Infertility

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Definitions:

Infertility is defined as the failure of a couple of reproductive age to conceive after at least 1 year of regular coitus without contraception.

Synonyms and related keywords:

- infertility, lack of pregnancy, fertility, in vitro fertilization, conception problems, pregnancy problems, assisted reproductive technologies (ART), gamete intra-fallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), partial zone dissection (PZD), sub zonal sperm injection, assisted hatching, etc.

Infertility is considered primary when it occurs in a woman who has never established a pregnancy and secondary when it occurs in a woman who has a history of one or more previous pregnancies.

Fertility is defined as the capacity to reproduce or the state of being fertile.

This term should be differentiated from fecundability, which is the probability of achieving a pregnancy each month, and fecundity, which is the ability to achieve a live birth within one menstrual cycle

Incidence:

- Infertility affects approximately 15% of couples of reproductive age. In recent years, there has been an increasing demand for infertility services.

The origin of infertility is similarly due to male or female factors; the causes are multiple. Female factors account for 32% of infertility. Male factors account for 18.8% of infertility. Male and female factors combined cause 18.5% of fertility. The etiology is unknown in 11.1%, and other causes are identified in 5.6%.

Causes of Male Infertility

- Low sperm count; normally, men produce at least 20 million sperms per milliliter of semen (that's around one sixth of the total ejaculate); fewer is judged to be subfertile.
- Poor sperm motility; sperms will then be unable to swim through the cervix to meet the egg in the fallopian tube.

Causes of Male Infertility:

- Poor shape (known as 'morphology'), so that an individual sperm is unable to penetrate the outer layer of an egg.
- Non-production of sperm. (because of testicular failure) or complete absence of sperm (perhaps because of an obstruction)

Causes of Female Infertility

- Hormonal disorders; as a result, egg follicles might not grow within the ovary, or an egg might not be released (ovulation).
- Damaged or blocked fallopian tubes, which will prevent an egg and sperm meeting.
- Endometriosis, in which womb tissue invades and damages neighboring reproductive tissue.
- Excessively thick cervical mucus, which prevents sperm passing through.

Evaluation.

- History and physical examination
- Semen analysis
- Sperm–cervical mucus interaction (postcoital testing)
- Testing for ovulation
- Evaluation of tubal patency
- Detection of uterine abnormalities
- Determination of peritoneal abnormalities

History:

- frequency and timing of intercourse
- character of menstruation,
- information regarding to impotence, dyspareunia, the use of lubricants,
- sexually transmitted diseases.

Physical examination

- BP, PR, body T.
- Height and weight to calculate the body mass index (body mass/height).
- Eye examination to establish the presence of exophthalmos (hyperthyroidism).
- The presence of epicanthus, lower implantation of the ears and hairline, and webbed neck can be associated with chromosomic abnormalities.
- Evaluation of thyroid gland to exclude enlargement or thyroid nodules.
- Breast examination: breast development and to seek abnormal masses or secretions (galactorrhea).

Physical examination:

- The abdominal examination should be directed to the presence of abnormal masses at the hypogastrium level.
- The examination of the extremities to rule out malformation (shortness of the fourth finger or cubitus valgus, which can be associated with chromosomal abnormalities and other congenital defects.
- Examine the skin to establish the presence of acne, hypertrichosis, and hirsutism.

After the completion of all these steps no abnormality or cause of infertility can be identified in 15% of couples. This group comprises a category known as "unexplained infertility."

Gynecological examination

- Evaluation of hair distribution, clitoris size, Bartholin glands, labia majora and minora, and any *condylomata acuminatum* or other lesions that could indicate the existence of venereal disease.
- The inspection of the vaginal mucosa may indicate a deficiency of estrogens or the presence of infection.

Gynecological examination

- The evaluation of the cervix should include a Papanicolau test (Pap smear) and cultures for gonorrhea, Chlamydia, and Ureaplasma urealyticum.

Bimanual examination:

- the direction of the cervix and the size and position of the uterus in order to exclude the presence of uterine fibroids, adnexal masses, tenderness, or pelvic nodules indicative of infection or endometriosis.

Pelvic ultrasonographic scan

- to establish an early diagnosis of adnexal masses; to determine the size and aspect of the ovaries; and to detect the presence of endometrial polyps, submucous fibroids, and hydrosalpinx.

Semen analysis

The semen sample should be collected after a period of abstinence of at least 48 hours and should be evaluated within 1 hour of ejaculation. The sample is obtained either by masturbation or by sexual intercourse with a silicone condom, as latex condoms are spermicidal.

Semen analysis

Normal parameters:

- Volume - 2-5 mL
- pH - 7.2-7.8
- Sperm concentration - 20 million or greater
- Motility - 50%, forward progression
- Morphology - Normal sperm (50% or greater)
- White blood cells - Fewer than 1 million cells/μL

- Azoospermia - absence of sperm that could be related to congenital absence or bilateral obstruction of the vas deferens or ejaculatory ducts, history of spermatogenesis arrest, Sertoli cell syndrome, or postvasectomy.
- Oligozoospermia indicates a concentration of fewer than 20 million sperm/mL and could be associated with ejaculatory dysfunction such as retrograde ejaculation.

