INFERTILITY

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Definition

- As 1 year of unprotected intercourse without conception.

- Subfertility– as women or couples who are not sterile but exhibit decreased reproductive efficiency.
- Cycle fecundability– is the probability that a cycle will result in pregnancy.
- Cycle fecundity– is probability that a cycle will result in a live birth.

Incidence

- 10 – 15 % of couples.

- Approx 85-90% of healthy young couples concieve within 1 year or most in 6 months.

fritz & speroff.

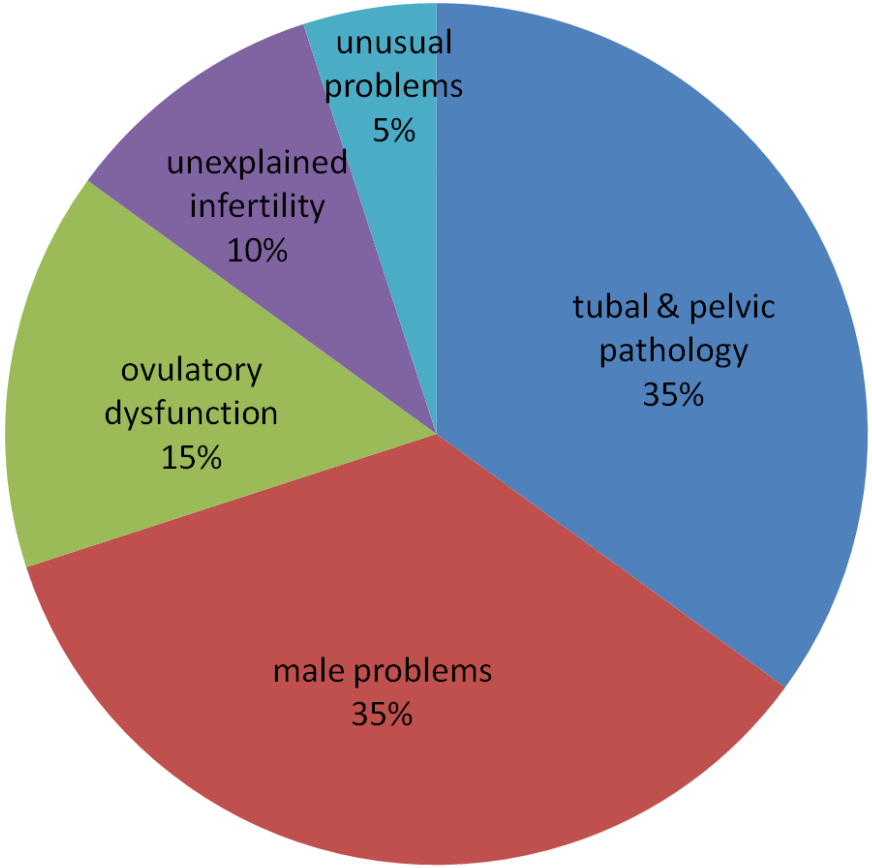
Types

- Primary— the inability to conceive after 1 year of unprotected intercourse for a woman younger than 35, or after 6 months of unprotected intercourse for a woman 35 or older.

