THE PCOS SOCIETY INDIA

PCOS TUTORIALS

A Post Graduate Certificate Course in PCOS Management

Module 4
PCOS and Infertility

Brought to you by The PCOS Society (India)

THE PCOS SOCIETY INDIA

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Module IV

PCOS and Infertility

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Module Overview

- Prevalence of polycystic ovarian syndrome (PCOS) has been reported as nearly 40% among women with infertility; while on the other hand prevalence of infertility has been reported as high as 72% in women with PCOS.[1] This signifies the high impact of PCOS on the reproductive career of a woman.
- This module is designed to provide in-depth understanding of the pathophysiology of infertility in PCOS.
- It would further discuss stepwise options beginning with easy to implement and those with lesser adverse effects to more specialised, sophisticated treatments of infertility in PCOS. The latter may need experts in the field to implement these treatments.
- Infertility in PCOS is associated with considerable psychological turmoil and it is important for the clinician providing holistic treatment to include the care for emotional well being of the patient. The same has been discussed briefly in this module.

Reference:

1. Joham AE, Teede HJ, Ranasinha S, *et al.* Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. *J Women's Health (Larchmt).* 2015;24(4):299–307.

Learning Objectives

At the completion of this module the participant is expected to be able to:

- Understand the burden of infertility associated with PCOS
- Understand the pathophysiology of infertility in PCOS
- Implement a stepwise management plan for infertility in PCOS
- Support the PCOS patients for their emotional well being

PCOS and Infertility

PRE-TEST

State whether the following statements are True or False

1. **PCOS will always be diagnosed way before the patient starts having infertility concerns.**

   True

   False

2. **Infertility issues arise in all patients with PCOS.**

   True

   False

3. **There is a link between nutrition and reproduction.**

   True

   False

4. **PCOS is linked largely with anovulatory infertility.**

   True

   False

5. **More severe sequelae of PCOS are seen among those who are obese when compared to those with normal BMI.**

   True

   False

6. **Insulin resistance and infertility are independent problems that can be dealt separately.**

   True

   False

7. **Weight loss is associated with improved fertility among obese PCOS patients.**

   True

   False

8. **Laparoscopic ovarian surgery is the first line of treatment for patients with PCOS.**

   True

   False

9. **Bariatric surgery can be considered for all obese patients with PCOS.**

   True

   False

10. **Myoinositol improves ovarian function and the pregnancy rate.**

    True

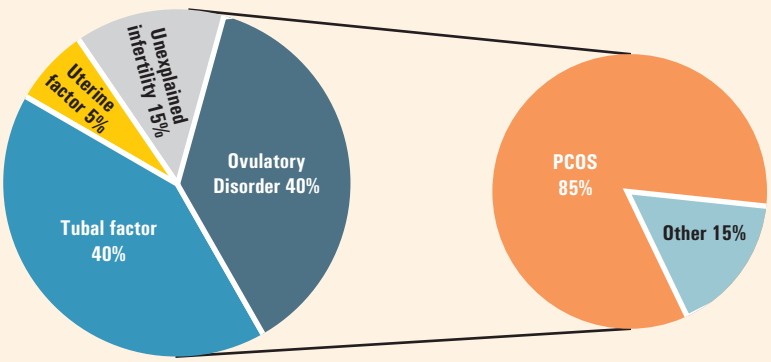
    False

Answers: 1. False; 2. False; 3. True; 4. True; 5. True; 6. False; 7. True; 8. False; 9. False; 10. True

Introduction

- Polycystic ovarian syndrome(PCOS) is one of the commonest endocrine disorder among the women.
- It carries an increased risk of metabolic aberrations that raise the likelihood of suffering from type 2 diabetes (T2DM), dyslipidemia, cardiovascular disease, and endometrial carcinoma.
- PCOS also hugely impacts the women's reproductive career and it's one of the primary causes of anovulatory infertility.
- In addition to menstrual irregularities and hyperandrogenic manifestations; infertility is one of the prime cause of concern and may be the presenting complaint among these women.
- In this module we shall focus on the infertility associated with PCOS and its management.

Causes of female infertility



- PCOS is one of the commonest gynaecological endocrine disorders.
- In addition to several metabolic dysfunctions and long term consequences such as diabetes, cardiac diseases and cancers, it is also a prime cause of anovulatory infertility.
- The basic pathology of arrest of ovulation in PCOS leads to infertility.
- Many patients may present in clinics with infertility as the presenting complaint.
- Thus, in all patients presenting particularly with infertility due to anovulation, screening for PCOS must be conducted.
- Rotterdam criteria,[1] discussed in module 1 and 2, are the most widely accepted diagnostic criteria for PCOS.

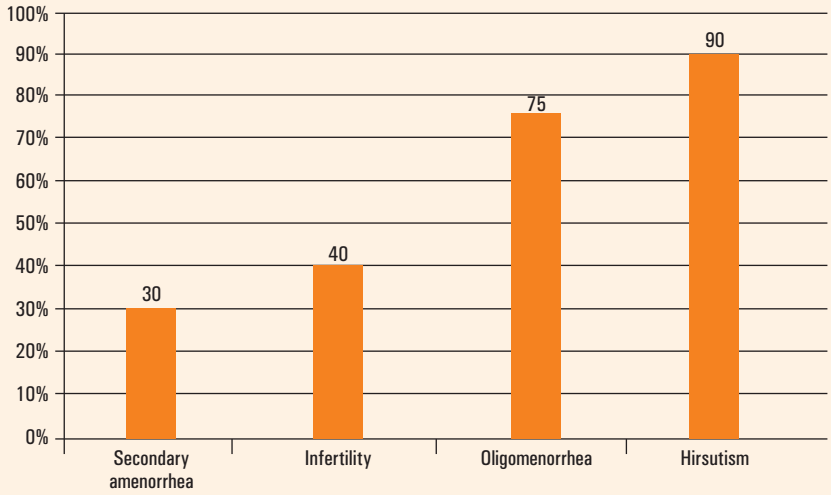
Reference:

1. The Rotterdam ESHRE/ASRM sponsored PCOS con-sensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction*. 2004;19:41–47.

Prevalence

PCOS in Cases of Infertility

- The reported prevalence of PCOS ranges between 2.2–26% in various countries. It varies due to differences in recruitment method, the kind of study population, the criteria used for PCOS definition and the methods used to define each criterion.
- The prevalence of PCOS has been reported as:



- Prevalence rate of PCOS is very high affecting nearly 1 in 5 women
- The prevalence of PCOS has been reported as:
  - Thirty percent in women with secondary amenorrhea
  - **Fourty percent in women with infertility**
  - Seventy five percent in women with oligomenorrhea, and
  - Ninety percent in women with hirsutism[1]

Reference:

1. Hussein B and Alalaf S. Prevalence and characteristics of polycystic ovarian syndrome in a sample of infertile Kurdish women attending IVF infertility center in maternity teaching hospital of Erbil city. *Open Journal of Obstetrics and Gynecology*. 2013; 3:577–585.

Infertility in PCOS Patients

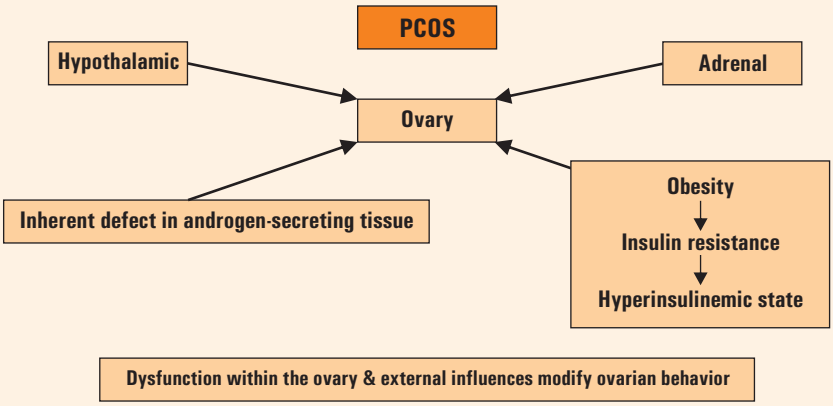
- The cross-sectional analysis of a longitudinal cohort study, the Australian Longitudinal Study on Women's Health (ALSWH) reports:
- Self-reported PCOS prevalence : 5.8% (95% CI: 5.3%–6.4%)
- Infertility was noted by:
  - o Seventy-two percent of 309 women reporting PCOS, compared with
  - o Sixteen percent of 4,547 women not reporting PCOS ($p < 0.001$)
- Infertility was 15-fold higher in women reporting PCOS, independent of body mass index (BMI)

- ALSWH [1] included women of 28–33 years of age from the general community, who were randomly selected from the national public insurance database.
- Mailed survey data were collected at multiple time points.
- Of 8,612 women with known PCOS status, 478 women reported having PCOS.
- Information regarding fertility status was available for 4856 women which was used in this analysis.
- Significantly higher prevalence of infertility was seen in women with PCOS. [2]

References:

1. The Australian Longitudinal Study on Women's Health (ALSWH), 2017. Available at: https://www.alswh.org.au/publications-and-reports/published-papers. Last accessed on: 19th July, 2017.
2. Joham AE, Teede HJ, Ranasinha S, *et al*. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. *J Women's Health (Larchmt)*. 2015;24(4):299–307.

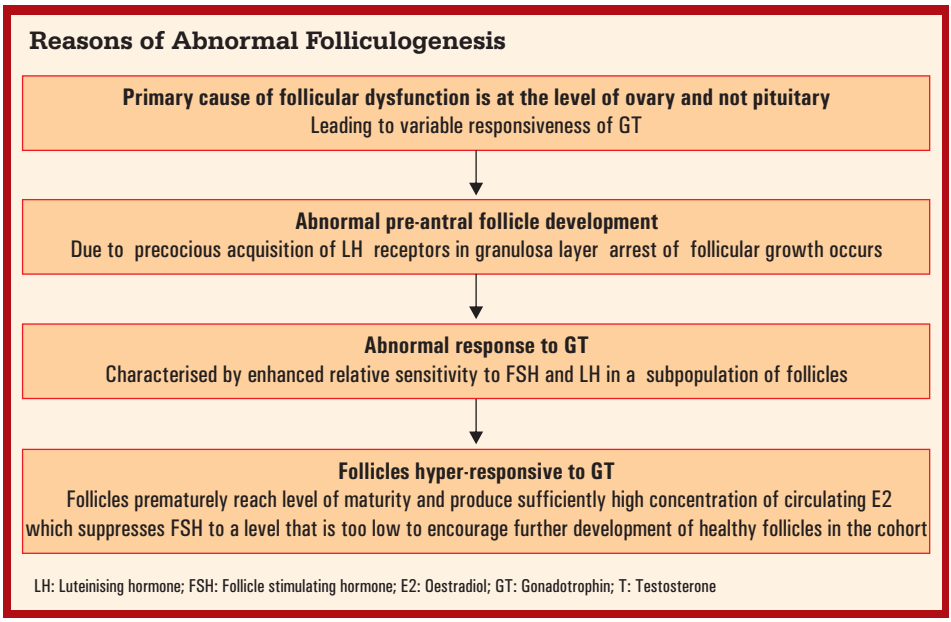
Pathophysiology of Infertility in PCOS



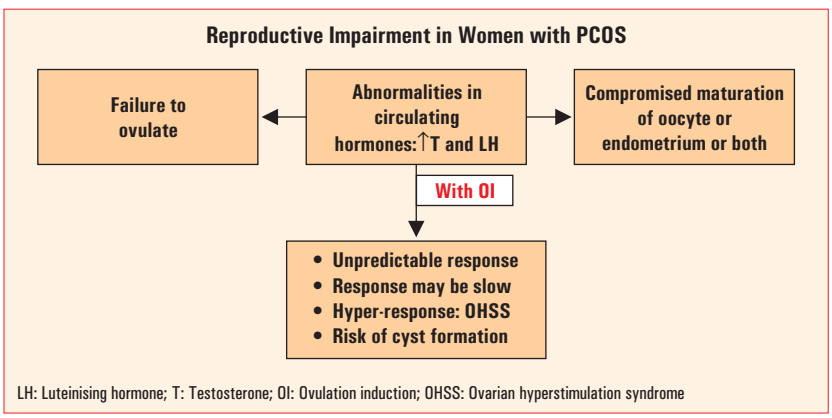
- Ovary is a dynamic multicompartmental organ, which is under the chief regulatory control of hypothalamic and pituitary hormones.
- However multiple internal and external factors influence these hormones.
- Obese women with PCOS are likely to experience more severe sequelae, such as hyperandrogenism and metabolic syndrome, than those with a normal BMI.
- Abnormal folliculogenesis is the primary cause of infertility in PCOS women.[1,2]

References:

1. Frank S, Stark J, and Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update.* 2008;14(4):367–378.
2. Chavez-Ross A, Franks S, Mason HD, *et al*. Modelling the control of ovulation and polycystic ovary syndrome. *J Math Bio.* 1997;36:95 –118.



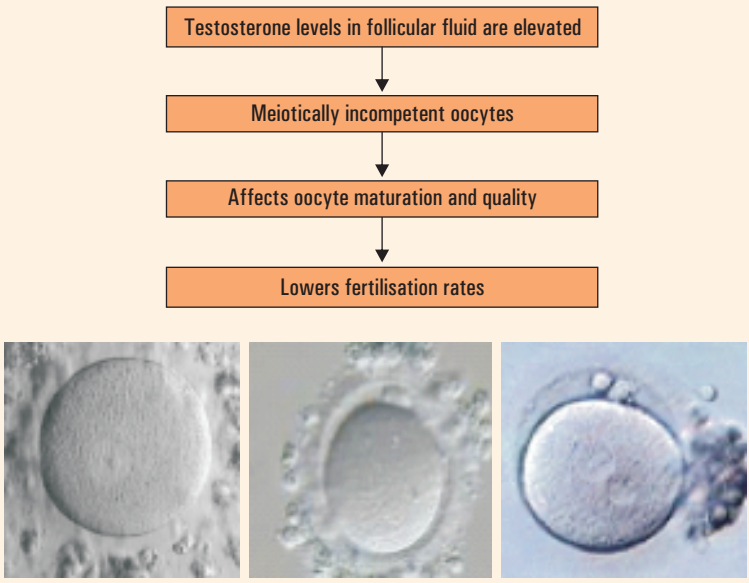
- Primary cause of follicular dysfunction is at ovarian level and not pituitary.
- This is influenced by various endocrine and paracrine factors.
- Hyperandrogenism and hyperinsulinism affects the competence of oocyte development.[1,2]



References:

1. Frank S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update.* 2008;14(4):367–378.
2. Chavez-Ross A, Franks S, Mason HD, *et al.* Modelling the control of ovulation and polycystic ovary syndrome. *J Math Bio*. 1997;36;95–118.

Effect of Androgens on Follicular Endocrine Micro-environment

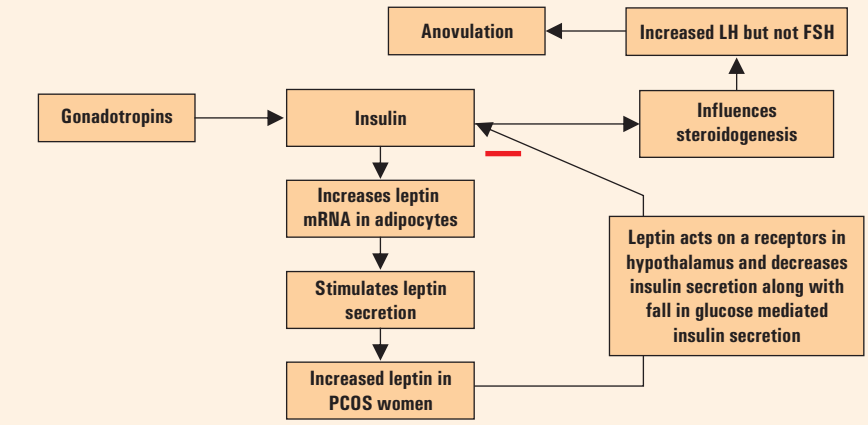


- In women with PCOS, testosterone (T) levels are higher in follicular fluid.
- T inhibits meiotic maturation and embryonic development, negatively affecting the fertilisation rate.
- Insulin also affect the competence of oocyte development.[1]

Reference:

1. Dumesic DA, Padmanabhan V and Abbott D. Polycystic ovary syndrome and oocyte developmental competence. *Obstet Gynecol Surv*. 2008;63(1):39–48.