- Asthenozoospermia indicates sperm motility of less than 50%. Extreme temperatures and delayed analysis after sperm collection are among the factors that decrease sperm motility.
- Teratospermia indicates an increased number of abnormal sperm morphology at the head, neck, or tail level.

- Hypospermia indicates a decrease of semen volume to less than 2 mL per ejaculation.
- Hyperspermia indicates an increase of sperm volume to more than 8 mL per ejaculation

Semen analysis:

- If abnormalities are present, the patient should be referred to a urologist specializing in infertility to be evaluated for reversible causes of male-factor infertility.

The postcoital test (PCT or Huhner test)

- Allows direct analysis of sperm and cervical mucus interaction and provides a rough estimate of sperm quality. The test is done between days 12 and 14 of a 28–30 day menstrual cycle (after 48 hours of abstinence).
- The mucus is examined within 2–3.5 hours after coitus for total number of sperm seen per high-powered field and percentage and quality of motility.

PCT (*continuation*)

- A satisfactory test is one in which more than 10 motile spermatozoa are seen per high-powered field.
- An unsatisfactory test: no or few spermatozoa seen; nonmotile spermatozoa or those with a “shaking” movement

PCT (continuation)

Possible reason of an unsatisfactory test:

- azospermia (no spermatozoa in ejaculate),
- poor inherent spermatozoa motility,
- hostile cervical mucus (infection, antidodies, or not enough estrogen),
- poor coital technique.

PCT (continuation)

Other causes include:

- cervical stenosis,
- hypoplastic endocervical canal,
- coital dysfunction

PCT *(continuation)*

- a finding of 5–10 progressively motile spermatozoa per high-power field and clear acellular mucus with a spinnbarkeit (the degree to which the mucus stretches between two slides) of 8 cm generally excludes a cervical factor.
- Fecundity rates do not correlate directly with number of motile sperm seen.

The sample can also be assessed for pH, mucus cellularity, WBC, ferning.

Testing for ovulation:

- 1.measuring a rise in basal body temperature (BBT),
- 2.identifying an elevation in the midluteal phase serum progesterone concentration, and detection of luteinizing hormone (LH) in the urine.
- 3. luteal phase endometrial biopsy

1.The basal body temperature (BBT)

- After ovulation, rising progesterone levels increase the basal temperature by approximately 0.22°C - 0.4°C through a hypothalamic thermogenic effect.

2.Midluteal phase progesterone level

- Is another test to assess ovulation
- a concentration greater than 3.0 ng/mL in a blood sample drawn between days 19 and 23 is consistent with ovulation,
- a concentration greater than 10 ng/mL implies adequate luteal support.

3.Urine LH kits

Unlike the rise in BBT and serum progesterone concentrations, which are useful for retrospectively documenting ovulation, urinary LH kits can be used to predict ovulation. Ovulation usually occurs 24 to 36 hrs after detecting the LH surge.

4.Endometrial biopsy

- **An endometrial biopsy evaluates the response of the endometrium to progesterone.**
- **The test is usually performed between days 24 and 26 of a 28 day menstrual cycle or 2–4 days before anticipated menstruation.**

Endometrial biopsy (continuation)

- A luteal phase defect may result from inadequate estrogen priming, progesterone secretion, or endometrial response.

Evaluation of tubal patency

- Tubal patency can be evaluated by hysterosalpingography (HSG) and/or by chromopertubation during laparoscopy.

The hysterosalpingogram (HSG):

- Shows uterine and fallopian tube contour and tubal patency.
- It is performed in the early follicular phase, within 1 week of cessation of menstrual flow.
- Radiopaque dye injected through the cervix. And passes through the uterine cavity into the fallopian tubes and peritoneal cavity. Permanent radiographic films are made under fluoroscopy to demonstrate patent or obstructed tubes

Diagnostic laparoscopy:

- assesses peritoneal and tubal factors (endometriosis and pelvic adhesions)

Treatment of cervical infertility

- An abnormal PCT because of chronic cervicitis: doxycycline 100 mg by mouth twice daily for 7 days
- Reduced secretion of cervical mucus due to destruction of the endocervical glands by previous cervical conization, freezing, or laser vaporization: low-dose estrogen therapy
- The most successful - IUI

Treatment of uterine factors

- Congenital absence of the uterus and vagina (Rokitansky-Küster-Hauser syndrome) - surrogate mother or gestational carrier.
- Uterine malformations: not require treatment /or plastic surgery/ART
- Myoma, endometriosis: medication/surgery

Tubal factor infertility:

- **tubal cannulation,**
- **microsurgical tubocornual reanastomosis,**
- **IVF.**

Treatment of anovulation:

stimulation of multiple ovarian follicles:

- clomiphene citrate (CC),
- human menopausal gonadotropins (hMG),
- purified follicle-stimulating hormone (FSH).

Clomiphene Citrate (CC)

- The standard dose of CC is 50 mg PO qd for 5 days, starting on the fifth menstrual cycle day or after progestin-induced bleeding.
- The CC response is monitored using pelvic US starting on the 12th menstrual cycle day. The follicle should develop to a diameter of 23-24 mm

Human menopause gonadotropins (hMG)

- **Brand Names:** Humegon, Organon, Pergonal, Serono, Repronex
- contains 75 U of FSH and 75 U of LH per mL, although the concentration may vary among batches (ranges from FSH at 60-90 U and LH at 60-120 U)
- injected once daily for 5 days or more.

