


The background of the slide is a close-up photograph of numerous small, light purple flowers with five petals and yellow centers, growing on green stems. A solid purple rectangular box is positioned on the left side of the slide, containing the title text in white.

# IUI TREATMENT

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# When is IUI Treatment Recommended

- Evaluation of the male partner should begin at the same time as in the female partner, generally when pregnancy fails to occur **after 1 year** of reasonably regular unprotected intercourse.
- Earlier evaluation is indicated whose partner **is age 35 or older** (where it is important to identify all potential infertility factors as quickly and efficiently as possible)

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- While recommending a treatment plan, an IVF specialist keeps the age, medical history and type of infertility of the couple in mind.
  - It's an ideal treatment for younger couples, but the success rate drops down in women who are over 35 years of age

# IUI is a simple Procedure

- It is usually preferred as the **first line** of treatment before (IVF) as it is cost-effective and less invasive.
- It involves selected sperm of higher motility through a catheter inside a woman's uterus near to the released egg during ovulation to facilitate fertilisation.
- A semen sample from a male partner is washed, processed in the laboratory to remove all the inactive or sluggish sperm and **only the ones with progressive motility are used**.
- IUI can be combined with fertility drugs if a woman has a problem with ovulation.





# IUI PROCESS

EGG MAKING


EGGS TRACKING

SPERM RINSING

INSEMINATION

PREGNANCY TEST



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- The best available evidence suggests that *treatment with IUI in natural cycles has no clinically important effects.*
  - Although clomiphene is commonly used as a treatment for unexplained infertility, the best available evidence indicates it has no significant benefit.
  - Combined treatment with **clomiphene + IUI is commonly recommended** for **unexplained infertility**

# CLOMIPHENE CITRATE



Non steroidal selective estrogen receptor modulator  
(SERM)

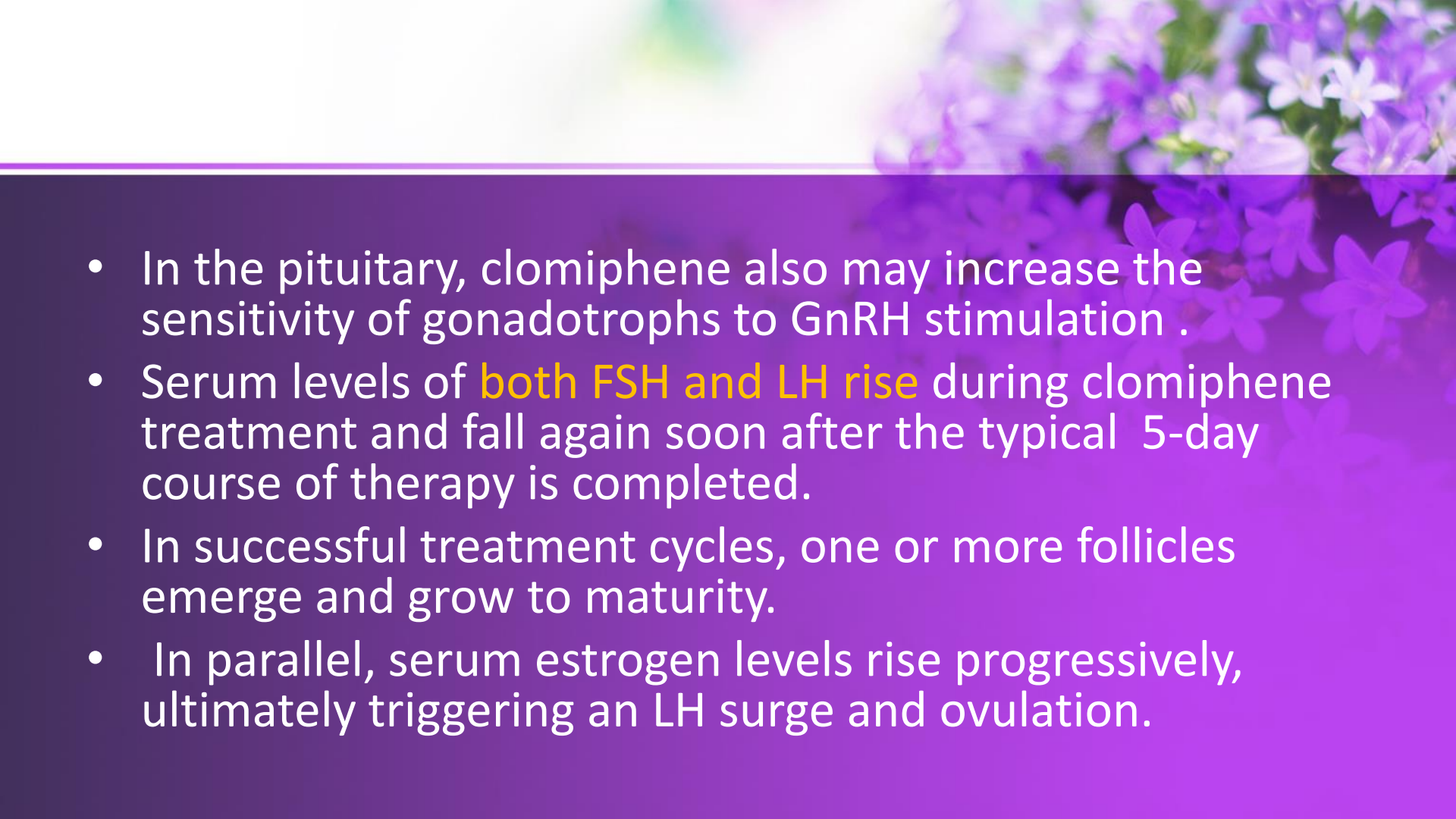
Having both estrogen agonist and antagonist properties.

It is cleared through the liver and excreted in the stool;  
approximately 85% is eliminated within a week, but traces  
can remain in the circulation for a longer time .

- Structural similarity to estrogen allows clomiphene to compete with endogenous estrogen for nuclear estrogen receptors at sites throughout the reproductive system.
- Unlike estrogen, clomiphene binds to nuclear estrogen receptors for an extended interval of time .
- Reduced negative estrogen feedback triggers normal compensatory mechanisms that alter the pattern of GnRH secretion and stimulate increased pituitary gonadotropin release, which, in turn, drives ovarian follicular development.





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- In the pituitary, clomiphene also may increase the sensitivity of gonadotrophs to GnRH stimulation .
  - Serum levels of **both FSH and LH rise** during clomiphene treatment and fall again soon after the typical 5-day course of therapy is completed.
  - In successful treatment cycles, one or more follicles emerge and grow to maturity.
  - In parallel, serum estrogen levels rise progressively, ultimately triggering an LH surge and ovulation.

