Fibroids and infertility

M Aboulghar
Cairo, Egypt
Uterine fibroids occur in up to 30% of reproductive age women (Verkauf 1992)
• Fibroids may cause infertility by obstructing the tubes and impairing gamete transport.
• Now it is thought that the critical factors are distortion of the endometrial cavity, abnormal endometrial receptivity and hormonal milieu.

(Donnez and Jadoul 2002)
The issue whether fibroids can be the sole cause of infertility has been poorly understood (Cook et al. 2010)
Intramural fibroids are myomas completely surrounded by muscular wall of the uterus, however, they vary in size, number and distance from endometrial cavity.
The problem of diagnosis of intramural fibroids
The problem of diagnosis of intramural fibroids (1)

• Transvaginal ultrasound:
  – Transvaginal ultrasound can precisely measure the size of the fibroids (Pritts et al. 2009).
  – Recent studies showed sensitivity as low as 69% in locating fibroids by vaginal US (Aida et al., 1997).
The problem of diagnosis of intramural fibroids (2)

• Hysteroscopy was found to be adequate in evaluating the uterine cavity to exclude a submucosal part of an intramural fibroid (Soares et al., 2000).
The problem of diagnosis of intramural fibroids (3)

- Direct hysteroscopic visualization of the uterine cavity may most accurately identify those fibroids with a submucosal component (Cicinelli et al., 1995)
The problem of diagnosis of intramural fibroids (4)

• Sonography, hysteroscopy and MRI are clearly the best techniques available to diagnose the presence of a part of an intramural fibroid in the uterine cavity (Protts et al., 2009).
The problem of diagnosis of intramural fibroids (5)

- Sonohysterogram can provide 100 percent sensitivity and specificity for identifying the exact location of the fibroid (Pritts et al. 2009).
The problem of diagnosis of intramural fibroids (6)

- Magnetic resonance imaging (MRI) may provide the best means by which to assess whether an intramural fibroid impacts the endometrial cavity either through actual distortion or through its relationship to the junctional zone (the anatomically distinct segment of the uterus that represents the endometrial-myometrial transition) (Somigliana et al 2007).
The problem of diagnosis of intramural fibroids (7)

- Intramural fibroids may disrupt the junctional zone of the myometrium without dramatically altering the contour of the uterine cavity. The junctional zone is structurally and hormonally different from the other layers of the uterine body and further research may elucidate its roles in fertility and how disruptive of this zone by fibroids and/or adenomyosis can reduce implantation (Somigliana et al 2007).
Relation between intramural fibroids and infertility
There is a general consensus that subserosal fibroids have no impact on infertility and that submucous fibroids have been associated with decreased pregnancy rates (Bernard et al., 2000)
The effect of intramural fibroids on fertility and the outcome of IVF treatment remain poorly understood with studies yielding conflicting results (Sunkara et al 2010).
Epidemiological evidence on the relationship between infertility and intramural fibroids is not conclusive due to methodological limitations.
Why studies on intramural fibroids are inconclusive?

• Most of studies are retrospective.
• Exact position of fibroids in the muscular wall of the uterus is not defined in most studies.
• Number and size of fibroids is not clear in the majority of studies.
• Distance between fibroid and endometrium is not specified in the studies.
In 2001, Pritts et al. performed a systematic review of controlled studies examining the issue of fibroids as a cause of infertility. The analysis failed to demonstrate any effect of fibroids on fertility outcomes except when the tumors deformed the endometrial cavity.
After 8 years, in another meta-analysis, the same authors reported that women with IM fibroids produced significantly lower clinical pregnancy rates, implantation rates, and ongoing pregnancy/live birth rates and significantly higher spontaneous abortion rates (Pritts et al., 2009).
Does myomectomy improve fertility?
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. More high-quality studies need to be directed toward the value of myomectomy for intramural fibroids, focusing on issues such as size, number, and proximity to the endometrium (Prittts et al 2009).
Recent evidence supports the opinion that IVF pregnancy rate is reduced in the presence of intramural fibroids and the pregnancy rate is not affected if the fibroids is removed (Somigliana et al 2007)
• In a Cochrane review, there was no sufficient evidence from randomized trials to evaluate the role of myomectomy to improve fertility.

