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The Mumbai Obstetric & Gynecological Society

MOGS MEDIA

Vol.3 | Optimising IUI Results

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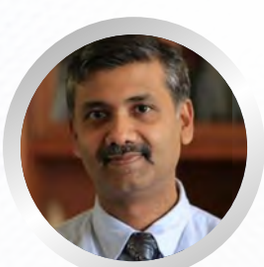

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President's Message

Dear Colleagues,

It gives me great pleasure to bring to you the third issue of MOGS MEDIA, a focused Enewsletter by the Mumbai Obstetric and gynaecological society. In our earlier e-newsletters we have given detailed updates on preterm birth, anaemia management and now we bring to you the latest information on the important subject of Intrauterine insemination. The editor Dr Pratik Tambe and all the contributors have made a lot of effort to bring you concise and precise information and we are thankful to them .

Mumbai Obstetric and Gynaecogical Society has been very active on many fronts presently. On 21st June 2020 we had the 'Focus on First Trimester' digital conference with a wonderful oration by Dr Asma Khalil from UK and many other national and international speakers. On 28th June 'Fresh Viewpoints in Infertility' an excellent focussed programme with an oration by the President of the World Endometriosis Society, Dr Neil Johnson was held online and thousands of doctors enjoyed these CMEs in the comfort of their home.

Our Outreach programmes and N A Purandare teaching programmes are much in demand.

On 19th July we bring to you the first ever Youngistan conference-by the young for the young at heart. Do tune in for this different summit.

MOGS V Care & Share programme has been started by us to support our frontline workers and the women whose health we look after. PPE, N95 masks, face shields, fetal dopplers, thermal scanners etc have been donated by us to all major and many peripheral municipal and government hospitals. We need your help and support for this . You can donate by online payment on our website or by bank transfer.

We have many different academic and fun activities planned this year Do visit our website for updates. www.mogsonline.org

Thank you once again for all your support and we look forward to a wonderful year at MOGS.

Dr Rishma Dhillon Pai
President MOGS.

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Editors' message

Dr Pratik Tambe
Editor

Dr Parikshit Tank
Co Editor

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Dr Rajendra Nagarkatti
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Dear MOGS members,

The MOGS Media series of newsletters have been one of the highlights of the MOGS year so far. The newsletter is themed on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists. The previous two issues on Preterm Birth and Anaemia and Nutrition in Pregnancy were well received and widely appreciated.

It is with great pride that we bring you the third issue on **"Optimising IUI Results"** which refers to recent publications and highlights the current evidence on this subject. Intrauterine insemination is a common modality of treatment for a wide range of infertile patients including cervical factor, male partner issues and unexplained infertility to name a few. We revisit the basics and highlight the important optimisations to achieve better success rates from the point of view of the practising gynaecologist.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative.We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

Dr Pratik Tambe
Dr Parikshit Tank
Dr Sudha Tandon
Dr Rajendra Nagarkatti
(Editors)

MOGS MEDIA
Vol.3 | Optimising IUI Results

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PATIENT SELECTION

Dr Riddhi Doshi MBBS DNB MNAMS DRM(Germany)
Fertility Consultant, Bavishi Fertility Institute, Mumbai

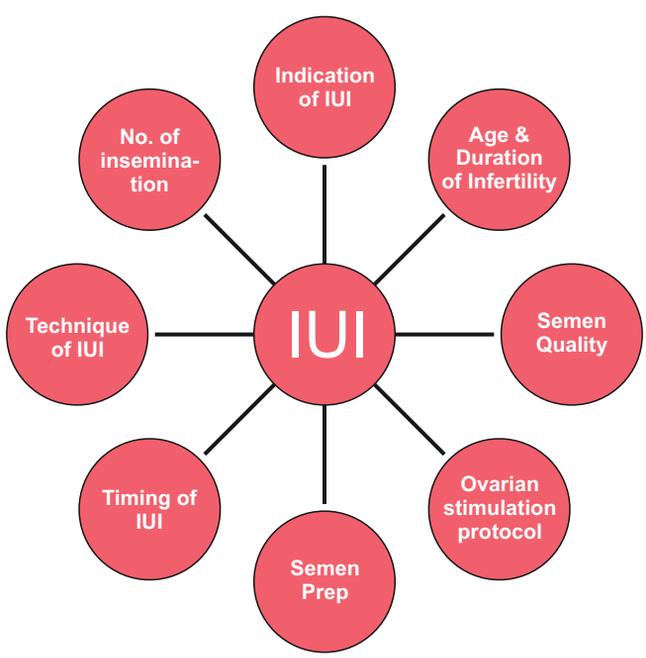
Introduction

Intrauterine insemination is an assisted conception technique in which processed semen sample is deposited in the uterine cavity with the rationale to make healthy sperms available at site of fertilisation in the ovulatory period. The pregnancy rate per cycle after IUI with husband sperm is on an average 12.4% and approximately 4% higher in donor insemination cycles.[1]

Over the years the technique of intrauterine insemination has remained the same, but increased understanding of follicular dynamics and advanced sperm preparation techniques have led to promising success in this area of fertility treatment. However, careful patient selection is essential so that this treatment methodology yields the best results.

IUI is a cost effective, non-invasive first line therapy for selected patients with functionally normal tubes and infertility due to cervical factor, mild to moderate male factor, ovulatory dysfunction, mild endometriosis, unexplained infertility, ejaculatory disorders, immunological factors, viral infections (HIV, HBsAg) and donor insemination. It is ineffective in cases of bilateral blocked/ damaged fallopian tubes, ovarian failure, severe OAT, severe endometriosis and long-standing unexplained infertility.

Fig 1 Factors predicting IUI success rate



Patient age and duration of infertility

Young women with normal ovarian reserve respond well to IUI. As age increases IUI success rates also naturally fall mainly attributable to decreasing ovarian reserve. In women >35 years with antral follicle count of <5, IUI may not be indicated and direct referral to IVF should be considered.[2] With age, duration of infertility also increases and has negative impact of overall pregnancy chances. Studies have shown IUI has limited success when duration of infertility is more than 6yrs.[3]

Semen parameters

There are several sensitive indicators with respect to different sperm parameters which determine prognosis of IUI and sometimes whether or not IUI should be performed at all or not. Though there is no overall consensus on cut-offs, most studies have determined impaired success rates in following scenarios:

Processed total motile sperm count	< 10 million/ml [4]
Normal sperm morphology	< 4 % [5]
Inseminating motile count	<1 million/ml [5]
Rapid progressive motility post wash	<= 25% [6]

Aetiology

Indication for which IUI is done is one of the most crucial factors for predicting the success rate as well as from a counselling standpoint. A large Indian retrospective study has assessed this well.[7]

Table 1 IUI success rates depending on indication

Etiologies	Cycles (patient)	Pregnancy	PR (%)
Female factor			
Ovulatory dysfunction	94 (106)	20	21.2
Tubal	69 (52)	8	11.5
Endocrinological	186 (55)	25	13.4
Unexplained	236 (261)	28	11.8
Male factor	149 (91)	22	14.7
Combined (both male and female)	66 (86)	10	15.1
Total	800 (651	113	14.1

PR=Pregnancy rate

Cervical factor

In case of cervical factor proven by post coital test in presence of normal sperm, COH-IUI success rate can be as high as 51% vs 33% in expectant management. Clinical pregnancy rate in 1st, 2nd and 3rd cycle in such cases is 19.7%, 36.8% and 36.8% respectively.[8]

Endometriosis

For minimal endometriosis, a pregnancy rate of 21% and mild endometriosis 18.9% has been observed. Success rates have been found to be lower with pathological uterotubal function or surgical resection performed even in minimal or mild endometriosis cases.[9]

Unexplained infertility

This is a very tricky and often distressing situation for the patient as well as the clinician as there is no demonstrable cause. The various modalities of treatment available are expectant treatment (planned intercourse with lifestyle changes), ovarian stimulation followed by intrauterine insemination, and in vitro fertilisation.

The ASRM practice committee has published an analysis of the previously available data to study the cost effectiveness of the various treatment options for patients with unexplained infertility.[10] The analysis showed that as the pregnancy rate/cycle increases so does the treatment cost. IVF has been found to be associated with a higher live birth but due to financial, social, or personal reasons the patient might opt for a less expensive and less invasive option.

A Cochrane review by Pandian et al has mentioned that IVF has a higher live birth compared to expectant management, unstimulated IUI and IUI + gonadotropins (pretreated with clomiphene + IUI) but in treatment-naive patients there is no conclusive evidence of difference in live birth between IVF and IUI + gonadotropins/clomiphene.[11]

Hence, treatment needs to be individualised and in such a scenario, IUI can be done to provide patient with the time that they need before moving on to IVF while providing a respectable chance of pregnancy.

Conclusion

Intrauterine insemination can be considered to be a cost effective and non invasive first line fertility enhancing technique with fairly acceptable pregnancy rates. Stringent patient selection criteria and tailor made stimulation protocols with sound semen preparation techniques form the main pillars for successful outcomes in IUI treatment.

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COUNSELLING

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Introduction

Intra uterine Insemination (IUI) is a type of artificial insemination in which actively motile sperms are injected directly into the uterine cavity near the time of ovulation. This procedure can be performed either with partner's sperms or with sperms from a donor. It is considered the first-line treatment for unexplained infertility, mild endometriosis, or mild male factor infertility. IUI may increase the chances of conception of the couple if the patient selection is done correctly. Often couples undergoing an IUI cycle need support and counselling because of the emotional stress they are going through.

Common queries

Couples who decide to opt for fertility treatments, tend to have a plethora of questions and often seek some guidance. Common questions that they tend to ask are

1. What is entire process be like?
2. Will the treatment or any step involved in it have any side effects or risks?
3. Is the decision for going for IUI the correct one?
4. What is the success rate of the procedure?
5. How many times do I need to undergo it?
6. What are the precautions or care we need to take while the cycle is going on?
7. What precautions do we need to take after the procedure is done?
8. What are the finances involved?

During this time proper counselling from the treating doctor and a fertility counsellor can help put at ease the couple and alleviate most of their concerns.

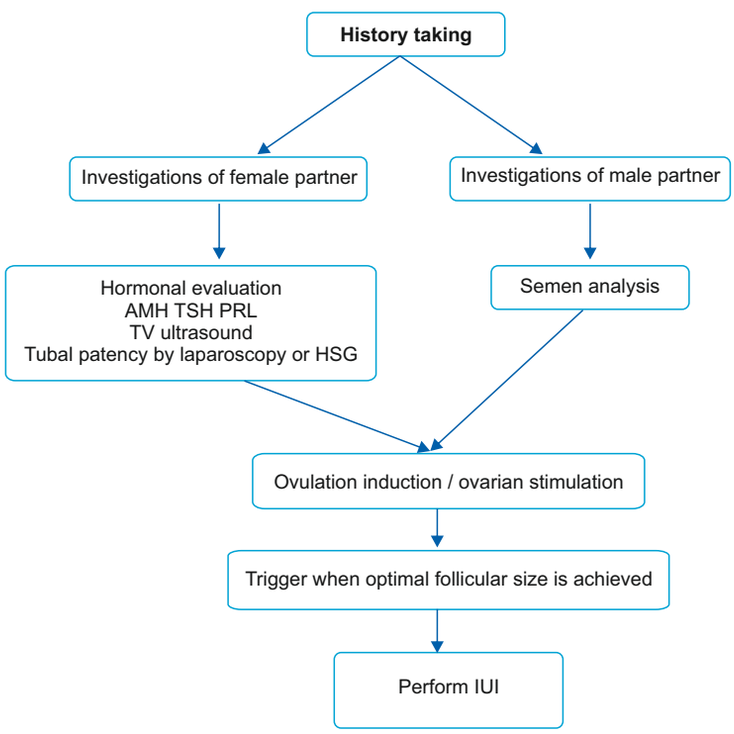
Role of counselling

Counselling sessions help to recognise various psycho-social and emotional problems faced by couples having fertility issues. The counsellors help to resolve their issues by conducting various therapies and counselling sessions. Pre-treatment counselling happens before starting the fertility treatment. The discussion involved in pre-treatment counselling includes:

- Discuss the specific cause of infertility in the couple.
- Discuss why IUI may be beneficial.
- Confirm investigations such as infection screen are done prior to the cycle.
- Talk about couple and disease-specific IUI success rates.
- Explain the day-to-day progress during the cycle and what to expect.
- Specifics of stimulation protocol and adjuvant therapies.

