Unexplained infertility – debate continues

Traditionally, a diagnosis of unexplained infertility is established only when all standard recommended clinical investigations yield normal results. In practice it has been seen that in patients labeled as having unexplained infertility, the couple actually has a real but unobservable defect, which was undetected due to misdiagnosis, the lack of specific tests, or because of limitations in the quantity and quality of tests. In addition, unexplained infertility leads to psychosexual effects and sexual dysfunction, because the patient believes that there is no effective treatment, because the cause is nonidentifiable. The current practice of including poorly performing and expensive tests to improve the diagnostic accuracy is logical but debatable.

The most frequent reasons for unexplained infertility are endometriosis, mild tubal abnormality, immunological causes, and POF. Hence, utero-tube peritoneal evaluation should be an integral part of infertility evaluation. Recapitulating the normal reproductive physiology will better explain the importance of uterotuboperitoneal factor. At the time of release of the ovum, the fimbrial processes cover the ovary; ciliary movement in the tubal lumen leads to the development of negative pressure that sucks the ovum from the follicle into the tubal lumen. The ovum then advances in the tubal lumen, where the sperms have reached already after a natural intercourse or intrauterine insemination (IUI). Fertilization occurs in the tube, and the embryo advances toward the uterine cavity for implantation. Thus, the fallopian tube, apart from being a conduit for the gametes and early embryos, plays an important role in many reproductive functions such as sperm transport and capacitation, ova retrieval and transport, fertilization, embryo storage, nourishment, and transport. Complex and coordinated neuromuscular activity, cilial action, and endocrine secretions are required for successful tubal function. Compromised tubal damage can occur after external or internal injury, inhibiting the normal transport of the gametes. The overall prognosis for fertility depends principally on the insult and the severity of the tissue damage; hence, the assessment of tubal damage plays a major role in predicting the occurrence of pregnancy and the likelihood of developing ectopic pregnancy. This explains that the tuboovarian relationship and tubal function in the form of tubal peristalsis and fimbrial function are as important as the patency of the fallopian tubes for the preservation of fertility.

Over the past decade, several advances have occurred in the diagnosis and treatment of reproductive disorders. In spite of extensive diagnostic procedures, in 15–30% of couples, the cause of infertility cannot be explained, and they are grouped as unexplained infertility.[1]

Current definition of unexplained infertility: Unexplained infertility remains a diagnosis of exclusion. It is idiopathic in the sense that its cause remains unknown even after an infertility workup, usually including semen analysis in the male and the assessment of ovulation and fallopian tubes in the female. The practice committee of the American Society of Reproductive Medicine has issued guidelines for standard infertility evaluation, which includes a semen analysis, an assessment of ovulation, a hysterosalpingogram, and, if indicated, tests for ovarian reserve and laparoscopy.[2] When the result of standard evaluation is normal, the couple is assigned as a case of unexplained infertility. However, there is a constant debate on the need to exclude endometrial and intraperitoneal abnormality by hysterolaparoscopy before a diagnosis of unexplained infertility is made. Even the practice committee of the American Society of Reproductive Medicine has not clearly deliberated on this issue. As per RCOG recommendations, an essential workup of infertility should consist of semen analysis, mid-luteal serum progesterone, and tubal patency by hysterosalpingography (HSG) or laparoscopy[3] These suggested diagnostic tests do not include the assessment of tuboperitoneal relations, endometriosis, and subtle defects in the endometrium, which are responsible for the failure of conception in a large number of cases.

Questions that need to be answered:

(1) Infertility related to the uterine cavity abnormalities has been estimated to be the causative factor in as many as 10–15% of couples seeking treatment. Moreover, abnormal uterine findings have been noted in 34–62% of infertile women.[4] However,

this fact is completely overlooked by the currently available recommendations. Hysteroscopy is the gold standard to evaluate the uterine cavity and might pickup subtle defects, which could be responsible for infertility, and in turn decrease the percentage of unexplained infertility cases. Therefore, it becomes pertinent to answer the question whether hysteroscopy should be included in the workup of infertility before it is termed as unexplained.

