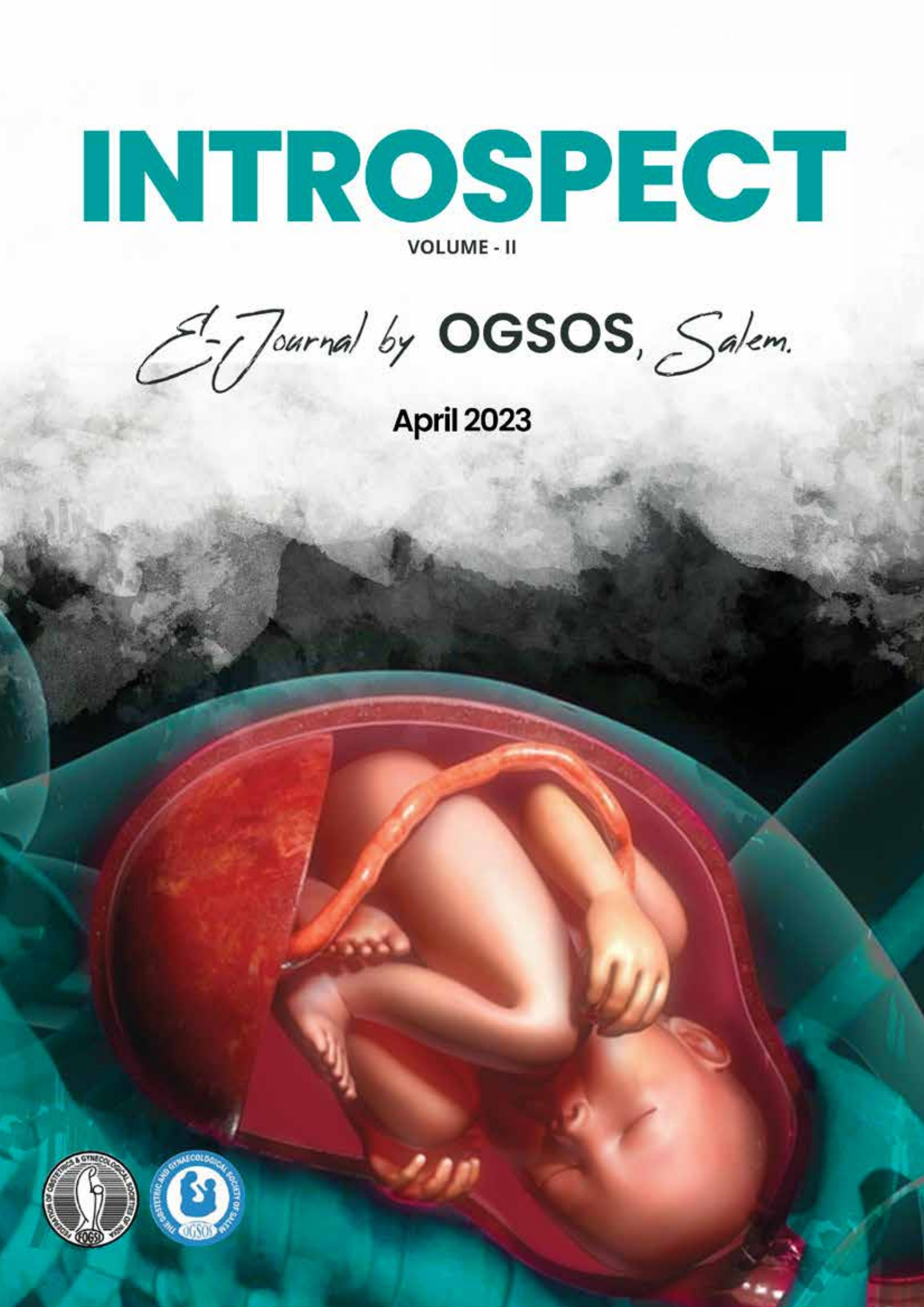
# INTROSPECT

VOLUME - II

E-Journal by OGSOS, Salem.

April 2023



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## EDITOR'S NOTE

We are pleased to proudly present to you "INTROSPECT" – Official online journal from Obstetric and Gynaecological Society of Salem (OGSOS), commenced in order to acknowledge and recognize the work done by our very own members.The online media has become a vital component for the dissemination of knowledge and an imperative vehicle for wide access.

With this in mind, the first edition of our E-Journal has been curated meticulously. Our OGSOS has always turned heads, be it academics, conferences, skills, culturals, etc. This is our next step, where our vision has taken shape and this endeavor marks a major milestone in taking our society to greater heights.The objective of this journal is to promote research, share ideas, help in day to day clinical practice and promote a spirit of oneness among us. This would provide an exciting opportunity to showcase our work and share our skills. The journal aspires to be vibrant, engaging and accessible, and at the same time integrative and challenging. It will continue to evolve with fresh ideas and guidance at each step,encouraging debates and discussions.

We hope that this journal will offer ample opportunity to our members to learn about and reflect upon the practices and possibilities and help in their achievements and challenges at work.We are privileged to have the expertise and enthusiasm of our authors and believe that every member will play a pivotal role in leading the journal through the exciting phase of its development. Finally we remain very grateful to our President, Vice President, Secretary and Patrons for constant encouragement and guidance. Let us all join together in solidarity and introspect our ideas, thoughts and practices,with the aim of better practices and better outcomes, following the footsteps of our seniors and setting examples for those next in line.

**HAPPY LEARNING!**

**DR. KAVITHA NAGARAJAN,**
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**DR. ANUREKHA J P,**
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**DR. MADHUMITHA ARUNKARTHIK**
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## PRESIDENT'S NOTE

Greetings from the desk of the President of OGSOS! It is indeed a proud moment to be in this chair amidst our highly talented and esteemed members!

CHANGE is the only CONSTANT thing in this world. Likewise, Medical practice is something that keeps changing with newer inventions, interventions and evidence based modalities. So, it is inevitable for us to keep up with the trend, update our knowledge and enhance our clinical skills especially in this era, where patients are Google doctors with first hand information. We try hard to update ourselves by attending conferences, CMEs, reference articles and juggle between busy practice and family needs.

With our team of Editors, it is our maiden effort to bring out an E-journal every 4 months authored by our very own members. Our aim is to provide evidence based protocols, interventions and practical points needed for our day to day practice. My vision is to bring near uniform practice amongst us which is evidence based, for the benefit of our women to get standard treatment. Evidence based practice and following guidelines protect us legally too.

We have tried to cover all subspecialities with the experts in each. Hope our efforts help you in your practice. We are open to any suggestions to improve our quality and content of the journal.

I thank my team of council members who share responsibility and for their sincere efforts in all our proceedings. My heartfelt gratitude to all the enthusiastic authors for their contribution to the first edition of our journal!

My sincere thanks to my team of editors for their enthusiasm and hardwork shown in bringing out this journal!

**Dr. G. JAYAMALA,**
DOWH (IRE), MRCOG (UK), MRCPI (OG)., DRM.,
CONSULTANT, RAINBOW HOSPITAL

## SECRETARY'S NOTE

Greetings and welcome to the first E-Journal of Obstetric and Gynaecological Society of Salem. I am honored to be the Secretary of our OGSOS family and I take this opportunity to thank our society members for their love and confidence on me and look forward to our continued teamwork to achieve greater excellence.

It's our proud moment in releasing the very first E-Journal of OGSOS and the credits are deeply shared by all the members of our OGSOS family. I am deeply obliged to Dr.G.Jayamala, the President of OGSOS who was the brain behind this baby.

My special thanks to the Journal committee members who played tremendous role in this beautiful compilation. In the months to come let us all join hands in making this E-Journal grow with impact factor and achieve its position among the indexed journals. For this, I kindly encourage all the OGSOS society members to actively contribute with original articles.

The culmination of our efforts in bringing out this first E-Journal shall lay the fundamental foundation of our society in uplifting the academic wing and thereby benefitting our society members by constant updation and knowledge upgradation. I believe that continued stability is dependent on continued support of its members and therefore I would encourage all members to actively participate and contribute to the upcoming issues.

**LONG LIVE OGSOS!**

**Dr. L. SHANMUGAVADIVU,** MD., (OG)
ASSOCIATE PROFESSOR, DEPARTMENT OF OG,
GMKMCH

# CONTENTS

# TOTAL LAPAROSCOPIC HYTERECTOMY SHORTENING THE LONG LEARNING CURVE!

**Dr. GNANA SANKER NATESAN,**
MD, DNB, MRCOG

Laparoscopic surgery has several significant advantages over laparotomy, and has become a mainstay of gynaecological surgery during the past 30 years .

One of the surgeries, we want to and need to master is the total laparoscopic hysterectomy. You are called a master when you are both safe and fast and are able to effectively manage complexities with tact.

Regarding safety Most large studies report a major complication rate to be less than 0.5% provided the surgeons are proficient.

Regarding speed, every surgeon follows a learning curve, which refers to the relationship between operating time and patient outcomes, including surgical complications.

This small write up of seven suggestions is to help interested gyn surgeons to get proficient and shorten the learning curve with Total laparoscopic Hysterectomy.

## SUGGESTION 1 -

Breakdown TLH into 7 seven steps and standardise the technique

After an intraperitoneal access and port placement of your choice, our first mental job is to assess the pelvis and make a surgical strategy.

Now we get additional requirements if needed (e.g., blood / staplers/ stents/ surgical support) and inform anaesthetist of our expected process and time.

Now is the time for the seven surgical steps.

1. Upper pedicle management (Round & Ovarian / Infundibulopelvic ligaments)
2. Taking down Bladder /Rectum
3. Sealing and dividing Uterine vessels
4. Cardinal Uterosacral complex division
5. Colpotomy

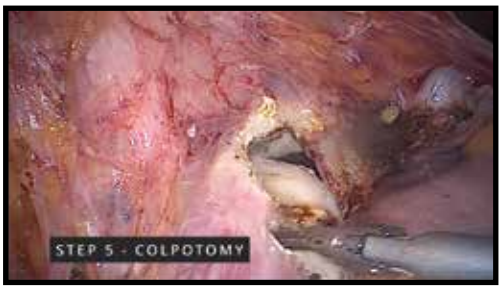
6. Specimen retrieval
7. Vault closure (Vaginal / Endo suturing)

Complete your conquest One at a time progressively. Being a free gyn surgeon in a high-volume centre with supportive team helps here.

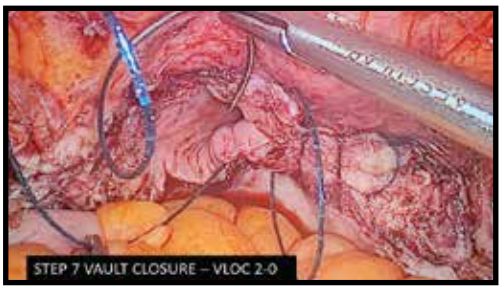
I can still remember that I did only the first step in my first two cases, then steps 1 & 2 for the next few cases before reaching out to step 3 with confidence for a lot of subsequent ones to come. (The rest portion of hysterectomy I would complete vaginally from below)









## SUGGESTION 2

Invest in high-resolution vision and advanced power sources.

Rapid technological innovations have allowed conventional laparoscopy to be safe and fast and also easy on the surgeons.

We all know how much a good vision helps us drive safe against all the dangers on the road. Similarly having a good High-Definition camera is must for anyone who wants to embark on an advanced laparoscopy journey. You have clear visibility, identify the vital structures better, protected from complications and in the process enjoy the whole operating process.

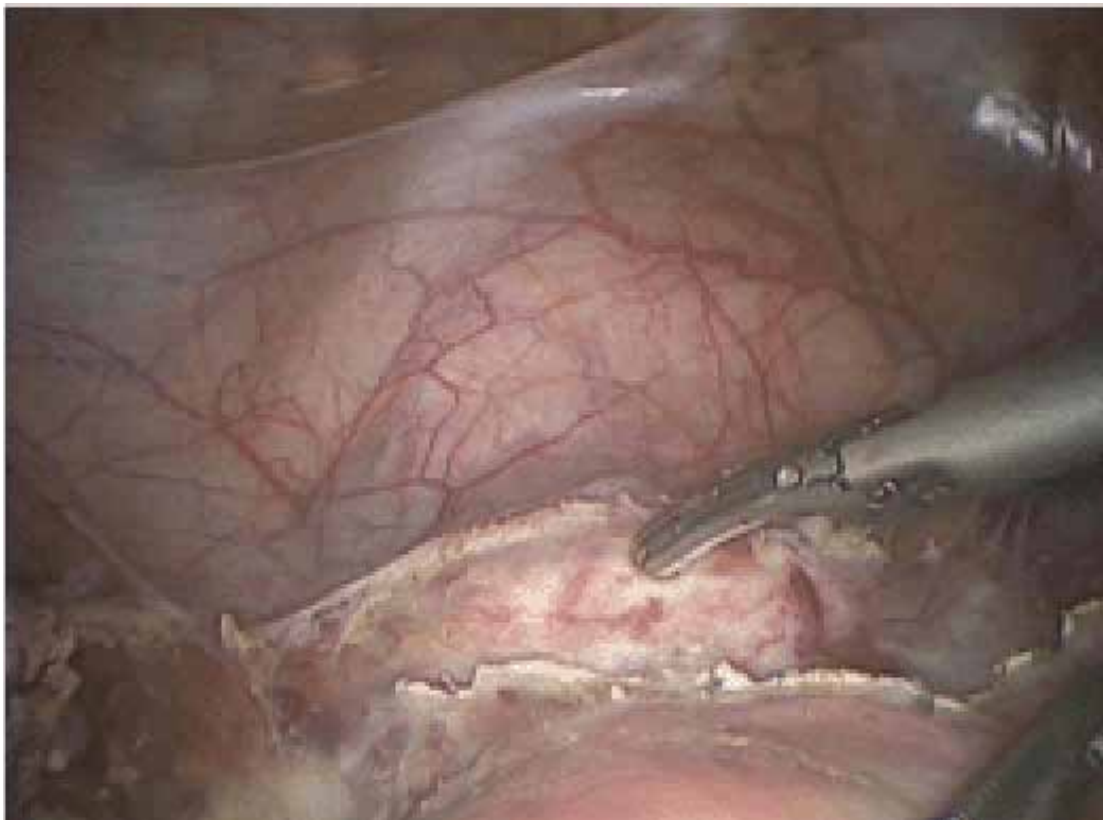
Although we can still confidently complete a TLH with a humble bipolar and a simple scissor ( we actually completed many of our initial TLH cases with this combo), We suggest beginners to invest in an Ultrasonic energy if you want to master TLH . We specifically need them while addressing (Step 2, and esp. 4 &5) the cardinal uterosacral ligaments and while making colpotomy, because here lateral spread could be detrimental to ureters which are running close. Also, the newer Ultrasonic units come with integrated advanced bipolar so that the vascular pedicles (step 1 & 3) i.e., the cornual structures or the infundibulopelvic and the uterine vessels can be addressed safely. Basically, this would be the only other instrument you will be needing inside the abdomen apart from a good grasper.

Harmonic HD 1000i

## SUGGESTION 3

Using manipulators.

Personally, we prefer using a myoma spiral for its versatility especially with large uteri. But for beginners I would recommend to try the RUMI® II Uterine Manipulator (Cooper-Surgicals) . This could ease the colpotomy phase Step 5 safe and easier.

Colpotomy delineator is visible between uterus corpus & bladder

## SUGGESTION 4

Choose simple cases to begin with.

Every successful completion of a procedure boosts your confidence, and converting to open can dent the same confidence. Hence early in your career choose cases that are not very challenging for a TLH. A mobile uterus in a parous woman around 6 - 8 weeks in size without previous surgeries is a good one to begin with. and at any point of challenge one can still finish the case by a vaginal route and maintain the confidence tempo. As days proceed choose cases with one challenge added at a time.

## SUGGESTION 5

Flight hours for pilots - On road hours for drivers – Lap hours for Gyn lap surgeons

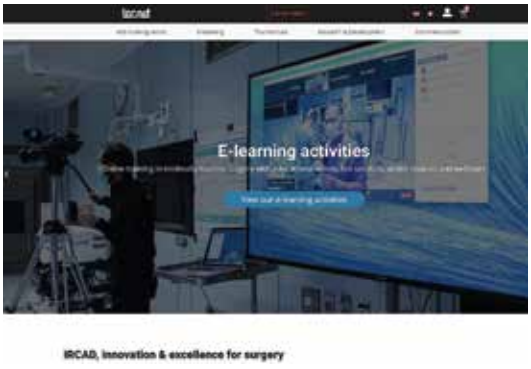
Success is the child of audacity. – Benjamin Disraeli

The longer we spend time training ourselves in a particular skill, decides the mastery we gain over the same. Hence utilise every opportunity to be inside the pelvis with a scope (for the right reason but) and practice, practice and practice. Try it out with an Endo trainer, on authorised live animal models and finally your patients. Studies conclude that around 75 cases are needed to get proficient with TLH and before the learning curve gets flat

## SUGGESTION 6

Internet a great asset. Observe many, try and adopt what is suitable for you.

Gone are the days when we had to register and run to watch top surgeons operate in live workshops at distant metros. Now we can readily watch them and many other experts in a web platform for free at your place and at your pace. Apart from these almost all endoscopic societies have good video libraries to learn from. We suggest you watch many and adopt the techniques that suits your settings and your personal physical stature and features.




## SUGGESTION 7

Find a good Mentor or at least a good likeminded colleague

Tell me and I forget. Teach me and I remember. Involve me and I learn. -Benjamin Franklin

Find a good mentor or at least a friendly motivated colleague to work with while you operate. Honour your mentor or colleague for the time and effort they spend for you.

You can even send your recorded videos for review with them and take open feedback. Willingness to be corrected and a keen interest to learn will take anyone in any field to heights all the more in the surgical arena.

# CERVICAL CANCER PREVENTION AND SCREENING

**Dr. R. KALAISELVI,**
MBBS, DGO

Cervical cancer is most common cancer in Indian women though breast is the leading cancer site globally. In India, cervical cancer accounted for 9.4% of all cancers and 18.3% of new cases in. Over 80% of the cervical cancer present at a fairly advanced stage and annually around 80,000 deaths are reported in India.

According to global cancer statistics, cervical cancer is now the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide. More than 85% of these cases occur in developing countries. India, the second most populous country in the world, accounts for 27% (77,100) of the total cervical cancer deaths. The disproportionately high burden of cervical cancer in developing countries and elsewhere in medically underserved populations is largely due to a lack of screening that allows detection of precancerous and early stage cervical cancer.

It is now well recognized that cervical carcinogenesis occur in a stepwise fashion. This transition of normal epithelium to pre-neoplastic lesions and invasive carcinoma occur sequentially and progress through well recognized stages and takes approximately 10–20 years to develop an overt malignancy. The natural history of the disease suggests that screening should initially target those women who have higher prevalence of high grade precancerous lesions (CIN2/CIN3) – women mostly in their 30s and 40s. In India, the incidence of cervical cancer significantly rises around the age of 45 years and peaks at 55 years of age.

HPV is the most common viral infection affecting the reproductive system & responsible for over 95% of cervical cancer cases. To date, more than 140 human and animal Papilloma virus genotypes have been characterized and sequenced. Approximately 30 HPVs that infect the ano–genital tract, of these 15 HPV types classified as 'high-risk' types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) are associated with high grade cervical cancer precursor lesions and invasive cervical cancers.

Molecular and clinico-epidemiological studies have demonstrated that HPV types 16 and 18 are the two most common oncogenic and 11 different HPV types

classified as 'low-risk' types (6, 11, 40, 42, 43, 44, 54, 61, 70, 81 and CP6108) are mainly associated with genital warts and benign cervical lesions.

In addition to HPV infection, co-factors such as parity, early age of marriage, genital hygiene, promiscuity, use of oral contraceptives, smoking, immune suppression (eg HIV), infection with other sexually transmitted agents and poor nutrition have been associated with the development of cervical cancer.

Prevention

Cervical cancer can be avoided through primary and secondary prevention measures

The primary prevention is by HPV vaccination

The most effective secondary preventive strategy is systematic screening of women through an organized program along with treatment and follow-up of the screen detected precursor lesions.

Cervical screening should be advocated for all ever sexually active women within a certain age group irrespective of whether they have any complaints, because there are often no signs and symptoms of cervical precancers.

The available screening tests are

VIA(visual inspection with acetic acid)

Pap smear (conventional, liquid based cytology)

Primary HPV testing

Cotesting (HPV testing & cytology)

The national guideline for cervical cancer screening in India advocates screening of women between 30 years to 59 years of age.

Women in the general population should start cervical cancer screenings at age 30 and have regular tests (every 5–10 years) using reliable HPV results. Women living with HIV should start at age 25.

