INTROSPECT

VOLUME IV

AUGUST 2024

E-JOURNAL BY

OGSOS

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,
MD OG, FRM, MRCOG, MICG.,

DR. ANUREKHA J P,
MD, DNB, FRM, FICOG

DR. MADHUMITHA ARUNKARTHIK
MS, DNB, FRM, FMAS.

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

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MS OG,, DNB., MNAMS., MRCOG.,

CONTENTS

Dr. Meenakshi Bhairavi Kannan
MS Medical Genetics (UK), PhD Molecular Medicine (Canada)
Genetics CentreKanshyaGenetics Consultant,

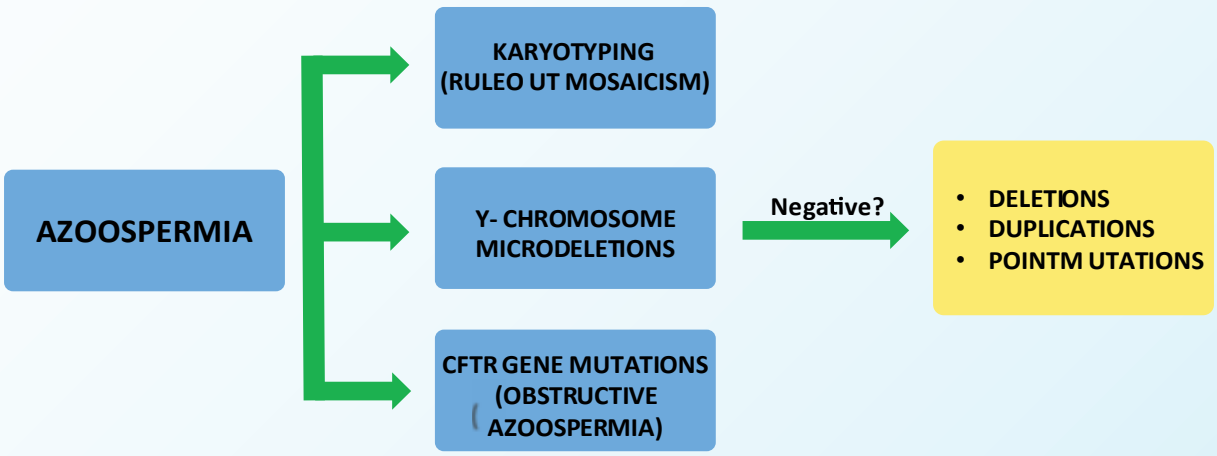
AZOOSPERMIA - THE ROLE OF THE X CHROMOSOME IN SOUTH INDIAN POPULATION

Infertility impacts approximately 15% of couples, and about 45% of infertility is caused by male factors. Up to 20% of infertile men receive a diagnosis of azoospermia. Disorders in spermatogenesis caused by genetic factors represent the most commonly encountered problems, accounting for 15%–30% of male infertility, and these typically manifest as severe oligospermia or azoospermia. The incidence of azoospermia is about 10%–15% in male infertility,which can be divided into obstructive azoospermia (OA; 15%–20%)and nonobstructive azoospermia (NOA; 80%–85%). NOA is spermatogenic failure, which is the absence of spermatozoa in the seminal fluid. Azoospermia is a heterogeneous condition with a varied range of histologic phenotypes.For OA patients, it is sometimes possible to restore reproductive function via surgery or other treatments,whereas NOA is understood as one of the most difficult diseases to treat in male infertility. Etiology and mechanisms of many NOA patients remain unclear, further limiting treatment options.Moreover, only limited genetic tests are currently available to help determine the etiology of infertile men, including karyotyping, Y chromosome azoospermia factor (AZF) microdeletion, and cystic fibrosis transmembrane conductance regulator (CFTR) mutation screening. The Y-microdeletion analysis does not assess other chromosomes and could be a drawback in genetic investigations of men with NOA. Up to 20% of men with nonobstructive azoospermia have a detectable chromosomal abnormality; these abnormalities include sex-chromosome anomalies (e.g., Klinefelter's syndrome), structural aberrations (e.g., translocations and inversions), and Y-chromosome microdeletions of azoospermia factors. However, the remaining 80% of men with nonobstructive azoospermia have negative results on these basic genetic tests and receive a diagnosis of "idiopathic" azoospermia, which makes patient counselling extremely difficult. Assessing other genetic factors in male infertility, and especially in NOA patients, is very likely to further clarify the causes and mechanisms of spermatogenesis disorders and to improve the capacity of clinicians to provide individualized diagnoses as well as comprehensive genetic counseling for patients with azoospermia.

POSITION	MUTATION	PROTEIN/RNA CHANGE	SPERM COUNT
Exon 6	349T→A	Missense mutation, W117R	No sperm
Exon 24	2047G→A	Missense mutation, A683T	Few sperms
Intron 3	-17T→C	Intronic alteration	No sperm
Exon 16	1258Ins (TT)	Frameshift mutation, 1258GATG→TTGGTA	No sperm
Exon 7	515A→G	Missense mutation, Q172R	No sperm

TEX11 mutations are mapped to isoform 2 (GenBank accession number, NM_031276

We have identified 5 different mutations in the testis-expressed 11 (TEX11) gene in 13 patients with azoospermia from the south Indian population. Testis-expressed 11 (TEX11) is a gene located on the X chromosome that is expressed specifically in germ cells.The incidence ofTEX11gene mutations in male primary infertility is high, at about 2-3%, andTEX11genedysregulation has been implicated in spermatocyte apoptosis, maturation disorders, and azoospermia. Work withTex11-/Y-null mice has shown that the lack ofTEX11causes meiotic arrest, andTEX11is known to regulate homologous chromosomal synapsis and the repair of DNA double-strand breaks.



Mutations in theTEX11gene were detected in 13 azoospermia patients based on whole-exome sequencing analysis, verified by Sanger sequencing analysis. Previous work has shown that TEX11 forms distinct foci on homologous chromosomes that synapse with each other, apparently forming components of meiotic nodules that are needed for recombination. The frequency of rare TEX11 mutations is significantly elevated in azoospermic men, suggesting that TEX11 may function

in human spermatogenesis. Mutations in this single X-linked gene cause infertility in 2-3% of azoospermic men. TEX11 mutations have also been associated with a higher rate of ICSI failure and ART success rates. It will be helpful to further explore the relative incidence of this TEX11 mutation in azoospermia in larger and more diverse cohorts. We propose TEX11 mutations as a common cause of meiotic arrest and azoospermia in infertile men in South India, with evidence from 13 patients. Although inversions and deletions involvingTEX11were not observed in our patients, they may occur frequently in other patients and could be associated with azoospermia. This report emphasizes on assessing point mutations and chromosomal microdeletions in men with azoospermia for more accurate diagnosis and enhanced patient counselling.

Dr Nithya Elango
DGO, PDF Maternal - Fetal Medicine, PG degree Fetal Cardiology,
Salem Fetal Medical Centre.

LATE FETAL ANOMALIES - WAS MISSED OR EVOLVING ONE?

WHY THIS TOPIC?

Most of us come across few repeated questions, either from patients or from referring doctors:

1. Why was the fetal defect not picked up in first- or second- trimester scans?
2. Was the person performing scan was trained well?
3. Was the machine used, not upgraded one?
4. If diagnosed before, we would have opted for termination.
5. How to counsel at this gestation. Too late!

INTRODUCTION:

Even with the most expert hands and best equipment, few fetal abnormalities will not be detected at the routine second-trimester anatomy scan. Reasons being; first defect was present but not seen, due to technical difficulties, such as increased maternal body mass index or fetal position. Second, the natural history of some fetal defects, they develop or become visible only after the second-trimester scan, commonly the genitourinary tract, central nervous system and heart.

INCIDENCE:

- Overall incidence of fetal abnormalities was 1.9% of these 67.7% were detected during first - or second trimester, 24.8% were detected for the first time at 35 to 37 weeks.
- Almost quarter of fetal defects are identified during routine scan at 35 to 37 weeks.

SIGNIFICANCE:

Such prenatal diagnosis and subsequent management, timing and place of delivery, appropriate

investigations, improve the postnatal outcome. Multidisciplinary team counselling which includes obstetrician, neonatologist, geneticist will improve the perinatal outcome.

Abnormalities first detected in third trimester ultrasound:

- Arachnoid cyst
- Urinary tract dilatation
- Microcephaly
- Ventriculomegaly
- Ovarian cyst
- Ventricular septal defect
- Duplex kidney
- Skeletal defects

Hence there is a definite place for third trimester ultrasound to detect the fetal abnormalities that were missed in previous first or second trimester scan or became apparent only during third trimester scan. Before going into third trimester scan, let us see short review of first- and second-trimester.

Fig.1 Fetal head showing Arachnoid cyst.

