies.

Despite a large number of series reporting on the pregnancy rate after myomectomy, randomized studies are lacking. A recent cochrane review on this issue failed to identify any randomized trial comparing surgery to expectant management (Griffiths *et al.*, 2006).

IVF Outcome after Myomectomy

Narayan and Goswamy (1994) investigated the effect of myomectomy on a small group of women with submucosal fibroids (n=27). They found that the delivery rate was not significantly different in women who underwent myomectomy compared to women without fibroids (37% and 22% respectively, *P*=0.13). Surrey et al (2005) reported a pregnancy rate of 62% and 68% respectively in women operated for submucous fibroids and controls without fibroids following IVF treatment. From these studies we can infer that although the overall evidence is scarce, myomectomy for submucous fibroids did not seem to negatively affect the pregnancy rate following IVF treatment.

A comparative study by Bulletti et al (2004) looked at the effectiveness of myomectomy prior to IVF treatment in women with intramural and/ or subserosal fibroids with at least one lesion > 5cm. Women were allocated to myomectomy (n = 84) or no surgery (n = 84) based on their decision. They reported a live birth rate of 25% and 12% respectively in women who did and did not undergo surgery prior to IVF treatment. It is worthy of note that this study involved small numbers and this evidence therefore does not justify advocating routine myomectomy for these women; as a favourable risk benefit analysis of this surgical intervention or any other interventions, in this clinical context is currently lacking.

From this evidence it can be concluded that fertility outcomes are decreased in women with submucosal fibroids, and removal seems to confer benefit. Subserosal fibroids do not affect fertility outcomes, and removal does not confer benefit. Intramural fibroids appear to decrease fertility, but the results of therapy are unclear.

Fibroids and Pregnancy

It has been claimed that the hormonal milieu of pregnancy can determine a rapid growth of fibroids and increased symptoms. In case-control studies, a history of miscarriage is more frequently reported by affected patients (Sheiner *et al.*, 2004) apart from placental abruption, placenta previa, intrauterine growth restriction and fetal malpresentation. Not surprisingly, a higher rate of caesarean section has also been repeatedly reported.

A role of fibroids in the determinism of pregnancy complications is also supported by the demonstration that the dimension and location of the lesions play a role in this regard (Qidway *et al.*, 2006). In particular, the location of the myomas in relation to the placental site has been reported to be a significant clue to the outcome of pregnancy.

Myomectomy and Pregnancy

The rate of pregnancy wastage significantly decreases after surgery. (Marchionni *et al.* (2004)). One of the major concerns about myomectomy is the low, albeit clinically relevant, risk of uterine rupture during pregnancy or labour. but studies aimed at precisely quantifying this risk are scanty and controversial (Serrachioli *et al.*, 2006). Regardless of the surgical approach, fear about the risk of uterine rupture certainly leads to a high rate of cesarean section in pregnant patients who previously underwent myomectomy.

On the other hand, surgery is not without complications. Even if very rare, major intraoperative and post-operative complications may occur.

Alternative treatments for Fibroids

Several non-surgical approaches for the treatment of fibroid associated symptoms have emerged over the last several years with medical therapies (GnRH agonists, danazol, the antiprogestogen mifepristone, the selective oestrogen receptor modulator raloxifene and the aromatase inhibitor fadrozole) as well as radiological interventions(fibroid embolisation, laparoscopic myolysis and MRI guided focused ultrasound) being proposed. However,their use in the context of infertility treatment remains questionable.

Conclusions

Available evidence also suggests that submucosal, intramural and subserosal fibroids interfere with fertility in decreasing order of importance. Although more limited, some data supports an impact of the number and dimension of the lesions. Drawing clear guidelines for the management of fibroids in infertile women is difficult due to the lack of large randomized trials aimed at elucidating which patients may benefit from surgery. At present, physicians should pursue a comprehensive and personalized approach clearly exposing the pros and cons of myomectomy to the patient, including the risks associated with fibroids during pregnancy on one hand, and those associated with surgery on the other hand.

At least four points have to be considered: (i) the age of the woman; (ii) the location, dimension and number of the fibroids; (ii) the concomitant presence of fibroids-related symptoms such as menorrhagia or hypermenorrhea and (iv) the presence of other causes of infertility and whether or not there is an indication to IVF. The ultimate aim is to assume a shared decision with the patient.

A personalised and individualised approach considering age of the patient, duration of infertility, treatment received till date, size/site/number of fibroids should be taken into consideration to optimize the outcome