(2) The prevalence of endometriosis increases dramatically to as high as 25–50% in women with infertility, and 30–50% of women with endometriosis have infertility. Patients with endometriosis without endometrioma are easy to go undetected on routine workup. As per current recommendations, because laparoscopy is the only means to diagnose these cases, should laparoscopy be mandatory before labeling the patient as a case of unexplained infertility?

Systemic approach to the management of unexplained infertility: As the diagnosis of unexplained infertility is by exclusion, it is important to observe the following principles.

- Check whether the evaluation of the couple is complete as per current diagnostic standards and whether all possible diagnostic tests to exclude detectable abnormalities have already been performed.
- Re-evaluate strategies after each cycle so to maximize the outcome.
- Consider the possibility of change in the diagnosis during the workup at a latter stage.
- Understand that many processes involved in conception are not accessible during routine and even advanced workup.

Diagnosis of unexplained infertility

The current evaluation of any infertile couple consists of a detailed history of both male and female partners including their sexual history, occupational history, menstrual history, and any history of sexual dysfunction, drug intake, smoking, and operative history or chronic illness. A detailed examination of male and female partners is also recommended to exclude any obvious abnormalities; diabetes, thyroid disorders, and hyperprolactinemia should be excluded by appropriate investigations. A basic scan on day 2–3 of cycle provides information about ovarian reserve and endometrial abnormalities and excludes any obvious abnormality; therefore, it is recommended.

Assessment of male infertility

The important elements of the history that need to be considered include prior paternity, a history of cryptorchidism, medical and surgical history, sexual dysfunction, and any use of medications, tobacco, alcohol, or illicit drugs. On physical examination, testicular abnormalities such as a varicocele or the absence of the vas deferens can be detected. Semen analysis as per World Health Organization guidelines is the basic test to exclude a male factor.

If the semen analysis is abnormal, it should be repeated after at least 15 days to 1 month by a laboratory that adheres to the WHO's guidelines. A number of commercial laboratories use a variety of ranges for the different components of the semen analysis. Careful attention should be paid to these ranges, and the semen values should be interpreted in the right context. Despite its limitations, semen analysis remains the most important tool in the investigation of male factor infertility.

Assessment of ovulation

Ovulation predictor kits are useful for women who do not have very long menstrual cycles. Ovulation is best detected by mid-luteal progesterone levels, which are measured around day 21 in women with regular (~28 day) cycles. However, they are often poorly timed if they are drawn on cycle day 21 in women with irregular menses. In such women, it is better to use an ovulation kit and measure the progesterone levels 7–8 days after the LH surge is detected. Serum progesterone levels higher than 3 ng/mL suggest that ovulation has occurred, and levels higher than 10 ng/mL are optimum for ovulation assessment. Serial transvaginal sonography starting from the 9–10th day of the cycle to detect follicular development and endometrial growth is a popular method for the documentation of ovulation.

Assessment of ovarian reserve

Another test added to the workup of couples with infertility includes the assessment of ovarian reserve. Women with advanced age or a history of prior ovarian surgery are at risk for diminished ovarian function or reserve. Because it is a key and noninvasive determinant, several practitioners are including the evaluation of ovarian reserve as first-line workup for infertility. The testing includes the following conventional markers: day 2–3 serum follicle-stimulating hormone and estradiol level or the relatively new markers AMH and ultrasonographic ovarian antral follicle count. The results of these tests are not the absolute indicators of infertility, but abnormal levels correlate with decreased response to ovulation induction medications and lowered live birth rates after

in vitro fertilization (IVF). In addition, young patients with diminished ovarian reserve are prone to have subtle immunologic factors leading to relative infertility, which may not be picked up in routine infertility evaluation.

