17

INTRAUTERINE INSEMINATION

Dr. Rishma Pai
M.D., D.N.B., F.C.P.S., D.G.O., F.I.C.O.G.
Consultant Gynaecologist
Lilavati and Jaslok Hospitals, Mumbai
Sr. Vice President FOGSI 2010
Treasurer - Indian Society of Assisted Reproduction
Member of Managing Committee MOGS, IAGE

Dr. Rutvij Dalal
M.D., D.G.O., D.N.B., F.N.B.
Current Fellow in Reproductive Medicine
at the Lilavati Hospital, Mumbai

Introduction

The prevalence rate of infertility in the general population is in the range of 10-15%. [1] The choice of treatment for these couples depends on multiple factors. Intrauterine insemination (IUI) is a method of assisted conception that can be used for treatment of infertility in certain groups of infertile couples. It is defined as the deposition of washed spermatozoa in the uterus at any point above the internal os, around the time of anticipated ovulation. The procedure helps in overcoming the problems of vaginal acidity and cervical mucus hostility, and allows deposition of a good number of highly motile and morphologically normal sperms in the uterus near the fundus. It is one of the simplest, safest and least expensive methods of assisted conception and is suitable as the first line of treatment for women with patent fallopian tubes.

Patient Selection, Indications And Contraindications Of Intrauterine Insemination

A detailed history and complete evaluation of the infertile couple should be done. Any contraindications to the procedure should be identified and alternative treatment should be advised to these couples accordingly. The various indications for the procedure are detailed below.

Indications Of Intrauterine Insemination

1. Unexplained Infertility

In this condition, there is no definite cause for infertility even after subjecting the patient to a complete work up.

The pregnancy rate in these patients is as follows:

a. Natural cycle + IUI: 6%
b. Clomiphene Citrate (CC) and/or gonadotropins + IUI: 18-19%

2. Cervical Factor

The use of IUI in patients with cervical factor infertility yields very good pregnancy rates, in the range of 14-18%.

3. Male Factor These can be classified as:

3.1 Subnormal Semen Parameters

These are cases of:

- Oligozoospermia
- Asthenozoospermia
- Teratozoospermia
- Hypospermia
- Highly viscous semen.

Zayed et al reported a pregnancy rate of 19% per cycle in patients with mild male factor.[2]

Patients with severe factor infertility should go directly for intracytoplasmic sperm injection (ICSI) or the use of donor sperms for insemination (artificial insemination by donor or AID).

3.2 Ejaculatory Failure

A) Anatomical: Severe hypospadias. In this condition, semen is collected by masturbation.

B) Neurological: Retrograde ejaculation and paraplegia. In retrograde ejaculation, urine is centrifuged and then washed to isolate sperms. In paraplegics,, the semen is collected by electroejaculation. In electroejaculation, a probe is inserted into the rectum and a stimulus is given to the seminal vesicles to bring about ejaculation. In both these conditions, the sperm quality especially its motility is hampered. Furthermore, debris, inflammatory cells and quite often bacteria abound in these samples. Good results are obtained with samples where the progressive motility is more than 20-30%.

C) Psychological conditions: Impotence and erectile dysfunction. In this the patient is given sex-psychotherapy. Drugs such as Viagra, Muse or papavarine may be given to bring about a good erection. Some patients benefit with the use of mechanical vibrators. Occasionally, the patients may have to be subjected to general anesthesia and electroejaculation. Following this, IUI may be performed.

D) Drug-induced: Drugs like sedatives, antidepressants, antihypertensive agents, cimetidine, etc. can cause ejaculatory dysfunction.

4. *Ovulatory Dysfunction*

It contributes to 30-40% of the female factor. In these cases, the first choice of treatment would be ovulation induction combined with timed intercourse or IUI. Many studies have shown that IUI gives better results as compared to timed intercourse.

5. *Endometriosis*

Patients with mild to moderate endometriosis have good pregnancy rates of 7-18% with IUI. However, if the pregnancy rates are very low (3-5%) as with severe endometriosis, it is best to opt for IVF/ICSI.

6. *Vaginismus*

7. *Allergy to Seminal Plasma*

8. *Cryopreserved Samples*

IUI using husband's frozen semen in the following cases:

- Absentee husband
- Post Anti-neoplastic treatment
- Vasectomy
- Poor semen parameters
- Drug therapy

9. *IUI with Donor Sperm*

- Severe abnormal semen parameters
- Azoospermia
- Hereditary disease in male
- Repeated failure at IVF/ICSI

Contraindications For Intrauterine Insemination

1. Tubal pathology
2. Genital tract infection
3. Severe male factor infertility
4. Severe endometriosis
5. Genetic abnormality in husband
6. Poor egg quality
7. Unexplained genital tract bleeding
8. Pelvic mass
9. Older women, more than 40 years
10. Multiple failures at IUI (more than 4-8 previous IUI cycles)

Prerequisites For Intrauterine Insemination

1. Age <40 years
2. Patient capable of spontaneous or induced ovulation
3. At least one patent fallopian tube with good tubo-ovarian relationship
4. Sperm count of more than 10 million/ml pre-wash or a post-wash count of > 3-5 million motile sperms with percentage motility of more than 40%.
5. Easy access to the uterine cavity via a negotiable cervical canal.

