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Little is known about “Ideal” monitoring of patients who conceive after IVF treatment. One thought would be that after a long period of living in preparation for a future pregnancy, patients should be well prepared. On the other hand the high anxiety levels of these patients (and not to mention their care providers) during pregnancy might make them over-utilize antenatal care which at times may lead to over / mis - treatment.

We should bear in mind that all conceptions should be considered “Precious”, whether natural or assisted. There are however a few marked differences that must be kept in mind while dealing with IVF Pregnancies. The list below although not exhaustive, states the common and important differences.

- The “Age” Factor: It is well documented that age of women conceiving by ART is significantly higher than age of women conceiving naturally. This lone variable accounts for an increase in the incidence of all materno-fetal complications known to exist.
- Miscarriages: It has been widely reported that the incidence of miscarriage in pregnancies resulting from ART is higher than in spontaneous pregnancies (1).
- Multiple pregnancies: In natural conceptions, one in 80 pregnancies results in twins. However in ART, rate of multiple pregnancies is more than one in five. In ESHRE report 2006, total multiple delivery rate was 24.5 % (2). Apart from the increased rate of twins, higher order births which are extremely rare in natural conceptions occur commonly in women undergoing ART.
- Obstetric complications: The incidence of first trimester bleeding, PIH, Placenta Previa, Preterm labour, IUGR, Intra Uterine fetal death, Caesarean Section is higher in IVF Pregnancies. Even when maternal variables such as age and parity are matched, the risk of these complications is higher therefore demanding extra vigilance (3).
- Congenital Malformations: Infants conceived by IVF and ICSI have twice the risk of a major birth defect as compared to naturally conceived children (5). The possible reasons are attributed to:
  - ❖ Increased maternal age: Oocyte and sperm abnormalities increase with increasing age. This may be an independent cause for infertility. Apart from this, the more the number of oocytes in a stimulated cycle, the higher is the incidence of aneuploidy.
  - ❖ ICSI in male infertility leading to transmission of genetic causes such as Y chromosomal microdeletions, ultra structural sperm defects with genetic basis etc (4).
  - ❖ Embryo is exposed to mechanical, thermal and chemical alterations which theoretically can increase the risk of congenital malformations.
  - ❖ Evidence is also suggestive of an Increased risk of Imprinting disorders such as Beckwith Wiedmann syndrome, Angelman syndrome etc.
  - ❖ Cryopreservation can theoretically increase this risk.

- Psychological factors: IVF parents are more anxious than matched controls about the survival and normality of the unborn babies. These findings of increased psychological stress necessitate intense counseling of patients undergoing IVF.

#### Monitoring:

There should be good communication between healthcare professionals and women who have conceived after ART. This should be supported by evidence-based, audio-visual information tailored to the woman's needs. Antenatal care should be provided by a small group of healthcare professionals with whom the woman feels comfortable and there should be continuity of care throughout the antenatal period.

A system of clear referral paths should be established so that pregnant women who require additional care are managed and treated by the appropriate specialist teams when problems are identified. This is of utmost importance considering the fact that medical disorders and obstetric complications are more common in women undergoing IVF.

#### FETAL MONITORING:

##### Monitoring In First Trimester:

Approximately 14 days after Embryo transfer if a quantitative B-HCG suggests implantation, confirmation of site of gestation on transvaginal ultrasound (TVS) should be done as soon as possible as ectopic pregnancies are known to occur and in this group of infertile patients and early diagnosis will prevent an additional surgery. This will also confirm viability and chorionicity. Very high levels of B-HCG are suggestive of multiple gestation and therefore should raise the level of suspicion for all future scans. Low / Borderline levels on the other hand may indicate a failing intra-uterine gestation or ectopic pregnancy, both of which need close monitoring.

If there are any concerns regarding fetal viability, transvaginal ultrasound scan findings can be correlated with serial quantitative beta-HCG estimations. An increase in the levels of more than two fold over a period of 48 hours suggests viable pregnancy. In cases of pregnancy of unknown location, serum progesterone estimation is useful but until a gestational sac is visible in-utero on TVS, all such cases should be considered as ectopic gestation unless proven otherwise.

With an increase in Blastocyst transfers being done, monozygotic twinning is now not uncommon. Early detection will demand more vigilance and intervention at appropriate times will result in favorable outcome.

