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History:

Throughout history, involuntary childlessness has been an unwelcome burden. After 1866, when Dr. Marion Sims first reported success with artificial insemination of husband's sperm (AIH), in 1890 there followed reports of artificial insemination of donor sperm (AID) by Robert L. Dickinson. Later with In-Vitro Fertilisation and its advances, the concept of donor sperm was further extended to the use of donor oocytes. But yet, in cases with an irreparable uterine factor, all medical assistance met with a blind end. This led to legalisation of the concept of surrogacy. There are records related to surrogacy since the biblical times. However, the first formal surrogacy agreement was not arranged until 1976, in the USA.

Introduction:

The essentials for procreation are the oocyte, the sperm and the uterus. And most couples i.e. two people; fulfil the requirements for these three essentials. There was a time when, in the absence of any one factor, (or due to its diseased state) couples were forced to lead childless lives, or consider adoption. Technology and the law, now provides for the possibility of individuals other than the intended parents to get involved and invest in conception of a wanted child. And so, today, if at least one of the three factors belongs to the intended parents desiring their own (or partly so) genetic offspring, the lacking factors can belong to a donor, or assigned party (person) and conception achieved.

According to the American Society of Reproductive Medicine (ASRM) information bulletin (2006), the phrase "third party reproduction" refers to the use of eggs, sperm, or embryos that have been donated by a third person (donor) to enable an infertile individual or couple (intended recipient) to become parents. Donors may be known or anonymous to the intended recipient. The phrase also includes traditional surrogacy and gestational carrier arrangements.

Social Issues:

The practice of assisted reproduction is influenced by cultural norms, religious beliefs and personal values related to how infertility is perceived. ⁽¹⁾ Some religions, such as Roman Catholicism and Islam are against third part reproduction. Because both sperm and egg donors are paid, and surrogates may receive a considerable amount of money, many feel that third party reproduction smacks of "baby-buying".

Legal Issues:

With regard to third party reproduction, regulations are required in the areas of quality control and monitoring, safety, record keeping, inspection and licensing, consent, the identification and obligations of mothers and fathers, and requirements for donor screening. Carefully thought-out laws and guidelines are important. ⁽²⁾

Third party reproduction could be a legal nightmare in cases going wrong. Couples considering it must seek legal help before contracting with a donor or surrogate.

The law involved in surrogacy is a 'contract law'. But it is an emotional issue, and multiple complexes could arise. Also in a class-stratified society, where the surrogate contractors are bound to have more power and resources, the possibility of economic exploitation of the surrogate has to be prevented.

Psychological and Ethical Issues:

There are significant psychosocial issues for all parties in third party reproduction: intended parents, gamete or embryo donors, gestational carriers, and the offspring. Not only these directly involved parties, but also the partners and offspring of the third party helper are affected; more so, if this third party helper is a family member – thereby affecting the whole family system. So, though technologically, the concept simplifies things to a great extent, psychosocially they are a lot more complex.

The following are important ethical issues:

- Availability of care in underdeveloped countries
- Cross-border care
- The potential for exploitation of third party helpers
- The rights of the child to information about their conception and pregnancy
- Cultural beliefs about privacy versus secrecy
- Inequity of counselling guidelines for egg and embryo donors versus sperm donors

Oocyte Donation:

Oocyte donation represents a special case in the treatment of infertility, since it involves some degree of risk to an otherwise uninvolved party, the oocyte donor.⁽³⁾ This differs considerably from sperm donors who are at little or no physical risk from the donation process.

The donor could be either anonymous donors, known or directed donors, or women undergoing IVF cycles who agree to donate or share their excess oocytes (also called as 'Oocyte sharing') generally for a financial discount on her own IVF cycle.⁽⁶⁾⁽⁷⁾

The indications for use of third party oocytes include:

1. Women with non-functioning ovaries

- Premature ovarian failure
- Ovarian agenesis
- Bilateral oophorectomy
- Sequelae of cancer chemotherapy
- Menopause.