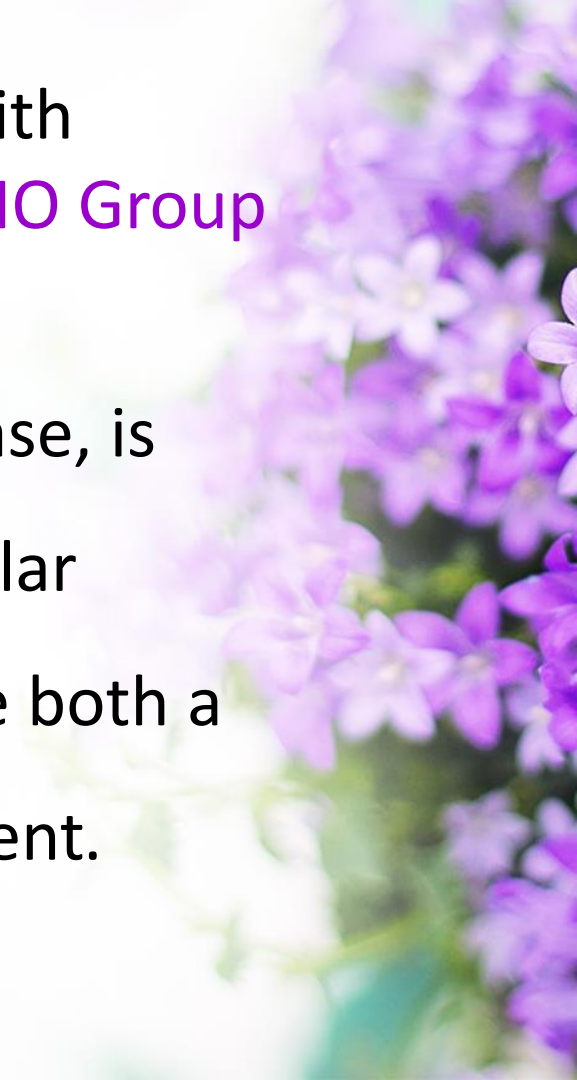
- **Impaired endometrial growth** has been reported in clomiphene-treated women.
- preovulatory endometrial thickness in clomiphene-induced cycles remains well within the range normally observed in spontaneous ovulatory cycles .



# Clinical Indications

- For I/O in anovulatory infertile women with
- NL thyroid function ,NL serum prolactin levels ,NL endogenous estrogen production, as determined by ,clinical observations (oligomenorrhea, estrogenic cervical mucus) ,serum E2 determination (  $> 40$  pg / mL) ,a normal menstrual response to a progestin challenge (WHO Group II)

- Clomiphene is **ineffective** in women with hypogonadotropic hypogonadism (**WHO Group I**).
- Poor luteal function, a short luteal phase, is associated with abnormally low follicular phase FSH levels, clomiphene could be both a logical and effective choice for treatment.



# WHO classification of anovulation

- *class 1* – Hypogonadotropic hypogonadal anovulation is the , occurring in **5 - 10 % of cases.** , (women with hypothalamic amenorrhea from functional etiologies such as excessive exercise or low body weight )
- *class 2* – Normogonadotropic normoestrogenic anovulation is the **most common**, accounting for **70 - 85 %** of cases.( Women with PCOS )
- *class 3* – Hypergonadotropic hypoestrogenic anovulation occurs in **10 - 30 %** .( Women with primary gonadal failure ( POF ) or gonadal dysgenesis ).
- *Hyperprolactinemic* anovulation is a separate category; gonadotropin concentrations in this condition are usually NI or ↓



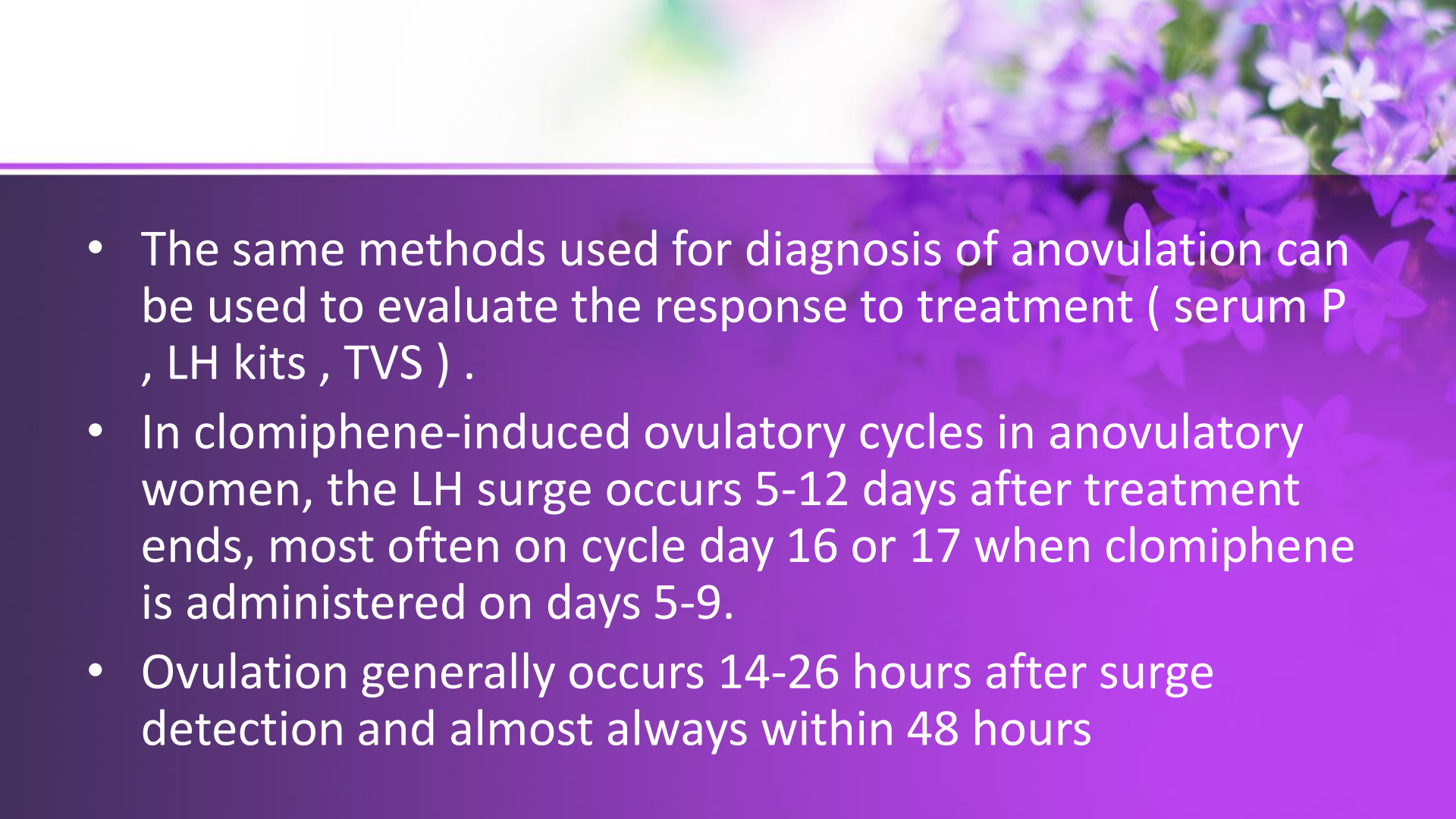
# Clomiphene citrate treatment is for

- Women with ovulatory dysfunction
- Normally ovulating women whose infertility remains unexplained( particularly in young women and short duration of infertility )
- Clomiphene alone **does not** significantly improve live birth rates or time to pregnancy compared to expectant management in unexplained infertility.
- Empiric clomiphene treatment for unexplained infertility is most effective when combined with IUI, in an effort to increase the numbers of both ova and sperm

# Clomiphene Treatment Regimens

- Clomiphene is orally, typically beginning on the 3 – 5 day after the onset of a spontaneous or progestin-induced menses.
- In women with amenorrhea, treatment can begin immediately,, if pregnancy has been excluded.
- The dose of clomiphene required to induce ovulation correlates with body weight .
- Treatment usually starts with a single 50-mg tablet daily for a 5-day interval and, if necessary, increases by 50 mg increments in subsequent cycles until ovulation is achieved.



