Unexplained Infertility

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1. Introduction

Definition

- Inability to conceive

after one year

with routine (standard, basic) investigations of infertility showing no abnormality.

(RCOG guidelines,1998; Randolph,2000)

- *Ideal definition*
  - *A couple with a real but unobservable defect : infertility which may be prolonged and permanent*
    (Ray et al, 2012)
  - *Term 'unexplained infertility' should be abandoned as it is so dependent on the quantity and quality of the diagnostic tests performed*
    (Gleicher and Barad, 2006)
  - *Diagnosis is due to:*
    lack of a specific test or misdiagnosis
  - *The most frequent reasons for misdiagnosis:*

1. *Endometriosis*
2. *Mild degrees of tubal infertility*
3. *POF*
4. *immunological causes...*

- *Whether improved diagnostic accuracy using little-performed and often expensive tests would actually improve the eventual prognosis.*

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation, or after six months in women 35 and older

Incidence

(NICE, 2013)

1 in 7 couples

- Male factors: 30%
- Female: 45%
  - Tubal: 20%
  - Ovulatory disorders: 25%
  - Uterine: 10%
  - Endometriosis: 5%
- Unexplained: 25%
- Combined male and female: 40%

Effect on psychosexual function

1. Frustration
{no explanation for the cause of infertility
no effective treatment}.
2. Prolonged & mutual agony
3. Depression

(Meller et al, 2002)

4. Sexual dysfunction

Recognition of the cause of infertility: acceptance of childlessness

Return to normal sexual behavior.

2. Causes

- It is possible to draw long list of putative & subtle causes of infertility,
- Many are uncertain
- Many have been found in couples of normal fertility.
- Few are actually treatable

(Balen,2003) .

- ±Arise in two ways.

1.Subtle, undetected defect in the reproductive process

2.Conception is delayed by chance alone, as the couples fecundity may be on the lower side of the normal distribution.

- *Current assessment of R system is far from complete.*

✓ *Many steps which are not routinely evaluated or unavailable*

I. Male fertility

✓ *Capacitation*

✓ *Ability of spermatozoa to negotiate the uterotubal junction.*

✓ *Acrosome reaction and the ability to bind to and penetrate the zona pellucida.*

✓ *No reliable test which can provide fertilization profiles of spermatozoa.*

II. Female fertility

- ✓ *Cervical mucus*
- ✓ *Defective oocytes, especially in ageing patients*
- ✓ *Tubal patency does not assess the characteristics of bidirectional tubal motility which is important for embryo transport.*
- ✓ *Tests for the evaluation of the chance for successful implantation are not available.*

I. Ovarian & endocrine factors:

1. Abnormal follicle growth

2. Lutenized unruptured follicle

3. Hypersecretion of LH.

4. Hypersecretion of prolactin in the presence of ovulation

5. Reduced growth hormone secretion/sensitivity

6. Cytologic abnormalities of in oocytes.

7. Genetic abnormalities in oocytes

8. Antibodies to zona pellucida

- *Putative*
- *Subtle*
- *Uncertain*
- *Found in fertile couples*

II. Peritoneal factors.

1. Altered macrophage & immune activities.
2. Mild endometriosis
3. Antichlamydial antibodies

- Putative
- Subtle
- Uncertain
- Found in fertile couples

III. Tubal factors

1. Abnormal peristalsis or cilial activity
2. Altered macrophage & immune activity

IV. Endometrial factors

1. Abnormal secretion of endometrial proteins
2. Abnomal integrin/adhesion molecule
3. Abnormal T cell & natural killer cell activity.
4. Secretion of embyotoxic factors
5. Abnormalities in uterine perfusion

- Putative
- Subtle
- Uncertain
- Found in fertile couples

V. Cervical factors

1. Altered cervical mucus
2. Increased cell-mediated immunity

VI. Male factors

1. Reduction in motility, acrosome reaction, oocyte binding & zona penetration

2. Ultrastructural abnormalities of head abnormalities

VII. Embryological factors

- Putative
- Subtle
- Uncertain
- Found in fertile couples

1. Poor quality embryo

2. Reduced progression to blastocyst in vitro

3. Abnormal chromosomal complement- increased miscarriage rate

3. Diagnosis

- By exclusion
- Consider the following

(Moghissi et al,2000)