***Luteal phase defects*:**

- intramuscular or intravaginal progesterone until the luteoplacental shift occurs at 8–10 weeks gestational age.

Treatment of Hyperprolactinemia:

- Inducing of ovulation : Bromocriptine in starting dose 2.5 mg each bedtime.
- CC is added if ovulation does not occur within 3 months after beginning treatment.

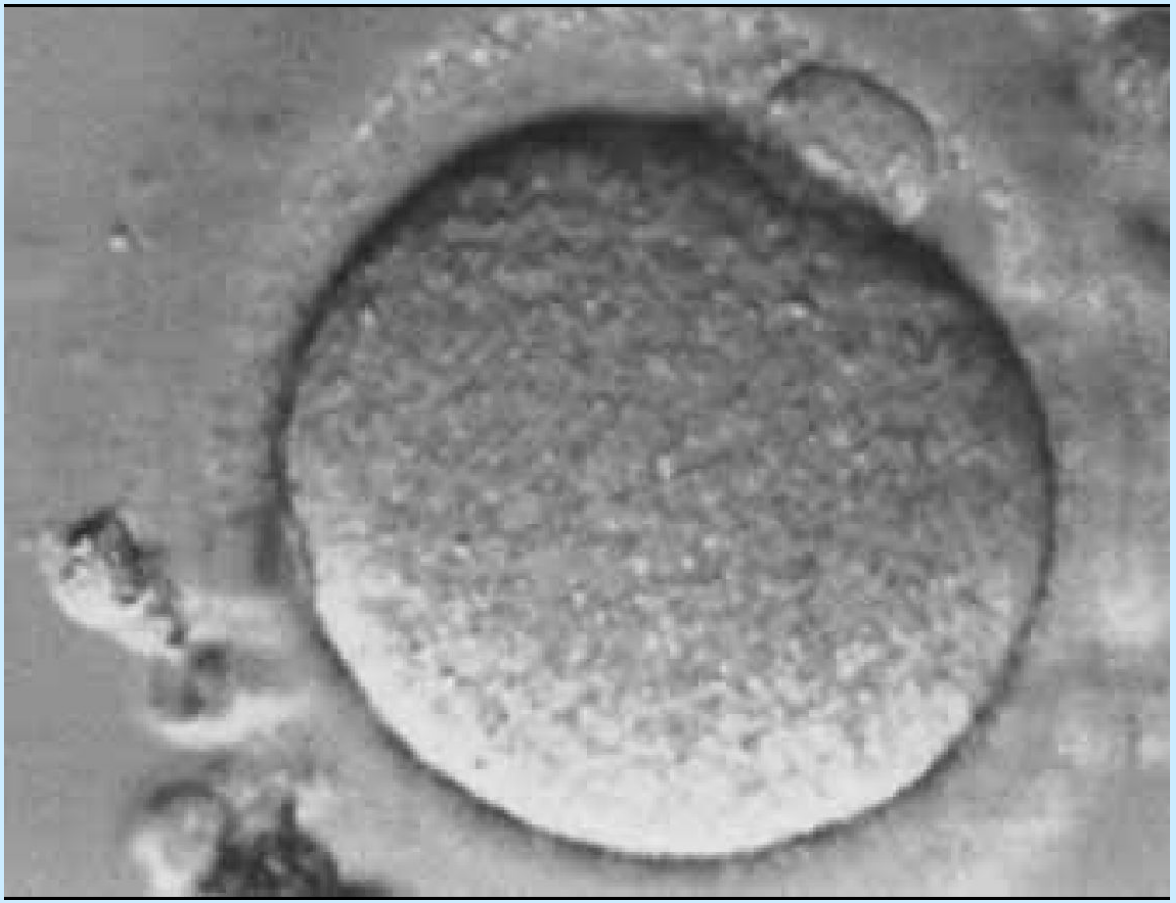
ASSISTED REPRODUCTIVE TECHNOLOGIES:

- Gamete intrafallopian transfer (GIFT): extraction of oocytes is followed by the transfer of gametes (sperm and oocyte) into a normal fallopian tube by laparoscopy.
- Zygote intrafallopian transfer (ZIFT): the placement of embryos into the fallopian tube after oocyte retrieval and fertilization

(continuation)

