Chapter 1

A Lifetime's Observations and Reflections as an IVF Doctor

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Considering life as an in vitro fertilization (IVF) doctor leads one to think that IVF has always been readily available, but this is not so. I did my first infertility clinic in 1959 as a Senior House Officer in Australia; it had already been differentiated from the gynecology clinic because of the number of patients. A hysterosalpingogram provided evidence for tubal macrosurgery, semen analysis was not standardized and there was no endocrine test for ovulation nor any means to stimulate it. A patient went abroad for donor insemination.

After extensive clinical training and research in endocrinology, I ran an infertility clinic in Wales in 1969, although tubal surgery was still the only treatment used. Urinary total estrogen and pregnanediol assays in 24-hour urine samples became possible and clomiphene and human menopausal gonadotropin (hMG) were introduced. Multiple pregnancies followed in spite of urinary estrogen monitoring that used the postal service to send samples to a distant lab, the results being phoned through the following day.

In 1973 I established my infertility clinic in Sheffield, by which time it was possible to measure serum hormones. Prolactin measurement led to a search for pituitary microadenomas, and bromocriptine was extensively used before it was fully appreciated that prolactin was also a stress hormone. Laparoscopy was developed into an important diagnostic tool and became essential to define peritubal and periovarian adhesions, better dealt with by microsurgery, as was tubocornual obstruction. Sperm cryopreservation using slow freezing became practical after earlier use in animal husbandry and sperm donation then became feasible. Sperm banks developed, so donors were screened, interviewed and counseled, as were the couples; it was recognized that counselors had a role and needed specific training. Sperm banks made donations available for sale to other clinics and trade flourished.

During this time the World Health Organization (WHO) developed its Task Force on the Diagnosis and Treatment of Infertility, began optimizing semen analysis and structured a formal evaluation of both female and male history, physical examination and investigation. The 1978 protocol was used in 23 countries and the project recruited about 10,000 patients. Features required for diagnosis of each cause were identified and resulted in the publication of the *Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction* and the *Manual for the Standardized Investigation and Diagnosis of the Infertile Couple*, which helped to regularize the clinical management. The former volume progressed to its fifth edition in 2010 and is the world reference standard for semen analysis, incorporating the major changes in evaluation of sperm morphology using strict criteria.

Ultrasound, which had been mostly used for obstetric measurement, began to be used for assessment of the nonpregnant pelvic organs and follicle growth was charted. Ovulation was timed more accurately by first urinary and then serum luteinizing hormone (LH) assays.

For 10 years Edwards and Steptoe had been researching human IVF. Edwards predicted that success would raise all sorts of ethical questions – and he was roundly ignored. Finally in 1978, they succeeded. Louise Brown was born after a non-stimulated cycle and laparoscopic oocyte retrieval and the world was changed.

Developments came slowly. In view of the poor results, ovarian stimulation was introduced and more oocytes were obtained. The Melbourne group refined the stimulation schedule, leading to more embryos being replaced and the inevitable rise in multiple births and associated prematurity causing pressure on neonatal units.

Laparoscopic egg retrieval was replaced by transurethral and then transvaginal aspiration under ultrasound control and aspiration pressures were reduced when syringes were replaced by low-pressure pumps. Human menopausal gonadotropin with its 1:1 ratio of

follicle-stimulating hormone (FSH) and LH (with added human chorionic gonadotropin [hCG] that was not highlighted) were gradually replaced by preparations containing more FSH until recombinant FSH was introduced with the claim that LH was unnecessary.

Around the same time, embryo cryopreservation, still with slow freezing, was introduced and seen as an answer to excess egg/embryo production. In the United Kingdom, social and political discussion led the Medical Research Council to set up a group to advise on research policy and Parliament to form the Warnock Committee of Inquiry into Human Fertilisation and Embryology, which recommended creating a Statutory Licensing Authority to regulate research and services. As little happened, the Medical Research Council and the Royal College of Obstetricians and Gynaecologists established a Voluntary (later Interim) Licensing Authority with a view to creating standards of clinical practice and as a stimulus to government to implement the Warnock recommendations. The Department of Health held discussions about the meaning of "proper counseling" and how it could be developed and practiced. After an unprecedented two white papers describing the government legislative intentions and then their revised proposals following public consultation, the Human Fertilisation and Embryology Act was passed in 1990. The Human Fertilisation and Embryology Authority was established in 1991 and quickly formulated its Code of Practice, instituting site visits and dialogue with practitioners and publishing its annual reports.