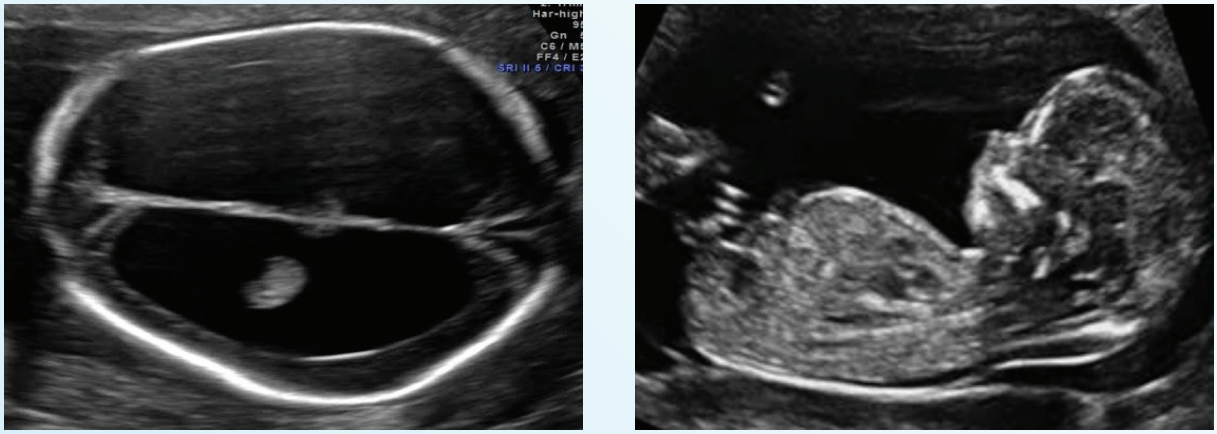


Fig. 2 Bilateral severe ventriculomegaly

FIRST TRIMESTER: [11-13weeks]

Fetal head on transverse section, intact calvarium, midline falx and 'butterfly shaped' choroid plexuses, a midsagittal view of face to demonstrate the nasal bone, midbrain and brainstem, orbits, premaxillary triangle, a sagittal section of the spine and overlying skin. On colour Doppler, transverse section of the thorax to assess the four-chamber view and 3 vessels trachea view and flow across the tricuspid valve, and stomach, kidneys, bladder, abdominal insertion of the umbilical cord, all long bones, hands and feet.

SECOND TRIMESTER :

In this scan, examination of fetal head on transverse section at the level of the cavum septum pellucidum, trans-thalamic and lateral ventricles; a suboccipito-bregmatic view to examine the midbrain, cerebellum and vermis; a midsagittal view of the face to examine the nasal bone and to exclude micrognathia; transverse views of the orbits, upper lip and palate; spine in sagittal, coronal and transverse views. A sweep through the heart in the transverse plane to view four-chamber view, outflow tracts and three-vessel view. Examination of the lungs, diaphragm, liver, stomach, bowel, umbilical cord insertion, kidneys, bladder and ureters on transverse and sagittal sections of thorax and abdomen; systematic examination of upper and lower limbs for length, shape of each bone, position and movement of each joint, both hands and feet. All the digit abnormalities, not completely ruled out in ultrasound scan. Examination of the genitalia, not a compulsory part of the protocol.

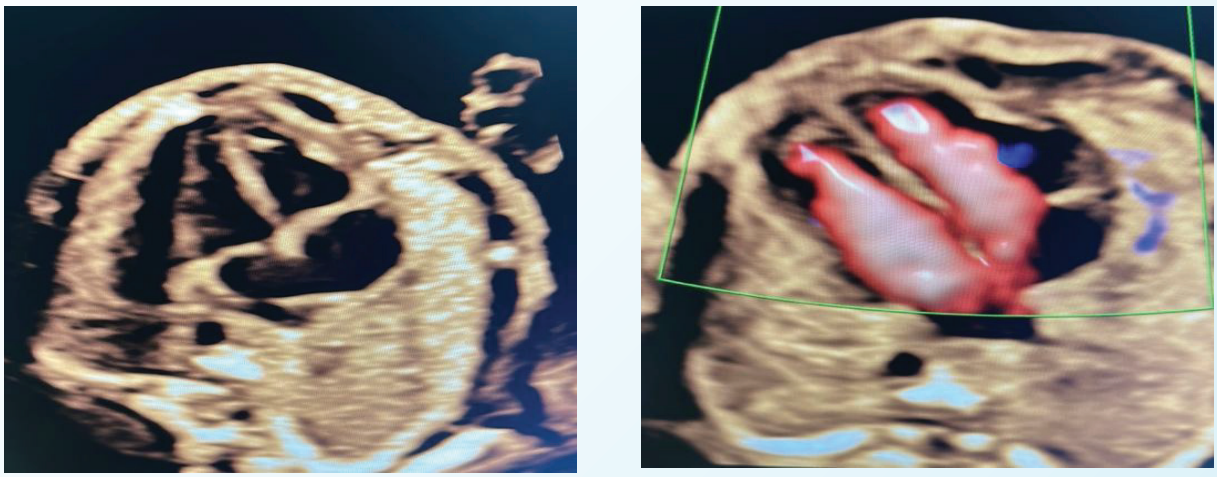


Fig.1 and 2 showing normal 4 chamber view of fetal heart, grey scale and color Doppler

THIRD TRIMESTER :

Aims primarily at assessing fetal growth, amniotic-fluid volume and Doppler measurements especially the uterine, umbilical and fetal middle cerebral arteries. Fetal anatomical survey can be performed in systematic way as in the second trimester, but it was accepted that, depending on the fetal position, examination of the fetal face, sacrum and extremities may not be possible. 3D and

4D scans can be very well performed at this gestation, it helps to confirm the 2D scan findings and easy to counsel the parents regarding the fetal external defects and also for better understanding of the defect.

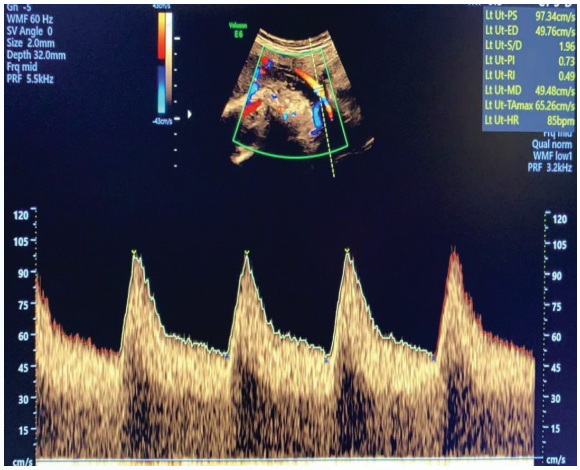


Fig.1 3D rendering image of third trimester fetus, Fig.2 showing Uterine artery Dopplers

EQUIPMENTS NEEDED :

Ultrasound examinations at third trimester usually performed transabdominally, using a 3–7.5-MHz curvilinear transducer, transvaginal scan (3 – 9 MHz), if there is technical difficulties in obtaining adequate views. Duration of scan 15 minutes to 30 minutes.

Most of the fetal abnormalities seen at 35 – 37 weeks had already been diagnosed in the first and/or second trimester ultrasound, except for few late fetal anomalies, classified according to the major organ system affected, are as follows:

Facial abnormalities:

- Dacryocystocele
- Cleft lip and palate, almost all cases diagnosed in the first or second trimester
- In contrast, isolated cleft palate or mucosal cleft difficult to detected prenatally

Fig.1 Dacryocystocele

Heart abnormalities:

- Ventricular septal defect [VSD]
- Of these ventricular septal defect around 18.3% were first diagnosed in the third trimester
- 4.2% of VSD were diagnosed Postnatally
- Rhabdomyoma, most cases were detected for the first time in third trimester.
- Coarctation of the aorta,
- Pulmonary or aortic stenosis,
- Anomalous pulmonary venous connections,
- Tricuspid valve defect, few were detected for the first time in third trimester and few diagnosed only postnatally

Gastrointestinal abnormalities:

- Oesophageal / trachea-esophageal fistula atresia
- Intra-Abdominal cysts
- Evolving Gastro-intestinal atresias'
- High anal atresia, can be detected but imperforate anus is postnatal diagnosis

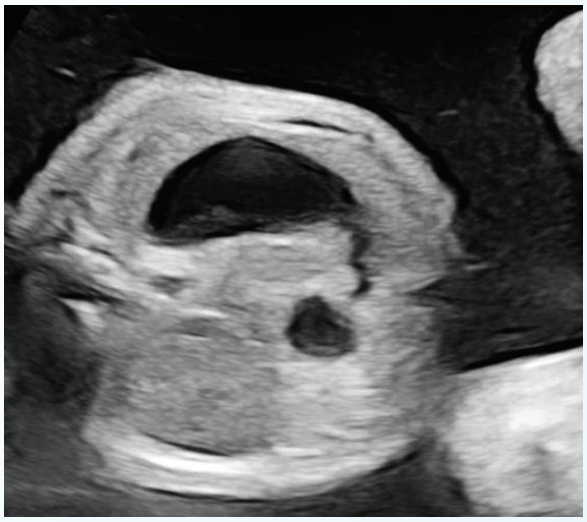


Fig.1 Duodenal atresia

Fig.2 Bilateral plueral effusion

Thoracic abnormalities:

- Congenital diaphragmatic hernia [evolving]
- Pleural effusion, most of the cases were first detected in the third trimester.

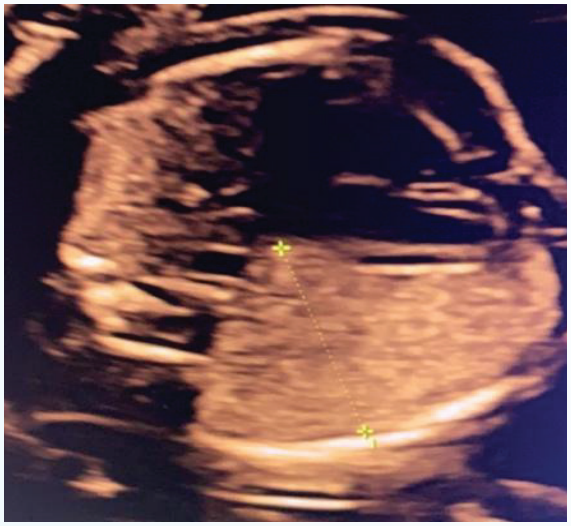



Fig.1 and 2 Congenital pulmonary airway malformation on axial and coronal views

GENITOURINARY TRACT:

- Hydronephrosis
- Unilateral renal agenesis with or without a pelvic kidney
- Duplex kidney
- Unilateral multicystic kidney, most cases of these, except hydronephrosis, usually diagnosed in second trimester scan.
- Most cases of megaureter and all cases of ovarian cysts and hematocolpos were first diagnosed in the third trimester.
- Prenatal examination of the genitalia, not a compulsory part of the protocol
- 93% of cases with ambiguous genitalia or hypospadias were diagnosed postnatally.