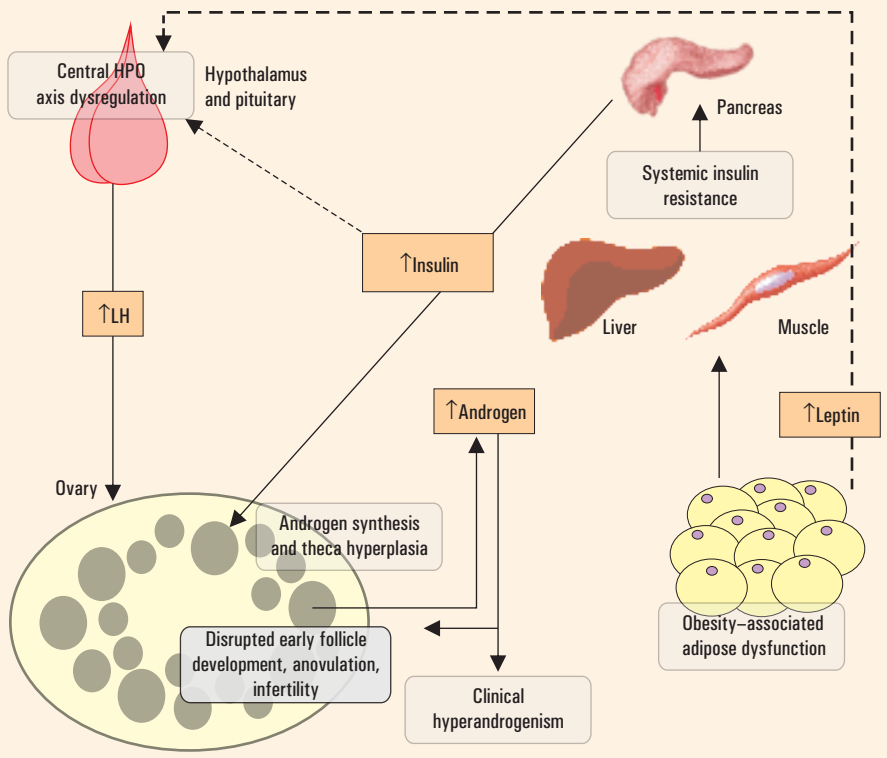
Influence of Insulin



LH: Luteinising hormone; FSH: Follicle stimulating hormone; PCOS: Polycystic ovarian syndrome

- Insulin has been shown to increase leptin mRNA in adipocytes, suggesting its possible role in stimulating leptin secretion
- Possibly elevated leptin in hyperinsulinemic PCOS women is a secondary consequence of insulin-stimulated synthesis of leptin.
- Leptin on the other hand, inhibits insulin-mediated promotion of gonadotropin(GT) stimulated steroidogenesis.
- There are reports that leptin decreases glucose-mediated insulin secretion through its receptors in the hypothalamus, and also attenuates its action at the cellular level
- In overweight women and/or those with polycystic ovary syndrome (PCOS), an increase in the number of fat cells results in above mentioned cascade of changes, involving increased leptin and insulin levels and a preferential increase in luteinising hormone (LH), but not follicle stimulating hormone (FSH) levels.
- The net effect of these changes is to stimulate the partial development of follicles that secrete supranormal levels of T, but which rarely ovulate (hence low levels of progesterone).[1,2,3]
- Disrupted endocrinal milieu in the ovary leads to failure of follicle development and ovulation.[1]

Schematic Representation of Metabolic and Reproductive Pathways in PCOS

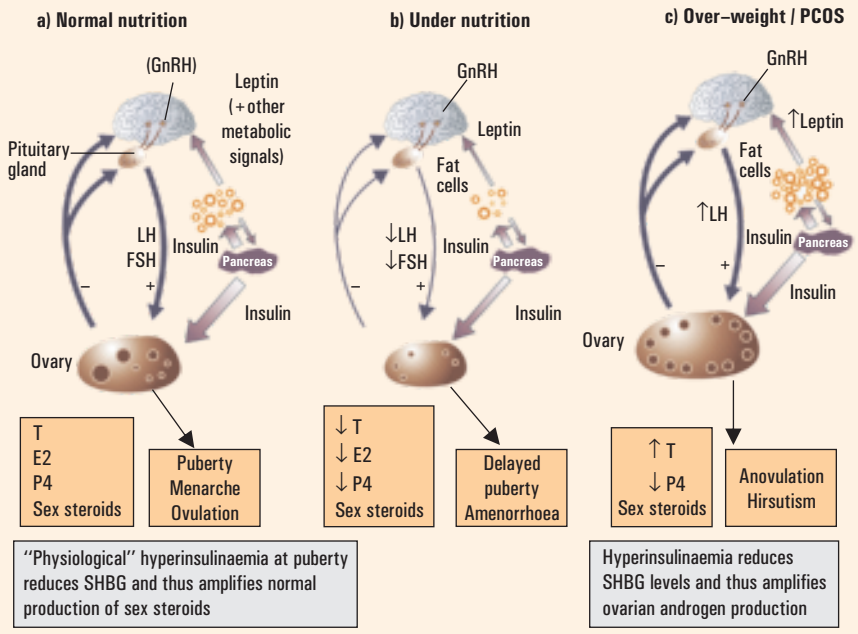


LH: Luteinising hormone; HPO: Hypothalamus

References:

1. Dumesic DA, Padmanabhan V and Abbott D. Polycystic ovary syndrome and oocyte developmental competence. *Obstet Gynecol Surv.* 2008;63(1):39–48.
2. Sharpe RM and Franks S. Environment, lifestyle and infertility — an inter-generational issue. *Nature Medicine*. 2002;8(S1);S33–S40.
3. Chakrabarti J. Serum leptin level in women with polycystic ovary syndrome: correlation with adiposity, insulin, and circulating testosterone. *Ann Med Health Sci Res*. 2013;3(2):191–196.

Obesity and PCOS



LH: Luteinising hormone; FSH: Follicle stimulating hormone; GnRH: Gonadotrophin relasing hormone; T: Testosterone; E2: Oestradiol; P: Progesterone; SHBG: Sex hormone-binding globulin

- Leptin mRNA and protein production is seen in:
  - o Granulosa cells that promote steroidogenesis
  - o Oocytes that have direct regulatory action in ovarian folliculogenesis
  - o Early cleavage stage embryos
- Leptin is found to be keenly interrelated with oestrogens, progesterone, androgens, and insulin[2,3]

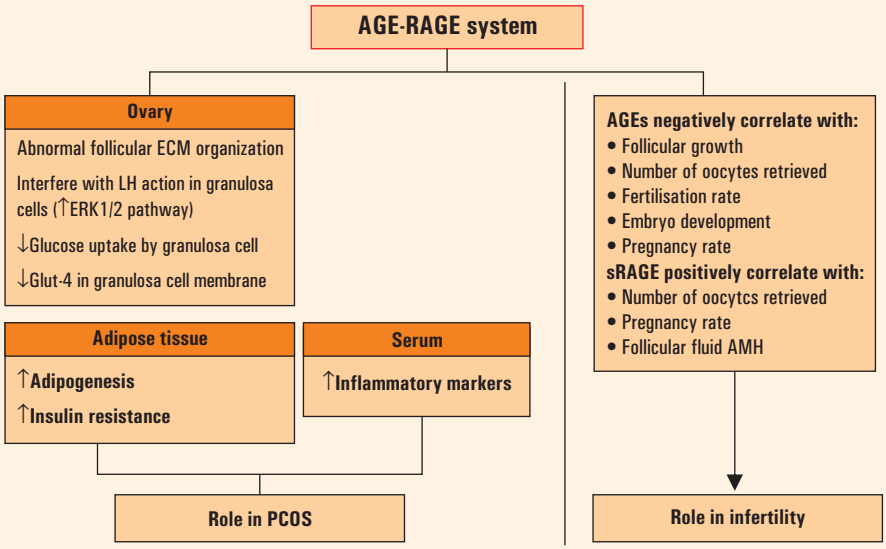
- Nutrition is linked to the female reproductive system through the effects of a hormone emanating from fat cells (leptin) and by insulin from the pancreas, which alters the bioavailability of oestradiol (E2) and T by affecting production of sex hormone-binding globulin (SHBG) from the liver.
- In addition, there is a genetic predisposition to PCOS.
- Several peripheral signals have been identified that form a link between adiposity and dysregulation in the gametogenic and steroidogenic potential of an ovary.
- Leptin and advanced glycation end (AGE) products have been identified as peripheral signals.
- They are the possible link between nutrition and reproduction.

- Reproductive potential in women undergoes adverse alteration following severe changes in nutritional status and energy availability in either direction.
- These adaptive changes are reversible when nutritional status is normalised.[1,2]

References:

1. Sharpe RM and Franks S. Environment, lifestyle and infertility — an inter-generational issue. Nature Medicine, 2002;8(S1);S33–S40.
2. Chakrabarti J. Serum leptin level in women with polycystic ovary syndrome: correlation with adiposity, insulin, and circulating testosterone. *Ann Med Health Sci Res.* 2013;3(2):191–196.

Advanced Glycation End Products Role in Infertility



AGE: Advanced glycation end products; RAGE: Receptor for AGE; ECM: Extracellular matrix; LH: Luteinising hormone; ERKs: Extracellular signal–regulated kinases; GLUT-4: Glucose transporter type 4; AMH: Anti-mullerian hormone; s-RAGE: Soluble RAGE

- Relationship of the advanced glycation end products-receptor for advanced glycation end products (AGE-RAGE) system with PCOS and infertility in shown in the above figure.
- Increased activity of this system is seen in PCOS in the serum, adipose tissue and in the ovary.
- In infertility, AGEs are negatively, while soluble RAGE form (sRAGE) are positively, correlated with assisted reproductive technology (ART) outcome and measures of ovarian reserve, as reflected by anti-mullerian hormone (AMH) level.[1]

- Multiple factors influence infertility in PCOS and several such pathways are being studied to understand this pathophysiology. However, to date, we do not understand completely the pathophysiology of infertility in PCOS .
- Deeper understanding will enable clinical researchers and scientists develop prevention and treatment modalities for infertility in PCOS.

Reference:

- Merhi Z. Advanced glycation end products and their relevance in female reproduction. *Hum Reprod*. 2014;29(1):135–145.

Management of Infertility in PCOS

Hormonal Testing in Infertility

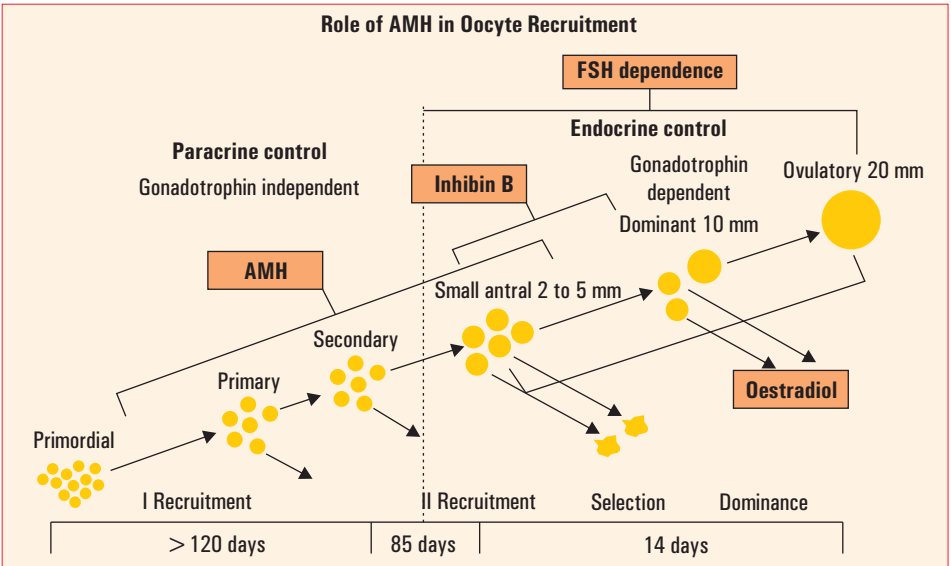
Table 1: Hormonal levels in PCOS

Hormone	In PCOS
• Follicle stimulating hormone	Normal or low
• Luteinising hormone	Elevated
• Testosterone	Elevated
• Oestrogens	Normal or elevated
• Sex hormone-binding globulin	Reduced
• Androstenedione	Elevated
• Anti-mullerian hormone	Elevated
• Human chorionic gonadotropin	Used to check for pregnancy; negative unless pregnant
• Insulin levels	Deranged hyperinsulinemia, Insulin resistance, T2DM
• Vitamin D	Reduced

Few other tests done in PCOS	To rule out
• Thyroid-stimulating hormone	Thyroid dysfunction
• Cortisol	Cushing syndrome
• Prolactin	Hyperprolactinemia
• 17-hydroxyprogesterone	The most common form of congenital adrenal hyperplasia
• Insulin-like growth factor 1	Acromegaly
• Dehydroepiandrosterone	Virilising adrenal tumour

- Hormonal testing is necessary for evaluating every case of PCOS.
- Few tests are done to rule out other possible dysfunctions before treating for PCOS.

- The above table provides the battery of hormonal testing necessary in a case of PCOS.
- AMH is an important biomarker for the oocyte quality and for further management of infertility in PCOS.[1]



FSH: Follicle stimulating hormone; AMH: Anti-mullerian hormone

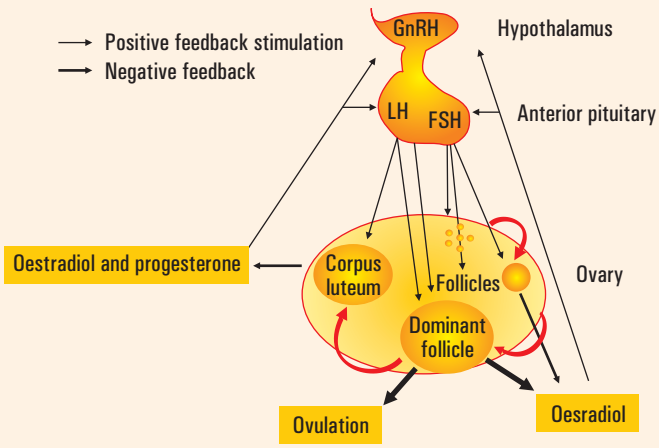
- In one of the studies published in the journal ''Human Reproduction''[1] the following results were noted:
  - o The mean serum AMH concentrations between women with PCOS (77.6 pmol/L) and those with polycystic ovarin morphology (PCOM) (52.2 pmol/L) were significantly higher than demographically similar controls (23.6 pmol/L) ($P < 0.001$)
  - o The combination of AMH >48 pmol/L and LH > 6 IU/L diagnosed 82.6% of women with PCOS.
  - o The mean serum FSH was lower in both PCOS and PCOM compared with controls, whereas LH was higher in PCOS compared with PCOM and controls, and correlated positively with AMH ($r = 0.321$, $P < 0.01$).[2]
- High-AMH concentrations present in women with PCOS play an integral role in causing anovulation due to its inhibitory influence on the actions of FSH that normally promotes follicular development from the small antral stage to ovulation.[3]
- A proper balance between FSH and AMH can be restored by cautious increase of FSH in PCOS which will have inhibiting physiological effect on AMH

References:

1. Lehmann P, Vélez MP, and Saumet J. Anti-Müllerian hormone (AMH): a reliable biomarker of oocyte quality in IVF. *J Assist Reprod Genet.* 2014;31(4):493–8.
2. Homburg R, Ray A, Bhide P, *et al.* The relationship of serum anti-Müllerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study, *Hum Reprod.* 2013;28(4):1077–1083.
3. Homburg R and Crawford G. The role of AMH in anovulation associated with PCOS: a hypothesis. *Hum Reprod.* 2014;29(6):1117–1121.

Consensus on Infertility Treatment Related to PCOS: ESHRE/ASRM, 2007

- Preconceptional counselling :
  - o Lifestyle modification
- Recommended first-line of treatment for ovulation induction (OI):
  - o Clomiphene citrate (CC)
- Recommended second-line of intervention:
  - o Exogenous gonadotrophins or
  - o Laparoscopic ovarian surgery (LOS)
- Recommended third-line treatment
  - o *In vitro* fertilisation (IVF)



GnRH: Gonadotrophin relasing hormone; LH: Luteinising hormone; FSH: Follicle stimulating hormone

- Before any intervention is initiated, preconception counselling should be provided emphasising the importance of life style, especially weight reduction and exercise in overweight women, abstinence or reduction in smoking and alcohol consumption.
- The recommended first-line of treatment for OI remains the anti-oestrogen CC and letrazole.
- Recommended second-line of intervention, if CC fail to result in pregnancy, are either exogenous GT or LOS.

