ISAR's

Times Of Gynaecology Conclave

Fertility Focus –1

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FOR LUTEAL PHASE SUPPORT IN ART

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IF IT'S ORALLY EFFECTIVE, IT'S†

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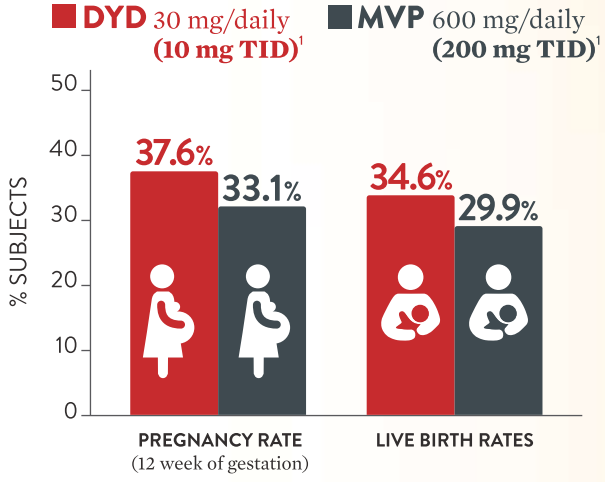
Dydrogesterone Tablets IP 10mg

FINDINGS FROM LOTUS-1 2017



ORAL DYDROGESTERONE MAY REPLACE MVP

AS THE STANDARD OF CARE FOR LUTEAL PHASE SUPPORT IN IVF DUE TO:[1]

- Good efficacy and safety profile[1]
- Improved patient compliance[1]

ART: Assisted reproductive technology. **LPS:** Luteal phase support. **TID:** Ter in die (Three times a day). **IVF:** In vitro fertilisation. **MVP:** Micronized vaginal progesterone. **DYD:** Dydrogesterone. † Schindler AE. Progestational effects of dydrogesterone in vitro, in vivo and on the human incidence of miscarriage endometrium. Maturitas.2009; 65(1):S3–S11. ‡ Internal calculations based on Quintiles IMS database, IMS Health Analytics Link MAT03 2017. * Data on file.

Reference: 1. Tournaye H. Sukhikh GT, Kahler E, Griesinger G. Aphase 3 randomised controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Human reproduction, Vol 32, no 5 pp.1019-1027,2017.

Abbreviated Prescribing Information: Dydrogesterone Tablets IP **Duphaston*** **LABEL CLAIM:** Each film coated tablet contains: Dydrogesterone IP 10 mg, Excipients q.s. Colour: Titanium dioxide IP. **INDICATION:** Progesterone deficiencies: Treatment of dysmenorrhoea; Treatment of endometriosis; Treatment of secondary amenorrhoea; Treatment of irregular cycles; Treatment of dysfunctional uterine bleeding; Treatment of pre-menstrual syndrome; Treatment of threatened miscarriage; Treatment of habitual miscarriage; Treatment of infertility due to luteal insufficiency; Luteal support as part of an Assisted Reproductive Technology (ART) treatment and Hormone replacement therapy. **DOSAGE AND ADMINISTRATION:** Dysmenorrhoea: 10 or 20 mg dydrogesterone per day from day 5 to day 25 of the menstrual cycle. Endometriosis: 10 to 30 mg dydrogesterone per day from day 5 to day 25 of the cycle or continuously. Dysfunctional uterine bleeding: When treatment is started to arrest a bleeding episode, 20 or 30 mg dydrogesterone per day is to be given for up to 10 days. Secondary amenorrhoea: 10 or 20 mg dydrogesterone per day, to be given daily for 14 days during the second half of the theoretical menstrual cycle to produce an optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogen. Pre-menstrual syndrome: 10 mg dydrogesterone twice daily starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Irregular cycles: 10 or 20 mg dydrogesterone per day starting with the second half of the menstrual cycle until the first day of the next cycle. The starting day and the number of treatment days will depend on the individual cycle length. Threatened miscarriage: An initial dose of up to 40 mg dydrogesterone may be given followed by 20 or 30mg per day until symptoms remit. Habitual miscarriage: 10 mg dydrogesterone twice daily until the twentieth week of pregnancy. Infertility due to luteal insufficiency: 10 or 20 mg dydrogesterone daily starting with the second half of the menstrual cycle until the first day of the next cycle. Treatment should be maintained for at least three consecutive cycles. Luteal support as part of an Assisted Reproductive Technology (ART) treatment: 10 mg Dydrogesterone three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed. Hormone replacement therapy: Continuous sequential therapy: An estrogen is dosed continuously and one tablet of 10mg dydrogesterone is added for the last 14 days of every 28-day cycle, in a sequential manner. Cyclic therapy: When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One tablet of 10 mg dydrogesterone is added for the last 12 -14 days of estrogen therapy. **CONTRAINDICATIONS:** Known hypersensitivity to the active substance or to any of the excipients. Known or suspected progestogen dependent neoplasms (e.g. meningioma). Undiagnosed vaginal bleeding. Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion /miscarriage. Contraindications for the use of estrogens when used in combination with dydrogesterone. **WARNINGS & PRECAUTIONS:** Before initiating dydrogesterone treatment for abnormal bleeding the etiology for the bleeding should be clarified. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy. If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with dydrogesterone and ceasing the treatment should be considered: Porphyria, Depression and Abnormal liver function values caused by acute or chronic liver disease. **PREGNANCY & LACTATION:** It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far there were no indications of a harmful effect of dydrogesterone use during pregnancy. Dydrogesterone can be used during pregnancy if clearly indicated. Breastfeeding: No data exist on excretion of dydrogesterone in mother's milk. Experience with other progestogens indicate that progestogens and the metabolites pass to mother's milk in small quantities. Whether there is a risk to the child is not known. Therefore, dydrogesterone should not be used during the lactation period. Fertility: There is no evidence that dydrogesterone decreases fertility at therapeutic dose. **ADVERSE REACTIONS:** The most commonly reported adverse drug reactions of patients treated with dydrogesterone in clinical trials of indications without estrogen treatment are migraines/headache, nausea, menstrual disorders and breast pain/tenderness. Undesirable effects in adolescent population: Based on spontaneous reports and limited clinical trial data, the adverse reaction profile in adolescents is expected to be similar to that seen in adults. Undesirable effects that are associated with an estrogen-progestogen treatment (see also 'Warnings and Precautions' and the product information of the estrogen preparation): Breast cancer, endometrial hyperplasia, endometrial carcinoma, ovarian cancer; Venous thromboembolism; Myocardial infarction, coronary artery disease, ischemic stroke

Issued on: Date (27/06/2018)

Source: Prepared based on full prescribing information (version 6) dated 27/Jun/2018

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For full prescribing information, please contact: Abbott India Limited, 16th Floor, Godrej BKC, Plot C-68, 'G' Block, Bandra-Kurla Complex, Near MCA Club, Bandra East, Mumbai-400 051. www.abbott.co.in

INDDUSTOI83104a 06th July 2018

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Preface

Dear Friends,

It gives me great pleasure to present to you this 'ISAR's, Times of Gynaecology conclave – Fertility Focus'

This publication contains subjects of importance to the practising gynaecologist and infertility specialists, in the form of simple algorithms. These are put together by a team of experts from across India who met, discussed and debated and finally came a consensus on the latest and best ways to manage issues such as an approach to managing an infertile couple, Intrauterine Insemination, Endometriosis in ART, Controlled Ovarian Stimulation etc. This will serve as a useful guide in your practice.

The Indian Society for Assisted Reproduction is the largest body of Infertility specialists in India and we organize many focused conferences, training workshops with hands-on experience, publish newsletters, give awards and encourage young gynaecologists to take up this interesting and challenging subspecialty.

These conclaves were an idea which I developed realizing that we doctors are all so busy that unless we take some time off and work in a group to focus completely on a subject, it will be difficult to arrive at a consensus. This concept has worked very well and now these 'Times of Gynaecology' conclaves have become an event that everyone looks forward to.

I hope you enjoy reading this as much as we enjoyed putting it together.

Develop a passion for learning. If you do, you will never cease to grow.
Anthony J. D'Angelo

Warm regards,

Rishma Dhillon Pai

Dr. Rishma Dhillon Pai
President ISAR 2018-2019
President IAGE 2018 – 2019
President FOGSI 2017
Vice President – Mumbai Obst & Gyn Society

APPROACH TO AN INFERTILE COUPLE

Moderators : Dr. Pratap kumar, Dr. Hrishikesh Pai

Panel Members : Dr. Kinjal Shah, Dr. Kedar Ganla, Dr. Shailendra Mahimkar, Dr. Shefali Jain

From left to right: Dr. Shailendra Mahimkar, Dr. Pratap kumar, Dr. Shefali Jain, Dr. Kinjal Shah, Dr. Kedar Ganla, Dr. Hrishikesh Pai

Introduction

Counseling forms an integral part of the management of an infertile couple as the first consultation is the best one. Sufficient time should be dedicated to understanding the couple's needs. Both the partners must be evaluated at the same time.[1]

Preliminary assessment[2,3]

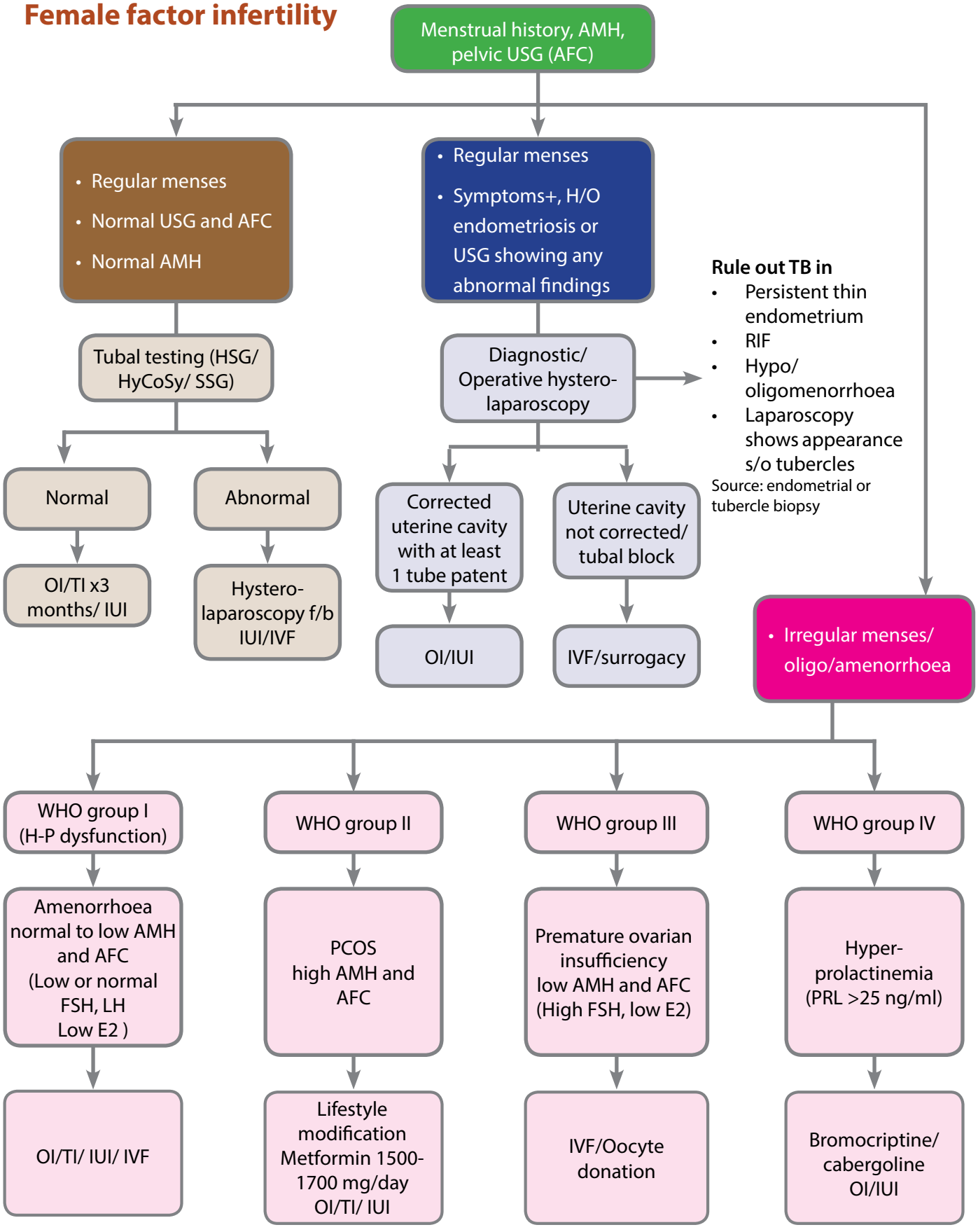
- Age of both partners
- Occupation
- Duration of infertility
- History of contraception used
- Menstrual history, details of prior conception if any, medical/surgical history, prior infertility treatment, the family history of early menopause and developmental anomalies
- Sexual history-timing, frequency, dyspareunia, erectile or ejaculatory disturbances in the partner
- History of alcohol, smoking, drugs, stress
- Physical examination of both partners-
  - » Body mass index [weight in kg/height (m^{20}]
  - » Evidence of thyroid swelling
  - » Breast examination
  - » Signs of androgen excess like acne, hirsutism, androgenic alopecia, acanthosis nigricans in the female
  - » Signs of androgen deficiency in the male
  - » General and local examination

Laboratory tests[4]

Female	Male
Complete blood count (CBC)	HIV, HBsAg, HCV, VDRL
HIV, HBsAg, HCV, VDRL	Random blood sugar
Blood group and Rh	Semen analysis
Random blood sugar, HbA1c In PCOS or suspected history of diabetes do GTT 75 g and 2 hrs PPBS	
Thyroid-stimulating hormone (TSH)	
Anti-mullerian hormone (AMH)	
Lipid profile	
Hemoglobin electrophoresis	
Ultrasound pelvis	
Optional (wherever indicated)	**Optional (wherever indicated)**
Serum prolactin	DNA fragmentation
Karyotyping	Hormonal tests: FSH, testosterone
Rubella IgG- if negative, then vaccinate and wait for 1 month *(RCOG)*	Genetic testing: Karyotype, Yq microdeletion, CFTR mutation
Vitamin D3	Ultrasound scrotum, TRUS
Pap smear (> 35 yrs)	Testicular biopsy /trial TESE
Serum progesterone (>10 ng/ml) 1 week prior to expected menses	
Breast imaging (> 40 yrs)	

CBC: Complete blood count; HIV: Human immunodeficiency virus; HbSAg: surface antigen of the hepatitis B virus; HCV: Hepatitis C virus; VDRL: Venereal Disease Research Laboratory; HbA1c: Glycated hemoglobin; PCOS: Polycystic ovarian syndrome; GTT: Glucose tolerance test; PPBS: Postprandial blood sugar; DNA: Deoxyribonucleic acid; FSH: Follicle stimulating hormone; CFTR: Cystic fibrosis transmembrane conductance regulator; TRUS: Transrectal ultrasound; TESE: Testicular sperm extraction.

Female factor infertility



If any of the above fails, then IVF to be done

AFC: Antral follicle count; AMH: Anti-Müllerian hormone; E2: Estradiol; FSH: Follicle-stimulating hormone; H/o: History of; H-P: Hypothalamic-pituitary; HSG: Hysterosalpingogram; HycoSy: Hysterosalpingo contrast sonography; IUI: Intrauterine insemination; IVF: In vitro fertilization; LH: Luteinizing hormone; OI: Ovulation induction; PRL: Prolactin; PCOS: Polycystic ovary syndrome; RIF: Recurrent implantation failure; SSG: Sonosalpingography; TB: Tuberculosis; TI: Timed intercourse; USG: Ultrasound; WHO: World Health Organization.

Recommendation for the management of obesity in women with infertility [5]

- Weight loss of 7% and increased physical activity to at least 150 minutes weekly of moderate activity such as walking is recommended.
- A 500–1000 kcal/day decrease from the usual dietary intake should lead to 1–2 pound/week weight loss with a low-calorie diet of 1000–2000 kcal/day achieving an increase of 10% in total body weight over 6 months.

Category	BMI (kg/m^2)
Underweight	< 18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obesity	> 30

Evaluation of the male factor[6]

- Male factor solely is responsible for approximately 20% of the infertile couples and contributes to another 30%–40% of the couples.
- Male infertility is termed as idiopathic when the cause of abnormal semen parameters cannot be identified.

WHO 2010

- Lower limits of the accepted reference values for semen analysis on at least two occasions one to three months apart (abstinence 2–7 days).

Parameter	Reference value
Ejaculate volume	1.5ml
pH	7.2
Sperm concentration	15 x 10^6 sperms per ml
Total sperm number	39 x 10^6 sperms per ejaculate
Percentage motility	40%
Forward progression	32%
Normal morphology	4% normal (strict Kruger criteria)
Sperm agglutination	Absent
Viscosity	< 2 cm thread after liquefaction

If a test is abnormal, repeat the test after 3 months (duration of spermatogenesis 70 days). However, if this is not practical, the test can be repeated after 1 month.

Semen culture

- Not to be done routinely in all cases
- Should be done only in men with suspected infection like epididymo-orchitis, prostatitis, etc (tenderness on local examination)

Total motile sperm count (TMSC)[7]

TMSC= volume of semen sample x total number of sperms x percentage of normal motility

Criteria	TMSC	Treatment
Pre wash TMSC	> 5 million /ml	Intrauterine insemination
Pre wash TMSC	1–5 million/ml	In vitro fertilization
Pre wash TMSC	< 1 million/ml	Intracytoplasmic sperm injection

DNA fragmentation tests[8]

- Direct tests are Comet (single-cell gel electrophoresis) and TUNEL (Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-nick end labeling). The sperm chromatin structure assay (SCSA) is an indirect test.
- Because the prognostic clinical value of DNA integrity testing may not affect the treatment of couples, the routine use of DNA integrity tests in the evaluation of male factor infertility is controversial.
- DNA fragmentation index (DFI): Indications
    - » Unexplained infertility
    - » Intrauterine insemination failures
    - » Severe oligoasthenoteratospermia
    - » Repeated IVF failures/poor outcome
    - » Recurrent implantation failure
    - » Recurrent pregnancy loss
    - » Abnormal DFI> 30%

Endocrine evaluation

- Minimal initial hormonal evaluation includes serum follicle-stimulating hormone (FSH) and total testosterone concentration
- Optional: Luteinizing hormone (LH), prolactin
- Endocrine evaluation is indicated for men having
    - » Abnormal semen parameters especially when sperm concentration is < 10 million per ml
    - » Impaired sexual function
    - » Other clinical findings s/o a specific endocrinopathy
- Pavlovich et al. identified a specific endocrine defect in men with severe male factor infertility due to a relative excess of estrogen (E) to testosterone (T). This is quantitatively measured as T: E ratio. A low T: E ratio is associated with defective spermatogenesis. Thus a T: E ratio less than 10:1 warrants treatment.
- Thus aromatase inhibitors (AIs) can be considered rational for the treatment in men with low serum testosterone levels and has been associated with an improved sperm concentration, increased serum testosterone, and suppressed estrogen levels.

Normal FSH does not necessarily mean normal spermatogenesis[9]

- Normal FSH = Normal spermatogenesis
    - » Not necessarily true
    - » Many men with primary testicular failure (PTF) will have normal FSH
- Normal FSH: Inconclusive
    - » Normal/abnormal spermatogenesis

High FSH = Testicular failure

- » Focal spermatogenesis may be present

Genetic evaluation[10,11]

- Genetic evaluation is not required in all patients with male factor infertility.
- Those who are at an increased risk of having a genetic abnormality are men with non-obstructive azoospermia (NOA) or severe oligozoospermia (<5 million/ml).
- Thus tests as a part of genetic evaluation are:
  - » Karyotyping (Fluorescent in-situ hybridization, FISH) and Yq microdeletion (polymerase chain reaction, PCR) should be offered to men with NOA and severe oligozoospermia before performing intracytoplasmic sperm injection (ICSI) with their sperms.
  - » Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation should be offered to men with congenital bilateral absence of the vas deferens (CBAVD).

Scrotal ultrasound

- Indications for a scrotal ultrasound:
  - » In case of doubtful clinical examination
  - » Testis located in the upper scrotum
  - » Small scrotal sac
  - » In men with risk factors for testicular cancer like cryptorchidism or a previous testicular neoplasm
- It should not be used as a routine screening procedure.
- Varicocele is seen in 15% of the normal male population and in 40% of men presenting with infertility.[12]
- Diagnosis of varicoceles is based primarily on physical examination.
- Only clinically palpable varicoceles have been clearly associated with infertility.

Trial TESE/testicular biopsy

Pros	Cons
Useful in counseling the couple. Only after the presence of sperms is confirmed, the female partner is subjected to hormonal stimulation.	If sperms are obtained on trial testicular sperm extraction (TESE), still there is a 20% chance that the sperms may not be obtained next time in nonobstructive azoospermia (NOA)
Sperms obtained in the trial TESE can be frozen and later thawed and used depending on the female partner's oocyte retrieval.	Efficient cryopreservation technique is required to cryopreserve the scanty sperms obtained.
Visiting andrologist is sufficient.	Andrologist has to be easily available.

Retrograde ejaculation[11]

- To exclude retrograde ejaculation, a post-ejaculatory urinalysis should be done in men having an ejaculate volume < 1.0 ml, except in those diagnosed with hypogonadism or CBAVD. Also r/o incomplete collection or a very short abstinence interval (<1 day).

- The post-ejaculatory urinalysis is done by centrifuging the urine specimen for 10 mins at 1500 rpm, f/b microscopic examination of the pellet at 400X magnification.
- In men with azoospermia, the presence of any sperm in the above analysis suggests a retrograde ejaculation.
- In men with low volume ejaculate and oligozoospermia, "significant numbers" of sperm must be seen to establish the diagnosis; there is no expert opinion on the minimum number required.

Conclusion

Counseling is an important part of management and both partners should be evaluated at the same time. Preliminary assessment should be detailed including age, occupation, duration of infertility, history of contraception, menstruation, and drugs, and physical examination of both partners. The laboratory test should also be administered to both partners and should include regular tests such as CBC, blood sugars, TSH, AMH, lipid profile for women and should include semen analysis for men. Some optional tests may be needed when indicated including karyotyping, serum prolactin, and Pap smear for women and DNA fragmentation, testosterone, scrotum scan, TRUS for men and may include others too.

Women with irregular menses/oligo/ menorrhea can be classified based on WHO groups and treated accordingly with lifestyle modification, metformin, and OI, timed intercourse or IVF. Obese women should be recommended to lose weight. For male factor infertility serum analysis is recommended on at least two occasions one to three months apart under abstinence of 2 to 7 days. The routine use of DNA fragmentation tests is controversial and has not shown to affect the treatment of couples. It is recommended to carry out an endocrine evaluation of men with male factor infertility with abnormal semen parameters especially sperm concentration is < 10 million per ml.

