



IUI TREATMENT

Dr sara saedi
Gynecologist
Fellowship of infertility

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)

- 
- 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

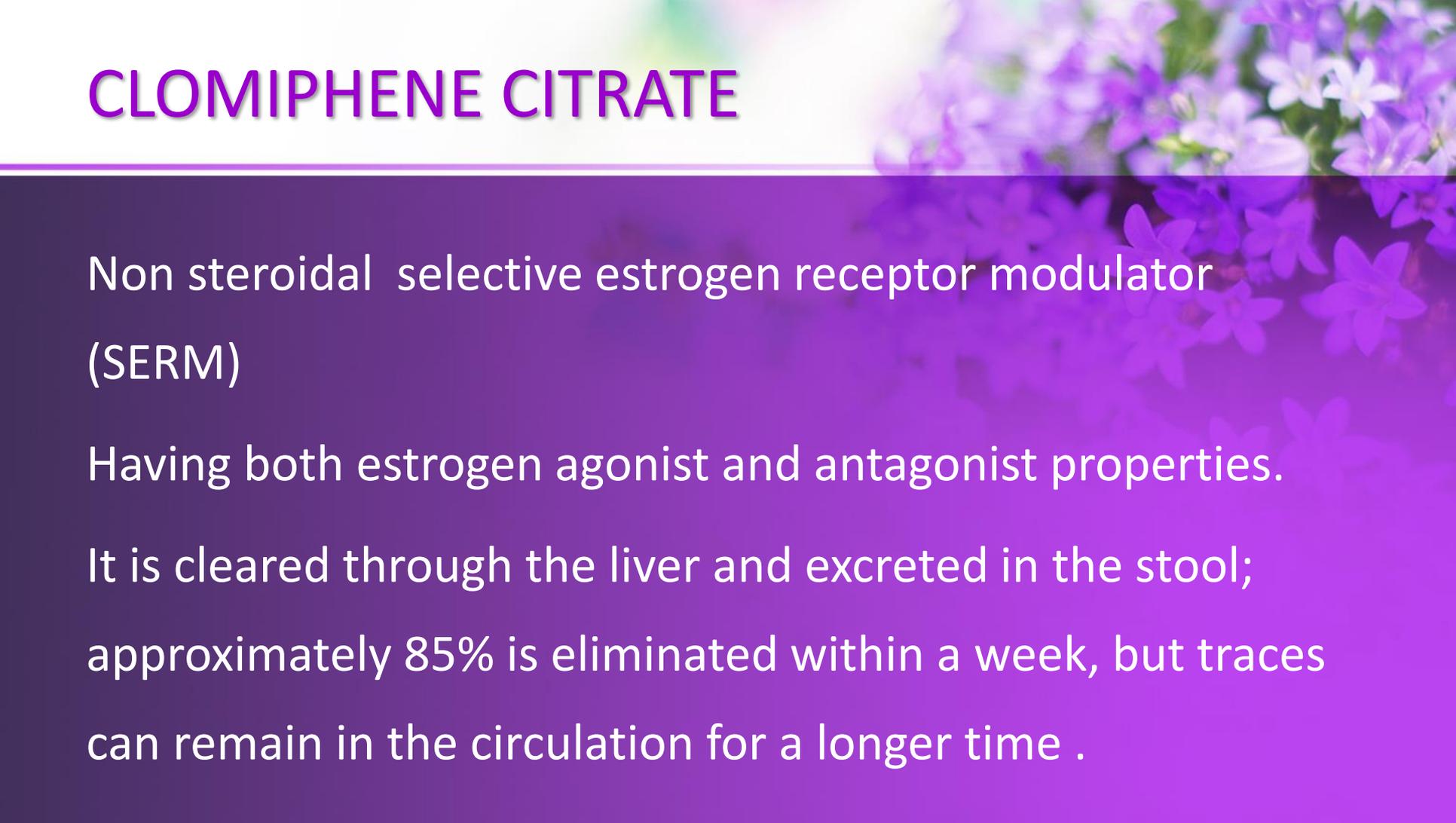
- It is usually preferred as the **first line** of treatment before (IVF) as it is cost-effective and less invasive.
- It involves selected sperm of higher motility through a catheter inside a woman's uterus near to the released egg during ovulation to facilitate fertilisation.
- A semen sample from 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.





- 
- 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.



- 
- A background image of purple flowers, possibly grape hyacinths, with a soft focus. The flowers are small and bell-shaped, with some showing white centers. The overall color palette is purple and white.
- 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.

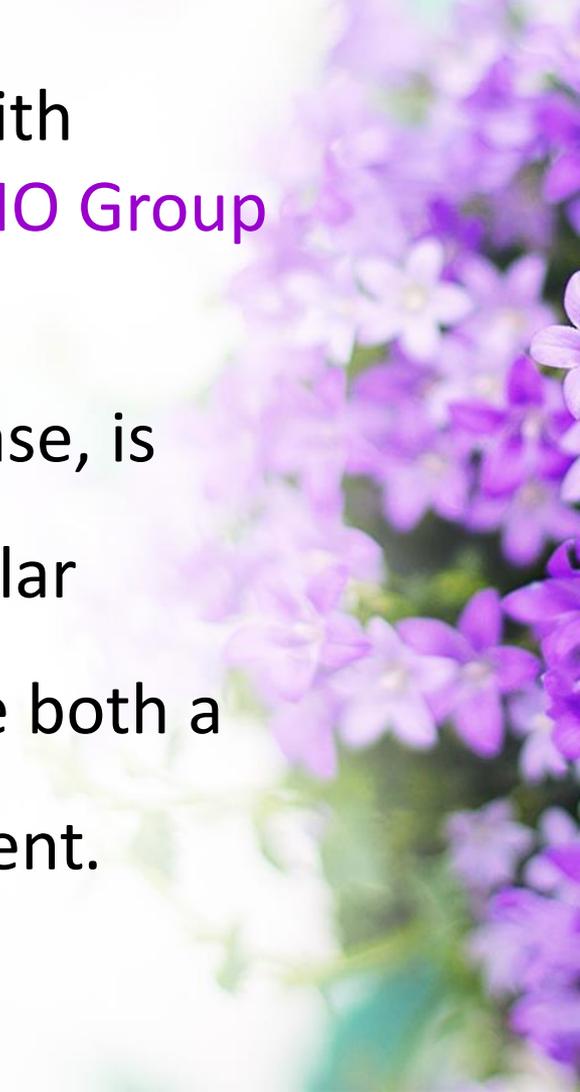
- **Impaired endometrial growth** has been reported in clomiphene-treated women.
- preovulatory endometrial thickness in clomiphene-induced cycles remains well within the range normally observed in spontaneous ovulatory cycles .