2. Women with functioning ovaries

- Risk of inheritable genetic disease in children



- Poor quality oocytes leading to multiple failed IVF attempts
- Inaccessible ovaries

The success rates of egg donation depend on many factors but are generally independent of the age of the recipient. ⁽⁴⁾⁽⁵⁾ The major risk for donor egg programs is multiple gestations.

Selection and Screening of oocyte donors according to the Indian Council of Medical Research (ICMR):

- Donors should be healthy, well screened, and in the age-group of 21 – 35 years.
- Relevant information regarding the donor, such as age, height, weight, blood group, educational qualifications, profession, colour of the skin and the eyes must be recorded.
- Detailed history to rule out hereditary disease and to exclude individuals who might be at high risk for HIV, sexually transmitted infections, or other infections that might be transmissible via gamete donation.
- Basic Investigations should include genetic karyotyping and haemoglobin electrophoresis to rule out conditions such as thalassemia.
- Psychological evaluation and counseling for the oocyte donor and her partner. In circumstances involving known donors, this counseling should be offered to the donor and her partner, as well as the recipient and her partner.
- The donor must be informed that the offspring will not know her identity.

Donor ovarian stimulation:

The long protocol, i.e. agonist downregulation method is generally used. Oral contraceptive pills are started in the previous cycle, with overlapping leuprolide acetate starting two days prior to stopping the pills. Gonadotropins (FSH or HMG) are administered with a starting dose of 150 IU per day from day 2 of the cycle, with adjustments of the dose according to the ovarian response, which is measured by ultrasound follicular tracking and serum estradiol levels. The criteria for hCG administration (10,000 IU) is the presence of at least three follicles of 17 mm with normally rising estradiol levels. Cycle cancellation is done if there is an inadequate response on day 5 of stimulation i.e. estradiol levels <150 pg/ml, and/or less than 6 follicles measuring smaller than 9 mm. Withholding Gonadotrophins i.e. "Coasting" is done if estradiol levels on the day of hcg are above 2000 pg/ml.

But then also, the aim being optimal stimulation with prevention of the Ovarian Hyperstimulation syndrome (OHSS), tailored protocols for every individual donor should be the norm. In donors at risk of OHSS, the use of the Antagonist protocol, and with replacement of the hCG trigger with recombinant LH or GnRH agonists (only in an Antagonist protocol cycle) helps in prevention of OHSS.

Recipient uterine preparation:

A normal uterine cavity is confirmed by means of a hysteroscopy or hystero-graph. Also, all recipients should ideally undergo a preparatory cycle to measure endometrial response to exogenous estradiol, as assessed by the standard Applebaum scoring (Endometrial scoring assessment by Ultrasonography). The recipient cycle is synchronised with the donor cycle using standard oral contraceptive pills. For hormonal synchronization, the recipients should be down-regulated with GnRH agonist daily/depot from midluteal phase of previous cycle (leuprolide acetate, 1mg s.c. per day or luprolide depot 3.75 mg single shot) to achieve pituitary suppression if there is evidence of spontaneous ovarian function. Measurement of estradiol levels (<30 pg/ml) and endometrial thickness (<6 mm) assessed by ultrasonography, is required to confirm pituitary downregulation

on day 2 of menstrual cycle or day 7-10 of GnRH analogue in case there are no menses. On day two of the menstrual cycle, estrogen supplementation is started by oral estradiol valerate tablets of 2 mg, given three times daily. On day 10 of taking these tablets, an Applebaum scoring is performed and if the score is more than 17, then progesterone supplementation (either vaginally or intramuscularly) is started to matching with oocyte retrieval. For a day 3 embryo transfer, four days of progesterone supplement is considered ideal. The embryo transfer can also be performed in a natural cycle, provided the exact timing of the endogenous LH surge is documented.

Sperm Donation:

Over the past 10 years, the utilisation of donor sperm has decreased as the utilisation of ICSI for the treatment of male infertility has become widespread. Artificial donor insemination is performed exclusively with frozen sperm. Current guidelines recommend that sperm be quarantined for at least six months before being released for use.