Intrauterine Insemination Steps

1. Patient selection and work-up (detailed earlier)
2. Ovarian stimulation
3. Monitoring of follicular growth and endometrial development
4. Timing of insemination
5. Number of inseminations (single v/s double)
6. Semen preparation
7. Insemination procedure
8. Luteal support
9. Detection of pregnancy

Though IUI can be carried out during the natural cycle, it has been observed that ovarian stimulation significantly improves the outcome of IUI cycles. Stimulating the ovaries results in the production of more than 1 oocyte, improves the chances of fertilization, and subsequent establishment of pregnancy in subfertile couples. There may be the added advantage of correction of unsuspected ovarian dysfunction[3] and luteal phase defects,[4] especially when ovarian stimulation is done in ovulatory patients.

There are various regimes that can be used to stimulate the ovaries prior to IUI. These are as follows:

1. Clomiphene citrate (CC)
2. Clomiphene + hMG (human menopausal gonadotropins)
3. Clomiphene + FSH (follicle stimulating hormone)
4. HMG

5. FSH
6. hMG + FSH
7. hMG/FSH + GnRH analogues
8. FSH + GnRH antagonists
9. CC + FSH + GnRH antagonist (the soft protocol)

Clomiphene Citrate (CC)

The drug is administered in a dosage of 50-150 mg/day for 5 days starting from the 2nd 5th day of cycle. Starting the drug from day 2 of the cycle reduces the anti-estrogenic effect of the drug by the time ovulation occurs by day 14. It is better to combine it with gonadotropins, rather than increasing the dose beyond 150 mg/day.

CC is known to exert anti-estrogenic effect: This can be in the form of poor cervical mucus or a thin endometrial lining. This may need the following measures:

- Oral supplementary estrogen (debatable benefit)
- CC to start on cycle day 1. This can cause better rapid follicular growth and can give a longer CC-free period before IUI, with better pregnancy rates.
- Introduce CC + gonadotropin sequence
- Start pure gonadotropin therapy

Normally the CC therapy can be combined with a CC challenge test in which S.FSH is done on cycle day 10. A high FSH indicates poor prognosis with only a 4.8% chance of pregnancy.

Clomiphene Citrate Failure:

It is defined as failure to ovulate in response to CC treatment. Direct ovarian stimulation with gonadotropins is the obvious alternative. However, many couples are reluctant or unable to pursue gonadotropin therapy once fully explained of the costs, logistical demands and risks. For such couples, there are certain other regimens which, though used uncommonly, can help some of them ovulate. These are:

Extended Course of Clomiphene Citrate Treatment:

Up to 50% of clomiphene-resistant patients may ovulate after longer duration of treatment (7 days).

Clomiphene Citrate and Glucocorticoids:

Numerous studies have shown that adjuvant treatment with glucocorticoids can successfully induce ovulation in many patients who fail to respond to CC alone. Either prednisolone (5 mg/d) or dexamethasone (0.5-2 mg/d) can be used in continuous or follicular phase treatment regimes (days 5-14). The exact mechanism of action of glucocorticoids is unclear. The effects can be due to androgen suppression, direct effect on developing oocyte and indirect effects on intrafollicular growth factors and cytokines that act synergistically with FSH.

Preliminary Suppressive Therapy:

With either OCP or a long-acting GnRH agonist can help restore the disturbed harmony of the hypothalamopituitary axis in patients with anovulation. Spontaneous resumption of ovulation sometimes follows, obviating the need for stimulation altogether.

Insulin-sensitizing Agents:

Patients with PCOS with signs and symptoms of insulin resistance can be started on metformin. It has been shown to restore ovulation in some of these anovulatory patients. Also in combination with CC, it may cause ovulation in those who are resistant to CC alone. In fact the authors advocate this therapy for all patients of PCO with/without associated metabolic disturbances. Oral metformin 1500 mg/d in 2-3 divided doses is given for 3-6 months. Rosiglitazone has a potentially teratogenic effect and is hence not advised. An Ayurvedic preparation called Hyponiid, containing D-Chiro-Inositol has been made available in

India. It is quite effective and can be given in combination with metformin (thus reducing metformin dose and GI side effects) or as an alternative to metformin (in patients who cannot tolerate metformin).