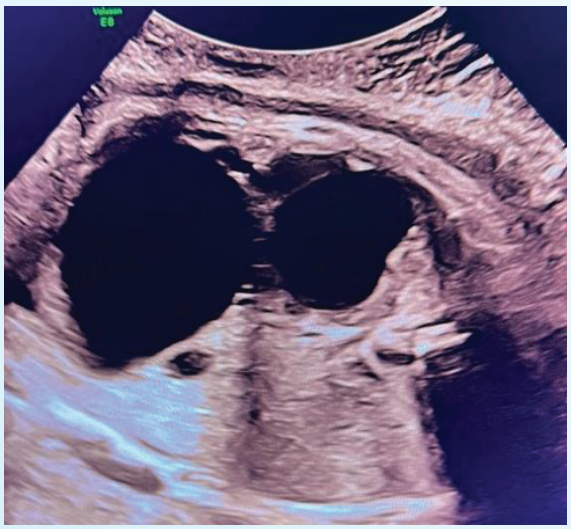



Fig.1 Cystic renal disease, Fig.2 Bilateral hydronephrosis (Urinary Tract Dilatation)

CONCLUSION AND SIGNIFICANCE:

Such diagnosis and subsequent management, timing and place of delivery, appropriate investigations, improve the postnatal outcome. Place of delivery plays a vital role, in cases of progressive heart abnormality, such as coarctation of the aorta and pulmonary or aortic stenosis, it may be advisable for delivery to be planned in a center with pediatric cardiac expertise; similarly, fetuses with diaphragmatic hernia, best delivered in centers with facilities for pediatric surgery. In other cases, such as those with hydronephrosis, megaureter, duplex kidney, ventriculomegaly, arachnoid or ovarian cyst, craniosynostosis, rhabdomyoma and hematocolpos, the pediatricians can be alerted to the need for appropriate postnatal investigations and follow-up.

How often do we identify fetal abnormalities during routine third-trimester ultrasound? A systematic review and meta-analysis

L Drukker et al. BJOG. 2021 Jan.

Conclusion:

Combining data form 13 studies and sample size of 140000 women, this systematic review showed that during routine third-trimester ultrasound, incidental fetal anomaly found in about 1 in 300 scanned women.

Late diagnosis of fetal central nervous system anomalies following a normal second trimester anatomy scan

Y. Yinon ✉, E. Katorza, D. I. Nassie, E. Ben-Meir, L. Gindes, C. Hoffmann, S. Lipitz, R. Achiron, B. Weisz

Conclusions:

Fetal brain continues to evolve throughout gestation, and therefore, some of the CNS anomalies can be diagnosed only during late second and third trimesters of pregnancy. Consequently, in patients who have a third trimester scan for any reason, assessment of the fetal CNS should be considered.

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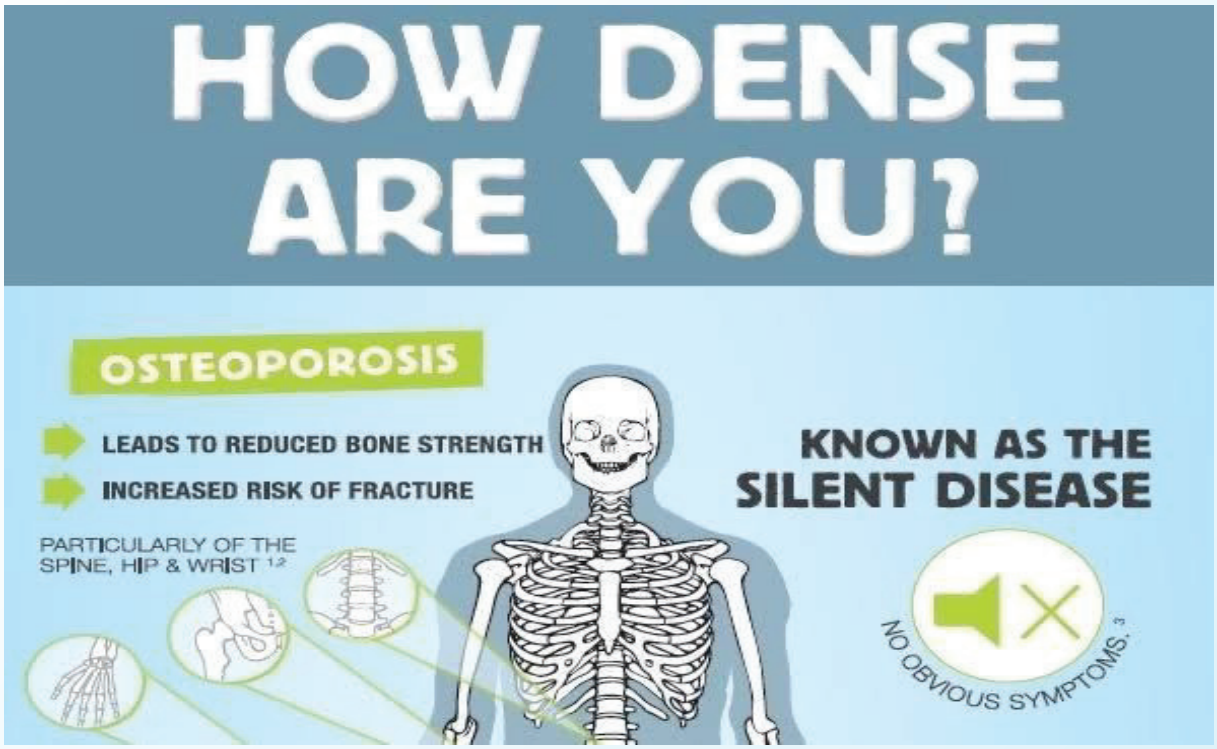
2. Value of routine ultrasound examination at 35–37weeks' gestation in diagnosis of fetal abnormalities. A. FICARA, A. SYNGELAKI , A. HAMMAMI, R. AKOLEKAR and K. H. NICOLAIDES Ultrasound Obstet Gynecol 2020
3. How often do we identify fetal abnormalities during routine third-trimester ultrasound? A systematic review and meta-analysis. L Drukker et al. BJOG. 2021 Jan
4. Third- trimester ultrasound finds undetected fetal abnormalities. Kate Madden Yee
5. How often do we incidentally find a fetal abnormality at the routine third- trimester growth scan? A population – based study. L Drukker, Angelo Cavallaro,et al. dec 2020.
6. Late diagnosis of fetal central nervous system anomalies following a normal second trimester anatomy scan. Y Yinon 1, E Katorza, D I Nassie, E Ben-Meir, L Gindes, C Hoffmann, S Lipitz, R Achiron, B Weisz

DR.DHIVYA.G
DGO, DNB, MRCOG, FICOG, MNAMS, FMAS, DMAS, CIMP, Diploma in Urogynecology
Sarvesh Medical Centre & Max Speciality Clinics

SIGNIFICANCE OF SCREENING FOR OSTEOPOROSIS IN ELDERLY WOMEN



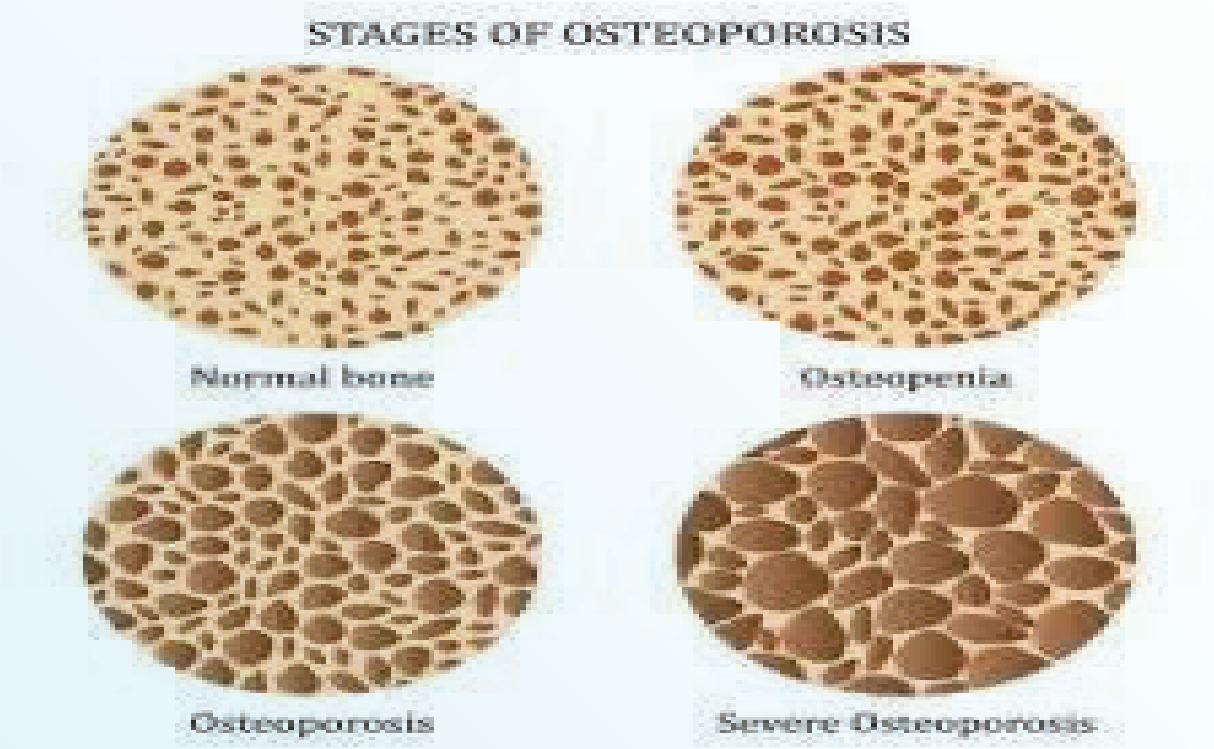
WorldHealthOrganization(WHO)defines osteoporosis as "a systemic skeletal disease characterized by low bone mass [measured as bone mineral density (BMD)] and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures involving the wrist, spine, hip, pelvis, ribsorhumerus.