- Recommended third-line of treatment is IVF.[1]

Reference:

1. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod.* 2008;23(3):462–477.

Lifestyle Modification

Obesity is associated with	**Weight loss of 5 – 10 % associated with**
• Anovulation • Pregnancy loss • Late pregnancy complications (pre-eclampsia, gestational diabetes) • Failure or delayed response to administration of o CC o GT and o Laparoscopic ovarian diathermy	• Reduction in insulin & LH concentration • Increase in insulin sensitivity • Increase in SHBG which leads to decreased free T • Improvement in reproductive /menstrual function and fertility • Reduced hirsutism and acne • Correction of defects in meiosis and early embryonic development

- Obesity is common in women with PCOS.
- Weight loss is recommended as first-line therapy in obese women with PCOS seeking pregnancy. [1]
- Both diet and physical activity play a vital role as a first step to improve fertility in obese PCOS patients with anovulatory infertility.
- Bariatric surgery may be considered in cases with BMI 35kg/m^2 and where lifestyle therapy has failed.
- Insulin sensitivity may be the prime factor associated with restoration of ovarian function by potentially acting through different mechanisms.[2]
- A study published in a well known journal also highlights increased energy intake, increased sitting time with low physical activity among women with PCOS. [3]
- The effects of calorie restriction, increased physical activity pharmacological and weight loss agents in the pre-conceptional period are unknown and can be potentially harmful.
- These interventions should be restricted prior to conception and not concurrently with infertility treatment.

- The risk benefit ratio of these therapies on pregnancy should be considered when applied concurrently with infertility treatments.[1,2,3]

References:

1. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod.* 2008; 23(3):462–477.
2. Palomba S, Giallauria F, Falbo A, *et al.* Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Hum Reprod.* 2008;23(3):642–650.
3. Moran LJ, Ranasinha S, Zoungas S, *et al.* The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome. *Hum Reprod.* 2013;28(8):2276–2283.

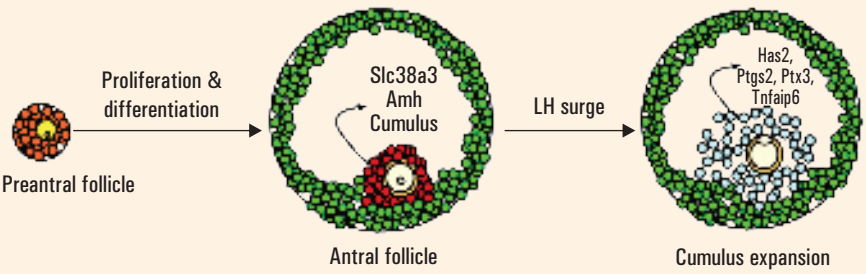
Ovulation Induction in PCOS

When

- Weight loss fails
- Anovulation and menstrual abnormalities are persistent
- Age > 35 years
- Other factors affecting fertility are present

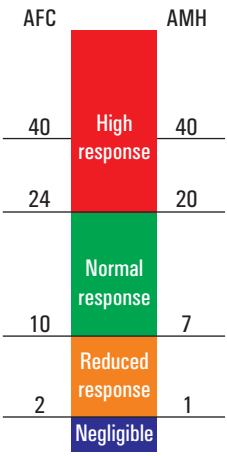
Before OI

- Analyse ovarian reserve
- Define the goal of ovarian stimulation
- Select correct protocol



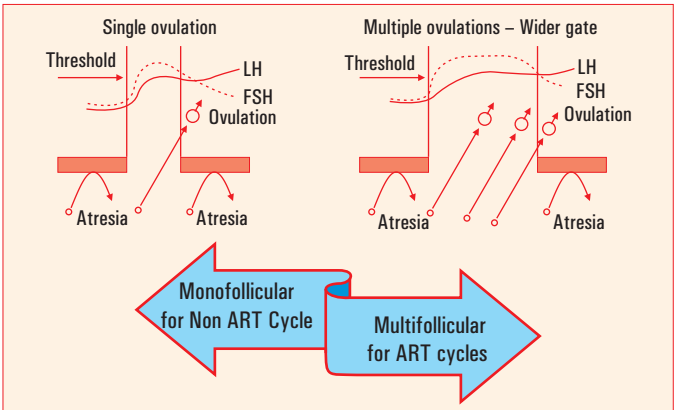
Analysing ovarian reserve

- Antral follicle count (AFC) and AMH are the currently preferred biomarkers for analysing the ovarian reserve.
- **AFC:** for ovarian reserve and predicts ovarian response
- **AMH:** apart from predicting response also assists in forecasting the reproductive lifespan and ovarian dysfunction in women with PCOS
- AFC and AMH are complementary and are used for:
  - **Pretreatment assessment/intervention**
  - **To decide stimulation dose and regimen, and**
  - **To select maturation trigger**



Goal of ovarian stimulation

- To convert the anovulation to normal ovulatory cycle
- The number of follicles that ovulate is determined by length of time that the level of FSH remains above the thresh hold value



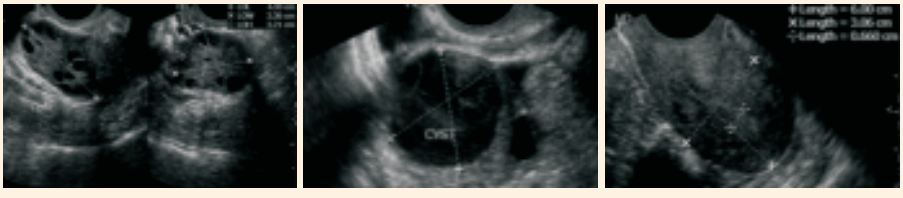
LH: Luteinizing hormone; FSH: Follicle stimulating hormone; ART: Assisted reproductive technology

Selecting the protocol

- The ovulation induction protocols are designed in the current clinical practise based on
  - o Ovarian reserve
  - o Age
  - o BMI
  - o Presence of other infertility factors
  - o Available resources
  - o Risk tolerance

Ovulation Induction Prerequisites

Follicular size is < 10 mm ; Absence of ovarian cyst; Endometrial thickness (ET) < 6 mm; E2 levels < 50 pg/mL and progesterone < 1.5 ng/mL

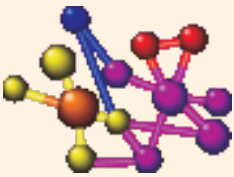


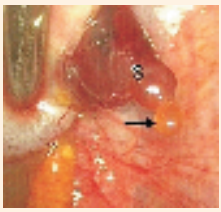
Selection of dominant follicle occurs in the follicular phase; hence OI is started within day 3 of the menstrual cycle. Given above are the prerequisites before initiating OI.

First Line/Oral Options

Anti-oestrogens: Clomiphene Citrate

- Started on day 2, 3, 4, or 5 of spontaneous or induced menses and given for 5 days
- Starting dose: 50 mg; Maximum dose:150–200 mg
- Dose correlates with body weight, age, indication for use (anovulation, PCOS, controlled ovarian hyperstimulation [COH]) and past history
- Dose cannot be accurately predicted
- Requires empiric incremental titration to establish lowest effective dose
- Treatment is discontinued if 2 consecutive cycles are anovulatory
- It induces
  - o Ovulation in 75%
  - o Pregnancy in 35%,
  - o Miscarriages in 20%
  - o Multiple Pregnancies (MP) in 8–10 %



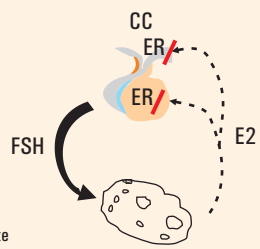


- CC remains the first choice of treatment for induction of ovulation in anovulatory women with PCOS.
- Cost, ease of administration, few adverse effects, supports its widespread use.
- The mechanism of action involves the blockade of the negative feedback mechanism which results in enhanced secretion of FSH.
- The main factors that predict responsiveness to CC are obesity, hyperandrogenemia, age, ovarian volume and menstrual status are additional factors that help to predict responsiveness to CC.[1,2,3]

Ultrasound (USG) Monitoring or Not for CC?

With U/S + hCG		No U/S or hCG
48%	Cumulative conception rate	34.7%
35.6%	Deliveries	26.7%
0	Multiple pregnancies	1

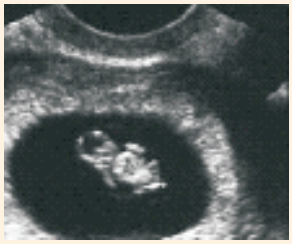
USG-monitored CC treated cycles produce better pregnancy rates compared with non-monitored cycles



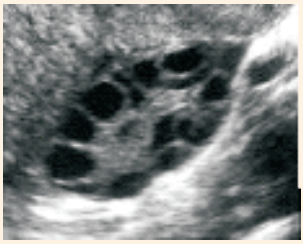
FSH: Follicle stimulating hormone; E2: Oestradiol; ER: Endoplasmic reticulum: CC: Clomiphene citrate

- USG monitoring is not mandatory in CC cycles
- However as noted better outcomes are seen with USG monitoring
- The outcome of use of hCG in mid cycle is not clear[4]

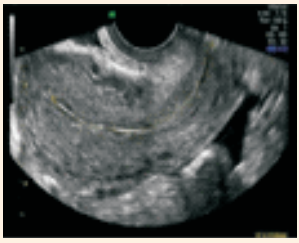
When to Stop CC ????



When 6 ovulatory cycles fail to yield a pregnancy

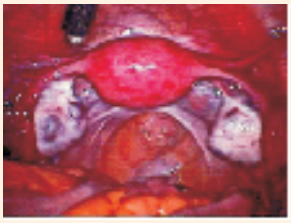


When no ovulation with 150 – 200 mg/day

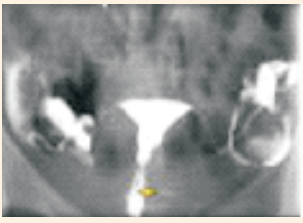


If ET < 7 mm at ovulation

- In all the above situations CC must be discontinued and further evaluation must be done for other infertility factors.



Diagnostic laparoscopy



Hysterosalpingography

- If this is already done next line of treatment should be considered.

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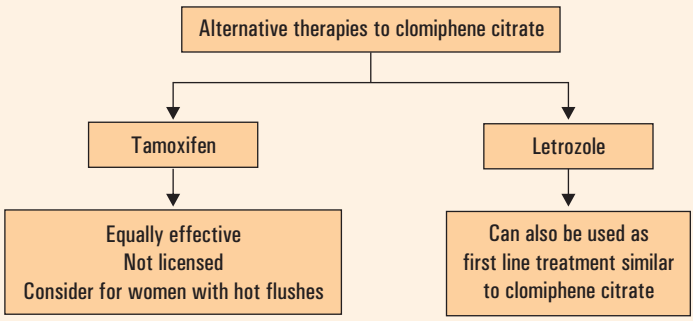
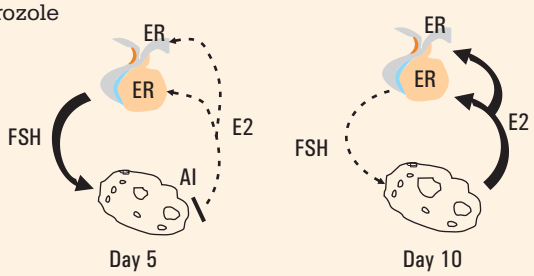
Alternative Therapies: Letrozole and Tamoxifen



- Anti-oestrogens other than CC: Tamoxifen appears to be as effective as CC for OI but is not licensed for that purpose.
- It may be considered as an alternative to CC in women who suffer intolerable side effects such as hot flushes.[1]
- Aromatase inhibitors: studies suggest that letrozole appears to be as effective as CC for induction of ovulation.[2]

Aromatase Inhibitors

- **Mechanism of action**
  - o Suppresses oestrogen biosynthesis
  - o Increase the follicular sensitivity to FSH secondary to high intra-follicular androgen levels
  - o Induction of high intra follicular insulin-like growth factor (IGF-I) concentrations
- **Merits**
  - o No anti-oestrogenic effect on the endometrium or cervical mucus
  - o Limited number of mature follicles
  - o Decrease ovarian hyperstimulation syndrome (OHSS) & multiple pregnancy
- **Demerits**
  - o There are concerns regarding increased rate of birth defects associated with use of letrozole



FSH: Follicle stimulating hormone; E2: Oestradiol; ER: Endoplasmic reticulum

- Aromatose inhibitor leads to:
  - o E2 suppression that peaks between day 5–7 of the cycle.
  - o After day 7, E2 levels rise steadily to trigger LH-surge; around day 12–14 of the cycle.
  - o Non supraphysiologic rise occurs as against that of CC[3]
- Letrozole is comparable to CC
  - o It is as effective as CC for OI in PCOS.[4]
  - o There is no statistical difference beteen letrozole and CC[5] for:
    - – Pregnancy rate per patient
    - – Live birth rate per pregnancy
    - – Miscarriage rate per pregnancy
    - – MP rate per patient
  - o Letrozole was better than CC for ovulation rate per patient[5]
- No difference was observed in effectiveness between letrozole and laparoscopic ovarian drilling (LOD).
- Occurrence of OHSS was rare.[6]
- A double blind randomised controlled trial (RCT) provides evidence of letrozole superiority over CC as a primary OI agent in PCOS women with a 40% increase in pregnancy rates and with a shorter time to pregnancy.
- This recent study recommends letrozole should replace CC as the first line OI agent in PCOS.[7,8]

Table 2: Outcome for letrozole versus CC as primary treatment-intention to treat analysis

Outcome	Letrozole (N = 80)	CC (N = 79)	Rate ratio (95% CI)	Absolute difference (95% CI)	*P*
Pregnancy rate	49/80 (61.2%)	34/79 (43.0%)	1.4 (1.1, 2.0)	18% (3 to 33%)	0.022
Live birth rate	39/80 (48.8%)	28/79 (35.4%)	1.4 (0.95, 2.0)	13% (–2 to 28%)	0.089
Ovulation rate	67/80 (83.8%)	63/79 (79.7%)	1.1 (0.9. 1.2)	4% (–8 to 16%)	0.513
Pregnancies per ovulating patient	47/67 (70.1%)	32/63 (50.8%)	1.4 (1.04, 1.9)	20% (3 to 30%)	0.024
Pregnancies-strata 1 (BMI < 30)	37/54 (68.5%)	25/53 (47.2%)	1.5 (1.04, 2.1)	21% (3 to 38%)	0.025
Pregnancies-strata 2 (BMI 30–35)	12/26 (46.2%)	9/26 (34.6%)	1.3 (0.7, 2.7)	12% (–14 to 35%)	0.397
Live births-strata 1 (BMI < 30)	29/54 (53.7%)	20/53 (37.7%)	1.4 (0.9, 2.2)	15% (–3 to 30%)	0.122
Live births-strata 2 (BMI 30–35)	10/26 (38.5%)	8/26 (30.8%)	1.3 (0.6, 2.7)	8% (–20 to 30%)	0.771
Pregnancies per cycle	49/261 (19.0%)	34/278 (12%)	1.5 (1.03, 2.3)	7% (0.4 to 1.3%)	0.036

Table 2: Outcome for letrozole versus CC as primary treatment-intention to treat analysis (table contd...)					
Outcome	**Letrozole (N = 80)**	**CC (N = 79)**	**Rate ratio (95% CI)**	**Absolute difference (95% CI)**	***P***
Live births per cycle	39/261 (15%)	28/278 (10%)	1.48 (0.95, 2.33)	5% (–0.7 to 11%)	0.087
Ovulation per cycle	196/261 (75%)	18/278 (67%)	1.1 (1.01, 1.2)	8% (1 to 15%)	0.045
Mono-ovulation	80/94 (85.1%)	64/77 (83.1%)	0.88 (0.4, 1.7)	–2% (–13 to 9%)	0.723
ET (mm)[median (IOR)]	8.4 (7.0, 10.2)	9.0 (8.0, 11.0)			0.002

References:

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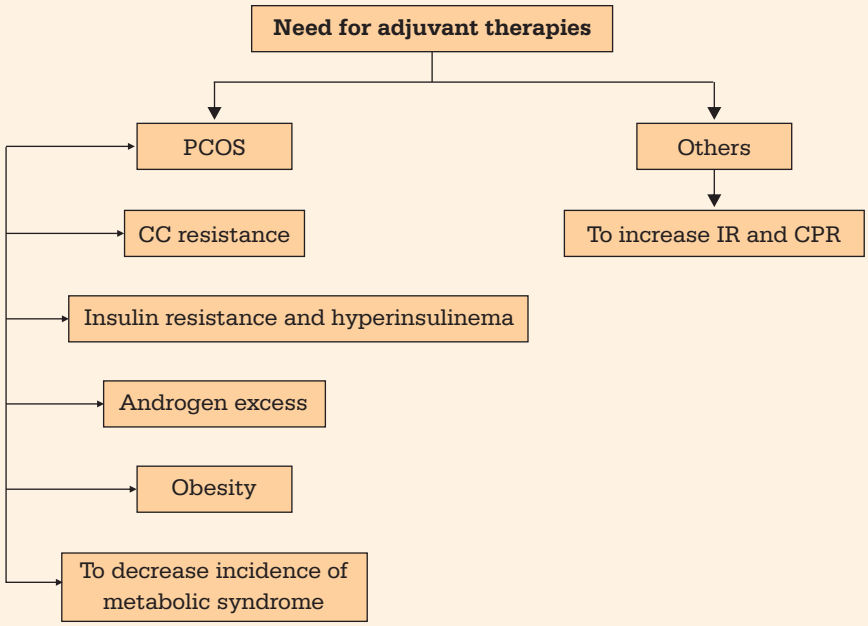
Adjuvants for Ovulation Induction

- **For treatment of PCOS**
  - o Androgen excess
    - – Glucocorticoids: prednisone, methyl prednisolone and dexamethasone
  - o Hyperinsulinemia/ Insulin resistance
    - – Metformin
    - – Myoinositol
  - o Others
    - – N Acetyl cysteine
    - – Melatonin
    - – Vitamin D
    - – Chromium polynicotinate
- **Others**
  - o Antioxidants
  - o Micronutrients
  - o Dopamine agonist
  - o Aspirin
  - o Sildinafil



IR: Implantation rate, CPR: Clinical pregnancy rate

- Not all adjuvant therapy is approved by FDA
- Many of them are used as OFF label drugs
- Off-label drugs have been evaluated in the phase I or phase II trials of clinical research but have not been fully assessed in phase III or phase IV trials

Use of Glucocorticoids

- For women with CC resistance and dehydroepiandrosterone (DHEAS) >200 micrograms/ dL
- For CC-resistant anovulatory patients add prednisone
- Addition of dexamethasone to CC significantly improved ovulation and pregnancy rates

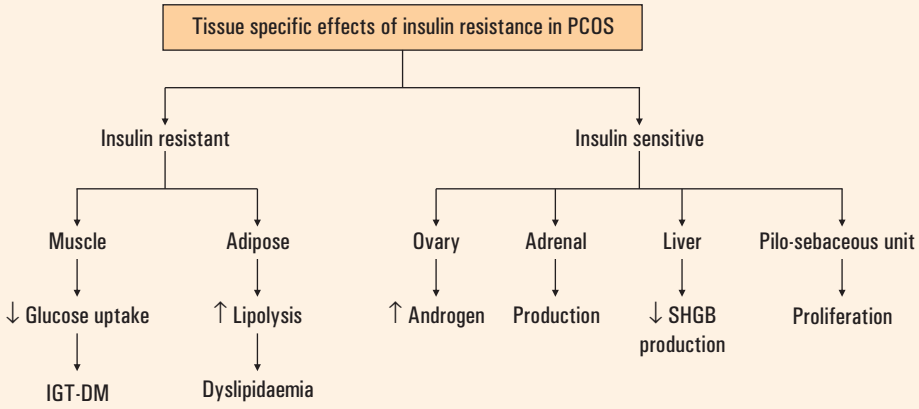
	CC alone	CC+ dexa	*P* value
Ovulation rate	15%	75%	$P < 0.001$
Pregnancy rate	4.2%	40.5%	$P < 0.01$

Recommended dose: Dexamethasone 2 mg/day days 5 to 14

- Glucocorticoids is now recommended for women with CC resistance irrespective of DHEAS values,[1] although early studies recommended benefits in women with DHEAS >200 micrograms/ dL.[2]
- CC-resistant anovulatory patients have high rates of ovulation and pregnancy after treatment with extended CC and prednisone.[3]
- Addition of dexamethasone to CC significantly improved ovulation and pregnancy rates when compared with CC alone.[2]
- This therapy offers a potential reduction in cost and risk and should be considered in this group of patients before GT stimulation or surgery.[2]
- Cochrane data review recommends the use of dexamethasone with CC in resistant cases.[4]
- Optimal dosing is not known, but the largest and best designed trial demonstrated benefit using dexamethasone 2 mg/day days 5 to 14.[5]

Insulin Resistance and PCOS

- Insulin resistance is intrinsic to PCOS
- It is independent of obesity (Thirty percent of PCOS women are not obese)
- It plays a central role in the pathogenesis of PCOS as insulin-induced hyperandrogenaemia is the underlying biochemical abnormality in PCOS
- Obesity when present (de novo or as a result of intrinsic insulin resistance is an extrinsic cause of insulin resistance in PCOS
- Insulin resistance in PCOS → Intrinsic
  → Extrinsic



IGT: Impaired glucose tolerance; DM: Diabetes mellitus; SHBG: Sex hormone-binding globulin

Insulin-sensitizing Agents: Metformins Role in Treatment of Hyperinsulinemic Hyperandrogenism

Potential advantages

- ↑Glucose tolerance
- ↑Insulin sensitivity
- ↓Blood lipid levels
- ↑Weight loss or stabilisation
- Improved fat distribution
- ↓Blood pressure
- ↓Androgen levels
- Restoration of regular menses
- Stimulates folliculogenesis
- Postponement of diabetes

Potential disadvantages

- Gastrointestinal disturbance in 1/3 of patients
- Generalised feeling of unwellness
- Decreased absorption of vitamin B_{12}
- Lactic acid buildup

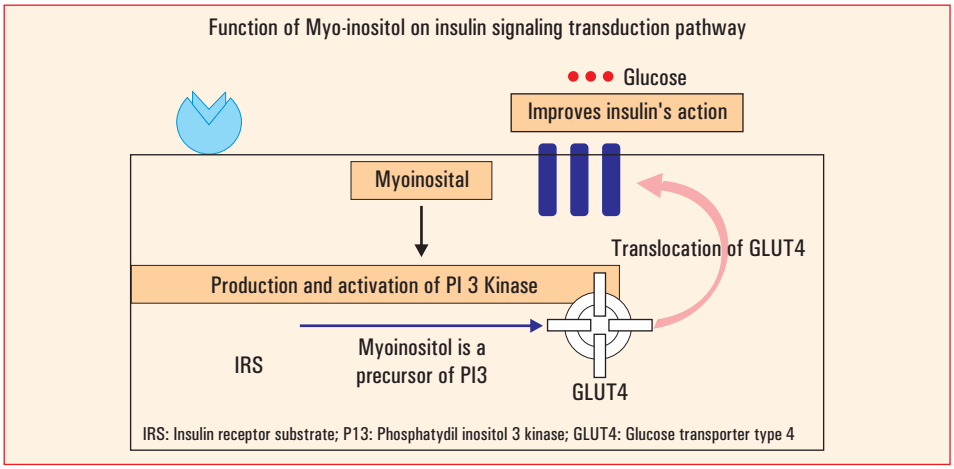
- There is no evidence that metformin treatment before or during ART cycle improved live birth rates (LBR) in women with PCOS.
- However, metformim increased clinical pregnancy rates and decresed the risk of OHSS.
- Obstetrician to decide about continuing insulin sensitizers during pregnancy in women with glucose intolerance.
- Metformin alone is less effective than CC in inducing ovulation in women with PCOS.

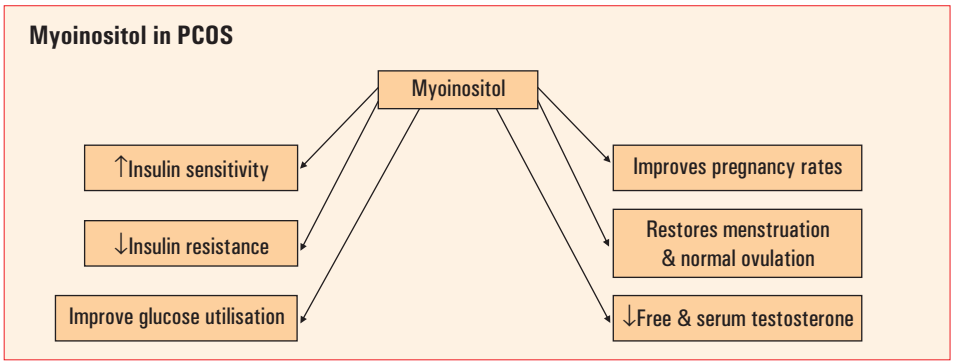
Table 3: Rate of LBR on PCOS treatment with metformin and/or CC	
PCOS medication	**Live birth rate**
Metformin only	7.2%
Clomiphene citrate only	22.5%
Clomiphene citrate/Metformin combination	26.8%

- Metformin increased clinical pregnancy rates only in GT cycles and decreased the risk of OHSS.[6]
- Two RCTs reported a live birth rate of 46% in the metformin group and 27% in the placebo group after three and six treatment cycles, respectively.
- Metformin use was associated with a higher LBR. For a control LBR of 27% after FSH, the addition of metformin resulted in a LBR ranging between 32%–60%.
- Metformin use was associated with a higher ongoing pregnancy rate vs placebo.
- No evidence of a difference in miscarriage rates between metformin and placebo.[7]
- Obstetricians must decide about continuing insulin sensitizers during pregnancy in women with glucose intolerance after careful evaluation of risks and benefits.
- Metformin alone is less effective than CC in inducing ovulation in women with PCOS as seen in the table above.[8,9]
- There is insufficient data to advise short-course metformin pretreatment as against long term treatment before initiation of CC for OI in infertile women with PCOS.

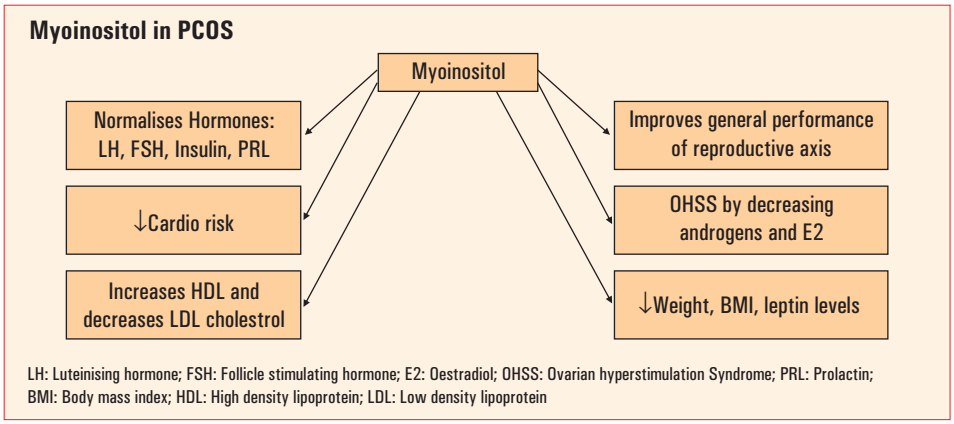
Inositol

- Inositol, is a member of the B-complex family of vitamins
- It's not an essential vitamin, as it can be manufactured by the body, but it tends to be deficient in women with PCOS
- It is present in cereals with high bran content, nuts, beans, and fruit, especially cantaloupe melons and oranges
- Human adults consume approximately 1 g of inositol per day in different biochemical forms
- Free inositol is actively transported across the intestinal wall by a mechanism dependent on sodium and energy, a process that can be inhibited by glucose
- Circulating free inositol is taken up by most tissues by a membrane-associated sodium-dependent inositol co-transporter

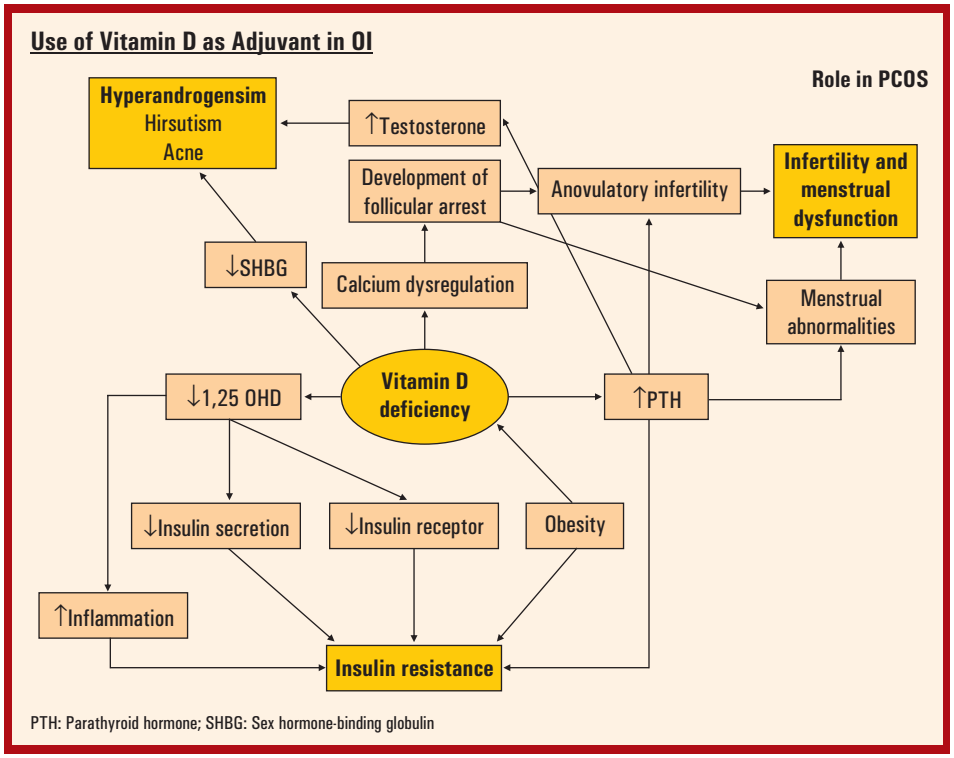




- Women with PCOS demonstrate low levels of inositol
- Myoinositol is an insulin sensitizer with beneficial effects on ovarian function and response to ART in women with PCOS
- Its use decreases insulin resistance, free and serum T
- It improves insulin sensitivity, glucose utilisation
- Its use leads to restoring normal menstruation and ovulation
- And all the above factors assist in improved pregnancy rates with myoinositol use[10]



- It induces nuclear and cytoplasmic oocyte maturation and promotes embryo development.[11]
- Myoinositol administration increases clinical pregnancy rates, lowers total recombinant FSH (rFSH) dose and the duration of the ovulation induction.[12]
- 2017 Cochrane review suggests that inositol appears to regulate menstrual cycles, improve ovulation and induce metabolic changes in PCOS; however, evidence is lacking for pregnancy, miscarriage or live birth.[12]



How Vitamin D Enhances Ovulation in PCOS?