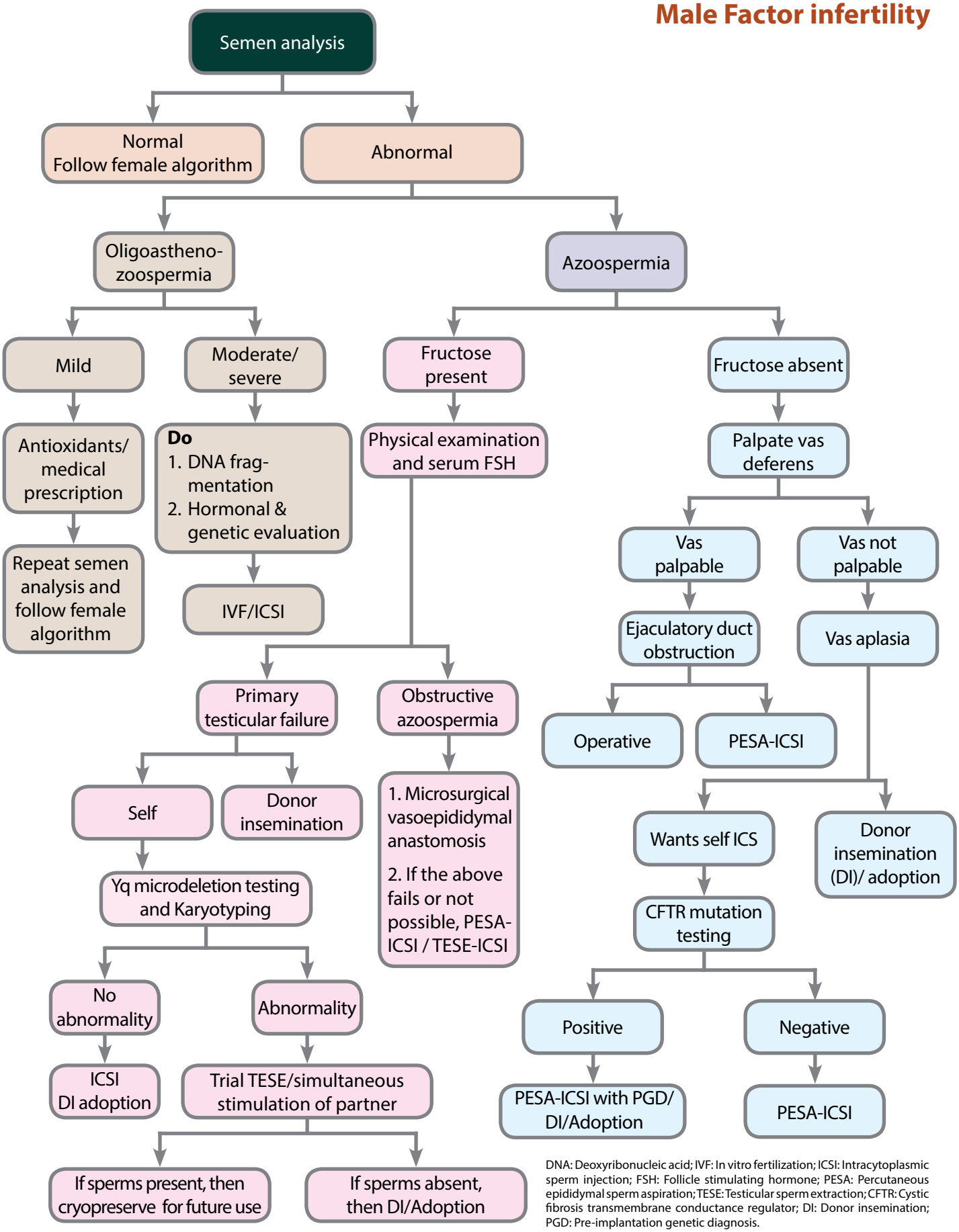
Aromatase inhibitors (AIs) can be considered in men with low serum testosterone levels, which has been shown to improve sperm concentration, serum testosterone, and suppress estrogen levels.

Genetic evaluation such as karyotyping or CFTR gene mutation is not required in patients with male factor infertility except when indicated.

References

1. Peterson B, Boivin J, Norré J, et al. An introduction to infertility counseling: A guide for mental health and medical professionals. J Assist Reprod Genet. 2012; 29(3): 243–48. **2.** Kamel RM. Management of the infertile couple: An evidence-based protocol. Reprod Biol Endocrinol. 2010; 8: 21. **3.** Frey KA, Patel KS. Initial evaluation and management of infertility by the primary care physician. Mayo Clin Proc. 2004;79(11):1439–43. **4.** Kakarla, N, Bradshaw, K, Glob. Evaluation and management of the infertile couple. libr. women's med., (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10321 **5.** Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: A committee opinion. Fertil Steril. 2015;104(5):1116–26. **6.** Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: A committee opinion. Fertil Steril. 2015;103(6):e44–50. **7.** Hamilton JA, Cissen M, Brandes M, et al. Total motile sperm count: A better indicator for the severity of male factor infertility than the WHO sperm classification system. Hum Reprod. 2015;30(5):1110–21. **8.** Jin J, Pan C, Fei Q, et al. Effect of sperm DNA fragmentation on the clinical outcomes for in vitro fertilization and intracytoplasmic sperm injection in women with different ovarian reserves. Fertil Steril. 2015 ;103(4):910–16. **9.** Ramaswamy S, Weinbauer GF. Endocrine control of spermatogenesis: Role of FSH and LH/ testosterone. Spermatogenesis. 2014; 4(2): e996025. **10.** Wosnitzer MS. Genetic evaluation of male infertility. Transl Androl Urol. 2014; 3(1): 17–26. **11.** Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: A committee opinion. Fertil Steril. 2015;103(3):e18-25. **12.** Mohammed A, Chinegwundoh F. Testicular varicocele: An overview. Urol Int. 2009;82(4):373–79.

Male Factor infertility



DNA: Deoxyribonucleic acid; IVF: In vitro fertilization; ICSI: Intracytoplasmic sperm injection; FSH: Follicle stimulating hormone; PESA: Percutaneous epididymal sperm aspiration; TESE: Testicular sperm extraction; CFTR: Cystic fibrosis transmembrane conductance regulator; DI: Donor insemination; PGD: Pre-implantation genetic diagnosis.

OVARIAN STIMULATION IN ART

Moderators : Dr. Nandita Palshetkar,
Dr. Kanthi Bansal

Panel Members : Dr. Sathy Pillai, Dr. Sanjay Makwana
Dr. Charumati Pekhale, Dr. Jiteeka Thakkar

From left to right: Dr. Jiteeka Thakkar, Dr. Sathy Pillai, Dr. Kanthi Bansal, Dr. Nandita Palshetkar, Dr. Charumati Pekhale, Dr. Sanjay Makwana

Introduction

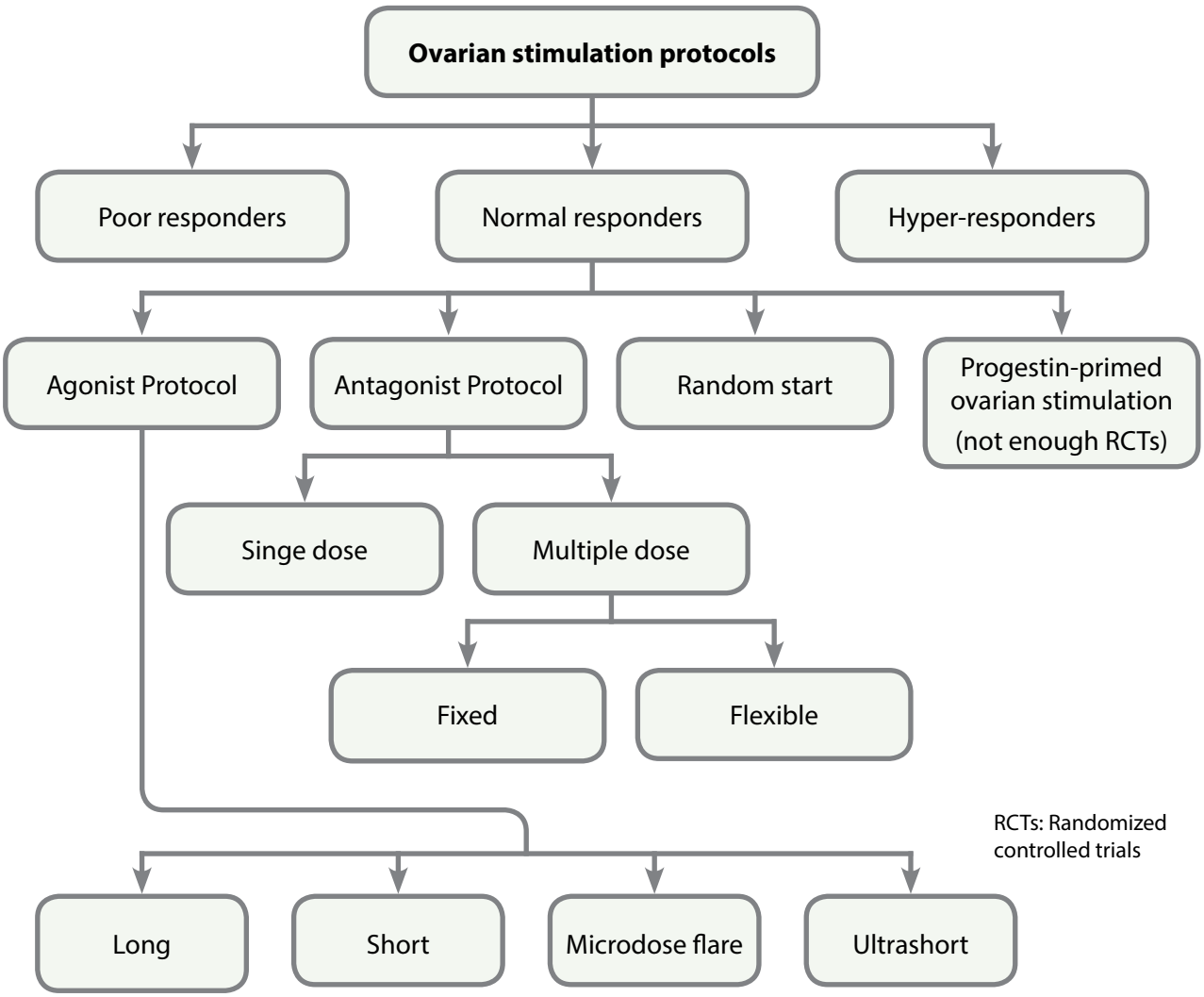
Ovulation stimulation is done in a woman who ovulates spontaneously but has unexplained infertility or associated male factor infertility issues which demands increasing the chance of conception. Aim of ovulation stimulation is to stimulate the production of multiple large follicles so that several eggs will be released.[1]

Controlled ovarian hyperstimulation (COH) is regulated super ovulation by turning off the patients own hypothalamic-pituitary-ovarian axis (HPO) system (down regulation) followed by stimulation.[1]

Individualization of response

	Poor responder	Normal responder	Hyper- responder
Menstrual cycles	Regular/short	Regular	Regular/irregular
Age	>35 yrs	<35 yrs	<35yrs
Anti-Müllerian hormone (AMH)	<1.4 ng/ml	1.5–3.5 ng/ml	> 3.5 ng/ml
Antral follicle count (AFC)	< 5–7	8–15	> 15
Previous response	Poor	Normal	Hyper response

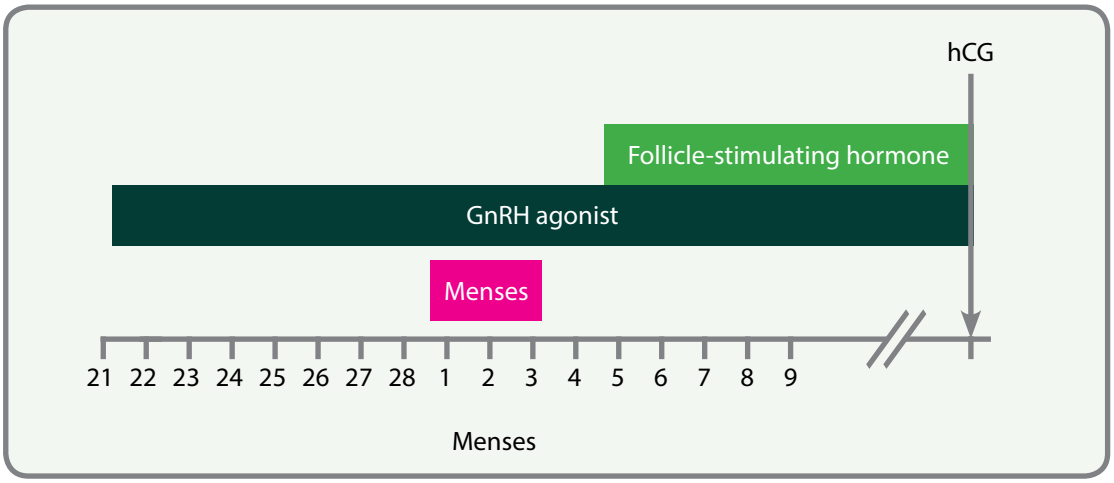
Ovarian stimulation protocols



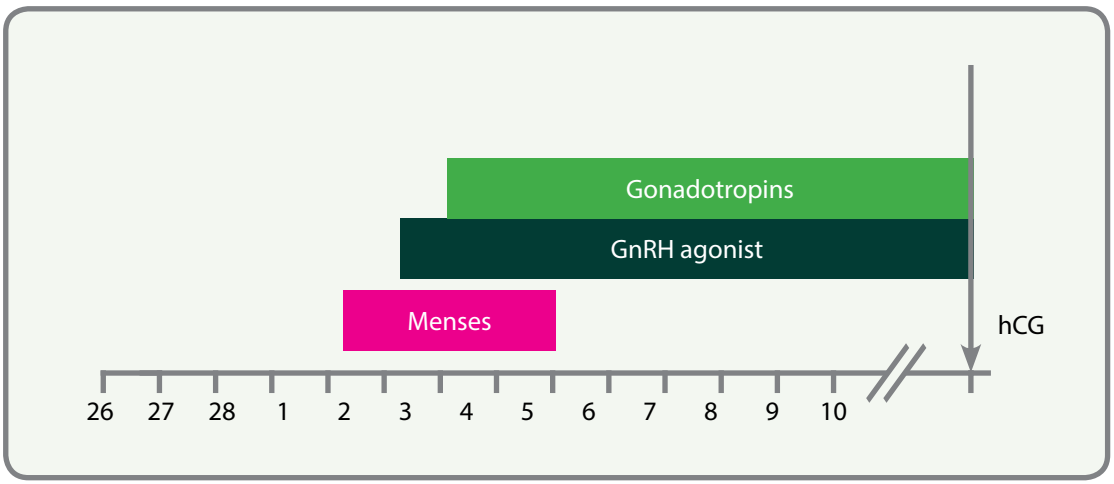
RCTs: Randomized controlled trials

GnRH protocols

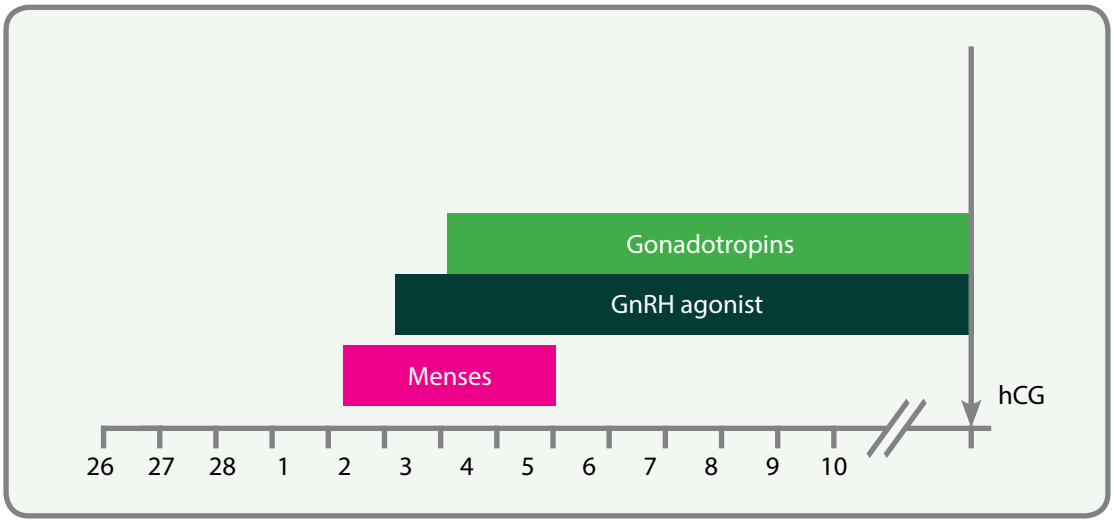
GnRH agonist-long protocol



GnRH agonist short protocol

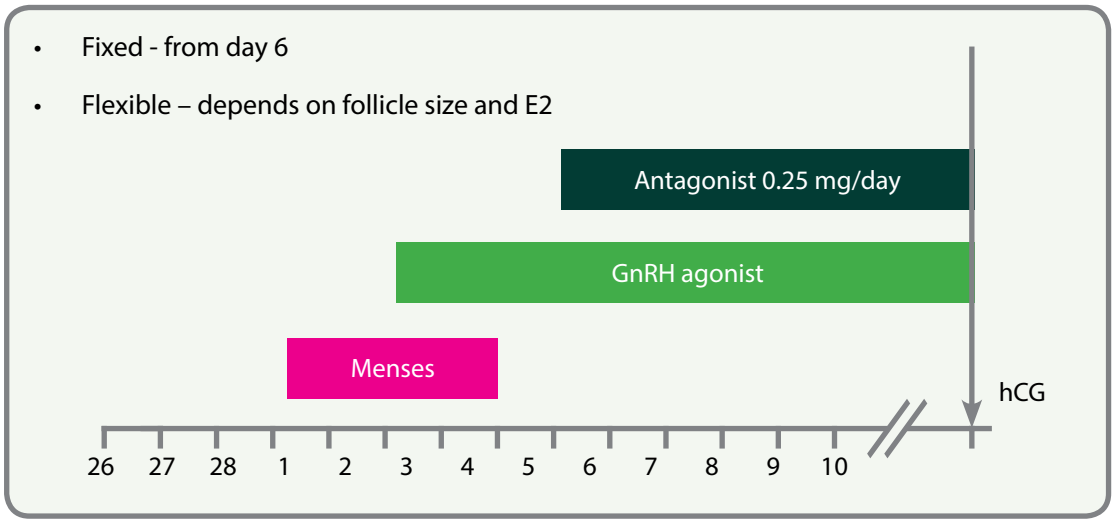


Microdose flare

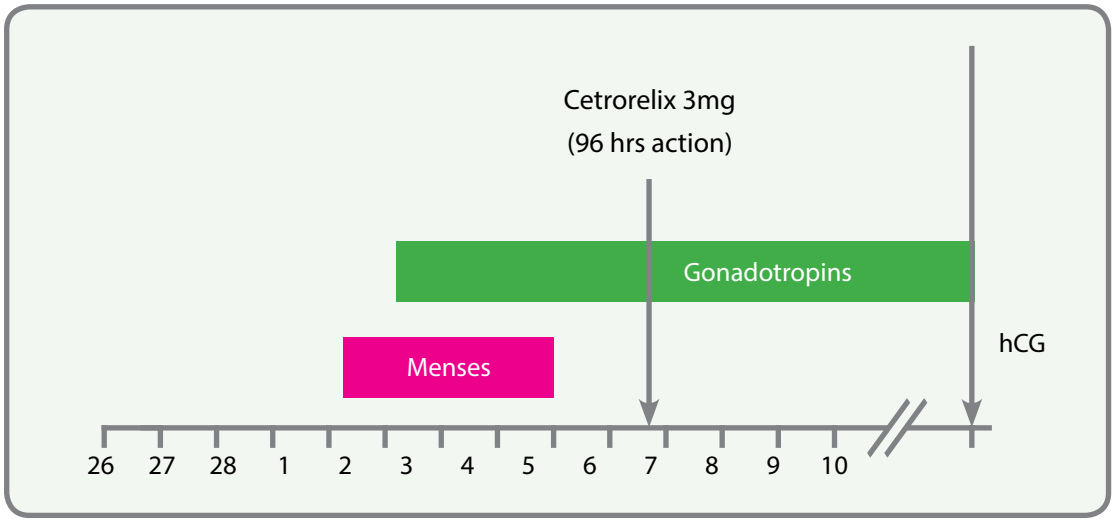


GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin

Multiple dose antagonist protocol



Antagonist – single dose



Dose of gonadotrophins

Age	PCOS-FSH hyperesponder	Normal responder	Hypo–responders (Poseidon 1,2)	Poor responder (B) (Poseidon 3,4)
AFC	> 15	5-15	5-15	< 5
AMH	>3.5 ng/ml	2-3.5 ng/ml	2-3.5 ng/ml	< 2 ng/ml
<30yrs	75 IU	75 IU	75 IU	225 IU
30-35 yrs	75 IU	150 IU	150 IU	300 IU
>35yrs	150 IU	225 IU	225 IU	300-450 /egg donation

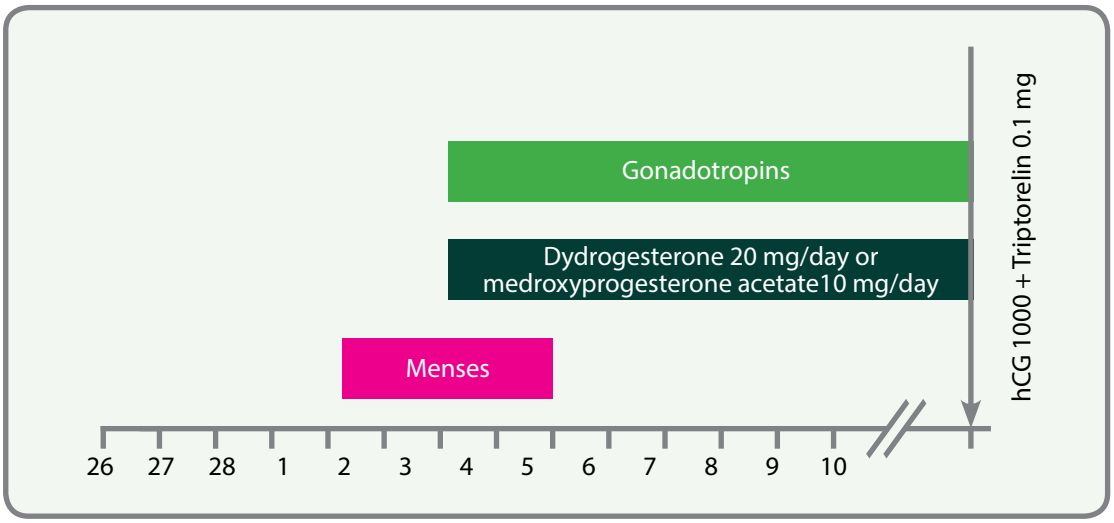
GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; AMH: Anti-Müllerian hormone; AFC: Antral follicle count; FSH: Follicle stimulating hormone; PCOS: Polycystic ovary syndrome

Trigger[1]

Trigger	DUAL Trigger
• Inj hCG 5000-10000 IU • Inj rec hCG 250 mcg • Inj triptorelin: 0.2 mg subcutaneously • Inj leuprolide acetate: 1 mg subcutaneously.	• Increases pregnancy rate in normal and poor responders • Dose hCG 5000–10000 + triptorelin 0.1
hCG: Human chorionic gonadotropin	

Progestest-primed ovarian stimulation (PPOS)

- Progesterone is used as an alternative to suppress premature luteinizing hormone surge during follicular phase[2]
- Oral administration, more flexible, economic
- Not enough randomized controlled trials