Once viable intrauterine gestation/s is confirmed on USG, All measures to detect early abnormalities should be undertaken. As stated earlier, abnormalities are more common in IVF conceptions therefore first Trimester Screening is preferable:

The 'combined test' (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) should be offered to screen for Down's syndrome between 11 weeks 0 days and 13 weeks 6 days in singleton and twin pregnancies. In higher order gestations, NT combined with Nasal Bone and flow in ductus venosus is used for screening.

If the screening test indicates high risk, invasive confirmatory testing in the form of Chorionic Villus Sampling must be offered.

##### Fetal Monitoring In Second And Third Trimester:

Monitoring in second and third trimester is similar to that offered in normal conception. Special attention must be given to targeted anomaly scan at 20 weeks and growth scans at 28 and 34 weeks.



### MATERNAL CARE:

#### First Trimester: Luteal Phase Support:

The Practice of luteal phase support is established beyond doubt in patients who have undergone IVF.

Whatever support is administered at the point of embryo transfer, should be continued till confirmation of cardiac activity on ultrasound. This includes Progesterone +Estrogen for oocyte recipients, embryo recipients and Frozen-Thawed Embryo transfer cycles.

The questions of when to end luteal supplementation is an area poorly studied in the literature. Most IVF practitioners arbitrarily start Progesterone supplementation after oocyte retrieval and elect to continue it, if the patient is pregnant, until 10 weeks of gestation. This practice is based mostly on relying on "experience" and a "comfort level" on the part of clinicians to do what is necessary to maximize the success rates. Progesterone being a relatively safe drug with minimal side effects may therefore be continued till 12 weeks. However prospective and randomized studies have reported no difference in the delivery rate between pregnant patients who discontinued Progesterone at 6 weeks and those who continued it until 10 weeks of gestation (6).

#### Maternal Care In Second And Third Trimester

Ante Natal Care after the first trimester in patients conceiving after IVF is no different than normal conceptions. In the second trimester cervical length assessment should be done at around 14 weeks both by USG and clinically keeping in mind risk factors such as congenital malformations of the uterus, previous second trimester losses and multiple gestation. In all patients who are at risk of developing threatened preterm, prophylactic tocolysis may be offered and continued till 34 weeks.

Apart from above mentioned, routine antenatal care should be provided with special attention towards high risk factors such as PIH, Gestational Diabetes, Multiple gestation etc.

All monitoring should be done at a tertiary referral center to ensure multidisciplinary care and also management of antenatal complications incase they arise.

#### Summary

More ART mothers use the possibilities of antenatal care and monitoring with regular visits to the obstetrician and with regular ultrasound examinations as compared to those who conceive spontaneously. It is the responsibility of the clinician to monitor such pregnancies appropriately and not to over treat them by labeling these pregnancies as "Precious". At the same time, realizing that complications that can occur, early detection and management is warranted to ensure desired outcome of a healthy baby and healthy mother.

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### Introduction

Contraception is defined as the intentional prevention of conception through the use of various devices, sexual practices, chemicals, drugs, or surgical procedures. The practice of contraception is as old as human existence. For centuries, humans have relied on their imagination to avoid pregnancy. Today, we have range of contraceptive methods which are effective, safe, easy to use with less side effects and reversible. The fertility after contraception may differ with different contraceptive methods. However, one should also consider the effects of endocrinological, medical, surgical and gynecological problems which increase with age and may significantly decrease the fertility potential, regardless of contraceptive use. Such problems may include diabetes, thyroid disease, polycystic ovary syndrome, obesity and exposure to sexually transmitted diseases.

Fertility after oral contraceptive pills :

Various studies have shown that after discontinuation of hormonal contraceptive pills, ovulation was resumed in 70% of cases in 1<sup>st</sup> post-treatment cycle and 94% in 3<sup>rd</sup> cycle. They also reported that persistent ovulatory defects are not associated with past OC use and that most hormonally attributable subfertility after OCs can be attributed to weight extremes, age, previous births and other endocrine or metabolic disorders. The possible correlation between duration of OC used and impaired fertility showed no statistically significant association between time to conception and duration of OC used.<sup>1,2,3</sup>

In a study of conception rates in 652 women who discontinued a combination OC pills, because of a desire to conceive, 84.2% of women who had used the OC for 1 to 6 cycles became pregnant within 12 months compared to 96.7% of those who had used the OC for 14 to 26 cycles.<sup>4</sup> In a large, prospective study of 12,106 pregnant women, 88.1% who had planned to conceive, got pregnant within 12 months of discontinuing OC and nearly all (99.5%) conceived by 3 years.