The National Institute of Health defnitionis "a disease characterized by decreased bone strength and propensity to fall".

RISK STRATIFICATION

In 2013, estimates suggested that ~50 million people in India had T-scores of - 1.3.

AGE	Pr evalence of lo w bone m ass
40 Years	40%
60 Years	62%
65 Years	80%



Screening for osteoporosis

- Do we have a cost effective screening method for the large scale whole population??????

NO!!!!!!!

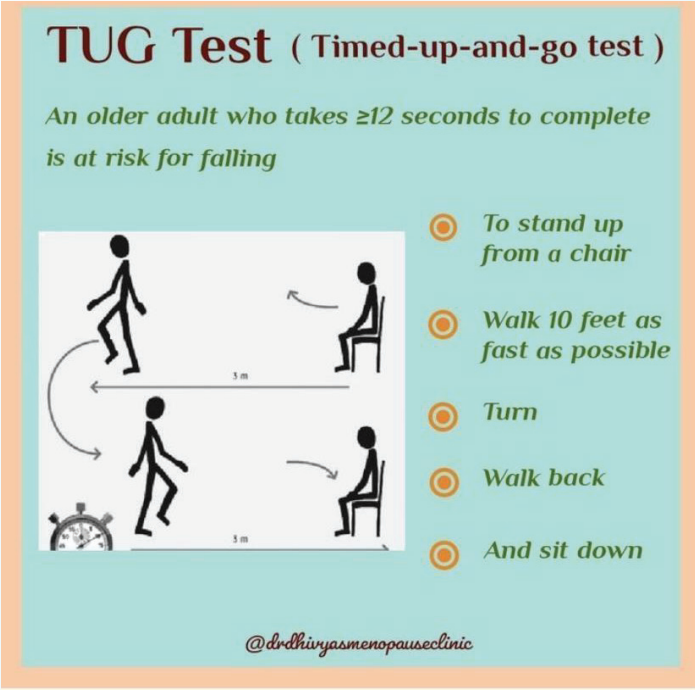
In the absence of a validated population screening tool for PostMenopausal Osteoporosis in India, Targeted Screening and Case finding strategy

SCREENING

- Evaluate all postmenopausal women age 50 years or older for osteoporosis risk
- Include a detailed history, physical exam, and clinical fracture risk assessment with FRAX in the initial evaluation for osteoporosis
- Consider BMD testing based on clinical fracture risk profile
- When BMD is measured, use DXA measurement (spine and hip)
- Osteoporosis should be diagnosed based on presence of fragility fractures in the absence of other metabolic bone disorders or a T-score of -2.5 or lower in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius even in the absence of a prevalent fracture
- Osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX country-specific threshold

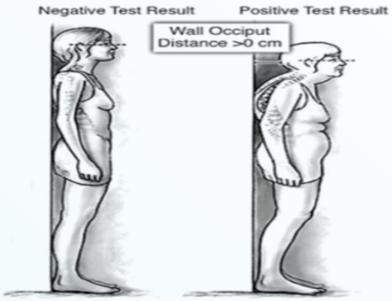
Rationale for screening for osteoporosis

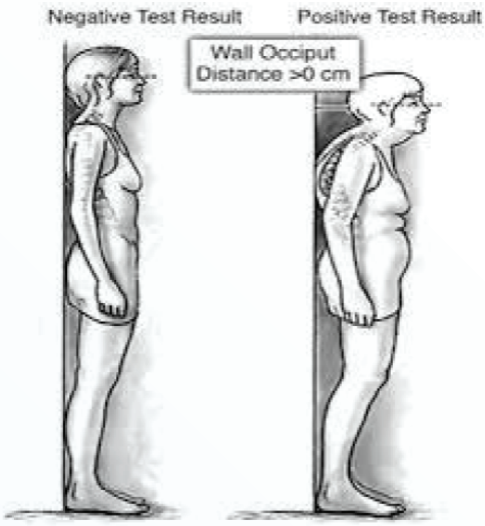
- To identify those at risk of fracture
- To provide treatment to increase bone mass and
- To prevent further losses
- Height and Weight annually
- Checking for balance and gait
- Get up and go test by asking the women to get up from the
- Chair without using their arms
- TUG Test



Physical Examination

- Measuring kyphosis (excessive outward curvature of the spine) and loss of height to detect vertebral fractures
  - One way to measure this is the *Occiput to Wall Test*. This test measures the distance between the back of the head and the wall when standing upright. A distance of greater than 5 cm suggests a vertebral fracture.





Rib-pelvis distance (RPD)

This is a quick method for screening subclinical compression fracture of the lumbar spine. Subjects are asked to stand with two arms raised to shoulder height, and the vertical distance between the lateral last rib margin and pelvis brim is measured. In normal individuals, it should be 2-3 fingerbreadths or >5 cm. A distance of <2 cm is highly confirmative for a spinal problem.

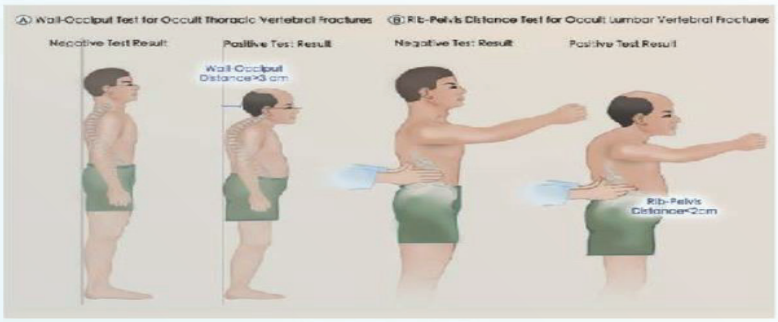


Fig.5-2 WOD and RPD

(Revised from: JAMA 2004; 292: 2890-2900)

LABORATORY STUDIES

Complete blood picture,

Erythrocyte sedimentation rate(ESR).

Random blood sugar.

Serum calcium.

Fasting serum phosphorus.

Serum creatinine.

Serum albumin.

Alkaline phosphatase.

Serum thyroid-stimulating hormone (TSH).

25-hydroxy-vitamin D.

X-ray of thoracolumbar spine (lateral view).

Parathyroid hormone (PTH)