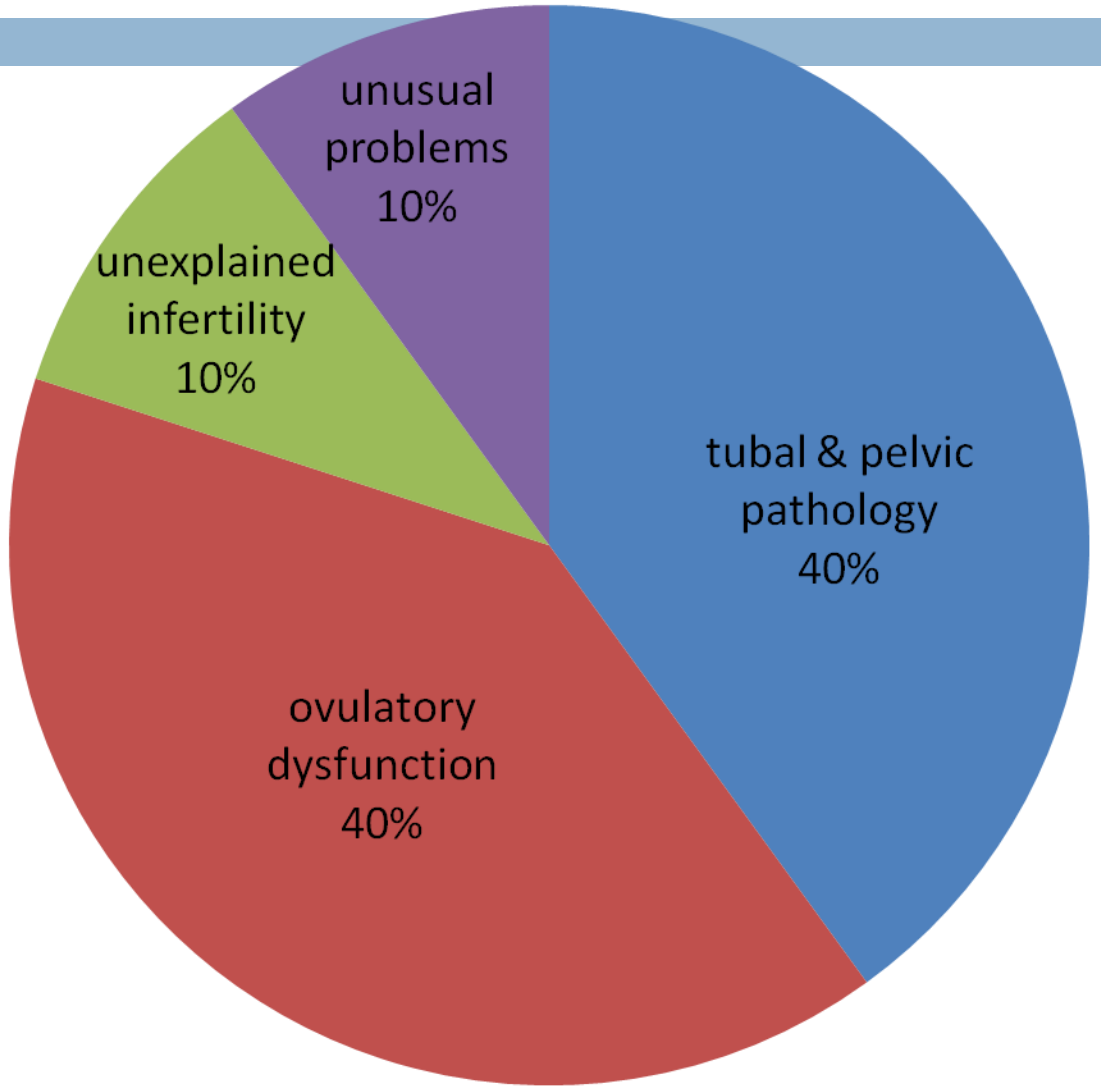
- Secondary– the inability of a woman to concieve who previously was able to do so.

fritz & speroff.

Causes - couples



Women


unusual problems 10%
unexplained infertility 10%
tubal & pelvic pathology 40%
ovulatory dysfunction 40%

Counselling

- Lifestyle & environmental factors—

obesity— causes

In women – menstrual dysfunction.

-- increased risk of abortion.

-- decreased fertility.

--obstetric & neonatal complications.

In men -- abnormal semen parameters.

-- decreased fertility.

contd.

factors

* Smoking– time of conception longer.
-- lower fecundibility.

Due to 1. accelerated follicle depletion
2. menstrual cycle abnormalities
3. gamete or embryo mutagenesis

*Substance abuse– alcohol.
-- marijuana.
-- cocaine.

Occupational harm

- Perchloroethylene – dye industry
- Toluene – printing business
- Ethylene oxide & solvents
- Radiant heat or heavy metals
- Herbicides & fungicides
- Pesticides & chlorinated hydrocarbons—incresase abortion.

So counsel--

- Smoking cessation.
- Achieve BMI between 20 – 25 kg/msq.
- Limit alcohol consumption to 4 or fewer drinks per week.
- Limit caffeine intake to 250 mg /day.

In **normally** fertile couples ,cycle **fecundity** averages **20%** and does not exceed **35%** even when intercourse is carefully timed.

Hence the benchmark for comparison is only **20-30%** and not 100%.

Induction of ovulation

- Identified in 18-25% of infertile women.

