The Association of Obstetricians & Gynaecologists of Delhi

43rd Annual AOGD Conference

19 20 21 NOVEMBER, 2021

VMMC & Safdarjung Hospital

THEME: SAFE PRACTICES, QUALITY SERVICES

Workshop Manual on Revisiting Basic Infertility Practices

Editor
Kavita Agarwal

Co-Editor
Bindu Bajaj

Organized by
AOGD Infertility Subcommittee
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Message

Its my pleasure to welcome you to the Post conference infertility workshop of 43rd Annual Conference of AOGD. The workshop with the theme "Revisiting Basic Infertility Practices" is very painstakingly planned, covering basics and as well as recent advances in semen analysis, drugs and surgical aspects of female infertility.

This workshop, with its eminent faculty is set to further strengthen your grasp of basic infertility practices by providing detailed and insightful updates. It is heartening to note that infertility workshop manual is being released for the benefit of participating delegates. I am sure it is going to be an asset and ready reckoner for delegates in day to day infertility practice. My heartiest congratulations to editors, all contributors and delegates. My best wishes for the success of the workshop.

Dr. Achla Batra
President AOGD
Professor & Consultant
VMMC & Safdarjung Hospital

Conveners Message

We are pleased to welcome delegates who are attending the AOGD Post-conference Infertility workshop 2021. We are extremely thankful to team AOGD for selecting VMMC & Safdarjung Hospital for this workshop and for trusting and giving us the opportunity to organize it.

The workshop is aimed at young gynaecologists interested in pursuing the practice of infertility. The focus will be on safe, efficient, and judicious use of technology in the field of infertility. It is a matter of great pride to have reputed National and International faculty to participate in the workshop and share their expertise and skill with the delegates.

We look forward for an active participation from the delegates in the workshop to make it a platform for shared learning. We sincerely hope that this workshop will provide rich academic experience and will be an event that all of us will cherish for a long time.

Dr. Kavita Agarwal
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VMMC & Safdarjung Hospital
Chairperson AOGD Infertility Subcommittee
Vice President IMA-SDB

Dr. Renu Misra
Director Kamna Fertility & IVF, Gurgaon
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Editorial

The workshop manual is dedicated to fresh postgraduates and young gynecologists who have started infertility practice or are beginners in the field of infertility. Most of the postgraduates are not well versed with the basic tests of infertility like semen analysis and tubal patency tests. There also exists a dilemma as to when to operate and when not to in certain cases of infertility. The manual has dedicated special chapters on basic tests and when to operate in infertile patients. The guidance provided in this manual will help to remove doubts in the minds of young practitioners in this field.

We are especially thankful to all stalwarts who have contributed chapters based on their extensive research, scientific papers and their rich experiences in this workshop manual. We also thank our publishers for printing and publishing the manual.

We hope that readers will find this manual with inputs from experts in the field, a very practical and useful ready reckoner.
Happy Reading

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CHAPTER 1

Semen Parameters, What is New in the WHO Manual 2021

Dr. Col (Prof) Pankaj Talwar, VSM; Dr. Meenu Vashisht Ahuja

Introduction

The WHO lab manual for the examination of human semen and cervical mucus interaction was first published in 1980. It has been revised four times since then, widely read and has become a recognized standard used by clinical and research labs throughout the world. The 5th edition published in 2010 has been the most popular edition. Clinical assessment plus semen analysis is crucial to guiding the investigation and management of a sub fertile couple.

The WHO MANUAL SIXTH EDITION (2021) encompasses 3 main components:

1. Semen Examination
2. Sperm preparation and cryopreservation
3. Quality assessment and quality control.

Experts from 43 countries in all 6 WHO regions participated and contributed to this edition. For declaring the various semen parameters, the semen samples were collected from a wider geographical region allowing representation of men from most populations.

Semen Parameters to be Assessed

The ejaculate has two major quantifiable attributes

1. The number of spermatozoa and
2. The fluid volume -secretions of the accessory glands.

The key patient factors affecting the ejaculate or semen parameters will include size of the testicles[1], endocrine status, medications being taken such as alpha blockers or SSRIs and supplements[2]. These variables and other largely uncontrolled factors contribute to well-known variation in semen composition among individuals[3].

A. Pre-Examination instructions:

1. Collection of samples is done by masturbation, coitus interruptus to be used in exceptional cases.

2. Ordinary latex condoms NOT to be used[4].
3. Lubricants to be avoided
4. Ejaculate should be completely collected, any spillage to be reported
5. ABSTINENCE PERIOD – minimum of 2 days, maximum of 7 days

B. Sample Collection:

1. The specimen container be kept at ambient temperature of 20 degrees to 37 degrees centigrade
2. The container be clean, wide mouthed and non-toxic for the sperms
3. The following information be recorded
   a. Identity of the man (name, date of birth, personal code number)
   b. Period of ejaculatory abstinence
   c. Date and time of collection
   d. Ejaculate volume
   e. Time between collection and start of examination (Preferably between 30 to 60 minutes)

Liquefaction

A temperature of 37 degrees will facilitate liquefaction, as also slow swirling movements of the container. Complete liquefaction is usually achieved between 15-30 minutes, maximum time taken should be one hour.

Volume

Volume is best measured by weighing the sample in the container in which it has been collected. Use a pre-weighed container, weigh the container with the ejaculate in it and subtract the weight of the empty container.
Calculate the volume from the sample weight, assuming the density of semen to be 1gm/ml. Semen density has been reported to vary between 1.03 and 1.04gm/ml[5],1.00 and 1.01g/ml, and an average of 1.01g/ml.
Normal Limits-1.4ml (1.4ml to 6ml).

Viscosity

It can be estimated by gently aspirating the semen into a wide bore (1.5mm) plastic disposable pipette allowing the semen to drop by gravity and observing the length of the thread. Normal sample would fall as discrete drops.
Graded as Normal,1,2,3 (most viscous being 3)
ABNORMAL would be if a drop would form a thread > 2cm

Ejaculate Odour

Normal smell of human ejaculate should be perceived. Note should be made of strong odor of urine or putrefaction.

Ejaculate pH

Measure in a fresh specimen. Preferably between 30-60 minutes. Mix the sample well, spread a drop of semen evenly on the pH strip. Wait for the color change to become uniform(<30secs). Compare the color with the calibration strip.
NORMAL pH is 7.2 TO 8.

Total Sperm Number

Dilute with a fixative to immobilize the spermatozoa.
The limit of normal sperm count is 39 million.

Assessment of Sperm Clumping

There are 2 types of clumping.