CC + Gonadotropin + hCG + IUI:

In case the follicle growth or number is inadequate with CC alone, one can give additional FSH/hMG injections from day 9 onwards. Inj. hCG 5000/10000 units is administered when leading follicle is 18-20 mm. In case there are more than 4 follicles of >16 mm or more than 8 of >12 mm, it is best not to give hCG as it can cause OHSS (ovarian hyperstimulation syndrome) and high order multiple births. In case of doubt, it is best to do a serum estradiol level. If the E2 level is <1500 pg/ml, one can give hCG. If E2 is >1500 pg/ml it is best to do the following to prevent hyperstimulation:

- Withhold hCG and wait for spontaneous rupture
- Instead of hCG, one can give Inj. GnRHa and perform the IUI after 36-40 hours. This can be done if there are not too many follicles.
- Alternatively one can start GnRH antagonist 0.25 mg subcutaneously every day till hCG injection, and convert the cycle into an IVF cycle, by performing oocyte retrieval after 36 hours of hCG injection.

Advantages of CC + Gonadotropin sequence:

1. This combination has pregnancy rate double than that of CC alone &is nearly the same as gonadotropins alone.
2. It is cost-effective, as fewer ampoules of gonadotropins are needed.
3. Multiple pregnancy rates are lesser than CC alone or gonadotropins alone.
4. There may be a lower incidence of OHSS, as compared to standard low-dose step-up or step-down Gonadotropin regimes.

Gonadotropin Therapy

- Conventional therapy
- Step-up regime
- Step-down regime

Conventional therapy:

Day 2 LH/FSH/E2 levels are usually performed prior to the stimulation so as to decide upon which kind of gonadotropins should be used for stimulation. If S.LH is elevated, FSH containing gonadotropins are used for stimulation. However, is S.FSH is elevated (>10mIU/ml), hMG is used for stimulation. For hypogonadotropic hypogonadism, hMG is used. The usual starting dose is 150 IU. However, a higher dose can be used for older women and in those with poor response to low doses. S.E2 levels and ultrasound monitoring of the follicles help in determining the further doses.

Step-Up regime: In this instead of 150 units a starting dose of 75 IU is given for 7 days starting from Day 2 of cycle. If day 8 serum E2 is >200 pg/ml or follicle >10mm, the dose is maintained. If not, the dose is increased by 37.5 (half ampoule) or 75 units (1 ampoule). hCG is given when leading follicle is > 16-18 mm and endometrial thickness is = 7mm. The rest of the precautions are as per the conventional regime.

Step-down regime: FSH therapy at a daily dose of 150 IU is started on day 2 and continued till a dominant follicle of > 10mm is observed on TVS. After this, the dose is decreased to 112.5 units IM per day for 3 days, followed by 75 units IM per day for 3 days.

This dose is continued till the day of hCG injection. The rest is the same as in the step-up regime.

GnRH analogue in combination with Gonadotropins

This protocol is used in the following situations:

- Patients undergoing IUI wherein the standard stimulation with CC or gonadotropins has failed to yield pregnancy after 2-4 attempts.
- In patients who have shown premature luteinization or premature LH surge while undergoing gonadotropin-only stimulation. Normally 20-24% patients undergo premature LH surge while being on stimulation on gonadotropins.
- In polycystic ovarian disease patients where there are highly elevated LH levels.
- History of premature luteinization or miscarriages

Disadvantages

1. Increased duration of therapy
2. Costly
3. Higher consumption of hormones with resultant higher chance of hyperstimulation syndrome and multiple pregnancy rates
4. Not much statistically significant increase in pregnancy rates as compared to the gonadotropin-only protocol

Monitoring of follicular growth and Endometrial development

The follicular growth can be monitored with the aid of serial trans-vaginal ultrasonography, serial E2 levels and urinary LH assays.

Trans-Vaginal Ultrasound

TVS provides the most practical method for assessing follicular development. Both the number as well as the sizes can be studied. The follicles normally grow at the rate of 2-3 mm/day once the leading follicle reaches 10-12 mm size. Serial ultrasound helps determining the exact time for triggering ovulation, specially in stimulated cycles. Counting the number of follicles also helps identifying the patients likely to develop OHSS. Usually a baseline scan is carried out on day 2 of cycle to exclude the presence of ovarian cysts or other pathologies such as PCOS, polyp, Endometriosis or hydrosalpinx. Serial ultrasound scanning is then performed from day 7 or 8 onwards. The endometrium is also assessed for thickness and reflectivity. A triple line endometrium with thickness of > 9 or > 10 mm is most conducive to pregnancy.

Serial Serum Estradiol Levels

Plasma estradiol correlates closely with the stage of development of the dominant follicle in natural cycle. This

is not true in stimulated cycles as the estradiol reflects the total output of all developing follicles irrespective of size. In most cycles ultrasound has replaced estradiol monitoring. Another problem of S.E2 estimation is the inconvenience of the repeat blood testing faced by the patient, both in terms of disruption of day-to-day routine as well as the costs.

Practically serum estradiol level is done in pure gonadotropin stimulated cycles with/without GnRH analog on day 8 of stimulation to assess follicular response.