- Couples may get confused about medications and their role during the cycle. Pre-treatment counselling helps them to understand the medical advice given.
- Helps the couple to understand the rights, psychosocial and ethical implications, responsibilities, and any legal considerations to be taken care of.
- The important details and information which the couple is not aware of are also clarified during this session.

Algorithm 1: Typical IUI cycle process



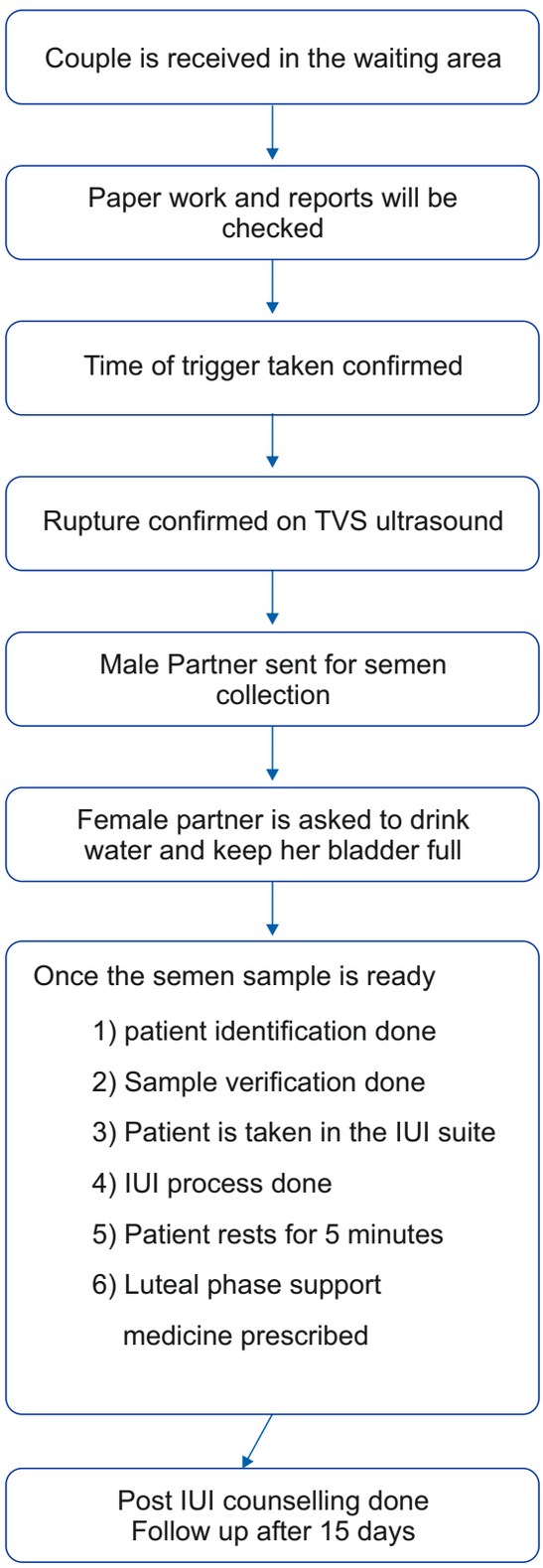
Treatment cycle specifics

While counselling, it is helpful to take the couple through the specifics of the treatment cycle as follows. After a thorough history taking and evaluation when an IUI treatment cycle is advised the treatment cycle is started on day 2/3 of the menstrual cycle. Ovarian stimulation is done with the help of either oral ovulogens or injectable gonadotropins. Regular transvaginal ultrasounds are done to monitor the growth of the follicles.Once the lead follicle reaches a desired size of 18 to 20 mm a trigger injection is given and an IUI is done 36 to 48 hours later.The follicle ruptures around 36 hours after the trigger injection and the egg can survive for about 24 hours.

The IUI can be done 36-48 hours after the trigger injection because the process of capacitation is done in thelaboratory.During the procedure, the male partner is asked to provide a semen sample about an hour or two before being scheduled for insemination. This is done by masturbating into a sterile container at the doctor's office or at home. The semen is processed to separate the sperm from the seminal fluid.

This must be done before the sperm can be injected directly into the uterus so that the success rates are better and because the seminal fluid contains substances that can irritate the uterus. The sample once processed should be inseminated within an hour of preparation.

Algorithm 2: What to expect on the day of the IUI



How does stimulating the ovaries for an IUI process help?

- Increasing the number of eggs available for fertilisation
- Overcoming subtle defects in ovulatory function and luteal phase
- Controlling the timing of ovulation
- We can time the insemination
- Stimulated ovaries come closer anatomically to the fimbrial end of the fallopian tubes hence facilitating egg pick up by the fallopian tube
- May affect tubal vascularity to enhance ovum pick up mechanisms

How does an IUI increase the chances of getting pregnant?

It reduces the effect of factors such as,

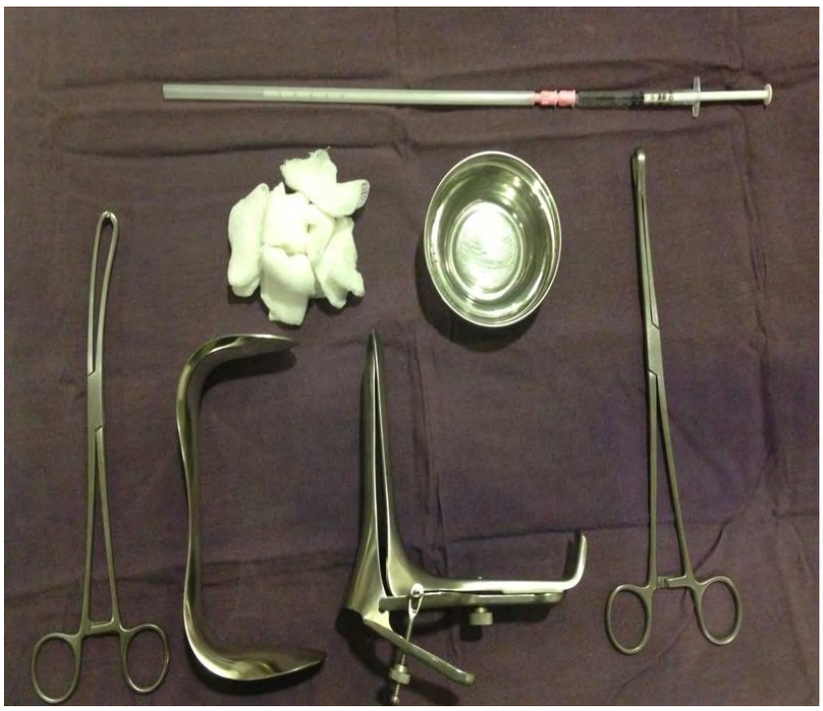
- Vaginal acidity
- Cervical mucus hostility
- Helps deposit good quality motile morphologically normal spermsclose to the oocyte around the time of ovulation
- Sperm wash techniques enhance fertilising capacity of the sperms
- IUI increases the number of sperms reaching the ampullo-isthmic junction

What is the role of semen processing before performing an IUI?

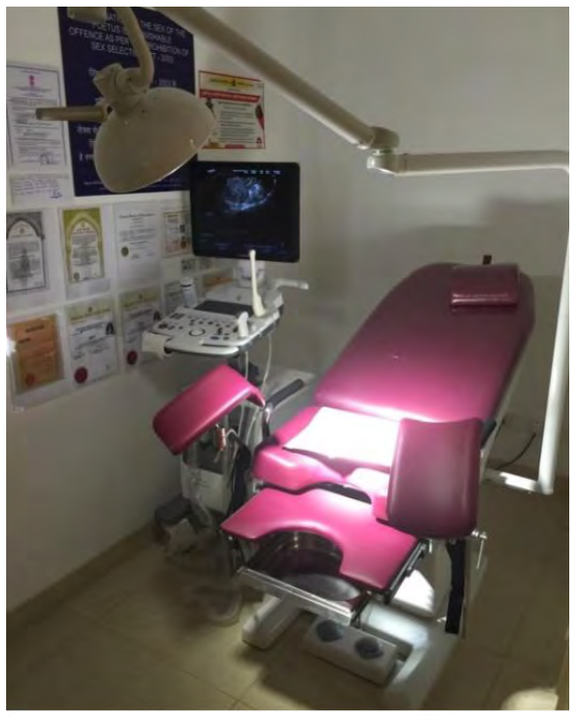
- Getting rid of debris, abnormal sperms, dead sperms, seminal plasma
- Picking up good motile sperms
- In vitro capacitation
- Concentrates the motile sperms into small volume
- Eliminates prostaglandin from the semen sample and thereby does away with any contractions that may occur in the uterus due to the prostaglandin reaction

How is the procedure of insemination performed?

The procedure is ideally carried out in a dedicated insemination room or the theatre with the sterilised instruments laid out on a trolley



A) Trolley set for an IUI process



B) A dedicated IUI suite

- Immediately after semen preparation (within 90 minutes of collection).
- Sample is maintained at 37°C in a test-tube warmer / held in a fist. Can be kept outside at room temperature, but not for long periods.
- Patient is asked not to void her bladder, to help correct the anteversion of the uterus
- Lithotomy position is given
- Cervix is exposed with a Cusco's speculum
- Patient and sample identification is done by the doctor and the embryologist
- Insemination is done with a plastic cannula with or without ultrasound guidance
- Patient is asked to rest for 5 minutes
- Luteal phase support is prescribed for the next 15 days
- UPT or beta hCG test is done after 15 days to confirm the result

What are the average success rates?

It is important to address the issue of average success rates that are currently prevalent at the clinic. The various factors which affect the IUI treatment success rate include:

1. Age of a woman
2. Status of the fallopian tube
3. Semen analysis reports

The average success rate is around 10 to 15%.The age-adjusted success rate is as follows:

10 to 15% if age	<35 years
10% if age	35- 40 years
2 – 5% if age is	40 years or more

Around 80% of the pregnancies occur within the first three IUI cycles. If the couple has not conceived in the first three cycles, they may need to be counselled regarding other advanced treatment options like IVF/ICSI.

Precautions

Since this is a relatively simple and safe procedure, it does not require any special precautions. A few minutes of rest are required after the procedure and then the woman can resume her routine.The woman needs to make sure that she takes her medication during the cycle including the injections and luteal phase support medication as prescribed.

Possible complications

Apart from mild pain and spotting on the day of an IUI, there are no major complications. Around 5-10% couples may land up with twin pregnancies. Very rarely, a patient may respond excessively to the medications and produce more eggs, putting her at risk for multiple pregnancies and a condition called ovarian hyper stimulation syndrome (OHSS). The couple is then advised accordingly and the cycle may be cancelled or converted to an IVF cycle. Infection is a very rare complication.

Conclusions

Most couples need counselling to determine whether IUI is the correct treatment for them or not. It is better to offer patient counselling as part of the process when IUI is offered. A patient clinician or trained counsellor who can show the right direction, answer queries and address couples' issues is of paramount importance.

STIMULATION PROTOCOLS AND CYCLE MONITORING

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Introduction

Intrauterine insemination (IUI) in conjunction with ovulation induction (OI) and ovarian stimulation (OS) has become an important component of infertility treatment. It is a simple, first-line, cost-effective treatment option in couples with oligo/anovulation, cervical, mild male factor and unexplained infertility.

Several drug regimens have been used for controlled ovarian hyper stimulation (COH) prior to IUI; however, there is as yet no ideal stimulation protocol and needs to be individualised on a per case basis. Controlled ovarian stimulation with low-dose gonadotropins and IUI offers significant benefit in terms of pregnancy outcomes compared with natural cycle or timed intercourse, while reducing associated COH complications such as multiple pregnancies and ovarian hyper stimulation syndrome.