The current indications for use of third party sperms include:

- Obstructive and non-obstructive azoospermia, which may be congenital or acquired.
- Severe oligospermia
- Ejaculatory dysfunction
- Risk of inheritable genetic disease in children
- If the female partner is Rh-sensitized and the male partner is Rh-positive.
- For a single woman who desires a pregnancy but who lacks a male partner.

The ICMR guidelines state that the age of the donor must not be below 21 or above 45 years with his semen analysis found to be normal according to the WHO method manual for semen analysis, if intended to be used for ART. The rest of the assessment would follow the guidelines as for an oocyte donor mentioned above.

Embryo Donation

Excess embryos (either fresh or frozen) donated by couples who have undergone an IVF cycle, after they have achieved conception or for altruistic reasons. Most commonly embryo donors have completed their family and have cryopreserved embryos that they wish to donate to other infertile couples. This is also resorted to when the male partner of a couple with an indicated oocyte donation, is diagnosed to have conditions such as primary germ cell failure or an inheritable genetic disorder. ICMR encourages embryo donation in such a scenario. Recipient preparation and investigations on the donor couple are the same as described in the section on oocyte donation.

Surrogacy

Traditional surrogacy refers to a treatment in which a woman is inseminated with sperm for the purpose of conceiving for an intended recipient. The surrogate has a genetic and biological link to the pregnancy she might carry. Traditional surrogacy, (also called partial surrogacy) arrangements often are perceived as controversial with the potential to be complicated both legally and psychologically. The ICMR does not allow traditional surrogacy in India.

In contrast, in gestational surrogacy (also called full surrogacy or IVF surrogacy) an individual acts as a uterine carrier in which embryos created by the intended parents are transferred. The gestational surrogate has no genetic link to the fetus she is carrying. Despite the requirement for in vitro fertilization (IVF) to create embryos,



the utilization of a gestational surrogate, legally, is a lower risk procedure and is the more common approach conducted in most countries. And if implantation happens, then by contract agreement, the surrogate woman carries the pregnancy till term in a normal course of events.

Use of a gestational carrier is indicated in women with the following medical conditions, to help them have their own genetic offspring.⁽⁹⁾

- Absent or congenitally abnormal uterus
- Absence of a uterus secondary to surgery
- Damaged uterus due to severe Asherman's syndrome
- Recurrent implantation failure
- Recurrent miscarriage.
- Women with a medical contraindication to pregnancy such as severe diabetes, heart or kidney disease.

Gestational surrogates can be relatives or friends of the intended parents who volunteer to carry a pregnancy for them. Alternatively, gestational surrogates can be identified through agencies that specialize in recruiting women to become surrogates.⁽¹⁰⁾ As per the ICMR regulations, commercial surrogacy is permitted in India.

According to ICMR (Indian Council of Medical Research):

- The surrogate should be in the age group of 21-45 years.
- Tested for Blood group, HIV, HBsAg, HCV and VDRL.
- A thorough medical history and extensive medical testing and physical examination.
- A complete personal and sexual history to exclude individuals who might be at high risk for sexually transmitted infections.
- Psychological evaluation and counseling by a qualified professional is recommended for the surrogacy and her partner, and immediate family.
- The surrogate should be well informed about the procedure and the possible complications.

ICMR Code of practice, and ethical considerations in gestational surrogacy (salient points):⁸

1. A child born through surrogacy must be adopted by the genetic (biological) parents, unless they can establish by genetic (DNA) fingerprinting that the child is theirs.
2. Advertisements regarding surrogacy should not be made by the ART clinic. The responsibility of finding a surrogate mother, through advertisement or otherwise, should rest with the couple, or a registered agency.
3. Legal papers regarding the contract agreement should be made by a lawyer, and as per the rules of the court.
4. Payments to surrogate mothers should cover all genuine expenses associated with the pregnancy. Documentary evidence of the financial arrangement for surrogacy must be available. The ART centre should not be involved in this monetary aspect.
5. A relative, a known person, as well as a person unknown to the couple may act as a surrogate mother for the couple. In the case of a relative acting as a surrogate, the relative should belong to the same generation as the woman desiring the surrogate. The consent of the surrogate's spouse is essential in all cases.