In 2008, Davis AR et al reported that in their series of 187 women who took 1 year of daily continuous levonorgestrel (LNG) 90 microg/ethinyl E(2) (EE) 20 microg , 181 returned to spontaneous menses and 4 became pregnant within 90 days after the last dose of LNG 90 microg/EE 20 microg.<sup>5</sup>

In 2009, Barnhart KT et al reported that after discontinuation of cyclic OC 72%-94% women conceived within 12 months which are similar to those observed in women discontinuing intrauterine devices (71%-92%), progestin-only contraceptives (70%-95%), condoms (91%), and natural family planning (92%). There is a limited amount of data on the time to conception in women stopping extended-cycle and continuous-use OCs, but the data suggest that subsequent return to fertility is generally comparable to that of cyclic OCs.<sup>6</sup>



## Injectable Hormones :

A study at the ICMR in India reported large differences in the cumulative pregnancy rates of ex-NET-EN users, when divided them by bleeding experience while using the methods (ICMR 1986). Women discontinued because of amenorrhea had a significantly slower cumulative conception rate over the ensuing 12 months compared to women who discontinued because of excessive bleeding. The 12-month conception rate for women discontinuing due to amenorrhea was 51%, compared with 73.5% among women who discontinued due to excessive bleeding.

When DMPA and NET-EN have been compared in the same population, with a common method for detecting ovulation, the 2-month injectable norethisterone enanthate (NET-EN) has a comparatively shorter time for the return of ovulation, relative to DMPA. The return of ovulation following discontinuation of DMPA occurred approximately 5 months after the expected effect of the last injection, but the variance extends over several months.<sup>7,8</sup>

The largest prospective study followed 796 Thai users of DMPA who stopped using the method to have a planned pregnancy, and reported a median time to conception of 5.5 months after the expected effect of the last injection. The same study included 427 women who stopped using oral contraceptives, and 125 women who had an IUD removed. The median time to conception after these methods were 3 months, and 4.5 months, respectively.<sup>9</sup>

## Combined Injectable Hormones :

The return of fertility following monthly injectables is considerably shorter than that observed for the progestogen-only injectables. Bahamondes et al (1997) reported observations on 70 Latin American women who had used between 1 and 19 injections of Cyclofem and discontinued to become pregnant. More than 50% were pregnant at 6 months, and the cumulative pregnancy rate was 82.9% at 12 months.<sup>10</sup>

## Hormonal Implants :

Return of fertility after hormonal implants has been found to be variable. Researchers at 15 Human Reproduction Centres of the Indian Council of Medical Research followed 627 women aged 18-35 who stopped using the subdermal Norplant-II system for different reasons, and thus were exposed to the risk of pregnancy, for 2 years to determine return of fertility. About 20% conceived within 1 month of Norplant-II implant removal. The 6-month, 1-year, and 2-year pregnancy rates were 63.4%, 80.3%, and 88.3%, respectively.<sup>11</sup> Neither duration of Norplant-II implant use nor bleeding patterns had an adverse effect on return of fertility.

The 1-year and 2-year cumulative pregnancy rates for women who stopped due to bleeding irregularities and other reasons were lower than those who stopped due to planning a pregnancy. Return of fertility was delayed in women whose implants were removed after age 30 compared to those younger than 30 (1-year pregnancy rate, 66.3% vs. 83%; median time to conception, 6 vs. 3.8 months;  $p < 0.05$ ). The difference was not significant at 2 years, however. 89.7% of women who wanted pregnancy, became pregnant within 2 years after discontinuation.

## Barrier method :

Studies support the highly expeditious return to fertility among barrier method users. A community-based study that assessed the time to conception following cessation of contraception of barrier method, specifically in order to conceive, demonstrated pregnancy within 12 months was 95% among 798 previous users of barrier methods.

### Intrauterine Devices:

Fertility returns rapidly after IUD removal, comparable to pregnancy rates after discontinuation of oral contraceptives. The pregnancy rate of the LNG-IUS ranges between 79% and 96% 12 months after removal.<sup>12,13</sup>

Study had reported that first-year pregnancy rates were essentially the same for women who had (copper and inert) IUDs removed in order to conceive and for women who had IUDs removed because of complications (85.8% and 82.8%, respectively), and both were equivalent to expected fertility rates.<sup>14</sup>

Studies had found that monogamous women who had used only copper IUDs had no increase in the risk of tubal infertility compared to women who had never used IUDs (relative risk [RR], 1.1; confidence interval [CI], 0.5–2.7). Among women who had had multiple sexual partners, copper IUD users had a statistically significant higher risk of tubal infertility compared to those who never used IUDs (RR, 2.8; CI, 1.7 to 4.5;  $p < .0001$ ).<sup>15,16</sup>