Vitamin D binds to vitamin D receptor

↓

Activates peroxisome proliferator activator receptor-δ (PPAR δ)

↓

Stimulates the expression of insulin receptor

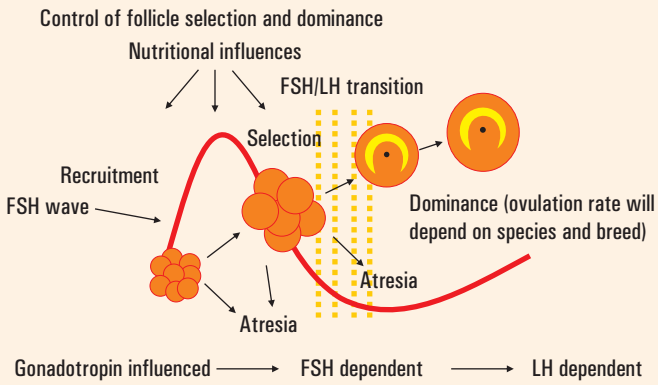
↓

Enhances insulin-mediated glucose transport

Vitamin D plays a physiologic role in reproduction including ovarian follicular development and luteinisation via AMH signalling, FSH sensitivity and progesterone production in human granulosa cells.[13]

- It also affects glucose homeostasis through manifold roles.
- Vitamin D supplementation can lower abnormally elevated serum AMH levels.[13]
- Vitamin D and calcium supplementation in women with PCOS could result in the beneficial effects on the menstrual regularity and ovulation.[13,14]

Role of N-acetyl Cysteine



LH: Luteinizing hormone; FSH: Follicle stimulating hormone

Mechanism of action

- Improves insulin sensitivity, quality of cervical mucus & decreases androgen level
- Prevents follicular cohort atresia

N-acetylcysteine: adjuvant to CC

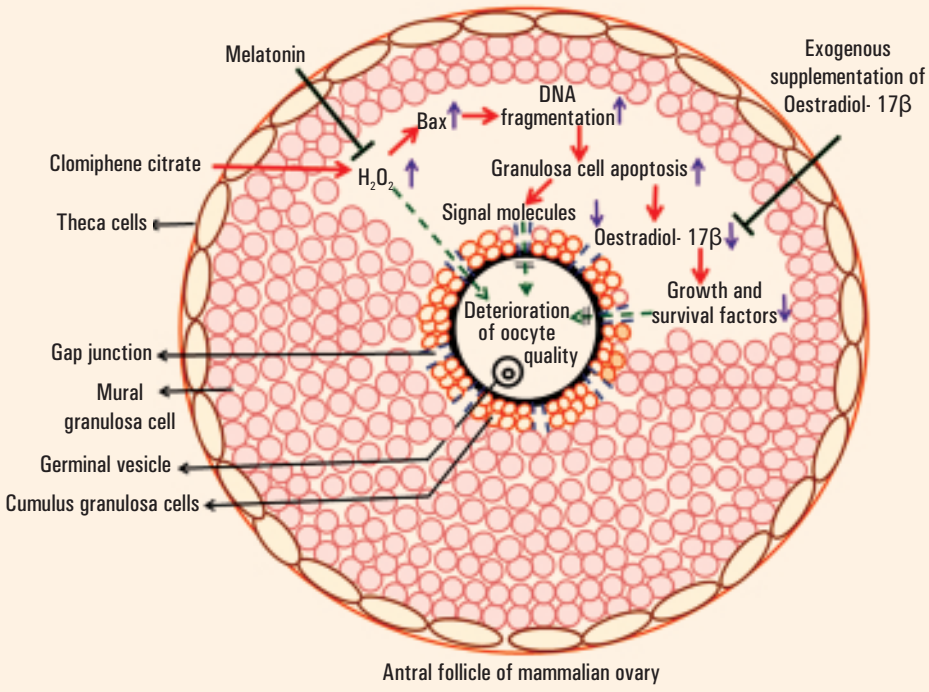
- Improves ovulation and pregnancy rates
- Beneficial impacts on embryo transfer

N-acetyl-cysteine: adjuncts to GT Therapy

- Improves the insulin sensitivity and hormonal profile and IVF outcomes
- Beneficial in improving ovarian response to ovarian stimulation

- N-acetyl cysteine improves insulin sensitivity and reduces hyperandrogenemia
- It is used as an adjunct for CC and GT therapy
- Its use has been associated with improvement in ovulation and pregnancy rates
- It may have beneficial effect on the ET as well[15,16]
- However at this time, there isn't enough evidence for use of supplemental oral antioxidants for subfertile women[16]

Melatonin as an Adjuvant



- Melatonin is taken up into the follicular fluid from the blood
- Reactive oxygen species (ROS) produced within the follicles, especially during the ovulation process, were scavenged by melatonin, and reduced oxidative stress involved in oocyte maturation and embryo development
- High intra-follicular melatonin concentrations, reduces intra-follicular oxidative damage
- Despite the antioxidant action of melatonin as per recent meta-analysis, there is no clarity regarding benefit of adding melatonin in all PCOS women[17]

Other Adjuvants

CoQ10[18]

- Promising adjuvant to oral ovulatory agents such as CC
- Effective, inexpensive and safe for stimulating follicular development in CC resistant PCOS

Phytoestrogens[19]

- Can be used as an alternative to CC for OI in women with PCOS
- No large trials yet

Alpha lipoic acid[20]

- Modulates insulin sensitivity

Vitamin B_{12}, folic acid pyridoxine

- Reduces homocysteine levels, which if raised can lead to defective ovulation

Iron

- Reduces risk of anovulatory infertility

Green Tea[22]

- Has positive effect on glucose metabolism

Zinc[23]

- Plays important role in ovulation

L arginine[21]

- Helps to optimise oocyte quality & maturation

Chasteberry[24]

- Used to treat hormonal imbalances in women because it has an immediate effect on pituitory gland

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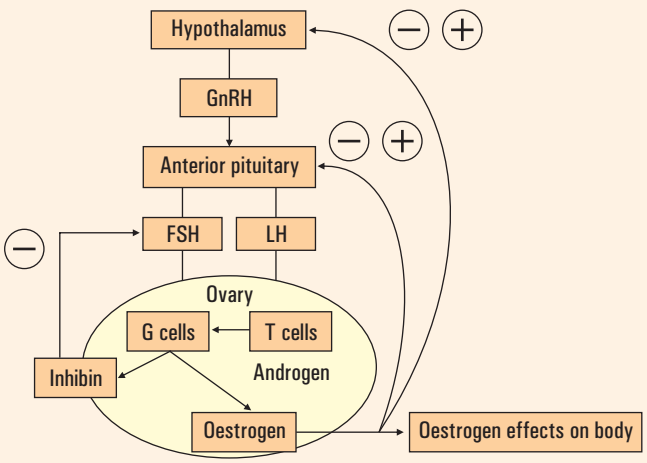
Second Line of Treatment

Gonadotropins

Laparoscopic ovarian drilling

- Infertile women who fail to conceive following clomiphene citrate, tamoxifen or with aromatase inhibitors require an alternative, second-line approach which includes
  - o GT
  - o LOD

Gonadotrophin action on ovary



LH: Luteinizing hormone; FSH: Follicle stimulating hormone; GnRH: Gonadotrophin relasing hormone

FSH and hMG (Human menopausal gonadotropins) are used for ovulation induction

- The aim of OI for women with anovulatory PCOS is to restore fertility and achieve a singleton live birth.
- The physiological concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles is the rationale behind GT use in OI.[1]

- Gonadotrophin relasing hormone (GnRH) analogues: prolonged activation of GnRH receptors by GnRH leads to desensitisation and consequently to suppressed GT secretion. FSH & hMG are GnRH analogues.
- GnRH antagonists: they compete with GnRH for receptors on gonadotroph cell membranes, inhibit GnRH-induced signal transduction and consequently GT secretion. They are free of agonistic actions.[2] Cetrorelix, ganirelix, abarelix, degarelix are GnRH antagonists.

Gonadotrophin

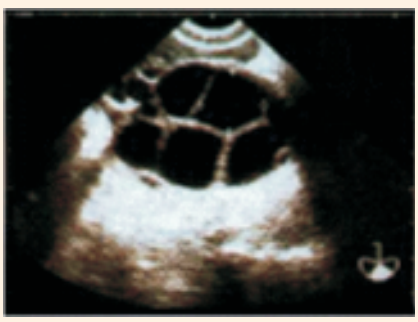
Indications

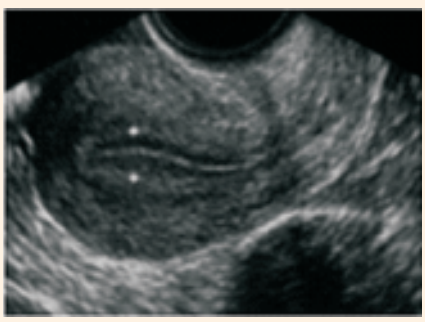
- CC/Tamoxifen resistance
- CC/Tamoxifen failure
- Persistent hypersecretion of LH
- Negative postcoital test
- Intrauterine insemination (IUI) or Assisted conception cycles

- FSH & hMG are GnRH analogues used alone or in combination with CC/Tamoxifen
- CC/Tamoxifen stimulates recruitment of number of small follicles & GTs sustain the growth of recruited follicles

Gonadotropin Protocols

- **Monitoring**
  - Transvaginal (TVS) ultrasound for follicular growth and endometrial thickness (ET)
  - Serial serum E2 if hypo or hyper response





- Stringent monitoring is essential when patient is on GT protocols.
- TVS is used for monitoring follicular growth and endometrial thickness ET

- Serial measurement of oestrogen hormone is done to assess hyper response
- It is necessary that specific protocols and stringent monitoring is performed for patient on GT.

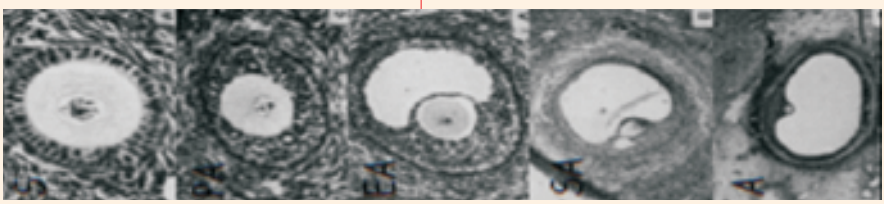
Gonadotropin to be used

GT

- Urinary (u-hMG) or
- Highly purified u-hMG
- Purified u-FSH or
- Highly purified u-FSH or r-FSH

Combinations

- GnRH agonists with hMG and/or FSH (long, short or ultra short protocol)
- GnRH antagonists with hMG and/or FSH (fixed or variable protocol)



LH on Day 2

< 1 mIU/L: Add hMG/ r-LH

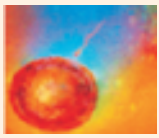
> 1 mIU/L: One can use pure FSH/ r-FSH

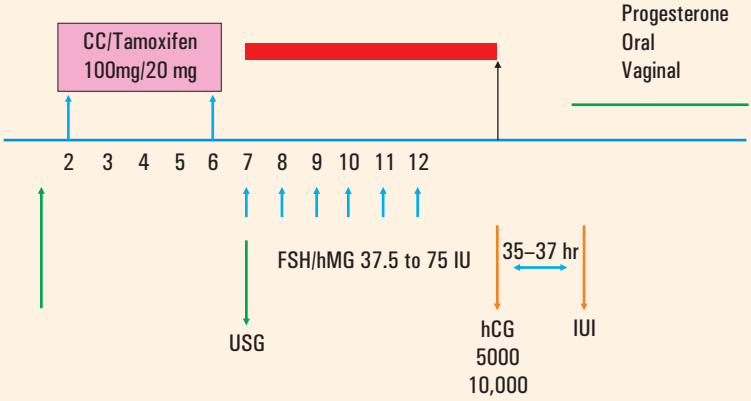
Fertility Treatments with Gonadotropin

- **Conventional regimen**
  - Starting dose of 150 IU a day
  - Increased risk of OHSS
  - No longer recommended
- **Low dose step up regimen**
  - Stepwise increase in FSH
  - Weekly dose of escalation based on USG monitoring
  - Chronic low dose regimen
  - Safer for monofollicular development
- **Low dose step down regimen**
  - Loading dose of FSH with stepwise reduction
  - USG monitoring
  - Requires more experience and skill
- **Combined approach**
  - Sequential use of step up and step down protocols

- Different regimens for use of GT are mentioned above[1]
- Conventional fixed dose regimen:
  - Fixed dose regimens comprise of constant daily dose of 75–150 U of GT from day 2 or day 3 with USG and E2 levels guiding further management.
  - Conventional regimen started with very high doses and increased the risk of OHSS and is hence no longer recommended.[3]

- **CC/ Tamoxifen + GT Protocol**

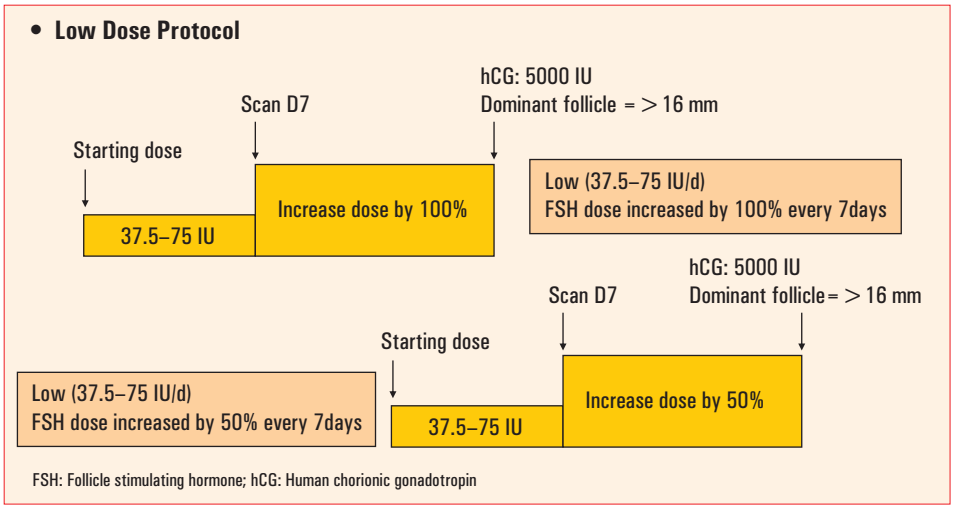




CC: Clomiphene citrate; FSH: Follicle stimulating hormone; hMG: Human menopausal gonadotropins; IUI: Intrauterine insemination; hCG: Human chorionic gonadotropin; USG: Ultrasound

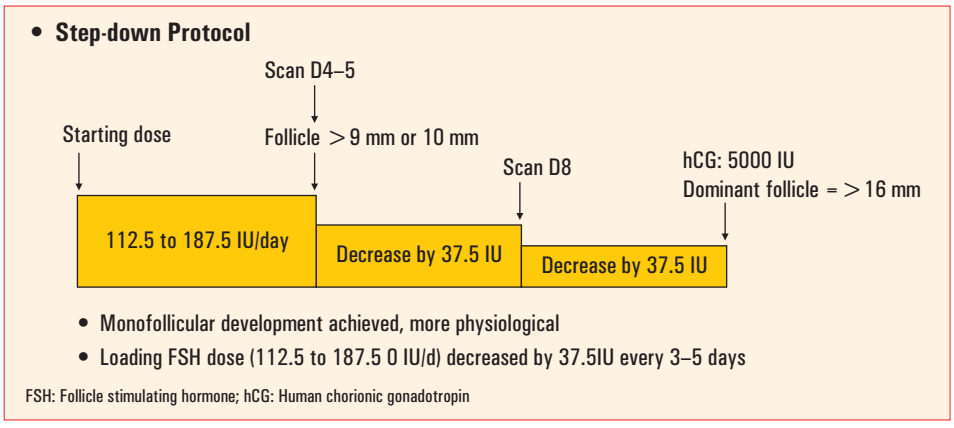
The commonest protocol used is:

- Five days of CC 100 mg or tamoxifen 20 mg, given once daily, from day 2 to day 6 followed by a injection of FSH 37.5 U/ hMG 75U from day 7, 8, 9 along with follicular monitoring by USG.
- When the leading follicle is 18–20 mm and serum E2 not more than 1500–2000 pg/mL, Injection hCG (5000/ 10,000 units) is given to trigger ovulation.[4]



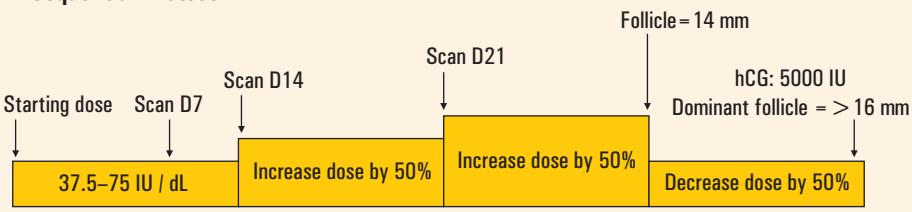
Low dose step up regimen

- The principle of this regimen is to find the threshold level of FSH which will lead to development of single preovulatory follicle
- Low dose regimens utilise (37.5–75 IU/day)
- Step up regimen starts with low dose and weekly dose is escalated
- The dose on the day the follicular growth is noted on USG and is continued as an optimal dose until the follicular selection is achieved
- For reducing the risk of ovarian hyper-responsiveness, the duration of the initial dose of FSH was extended (from 7 to 14 days) and the weekly dose increment was reduced (from 100 to 50% of the dose), leading to the so-called ''chronic low-dose regimen''[5]



- Step down regimen is designed to achieve the FSH threshold through a loading dose of FSH followed by stepwise reduction as soon as follicular development is observed on USG.