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 ↓



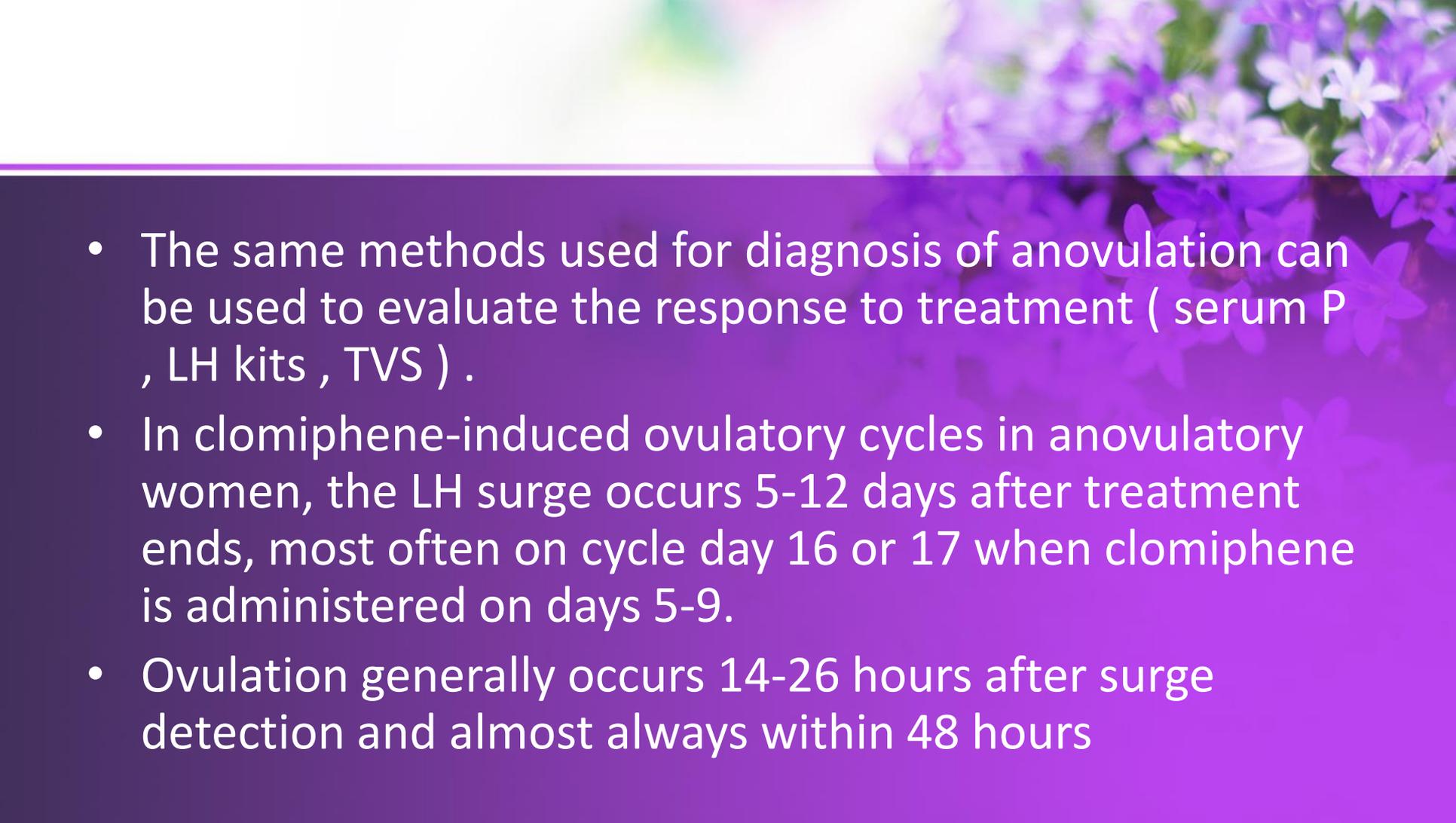
Clomiphene citrate treatment is for

- 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.



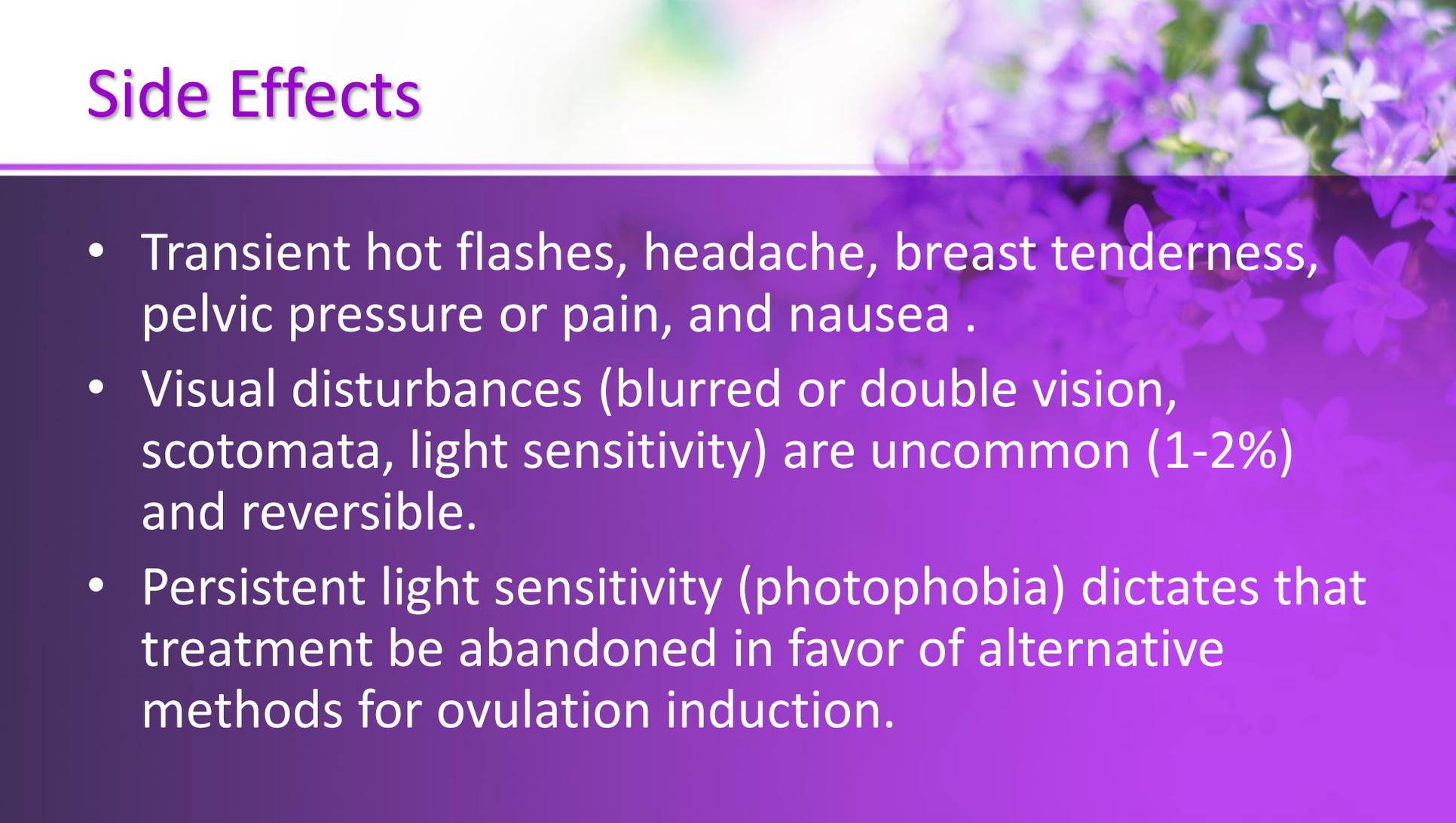
- 
- The same methods used for diagnosis of anovulation can be used to evaluate the response to treatment (serum P , LH kits , TVS) .
 - In clomiphene-induced ovulatory cycles in anovulatory women, the LH surge occurs 5-12 days after treatment ends, most often on cycle day 16 or 17 when clomiphene is 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



- 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

A cluster of small, light purple flowers with white centers, likely from a plant like Salvia, is shown in the top right corner of the slide. The background of the slide is a solid purple color.

- 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

A cluster of small, light purple flowers with five petals and yellow centers, set against a blurred background of green foliage. The flowers are in sharp focus in the upper right corner of the slide.