## THE BETHESDA SYSTEM FOR REPORTING CYTOLOGY

NILM -Negative for Intra-epithelial Lesion or Malignancy

ASCUS- Atypical Squamous Cells of Undetermined Significance

ASC-H- Atypical Squamous Cells: cannot exclude HSIL

LSIL- Low-grade Squamous Intra-epithelial Lesion

HSIL- High grade Squamous Intra-epithelial Lesion

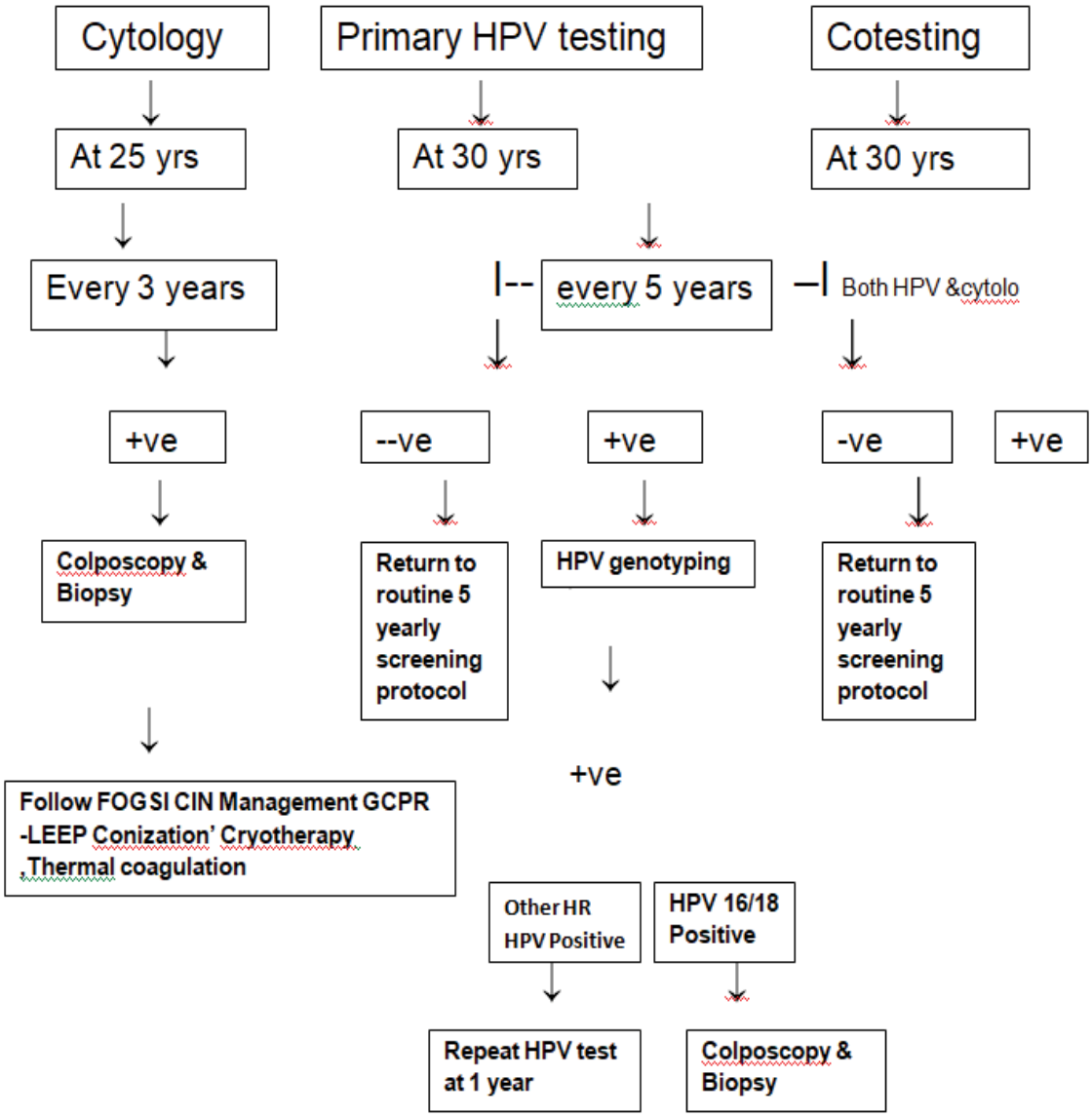
SCC Squamous Cell Carcinoma

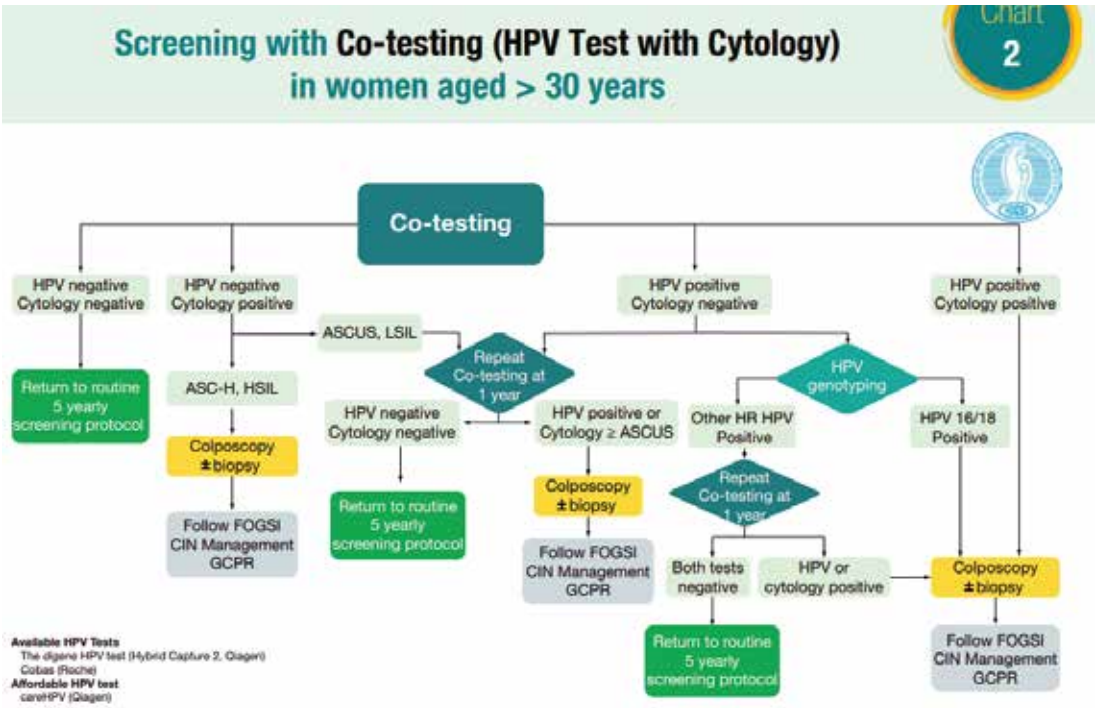
FOGSI India recommends based on resource setting

**Low resource setting**

VIA -- start at 30 years, every 5 yrs, at least 1-3times in life time.

**High resource setting**






## THE USPSTF 2022, RECOMMENDED SCREENING

Women aged 21 - 29 yrs - Pap test alone every 3 years

Women aged 30 – 65 yrs should have either

- Pap test alone every 3 years
- HPV test every 5 years
- HPV/Pap cotest every 5 years

Women should stop having cervical cancer screening after age 65 if

- they do not have a history of moderate or severe abnormal cervical cells or cervical cancer, and
- they have had either three negative Pap test results in a row, two negative HPV tests in a row, or two negative co-test results in a row within the past 10 years. The most recent test should have been performed within the past 3 or 5 years, depending on the type of test.

Women who have had a hysterectomy may still need to have screening if they had an abnormal cervical cells.

## MEASURES TO PREVENT CERVICAL CANCER INCLUDE:

- Delaying first sexual intercourse until the late teens or older
- Limiting the number of sexual partners
- Practicing safer sex by using condoms and dental dams

- Avoiding sexual intercourse with people who have had many partners
- Avoiding sexual intercourse with people who are infected with genital warts or who show other symptoms
- Quitting smoking

## HPV VACCINATION

Three types of HPV vaccines available

1. Bivalent HPV vaccine (Cervarix, 2vHP)
2. Quadrivalent HPV vaccine (Gardasil, 4vHPV),
3. 9-valent HPV vaccine (Gardasil 9, 9vHPV),

All three HPV vaccines protect against HPV types 16 and 18 that cause most HPV cancers.

## FOGSI RECOMMENDS

Two or three doses at 0&6 months ,or 0,1,6 months interval (bivalent) and 0,2,6 months for Quadrivalent for aged 9-26 years

Women >26 should be counseled regarding reduced efficacy and importance of screening

HIV positive or immune compromised girls also should receive three doses

In interrupted doses ,continue with the remaining dose, need not restart the schedule

Not recommended during pregnancy

## WHO NOW RECOMMENDS:

- A one or two-dose schedule for girls aged 9-14 years
- A one or two-dose schedule for girls and women aged 15-20 years
- Two doses with a 6-month interval for women older than 21 years

Vaccination is not recommended for everyone older than age 26 years.

For adults ages 27 through 45 years, clinicians can consider discussing HPV vaccination with people who are most likely to benefit.

Gardasil 9 protects against 9 types of HPV: 6, 11, 16, 18, 31, 33, 45, 52 and 58

The protection against HPV 16 and 18 has lasted at least eight years after vaccination for Gardasil and more than nine years for Cervarix.

- 9-valent HPV vaccine is produced in Saccharomyces cerevisiae (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast.
- No serious adverse events have been associated with any HPV vaccine.
- The most common adverse reactions reported during clinical trials of HPV vaccines were local reactions at the site of injection

The elimination programme by WHO aims to achieve the following targets by 2030:

90% girls fully vaccinated by 15 years of age with two doses of HPV vaccine;

70% women screened with a high-performance test at 35 and 45 years of age; and,

90% of women with cervical pre-cancer and cancer receive treatment to achieve a goal of less than four cases per 100,000 women.



# INTROSPECT E-JOURNAL RELEASE

January 2023

## HERE ARE A FEW MEDICAL RIDDLES FOR YOU:

1. I am not alive, but I grow. I don't have lungs, but I need air. I don't have a mouth, but water kills me. What am I?

2. What has a heart that doesn't beat?

3. What goes up but never comes down?

4. What is always in front of you but can't be seen?

5. I am taken from a mine and shut up in a wooden case, from which I am never released, and yet I am used by almost every person. What am I?

6. What starts with an E, ends with an E, but only contains one letter?

7. What has four legs in the morning, two legs in the afternoon, and three legs in the evening?

**HOPE YOU ENJOY THESE RIDDLES!**

### ANSWERS

1.Fire

2. An artichoke

3. Age

4. The future

5. Pencil lead

6. An envelope

7. A human - crawling on all fours as a baby, walking on two legs as an adult, and using a cane in old age.

# INSTRUMENTAL DELIVERY: CURRENT SCENARIO

**Dr. SENTHIL PRIYA,**
MD,DNB.

## OVERVIEW: INSTRUMENTAL DELIVERY

An instrumental delivery is a major intervention similar to other surgical procedures. Both an appropriate indication and the consent of the mother are mandatory prerequisites. The basic requirements for the operation include careful choice of cases, adequate operator training and experience, acceptable anesthesia, meticulous technique, and the willingness to abandon the attempt if it does not proceed easily

## INDICATIONS FOR INTERVENTION

The indications for operative vaginal delivery are either fetal or maternal. These indications include a prolonged second stage of labor, shortening of the second stage for maternal benefit, and suspicion of immediate or potential fetal compromise.

- PROLONGED SECOND STAGE
- SHORTENING OF SECOND STAGE
- SUSPICION OF FETAL COMPROMISE

## EQUIPMENT

- Classic outlet forceps
- Modified classic forceps
- Axis-traction forceps
- Specialized forceps
- Vacuum extractors — rigid cup
- Vacuum extractors — soft cup

## CLINICAL ISSUES

The first step in evaluating an assisted delivery is an abdominal examination. A Hills Muller maneuver can be performed by applying fundal pressure during a contraction, noting the descent of the presenting part. In addition, during pelvic examination fetopelvic degree of cranial molding is estimated by the overlap of the bones of the fetal skull at the occipitoparietal and parietal-parietal junctions

## PREREQUISITES FOR INSTRUMENTAL DELIVERY OPERATIONS

- Informed consent and an acceptable indication
- Application of vacuum extractor cup or forceps centered at the cranial pivot point
- Analgesia (as clinically required)
- Local infiltration with vocal reinforcement
- Pudendal nerve block
- Epidural anesthesia
- Operator certain of fetal station and position. Pelvic examination to establish the station, position, and deflection of the fetal head
- Empty maternal bladder (Recent voiding, or catheterization)
- Full cervical dilation
- Ruptured membranes
- Knowledge of fetal heart rate or pattern
- The decision to abandon the procedure unless it proceeds easily

## CONDUCTING AN INSTRUMENTAL DELIVERY:

The procedure begins with a ghosting or phantom application. The surgeon holds the chosen delivery instrument in front of the maternal pelvis and rotates it to the position that it will occupy when the correct cephalic application is made. The instrument is then introduced into the birth canal. Once the correct application has been made, traction is applied. The dorsal lithotomy position is most common for instrumental delivery but is not absolutely necessary, especially if a vacuum extraction operation is performed.

Prophylactic antibiotics may be considered. Traction is timed to contractions, with only a single sustained traction effort accompanied by maternal bearing-down efforts during each uterine contraction.

When the forceps are used, the force for delivery is provided by the operator's arm, with the elbow bent at a right angle. The other hand rests on the shank

of the blades and presses downward (Saxtorph-Pajot or Osiander maneuver) This maneuver creates a vector of force guiding the fetal head through the pelvic curve (curve of Carus). The forceps handles should not be rocked up and down during the delivery because the posterior toe of the blade can injure the posterior vaginal vault as the fetal head descends. The fetal heart should either be auscultated or checked, a hand-held Doppler device, before the operation begins, and between contractions/pulls. The blades are relaxed and disarticulated between contractions at the operator's discretion.

For vacuum extraction, once a correct cup application is established, full suction and traction immediately follow. For rigid-cup instruments, either metal or plastic, the classic technique was to increase the vacuum by 0.2 kg/cm² every 2 minutes once the cup was correctly applied until the full vacuum force was reached. An alternative approach is to apply full vacuum within 2 minutes of the cup application and without additional delay for chignon formation. Both techniques are acceptable. A two-handed technique for vacuum extraction is recommended. During the extraction, the surgeon places the non-dominant hand within the vagina, palpating the fetal scalp with one or more fingers while placing a thumb and remaining fingers on the extractor cup to gauge the relative position of the cup edge to the scalp. The bimanual technique reduces the risks from sudden cup displacement and is recommended for all vacuum extraction operations.

For both forceps operations and vacuum extractions, an episiotomy is electively performed as the posterior perineum bulges, but only if maternal soft tissue impedes the descent of the presenting part. As a general rule, vacuum cups should not be left applied to the scalp for longer than 20 to 30 minutes. Prolonged extraction time risks shoulder dystocia and an increased risk for fetal scalp injury. The level of risk for a scalp injury is probably lower with soft-cups than with the rigid-cup devices.

Regardless of the instrument chosen, descent must begin with either the first or at least by the second traction effort. Otherwise it requires immediate reassessment.

## APPLICATION

Proper application of both the forceps and the vacuum extractor is critical to safety and success. A correct forceps application (biparietal bimalar) evenly distributes the compressive force generated by the blades over the fetal head. The fit between the fetal head and the fenestration of the blades, the location of the posterior fontanelle, in reference to the plane of the shanks, and the position of the sagittal suture are the components of the classic "checks" for forceps. This is a cephalic application and distinct from a pelvic application. In the latter, the forceps are applied independently of knowledge of the exact position of the fetal head. The only currently acceptable pelvic application occurs when Piper or Kjelland forceps are applied to the aftercoming head in a breech presentation.

When the forceps blades are correctly applied, the tips of the forceps blades lie over

the fetal cheeks, with the upper or concave border of the blade directed either toward the fetal occiput in anterior positions, or toward the face in posterior positions.

The biparietal diameter of the fetal head fits in the center of the cephalic curve of the instrument. For both the vacuum extractor and forceps, when the application is correct, the vector of traction force passes through the flexing or pivot point of the fetal skull. The pivot point is an imaginary site approximately 6 cm behind the edge of the anterior fontanelle or approximately 1.5 cm to 2.5 cm in advance of the posterior fontanelle centered over the sagittal suture. If one blade is misapplied over the brow and the other over the occiput, the instrument cannot be locked or articulated, or, if somehow approximated, the blades usually slip off when traction is applied and could injure the infant.

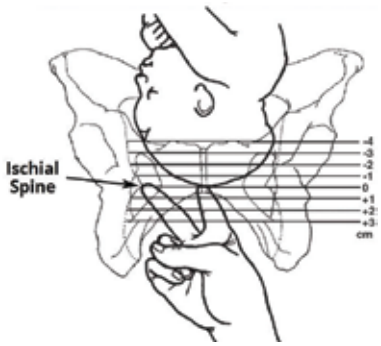



Fig 3: Assessment of fetal station by Digital Examination

When correctly placed, a standard 60-mm vacuum cup is positioned midline over the sagittal suture, with the edge of the cup lying approximately 3 cm from the edge of the anterior fontanelle. Thus in vacuum extraction operations, the anterior fontanelle becomes the reference point for checking instrument applications.

## SEQUENTIAL INSTRUMENTAL USE

Most data indicate that sequential operations (forceps operations followed by vacuum extraction or vice versa) are associated with an increased risk for fetal intracranial hemorrhage (ICH), exceeding the risk when either forceps or vacuum extraction is used alone. When one type of instrument is applied and fails, there is no absolute prohibition in trying a different device.

Injuries from multiple instrument use are mostly likely when a degree of unrecognized fetopelvic disproportion is present and despite difficulty, the clinician cannot refrain from pursuing a vaginal operative delivery. Whenever a vaginal delivery becomes difficult and sequential instrument is considered, the alternative of cesarean delivery must be entertained.

## CONTRAINDICATIONS AND SPECIAL APPLICATIONS:

The most important contraindications to vaginal delivery operations are operator

inexperience and the inability to achieve a proper application, uncertainty concerning fetal position or station, or the patient or her family are reluctant to undergo instrumentation. There are also clinical settings in which specific instruments should not be used. Examples include vacuum extraction applications to the aftercoming head in breech presentations or to the fetal face. The vacuum extractor should also be used with caution in preterm pregnancies, because the data on safety are limited. It is recommended that vacuum extraction operations not be performed on infants less than 32 to 33 weeks' gestation, and that a soft-cup extractor be preferentially employed if a vacuum procedure is performed on any fetus of less than 37 weeks' gestation.

At cesarean delivery, either the vacuum extractor or the forceps can be used to assist cranial extraction. In most circumstances, extraction problems occur because of an initially inadequate incision or a deeply engaged presenting part. It is best to either extend the incision sufficiently to avoid struggling. Request assistance in displacing the presenting part, or resort to an instrumentally assisted delivery. When instrumental assistance is needed during a cesarean delivery and the fetus is cephalic, a Vectis blade such as a Murless or a classic forceps are the most convenient instruments. A vacuum extraction during a cesarean delivery is most appropriate when the fetal head is positioned high in the uterus and difficult to grasp despite an adequate uterine incision.

## PROGNOSTICALLY POOR SIGNS FOR SUCCESSFUL INSTRUMENTAL DELIVERY BY EITHER FORCEPS OR THE VACUUM EXTRACTOR

- Estimated fetal weight >4,500 g
- Prolonged second stage of labor
- Dysfunctional active phase of labor
- Advanced cranial molding
- Station above +2/5 cm
- Position: occiput posterior, OT, especially if deflexed
- Poor maternal expulsive efforts/exhaustion or an overly dense epidural anesthetic

## CONCLUSION

Instrumental delivery remains a useful procedure despite the complications. Perhaps, the issue is not primarily of choice of instrument but of appropriate and careful use. In 1793, Thomas Denman, a prominent man-midwife of the era, wrote "It behoveth every person who may use an instrument in the practice of midwifery to be well convinced of the necessity before they are used, and to be extremely

careful in their use that he does not create new evils or aggravate those that might be existing. These words remain true today.

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# TIFFA –ALONE WILL DO ?

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The Midtrimester Fetal ultrasound evaluation (TIFFA-Targeted Imaging For Fetal anomalies )is considered as the essential step in antenatal care . In this article we will discuss whether TIFFA alone is sufficient for routine obstetric care .

Before moving on to that , let's try to understand some current concepts about TIIFFA scan .