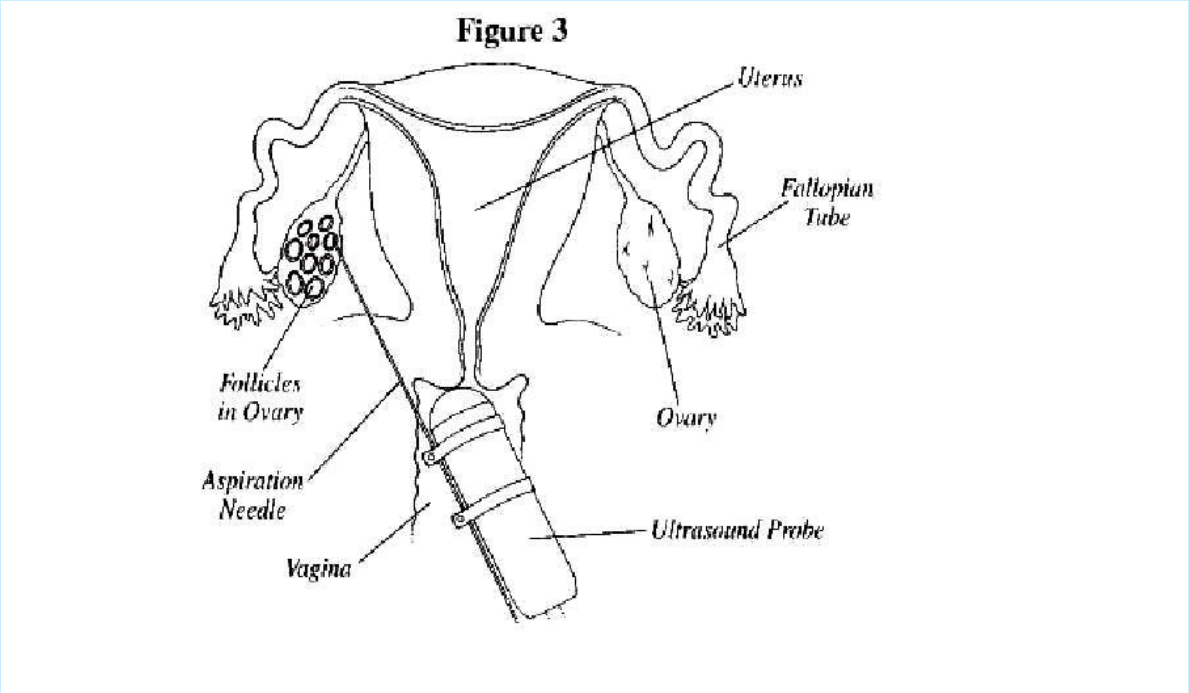
- In vitro fertilization (IVF): controlled ovarian hyperstimulation, ultrasonographically guided aspiration of oocytes, laboratory fertilization with prepared sperm, embryo culture, and transfer of the resulting embryos into the uterus through the cervix.