- 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

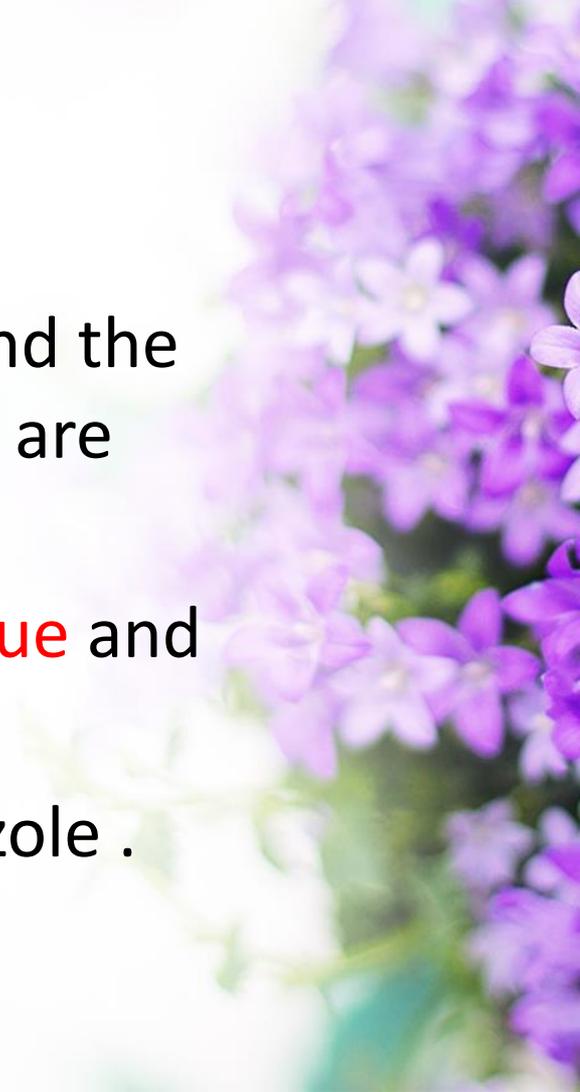


Results of Treatment with Aromatase Inhibitors

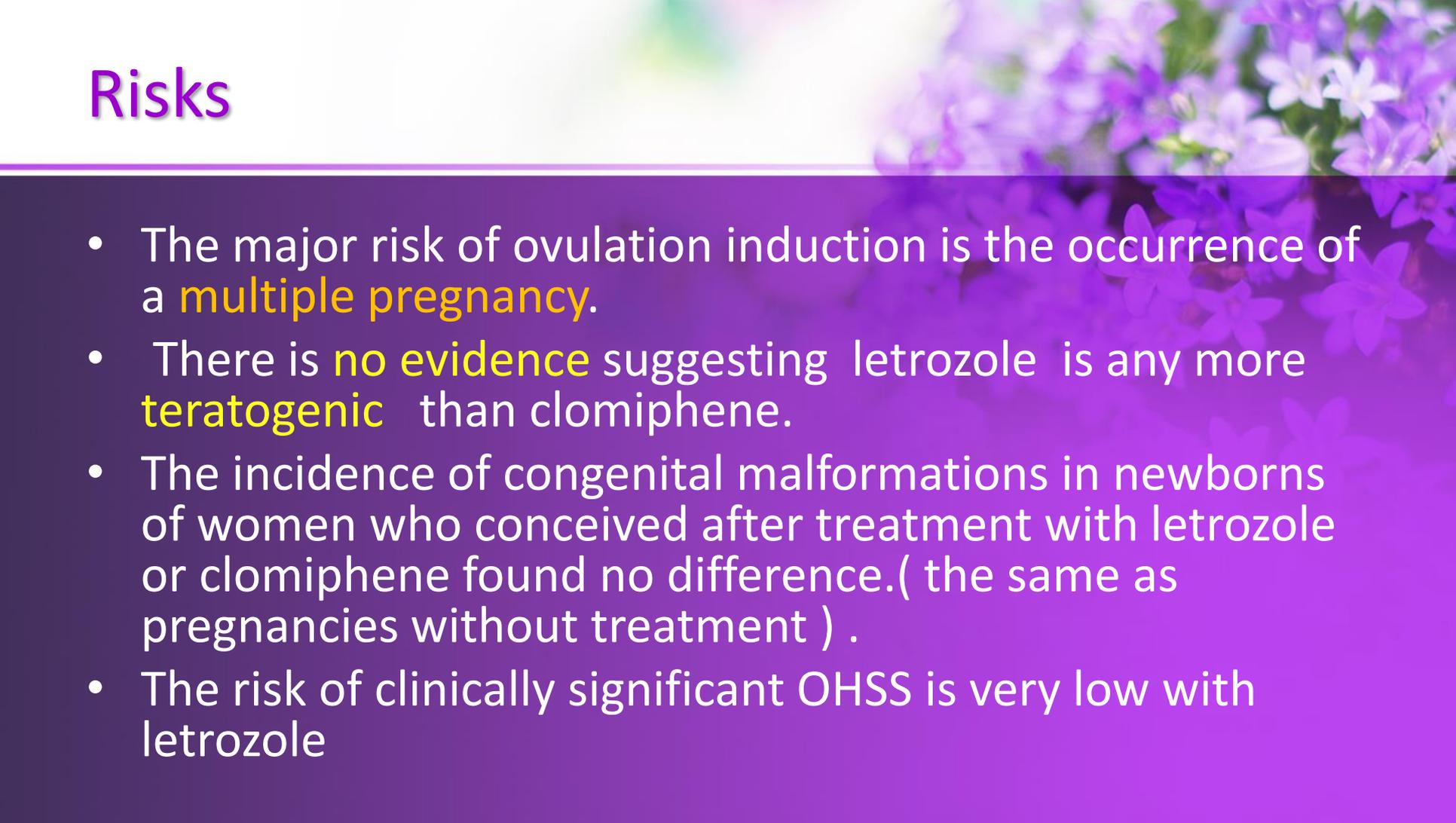
- Letrozole seems independent of BMI , despite ↓ overall LBR with ↑ BMI .
- Miscarriage per pregnancy and multiple pregnancy rates are also similar between letrozole and clomiphene-induced cycles.
- Aromatase inhibitors can also be effective in anovulatory women who fail to ovulate in response to clomiphene 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 .

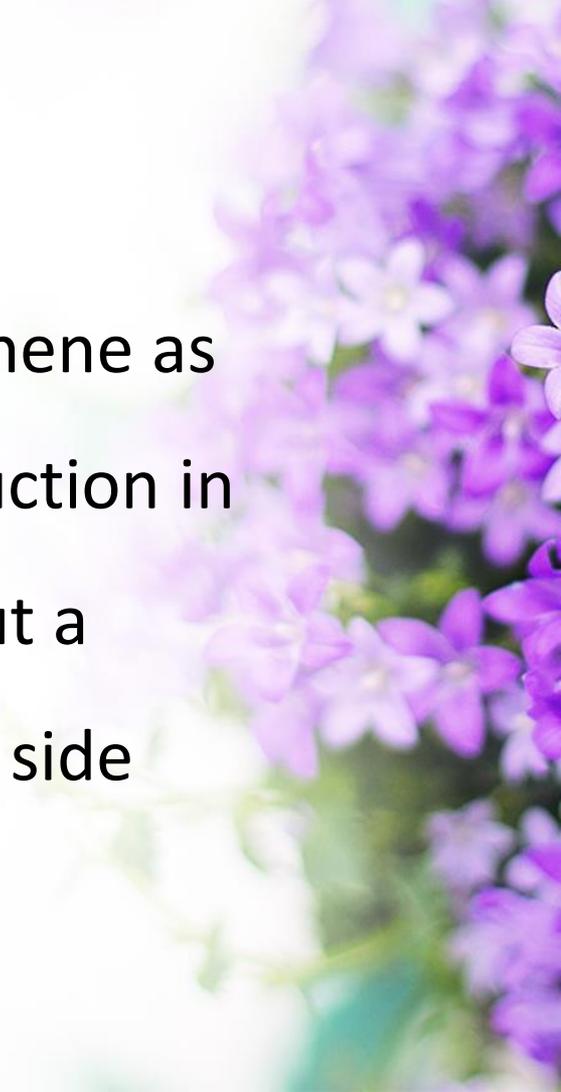


Risks



- 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 .



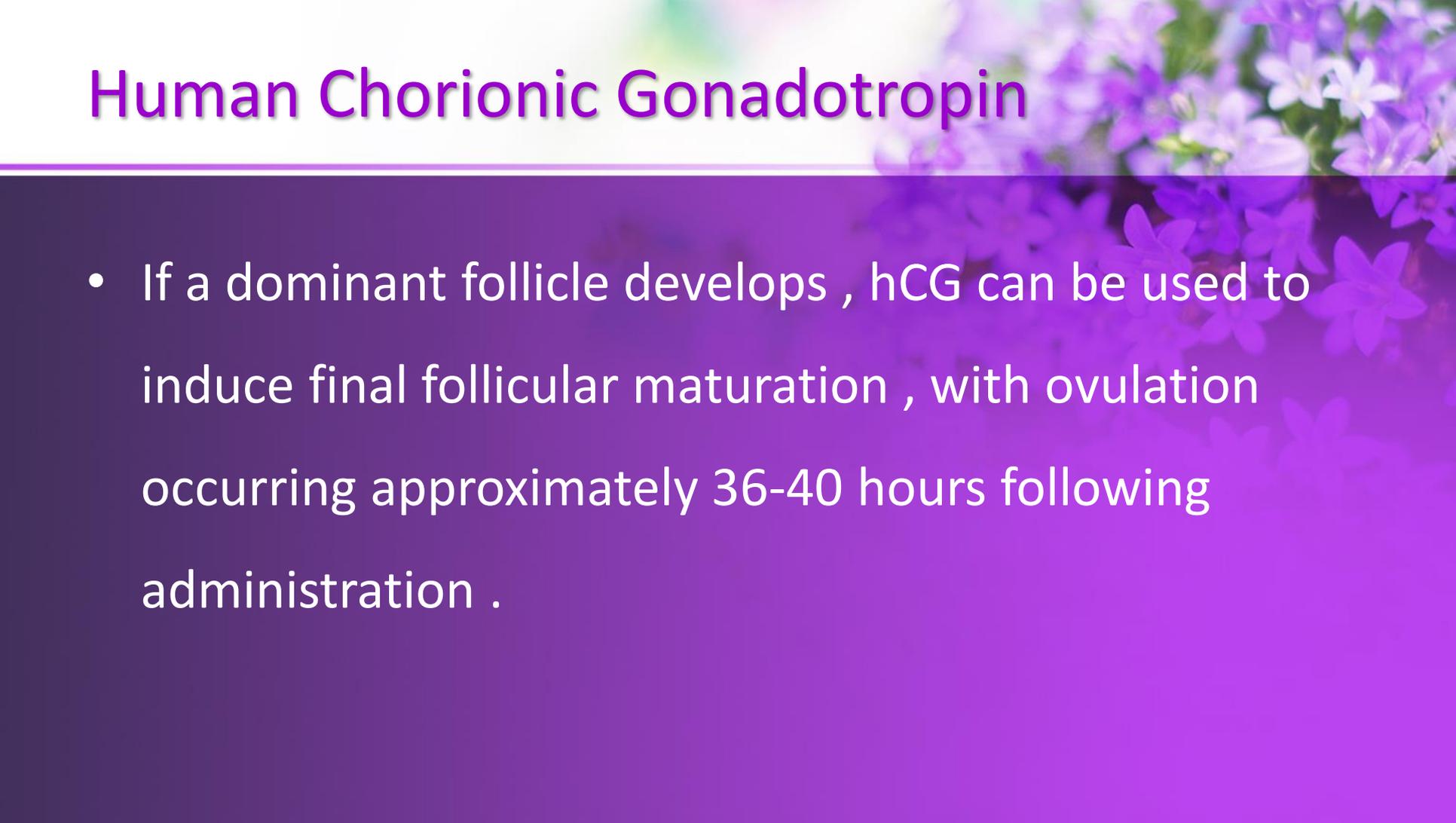
Monitoring Ovulation Induction Therapy

- 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

The background of the slide features a close-up photograph of numerous small, five-petaled purple flowers with yellow centers, set against a soft-focus green background. The flowers are densely packed in the upper right corner and extend towards the center of the frame.