Surrogacy And Third Party Options

6. A surrogate mother should not be over 45 years of age.
7. No woman may act as a surrogate more than thrice in her lifetime.
8. Sex selection at any stage after fertilization, or abortion of the foetus of any particular sex should not be permitted, except to avoid the risk of transmission of a genetic abnormality assessed through genetic testing of biological parents or through preimplantation genetic diagnosis (PGD).
9. A surrogate mother carrying a child biologically unrelated to her must register as a patient in her own name. The birth certificate shall be in the name of the genetic parents.
10. The surrogate mother must relinquish in writing all parental rights concerning the offspring and vice versa.

Conclusion:

The use of third party reproduction has grown worldwide, the reasons being primarily related to individuals opting for it, and not so much due to subfertility. Patients may be single men or women, homosexual or lesbian couples, in addition to traditional heterosexual couples. The indications also vary from chronic illnesses or congenital anomalies, advanced maternal or paternal age, posthumous conception and cultural or religious factors.

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I. Introduction

The recent option of integration of oocyte cryopreservation into the standard IVF programme has clearly improved the medical care for women at risk of losing ovarian function (1). During the past 2 decades, due to the greater than ever safety of oncology treatment the number of long-term cancer survivors has risen appreciably (2)(3). With the newer option of Oocyte freezing, many of these cancer survivors are able to achieve motherhood (4). The other common indications for oocyte freezing are enumerated in (Table 1)

Successful oocyte cryopreservation programme may in due course allow the creation of egg banks similar to present day sperm banks where the prospective Oocyte recipients would have wider choice over the selection of the donor's characteristics.

II. Peculiarities of oocyte freezing

The metaphase-II oocyte is extremely fragile due to its large size, water content, and peculiar shape (table 2). In the mature oocyte, the metaphase chromosomes are lined up by the microtubular spindle along the equatorial plate. It has been observed that the spindle apparatus is easily damaged by intracellular ice formation during the freezing or thawing process (table 3). Recent advances in embryology techniques, fertilization, use of intracytoplasmic sperm injection (ICSI), and standardization of cryoprotectants, have made oocyte cryopreservation a practical application.

III. Back ground

The initial pregnancies resulting from frozen oocytes were reported in the 1980s (7, 8), but latter for a long time only infrequent case reports were available, suggesting that the technique of oocyte cryopreservation was still experimental with debatable clinical application. In the subsequent years, some important technical modifications have been suggested including an increased concentration of sucrose in the freezing and thawing solutions (9, 10). The use of cryo freezing media in which choline has replaced sodium has also been suggested (11, 12).

IV. Current Methodologies

a. Slow Freezing

Slow programmable freezing techniques are based on the procedure first described by Willadsen (13) for the freezing of other mammalian embryos. The equilibration period, type of permeating cryoprotective agent (CPA) as well as the concentration of sucrose are various outcome influencing factors.

b. Ultra Rapid Freezing (Vitrification)

Vitrification is a prospective alternative to slow freezing technologies (14). This is accomplished by exposing the cell to high concentrations of CPAs for a short equilibration period followed by very short exposure of oocytes to

vitrification solution & then rapidly cooling the oocytes by plunging them into liquid nitrogen thus not allowing ice formation to take place (figure 1,2,3,4). (15) (16). Several recent reports describe these techniques resulting in birth healthy children from vitrified oocytes using varied types of cryo-carriers (17,18,19,20). (Table 4)

V. Oocyte banking

One of the most remarkable benefits of the Egg banking is the availability of frozen eggs for use in self or egg sharing recipient's at short notice. The Survival rate after warming is over 90%. The potential of vitrified oocytes is comparable to the one attained for fresh ones: with fertilization rate (73.1% vs 74.6%), clinical pregnancy rate (50.2% vs. 49.8.6%) and implantation rate of (39.9% vs. 40.9%) for vitrified and fresh oocytes respectively. It also provides additional advantages of being more economical, easier for both donors and recipients and potentially safer, because eggs can now be quarantined for 6 months or more to retest for infectious diseases in the donors. (21)

VI. Conclusion

There is a continuous debate about the appropriateness of human oocyte banking or about its prospects. Unfortunately, egg banking is inefficient presently and oocytes often fail to survive freeze–thawing techniques in majority of hands. However, these technologies are improving, and egg banking will sooner or later become an option for patients seeking fertility preservation or egg sharing.