At the same time intrauterine insemination began to be used as a treatment for selected couples prior to moving on to IVF, particularly for those couples with a mild male factor, mild endometriosis or unexplained infertility. Endometriosis was increasingly being diagnosed with more rigorous application of the revised American Fertility Society classification. Laparoscopic salpingostomy began to replace microsurgery and there was debate about the optimal way to manage endometriotic cysts.

The European Society of Human Reproduction and Embryology (ESHRE) held its first annual meeting in Bonn, Germany, in 1985, and its journal, *Human Reproduction*, was published in 1986, climbing to be the principal one in its field as evidenced by its impact factor. In Italy the law forbade embryo cryopreservation, so efforts were directed to oocyte freezing. Data collection began to be taken seriously and national data were aggregated into European IVF-monitoring (EIM) program reports, leading to the development of the International Committee for Monitoring Assisted Reproduction (ICMART) and its efforts to collate world data. Capri workshops of international experts provided an opportunity to synthesize knowledge in infertility.

The British Infertility Counselling Association was founded to promote professional standards and somewhat later, embryologists formed the Association of Clinical Embryologists in the United Kingdom to standardize practice, training and certification and develop continuing education.

Although WHO had published a technical bulletin in 1990 reviewing the field of assisted reproduction and putting forward a series of suggestions for research, it evinced little further interest until a large meeting was convened in Geneva in 2001 on "Current Practices and Controversies in Assisted Reproduction." A global perspective was framed and the importance of low-cost methods was emphasized. As well as the scientific and clinical perspectives, attention was given to social and psychological issues, ethical aspects of infertility and assisted reproductive technology (ART) and national and international data surveillance. In 1998 the International Federation of Fertility Societies (IFFS) had begun its surveillance of laws and guidelines relating to ART and has published data relating at its peak to 102 countries (2010), those with laws, guidelines, both or neither. Its documentation extended to the status of conception, embodying religious and ethical dimensions, and its triennial publications have continued [1]. These aspects were explored progressively from 2001 in a series of publications by ESHRE's Task Force on Law and Ethics [2].

The novel intracytoplasmic sperm injection (ICSI) allowed poor-quality semen to be used, but its indications were soon distorted and it has been used more widely, particularly in some parts of the Middle East, as the routine approach.

The Cochrane Collaboration, founded in 1993 and developed from its initial reviews in perinatal medicine, has embraced ART. An examination of the 59 reviews of randomized controlled trials covering many areas of ART practice (up to July 2015) was produced using A Measurement Tool to Assess Systematic Reviews (AMSTAR) criteria and it concluded that most were of a high standard, although there was evidence of publication bias [3].

Anxiety about the high frequency of multiple births soon emerged and single embryo transfer

(SET) was pioneered in Scandinavia; it was shown that live birth rates could be sustained and this has led to an effort in many parts of the world to reduce the number of embryos transferred. In Belgium regulation was introduced so that patient reimbursement was dependent on SET under defined circumstances, including maternal age and the number of attempts. A steady improvement in laboratory standards and competence has also helped lead to a reduction in the frequency of multiple births. Later, in vitro culture of embryos to blastocyst helped the selection for transfer and time-lapse imaging has improved understanding of the variety of embryological stages, but improvement in "take home baby" rates remains to be demonstrated.

Although embryo cryopreservation has been essential to the support of the SET concept, it was realized that too many embryos were being produced using the gonadotropin-releasing hormone (GnRH) agonist protocols and longer-term storage was becoming a problem. Gentler stimulation regimes were proposed to reduce the number of oocytes and embryos with some evidence that this led to better-quality embryos. Ovarian hyperstimulation syndrome (OHSS) was also occurring too frequently and antagonists caused less impact on the woman and markedly reduced the frequency of OHSS.