1. **Sperm Aggregates**
   Adherence of immotile sperms to one another or of motile sperms to mucus strands, Non sperm cells or debris is defined as nonspecific aggregation.
2. **Sperm Agglutinates**
   Refers to motile sperms sticking to each other, head-to-head, tail-to-tail or in a mixed manner, the motility being vigorous.The types of sperm agglutination are
   a. Isolated (<10sperms/agglutinate, many free sperms)
   b. Moderate (10-50 sperms/agglutinate, free sperms)
   c. Large (>50 sperms/agglutinate, some sperms are still free)
   d. Gross (all sperms agglutinated and agglutinates are interconnected)

Sperm Concentration

Use of hemocytometer chambers with improved NEUBAEUR ruling is RECOMMENDED. Labs should not stop assessing if the number of sperms is as low as 2 million/ml. LOWEST reference range -16 million/ml.

In order to increase the prognostic value of routine Semen Analysis, the sperm count have been combined to provide:

TOTAL SPERM COUNT=Sperm Conc. x Volume of semen

TOTAL MOTILE SPERM COUNT=Total sperm in ejaculate x % motility

Or MOTILE SPERM/ml (sperm/ml x % motility

Sperm Motility

The extent of progressive sperm motility is related to pregnancy rates[6]. It is obtained by multiplying the total number of spermatozoa in the ejaculate by the percentage of progressively motile sperms. Back to 4 pointer system:

1. RAPIDLY PROGRESSIVE->=25micrometres/sec or at least half tail length per sec.
2. SLOW PROGRESSIVE- 5 TO 25 micrometers per sec or at least one head length to less than half tail length/sec
3. NON PROGRESSIVE-<5 micrometers/sec or less than one head length
4. IMMOTILE-no tail movement

Lowest Reference Value -total motility-42%. Progressive motility-30%

Sperm Morphology

Lowest reference value of morphology: 4%

In this more and better-quality micrograph of spermatozoa from unprocessed semen samples considered normal, borderline or abnormal are included, accompanied by explanations of why each spermatozoon has been classified the way it has.

Sperm Vitality

The recommended test for diagnostic use is the Eosin-Nigrosin test. Alternative vitality is also described. Lowest reference value: 54%.

Conclusions

THE MAIN DIFFERENCES IN SEMEN PARAMETERS –5th Edition Vs 6th Edition

WHO Edition	5th Edition	6th Edition
YEAR	2010	2020
VOLUME	1.5ml	1.4ml
TOTAL SPERMNUMBERS(M)	39	39
SPERM CONC (M/ml)	15	16
TOTAL MOTILITY	40	42
PROGRESSIVE MOTILITY	32	30
VITALITY	58%	54%
NORMAL FORMS (%)	4%	4%

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2
CHAPTER

Leucocytospermia: To treat or not to treat

Dr. K. D. Nayar

Introduction

Leukocytospermia is a condition in which there is abnormally high concentration of WBCs within the semen. Leukocytospermia has been shown to be a negative prognostic factor for fertility. Current methods for detecting leukocytospermia include identification of round cells, immunohistochemical staining using monoclonal antibodies, the Endtz test, the peroxidase test, and flow cytometry. Studies have evaluated the use of antibiotics, anti-inflammatory agents, and antioxidants as treatment.

Definition

In healthy men, WBCs are usually found in small amounts in semen samples. The World Health Organization (WHO) defines leukocytospermia as $>1\times10^{6}$WBCs/mL in a semen sample. In order to define the etiology of leukocytospermia, people who present with this finding can be divided in two groups:
Group 1, Leukocytospermia without genital tract infection (GTI)
Group 2, Leukocytospermia with GTI

The etiology of leukocytospermia in people without a GTI remains unclear but GTI can affect the urethra, epididymis, testicles, and prostate.

Leukocytospermia is considered an inflammatory disease. In most cases, the inflammatory syndrome is secondary to a urogenital bacterial disorder. However, other conditions may also lead to leukocytospermia, including viral infections, varicocele and therefore confirmatory tests are recommended. Numerous etiologies and various implications on fertility have been identified. In a small proportion of men, the presence of white blood cells or red blood cells can adversely affect sperm quality by the production of reactive oxygen species.

Detection

Several methods have been used to assess the presence of white blood cells and red blood cells in samples, such as identification of round cells.

The American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) recommend wet mount microscopy confirmed with immunohistochemistry for diagnosis of leukocytes in a semen sample. In contrast, the European Association of Urology (EAU) recommends wet mount microscopy confirmed with peroxidase positive staining. The WHO also recommends the peroxidase test, although this test distinguishes only granulocytes and no other WBC types. The gold standard for assessment of WBCs in semen is immunohistochemical staining using monoclonal antibodies against specific WBC subpopulations, but this method is expensive, time-consuming, and not standardized. Monoclonal antibodies targeted against CD45 are used as a pan-leukocytic marker in both immunohistochemical staining and flow cytometry. 30% of infertile males have leukocytospermia, although in 80% of leukocytospermic infertile males, no microbial infection can be detected in their semen.

Treatment

There is no clear agreement on the treatment for leukocytospermia. The AUA and ASRM provide no guidelines for treating leukocytospermia, while the Canadian Urological Association (CUA) believes that there is no indicated treatment for leukocytospermia, but antimicrobial therapy can be considered in an infertility setting.

Systematic review of treatments for leukocytospermia found that antibiotics might improve sperm parameters, the rate of resolution of leukocytospermia, the bacteriological cure rate, and even the pregnancy rate, although reports were conflicting.[4] In vitro studies have shown that antioxidants may also have clinical benefit for sperm function. However, the data were insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia were effective or not.

Various treatments, including antibiotics, anti-inflammatory medications, and ejaculation at least once a month.[5] Caution has been advised in the use of antibiotics, as animal studies have found that antibiotics can arrest spermatogenesis and disturb other semen parameters. Thus, care should be taken to administer the appropriate dose and duration of antibiotic therapy to prevent these complications.

Other agents have been used in the treatment for leukocytospermia. For example, ketotifen, an antihistamine-like drug, was found to improve sperm motility and morphology in men with leukocytospermia and unexplained infertility. Antioxidants have been used to reduce the production of ROS by seminal leukocytes and improve sperm quality. Nonsteroidal anti-inflammatory

drugs (NSAIDs) were found to recover sperm count, motility, and morphology in asthenoteratozoospermic men with leukocytospermia.