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- The same methods used for diagnosis of anovulation can be used to evaluate the response to treatment ( serum P , LH kits , TVS ) .
  - In clomiphene-induced ovulatory cycles in anovulatory women, the LH surge occurs 5-12 days after treatment ends, most often on cycle day 16 or 17 when clomiphene is administered on days 5-9.
  - Ovulation generally occurs 14-26 hours after surge detection and almost always within 48 hours

# Results of Clomiphene Treatment

- Clomiphene will induce ovulation successfully in 70-80% of selected women.
- In anovulatory women the likelihood of response **decreases** with ↑ age , ↑ BMI, hyper androgenemia.
- Women with **amenorrhea** are more likely to conceive than those with oligomenorrhea, because infertile women who menstruate also likely ovulate, albeit infrequently, and are more likely to have other coexisting infertility factors



# Side Effects

A decorative background featuring a dense cluster of small, light purple flowers with yellow centers, set against a soft, out-of-focus background of more flowers and greenery. The flowers are in sharp focus in the upper right corner, while the rest of the background is blurred.

- Transient hot flashes, headache, breast tenderness, pelvic pressure or pain, and nausea .
- Visual disturbances (blurred or double vision, scotomata, light sensitivity) are uncommon (1-2%) and reversible.
- Persistent light sensitivity (photophobia) dictates that treatment be abandoned in favor of alternative methods for ovulation induction.



# Risks

- Increased risk for a multiple pregnancy (7-10% ) .
- There is no evidence that increases the overall risk of birth defects , developmental delay or learning disability in children conceived during clomiphene treatment.
- Mild symptoms of OHSS (transient abdominal discomfort, mild nausea, vomiting, diarrhea, and abdominal distention) are not uncommon but require only expectant management.
- **No causal** relationship between ovulation-inducing drugs and **ovarian, breast, or endometrial cancer** has been established

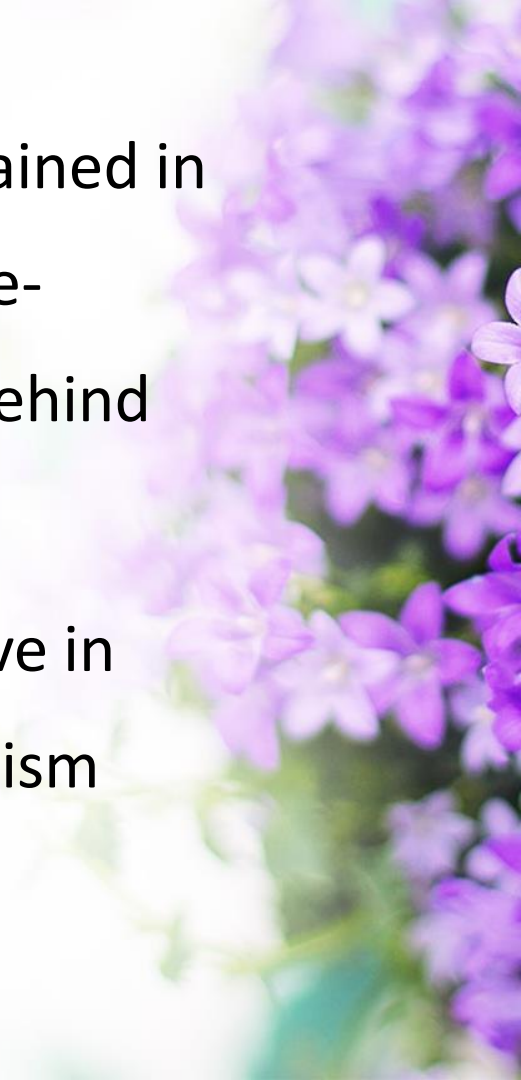


# AROMATASE INHIBITORS



- Letrozole is now considered the first-line therapy for ovulation induction in women with PCOS, as it provides significantly higher live birth rates compared to clomiphene .
- Anastrozole and letrozole are triazole (antifungal) derivatives that act as potent, **competitive, non steroidal** inhibitors of aromatase, the enzyme that catalyzes the rate-limiting step in estrogen production.
- They block estrogen production both in the periphery and brain, resulting in a compensatory  $\uparrow$  in pituitary gonadotropin secretion that stimulates ovarian follicular development .

- ↓ E2 levels and ↑ luteal phase P levels attained in letrozole stimulated cycles than clomiphene-stimulated cycles may be the mechanism behind ↑ LBR with letrozole.
- Similar to clomiphene, letrozole is ineffective in women with hypogonadotropic hypogonadism (WHO Group 1 ) .



# Peripheral Actions

The slide features a decorative background of purple flowers, likely bellflowers, in the upper right corner. The main content area has a solid purple background with white text.

- Despite ↓ serum E2 levels in letrozole-stimulated cycles than in clomiphene-stimulated cycles, letrozole could have been expected to have less of an adverse effect on endometrial growth, since it does not block estrogen receptors.

# Aromatase Inhibitor Treatment Regimens

- Letrozole (2.5-7.5 mg daily) and anastrozole (1 mg daily) administered for a 5-day interval.
- Letrozole is administered orally, typically beginning on the 3 – 5 day after the onset of a spontaneous or progestin-induced menses.
- Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 3 and 5.
- In women with amenorrhea, treatment can begin immediately, pregnancy must be excluded





# Results of Treatment with Aromatase Inhibitors

- Letrozole seems independent of BMI , despite ↓ overall LBR with ↑ BMI .
- Miscarriage per pregnancy and multiple pregnancy rates are also similar between letrozole and clomiphene-induced cycles.
- Aromatase inhibitors can also be effective in anovulatory women who fail to ovulate in response to clomiphene treatment.
- Aromatase inhibitors also might be considered for women who respond to clomiphene but exhibit grossly poor endometrial proliferation ,letrozole is associated with a significantly thicker endometrium.