Diagnosis:

Women with –

- Irregular ,
- Unpredictable &
- Infrequent menses.
- BBT recordings having no sustained interval of temp elevation,preceeding onset of menses.
- Ovulatory cycles have typical 'biphasic pattern' of BBT.
- Short luteal phase & progesterone **<3ng/ml.**

Classification – WHO.

Hypogonadotropic Hypogonadal Anoovulation

Group I:

- 5-10% of anovulatory women.
- Low/low normal sr. FSH .
- Low sr.estradiol .
- Absent or abnormal hypothalamic GnRH secretion or pituitary insensitivity to GnRH.

INCLUDES-

Weight loss

Physical, emotional,nutrional stress

contd.

Classification – WHO.

Anorexia nervosa

Excessive execrcise

Kallmann syndrome

Isolated gonadotrophin deficiency

These women may require hypothalamic-pituitary imaging for any **mass** lesion.

Group-II

Eugonadotropic Euestrogenic Anovulation

- Largest -75-85% women
- Normal sr.FSH and estradiol levels
- Normal or elevated sr.LH levels

INCLUDES:

PCOS

Screen for Type 2 DM before treatment.

Advice strict wt reduction.

Group-III

Hypergonadotropic Anovulation

- 10-20% of women
- Present with amenorrhea
- Elevated sr.FSH levels

INCLUDES:

Premature ovarian failure

Follicular depletion

Few respond to **ovulation induction.**

Hyperprolactinemic Anovulation

- 5-10% anovulatory women
- Low GnRH levels
- Low/low normal sr.FSH levels
- Low sr. estradiol levels
- Present with oligomenorrhea/ amenorrhea.
- Hypothyroidism or medication

May require hypothalamic imaging for **prolactinomas.**

Pretreatment evaluation

- Screen for IGT / DM in obese women.
- PCOS
- Semen analysis
- HSG / TVS-USG for history with-

-Pelvic infection

-Surgery

-Ectopic pregnancy

-IBD

-Endometriosis

-Abnormal physical examination

Clomiphene citrate

- Synthesised in 1956.
- Introduced for clinical trials in 1960.
- Approved for use in U.S in 1967.
- 80% success rate.

Mechanism of action

- Non-steroidal triphenyletylene derivative– SERM.
- Has antiestrogenic effect more than estrogenic one.
- Cleared through liver & stools.
- 85% within a week.
- Racemic mixture– enclomiphene & zuclomiphene.
- Enclomiphene—more potent,ovulation inductin action,short half life,serum concentrations rise &fall quickly .

- Reduced negative estrogen feedback triggers normal compensatory mechanism that alter the pattern of GnRH secretion and stimulate increased pituitary gonadotrophin release which in turn drives ovarian follicular development.
- In ovulatory women it increases GnRH pulse frequency.
- In anovulatory women with PCOS ,with increase GnRH frequency ,it increases only pulse amplitude.

Clinical indications

- Ovulation induction in anovulatory infertile women with— normal
- Thyroid function
- Sr. prolactin levels
- Endogenous estrogen production
- Sr.estradiol levels(more than 40pg/ml)
- Normal response to a progestin challenge(WHO Group-II)
- In unexplained infertility for multi-follicular developmen in combination with IUI.

- Ineffective in Hypogonadotropic Hypogonadism (WHO Group-I).

SIDE EFFECTS—

Well tolerated

- Hot flushes,mood swings,headache,reast tenderness,pelvic pain,nausea.
- Visual-light sensitivity,blurred vision,scotoma.
- All are reversible.
- If not change treatment type.

Regimens

- 50 mg tablet daily for 5 days
- Can increse by 50 mg increments in subsequent cycles.
- Most respond to 50mg (52%), 100mg (22%).
- Lower doses 12.5-2.5mg daily.for women with high sensitivity and prone for large ovarian cysts.
- Longer duration of 7-10days can succeed.
- In anovulatory women ,LH sorge occurs at 5-12 days after treatment ends.
- Most often on day 16/17 when given on day 5-9.

Results

- 70-80% in properly selected women.
- In anovulatory women cycle fecundability is approx 15%.
- In others it is 22%.
- 70-75% pregnancy rates in 6-9 cycles of treatment.
- If this fails expand the investigations to rule out other factors.
- Prolonged treatment in women after 35yrs,not appropriate.

Risks

- Multiple pregnany.
- Spontaneous abortions.
- Ovarian hyperstimulation syndrome.
- No causal relationship between ovulatio –induction drugs and ovarian or breast cancer is established.
- No evidence of teratogenecity.