Presence of WBCs and RBCs can significantly affect semen quality and fertility. ROS production is the most prominent issue and is further exacerbated when these specimens containing WBCs or RBCs are cryopreserved. Proper diagnostic methods should be utilized, and underlying etiologies should be ruled out using more extensive urological workups in recurrent and high-risk cases. Treatment options for these conditions have proven controversial as studies have demonstrated conflicting results. Currently, no clear clinical strategies exist for how to manage the cryopreservation of samples with leukocytospermia or hematospermia. However, appropriate strategies to eliminate WBCs in semen samples can improve outcomes for cryopreservation and ART.

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CHAPTER 3

Is HSG the preferred tubal patency test?

Dr. Surveen Ghumman Sindhu

Tube blockage is one of the most frequent causes of infertility in women. One third of infertility cases are due to anatomical abnormalities of the female reproductive tract such as tubal blockage. The degree of tubal pathology determines the possibility for fertility. The evaluation of the fallopian tube is necessary to determine the management plan of infertility. A number of diagnostic tests are being used in clinical practice to assess tubal patency as part of the work-up for subfertility. In clinical practice, the principle modes of imaging to evaluate infertile women are hysterosalpingography using X-rays, ultrasonography, hysterosonography, and pelvic magnetic resonance imaging. Although laparoscopic evaluation of fallopian tubes using methylene blue is considered the gold standard, tubal patency is most often evaluated with a hysterosalpingogram (HSG).[1]

HSG is a minimally invasive and low-cost outpatient procedure with a reported sensitivity and specificity for detecting tubal pathology of 65% and 83%, respectively.[2] The relatively low sensitivity of HSG with respect to its specificity is due to its inability to differentiate between transient and pathological tubal obstructions. Another drawback of HSG is that even if tubal patency is demonstrated, information about the function of the tube cannot be obtained. In patients with hysterosalpingographic findings of a bilateral tubal obstruction, the patient is either offered a laparoscopic evaluation for tubal patency and pelvic pathology and subsequent reconstructive surgery or is referred directly for in vitro fertilisation (IVF) treatment. For those with unilateral tubal patency laparoscopic surgery, direct referral of the patient for IVF or ovulation induction (OI) and intrauterine insemination (IUI) has been suggested as an acceptable approach. However, OI and IUI seems to be the preferred initial treatment approach for such patients in many centres due to its non-invasive nature and lower cost compared to IVF or tubal surgery. Several studies have reported similar pregnancy rates among patients with unexplained infertility and unilateral tubal patency following OI and IUI.[3] Although, patients with proximal

tubal occlusion appear to have more favourable pregnancy outcomes than those with a distal tubal obstruction, a statistically significant difference has not been demonstrated.[4]

Venous intravasation is a complication and potential pitfall during HSG. It can, if not interpreted properly be a cause for an erroneous diagnosis. The sensitivity and specificity of HSG on bilateral tubal patency or no bilateral tubal patency were 92.1% and 85.7% respectively. The positive and negative predictive values were 97.2% and 66.7%, and the accuracy was 91.1%.[5]

Some studies have shown that it is possible to evaluate tubal permeability through MRI utilizing the same technique as HSG, using a saline solution with gadolinium instead of iodine contrast. For those patients who had been recommended for a pelvic MRI for a more detailed infertility study, a simultaneous hysterosalpingography using the same method (HSG-MRI) enabled a single and complete exam in addition to not being subjected to ionized radiation.[6]

HSG is considered to have a high sensitivity and specificity. HSG and laparoscopy are not alternative, but are the complementary methods in the examination of tubal patency.

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4
CHAPTER

Ideal Progesterone for Luteal Phase Support: When, How Much, How Long?

Dr Renu Misra

Progesterone plays a crucial role in implantation and continuation of pregnancy. It was isolated in 1933 and recognized to be the "hormone of pregnancy, therefore called "Pro-gestational" or progesterone. It causes decidualization of the endometrium which has been primed by estrogen, by blocking the proliferative effect of estrogen and inducing genes that allow the endometrium to permit embryo attachment. With its genomic and non-genomic actions, progesterone helps in preparing the endometrium for implantation and also in regulating trophoblast invasion and migration.

Which is the ideal progesterone?

Progesterone is available as tablets, vaginal gel and rings, topical creams and injections. The tablets can be used for oral, sublingual, vaginal or rectal administration. The non-enteral preparations include vaginal gels, transdermal creams and injections (oil and aqueous preparation). The question -which is the ideal progesterone - can only be answered by knowing the pharmacokinetics of progesterone with different routes of administration, and finally the implantation rates, as that is the end-point of interest.

Orally administered progesterone is absorbed through the bowel and reaches the liver via the portal vein, where it is rapidly converted to metabolites. Significantly higher dosage of progesterone is therefore required to be ingested to achieve adequate plasma levels,hence it is not the preferred route of administration for luteal phase support (LPS). The sublingual administration route is inconvenient because more daily doses are required. Dydrogesterone has been studied recently as an oral alternative for LPS in IVF cycles and has shown promise. In a metaanalysis, 20-40 mg of dydrogesterone compared to micronized vaginal progesterone 600-800 mg/day and vaginal gel 90 grams/day showed a higher pregnancy and live birth rate in the dydrogesterone arm.[1]

Nevertheless, it will take more studies done worldwide to gain confidence before dydrogesterone will be used as the sole progesterone for LPS in ART cycles.

Transdermal administration would offer good patient compliance, but it does not provide adequate plasma level of circulating progesterone. In contrast, with vaginal administration, though the serum progesterone levels are lower, the concentration in the endometrium is higher due to the "uterine first-pass". Injectable progesterone has been considered the gold standard for a long time, as it achieves good plasma levels that can be monitored by serum level measurements. However, the patient compliance is poor because oil based intramuscular progesterone injections are quite painful. Aqueous progesterone has now become available which has the advantage that it can be administered subcutaneously which is comparatively less painful and can be self-administered.

A recent prospective randomized multicentre trial to study the non-inferiority of vaginal to intramuscular progesterone showed that vaginal progesterone gel showed good efficacy and safety.[2] Vaginal progesterone therefore provides a good alternative to injectable progesterone.Aqueous injectable progesterone 25 mg daily was compared to micronized vaginal progesterone 400 mg daily in a randomized study in IVF cycles. There was no statistically significant difference between clinical, chemical and ongoing pregnancy rates, and early abortions.[3]

When should luteal phase support be given?

Regular ovulatory cycles in young women with good follicular development are likely to produce optimally functioning corpus luteum, and progesterone levels enough to provide adequate support for implantation and ongoing pregnancy. Routine luteal phase supplementation to increase pregnancy rates in such women therefore does not seem to be justified.