Assessment of the uterus and fallopian tubes

HSG is the primary investigation method for uterine cavity and tubal evaluation. Any irregularity in the cavity or any suspected tubal abnormality or tuboperitoneal abnormality should be further evaluated by more definitive video hysteroscopy/laparoscopic as per the current protocol. Intrauterine subtle lesions such as periosteal adhesions, focal atrophy, and chronic endometritis and adhesions, submucous polyps, and myoma are best detected by hysteroscopic evaluation. It also provides an opportunity to correct these defects. Endometriosis and intraperitoneal adhesions are best assessed by laparoscopy along with dye perturbation. It is suggested but remains debatable that the inclusion of hysteroscopy and laparoscopy should be mandatory before labeling a patient as a case of unexplained infertility and can help in explaining the unexplained and can reduce the incidence of unexplained infertility up to a certain extent.

Ultrasound evaluation in the follicular phase is used to identify uterine fibroids, polyps, and congenital cavitary anomalies such as a septate uterus. At the same time, information on ovarian volume and antral follicle counts can be obtained, making pelvic ultrasound a part of the initial workup for infertility.

The role of laparoscopy in the infertility evaluation

The role of laparoscopy in the investigation of infertility has changed over the past decade. Given that it allows a direct visual examination of the pelvic reproductive anatomy, it is the test of choice to identify otherwise unrecognized peritoneal factors that influence fertility, specifically endometriosis and pelvic adhesions. According to the guidelines of the ASRM, laparoscopy should be performed in women with unexplained infertility or signs and symptoms of endometriosis, or in whom reversible adhesive tubal disease is suspected.[3]

Newer investigations in unexplained infertility: Standard investigations, which form a part of the basic evaluation of any infertile couple, are not able to explain the cause of infertility in many cases, and these continue to be termed as unexplained. It is postulated that the important cause of infertility in these cases is the failure of sperm oocyte contact and oocyte fertilization. Possible etiological factors could be the following: (a) functional defect in the spermatozoa or (b) functional defect in the ovum. However, these defects cannot be assessed in routine laboratories, and their detection is possible only in specialized andrology or IVF laboratories. Various investigations that are suggested for workup include the following:

(1) Hypo-osmotic swelling test − for plasma membrane integrity.
(2) DNA fragmentation test: tunnel assay, comet assay, and acridine orange assay.
(3) Test for acrosin competence.

Oocyte defects are difficult to assess and at present are indirectly assessed by failed fertilization during ART cycles.

Treatment of unexplained infertility

A diagnosis of unexplained infertility is made after the above-recommended testing fails to reveal any abnormality. The treatment for unexplained infertility is, therefore, by definition, empiric, because it does not address a specific defect or functional impairment. The principal treatments for unexplained infertility include the following:

(1) Expectant observation with timed intercourse and lifestyle changes;
(2) Clomiphene citrate and IUI;
(3) Controlled ovarian hyperstimulation (COH) with IUI; and
(4) IVF/Intracytoplasmic sperm injection (ICSI).

Expectant management and lifestyle changes

Expectant management is not the ideal treatment suggested, because the fecundity remains low with expectant approach. However, it can be suggested in young patients with a minimal duration of infertility. The likelihood of pregnancy without treatment among couples with unexplained infertility is less than that of fertile couples, but greater than zero. It is possible that unexplained infertility represents the lower extreme of the normal distribution of fertility with no defect present. However, it could also be due to the fact that the routine infertility evaluation misses subtle defects because of imperfect or incomplete testing methods. Studies of couples with unexplained infertility who were followed up without any treatment reported a broad variation in cumulative pregnancy rates (PRs). A retrospective review of 45 studies by Guzick *et al.* found an average cycle fecundity of 1.3–4.1% in the untreated groups, which was lower than most treatment interventions.[5] In a recent

study, couples with unexplained infertility on a waiting list for IVF in the Netherlands had a 10–15% cumulative chance of pregnancy over a 12-month period. As expected, the age of the female partner influenced the PR associated with expectant management.[6] It is advisable that couples should be counseled in detail about the low fecundity of expectant management and option for other better modalities available, and they should be encouraged to make a conscious decision keeping all factors in mind.