Freezing was extended to oocytes, particularly in Italy, which created laws based on religious dogma in order to restrict the number of oocytes fertilized and mandated their replacement, although these were ultimately struck down. The slow cryopreservation technique has largely been replaced by vitrification, although more extensive longer-term data on ovarian tissue preservation are awaited.

Surrogacy was introduced, leading to cross-border activity, complicating the ethical debate and raising legal issues about the adoption process. Some countries have responded by restricting its practice within their borders.

The Royal College of Physicians and the Universities of Leeds and York published their Effective Health Care Bulletin on the Management of Subfertility based on systematic reviews in 1992. This was followed by the Royal College of Obstetricians and Gynaecologists' series of evidence-based Guidelines for the management of infertility in primary, secondary and tertiary care. The ESHRE Capri Workshop set out its Guidelines on Prevalence, Diagnosis and Management of Infertility and the National Institute for Health and Care Excellence (NICE) issued its Fertility Assessment and Treatment for People with Fertility Problems extensively using systematic reviews and publishing its evidence base. Those recommendations were subsequently reviewed and have significantly influenced national criteria for funding within the National Health Service. WHO is currently finalizing its Guidelines. It defined the questions for systematic reviews using the Patient/Problem/Population; Intervention; Comparison; Outcome and Setting [4] (PICOS) system using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to determine the level of the Recommendations [5] and these seem likely to determine the standard of future Guidelines.

The impacts of the procedures and monitoring on patients have both physical and mental dimensions, with anxiety and stress playing a significant role. Recognition has led to efforts to improve the procedures and designate "patient-friendly" IVF with emphasis on communication and support. ESHRE has recently published its Guideline on Psychosocial Care in Infertility and Medically Assisted Conception and has issued a pocket guideline for use by professionals in their routine care delivery [6].

Although the isolation of embryonic stem cells, derived from the inner cell mass of blastocysts grown for research, has stimulated the new field of organ replacement therapy, the ethical constraints have helped to push research into pluripotent cell derivatives of somatic cell lines. This research field has emphasized the segregation of opinion driven by religious principles, a problem recognized early on in reproductive medicine by Dr. Mary (later Baroness) Warnock. IFFS Surveillance publications regularly underscore this, identifying those countries where specific practices, such as donor gametes, are forbidden by law. Costa Rica was the only country to pass a law prohibiting IVF, but an appeal by citizens to the Inter-American Court of Human Rights resulted in a judgment supporting them and instructing the government to repeal the law and provide IVF. The Court gave a robust refutation of the biological and philosophical premises underlying the law, providing reassurance that science and rationality can lead to progress [7].

Huge advances have been made in the science and clinical practice of reproductive medicine and the latest

evidence is presented in this volume. However, to make further progress, such as by the creation of artificial gametes, there will need to be high-quality communication in extending the public understanding not only of science but also of the ethical basis of both the science and its clinical application. At the other end of the spectrum, more attention will need to be given to the politics of health and the financial aspects of clinical service. Access may seem a problem in the developed world, but this problem has hardly been touched in low-resource economies, where appropriate forms of ARTs have not been available for the general population. They really have to be part of the WHO approach of universal health coverage [8] at the same time as greater efforts must be made to reduce the massive burden of tubal damage from unsafe abortion and lack of obstetric care [9].

It is a privilege to have been part of the revolution in fertility care. These selective memories highlight the fact that the discussions have been on a much broader stage than clinical science alone. We need to keep that perspective. The technology has not reached most people in the world. It remains a challenge to deliver to them affordable reproductive health care and extend the gains made in the delivery of contraception, so that fertility care truly covers the life course for everyone [10].

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Chapter 2

The Patient's Perspective of Assisted Reproduction

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Working in health care, it is natural to be in "professional mode," and sometimes we forget about the most important person – the patient. While in vitro fertilization (IVF) and everything associated with it might be second nature, it is important to remember that it might be the first time that the patient has encountered this new and intimidating world. I have been on both sides of the coin.