There is good evidence that women receiving clomiphene citrate for ovulation induction with or without IUI have a good luteal phase progesterone, and do not require additional LPS.[4] Women treated with letrozole may benefit with LPS, particularly those with polycystic ovarian syndrome.[5]

Use of gonadotropins has different impact and is known to be associated with luteal phase defect. Supraphysiological estradiol levels produced due

to multi-follicular development with gonadotropins leads to reflex inhibition of LH and hence decreased progesterone secretion. Consequently, IUI cycles with gonadotropin stimulation are benefited with LPS.[6] The effect is more pronounced in IVF cycles as gonadotropins are given in higher doses, and it is well accepted that LPS increases pregnancy rates. Injectable or vaginal progesterone is therefore part of a standard protocol for LPS in IVF cycles. Higher doses of progesterone may be required when follicle maturation is triggered by GnRH agonist instead of HCG. Progesterone supplementation is also critical in frozen embryo transfers when endometrium is prepared by hormone replacement as there is no corpus luteum and endogenous production of progesterone.

How much progesterone supplementation is required?

The importance of progesterone in establishing and maintaining pregnancy is beyond doubt. However, the minimum level of progesterone required to support pregnancy is not known. As a result, there are no absolute dosage recommendations for progesterone for LPS. The commonly used doses of various progesterone preparations are as follows:

Micronized progesterone tablets – 400-800 mg/day

Dydrogesterone tablets – 40-80 mg/day

Vaginal gel 8% - 90 mg once or twice daily

Inj Progesterone (oil based) – 50-100 mg/day

Inj Progesterone (aqueous) – 25-50 mg/day

According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines, the daily administration of 50 mg of intramuscular progesterone, 25 mg of subcutaneous progesterone and 600 mg of micronized vaginal progesterone may be equally effective.[7]

How long should LPS be continued?

In the event of successful implantation and pregnancy, the HCG produced by the trophoblast rescues the corpus luteum and prevents luteolysis. Under physiological conditions, no matter how the pregnancy is achieved, progesterone production from corpus luteum shifts to placenta around the seventh week of pregnancy.[8]

Progesterone supplementation can be started on the day of oocyte retrieval or up to two days after the procedure. However, there is great variation in the duration of LPS in clinical practice. A randomised trial comparing progesterone supplementation for 11 days (positive pregnancy test) to six weeks of pregnancy found no difference in pregnancy and live birth rates.[9] Another metaanalysis showed similar results finding no difference between cessation of progesterone on the day of positive pregnancy test compared to prolonged therapy up to 5-7 weeks of gestation.[10] However most IVF clinicians continue LPS up 10-12 weeks of pregnancy. In a recent worldwide survey of practices regarding the choice and duration of LPS, it was reported that 80% preferred to use vaginal progesterone alone for LPS, and 52% continued LPS until 12 weeks.[11]

Key Points

1. Injectable and intravaginal progesterone are equally effective in providing adequate luteal phase support, and are the preferred route for administration in ART cycles. Oral dydrogesterone and aqueous progesterone have shown promise, and may be used for LPS in ART cycles in the future.
2. Natural ovulatory cycles and clomiphene induced cycles do not routinely require LPS. Gonadotrophin induced cycles for IUI may benefit from LPS, but IVF cycles must be supported with progesterone.
3. Although evidence does not show significant difference in pregnancy outcomes when progesterone supplementation is stopped at the time of pregnancy test, majority of clinicians worldwide continue LPS up to 12 weeks.

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5
CHAPTER

Adjuvants in Thin Endometrium

Prof. Sudha Prasad

Endometrial thickness (EM) is one of the strongest predictors of implantation rate and ongoing pregnancy success rate. The endometrial growth is dependent on the uterine blood flow and angiogenesis. Hence, assessment of the endometrium is an essential and a prognostic component for success in assisted reproduction.

Adequate endometrial thickness (ET ≥ 7 mm) at the day of embryo transfer represents the "fertile soil" for an implanting embryo, which is essential to accomplish a successful pregnancy[1]. When the endometrium is assessed to be 'thin', physicians and patients face a decision of whether to proceed with the treatment cycle. At present, there is no consensus on the exact definition of thin endometrium. The most widely acceptable measure is 7 mm, as an ET < 7 mm is negatively associated with the chance of implantation and pregnancy[2].

Estrogen-induced endometrial proliferation after menstruation is mainly dependent on blood flow to the basal endometrium[3]. Estrogen regulates the proliferative phase and estrogen-primed endometrium produces progesterone receptors, which are necessary for the secretory phase endometrial growth regulated by progesterone[4].

Endometrial growth is regulated by these hormones and growth factors such as vascular endothelial growth factor (VEGF)[5]. Some of these factors are produced locally and act via paracrine mechanisms; others have to be transferred to the endometrium. Sufficient uterine blood supply is required for these factors to reach the endometrium, especially to its functional layer[6].

Adjuvant therapy, also known as adjunct therapy or add-on therapy, is given in addition to the primary or initial therapy to maximize its effectiveness. These additional processes vary from simple medications through complex laboratory procedures through to surgical procedures. Add-ons have become ubiquitous with the process of assisted reproduction (ART). Many adjuvant therapies are used empirically to enhance pregnancy outcomes during assisted reproductive

technology cycles. However, disputes still exist regarding the validation of these practices; vaginal/oral oestradiol has been used to augment the oestrogen effect on the uterus necessary for uterine endometrial thickness and receptivity. Low-dose (75-150 mg) aspirin was reported to improve ovarian responsiveness, uterine and ovarian blood flow and pregnancy rates in patients undergoing IVF whereas heparin have been evaluated by several groups and was found to improve pregnancy rates among women with thrombophilia and recurrent abortions[7].

Others included L-arginine, Vitamin E, nitrates, sildenafil, estrogen, pentoxifylline, tocopherol, and intrauterine infusion of growth factor such as Granulocyte-colony stimulating factor and Platelet-rich plasma.

Sildenafil, a phosphodiesterase 5 (PDE-5) inhibitor is now one of the standard treatments for erectile dysfunction (ED) since decades. Beyond its urological scope, new therapeutic applications are being explored because of its vasodilatory property. Recently, the use of sildenafil citrate (SC) has been gradually extended, and attention has also been paid to the adjuvant use of SC in IVF. SC prevents the breakdown of cGMP and potentiates the effect of nitric oxide (NO) on vascular smooth muscles.

Granulocyte colony–stimulating factor (G-CSF) is a cytokine that stimulates the production of a range of inflammatory cells and is thought as a result to have a role in several aspect of reproduction including implantation although the exact mechanism is not understood. [8]

Steroids have also been proposed as an adjuvant because of their immunomodulatory activity. A recent systematic review of the use of glucocorticoids in ART concluded that they did not improve the overall chance of live birth[9]. However, the use of glucocorticoids in women undergoing IVF, rather than ICSI, was associated with an improvement in pregnancy rates of borderline significance (OR, 1.53; 95% CI, 1.07–2.19).