Terminology

Ovulation induction is pursued in patients who are not ovulating; the aim is to achieve mono-follicular growth. Superovulation/ Controlled ovarian hyperstimulation is for women who are ovulating but are still infertile; aim in IUI cycles is to recruit maximum of 2 or 3 follicles.

Physiology

A brief review of physiology of follicular recruitment is essential to achieve an effective yet safe stimulation using ovulation induction agents. Falling luteal steroid and inhibin A level in the late luteal phase leads to increase in FSH bioactivity. A certain “threshold” level of FSH is required is required to initiate follicular recruitment. Once this level is achieved, it is maintained for a brief period —the“FSH window”to sustain follicular growth.

With rising estradiol levels there is a negative feedback effect and FSH levels start declining.This allows for selection of the dominant follicle with atresia of the remaining cohort. The wider the FSH window greater is the follicular recruitment. Larger doses of exogenous gonadotropin widen the FSH window leading to recruitment of multiple follicles. Recruitment of not more than three follicles in subfertile patients requires meticulous manipulation of the FSH window.

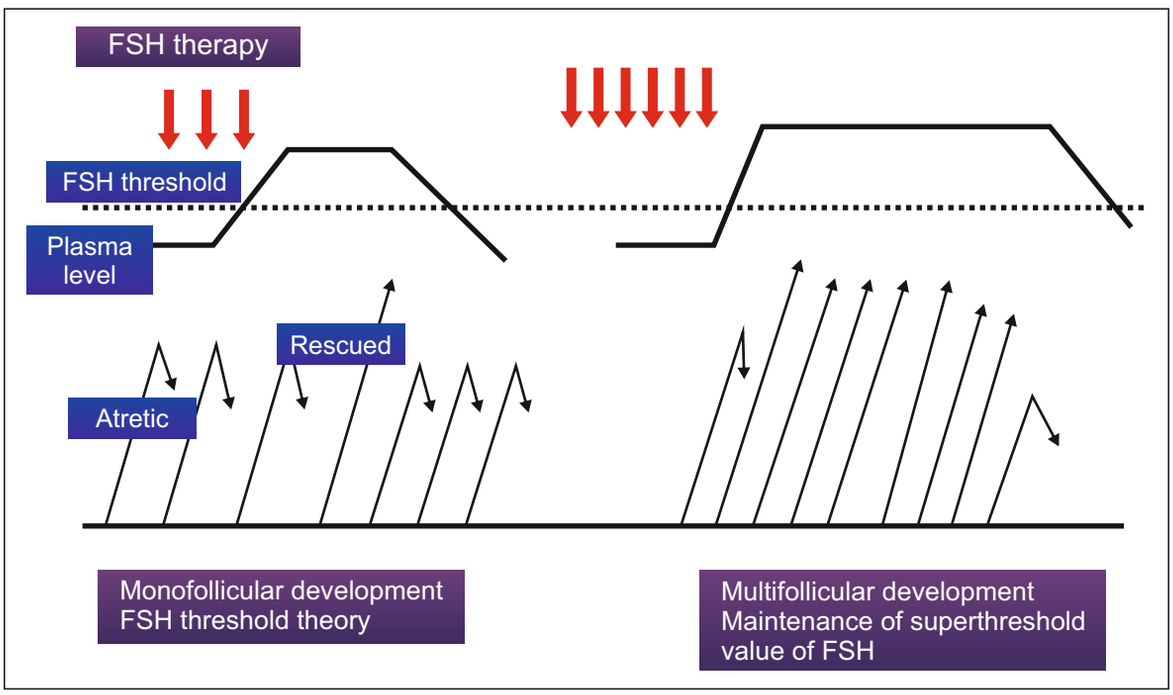

Fig 1 Follicle stimulating hormone (FSH) threshold[1]

Protocols[2]

- Natural cycle – where no agents are used
- Oral ovulation induction agents: Clomiphene citrate/Letrozole/Tamoxifen
- Gonadotropins
- Clomiphene citrate/Letrozole+ Gonadotropins

Clomiphene

Nonsteroidal, SERM agent with both agonist and antagonist site specific action. The mode of action is by binding and depletion of estrogen receptors in hypothalamus, thus reducing negative feedback and leading to 3-4 fold rise in release of pituitary gonadotropins. For five decades, it has been used in doses of 50-100 mg from day 2/3 of menses for ovulation induction with fairly good ovulation rates but poor conception rates.

Letrozole

Third generation aromatase inhibitor, inhibits conversion of androgen to estrogen thus leading to fall in negative feedback and release of pituitary gonadotropins. Main advantages its short half-life [45 hours], monofollicular recruitment due to intact central mechanisms, lower risk of OHSS, lack of antiestrogenic side effects on endometrium. As per the most recent published ESHRE ASRM guidelines, letrozole is the first line treatment for oral ovulation induction in PCOS women.

Recommended regimens include

1. 2.5 to 5 mg/day from day 2/3 of menses for 5 days
2. Single dose of 20 mg letrozole
3. Extended long protocol for 10 days in PCOS: higher ovulation rates in CC resistance
4. Step up protocol: 2.5 mg, 5 mg, 7.5 mg, 10 mg on day 2,3,4,5 respectively leads to multifollicular growth, higher ovulation rates and pregnancy rates in patients with CC resistance.[3]

Novel protocols

Combination of clomiphene 50 mg with letrozole 2.5 mg from day 3 of menses has been proposed as both agents have different actions which complement each other resulting in higher ovulation rates.[4]

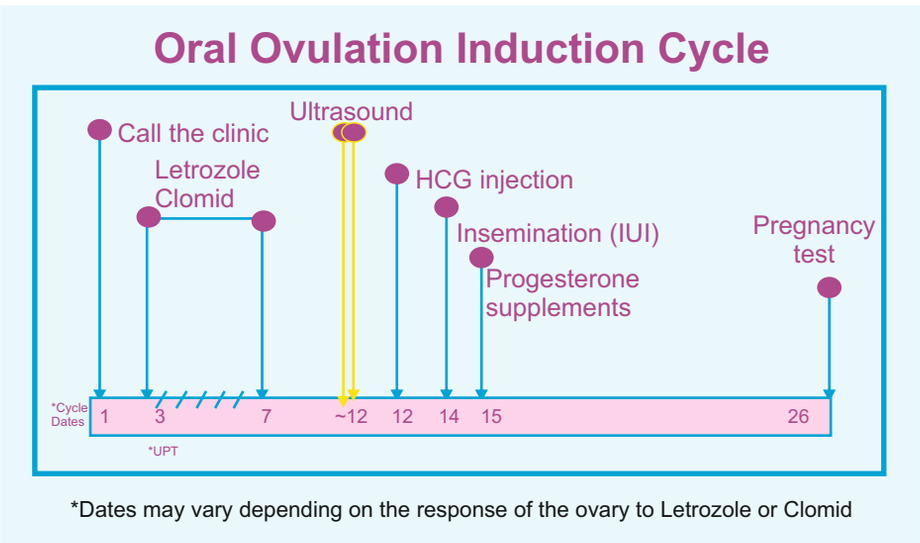

Fig 2 Oral ovulogens for ovulation induction [ASRM Practice Committee 2003]

In clinical practice, IUI should almost never be performed in a pure oral ovulogen cycle as combination protocols with gonadotropins or pure gonadotropin protocols yield better ovulation and conception rates. This is true except in cases of azoospermia with donor IUI cycles, very young patients, BMI <23 and hyper-responders where oral ovulogens alone may be preferred.

Oral ovulogens and gonadotropins

Advantages are cost effectiveness, requires lesser dose of gonadotropinsand endometrium is not adversely affected as in CC cycles.

A study by J Liu et al in 2016 analysed 8,893 cycles of IUI treatment. In ovulatory women undergoing IUI, ovarian stimulation with L and hMG, but not with CC, L, hMG or CC with hMG, significantly improved the pregnancy and live birth rates. Pure gonadotropin stimulation resulted in a higher risk for twins.[5]

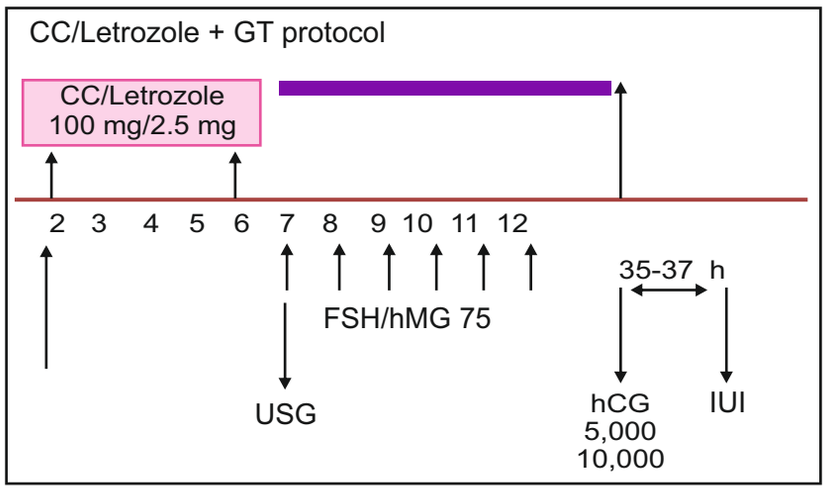

Figure 3 Combination of oral ovulogens and gonadotropins

Gonadotropins

Rationale for their use is to increase the number of oocytes available and increase in steroid production thus increasing the chance of implantation. In a natural cycle the time period for which FSH remains above the threshold value is less resulting in mono follicular development. If the time period for which FSH remains above the threshold value is extended by administering exogenous FSH in the mid-follicular phase, it results in multi-follicular development.

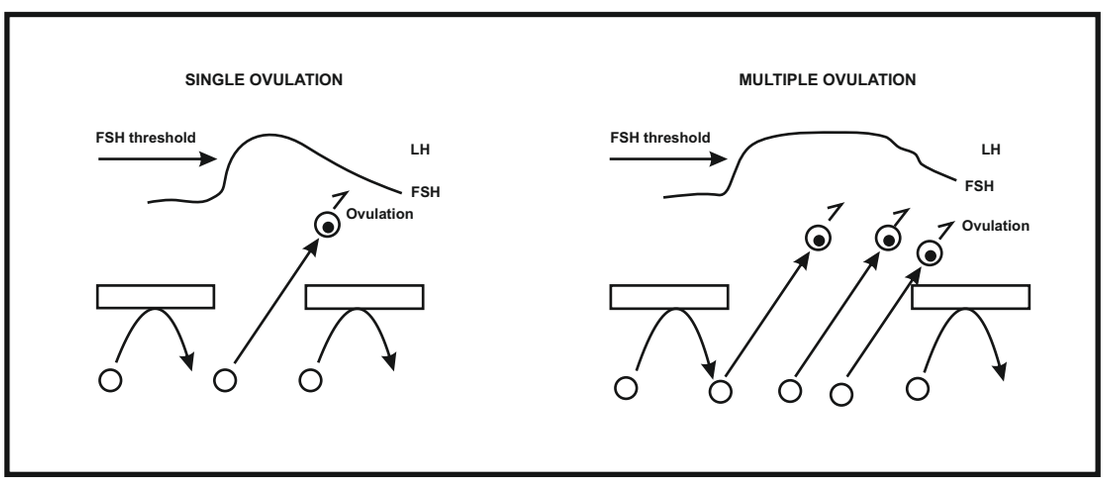

Figure 4 Multifollicular development with change in FSH threshold and window

Pure gonadotropin protocols

While a variety of protocols have been described including the fixed dose, step up, step down and chronic low dose protocols, in IUI treatment cycles the most commonly used and safe option is the fixed dose protocol. In this protocol, a constant daily dose of 75–150 IU of gonadotropins is started from Day 2/3, utilising the same strength throughout the stimulation with USG monitoring.

Chronic low dose step up protocol

With a view to preventing OHSS in hyper-responders, this protocol was devised. The key feature of this regimen is the low starting dose (37.5–75 IU/day) and a stepwise increase only after 7 days, if necessary. With this protocol, it is possible to achieve monofollicular development and prevent multiple pregnancies. However, hyper-responders are best treated by experts, especially where pure gondatropin stimulation protocols are involved.