### Is there any standard protocol / Guidelines for TIFFA scan performance?

Yes.For Midtrimester Fetal ultrasound evaluation we follow ISUOG guidelines(The International Society of Ultrasound in Obstetrics and Gynecology) for fetal evaluation.

## WHAT IS ISUOG GUIDELINES ?

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) is a scientific organization that encourages sound clinical practice, and high-quality teaching and research related to diagnostic imaging in women's healthcare. The ISUOG Clinical Standards Committee (CSC) has a remit to develop Practice Guidelines and Consensus Statements as educational recommendations that provide healthcare practitioners with a consensus-based approach, from experts, for diagnostic imaging(1).

A routine mid-trimester fetal ultrasound examination includes an evaluation of the following: -

### Survey:

1. Placental appearance and location; -
2. Amniotic fluid volume,
3. Cardiac activity; -
4. Fetal number (and chorionicity and amnionicity in cases of multiple pregnancy);

5. Gestational age/fetalBiometry ; -
6. Basic fetal anatomy; - (Table 1)
7. Transvaginal Cervical length assessment (1)

| Table :1 | TIFFA scan | |
|---|---|---|
| | ISUOG guidelines –sections | Anomalies Detection (Brief) |
| Head | Intact Cranium | Anencephaly, Encephalocele |
| | Head shape | craniosynostosis |
| | Cavum septum pellucidum | Agenesis of corpus callosum , septo optic dysplasia |
| | Choroid plexus in normal position | Choroid plexus cysts ,lipoma |
| | Midline falx | Holoprosencephaly |
| | Thalami in normal appearance | Holoprosencephaly |
| | Lateral ventricles | Ventriculomegaly |
| | Cerebellum | Open neural tube defects , Hypoplasia |
| | Cisterna magna | Posterior fossa abnormalities |
| Face | Both orbits | Anophthalmia , Hyper /Hypotelorism |
| | Profile | Micronagthia ,Midline cleft , frontal bossing /receding |
| | Nasal bone | Unossified nasal bone |
| | Upper lip intact | Cleft lip |
| Neck | Absence of neck masses | Cystic hygroma ,goiter |
| Chest /Heart | Chest and lung appearing normal in shape | Thoracic /lung hypoplasia / Diaphragmatic Hernia |
| | Heart activity present | Intrauterine demise /Arrhythmias |
| | Four chamber view | Chamber asymmetry, Valve ,offset abnormalities , |
| | Outflow tracts | Outflow tracts abnormalities |
| | 3 vessel view , 3 vessel trachea view | Outflow tracts abnormalities, venous anomalies |
| Abdomen | Stomach in normal position | Absent –Tracheoesophageal fistula<br>Abnormal-Duodenal obstruction<br>Displaced into thorax-Congenital diaphragmatic hernia |
| | Bowel | Echogenic/Dilatation |
| | Gallbladder (Right side ) | Situs abnormalities |
| | Both kidneys | Absence /Dysmorphic/Pelvic dilatation |
| | Urinary bladder | Bladder exstrophy /Lower urinary tract obstruction |
| | Cord insertion site | Abdominal wall defects |
| Skeletal | Spine | Spinal defects /masses |
| | Arms & hands with normal joint position | Limb reduction defects ,Arthrogryposis |
| | Legs & Feet hands with normal joint position | |
| Placenta | Position in relation with cervix | Masses/low lying placenta |
| Umbilical cord | 3 vessel cord | Single umbilical artery |
| | Cord insertion placental site | Marginal /velamentous cord insertion site |
| | | |

Table 1 describes the anatomical checklist by ISUOG guidelines for TIFFA (Mid trimester )scan and potential anomalies which can be detected by it.

## WHAT IF THE EXAMINATION CANNOT BE PERFORMED IN ACCORDANCE WITH THESE GUIDELINES?

These Guidelines represent an international benchmark for the second-trimester ultrasound scan, but consideration must be given to local circumstances, protocols and medical practice. If the examination cannot be completed in accordance with these Guidelines, it is advisable to document the reasons for this.

Example : According to the guidelines , external genitalia documentation is a part of checklist . But according to our PCPNDT law, sex determination is punishable. Hence , we are not documenting the external genitalia unless indicated in special situations.

In most circumstances, it will be appropriate to repeat the scan, or to refer the case to another healthcare practitioner if the checklist could not completed . This should be done as soon as possible, to minimize unnecessary patient anxiety and any associated delay in achieving the desired goals of the initial examination(1)

## WHETHER THESE GUIDELINES ARE SUFFICIENT FOR ALL PREGNANT WOMEN?

These recommendations represent minimum suggested Practice Guidelines for the mid-trimester fetal ultrasound scan. If time, equipment and skills allow, more comprehensive evaluation is encouraged.

The patient with significant History or risk factors for particular anomaly, extended examination of that system is encouraged .

Eg: Pregnant with Diabetes /Previous child or mother with cardiac anomaly – Detailed Fetal Echo to be performed .

If there a suspicion of cardiac anomaly in routine sections of checklist –we should proceed with Detailed Fetal Echocardiography to pinpoint the exact pathology

Eg:Abnormal 3 vessel view araises the suspicion of outflow tract anomaly which necessitates the detailed Fetal Echocardiography evaluation.

## CAN WE WAIT TILL TIFFA (MID TRIMESTER) SCAN TO DIAGNOSE THESE ANOMALIES (MENTIONED IN TABLE 1)?ANY OTHER POSSIBILITIES OF DIAGNOSING THESE ANOMALIES IN EARLIER GESTATION ?

Like TIFFA scan guidelines , there is new updated ISUOG guidelines for First trimester (11-13weeks ) scan also (2).By following that , we can diagnose most of the lethal anomalies in first trimester itself (Table 2).

| Table :2 | 11-13 weeks scan | |
|---|---|---|
| | **ISUOG guidelines –sections** | **Anomalies Detection (Brief)** |
| **Head** | Intact Cranium | Anencephaly, Encephalocele |
| | Choroid plexus in normal position | Holoprosencephaly |
| | Midline falx | Holoprosencephaly |
| | Thalami in normal appearance | Holoprosencephaly |
| | Cerebral peduncles with aqueduct of Sylvius | Open neural tube defect |
| | Intracranial translucency (fourth ventricle) | Open neural tube defect, possibilities of posterior fossa abnormality |
| | Cisterna magna | possibilities of posterior fossa abnormality |
| **Face** | Both orbits | Anophthalmia , Hyper /Hypotelorism |
| | Profile | Micronagthia ,Midline cleft , frontal bossing /receding |
| | Nasal bone | Unossified nasal bone |
| | Upper lip intact | Cleft lip |
| **Neck** | Jugular sacs /Nuchal translucency | Cystic hygroma /Marker for chromosomal abnormalities |
| **Chest /Heart** | Chest and lung appearing normal in shape | Diaphragmatic Hernia |
| | Heart activity present | Intrauterine demise /Arrhythmias |
| | Four chamber view (B mode & Colour flow) | Chamber asymmetry, Valve ,offset abnormalities , |
| | Left ventricular outflow tract (B mode or color) | Outflow tracts abnormalities |
| | 3 vessel trachea view (B mode or color) | Outflow tracts abnormalities,venous anomalies |
| | Tricuspid valve flow & ductus venosus flow in Pulse Doppler | Markers for Genetic abnormalities/cardiac anomalies |
| **Abdomen** | Stomach in normal position | Displaced into thorax-Congenital diaphragmatic hernia |
| | Both kidneys | Absence /Dysmorphic/Pelvic dilatation |
| | Urinary bladder | Bladder exstrophy /Megacystis |
| | Cord insertion site | Abdominal wall defects |
| **Skeletal** | Spine | Spinal defects /masses |
| | Arms & hands with normal joint position | Limb reduction detects ,Arthrogryposis |
| | Legs & Feet hands with normal joint position | |
| **Placenta** | Position in relation with cervix & relation with previous Cesarean# Scar | Masses/low lying placenta |
| **Umbilical cord** | 3 vessel cord | Single umbilical artery |

## WHAT IS THE SCOPE OF DIAGNOSING THESE ANOMALIES IN EARLIER GESTATION ? CAN WE OFFER FETAL ANATOMICAL EXAMINATION ONLY FOR HIGH RISK GROUP ?

Earlier detection of an anomaly ,both in low and high risk group gives the opportunity to ascertain any family history of genetic syndromes or anomalies that warrant further investigations.This is an important fact particularly in the countries which have stringent laws of gestational age for pregnancy termination(3).

The concept of turning the pyramid of care was introduced by Kypros Nicolaides in 2011.He recommended that the prediction of many pregnancy complications in 11-13 weeks integrated visit itself. He proposed that instead of closely following with frequent visits in third trimester ,the mode of prenatal care should get inverted and the emphasis should be on first trimester (4)

The first trimester diagnosis of fetal anomalies allows safer,earlier termination of pregnancy .Eg: Previous LSCS pregnant women

Because of the above reasons , it is reasonable to perform fetal anatomical examination in first trimester for every pregnant women .

## BY FOLLOWING THESE PROTOCOLS BY ISUOG GUIDELINES FOR FETAL ANATOMICAL EVALUATION IN FIRST TRIMESTER /TIFFA SCANS –WHETHER IT MAY HARM THE FETUS OR NOT?? BECAUSE OF INCREASE IN THE FETAL EXAMINATION DURATION ...

Prenatal ultrasonography appears to be safe in clinical practice; however, it should follow the ALARA principle and not be performed solely for parental entertainment purposes . Nonetheless, fetal exposure times should be minimized, using the lowest possible power output needed to obtain diagnostic information, following the ALARA principle (As Low As Reasonably Achievable)(5)

The fetal period commences at 11 weeks (after the lastmenstrual period; corresponding to a crown – rump length≥45 mm). By this stage, organogenesis is complete and the fetal – placental circulation is established. There are no indications that the use of B-mode or M-mode prenatal ultrasonography may be harmful during the first trimester, due to their limited acoustic output(6,7) However, scanning time should be limited and the lowest possible power output should be used to obtain diagnostic information according to the ALARA (As Low As Reasonably Achievable) principle

From 11+0 to 13+6 weeks, spectral Doppler, color flow imaging, power imaging and other Doppler ultrasound modalities may be used routinely for certain clinical indications, such as screening for trisomy and cardiac anomalies. When performing Doppler ultrasound, the displayed thermal index (TI) should be≤1.0 and exposure time should be kept as short as possible (usually no longer than5 – 10 min).Uterine artery Doppler when scanning maternal uterine arteries at any point inthe first trimester, there are unlikely to be any fetal safety implications as long as the embryo/fetus lies outside the Doppler ultrasound beam. (8)The exact same principles applicable to TIFFA scan too.

## CAN 11-13 WEEKS SCAN REPLACE THE TIFFA SCAN ?

Absolutely not .The Evolving structures like Cavum septum pellucidum , spine development , Anomalies of lung (Pulmonary sequestration , Congential pulmonary airway malformation)can be assessed only in second trimester . So we can replace the role of TIFFA scan by 11 -13 weeks scan .

## CAN WE RULE OUT ALL CONGENITAL ANOMALIES IN TIFFA SCAN ? CAN WE GIVE 100% REASSURANCE TO THE COUPLE ONCE THE TIFFA SCAN IS NORMAL ?

No, Even though most of the anomalies can be diagnosed in TIFFA scan , some of the anomalies cannot be diagnosed like Tracheo-oesophageal fistula , Imperferate anus , Partial anomalous pulmonary venous connections , soft palate cleft , Atrial septal defect , patent ductus arteriosus , small ventricular septal defects .

Newly onset findings like Ventricular hemorrhage , Intracranial calcifications due to fetal infections can occur in any trimester.

Some of the anomalies can be diagnosed only in that particular gestation due to its evolving nature like Lissencephaly ,progressive microcephaly , Talipes due to evolving arthrogyposis , outflow tract disproportion , intestinal obstruction will manifest only in third trimester . Hence the third trimester fetal evaluation also becomes mandatory .

Some anomalies become evident in any of the gestation depend on their severity like congenital diaphragmatic Hernia (more severe –early onset gestation ).

## WHAT ARE THE LIMITATIONS OF ANTENATAL SCANS? WHAT FACTORS INFLUENZING ON ANTENATAL SCANS ANOMALY DETECTION ?

1. Visibility of the fetal parts depends numerous factors like Maternal BMI ,thick abdominal wall,Presence of anterior wall fibroid , Multiple pregnancy,unfavourable fetal position
2. Successful early detection of fetal structural anomalies is also dependent on the standard of equipment available for screening, the skill set of the imaging person and the prevalence of the anomalies in the population (2)
3. The natural history of an particular anomaly influences on its detection rate Because of the evolution nature of some anomalies ,the ultrasonography at later gestation becomes mandatory.

## WHETHER TO INFORM THE COUPLE REGARDING THE LIMITATIONS OF ANTENATAL SCANS ? WHAT IS THE IDEAL TIME TO INFORM ? HOW IT CAN HELP IN OUR DAY TO DAY PRACTICE ?

Yes. The couple must be aware of the limitations .Before referring every pregnancy women for antental scan , the couple should be counseled by Health care professional regarding the purpose , advantages and limitations of scan .After explaining and obtaining consent only , the patient should be referred . This pretest counseling is the crucial step , which can avoid many postanatal issues due to misbelieves regarding antenatal scans .So this initiative , must integrate it in our routine practice .

## CAN WE DIAGNOSE ALL GENETIC DISORDERS BY ANTENATAL USG ?

No , only some of chromosomal /genetic disorders will manifest with antenatal scan findings like Trisomy 13 , Meckel Gruber syndrome . But most of the genetic disorders like Hemoglobinopathies, in born errors of metabolism need prenatal invasive testing to ruleout their possibility in the presence of proven familial inheritance .

## CAN WE RULE OUT DOWN SYNDROME BY TIIFA SCAN ?

Trisomy 21 is associated with nasal hypoplasia, increased nuchal fold thickness, intracardiac echogenic foci ,echogenic bowel, hydronephrosis, shortening of the femur ,humerus, sandal gap , clinodactyly or mid-phalanx hypoplasia of the fifth finger.But the presence of each individual markers significance depend on their Isolated likelihood ratios-according to that further decision to be taken .

In the presence of soft markers, the risk of Down syndrome is recalculated as new risk = baseline risk x likelihood ratio (LR). The new LR is calculated by multiplying all positive LRs (of markers present) and all negative LRs (of markers absent).

Note: if a single marker is present, then isolated LR is considered.

In the presence of Ultrasound features of anomalies like cardiac defects , duodenal atresia –Direct invasive testing to be considered .

As we all know , all down syndrome children need not to manifest with ultrasound features in antenatal scans .Hence , the first trimester combined screening (Includes biochemical markers )plays the vital role in screening the above subset also.

## CONCLUSION :

Around 60 % of the major anomalies detected by TIFFA scan can be diagnosed

in 11-13 weeks nowadays . But the role of TIFFA scan still stands in detecting evolving anomalies of second trimester . But the TIFFA scan is not sufficient to pickup evolving anomalies of third trimester and evolving growth issues . Hence third trimester scan also plays the vital role . Regarding chromosomal / genetic disorders detection , the role of First trimester combined screening and invasive testing for prenatal diagnosis cannot be replaced only by TIFFA scan . So obviously, the TIFFA scan alone won't be sufficient . But It is one of the integral part of standard obstetric care .

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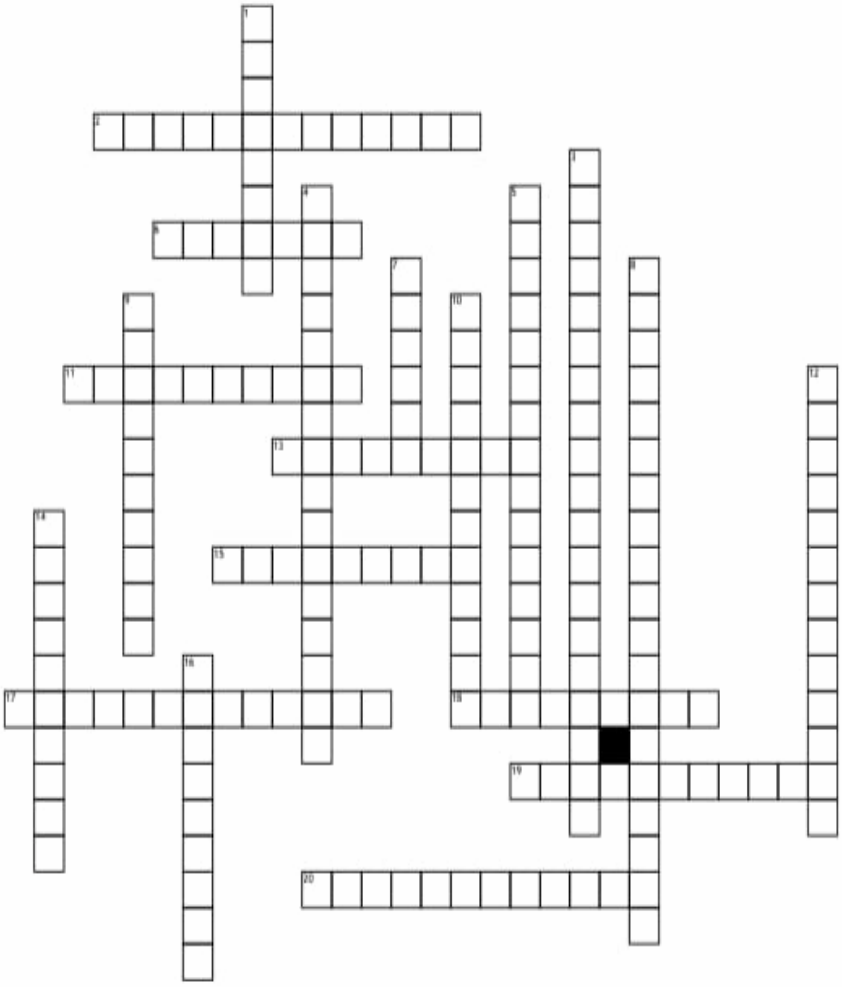
# CANCER AWARENESS PROGRAMMES

March 2023

# CROSS WORD

## Obsetrics and Gynecology



**Across**

**2.** Modulator of the biochemical activity in tissues

**6.** Oxygen deficiency

**11.** Destroyed by means of an electric current

**13.** Period of development from fertilization to birth

**15.** A bacterium that causes one of the most prevalent sexually transmitted diseases

**17.** Voluntary prevention of pregnancy prescriptions

**18.** To rupture during labor when your water doesn't break

**19.** Painful intercourse

**20.** Usual method for calculating expected date of birth

**Down**

**1.** Expansion of an orifice or organ

**3.** A biopsy of the uterine cervix using an instrument

**4.** Inherited blood disorder that may shorten life span

**5.** Delivery of the fetus through surgical incision into the uterus

**7.** Vaginal discharge appears during postpartum puerperium

**8.** Being born with existing at time of birth

**9.** Cysts on the ovaries

**10.** A women pregnant for the first time

**12.** Painful menses

**14.** Emergency contraception also called preven or plan B

**16.** Complication of pregnancy that includes general edema, hypertension and proteinuria

**Word Bank**

| | | | |
|---|---|---|---|
| Amniotomy | Fulgurated | Lochia | Contraception |
| Cervical punch biopsy | Cesarean section | Chlamydia | Congenital anomalies |
| Dysmenorrheal | Dilation | Dyspareunia | Eclampsia |
| Gestation | Hypoxia | Nagele's Rule | Polycystic |
| Postcoital | Primigravida | Prostaglandin | Sickle cell anemia |

# NON-SURGICAL APPROACHES FOR UTERO-VAGINAL PROLAPSE

**Dr. B. JEYAMANI,**
**MD, OG**

Pelvic Organ Prolapse (POP) is one of the common gynecological problems especially in post-menopausal age group, one of the curse of increasing life expectancy. Women in the United States have a 13% lifetime risk of undergoing surgery for POP and it is expected that by 2050 50% women would be suffering from POP. Pelvic organ prolapse is non- life threatening but can be distressing to one's self-respect due to associated bowel and bladder disturbances.

Hence Non-Surgical Management is recommended by the Agency of Health Care Policy and Research and the American College of Obstetricians and Gynecologists (ACOG) especially in women whom is surgical management couldn't be attempted.

## INDICATIONS FOR NON-SURGICAL MANAGEMENT OF POP

1. Mild to Moderate Asymptomatic UV Prolapse.
2. Those waiting for Surgery – In view of medical problems like Diabetes Mellitus, Anaemia, Heart Disease.
3. Not willing to undergo surgery.
4. Wish to have some children.