- ***A mature, unfertilized egg.***

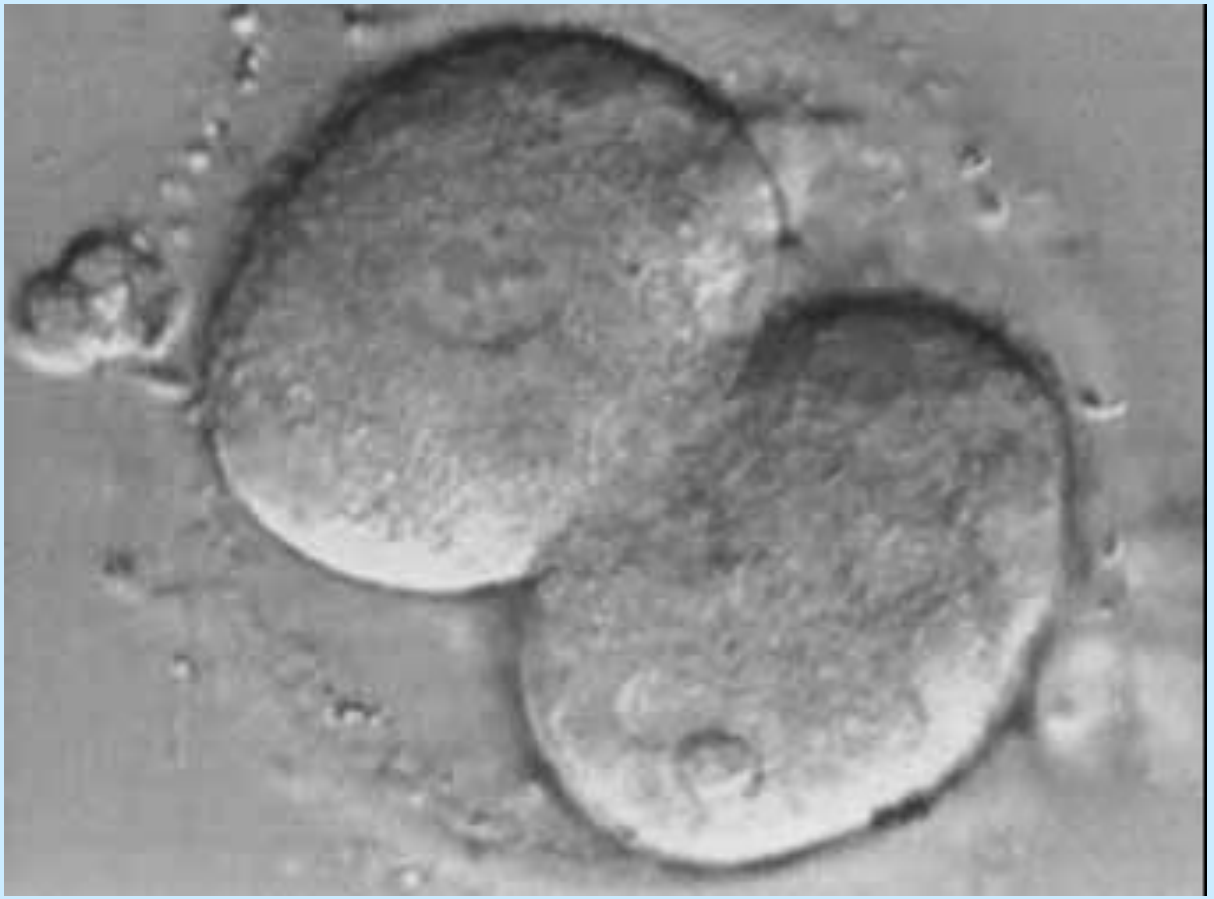


EGG retrieval

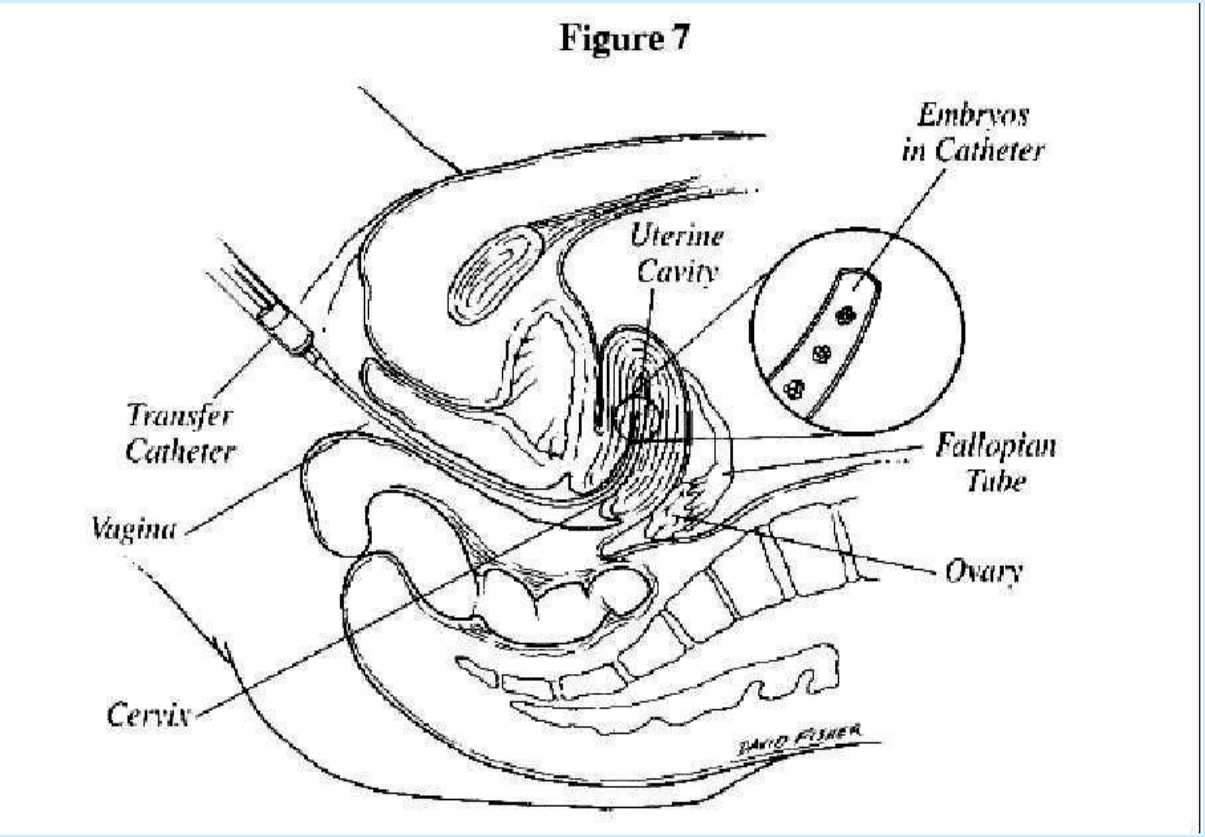
- *Egg retrieval is usually performed through the vagina with an ultrasound-guided needle.*