- **Sequential Protocol**



hCG: Human chorionic gonadotropin

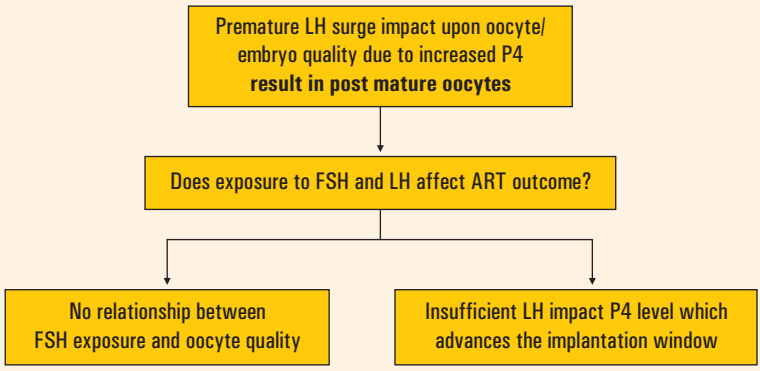
- Risk of multifolliculogenesis & OHSS reduced
- FSH threshold dose decreased by 50% when leading follicle is 14 mm

Principle

- FSH dependence of leading follicle decreases as follicle grows
- Decrease in FSH threshold contributes to the escape of the leading follicle from atresia when FSH concentrations start to decrease due to negative feedback of rising E2

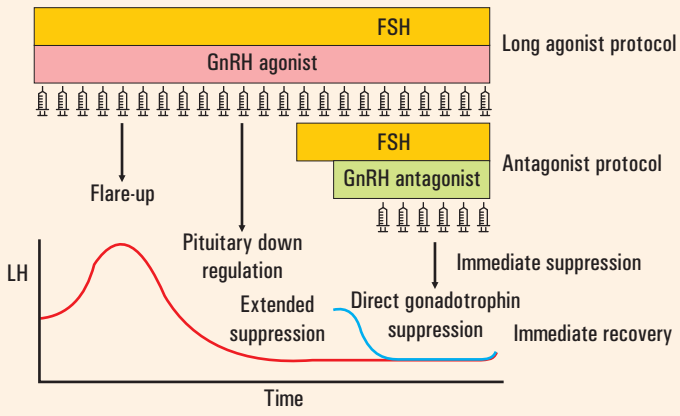
- Combined approach is sequential use of both the regimens- step up and step down.
- Strict cycle cancellation criteria should be agreed upon with the patient before therapy is started.
- MP and OHSS may still occur.
- Routine use of GnRH agonists is not recommended due to significantly higher hyperstimulation rate, the associated risk of multiple pregnancies and the additional inconvenience and cost in women with PCOS.[1,3,5]
- It is often prudent to refer patients who need GT for OI to the infertility specialists.

Why do we Require GnRH Analogues in OI?



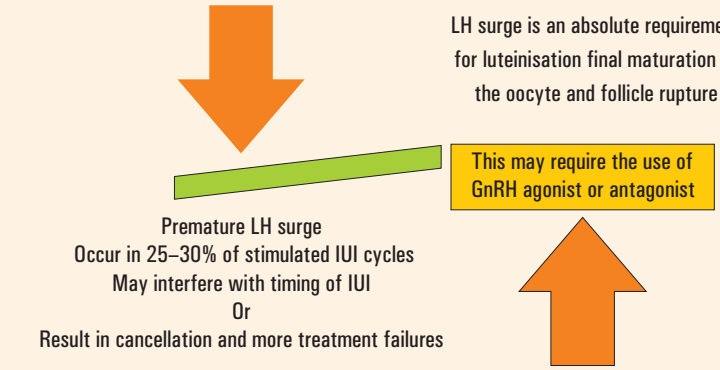
LH: Luteinising hormone; FSH: Follicle stimulating hormone; GnRH: Gonadotrophin relasing hormone; P4: Progesterone; ART: Assisted reproductive technology

Methods to Prevent Premature LH surge



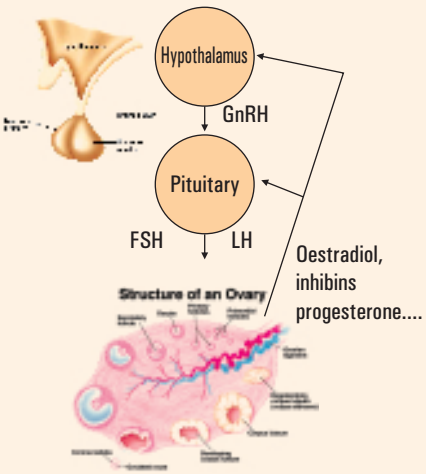
- In PCOS with CC resistance or CC failure, no evidence of a difference in LBR and OHSS rates was seen between urinary-derived GTs and rFSH or hMG/highly purified hMG (hp-hMG). One needs to weigh costs and convenience in the decision to use one or the other[6]
- In order to minimise this side effect, ovarian stimulation should be initiated with low doses of GT (100 to 150 IU of follicle stimulating hormone receptor [FSHr])
- Addition of hMG to recombinant FSH cycles on Day 8 – 9 enhances follicular growth & increases E2 levels
- Pituitary should be suppressed with a gonadotropin-releasing hormone (GnRH) antagonist because this method is associated with a reduced risk of OHSS compared with an agonist[7]

- **Is there Role of GnRH Analouges in IUI cycles**



GnRH: Gonadotrophin relasing hormone;LH: Luteinizing hormone; IUI: Intrauterine insemination

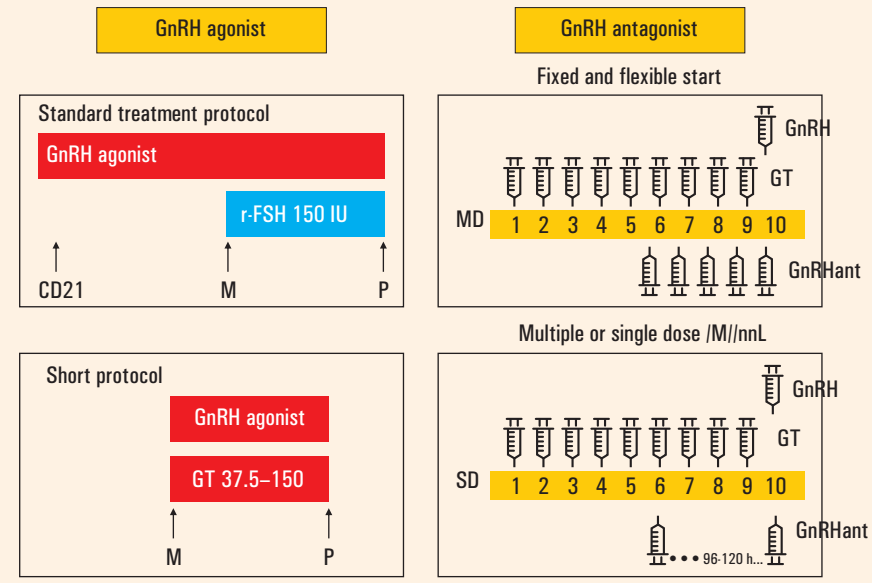
- **Use of GnRH Analogues in Intrauterine Insemination (IUI)**



- In comparison of GT alone vs GT with GnRH agonists it was seen that pregnancy rate was higher with use of GnRH agonists, however it was also associated with higher rate of MP and OHSS.
- In seven RCTs average ongoing pregnancy rate was 5.3% greater with use of GnRH antagonist
- Number-needed-to-treat (NNT): 20 cycles of GnRH antagonist for one additional pregnancy

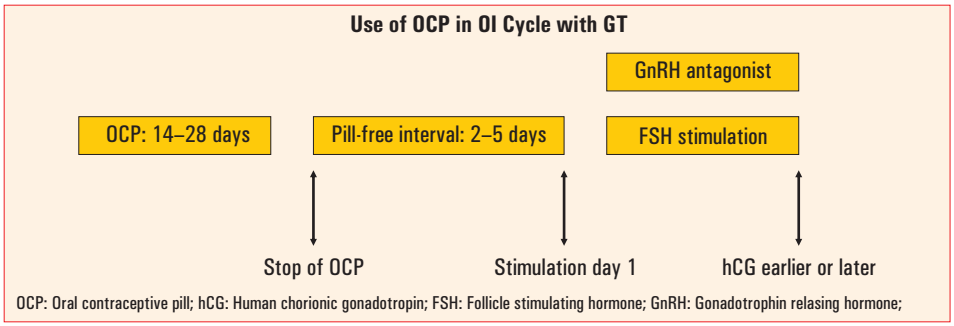
LH: Luteinising hormone; FSH: Follicle stimulating hormone; GnRH: Gonadotrophin relasing hormone;

- **How to Choose Between GnRH Analogues in ART cycle ?**



GnRH: Gonadotrophin relasing hormone; FSH: Follicle stimulating hormone; GnRHant: GnRH antagonist ; GT: Gonadotrophin

- Choice between GnRH analogues will depend on :
  - Ovarian reserve: based on AMH and AFC
  - Hormonal profile
  - E2 levels
  - Number of growing follicles
- The use ovarian biomarkers to select the appropriate treatment is recommended.
- AMH stratified treatment for choosing the GnRH analogue and dose of FSH is helpful for generating customised individualised stimulation protocols.
- Use of oral contraceptive pill (OCP) with GnRH agonists assists in prevention of asynchronous development of follicles which is found when GnRH antagonists are used.



OCP: Oral contraceptive pill; hCG: Human chorionic gonadotropin; FSH: Follicle stimulating hormone; GnRH: Gonadotrophin relasing hormone;

References:

1. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod.* 2008;23(3):462–477.
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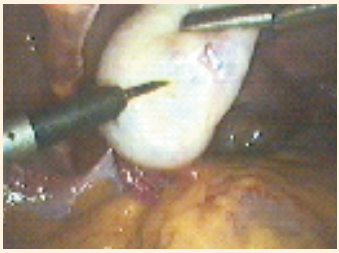
Laparoscopic Ovarian Drilling



Basic technique

- Grasp ovarian ligament
- Stabilise ovary
- Ovarian drilling
- Electrocautery: monopolar coagulation
  - 3–50W, 4–5 punctures,
  - 5–7mm in depth
  - 4–5 sec for each penetration
- Laser coagulation: CO2 laser, continuous mode
  - 10–25W, 10–30 holes,
  - 5 sec for each hole

Laparoscopic Ovarian Drilling (contd...)

- Avoid the hilum
- Prevention of adhesions by
  - o Abdominal lavage
  - o Early II look scopy

Indications

- CC resistance in women with anovulatory PCOS
- For patients who persistently hypersecrete LH
- For women with PCOS who need laparoscopic assessment of their pelvis or
- For those who live too far away from the hospital for the intensive monitoring required during GT therapy.

Mechanism of action:

- Promotes ovulation through changes in intra-ovarian hormonal environment
- Decreased LH leads to increased sensitivity of ovaries to GT resulting in ovulation

Merits:

- Avoids or reduces the need for GT
- It is beneficial in lean women with high LH and androstenedione (ASD) concentrations

Demerits:

- Possibility of ovarian tissue destruction and reduction can lead to premature ovarian failure
- Non permanent ovulatory effect
- Possible post-operative adhesions

Results:

- Ovulation rate: 70 – 80 %
- Pregnancy rate: 40 – 47 %
- Miscarriage rate: 14 %

Gonadotropins vs. Laparoscopic Ovarian Drilling		
	Parameter	**Inference**
1.	LBR per couple	No difference
2.	MPR	Lesser with LOD
3.	OHSS	No difference

- Use of LOD for OI in women with PCOS:
  - Beneficial for CC resistant PCOS
  - As effective as OI with FSH in terms of live births, and
  - Reduces the need for OI or ART in a significantly higher proportion of women

- It is not the first line of treatment and should be reserved for CC failure cases.
- Surgical approaches to OI have progressed from historical wedge resection to modern day minimal access techniques, usually employing laparoscopic ovarian diathermy or laser
- Multiple ovarian puncture performed either by diathermy or by laser is known as ''ovarian drilling''
- LOD can achieve unifollicular ovulation with no risk of OHSS or high-order multiples
- Does not require intensive monitoring of follicular development
- Indications for its use are mentioned above
- LOD is a single treatment using existing equipment
- The risks of surgery are minimal and include the risk of laparoscopy, adhesion formation and destruction of normal ovarian tissue
- Surgery should be performed by appropriately trained personnel
- LOD should not be offered for non-fertility indications
- There was no evidence of a significant difference in rates of clinical pregnancy, live birth or miscarriage in women with CC resistant PCOS undergoing LOD compared to other medical treatments
- The reduction in MPR in women undergoing LOD makes this option attractive[1]
- However, there are ongoing concerns about the long-term effects of LOD on ovarian function[2,3]

References:

1. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod*. 2008;23(3):462–477.
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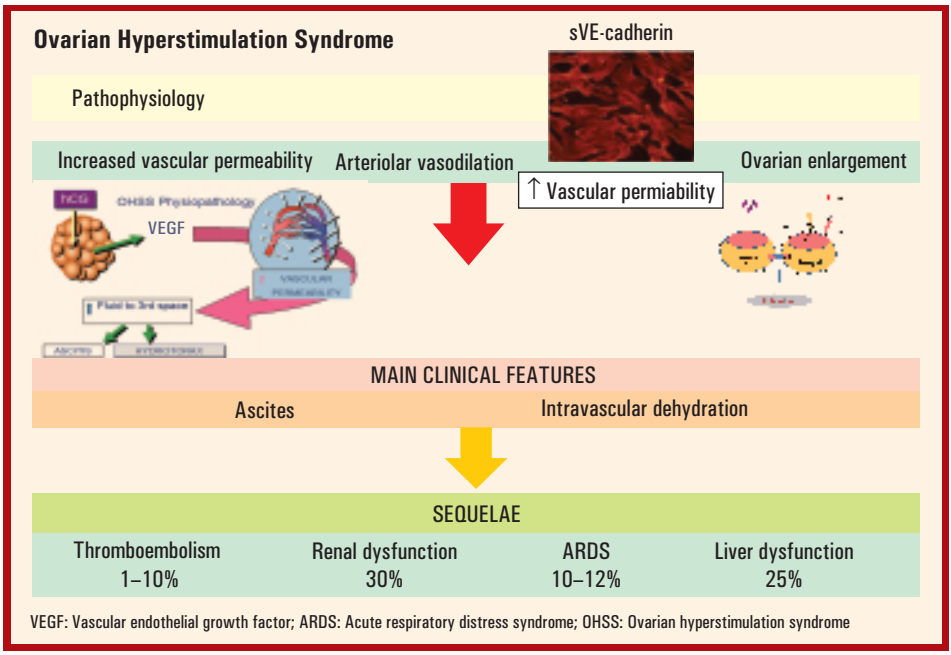
Complications

Problems associated with GT use

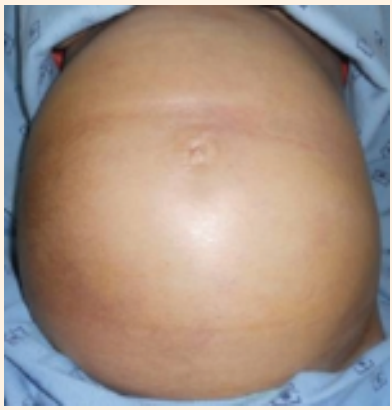
- OHSS
  - Leads to cycle cancellation
  - Severe morbidity
  - Risk of mortality
- MP
  - Higher maternal morbidity and mortality
  - Increased complications and fetal mortality

- GT use is associated with higher risk of:
  - OHSS
  - Multifetal gestation
- Both raise the risk of maternal morbidity and can turn fatal
- The new definition of success of ART cycles defines successful singleton pregnancy and not live births
- With the rise in order of multifetal gestation the complications associated with triplet pregnancy are greater than complications with twin pregnancy



- OHSS is an iatrogenic complication of ART and is dependent on hCG administration.
- The relationship between hCG and OHSS is thought to be mediated via the production of the angiogenic molecule Vascular endothelial growth factor (VEGF).
- It is characterised by cystic enlargement of the ovaries and a fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neoangiogenesis.
- It has profound impact on the patient's general health and can turn fatal.[1]

Classification of Severity



Mild

- Abdominal bloating/discomfort
- Mild pain
- Mild nausea/vomiting/diarrhea
- Enlarged ovaries but <8 cm