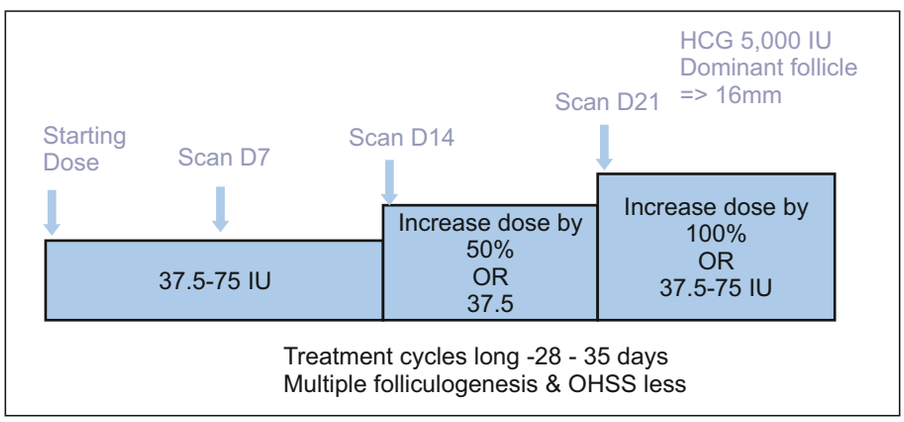

Figure 5 Chronic low dose step up protocol

Salient features

The highest success rates per started cycle and significantly better pregnancy rates per cycle can be achieved with gonadotropins compared to oral ovulogens. While the various preparations available yield comparable success rates, the rates of multiple pregnancies are higher when compared to oral ovulogens.

Cycle monitoring

Follicular monitoring is an absolute essential for any fertility therapy in which ovulation induction is done. This chiefly is about assessing the maturity of the follicle and receptivity of the endometrium to decide the time of ovulation trigger. This can be done by hormonal assessments and/ or ultrasound.

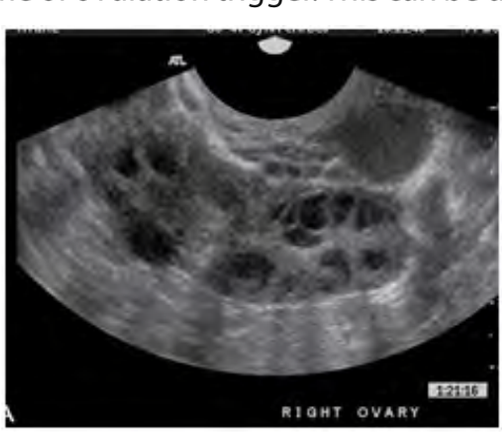

Fig 6 Baseline scan for AFC, ovarian cysts or pathology

Day 2/3 scan: assess the antral follicle count, rule out any ovarian cysts and check if thin endometrium before starting cycle, rule out uterine factors and anatomical defects.

AFC is the sum of antral follicles (2-10 mm) in both ovaries, during a transvaginal ultrasound during the early follicular phase and it helps to define the patient as a normal responder (8-14), hyper-responder (>15) or poor responder (<4). Helps to decide protocol and dose of gonadotropins.

Ovulation induction may be started on Day 2/3 if

1. follicular size is < 10 mm
2. ovarian cysts are absent
3. endometrial thickness<6 mm
4. estradiol level <50 pg/ml and
5. progesterone level <1.5 ng/ml

The ovarian follicles normally grow at the rate of 2-3mm/day once the leading follicle reaches10- 12 mm size. Serial transvaginal ultrasound is performed from Day 7/8/9 onwards. The endometrium is also assessed for thickness as well as echogenicity. A triple line endometrium with thickness of >7 mm is most conducive to pregnancy.

Conclusions

Ovarian stimulation protocols for IUI cycles should be mild. Letrozole is adequate as a first line agent for ovulation induction. For the purpose of multifollicular development essential in IUI cycles, combination of oral ovulogens with gonadotropins or pure gonadotropin cycles work best. Gonadotropin protocols are the most effective, but add to cost, need stringent monitoring, and are associated with increased risk of OHSS and multiple pregnancy.

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GnRH ANALOGUES: UTILITY IN IUI CYCLES

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Background

IUI is a procedure which is often offered to women suffering from infertility resulting from a diverse range of aetiologies. While results vary from one practitioner to another, they are generally in the 7-12% success rate range in large series. Hence, optimisation is essential and one of the methodologies aimed at this is the utilisation of GnRH analogues in IUI cycles. The substitution of the traditional hCG trigger for oocyte maturation by GnRH agonists is one option, while the addition of GnRH antagonists to traditional stimulation protocols is another. In this article, we summarise the current evidence on both these fronts so the reader can make an evidence-based choice as regards the utility of these methodologies in their own daily practice.

GnRH agonists as trigger

In a landmark article in 2014, the Danish investigator Peter Humaidan suggested that the GnRH agonist trigger has helped substitute for the traditional hCG for the final oocyte maturation at the end of the stimulation cycle, resulting in significant reduction or complete elimination of ovarian hyperstimulation syndrome.[1] However, early trials showed a significant consequent luteal phase insufficiency and robust support was required rather than standard luteal phase support protocols. It wasn't long before the GNRH agonist trigger was applied to IUI cycles and we present below a literature review in this context.

MT Le et al from Vietnam in 2018 presented a case series of 197 women randomised to GnRHa trigger (n=98, decapeptyl 0.1 mg 2 vials) vs hCG trigger (n=99, 5,000 IU). The aim was to study the clinical pregnancy rates (CPR) in these two populations. A clinical pregnancy was defined as the presence of gestational sac with fetal cardiac activity. There was no difference in ovulation rates in either group receiving GnRHa or hCG trigger for ovulation. After adjusting for body mass index (BMI) and infertility duration, there was no difference in CPR between the two groups (OR 0.58, 95% CI 0.27-1.25, p = 0.163). They concluded that the use of the GnRHa to trigger ovulation in patients undergoing ovulation induction may be considered in patients treated with IUI and it appears to be equivalent to the traditional hCG trigger.[2]

Table 1 Success rates GnRHa vs hCG

Table 3: Intervention outcomes after adjustment for BMI and infertility duration in GnRHa - and hCG-triggered cycles

Outcomes	GnRHa-triggered cycles (n=98)	hCG-triggered cycles (n=99)	p value
Ovulation rate	OR 0.56 CI: 95% (0.23-1.38)		0.207
Biochemical Pregnancy rate	OR 0.47 CI: 95% (0.23-0.98)		0.044
Clinical pregnancy rate	OR 0.58 CI: 95% (0.27-1.25)		0.163

GnRHa : gonadotropin receptor hormone against; hCG human chorionic gonadotropin

R Taheripanah et al from Iran in 2017 performed an RCT on 110 infertile women comparing 0.1 mg GnRHa (Group I) vs 10,000 IU hCG (Group II). They measured E2, FSH and LH 12 and 36 hours after injection. An LH surge was detected in all patients. LH levels at 12 and 36 hr after triggering were higher in Group I and were washed out earlier than group II. The pregnancy rate was higher in Group I, but the difference was not statistically significant (26.9% vs. 20.8%, respectively p=0.46). Also, the incidence of ovarian hyperstimulation syndrome was not different between the two groups (p=0.11). There was a significant difference regarding the estradiol levels at 36 hours after triggering (p=0.00). They concluded that the effects of GnRH on endogenous LH surge is sufficient for oocyte releasing and final follicular maturation. Pregnancy rates and ovarian hyperstimulation syndrome incidence were similar and suggested that GnRH agonists might be used as an alternative option instead of hCG in IUI cycles.[3]

Tables 2 and 3 Clinical characteristics GnRHa vs hCG

Table I. Demographic data of GnRH-agonist versus HCG in IUI cycles among infertile patients

Variable	Groups		p-value
	GnRH-a (n=51)	HCG (n=53)	
Mean Age (years)	29.4 ± 4.3	29 ± 3.9	0.58
Mean Clomiphene number	13.7 ± 2.9	13.6 ± 2.2	0.82
Mean rFSH number	8.9 ± 3.7	7.4 ± 1.8	0.01
Mean BMI (Kg/m^2)	23.3 ± 3.2	23.9 ± 3.9	0.24
Mean FSH base (mIU/ml)	7.5 ± 1.9	6.8 ± 1.5	0.12

Data are presented as Mean ± SD. Independent t-test was used.
rFSH: recombinant Follicle-Stimulating Hormone BMI: Body Mass Index HCG: Human Chorionic Gonadotropin
GnRH-a: Gonadotropin Releasing Hormone-agonist FSH: Follicle-Stimulating Hormone

Table II. Hormonal and follicular monitoring of GnRH-agonist versus HCG in IUI cycles among infertile patients

Variable	Group		p-value**
	GnRH-a (n =51)	HCG (n=53)	
Mean Ro follicles (No)*	5 ± 3.70	4.5 ± 3.00	0.45
Mean Lo follicles (No)*	4.30 ± 3.30	4.7 ± 2.00	0.58
Mean Trigger day (No)*	13.10 ± 1.30	14.40 ± 1.40	0.51
Serum LH 12 hr (mIU/ml)*	64.16±26.95	40.15 ± 13.75	0.00
Serum FSH 12 hr (mIU/ml)*	33.10 ± 11.25	17.99 ± 5.25	0.00
Serum Estradiol 12 hr (pg/ml)*	1119.93 ± 600.25	1206.69 ± 809.77	0.53
Mean Serum LH 36 hr. (mIU/ml)*	11.92 ± 6.01	15.52 ± 6.14	0.00
Mean Serum FSH 36hr (mIU/ml)*	11.07 ± 6.27	11.24 ± 3.88	0.87
Pregnancy Rate (%)*	14 (26.9%)	11 (20.8%)	0.46

Data are presented as Mean ± SD. ** Independent t-test.
LH: Luteinizing Hormone HCG: Human Chorionic Gonadotropin
GnRH-a: Gonadotropin Releasing Hormone-agonist
Ro: Right Ovary and etc Lo: Left ovary FSH: Follicle-Stimulating Hormone

A recent study published 2019 by Li M et al included 341 couples seeking for their first or second IUI cycle from July 2016 to June 2018in Zhejiang. Ovulation was triggered by hCG 10,000 IU in 154, by 0.1/0.2 mg triptorelinin 94 cases and by hCG combined with triptorelinin in 93 cases. The primary outcome was clinical pregnancy rate and ongoing pregnancy rate beyond 28 gestational weeks, secondary outcomes included biochemical pregnancy, miscarriage rate, ectopic pregnancy rate and multiple pregnancy rate. Their results showed no significant difference in between the three groups.[4]

A prospective observational Indian study by Bathwal S et al published 2018 studied 631 women with unexplained infertility and follicular-endometrial asynchrony (follicle ≥ 18 mm, endometrial thickness (ET) < 7 mm) in previous two failed clomiphene/IUI cycles. 76 patients with persistent issues were excluded and the remaining women (n=555) were divided into two groups: Group A (n=285) received GnRHa and Group B (n=270) received hCG ovulation trigger. Finally, 513 patients who underwent IUI were analysed.Cancellation due to luteinised unruptured follicle was more in hCG group (p=0.01). Higher clinical pregnancies (10.33 vs. 4.96%, p=0.03) and live birth rates (8.86 vs. 4.13%, p=0.03) were noted with GnRHa trigger. Miscarriage rate was comparable in both the groups (10.71 and 16.67% respectively).[5]

In conclusion, while the majority of international publications support the use of the GnRHa trigger for final follicular maturation and demonstrate non-inferiority versus the traditional hCG trigger, one large publication from India has shown better clinical pregnancy rates and live birth rates with the GnRHa trigger. Similar large volume data from other studies is still awaited.

GnRH antagonists in IUI cycles

GnRH antagonists have traditionally been added to conventional ovarian stimulation protocols for IUI with a view to postponing ovulation trigger and avoiding work on the weekends. In more recent times, they have also been used as an agent to allow greater number of follicles to mature, postponing ovulation and IUI with a view to enhancing IUI success rates.