Risk assessment tools

For screening asymptomatic postmenopausal women

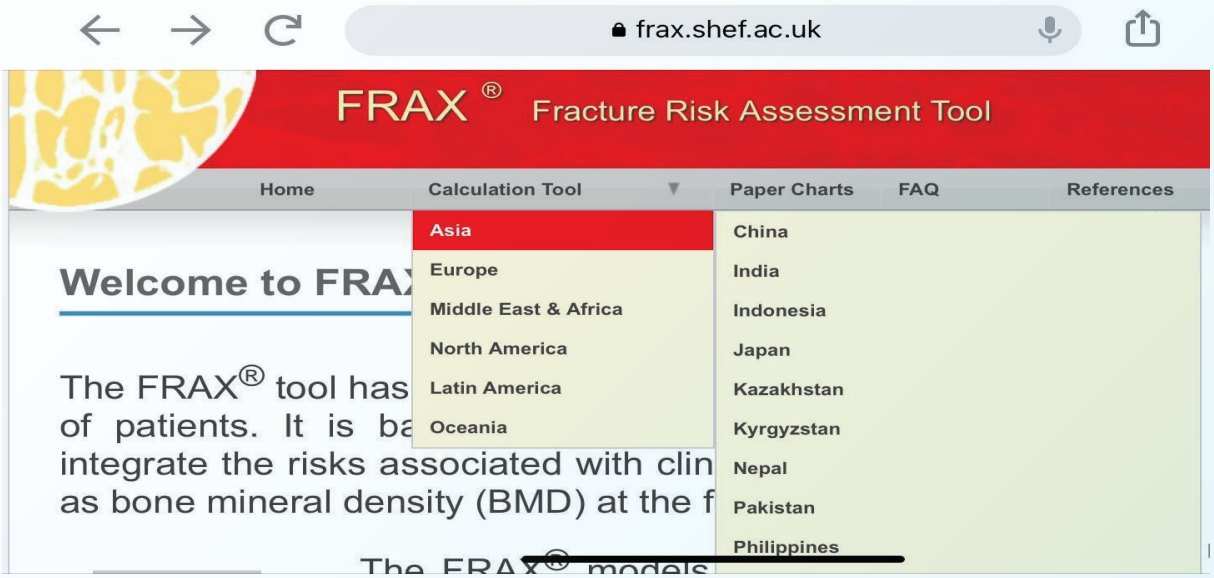
FRAX

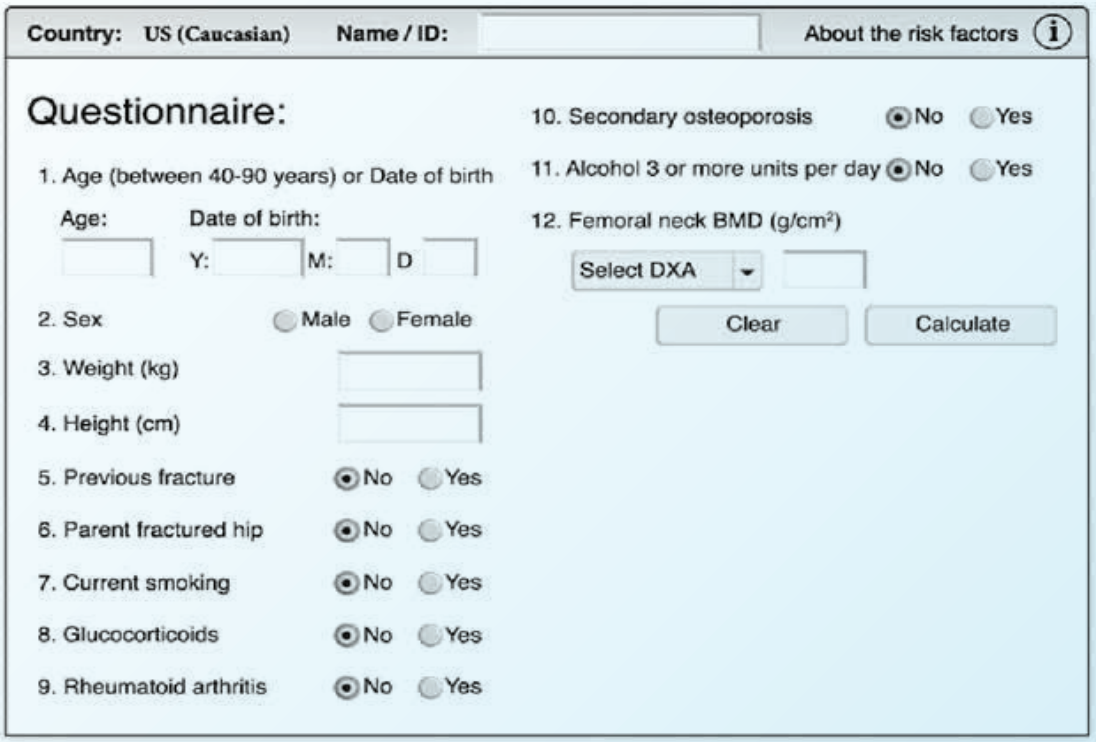
SCORE

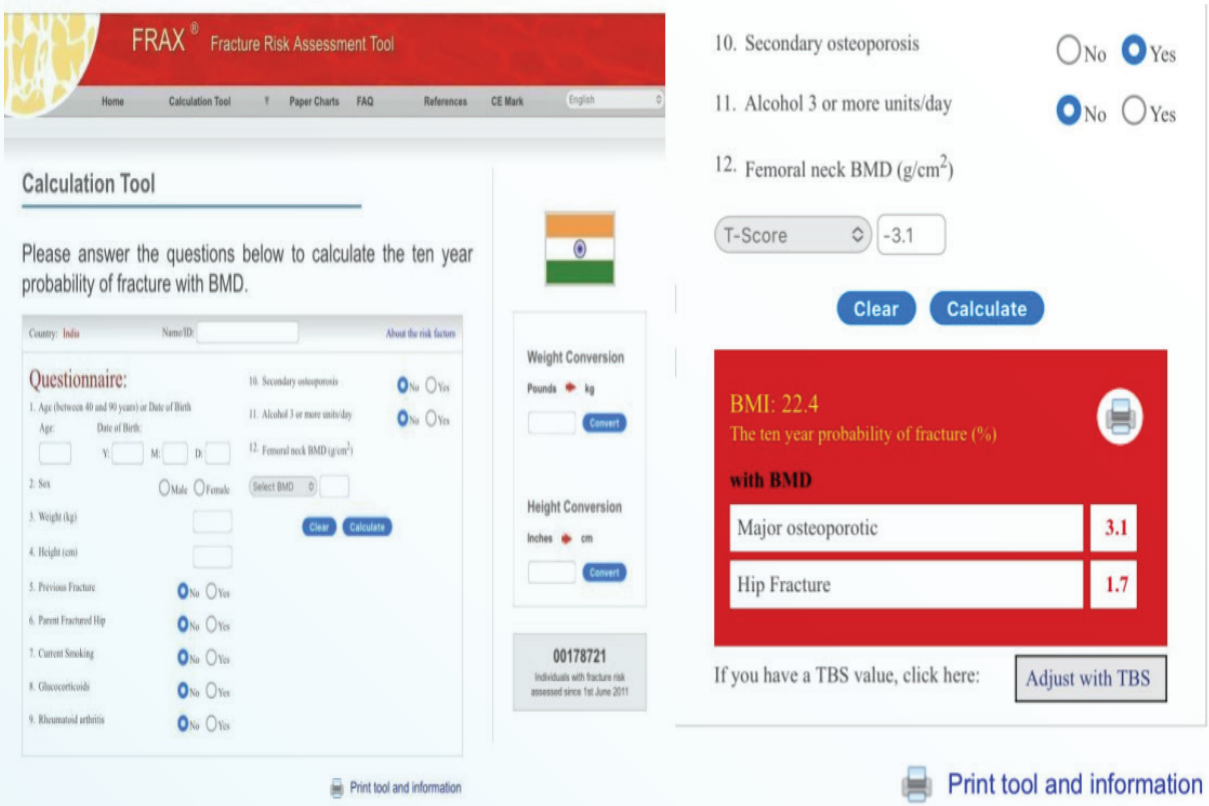
OSTA

The FRAX (WHO Fracture Risk Assessment Tool)

Country-specifc, FRAX is available for use for Indian population







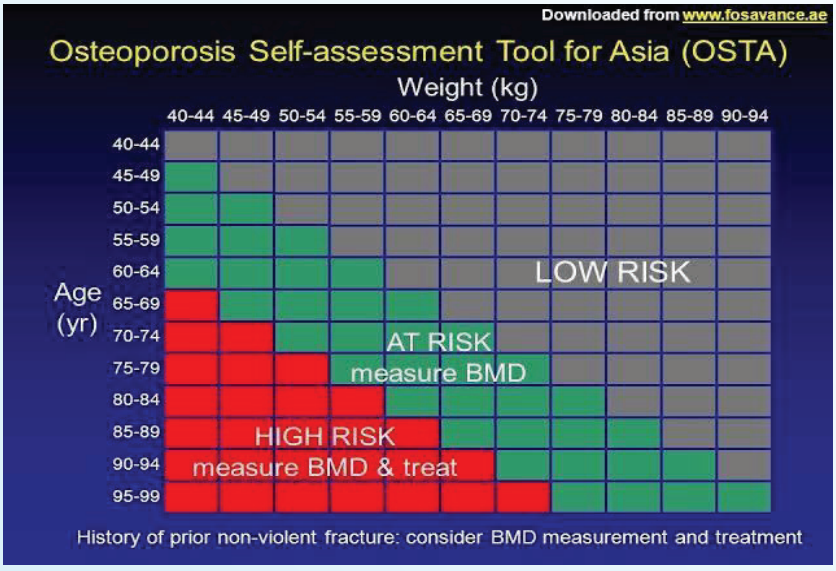
OSTA

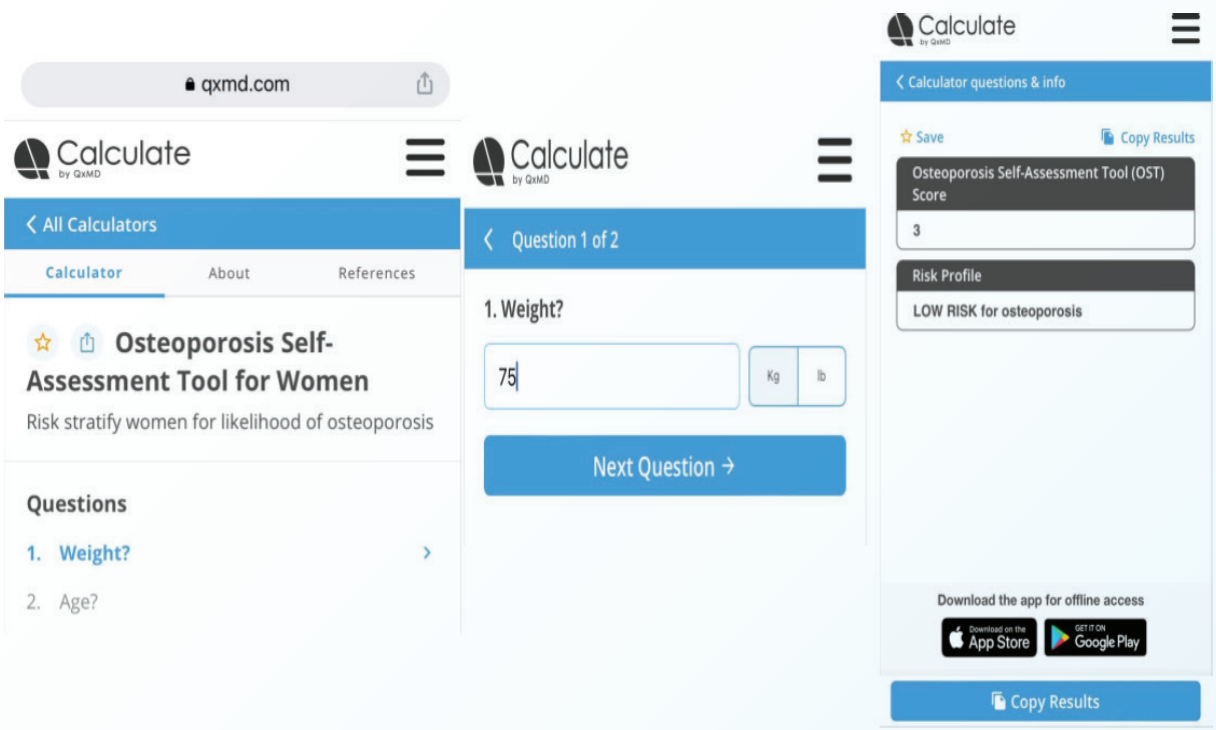
Osteoporosis Self-assessment Tool for Asians (OSTA)

Conclusions: The OSTA index, a simple and free risk assessment tool, can be used to estimate the prevalence of low QUS values in Nepalese women and may help to increase awareness and prevention of low bone mineral density.