By the time the patient is sitting in your clinic, she may be further down the investigative line and know what the issues are. The discovery of an issue and the need to have investigations and intervention can come as quite a shock. The devastating effect that this news can have should not be underestimated. As a patient, it can be a scary time and the feeling of isolation simply adds to emotions.

After having the investigations in our local hospital and learning that we would need IVF, we looked into local clinics and went along to an open evening. We found this very informative. All the staff came across as professional and, just as important, friendly and approachable. You might be a professor in your field, but if you appear standoffish, that is likely to put some people off. It was also interesting to hear from all the different specialties (the lab team, the nurses and the counselor) and see how they worked as a team and genuinely seemed to respect each other. Combined with the tour, this made us feel so sure we were in good hands, we actually didn't bother going to any other clinics.

Subsequently, I have been lucky enough to go along and talk for a few minutes at these open evenings as I feel that clinics will easily be able to "big themselves up," but it helped to hear from someone who had been in their shoes and actually been through it. It's all well and good that you have the most up-to-date lab or an embryoscope, but what's it like to have to go through the ups and downs, or to inject yourself? I also felt reassured that we weren't the only couple going through this.

It's a strange stage to be at, with a mix of trepidation and excitement that you have finally started on the journey. At all the consultations with both the consultants and the nursing team we had everything explained to us in a language and at a level we understood. This is another important point from a patient's point of view. We weren't being spoken down to or impressed by big, fancy words. Explaining all the options to patients and making them part of the decision-making process can give them some element of feeling in control. When we were told something, it was made clear and explained to us, and we were frequently asked if we had any questions before we moved on. We were often reminded that we could call the clinic at any point if we had any questions.

The day that the drugs arrived was a bit of a reality check. I remember opening the box and seeing the different drugs, syringes and needles (so many needles …). I must admit I had a bit of a wobble, but it wasn't long until our first ultrasound scan and a meeting with our lovely, reassuring, friendly nurses.

During all our scans, the results and how things were progressing were discussed. One of the most important things to me, and to others that I've spoken to, is that the partner is included. They may not be going through the actual interventions, but they are emotionally invested in the procedure and are a very important part, especially to the patient.

The day of egg collection can be another mixed bag of emotions. It is another step forward, but there can also be disappointment if fewer eggs than expected are collected. On one occasion, my left ovary was inaccessible, which obviously had an effect. The staff members were upbeat, though, and we left with a promise of a phone call from the embryologists the next day. We have been through IVF more than once and had both fresh and frozen cycles. Waiting for that call doesn't get any easier.

Embryo transfer day was made to feel as relaxed as possible for us. We got to see the embryo and were

given a picture to take home. This may seem like a small thing, but it was huge for us, and, if successful, many people have a baby photograph that early!

The time between transfer and getting the results was perhaps the strangest time of all. After having injections every day and scans every other day, suddenly nothing. Luckily we had been warned about this, and once again the offer of help and support being only a phone call away was reiterated.

We have had the best and the worst outcomes through IVF. Poor egg numbers, poor embryo quality, positive and negative pregnancy blood test results, the first scans with a heartbeat, the loss of twins, the birth of our rainbow baby. Throughout all of this our clinic was there to support us. Counseling was included in the package, and having a specialist that dealt with these highs and lows every day was invaluable.

We have been blessed with our clinic, but I know others have not been so lucky. The technology involved is impressive, but the majority of patients I've spoken to are more interested in something far more basic – being treated as an individual and not just another patient on a conveyor belt. Due to the way that the National Health Service is funded, there are likely to be a significant number of patients who are paying privately. IVF isn't cheap, understandably so, but some patients won't have money to splash around and a significant amount of savings will be necessary. They may be able to afford only one attempt. There are so many extra add-ons available out there that patients can find out about, thanks to Dr. Google. It is important that what is being offered at clinics is through evidence-based medicine and not seen as either trying to get more money or offering false hope to people who are often in a desperate situation.

These may sound like simple points, but I think in the world of health care, with time pressures and targets to hit, we often forget the basics and it does no harm to be reminded of them on occasions. To sum the whole experience up in one word would be difficult, but I'd say "emotional." Remembering that the patient may be experiencing excitement to fear, and everything in between, is important. Whether she is going through this for the first or fifth time, the patient should always be at the center of the decisions made.