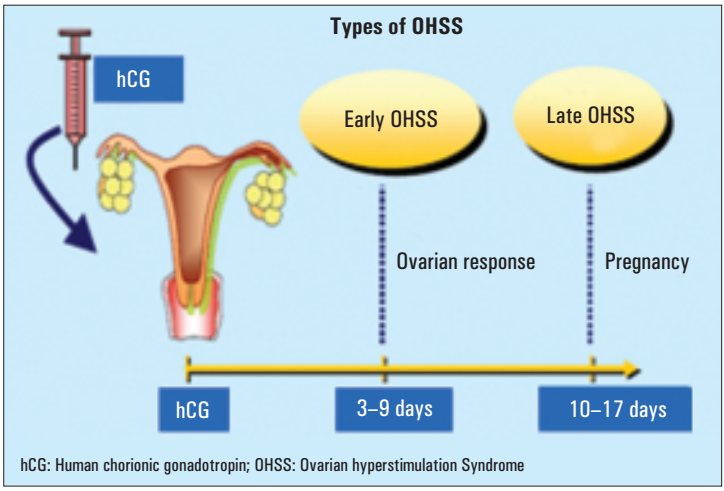
Moderate

- Moderate abdominal pain
- Nausea/ vomiting/ diarrhea
- USG evidence of ascites
- Ovaries usually 8–12 cm
- Haemoconcentration (Hct) >41%
- Elevated WBC >15,000 mL

Severe

- Clinical ascites
- Hydrothorax, severe dyspnea
- Intractable nausea/vomiting
- Hct >45%, WBC >25,000/mL
- Oliguria, liver dysfunction (elevated liver enzymes)
- Ovaries usually >12 cm
- CrCl <50 mL/min; Cr >1.6 mg/dL
- Na+<135 mEq/L ; K+ >5 mEq/L

- The incidence of moderate OHSS is estimated to be between 3 and 6%, while the severe form may occur in 0.1–3% of all cycles.
- OHSS has been recognised in two forms:
  - The early form of OHSS, (within days after the ovulation triggering injection of hCG) although elicited by hCG, is related to an exaggerated ovarian response to GT stimulation
  - The late form (10 days after hCG) is mainly related to the secretion of placental hCG[1]



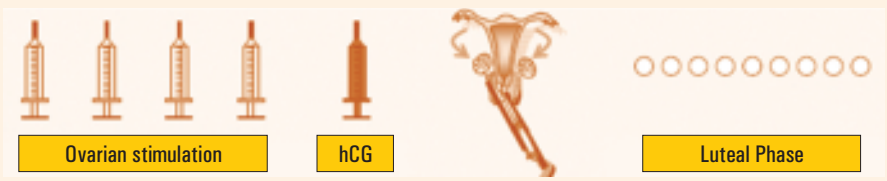
hCG: Human chorionic gonadotropin; OHSS: Ovarian hyperstimulation Syndrome

Prevention

Before
• Identification of risk factors to individualise controlled ovarian stimulation (COS)
• Correct adaptation of stimulation protocols
• Limit the dose or concentration of hCG
• Monitoring COS using USG and E2 assays constitutes the `gold standard'
• Use of GnRh antagonist
• Cycle cancellation or coasting

During
• Limit the dose or concentration of hCG
• Use r-LH/ GnRH agonist to trigger ovulation
• *In vitro* maturation (IVM)
• Prophylactic albumin in high risk
• Transfer of single embryo ↓MPR thus OHSS

After
• Cryopreservation of all embryos for transfer in subsequent cycle
• Using progesterone instead of hCG for luteal phase support
• Dopamine agonist
• Use of antagonist post cryofreezing all embryos or with fresh embryo transfer?



hCG: Human chorionic gonadotropin

- In the past, apart from cycle cancellation, none of the approaches were totally efficient, although they decrease the incidence in patients at high risk of OHSS.
- But today we have a option of GnRH agonist trigger in a GnRH antagonist cycle with cryopreservation of all embryos to be transferred in the subsequent cycles.
- HCG is a primary stimulus for the syndrome, with holding hCG is the main preventive measure against OHSS.

Management

Examination

- General: assess for dehydration, edema- pedal vulval, sacral, heart rate (HR), respiratory rate (RR), blood pressure (BP), body weight
- Abdominal: assess for ascites, palpable mass, peritonism and measure girth
- Limit the dose or concentration of hCG
- Respiratory: assess for pleural effusion, pneumonia, pulmonary oedema

Investigation

- Full blood count (FBC), packed cell volume (PCV), C-reactive protein (CRP)
- Urea and electrolytes, serum osmolarity,
- Liver function test (LFT), coagulation profile
- USG

Additional tests

- Arterial blood glucose (ABG), D- dimers
- Electocardiography (ECG)
- Chest radiograph (CXR)
- USG: ovarian size, pelvic and abominal free fluid

- In most cases OHSS is self-limiting and requires supportive management and monitoring while awaiting resolution.
- Women with more severe OHSS may require inpatient treatment to manage the symptoms and reduce the risk of further complications.
- The key principles of OHSS management therefore are early recognition and the prompt assessment and treatment of women with moderate or severe OHSS.[1]

Treatment

- Nonsteroidal anti-inflammatory drugs (NSAIDS) should be avoided, as they may compromise renal function.
- Women with severe OHSS should receive thromboprophylaxis with Low-molecular-weight heparin (LMWH).
- Paracentesis of ascitic fluid by the abdominal or TVS route under USG guidance.
- There is insufficient evidence to support the use of GnRH antagonists or dopamine agonists in treating established OHSS.

Out patient department management for mild to moderate cases

- Review in 2–3 days
- Early follow up in case of increased severity of symptoms
- Paracentesis can be done on OPD basis
- LMWH

In patient department management for severe cases

- Analgesia- paracetamol and opiates, avoid NSAIDS
- Maintain fluid balance – replace with intravenous colloids, avoid diuretics
- Paracentesis
- LMWH prophylaxis
- Surgery only for coincident problems such as adnexal torsion, ectopic pregnancy rupture or ovarian rupture

- NSAIDS should be avoided, as they may compromise renal function.
- Fluid replacement by the oral route, guided by thirst for correcting intravascular dehydration.
- Women with persistent Hct despite volume replacement with intravenous colloids may need invasive monitoring with anaesthetist's input.
- Paracentesis of ascitic fluid may be carried out on an outpatient basis by the abdominal or TVS route under USG guidance.
- There is insufficient evidence to support the use of GnRH antagonists or dopamine agonists in treating established OHSS.
- Mild and moderate cases can be managed on OPD basis.
- Women with more severe OHSS may require inpatient treatment to manage the symptoms and reduce the risk of further complications.
- Women with severe OHSS should receive thromboprophylaxis with LMWH.

- The duration of treatment should be individualised, taking into account risk factors and whether or not conception occurs.
- Surgery is only indicated in patients with OHSS if there is a coincident problem such as adnexal torsion, ovarian rupture or ectopic pregnancy and should be performed by an experienced surgeon.
- The treating doctor should be aware, and patient should be informed, that pregnancies complicated by OHSS may be at increased risk of pre-eclampsia and preterm delivery.[1]

References:

1. Kumar P, Sait SF, Sharma A, *et al.* Ovarian hyperstimulation syndrome. *J Hum Reprod Sci.* 2011;4(2):70–75.
2. Practice committee of ASRM. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertility and Sterility.* 2016;106(7):1634–1647.
3. Banker M and Velasco JAG. Revisiting ovarian hyper stimulation syndrome: towards OHSS free clinic. *J Hum Reprod Sci.* 2015;8(1):13–17.
4. Royal College of Obstetricians and Gynaecologists, The Management of Ovarian Hyperstimulation Syndrome. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_5_ohss.pdf . Last accessed on: 28th August, 2017.

Multifetal Gestation

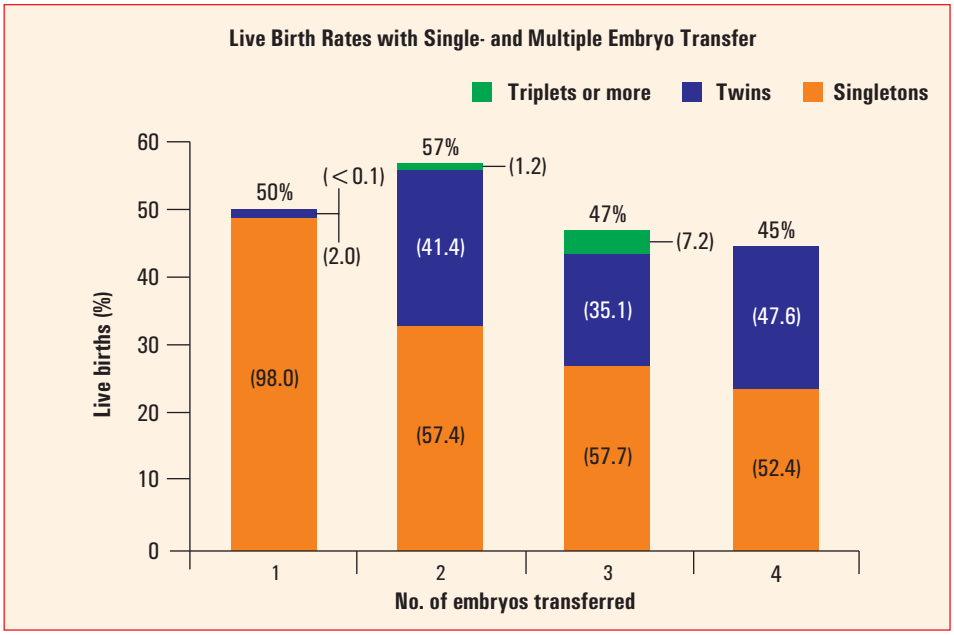
- Maternal morbidity and mortality is higher in twins and higher order pregnancies
- Fetal morbidity mortality is also higher in twins and higher order pregnancies
- All complications are higher in triplets compared to twins
- Multiple birth parents face higher financial and psychosocial stress which tends to persist long after the newborn stage

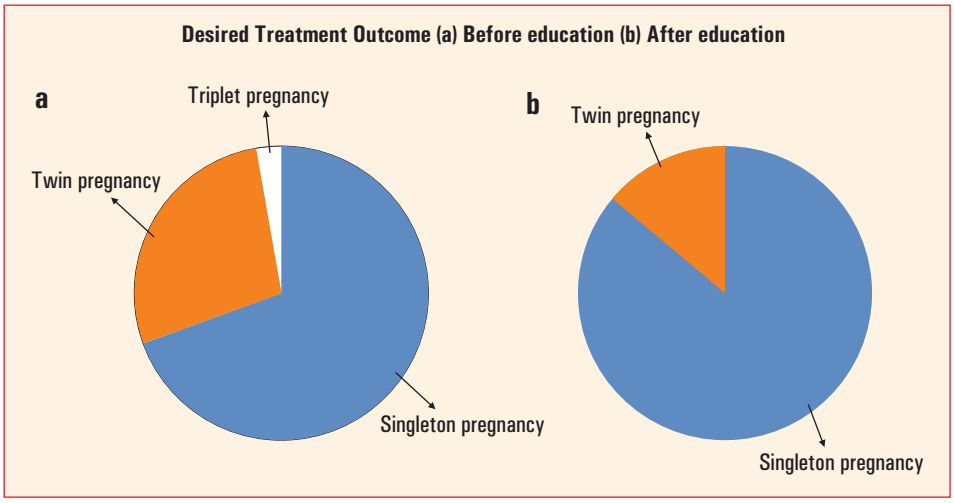
Maternal mortality X 2 or 3	Infant mortality X 5

- The presence of multifetal gestation blemishes the outcomes of ART.
- Prevention of MP is essential to prevent maternal and neonatal complications.
- Multifetal gestation leads to higher maternal mortality and morbidity as stated in the table below and higher infant mortality and morbidity as well.
- They also face higher financial and psychosocial stress which extends beyond the newborn stage.

Table 4: Effects of multifetal gestation on mother, infant and the family		
Maternal health	**Infant health**	**Psychosocial effects on the family**
• Pre-eclampsia • Gestational diabetes • Placental previa • Placental abruption • Preterm premature rupture of the membranes • Cesarean delivery • Postpartum haemorrhage • Death	• Placental problems o Premature aging o Twin-to-twin transfusion syndrome • Spontaneous abortion • Intrauterine growth restriction • Preterm (< 37 weeks), very preterm (< 32 weeks), and extreme preterm (< 28 weeks) birth • Perinatal and infant mortality • Low (< 2500 g) and very low birth weight (< 1500 g) • Intraventricular haemorrhage • Periventricular leukomalacia • Respiratory distress syndrome • Bronchopulmonary dysplasia • Hypoxic-ischemic encephalopathy • Necrotising enterocolitis • Sepsis • Jaundice • Retinopathy of prematurity • Cerebral palsy • Neural tube defects, heart malformations, and other birth defects • Developmental delays	• Postpartum depression (mother and father) • Relationship stress • Financial stress o Obstetric costs and neonatal intensive care admission o Costs for caring for multiple children throughout childhood

- When the goal is to minimize IVF complications, multiple embryo transfer (MET) does not necessarily translate to a superior outcome.
- The goal of infertility treatment should be the delivery of a healthy single baby, with fewer twin and higher-order births.
- The new guidelines promote single embryo transfer (SET).
- The voluntary transfer of a single high quality embryo, elective single embryo transfer (eSET), has significantly reduced multiple gestation rates and maximised the rate of singleton pregnancy without compromising overall success rates.
- Thus reduces the risk of iatrogenic twins and higher order pregnancies.





- A mandatory single blastocyst transfer policy with educational campaign in a United States IVF program reduces multiple gestation rates without sacrificing pregnancy rates as shown in the figure above.[2]
- SET is an effective method for reducing MP resulting from IVF and should be consistently encouraged for the majority of patients to improve the likelihood of delivering a healthy baby.
- A multi-faceted approach incorporating patient education and counselling, reimbursement offers or other financial incentives, and IVF success prediction tools can be used to improve eSET rates in clinical practice.[1]

Monitoring OI Cycles can Improve Outcome

Patient's initial parameters
• Base line scan: to rule out ovarian or uterine pathology, AFC
• Base line hormonal profile: ovarian reserve, FSH:LH ratio, androgen excess, thyroid profile and hyperprolactenemia
• Choose appropriate stimulation regime to prevent OHSS, multiple pregnancy and predict responses to ovarian stimulation

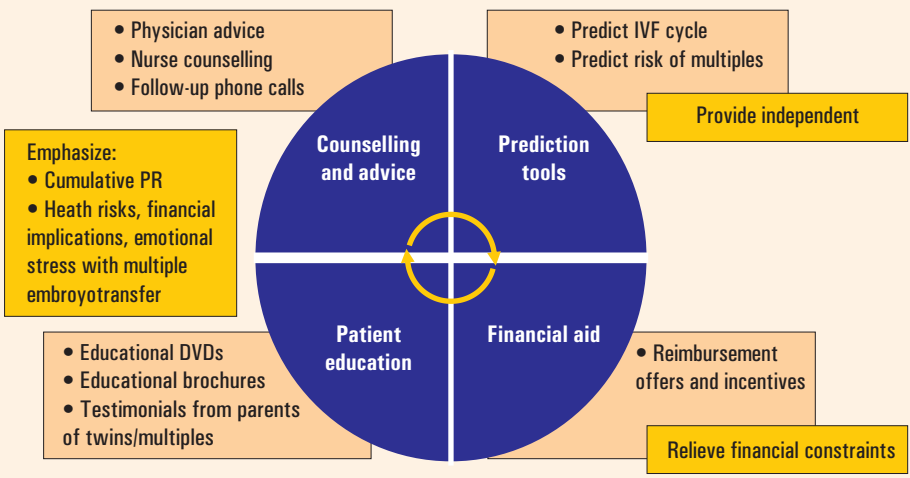
↓

Ovarian responses to OI
• Confirmation of down-regulation after GnRH agonist
• Determine response to drug
• Determine the dose and length of GT treatment
• Determine optimal time for hCG administration
• Detect ovulation
• Time ova-reduction
• Identify poor responders and women at risk of OHSS

↓

Completion of therapy
• Diagnose complications of OI o Premature lutenisation o Lutenised unruptured follicle (LUF) o Endogenous LH surge o Retention/functional cysts
• Confirm pregnancy
• To rule out MP
• To rule out latest onset OHSS

Holisitc View of IVF Management

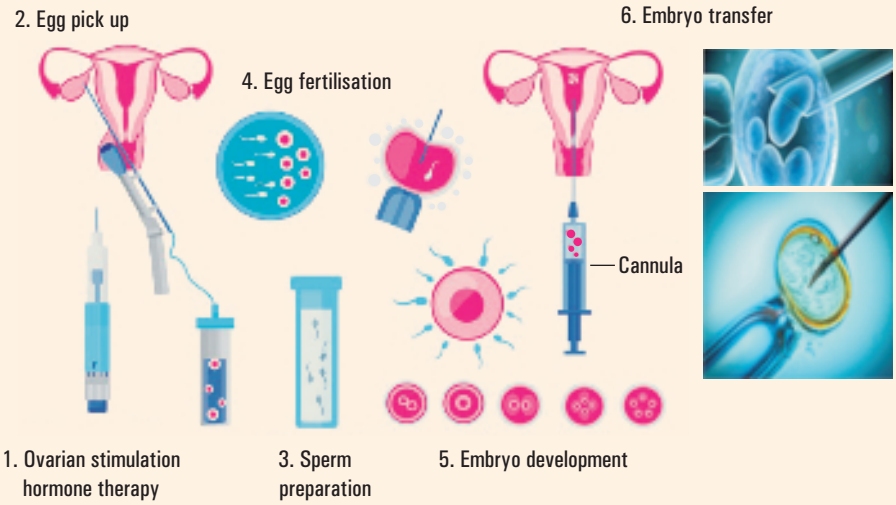


- Patient' initial parameters such as base line scan, AFC, AMH, hormonal profile help in choosing the appropriate regimen with successful outcomes and fewer complications.
- Monitoring is necessary for confirming the down regulation, determining response to drugs used for OI, determining the optimal time for hCG administration, detecting ovulation, timing ova reduction and identifying poor responders/ women at risk of OHSS.
- It is important to diagnose complications and treat them promptly if they occur and confirm pregnancy and provide adequate support to the pregnancy.[1,2]

References:

1. Tobias T, Sharara FI, Franasiak JM, *et al.* Promoting the use of elective single embryo transfer in clinical practice. *Fertility Research and Practice*. 20162:1.
2. Ryan GL, Sparks AE, Sipe CS, *et al.* A mandatory single blastocyst transfer policy with educational campaign in a United States IVF program reduces multiple gestation rates without sacrificing pregnancy rates. *Fertil Steril.* 2007; 88(2):354–60.