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

HCG

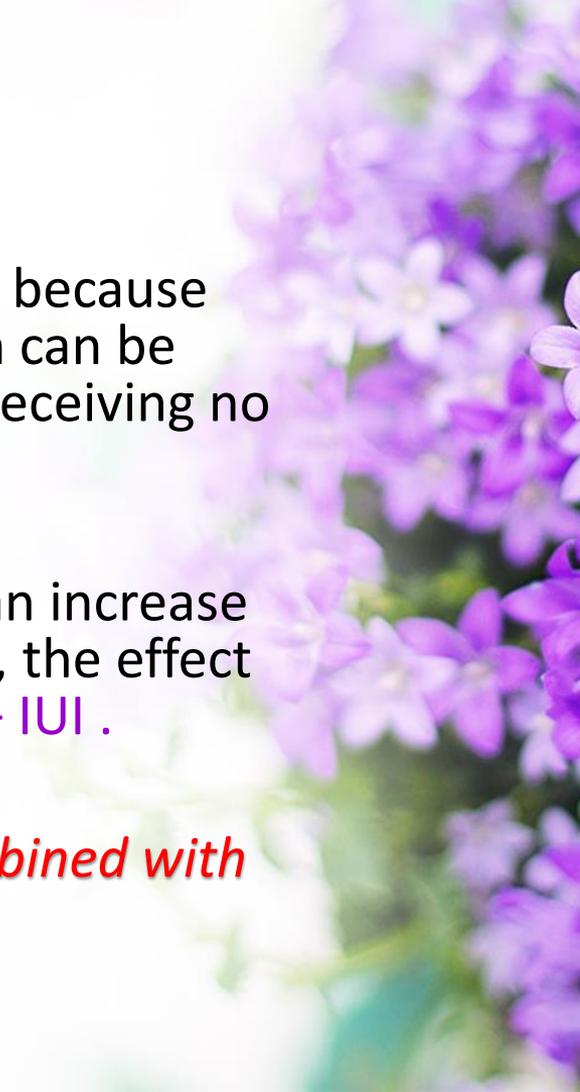
- HCG is recommended is used when 1 - 2 follicles are 16 to 18 mm diameter and the E2 level per dominant follicle is 150 to 300 pg/mL .
- Ovulation is expected 24 - 48 hours after the hCG trigger.
- Intercourse should be recommended within 24 - 48 hours of ovulation triggering or IUI 24 - 36 hours after 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.