Practically it is done in pure gonadotropin stimulation cycles with/without GnRH analogue on day 8 of stimulation to assess follicular response. A value of > 200 pg/ml indicates adequate dose of gonadotropins. It

is also indicated when there are > 4 follicles of > 16 mm size or > 8 follicles of = 12 mm on the day of ovarian stimulation. An estradiol level of > 1500-2000 pg/ml would indicate withholding of ovulation trigger and cancellation of cycle. In case the estradiol level is < 1500 pg/ml, one can use a GnRH analog to trigger ovulation, provided that the ovarian stimulation is not in downregulated cycle.

Urinary LH Assay

In patients who are undergoing ovarian stimulation, and who are not using GnRHa for downregulation, there is possibility of having a premature endogenous LH surge prior to the administration of hCG to bring about ovulation. In case of premature LH surge, ovulation will occur in relation to the surge, rather than occurring in relation with the hCG injection. In such conditions IUI will have to be planned prematurely to time with the LH based ovulation.

LH surge is known to occur after the leading follicle reaches 16 mm. This is known to occur in 20-24% of patients undergoing ovarian stimulation. The LH surge can be detected either by doing a daily blood or urinary LH assay, once the leading follicle exceeds 16 mm diameter. If the LH surge is detected, Inj hCG 10,000 units is given immediately, and an insemination is carried out on the same day. A repeat insemination is carried out the next day. The hCG injection is necessary as the LH-secreted by the body is not high enough as would occur during a natural cycle. Furthermore the body LH may not be adequate enough, to induce the necessary maturational changes in all oocytes, if there are many follicles in the ovary. Numerous urinary LH kits are available to detect LH surge. They are easy to use and are cost effective.

LH surge is known to occur in 20% of all IUI cycles. The remaining 80% cycles do not experience any LH surge. In these cycles, hCG 10,000 units are given when the leading follicle reaches 18-20 mm. IUI is carried out 36-40 hours after hCG administration.

<u>Ovulation Trigger And Timing Of Insemination</u>

The ovulation is triggered by administration of hCG injection when the following conditions are met:

- Leading follicle is 18-20 mm.
- Less than 4 follicles of 16 mm or less than 8 follicles of 12 mm.
- Serum E2 is not more than 1500-2000 pg/ml (serum estradiol is done only if the total number of follicles exceed 12 and there is a potential chance of OHSS).
- There is no LH surge as seen by testing the morning sample of urine.

There are various ovulation triggers available:

- HCG: Inj. hCG 5000 IU or 10,000 IU i.m. IUI is done 34-36 hours after the dose of hCG injection.
- Recombinant hCG

- Recombinant LH
- GnRH analog: Inj. Leuprolide 500 µg s.c. and repeat 500 µg s.c. after 12 hours. The insemination is done 36 hours after the first injection.

Timing Of Insemination

The main objective is to time the insemination as near to the ovulation as possible 4 hours before or within 12 hours after ovulation is good enough to yield pregnancy. Ovulation normally occurs about 40-45 hours after the onset of LH surge.[5] All follicles do not ovulate at one time; they rather do so in waves. This consideration has led many practitioners to carry insemination twice at the interval of 24 hours, around the time of ovulation.

Single Insemination

IUI is carried out between 32-40 hours after hCG injection. Normally it is done 34-36 hours after hCG injection. An ultrasound examination is carried out at the time of or after the insemination. If there is no rupture of the follicle, an additional insemination is carried out the next day, 24 hours later.

Double Insemination

IUI is carried out 24 and 48 hours after hCG injection. Some units carry out double insemination at 12 and 34 hours post hCG. Many meta-analysis have been done comparing simple versus double insemination. Efficacy of two versus one insemination has not been proved. Numerous studies have shown no difference in outcome. However some studies have shown better results with double insemination whereas certain others have shown single insemination to be more efficacious.[6,7] However, it is better to avoid double insemination in patients with male factor infertility.

Sperm Preparation

It is important not just to obtain an enriched fraction of the maximum number of motile and morphologically normal spermatozoa by using the correct semen washing technique but it is also important to obtain a reduction or removal of seminal plasma and other harmful cellular components (leukocytes, debris, microbase) from the ejaculate. Seminal plasma components are rich in prostaglandin as well as contain factors that prevent capacitation of the sperm. A normal ejaculate contains a large number of defective sperms and granulocytes which on centrifugation disintegrate, and generate a high number of ROS (reactive oxygen species). These, in turn, attack the unsaturated fatty acids in the plasma membrane of the sperm, resulting in causing an oxidative stress, which can functionally damage the sperm.

Semen Preparation Techniques

There are three conventional methods of sperm washing techniques:

1. Direct swim up
2. Pellet and swim up method
3. Density gradient

The method used to prepare sperm will depend upon the following:

1. The motile count
2. Volume
3. Presence of leukocytes, other cells and debris
4. Viscosity
5. Whether it is for IUI, IVF or ICSI

The direct swim up is used for semen with normal parameters. It is not used for viscous samples. The pellet and swim up method is used for normal or marginally abnormal semen samples. It is the method of choice for viscous samples.

