Factors and Management of Infertility -A Review

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Abstract

Infertility Management depends on accurate prognosis or the reasons concerning a failure to conceive. By classical definition, infertility is the inability to commence process of reproduction within one year of attempt by a couple. Rapid advances in the field of reproductive biology has rendered the traditional approach of infertility management obsolete. Comparative biology, endocrinology, immunology, genetics, several aspects of plastic surgery must be considered in the investigation and treatment of infertile couple. The purpose of this review is to draw attention towards the factors and management of infertility and the clinical applications.

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BACKGROUND: Clinical studies regarding the months of contraception has established one fourth of couples will conceive within a month to eighty percent in a year[1]. Customarily infertility is defined as either primary or secondary [in case pregnancy has been achieved previously one or multiple times but cannot be initiated any longer]. Technological advancement in the field of reproductive science has produced Assisted Reproductive technology (ART). ART is a number of different treatments such as Intra-Uterine Insemination, In Vitro Fertilization, In Vitro Maturation Vitrification, and Intra-Cytoplasmic Sperm Injection that can induce pregnancy.

Etiology of Infertility

The etiological factors relating to infertility are summarized in the following table[2]:

	Female Factors	Male Factors
General	Dietary Dysfunction Severe Anemia Stress induced Anxiety	Excessive alcohol consumption Excessive intercourse Fatigue Impotence Stress
Developmental	Uterine Anomalies Gonadal dysgenesis Uterine Anomalies	Undescended testicles Hypospadias Kinefelter's syndrome
Endocrine	Polycystic Ovary Thyroid imbalance	Thyroid imbalance Adrenal deficiency

	Adrenal hyperplasia Pituitary failure	Pituitary failure
Genital Maladies	Tuberculosis Vaginitis Endometriosis	Mumps Venereal disease
Factors concerning male and female: *Lack of sex education, low fertility, immunological incompatibility, marital maladjustments*		

The advanced etiology concept attributes equal responsibility towards male and female partners. Several etiological factors are considered to be the result of an infertile union. The classic opinion held as a single partner possessing defect instead of a myriad of other factors in one or both partners. Through the mechanism of conception the complexity of causes of infertility can be brought down to three conditions.

- The cyclical production of a healthy ovum that enters fallopian tube for fertilization, to be later implanted in the endometrium.
- In a sustainable transport medium a particular number of quality sperm should be available repeatedly.
- Fertilization of ovum in the tubes is enabled through proper insemination of the cervix and ascension of Spermatozoa through uterine cavity and cervix.

Any interference with these processes are identified as an etiological factor in infertility. This scheme has been utilized in determining the five major etiological factors as listed by Israel[3]:

1. Pelvic conditions - tumors and infections, obstructing the initiation and maintenance of pregnancy.

2. Insemination of the cervix.

3. Complete/partial occlusion of the fallopian tubes.

4. Menstrual abnormalities, incomplete progesterone preparation of the endometrium for implantation.

5. The male factor.

Pelvic Disorders

The clinical interpretation of the preliminary step – a complete menstrual health assessment is a fairly decent indicator of a normally functioning ovary. Irregular/prolonged menstrual cycle, delayed menarche, amenorrhea lasting longer than usual points to endocrine dysfunction. In an estimated five percent couples gross pelvic disorders are the primary causal factor of infertility.

Uterine leiomyoma, endometriosis, ovarian tumors, chronic pelvic inflammatory disease, and congenital malformations of the reproductive tract. Up to 60 percent of women afflicted by endometriosis are rendered infertile. In such cases peri-salpingeal and peri-ovarian adhesions occur frequently. Shift of uterus and cervix are often accompanied by the same as well as occasional ovary fixation. This causes the inability of ovum from entering and propelling through the tubes.

Endometrial cysts and edema also often immobilize the ovaries and cause extraovarian pressure which is deemed as a major cause of ovarian dysfunction. The treatment traditionally has been surgery in such cases. However, modern research is more lenient towards individualized management. For some women the approach could be as simplified as wait-and-see emphasizing six month follow ups and early pregnancy. The failure of this approach calls for specific therapy. Severe symptoms include retroverted uterus, adnexal masses and can be assessed for surgery. The uteri is suspended, freed from pre-ovarian adhesions.

Most patients abide between these two extreme categories and should be induced to pseudo-pregnancy for at least nine months. Combinations of progestin-estrogen therapies are available on the market for the same. Enovid is one such schedule that begins by a low dosage of 2.5 mg to be gradually upscaling to 20 mg on indefinite basis. This regimen has performed brilliantly along with other progestin.