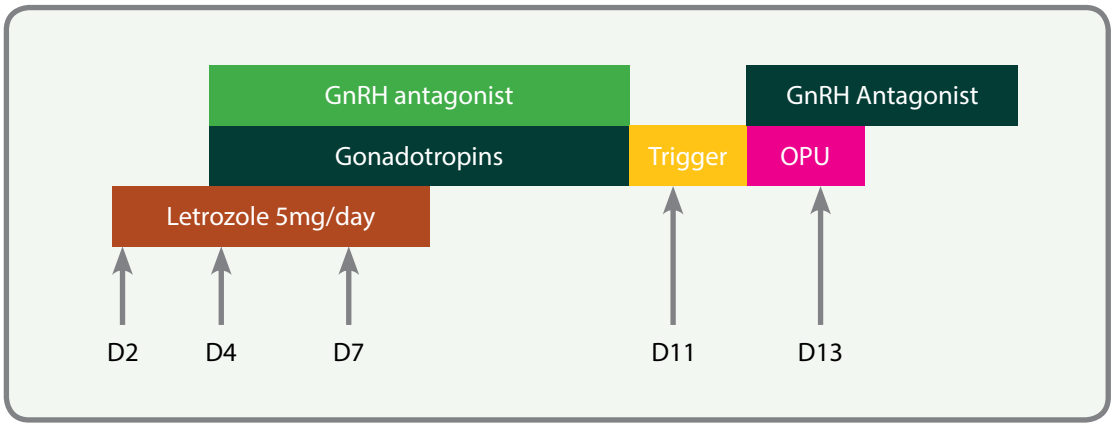


International Society for Mild Approaches in Assisted Reproduction (ISMAAR) classification[3]

Protocol	Aim	Methodology
Natural cycle IVF	Single oocyte	No medication
Modified natural cycle IVF	Single oocyte	hCG only, GnRH antagonist with/without FSH/HMG add back
Mild or minimal stimulation IVF	2 to 7 oocytes	Low dose FSH/hMG, oral compounds like clomiphene citrate and GnRH antagonist. Can be used for patients with a decreased ovarian reserve and also for hyperresponders.
Conventional IVF	≥ 8 oocytes	GnRH agonist or antagonist conventional FSH/hMG dose

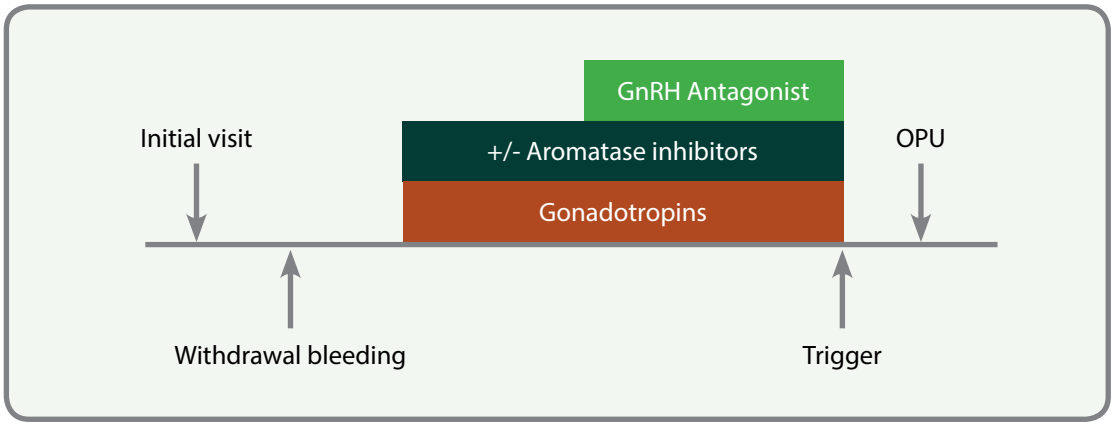
IVF: In vitro fertilization; hCG: Human chorionic gonadotropin; GnRH: Gonadotropin-releasing hormone; FSH: Follicle stimulating hormone; hMG: human menopausal gonadotropin

COH in breast cancer patients[4]



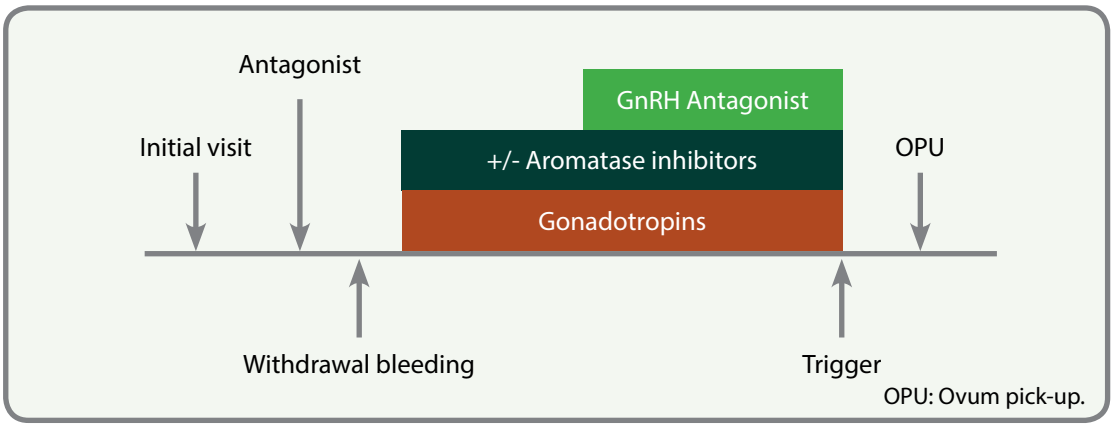
COH: Controlled ovarian hyperstimulation.

Spontaneous menses: Conventional start



GnRH: Gonadotropin-releasing hormone; OPU: Ovum pick-up

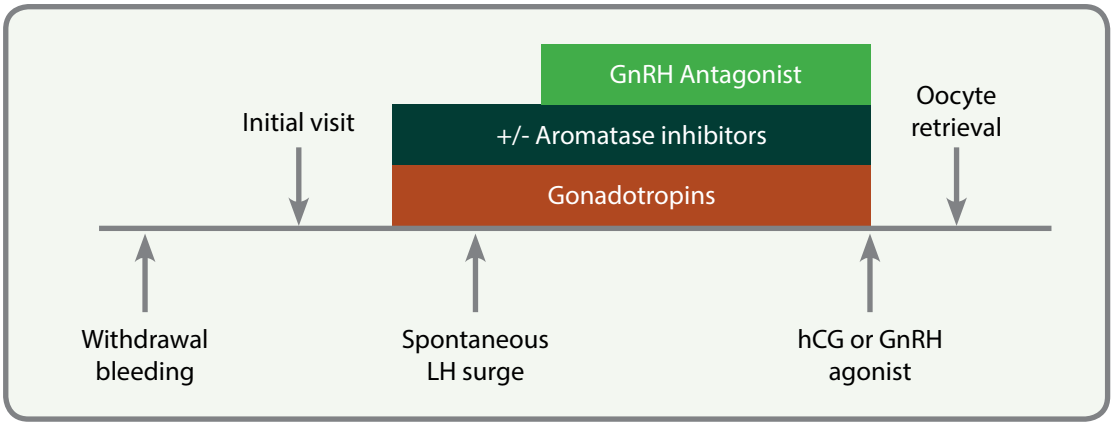
Menses following luteolysis by GnRH antagonist[5]



OPU: Ovum pick-up.

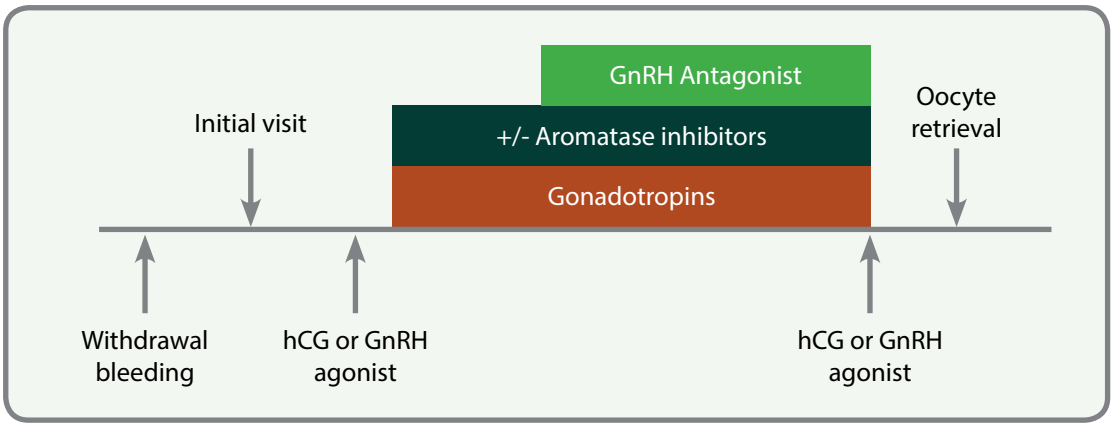
Random start in late follicular phase

Stimulation is started without GnRH antagonist if the lead follicle was <12 mm and continued to be <12 mm before spontaneous LH surge. After the LH surge, GnRH antagonist is started later when the secondary follicle cohort reached 12 mm to prevent premature secondary LH surge.[5]



Random-starting COS after inducing ovulation

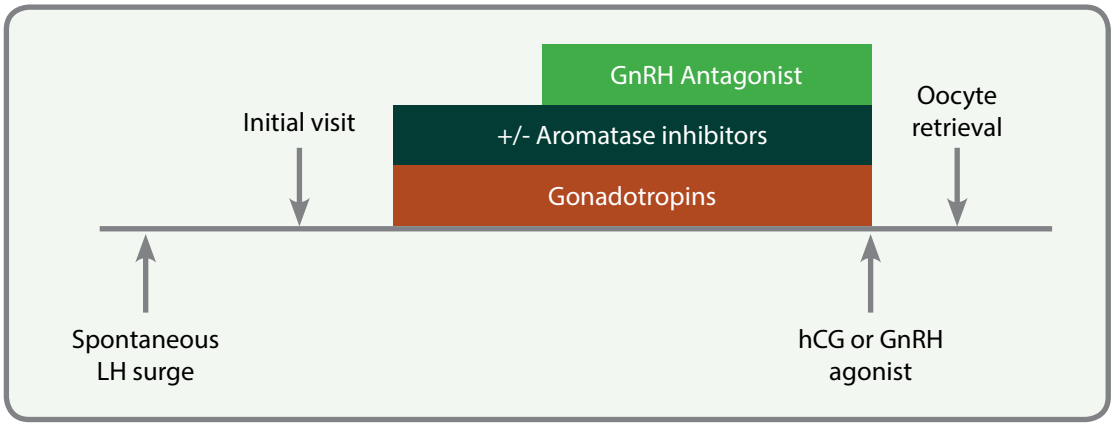
Ovulation is induced with hCG or GnRH agonist and ovarian stimulation is started in 2–3 days in the luteal phase.[5]



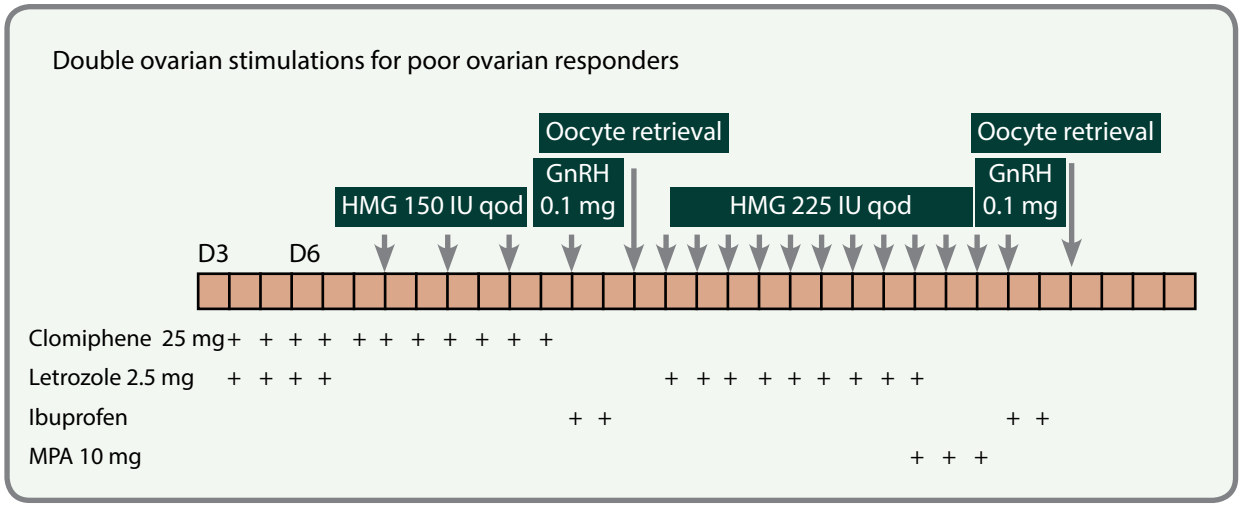
GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; LH: Luteinizing hormone

Random-luteal phase start

If the cancer patient presented in the luteal phase or the ovulation was induced, GnRH antagonist administration is initiated similarly to conventional ovarian stimulation later in the cycle when the secondary follicle cohort reached 12 mm to prevent premature secondary LH surge.[5]



Double stimulation (Shanghai protocol)[6]



1st ovum pick-up (OPU) - do not aspirate follicles <10 mm

2nd stage- continue only if ≥ 2, antral follicle count (AFC) 2-8 mm

GnRH: Gonadotropin-releasing hormone; hCG: Human chorionic gonadotropin; LH: Luteinizing hormone; qod: Every other day.

Conclusion

Ovarian stimulation is required in ART to increase the pregnancy rate as ART with natural cycle has a very low pregnancy rate. Optimizing pregnancy rates per cycle is the basis for ovarian stimulation protocols in ART. It is important to reliably predict ovarian response to stimulation, to tailor stimulation protocols optimizing the probability of pregnancy, and keep the risks of complications minimum. Individualization starts from an assessment before the start of IVF cycle of the ovarian reserve by assessing AMH, FSH, and age of the patient. Once the patient is categorized as a hypo, hyper-, or normo-responder the dose of gonadotropin should be decided. The dose selection is important for the optimal outcome of ovarian stimulation. In case of poor responders and hyper-responders, GnRH antagonist regimes are preferred. Cycle monitoring is important to decide any alteration in dose or when to add GnRH antagonist. In women at high risk for ovarian stimulation, it is important to start with low doses and intensive monitoring. In case there are indications of hyperstimulation, the regime may be altered by decreasing dose or coasting. Many factors are interdependent, and hence, a careful selection of the type of ovarian stimulation will be the key factor in deciding the success of the same.

References

1. Ding N, Liu X, Jian Q, Liang Z, Wang F. Dual trigger of final oocyte maturation with a combination of GnRH agonist and hCG versus a hCG alone trigger in GnRH antagonist cycle for in vitro fertilization: A Systematic Review and Meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2017;218:92–98.
2. Kuang Y, Chen Q, Fu Y, et al. Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Fertil Steril. 2015;104(1): 62–70.e3.
3. Nargund G. ISMAAR: The International Society for Mild Approaches in Assisted Reproduction. Facts Views Vis Obgyn. 2011; 3(1): 5–7.
4. Kim SS, Klemp J, Fabian C. Breast cancer and fertility preservation. Fertil Steril. 2011; 95(5): 1535–543.
5. Cakmak H, Katz A, Cedars MI, Rosen MP. Effective method for emergency fertility preservation: Random-start controlled ovarian stimulation. Fertil Steril. 2013;100(6):1673–80.
6. Kuang Y, Chen Q, Hong Q, et al. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). Reprod Biomed Online. 2014;29(6):684–91.

INTRAUTERINE INSEMINATION

Moderators : **Dr. Sanjeeva Reddy, Dr. Mamta Deendayal**

Panel Members : **Dr. Suresh Kumar, Dr. Nimish Shelat, Dr. Manisha Kundnani, Dr. Swarnalatha**

From left to right: Dr. Manisha Kundnani, Dr. Mamta Deendayal, Dr. Nimish Shelat, Dr. Suresh Kumar, Dr. Sanjeeva Reddy, Dr. Swarnalatha

Introduction

Intrauterine insemination (IUI) is an assisted conception technique that involves the deposition of a processed semen sample in the upper uterine cavity, overcoming natural barriers to sperm ascent in the female reproductive tract. It is a cost-effective, noninvasive first-line therapy for selected patients with functionally normal tubes, and infertility due to a cervical factor, anovulation, moderate male factor, unexplained factors, immunological factor, and ejaculatory disorders with clinical pregnancy rates per cycle ranging from 10% to 20%.[1]

IUI: PROS and CONS

PROS	CONS
• First-line procedure • Simple and easy • Relatively economical • Less invasive • Reduced psychological burden • Good couple compliancy • Low risk for serious complications • Minimal infrastructure required	• Limited indications • Low success rates • High order multiple pregnancy • Ovarian hyperstimulation syndrome (OHSS)

Work up prior to IUI[2]

Female partner	Male partner
• Baseline ultrasound for antral follicle count (AFC) • At least one normal patent tube [Hysterosalpingography (HSG)/Laparoscopy] • Anti-mullerian hormone (AMH)	• Basic semen analysis • Minimal semen parameters » Total motile sperm count (TMSC) (pre wash): >5–10 million » Total motility (pre wash): >30% » Morphology: > 4% normal » DNA fragmentation index (DFI): If indicated

Work up prior to IUI[3]

Male factor infertility	• Subnormal semen parameters • Sexual dysfunction: Ejaculatory dysfunction, hypospadias, impotence HIV discordant couples
Female factor infertility	• Minimal and mild endometriosis cervical hostility: Previous cervical operations (loop electrosurgical excision procedure, cryotherapy, and cone biopsy) • Anovulation
Combined	• Unexplained infertility
IUI with donor	• Azoospermia, hereditary disease • Severe Rh incompatibility • Severe male factor, not ready for IVF
HIV: intrauterine insemination; IUI: intrauterine insemination; IVF: In vitro fertilization.	

Ovarian stimulation for IUI

Zeng et al., analyzed a single center data from 458 patients underwent the first IUI cycle and had only one mature follicle. There were 79.3% patients allocated to controlled ovarian stimulation (COS) cycles, and most were gonadotropins protocol. No significant differences were found regarding pregnancy rate between COS group when there was only one mature follicle.[4]

Protocols[5]

- Natural cycle
- Oral ovulation induction agents: Clomiphene citrate/Letrozole
- Gonadotropins
- Clomiphene citrate/Letrozole+ Gonadotropins
- Gonadotropin releasing hormone (GnRH) agonists and antagonists

Evidence lacking as to which protocol is the best.

Optimal ovarian stimulation[6,7]

- Ovarian stimulation should be mild.
- Controlled ovarian hyperstimulation has independent positive effect on pregnancy rate when combined with IUI.
- Clomiphene citrate/Letrozole seems to be the most cost effective, specially considering the cost of monitoring and risk of ovarian hyperstimulation syndrome.
- Antagonist or agonist use in IUI cycles did not show any significant increase in pregnancy rates and are not cost effective for all IUI cycles.
- GnRH antagonists are useful in selected patients.

Optimal ovarian stimulation[8]	
1–2 follicles	• 18 – 20 mm
Endometrium	• ≥ 7 mm thick & trilaminar
Cancel or resort to IVF if	• ≥ 4 follicles ≥ 16 mm or ≥ 8 follicles ≥ 12 mm • Estradiol ≥ 1500 pg/ml

Timing of IUI

- Human chorionic gonadotropin (HCG) trigger 5000–10000/recombinant human luteinizing hormone (rec-hLH) -250 mcg SC /GnRH agonists
- Trigger when dominant follicle (DF) is 22–23 mm with clomiphene citrate/Letrozole cycles
- If the follicle size is 18 mm induce by gonadotropin
- IUI 36–38 hours later
- Gheit SA et al., showed that there was no difference in pregnancy rates when IUI was performed 24, 36, or 48 hours after the HCG trigger[9]

Semen preparation technique

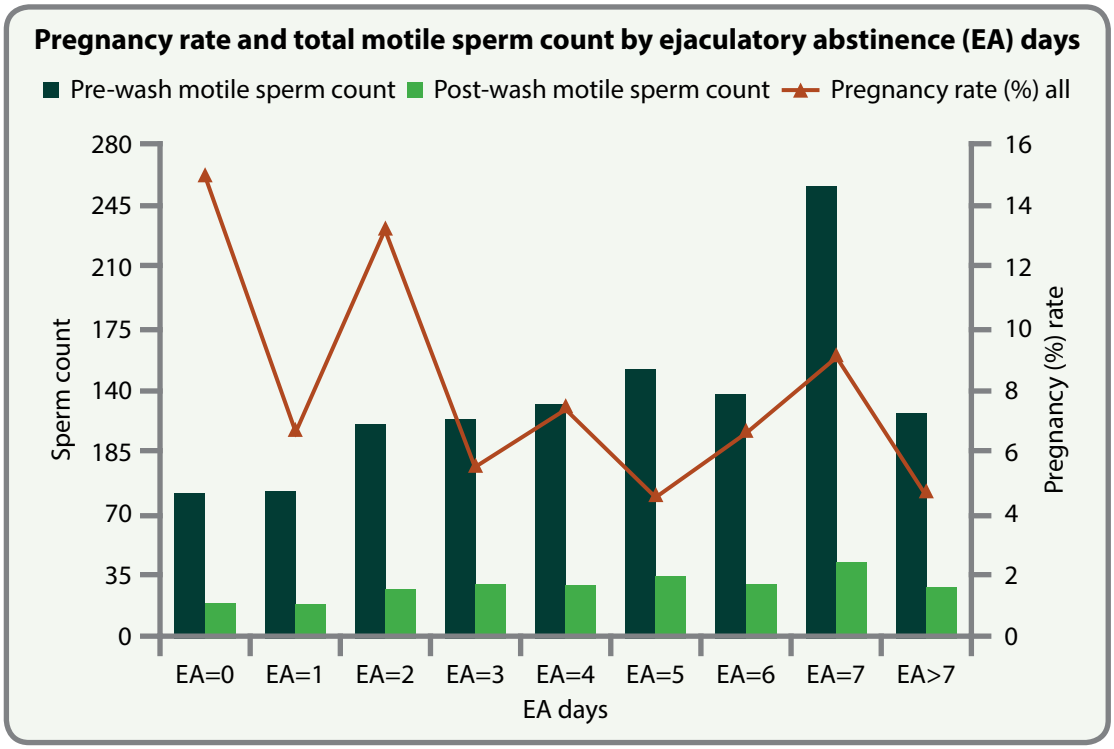
- Semen preparation technique would depend on quality of native sperm
- Swim-up is simple and cheap
- Density gradient centrifugation (DGC) is superior to swim-up and simple wash technique in laboratory outcomes
- Boomsma et al., showed that there is no significant difference in clinical pregnancy rates with any method of semen preparation.[10]

Threshold levels of semen parameters

Parameter	Threshold
Total motile sperm count (TMSC)	5–10 Million
Total notility in native sample (TM)	30%
Morphology	4%
Inseminating motile count (IMC)	1 Million

Sperm preparation time[11]

- An IUI pregnancy outcome is enhanced by the shorter intervals from semen collection to sperm wash, from sperm wash to IUI time, and from semen collection to IUI time.
- Semen specimens should be processed as soon as possible, just after liquefaction and within 30 minutes of collection.
- IUI performed as soon as possible just after processing and within 90 minutes of collection.



Abstinence of < 2 days is advisable.