Available from:

https://reference.medscape.com/calculator/osteoporosisself_x0002_assessment-women.





OSTA INDEX CALCULATION

OSTA Index = (Weight in kg- Age) x 0.2

OSTA RESEARCH GROUP CLASSIFICATION

A. High risk subgroup (index < -4)

B. Intermediate risk subgroup (index -1 to -4)

C. Low risk sub group (index > -1)

Simple Calculated Osteoporosis Risk Estimation (SCORE)

A. Race not black: 5 points

B. Rheumatoid Arthritis: 4 points

C. Fracture after age 45 of wrist, hip or rib: 4 points per Fracture

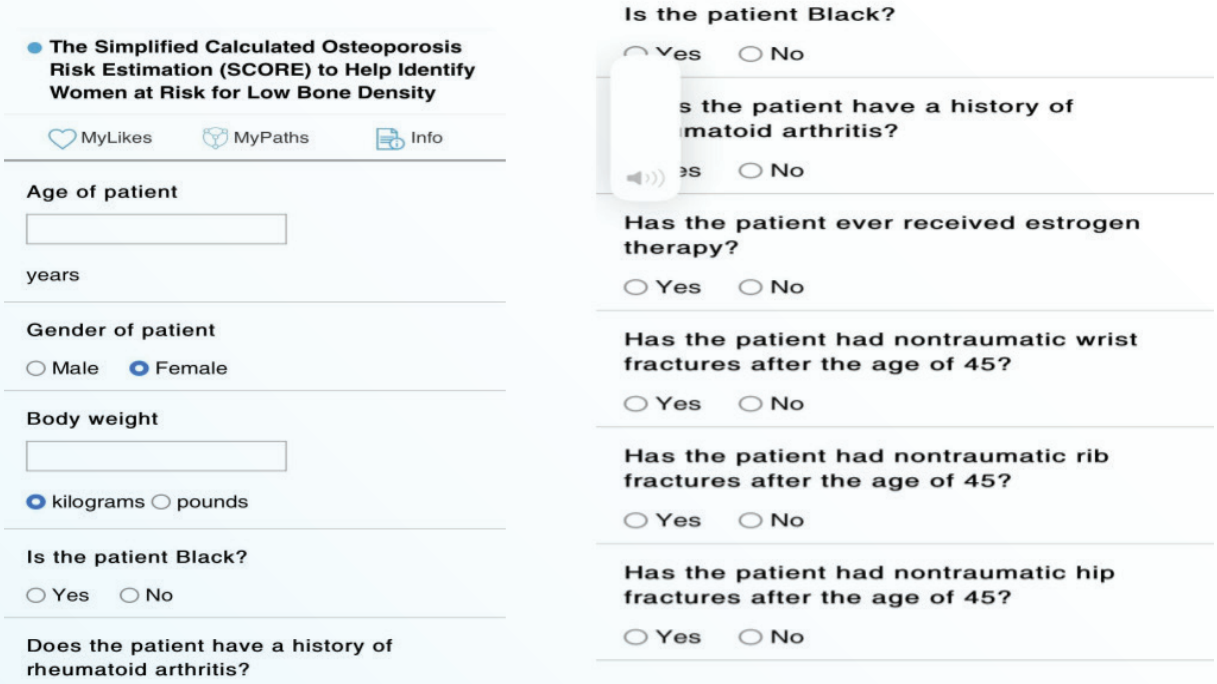
D. Age over 65: Calculate 3 x (1st digit of age)

Example for age 70: 21

E. Weight: Calculate (-1 x weight in pounds)/10

Example for weight 200 pounds: -20

F. Estrogen therapy never used: 1 point



Interpretation

A. Score of 6 or above is associated with T-Score below -2

B. Osteoporosis testing with DXA Scan is recommended if Score of 6 or above

Effcacy

Test Sensitivity: 91%

Test Specifcity: 40%

OTHER MODALITIES

DXA

Quantitative ultrasound

X-Ray

Quantitative CT and MRI

Bone turnover markers

DUAL-ENERGY X-RAY ABSORPTIOMETRY

Indications for DXA (GRADE B)

All postmenopausal women more than 5 years of menopause.

Postmenopausal women less than 5 years of menopause with risk factors.

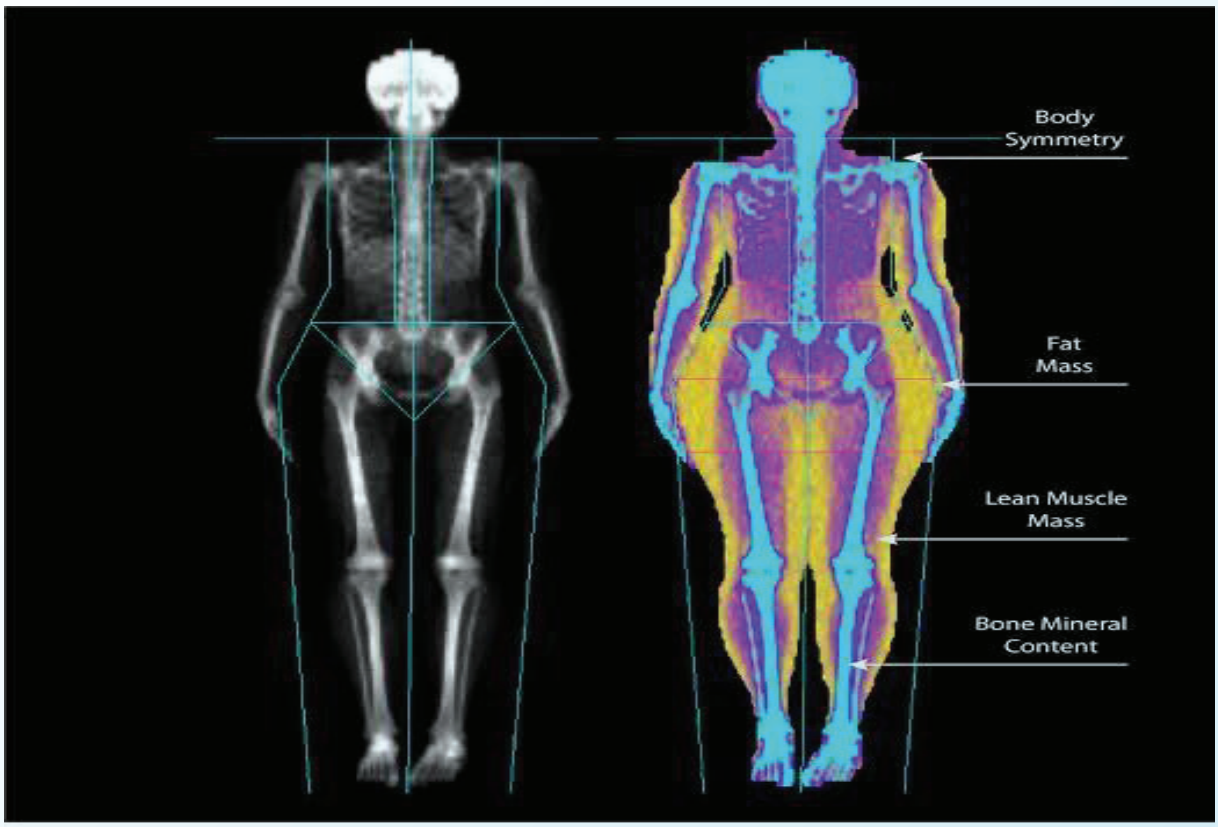
Women in menopause transition with secondary causes.

Radiological evidence of osteopenia and presence of vertebral compression fracture (VCF).

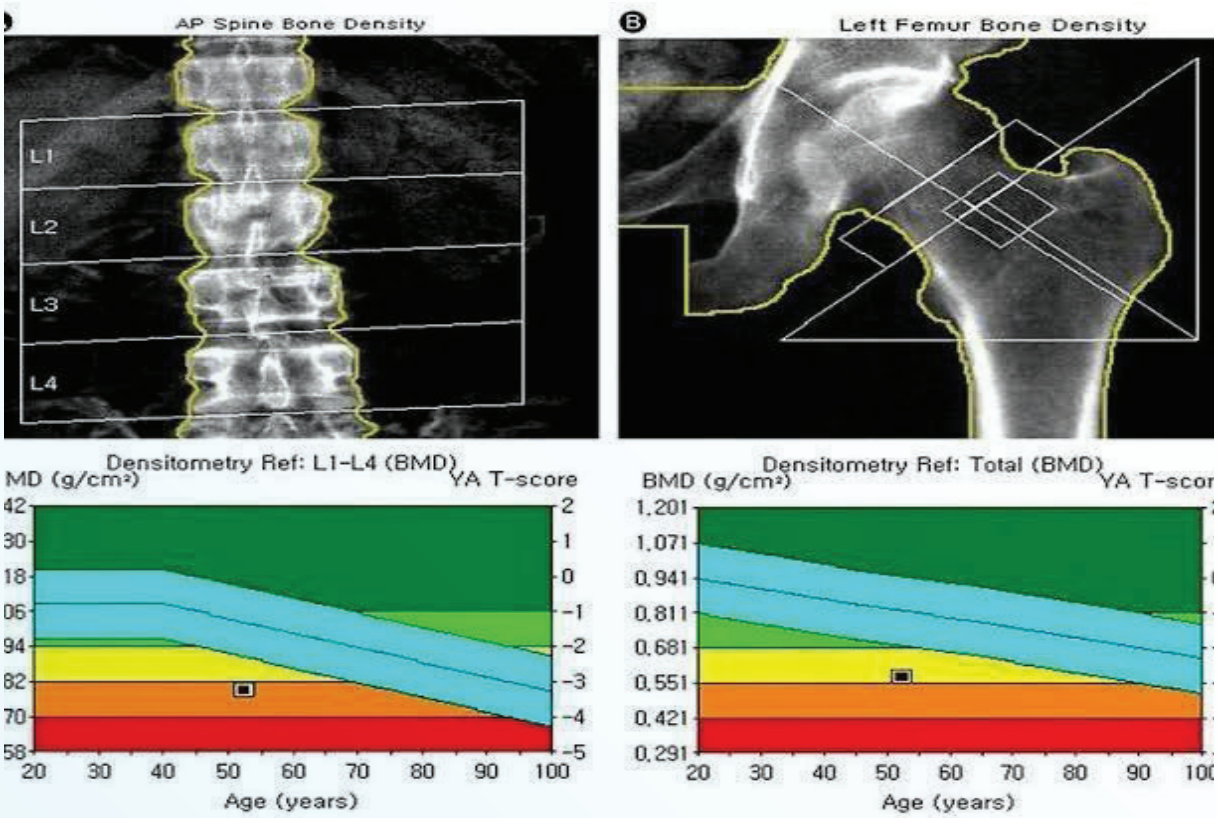
Women with fragility fractures.