Adjuvant treatments

- Glucocorticoids-

Prednisolone-5mg or dexamethasone 0.5-2mg .

As continuous and more limited follicular phase treatment.

Effective in those with elevated DHEA-S levels.

- HCG-

As a surrogate LHsurge to trigger ovulation in those when IUI is done.

Serial TVS-USG done to know follicular size.

Given when lead follicle reaches 18-20mm.otherwise can cause atresia .

Ovulation occurs 34-46 hours after HCG injection so IUI performed 36 hours later.

When LH surge detected this therapy has no value but only adds expense and inconvinience.

- Metformin-

Combined treatment proves good in women woth clomiphene resistant before proceeding to ovarian drilling or treatment with GnRH analogues.

Begin with 500mg daily increasing gradually weekly upto 1500-2000mg as tolerance allows.

Found to have low risk of abortion in women with PCOS.

Assited Reproductive Technology

- Practiced since a centuary.

IN- VITRO FERTILISATION and EMBRYO TRANSFER

- Indications-
- Unexplained infertility
- Treated endometriosis
- Male factor infertility
- Cervical hostility
- Therapy for female cancer
- Occluded or damaged fallopian tubes

Advantages

- Stimulation of superovulation by clomiphene/gonadotrophins.
- Downregulation of HPO- axis by GnRH agonists.
- All help in maximum oocyte retrieval.

Only—

1. Expensive
2. Specialised laboraory facilities
3. Skilled team workers

Controlled ovarian stimulation

- 3 categories—

NORMAL RESPONDER-

- LONG protocol used.
- GnRH analogues are used in mid –luteal phase of previous cycle, as follicle recruitment normally starts at this time and falling levels of FSH, ostrogen and inhibin.
- This is continued till hCG is administered.
- Gonadotrophins are started after menses.
- Monitoring –by serial USG, sr.FSH, LH,estradiol & progesterone levels.

DOSE—Leuprolide 0.1mg daily subcutaneously or Naferelin 200mcg bd intranasally.

POOR RESPONDERS—

- MICRODOSE FLARE PROTOCOL
- Leuprolide 20mcg s/c bd started from day 2/3 of cycle.
- Gonadotrophin started from day 6
- Assisted zona hatching may improve preg rates here.

HYPER RESPONDERS—

- Like PCOS
- COASTING PROTOCOL
- GnRH analogues started from 3rd week of previous cycle.
- Low dose gonadotrophins started after menses.
- If sr.estradiol is >3000pg/ml gonadotrophin is discontinued while if <3000pg/ml Hcg is started.

Oocyte retrieval

- Done transvaginally under USG guidance with transducer.
- Easiest,accurate & pt friendly.
- Warm flushing medium- Earle's with heparin or warmed normal saline used
- If oocyte not recovered follicle is flushed with solution and aspirated.
- Last fluid and blood collected on pouch of Douglas aspirated.

Insemination

- In –vitro by fresh or cryopreserved sperm
- Sperms are incubated under controlled conditions.
- After 16-18 hrs examined for 2 pronuclie that confirms fertilisation.
- Zygotes are returned to incubation to allow cleavage to 2-4 cell stagewhen are ready for transfer to uterus.

Embryo transfer

- Done 46-48 hrs after insemination or 48-50 hrs after oocyte recovery.
- An embryo catheter used flushed with Earle's medium.
- 2-3 embryos suspended in 15-25mcl of fluid transferred 1 cm away from fundus i.e 5-6 cms from external os.
- Pt is made to lie down half an hour
- Post –transfer pt recieves progesterone vaginal suppositories twice daily or i/m progesterone 12.5 mg daily.

Outcome

- Clinical pregnancy rate is 26%.
- Live birth rate 9-26% per cycle.
- Cumulative conception rate in >35yrs is 56-72% whereas in normal poulation is 55%.
- Ectopic preg in 4-6%. -- pre-existing tubal damage, multiple embryo transfer, retrograde migration to tubes.
- Maternal complications–
- OHSS
- Risk of anaesthesia
- Risk of damage to adjacent organs

OTHER TECHNIQUES

- Cryopreservation
- Oocyte donation
- Embryo donation
- Surrogacy
- IUI
- GIFT
- DIPI
- IFI
- ZIFT
- ICSI

ADOPTION