IUI procedure

Types of catheter	• No significant difference in PR with type of catheter.[12] • Gentle, atraumatic technique with no touch to fundus is the essence of successful IUI.[12]
Ultrasound guided	• No difference in cumulative pregnancy rates. • Ultrasound guided helpful in case of difficult IUIs.
Single or double insemination	• Single well timed IUI recommended.[13] • Double IUI in cases of male factor infertility.[14] • Routine double IUI increases cost and psychological burden.[14]
Fallopian tube sperm perfusion vs IUI	• No clear evidence to suggests any difference between IUI and fallopian tube sperm with respect to their effectiveness and safety for treating couples with non-tubal subfertility.[15] • However, a high level of uncertainty is evident in the findings, and an additional research may be useful.[15]
Bedrest after IUI	• 10–15 min immobilization after IUI, with or without COS, Improves cumulative ongoing PR and LBR[16,17]

ART: Artificial reproductive technology; CRP: Clinical pregnancy rate; COS: Controlled ovarian stimulation; IUI: Intrauterine insemination; LBR: Live birth rate; LPS: Luteal phase support; MVPs: Micronized vaginal progesterone; OI: Ovulation induction; PR: Pregnancy rate.

LPS after IUI: Oral vs vaginal[18]

- Oral dydrogesterone 30 mg (10 mg TID) was as effective as 600 mg (200 mg TID) micronized vaginal progesterone (MVP) with no significant difference in clinical pregnancy rate (CPR) and live birth rate in both groups until 12 weeks of gestation.
- Oral dydrogesterone was better tolerated and had similar safety profile as MVP, and may replace MVPs as standard of care in ART.

Luteal phase support (LPS) after IUI[19,20]

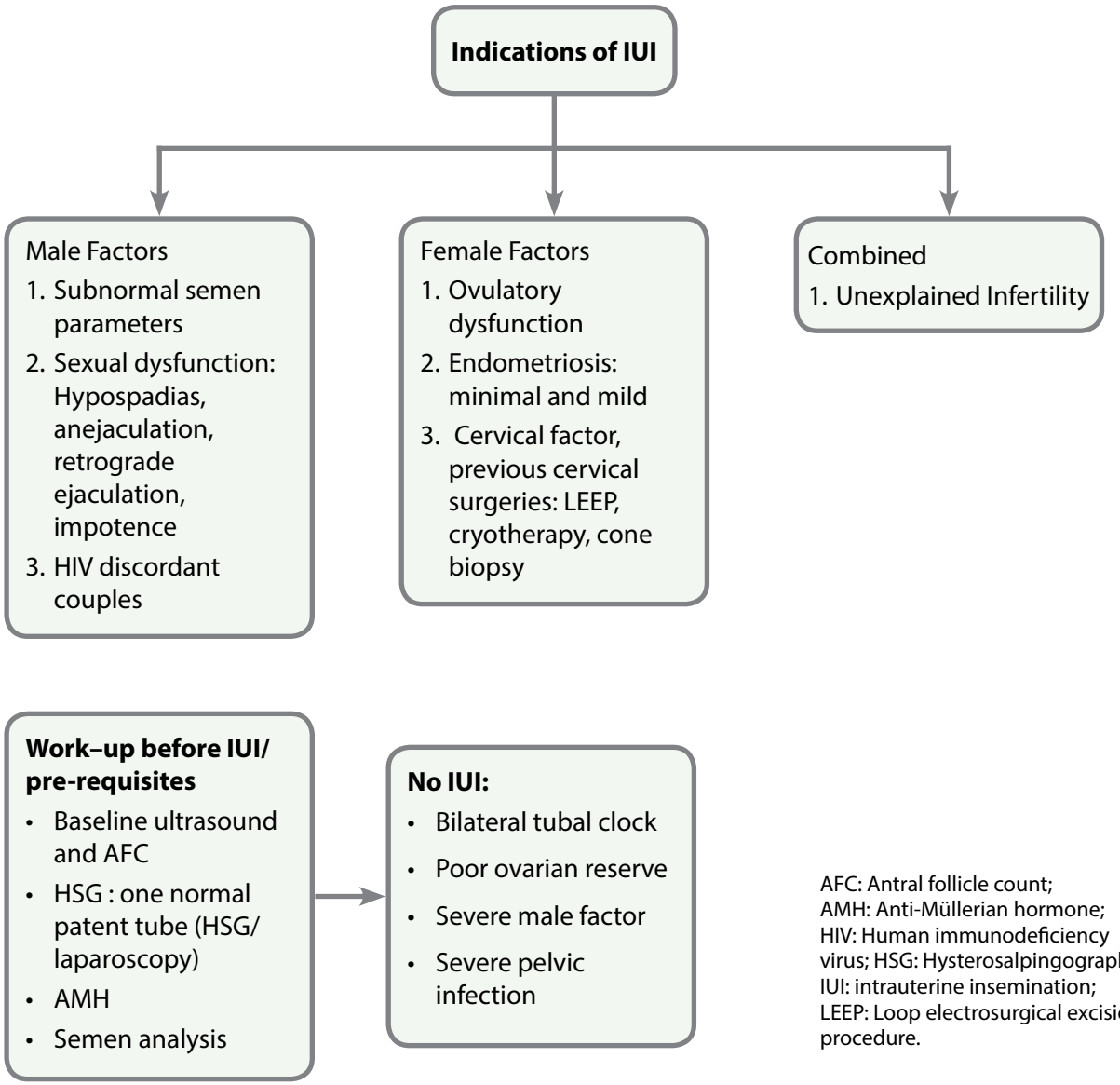
- Progesterone LPS is beneficial to patients undergoing OI with gonadotropins in IUI cycles.
- Started from second day of IUI or after ovulation is confirmed on ultrasound.
- Given for two weeks, if pregnant continued till 10–12 weeks of gestation.

Recent data (LOTUS study)[18]

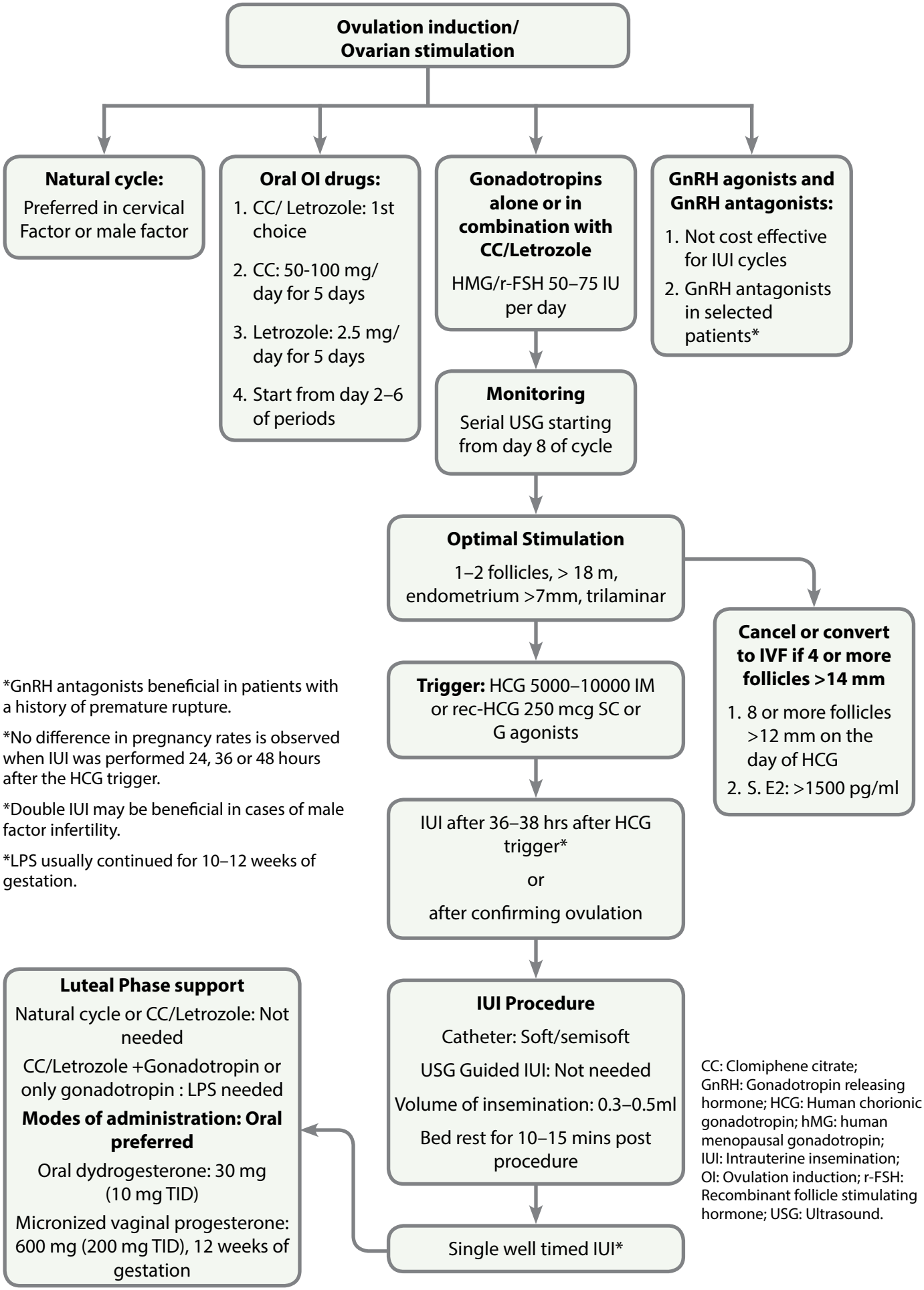
Lotus trial was a robust study which provided appropriate evidence that dydrogesterone is as effective as the current standard of care in women undergoing ART. Oral dydrogesterone 30 mg (10 mg TID) vs. 600 mg (200 mg TID) MVP for LPS in IVF cycles was compared. A total of 1,031 subjects were randomized. Luteal support was started on the day of oocyte retrieval and continued until 12 weeks of gestation. Oral dydrogesterone

30 mg (10 mg TID) was as effective as 600 mg (200 mg TID) MVP with no significant difference in CPR, LBR in both groups. Oral dydrogesterone was better tolerated, and had similar safety profile as MVP. Dydrogesterone may replace MVP as standard of care in ART.

Efficacy		
	Dydrogesterone	**Micronized vaginal progesterone**
Implantation rate	37.6%	33.1%
Live birth rate	34.6%	29.8%



AFC: Antral follicle count;
AMH: Anti-Müllerian hormone;
HIV: Human immunodeficiency virus; HSG: Hysterosalpingography;
IUI: intrauterine insemination;
LEEP: Loop electrosurgical excision procedure.



*GnRH antagonists beneficial in patients with a history of premature rupture.

*No difference in pregnancy rates is observed when IUI was performed 24, 36 or 48 hours after the HCG trigger.

*Double IUI may be beneficial in cases of male factor infertility.

*LPS usually continued for 10–12 weeks of gestation.

CC: Clomiphene citrate; GnRH: Gonadotropin releasing hormone; HCG: Human chorionic gonadotropin; hMG: human menopausal gonadotropin; IUI: Intrauterine insemination; OI: Ovulation induction; r-FSH: Recombinant follicle stimulating hormone; USG: Ultrasound.

Conclusions

- IUI has a major role as first-line treatment of infertility, provided there are sufficient sperms and there is no tubal disease.
- Success rates averages between 8% to 14% per cycle.
- Critical factors for success include patient selection, using ovarian stimulation, and timing the insemination accurately, post wash total motile sperms.
- Ovarian stimulation for IUI should be mild, targeting two follicles >16 mm, and estradiol of 500 pg/ml
- IUI performed 12–36 hours after HCG. Altering the timing of IUI does not affect the pregnancy rates.
- No significant difference in clinical pregnancy rates with any method of semen preparation.
- IUI success is affected by semen preparation time.
- Minimal threshold for semen parameters above which IUI can be performed with acceptable success rates are total motile sperm count >5–10 million, motility >30%, morphology >4%, inseminating motile count 1–5 million.
- Single well timed IUI is recommended, double IUI in male factor infertility.
- Gentle atraumatic technique is important.
- Bed rest of 10–15 mins after procedure improves success rates.
- Luteal phase support is needed in gonadotropin cycles.
- Oral dydrogesterone may replace micronized vaginal progesterone as the standard of care for luteal phase support in assisted reproduction due to good efficacy and safety profile and improved patient compliance.

References

1. Allahbadia GN. Intrauterine insemination: Fundamentals revisited. J Obstet Gynaecol India. 2017;67(6):385–92.
2. O'Flynn N. Assessment and treatment for people with fertility problems: NICE guideline. Br J Gen Pract. 2014; 64(618): 50–51.
3. Aboulghar M, Collins J, Crosignani PG, et al. Intrauterine insemination discussed by the ESHRE Capri Workshop Group. The ESHRE CampuS 2009 Artificial insemination: An update. 2009
4. Zeng M, Wen Y, Jiang M, et al. Doctors' preferences for controlled ovarian stimulation protocols in intrauterine insemination.Mater Sociomed. 2015; 27(4): 248–50.
5. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev. 2007;(2):CD005356.
6. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev. 2007;(2):CD005356.
7. Cantineau AE, Cohlen BJ, Klip H, Heineman MJ; Dutch IUI Study Group Collaborators. The addition of GnRH antagonists in intrauterine insemination cycles with mild ovarian hyperstimulation does not increase live birth rates--a randomized, double-blinded, placebo-controlled trial. Hum Reprod. 2011;26(5):1104–11.
8. Merviel P, Heraud MH, Grenier N, et al. Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature. Fertil Steril. 2010;93(1):79–88.
9. Gheit SA. Pregnancy rates following three different timings of intrauterine insemination for women with unexplained infertility: A randomised controlled trial. Middle East Fertility Society Journal. 2010; 15(4):265–68.
10. Boomsma CM, Heineman MJ, Cohlen BJ, Farquhar C. Semen preparation techniques for intrauterine insemination. Cochrane Database Syst Rev. 2007;(4):CD004507.
11. Fauque P, Lehert P, Lamotte M, et al. Clinical success of intrauterine insemination cycles is affected by the sperm preparation time. Fertil Steril. 2014;101(6):1618-23. e1–3.
12. Abou-Setta AM, Mansour RT, Al-Inany HG, et al. Intrauterine insemination catheters for assisted reproduction: A systematic review and meta-analysis. Hum Reprod. 2006;21(8):1961–67.
13. Cantineau AE, Cohlen BJ, Heineman MJ. Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility. Cochrane Database Syst Rev. 2009;(2):CD001502.
14. Polyzos NP, Tzioras S, Mauri D, Tatsioni A. Double versus single intrauterine insemination for unexplained infertility: A meta-analysis of randomized trials. Fertil Steril. 2010;94(4):1261–66.
15. Cantineau AE, Cohlen BJ, Heineman MJ, Marjoribanks J, Farquhar C. Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility. Cochrane Database Syst Rev. 2013;(10):CD001502.
16. Saleh A, Tan SL, Biljan MM, Tulandi T. A randomized study of the effect of 10 minutes of bed rest after intrauterine insemination. Fertil Steril. 2000;74(3):509–11.
17. Cordary D, Braconier A, Guillet-May F, et al. Immobilization versus immediate mobilization after intrauterine insemination: A systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2017;46(10):747–51.
18. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Hum Reprod. 2017;32(5):1019–027.
19. Hill MJ, Whitcomb BW, Lewis TD, et al. Progesterone luteal support after ovulation induction and intrauterine insemination: A systematic review and meta-analysis. Fertil Steril. 2013;100(5):1373–80.
20. Miralpeix E, González-Comadran M, Solà I, et al. Efficacy of luteal phase support with vaginal progesterone in intrauterine insemination: A systematic review and meta-analysis. J Assist Reprod Genet. 2014;31(1):89–100.

POLYCYSTIC OVARY SYNDROME

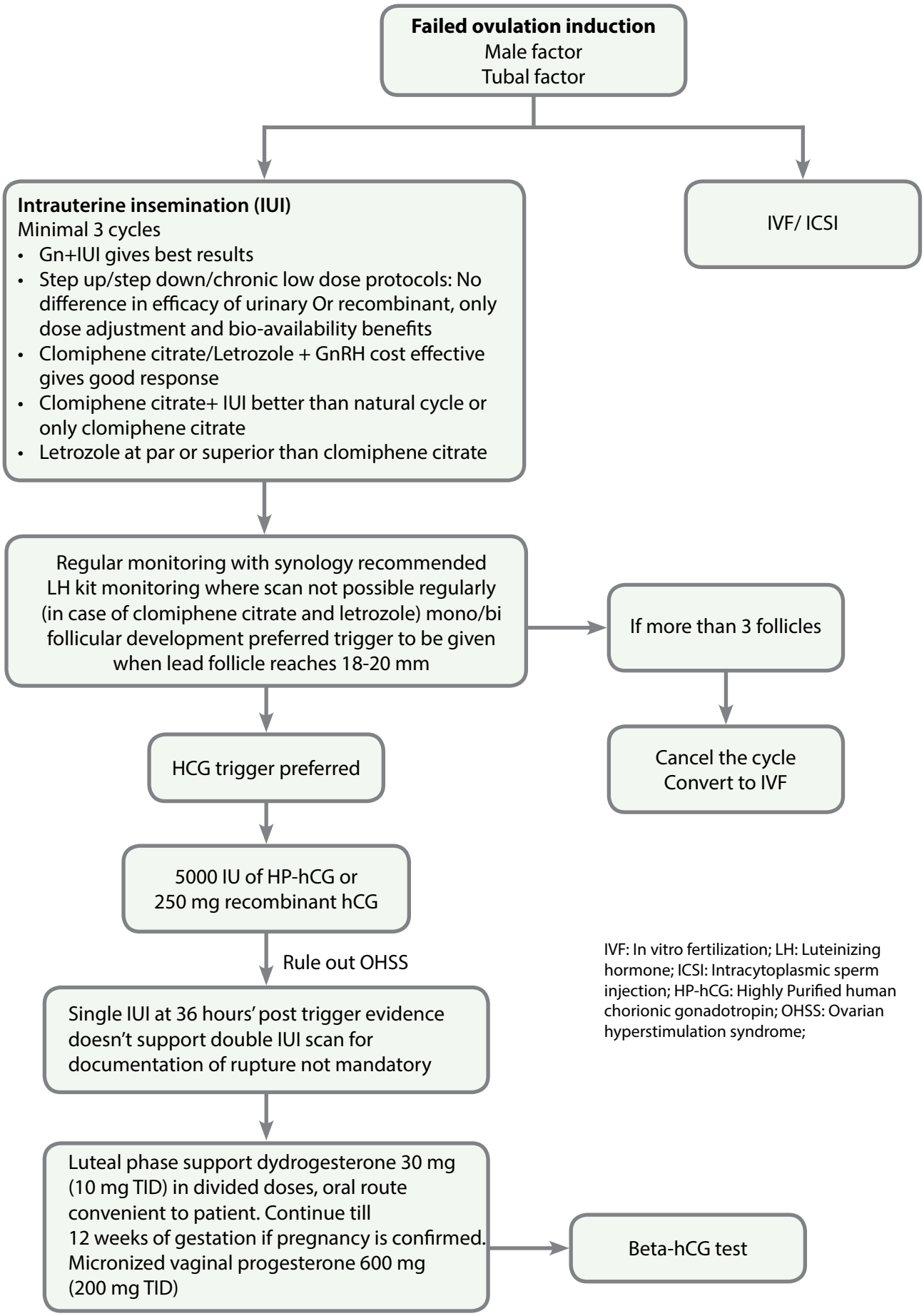
Moderators : Dr. Kaberi Banerjee, Dr. Maninder Ahuja

Panel Members : Dr. Jatin Shah, Dr. Seema Pandey, Dr. Sarita Sukhija

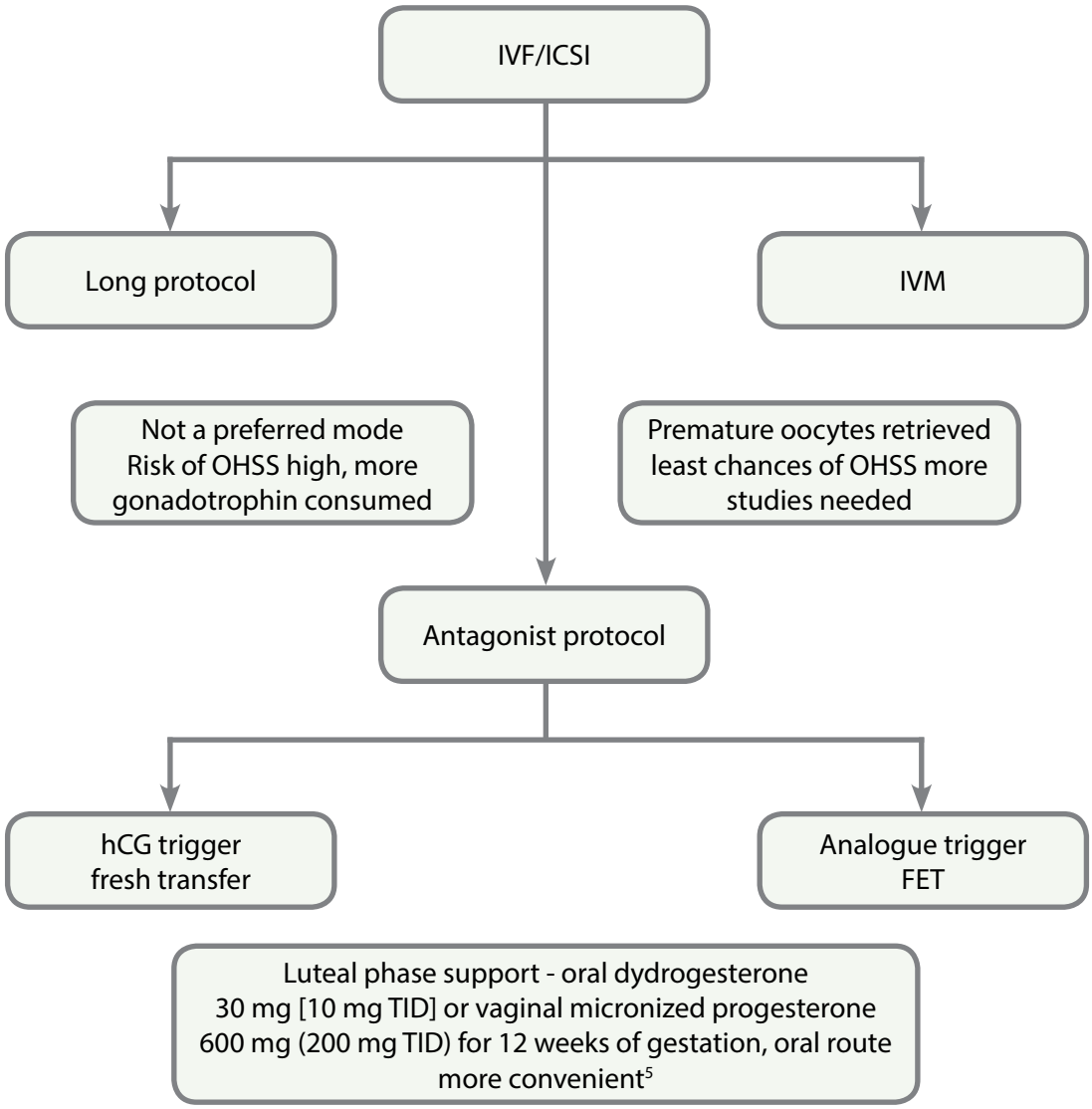
From left to right: Dr. Seema Pandey, Dr. Jatin Shah, Dr. Sarita Sukhija, Dr. Maninder Ahuja

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women.[1] It affects about 12%–21% of the women of reproductive age and about 70% of women with PCOS remain undiagnosed.[2] Guidelines from the Endocrine Society recommend the use of Rotterdam criteria for diagnosis, which mandates the presence of two of the following three findings—hyperandrogenism, ovulatory dysfunction, and polycystic ovaries—plus the exclusion of other diagnoses that could result in hyperandrogenism or ovulatory dysfunction.[3] Increased BMI and age can also contribute to infertility, and women should be counselled about the importance of maintaining a healthy weight (BMI <30 kg/m^2) and optimal timing of family initiation.[2] If lifestyle measures are unsuccessful pharmacological treatment is required. The ovulation induction (OI) protocols and treatment modalities must be balanced for optimal results. Drugs used for OI include clomiphene citrate (CC), letrozole, CC/letrozole + gonadotrophins, gonadotrophins, gonadotrophin-releasing hormone (GnRH) agonist + gonadotrophins.[4]



IVF: In vitro fertilization; LH: Luteinizing hormone; ICSI: Intracytoplasmic sperm injection; HP-hCG: Highly Purified human chorionic gonadotropin; OHSS: Ovarian hyperstimulation syndrome;



IVF: In vitro fertilization; LH: Luteinizing hormone; ICSI: Intracytoplasmic sperm injection; hCG: Human chorionic gonadotropin; OHSS: Ovarian hyperstimulation syndrome; IVM: In vitro maturation of oocytes; FET: Frozen embryo transfer.