Was the infertility evaluation

1. Complete?
2. Performed correctly?
3. Interpreted appropriately?

❑ESHRE (2000)

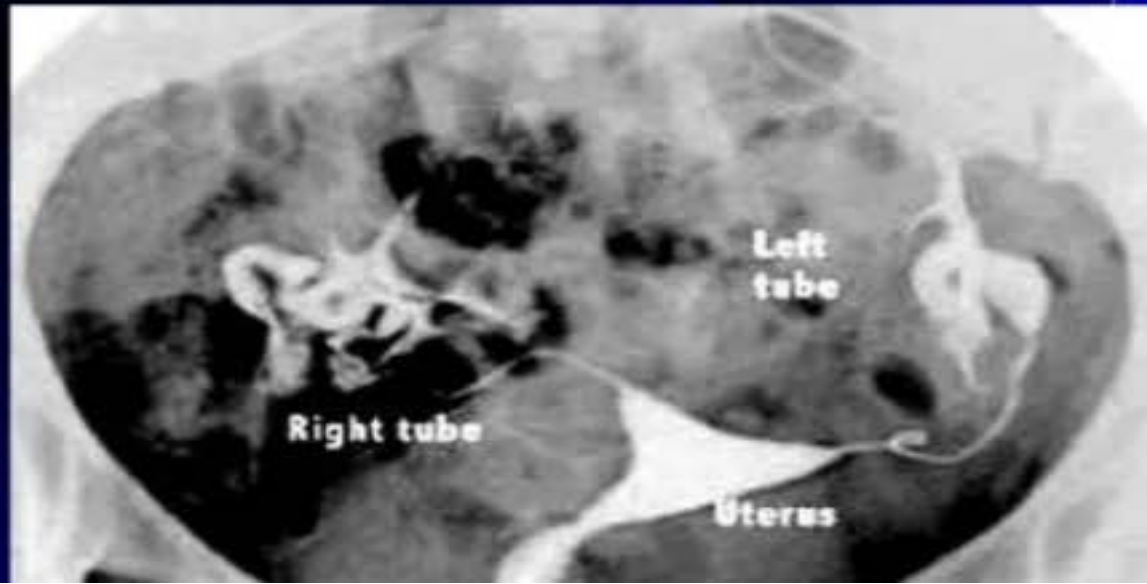
Infertility testing should be classified into 3 groups depending on correlation with pregnancy rates

I. Tests that have an established association with pregnancy:

Conventional semen analysis

Tubal patency tests

Tests of ovulation



II. Tests that are not consistently associated with pregnancy:

Post-coital test

Antisperm antibody tests

Zona-free hamster egg penetration test

III. Tests that have no association with pregnancy:

Endometrial biopsy

Varicocele assessment

Chlamydia testing

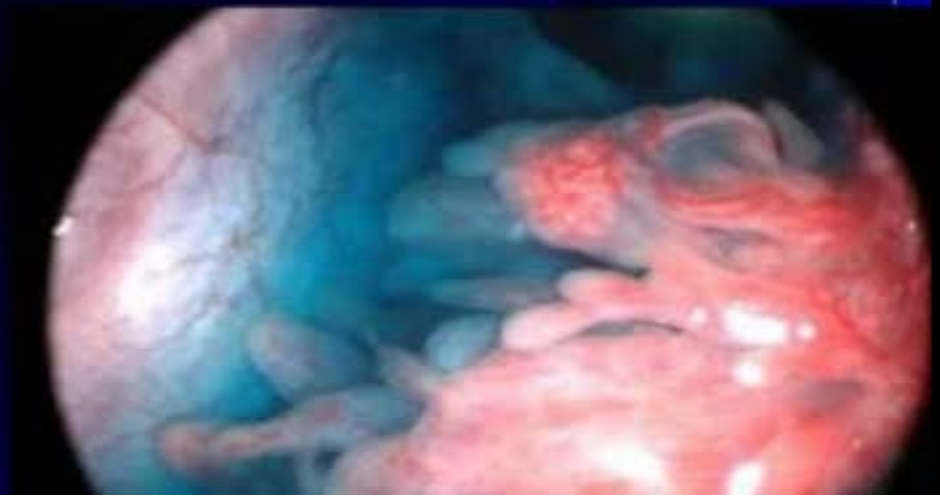
❑Laparoscopy and dye test:

- Indicated

1. Abnormal HSG
2. History or symptoms suggestive of pelvic disease.

{Normal HSG or without history suggestive of tubal disease, The probability of clinically relevant tubal disease or endometriosis is very low & laparoscopy is not justified or cost effective}

(Fatum et al, 2002).