Ideally before initiating pharmacotherapy for osteoporosis.

Emerging indications are to measure total body fat an lean tissue mass.



DEXA Scan Results



Follow-Up and Monitoring with DXA

- To monitor therapy, the interval is mostly scheduled between 1 year and 5 years later.
- It is suggested that DXA should be performed every 2 years on the same machine in order to monitor osteoporosis therapy (Grade B).
- Measurement of bone density using DXA has become the gold standard for the diagnosis of osteoporosis and for guiding decisions about which patients to treat.
- DXA of the femoral neck is considered the best predictor of hip fracture

Quantitative Ultrasonography

- The most commonly used test in the United States after DXA is quantitative ultrasonography of the calcaneus.
- Quantitative ultrasonography is less expensive than DXA,does not involve radiation, and can feasibly be implemented in primary care settings.
- Recent studies demonstrate can predict fractures as effectively as DXA in postmenopausal women and in men.
- WHO's diagnostic criteria of –2.5 standard deviation (SD) does not apply for non-DXA techniques (GRADE A).
- In the absence of calibrated ultrasound machines, it is not recommended for population screening (GRADE A).

Bone mass assessment

Bone mass was assessed by broad band ultrasound attenuation using a QUS device. This device is small and portable, with a gel-coupled (dry) system that can measure BUA and speed of sound at the calcaneus. For

Figure 1. QUS device and Measurement of bone dens

Quantitative computed tomography (QCT) and magnetic resonance imaging (MRI)

It gives an additional advantage of three-dimensional (3D) structural assessment of bone tissue (GRADE A).

Radiography

- X-ray abnormality is a feature of advanced bone disease.
- It is recommended that X-rays be used in all the diagnostic protocols for osteoporosis (GRADE A).
- Vertebral fractures are mostly clinically silent,-

  - lateral X-ray of the spine is clinically important

- Radiographic techniques are easily available and we recommended their usefulness in epidemiological screening (GRADE B).
- Radiographic techniques cannot be used in monitoring drug therapy (GRADE A).

EMERGING ROLE OF BONE TURNOVER MARKERS AT MENOPAUSE TRANSITION

- Normal values are reference values established in healthy premenopausal women aged 30–45 years.
- Bone turnover markers are not a part of the routine tests to be used for clinical diagnosis (GRADE B).
- This may help identify women at greatest risk who would beneft from therapeutic intervention at menopause.

Type of Marker

- Bone resorption: Serum carboxy-terminal cross-linked telopeptide (CTX) of type 1 collagen or urine CTX.
- Bone formation: N-terminal propeptide of type 1 procollagen (PINP), bone-specifc alkaline phosphatase or osteocalcin.

Use one marker of bone resorption and one marker of bone formation.

More specifcally,

Markers for bone resorption -on antiresorptives

Bone formation markers -on anabolic agents.

Osteoporosis Screening Recommendations of Organizations

- **National Osteoporosis Foundation**
- BMD testing for all women _> 65 yrs and postmenopausal women <65 yrs, based on risk factor profile

Screening for Osteoporosis, U.S.Preventive Services Task Force Recommendations:

- The USPSTF recommends screening for osteoporosis in women aged 65 years or older and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors. (Grade B recommendation)
- World Health Organization
- Indirect evidence supports screening women > 65 yrs, but no direct evidence supports widespread screening programs using BMD testing
- American Congress of Obstetricians and Gynecologists
- BMD testing for all women >/= 65 yrs and postmenopausal women < 65 yrs who have >/= 1 risk factor

Annals of Internal Medicine

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SCREENING FOR OSTEOPOROSIS
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Women aged ≥65 years without previous known fractures or secondary causes of osteoporosis	Women aged <65 years whose 10-year fracture risk is equal to or greater than that of a 65-year-old white woman without additional risk factors	Men without previous known fractures or secondary causes of osteoporosis
Recommendation	Screen		No recommendation
	Grade: B		Grade: I (insufficient evidence)
Risk Assessment	As many as 1 in 2 postmenopausal women and 1 in 5 older men are at risk for an osteoporosis-related fracture. Osteoporosis is common in all racial groups but is most common in white persons. Rates of osteoporosis increase with age. Elderly people are particularly susceptible to fractures. According to the FRAX fracture risk assessment tool, available at www.shef.ac.uk/FRAX/, the 10-year fracture risk in a 65-year-old white woman without additional risk factors is 9.3%.		
Screening Tests	Current diagnostic and treatment criteria rely on dual-energy x-ray absorptiometry of the hip and lumbar spine.		
Timing of Screening	Evidence is lacking about optimal intervals for repeated screening.		

Dr Pachaiyappam
Associate Professor Department of Cardiology
GMKMCH, Salem

WOMEN AND HEART DISEASE WHAT MAKES THE DIFFERENCE

INTRODUCTIONS:

Cardiovascular disease (CVD) has now become the leading cause of death among women, 1 In 4 female deaths in US. A 40 yrs old women has a lifetime risk-of developing CVD is 1 in 2.1 in 3 has risk of developing coronary artery disease and 1in 5 has risk of developing heart failure. Cardiovascular disease has difference in outcome between women and men due to number of variables such as sex specific risk factors for CVD, difference in management strategies for women both in primary and secondary prevention and pathophysiological difference in CVD.

WHAT MAKES CORONARY ARTERY DISEASE DIFFERENT IN WOMEN

1. Hormone Changes – Estrogen provides benefit against heart disease by keeping arteries flexible and beneficial effect on lipid profiles
2. Size and Structure of the heart – women's heart and blood vessels are smaller and muscular walls are thinner
3. Women are more likely to develop coronary microvascular disease compared to men and it makes harder to identify and treat CVD in women.

RISK FACTORS AFFECT'S DIFFERENTLY IN WOMEN

4. DIABETES - increase the risk of coronary heart disease (CHD) by 3 to 7 folds in women compared to 2 to 3-fold in men and Diabetic women has 3.5 times increased risk of fatal coronary heart disease compared to non-diabetic women.
5. HYPERTENSION - Has an adverse impact on CVD in women over the age of 60 yrs compared to men and increases the risk of developing congestive heart failure

6. DYSLIPIDEMIA - common in women, women of less than 40 yrs of age will have low total cholesterol compared to men. High density lipoprotein levels are high in women compared to men and its inversely associated with ASCVD Risk. Adverse changes in lipid profiles in women follows menopause and include increased levels of total cholesterol LDL-C, Triglycerides and decreased levels of HDL -C.
7. CIGARETTE SMOKING - Women smokes less than men but smoking is more detrimental in women compared to men. Female smokers die 14.5 years earlier than female nonsmokers and men smokers die 13.2 yrs earlier than male nonsmokers. The use of oral contraceptives and smoking imparts greater risk than smoking alone likely related to pro thrombotic effects.
8. PHYSICAL ACTIVITY/PHYSICAL FITNESS - Exercise capacity also known as physical fitness, strongly and independently predicts all-cause mortality. Physical activity benefits cardiovascular health but physical inactivity is common, women more likely to report not meeting the physical activity guidelines than men.
9. METABOLIC SYNDROME – Women with metabolic syndrome has increased risk of developing CVD and myocardial infarction compared to men.

SEX SPECIFIC RISK FACTORS

1. AGE OF MENARCHE: Early (before 12 years) and Late (>15 years) onset menarche have shown to increase the risk of myocardial infarction, stroke and heart failure hospitalizations.
2. PREGNANCY ASSOCIATED CONDITIONS: Preterm delivery, Eclampsia and pre-eclampsia, gestational hypertension, gestational diabetes and assisted reproductive therapies.
3. PREMATURE MENOPAUSE AND PREMATURE OVARIAN INSUFFICIENCY
4. ORAL CONTRACEPTIVE THERAPY: The women with healthy heart and free of CVD risk factors. The use of combination estrogen-progestin oral contraceptives associates with low relative and absolute risk of CVD. Women with uncontrolled hypertension, smoking and a history of thromboembolic disease have an unacceptable level of CVD risk associated with oral contraceptives.
5. AUTOIMMUNE DISEASE AND BREAST CANCER THERAPY

WOMEN AND MYOCARDIAL ISCHEMIA

Women were more likely to present with a myocardial infarction without any chest pain at all, particularly young females, symptoms of ischemia may be more nonspecific and less severe compared to men and can includes breathing difficulty, pain in the arm, shoulder, middle back, jaw or epigastrium; Indigestion, vomiting, fatigue, generalized weakness or palpitations. Women are more likely to have angina with routine activity such as shopping, cooking and resting rather than during exercise and in men angina is worsens with physical activity.