Conclusion

- In women who have failed ovulation induction or if there is tubal factor involved or in case of male factor infertility should be offered intrauterine insemination, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Intrauterine insemination should be offered for a minimal 3 cycles with gonadotropin to get best results. Clomiphene citrate/letrozole with gonadotropin is cost effective and show good response.
- Clomiphene citrate with IUI is better than natural cycle or only clomiphene citrate and letrozole is reported to be equally effective or superior to clomiphene citrate. These cycles are carried out under regular monitoring and when there is mono or bi follicular development HCG is use to trigger and post trigger luteal phase support is given with dydrogesterone and micronized vaginal progesterone.
- In case of IVF/ICSI long protocol may result in risk of ovarian hyperstimulation syndrome. Antagonist protocol with HCG trigger and fresh transfer or analogue trigger with frozen-thawed embryo transfer can be carried out and luteal phase support is give with oral dydrogesterone 10 mg TID or vaginal micronized progesterone 200 mg TID for 12 weeks of gestation is recommended, but oral route of progesterone is more convenient.

References

1. Jalilian A, Kiani F, Sayehmiri F, et al. Prevalence of polycystic ovary syndrome and its associated complications in Iranian women: A meta-analysis. Iran J Reprod Med. 2015; 13(10): 591–604.
2. Boyle J, Teede HJ. Polycystic ovary syndrome: An update. Aust Fam Physician. 2012;41(10):752–6.
3. Williams T, Mortada R, Porter S. Diagnosis and treatment of polycystic ovary syndrome. Am Fam Physician. 2016;94(2):106-13.
4. Xi W, Liu S, Mao H, et al. Use of letrozole and clomiphene citrate combined with gonadotropins in clomiphene-resistant infertile women with polycystic ovary syndrome: A prospective study. Drug Des Devel Ther. 2015; 9: 6001–008.
5. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Hum Reprod. 2017;32(5):1019–027.

ENDOMETRIOSIS IN ART

Moderators : Dr. Prakash Trivedi, Dr. Krishnakumar

Panel Members : Dr. S. Shanthakumari, Dr. Sunita Arora, Dr. Sapna Hosur, Dr. Gouri Gupta, Dr. Jayshri Padte

From left to right: Dr. S. Shanthakumari, Dr. Sunita Arora, Dr. Gouri Gupta, Dr. Krishnakumar

Introduction

Endometriosis being a recurrent disease of unknown etiopathogenesis, with no conclusive definite management in the infertile group, a proper scientific knowledge of endometriosis surgery and assisted reproductive technology (ART) is required. It is an inflammatory condition characterized by the presence of tissue resembling endometrium in sites other than uterine cavity.[1]

Incidence of endometriosis[2]

- 6%–10% in reproductive age group
- 9%–50% incidence on laparoscopy. Varies as per geographical distribution phenotype and genotype.

Endometriosis causes infertility (various theories)[3]

- Chronic inflammation
- Distorted pelvic anatomy with altered uterotubal transport
- Reduced endometrial receptivity and impaired implantation
- Decreased ovarian reserve
- Compromized oocyte and embryo quality

Symptoms[3]

Endometriosis can range from asymptomatic to classical triad of symptoms:

- Chronic pelvic pain
- Dyspareunia
- Dysmenorrhea
- Also may have urinary and bowel complaints

Diagnosis[4]

- Symptoms: Varies from asymptomatic to classical symptoms
- Diagnosis by clinical examination pervaginal/per rectal (level D)
- Diagnosis of deep endometriosis if painful induration/nodule in rectovaginal wall (level C)
- Transvaginal scan aids in diagnosis especially if an endometrioma is suspected (Level A)
- Cancer antigen (CA)-125 levels not recommended for diagnosis (level A)
- Laparoscopy per se need not be used for making only the diagnosis
- Role of magnetic resonance imaging (MRI) and computed tomography (CT) in diagnosis – not well established (Level D)
- Additional imaging helps if rectal or bowel involvement suspected (Level D)

Staging of endometriosis[4]

Stage 1

- Minimal/mild endometriosis
- Isolated implants
- No significant adhesions
- Superficial implants <5 cms

Stage 2

- Moderate endometriosis
- Multiple implants both superficial + deep, > 5 cms peritubal + periovarian adhesions
- Small, <4 cms: endometriomas

Stage 3

- Severe endometriosis
- Multiple superficial + deep implants
- Large ovarian endometriomas
- Flimsy + dense adhesions

Stage 4

- Advanced + extensive
- Rectovaginal infiltrates + frozen pelvis

Medical management[5]

Different drugs used for various indications of endometriosis are:

- Oral contraceptive pills (OCPs) dienogest, medroxyprogesterone acetate, gonadotropin-releasing hormone (GnRH) agonists, levonorgestrel-releasing intrauterine system (LNG-IUS), danazol, and dydrogesterone.

All of these drugs except dydrogesterone, inhibit ovulation, and hence may not have beneficial effect in patients having endometriosis planning for immediate conception.

Surgical management[4]

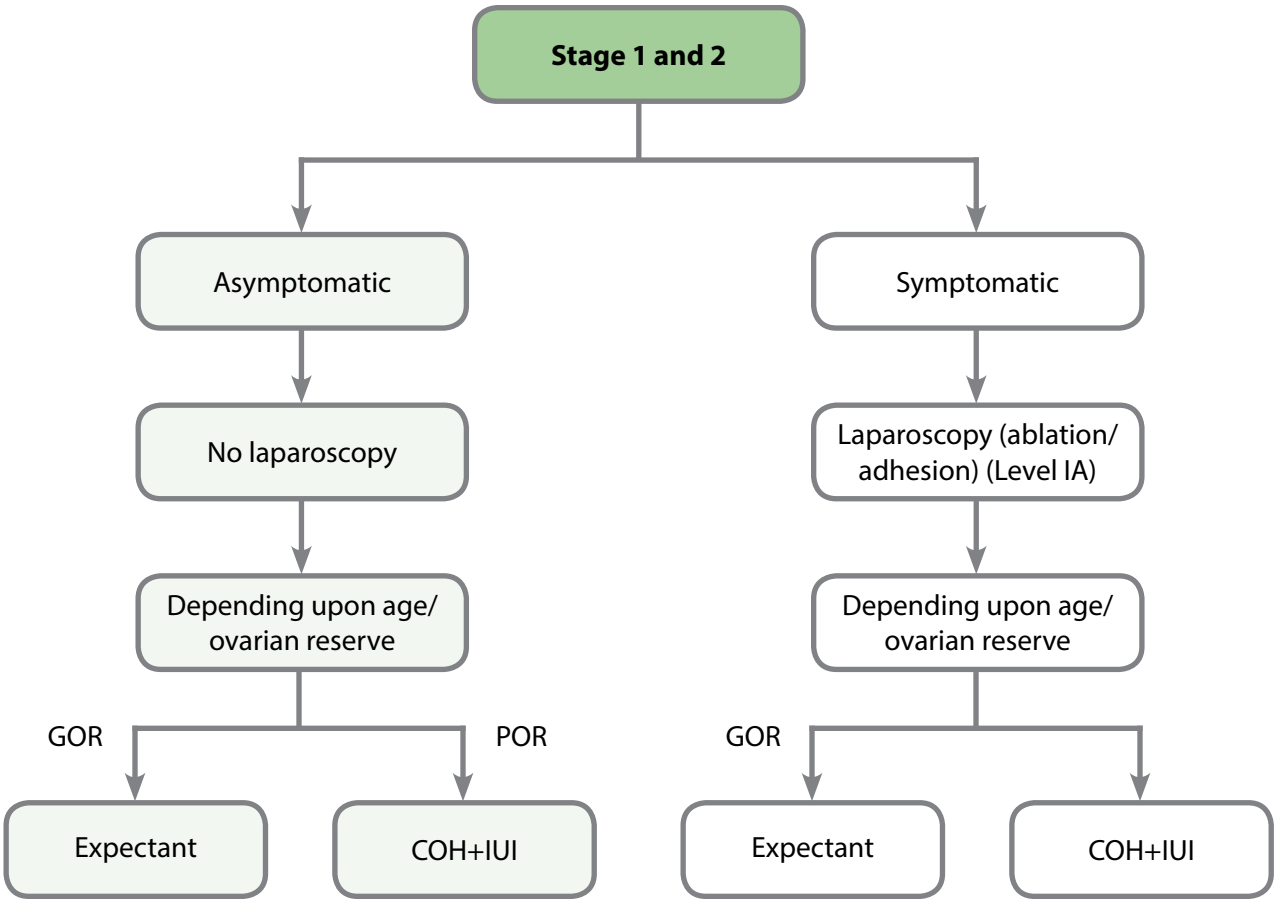
- Stage 1 and 2: Laparoscopic ablation has been shown to be associated with small but significant improvement in live birth rate (incidental finding during diagnostic laparoscopy or laparoscopy for some other indication) (level C)
- Stage 3 and 4: Conservative surgery by laparoscopy improves pregnancy rates even with expectant management (level B)
- Endometrioma (evaluate ovarian reserve)
- Cystectomy better than ablation and coagulation in > 4 cms (level A)
- Avoid cystectomy in endometrioma <4 cms and B/L endometriomas
- Repeat surgery does not improve fertility rates (level D)

Combination of medical and surgical therapy[4]

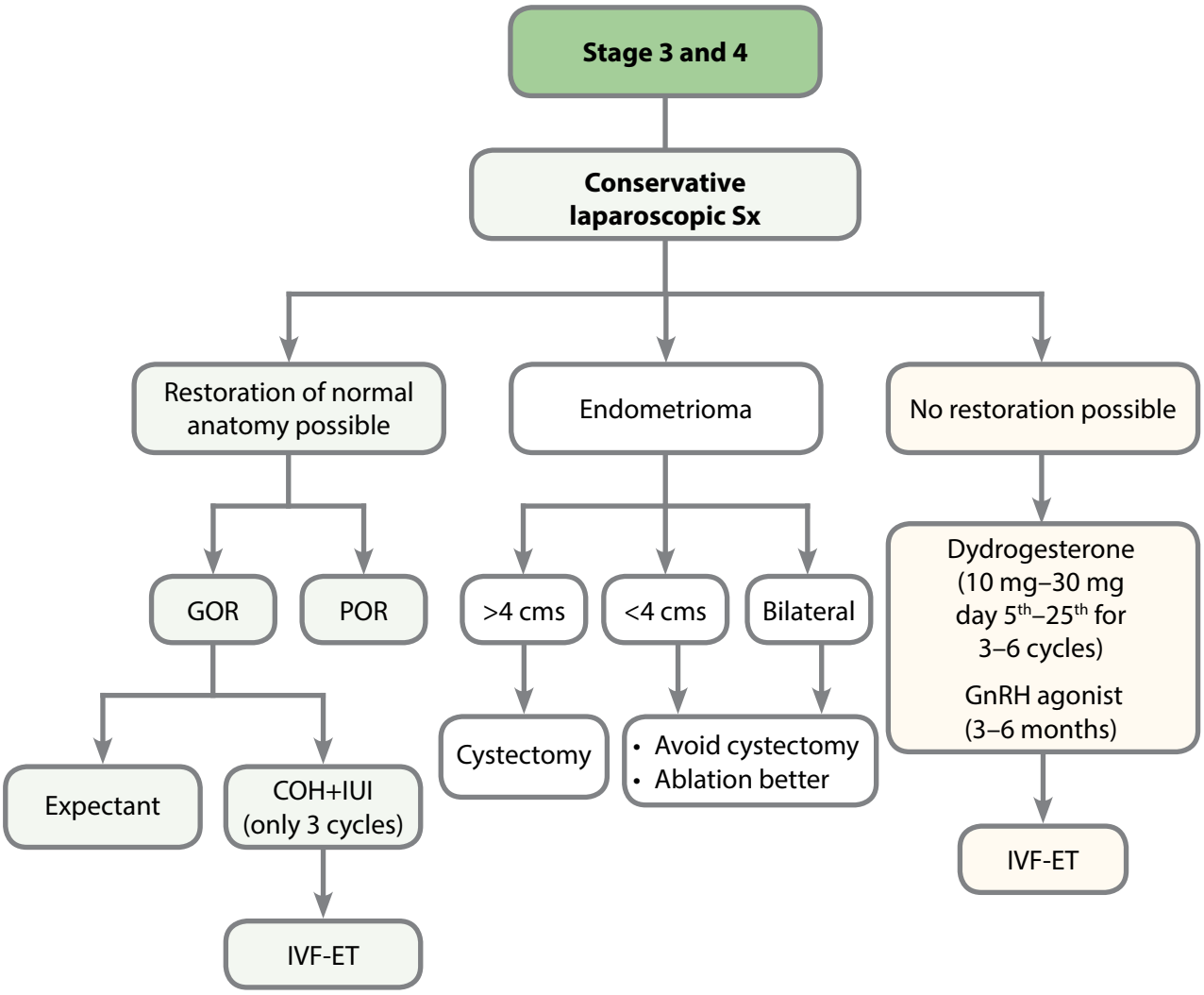
- The combination of medical and surgical therapy does not improve fertility.
- Preoperative therapy may reduce vascularity and the size of endometriotic implants. Since surgical therapy may miss endometriotic implants, its role is controversial.
- Adjunctive hormone before surgery does not improve spontaneous pregnancy rates (level D).
- Postoperatively agonist therapy should be planned only if ART is planned. It increases pregnancy rate by 4-fold (level A).

Algorithms

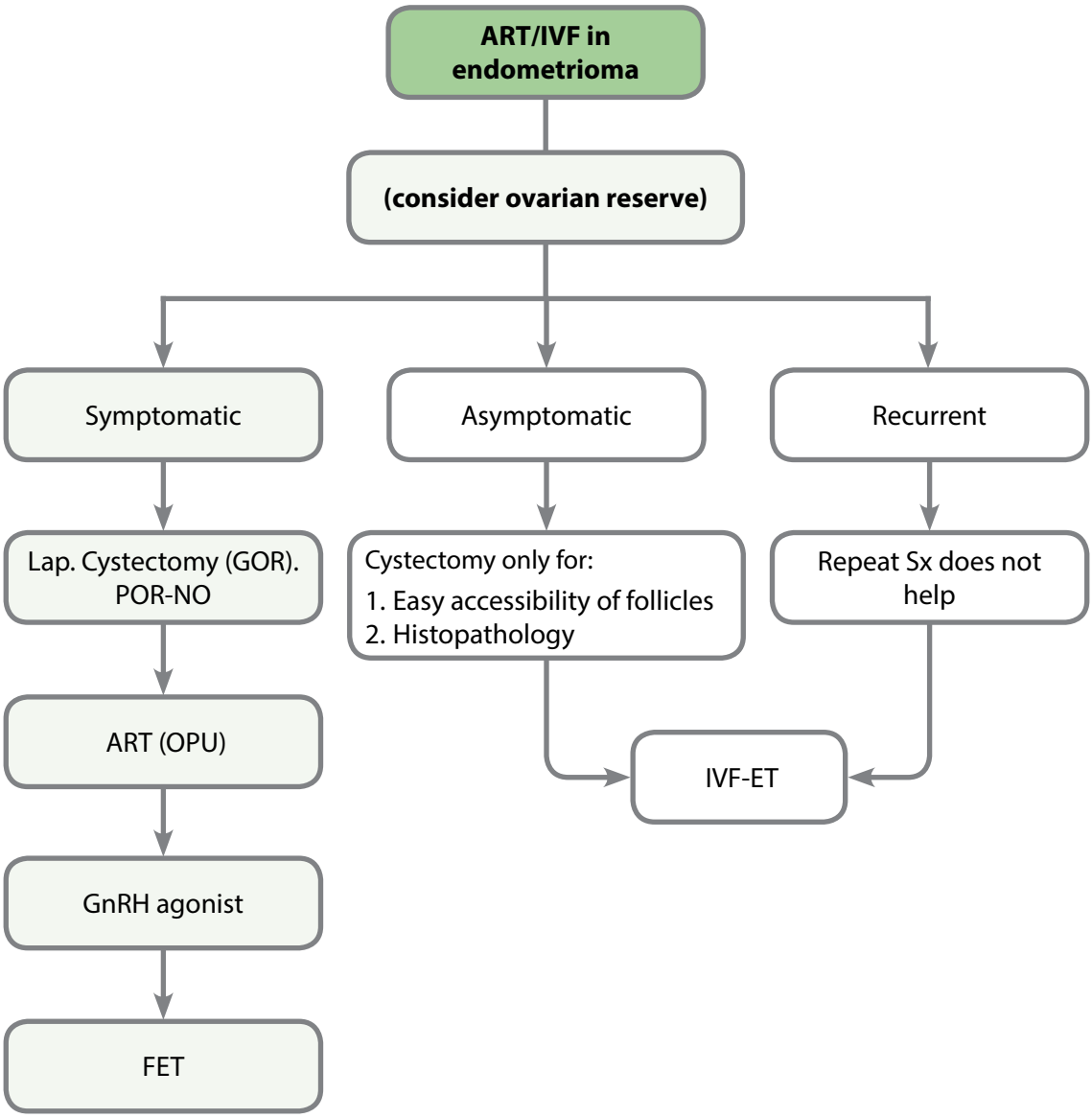
- Counselling: Age/ovarian reserve/pain (all factors to be considered)



COH: Controlled ovarian hyperstimulation; GOR: Good ovarian reserve; IUI: Intrauterine insemination; POR: Poor ovarian reserve, Sx: surgery.



COH: Controlled ovarian hyperstimulation; GOR: Good ovarian reserve; IUI: Intrauterine insemination; IVF-ET: In vitro fertilization and embryo transfer; POR: Poor ovarian reserve, Sx: Wurgery.



ART (OPU): Assisted reproductive technology oocyte pick-up (OPU); COH: Controlled ovarian hyperstimulation; FET: Frozen embryo transfer; GnRH: Gonadotropin-releasing hormone; GOR: Good ovarian reserve; IUI: Intrauterine insemination; IVF-ET: In vitro fertilization and embryo transfer; POR: Poor ovarian reserve, Sx: Surgery.

Medical management[6,7]

- Molecules used: Dienogest, OCPs, Dydrogesterone, and GnRH.
- Dydrogesterone is preferred in patients of endometriosis planning for immediate conception as it does not inhibit ovulation.

Endometriosis and ART[8]

- Women with endometriosis undergoing ART have been found to have similar live birth rate and clinical pregnancy rates as compared to other infertility causes.
- Although there is lower oocyte retrieval rate and higher cancellation rates in endometriosis.
- Risk of recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage 3/4 since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF.

Conclusion

- Hormonal treatment for suppression of ovarian function – Not recommended (Level A)
- American Society for Reproductive Medicine (ASRM)/American Fertility Society (AFS) Stage I/II: Operative laparoscopy (excision or ablation) including adhesiolysis rather than diagnostic laparoscopy increases ongoing pregnancy rates (Level A)
- In infertile women with endometrioma excision rather than drainage increases spontaneous pregnancy rates (Level A)
- Decision for surgery should be considered carefully if there is previous ovarian surgery (Level D)
- Stage III/IV: Operative laparoscopy instead of expectant management increases spontaneous pregnancy rates (Level B)
- AFS/ARSM I/II stage: IUI with controlled ovarian stimulation better than expectant management (Level C)
- ART should be given if tubal function is compromised or male factor in (AFS/ASRM I/II) or other treatment failed (Level B)
- Recurrence rates of endometriosis is not increased with controlled ovarian stimulation (Level C)

References

1. Acién P, Velasco I. Endometriosis: A disease that remains enigmatic. ISRN Obstetrics and Gynecology. Volume 2013, Article ID 242149, 12 pages
2. Practice bulletin no. 114: management of endometriosis. Obstet Gynecol. 2010;116(1):223–36.
3. The Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. 2012; 98(3): 591–98.
4. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29(3):400–12.
5. Rafique S, DeCherney AH. Medical management of endometriosis. Clin M Obstet Gynecol. 2017; 60(3):485–96.
6. Akashi D, Todo Y, Shimada C, et al. Successful use of dydrogesterone as maintenance therapy in recurrent endometrial stromal sarcoma: A case report. Jpn J Clin Oncol 2013;43(11)1145–149.
7. Schweppe KW. The place of dydrogesterone in the treatment of endometriosis and adenomyosis. Maturitas. 2009; 65S (2009) S23–S27.
8. ESHRE Guideline for the diagnosis and treatment of endometriosis. Assisted reproduction in endometriosis. Available from http://guidelines.endometriosis.org/concise-art.html

POOR OVARIAN RESERVE

Moderators : **Dr. Manish Banker, Dr. Sudha Prasad**

Panel Members : **Dr. Amiti Agrawal, Dr. Kedar Padte, Dr. Monika Doshi, Dr. Rakhi Singh, Dr. Sheetal Sawankar, Dr. Ritu Hinduja**

From left to right: Dr. Monika Doshi, Dr. Amiti Agrawal, Dr. Sudha Prasad, Dr. Manish Banker, Dr. Kedar Padte, Dr. Sheetal Sawankar, Dr. Rakhi Singh, Dr. Ritu Hinduja

Introduction

Poor ovarian reserve (POR) is most challenging area of reproductive medicine. It lacks uniform definition. There is lot of low quality or empirical data.[1]

Bologna criteria for poor responders[2]

At least 2 of the following:

1. **Advanced maternal age**
   ≥ 30 years or risk factor for poor ovarian reserve
2. **Previous poor ovarian reserve**
   ≤3 oocytes with conventional stimulation
3. **Abnormal ovarian reserve biomarker**
   AFC<5-7; AMH <0.5-1.1 ng/ml

OR Two episodes of poor ovarian reserve after maximal stimulation

POSEIDON GROUP 1

Young patients <35 years with adequate ovarian reserve parameters (AFC ≥ 5; AMH≥ 1.2 ng/ml) and with an unexpected poor or suboptimal ovarian response.