- *laparoscopy should be omitted in couples with UI.*

{1.Laparoscopy may reveal minimal or mild endometriosis or peritubal adhesions: Surgery or medical tt has not been proven to improve fecundity.

2. These patients should be treated as UI (by 3 cycles of combined gonadotropins & IUI & if unsuccessful ART) Treatment indicated if duration > 2 y or >35 y}

(Bhattacharya et al., 2008; Collins et al., 1995).

Hormonal assay

(NICE, 2013)

1. Midluteal progesterone

in regular and irregular cycles

{confirm ovulation}

In irregular prolonged cycles

Depending upon the timing of menstrual periods, conducted later in the cycle (for example day 28 of a 35-day cycle) and repeated weekly thereafter until the next menstrual cycle starts

2. Basal FSH and LH

- Only in

irregular prolonged cycles

Evidence of ovulation:

a. Mid-luteal srerum progesterone:

- ✓ *less invasive way to assess luteal function,*
- ➢ *controversy persists regarding lower limit of normal.*

b. LH surge in urine:

- ✓ *sensitive, relatively inexpensive,*
- ✓ *pinpoint the day of ovulation &*
- ✓ *reduced uncertainty in interpretation of progesterone levels by better-identifying the time of peak progestrone secretion at which to obtain serum*

3. Prolactin

Only in
ovulatory disorder
galactorrhoea or
pituitary tumour

4. TSH:

only if
symptoms of thyroid disease

5. Ovarian reserve testing

- Woman's age:

An initial predictor of overall chance of success through natural conception or with IVF

- Predictors of ovarian response to Gnt stimulation in IVF:

	Low response	High response
Total AFC	4 or less	16 or more
AMH		
ng/ml	0.8 or less	3.5 or more
pmol/l	5.5	25
Conversion ratio:7		
FSH IU/L	8.9 or more	4 or less

4. Treatment

Prognosis

1. Good:

If the duration of infertility: ≤ 2 y even without therapy, unless the female partner is >35 years.

2. Worse:

when the duration of infertility: > 3 y and
the female partner: >35 y
(Collins et al.,1995).

- *A nonhomogenous hyperechogenic endometrial pattern predicts lower fertility potential in women who are not receiving follicle maturing drugs in UI*

(Check et al, 2003)

Aim of the treatment

To increase the monthly PR above the natural rate of 1.5-3%

How?:

improve gamete quality

increase gamete number

facilitate gamete interaction.

Treatment

- By definition: **empiric**
- {does not address a specific defect or functional impairment, disease is not defined}

(Soules,2000 , Balen,2003; ASRM, 2006)

- Dependent on:
  - Availability of resources
  - Patients' age
  - Duration of infertility.
- *The standard protocol is to:*
  - *Progress from simple to complex*
  - *Balance the effectiveness against the cost and side effects.*

(Ray et al,2012)

Strategy of treatment

1. ≤35

≤2y: Expectant for 2y

≥2Y: Active

2. 35-39

≥ 1 y: Active

3. ≥40 y:

Active

Lines of treatment

I. Expectant management (EM)

II. Tubal flushing or perturbation

III. Ovulation-inducing agents

1. CC:
2. Aromatase inhibitors (AI)
3. Gonadotropins

IV. IUI

V. Fallopian tube sperm perfusion

VI. ICSI

I. Expectant management (EM)

- *Spontaneous PR*

- *After one month: 1.8-3.8%* (Guzick et al., 1998).
- *After one y: 27.4%* (Snick et al.1997)
  14.3% (Collins et al. 1995).
  19.9% (Gleicher et al., 1996)
- *After 3y: 60%* (Godon & Sperof,2002)
- *After 5 y: 80%* (Randolph,2000)
- Chance of spontaneous pregnancy with EM is low but never zero.