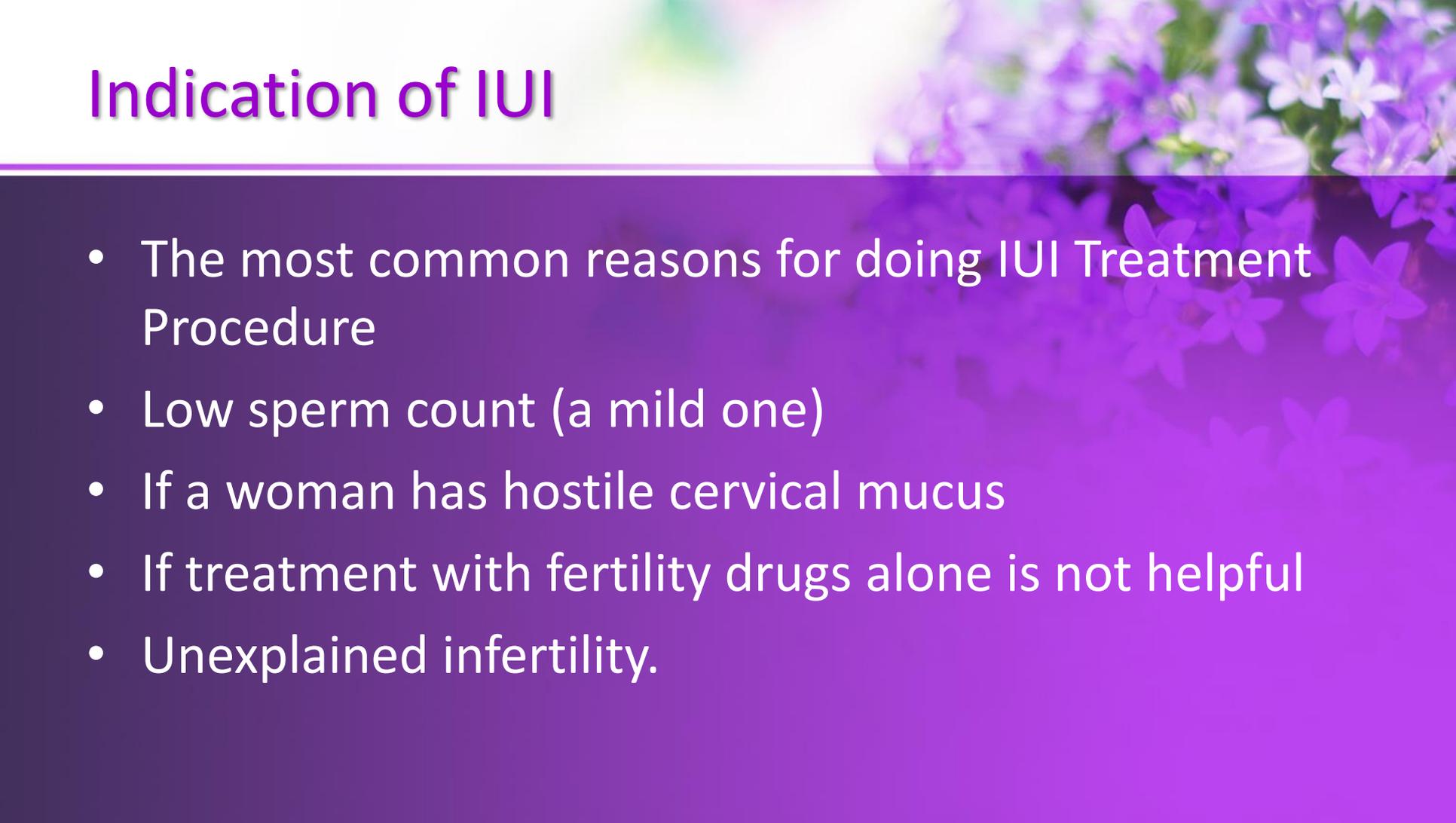


Treatment idiopathic subfertility



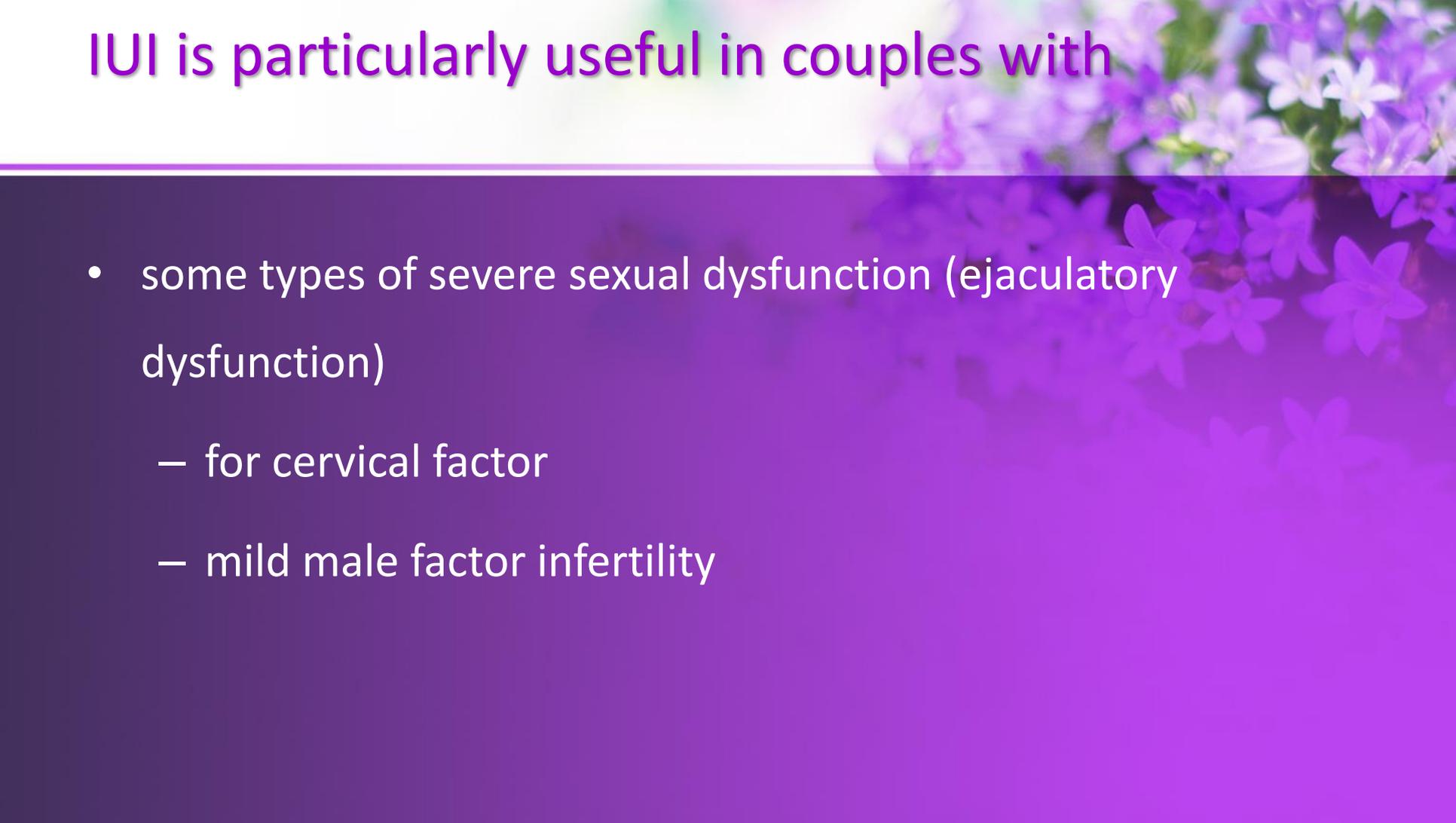
- **Exogenous FSH** may improve semen quality in a subset of men with idiopathic oligospermia in whom testicular biopsy reveals maturation arrest and serum FSH and inhibin B levels are normal.
- Empiric treatment (3–6 months) with either **clomiphene citrate** (25 mg daily) or **tamoxifen** (20 mg daily)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