Table 1. Indication for Oocyte banking

1	Husband is unavailable or unable to provide semen sample on the day of egg harvesting (5).
2	Preservation of reproductive competence of young cancer patients who need pelvic radiation or chemotherapy.
3	Surgical intervention before or during the reproductive age involving removal of ovaries.
4	Patients at risk of loss of ovarian function with impending premature menopause.
5	Ovarian hyperstimulation syndrome.
6	Legal, ethical and social issues may also warrant oocyte cryopreservation. (6).
7	When the women wish to delay motherhood due to personal reasons.
8	Cryobanking oocytes for egg donation programs or for research purposes.
9.	Inadequate number of good morphology sperms obtained after testicular or epididymal aspiration with large number of oocytes.



Table 2 : Peculiarities of Oocyte Freezing

Structural	Remarks
Large volume	The large cell mass and high water content with spherical shape of the oocyte makes dehydration difficult and necessitates the use permeable /non permeable cryoprotectants with low toxicity.
Spherical shape	The almost perfect sphere slows down permeation and equal distribution of any cryoprotectants in the oocyte. This continuous concentration gradient from the periphery to the center of the oocyte or vice versa exists for long time resulting in prologed exposure to the cryoprotectants.
low cell number	No second chance as the number of oocytes is low and it is a single cell structure with morphological peculiarities.

Table 3 : cryo damage

Structural	Remarks
<p>Nucleus & nuclear membrane/envelope(NE) Role: (DNA replication, trans- cription, RNA processing and ribosomal sub unit assembly)</p> <p>CYTOPLASM Role: (Protein synthesis, cytoskeleton formation & support)</p>	<p>cryopreservation can effect the structural integrity of the NE and thus affect DNA replication and transcription.</p> <p>MICROTUBULES Microtubules form the spinde apparatus in oocytes which is responsible for spatial organization and subsequent migration of chromosomes during meiotic divisions. Cryopreserved oocytes depict grave disturbances of the microtubules immediately after thawing.</p> <p>MICROFILAMENTS Microfilaments In human oocytes have been found organized in a uniform layer enveloping the cortex. During oocyte maturation , microfilaments have an pivotal role in polar body extrusion, pronuclear body migration , intracellular movement of organelles, and cell divison. Cryopreservation may affect microfilament function leading to disordered intracellu-lar organelle migration, premature cortical granules release & polar body extrusion.</p>
Zona pellucida (blockage of polyspermy)	<p>The zona pellucida is a glycoprotein membrane surrounding the oolemma of oocytes. it is composed of three glycoproteins termed ZP1, ZP2, and ZP3.</p> <p>The exposure to cryoprotectants in oocyte cryopreservation may lead to premature cortical granule release and zona hardening.</p>