- EM Vs CC or natural IUI:

Comparable results

(Wordsworth et al., 2011)

- EM does play an important role in a situation where limited resources are available.

❖ Unfortunately, it is not possible to predict which couples will conceive spontaneously or in what time frame.

II. Tubal flushing or perturbation

- *Indications*

UI

Early stages of endometriosis.

(Johnson et al., 2005).

- *Mechanism:*

1. *Mechanical*
2. *immunological*

(Edelstam et al., 1998).

It affects the concentration of peritoneal factors such as cytokines

(Oak et al., 1985; Agic et al., 2006).

- *Methods:*

1. Hysterosalpingo contrast sonography

With the use of lignocaine, treatment was well tolerated.

(Johnson et al., 2005).

2. Oil-based tubal insufflation media

significant improvement in PR

(Watson et al., 1994; Nugent et al., 2002)

{1. removal of tubal debris

2. an underlying immunological cause {in vitro it was shown that lipiodol prevents peritoneal mast cell phagocytosis of the spermatozoa}

(Watson et al., 1994).

Results

- *Absolute increase in PR: 11.7%*
- *Relative increase in PR: 4.5 times.*
- *Lipioidol: increased cycle fecundity when compared with water soluble*

(Cochrane,2001).

III. Ovulation-inducing agents

1. CC:

- *Enhances fertility by:*

1.Correcting subtle defect in ovarian function-either follicular development or luteal phase defect

2. Increasing the number of follicles that develop & consequently oocyte that are released

(Balen,2003).

❑Results:

- No better (and even inferior) live-birth rates than EM (14% vs 17%).

(Bhattacharya et al., 2008)

- Number of cycles needed under CC for one additional pregnancy was 40 compared with placebo

(ASRM, 2006).

- No evidence that CC was more effective than no tt or placebo for live birth or for clinical pregnancy

(SR by Hughes et al.;2010)

❖Do not offer oral ovarian stimulation agents (such as CC, or anastrozole letrozole). {no increase the chances of a pregnancy or a live birth}

(NICE, 2013)

Offer IVF after 2 years

2. Aromatase inhibitors (AI)

- *Mechanism*

Release of the estrogen negative feedback, increase GnTR, stimulate ovarian follicle development

(Casper and Mitwally, 2006).

2. Increase sensitivity of follicles to FSH. increasing follicle recruitment in UI (Mitwally & Casper,2000)

- *Advantages over CC:*

Because of the short half life (45h) & absence of ER depletion

No effect on the endometrial thickness or cervical mucous

Letrozole:

Dose: 2.5 mg/d from day 3-7

- *Results:*
  - *supports the role of AI in UI*

(Polyzos et al. ,2008)

- Available data: limited

Current evidence: use of these drugs for UI is weak

PR: comparable with use of CC. (MA)

3. Gonadotropins:

- PR:

7.7% *(Guzick et al,1998).* 8%. *(Veltman-Verhulst et al., 2009).*

- CC Vs HMG
- significantly higher CPR in the group treated with HMG

PR/cycle: 8% (CC) and 25% (HMG).

(Karlstro¨m et al., 1993; Echochard et al., 2000 Balasch)

- Oral Vs injectable ovulation

insufficient evidence to prefer either of the methods

(Cochrane database, Athaullah et al., 2009)

- Letrozole plus FSH:

improved response to FSH: lower FSH dose & higher number of mature follicles UI

IV. IUI

I. IUI alone

- does not significantly increase PR

(ESHRE, 2009)