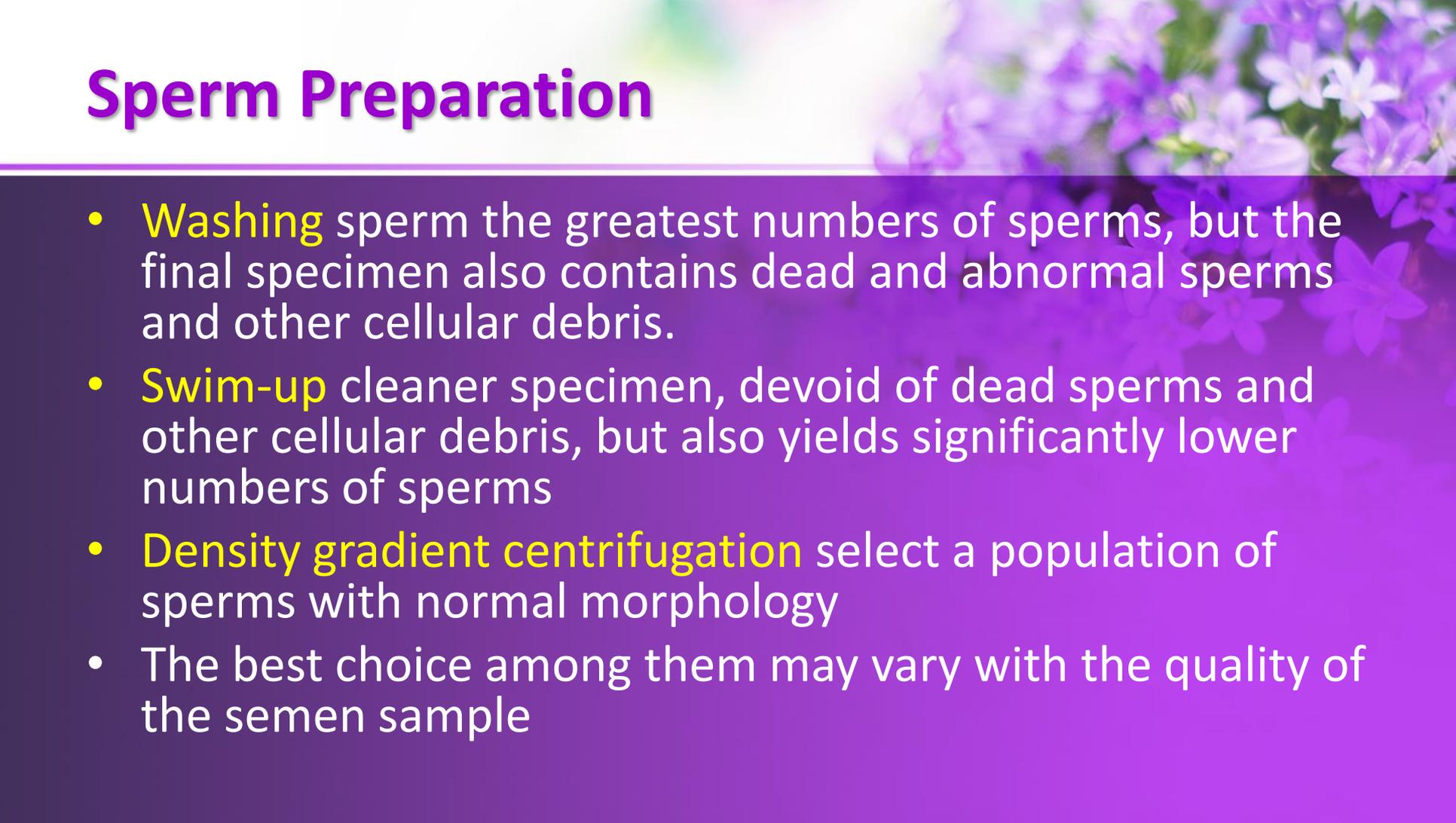
Retrograde Ejaculation

- 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

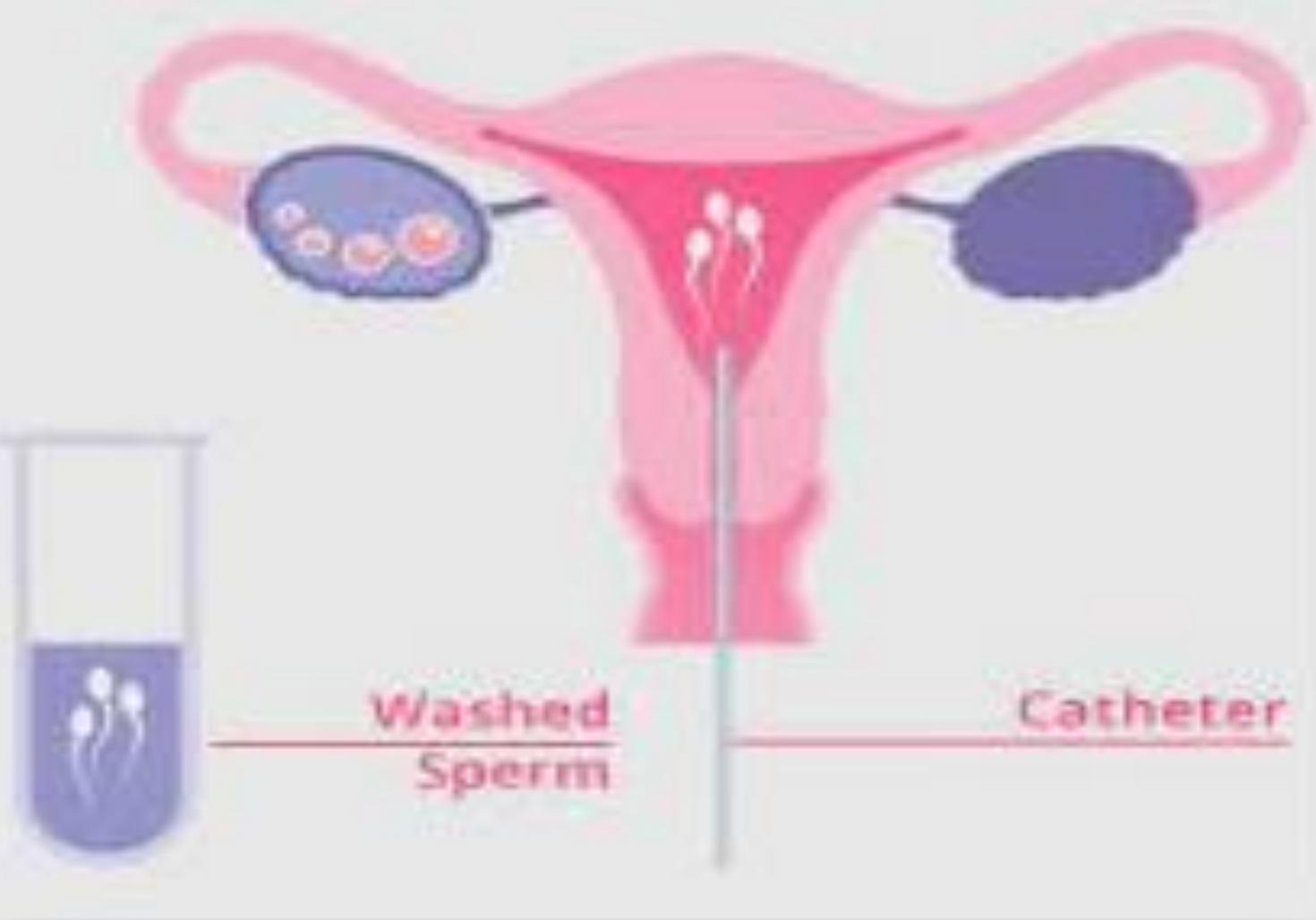


Intracytoplasmic Sperm Injection (ICSI)