Cervical Factor

Cervical factors could also be assessed by a physician. Various psychological and anatomical factors pertaining to cervix possess a significant factor in infertility. Through a smear the viscosity, volume and alkalinity demonstrates spinnbarkeit and ferning. Ideal test of which can be conducted when ovulation occurs as the cervix influences estrogen stimulation at the peak during this period, dilating the cervical canal. The quality of mucus ferning in middle of the cycle, as well as of low volume/viscosity suggests dysfunction in proper stimulation of estrogen. In such cases inflammatory processes are important to overrule. An estrogen replacement therapy could be the answer for stimulating cervical glands.

A regimen constituting of daily 0.2 mg of diethylstilbestrol from the 15^{th} to 28^{th} day of menstrual cycle recuperates the mucus quality without suppressing ovulation. In patients perceived to have low alkalinity rendering sperm survival difficult can be introduced to an alkaline douche prior intercourse. Any other cervical dysfunction inducing infertility completely or partially, i.e. polyps, cervix, synechiae etc. must be put into consideration by the physician. The Sims Huhner test and a thorough examination during the middle of cycle of cervical mucus, from external, mid and internal os can be initiated to examine mobility and sperm count. To achieve most accurate results of Sims Huhner test, an analysis of female cervical mucus and male partner's semen is necessary. These samples reveal hostile cervical mucus or presence of obstructive polyps or stenosis. The reasons pertaining to this could be inhospitable pH or inadequate estrogen

stimulation. Absence of spermatozoa in vaginal pool indicates a failure of semen deposition due to faulty technique or otherwise.

Sperm Antibody

The earliest discovery of existence of sperm antibodies was in 1899. But only recently the role of sperm antibodies resulting in agglutination, immobilization and crystallization of sperm. Before the sperm is sufficiently transformed if it is absorbed from female genital tract the female body recognizes sperm as a foreign protein. Eventually, enough absorption of sperm material becomes antigenic causing higher titres of antibodies. Antispermatazoal antibodies have been deemed successful for therapeutic purpose in such patients. A test for antibodies causing sperm immobilization is thus now routinely performed mid cycle.

Inadequate Luteal Phase

This is identified by inadequate progesterone production, a defect that has been clearly identified in groups of patients with abnormal ovarian function. Characterized by repeated abortions in the first trimester, sometimes this has also been associated with primary infertility. When accessed through BBT charts patients with extreme early abortions in their pregnancy without having missed a menstrual cycle. Etiology dictates an inadequate production of pituitary LH by Hypothalamus. The diagnosis can be determined by endometrial biopsy during luteal phase. Progesterone therapy can be administered during luteal cycle as a choice of treatment. Administering 5 mg Diphaston on 14^{th} to 24^{th} day is usually preferred.

Tubal Factor

Determination of tubal factor requires admitting the patient to a hospital. The two factors to consider in analyzing tubal function are: physiological – a suitable environment for the gametes, and anatomical – relating to the transportation of both ovum and sperm. Detection of tubal anatomy can occur through detection of deformity and occlusion. Rubin's test is the most widely accepted process for screening. PID or any other genital tract infection are inhibitory factors in producing results in this test. The test should ideally be performed after a week of commencement of menstrual cycle. In the past decade several plastic operative procedures have been utilized as well as salpingolysis, tubal resection and anastamosis, cornual resection. In the Royal Victoria Hospital Clinic in Montreal[4], 61 out of 173 contraception have been reported in patients following tubal dysfunction surgery.

Failure of Ovulation

Identified by severely irregular menstrual cycle, oligomenorrhea, amenorrhea could project a failure in ovulation. A myriad of tests would be applicable to women with above abnormalities

that must be carried out. Basal body temperature is one such deciding factor in the determination as ovulation gives a rise of 0.2 to 0.8 degrees during the menstrual cycle luteal phase. Endometrial biopsy the cornerstone of ovulation study. Discovery of nonsecretory endometrium prior or at the end of menses is positive confirmation of anovulation. The laboratory diagnosis of ovulation could be determined by estimating total urinary pregnanediol in urine collected during 22-23rd day of menstrual cycle. Adjunctive tests include evaluation of cervical mucus at mid cycle, evaluation of vaginal smears throughout the cycle, maximum estrogen stimulation etc.