- *A fertilized egg that has divided once and is now a two-cell embryo.*



- *Embryo transfer is performed through the cervix.*



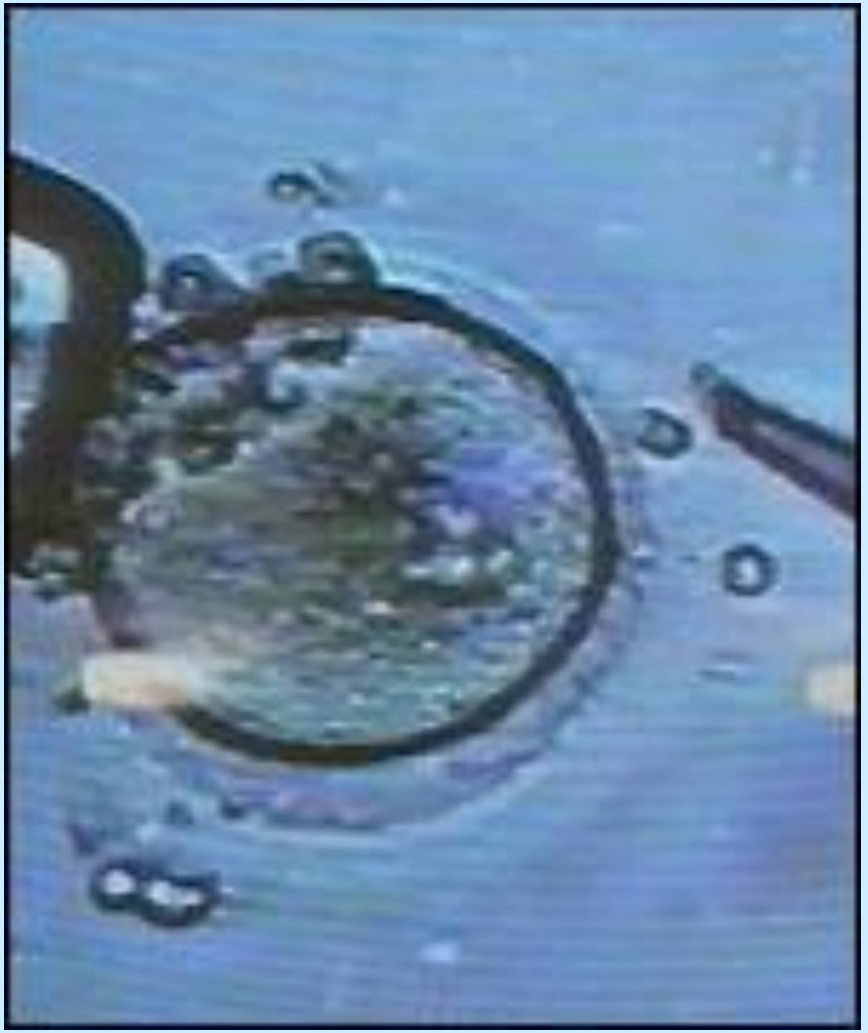
Indications for in vitro fertilization:

- **Tubal conditions**
- **Endometriosis**
- **Unexplained infertility**
- **Male factor infertility**
- **Uterine malformations**

ASSISTED REPRODUCTIVE TECHNOLOGIES (*continuation*)

- **intracytoplasmic sperm injection: single spermatozoon is injected into each oocyte, and the resulting embryos are transferred transcervically into the uterus.**