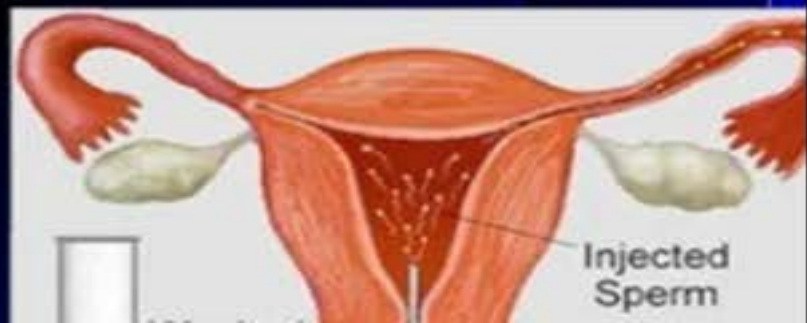
- *No evidence of effect of IUI in natural cycles compared with EM*

(Cochrane, 2012)

- *IUI without stimulation was no better than EM*

The evidence does not support the use of IUI as an alternative to EM in the belief that doing something was better than doing nothing.

(NICE, 2013)



II. *Stimulated IUI*

- *Mechanism*

increasing the density of the motile spermatozoa available to these eggs: increase the monthly probability of pregnancy.

1. IUI with CC

5–7% PR/cycle even after 7 cycles

*(**ESHRE, 2009**)*

Not proved to be effective

(Hughes et al, 2010)

2. IUI with Letrozole

can replace CC in patients with UI undergoing ovulation induction & IUI

(Sammour,2001).

3. IUI with Gnt

- *ESHRE, 2009*

▪PR: 12%/cycle but multiple birth rates13%.

High multiple PR mean that it is no more than a poor substitute for IVF.

▪IUI in stimulated cycles may be considered

1. while waiting for IVF or
2. when in women with patent tubes and IVF is not affordable

- *ESHRE, 2004*

▪*UI or stimulated ovary/IUI is indicated as empiric treatment for all categories of UI*

- *Cochrane, 2012*
  - IUI with OH increases the live birth rate compared to IUI alone.

PR increased with IUI compared to TI in stimulated cycles

- *NICE, 2013*
  - *IUI with stimulation was better than EM in all groups of women, but it was clear that it significantly increased the risk of multiple pregnancies.*
  - IUI (with or without stimulation) should not be routinely offered for couple with UI
  - Exceptions: when people have social, cultural or religious objections to IVF
- *NICE, 2004*
  - *IUI stimulated or unstimulated more effective than EM*
  - *ovarian stimulation should not be offered, even though it is associated with higher PR than un stimulated IUI {risk of multiple pregnancy}*

VI. **IVF/ICSI**

- *Rationales:*

1. To increase the number & quality of oocytes available for fertilization,

2. To facilitate the sperm-oocyte interaction & enhance fertilization,

3. To document the occurrence of fertilization, & to evaluate embryo quality

(Randolph,2000) .

- *Cycle fecundity rate:*

25.7% (ESHRE).

1. IVF Vs EM:

- Higher PR than EM

A Cochrane review (Pandian et al., 2005)

- Live-birth rate/woman with a single cycle of IVF was also significantly higher than with EM

(Hughes et al., 2004).

2. IVF Vs IUI

- IVF success rates are much higher than they were before 2000, while success rates with stimulated IUI have not changed

(ESHRE, 2009)

- *No evidence of difference in live birth rates between IVF & IUI either without or with ovulation stimulation. The effectiveness of IVF in UI remains unproven*

(Pandian et al,2003, Cochrane review).

- *The initial treatment of UI should be IUI as opposed to IVF*

(Homburg,2003)

3.IVF Vs ICSI:

- Complete fertilization failure was higher in conventional IVF (34.3%) than ICSI (10.3%) cycles in UI

(Jaroudi et al,2003).

- ICSI should be the first option for in vitro fertilization in UI

(Sertac et al,2000).

- ICSI should be the first line therapy for women over 35 yrs

(Balen,2003)

❑ *IVF*

- *Expensive and invasive*
- *Most effective method.*

Success rate for IVF
28.2% for women <35,
23.6% for women aged 35–37,
18.3% for women aged 38–39 and
10.6% for women aged 40–42
(HFEA, 2006–2007)

- *live-birth rate in UI: 30.4%*

(ASRM, 2006).