Chapter 3

How to Manage Intramural Fibroids before an IVF Cycle

Ertan Saridogan

Fibroids are frequently encountered prior to or during in vitro fertilization (IVF) cycles due to their high prevalence in the female population. The estimated cumulative incidence of fibroids by age 50 years is >80 percent in black women and almost 70 percent in white women [1]. However, many fibroids are completely harmless and have no clinical relevance. When clinically relevant fibroids are taken into account to include uteri nine weeks gestation size or larger, at least one submucosal fibroid or at least one fibroid of ≥4 cm, the prevalence is 10–15 percent in white women and 30–40 percent in black women between the ages of 35 and 39 years. In contrast, 35 percent of white women and 50 percent of black women aged 40–50 years have clinically relevant fibroids [1]. It is, however, debatable how clinically relevant are the inclusion criteria used to produce these figures.

The impact of fibroids on IVF outcome is very controversial; a number of published systematic reviews and meta-analyses in the past decade have come up with different conclusions [2–6]. This is probably a reflection of the differences in the methodology of reviews and how stringent are the inclusion/exclusion criteria that have been used. Furthermore, and probably more importantly, the differences may stem from the fact that the number, size, shape, location and consistency of fibroids vary and their impact on reproduction would be almost impossible to stratify.

In general, there is consensus that submucosal fibroids or those that distort the uterine cavity do have a detrimental impact on fertility outcome. However, the quality of evidence to support this is weak and the significance of benefit has been brought into question in a recent Cochrane review [7]. An additional issue is that uterine cavity distortion is not restricted to submucosal fibroids and some intramural fibroids do cause significant distortion to the uterine cavity. Studies that set out to examine the impact of intramural fibroids go to great lengths to ensure that uterine cavity distortion is excluded with a high-quality or reliable test. This may have resulted in exclusion of a subgroup of women who have intramural fibroids with cavity distortion, and the published systematic reviews do not provide a clear outcome analysis for this group.

In this chapter, the evidence from published literature is critically analyzed to attempt to provide guidance to clinicians as to how intramural fibroids can be managed in women undergoing IVF treatment.

Data from Published Systematic Reviews

Several major reviews have been published on the impact of fibroids on reproductive outcomes in the past decade [2–6]. Three of these reviews included studies that looked at the impact of all types of fibroids on both spontaneous pregnancy and IVF treatment outcomes [2–4], whereas the other two specifically looked at studies that analyzed the impact of intramural fibroids not distorting the uterine cavity on the outcome of IVF treatment [5, 6].

Somigliana et al. [2] reviewed the published literature related to fibroids and reproduction. In one of their analyses, they carried out a meta-analysis of 15 articles on IVF outcome and fibroids. Seven of these articles reported IVF outcome separately for intramural fibroids and the meta-analysis showed a small but significant detrimental impact of intramural fibroids on conception (OR 0.8, 95% CI 0.6–0.9) and delivery (OR 0.7, 95% CI 0.5–0.8) rates following IVF/intracytoplasmic sperm injection (ICSI) treatment. They noted that the mean or median diameter of fibroids in the included studies was rarely above 3 cm and that the detrimental impact emerging from the published articles may have been an underestimation of the real impact. The latter opinion was based on the finding that the negative impact was seen in women

with fibroids > 4 cm [8]. Somigliana et al. also made reference to a nonrandomized comparative study by Bulletti et al. [9], who found higher cumulative clinical pregnancy (33 percent versus 15 percent) and delivery (25 percent versus 12 percent) rates after one to three cycles of IVF treatment in women who underwent myomectomy for intramural fibroids > 5 cm compared to those who decided against myomectomy.

Klatsky et al. [3] carried out a similar meta-analysis of 19 studies that were mostly included in the previous systematic review. These studies compared the IVF outcome in women with intramural fibroids of 1–8 cm with those controls without fibroids. Most studies included women with relatively small fibroids of 2–3 cm. The meta-analysis showed a significant decrease in implantation (OR 0.79, 95% CI 0.71–0.88) and clinical pregnancy rates (OR 0.84, 95% CI 0.74–0.95) and an increase in miscarriage rates (OR 1.82, 95% CI 1.43–2.30). The authors urged caution in interpreting the results as they pointed out that meta-analysis may replicate and amplify biases in each study.