- Intracytoplasmic sperm injection

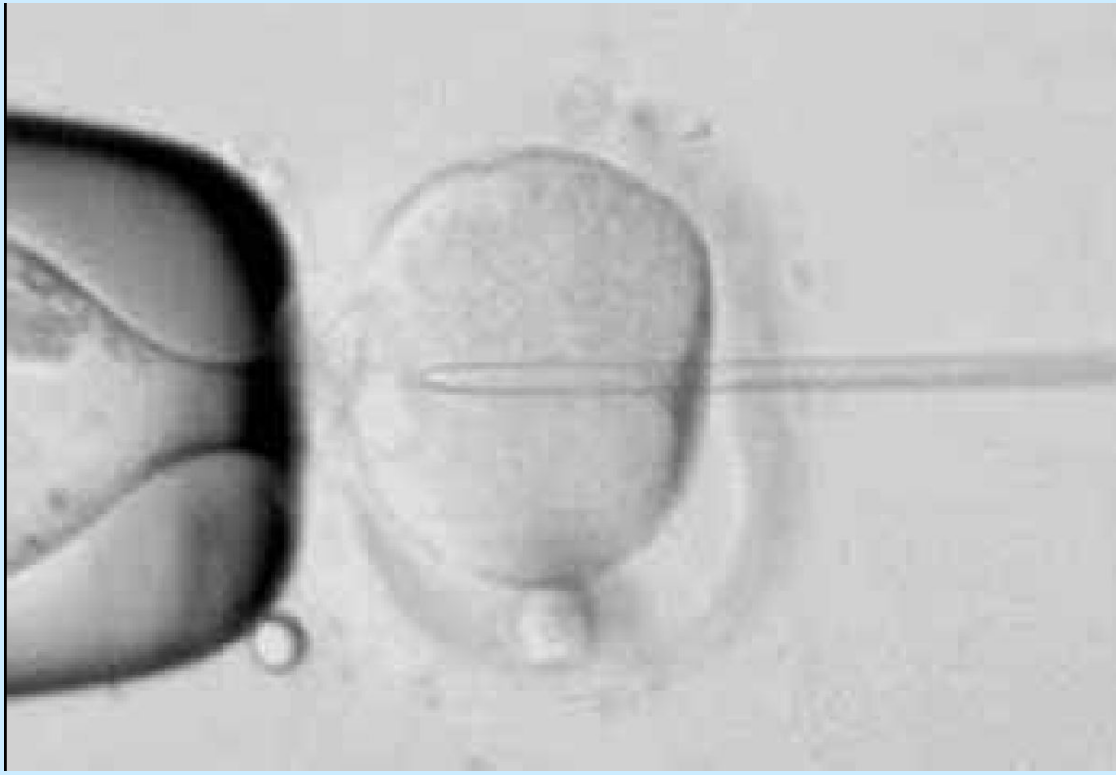


Indications for Intracytoplasmic Sperm Injection

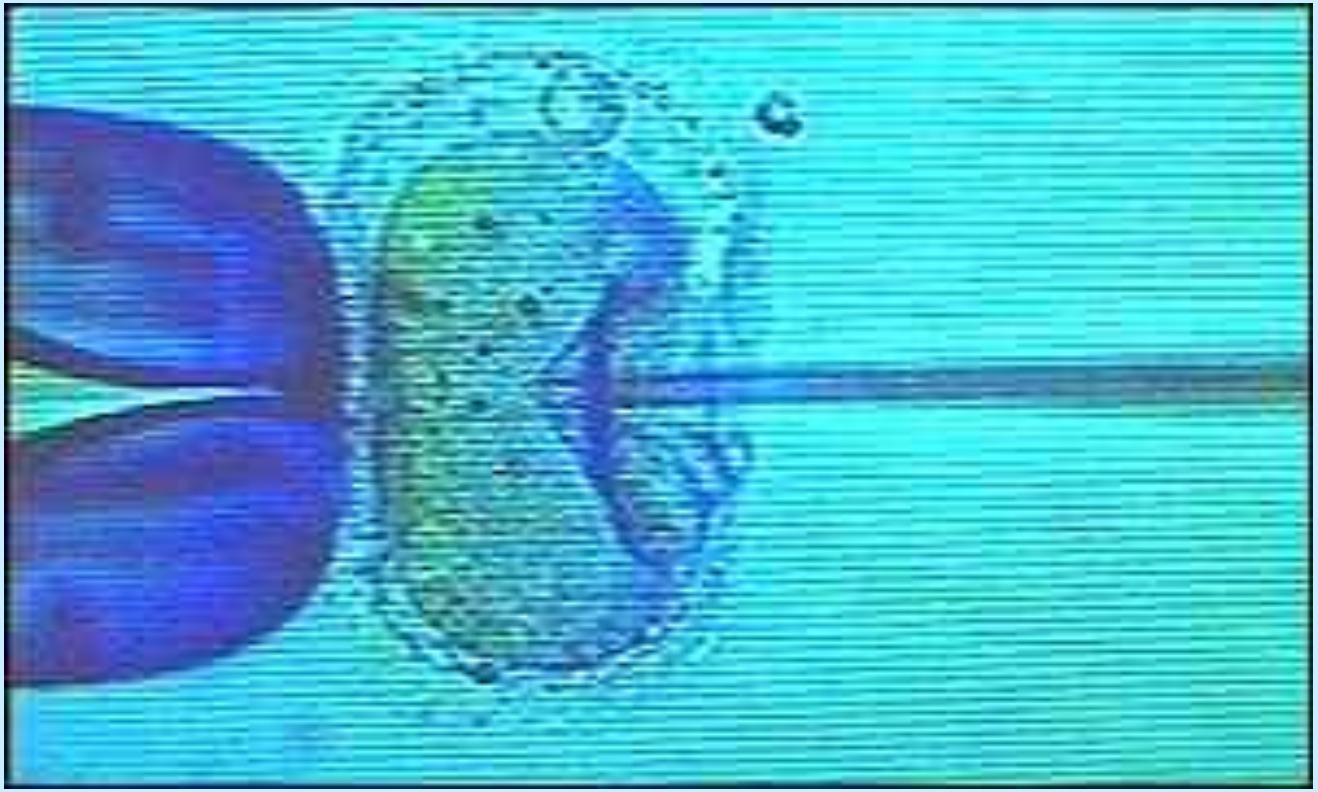
- Very low numbers of motile sperm.
- Severe teratospermia.
- Problems with sperm binding to and penetrating the egg.
- Antisperm antibodies thought to be the cause of infertility.
- Prior or repeated fertilization failure with standard IVF methods.
- Frozen sperm limited in number and quality.
- Obstruction of the male reproductive tract not amenable to repair. Sperm may then be obtained from the epididymis by a procedure called microsurgical epididymal sperm aspiration (MESA), or from the testes by testicular sperm aspiration (TESA).

ICSI

- *Intracytoplasmic sperm injection (ICSI), in which a sperm is injected directly into an egg to facilitate fertilization.*



- ICSI involves injecting sperm directly into the egg



Controlled ovarian hyperstimulation (protocol):

- CC is given on days 5–9 of the menstrual cycle in dose 50 mg/day for 5 days. If no effect, the dose is increased to 100 mg/day. The maximum dose is 250 mg/day.
- Human chorionic gonadotropin (hCG), 5000 IU to 10,000 IU, may be used to simulate an LH surge