## NON – SURGICAL APPROACH

1. Lifestyle Advice.
2. Pelvic Floor Muscle Training.
3. Vaginal Pessaries.

## LIFESTYLE ADVICE

1. Weight Loss – To maintain BMI less than 30.
2. Avoid heavy lifting.
3. Avoid constipation and straining.

4. Treat persistent cough.
5. Posture maintenance.
6. Daily Vitamin D3 supplement and HRT.
7. Avoid high impact exercise.

## PELVIC FLOOR MUSCLE TRAINING

Daily Pelvic Floor Exercises – Kegel's Exercises to improve the strength and function


Fig. 1 Kegel's exercises - steps


Fig. 2 Pelvic floor exercises

of Pelvic floor muscle, most commonly used to treat Stress urinary incontinence (SUI). To make Kegel's more effective Electronic Pelvic Toner, Biofeedback Machine – Using weighted vaginal cones or Neuromuscular electric stimulation can be attempted. It's advisable to do Pelvic Floor exercises at least once daily or as and when possible throughout the day. A one-to-one monitored pelvic floor muscle training program/ involvement of physiotherapist will improve the effect.

## PESSARY

Vaginal pessaries, may be used along with Pelvic floor muscle exercises. It can be used during pregnancy or following childbirth

## TYPES

- Supportive – Ring or Smith Hodge Pessary.
- Space Filling –Doughnut, Gelhorn, Cube Pessaries

With available evidence either supportive or space filling pessaries could be used for pelvic organ prolapse while waiting for surgery.

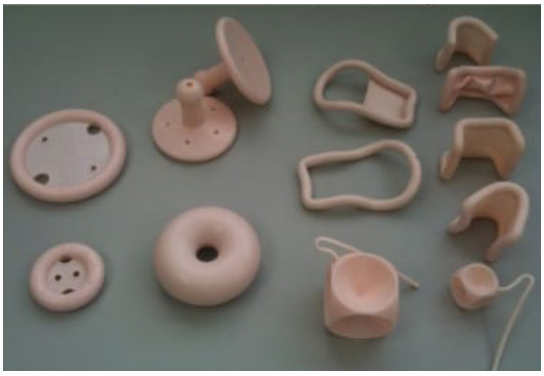


Fig. 3 Pessaries for pelvic organ prolapse

## ADVANTAGES

1. Inexpensive.
2. Simple/ ease of use
3. Effective and Safe
4. High patient satisfaction

## RISK OF PESSARIES

1. Risk of Infection.
2. Ulceration of vaginal wall.
3. Unpleasant vaginal discharge.
4. Actinomycosis & Bacterial Vaginosis.
5. May get displaced- No longer beneficial.
6. May get impacted in the vagina
7. Neglected pessary may complicate as Fistula/ Peritonitis

To sum up, Non-surgical management should be attempted before surgery is contemplated for Pelvic Organ Prolapse; May be offered for women in whom surgical management is contraindicated or delayed and as a supportive measure along with surgical management of POP.

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# FAQS ABOUT FGR

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## WHAT IS FGR? WHY IS IT IMPORTANT TO OPTIMIZE OUTCOMES IN FGR?

Fetal growth restriction (FGR) indicates a fetus that has not attained its full biological potential for growth due to a pathological factor. This term has replaced the earlier terms Intra Uterine Growth Retardation and Intra Uterine Growth Restriction.

Affects approximately 10% of all pregnancies and is the leading cause of perinatal morbidity, mortality and has long term neuro developmental and cardio vascular consequences. Unfortunately, even in high resource setting the diagnosis is often missed.

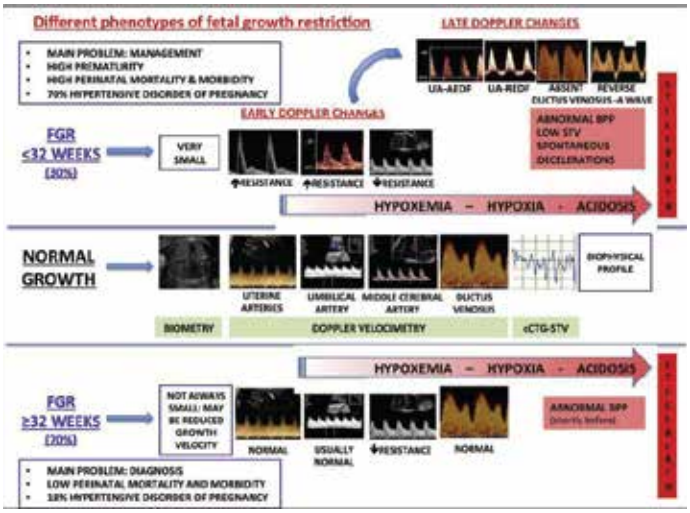
## WHAT IS THE DIFFERENCE BETWEEN SMALL FOR GESTATIONAL AGE SGA BABY AND FGR?

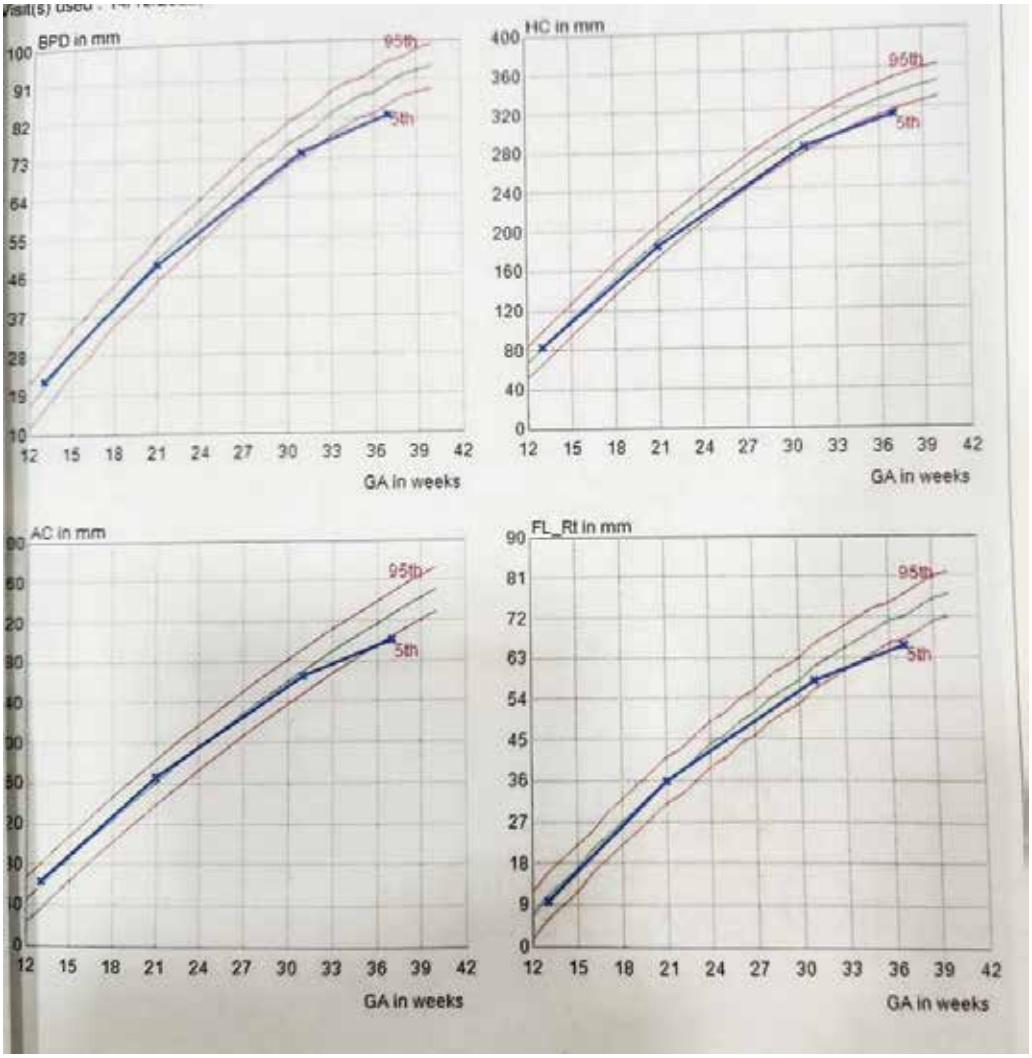
A new born that weighs < 10 centile for that gestational age is considered SGA. It could be a constitutionally small, otherwise healthy baby without having suffered from nutrient deficiency or hypoxia. The term is SGA can also include FGR where the fetus has suffered nutrient deficiency and hypoxia. The constitutionally small SGA baby does not suffer the same morbidity or mortality or long- term neurological defects like the FGR baby.


FGR BABIES

## WHAT IS THE MOST ACCEPTED DEFINITION OF FGR? WHAT ARE ITS PHENOTYPES?

Different societies like MFM, AAFP and ISUOG have defined FGR differently.The SMFM definition of FGR is estimated fetal weight (EFW) or abdominal circumference (AC) < 10th percentile. The ISUOG-FGR definition follows the Delphi consensus criteria (see annexure 1) and includes either EFW or AC < 3rd percentile or EFW or AC < 10th percentile combined with abnormal Doppler findings or a decrease in growth centiles. It is generally agreed that considering fetal weight < 10 centile for the gestational age will miss many cases of FGR as fetal growth velocity is a dynamic entity. Considering suspected FGR only in terms of fetal AC or EFW size of <10th percentile assumes that fetal size predicts fetal well-being in terms of oxygenation and acid-base status. Approximately 60% to 70% of fetal deaths, especially toward term, occur in AGA fetuses, and a recent case-control study showed that 88% of stillbirths had histologic features of hypoxia on postmortem or placental examination. Individualized growth assessment is a method for the evaluation of fetal growth and neonatal growth outcome in which each fetus is its own control, based on estimates of individual growth potentials. This type of longitudinal evaluation addresses the concept of possible fetal growth failure even if the EFW is >10th percentile Hence growth charts [ preferably customised for the local area] and fetal doppler parameters including umbilical artery and middle cerebral artery have been included in the ISUOG definition.






Earlier FGR was classified as symmetrical and asymmetrical but this could not provide clear guidelines or prognosis. Currently FGR is classified as early onset FGR (diagnosed less than 32 weeks gestation) and late onset FGR [Diagnosed after 32 weeks of gestation]. Early onset FGR is usually progressive and predictable – accounts for 20 – 30% cases of FGR. Late onset is difficult to diagnose, often unpredictable as far as perinatal morbidity and mortality is concerned. Many antepartum and intrapartum still births are due to undiagnosed late onset FGR

## WHAT IS THE AETIOLOGY OF FGR?

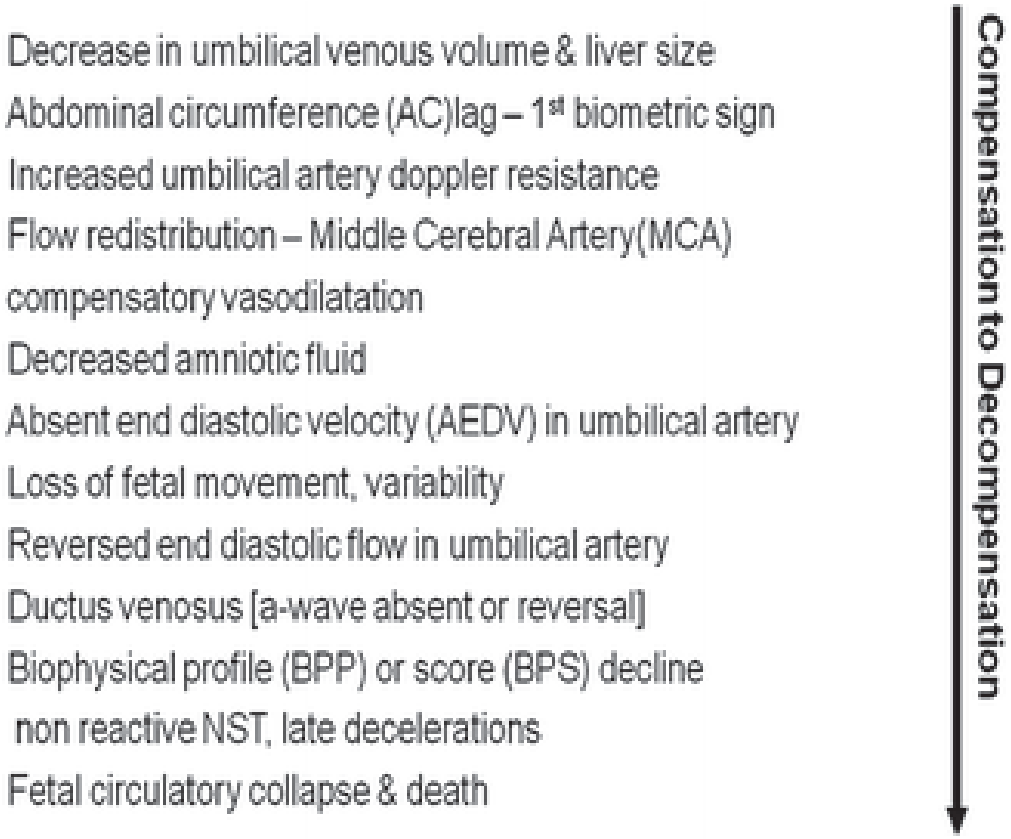
Most common causes are:

Placenta related. Abnormal placentation, placenta praevia, vasculopathies, infarcts, chorioangiomas and single umbilical artery.

Maternal causes: Hypertensive disorders of pregnancy, long standing DM, SLE and other autoimmune disorders, malnutrition, drugs and substance abuse.

Fetal causes: TORCH group infections, syphilis, chromosomal/genetic defects, congenital malformations, and multiple pregnancies

## HOW DOES FGR EVOLVE AS GESTATION ADVANCES?




## WHAT ARE THE BASIC PRINCIPLES OF MANAGING EARLY ONSET FGR?

First step is accurate dating & establishing FGR

Second step is to do Level 2 scan& rule out chromosomal & developmental anomalies, infections

Third step is to identify & treat specific conditions like malnutrition, PE, autoimmune conditions . Low dose aspirin[100-150mg] can be started in patients prone for PE & FGR around 12 -16 weeks .Inj.LMWH is indicated only in APLA & Thrombophilias..Detailed history is extremely important.

Fourth step is periodic monitoring of interval growth, multiple vessel Doppler changes [UA, MCA, Ut A ,DV] & behavioural response[CTG, BPP]

In early-onset suspected FGR, fetal deterioration is heralded by progressively increasing UA impedance, most expressed as PI, resistance index or S-to-D (systolic-to-diastolic) ratio. This change may occur during many weeks before severe fetal cardiovascular and metabolic deterioration and may be less predictable if pre-eclampsia supervenes. The absence of umbilical end-diastolic velocities AEDV as a reflection of worsening uteroplacental insufficiency precede reversed end-diastolic velocity REDV in the UA and eventually ductus venosus DV abnormalities

Computerised CTG where available is a more objective &reproducible method of predicting fetal hypoxia and acidemia. STV [SHORT TERM VARIATION] <2.6 milliseconds (ms) at 26 0/7 to 28 6/7 weeks of gestation and <3 ms at 29 0/7 to 31 6/7 weeks of gestation is considered threshold for delivery.

The TRUFFLE study of early-onset suspected FGR was conducted in 20 European centers between 2005 and 2010, and all women received surveillance using UA Doppler and computerized cardiotocography (cCTG). . The TRUFFLE study concluded that timing delivery based on ductus venosus Doppler measurement in conjunction with STV obtained from cCTG led to the best long-term (2-year neurodevelopmental) outcome in survivors. This constitutes the strongest evidence in favor of the use of ductus venosus Doppler combined with cCTG for monitoring and triggering delivery in early suspected FGR.

FGR fetuses are at high risk of hypoxia, acidemia & stillbirth. From the second trimester onward, the biophysical profile [BPP] score correlates over 90% with the current fetal pH, and a normal score predicts a pH >7.25 with a 100% positive predictive value; an abnormal score on the other hand predicts current fetal acidemia with similar certainty. Between 30% and 70% of growth-restricted fetuses with a nonreactive heart rate require biophysical profile scoring to verify fetal well-being, and an abnormal score in 8% to 27% identifies the need for delivery, which is not suspected by Doppler findings.

Fifth step is Timely delivery of the fetus when the risk of intra uterine stillbirth exceeds risk of neonatal death This trigger should be based on interval growth, amniotic fluid, Dopplers ,CTG ,& BPP as well as maternal condition.[ See Annexure FIGO Guidelines]

Severe FGR especially less than 32 weeks gestation should be delivered in materno fetal medicine centres with good NICU facilities

## WHAT IS THE ROLE OF ANTENATAL STEROIDS, MAGNESIUM SULPHATE AND ADJUVANTS IN THE THERAPY OF FGR?

Antenatal corticosteroids and magnesium sulphate are of proven benefit in reducing serious neonatal morbidity & mortality. Same protocol is followed as in other cases.

All other therapies like nutrients, plasma volume expansion, bed rest, oxygen, sildenafil ,TENS, tocolytics have no proven benefit hence NOT recommended

## WHAT ARE THE ABSOLUTE INDICATIONS FOR DELIVERY IRRESPECTIVE OF GESTATIONAL AGE IN FGR?

Abnormal CTG [ loss of baseline variability, unprovoked ,persistent late decelerations ,prolonged bradycardia], BPP<=4, Severe PE with uncontrolled HT,HELLP syndrome or other end organ damage. Problem is CTG changes often occur quite late and fetus is already compromised with severe neonatal morbidity.

## HOW DO YOU MANAGE LATE ONSET FGR?

In late onset FGR, umbilical artery Doppler remains normal or mildly altered in late preterm and term fetuses. Cerebral vascular redistribution plays a vital role. CPR RATIO provides valuable information of fetal Hypoxia and acidosis compared to Umbilical A OR MCA Doppler changes alone. Altered CPR ratio does not warrant immediate delivery but calls for inpatient monitoring with twice weekly monitoring with NST/BPP to increase safety net till the fetus is safe enough to be delivered.

## HOW DO YOU COUNSEL WOMEN WITH FGR POSTPARTUM?

FGR infants should be closely followed up as they are at high risk of developing long term cardiovascular or neurodevelopmental abnormalities

Mothers have risk of recurrence in subsequent pregnancies and are recommended LDA from 12 -16 weeks. Fetal surveillance should start from 24 – 28 weeks in subsequent pregnancies

Mothers with associated conditions like PE, chronic diseases or autoimmune disorders need to be appropriately advised.