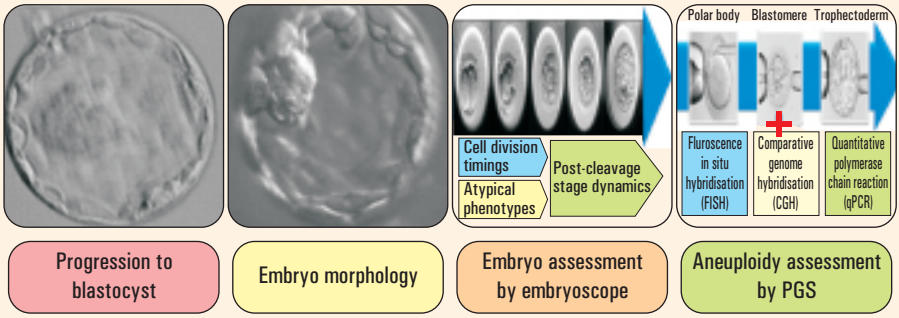
In vitro Fertilisation



- IVF is a reasonable option, to limit the number of MP by transferring small numbers of embryos
- The optimal stimulation protocol is debatable
- Implantation is not compromised in PCOS
- The increase in the cycle cancellation rate in women with PCOS appears to be due to absent or limited ovarian response or due to increased OHSS

- IVF is a reasonable option, because the number of multiple pregnancies can be kept to a minimum by transferring small numbers of embryos.
- The optimal stimulation protocol is still under debate.
- It is reassuring that in the published data the pregnancy rates in women with and without PCOS is similar. This observation suggests that implantation is not compromised in PCOS.
- The increase in the cycle cancellation rate in women with PCOS appears to be due to absent or limited ovarian response or due to increased OHSS.[1]
- Use of GnRH agonist vs antagonist and various other protocols for ART are beyond the scope of this module.
- Further patients needing IVF need to be referred to the infertility specialists for further management.

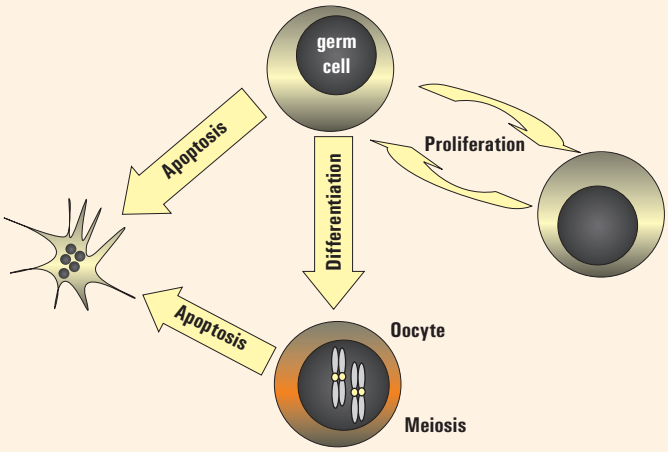
IVF Tools for Selection of Best Embryo



PGS: Preimplantation genetic screening

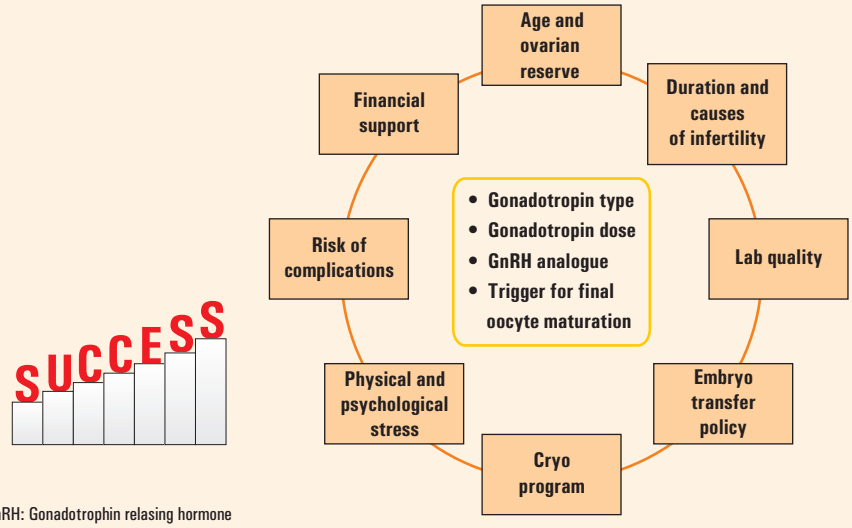
- Advancement in embryo cryopreservation, extended embryo culture with blastocyst selection, and preimplantation genetic screening supports the successful outcomes of elective single embryo transfer.[2]
- Preimplantation genetic screening (PGS), including comprehensive chromosomal screening (CCS) technologies, allows clinicians to assess embryos for aneuploidy (i.e., an abnormal number of chromosomes) prior to transfer.
- CCS is highly predictive of the reproductive potential of human embryos.

The Choice of Treatment will Depend on



- Presence of other infertility factors
- Available resources
- Risk tolerance

Success of OI in an ART Cycle Depends on



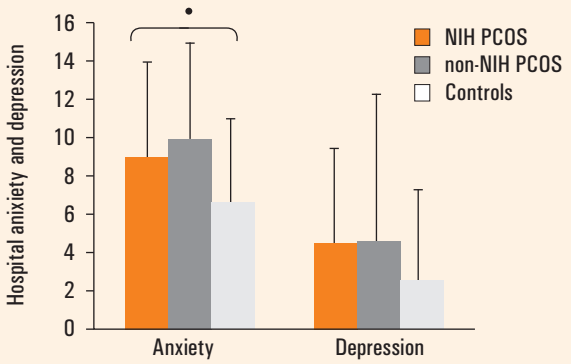
GnRH: Gonadotrophin relasing hormone

- Success of OI in an ART cycle depends on several factors as mentioned above

References:

1. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod*. 2008;23(3):462–477.
2. Lee AM, Connell MT, Csokmay JN, *et al.* Elective single embryo transfer- the power of one. *Contraception and Reproductive Medicine.* 2016;1:11.

Emotional Well-being



PCOS: Polycystic ovary syndrome; NIH: National Institute of Health

Women with PCOS when compared with those without PCOS showed

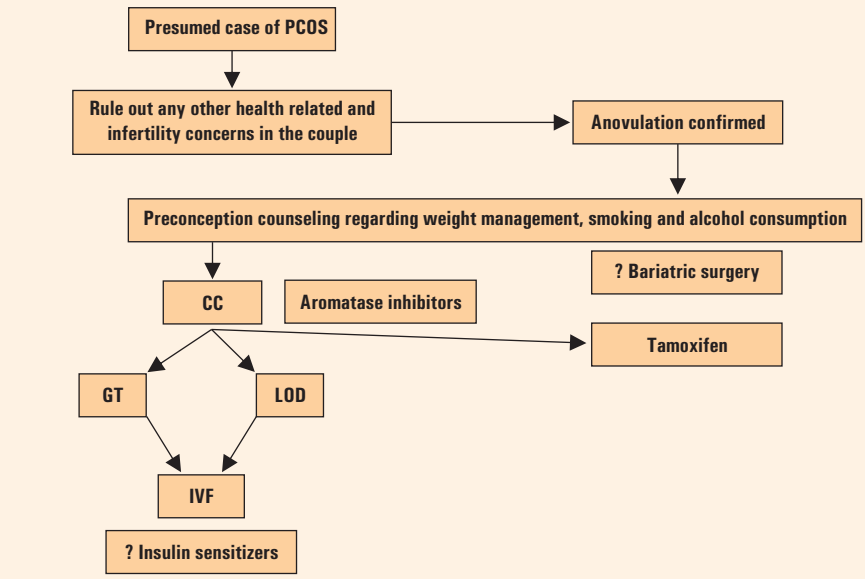
- Worse anxiety
- Higher rate of depression
- Worse health related quality of life

- Women with PCOS had worse anxiety ($P = 0.007$) and depression ($P = 0.048$) compared with women without PCOS.
- Both PCOS phenotype displayed higher rate of depression and anxiety than controls
- They had worse health-related quality of life (HrQOL) compared to controls[1]
- Obese and hirsute women had worse HrQOL
- Reduced sexual self worth, and inability to conceive with existing desire to conceive are the important factors that influence emotional well being.[2]
- OCP normalised the hormones but did not improve the distress symptoms among women with PCOS.[3]
- Appropriate interventions by experts to improve psychological function in all women with PCOS must be employed.
- Education plays an important role in help reduce the likelihood of depression and anxiety among women with PCOS.
- Psychopharmacotherapy may be considered for modifying influence of psychosocial function in women with PCOS.[3]
- Multidisciplinary team must be utilised for holistic treatment of women with PCOS.[2,3]

References:

1. Moran LJ, Deeks AA, Gibson-Helm ME, *et al.* Psychological parameters in the reproductive phenotypes of polycystic ovary syndrome. *Hum Reprod.* 2012;27(7):2082–2088.
2. Tan S, Hahn S, Benson S, *et al.* Psychological implications of infertility in women with polycystic ovary syndrome. *Hum Reprod.* 2008;23(9):2064–2071.
3. Rowlands IJ, Teede H, Lucke J, *et al.* Young women's psychological distress after a diagnosis of polycystic ovary syndrome or endometriosis. *Hum Reprod.* 2016;31(9):2072–2081.

Conclusion



CC: Clomiphene citrate; PCOS: Polycystic ovarian syndrome; GT: Gonadotrophin ; IVF: *In vitro* fertilisation; LOD: Laparoscopic ovarian drilling

Key Points

- While examining women with presumed polycystic ovarian syndrome desiring pregnancy any other health issues or infertility problems in the couple should be excluded.
- Before any intervention is initiated, preconception counselling should be provided emphasising the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption.
- Bariatric surgery may be considered in those with body mass index 35 kg/m^2 and when lifestyle therapy fails.
- The recommended first-line treatment for ovulation induction remains the anti-oestrogen clomiphene citrate.
- For cases where clomiphene citrate fails, recommended second-line intervention is either exogenous gonadotrophins or laparoscopic ovarian drilling. Both carry their own advantages and drawbacks. Treatment needs individualisation. Exogenous gonadotrophins are associated with higher risk of multiple pregnancies and intense monitoring of ovarian response is necessary. Laparoscopic ovarian drilling is usually effective in <50% of women however further ovulation induction may be required.
- Overall, ovulation induction is highly effective with a cumulative singleton live birth rate of 72%.
- *In vitro* fertilisation is the recommended third-line treatment as it is effective in women with polycystic ovarian syndrome and may significantly reducing chances of multiple pregnancies by restricting to single embryo transfer.
- Metformin alone has limited benefits in improving live birth rate
- Metformin should be used for women with glucose intolerance.
- If a gonadotrophin relasing hormone agonist protocol is used, metformin as an adjunct may reduce the risk of ovarian hyperstimulation syndrome.
- Health professionals should be aware of the potential psychosocial needs among women with polycystic ovarian syndrome and infertility, particularly women with polycystic ovarian syndrome who are obese and provide appropriate interventions.
- Even singleton pregnancies in polycystic ovarian syndrome are associated with increased health risk for both the mother and the foetus which will be discussed in our next module on polycystic ovarian syndrome and pregnancy.

Suggested Readings

1. The Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod.* 2008;23(3):462–477.
2. Frank S, Stark J, and Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. *Hum Reprod Update.* 2008;14(4):367–378.
3. Practice committee of ASRM. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertility and Sterility.* 2016;106(7):1634–1647.
4. I.J. Rowlands, H. Teede J. Lucke, *et al.* Young women's psychological distress after a diagnosis of polycystic ovary syndrome or endometriosis. *Hum Reprod.* 2016;31(9):2072–2081.
5. Emekçi-Özay Ö, Özay AC, Çağliyan E, *et al.* Myo-Inositol administration positively effects ovulation induction and intrauterine insemination in patients with polycystic ovary syndrome: a prospective, controlled, randomized trial. *Gynecol Endocrinol.* 2017;33(7):524–528.

Notes

Notes

Notes

PCOS and Infertility

POST-TEST

1. **The commonest infertility issue with PCOS is:**

   a. Tubal infertility

   b. Unexplained infertility

   c. Anovulatory infertility

   d. All the above

2. **The prevalence of PCOS has been reported as_____% in women with infertility.**

   a. 40%

   b. 50%

   c. 60%

   d. 70%

3. **Infertilty in PCOS is due to:**

   a. Ovarian dysfunction

   b. Hyperandrogenemia

   c. Hyperinsulinemia

   d. All the above

4. **Leptin is one of the peripheral signal that forms the link between adiposity and dysregulation in the gametogenic and steroidogenic potential of an ovary.**

   a. True

   b. False

5. **For checking ovarian reserve following test must be done:**

   a. AMH

   b. AFC

   c. Both (a) and (b)

   d. None of the above

6. **Which of the following is incorrect about hormonal testing in PCOS?**

   a. Hormonal testing is necessary for evaluating every case of PCOS

   b. Few tests are done to rule out other possible dysfunctions before treating for PCOS

   c. Any one hormone test such as FSH/ LH/ AMH/ Oestrogen/ Testosterone is sufficient

   d. All of the above

7. **AMH is biomarker for PCOS. Which of the following is correct?**

   a. AMH is raised in PCOS women

   b. AMH levels fall in PCOS

   c. AMH does not influence FSH

   d. It has no role in anovulation of PCOS

8. **Management of infertility in PCOS starts with:**

   a. Gonadotropins

   b. IVF

   c. Clomiphene citrate

   d. Weight loss

9. **In an obese woman with PCOS and anovulatory infertility, living in the interiors who needs to travels three hours to reach the clinic and has failed to conceive on clomiphene citrate protocols, what would be your next step?**

   a. Gonadotropins

   b. Laparoscopic ovarian drilling

10. **For IVF in PCOS women with infertility. Which of the following is incorrect?**

    a. It is recommended as the third step of intervention

    b. It can help restrict to singleton pregnancy

    c. It has poorer results among PCOS women

    d. All of the above

Answers: 1. c; 2. a; 3. d; 4. a; 5. c; 6. c; 7. a; 8. c; 9. a; 10. c

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This initiative is supported by an unrestricted educational grant from

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