In the 4-year study period, done in Newzealand, there were 887 removals for purposes of conception and 164 due to complications. 64% of these removals involved gravid women, and 36% involved nulligravidae. At 36 months after removal of the IUD, 92% of women who underwent removal because of complications had conceived compared with 94% of women who had removal to become pregnant. There were no significant differences in conception rates according to the complication that led to removal due to pain and bleeding, pelvic inflammatory disease, and vaginal discharge.<sup>3</sup>

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*Science can help to create life, but lives are often ruined in the process  
~ Pip Cummings*

1977 will remain a landmark year in reproductive medicine, as IVF became a legitimate treatment following the birth of Louise Brown. Over the years there have been several refinements in treatment - protocols, drugs and techniques, offering renewed hope to a vast number of infertile couples. With the advent of third party reproduction it seems that infertility specialists have an answer to every couple's problem/ dream. Be that as it may, the reality is far less rosy.

Unfortunately infertility treatments do not guarantee success. The success of IUI is approximately 10-20% / cycle- a plateau is reached after 4 cycles. In IVF the pregnancy and take home baby rate is 40% - 50% and 35%/cycle respectively. A cumulative PR of 60% is reached after 3 cycles and there is a drop in PR after 4 cycles to about 15%. Women who conceive after infertility treatment sadly have a higher rate of reproductive loss. *Approximately one third of patients will fail to achieve a pregnancy despite repeated treatment.*

The couple may spend months to years going through the various tests and basic treatments before they reach IVF. The management trajectory would be - Consultation - basic Investigations - Simple treatments eg. OI & IUI - Invasive investigations eg. Diagnostic laparoscopy and hysteroscopy - Invasive treatments – operative procedures (endometriosis, LOD, myomectomy, IU –adhesiolysis etc) and finally IVF.

IVF is perceived as the last bastion of infertility treatment. Many patients who are offered IVF as a first line of treatment are devastated – they fear that if this fails they have nothing else left. Failure of treatment especially IVF, is incomprehensible (especially to *Indian* couples) and despite counselling there are unrealistically high expectations. In a study done by Melamed et al(1) it was seen that 25% of couples after professional psychological counselling believed in real pregnancy success after ART (25-35%), compared to couples not in previous counselling (routine-no-counselling group: 8% and social-no-counselling group: 6%). 56.2% of couples whose did not participate in psychological counselling believed in 100% of pregnancy chance. (Melamed et al FS).

Infertility treatment is often described as a "roller coaster" experience with cycles of hopeful anticipation - once the decision to start therapy is taken, followed by anxiety during the procedure and subsequent despair if the result is negative. Couples desperate to have a child go through this cycle again and again in the hope that their patience and perseverance will be rewarded one day. Like gambling – the last try is never the last! Couples are lured by stories of others who conceived after extensive treatment or sensational success stories in media. Sometimes not letting go is an unconscious way of avoiding grief.

Apart from the financial and physical strain the couple especially the woman, goes through an enormous psychological and emotional upheaval. So there is need to define a time to stop and move on with life.

'When to say enough is enough – decision making time'.

What is enough for one couple may be too much for another and not enough for a third. Making a decision to stop treatment is extremely difficult, made more so by the fact that science is forever offering hope by coming

up with new technologies. It takes enormous courage to undertake infertility treatment and much more to reassess and end it.

So how can the couple decide? There are 3 levels at which they can seek help and guidance.

1. Evaluating their position by answering a questionnaire honestly.
2. Discussion with Self-help groups and counsellors.
3. Discussion with their physician.

Answering questions on this check list (2) can make it easier to deal with the situation.

1. Do I have complete information on my condition and the treatment options available? Have we given the treatment a reasonable chance of working?

This information should be sought from professionals, not from neighbours, friends, sensational media reports, clinic advertisements etc. Review past treatment with the treating physician and ask if there are any other reasonable options to explore. Taking a second opinion from another specialist may help to crystallize the decision.

2. Do you resent treatment? Is it having a detrimental effect on you personally?

Infertile women often report feelings of anger, resentment, envy, and guilt. As treatment failures mount, feelings of powerlessness and lack of control begin to predominate and the uncertainty creates tension and dissatisfaction (3). Men also report high levels of stress, but infertility was found to be overall more stressful for women. (4)

The ten most significant difficulties reported (n 174).