Routine screening for APLA is not recommended unless there is fetal loss or thromboembolic event

## ANNEXURE

1.DELPHI Consensus criteria for definition of FGR

## REFERENCES

1.FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: Best practice advice for screening, diagnosis, and management of fetal growth restriction

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PMCID: PMC8252743

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Christoph C. Lees, Roberto Romero, Tamara Stampalija et al

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3.Fetal growth restriction and stillbirth: Biomarkers for identifying at risk fetuses

Victoria J. King, Laura Bennet, Peter R. Stone, et al

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4.Current practice in the diagnosis and management of fetal growth restriction: An international survey

Ilaria Fantasia, Giulia Zamagni, Christoph C Lees et al

Acta Obstet Gynecol Scand. 2022 Dec; 101(12): 1431–1439. Published online 2022 Oct 10. doi: 10.1111/aogs.14466

PMCID: PMC9812103

5.The role of biophysical profile in the management of fetal growth restriction

Ahmet A Baschat,Henry L Galan,Wesley Lee et al

Am J Obstet Gynecol2022 April, Vol 226

6.ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 227 (Replaces Practice Bulletin Number 204, February 2019) Committee on Practice Bulletins—Obstetrics and the Society for Maternal-Fetal Medicine .This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics and the Society for Maternal-Fetal Medicine Publications Committee with the assistance of Henry Galan, MD, and William Grobman

7.Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction

J T Roeckner 1, K Pressman 1, L Odibo 1,et al

Ultrasound Obstet Gynecol 2021, June

| **Early FGR**: GA < 32 wk, in the absence of congenital anomalies | **Late FGR**: GA > 32 wk, in the absence of congenital anomalies |
|---|---|
| AC or EFW of < third percentile or UA-AEDF Or<br>1. AC or EFW of < 10th percentile<br>combined with<br>2. Uta-PI of > 95th percentile<br>and/or<br>3. UA-PI of > 95th percentile | AC or EFW of < third percentile Or at least 2 of 3 of the following:<br>1. AC or EFW of < 10th percentile<br>2. AC or EFW crossing percentiles<br>of > 2 quartiles on growth percentiles<br>3. CPR of < 5th percentile or UA-PI of<br>> 95th percentile |

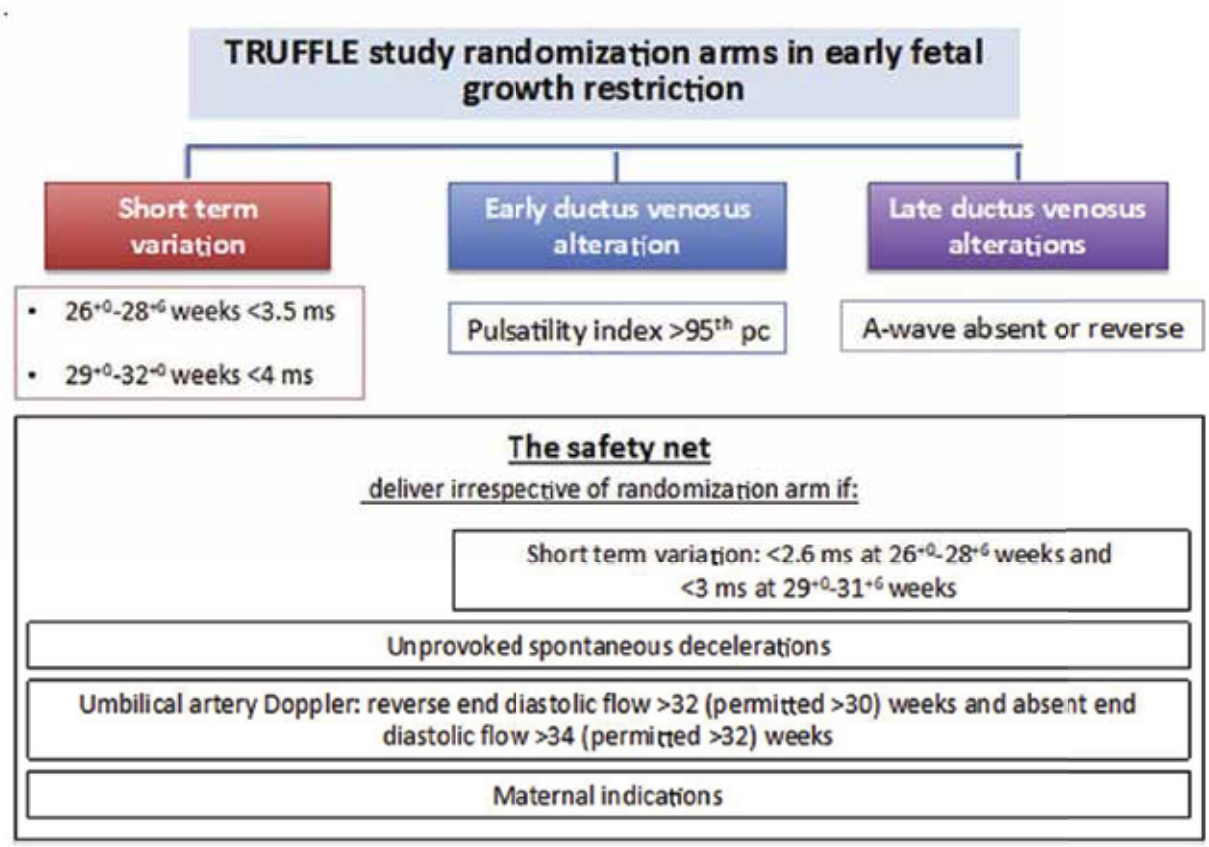
**2. FIGO Recommendations** for monitoring, timing, and mode of delivery in cases with suspected fetal growth restriction. Int J Gynaecol Obstet. 2021 Mar; 152(Suppl 1): 3–57. Published online 2021 Mar 19. doi: 10.1002/ijgo.13522

| **Findings** | **Risk of stillbirth** | **Suggested monitoring** | **Timing and mode of delivery** |
|---|---|---|---|
| SGA (EFW at 3rd–9th percentile, normal fluid and Doppler studies) | Low | • Doppler (UA, MCA) every 1–2 weeks<br>• Growth every 2 weeks | • 37–39 weeks<br>• Mode of delivery: induction |

| | | | |
|---|---|---|---|
| | | • At ≥37 weeks consider BPP/NST 1–2 times per week | |
| Uncomplicated FGR at <3rd percentile (normal fluid and Doppler studies) | Low | • Doppler (UA, MCA) 1–2 times per week<br>• Growth every 2 weeks<br>• At ≥37 weeks consider BPP/NST 1–2 times per week | • 36–38 weeks<br>• Mode of delivery: induction |
| FGR with mild abnormalities:<br>• Early Doppler changes:<br>a. UA PI >95th percentile, or<br>b. MCA PI <5th percentile, or | Low | • Consider inpatient monitoring<br>• Consider steroids for fetal lung maturation<br>• BPP/NST 1–2 times per week | • 34–37 weeks<br>• Mode of delivery: cesarean section or induction |

| | | | |
|---|---|---|---|
| c. CPR <5th percentile, or<br>d. UtA PI >95th percentile<br>• Oligohydramnios<br>• Suboptimal interval growth<br>• Suspected pre-eclampsia | | • Doppler (UA, MCA, DV) 1–2 times per week<br>• Growth every 2 weeks | |
| FGR with umbilical artery AEDV/REDV | • Overall risk of stillbirth<br>a. AEDV: 6.8%, OR 3.6 [2.3–5.6]<br>b. REDV: 19%, OR 7.3 [4.6–11.4]<br>• Risk of stillbirth with strict monitoring protocol with a safety net<br>a. AEDV: 0%–1% | • Inpatient monitoring<br>• Steroids for fetal lung maturation<br>• BPP/NST 1–2 times per day<br>• Doppler (UA, MCA, DV) every 1–2 days<br>• Growth every 2 weeks | • AEDV: 32–34 weeks[d]<br>• REDV: 30–32 weeks<br>• Mode of delivery: cesarean section |

| | | | |
|---|---|---|---|
| | b. REDV: 1%–2%<br>• Median time for deterioration:<br>a. AEDV: 5 days<br>b. REDV: 2 days | | |
| FGR with abnormal ductus venosus Doppler | • Overall risk of stillbirth<br>• 20%, OR 11.6 (6.3 19.7)<br>• Risk of stillbirth with strict monitoring protocol with a safety net<br>a. Elevated DV PIV. 2%<br>b. Absent-reverse a wave in DV: 4% | • Inpatient monitoring<br>• Steroids for fetal lung maturation<br>• BPP/NST twice per day<br>• Daily Doppler | • 26 30 weeks<br>• Mode of delivery: cesarean delivery |




**Schematic representation of the TRUFFLE randomization and the "safety net"**
The inclusion criteria were singleton fetus between 26 0/7 and 31 6/7 weeks of gestation with an estimated fetal weight >500 g, an abdominal circumference <10th percentile, and an umbilical artery >95th percentile, with a normal ductus venosus pulsatility index and short-term variation. Chromosomal and congenital anomalies constituted an exclusion criterion.
***TRUFFLE*, Trial of Umbilical and Fetal Flow in Europe.**


Colposcopy work shop
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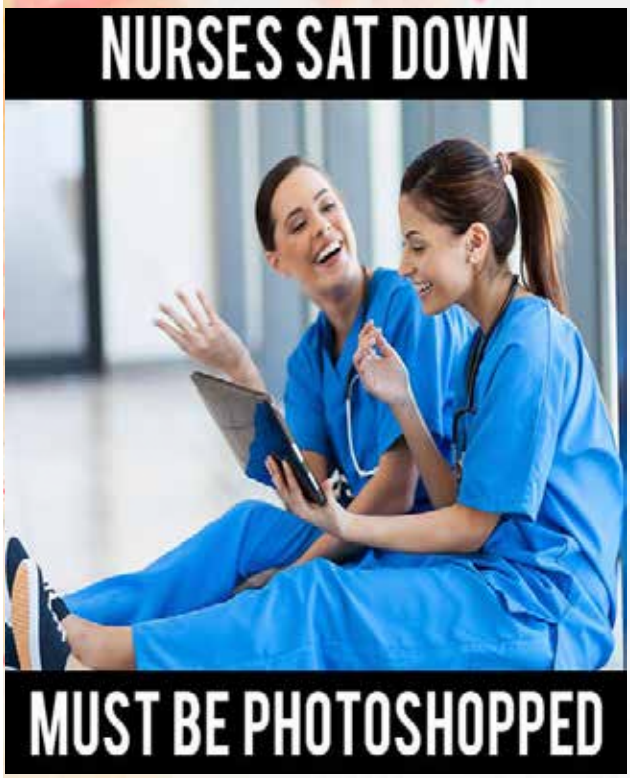
# BREAK


NURSES SAT DOWN
MUST BE PHOTOSHOPPED


1%
PRIORITIES


In order to follow privacy requirements we can't call our patients by their name.
The lady with hemorrhoids, please come in.


WHEN SOMEONE ASKS: "WHY DID YOU BECOME A MALE NURSE?"
REPLY: "THE OPERATION TO BE A FEMALE NURSE WAS TOO EXPENSIVE."

# EVALUATION OF MALE INFERTILITY : BASICS AND BEYOND

**Dr. SURESH KRISHNAAMORTHI, MD**

Among the causes of infertility male factor contributes about 50% and it is increasing day by day.

The goals of the evaluation of male infertility are to identify and treat correctable causes of male infertility and result in natural pregnancy.

Evaluation of male infertility includes a detailed history good clinical examination and semen analysis.

Semen analysis is a corner stone in the evaluation of male infertility.

Further evaluation of male infertility are directed by the initial screening evaluation.

Detailed history of the male should include coital frequency, timing, usage of lubricants, history of knowledge of fertile period.

Developmental history and childhood illness like hypospadias, congenital anomalies and onset of puberty.

Medical History of diabetes mellitus, history suggestive of cystic fibrosis,

Surgical history on scrotum, pelvic, retroperitoneal and inguinal surgeries.

Family history of infertility, cryptorchidism, hypogonadism.

Social history with frequent alcohol, tobacco or recreational drugs, exposure to chemical and environmental gonadotoxins.

Physical examination like obesity, secondary sexual characters, hair distribution has to be noted.

Genital examination should include phallus which should be examined for curvature of penis, hypospadias, any ulcer, plaques.

Both testis should be examined for size, consitency and presence of masses.

Normal adult testis is of 4cm x 3cm in size and the normal volume of testis is 20ml. 85% of testicular volume is made up of seminiferous tubules in which spermatogenesis occurs.

Epididimis should be palpated behind the testis and its presence, consistency, and nodularity has to be assessed to identify obstruction or infection.

Palpation of both vas deferens to rule out absence of vas, agenesis or atresia. CBAVD is a clinical diagnosis which can be easily diagnosed by palpation.

Palpation of both spermatic cords both in supine and in standing position with and without valsalva enables diagnosis of varicocele.

Finally a per rectal examination to identify dilated seminal vesicles, ejaculatory duct cysts or utricular cysts which may contribute to obstructive etiologies can be diagnosed.

## SEMEN ANALYSIS

The first step in assessment of infertility should be semen analysis.

Semen sample is collected after abstinence for 3 to 5 days in a wide bore sterile container by masturbation or by intercourse with the use of semen collection condoms, lubricants has to be avoided. Collection of the first few ejaculate of the sample is important as it contains maximum amount of sperms.

The key parameters of semen analysis is divided into macroscopic features which include semen volume, viscosity, color, PH, coagulation and microscopic features include sperm count, concentration, motility and sperm morphology.

## INTERPRETATION OF SEMEN ANALYSIS

VOLUME: The normal volume of semen is ≥ 1.4 ml. The contribution of seminal plasma is from seminal vesicles (65%), prostate (30%), bulbo urethral glands (5%). If there is low volume eg. 0.5ml with sperm count of 4 million then the patient would have ejaculated the previous night so redo the semen analysis. Low volume of semen with azoospermia with absent fructose is diagnostic of CBAVD. Some medications liked blockers (antihypertensive drugs), SSRI (anti depressants) can inhibit vas deferens motility and accessory gland emptying.

LIQUEFACTION : The liquefaction time is usually 30 to 60 minutes. Liquefaction and viscosity of the seminal fluid depends on the secretion from the prostate and seminal vesicles, so any alteration in these may lead to alteration in the viscosity . Viscosity can be assessed by gently aspirating the semen into a wide bore pipette approx 1.5 mm diameter pipette and allowing the semen to drop by gravity or by observing the length of the thread. Infection may alter the viscosity so look for puscells, leukocytes or any history of UTI. In these cases treat them with antibiotis for 3- 4 weeks. In high viscous samples the patient may be prescribed with liquefying agents like bromhexine. But most of the times alteration of viscosity and abnormal liquefaction is idiopathic.

PH: The clinical interest of ejaculates PH is of low value. NormalPH is 7.2 – 8.0

SPERM COUNT : According to WHO 2021 the total count should be ≥ 39 millions, and the sperm concentration is 16 millions/ ml. When we use a makler counting chamber examine under 10 X power and count 10 boxes and it is equal to the number in millions/ ml. In case of azoospermia centrifuge the sperm, form a pellet and examine the pellet for any spermatozoa. Only if there is no sperm in the pellet it can be reported as azoospermia, but atleast two samples has to be examined.

MOTILITY: Motility of sperm should be examined without any staining of the sample.

Rapidly progressive motility > 25 micro metre / sec which is equal to that of the length of the tail.

Slow progressive 5 to 25 micro metre/sec

Non progressive motility < 5 micro metre /sec which is equal to one head length.

Total motile sperm count (TMSC} is a parameter which is more informative than motility and count alone.

TMSC = Total count x active motility / 100 = number in millions.

TMSC > 15 millions is necessary for spontaneous conception.

SPERM MORPHOLOGY: Morphology is assessed by papanicolaou staining and viewing in oil immersion under 100 power. Evaluate 200 sperms to achieve an acceptably low sampling error. The head, midpiece, tail and cytoplasmic residue must be considered normal. The normal range of normal forms is 4%.

VITALITY: Vitality is assessing the membrane integrity of the cells. It is not necessary to do vitality testing if at least 40% of spermatozoa is motile. Vitality helps in differentiating immotile dead sperms and immotile live sperms. High percentage of immotile dead cells may indicate epididimal pathology or an immunological reaction to infection. Sperm vitality should be assessed immediately after liquefaction that is within 30 minutes to 60 minutes to limit the deleterious effects of dehydration or change in temperature.

AGGLUTINATION: Sample showing agglutination occasionally is not significant but if all samples show agglutination then look for infection , antibodies and it may be idiopathic also.

PUS CELLS: 3 types of round cells are seen.

leukocytes indicate infection

macrophages – normally present

spermatocytes – normally present

To find leukocytes do peroxidase staining, only peroxidase stained cells are leukocytes.

## EXTENDED SEMEN EXAMINATION:

I. There are many indices of multiple sperm defects which are used for more detailed assessment of the morphological abnormalities.

Teratozoospermic Index

Multiple abnormality index

Sperm deformity index

II. DNA FRAGMENTATION INDEX

DNA fragmentation index is defective packaging of the DNA during speramatogenesis and oxidative stress associated with several pathological and environmental conditions.

Role of DFI: It is not used as a routine but it can be done in idiopathic infertility, recurrent ICSI failure and recurrent early abortions.

III. SEMINAL OXIDATIVE STRESS AND REACTIVE OXYGEN SPECIES TESTING

There is still no any landmark study with decisive evidence for a certain test or proof of a relationship between REDOX and natural or assisted conception outcomes.

IV. ASSESSMENT OF ACROSOME REACTION

This test is done to find out the integrity of the acrosome structure and ability to undergo acrosomal reaction.

V. ASSESSMENT OF SPERM CHROMATIN

The stability of sperm chromatin structure is of fundamental importance for embryo development and quality. Disturbance of the stability of sperm chromatin is associate with lower fertiization in Assisted Reproduction.

VI. CASA

CASA system are best used for kinematic analysis of spermatozoa as they can detect and analyse mobile cells.

CASA system for morphological assessment relies on a high level of standardization and quality of staining of cells.

## HORMONAL EVALUATION IN MALE INFERTILITY

In case of azoospemia or severe oligozoospermia FSH and Total Testrosterone assay is done. FSH is considered to be an indicator of germinal function. LH assay is done only when there is abnormality in Testosterone level. Testosterone is measured between 7 AM to 9 AM as ths is the time when the serum testosterone is high. The normal testosterone level is 300 ng/dl

When FSH and LH levels are high with low testosterone it indicates testicular failure.

FSH, LH and Testosterone is low it indicates hypogonadotrophic hypogonadism.

An increase in LH with normal FSH indicates a disturbance of androgen receptivity.

Normal FSH and LH values suggest obstructive etiology.

Prolactin is indicated when associated with low libido or erectile dysfunction.

Estradiol is measured especially in obese, the normal value is 45 pg/ml and ratio between total testosterone and estradiol is calculated. Normal ratio is 10:1. If the ratio is less then treating those patients with aromatase inhibitors may help in reversing the ratio.

USG : USG is done for detecting duct obsructions in the prostate , scrotum, seminal vesicles and ejaculatory ducts. Varicocoele diagnosed only by usg and not clinically evident is not significant.

## OTHER TESTS

Seminal fructose test – identifies whether fructose is being added from seminal vesicles.

Post ejaculatory urinalysis- to determine if obstructions or retrograde ejaculation

Genetic testing : To rule out underlying mutations in one or more genes of the Y chromosome or to test for cystic fibrosis in men with absent vas deferens.

Vasography - to check the structure of duct system and to identify any obstructions.

Anti sperm antibodies : To identify the presence of antibodies, routine testing is not necessary. ELISA test is irrelevant, immunobead test/ MAR test can be done but they are expensive and not easily available.

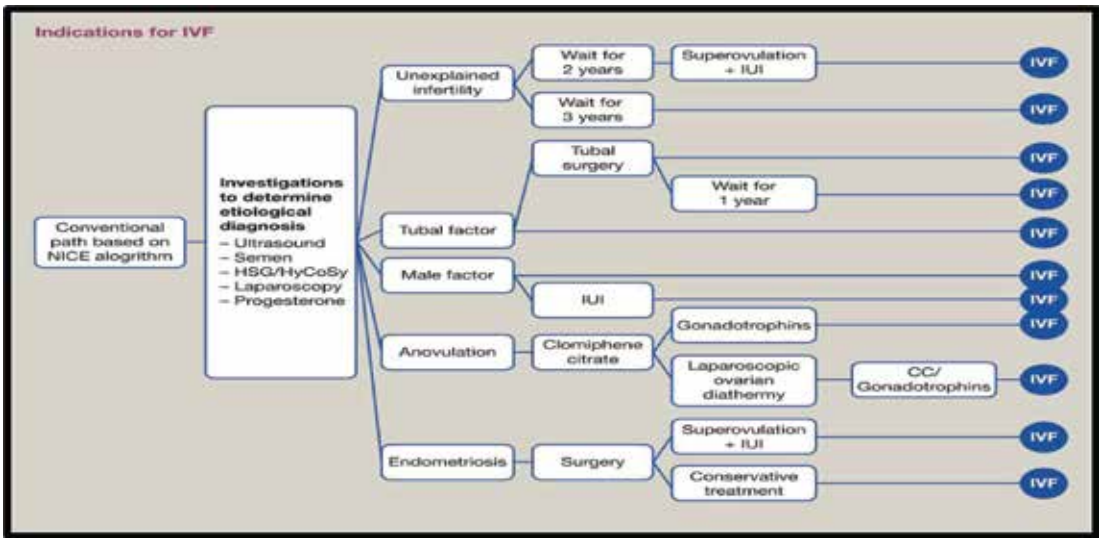
It is hoped that by combined application of history, clinical examination and proper semen analysis we can evaluate the male factor infertility.