# Side Effects

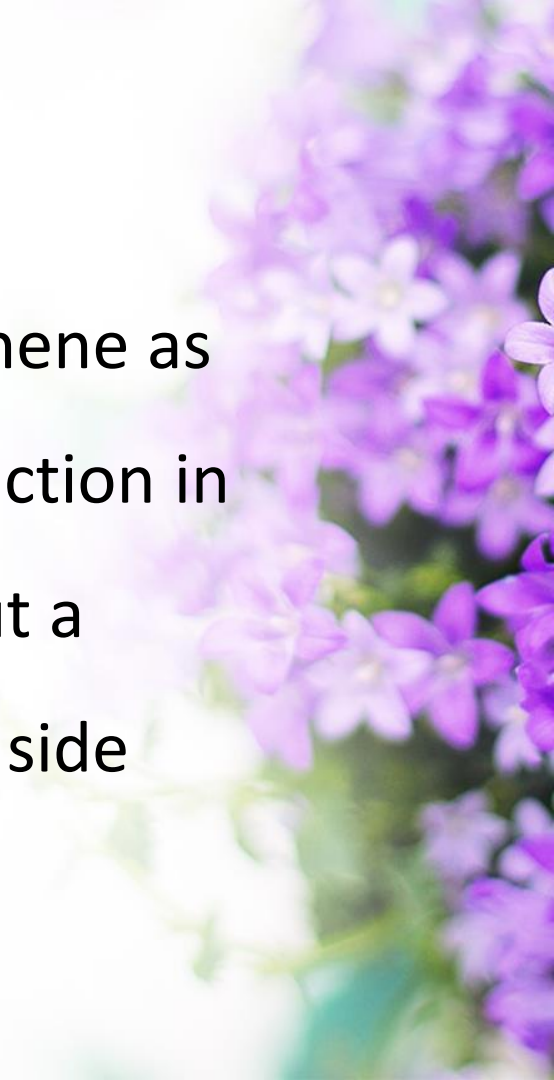
- Letrozole is generally well tolerated, and the most common side effects of letrozole are **headaches and cramps**.
- Women on letrozole report more **fatigue** and **dizziness** than women on clomiphene.
- Hot flushes are ↓ common with letrozole .



# Risks

- The major risk of ovulation induction is the occurrence of a **multiple pregnancy**.
- There is **no evidence** suggesting letrozole is any more **teratogenic** than clomiphene.
- The incidence of congenital malformations in newborns of women who conceived after treatment with letrozole or clomiphene found no difference.( the same as pregnancies without treatment ) .
- The risk of clinically significant OHSS is very low with letrozole

- In sum, the available data suggest that **letrozole** is more effective than clomiphene as a first-line treatment for ovulation induction in anovulatory women with PCOS, without a significant increase in complications or side effects.



# Gonadotropin Therapy

- Anovulatory PCOS patients who fail to ovulate or conceive with oral agents may be considered for ovulation induction with exogenous gonadotropin injections .
- Typical protocols monitor at baseline, 4 - 5 days after treatment initiation, and every 1 - 3 days until follicular maturation.
- Expected follicle growth is 1 - 2 mm daily after achieving 10 mm diameter .
- Given the goal of promoting growth of a single mature follicle, low initial gonadotropin doses of 37.5 – 75 IU / day are generally recommended, with increases in doses by 50% of the previous dose after 7 days if no follicle >10 mm is observed .





# Monitoring Ovulation Induction Therapy

- Although no clear advantage has been demonstrated for any ovulation monitoring technique, **regular contact** should be maintained with patients to review response to therapy .
- The urinary LH surge may be detected 5 - 12 days after treatment is completed .
- When clomiphene or letrozole is given on cycle days 5 - 9, the surge typically occurs on cycle days 16 - 17

- With US monitoring, treatment should be withheld if large cysts are seen on baseline testing.
- Following ovulation induction use, follicles typically reach a pre ovulatory diameter of 19 - 25 mm by US, but may be as large as 30 mm.
- A combination of LH testing and US can be used, with LH kits starting when the largest US-measured follicle reaches 14 mm in diameter .



# Human Chorionic Gonadotropin



- If a dominant follicle develops , hCG can be used to induce final follicular maturation , with ovulation occurring approximately 36-40 hours following administration .

# HCG

- HCG is recommended is used when 1 - 2 follicles are 16 to 18 mm diameter and the E2 level per dominant follicle is 150 to 300 pg/mL .
- Ovulation is expected 24 - 48 hours after the hCG trigger.
- Intercourse should be recommended within 24 - 48 hours of ovulation triggering or IUI 24 - 36 hours after triggering .
- Testing for pregnancy is performed within 15 - 16 days after ovulation triggering
- Gonadotropin dosage in future cycles should be altered if the prior response was inadequate or excessive.

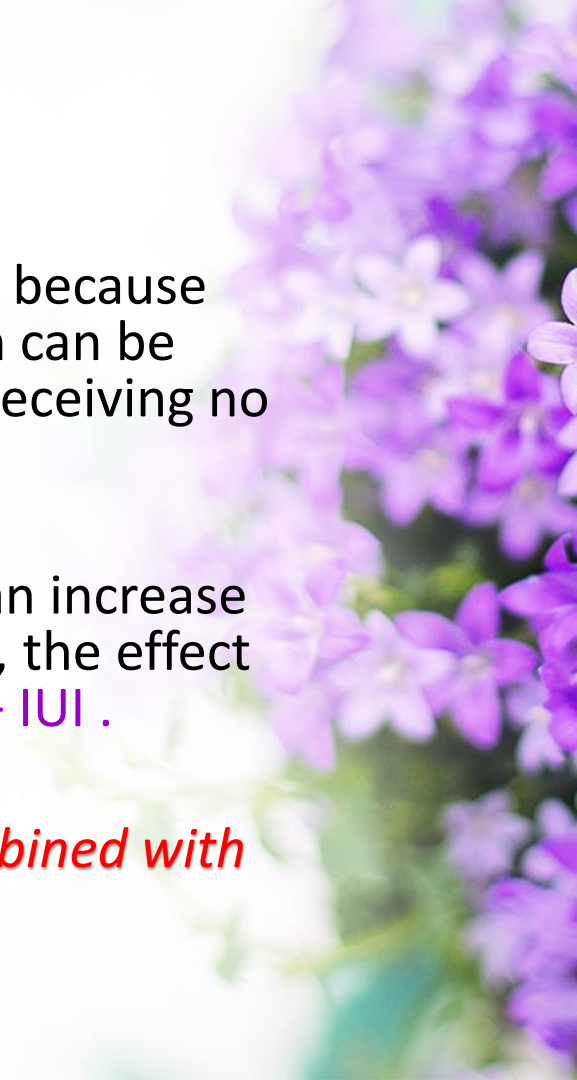
# Timing and Technique

- **Normal sperms** can survive in the female reproductive tract and retain the ability to fertilize an egg for **at least 3 days**
- **Oocyte** can be successfully fertilized for only approximately **12–24 hours** after it is released.
- When ovulation is triggered by injection of exogenous hCG in natural or stimulated cycles, IUI generally is best performed approximately 34–40 hours later.



# Clomiphene + IUI

- Treatment with **clomiphene + IUI** can be justified because the cycle **fecundability is significantly higher** than can be expected in couples with unexplained infertility receiving no treatment.
- Although treatment with **gonadotropins alone** can increase cycle fecundability, compared with no treatment, the effect is quite modest and **no better than clomiphene + IUI** .
- *More commonly, gonadotropin treatment is combined with IUI for the treatment of unexplained infertility.*



# Gonadotropins + IUI

- Treatment with **gonadotropins + IUI** is modestly effective treatment for couples with :
  - longer durations of unexplained infertility ( >3 years )
  - couples who fail to conceive with clomiphene + IUI
  - clomiphene treatment fails to stimulate multiple follicular development
  - when IVF is not a viable option

# Idiopathic Male Infertility

- Unfortunately, no medical treatment has proven reliably effective for improving semen parameters or fertility in men with idiopathic subfertility.
- There is no substantial evidence that androgen therapy is an effective treatment for idiopathic male infertility.