The density gradient method is effective for abnormal sperm. It not only removes the abnormal sperm but also microbes, debris and other cell contaminates from the sample. It is also used in processing semen samples prior to freezing them and for processing non-processed frozen semen samples. It can also be used for normal semen samples.

Once the semen sample is processed, IUI should be carried out as soon as is possible. The ejaculation to insemination interval should not exceed 1 hour and 15 minutes.

Advantages of Density Gradient

1. Improves yield and recovery compared to swim up technique especially in oligospermic semen samples.
2. Removes morphologically abnormal sperms.
3. Removes dead sperms.
4. Removes sperms with abnormal DNA.
5. Increases sperm survival time.
6. Improves cryosurvival, hence better to perform density gradient prior to freezing sample.
7. Removes bacteria.
8. Removes sources of ROS.
9. Removes viral infectivity such as HIV and hepatitis C.

Disadvantages of Density Gradients

1. Poor sperm recovery in patients with severe oligoasthenospermias.
2. Poor sperm recovery in patients with viscous samples.
3. Poor recovery in semen samples with high degree of cellular debris.
4. Relatively costlier than standard swim up method.
5. Not much advantage in patients having normal semen parameters.
6. Vaginal irritation following improper washing of the final sample prior to IUI, due to residual colloidal silica particles.

<u>The Insemination Procedure</u>

Semen sample is prepared by the appropriate method. The woman lies in the lithotomy position. Cervix is exposed using Cuscos bivalve speculum or Sims speculum with anterior vaginal wall retractor. Cervix is cleaned using sterile gauze pieces soaked in normal saline. The IUI cannula is flushed with 1-2 ml of flushing media to wash away any toxic factors present. The sperm suspension is then drawn in the cannula. Normally an insemination volume of 0.4-0.6 ml is used. A minimum concentration of 1 million motile sperms is essential. Good results are seen with inseminate having more than 5 million motile sperms. It is best to deposit inseminate very slowly into the uterine cavity over 3-minute period. After the deposit, the cannula is withdrawn very slowly. This prevents the sudden gushing out of inseminate which may happen if cannula is

suddenly withdrawn. Once the procedure is complete, all instruments are withdrawn and patient is allowed to lie in couch for about 10-15 minutes. It is important to have an atraumatic transfer for successful implantation. In difficult inseminations, where it is difficult to negotiate the canal, one can try to use more rigid cannulas.

Luteal Support

Usually prophylactic luteal support is given to all patients undergoing IUI. Alternately, one can support the luteal phase in those patients who have day 21 serum progesterone < 10 ng/ml. Any of the following drugs can be given for the same:

1. Oral dydrogesterone 10 mg BD from day of IUI
2. Micronized progesterone 100 mg BD orally or vaginally
3. Inj. Progesterone 25-50 mg i.m. every day
4. Inj. hCG 3000 IU i.m. once every 3 days

The luteal support is given for 14 days. At the end of 14 days, a serum â-hCG is done for detection of pregnancy.

If patient is pregnant luteal support is continued till 12 weeks.

Complications Of Iui Treatment

1. Failure of treatment
2. Pelvic infection: 0.01-0.2%
3. Uterine contractions and anaphylaxis
4. OHSS <1%
5. Multiple pregnancy
6. Ectopic pregnancy
7. Miscarriages

Success Of Treatment

The results of IUI in terms of pregnancy rates per treatment cycle vary considerably with different studies. Analysis of pregnancy rates is difficult due to the variability in populations studied, differences in etiology of infertility, and multiplicity of ovarian stimulation protocols. The overall success rates vary between 10-15% per treatment cycle. Patients with cervical factor and unexplained infertility as well as those undergoing donor IUI demonstrate higher pregnancy rates. Most patients who get pregnant with IUI do so within the first four cycles. This number of cycles can be completed within a year's time. It is advisable to recommend IVF/ICSI to patients who fail to become to pregnant after 1 year of IUI therapy.

A minimum concentration of 1 million motile sperms is essential. Good results are seen with inseminate having more than 5 million motile sperms.

Conclusion

Intrauterine insemination has an established role as a low-risk, low-cost and first line treatment method yielding pregnancy rates of 10-15%. Pregnancy rates of 20% in patients with cervical factor and unexplained infertility seem to be realistic based on present literature. Patient selection is very important. Males with

pronounced semen abnormalities and older patients > 40 years of age with long-standing infertility may not be suitable for IUI. The patients should be given the option of IUI for 4-6 treatment cycles prior to recommending them for ART.