# PATIENT SELECTION FOR IVF & PRE ART EVALUATION OF THE COUPLE

**Dr. KAVITHA NAGARAJAN.**
MD, MRCOG, FRM, MICG

## INDICATIONS FOR ASSISTED CONCEPTION

| | | | |
|---|---|---|---|
| UNEXPLAINED INFERTILITY | OVULATORY DYSFUNCTION | TUBAL FACTOR | ENDOMETRIOSIS |
| MALE FACTOR | THIRD PARTY REPRODUCTION | PGT | OTHER FAILED TREATMENTS |

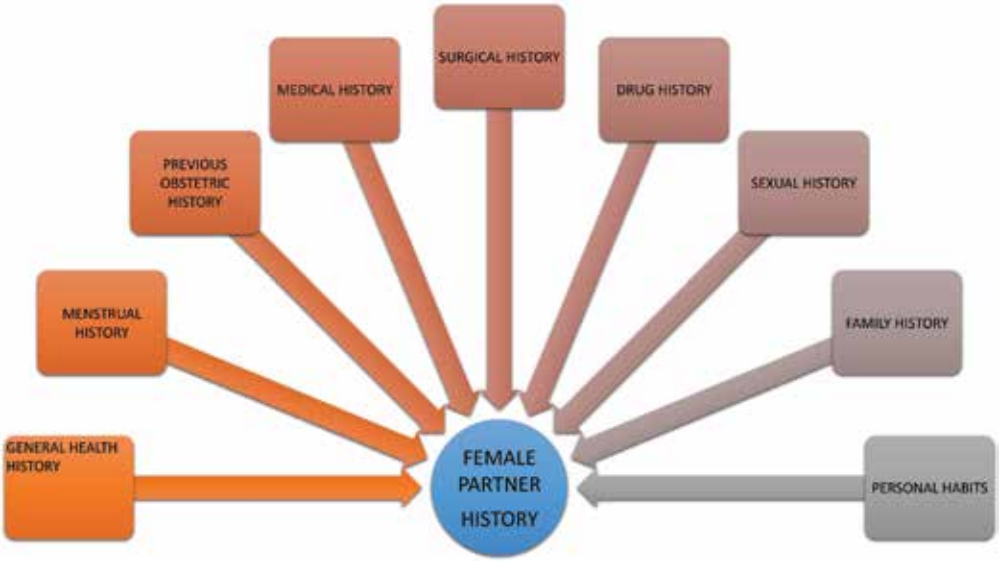



- Tubal surgery is not a realistic optionprimary investigations
- In case of impaired tubal function but no occlusion is present,
- Following tubal surgery - after an infertility duration of two years or longer.
- Depending on the female age, IVF can be done after a shorter duration of infertility.
- Anovulatory cycle abnormalities are indications for IVF if 12 cycles of treatment with ovulation induction have been unsuccessful.
- In case of mild or moderate endometriosis, treat as unexplained infertility
- In case of severe endometriosis, policy is to treat as tubal pathology

## MALE INFERTILITY

- TMC <1 million: first treatment of choice is ICSI.
- TMC >1 and <10 million: IVF can be performed if infertility duration is two years or longer
- TMC >10 million: treat as unexplained infertility.
- AZOOSPERMIA
- SURGICALLY RETRIEVED SPERMS

## EVALUATION OF FEMALE PARTNER




## PHYSICAL EXAMINATION

## PRIMARY INVESTIGATIONS


## AGE – SINGLE MOST IMPORTANT FACTOR?

- Chronological age is not same as biological age
- Age reflects the oocyte quality
- Assessment of the biological ovarian age would be necessary

**Table III Comparison of characteristics of the most widely used markers of ovarian reserve (modified with permission from La Marca et al. (2010)).**

| Characteristics for a Good Marker | Age | AMH | FSH | AFC |
|---|---|---|---|---|
| Prediction of poor response | + | +++ | ++ | +++ |
| Prediction of hyper response | + | +++ | + | +++ |
| Low inter-cycle variability | +++ | ++ | – | ++ |
| Low intra-cycle variability | +++ | ++ | – | ++ |
| Applicable to all patients | +++ | ++ | + | + |
| Economic | +++ | – | – | – |

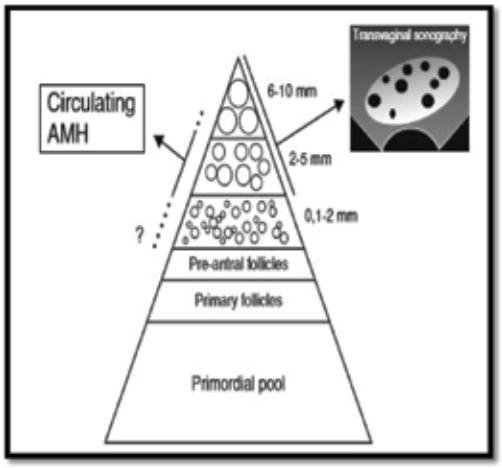
–, not appropriate; +, not very appropriate; +++, very appropriate. AFC, antral follicle count; AMH, anti-Mullerian Hormone.

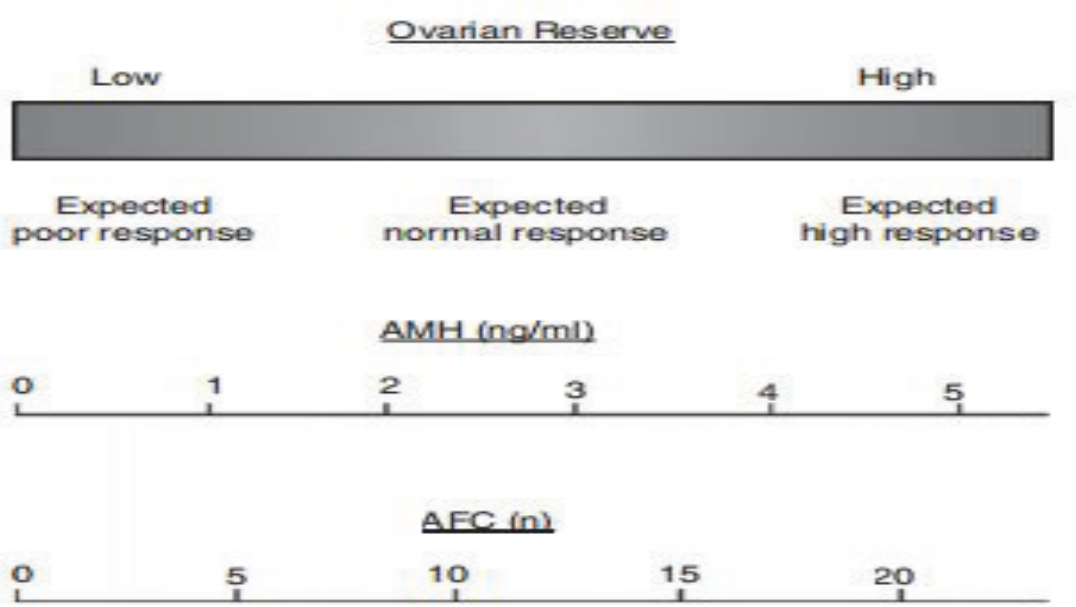
## AMH AND AFC :TWO FACES OF MOON

- Stronger & similar correlation with primordial foll.Counts and foll. recruitment rates
- Frequently pitted against each other as alternatives ,both may contribute and be synergistic

**Table 3 Characteristics of potential markers for response to COS (where +++ = degree to which a characteristic is present)**

| Characteristics of an effective marker | Age | AMH | FSH | AFC |
|---|---|---|---|---|
| Prediction of poor response | + | +++ | ++ | +++ |
| Prediction of hyper response | + | +++ | - | ++ |
| Low inter-cycle variability | +++ | ++ | - | ++ |
| Low intra-cycle variability | +++ | ++ | - | ++ |
| Applicable to all patients | +++ | +++ | + | + |
| Low cost of applying test | +++ | - | - | - |




## GENETIC BIOMARKERS

- Genetic polymorphisms may alter ovarian response to gonadotropins
- FSH RECEPTOR POLYMORPHISM
- LH RECEPTOR POLYMORPHISM

## FSHR POLYMORPHISM

SNP in position 680 of FSHr asp680 ser is asso. with altered response to stimulation

Asn680 is asso.with increased severity of OHSS

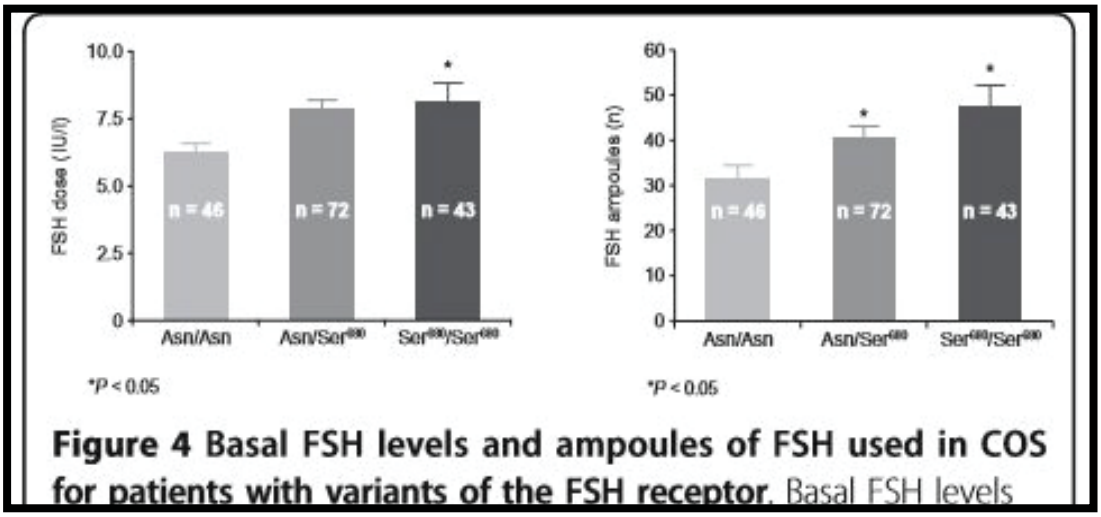



**Figure 4 Basal FSH levels and ampoules of FSH used in COS for patients with variants of the FSH receptor.** Basal FSH levels

Characterized by higher basal FSH , higher administered amounts of FSH required and higher risks of hypo- or hyper-responses.

Up to 35% of patients requiring ART are detected with alternatively spliced FSHR products

## LHR POLYMORPHISM

- Mutation in gene coding of LH is common in certain North European population.
- Common variant of the b subunit of the LH molecule (v-LH) is identified by an additional sulphonated sugar at asparagine (Asn)-13
- v-LH genotype may help to identify hyporesponders who are less sensitive to FSH - benefit from LH supplementation

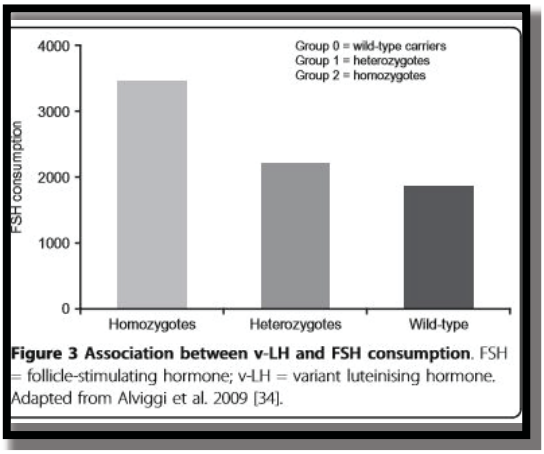



**Figure 3 Association between v-LH and FSH consumption.** FSH = follicle-stimulating hormone; v-LH = variant luteinising hormone. Adapted from Alviggi et al. 2009 [34].

## HOW TO INTERPRET?

Normal genetic profile with very low AMH/AFC:

NO DOSE WILL COMPENSATE

Bad genetic profile for FSHR with normal AMH/AFC:

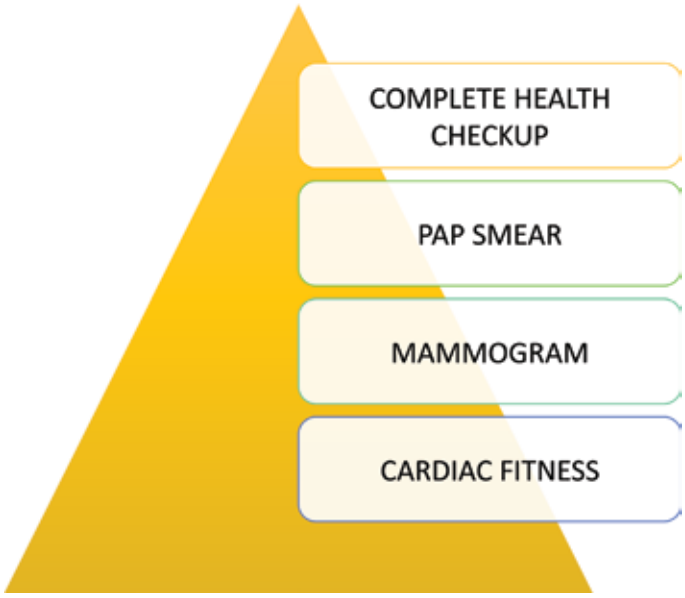
INCREASE THE DOSE OF FSH

Bad genetic profile for LH/LH-r with normal AMH/AFC:

ADD LH RATHER THAN INCREASING FSH

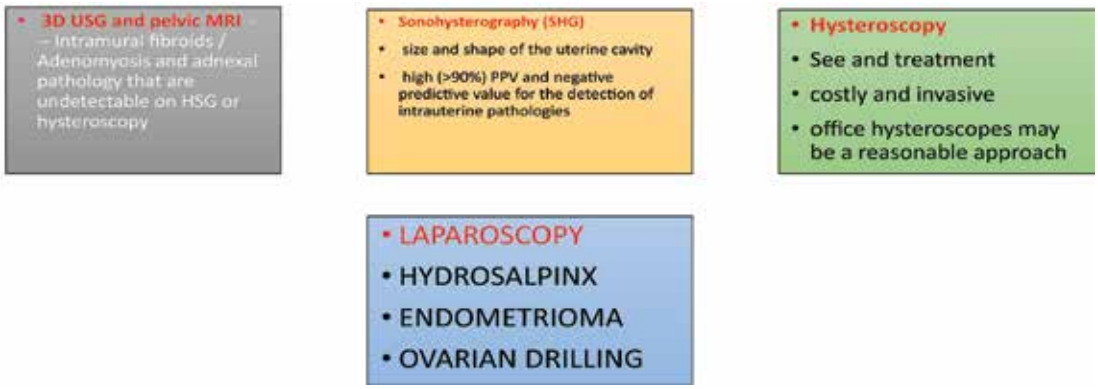
- Hormonal and functional biomarkers are more established tools to predict ovarian response
- In future, genetic biomarkers may be the best predictive tool to guide individualised treatment

## ADDITIONAL TESTS IN ADVANCED AGE



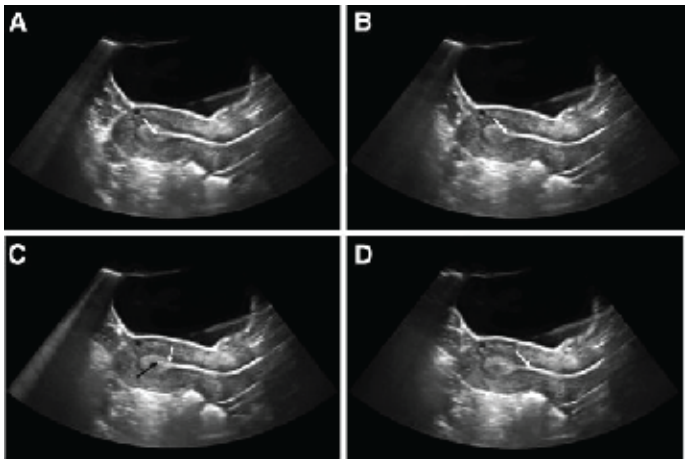

## SECONDARY INVESTIGATIONS

## UTERINE CAVITY EVALUATION




## TRIAL TRANSFER

- Measurement and mapping of the endometrial canal
- ET Catheters
- Under ultrasound guidance



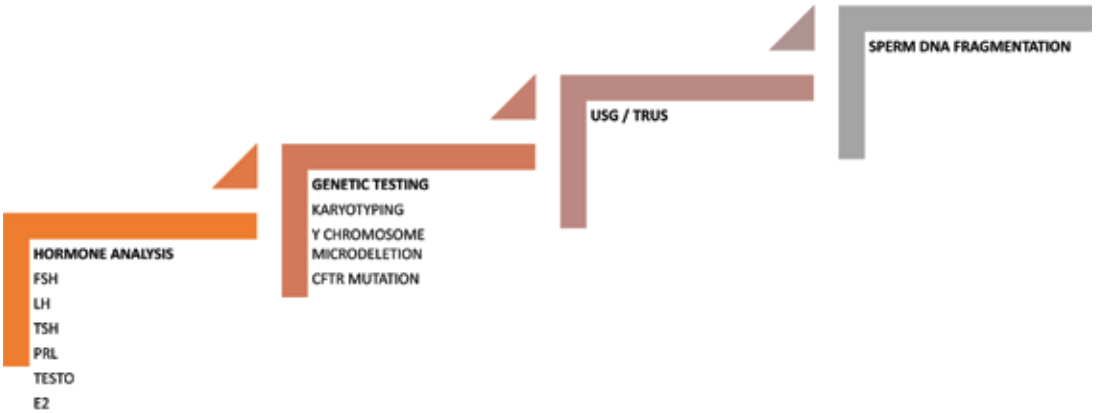

## SECONDARY INVESTIGATIONS

## MALE PARTNER


## PHYSICAL EXAMINATION


## PRIMARY INVESTIGATIONS


## SECONDARY INVESTIGATONS



## INDICATIONS FOR SPERM DNA FRAGMENTATION TEST

- RECURRENT IMPLANTATION FAILURE
- RECURRENT PREGNANCY LOSS
- SMOKING
- ADVANCED PATERNAL AGE
- UNEXPLAINED OR PERSISTANT INFERTILITY
- VARICOCELE

## MALE INFERTILITY – GENETIC ABNORMALITIES

INDICATIONS

- Non obstructive azoospermia/severe oligospermia < 5mil/m
  - Karyotype analysis
  - Y Chromosome micro deletions
- Obstructive azoospermia – CBAVD
  - CFTR gene mutation - chromosome 7

## IDENTIFICATION OF PATIENT SUBGROUPS REQUIRING AN ALTERED APPROACH BEFORE IVF

ART AND OBESE WOMEN

- Adverse effect on the outcomes of assisted conception
- Higher doses of gonadotropins are required
- Increased risk of early pregnancy loss, gestational diabetes and hypertensive disorders
- Management options:
- Dietary and lifestyle changes
- Pharmacologic agents for weight loss (orlistat)
- Bariatric surgery: laparoscopic adjustable gastric band
- Increasing doses of gonadotropins for ovulation induction and superovulation

## OLDER COUPLE UNDERGOING ART

- Mean age of women and men attending IVF clinics is increasing.
- Female aging adversely affects oocyte quality and oocyte yield after superovulation, reduces pregnancy rates and increases miscarriage rates.
- Chromosomal defects are increased with increasing female age.
- Obstetric risks such as preeclampsia and preterm birth are higher in older women.
- There is conflicting evidence on the effect of male age on IVF outcomes, with some studies showing no difference, while others show a reduction in pregnancy rates with increasing male age.
- Miscarriage rate appears to be increased with advancing male age
- Small but significant increase in abnormalities in children with older fathers; these include certain forms of autism, schizophrenia and, rarely, retinoblastoma.
- PGT-A may decrease the miscarriage rate, but with no effect on the cumulative live birth rate

## PCOS AND ART 20 TO 30%

- ounsel for increased obstetric risk (gestational diabetes, preeclampsia and fetal morbidity) if overweight - WEIGHT LOSS
- Treatment plan aimed to minimize risk of OHSS
- Use low dose stimulation in a short GnRHantagonist protocol.
- Metformin therapy may reduce the risk of OHSS in a long GnRH-agonist protocol

## PATIENT WITH AN ENDOMETRIOMA - 5 %

- Establish outcomes of previous surgical and/or medical treatments.
- Check ovarian reserve (AMH, AFC).
- Evaluate access for oocyte retrieval. consider segmentation of the cycle.
- Avoid surgery in patients with previous history of surgeries and reduced ovarian reserve.

## HYDROSALPINX

- Associated with a significant reduction in pregnancy and implantation rates
- Laparoscopic salpingectomy or tubal occlusion prior to IVF significantly improves results
- Prior to starting IVF:
- Salpingectomy through laparoscopy
- Tubal occlusion through laparoscopy if adnexal adhesions are present

During ovarian stimulation:

- Transvaginal aspiration of hydrosalpingeal fluid at the time of oocyte retrieval.
- Freeze all embryos, abandon fresh cycle, surgery for hydrosalpinx and then freeze thaw cycle.

## FIBROID - 20 TO 40 %

- Surgical removal of submucous fibroids is likely to improve pregnancy rates in ART patients.
- Evidence on surgical treatment for intramural fibroids is limited.
- If significant distortion is observed without uterine distention, excision should be considered
- Common practice, surgical treatment for intramural fibroids that distort the endometrial cavity or greater than 4 cm

## ADENOMYOSIS - 7% TO 34%

- Associated with endometriosis, subfertility, implantation failure, miscarriages, and a poor obstetric outcome such as preterm delivery, and preterm premature rupture of membranes.

- Normal ovarian reserve, the long GnRH agonist protocol - fresh ET
- FET , pretreatment with GnRH agonists for 3 TO 6 months
- Reduced ovarian reserve - freeze-all approach may be considered.