Table 4: types of cryocarriers for vitrification

Structural	Remarks
standard 0.25ml insemination straw loading volume : (>5 μ L)layer. warming rates 1300°C/min.	thick plastic wall of the sealed straw that presents considerable the rmoinsulating Cooling rate is low-2500°/min
open pulled straw (OPS) technique glass micropipettes, GMP super-finely pulled OPS ,SOPS gel-loading tips sterile stripper tip loading volume : (<1 μ L)	filled with a tiny amount of solution containing the sample by using of the tool & plunging it into liquid nitrogen . The achiev-able cooling & warming rates with these tools may be as high as 20,000 °C/min.
Cryoloop A 20- μ m nyl-on loop, 0.5mm in diameter, mounted on a 20mm steel tube, which is attached to the lid of the cryovial. loading volume (<0.3 μ L)	cooling and warming rate may reach the estimated level of 7,00,000°C /min
Minimum drops size (MDS) loading volume: (<0.5 or even 0.1 μ L)	very small droplet containing the sample is placed onto a solid surface and immersed into the liquid nitrogen.
Nitrogen slush cooling	approach is the elimination of the vapor-coat that arise around the sample in the liquid nitrogen for cooling (Vlt Master)
High security vitrification Kit (HSV kit) loading volume: (<0.5 μ l)	Straw is heat sealed using a special welder which ensures a leak-proof seal .
Cryotop The Cryotop consists of a 0.4 mm wide, 20 mm long, 0.1 mm thick flexible filmstrip attached to a rigid plastic handle. loading volume : 0.1 μ l	Cooling rates (23000°C/min). Warming rate (42, 000°C/min).
Cryo tip A plastic straw container that can be sealed as a closed device to hold gametes or embryos during cryopreservation. loading volume: 1 μ l	Cooling rates 1200 °C/min. Warming rate 2400°C/min.
Electron microscope grids	Biological EM work is done on small (several millimeters) copper discs called grids cast with a fine mesh. Oocytes are placed on the electron microscopeand directly plunged into liquid nitrogen (Ln ₂).



Figure 1

A closer view of the freshly denuded oocyte at 200x. Regular zonapellucida with normal perivitelline space an healthy polar body is seen.

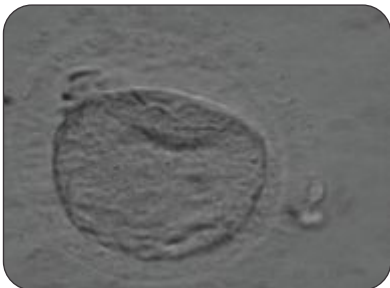


Figure 2

Oocyte in equilibration media during vitrification, shrinking and irregularity of oolemma occurring immediately after contact of oocyte with the media. Intact polar body is seen at 11'O clock position.



Figure 3

Oocyte as seen in the warming media. Ooplasm here is contracted and oolemma is wrinkled. wide perivitelline space is observed and zona pellucida is intact.

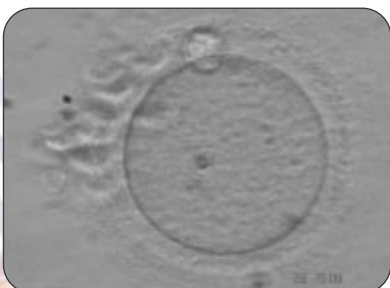


Figure 4

Oocyte is further recovering in the washing media 1. Perivitelline space is decreasing and oolemma is expanding circumferentially. Zona pellucida is healthy and polar body is seen at 11'oclock position.

Oocyte Banking

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Fertility drugs are extensively used in treating infertility. Drugs are usually the first line of therapy in treating male and female infertility. Too often, doctors give clomiphene to women with infertility even before the couple has had a complete fertility workup. It is also prescribed after a workup when there is no evidence of an ovulation disorder. This empirical therapy may create new problems and often delays further evaluation that can lead to a specific diagnosis & proper treatment. For a woman who has normal, spontaneous ovulation, driving the pituitary harder won't make ovulation any more normal.

Clomiphene is a good first choice when there is anovulation or evidence of luteal phase defect (LPD). However, since it is relatively cheap, easily available & well tolerated, clomiphene citrate is often prescribed for long duration of periods, in some cases without medical supervision. Ovulation induction agents increase the risk of twin pregnancy by 10% & risk of multiple order pregnancy by 1-2%. Clomiphene is an easy drug to misuse & on occasions can lead to serious complications including OHSS, endometrial problems and retention cysts leading to unnecessary interventions.

Gonadotrophins are usually the main culprits for OHSS (1-3%) which can be potentially life threatening & multiple pregnancies (20%). In addition these drugs can cause other adverse reactions like allergic sensitivity, rash, swelling and pain at the injection site and on occasions cancellation of treatment due to over stimulation. Hence gonadotropins and other injectable ovulation inducing drugs are to be used with proper supervision.