# Treatment idiopathic subfertility



- **Exogenous FSH** may improve semen quality in a subset of men with idiopathic oligospermia in whom testicular biopsy reveals maturation arrest and serum FSH and inhibin B levels are normal.
- Empiric treatment (3–6 months) with either **clomiphene citrate** (25 mg daily) or **tamoxifen** (20 mg daily) commonly is offered to stimulate increased gonadotropin secretion and spermatogenesis in men with idiopathic subfertility.

# Indication of IUI



- The most common reasons for doing IUI Treatment Procedure
- Low sperm count (a mild one)
- If a woman has hostile cervical mucus
- If treatment with fertility drugs alone is not helpful
- Unexplained infertility.



# IUI is particularly useful in couples with

- some types of severe sexual dysfunction (ejaculatory dysfunction)
  - for cervical factor
  - mild male factor infertility

# Indication for IUI

- Severe hypospadias
- Retrograde ejaculation
- Neurologic impotence
- Sexual dysfunction
- Oligospermia, asthenospermia mild
- Low ejaculate volumes
- Sperm autoantibodies
- Cervical factors



# Retrograde Ejaculation

- Medical treatment :
- Imipramine 25 mg twice daily or 50 mg at bedtime,
- Pseudoephedrine 60 mg
- Ephedrine 25–50 mg four times daily,
- Phenylpropanolamine 50–75 mg twice daily), directed at control of the internal sphincter. for best results,
- Urine pH and osmolality (300–380 mOsm/L) must be carefully controlled by alkalinizing the urine (sodium bicarbonate 650 mg four times daily, beginning 1–2 days before collection) and managing fluid

# Semen Parameters and Prognosis

- **Best results** are achieved when the number of total motile sperms exceeds a approximately 10 million.
- **Combining the yield from two ejaculates** obtained approximately **4 hours apart** may increase the numbers of sperms available from oligospermic men.
- **Success rates with IUI are highest when 14% or more of normal morphology**, intermediate with values between 4% and 14%, and generally quite poor when fewer than 4% of sperms are normal.

# Sperm Preparation

- **Washing** sperm the greatest numbers of sperms, but the final specimen also contains dead and abnormal sperms and other cellular debris.
- **Swim-up** cleaner specimen, devoid of dead sperms and other cellular debris, but also yields significantly lower numbers of sperms
- **Density gradient centrifugation** select a population of sperms with normal morphology
- The best choice among them may vary with the quality of the semen sample



# The principal indication for ICSI male infertility

- Severe oligospermia (<5 million sperm/mL)
- Asthenospermia (<5% progressive motility)
- Teratospermia (<4% normal forms by strict criteria)
- Using surgically retrieved sperm
- Treatment includes PGD
- couples with previous failed or poor fertilization with conventional IVF

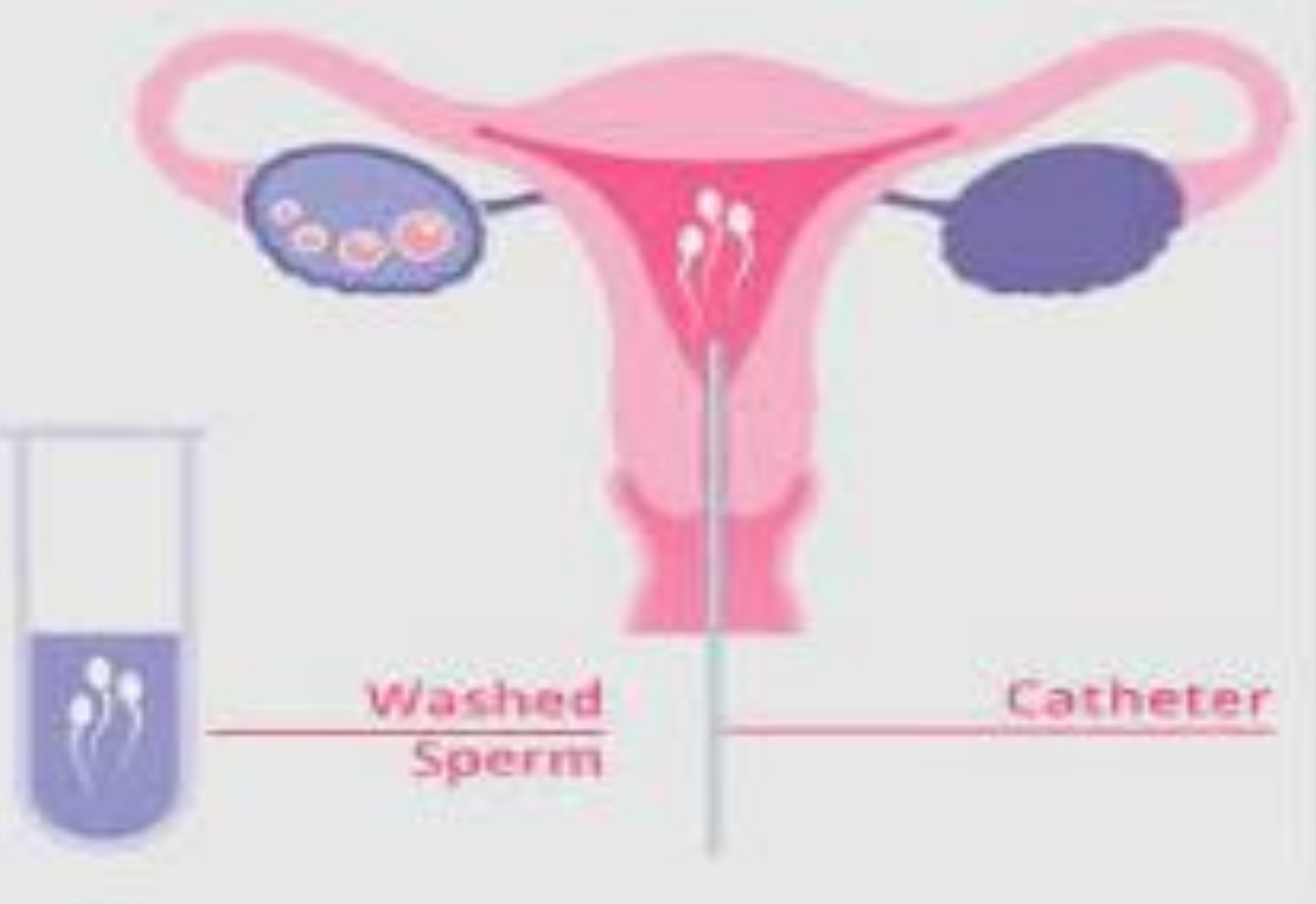


## Intracytoplasmic Sperm Injection (ICSI)

# Min requirements

- ovulation in the IUI cycle
- patency of at least one fallopian tube
- inseminate with an adequate number of motile sperm
- absence of documented or suspected active infection