Subgroup 1a: <4 oocytes*

Subgroup 1b: 4-9 oocytes retrieved*

*after standard stimulation

POSEIDON GROUP 2

Older patients ≥ 35 years with adequate ovarian reserve parameters (AFC ≥5; AMH≥ 1.2 ng/ml) and with an unexpected poor or suboptimal ovarian response.

Subgroup 2a: <4 oocytes*

Subgroup 2b: 4-9 oocytes retrieved*

*after standard stimulation

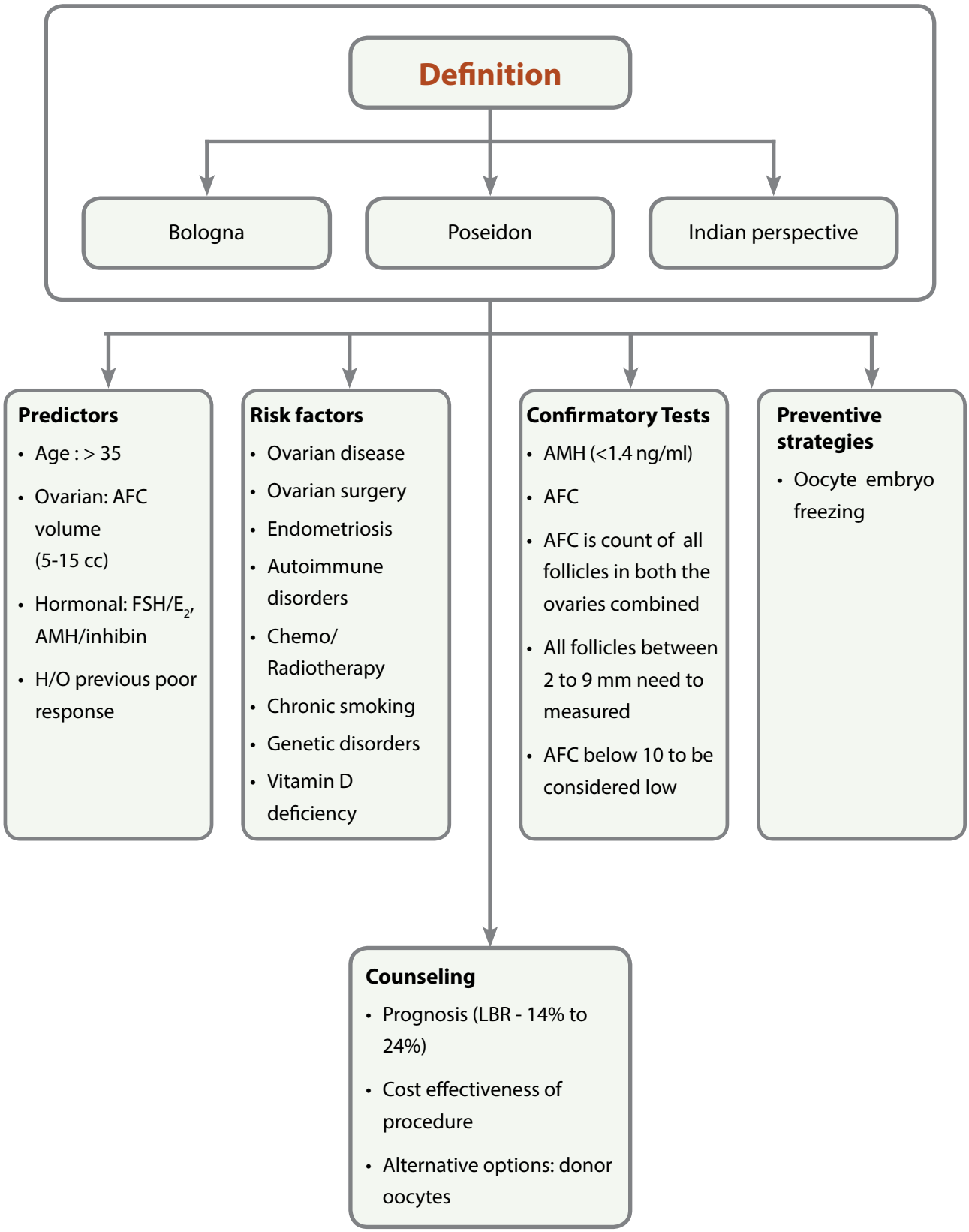
POSEIDON GROUP 3

Young patients (<35 years) with poor ovarian reserve pre-stimulation parameters (AFC < 5; AMH < 1.2 ng/ml)

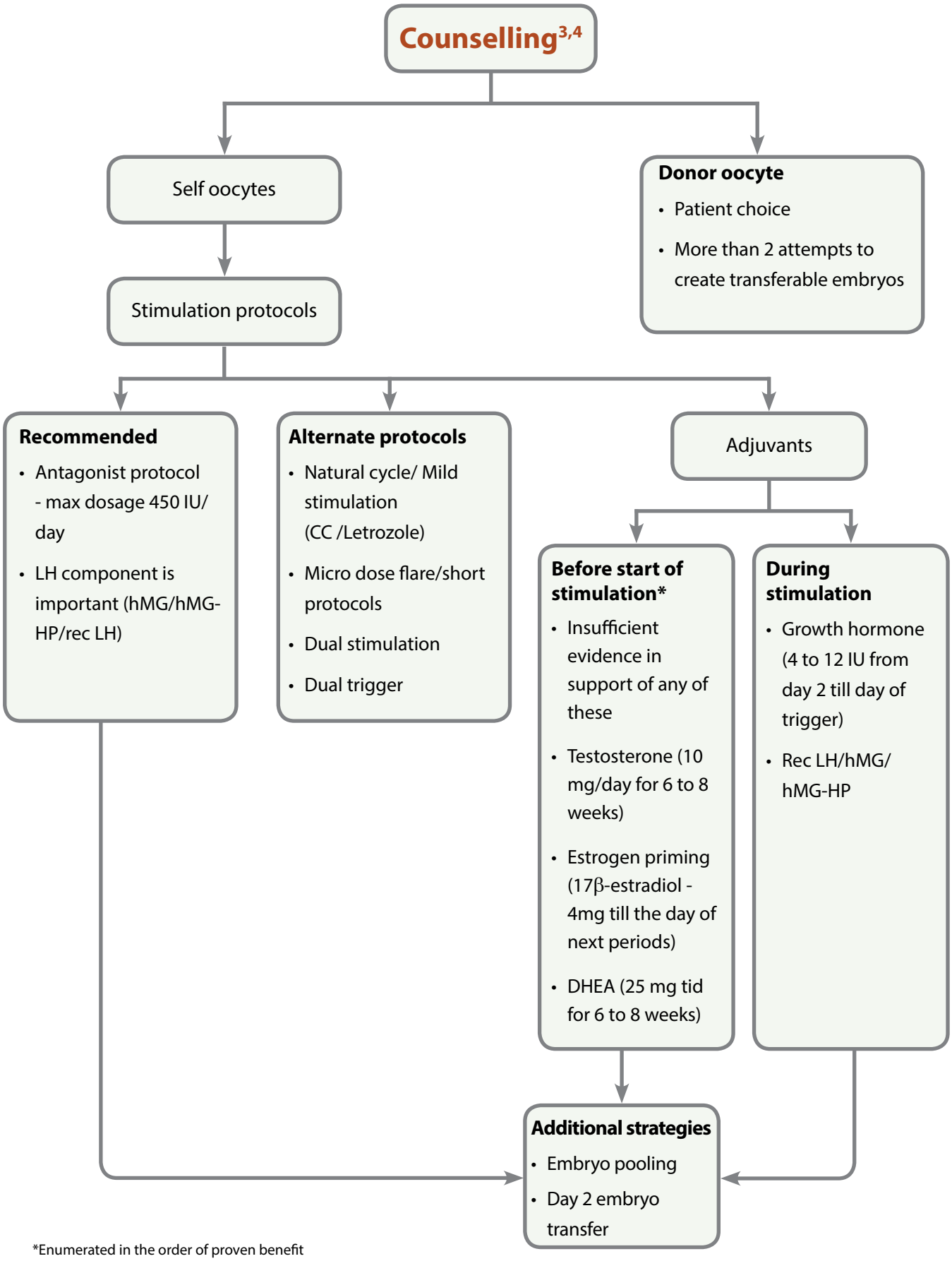
POSEIDON GROUP 4

Young patients (≥35 years) with poor ovarian reserve pre-stimulation parameters (AFC < 5; AMH <1.2 ng/ml)

AMH: Antimüllerian hormone; AFC: Antral follicle count



AMH: Antimüllerian hormone; AFC: Antral follicle count; FSH: Follicle stimulating hormone; E_2: Estradiol; LBR: Live birth rates



*Enumerated in the order of proven benefit

LH: luteinizing hormone; hMG: human menopausal gonadotropin; HP: highly purified; rec: recombinant; CC: Clomiphene citrate; DHEA: dehydroepiandrosterone.

Conclusion

Treating women with poor ovarian reserve is challenging. Evaluating ovarian reserve and individualizing the therapeutic strategies are important for optimizing the success rate. Bologna criteria offer right direction to identify homogenous groups for evaluating efficacy of various therapies. Avoiding prolonged pituitary suppression, prevention of premature luteinizing hormone (LH) surge, and controlled ovarian stimulation (COS) to maximize oocyte yield and achieve embryos with good implantation potential form the basis of all therapeutic interventions in poor responders.

References

1. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian failure, poor ovarian responder—A plea for universal definitions. J Assist Reprod Genet. 2015; 32(12): 1709–712.
2. Ferraretti AP, La Marca A, Fauser BC, et al; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: The Bologna criteria. Hum Reprod. 2011;26(7):1616–624.
3. Jeve YB, Bhandari HM. Effective treatment protocol for poor ovarian response: A systematic review and meta-analysis. J Hum Reprod Sci. 2016;9(2):70-81.
4. Pandian Z, McTavish AR, Aucott L, Hamilton MP, Bhattacharya S. Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF). Cochrane Database Syst Rev. 2010;(1):CD004379.

LUTEAL PHASE SUPPORT IN ART

Moderators : Dr. Rishma Pai,
Dr. Pankaj Talwar

Panel Members : Dr. Nikita Lad, Dr. Rohan Palshetkar,
Dr. Pritimala Gangurdhe,
Dr. Ashish Kale, Dr. Rajul Tyagi

From left to right: Dr. Rajul Tyagi, Dr. Pritimala Gangurdhe, Dr. Rohan Palshetkar, Dr. Ashish Kale, Dr. Pankaj Talwar, Dr. Rishma Pai, Dr. Nikita Lad

Physiology of corpus luteum (CL) function and disruption

- After ovulation is induced by the mid-cycle luteinizing hormone (LH) surge the luteinized granulosa cells collectively forming the CL start producing estradiol (E_2) and progesterone. [1]
- The hormonal activity of CL is tightly controlled by the pulsatile production of LH by the anterior pituitary
- Numerous hormonal changes caused by controlled ovarian stimulation (COS) interfere with the normal function of the anterior pituitary, causing a disruption of CL function and progesterone secretion.
- In assisted reproductive technologies the factors interfering with the normal support of CL function by the anterior pituitary notably are[2]
    - » Excessive levels of E2 induced by COS leading to Negative feedback to hypothalamic pituitary axis and suppression of the LH pulsatile secretion.
    - » Damage to the granulosa cell apparatus.
- There is now overwhelming evidence that assisted reproduction techniques (ART) outcomes, pregnancy rates and live birth rates are improved by luteal-phase support (LPS)

Drugs used for LPS

- Drugs used for LPS are progesterone, estrogens, gonadotropin-releasing hormone (GnRH) agonist, and human chorionic gonadotropin (hCG)[3]
- LPS can be accomplished by either an intermittent administration of hCG or daily progesterone replacement via oral, intramuscular, subcutaneous, and vaginal route.
- Some studies have used adding estrogen to the progesterone but only benefit observed is in the clinical pregnancy (CPR)[4]
- The hCG has been abandoned due a several-fold increase in the risk of ovarian hyperstimulation syndrome and a lack of demonstrated superiority over simple progesterone supplementation.[2]

Progesterone[5]

Drug preparation	Dose	Benefits
1. <u>ORAL</u> Dydrogesterone	30 mg/day (10 mg TID) till 12 weeks of gestation	1. Better bio-availability 2. 10-20 times more potent 3. Lesser side effects 4. Comparable live birth rate 5. Oral compliance 6. No estrogenic, androgenic, glucocorticoid activities 7. Better pregestational and immuno modulator activity
2. <u>Vaginal progesterone</u> a. Micronized progesterone capsules	600 mg/day (200 mg TID)	1. By passing first- pass metabolism 2. Higher concentration in uterine circulation
b. Micronized progesterone (Gel)	90 mg / day	Same as above
3. <u>Injectable</u> a. Sustained release depot (17 alpha hydroxy progesterone caproate)	250 mg every 3 days OR 341 mg every 3 days	High plasma concentration
b. Micronized progesterone (Oil based)	100 mg/day	High plasma concentration
c. Micronized progesterone (Water based)	50 mg/day	1. High plasma concentration 2. No pain at Injection site

Dydrogesterone

- Compared with progesterone, dydrogesterone has a greater affinity for the progesterone receptors and can be used at lower oral doses to promote endometrial proliferation, owing to its better bioavailability and to the progestogenic activity of its metabolites.[6]
- Dydrogesterone also appears to have no affinity for androgenic, estrogenic, glucocorticoid, or mineralo-corticoid receptors.
- Favorable safety and tolerability profile in pregnancy.

Estrogen

	Dose	Benefits	Side-effects
1. Oral			• Nausea • Vomiting • Deep vein thrombosis (DVT) • Breast tenderness • Loss of appetite • Migraine, headache, dizziness • Bloating • Venous thromboembolism (VTE)
a. Estradiol valerate 2 mg	6–12 mg[2]	Better compliance	
b. Estradiol hemihydrate 2 mg	6 mg[2]	Better compliance	
2. Transdermal			
a. 17-beta-estradiol	6 mg[7,8]	Decreases chance of DVT and VTE in post menopausal women or older women[9]	
3. Vaginal			
a. Estradiol valerate 2 mg	6–12 mg[10]	Increases clinical pregnancy rate but no other parameters[10]	

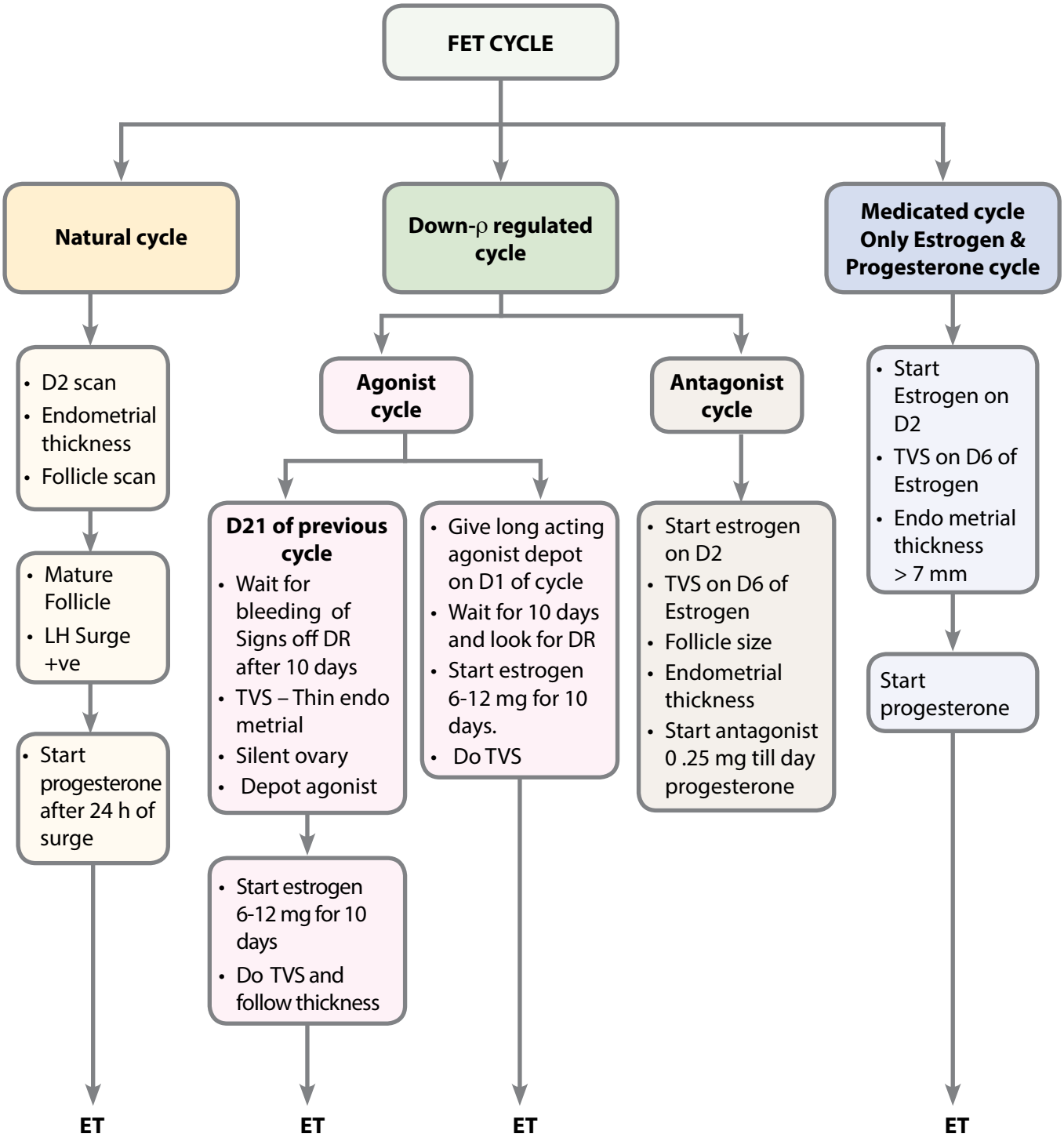
Antagonist

- 0.1 mg of agonist on Day 6 of oocyte pick-up (OPU).[11]

Onset of treatment[2]

- ART - Initiate on the evening of oocyte retrieval or the day after. Relaxing properties of progesterone tend to reduce uterine contractions (UCs) at the time of embryo transfer (ET)
- Frozen embryo transfer (FET) cycles – Endometrium - More than 7 mm, triple layer pattern with adequate blood flow.
- Intrauterine insemination (IUI) cycles the LPS - Day of IUI, If COH has been done.

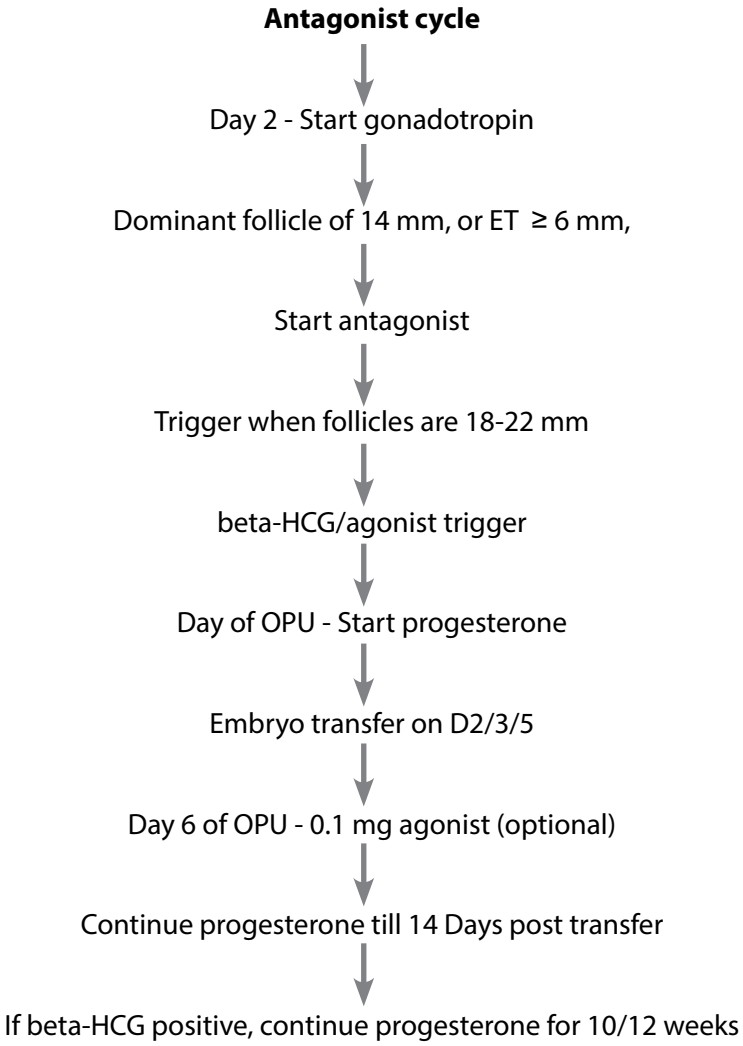
Algorithm of LPS in FET cycle



Continue estrogen and progesterone till 10 weeks of pregnancy

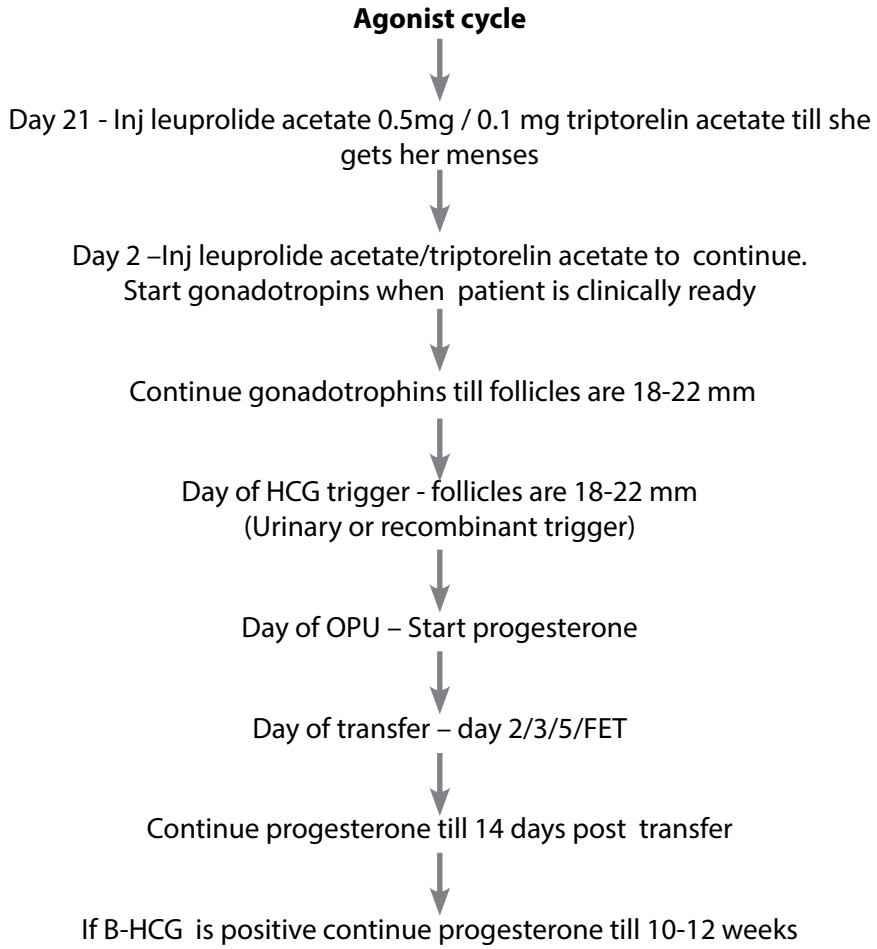
DR: Down regulation; FET: Frozen Embryo Transfer; LH: Luteinizing hormone; TVS: Transvaginal sonography.