References

1. Mosher WD, Pratt WF, Fecundity and Infertility in United States: Incidence and trends. *Fertil Steril* 1991;56:192-3.
2. Zayed F, Lenton EA, Cooke ID. Comparison between stimulated in-vitro fertilization and stimulated intrauterine insemination for the treatment of unexplained and mild factor infertility. *Hum Reprod* 1997;12:2408-13.
3. Arici A, Byrd W, Bradshaw K, et al. Evaluation of clomiphene citrate and human chorionic gonadotrophin treatment: a prospective, randomized, crossover study during intrauterine insemination cycles. *Fertil Steril* 1994;61:314-8.
4. Edwards RG, Brody SA, eds. Natural cycle and ovarian stimulation in assisted conception. *Principles and Practise of Assisted Human Reproduction* Philadelphia: WB Saunders, 1995:233-84.
5. Lenton, et al. Ovulation timing. In: *Donor Insemination* Bairrati CLR, ed., Cambridge, 1993:97-110.
6. Centola GM, Mattox JH, Raubertas RF. Pregnancy rates after double versus single insemination with frozen donor semen. *Fertil Steril* 1990;54:1089-92.
7. Khalifa Y, Redgment CJ, Tsirigotis M, et al. The value of single versus repeated insemination in intra-uterine donor insemination cycles. *Hum Reprod* 1995;10:153-4.

18 LUTEAL PHASE SUPPORT

Dr. Mandakini Parihar
MD, DGO, FICOG
Director , Mandakini IVF Centre
1st Vice-President Elect, FOGSI 2012
Chairman Elect, Maharashtra Chapter ISAR 2013
Jt. Treasurer, IMS
Associate Professor, K.J. Somaiya Medical College

Physiology of luteal phase

The luteal phase is defined as the period between ovulation and either the establishment of a pregnancy or the onset of menses two weeks later. (Fauser 2003). After ovulation, the corpus luteum is formed. This new structure derives from the Graafian follicle after changes induced by gonodotrophin surge. These changes include vascularization of the previously avascular granulosa cell layer and the acquisition of the capacity for de Novo steroids biosynthesis by the granulosa cells. The main steroids produced are estradiol and progesterone. Endometrial glands undergo a secretary differentiation (the secretary phase) an important event in preparation for implantation of the fertilized egg. LH is necessary for the maintenance of the corpus luteum throughout its life span. This reflects the fact that the corpus luteum is a transient endocrine organ, having an inherent 12-15 day life span. (Figure 1)

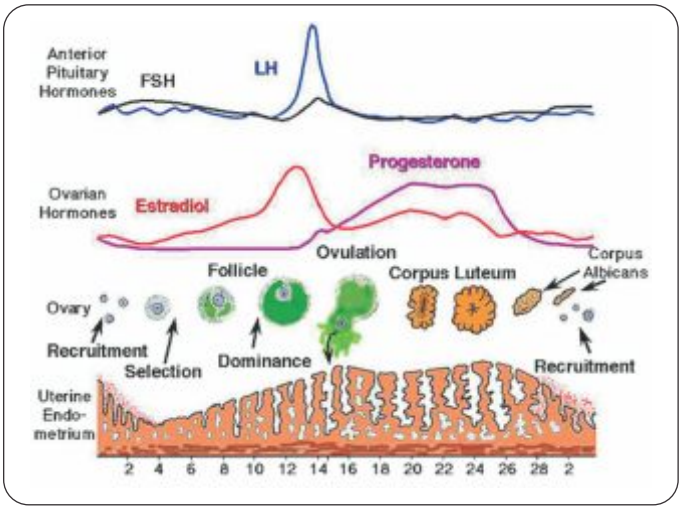

Figure1: Pituitary and ovarian hormonal pattern with ovarian and endometrial cycle

When there has been a successful pregnancy there is a corpus luteum rescue by the HCG from the pregnancy and the corpus luteum does not undergo luteolysis. In the non-fertile cycle, its regression, the process of luteolysis is inevitable. During the final days of the luteal phase and in the absence of implantion of a fertilized egg, ovarian steroid secretion decreases dramatically. Because of this withdrawal of hormonal support, the endometrium undergoes necrotic changes menstrual bleeding results. If conception and implantation occur, the developing blastocyst secretes human chorionic gonadotrophin (hCG). The role of hCG produced by the embryo is to maintain the corpus luteum and its secretions (Penzias, 2002).

In what way, luteal phase in stimulated cycle is different from natural cycle As early as 1949, the premature onset of menses was recognized as indicative of a luteal phase deficiency of progesterone production, which was shown to be correctable by exogenous progesterone administration.

Stimulated cycle luteal phase is different from natural cycles

1. Ovarian stimulation produces multiple corpora lutia, the levels of both E and P in the early part of the luteal phases are supra physiological.
2. Duration of ovarian steroid production in stimulated cycles is usually shorter than normal menstrual cycle by one to three days. Menstruation on occasion is observed to occur as early as 10 days after egg retrieval
3. The decline of serum E and P is also more abrupt than the natural cycle.
4. It was also suggested that the hCG administered for the final oocyte maturation in stimulated IVF cycles could potentially cause a luteal phase defect by suppressing the LH production via a short-loop feedback mechanism (Tavaniotou and Devroey,2003).