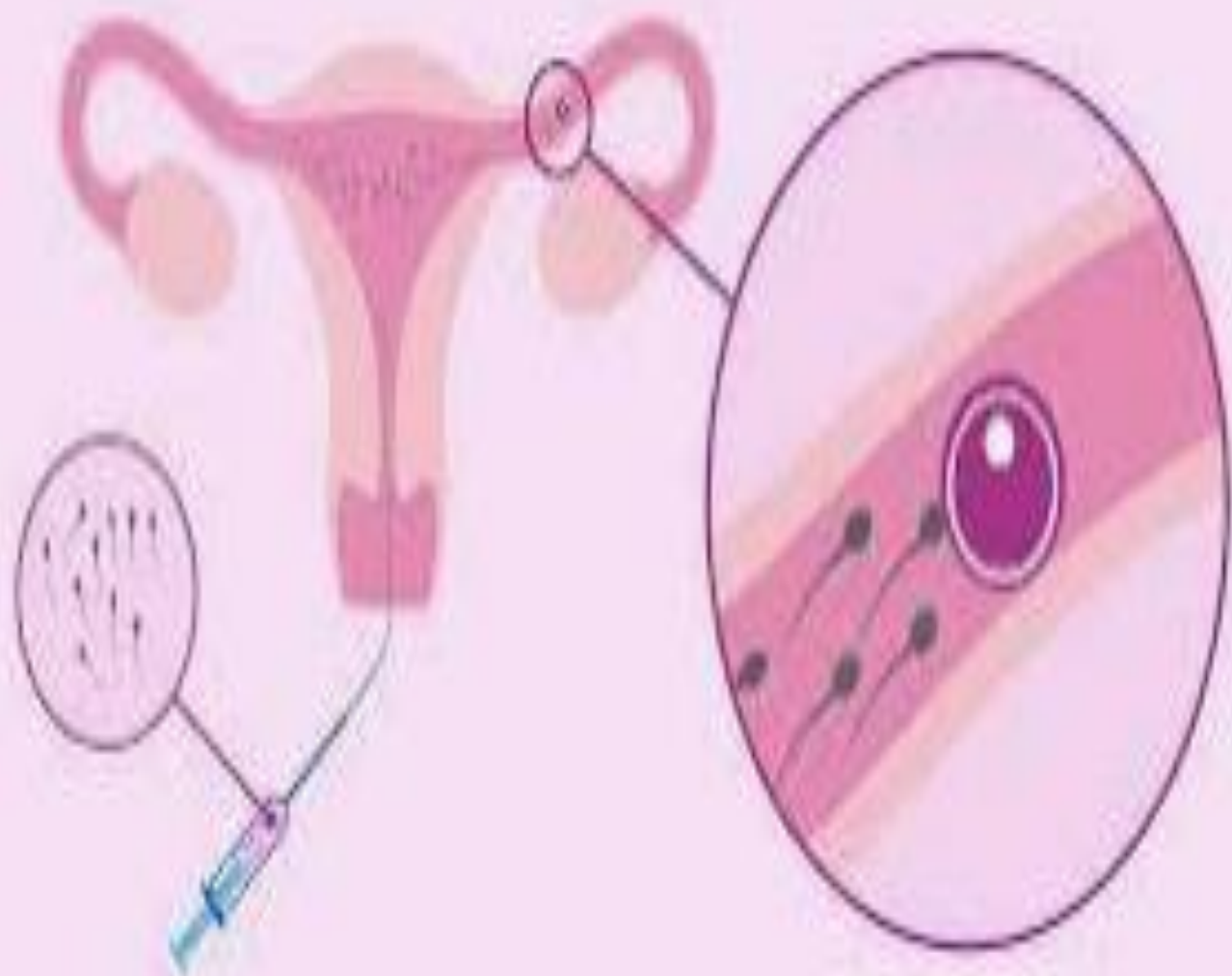


# IUI



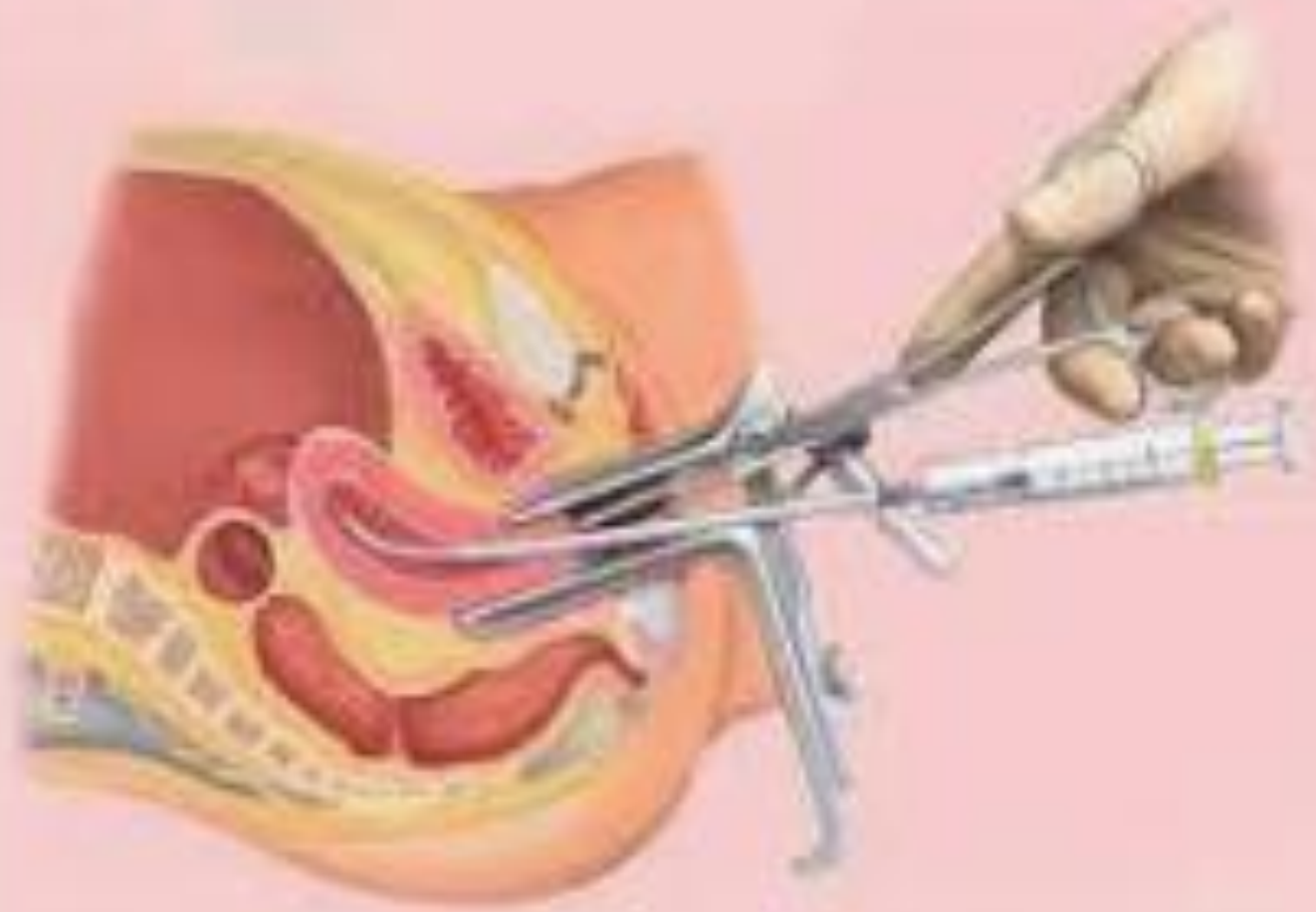
- IUI is usually performed with fresh sperm (morning after 2 - 3 days of sexual abstinence )
- The LH surge can be detected in serum 36 hours before ovulation and in urine 24 hours before ovulation.
- The oocyte can be fertilized up to 24 hours after ovulation; sperm are most capable of fertilization up to 48 hours after entering the female genital tract.