Laparoscopy as a treatment

Whether laparoscopy should be offered as diagnostic tool for unexplained infertility or to treat the condition is a matter of debate. There is constant suggestion that laparoscopy should be a part of the diagnostic protocol in patients who are having no other detectable cause. The roadblock in including laparoscopy in diagnostic workup is its invasive nature and cost involved. Whether operative laparoscopy improves pregnancy outcomes in unexplained or minimal/mild endometriosis is a subject of debate, but is acceptable. In 1997, Marcoux *et al.* reported the results of a randomized, controlled trial (RCT) in a population of 341 infertile women 20–39 years of age with minimal or mild endometriosis.[5] During diagnostic laparoscopy, the women were randomly assigned to undergo resection or ablation of visible endometriosis or diagnostic laparoscopy only. They were followed up for 36 weeks after the laparoscopy or, for those who became pregnant during that interval, for up to 20 weeks of pregnancy. In the intervention group, 50 of the 170 women became pregnant in the follow-up period, compared with only 29 of 169 in the diagnostic laparoscopy group. The corresponding rates of fecundity were 4.7 and 2.4 per 100 person-months (rate ratio, 1.9; 95% confidence interval, 1.2–3.1). The authors concluded that "laparoscopic resection or ablation of minimal and mild endometriosis enhances fecundity in infertile women."[6] Contradicting this finding, a smaller RCT from Italy with a similar study design could not confirm these results. In the study reported by Parazzini,[7] the 1-year birth rate in the resection/ablation group was 10 out of 51 women (19.6%) compared with 10 out of 45 women (22.2%) in the no-treatment group. A Cochrane review on the topic published in 2002 concluded that laparoscopic surgery in the treatment of minimal and mild endometriosis may improve pregnancy success rates, but that the "relevant trials have some methodological problems and further research in this area is needed."[8] If laparoscopy is performed in a patient with unexplained infertility and minimal/mild endometriosis is identified, it is recommended to ablate endometriosis.

INTRAUTERINE INSEMINATION

IUI involves the placement of washed sperm into the uterine cavity around the time of ovulation. It should be performed with ovulation induction using clomiphene citrate or injectable gonadotropins. Few data exist on the use of IUI without ovarian hyperstimulation. It has been estimated that 37 cycles of IUI without additional ovarian stimulation would be needed to obtain an additional pregnancy compared with control cycles.[1] A recent Cochrane review on this topic confirmed that IUI with ovulation induction increased the live birth rate compared with IUI alone.[9] Therefore, IUI without additional treatment with clomiphene citrate or gonadotropins is not routinely performed in couples with unexplained infertility.

CONTROLLED OVARIAN HYPERSTIMULATION AND INTRAUTERINE INSEMINATION

In the past decades, there has been a marked increase in the use of COH, with or without IUI, in the treatment of unexplained infertility. Both clomiphene citrate and gonadotropins have been used for COH in combination with IUI or alone. The theoretical rationale for COH in women with a normal ovulatory assessment is that subtle ovulatory defects missed by standard testing may be overcome, and that an increased number of eggs available for fertilization may increase the likelihood of pregnancy. In a similar fashion, introducing washed sperm into the uterine cavity using IUI may increase the density of motile sperm available to the ovulated oocytes, which should maximize the chance of fertilization.