Reason for abnormal luteal function after ovarian stimulation for IVF remains open for speculation

Possible mechanisms involved include

1. Continued down regulation, by GnRH agonist co-administration may retard pituitary recovery
2. Initially, it was thought that the removal of large quantities of granulosa cells during the oocyte retrieval (OR) might diminish the most important source of progesterone synthesis by the corpora lutea, leading to a defect of the luteal phase. (Smitz,1992)
3. Supra physiological levels of steroids due to higher number of corpora lutia during the early luteal phase could directly inhibit LH release the HPO axis.

Effects of GnRH agonist & antagonist on the luteal phase

Use of GnRH agonist causes suppression of pituitary LH secretion for as long as 10 days after the last injection. Without this LH signal the corpus luteum may be dysfunctional and hence the progesterone secretion may be abnormal. This compromises the endometrial receptivity leading to decreased pregnancy rate unless supplementation with progesterone is done. In addition the agonist themselves create an iatrogenic luteal phase defect by early luteolysis. (Friedler, 2006).

In GnRH antagonist cycle, the exact role is not well defined. However, there is need for supplementation of the luteal phase especially when HCG is used as ovulation trigger, as it causes pituitary LH suppression indirectly (Friedler, 2006).

Drugs used for luteal phase support

Progesterone supplementation

Progesterone is the most important steroid for implantation and it induces the pinopode formation of the endometrium and hence assists implantation. In a natural cycle, the implantation window is usually 7 days post ovulation. Starting progesterone supplementation from the day of oocyte retrieval in stimulated cycle or in recipient cycle even earlier has got a quieting effect on the uterus. In addition, the dys-synchrony between gland and stroma is eliminated if progesterone is started 2 to 4 days before embryo transfer. It has been shown that highest pregnancy rates occurred when 2-day-old embryos were transferred on the 4^{TH} or 5^{th} day of progesterone therapy.

Routes of progesterone support

Progesterone can be delivered in different ways to the body. Possible routes of progesterone are trans-dermal, oral, intra-muscular, transvaginal , sublingual, nasal or rectal. In clinical use for luteal support, only oral, IM, transvagial routes are commonly used. (Simunic 2007, Kolibianakis & Devroey 2002a,b)

Figure 2 gives the advantages and disadvantages of the 3 options.

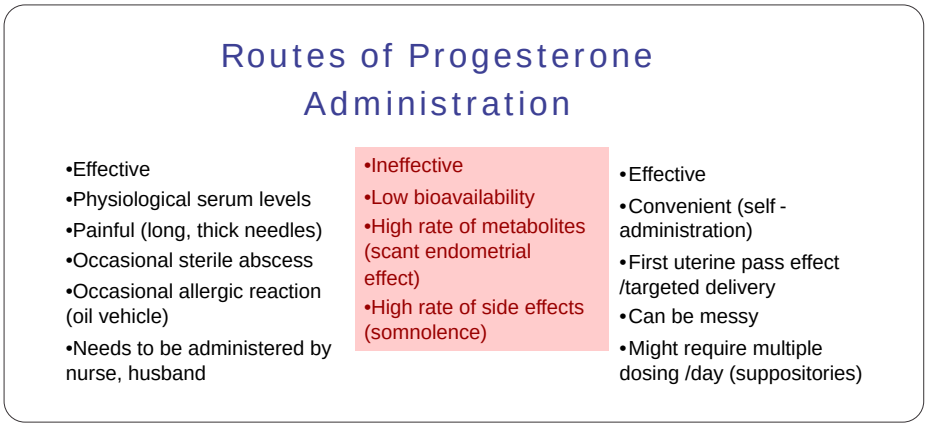

Figure 2: Routes of Progesterone Administration with advantages and disadvantages

Vaginal route

This is the most preferred route. Vaginal progesterone preparations are available as suppository, rings, 8%gel or micronized gelatin capsules, micronized vaginal tablets and the most recent is the dispersible vaginal tablets. The dosage is between 400-800mg per day in divided doses.

Role of Estrogen in luteal phase support

Addition of estrogen to the progesterone in luteal phase improves pregnancy rate by increases progesterone receptors. (Fatemi, 2006).

It was seen that those patients where there is precipitous drop of luteal phase serum estradiol levels by more than 50% over a 48 hour period from hCG administration benefited when estradiol was added along with progesterone in luteal phase.

Role of HCG

It was used earlier routinely for luteal support. It helps to stimulate secretion of estradiol and progesterone receptors. However, it is associated with a high risk of OHSS and hence is no longer recommended for use in luteal phase. (Nosarka 2005)

GnRH agonist: a novel luteal phase support?