Pritts et al. [4] analyzed 23 studies that mostly gave IVF/ICSI-related outcomes. Twelve of these studies included outcomes related to intramural fibroids. These studies showed lower clinical pregnancy rates (OR 0.81, 95% CI 0.70–0.94), ongoing pregnancy/live birth rates (OR 0.70, 95% CI 0.58–0.85) and implantation rates (OR 0.68, 95% CI 0.59–0.80) and higher miscarriage rates (OR 1.75, 95% CI 1.23–2.49) compared to control women without fibroids. When only prospective studies or studies that assessed the uterine cavity distortion with hysteroscopy or sonohysterography were examined, clinical pregnancy rates were no longer significantly different, while the implantation rates remained significantly lower in women with intramural fibroids. Two studies that assessed the clinical pregnancy rates and one that gave the ongoing/live pregnancy rates showed that myomectomy for intramural fibroids did not improve the outcomes compared to controls with in situ fibroids.

Sunkara et al. [5] published an analysis of 19 studies on the impact of non-cavity-distorting intramural fibroids on IVF outcome. They found significant reductions in live birth (OR 0.79, 95% CI 0.70–0.88) and clinical pregnancy (OR 0.85, 95% CI 0.77–0.0.94) rates in women with fibroids compared to women without fibroids. Implantation and miscarriage rates were not statistically different. The studies included in this article had analyzed data from women with fibroids of 0.4–8.0 cm, the majority being less than 5 cm.

Metwally et al. [6] carried out a further analysis of the published studies on the effect of intramural fibroids on assisted reproduction technology (ART) treatment using stricter criteria. Inclusion criteria were presence of a control group, analysis of intramural fibroids separately (not grouping them together with subserosal fibroids) and exclusion of submucosal fibroids by assessing the endometrial cavity with an objective method (hysteroscopy, hysterography, ultrasonography and sonohysterography). With this approach they included only 10 studies from a similar period of publication year to the previous four systematic reviews. The analysis of nine studies that gave the outcome of ART treatment showed no differences in live birth and miscarriage rates, but demonstrated lower clinical pregnancy rates in women with fibroids (OR 0.60, 95% CI 0.42–0.87). When further sensitivity analyses were carried out to include only the studies where age was not a confounding factor and/or studies that used a high-quality method (hysteroscopy or sonohysterography) to exclude cavity involvement, no differences in the live birth, clinical pregnancy or miscarriage rates were found between women with and without fibroids. Importantly, four studies that gave the size of fibroids included women with fibroid size of 5 cm or less.

It appears that, despite some degree of differences in the conclusions of these systematic reviews, the common finding is that the presence of fibroids probably has a detrimental impact on the outcome of IVF.

Significance of Size of Fibroids

As mentioned earlier, a common feature in these reviews is that the majority of studies included only women with relatively small intramural fibroids, probably because women with larger fibroids underwent a myomectomy. Hence, the published literature may be underestimating the impact of intramural fibroids, particularly the larger ones. Only a few studies attempted to assess the impact of fibroid size.

Oliviera et al. [8] found significantly lower clinical pregnancy rates after IVF/ICSI in women with intramural or subserosal fibroids of 4.1–6.9 cm compared to women with no fibroids or fibroids ≤ 4 cm. There was no difference in pregnancy rates between the control group and women with fibroids ≤ 4 cm. Women with fibroids of ≥ 7 cm were excluded.

Another retrospective study of impact of fibroids not distorting the cavity found that delivery rates were lower in the presence of fibroids > 2.85 cm whilst there was no detrimental impact in the presence of smaller fibroids [10].