Metformin is another drug that is commonly given to the patients on the basis of mere suspicion of PCOS. This is without the understanding whether any hormonal proof of PCOS exists or any insulin resistance has been documented. Metformin is a drug which is very useful for PCOS patients with insulin resistance. In other cases, it is not effective. This indiscriminate use should be avoided.

The new drug available i.e. DHEA is also now used for a lot of patients. DHEA should be used only for those patients with a documented poor ovarian reserve i.e. a poor antral follicular count and low AMH levels. Only a subset of patients will respond to this drug. The drug should be given for a period of 3-4 months and its effect has to be assessed. If there is no effect, it should be stopped rather than continuing it indiscriminately and hoping for the results

Various other treatment modalities like growth hormones, corticosteroids, insulin sensitizers have shown to be of limited help in achieving pregnancy particularly in ovulatory disorders and hence their randomized or indiscriminate usage without appropriate indications would result in dangerous metabolic complications.

Mention must be made of empirical addition of desiccated thyroid extract to treatment schedules of the infertile women. Desiccated thyroid extract differs from thyroxine compounds since it also contains thyronine (T3). Large amounts of T3 can be under productive in terms of ovulatory dysfunction. Over treating a patient with hypothyroidism or providing empirical thyroid hormone for a euthyroid patient is potentially harmful. Hyperthyroidism, even though it is through over treatment is associated with osteoporosis.

As far as male infertility is concerned majority of men presenting with infertility have (OAT) Oligoasthenoteratospermia of unknown cause. Hence there are wide ranges of therapies available. However there is a consensus that only randomized controlled trials with the outcome parameter "pregnancy" can be accepted

Misuse of Drugs In Infertility Treatment

for efficacy analysis. Sadly none of the drugs could show the end result as increase in pregnancy rates. Hence medical management in most cases is empirical. Most doctors are pressurized into prescribing some medications, since most patients want medical treatment to increase sperm counts. The problem with medical treatment for low sperm count is that for most people it simply doesn't work. This is clearly seen in the wide range of medicines presently available to treat male infertility. Some patients are not willing to accept that there is really no effective treatment available as yet for increasing sperm counts. Hence medical literature is filled with small sample trials of various drugs increasing sperm counts that there is no effective method available. It also has to be taken into consideration of duration of the treatment like in male infertility if one has to give treatment for at least one spermatogenetic cycle that is minimum of 70 days and then reassess the progress. If improvement is seen then one can continue the same treatment and see the result in terms of pregnancy in next few cycles. If no results are observed then new medication in view with the evidence based medicine should be considered. Empirical treatment inhibits the patient from exploring effective methods of alternate therapy such as IVF / ICSI and often leads to increased anxiety and depression due to failure of assumed or assured benefits.

With growing number of patients undergoing infertility treatments the systematic evaluation of the drugs used and their obstetric and prenatal outcomes and long term outcomes in the children has taken even more importance. There is an acute need for multicentric data collection and analysis to realize potential ill effects of drugs used in infertility.

Gynecologists should also be cautious of using drugs not approved for infertility treatment (i.e off license use). Some of the drugs are acknowledged to be toxic to the embryos and fetus. Use of such drugs could be seen as unlawful and can attract medico-legal complications. Off license use of drugs or use of new drugs need proper permission from concerned authorities prior to even conducting trials. A time has come for physicians treating the infertile couple to discuss and counsel couples regarding infertility management and explain the pros and cons of empirical drug therapy.

The drugs and their uses should not be based on isolated studies. A small study is done on a research molecule and the benefits are advocated to the doctor. The undesirable effects of the drug are not studied or highlighted to the doctor. The trials done are generally on a small population and proper randomized controlled trials are lacking. So before giving a drug we should check and counter check the trials conducted, be assured of the benefits of the drug and also be aware of the possible side effects of the drug. This policy should be adopted while starting any drug to prevent the misuse of the drug.

The ultimate aim should be safety of the patient and the motto to be followed should be 'Primum non nocere' - the Latin words for medical slogan "First do no harm," a fundamental medical precept of Hippocrates.