In a prospective randomized study, (Tesarik2006) evaluated the effect of GnRH agonist (0.1 mg triptorelin) administration in the luteal phase on outcomes in both GnRH agonist (*n* = 300) and GnRH antagonist (*n* = 300) ovarian stimulation protocols. They were randomly assigned to receive a single injection of GnRH agonist (study group) or placebo. Luteal-phase GnRH agonist administration additionally increased the luteal-phase serum hCG, E_2 and progesterone concentrations in both ovarian stimulation regimens and had a significantly higher implantation rate in both groups. It was postulated that the beneficial effect may have resulted from a combination of effects on the embryo and on the corpus luteum.

Length of Administration of Luteal Support

Once the pregnancy test is positive, how long should one continue the progesterone support?

Controversy still persists as to when to stop the luteal support. Most clinics stop the luteal support at the end of thirteen weeks. The question asked is when to stop?

- at 12-13 wks or
- once fetal heart is seen or
- as soon as the HCG test is positive?

Recent evidence suggests that one can safely stop luteal support as soon the pregnancy test is positive. (Bourgtain 2003) (Fatemi 2007)

Conclusion : Evidence today for ideal luteal support

- Implantation rates (IR) were increased in women receiving vaginal progesterone when compared with oral progesterone in the luteal phase (Bourgtain 2003)
- Intramuscular progesterone versus vaginal progesterone in the luteal phase conferred no obvious benefit upon Clinical Pregnancy Rate.
- Vaginal progesterone should be the standard choice for luteal phase support. Vaginal progesterone is the treatment of choice for Luteal Support and can be given as tablets, gelatin caps, dispersible caps or vaginal gel.
- Addition of E2 to p4 is the luteal phase also seemed to confer benefit at least in terms of implantation rate in select cases
- There is no evidence of the benefit of oral dedydrogestone in luteal phase as per current evidence. Larger trials needed. (Fatemi 2007)
- HCG does not provide better results than progesterone and it is associated with a greater risk of OHSS.
- There may be some role of GnRH agonist in luteal phase in improving implantation rates but larger trials are needed (Kyrou D 2011)
- A well managed luteal phase goes a long way in optimizing ART results

References:

1. Fauser BC, Devroey P. . Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab 2003;14:236-242.
2. Penzias AS. Luteal phase support. Fertil Steril 2002;77:318-323.
3. Tavaniotou A, Devroey P. Effect of human chorionic gonadotropin on luteal luteinizing hormone concentrations in natural cycles. Fertil Steril 2003;80:654-655.
4. Smitz J, Devroey P, Faguer B, Bourgain C, Camus M, Van Steirteghem AC. A randomized prospective study comparing supplementation of the luteal phase and early pregnancy by natural progesterone administered by intramuscular or vaginal route. Rev Fr Gynecol Obstet (a) 1992;87:507-516.
5. Friedler S, Gilboa S, Schachter M, Raziel A, Strassburger D, Ron El R. . Luteal phase characteristics following GnRH antagonist or agonist treatment—a comparative study. Reprod Biomed Online 2006;12:27-32.
6. Simunic V, Tomic V, Tomic J, Nizic D.Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal phase support. Fertil Steril 2007;87:83-87.
7. Kolibianakis EM, Devroey P. The luteal phase after ovarian stimulation. Reprod Biomed Online (a) 2002;5(Suppl 1):26-35.
8. Kolibianakis EM, Devroey P. Blastocyst culture: facts and fiction. Reprod Biomed Online (b) 2002;5:285-293.
9. Fatemi HM, Kolibianakis EM, Camus M, Tournaye H, Donoso P, Papanikolaou E, Devroey P. Addition of estradiol to progesterone for luteal supplementation in patients stimulated for IVF: a randomized controlled trial. Hum Reprod 2006;21:2628-2632.

10. Nosarka S, Kruger T, Siebert I, Grove D. Luteal phase support in in vitro fertilization: meta-analysis of randomized trials. Gynecol Obstet Invest 2005;60:67-74.

11. Tesarik J, Hazout A, Mendoza-Tesarik R, Mendoza N, Mendoza C. Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles. Hum Reprod 2006;21:2572-2579.

12. Fatemi HM, Bourgain C, Donoso P, Blockeel C, Papanikolaou EG, Popovic-Todorovic B, Devroey P. Effect of oral administration of dydrogestrone versus vaginal administration of natural micronized progesterone on the secretory transformation of endometrium and luteal endocrine profile in patients with premature ovarian failure: a proof of concept. Hum Reprod 2007;22:1260-1263.

13. Daya S and Gunby. Luteal Phase Support in assisted reproduction cycles Cochrane data base reviews, 2006

14. Kyrou D, Kolibianakis EM, Fatemi HM, Tarlatzi TB, Devroey P, Tarlatzis BC. Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis. Hum Reprod Update. 2011

15. Bourgtain c Devroey P. The endometrium in stimulated cycles for IVF human rep update 9,515-522, 2003.