Endometrial injury produced either as an isolated procedure or as part of an investigative procedure such as hysteroscopy has become part of routine practice in some centres. Its action is unclear but thought to be modification of the endometrial inflammatory response to implantation or timing of decidualization. Evidence for benefit has been inconsistent.[10]

Platelet-rich plasma (PRP) derived from fresh whole blood and has anti-inflammatory and pro-regenerative functions. After the activation of the platelets in PRP, growth factors as vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) are actively secreted and transformed

into their bioactive forms within 10 minutes after clotting.[11] These growth factors are known to regulate cell functions such as attachment, migration, proliferation, differentiation and promote extracellular matrix accumulation.[12] PRP efficiently improved the endometrium proliferation, implantation rate, and clinical pregnancy rate. The high concentrations of various growth factors in PRP Immuno-histochemical analysis showed increased micro-vessel density, upregulated expression of Ki67, estrogen receptor alpha, and progesterone receptor, indicating an improvement in endometrial angiogenesis, proliferation, and response to hormones. PRP were proposed to be the possible mechanism.

The effect of transplantation with collagen scaffold/umbilical cord mesenchymal stem cells (CS/UC-MSCs) is on also on trial in thin endometrium caused by asherman's syndrome[13].

Therefore, the results suggest there is no robust evidence that these add-ons are effective or safe for thin endometrium in women who are waiting for embryo transfer.Stem cell therapy seems to be promising. If the endometrium is constantly thin and unresponsive, proper counselling must be done regarding the very low live birth rate. Hence, alternatives means such as surrogacy and adoption may be offered.

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6
CHAPTER

Role of Inositols in PCOS

Dr. Kavita Agarwal

Introduction

Polycystic ovarian syndrome (PCOS) has varied presentation ranging from irregular cycles, ovulatory dysfunction, polycystic ovarian morphology on ultrasound to features of hyperandrogenism and metabolic features, including insulin resistance, obesity, metabolic syndrome, prediabetes, type 2 diabetes and dyslipidemia[1]. As insulin resistance is a major contributor for metabolic, endocrinal and reproductive disorders in PCOS[2], therefore, insulin sensitisers, inositols are now being considered in management of PCOS.

Inositols in metabolic and endocrine abnormalities

Inositols are commonly found in fruits, beans, almond, walnuts and vegetables. Myoinositol (MI) and D-chiro- inositol (DCI) are the stereoisomers of Inositol belonging to a group of sugar alcohols (cyclic polyols)[3].MI promotes cellular glucose uptake and inhibits lipolysis. DCI mediates glycogen synthesis and decreases hepatic gluconeogenesis. Tissues that use more glucose such as brain, heart and ovary have low concentration of DCI and high concentration of MI whereas muscles, fat and liver (glycogen storage tissues) have high concentration of DCI. The physiological ratio of MI/DCIis 40:1in plasma[3].

Combined therapy of MI and DCI regulates glucose metabolism and ameliorates insulin resistance in PCOS women. A large number of reviews, meta analysis, studies have found that combined treatment in a ratio of 40:1improves lipid profile, led to weight loss, significantly reduced fasting Insulin and homeostasis model assessment (HOMA) index, improvement in insulin resistance, metabolic and endocrine profile of PCOS patients[4-5].

Inositols in oogenesis

Inositol deficiency leads to decreased glucose uptake, leading to hyperglycemia and hyperinsulinemia in PCOS women. The specific epimerase that coverts MI into DCI[3] is under insulin control. Due to hyperinsulinemia, there occurs increased

epimerisation of MI to DCI in ovary of PCOS women resulting in deficiency of MI and increased production of DCI. This disturbs the normal physiological ratio of 40:1[6].

MI improves oocyte quality in two ways- one is increasing availability of glucose in ovary for follicular cells and oocytes by cellular glucose uptake and secondly as Inositol 3 Phosphate plays an important role of second messenger of FSH and hence promotes maturation of oocyte. DCI reduces aromatase gene expression leading to decreased estrogen and increased testosterone levels which explains the detrimental effects on blastocyst and oocyte quality seen with high DCI concentrations in follicular fluid[3].

Many studies have concluded that best results in terms of normalisation of estradiol, testosterone, progesterone, sex hormone binding globulin (SHBG), ovulation, IVF outcomes, better quality of oocyte and embryos were obtained by MI/DCI ratio of 40:1. Inositol in PCOS women undergoing IVF decreases rFSH (recombinant Follicle stimulating hormone) requirement and reduces the days of stimulation. Studies have found that total number of follicles and peak estradiol levels were significantly lower on the day of Human chorionic gonadotropin (HcG) administration in the inositol group. It reduces risk of ovarian hyperstimulation syndrome and cycle cancellation rates. Myoinositols improved implantation rate and was associated with more number of clinical pregnancies. Therefore, many studies have suggested the use of myoinositols in PCOS women undergoing IVF cycles[7-8]. Studies have concluded that 2g twice a day to cover 24 hours compared to single 4g dose is a better approach[9].

Safety profile

Safety of inositols has been proved in many studies. Recently, an International trial was done on women with previous NTD pregnancy and were planning next pregnancy. There were 2 recurrences of NTD in women on only folic acid compared to no recurrence in women on inositol and folic acid[10].

Recommendations

International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 recommends Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.

Summary

Insulin resistance plays a vital role in pathogenesis of PCOS. Inositols are insulin sensitisers and there is enough evidence to support that MI/DCI in ratio of 40:1

significantly improves metabolic, endocrine profiles and restores ovulation in PCOS women. Also, it is a nutritional supplementation without any significant side effects. Therefore, it should be considered as an alternative therapy for PCOS women.

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7
CHAPTER

To Knife or Not to Knife: Intramural Myoma

Dr. Neena Singh Kumar

Fibroids are the most common uterine tumour in the reproductive age group affecting 20–50% of women. Their relation with infertility, although controversial is always a great concern to the clinician as well as the patient. The various mechanisms by which fibroids are implicated in infertility are as follows: uterine cavity distortion (myoma types 0, 1, 2, 2–5); impaired endometrial and myometrial blood supply; greater uterine contractility; hormonal, paracrine, and molecular modifications; defective endometrial receptivity and gene expression, role of transforming growth factor beta-3 and HOXA-10; and a thicker capsule.