Rank	Type of difficulty %
1. The monthly anticipation of treatment result	40
2. Lack of spontaneity in our sexual relationship	30
3. Uncertainty regarding the future	29
4. Negative feelings aroused by the infertility problem	21
5. Not being able to solve the problem myself	16
6. Disruption of my daily routine	15
7. Feeling lack of control over my life	14
8. Pain and physical discomfort involved in treatment	13

3. Is it affecting my relationship?

Treatment can take its toll on any relationship. 'Programmed sex' distorts the natural libido. Stopping treatment removes this pressure and enables couples to rekindle their relationship.

4. Is it a drain on our finances?

If so then it is time to reassess whether further expenditure is really worth it. It may give the couple a tangible, convincing reason to let go. Studies show that financial reasons are not the prime reason for discontinuing. (Netherlands, Sweden, Australia).





5. Am I putting my life on hold – are all important life decisions secondary to my treatment?

Quit your job. Take indefinite leave from work. Put off holidays. Put on hold all other activities in your life. If “yes” then, how much longer am I prepared to wait “until my/our real life begins”?

6. How important is it to have my genetic child.

7. Is donor gamete an option that I am willing to accept?

Personal & religious reasons for non- acceptance of donor gametes. Social, emotional, ethical, financial and availability issues.

8. Am I willing to accept surrogacy?

given the emotional, ethical and financial problems associated with surrogacy.

If after deliberating on these questions you are 'Still Undecided' and are not ready to stop treatment now, then give yourself a deadline. That way you will be less inclined to “just have one more try”. This deadline could be:

- Number of treatment cycles.
- Age
- Keep aside a fixed amount of money for treatment.
  - "Remember it is not you who have failed but the treatment".

Responsibility of the physician:

The treating physician has an enormous responsibility in guiding the patients and helping them come to a rational decision. He/She must have a detailed discussion on the patient's condition, the pros and cons of all treatments available and an honest presentation of the possibility of conception. Give realistic hope, do active censoring when the situation demands and take note of the patients emotional status before advising further treatment. Discuss alternative options and give the patient time to consider them.

It has been proposed that the patient's mental health be considered an integral component of her infertility care. Just as a patient's evaluation would be considered incomplete without a hysterosalpingogram, her level of anxiety and depression and her ability to cope during crises should be assessed as well. (5) Domar et al FS.

When patients do discontinue treatment emotional stress is cited as the most important. Physical discomfort and financial reasons are cited last.

A study conducted was conducted by the 'Institute of Medical Ethics and Medical history' to investigate the views of patients and experts in Germany on information provision and decision-making in assisted reproduction treatment. A Standard questionnaire techniques was used for interviewing Reproductive Physicians, Psychosocial Counsellors and Patients. The conclusion of this study was that a significant number of patients in reproductive care *are not well informed on all the aspects that are relevant for treatment decision-making*, are overwhelmed by their desire for a child, lose control over the situation, and *are limited in their capacity to end unsuccessful treatment*.

It was suggested that information provision should be ensured and monitored during treatment by standardized safeguards. A strategy for stopping ART and embarking on alternative ways of coping with infertility should be installed from the outset of every treatment. (6)

### *When to stop Infertility treatment*

#### Coping with failure

Some form of closure regarding the ending of treatment is required. Acceptance of a major disappointment, reassessment and readjustment of life is the key to coping. One of the important aspects of coping is to allow time for grieving. The grief is for the loss of something they hoped for but did not have. Some couples write a letter to their unborn child, others have planted a rose or a tree, other couples have gone away together to mark the end of their treatment and to plan a new beginning together. Some couples are able to reinvent life goals and re-establish their relationships; however, a significant number of couples struggle to adapt to life without the child they had anticipated leading to a breakdown of relationships (7). Encouraging adoption should be a prime part of counselling.

#### Conclusion

Infertility is experienced as a stressful situation by couples all around the world. The stress in Asian societies is increased manifold as childlessness carries a huge stigma. Women are more affected as they feel a strong pressure to fulfil the societal norm of motherhood. They suffer from a sense of low self esteem and an intense feeling of failure of her perceived role as a woman. ART offers hope to many couples but when treatment fails repeatedly the couple must be counselled to move on with their lives. Medical treatment has unfortunately not paid enough attention to the emotional responses that couples experience. It is imperative that when a treatment strategy is outlined for infertility it should include a design for stopping ART and embarking on alternative ways of coping with infertility.

We must be willing to let go of the life we have planned, so as to have the life that is waiting for us. -E.M. Forster

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