Semen analysis

Evaluation of the male partner in an infertile couples is primarily done by semen analysis5. Despite the widely used thresholds published by WHO measurements of sperm mobility, concentration and morphology the available norms fail under rigorous technical, clinical and statistical standards6. To increase the predictability of semen analysis, complex prediction models have been incorporated. Despite that the results must be considered conservatively to bridge the last confidence interval. Normal sperm concentration is currently defined between 20 _ 106/ml containing greater than 50% progressively motile sperm and sperm as ascribed by standard morphology. The results of semen analysis still remain variable as often majority of laboratories don't possess accurate methodology or training and in dire need of stringent quality control, which otherwise undermines the prognostic values of the test. The evaluation guides management decisions regarding the choice of insemination by in vitro fertilization, intracytoplasmic sperm injections or intrauterine insemination.

Evaluation of ovarian reserve

In ART, ovarian stimulation is utilized for stimulating multifollicular development and enabling multiple oocyte retrieval[7]. The major determinant of the success of IVF is dependent on the woman's ovarian response to gonadotrophin stimulation[8]. Ovarian reserve can be defined by antral follicle count in the ovaries present for response to a stimulant to grow into dominant follicle by exogenous follicle-stimulating hormone (FSH). Conventional ovarian stimulation will influence development of 8-10 dominant follicles in women with normal ovarian reserve. Accurate ovarian reserve tests predicts oocyte yield and ART outcome in ongoing pregnancies in individuals. Ovarian reserve evaluation enables identification for patients with better or worse response to gonadotrophin stimulation by age, essentially enabling clinicians to personalize appropriate treatment.

Management strategy selection

Expectant or active therapy

Infertile couples can be categorized in two groups: unable to conceive without therapy and likely to conceive with time despite reduced fertility[9]. It's the most apt method with a decent prognosis rate for couples with infertility for spontaneous pregnancy. Enabling clinicians is essential to decide if active of expectant management should be the method for a couple. In 76-79% infertile couple in a primary care setting statistical analysis of this therapy would be a good predictor of a live birth.

Active ART treatment options

For female and male fertility respectively IVF and ICSI are effective treatment options. Evidence supporting the effect of these treatments in cases of PCOS, male infertility, unexplained infertility and bilateral tubal occlusion is charted below.

Polycystic ovarian syndrome (PCOS)

After ovulation induction and laparoscopic ovarian surgery, IVF is currently considered a treatment option for women who suffer from anovulatory infertility caused by PCOS. But IVF is considered to be beneficial to older women in earlier stages[13].

Male infertility

Treatment with ICSI can help couples afflicted by male infertility related to obstructive or non-obstructive azoospermia, to achieve pregnancy. However the treatments available for male fertility vary widely as it's an area which requires more research. IUI after clomiphene citrate stimulation has shown little result as first line therapy and calls for high-quality, randomized controlled trials to investigate the issue.

Bilateral Tubal Occlusion

A sibling oocyte design study in couples with tubal infertility and normal semen has shown to have a 53% and 62% mean fertilization rates in IVF and ICSI[14].

Unexplained infertility

IUI the common treatment strategy for couples who suffer from unexplained fertility. IUI and ovarian stimulation has shown a slightly higher live birth rate than only IUI[15].

Individualized ovarian stimulation

Evaluation of ovarian response to stimulation

There is no universal standards of standard ovarian stimulation with acceptable definitions of what can be considered as normal, poor or excessive. This has hampered experiments to compare different treatment outcomes[10]. Most definitions refer oocyte number as a crude marker of response when used in isolation.

Excessive ovarian response

Severe OHSS is the most serious consequence of multifollicular ovarian stimulation and it's predominantly triggered by Human Chorionic Gonadotrophin (hCG)[11]. This condition could be life threatening resulting in haemoconcentration and hypovolaemia. An increased understanding of the metabolic needs of embryos and improvements in cell culture media have enabled prolonged in vitro culture of embryos. Transfer of blastocyst-stage compared with cleavage-stage embryos has shown a significantly higher rate of clinical pregnancy. To explain the best practices for maximal embryo viability is important for procedures and outcomes must be compared considering the advancements of laboratory techniques.

Cryopreservation techniques

Gamete, blastocysts and embryo cryopreservation is a vital part of modern ART. It's proven to increase pregnancy rates per oocyte by proper storage of unused embryos, and by allowing delay in transferring embryo during a menstrual cycle. The conventional cryopreservation methods include Vitrification and the slow cooling method.

Compared with standard cryopreservation, Vitrification improves survival of pregnancy rates and frozen-thawed cleavage state blastocysts. The only matter of concern is the high concentration of cytotoxic cryoprotectants that are used during the process of Vitrification. The long term safety of cryopreservation must be performed by high-end studies considering the rapid development in the field. Frozen-thawed embryo transfer can be performed during spontaneous ovulatory cycles all with or without use of GnRH agonist[12].

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