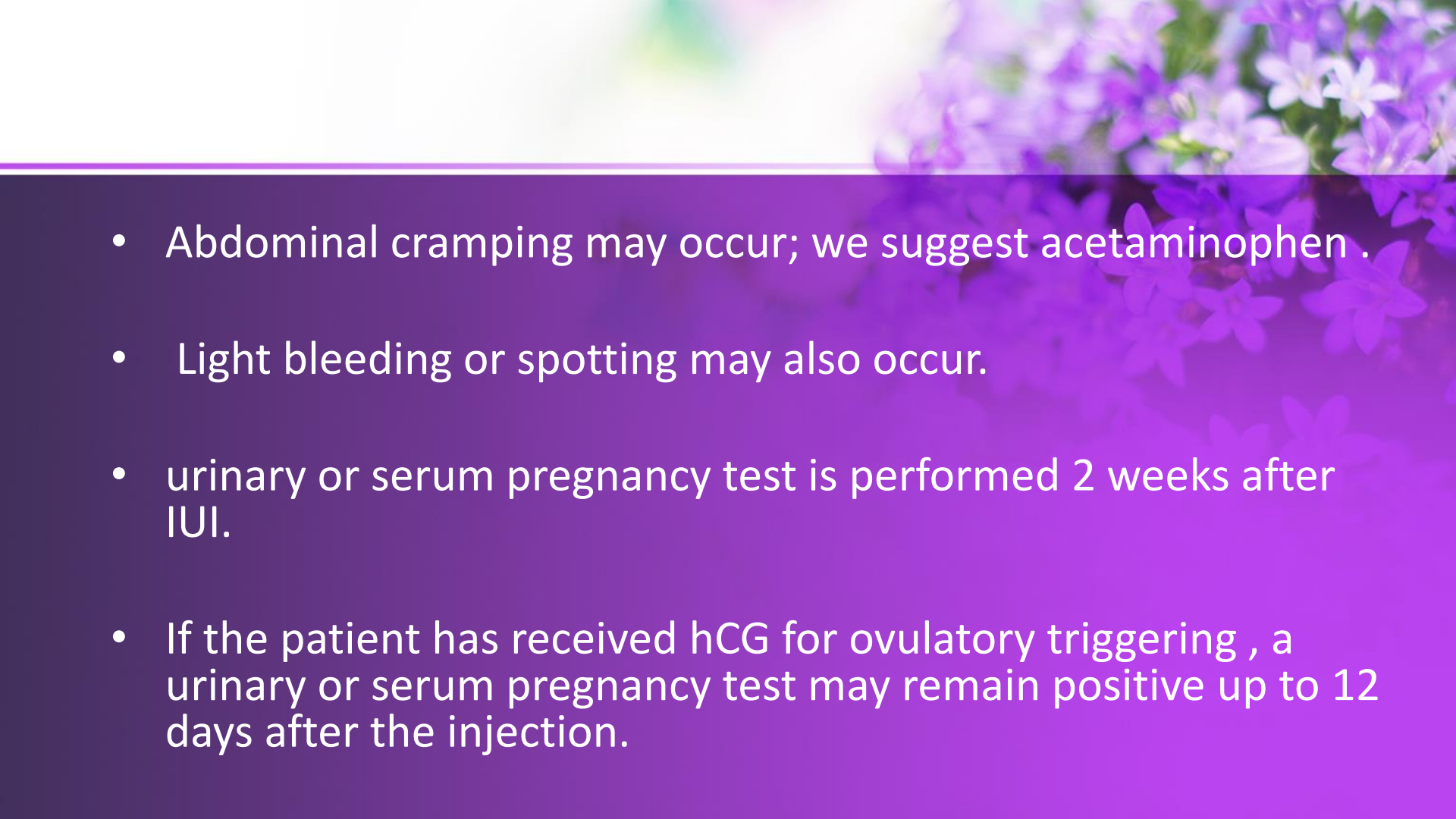




- Proper identification of both the patient and sperm sample in the laboratory and the clinic is essential.
- Antibiotic prophylaxis is unnecessary.
- Povidone iodine should not be used to cleanse the cervix because it is toxic to sperm.
- The sperm is suspended in a small volume of media, no > 0.5 mL, to prevent expulsion from the cervix and uterine contractions .
- The patient may resume her normal activities after insemination.