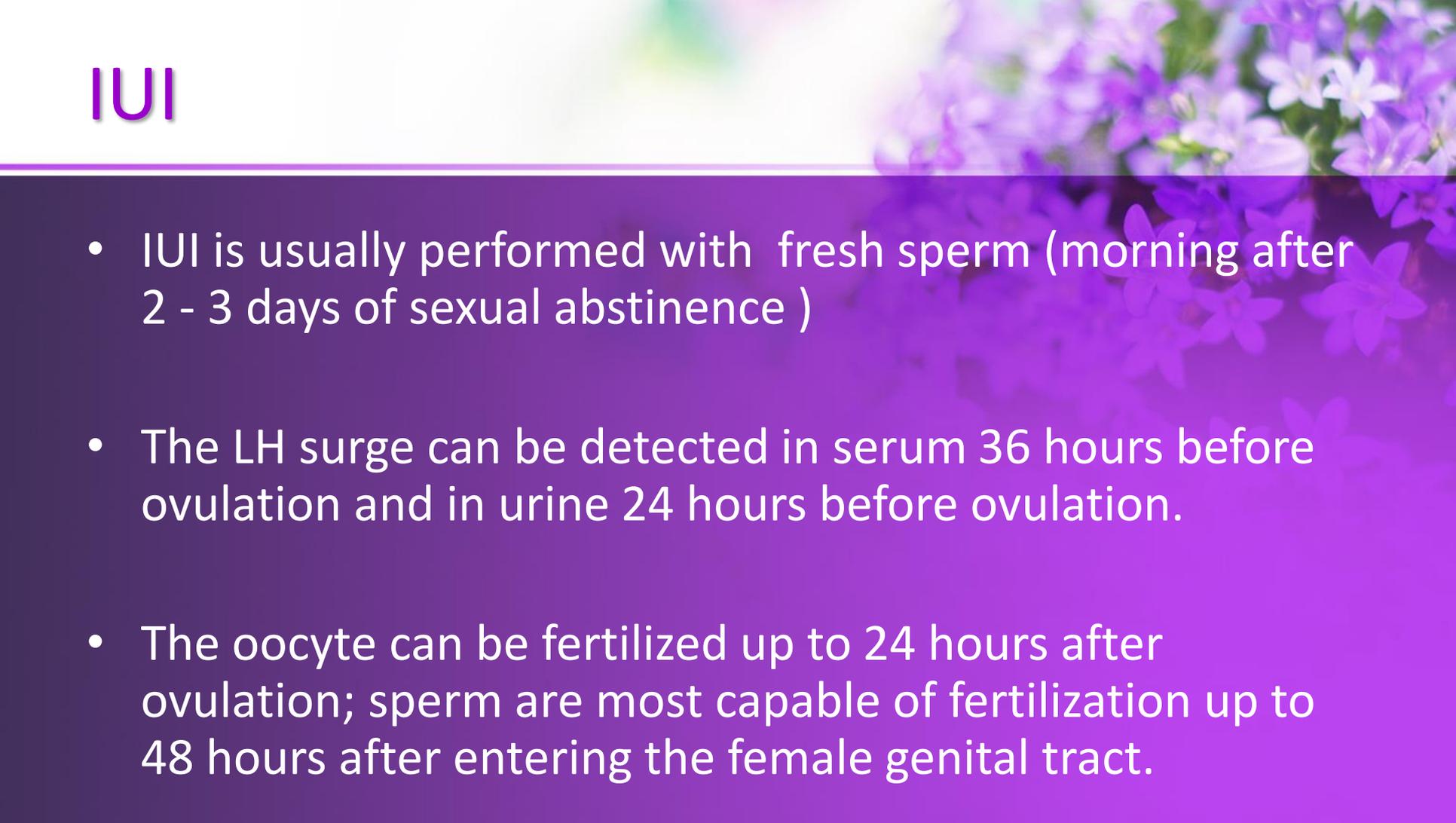
Min requirements

- 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

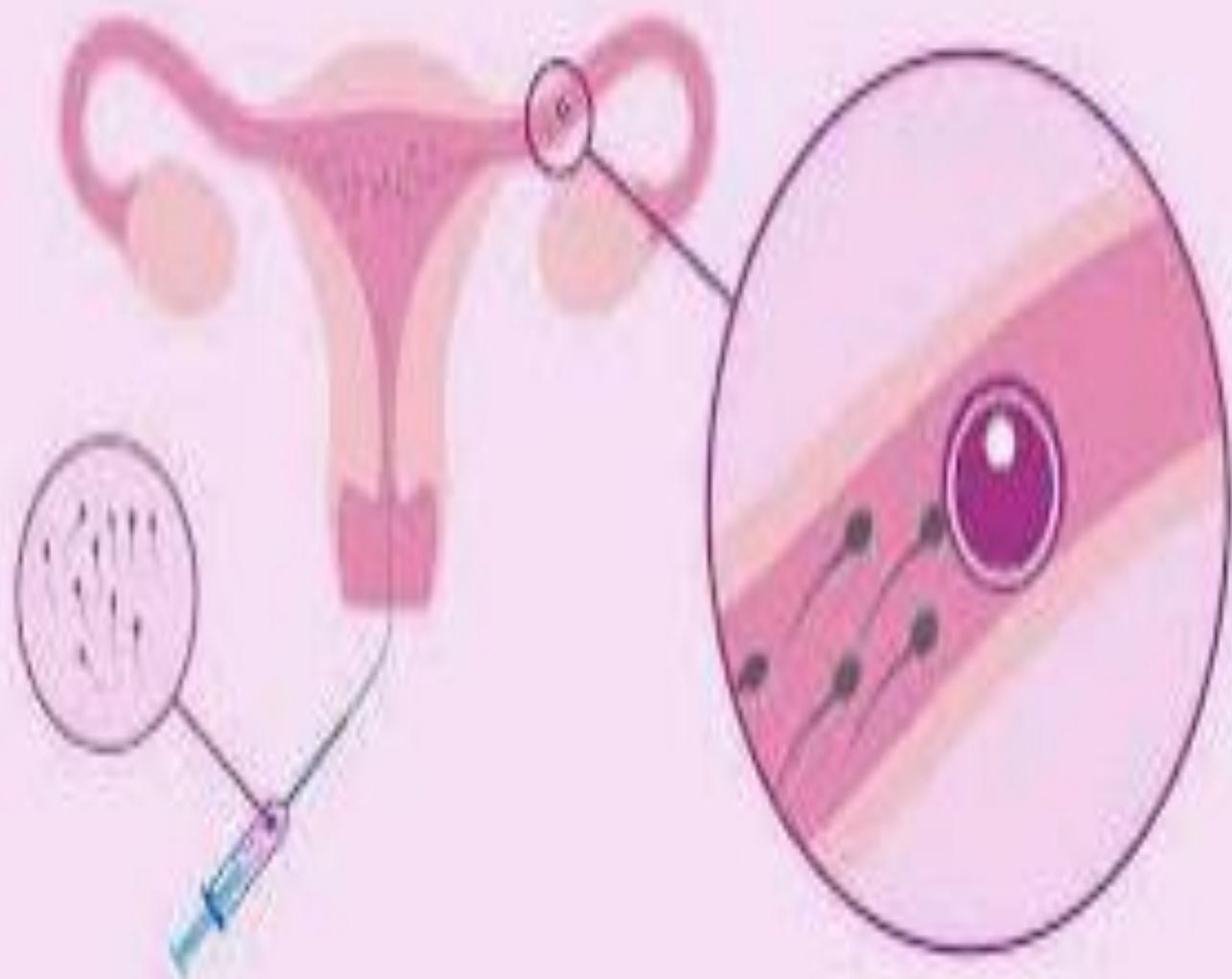




IUI

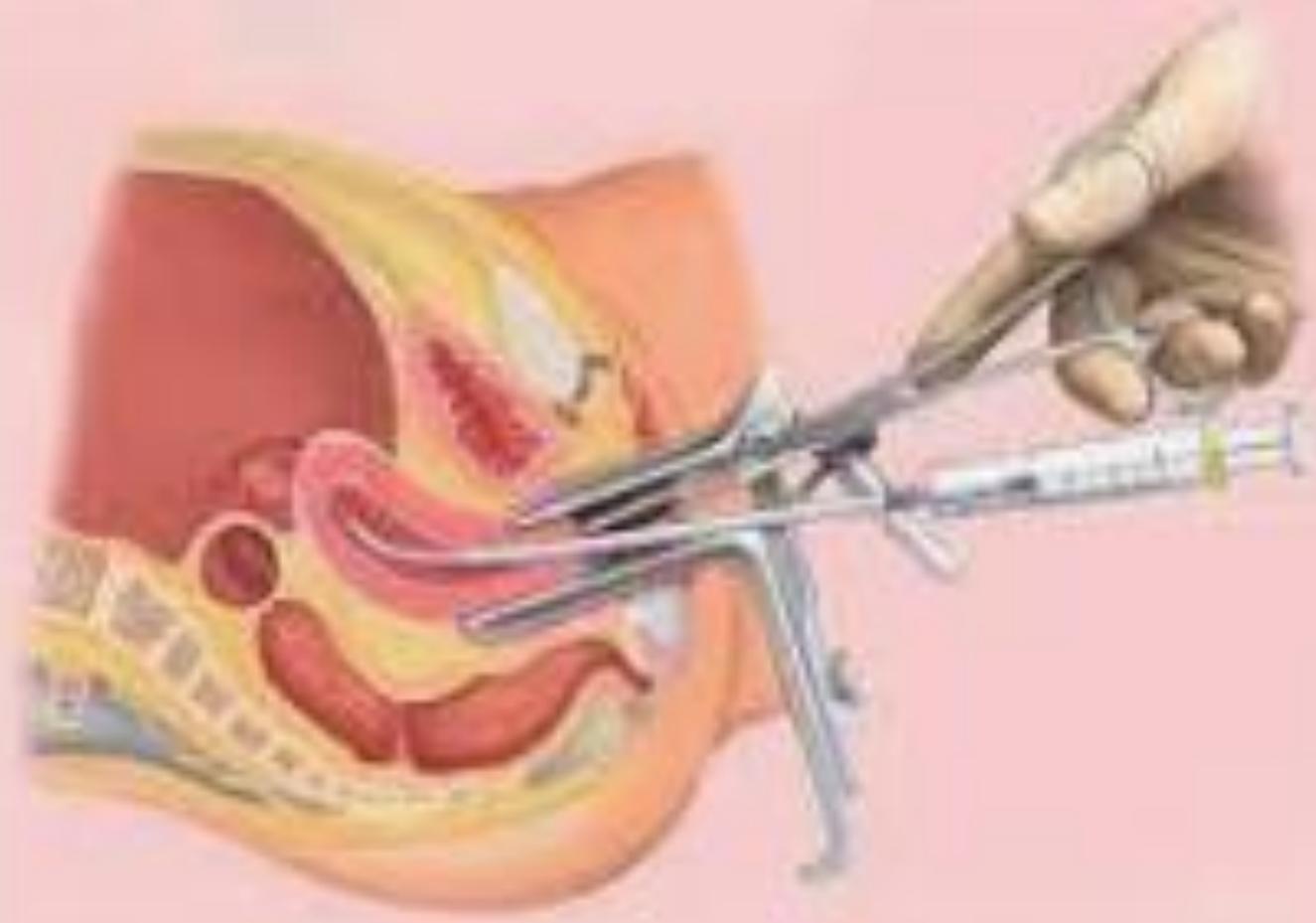


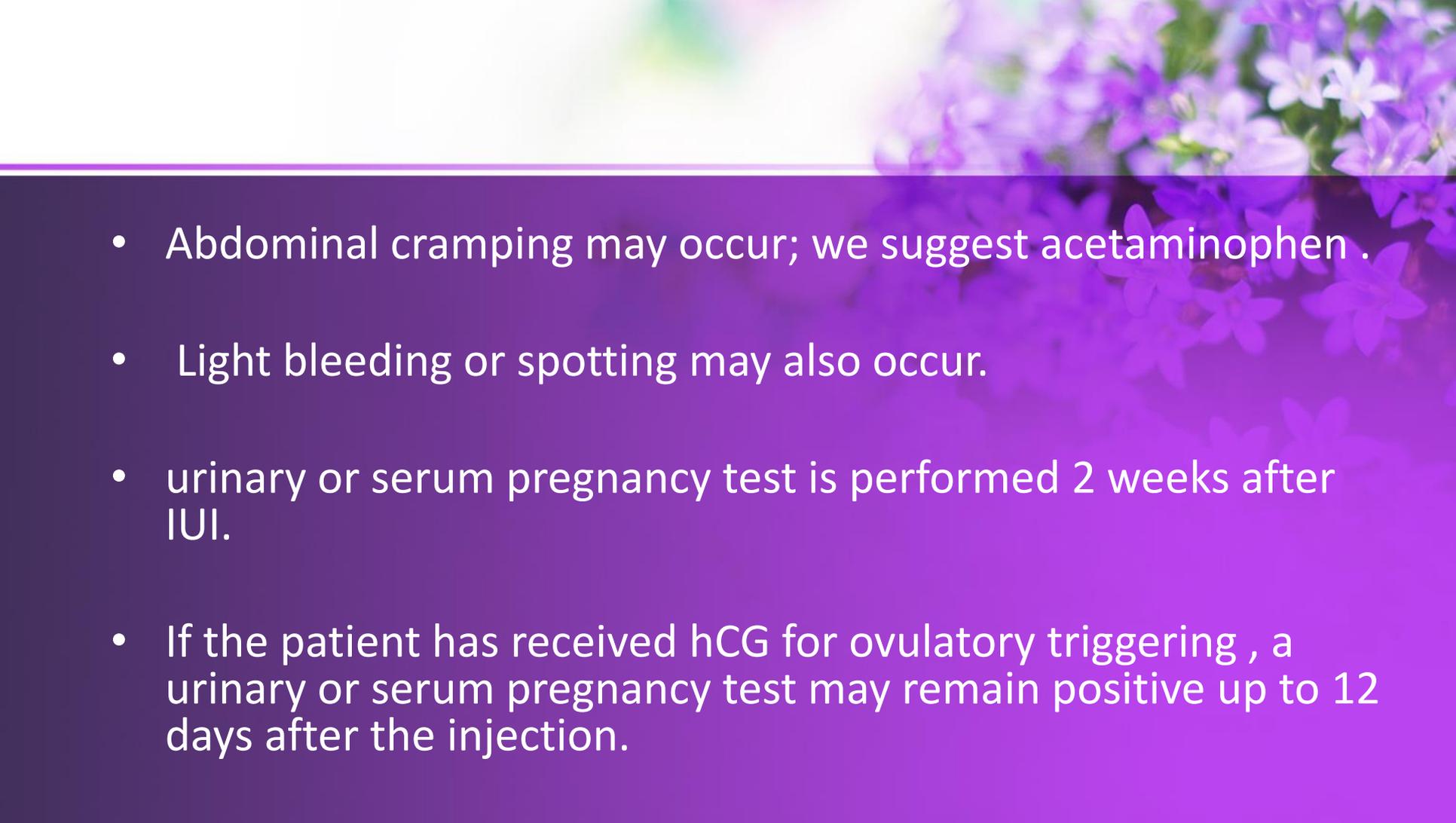
- IUI is usually performed with fresh sperm (morning after 2 - 3 days of sexual abstinence)
- The LH surge can be detected in serum 36 hours before ovulation and in urine 24 hours before ovulation.
- The oocyte can be fertilized up to 24 hours after ovulation; sperm are most capable of fertilization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