Algorithm of LPS in antagonist cycle



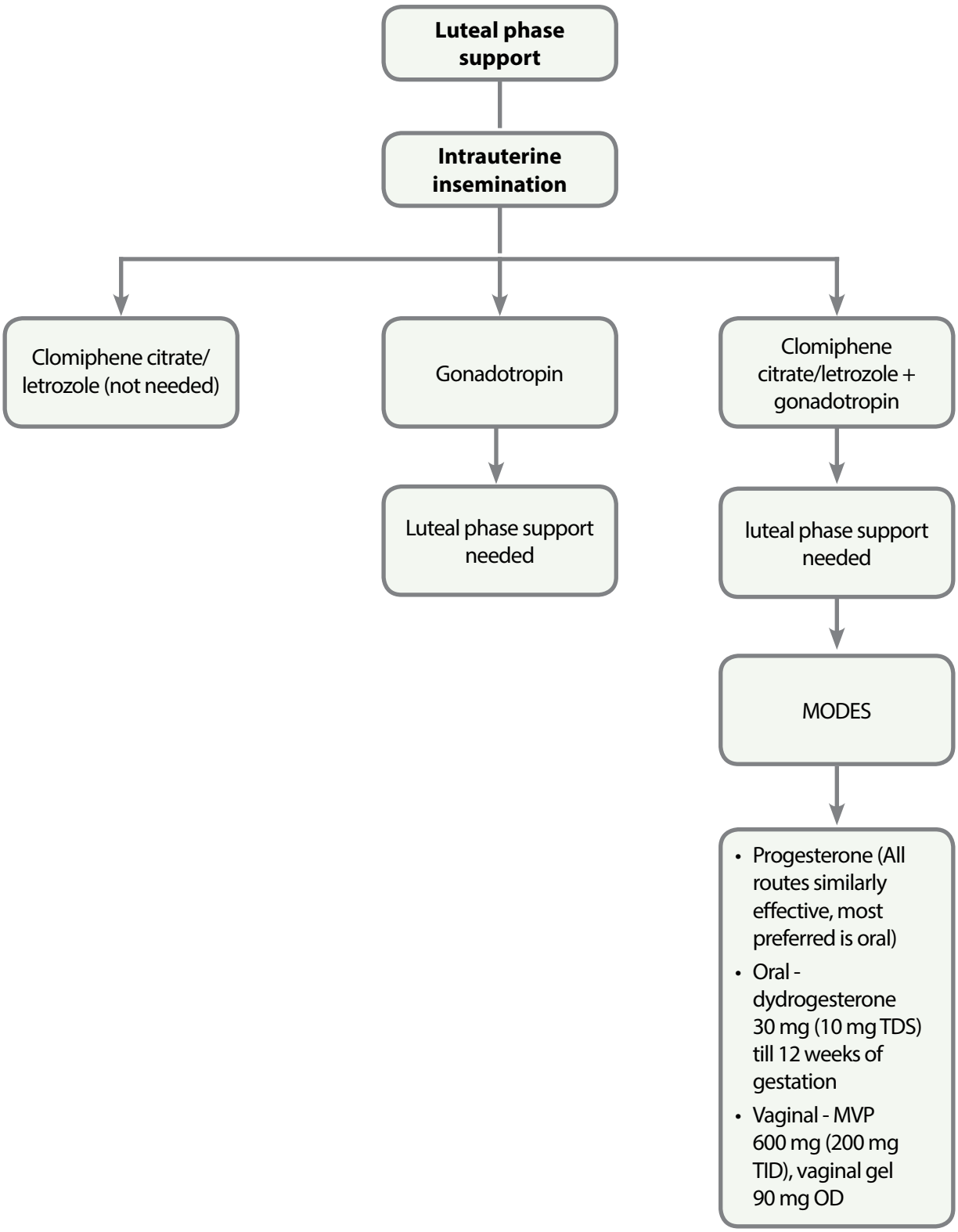
OPU: Ovum pick-up; ET: Endometrial thickness;
HCG: Human chorionic gonadotropin.

Algorithm of LPS in agonist cycle



OPU: Ovum pick-up; HCG: Human chorionic gonadotropin.

Algorithm of LPS in IUI cycle



MVP: Micronized vaginal progesterone; OD: Once daily; TID: Thrice daily.

How to choose a progesterone?[12-15]

Choice depends upon the following four factors:

- Bioavailability
- Side effects
- Ease of use
- Clinical outcome

Route and type of progesterone	Side effects and tolerability	Advantages and ease of use
Oral dydrogesterone	• Well tolerated, oral compliance, lesser side effects	• Better bio-availability • 10-20 times more potent • Well-tolerated • Comparable live birth rate • Oral compliance • Less estrogenic, androgenic, glucocorticoid activities • Better progesterone and immunomodulatory activity
Vaginal (MVP)	Vaginal irritation, discharge, and bleeding	• Good bioavailability, messy to use
Intramuscular	Pain at the injection site, local abscess	• Good bioavailability, lacks compliance

- Oral dydrogesterone may replace MVP as standard of care in ART due to comparable efficacy, better bioavailability, and well-tolerated oral compliance.

Role of adjuvants for thin ET[16-18]

- Presently used - Aspirin, sildenafil, arginine, granulocyte colony- stimulating factor (G-CSF)
- Not recommended – Usage part of empirical treatment for thin endometrial thickness

Termination of LPS

Termination of treatment

- LPS would only need to be administered – till Positive pregnancy test logically.
- Later the hCG produced by the developing embryo, sustains proper corpus luteum function.
- This corresponds to the moment of luteo-placental transition when hormone production (E_2 and progesterone) is entirely taken over from the corpus luteum by the placenta.
- The extended duration of LPS prescribed by many groups is not supported by evidence.

- The primary reason that leads many groups not to interrupt LPS upon a positive pregnancy test, which includes our own, is a clear lack of courage.
- It has been amply documented that LPS can be stopped after the first positive ultrasound finding or even positive pregnancy test or at 10 or 12 weeks of gestation.

Conclusion

- LPS has been proven to be necessary in artificial reproductive technique.
- The modalities may be adding progesterone, GnRH agonist, and estrogens.
- Progesterone supplemental doses either by oral preparation or vaginal administration is recommended, oral is preferred.
- Use of antagonist leads to better outcome as per some studies but need more corroboration.
- Aqueous progesterone preparation allows self-administration by subcutaneous route.
- Dydrogesterone is recommended for LPS as it has minimal side effects, better bioavailability and comparable outcome .
- We recommend continuing the LPS till 12 weeks.

References

1. Kumar P, Sait SF. Luteinizing hormone and its dilemma in ovulation induction. J Hum Reprod Sci. 2011; 4(1): 2–7.
2. Gardner DK. Textbook of Assisted Reproductive Techniques, Fifth Edition. dited by Ariel Weissman , Editors Howles CM, Shoham Z. CRC Press. Published January 22, 2018, 518 Pages
3. de Ziegler D, Pirtea P, Andersen CY, Ayoubi JM. Role of gonadotropin-releasing hormone agonists, human chorionic gonadotropin (hCG), progesterone, and estrogen in luteal phase support after hCG triggering, and when in pregnancy hormonal support can be stopped. Fertil Steril. 2018;109(5):749-55.
4. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: A meta-analysis of the randomized trials. Hum Reprod. 2002;17(9):2287–99.
5. Daniel Shapiro et al. Examining the evidence: Progesterone supplementation during fresh and frozen embryo transfer. Reproductive Bio Medicine Online. 2014;29:S4-S14.
6. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5400051/"A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Hum Reprod. 2017; 32(5): 1019–027.
7. Shahrokh Tehrani Nejad E, Bakhtiari Ghaleh F, Eslami B, et al. Comparison of pre-treatment with OCPs or estradiol valerate vs. no pre-treatment prior to GnRH antagonist used for IVF cycles: An RCT. Int J Reprod Biomed (Yazd). 2018;16(8):535–40.
8. Sun et al. J Reprod Med, 2014,
9. Mohammed K, Abu Dabrh AM, Benkhadra K, et al. Oral vs transdermal estrogen therapy and vascular events: A systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(11):4012–20.
10. Lias et al. Int Journal of Clinical Path, Sept 2014.
11. Zafardoust S, Jeddi-Tehrani M, Akhondi MM, et al. Effect of administration of single dose GnRH agonist in luteal phase on outcome of ICSI-ET cycles in women with previous history of IVF/ICSI failure: A randomized controlled trial. Journal of Reproduction & Infertility. 2015;16(2):96–101.
12. Ludwig M, Schwartz P, Babahan B, et al. Luteal phase support using either Crinone 8% or Utrogest: Results of a prospective, randomized study. Eur J Obstet Gynecol Reprod Biol. 2002;103(1):48–52.
13. Shapiro D, Boostanfar R, Silverberg K, Yanushpolsky EH. Examining the evidence: Progesterone supplementation during fresh and frozen embryo transfer. Reprod Biomed Online. 2014;29 Suppl 1:S1-14; quiz S15–6.
14. Ghanem ME, Al-Boghdady LA. Luteal phase support in ART: An update. Chapter 7. 2012; http://dx.doi.org/10.5772/51093
15. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. Hum Reprod. 2017;32(5):1019–027.
16. Wang L, Huang X, Li X, et al. Efficacy evaluation of low- dose aspirin in IVF/ICSI patients evidence from 13 RCTs: A systematic review and meta-analysis. Medicine. 2017;96:e7720
17. Takasaki A, Tamura H, Miwa I, et al. Endometrial growth and uterine blood flow: A pilot study for improving endometrial thickness in the patients with a thin endometrium. Fertil Steril. 2010; 93(6): 1851–812.
18. Gutarra-Vilchez RB, Urrútia G, Glujovsky D, et al.Vasodilators for women undergoing fertility treatment. Cochrane Database of Systematic Reviews. 2014, (10): CD010001.

SETTING OF ART LAB

Moderators : Dr. R S Sharma, Dr. Srinivas

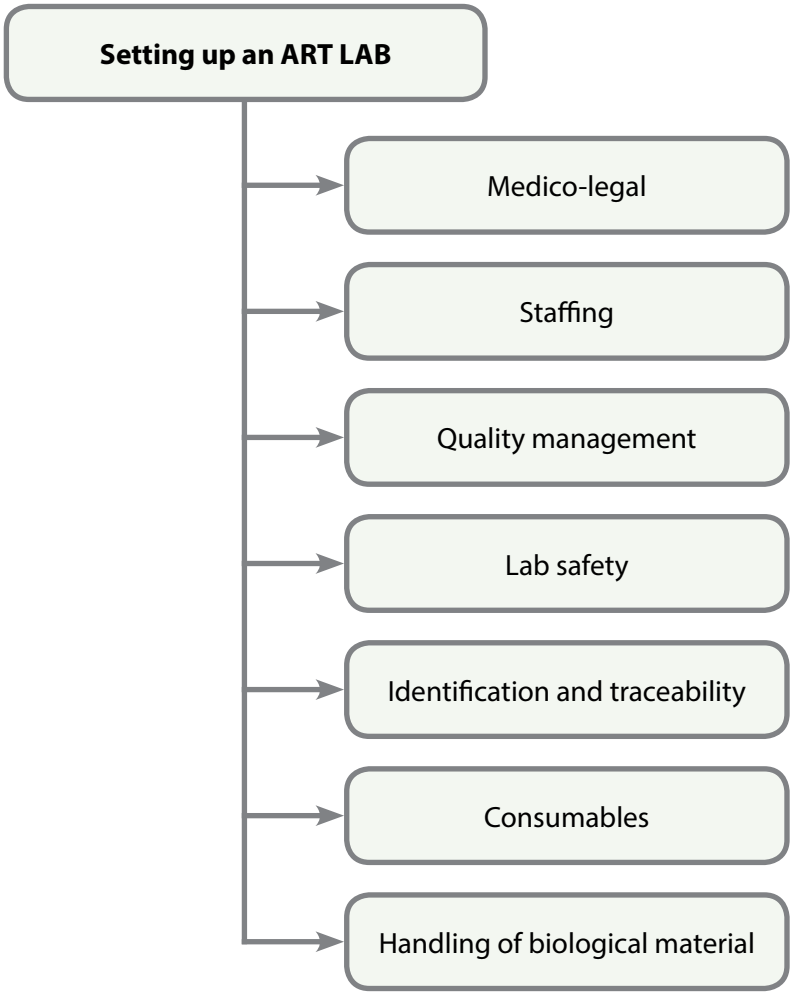
Panel Members : Dr. Rajnikant, Dr. R B Agarwal, Dr. Meenu Handa, Dr Rutvij Dalal, Dr. Keshav Malhotra

From left to right: Dr. Meenu Handa, Dr. R S Sharma, Dr. Srinivas, Dr. Rajnikant, Dr. R B Agarwal, Dr. Keshav Malhotra, Dr Rutvij Dalal

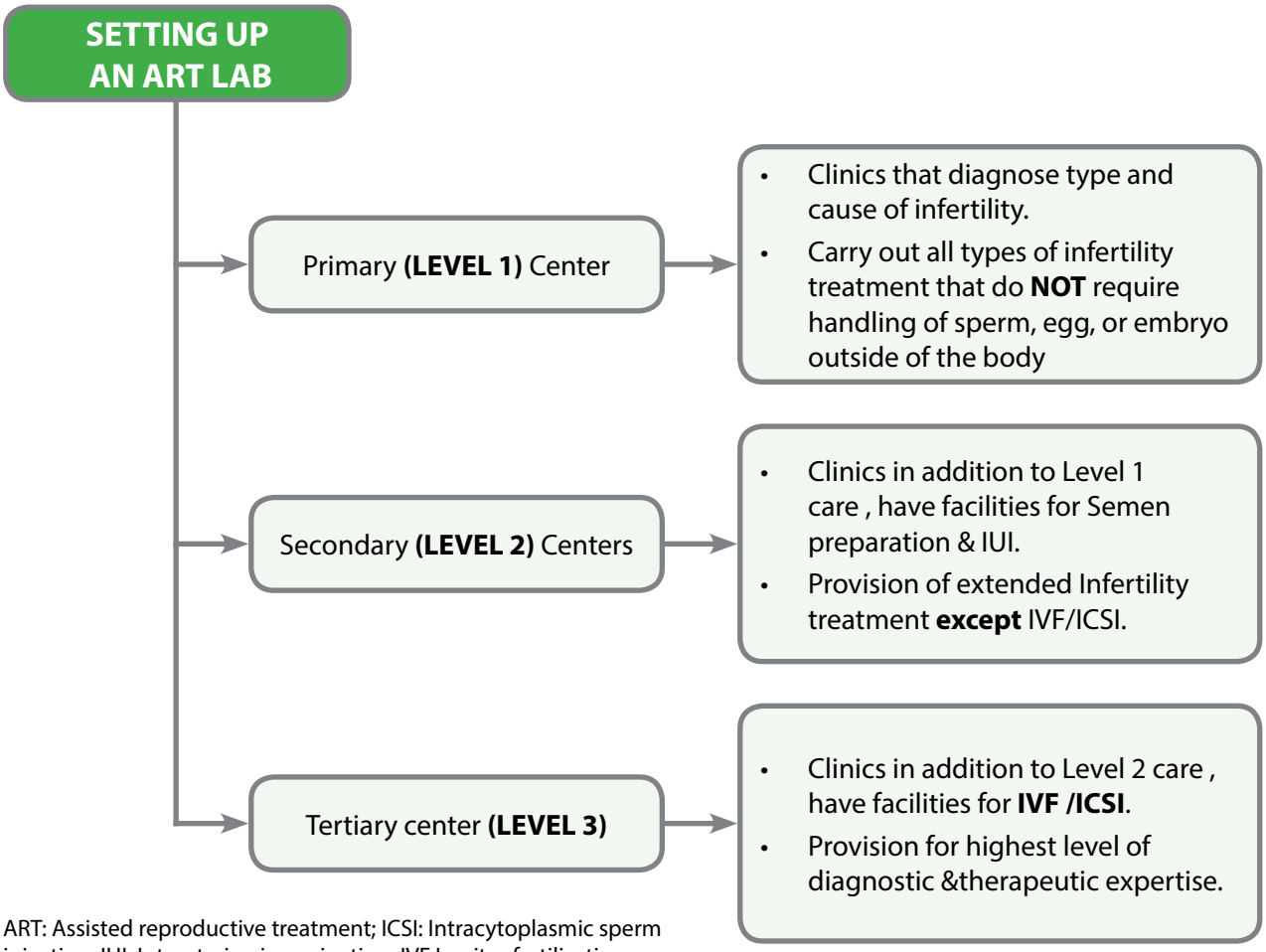
Introduction

Designing and equipping an IVF lab is very daunting process, as numerous factors have to be considered to ensure optimal working conditions.[1]

There are a number of ways to set up and operate a successful assisted reproduction technology (ART) laboratory; one set-up may have little in common with another but prove to be equally successful.[2]

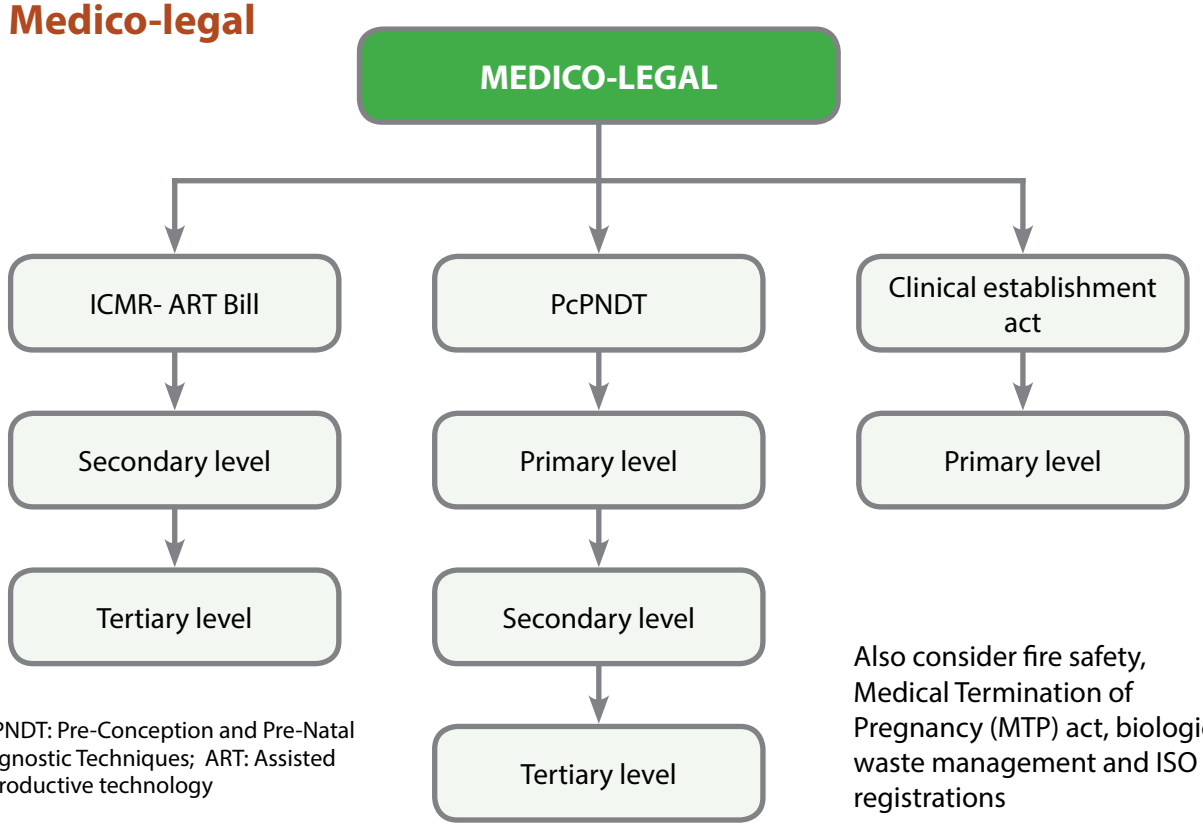


The Indian Council for Medical Research (ICMR) guidelines[3]



ART: Assisted reproductive treatment; ICSI: Intracytoplasmic sperm injection; IUI: Intrauterine insemination; IVF:In-vitro fertilization.