## ENODOMTRIAL POLYP - 7% TO 8%

- Subfertility, implantation failure and miscarriages.
- For polyps identified before IUI or IVF, polypectomy is recommended.
- If the polyp is small (< 1.5 cm), and the woman has no history of implantation failure or recurrent miscarriage, then continuation of IVF treatment with fresh embryo transfer can be considered.
- If the polyp is large (>1.5 cm), or if there is a history of implantation failure or recurrent miscarriage, then the option of freeze all embryos, polypectomy, followed by FET

## UTERINE ANOMALIES

- Surgery is indicated in the case of a functioning rudimentary horn
- Metroplasty is not recommended for partial or complete bicorporeal uterus
- It remains unknown whether hysteroscopic resection of a uterine septum improves fertility and pregnancy outcomes
- For women with severe uncorrectable uterine anomalies or absent uterus, surrogacy should be considered
- Uterine transplants are becoming more commonly performed but are associated with significant risks
- Partial bicorporeal uterus having IVF treatment - single embryo transfer (to reduce the risks of pregnancy loss and preterm births) into the larger of the two horns

## RECURRENT IMPLANTATION FAILURE

- RIF is a multifactorial condition
- No standard set of tests for RIF exist and these differ by clinic, but should be adjusted according to the suspected underlying cause.
- Optimize subsequent controlled ovarian hyperstimulation protocol to safely obtain as many oocytes as possible in order to assure a good number of top-quality blastocysts
- Perform thyroid function test, and consider testing for APS
- Consider removing polyps >1.5cm and submucous fibroids

- If there is evidence of hydrosalpinx, recommend laparoscopy and tubal clipping or removal
- If the patient has thin endometrium on ultrasound scan, consider a hysteroscopy
- If there is adenomyosis, consider prolonged pituitary downregulation with GnRH agonists for 6–8 weeks before ovarian stimulation / FET
- ERA - PROPER SCIENTIFIC VALIDATION IS AWAIED BEFORE RECOMMENDING THEIR USE

## LIFESTYLE FACTORS IMPORTANT IN MAXIMIZING IVF OUTCOMES


## PSYCHO-SOCIAL ASPECTS

- Stress, anxiety, and depression have been linked to lower IVF outcomes , and intervention improves the chance of success
- Paying attention to these factors will also improve interactions between patients and staff, and will help couples' adjustment to the stresses of child rearing
- COUNSELLING

## SUPPLEMENTS

- Antioxidants and omega-3s can be augmented by diet or by supplements
- Mitochondrial function decreases with age
- Oocyte mitochondria provide energy for chromosomal segregation and cell division until the blastocyst stage, when new mitochondria again start to be produced
- Co-enzyme Q10, a mitochondrial nutrient and cofactor in energy production, associated with improved chromosome segregation
- Small trial in the female, with a trend toward an increased pregnancy rate

# 2023

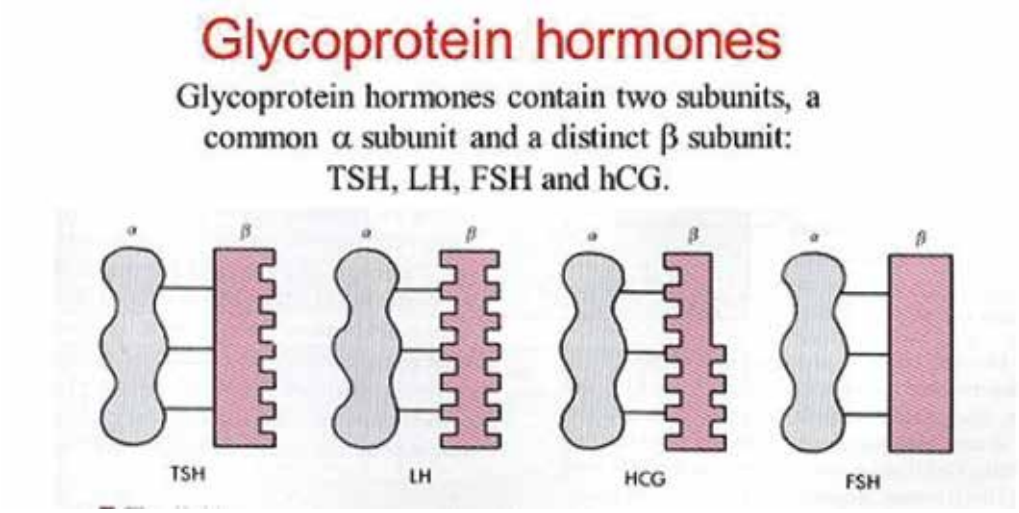

Spinal குடுக்கணும்,
Hypotension manage பண்ணனும்,
Anaesthetist
Fundal pressure குடுக்கணும்,
Synto load பண்ணனும்,
Baby resuscitate பண்ணனும்,
AL memes
இதுக்கு மேல baby delivery time ம்
பாக்கணும்னா எப்படி..?

# NEWER FSH

ADHUMITHA ARUNKARTHIK
NB, FMAS

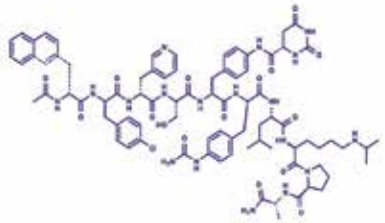
## FSH

- FSH is a glycoprotein dimer with alpha and beta subunits.
- The beta subunit is unique to FSH, while the alpha subunit is the same as in TSH, hCG, and LH.




## FSH IN ART

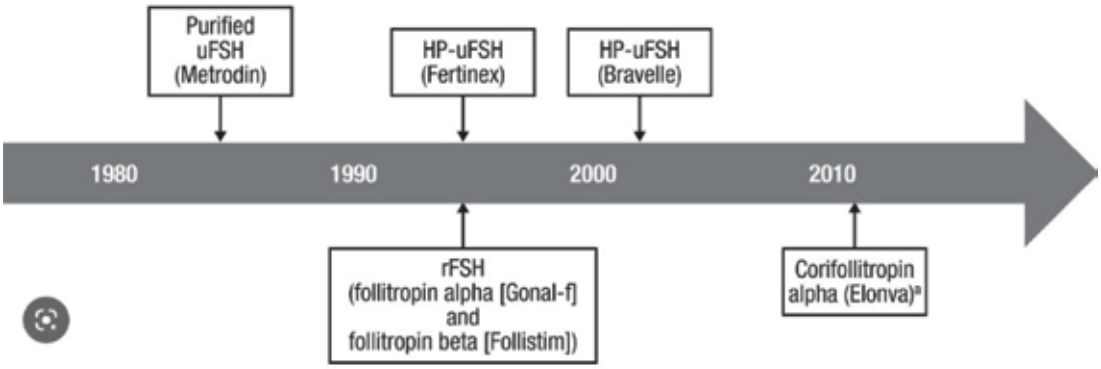
- The use of FSH is an indispensable part of fertility treatment.
- It is well established that the oocyte yield in patients undergoing ovarian stimulation is positively correlated with the extent of exposure to exogenous FSH.



## FSH IN ART

- There are a number of FSH preparations commercially available or in development, including both uFSHand rFSH.
- Differences in the glycosylation patterns of FSH gives rise to a number of naturally occurring isoforms that may differ functionally.

## TIMELINE




## SEARCH FOR NEWER FSH

- Injectable form
- Once daily injections for 9-12 days
- Aim to improve Follicular output rate (FORT) and Follicle-to-oocyte index (FOI)
- Better quality of oocytes and embryos
- Better FR, CPR and LBR
- To avoid OHSS

## FSH PREPARATIONS

Table 1. Currently available FSH products.

| Generic name | Active substrate | FSH:LH ratio | Trade name |
|---|---|---|---|
| Menotropin | uFSH and uLH | 1:1 | hMG-Ferring®, Humegon™, Menogon®, Pergonal®, Repronex® |
| Purified menotropin | uFSH and uLH | 2:1 | Menopur® |
| Urofollitropin | uFSH and uLH | 1:<0.01 | Metrodin®, Follegon® |
| Purified urofollitropin | uFSH and uLH | 1:<0.001 | Metrodin HP/Fertinex®, Bravelle® |
| Follitropin α | rhFSH | 100% FSH | Gonal-F® |
| Follitropin β | rhFSH | 100% FSH | Follistim®, Puregon® |

*FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; rhFSH: Recombinant human follicle-stimulating hormone; uFSH: Urinary follicle-stimulating hormone; uLH: Urinary luteinizing hormone.*
*Adapted from Huirne et al. (2004) [2] by kind permission of Adis International.*

## -FSH AND -FSH

- Both preparations are synthesized by the same recombinant technology resulting in identical dimeric-FSH and-FSH subunits.
- They differ in the glycosylation and purification procedures.
- Genes encoding the - and - subunits of human FSH and transfected these into Chinese hamster ovary (CHO) cells.
- Slightly more acidic follitropin- compared with follitropin - with the consequent different metabolic clearance, half-life and biologic activity.

RAPID COMMUNICATION | VOLUME 91, ISSUE 4, SUPPLEMENT , 1522-1525, APRIL 2009

Follitropin-α (Gonal-F) versus follitropin-β (Puregon) in controlled ovarian hyperstimulation for in vitro fertilization: is there any difference?

Raoul Orvieto, M.D., M.M.Sc. • Ravit Nahum, M.D. • Jacob Rabinson, M.D. • Jacob Ashkenazi, M.D. • Eyal Y. Anteby, M.D. • Simion Meltcer, M.D.

Published: October 13, 2008 • DOI: https://doi.org/10.1016/j.fertnstert.2008.08.112

TABLE 1

Comparison between IVF cycles in patients undergoing COH with GnRH agonist or antagonist using either follitropin-α or follitropin-β.

| | All patients | | | Agonist group | | | Antagonist group | | |
|---|---|---|---|---|---|---|---|---|---|
| | Follitropin-α | Follitropin-β | *P* value | Follitropin-α | Follitropin-β | *P* value | Follitropin-α | Follitropin-β | *P* value |
| No. of cycles | 198 | 68 | | 75 | 30 | | 123 | 38 | |
| Patient age (y) | 28.9 ± 4.0 | 29.3 ± 4.7 | NS | 28.9 ± 4.2 | 28.7 ± 5.0 | NS | 28.9 ± 3.9 | 28.9 ± 4.4 | NS |
| BMI (kg/m$^2$) | 23.6 ± 5.5 | 23.3 ± 5.8 | NS | 24.8 ± 5.2 | 21.8 ± 6.9 | NS | 22.8 ± 6.1 | 24.4 ± 4.8 | NS |
| Day 3 FSH (IU/L) | 6.5 ± 2.6 | 7.0 ± 2.3 | NS | 6.6 ± 2.4 | 6.2 ± 2.4 | NS | 7.4 ± 3 | 8.3 ± 3 | NS |
| Length of stimulation (d) | 9.6 ± 1.9 | 10.0 ± 1.9 | NS | 10.1 ± 1.9 | 10.5 ± 1.9 | NS | 9.3 ± 1.9 | 9.7 ± 1.9 | NS |
| Cumulative dose of recombinant human FSH (IU) | 1,980 ± 817 | 1,620 ± 645 | <.001 | 2,227 ± 1,035 | 1,763 ± 607 | <.01 | 1,845 ± 630 | 1,515 ± 667 | <.01 |
| Peak $E_2$ levels on day of hCG administration (pg/mL) | 1,605 ± 932 | 2,081 ± 1,063 | <.001 | 2,052 ± 1,074 | 2,219 ± 795 | NS | 1,361 ± 743 | 1,985 ± 1,218 | <.001 |
| Progesterone levels on day of hCG administration (ng/mL) | 0.7 ± 0.6 | 0.7 ± 0.4 | NS | 0.8 ± 0.6 | 0.7 ± 0.5 | NS | 0.7 ± 0.6 | 0.6 ± 0.3 | NS |
| No. of oocytes retrieved | 13.0 ± 6.9 | 13.9 ± 6.3 | NS | 14.8 ± 6.7 | 13.2 ± 1.3 | NS | 11.9 ± 6.7 | 14.5 ± 6.4 | <.04 |
| Fertilization rate (%) | 54 ± 23 | 57 ± 24 | NS | 58 ± 22 | 55 ± 26 | NS | 51 ± 23 | 58 ± 22 | NS |
| No. of embryos transferred | 2.0 ± 0.5 | 2.0 ± 0.4 | NS | 2.2 ± 0.6 | 2.1 ± 0.5 | NS | 1.9 ± 0.4 | 2.0 ± 0.3 | NS |
| Clinical pregnancy rate | 32.8% (65/198) | 22.1% (15/68) | .07 | 38.7% (27/68) | 23.3% (5/25) | 0.1 | 29.3% (35/118) | 21.1% (8/35) | .3 |

*Note:* COH = controlled ovarian hyperstimulation; BMI = body mass index; NS = not significant.

Clinical Trial > Hum Reprod. 1999 Nov;14(11):2709-15. doi: 10.1093/humrep/14.11.2709.

# Comparison of two recombinant follicle-stimulat hormone preparations in in-vitro fertilization: a randomized clinical study

M Tulppala [1], M Aho, T Tuuri, S Vilska, T Foudila, T Hakala-Ala-Pietilä, J Moilanen, T Bützow, S Kaukoranta, V Söderström-Anttila, R Siegberg, A M Suikkari, O Hovatta

Affiliations + expand

PMID: 10548606 DOI: 10.1093/humrep/14.11.2709

## Abstract

A randomized comparison of two recombinant human follicle-stimulating hormone (recFSH) preparations (Gonal-F and Puregon) in ovarian stimulation for in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was carried out at the Infertility Clinic of the Family Fed of Finland. A total of 348 women (aged 22-43 years) suffering from infertility due to miscellan causes was recruited. Of these, 344 underwent stimulation using equal starting doses (150 IU/ Gonal-F n = 164, Puregon n = 158 or 300 IU/day: Gonal-F n = 8, Puregon n = 14) after down- regulation with intranasal buserelin from the mid-luteal phase. Similar clinical pregnancy rates achieved with both preparations; 33.5% per cycle and 37.4% per embryo transfer (24.5% one- and 75.5% two-embryo transfers, n = 147) with Gonal-F (150 IU/day) and 32.9% per cycle and per embryo transfer (30.1% one-embryo and 69.9% two-embryo transfers, n = 145) with Pure (150 IU/day). The ongoing cumulative pregnancy rates after frozen-thawed embryo transfer w 35.4% with Gonal-F and 37.7% with Puregon. Six cycles were cancelled because of a low respo (three in each group). Similar numbers of oocytes were obtained in both groups; 13.0 with 150

FERTILITY AND
VOL. 73, NO. 1,


# A comparison of the efficacy and tolerability of two recombinant human follicle-stimulating hormone preparati in patients undergoing in vitro fertilization-embryo transfer

*Peter Brinsden, M.D.,* Fidelis Akagbosu, M.D.,* Lisa M. Gibbons, M.D.,* Susan Lancaster, Ph.D.,† Dominique Gourdon, Pharm.D.,† Patrick Engrand, P Ernest Loumaye, M.D., Ph.D.†*

*Bourn Hall Clinic, Bourn, Cambridge, United Kingdom; and Ares-Serono International S.A., Gen Switzerland*

**Objective:** To compare the efficacy and tolerability of two recombinant human FSH (r-hFSH) follitropin-α (Gonal-F; Ares Serono, Geneva, Switzerland) and follitropin-β (Puregon; Orga Netherlands), for superovulation in patients undergoing IVF-ET.

**Design:** Randomized, parallel-group, assessor-blind, single-center trial.

**Setting:** Outpatient tertiary referral center for assisted reproductive techniques.

**Patient(s):** Forty-four infertile women undergoing IVF-ET.

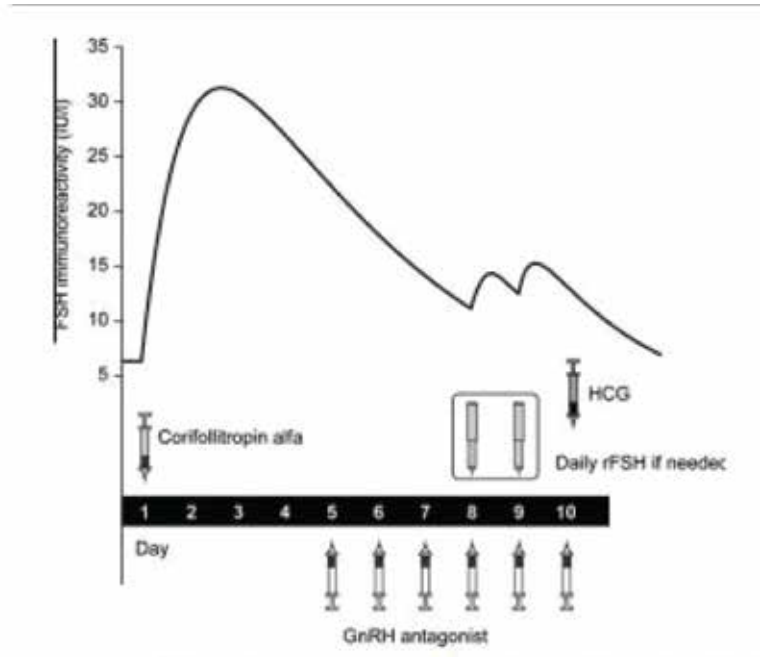
## FOLLITROPIN + LUTROPIN

- 2:1 ratio.
- Use of r-hLH supplementation during controlled ovarian stimulation remains a topic of ongoing debate.
- ESPART trial is to explore the possible superiority of a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio over rFSH monotherapy in patients with a POR, (ESHRE Bologna criteria).
- Not superior in terms of number of oocytes retrieved, the LBR per cycle were similar in both groups.
- Total pregnancy outcome failure was significantly lower in the rFSH/rLH group than in the rFSH group.
- rFSH/rLH treatment may have added clinical value compared with rFSH alone in women with POR, but additional studies are needed to validate and confirm these observations.

## CORIFOLLITROPIN ALPHA

- Similar pharmacodynamic properties as rFSH but maintains prolonged follicle-stimulating activity.
- Glycosylation sites have been inserted into FSH to generate a longer half-life agonist.
- Corifollitropin alfa is a recombinant fusion molecule composed of an a-subunit identical to that in human FSH and a b-subunit, which is a hybrid composed of the FSH b-subunit and carboxyterminal peptide of human chorionic gonadotrophin (HCG) b-subunit.
- Unlike rFSH, the dose of corifollitropin alfa cannot be converted into international units and is expressed in micrograms.
- Time to serum peak concentrations is approximately 44 h and its elimination half-life is approximately 69 h (compared with 34 h for conventional rFSH).
- Less suitable to induce monofollicular growth and ovulation, as even low doses of corifollitropin alfa easily result in multiple follicular growth.
- Higher patient cooperation and compliance, lower risk of errors.
- A single SC injection of corifollitropin alfa has the capacity to initiate and sustain multiple follicular growth for the first 7 days of COS, reducing the number of injections required in one treatment cycle.
- Corifollitropin alfa is administered as a single injection on menstrual cycle day 2 or 3 (stimulation day 1).

- Daily injections of FSH are started on the eighth day of stimulation if necessary.
- A GnRH antagonist is associated with day 5 or 6 of stimulation to prevent a premature surge in LH.




Fertility and Sterility asrm

ORIGINAL ARTICLE | VOLUME 111, ISSUE 4, P722-733, APRIL 2019

## Corifollitropin alfa for ovarian stimulation in in vitro fertilization: a systematic review and meta-analysis of randomized controlled trials

Mauro Cozzolino, M.D. • Amerigo Vitagliano, M.D. • Gustavo Nardini Cecchino, M.D. • Guido Ambrosini, M.D. • Juan Antonio Garcia-Velasco, Ph.D.

DOI: https://doi.org/10.1016/j.fertnstert.2018.11.047 • Check for updates

**Result(s):** Eight randomized controlled trials were included; 2,345 women were assigned to the intervention group and 1,995 to the control group. The analysis of 4,340 IVF cycles did not reveal any difference in live birth rate and/or ongoing pregnancy rate between groups (risk ratio [RR], 0.92; 95% confidence interval [CI], 0.80–1.05). Similarly, no difference was found in clinical pregnancy rate (RR, 0.96; 95% CI, 0.88–1.05; $I^2 = 0\%$), miscarriage rate (RR, 0.94; 95% CI, 0.71–1.25; $I^2 = 0\%$), or multiple pregnancy rate (RR, 1.22; 95% CI, 0.99–1.50; $I^2 = 0\%$). Also, the rates of cycle cancellation, ovarian hyperstimulation syndrome, and ectopic pregnancy were similar in both groups. Sensitivity and subgroup analyses did not provide statistical changes to pooled results.