The use of clomiphene citrate with timed intercourse in patients with unexplained infertility has been shown to have a small effect on PRs; a combined analysis of the available evidence revealed that 40 cycles with empiric clomiphene citrate therapy were necessary to achieve one additional pregnancy. Gonadotropin therapy is superior to clomiphene citrate therapy, and both are most effective when combined with IUI. A meta-analysis of 27 studies involving 2939 cycles revealed that the PR per cycle was 8% with gonadotropin treatment alone and 18% with gonadotropin treatment combined with IUI.[5] The cumulative PR rises with the number of attempted COH/IUI cycles; however, there is some evidence suggesting that the number of COH/IUI cycles prior

to treatment with IVF should be limited to 3. Aboulghar *et al*. performed an observational prospective study on 594 couples with unexplained infertility to determine the optimum number of COH/IUI cycles. They found that 1–3 cycles of COH/IUI resulted in 182 pregnancies, with a cycle fecundity of 16.4% and a cumulative PR of 39.2% (a total of 1112 cycles with a mean of 1.9 cycles/patient).[10] Up to three further trials of COH/IUI in 91 of these women resulted in only nine more pregnancies, with a cycle fecundity of 5.6%, which was significantly lower than that in the first three attempts (additional 161 cycles with a mean of 1.8 cycles/patient). The cumulative PR rose to 48.5% by cycle 6, which is a further increase of only 9.3%. A historical comparison group with 131 patients with three failed cycles of COH/IUI who underwent 1 cycle of IVF at the same center resulted in 48 pregnancies, with a cycle fecundity of 36.6% per cycle, suggesting that patients should be offered IVF if they fail to conceive after three trials of COH and IUI.

Although some studies suggested the marginal benefits of double IUI over single, the most recent randomized trial concluded that among patients undergoing COH/IUI, the results of single and double IUI do not statistically differ.[11] Therefore, double IUI is not routinely offered.

In vitro fertilization/intracytoplasmic sperm injection

Not only the most expensive, but also the most successful treatment of unexplained infertility consists of the spectrum of assisted reproductive technology including IVF, with or without ICSI. IVF is the treatment of choice for unexplained infertility when the not only less costly, but also the less successful, treatment modalities outlined above have failed. In the 2006 society of assisted reproductive technology (SART) data for unexplained infertility, there were 126,726 completed cycles with 40.4% live birth rate for women younger than 35 years of age and 38.9% for women 35–37 years of age. In addition to offering the highest success rate, IVF also explains infertility in some of these couples. In some IVF programs, ICSI is performed in all couples with unexplained infertility (for an undetected fertilization problem), whereas other programs may perform ICSI in 50% of the retrieved oocytes.

COMPARISON OF DIFFERENT TREATMENTS FOR UNEXPLAINED INFERTILITY

A randomized trial comparing treatment alternatives against one another and a nontreated control group and the cost effectiveness of various treatment modalities is not available. Therefore, depending on the individual couple and their particular clinical situation, COH with IUI may be attempted first, with transition to IVF/ICSI if pregnancy is not achieved in a timely manner. It is recommended to go for an accelerated approach − 3 cycles of IUI with CC/letrozole/gonadotropins and followed by ART in the case of failure to reduce median time to pregnancy.[12]

Summary and conclusion Unexplained infertility is a diagnosis of exclusion; therefore, a thorough, but time-efficient, investigation of the infertile couple is required prior to labeling them as a case of unexplained infertility. Comprehensive time-bound evaluation including semen analysis, ovulation testing, the assessment of ovarian reserve, and imaging to assess for tubal and uterine factors are essential before a diagnosis of unexplained infertility is made. However, there is an emerging school of thought recommending the inclusion of hysteroscopy and laparoscopy in the diagnostic workup. The various treatment modalities include expectant management with lifestyle changes, operative laparoscopy, COH (clomiphene citrate or letrozole or gonadotropins) with IUI, and IVF (with or without ICSI). However, the optimal treatment strategy needs to be based on individual patient characteristics such as age, treatment efficacy, side effect, and cost.

Kuldeep Jain

Editor-in-Chief
KJIVF and Laparoscopy Centre, Delhi, India

Address for correspondence: Dr. Kuldeep Jain, KJIVF and Laparoscopy Centre, 24, Gagan Vihar, Delhi-110051, India.
E-mail: Jainravi6@rediffmail.com

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