• From two randomized studies, there was no significant difference between laparoscopic and open approach regarding fertility performance. (Metwally et al., 2012)
A randomized study evaluating spontaneous conception with and without fibroids (Bullett et al, 1999), spontaneous pregnancy was 11% with fibroids versus 25% without.

Myomectomy improved the pregnancy rate to 42% (Bulletti et al. 1999)
if IM fibroids do indeed decrease fertility, it is not a given that their removal will reverse the process and normalize fertility or even be beneficial to the patient. Abdominal or laparoscopic myomectomy can be associated with significant morbidity, including infection, high rate of postoperative adhesion formation (Pritts 2009)
The current results show, there is no clear evidence at this time that myomectomy for IM fibroids is beneficial (Somigliana et al 2007)
Buttram and Reiter (1981) reported a 40% pregnancy rate following abdominal myomectomy (480 out of 1202 cases). A more recent comprehensive review of articles published between 1982 and 1996 on the success rate after abdominal myomectomy confirmed this rate of success. The post-surgical pregnancy rate across prospective studies was 57% (95% CI 48–65) (Sunkara et al 2010).
Patients with intramural fibroids were divided into myomectomy versus expectant treatment, based on their own wish. Each group had 84 patients. The cumulative delivery rate was 25% in myomectomy arm versus 12% in no treatment arm (P=0.01) (Bulletti et al. 2004)
Adhesions after myomectomy

- Adhesions after abdominal myomectomy are particularly disturbing in infertility patients; adhesions involving the uterus and fallopian tubes may cause infertility, when paradoxically the surgery was performed for fertility enhancement.
Preoperative GnRH before open myomectomy (Coddington et al. 2009)

• To determine if 3 months of preoperative gonadotropin-releasing hormone agonist (GnRH-a) treatment decreases postoperative uterine adhesions after open abdominal surgery for the removal of uterine fibroids.
Coddington et al. 2009 (Continued)

- Prospective, randomized, clinical study.
- Women of reproductive age with symptomatic uterine fibroids not amenable to hysteroscopic removal.
- Twenty patients underwent an initial abdominal myomectomy followed by a second-look laparoscopy for evaluating uterine adhesions after random allocation to groups receiving either GnRH analog or placebo.
- for 3 months before the initial surgery.
• For every additional centimeter of incision length, the total adhesion area over the uterine serosal surface increased by 0.55 cm². The number of myomas removed and the number of incisions were positively correlated with total adhesion area.
Gonadotropin-releasing hormone agonist pretreatment versus placebo did not decrease postoperative adhesion formation after abdominal myomectomy in a randomized control trial (Coddington et al 2009)
Post operative adhesions

- 3 months of preoperative GnRH-a had an increased adhesion area/incision length. This was an unexpected finding as GnRH-a is known to shrink fibroids and thus was likely to reduce incision length.
Post operative adhesions

• Fibroids after GnRH-a administration are sometimes more difficult to extract from the surrounding compressed myometrium (the pseudo-capsule). The increased manipulation of the incision site can result in additional peri-incisional trauma and potentially can result in more adhesions.
What is the effect of intramural fibroids on IVF outcome? and does myomectomy improve IVF outcome?
Sunkara et al (2010) identified 19 observational studies comprising 6087 IVF cycles. Meta-analysis of these studies showed a significant decrease in the live birth (RR = 0.79, 95% CI: 0.70–0.88, $P < 0.0001$) and clinical PRs (RR = 0.85, 95% CI: 0.77–0.94, $P = 0.002$) in women with non-cavity-distorting intramural fibroids compared with those without fibroids, following IVF treatment.
Clinical evidence support the vision that fibroids may interfere with fertility. IVF suggests a detrimental effect on implantation: the delivery rate is reduced in patients with fibroids, while it is not affected in patients who had undergone myomectomy. Second, surgical treatment appears to increase the pregnancy rate (Sunkara 2009).
However, the effect of fibroids not distorting the uterine cavity on the outcome of IVF treatment remains poorly understood with studies yielding conflicting results.
Moreover, 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.
The effect of small intramural uterine fibroids on the cumulative outcome of assisted conception (Khalaf et al 2006)