Mechanism of Action

The actual mechanism of how intramural fibroids may affect ART outcome is not known. It is possible that the presence of fibroids affects uterine contractility, intrauterine environment or endometrial receptivity through endocrine, paracrine mechanisms or inflammatory pathways [2]. In addition, larger fibroids may affect ovarian accessibility for the purpose of egg collection. This latter point is less well recognized in the published literature, but is an important clinical challenge in the presence of some fibroids. This may result in a lower number of collected oocytes and may occasionally force clinicians to perform transabdominal egg collections.

Impact of Myomectomy

Evidence on the potential benefit of myomectomy prior to ART for women with intramural fibroids is scarce. Only one comparative nonrandomized study assessed the potential benefit of myomectomy prior to IVF [9]. One hundred sixty-eight women with at least one fibroid > 5 cm were allowed to choose between myomectomy and expectant management prior to IVF. Submucosal fibroids were excluded, but it is likely that some women had subserosal fibroids. In the 84 women who had a myomectomy, clinical pregnancy (33 percent versus 15 percent, $0.05 < p$) and delivery (25 percent versus 12 percent, $p < 0.05$) rates were significantly lower compared to the other 84 women who did not have surgery after one to three cycles of IVF treatment.

Myomectomy is a relatively frequently performed procedure, particularly in the presence of symptomatic fibroids. However, questions remain as to its effect on fertility and outcome of ART. While the potential harm of postoperative pelvic adhesions on spontaneous conceptions is well recognized, the impact of myometrial trauma or intrauterine adhesions after myomectomy on IVF is less recognized.

Potential benefits of laparoscopy against laparotomy for myomectomy have been well established in a number of randomized controlled trials. In comparison to traditional open myomectomy, the laparoscopic approach is associated with less postoperative pain and fever, and shorter hospital stay at the expense of longer operating times [11]. Other potential advantages of the laparoscopic approach include a shorter recovery time with a quicker return to activities of daily living [12]. Nevertheless, myomectomy is still a major operation and is associated with significant morbidity. Furthermore, the women are usually advised to avoid a pregnancy for at least three months postoperatively, resulting in delays in the planned IVF treatment. This may potentially be an issue for older women, particularly for those with reduced ovarian reserve.

Conclusions and a Practical Approach to Management in Clinical Practice

The published evidence on the impact of intramural fibroids on IVF outcome is suggestive of a detrimental impact; however, this is based on relatively low-quality studies that show significant variability in inclusion/exclusion criteria and outcome parameters. This is hardly surprising, considering that fibroids come in different numbers, size and consistency. While there is a need to perform prospective randomized studies in this field, this is likely to be extremely challenging due to a high number of confounding factors. The majority of published studies included women with relatively small intramural fibroids, hence there is a significant possibility that the detected impact in the systematic reviews is an underestimation.

Currently there is very little evidence from controlled studies on the benefit of myomectomy for intramural fibroids prior to IVF treatment, although the procedure is relatively frequently performed. It is quite likely that numbers needed to treat (NNT) for this purpose would be very high for small fibroids, while the NNT would be lower for larger fibroids. This point would need to be taken into account when decisions are made on myomectomy, and potential benefits should be weighed against the associated morbidity, cost and delay in treatment.

In our practice we take a number of factors into account when we counsel our patients who have intramural fibroids that do not distort the cavity prior to IVF treatment. These include the age of the woman, her ovarian reserve, the number and size of fibroids, the overall size of the uterus, history of previous surgery and ovarian accessibility. We try to avoid

surgery in the presence of fibroids < 5 cm when the uterine cavity is regular. We tend to offer surgery first to women with fibroids ≥ 7 cm but proceed with IVF treatment without surgery in the presence of fibroids of 5–6 cm in the first IVF attempt. We usually offer surgery for fibroids of 5–6 cm, if the woman had one or two failed IVF attempts. With this approach we aim to keep the NNT as low as possible per additional pregnancy achieved.

If there are difficulties with ovarian accessibility due to fibroids, we prefer surgery before IVF. We usually wait for three months before proceeding with IVF postoperatively but in older women with reduced ovarian reserve, we proceed with IVF earlier and freeze embryos for delayed transfer.

Suggested Standard Operating Protocol (SOP)

– Management of women with subfertility and fibroids

Suggested Patient Information Sheet

– Subfertility and fibroids

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