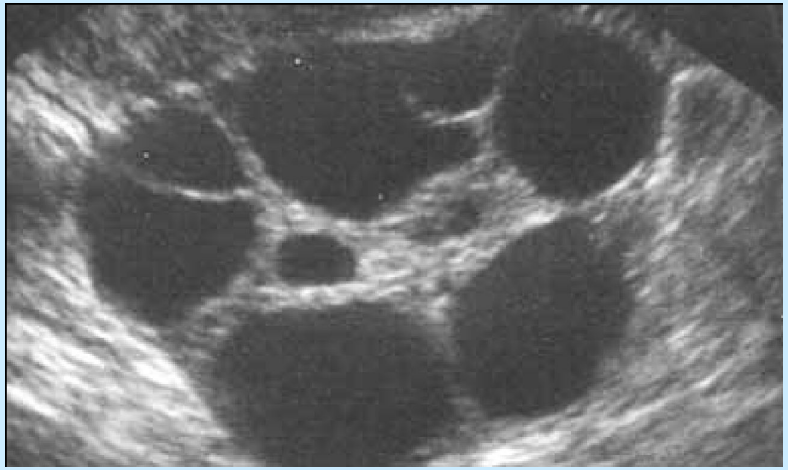
Controlled ovarian hyperstimulation (continuation):

- CC/hMG combinations - The hMG is given for 2–7 days after the clomiphene. Trade names for hMG include Humegon, Pergonal, and Repronex.
- To complete oocyte maturation, hCG needs to be given once the follicles have reached 17–18 mm in diameter.
- Aspiration of follicles should be timed 35–36 hours after the hCG injection.

- *Ovarian follicles, stimulated by ovulation drugs,*

  visible on ultrasound. The dark, circular areas

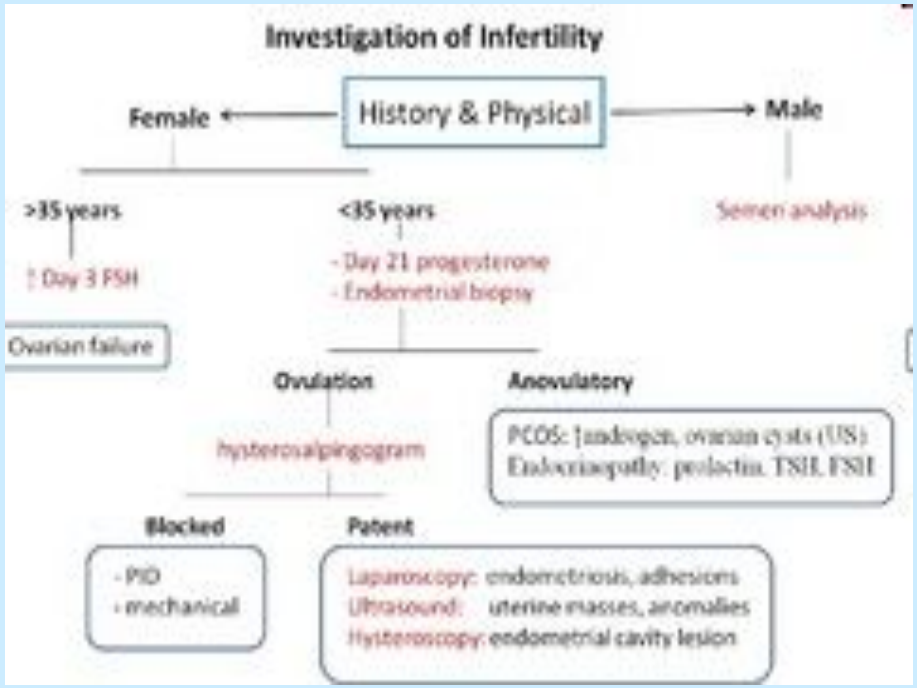
  are the follicles.



IVF RESULTS 1996 - 1997

Year	Patients	Treatment cycles	Live births*	Babies	Live birth rate
1985	3,717	4,308	364	444	**8.6%**
1986	4,687	7,043	605	754	**8.6%**
1987	7,488	8,890	760	1,013	**10.1%**
1988	7,515	10,489	956	1,345	**9.1%**
1989	8,790	10,413	1,157	1,552	**11.1%**
1990	9,964	11,583	1,443	1,899	**12.5%**
1991-1992†	15,087	17,017	2,155	3,062	**12.7%**
1992-1993	14,996	19,553	2,546	3,343	**13.0%**
1993-1994	17,124	22,524	3,205	4,206	**14.2%**
1994-1995	20,077	25,878	3,733	4,887	**14.4%**
1995-1996	23,317	30,432	4,620	6,130	**15.2%**
1996-1997	25,563	33,517	5,601	7,292	**16.7%**
Total	**158,325**	**201,647**	**27,145**	**35,927**	**13.5%**

*There are more babies than live births because of multiple births
†Data cover 15-month period 1 January 1991 to 31 March 1992
SOURCE: Human Fertilisation and Embryology Authority


Investigation of Infertility
History & Physical
Female
Male
>35 years
<35 years
Semen analysis
↑ Day 3 FSH
- Day 21 progesterone
- Endometrial biopsy
Ovarian failure
Ovulation
Anovulatory
hysterosalpingogram
PCOS: ↑androgen, ovarian cysts (US)
Endocrinopathy: prolactin, TSH, FSH
Blocked
Patent
- PID
- mechanical
Laparoscopy: endometriosis, adhesions
Ultrasound: uterine masses, anomalies
Hysteroscopy: endometrial cavity lesion

Thank you