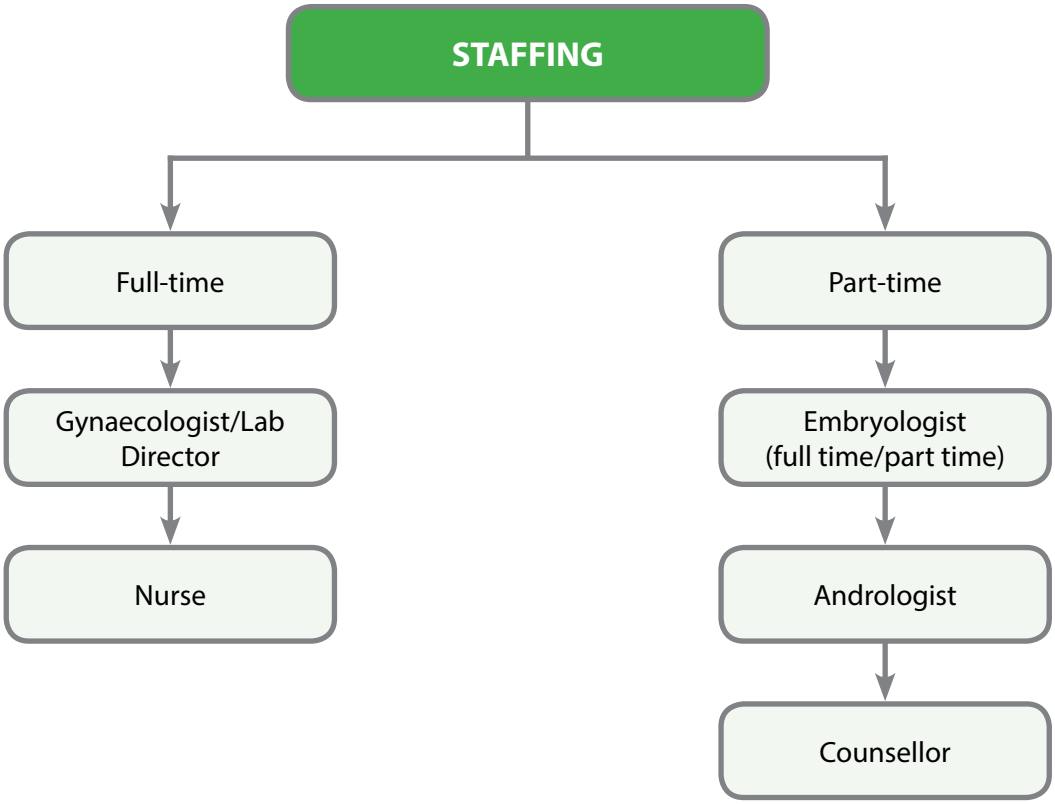
1. Medico-legal



PCPNDT: Pre-Conception and Pre-Natal Diagnostic Techniques; ART: Assisted reproductive technology

Also consider fire safety, Medical Termination of Pregnancy (MTP) act, biological waste management and ISO registrations

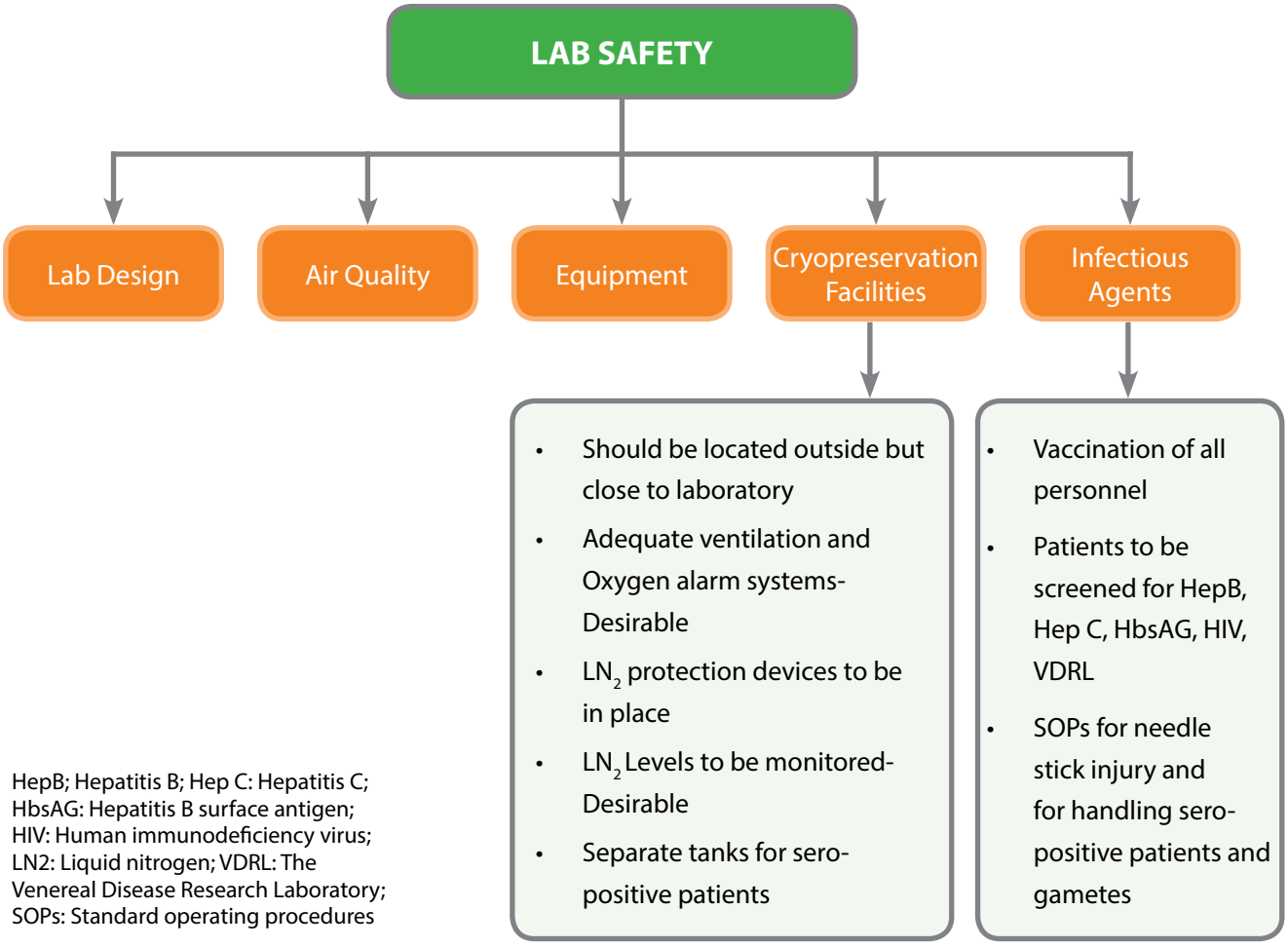
2. Staffing[4]



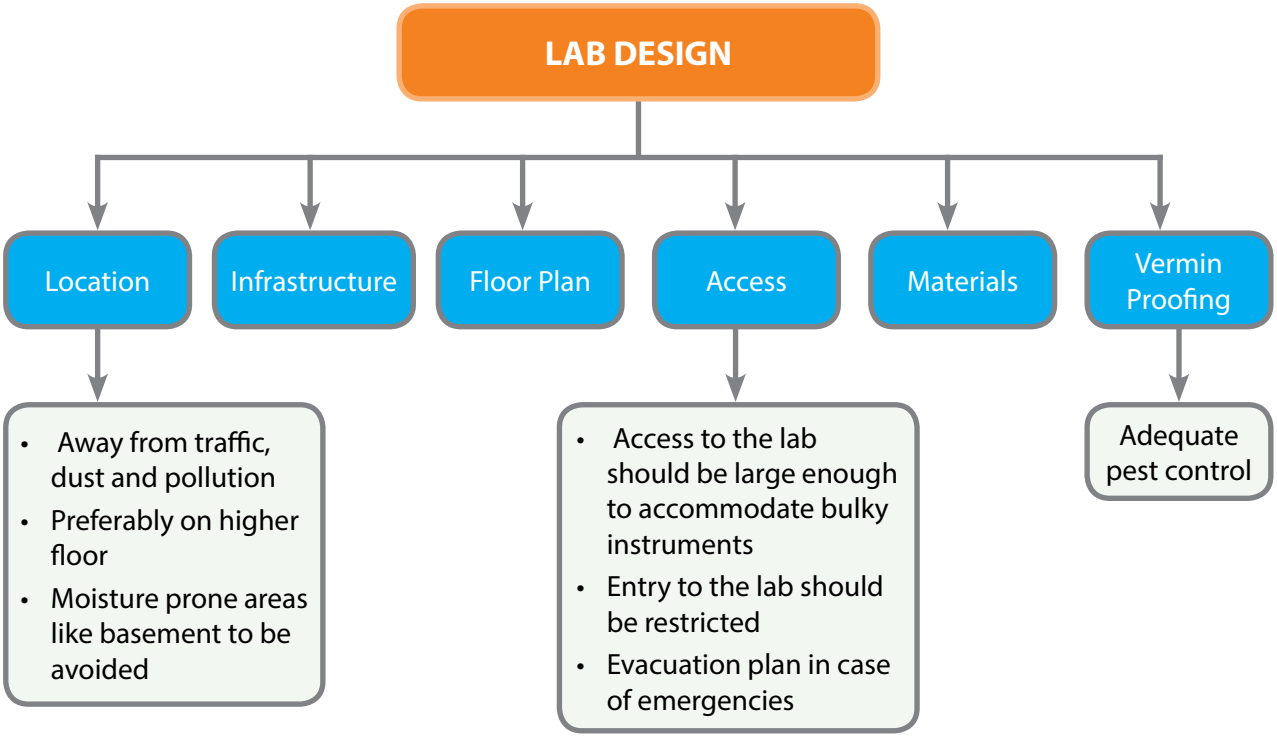
3. Quality management[4]

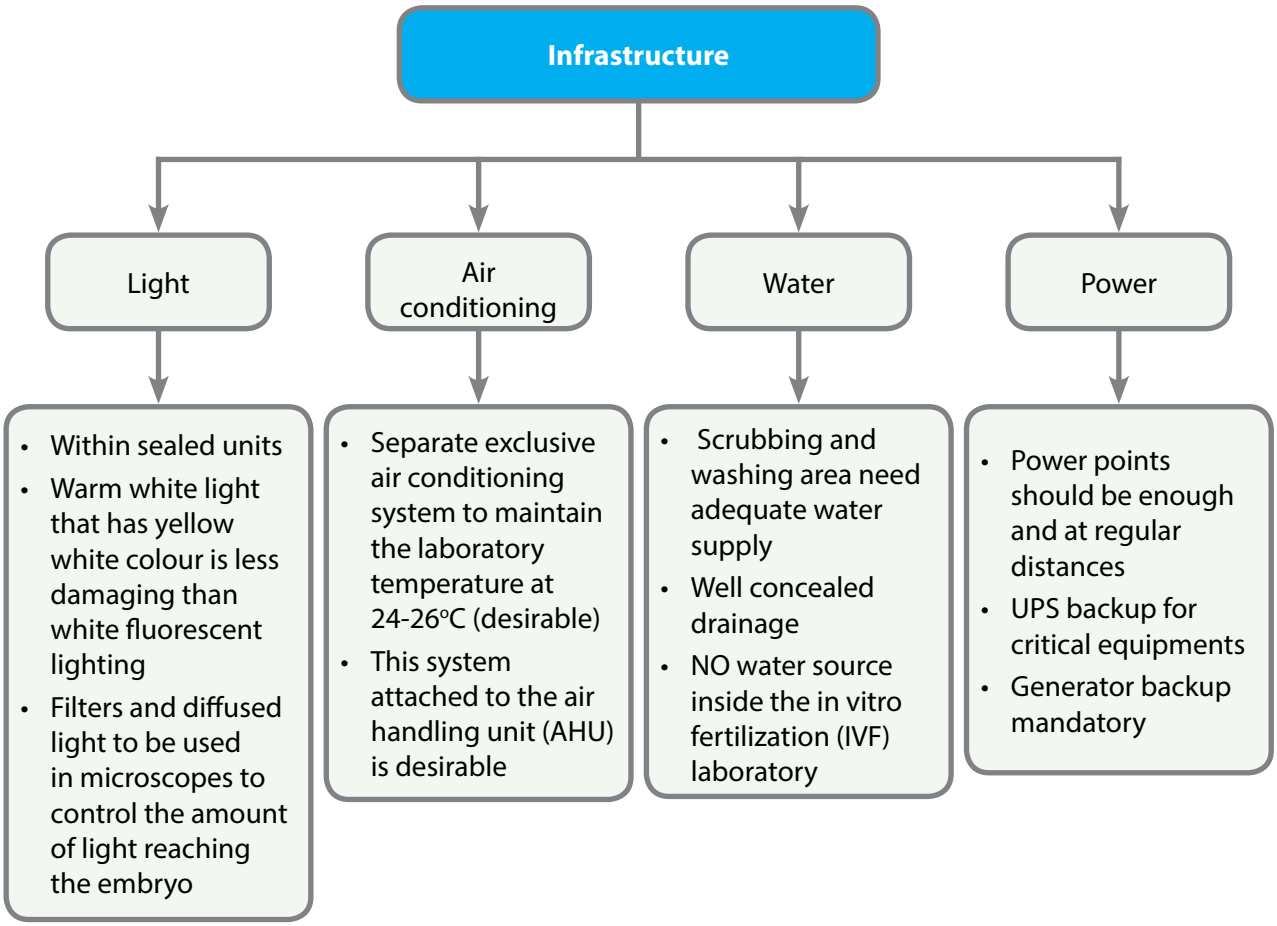
SOPs: Standard operating procedures; AMC: Annual maintenance contract; KPI: Key performance indicator.

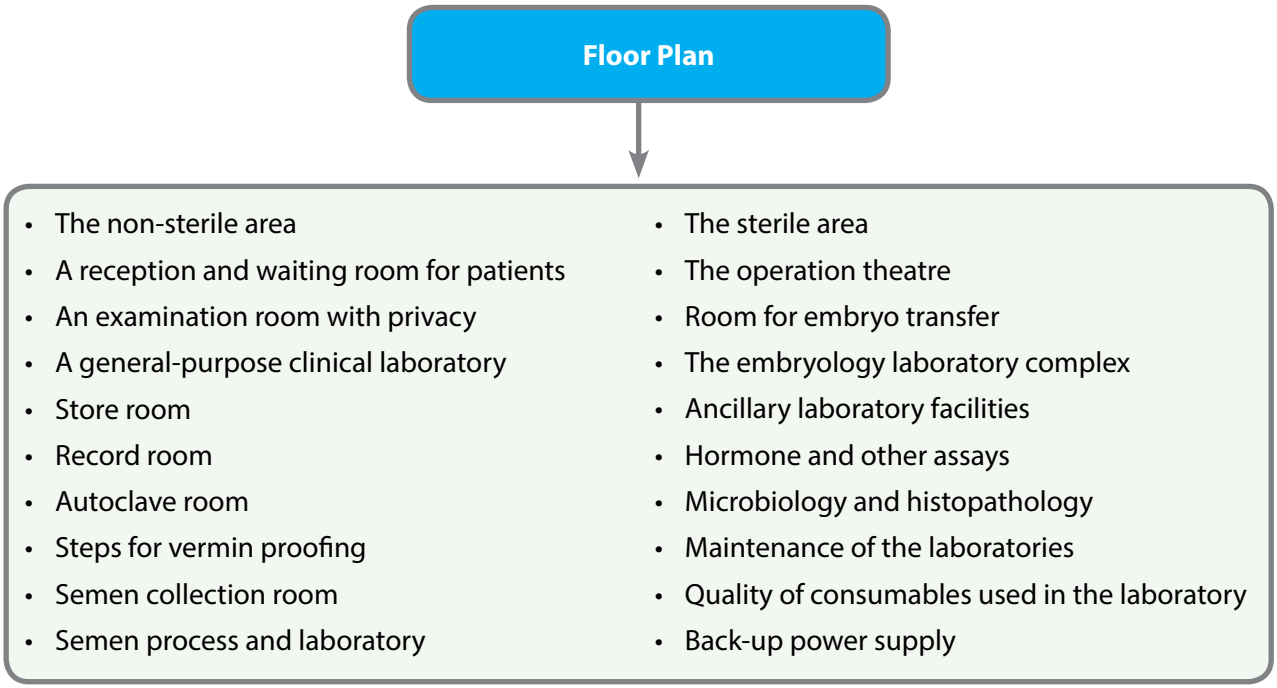
4. Lab safety[4]



HepB; Hepatitis B; Hep C: Hepatitis C; HbsAG: Hepatitis B surface antigen; HIV: Human immunodeficiency virus; LN2: Liquid nitrogen; VDRL: The Venereal Disease Research Laboratory; SOPs: Standard operating procedures







- Minimum area not defined in the ICMR guidelines as of now.
- In hospitals some of the facilities can be shared with IVF department (Record room/Autoclave room),

Materials[4]

Low or no volatile organic compounds (VOCs)

- Flooring/adhesives - sheet vinyl with welded seems, low-VOC adhesive
- Insulation - avoid around perimeter of laboratory; formaldehyde free product or mineral wool if required
- Paint - no-VOC latex paint product for all laboratory spaces
- Cabinetry - powder-coated/painted-metal cabinetry, no particle board or laminate
- Countertops - Low-VOC hard material without adhesives
- Furniture - medical- or laboratory-grade furniture with vinyl covering and low VOC materials
- Avoid use of printers, corkboards, xylene markers inside the laboratory space
- Copper piping for gas lines with brazed connection; stainless steel piping also appropriate
- High-density polyethylene fibers wrap around lab perimeter behind drywall to help maintain positive pressure

- Insulation: Insulation is often used in construction. However, chemicals such as formaldehyde are often present. Presence of insulation on the direct periphery of the IVF laboratory should be avoided if possible. If unable to avoid due to the presence of an outside wall, use of formaldehyde -free product is recommended. Alternatives for sound dampening include mineral wool.
- Flooring: Welded instead of glued seems of sheet vinyl flooring are recommended for sanitary reasons as well as minimal VOC release. Prior to clinical use, floors need to be cleaned with appropriate cleaners, such as hydrogen peroxide, along with simple regular sweeping, vacuuming or steam mopping. Avoid the use of any potentially harmful cleaners or waxes inside the laboratory.
- Paints: Latex-based no-VOC paints should be used on all painted surfaces.
- Cabinetry: Powder-coated metal cabinetry or stainless steel is suggested to avoid concerns with laminate and particle board, which would likely contain adhesives with high levels of VOCs.
- eFurniture: Purchase all medical- or laboratory-grade chairs with vinyl-coated seating surfaces that are easily cleaned of any contamination. Tables and countertop should be made of either epoxy resin material, solid stone and plastic mix, stainless steel or some other hard material devoid of adhesives (laminate).
- Cleaners: Alcohol is discouraged due to VOCs. 3% Hydrogen peroxide -based cleaning solutions are recommended.

AIR QUALITY

- VOC count of less than 0.5 ppm is required. 0 is preferable but 0.2 is ideal
- Positive pressure to be maintained (DESIRABLE)
- High efficiency particulate air (HEPA) filters and CODA filter.
- Air handling unit (AHU) is DESIRABLE.

Devices to ensure good air quality is MANDATORY.

EQUIPMENTS

MINIMUM EQUIPMENT REQUIRED

- Ultrasound machine
- Ovum aspiration pump
- Laminar flow
- CO_2 incubator
- Heated stage
- Centrifuge
- Microscopes
- Sperm counting chamber
- Micromanipulator (if ICSI is done.)

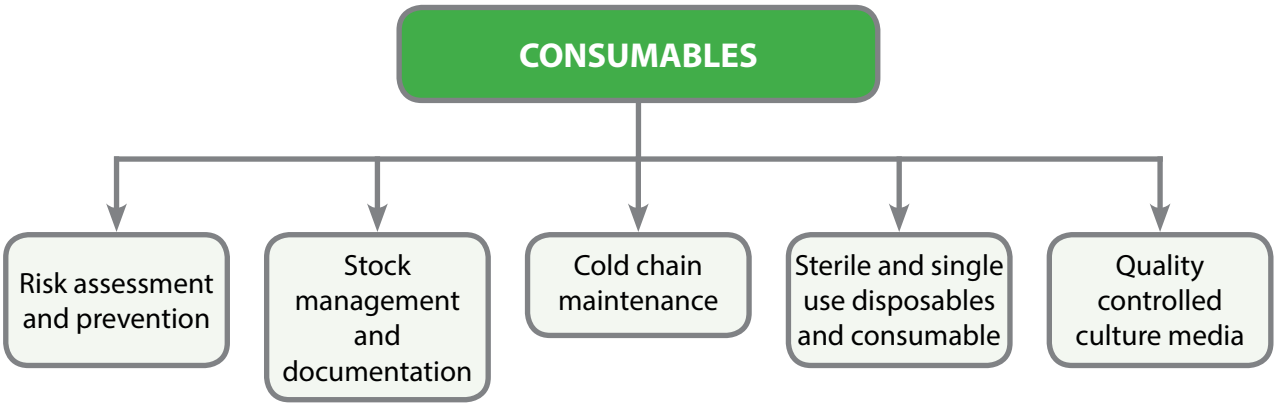
Equipment Number based on number of cycles

Equipment Validation, calibration and AMC to be mandatory and be documented

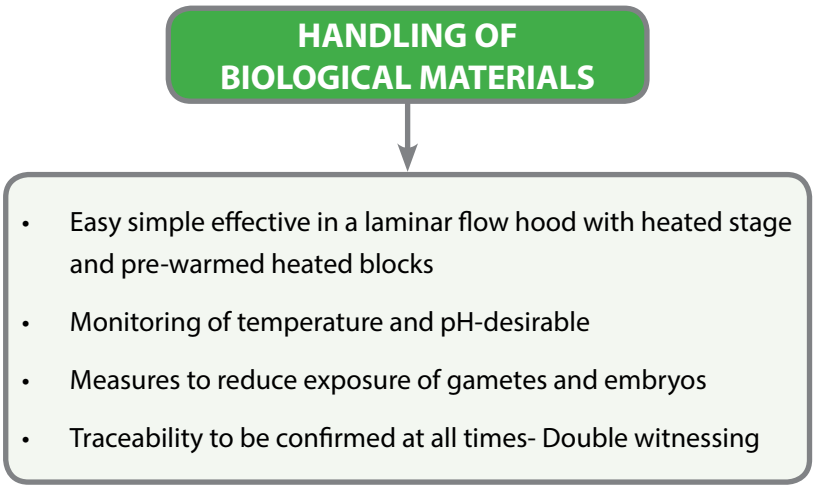
Equipment SOPs and Instruction Manuals to be in place

SOPs: Standard operating procedures; AMC: Annual maintenance contract; ICSI: Intracytoplasmic sperm injection

5. Consumables



6. Handling of biological materials



7. Safety and security

8. Desirable strategies

Risk	Mitigation strategy
Loss of power	Generator/UPS
CO_2/Special gas mix failure	Automatic gas changeover manifold; Regulators
liquid nitrogen (LN_2) storage tank emptying	LN_2 Level alarms; regular measuring/top up of tanks; replacement at end of life span; safety training
Staff member injured	Low O_2 level & high CO_2 alarms; Personal Protective Equipment; fire alarms/extinguishers
Break in to laboratory	Security monitoring; Security response; Locks on LN_2 tanks
Equipment failure	Back to base alarm system; spare equipment; service/ maintenance contracts; arrangements with competitors
IT virus/hacking–loss of data	Regular backups (stored offsite); antivirus software

Conclusion

Setting up an ART laboratory is a challenging task that involves numerous factors for the optimal working condition. The main initial aspects to look into involves medico-legal, staffing, quality management, lab safety, identification and traceability, consumables, and handling biological material.

The ICMR guidelines have given a clear recommendation on setting up an ART laboratory at all three levels. Along with all medico-legal requirements we recommend fire safety, MTP act, management of biological waste, and ISO registration. Staffing should be optimal with both full-time and part-time. The full-time gynaecologist or a lab director and nurse is a must and a part-time embryologist, andrologist and a counselor will be required. For quality management jobs and roles of all individuals should be defined, SOP will be required for all procedures along with full traceability, audits, reviews, risk assessment, and analysis are some of the requirement for quality management. The safety of a laboratory should start at its design levels itself (location, infrastructure, access, material, and vermin proofing), and extend to air quality, equipment, and cryopreservation facilities. All laboratory personals should be vaccinated and patients should be screened for infectious diseases. For air quality devices to ensure good air quality is a must. Handling biological material should be easy simple and effective, temperature and pH should be desirable. Traceability confirmed at all times with double witnessing.

References

1. Lagunov A, Crowe M, Swain JE. Edited by Montag MHM, Morbeck DE. Chapter 1 - Establishing and equipping a new IVF Laboratory from Section 1 - Starting a New Laboratory and Training Protocols. pp 1-7. Cambridge University Press. doi.org/10.1017/9781316569238.003
2. Gardner DK, Weissman A, Howles CM, Shoham Z. (2017) Textbook of Assisted Reproductive Techniques. Cohen J, Alikani M, Gilligan A, Schimmel T. Chapter 1. New guidelines for setting up an assisted reproduction technology laboratory. CRC Press. Pages 9.
3. Indian Council of Medical Research New Delhi. The Assisted Reproductive Technologies (Regulation) Rules. 2010. Ministry of Health & Family Welfare Govt. of India, New Delhi.
4. ESHRE Guideline Group on good practice in IVF labs. Revised guidelines for good practice in IVF laboratories (2015).https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Revised-guidelines-for-good-practice-in-IVF-laboratories-(2015)

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† Schindler AE. Progestational effects of dydrogesterone in *vitro, in vivo* and on the human endometrium. *Maturitas.* 2009;65(1):S3-S11. # Data on file. ^ Novel - Estradiol hemihydrate first time in India. + Safer - As compared to conjugated equine estrogens. Smith NL *et al* Lower risk of cardiovascular events in postmenopausal women taking oral estradiol compared with oral conjugated equine estrogens. *JAMA Intern MED.* 2014; 174(1):25-31.

Further information available on request: Abbott India Limited, Floor 16, Godrej BKC, Near MCA Club, BKC, Bandra (East), Mumbai 400051. www.abbott.co.in

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