Prior to attributing fibroids as the only cause for infertility and rushing to surgery, one must investigate for other causes of infertility. All patients should complete preliminary investigations including assessment of ovarian reserve and ovulation, seminal fluid analysis and tubal patency tests even though tubal patency tests in the presence of fibroids are inaccurate. Furthermore, accurate fibroid mapping i.e. description of size, location and nature of fibroids, using ultrasound scan is a critical step in such an assessment. Saline infusion sonography (SIS) can be used to rule out submucosal involvement and MRI reserved for complex cases or to differentiate from adenomyosis. It is desirable to know the extent of an intramural fibroid (<50% myometrial invasion or more) and whether or not the fibroid distorts the endometrial cavity before a decision regarding myomectomy can be concluded on. The overall chance of conception is also an important factor in decision making. For example, the removal of submucous or large intramural fibroids is likely to be successful in a woman age <40 years with otherwise unexplained infertility, as opposed to a woman age 40 years or more with low/poor ovarian reserve, where myomectomy irrespective of size and location of fibroids is unlikely to be of major benefit. Also, women who receive treatment early are most likely to have successful outcomes, whereas those who suffer long duration of infertility are the residuals whose

prognosis is worse irrespective of treatment.

What are the pros and cons of myomectomy in patients with an intramural fibroid?

PROS	CONS
1. No interference with sperm transport by reshaping the endometrial cavity and removing distortions.	1. Inconclusive evidence whether myomectomy improves the postoperative clinical pregnancy rate in case of intramural fibroids.
2. Improved endometrial and myometrial vascularity	2. Myomectomy exposes women to nearly 10% rate of surgical complications which include excessive blood loss, myometrial hematoma (1.3%–29.2%), blood transfusion (0.1%–1.3%), and conversion to laparotomy (0.3%–2.7%).
3. Reduced endometrial inflammation	3. Associated with the formation of both intrauterine and intra-abdominal de novo adhesions that can reduce fertility
4. Reduced myometrial contractility associated with fibroids causing successful implantation	4. Long-term complications include the risk of uterine rupture in subsequent pregnancies.
5. Restoring the tubo-ovarian relationship improving ovum pick up and fertilization	5. High recurrence: almost 60% after an interval of 4–5 years and need for repeat surgery.
6. Better expression of molecular markers of endometrial receptivity - HoxA-10 and LIF.	6. Adverse pregnancy outcomes: preterm birth, hospitalization for threatened preterm birth, preterm premature rupture of membranes, intrauterine growth retardation, preeclampsia, and cesarean delivery. To date, there is no evidence in the literature of obstetrical risk reversibility after myomectomy.

What size and type of intramural fibroid should be considered for myomectomy?

Recommendations for myomectomy are less clear for asymptomatic women with infertility who have intramural fibroids that do not distort the endometrial lining (types 3–4) . Type 3 myomas (intramural abutting the endometrial cavity) ranging from 2 to 4 cm in diameter should have these fibroids removed hysteroscopically in patients with recurrent implantation failure and unexplained infertility as supported by a large retrospective cohort in 2018, Yan et al.

Kolankayaet al. reported that most surgeons recommend surgery for fibroids >7 cm or women with multiple failed IVF cycles. Vimercatiet al. supported pre-IVF myomectomy for fibroids >4 cm . Bulletti et al. demonstrated higher success

rate among patients with IM fibroids >5 cm and underwent laparoscopic myomectomy prior to IVF.

Even though intramural fibroids are implicated in sub-fertility however benefit of myomectomy remains debated. There is insufficient evidence to determine that a specific myoma size, number, or location (excluding submucosal myomas or intramural myomas impacting the endometrial cavity contour) is associated with a reduced likelihood of achieving pregnancy or an increased risk of early pregnancy loss.

Do intramural fibroids not distorting the endometrial cavity also cause infertility?

The prospective controlled study by Casini et al. showed the importance of the localization of the myoma in relation to the junctional zone, in which importance in implantation and deep placentation is well known . This is reflected in the significant impact of intramural non-cavity- distorting myomas on placental histopathology . The importance of uterine dysperistalsis in the presence of intra- mural myomas in achieving pregnancies and normalization after surgery was clearly demonstrated by Yoshino et al.

What are the international recommendations on this issue?

As per the SOGC (Society of Obstetricians and Gynaecologists of Canada) :

There is fair evidence to recommend against myomectomy in women with intramural fibroids (hysteroscopically confirmed intact endometrium) and otherwise unexplained infertility, regardless of the size of the fibroids. (II-2D) If the patient has no other options, the benefits of myomectomy should be weighed against the risks, and management of intramural fibroids should be individualized. (III-C).

Reaching a consensus…

We can perform myomectomy in patients undergoing ART and not otherwise in patients diagnosed incidentally with an intramural fibroid and trying to conceive. We can consider myomectomy for intramural fibroids in cases of:

1. Long standing unexplained infertility
2. Recurrent implantation failures
3. Fibroids abutting and distorting the endometrial cavity
4. Patients with previous bad obstetric history now wanting to conceive

through IVF

5. Age of patient>35 yrs resorting to pregnancy via ART

The management of intramural fibroids should be individualised on a case to case basis, weighing the risks and benefits in each patient.

Road ahead- further research needed…

In women of reproductive age, MRI has shown three distinct layers in the myometrium: a high-signal-intensity endometrial stripe, a medium-signal-intensity outer myometrium, and between the endometrium and outer myometrium, a low-signal-intensity junctional zone (JZ) which compared with the outer myometrium has a threefold increase in nuclear area per unit area, a decreased extracellular matrix per unit volumeand a lower water content. This zone may affect fertility by two different mechanisms. Firstly, the origin of myometrial peristalsis in the JZ . Disruption of this zone by fibroids may lead to increased peristalsis. Secondly, IM fibroids may cause thickening or disruption of the JZ leading to poor reproductive outcome. Since JZ plays an important role in implantation and its disruption may lead to implantation failure, we propose that type 4 fibroid can be further classified into type 4a and 4b

- 4a are fibroids that disrupt the JZ but does not reach the endometrium (should be considered for myomectomy)
- 4b are fibroids that do not disrupt the JZ.

8
CHAPTER

Adenomyosis - Is Intervention of Any Benefit

Dr. Rita Bakshi

ADENOMYOSIS is commonly seen in nearly in 30 to 40% of infertile patients it is an enigmatic disease. Various methods of treatment are advocated. Following is a synopsis of the same.