In one of the largest series of its kind, 4,782 inseminations were performed in 1,650 women at Valladolid University Clinic in Spain between January 2007 and December 2015. Of these, 911 IUIs corresponding to 695 women would have fallen on the weekend. When a member of the Reproduction Unit was available (n=685, control group) IUI was performed as planned and when not available (n=695), IUI was postponed using 0.25 mg GnRH antagonist.

There were no differences in the clinical pregnancy rate (13.7 vs. 16.2 %, p = 0.371) or in the ongoing pregnancy rate between groups (11.9 vs. 14.9 %, p = 0.271). The multiple pregnancy rate was also comparable in both groups (14.7 vs. 18.5 %, p = 0.77). They concluded that women with a planned IUI which cannot be performed at the ideal date can be offered postponement for two days with the support of GnRHa treatment, with results that are not inferior to those expected applying the regular protocol.[6]

Table 4 GnRH antagonist to postpone IUI vs control group

Table 1 Results of IUI in the study group receiving GnRHa to bridge the weekend (n=226, with IUI on Monday, and the control group (n=685), with IUI during the weekend as scheduled

	Study group	Control group	*p*-value
Age (years)	33.4±2.8	33.2±3.1	0.614
total rFSH per cycle	696.2±295.5	596.5±304.4	<0.001
Duration of stimulation (days)	10.3±2.8	8.4±2.8	<0.001
n follicies 14-17 mm	1.4±0.9	1.2±1.2	0.031
Endometrial thickness (mm)	9.0±2.1	9.2±3.3	0.554
Mobile sperm count (million)	14.5±12.5	15.6±13.3	0.230
Medication expenses	452.72±157.60	303.22±132.93	<0.001
Clinical pregnancy (%)	31 (13.7%)	111 (16.2%)	0.371
Clinical pregnancy OR	0.78 (0.49-1.22)		
Ongoing pregnancy (%):	27 (11.9%)	102 (14.9%)	0.271
Ongoing pregnancy OR	0.82 (0.53-1.26)		

A Turkish group led by R Ozelci published their results in 2018. A total of 175 IUI cycles in women with PCOS were included. Women in the control group (n=87) underwentcontrolled ovarian stimulation (COS) with recombinant follicle stimulating hormone (r-FSH) only, whilewomen in the study group (n=88) were administered r-FSH plus cetrorelix.

The mean values of luteinising hormone and progesterone on the day of hCG administration were statistically significantly lower in patients receiving GnRHantagonist than the control group (p=0.002). Premature luteinisation occurred in only one of the patientsin the GnRH antagonist group (1.1%) and in 15 of the 88 cycles in the control group (17.2%),showing a significant difference between the two groups (p=0.001). The clinical pregnancy rate percycle was higher in GnRH-antagonist group compared to the control group but the difference did notreach statistical significance (25 vs 14.9%, p=0.096). They concluded that adding GnRHantagonist in COS/IUI cycles in women with PCOS resulted in a lowerincidence of premature luteinisation but did not improve pregnancy rates.[7]

An Indian RCT conducted by Kamath MS et al in 2013 studied 141 patients divided into 70 (Group A GnRH antagonists) and 71 (Group B control arm). The incidence of premature LH surge and premature luteinisation was lower in the antagonist group as compared to the control group (5 vs. 10.3%, p=0.45 and 5 vs. 13.8%, p=0.31) but not statistically significant. The clinical pregnancy rates were lower in the antagonist group (2.8 vs. 10%, p=0.12), which was also not statistically significant.They concluded that the addition of GnRH antagonist during controlled ovarian stimulation and intrauterine insemination cycles does not lead to improvement in clinical pregnancy rates.[8]

A meta-analysis of 12 studies with 2,577 cycles published in 2014 suggested that GnRH-ant can significantly increase CPR(OR=1.42; 95% CI, 1.13–1.78) and decrease the premature luteinisation (PL) rate (OR=0.22, 95% CI, 0.16–0.30) in COS/IUI cycles. Subgroup analysissuggested statistically significant improvement in the CPR in non-PCOS patients (OR=1.54; 95% CI, 1.03–2.31) butnot in the PCOS population (OR = 1.65; 95% CI, 0.93–2.94) and multiple mature follicle cycles (OR=1.87; 95% CI, 0.27–12.66).There were no differences in the miscarriage and multiple pregnancy rates between the groups.[9]

Fig 1 Forest plot comparing CPRs in GnRH antagonist to control group

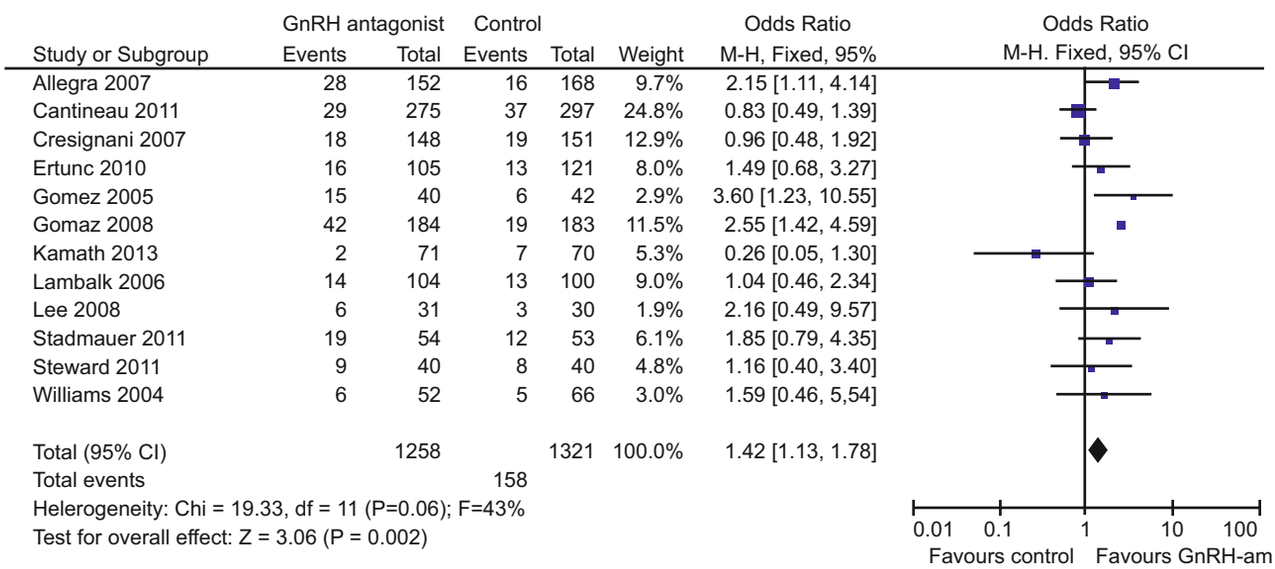

Figure 2. Forest plot of odds ratios (Ors) and 95% confidence interval (CI) of pooled trials comparing GnRH antagonist and control for clinical pregnancy rate.
doi; 10.137/journal, pone.0109133,g002

In conclusion, there is robust evidence to now support the use of GnRH antagonists to prevent premature luteinsation, postponement of IUI over weekends by two days, and for enhancement of clinical pregnancy rates in IUI cycles. There is as yet insufficient evidence whether their use decreases miscarriage rates and regarding the incidence of multiple pregnancies which appear to be similar to control groups.

Conclusions

GnRH analogues are a class of drugs which are more readily available and easily accessible to all of us in modern practice. While the GnRH agonist trigger has been shown to be non-inferior to the traditional hCG trigger, GnRH antagonist use has been more widely embraced with most studies demonstrating better clinical pregnancy rates or similar success rates even after postponing ovulation for two days over the weekend.

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SEMEN PROCESSING TECHNIQUES

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Introduction

The human ejaculate consists of the seminal plasma, spermatozoa, non-specific debris, microorganisms and other non-reproductive cells. The seminal plasma provides nutrition to the spermatozoa that helps the sperm penetrate and pass through the cervical mucus. However, it also contains harmful substances like zinc, prostaglandins that may interfere in the fertilisation,thus hampering the pregnancy results.

The aim of the semen preparation/ processing techniques is to separate the motile, morphologically normal, most fertilisable sperm from the surrounding milieu containing debris, other non-germ cells and dead sperms for assisted reproductive techniques. The basic sperm preparation techniques include – sperm dilution and centrifugation, swim up and density gradient technique for sperm preparation.

Which technique?

The selection of the technique for the processing of the semen sample is decided as per the semen parameters. The absolute sperm count, the number of motile sperms, percentage of the morphologically normal sperms in the semen sample are used to assess the efficiency of the procedure. Lower recovery of motile sperms is seen in the swim up technique in comparison of the density gradient technique.

The direct swim up technique is used for the normozoospermic semen samples, whereas the density gradient is preferred in case of severe oligozoospermia, teratozoospermia or asthenozoospermia. Density gradients can be altered according to the individual samples to optimise the results.

For samples with high viscosity, the centrifugation time may be increased. When the sperm count is extremely low, the centrifugation time and the force should be modified so as to get the maximum number of sperms.All the laboratories and the embryologists handling the samples should individually identify the centrifugation time and force to attain a manageable sperm pellet.

General principles

Simple sperm preparation techniques are described in the following sections. Preparation methods that do not use centrifugation are in general advantageous. A normal ejaculate contains a large number of defective spermatozoa and granulocytes which on centrifugation 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 collection

1. The collection jar should be sterile and non-toxic.
2. Name of the partner/husband should be written on the lid as well as the side of the container. This writing has to be done in front of the partner, in order to avoid mix up.
3. Sample to be collected on the premises, ideally.
4. Volume, viscosity, presence of other cells should be noted.
5. Allow sperm sample to liquefy for 20 minutes. If it does not, pass it through a 23-gauge needle.
6. A drop of semen is put on Makler chamber and examined under a microscope. The number of sperm in ten squares on the chamber grid is the count in million/ml.
7. The number of motile sperms in the same squares is counted and percentage of motility noted.

Sperm preparation

Four conventional methods are available:

1. Direct swim up
2. Pellet and swim up method
3. Density gradient
4. Iso care – one step

Direct swim up

1. Take a 10 ml round bottom plastic test tube and label it.
2. Pipette 2ml of culture medium.
3. Gently pipette 1.5ml of neat semen underneath the medium.
4. Cap the test tube and put in an incubator for 30minutes – 1 hour.
5. Pipette the top layer and cloudy middle layer of supernatant and discard the rest.
6. Supernatant used for IUI after checking the count and motility.

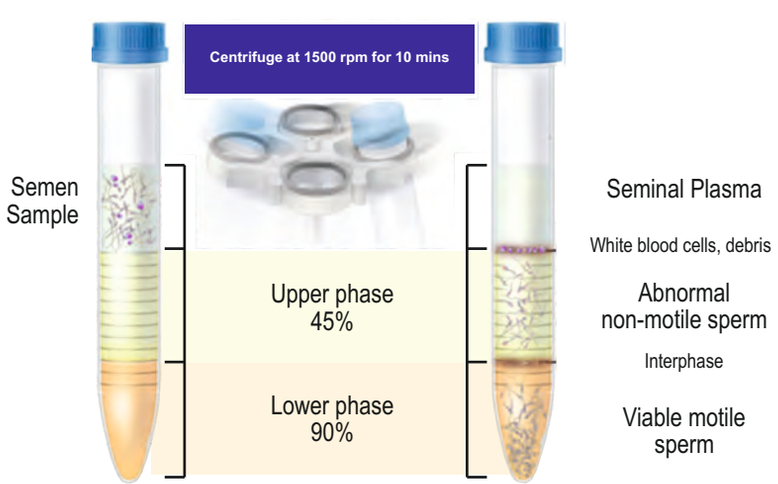
Pellet and swim up

1. Take one drop and put it on Makler Chamber for count and motility.
2. Take 2 test tubes, label them, put 1ml sperm sample in each.
3. Add 2ml flushing media in each tube and mix.
4. Centrifuge for 10 minutes at 1500 rpm.
5. Aspirate out the supernatant.
6. Gently layer the pellet with 1ml flushing media/culture media and place the tubes in the heating block or container, then place the block in a heater or incubator.
7. After 30-40 minutes remove 0.5ml of the supernatant from each tube to make it 1ml and put it another clean tube.
8. Determine the count and motility of the supernatant on the Makler chamber.
9. The supernatant is used for intra-uterine insemination.