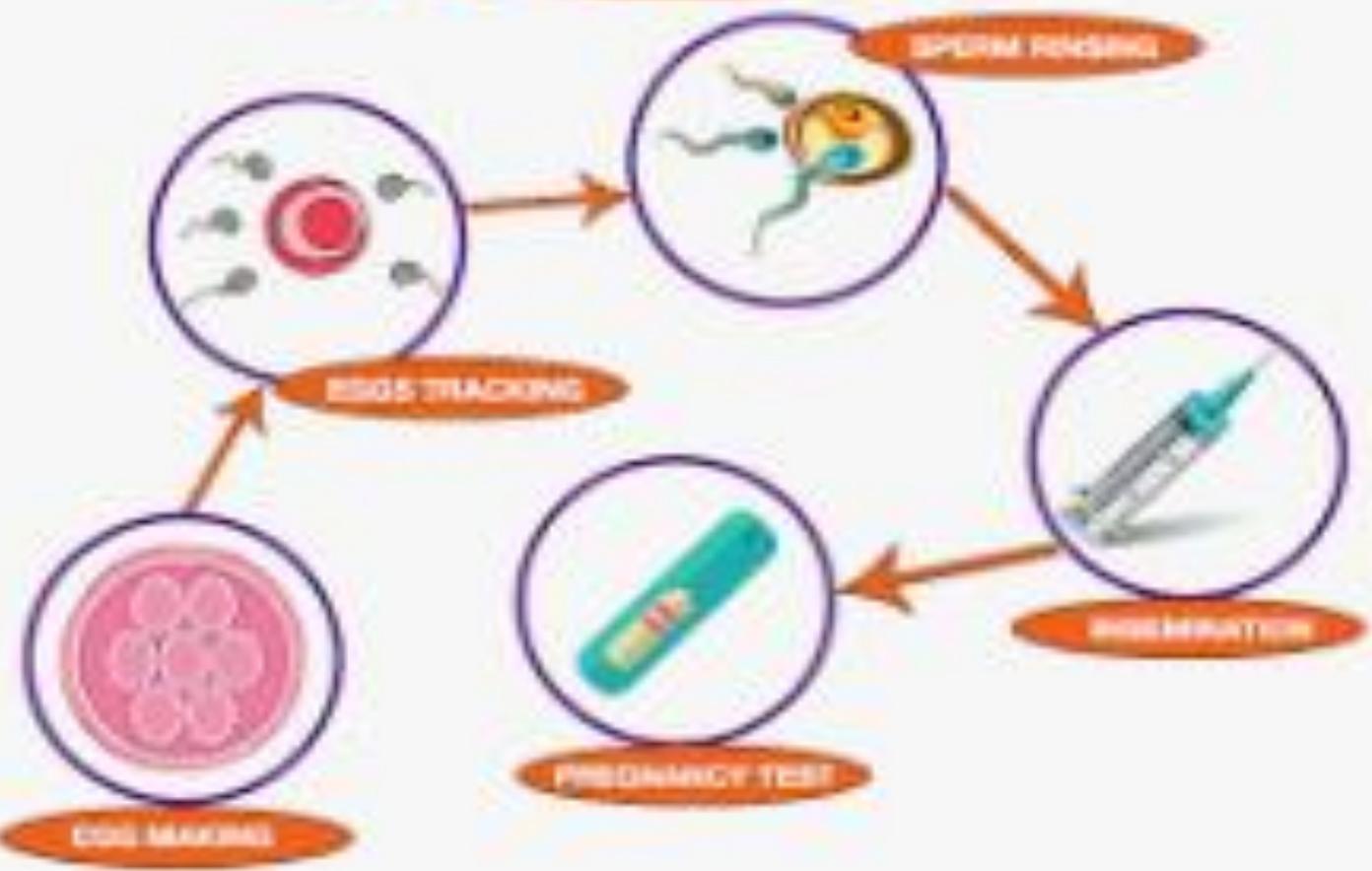
- Proper **identification of both the patient and sperm sample** in the laboratory and the clinic is essential.
- **Antibiotic** prophylaxis is **unnecessary**.
- **Povidone iodine** should not be used to cleanse the cervix because it is toxic to sperm.
- The sperm is suspended in a small volume of media,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



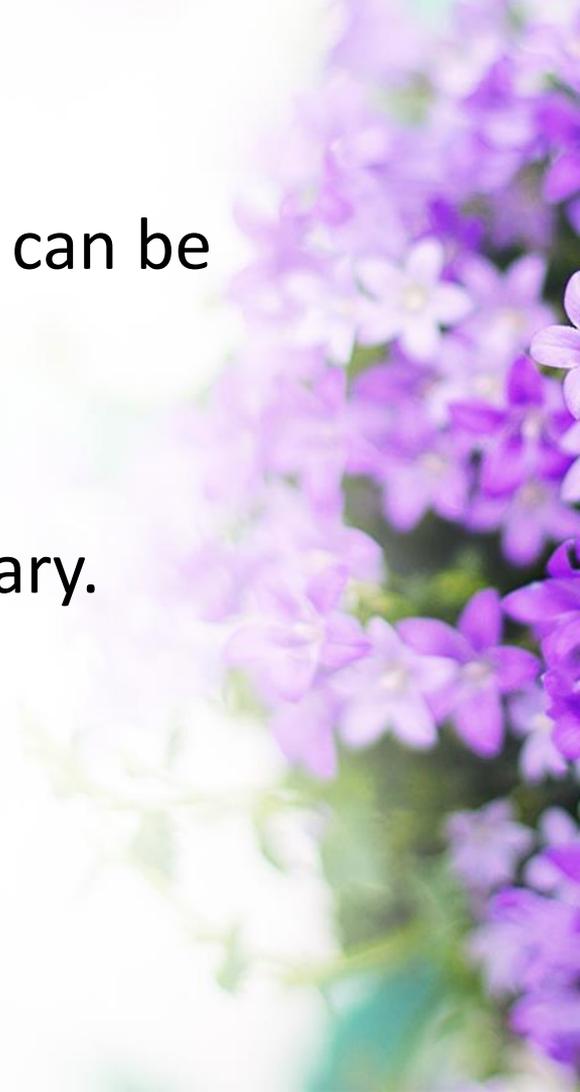


- 
- Abdominal cramping may occur; we suggest acetaminophen .
 - Light bleeding or spotting may also occur.
 - urinary or serum pregnancy test is performed 2 weeks after IUI.
 - If the patient has received hCG for ovulatory triggering , a urinary or serum pregnancy test may remain positive up to 12 days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

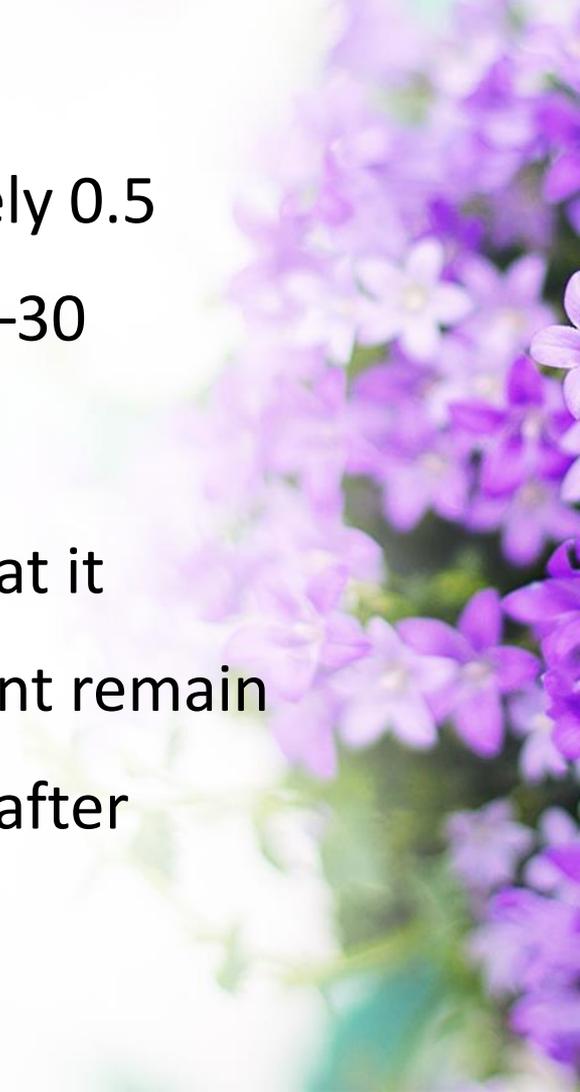
IUI PROCESS



- 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.





Thank you for
your attention