Surgical Approach

Hysteroscopic procedures form the main stay of conservative uterine surgeries. Hysteroscopic Resection- Limited to only superficial lesion not exceeding 2.5mm as there is risk of causing significant bleeding & risk of pregnancy failure. Complete excision of ectopic endometrium of adenomyotic foci is a moderately good therapeutic modality, however the lesions often are not clearly defined & adenomyosis is present diffusely throughout the myometrium. One of the largest studies of adenomyomectomy included 165 women treated with surgery alone or with combined surgical and medical treatment (Surgery followed with 6 months GNRH agonist).The advantage of surgery was clinical pregnancy rate of 77.5% & 69 % had a successful delivery. But disadvantage of surgery is the relapse and rupture following pregnancy.

Uterine Artery Embolism (UAE): - effectiveness of UAE in management of adenomyosis & pregnancy give a live birth rate of 83.3% after a follow up 35 months.

Only Surgery – conservative Surgery described in all studies involving excision of adenomyosis tissue hysteroscopically, laparoscopically or laparotomy had overall live birth rate of 36.2%.

There are no formal guidelines; surgical modality is not preferred modality in patients of infertility as there is lack of evidence.

Medical Management

Currently accepted Rx of adenomyosis in infertility patient is GnRh agonist and

has resulted in good results.

However, problem facing management of adenomyosis surgically are selection of appropriate patient. Postoperative complication such as pelvic uterine adhesion, reduced uterine capacity and uterine deformity, decrease tissue strength predisposing it to uterine rupture during pregnancy. Hence caution decision need to be undertaken in management by surgery.

Combined Therapy

Combined therapy seems to have better pregnancy rate. They may be appropriate in patient failing GNRH agonist alone. Secondly in severe adenomyosis causing severely deformed uterus.

Conclusion

No one particular method of Rx is wholly satisfactory to achieve pregnancy in an infertile patient.

9
CHAPTER

To Knife or Not to Knife: Endometrioma 4cm

Dr Leena Wadhwa, Dr Sonam Yadav

The most common procedure for treatment of ovarian endometrioma and/or "chocolate cysts" is either excision of the cyst capsule or drainage and electrocoagulation of cyst wall." Small ovarian endometrioma of (<3cm diameter) can be treated by drainage and electrocoagulation i.e. it is aspirated and irrigated and inspected with ovarian cystoscopy for intracystic lesion and the mucosal lining of the cyst wall is destroyed by vaporization. Large ovarian cysts greater than 3 cm in diameter can be aspirated and excision and removal of cyst wall done. Cystectomy of endometriomas involves the opening of the cyst (using scissors or electrosurgical or laser energy). After identifying the plane of cleavage between the cyst wall and ovarian tissue, the cyst wall is then excised or "stripped away" by applying opposite bimanual traction and counter action with two grasping forceps. The ovarian edges could be sutured or inverted by light application of bipolar coagulation or kept as they are.

Surgical management is warranted for women with symptoms of dysmenorrhea, dyschezia and chronic pelvic pain.For women who are found to have an asymptomatic endometrioma and who are planning to undergo IVF/ICSI, there is insufficient evidence to suggest that removal of the endometrioma will improve IVF success rates.

In women with endometrioma larger than 3 cm, the ESHRE GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles. The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery

- Benefits of surgical treatment prior to IVF, especially for large endometriomas, include prevention of possible rupture of endometrioma, facilitation of oocyte retrieval, detection of occult malignancy (particularly in view of a large study confirming an association between endometriosis and

certain ovarian cancers), avoidance of contamination of follicular fluid with endometrioma content during oocyte retrieval, and prevention of progression of endometriosis

- Disadvantages of surgery include surgical trauma, surgical complications, economic costs, potential decreased ovarian response, and lack of evidence for improved IVF pregnancy rates.

For ovarian endometriomas greater than 4 cm if surgery is planned then laparoscopic cystectomy with excision of the cyst wall is preferred as it improves fertility compared to cyst drainage and coagulation, which is associated with a high risk of cyst recurrence. Intraoperative steps should be taken to prevent complications.

- Preservation of the vascular blood supply to the ovary is important, as proper blood supply is vital for the preservation of ovarian volume and antral follicular counts. So it is postulated that when approaching the hilus, where the ovarian tissue is more functional and the plane of cleavage is less visible, partial cystectomy is performed and the remaining tissue is electro coagulated or CO2 Laseris used for vaporization
- Strict adherence to the principles of microsurgery
- To remove all visible endometriotic disease.
- Plane of dissection should be identified clearly between cyst wall and normal ovarian tissue to avoid inadvertent injury to normal ovarian tissue, for this hydro dissection or dilute vasopressin injection can be used beneath the capsule
- During adhesiolysis and release of ovaries from ovarian fossa, ureters should be identified clearly.
- Avoid spillage of endometriotic contents as this may increase the risk of recurrence of the disease and adhesion formation

Conclusion

Moderate –severe endometriosis with prior one or more infertility operations, IVF-ET is better therapeutic option than another infertility operation. Second line surgery not recommended.

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10
CHAPTER

Unresponsive PCOS- Ovarian Drilling

Dr Tanya Buckshee Rohatgi

LaparoscopicOvarian Drilling (LOD) works on the principle of removing the intra-ovarian block to follicular maturation by surgically ablating the ovaries. Unipolar or Bipolar energy is used and the number of punctures are chosen depending on ovarian size. The methods to ablate can be the fixed dose or adjusted dose based on ovarian volume. The usual indications are-

- RCOG/ ACOG/ SOGC/and the recent PCOS consensus working group— All recommend its use in highly selected cases of Clomiphene Citrate (CC) Resistant patients
- Hypersecretion of luteinizing hormone (↑LH)
- Those needing laparoscopy for tubal evaluation or any other indication.
- Who live too far away from the hospital for the intensive monitoring required during gonadotropin therapy.
- Poor response to Ovulation induction(OI) agents

Controversies with this procedure entail whether drilling should be unilateral or bilateral, the type of energy source-laser versus electrocautery and whether it should be done before IVF or not?

This is a competency-based procedure with the skill of surgeon playing a crucial role in positives outcomes. The advantages includes is that it is a one-time procedure which increases the sensitivity of the ovaries to OI with decrease risks of OHSS, multilple pregnancies and avoids the need for invasive monitoring. However the down side includes invasive surgery, cost with risks of ovarian damage. Approximately 20-30% of anovulatory PCOS women fail to respond to LOD. Unfavourable factors include -high BMI or any associated tubal factor infertility.

With new and novel oral OI protocols for unresponsive PCOS patients like the extended CC / Letrozole protocol or the stairstep protocol the value of this procedure needs reappraisal. Gonadotropins are a comparable alternative

however need careful monitoring and tailoring of cost effective treatment to avoid risks of OHSS and multiple pregnancies. Lifestyle modification would always remain as the first step towards improvement in unresponsive PCOS. Adjuvants using metformin have shown varied results with some studies showing the combination of Metformin and CC to be comparable to LOD.