Advantages: simple, easy to perform and cost effective.

Disadvantages: Restricted to normal or marginally normal semen samples.It cannot separate the morphologically normal sperms from the abnormal ones.Some sperms may get trapped in the pellet if the pellet is concentrated.Centrifugation produces reactive oxygen species which cause damage to the plasma membrane of the sperm and damage the sperm DNA.

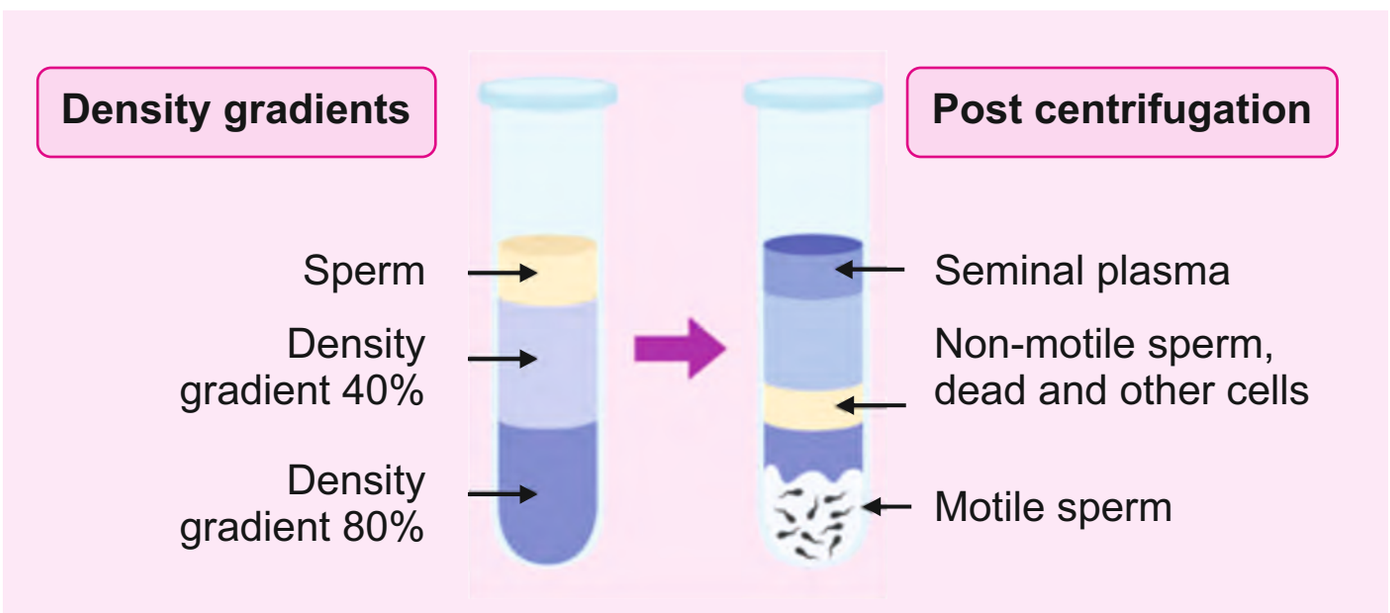
Fig 1 Swim up technique



Density gradient

1. Allow the sperm sample to liquefy for 20 minutes. If it does not, then pass it through a 23-gauge needle.
2. Take one drop and put it on the Makler chamber to measure the sperm count & determine the motility.
3. Take two test tubes and label them with patient ID.
4. 1ml of 90% sperm gradient is layered in each conical tube with a sterile pipette.
5. 1ml of 45% sperm gradient is then gently layered on top of it with another sterile pipette.
6. 1-2ml of sperm sample is then gently layered on top of the two layers. Care is taken not to add too much sample as it results in poor separation.
7. Without disturbing the layers, the tubes are centrifuged at 300g (1500 rpm) for 20 minutes.
8. The supernatant is then pipetted out and discarded leaving the pellet with as little of the 90% solution as possible.
9. Take a new test tube and add 5-10ml of flushing medium to it and transfer the pellet to this tube.
10. It is then centrifuged at 300g for 10 minutes. The supernatant is pipetted out and discarded. Add 5ml media and repeat this step.
11. For samples with good motility, a swim up procedure is now carried out in a 6ml test tube, the pellet is layered with 1ml culture medium and incubated for 30 minutes in a CO_2 incubator. The upper layer is carefully pipetted out in another clean test tube.
12. For samples with poor motility, the pellet is gently layered with 0.8ml culture medium and incubated for 60 minutes. The supernatant is carefully pipetted out in a clean test tube.
13. Alternately, the pellet is resuspended in 0.5-1ml of culture media or flushing media.
14. It is then checked for motility and concentration and is ready for IUI.

Fig 2 Density gradient technique



Microfluidics

This refers to the behaviour of the fluid constrained in a small space at which the capillary penetration governs the transport through the microchannels made up of sub millimeters. Microfluidics is a technology that utilises the micro manipulation of the semen sample through microchannels of micrometers which in turn helps in sorting the morphologically normal, highly motile sperms from the sample. It relies on the various variables like the fluid density, viscosity, velocity and geometry of environment.

Various types of microfluidic devices are available for use. After sperm sorting, the sorted sperm is then analysed by strict Kruger criteria and used for IUI. This method has given promising results in male factor infertility. However, more randomised controlled trials are required for the same.

Advantages

1.This method is beneficial as it removes the sperm damage associated with sperm washing, swim up and gradient centrifugation techniques.

2. It exhibits less damage to the sperms in terms of DNA fragmentation, ROS levels and has better sperm morphology.

3.The risk of contamination is low as preprocessing is not required.

4. It is simple to use, does not require extensive training and provides the excellent sorted sample within 30 minutes.

Magnetic assisted cell sorting (MACS) device

It is a novel method that separates the sperm by density gradient and molecular filtration that helps in differentiating the apoptotic sperms, associated with DNA damage.It has been observed that phospholipid phosphatidylserine is one of the early markers of apoptosis, and this phospholipid is known to have high affinity for annexin V. Annexin V, conjugated with magnetic microspheres when exposed to a magnetic field in an affinity column can separate apoptotic from non-apoptotic sperms.

Conclusions

Various semen processing techniques are now available to us which have evolved over a period of time. Utilising the appropriate method for any given sample is where the embryologist and clinician's expertise is of paramount importance. Besides being able to segregate the best quality, highly motile and morphologically normal sperm, these techniques not only enhance success rates in IUI but also indirectly help to reduce the chances of fertilisation with abnormal sperm, fetal aneuploidies and early first trimester losses.

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INSEMINATION PROCEDURE

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Introduction

The deposition of spermatozoa in the uterus at any point above the internal os is considered as intrauterine insemination or IUI. While the procedure is fairly straightforward, appropriate care and attention to detail is essential to achieve good and consistent results with IUI.

Procedure specifics

1. Proper cleaning and sterilisation of equipment. Avoid chemicals in the procedure room.
2. Treatment of vaginal infections in previous cycle.
3. IUI room preferably to be next to the laboratory where the sample is being processed.
4. The time interval between sample collection and insemination should preferably not be more than one hour.
5. Sterile disposable plastic gloves preferred as powder used with latex gloves can be toxic.
6. Cervix to be exposed with Cusco's Speculum or Sim's speculum with anterior vaginal retractor. Try to avoid holding the cervix with a sharp instrument or tenaculum forceps.
7. Prepare vagina with normal saline (preferably warm saline). Avoid using Savlon, betadine or any disinfectant as it will harm the sperms.
8. Flush the IUI cannula with flushing media to wash away any toxic factors.
9. The IUI cannula has to be loaded properly to avoid dead space, which can be as much as 0.5 ml. Attach the canula to the 1ml BD Syringe and load the sample from the falcon tube by dipping the cannula into the prepared sample.
10. Minimum handling of the cervix is ideal. Generally, it is quite easy to negotiate the cervical canal. However, in case of difficulty, the anterior lip of the cervix may be held with a vulsellum or Allis' forceps. Care has to be taken not to close the clamp, as it would cause release of prostaglandins, causing pain and uterine contractions. The main purpose of the instrument is to only straighten the cervical canal, especially in case of an acutely anteverted uterus.
11. In some cases where it is difficult to negotiate the canal, one may use more rigid cannulas like the Makler cannula or even an embryo transfer catheter. Lastly, one could also use a steel curved canula with a bullous tip which could be easily negotiated through the cervix. In case of this, one should flush the canula several times with distilled water, dry it with compressed air and then send it for sterilisation.

12. Normal insemination volume is 0.5 to 1 ml. Good results have been observed with the inseminate having more than 5 million sperms, but a minimum concentration of 1 million motile sperms is essential.
13. Deposit the inseminate slowly over a period of 1 to 2 mins. After the deposit, the canula is withdrawn slowly to prevent gushing out of the inseminate.
14. In spite of slow withdrawal, one may see the inseminate coming out of the cervical canal. If this happens, one can give a steep head low position.
15. Once the procedure is completed, the speculum may be removed, head low is given and patient is kept in this position for 15 mins. Thereare better results with significant difference in ongoing pregnancy rates highlighting the importance of immobilisation for 15 mins after IUI.
16. Luteal phase support is important in deciding the outcome and will be covered in another article. Normally one of the following protocols is used
17. Antibiotic coverage is controversial and not generally recommended.

Laboratory and procedure related factors

1. Setting up a proper lab with good quality control is of prime importance.
2. Standardised equipment -a good centrifuge machine and a CO2 incubator.
3. The ideal cannula should be easy to use, semi-rigid so as to easily negotiate the cervical canal, made of non-toxic materials like Teflon, small intra-cannula volume to minimise dead space, rounded tip to minimise trauma.
4. Technique of insemination -use warm saline, strict asepsis, minimal handling of cervix, cervical mucus removal and minimal trauma to the endometrium.
5. Selecting proper sperm processing technique is recommended.
6. Maintaining good air quality - Air conditioners, HEPA filters, medical grade CO2 and laminar air flow.
7. Readymade standardised culture media.
8. Use disposable, sterile and toxicity tested semen containers, tubes and pipettes.
9. Avoid major chemicals like methyl alcohol, formalin, powdered latex gloves etc.
10. Cleaning the laboratory surfaces with 70-100 % ethyl alcohol or isopropyl alcohol is recommended.

Conclusion

It is becoming more apparent that IUI if practised efficiently can provide good pregnancy rates to the over 74 million couples worldwide, all of who may not have access to the complex and costly IVF treatments. Clinics should maintain records, create a database to allow realtime monitoring of their own progress. The biggest determinant of success is the clinical management of the patient and properly optimised IUI cycle.

LUTEAL PHASE SUPPORT

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Background

The utility of luteal phase support (LPS) has been extensively studied in a variety of clinical scenarios including – but not limited to – modified natural cycles, IVF/ICSI, recurrent miscarriages and so on. The overwhelming evidence has been in favour of implementing some form of luteal phase support with progesterone in IVF/ICSI cycles and patients with recurrent losses.