• 322 women without fibroids and 112 women with fibroids underwent 606 IVF/ICSI cycles. Live birth rates in the study group 14.8% compared to 24% in the control group, (P<0.05). The cumulative ongoing pregnancy rate was reduced by 43% (HR=0.57, 95% CI=0.35-0.91, P=0.018), and the cumulative live birth rate was reduced by 47% (HR=0.53, 95% CI=0.32-0.87, P=0.013)
The ability to correctly identify the location and size of a patient’s fibroids is critical for determining which patients require surgical management, as the current literature suggests that certain fibroids have a greater impact on fertility than others.
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, gamete migration or myometrial/endometrial gene expression (Arslan et al., 2005)
The Practice Committee of the American Society for Reproductive Medicine (2006) revised their earlier report and recommends surgical treatment after complete evaluation of other potential factors of infertility.
Effect of fibroids on pregnancy and its outcome
In a review of 1941 patients who underwent myomectomy, the spontaneous abortion rate improved from 41% prior to surgery to 19% following myomectomy (Buttram and Reiter, 1981).
More recently, four independent studies used a similar study design to investigate the impact of intramural and/or subserosal fibroids in the miscarriage rate. Results from all these studies tend to confirm a strong benefit of surgery (Somigliana et al 2007).
Unfortunately, due to the lack of a control group, the study design of all these reports is inadequate to provide a definite answer to the question (Somigliana et al 2007).
Conclusion I

• The current literature support the contention that fibroids decrease fertility in general, as well as IVF pregnant rates more specifically? Specific characteristics of fibroids (size, location or both) may predict the type of fibroid that alters fertility?, and Does removal of such fibroids may return fertility and IVF success to normal?
Conclusion II

• The question when to advise removal of an intramural fibroid is a frequent clinical dilemma, but making conclusions base upon the available literature has been problematic.
Conclusion III

–We need prospective randomized studies to answer all questions.
Personal Recommendations 1

• Young Women with short infertility period: for conservative treatment
• Women 30-35 years:
  AMH assay
  Expectant treatment for 6 months
  Surgery
• Women over 35 years: Myomectomy followed ART
Personal Recommendations 2

- All intramural fibroids, 5 cm in diameter or more and fibroids less than 10 mm for endometrium better be removed

- Myomectomy done using microsurgical technique
The Egyptian IVF-ET Center

- **Clinical directors:**
  - M. Aboulghar, M. D.
  - G. Serour, M. D.

- **Clinical associates:**
  - Y. Amin, M. D.
  - M. Sattar, M. D.
  - A. Ramzy, M. D.
  - L. Mansour, M. D.
  - M. Aboulghar, M. D.
  - A. Kamel, M. D.
  - H. Marie, M.D.
  - N. Elish, M. D.
  - M. Farahat, M.D.
  - Y. El-Faysal, M.D.
  - W. Saber, M.D.

- **Cryobiology and Andrology:**
  - D. Saad, B.Sc.
  - Y. Demeiry, B.Sc.
  - A. Mohamed, B.Sc.
  - N. Salah, B.Sc.
  - M. Abdel Fattah, B.Sc.
  - A. Sabry, B.Sc.
  - S. Nabawy, B.Sc.
  - P. Mahmoud, B.Sc.

- **Scientific director:**
  - **IVF / ICSI:**
    - A. Serour, M. D.
    - A. Mostafa, M. D.
    - N. Tawab, B.Sc.
    - G. Afifi, B.Sc.
    - Menna Serour, B.Sc.
  - **Cytogenetics:**
    - H. Fayek, Ph. D.
    - Somia Mohamed, Ph.D
    - A. Abdel-Razek, M. D.
    - A. Amer, B.Sc.
    - A. Naser, Ph. D.
    - O. Kamal, Bio m En.
    - S. Mostafa, Tech.Sc.

- **Andrology:**
  - I. Fahmy, M. D.
  - A. El-Gendy, M.D.
  - E. Fathi, M.D.
  - H. Elenany, M.D.

- **Clinical Psychologist:**
  - Shams Ramez