LOD should be reserved to well chosen anovulatory CC-resistant PCOS cases — Those with young age, raised LH levels, exaggerated response to gonadotropins, noncompliance or nonfeasibility with frequent, intensive monitoring or needing laparoscopic assessment of the pelvis.

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CHAPTER

To Knife or Not to Knife: "Subcentimeter Endometrial Polyp"

Dr Rhythm Ahuja Gupta

The success of infertility treatment is multifactorial. Assessment of microscopic and macroscopic uterine causes of infertility is as important as ovulatory and tubal disorders. However, to correct or not to correct a uterine pathology like small polyps, fibroids, septa etc. has always been a dilemma.

Endometrial polyps are usually benign overgrowths of endometrium containing glands and stroma, can be sessile or pedunculated, variable in size, number, can be symptomatic or asymptomatic. Up to 25 % women who undergo hysteroscopy with unexplained infertility have endometrial polyp[1]. The sensitivity and specificity of different modalities to pickup uterine pathology is 89% & 56% for ultrasound, 91.3% & 60% for saline infusion sonography and 97.3% & 92% for hysteroscopy. Also, hysteroscopy provides an opportunity for simultaneous correction[2,3].

Polyps & Endometrial Receptivity

It is observed that presence of polyp reduces expression of HOXA 10 and HOXA 11 gene expression, changes endometrial signalling pathways thus altering endometrial receptivity[4]. A prospective randomised study on 215 women showed significant improvement in pregnancy rates in IUI cycles post hyteroscopic polypectomy[5]. However routine use of hysteroscopy for diagnosing uterine pathology pre IVF has been controversial (inSIGHT& TROPHY trial)[6,7].

Subcentimeter Polyps

Small polyps are many a times picked up on ultrasound. In symptomatic women, hysteroscopy with polypectomy and endometrial curetting is the treatment approach. While in others there have been case series of spontaneous regression of small polyps over a couple of months[8].

Depending upon the fertility treatment and time of detection of endometrial polyp, management should be individualised. Polyps less than 1.5 cm did not seem to affect the pregnancy outcomes in ICSI cycle in a study[9]. Another study showed that polyps less than 1.5 cm which developed during an ovarian stimulation in an IVF cycle did not affect the pregnancy outcomes, also polyps detected and resected before the start of an IVF cycle had similar outcome as women with no polyps[10].

Having said that in lack of randomised controlled trials and conclusive evidence on this, patient should be informed about the affect of polyps on receptivity, possibility of regression, treatment option of polypectomy, cancellation or freezing followed by polypectomy and then frozen embryo transfer, based on embryo quality, previous reproductive history, time in hand and financial background and informed decision should be made.

Key Points

1. Assessment and correction of uterine factors is necessary for optimal outcomes with fertility treatment
2. Routine pre IVF hysteroscopy is controversial
3. When detected on routine hysteroscopy, polyps should be resected
4. Pre procedure detected polyps should be removed
5. Small polyps picked up during stimulation have shown not to affect the pregnancy rates significantly.
6. Couples to be counselled about the pros and cons of polypectomy, even for small polyps detected during treatment and informed decision to be made based on the embryo quality, previous reproductive history.

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CHAPTER

Role of Laparoscopy in Unexplained Infertility

Dr. Shalini Chawla Khanna

Diagnosing and managing unexplained infertility still remains an enigma. The frequency of infertility is about 1 in 10 couples and unexplained infertility accounts for about 20% of cases. Diagnosis isusually made when the female partner ovulates regularly, has patent Fallopian tubes, and has a partner with normal sperm count and function.Hysterosalpingography (HSG), Laparoscopy or both can be used to assess tubal patency. When laparoscopy is used as a standard test for tubal function , instead of HSG, incidence of unexplained infertility would apparently reduce from 10 to 3.5%. When laparoscopy is performed for infertile patients with normal HSG findings, 21%-68% of patients were shown to have pathologic abnormalities which may include endometriosis and tubal disease and peritubal adhesions (Corson et al. 2000). Laparoscopy is a reliable procedure in detecting infertility causes in the pelvic cavity, which could then be treated, allowing postoperative pregnancies. Therefore, laparoscopy has both diagnostic and therapeutic importance.

Once these pathologic abnormalities are treated by laparoscopic surgery, COH and IUI can be performed again and where spontaneous conception is deemed impossible because of severe adhesions in the pelvic cavity, they should be switched to ART. Sandra et al. (2003) reported that laparoscopy changed the management plan in 25% of infertile patients with normal HSG findings. In 8 (14.0%) of 57 patients, the management plan was switched to ART because of severe tubal disease. Even cases with severe endometriosis were able to achieve pregnancy rates of 40%-50%, demonstrating that spontaneous pregnancy can be expected even in severe cases of endometriosis by correcting the anatomic abnormalities by laparoscopic intervention .

Other school of thought, Fatum et al. (2002) suggests that diagnostic laparoscopy should be omitted in patients with unexplained infertility. These patients should be treated with 3-6 cycles of ovulation Induction and IUI, and if the treatment is unsuccessful, they should be switched to ART. The fecundity rate of women with minimal or mild endometriosis who undergo laparoscopic surgery

(6.1%) is much lower than fertile women (20%). Moreover, patients with mild tubal disease can expect pregnancy following adhesiolysis; however, if they do not achieve pregnancy, the final solution will be ART. Patients with severe tubal disease accompanying abnormal HSG findings are best advised to proceed to ART. Consequently, reasons supporting ART bypassing diagnostic laparoscopy are as follows: (1) improved outcome of ART, (2) lower pregnancy rate following diagnostic laparoscopy for patients with suspected unexplained infertility and normal HSG findings than following ART, and (3) lack of a contribution from diagnostic laparoscopy in the management plan for patients with suspected unexplained infertility and normal HSG findings.

Conclusion: Clinical history is very important for the selection of the more appropriate diagnostic tool. Its important to classify patients as high risk and low risk. High risk patients with past history of infection, prolonged infertility and positive clinical findings usually warrants early laparoscopy whereas HSG be initially indicated as the less invasive procedure in low risk patients. Omitting laparoscopy from the infertility work-up when HSG is normal and there is no contributing past history can reduce the cost of fertility treatment without compromising success rates. Laparoscopy and laparoscopic surgery for adhesiolysis or ablation of endometriotic lesions should be reserved for cases where ART is not easily available or covered by health care services.

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