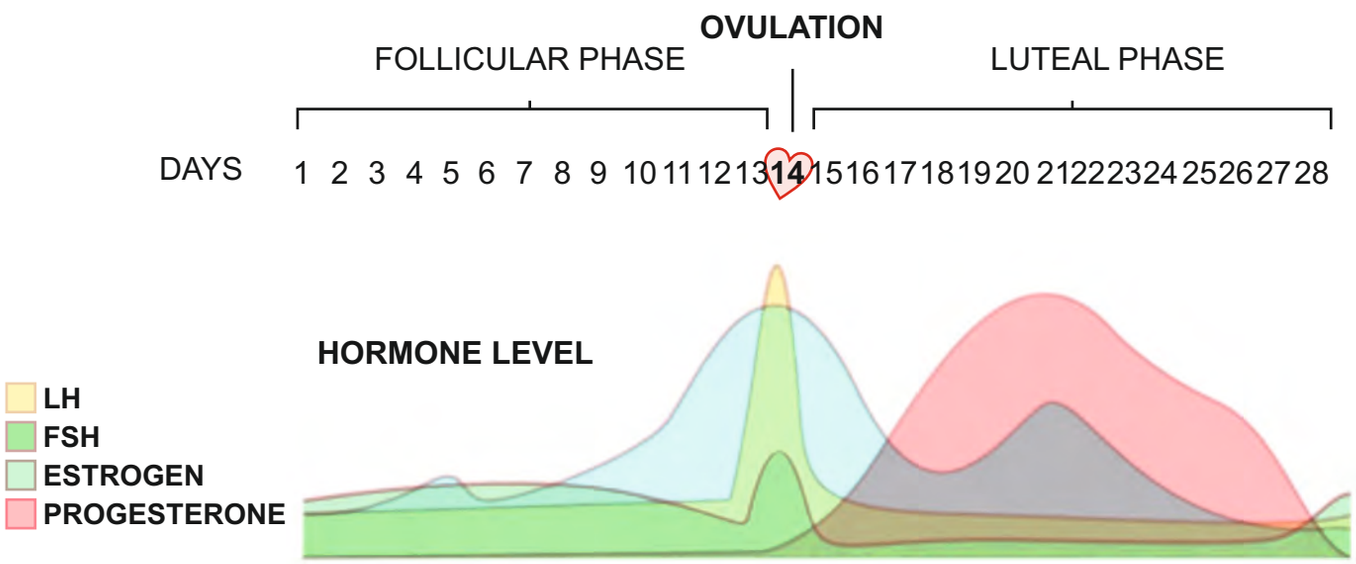
However, the evidence for luteal support with progesterone and other agents in clomiphene cycles, clomiphene + gonadotropin stimulated cycles and treatment-naïve patients is as yet unclear. We present a review of the literature as it stands vis-à-vis IUI and luteal support with some practical considerations at the end.

The rationale for progesterone

When we analyse the normal menstrual cycle, it is well known that an LH surge is needed for oocyte maturation and follicular rupture. It is also similarly well known that progesterone produced by the corpus luteum is needed to support an early pregnancy and implantation. Progesterone regulates the secretory transformation of the endometrium during the luteal phase. In order for progesterone receptors to diffuse, a sufficient amount of estrogen is also needed. In all cycles with multifollicular development, the supraphysiological estradiol levels block the hypothalamo-pituitary-ovarian axis with negative feedback. Therefore, LH levels are erratic and corpus luteum function function does not occur; leading to inadequate progesterone levels.[1]

An analysis of the available observational studies has revealed that the luteal phase in gonadotropin-stimulated cycles is 20% shorter and patient groups receiving LPS have significantly higher levels of mid-luteal progesterone than those receiving no support. Also, ovarian stimulation and multifollicular development are associated with abnormal endometrial progression during the early luteal period in almost 50% of cases.[2]

Fig 1 Hormonal fluctuations during the menstrual cycle



Clomiphene only cycles

Way back in 2010, the Belgian group led by Human Fatemi and Prof Devroey questioned the empirical usage of progesterone in clomiphene stimulated IUI cycles. They performed a prospective randomised controlled trial at a tertiary referral centre to assess the effect of intravaginal micronised progesterone as luteal support on the probability of ongoing pregnancy in patients stimulated with clomiphene citrate for IUI. Normo-ovulatory women ≤ 36 years of age undergoing ovarian stimulation with clomiphene citrate (50 mg) for IUI (n=468) were randomised either to receive luteal phase support (n=243) in the form of vaginal micronised progesterone in three separate doses (200 mg 3 times a day), or to a control group who did not receive luteal phase support (n=225).

No difference was observed in ongoing pregnancy between both groups of patients who did, or did not receive vaginal progesterone as luteal support [8.7 vs 9.3% p=0.82; 95% CI: -6.4, 5.2]. Additionally, the early pregnancy loss rate did not differ between groups (1.5 vs 2%,p=0.78, 95% CI: -3.6, 2.7). They concluded that routine supplementation of the luteal phase with vaginal progesterone does not seem to improve pregnancy rates in normo-ovulatory women stimulated with clomiphene citrate for IUI.[3]

As a corollary, this well constructed study also demonstrates why IUI cycles should not be initiated using clomiphene alone for ovulation induction since the results are so abysmally poor.

Gonadotropin stimulated cycles

Peeraer, D'Hooghe et al in 2016 reported in Fertil Steril a multicentric trial with 339 normo-ovulatory patients <43 years, with body mass index ≤30 kg/m2, in their first IUI cycle with at least one patent tube, a normal uterine cavity and a male partner with total motile sperm count ≥5 million after capacitation. They were stimulated with gonadotropins and after IUI were randomised to LPS using vaginal progesterone gel (n=202) or no LPS (n=191).

The primary outcome - clinical pregnancy rate, was not statistically different between the treatment group and the control group ((16.8 vs 11%) (RR 1.54; 95% CI, 0.89-2.67). Similarly, the secondary outcome, the livebirth rate, was 14.9 vs 9.4% (RR 1.60; 95% CI, 0.89-2.87). The mean duration of the luteal phase was about 2 days longer in the treatment group (16.6 ± 2.2 days) compared to the control group (14.6 ± 2.5 days) (mean difference 2.07; 95% CI, 1.58-2.56).
The investigators concluded that a trend toward a higher clinical pregnancy rate as well as live-birth rate was observed in the treatment group but the difference was not statistically significant.

An updated systematic review and meta-analysis of 11 trials involving 2,842 patients undergoing 4,065 cycles was published in 2017. In patients receiving gonadotropins for ovulation induction, clinical pregnancy (RR 1.56, 95% CI 1.21-2.02) and live birth (RR 1.77, 95% CI 1.30-2.42) were more likely in P supplemented patients. Similar findings persisted in live births per IUI cycle (RR 1.59, 95% CI 1.24-2.04). There was no benefit on clinical pregnancy with P support for patients who underwent OI with clomiphene (RR 0.85, 95% CI 0.52-1.41) or clomiphene plus gonadotropins (RR 1.26, 95% CI 0.90-1.76).

The researchers concluded that progesterone luteal phase support is beneficial to patients undergoing ovulation induction with gonadotropins in IUI cycles. The number needed to treat (NNT) is 11 patients to have one additional live birth. Progesterone support did not benefit patients undergoing ovulation induction with clomiphene citrate or clomiphene plus gonadotropins.[5]
In the Indian scenario, progesterone support has been extensively empirically prescribed even for patients with clomiphene-IUI and clomiphene plus gonadotropin-IUI cycles.

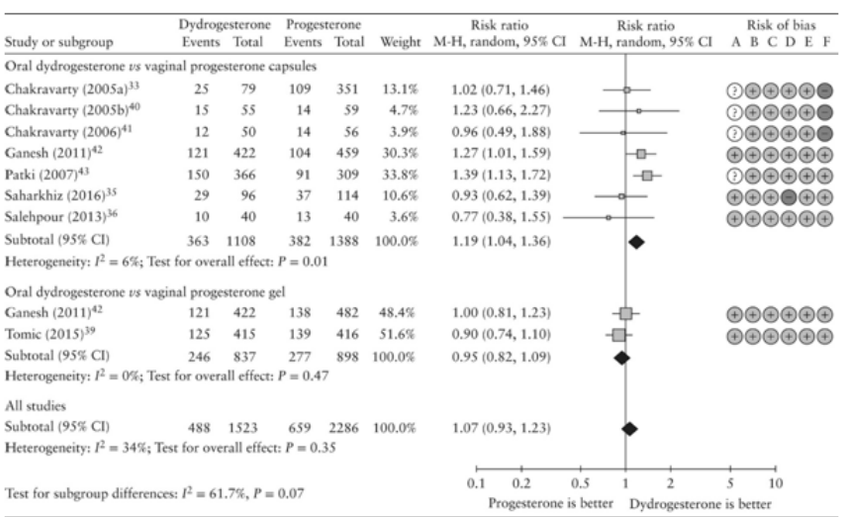
Vaginal or oral progesterone?

A study by at Turkish group published Jan 2020 evaluated vaginal micronised progesterone vs oral dydrogesterone in 432 patients with unexplained infertility stimulated with rFSH and who underwent IUI. Dydrogesterone was used in 233 participants (54%) and 337 cycles, while 199 participants (46%) and 233 cycles received vaginal micronised progesterone. The proportion of clinical pregnancies (7.4 vs. 10.2%, p = .213), live births (68 vs. 73%, p = .286) were similar in the two groups.

The study concluded that oral dydrogesterone and vaginal micronised progesterone provide similar pregnancy outcomes in terms of clinical pregnancy and live birth rates in women undergoing IUI in conjunction with ovarian stimulation with rFSH. Given the simple and easy administration, lack of safety concerns and better patient tolerability, they suggested that oral dydrogesterone might be preferred for luteal phase support in IUI. This study clearly demonstrates that dydrogesterone is also a progesterone and is at least non-inferior to vaginal micronised progesterone pessaries.

An older publication from 2016 published a three-arm study with 1,779 patients randomised to Group A: dydrogesterone, Group B: oral micronised progesterone and Group C: vaginal micronised progesterone. The pregnancy outcomes, including clinical pregnancy rate, early miscarriage rate, biochemical pregnancy rate and ectopic pregnancy rate were compared in the three groups. There was no significant difference in pregnancy outcomes in all groups.Subsequent stratified analysis demonstrated that pregnancy outcomes in subjects of natural cycle and ovulation cycle still showed no significant difference(p>0.05). They concluded that all three methods of LPS had similar clinical implications.

Fig 2 Dydrogesterone vs Vaginal progesterone in ART



What dose should we use?

There is currently no consensus as to the appropriate dosage of progesterone in IUI cycles. Current best practice options include 200, 300, 600, 800 mg of vaginal progesterone and 90 mg progesterone gel per day. A Turkish group performed an RCT where they studied the effect of 300 mg vs 600 mg intravaginal progesterone on 100 women.

The mean age of the women, duration of infertility, basal and day of hCG injection hormone levels in the female and sperm parameters were similar in the two study groups. Also, duration and dose of gonadotropin given, number of follicles, endometrial thickness, the total, ongoing and multiple pregnancy rates were comparable in both groups. This dose finding study therefore concluded that that 300 mg of intravaginal micronised progesterone should be the maximum dose of LPS in IUI cycles.

Other agents

LPS with hCG and the utility of estradiol, steroids, aspirin and LMWH with a view to enhance success rates is beyond the scope of this article and the evidence for these agents is scant, at best. They are primarily of use in certain specialised case scenarios which we are unable to address in this publication.

Conclusions

The rationale for the use of progesterone for luteal phase support is clear from our understanding of the hormonal interplay during the menstrual cycle. It is also abundantly clear that manipulating the follicular phase with a view to ovulation induction and multifollicular development may have unintended consequences on the endometrium and the corpus luteum.

Current evidence supports the use of progesterone for luteal phase support in patients with gonadotropin stimulated IUI cycles or with multifollicular development. The evidence for its usage in clomiphene/letrozole or comiphene/letrozole with gonadotropin treatment cycles is at the moment unclear. In day-to-day practice with most patients having multifollicular development, it may be practical to supplement the luteal phase with progesterone even in these latter two groups of patients.

RCTs show that oral dydrogesterone and vaginal micronised progesterone are comparable in terms of benefit in IUI cycles and patient choice should probably dictate the clinician's prescribing practices.

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ROLE OF ENDOSCOPIC SURGERY

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Introduction

Hysteroscopy and laparoscopy both have a definitive role in the management of infertility and ART. Intrauterine insemination (IUI) warrants the presence of a fairly normal reproductive pelvic organ structure and function, especially the patency of the fallopian tubes. The role of endoscopic surgery before IUI has been established in case of known correctable pelvic pathology. Its role has been debated in case of unexplained infertility especially when there is failure of IUI due to unknown reasons.