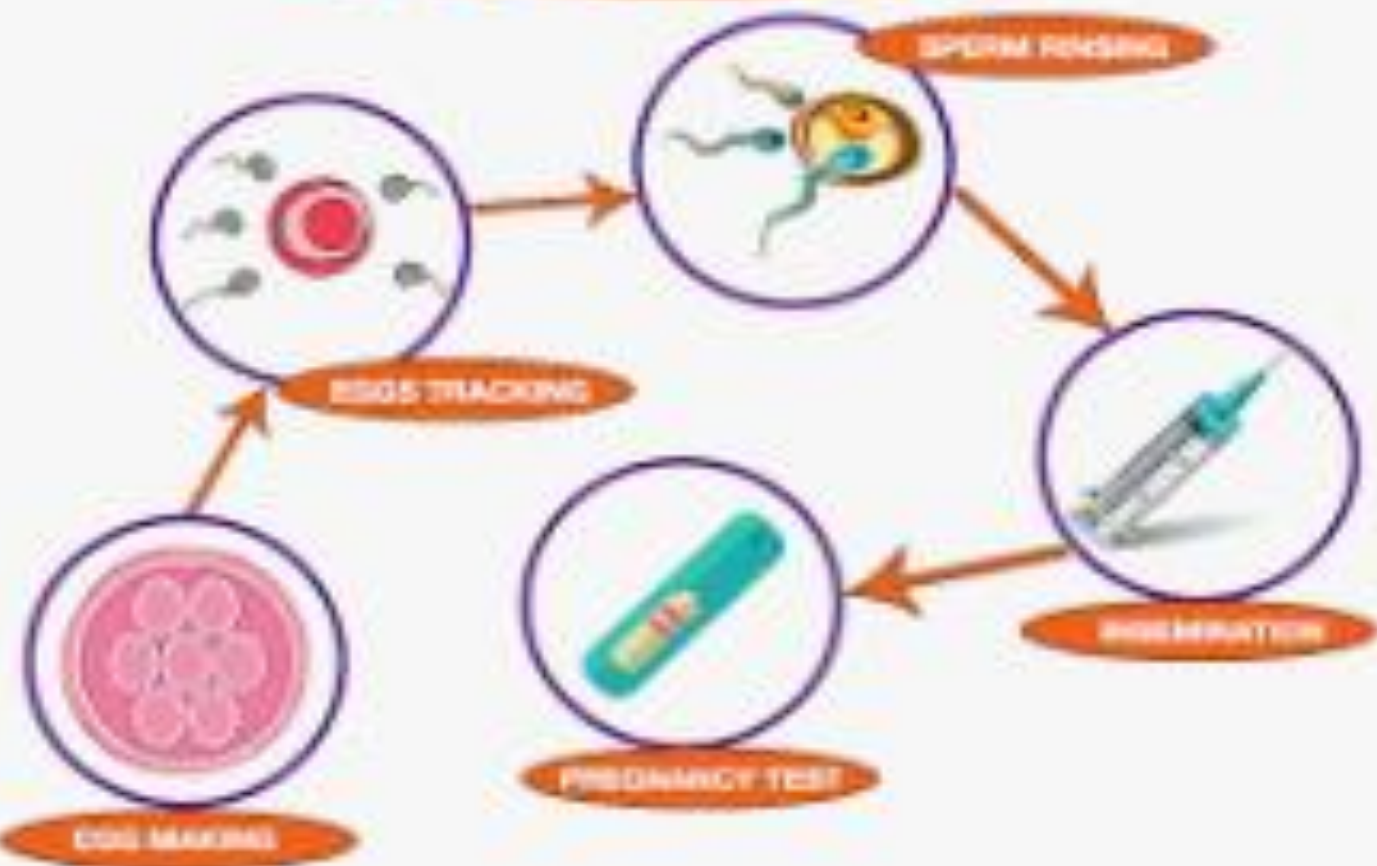




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- Abdominal cramping may occur; we suggest acetaminophen .
  - Light bleeding or spotting may also occur.
  - urinary or serum pregnancy test is performed 2 weeks after IUI.
  - If the patient has received hCG for ovulatory triggering , a urinary or serum pregnancy test may remain positive up to 12 days after the injection.

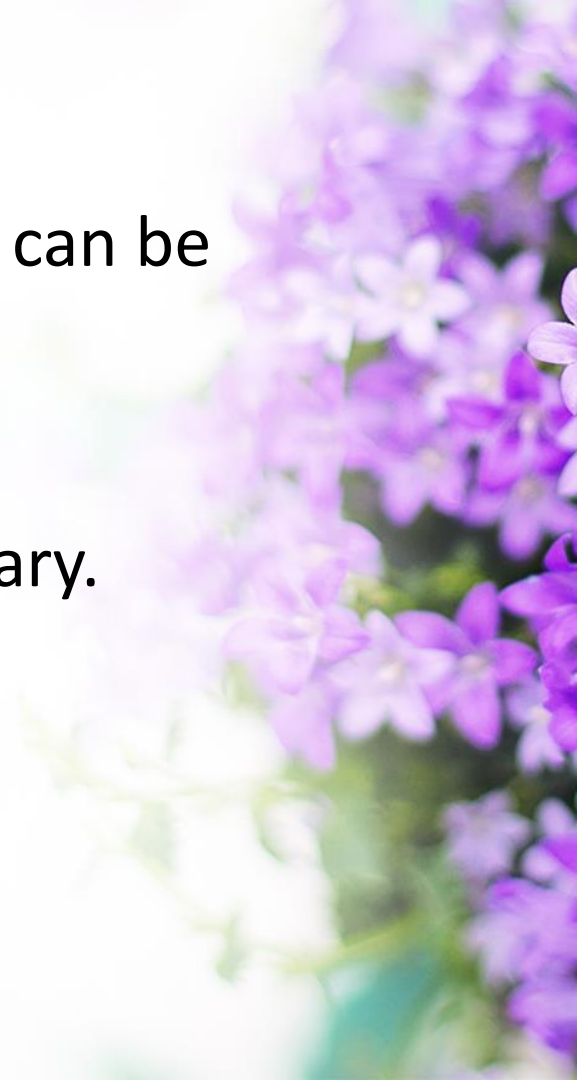


# IUI PROCESS

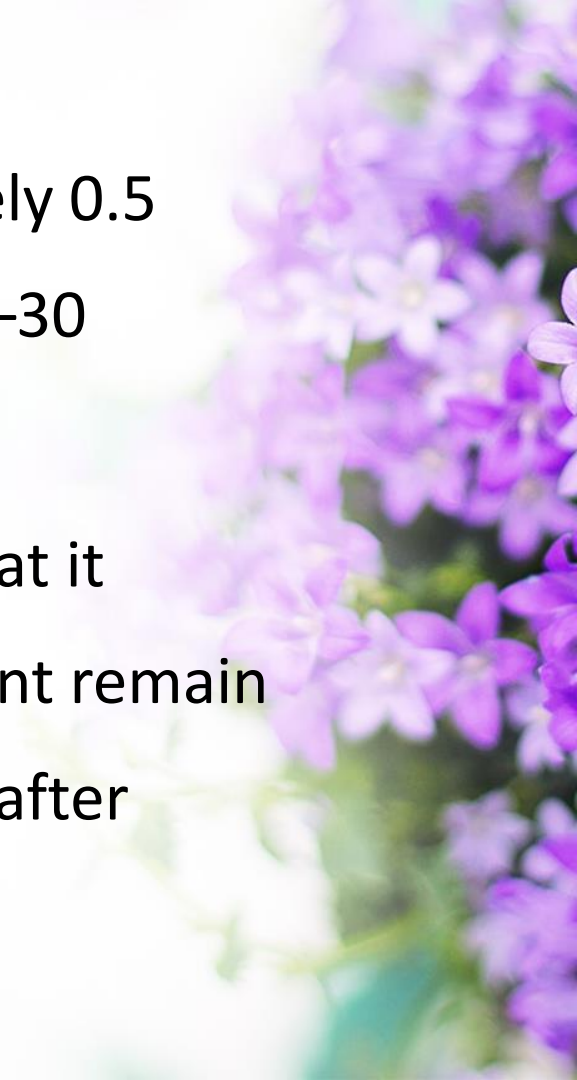




- If sufficient numbers of motile sperms can be recovered, **IUI** may be performed
- And if not, IVF and ICSI may be necessary.



- The insemination specimen (approximately 0.5 mL) should be introduced slowly over 10–30 seconds.
- Although there are no data to indicate that it matters, it is customary to have the patient remain supine for approximately 10–15 minutes after insemination.



## Other Prognostic Factors

- Maternal Age
- Ovulatory Function
- Uterine and Tubal Factors
- When male factor infertility is the diagnosis, and ovulatory function is normal, treatment with IUI alone is reasonable and appropriate.



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Thank you for  
your attention