**Conclusion(s):** Corifollitropin alfa seems to be an alternative for daily recombinant FSH injections in normal and poor responder patients undergoing ovarian stimulation in IVF/ICSI treatment cycles. (Fertil Steril® 2019;111:722-33. ©2018 by American Society for Reproductive Medicine.)


RBMO

ARTICLE | VOLUME 33, ISSUE 1, P56-60, JULY 2016

Corifollitropin alfa versus recombinant follicle-stimulating hormone: an individual patient data meta-analysis

Georg Griesinger • Robert Boostanfar • Keith Gordon • Davis Gates • Christine McCrary Sisk • Barbara J. Stegmann

Published: April 20, 2016 • DOI: https://doi.org/10.1016/j.rbmo.2016.04.005 • Check for updates

Corifollitropin alfa is a recombinant gonadotrophin with sustained follicle-stimulating activity, such that a single dose is able to initiate and sustain the growth of multiple follicles for the first 7 days of ovarian stimulation (Fauser et al, 2009). Three separate randomized, double-blind, phase III trials of women undergoing ovarian stimulation with either corifollitropin alfa or recombinant FSH (rFSH), Engage (Devroey et al, 2009), Ensure (Corifollitropin alfa Ensure Study Group, 2010) and Pursue (Boostanfar et al, 2015) showed that a single injection of corifollitropin alfa for the first 7 days of ovarian stimulation was either equivalent (Engage and Ensure) or non-inferior (Pursue) to daily injections of rFSH regarding the number of oocytes retrieved, and equivalent (Engage) or non-inferior regarding vital pregnancy rates (Pursue), equivalent (Engage) or non-inferior (Pursue) regarding ongoing pregnancy rates, and non-inferior regarding live-birth rates (Pursue). In addition, there were no significant differences in the incidence of ovarian hyperstimulation syndrome (OHSS) between corifollitropin alfa and rFSH in the three trials.


RBMO

REVIEW | VOLUME 23, ISSUE 2, P159-169, AUGUST 2011

Corifollitropin alfa doses based on body weight: clinical overview of drug exposure and ovarian response

William L. Ledger • Bart C.J.M. Fauser • Paul Devroey • Anthe S. Zandvliet • Bernadette M.J.L. Mannaerts

Published: April 18, 2011 • DOI: https://doi.org/10.1016/j.rbmo.2011.04.002

Corifollitropin alfa is a new sustained follicle stimulant, a single injection of which can replace the conventional first seven daily injections of recombinant FSH in ovarian stimulation for IVF or intracytoplasmic sperm injection. This review is based on the results of clinical trials testing two selected doses of corifollitropin alfa for patients of different body weights, 150 g for patients weighing more than 60 kg, and 100 µg for patients weighing up to 60 kg. The relationships between patient body weight, drug exposure and ovarian response are discussed. These selected doses of corifollitropin alfa, administered according to the patient's body weight, provide, on average, equal drug exposure and a similar ovarian response in terms of the number of growing follicles and number of eggs retrieved. It is recommended that patients should be treated with the appropriate dose of corifollitropin alfa according to their body weight as a lower dose does not result in milder stimulation and a higher dose does not result in an improved ovarian response. Successful use of corifollitropin alfa requires assessment of patient suitability and dosing before the start of stimulation. After decades of daily dosing with FSH preparations, corifollitropin alfa allows a simpler IVF/intracytoplasmic sperm injection treatment regime with fewer injections.

Table 3 Summary of dose recommendations of corifollitropin alfa in relation to body weight.

| Dose | Women ≤60 kg | Women >60 kg |
|---|---|---|
| 100 µg | Optimal sustained multiple follicular development for 7 days | Not indicated<br>Results in too low corifollitropin alfa exposure and therefore increases the risk of cycle cancellation<br>Will not result in milder stimulation |
| 150 µg | Not indicated<br>Results in too high corifollitropin alfa exposure beyond stimulation day 8<br>Will not result in a higher ovarian response | Optimal sustained multiple follicular development for 7 days |

## FSH DELTA

- First rFSH derived from a human cell line (PER.C6 cell line).
- While follitropin alfa and follitropin delta have the same amino acid FSH sequence, they vary in their glycosylation.
- First rFSH with defined dose algorithm.

## DEFINED DOSING ALGORITHM

- First rFSH derived from a human cell line (PER.C6 cell line).
- While follitropin alfa and follitropin delta have the same amino acid FSH sequence, they vary in their glycosylation.
- First rFSH with defined dose algorithm.

| Serum AMH concentration (pmol/L) | Daily dose[a] (fixed throughout stimulation) |
|---|---|
| <15 | 12 μg |
| 15–16 | 0.19 μg/kg |
| 17 | 0.18 μg/kg |
| 18 | 0.17 μg/kg |
| 19–20 | 0.16 μg/kg |
| 21–22 | 0.15 μg/kg |
| 23–24 | 0.14 μg/kg |
| 25–27 | 0.13 μg/kg |
| 28–32 | 0.12 μg/kg |
| 33–39 | 0.11 μg/kg |
| ≥40 | 0.10 μg/kg |

[a] Maximum daily dose is 12 μg.

*Nyboe Andersen. Individualized ovarian stimulation. Fertil Steril 2016.*

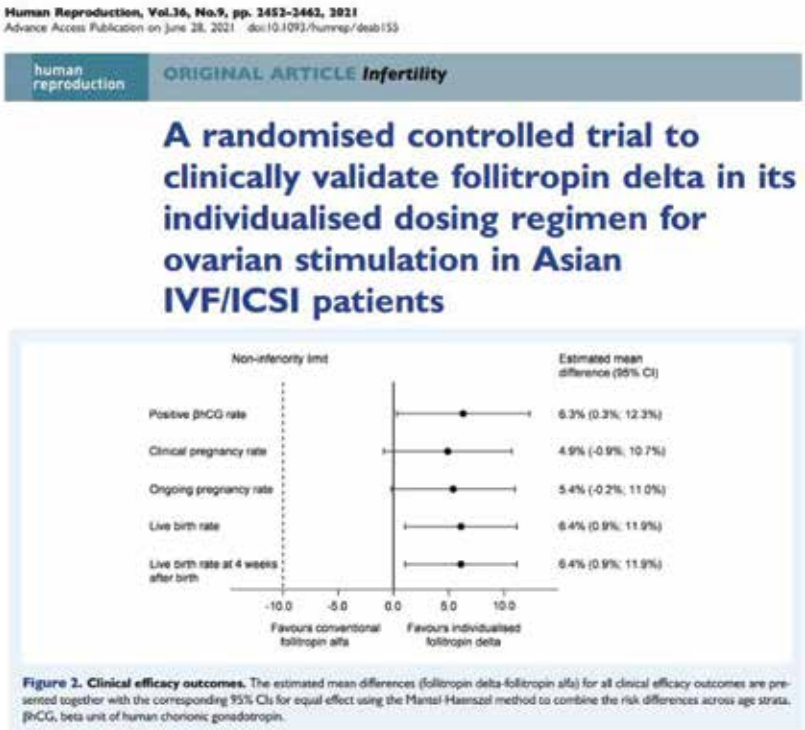



**Figure 2. Clinical efficacy outcomes.** The estimated mean differences (follitropin delta-follitropin alfa) for all clinical efficacy outcomes are presented together with the corresponding 95% CIs for equal effect using the Mantel-Haenszel method to combine the risk differences across age strata. βhCG, beta unit of human chorionic gonadotropin.

RBMO

ARTICLE | VOLUME 42, ISSUE 5, P909-918, MAY 2021

## Individualized follitropin delta dosing reduces OHSS risk in Japanese IVF/ICSI patients: a randomized controlled trial

Osamu Ishihara • Joan-Carles Arce • for the Japanese Follitropin Delta Phase 3 Trial (STORK) Group

Open Access • Published: February 08, 2021 • DOI: https://doi.org/10.1016/j.rbmo.2021.01.023 •

**Design:** This randomized, controlled, assessor-blind, multicentre, non-inferiority trial was conducted in 347 Japanese IVF/intracytoplasmic sperm injection patients. They were randomized to individualized follitropin delta (AMH <15 pmol/l: 12 μg/day; AMH ≥15 pmol/l: 0.10–0.19 μg/kg/day; minimum 6 μg/day; maximum 12 μg/day) or conventional follitropin beta (150 IU/day for the first 5 days, with potential subsequent dose adjustments). The primary end-point was the number of oocytes retrieved with a pre-specified non-inferiority margin (−3.0 oocytes).

**Results:** The primary trial objective was met, as non-inferiority was established for number of oocytes retrieved for individualized follitropin delta dosing compared with conventional follitropin beta dosing (9.3 versus 10.5; lower boundary of 95% confidence interval −2.3). The occurrence of ovarian hyperstimulation syndrome (OHSS) was reduced to approximately half with individualized compared with conventional dosing, with an incidence of 11.2% versus 19.8% ($P = 0.021$) for OHSS of any grade and 7.1% versus 14.1% ($P = 0.027$) for moderate/severe OHSS. The live birth rate per started cycle was 23.5% for individualized dosing and 18.6% for conventional dosing.

**Conclusions:** Dosing with individualized follitropin delta in Japanese women is non-inferior to conventional dosing with follitropin beta for number of oocytes retrieved. The individualized approach shows a favourable benefit–risk profile, providing a statistically significant and clinically relevant reduction in the incidence of OHSS, without compromising live birth rates.

ORIGINAL ARTICLE

## Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial

Anders Nyboe Andersen, M.D., Ph.D. • Scott M. Nelson, M.R.C.O.G., Ph.D. • Bart C.J.M. Fauser, M.D., Ph.D. • Bjarke M. Ravn, Ph.D. • Joan Carles Arce, M.D., Ph.D. • for the ESTHER-1 study group • Show all authors

Open access • Published: November 29, 2016 • DOI: https://doi.org/10.1016/j.fertnstert.2016.10.033 •

**Objective:** To compare the efficacy and safety of follitropin delta, a new human recombinant FSH with individualized dosing based on serum antimüllerian hormone (AMH) and body weight, with conventional follitropin alfa dosing for ovarian stimulation in women undergoing IVF.
**Design:** Randomized, multicenter, assessor-blinded, noninferiority trial (ESTHER-1).
**Setting:** Reproductive medicine clinics.
**Patient(s):** A total of 1,329 women (aged 18–40 years).
**Intervention(s):** Follitropin delta (AMH <15 pmol/L: 12 μg/d; AMH ≥ 15 pmol/L: 0.10–0.19 μg/kg/d; maximum 12 μg/d), or follitropin alfa (150 IU/d for 5 days, potential subsequent dose adjustments; maximum 450 IU/d).
**Main Outcome Measure(s):** Ongoing pregnancy and ongoing implantation rates; noninferiority margin −4.6%.
**Result(s):** Ongoing pregnancy (30.7% vs. 31.6%; difference −0.9% [95% confidence interval (CI) −5.9% to 4.1%]), ongoing implantation (35.2% vs. 35.8%; −0.6% [95% CI −6.1% to 4.8%]), and live birth (29.4% vs. 30.7%; −0.9% [95% CI −5.8% to 4.0%]) rates were similar for individualized follitropin delta and conventional follitropin alfa. Individualized follitropin delta resulted in more women with target response (8–14 oocytes) (43.3% vs. 38.4%), fewer poor responders (fewer than four oocytes as patients with AMH < 15 pmol/L) (11.8% vs. 17.9%), fewer excessive responses (≥ 15 or ≥ 20 oocytes in patients with AMH ≥ 15 pmol/L) (17.9% vs. 35.1% and 10.1% vs. 15.6%, respectively), and fewer measures taken to prevent ovarian hyperstimulation syndrome (2.3% vs. 4.5%), despite similar oocyte yield (10.0 ± 5.6 vs. 10.4 ± 6.5) and similar blastocyst numbers (3.3 ± 2.8 vs. 3.5 ± 3.2), and less gonadotropin use (90.0 ± 25.3 vs. 933.7 ± 33.6 μg).
**Conclusion(s):** Optimizing ovarian response in IVF by individualized dosing according to pretreatment patient characteristics results in similar efficacy and improved safety compared with conventional ovarian stimulation.

MO

ARTICLE

## An eight centre, retrospective, clinical practice data analysis of algorithm-based treatment with follitropin delta

Annette Ravn Jensen, A. M. • Stefan Kircher • Ivo Laubert • ... David Sebastian Sauer • Sascha Sauerbrei • Alexandra Petra Rothuß • Show all authors

Published: December 21, 2021 • DOI: https://doi.org/10.1016/j.rbmo.2021.12.013 • Check for updates

Design

In eight reproductive medicine centres in Germany, observational data of 360 women who underwent ovarian stimulation with follitropin delta were evaluated as part of the quality control from January 2018 to June 2019. The data were analysed retrospectively.

Results

Mean age of patients was 33.5 (±3.8) years. Pretreatment AMH concentrations ranged from <0.6 ng/ml or 3.6 pmol/l (2.5%) to >5.6 ng/ml or 40 pmol/l (19.7%), with 79.7% of all AMH measurements above 2.0 ng/ml or 14.5 pmol/l. The mean number of oocytes obtained in n = 359 first follitropin delta cycles was 11.2 (±6.7) oocytes with 42.1% of patients having between eight and 14 oocytes retrieved at oocyte retrieval. The average clinical pregnancy rate in the first cycle with a fresh embryo transfer was 38.2% with a mean of 1.4 embryos per transfer. The cumulative pregnancy rate was 49.4% for the first stimulation cycle (including cryopreservation cycles generated from the first stimulation cycle).

Conclusion

The goal of obtaining an adequate number of oocytes (8–14 oocytes) using the follitropin delta dosing algorithm was reached in 42.1% of patients despite a wide range of pretreatment AMH values, while achieving very good clinical pregnancy rates. Hence, algorithm-based ovarian stimulation with follitropin delta remains highly effective in clinical practice.

## UNDER TRIAL

- Oral drugs, TOP5668, TOP5300 were evaluated in vitro in Chinese hamster ovary cells.
- TOP5668 was found to have solely FSHR-AA activity while TOP5300 was found to have mixed FSHR-AA and LHR-AA activity.
- In pooled human granulosa cells obtained from patients undergoing IVF, TOP5300 stimulated 7-fold greater maximal E2 response than rFSH and TOP5668 was 10-fold more potent than TOP5300.

# ESTETROL/DROSPIRENONE –THE NEWER CONTRACEPTIVE

**DR ASHWIN RAO**
MS, DNB, FMAS

## ABSTRACT:

Estetrol/Drospirenone is a combination of new plant based estrogen Estetrol with an established progestin Drospirenone showing low affinity to estrogen receptor . This low oestrogenicity has potentially low risk of thrombosis. Estetrol/drospirenone is well tolerated in metrorrhagia which is similar to the other combined oral contraceptive agents. It is also seen that there is a decreased increased of hyperkalemia, depression and migraines.

## INTRODUCTION:

Drospirenone has long been used along with ethinyl estradiol as a combined oral contraceptive pill with a potential risk of thrombosis. Now a new combination of estetrol instead of ethinyl estradiol has been introduced. Estetrol being a plant synthesized estrogen has a lesser affinity to the ER- (estrogen receptor alpha) in contrast to estradiol. It has antagonistic action on other tissues like the breast. [1] This lower affinity of estetrol may potentially have a lower risk of thrombosis. This combination is also better tolerated in metrorrhagia when compared to other combined oral contraceptive pills. It is also associated with lower risks of migraines, hyperkalemia, depression and deep vein thrombosis.[2]

## PHARMACODYNAMICS:

The combination of estetrol with drospirenone suppresses ovulation thereby preventing pregnancy. Both estetrol and ethinylestradiol bind to the same estrogen receptor and have similar modes of expression on the uterine gene. Estetrol have better action in the promotion of endometrial growth. Estetrol partially antagonizes steroid signaling and also inhibited tyrosine kinase in cell lines of breast cancer. [3]

Studies showed that estetrol/drospirenone had a lower chance of ovulation when compared to ethinylestradiol (20µg)/drospirenone and there was better suppression of the pituitary ovarian axis. The estetrol/drospirenone combination did not affect the lipid profile and carbohydrate metabolism when compared to other COCPs. Estetrol was also found to have limited effects on cortisol, FSH and LH. The pro-thrombotic effects of estetrol was also found to be lower than

ethinylestradiol. [4] It was also seen that there was no relevant QT prolongation when the dose was increased to 5 times the recommended dose.

## DOSAGE:

The dosage recommended in the USA and Europe for contraception is that the combination is taken as a once daily tablet at the fixed time in a 28 day cycle. Each pack consists of 24 active tablets wherein each tablet contains 14.2 mg of estetrol and 3 mg of drospirenone and four inert tablets. Other modes of barrier or non-hormonal contraceptives are advised in case of a missed pill by more than 24 hours. The missed pill may the taken immediately even if it falls on the same day as the next pill. It was found that after a missed pill, the contraceptive effect was restored after seven days of uninterrupted usage.[5]

## EFFICACY OF ESTETROL/DROSPIRENONE:

The phase II FIESTA trial which evaluated the estetrol/drospirenone combination showed the best cycle control and bleeding pattern. In the phase II FIESTA trial, estetrol/drospirenone 15 mg/3 mg was similar to estradiol valerate/dienogest with respect to user satisfaction, acceptability and bodyweight control. Overall satisfaction was assessed using combined data from cycles 1–4 and 6 as an aggregate of the following domains; general feeling, mood, sexual life, premenstrual complaints and overall effect. The odds ratio for overall satisfaction with estetrol/drospirenone 15 mg/3 mg versus estradiol valerate/dienogest was 0.69 (95% CI 0.39–1.25). At cycle 6, the proportion of women who were reported to be satisfied or very satisfied with the study drug were 73.1% versus 67.6%, respectively. The proportion of women who gained or lost ≥ 2 kg of body weight by cycle 6 were generally similar across the estetrol/drospirenone 15 mg/3 mg and estradiol valerate/dienogest treatment arms. [6]

Similar studies like the E4 FREEDOM study evaluated the efficacy of estetrol/drospirenone on heterosexually active women between 16-50 years whose BMI was less than 35kg/m2 with primary intention of contraception for 12 months. It was seen that there was lower rates of cerebrovascular, cardiovascular and thromboembolic phenomena.[7]

## CONTRAINDICATIONS:

- Estetrol/ Drospirenone although low but still has a risk of venous and arterial thromboembolism and hence contraindicated in women with thrombotic diseases.
- It is not recommended in cases of current or past history of hormone sensitive malignancies like breast cancer.
- Renal impairment
- Adrenal insufficiency

- Liver disorders like hepatic adenoma, hepatocellular carcinoma, acute hepatitis, decompensated cirrhosis etc.,
- Patients on Hepatitis C drugs co-administration containing ombitasavir, paritaprevir or ritonavir.
- It is also contraindicated in abnormal uterine bleeding with an undiagnosed etiology.[8]

## PRECAUTIONS WITH ESTETROL/DROSPIRENONE:

- Hyperkalemia: Serum potassium levels may increase in women on long term treatment with estetrol/drospirenone.
- Hypertension: Blood pressure needs to be checked periodically and estetrol/drospirenone needs to be stopped in case of significant increase.
- Migraines: Discontinue in case recurrent, severe or persistent migraines.
- Hypertrigyceridemia and hyperglycermia: Serum glucose levels and triglycerides needs to be periodically monitored. Alternative contraceptive methods can be considered in case of prediabetes and hypertriglyceridemia.
- Hormone sensitive malignancy: Estetrol/Drospirenone needs to be discontinued in case of a hormone sensitive malignancy is diagnosed.
- Liver disorders: Periodic liver function tests are mandatory and the drug needs to be discontinued or withheld in case of persistent elevation of liver enzymes.
- Detection of gallstones or cholestatic disease also mandates discontinuation.
- All cardiovascular risk factors need to be evaluated before starting estetrol/drospirenone. In case of any history of thromboembolic event, other modes of contraception needs to be considered.

## ADVERSE REACTIONS:

The most common adverse effects include mood swings, breast symptoms, dysmenorrhea, acne, decreased libido, bleeding irregularities and acne.

## DRUG INTERACTIONS:

- CYP3A Inducers may lead to failure of contraception or chances of breakthrough bleeding.
- Concomitant usage with Hepatitis C drugs needs to be avoided.

## USE IN PREGNANCY AND LACTATION:

- Estetrol/Drospirenone needs to be discontinued in pregnancy.
- It can decrease milk production and hence avoided in lactation.[9]

## CONCLUSION:

In conclusion, Estetrol/drospirenone is a well-tolerated and effective combined oral contraceptive agent which hence increases the available options for contraception with lower risk of thromboembolism compared to the other combined contraceptive agents.

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