Endoscopy vs other modalities

Advances in imaging techniques with 2D and 3Dultrasound, saline infusion sonography, computerised tomography (CT), and magnetic resonance imaging (MRI) for the evaluation of uterine and pelvic disease have decreased the use of diagnostic hysterolaparoscopy as a first line investigation in patients with infertility. Hysterosalpingography (HSG) and hysterosalpingo-contrast-sonography (HyCoSy) are inexpensive, less invasive, welltoleratedmethods of determining tubal patency, but their accuracy compared to laparoscopy is unclear. Several studies suggest that diagnostic hysterolaparoscopy may be of additional value over the standard first line investigations, because it indicates intra-abdominal pathologicalabnormalities in 36 - 68 % of cases even after a normal HSG. It is accepted as the most accurate method for evaluating tubal pathological and other pelvic causes of infertility.[1]

Which patients benefit from diagnostic endoscopic surgery?

A study evaluating the accuracy of diagnostic laparoscopy after normal hysterosalpingography (HSG) before intrauterine insemination (IUI) with respect to laparoscopic findings leading to a change of treatment decisions concluded that in about 25% of the couples it led to an alteration in treatment plan. In 21%, intervention at the time of diagnostic laparoscopy such as adhesiolysis of periadnexal adhesions and treatment of minimal/ mild endometriosis could be performed. This eventually led to an overall increase in live birth rates.[2]

An Indian study by Jayakrishnan et al in 2010 [3], evaluated the role of hysterolaparoscopy in patients who had unexplained infertility treated for >=3 cycles with IUI. Of 127 women, only 12.6% (n=16) had no detectable pathology on laparohysteroscopy. The incidence of endometriosis was 77.2% (n=98); of which 70.9% had minimal to mild disease. 5.5% of patients had pelvic inflammatory disease (PID) with unilateral and bilateral tubal adhesions and tubal blocks It is important to note that the cost of IVF is high and one attempt usually offers only one chance of successful pregnancy. On the contrary, in a young infertile woman <35 years of age with treatable pelvic pathology, laparoscopic correction can help improve the chance of natural conception and success rates of IUI.

When to perform endoscopic surgery?

The timing of endoscopic surgery in the management of infertility is controversial. Performing a laparoscopy prior to initiating treatment looks attractive, but the cost of this surgical procedure is high andmostfertility specialists prefer to treat couples with unexplained infertility with a few cycles of IUI before proceeding to laparoscopy.

A prospective randomised reallocation study to investigate the timing of laparoscopy after a normal hysterosalpingography was performed.[4] This showed no significant difference in the prevalence of abnormalities with clinical consequences at laparoscopy before IUI when compared to laparoscopy after six cycles of IUI. The authors concluded that the impact of detection and laparoscopic treatment of pelvic pathology prior to IUI did not seem to affect IUI outcome.

Clinical scenarios

Endometriosis and endometriomas

The most common finding on laparoscopy in patients who are unable to conceive with IUI and apparently normal findings on imaging techniques is minimal to mild endometriosis. Laparoscopy is the gold standard for more subtle lesions of endometriosis like superficial endometriosis. These superficial lesions can be treated with fulguration/ ablation/excision and adhesiolysis to restore the tubo-ovarian anatomy during laparoscopy.

For endometriomas, the management is controversial. Most international guidelines suggest endometriotic cyst excision over drainage of a cyst above the size of 4cm prior to IVF, but there is a risk of lowered ovarian reserve. Most ART specialists prefer IVF over surgical treatment of endometriomas, especially if the patient has already undergone endometriosis surgery earlier. There is limited evidence on the treatment of endometriomas prior to IUIand most clinicians would recommend surgery followed by ART in women with endometriomas.[5] Surgery for deep infiltrating endometriosis is recommended only for symptom relief and has not been shown to improve pregnancy rates with or without ART.

Tubal surgery

Proximal tubal blockage accounts for 10–25% of tubal disease. It may be due to obstruction resulting from plugs of mucus and amorphous debris, due to spasm of the ostium or due to occlusion/ blockage resulting from fibrosis due to salpingitis isthmica nodosa (SIN), pelvic inflammatory disease or endometriosis.

Tubal cannulation to treat proximal tubal block can be done via hysteroscopy with laparoscopic confirmation once distal tubal pathology is ruled out. Gentle pressure is needed to overcome the obstruction by tubal cannulation and if force is required then anatomical occlusion is assumed and the procedure should be abandoned.6A meta-analysis of studies treating patients with bilateral proximal tubal occlusion showed that the obstruction is relieved in approximately 85% of the tubes with tubal cannulation and that approximately half of the patients conceive.[7]

Distal tubal diseaseincludes hydrosalpinx and fimbrial phimosis. A good prognosis is seen in patients who have limited filmy adnexal adhesions, mildly dilated tubes (<3 cm) with thin and pliable walls and a lush endosalpinx with preservation of the mucosal folds. Laparoscopic neosalpingostomy and fimbrioplasty are carried out by opening/ draining a hydrosalpinx or increasing the opening for fimbrial phimosis, respectively. Pregnancy rates after these procedures depend on the degree of tubal disease.Intrauterine and ectopic pregnancy rates after neosalpingostomy for mild hydrosalpinges range from 58-77% and from 2-8%, respectively.[8]

Tubal surgery should be the firstline management option for young women <35yearswith minor tubal pathology. The second option should be IVF if there are other concurrent factors affecting fertility, if the patient'sage is >38years, if the patient has moderate to severe tubaldisease and if one year or more has passed post-surgery for tubal pathology.[9]

Laparoscopic ovarian drilling (LOD)

The proposed mechanisms by which LOD helps is by destruction of androgen producing stroma, causing reduction in the intraovarian and circulating levels of androgens and LH.PCOS women who have a high LH value, lean PCOS and non-insulin resistant are known to have a better response to LOD. It is usually done in women who are resistant to clomiphene citrate as an alternative to use of gonadotropins. Use of gonadotropins with IUI is second line treatment in CC resistant PCOS women. A Cochrane review in 2012 found that LOD is as effective as ovulation induction in terms of clinical pregnancy or live birth rates, but the risk of multiple pregnancy is lower with LOD.[10] The concerns about LOD are risk of adhesions and ovarian failure following LOD. The hilar region should be avoided and the ovary should be raised before the application of energy and saline wash should be done after

the procedure to lower the risk of injury. The usual dictum is application of 4 diathermy points to each ovary for 4 seconds each, and using a power of 40 watts.[11]

Regarding the efficacy of ovarian drilling, observational studies have demonstrated that the ovulation rate was between 54-76% in the 6 months after the procedure and 33-88% in the 12 months after the procedure. During these periods, the spontaneous pregnancy rate ranged between 28-56% and 54-70%, respectively.[12]

Hysteroscopic surgery

Hysteroscopy is the most accurate method to diagnose and treat unsuspected and subtle intrauterine pathologies in infertile women. Uterine pathologies like endometrial polyps, uterine septa, intrauterine adhesions and submucous fibroids cause infertility by impairing embryo implantation and growth due to poor vascularisation, affecting sperm migration or by causing an inflammatory endometrial response.

Hysteroscopic polypectomy

Perez-Medina et al[13] randomised women with a clear sonographic diagnosis of endometrial polyps and at least 1 year of infertility to hysteroscopy and polypectomy or diagnostic hysteroscopy and polyp biopsy prior to planned IUI. The mean polyp diameter in the treated group was 16 mm (3–24 mm). The pregnancy rates after four cycles of stimulated IUI starting at least 3 months after surgery were significantly higher in the polypectomy group (63 vs 28%).

Similarly, another study by Kalampokas et al[14] on 86 women who under went a hysteroscopic polypectomy vs a control group of 85 women who chose not to undergo polypectomy before IUI. There was a statistically significant difference in cumulative pregnancy rates between the two groups. Thus, hysteroscopic removal of polyps has shown to improve the pregnancy rates after IUI.

Intrauterine adhesions

A more recent study by Chen et al[15] evaluated reproductive outcomes in 357 patients with mild, moderate and severe Asherman's syndrome who underwent hysteroscopic adhesiolysis. The reproductive outcomes of 332 women (93%) were followed for an average duration of 27±9 months and the overall conception rate after hysteroscopic adhesiolysis was 48.2%, which decreased with increased intrauterine adhesions (IUA) severity (mild 60.7%, moderate 53.4%, severe 25%). The mean time to conception following hysteroscopic adhesiolysis was 9.7±3.7 months. The miscarriage rate was 9.4%, and the live birth rate was no lower than 85.6%. Eleven patients (7.9%) had postpartum hemorrhage, including 6 (4.3%) due to adherent placenta and 3 (2.1%) due to placenta

accreta.Hysteroscopic adhesiolysis is a feasible and effective way to improve fertility in patients with Asherman's syndrome. Hysteroscopic division of adhesions with scissors or electrosurgery is usually recommended. Some women may require multiple procedures to achieve a satisfactory anatomical result due to the high recurrence rate. Postoperative mechanical distension of the uterine cavity with an intrauterine device or a paediatric Foley catheter along with estrogen therapy to facilitate endometrial regrowth and proliferation are commonly used to decrease the high rate of recurrence.

Other surgeries

The other fertility enhancing endoscopic surgeries like hysteroscopic myomectomy for submucous fibroids, hysteroscopic septal resection and laparoscopic myomectomy are known to improve fertility outcomes and hence indirectly also improve success rates of IUI.

Conclusion

Endoscopic surgeries have a role in optimising the outcome of IUI, provided they are done for the correct indication and with standard techniques as suggested by research. Couples who fail to conceive with ovulation stimulation with IUI should be counselled that there is evidence to show that hysterolaparoscopy is of benefit before proceeding to IVF. At the same time, the use of empirical treatment in the form of ovulation stimulation and IUI prior to laparoscopy might reduce the number of patients requiring the procedure, reduce the number of negative laparoscopies and optimise resource utilization.

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Abbreviated Prescribing information for Uniprogestin (Hydroxyprogesterone Injection IP) [Please refer the complete prescribing information available at www.torrentpharma.com] **PHARMACOLOGICAL PROPERTIES:** Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known. Hydroxyprogesterone caproate is an ester of the naturally occurring hydroxyprogesterone and possesses progesterone-like progestogenic effects such as antigonadotropic effects, the secretory transformation of the endometrium and thickening of the cervical mucus. The transformation of the endometrium facilitates the implantation of a fertilized ovum and creates favorable conditions for the maintenance of any pregnancy. **INDICATIONS:** Uniprogestin is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. To prevent premature birth and threatened abortion **DOSAGE AND ADMINISTRATION:** Dosage: As directed by the Physician. **CONTRAINDICATION:** Hypersensitivity to the active substance or to any of the excipients listed **WARNINGS & PRECAUTION:** Thromboembolic Disorders: Discontinue Uniprogestin if an arterial or deep venous thrombotic or thromboembolic event occurs. Allergic Reactions: Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Uniprogestin or with other products containing castor oil. Consider discontinuing the drug if such reactions occur. Decrease in Glucose Tolerance: A decrease in glucose tolerance has been observed in some patients on progestin treatment Fluid Retention, Depression, Jaundice, Hypertension **DRUG INTERACTIONS:** Reported In vitro drug-drug interaction studies were conducted with Hydroxyprogesterone caproate. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The need for oral antidiabetics or insulin may change. **ADVERSE REACTIONS:** Precaution). The following adverse reactions have been identified following use of hydroxyprogesterone caproate. Body as a whole: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes Page 5 of 11 Digestive disorders: Vomiting Infections: Urinary tract infection Nervous system disorders: Headache, dizziness Pregnancy, puerperium and perinatal conditions: Cervical incompetence, premature rupture of membranes Reproductive system and breast disorders: Cervical dilation, shortened cervix Respiratory disorders: Dyspnea, chest discomfort Skin: Rash

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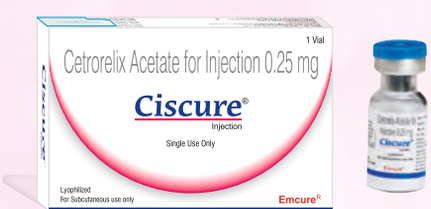

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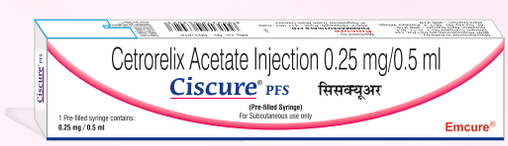

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