- *For women over 40 years*

(Tsafrir et al., 2009)

CC: ineffective

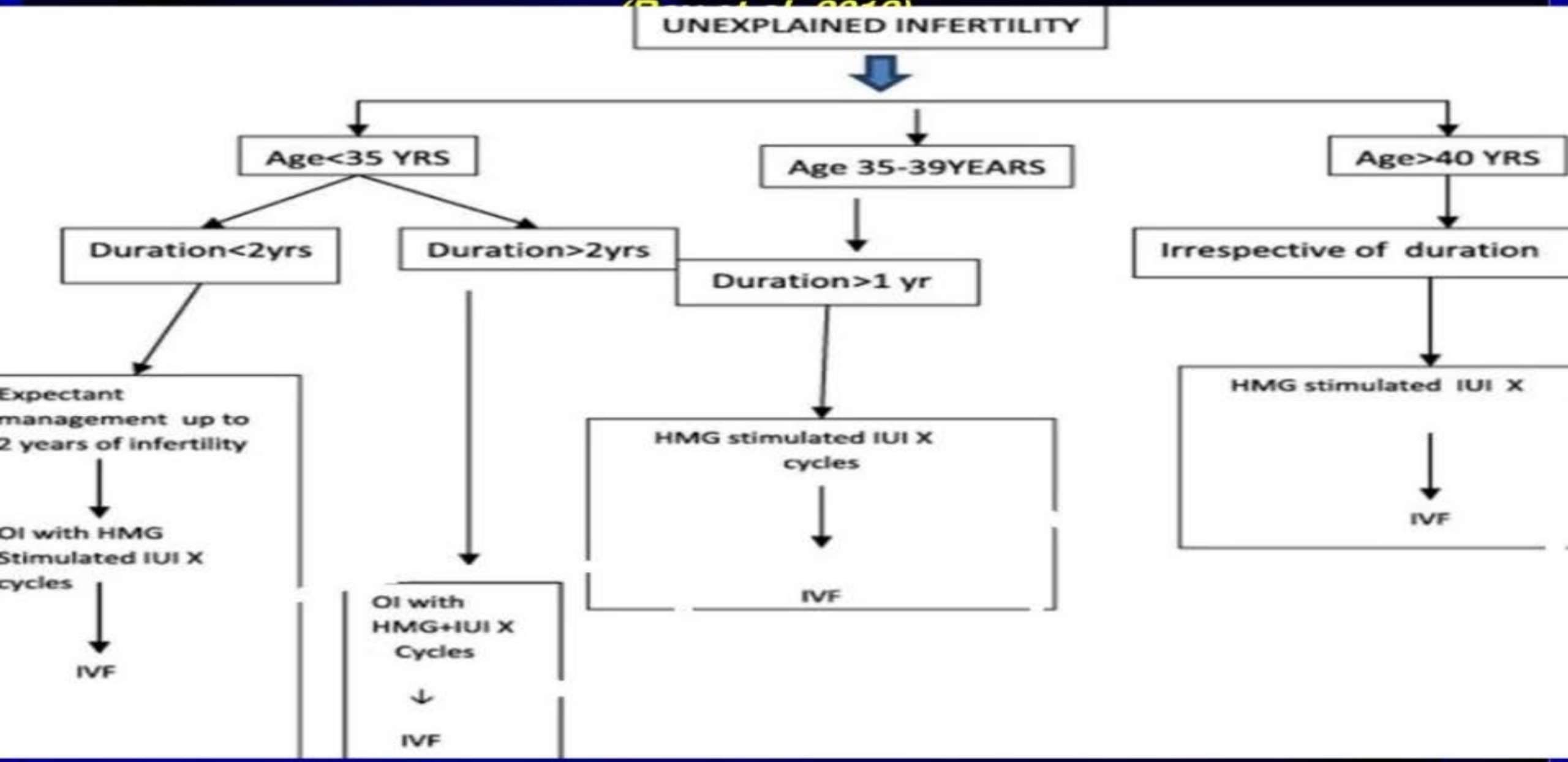
Gnt in IUI: PR≤ 5% .

{Chance of pregnancy reduces every year after the age of 40} all women should be referred for IVF after a short trial of Gnt and IUI.

IVF: 7-fold higher likelihood of pregnancy

(ESHRE, 2007)

Protocol for Management



Thank you