ISCHEMIC HEART DISEASE RISK IN WOMEN

1. LOW RISK WOMEN: Pre-menopausal women with symptoms.
2. LOW TO INTERMEDIATE RISK WOMEN: Women in fifth decade and able to perform routine activities of daily living (ADL)
3. INTERMEDIATE RISK WOMEN: Women in her 50s and unable to perform routine activities of daily living and women in their 60s.

   Low to intermediate and intermediate risk women is a candidate for exercise ECG and intermediate risk women with abnormal ECG should be referred for noninvasive modalities like Myocardial perfusion imaging (MPI), ECHO, cardiovascular magnetic resonance (CMR) and coronary computed tomography angiogram (CCTA).
4. HIGH RISK WOMEN: Women in their 70s and older. High risk women with stable symptoms may be referred for a stress imaging modality for function assessment.

RISK ASSESSMENT

1. High risk- The presence of CVD, Diabetes mellitus, end-stage renal or chronic kidney disease, or 10-year CHD risk of greater than 20 percent.
2. At risk- the presence of at one major risk factor (metabolic syndrome, evidence of subclinical vascular disease or poor exercise tolerance on treadmill testing.
3. Optimal risk- absence of major risk factors, a Framingham risk score of less than 10% and a healthy lifestyle.

HEART FAILURE IN WOMEN

The prevalence of heart failure is increasing and affects around 3.2 million women in US and heart failure related admissions are increasing due to heart failure with preserved ejection fraction (HFpEF), which is more common in women.

IMPACT OF DIFFERENT ETIOLOGICAL FACTORS: DIFFERENCE IN SYMPTOMS

- Women are more dyspneic on exertion.
- Quicker relief in dyspnoea on treatment in women
- Higher chance of oedema in females.

The Framingham study has shown reduction in the incidence of HF in women, but not in men over the last 50 years. Best survival is with non-ischemic HF.

INDIAN STUDIES ON HEART FAILURE

Unlike Western World, RHD is the commonest cause of HF in India (52% of hospitalized patients followed by CAD 17%) (Chaturvedi et al). Women contributed 43% of HF, CAD as cause of HF was more common in men (67.4%) versus 46% in women. Since RHD affects young population, 22.5% patients were <30 years of age and 14.9% > 50 years. Valvular heart disease and Dilated CMP are causes of HF and more common in women (18.8% and 22% than men 10.6% and 15%).

- Another important thing in India is that anaemia also causes HF or acts as contributor of HF in women especially in rural areas.

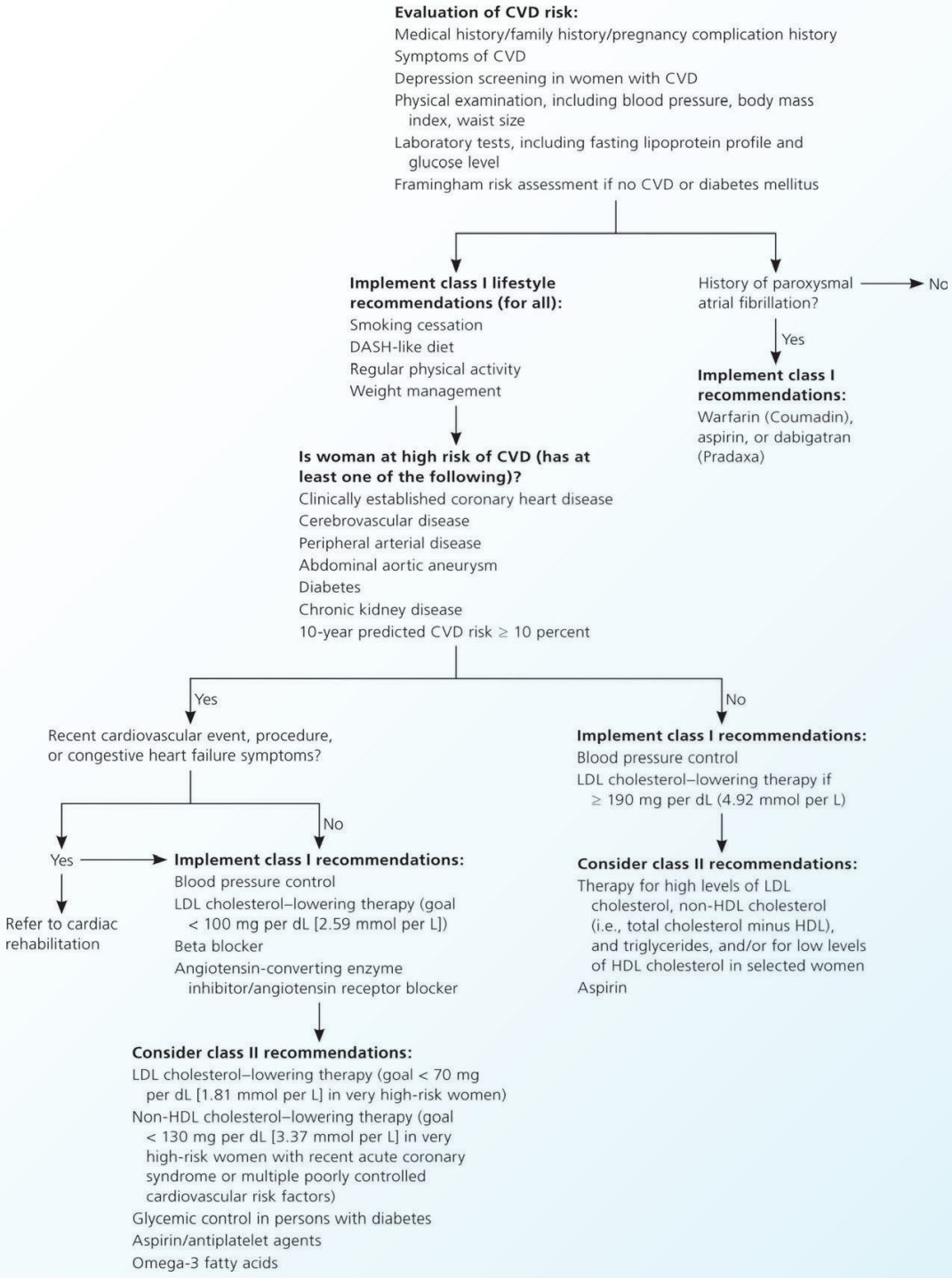
ACUTE BALLOONING SYNDROME (ALSO CALLED STRESS, CMP, AND BROKEN HEART SYNDROME)

- In 90% cases it occurs in females, especially post-menopausal women average at 61-76 years of age. Ballooning of LV occurs. LVEF is usually 35-50% which returns to normal in 95 cases in a few weeks.

PREGNANCY AND HEART DISEASE

1. Cardiovascular disease complicates 1 to 4 % of pregnancy and in the principal cause for maternal mortality. Older maternal age with associated risk factors like DIABETES MELLITUS, SYSTEMIC HYPERTENSION and OBESITY as well as improved longevity of patient with congenital heart disease have increased the burden of cardiovascular disease complicating pregnancy.
2. The knowledge of the unique haemodynamic changes of pregnancy will help us to understand the pathophysiology, signs and symptoms and the-noted history of each heart disease. Then requires a multi-disciplinary approach to anticipate the and manage the complications that may arise during ante partum, intra partum and post-partum periods.
3. Pregnancy is not advised in certain cardiac conditions such as SEVERE LV DYSFUNCTION, PERIPARTUM CARDIOMYOPATHY WITH PERSISTENT LV DYSFUNCTION, PULMONARY HYPERTENSION, SEVERE MITRAL STENOSIS, COARCTATION OF AORTA, SEVERE AORTIC STENOSIS and ANY CYANOTIC CONGENITAL HEART DISEASE

PREVENTION OF CVD IN WOMEN



LOWER AFFORDABILITY OF TREATMENT IN WOMEN

- In women less angiotensin – converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), and statin were prescribed.
- Referral to higher centre was less.
- Revascularization was less in CAD cases.

Dr R Shinika
MD(Psy), DNB, Fellowship in Child Psychiatry (CMC, Vellore)
Consultant Child & Adolescent Psychiatrist

ANTENATAL DEPRESSION: THE ELEPHANT IN THE ROOM

FAQs

1. Is antenatal depression common?
2. How common is that?
3. Why are antenatal mental illnesses under-diagnosed?
4. What are the risk factors?
5. What are the symptoms of antenatal depression?
6. Why is it important to address antenatal depression?
7. How to screen for antenatal depression in busy OPs?

1. Is antenatal depression common?

    - Yes, antenatal depression and anxiety disorders are common.
    - Largely under-diagnosed and untreated.

2. How common is that?

    Statistics are truly shocking!!

    - Overall prevalence of antenatal depression ranged from 3.8% to 65% and antenatal anxiety from 13 to 55% (1). This wide range of prevalence is due to variability in socio-demographic factors, study settings and study tools used.
    - The National Mental Health Survey 2016 (NMHS) revealed that one in every tenth Indian suffers from depression and anxiety, and 20% of these depressed Indians are pregnant women(2).
    - Current data from South-Asian countries suggest one in four pregnant women is likely to experience antenatal depression in the region(3).

3. Why are antenatal mental illnesses under-diagnosed?
    - Mental health stigma
    - Poor awareness among health care providers, public and across all health care sectors(4).
    - Referrals to Psychiatrists is often considered as stigma and hence reluctant to seek help (4).
    - Misconceptions related mental health treatment.
    - Lack of trained mental health professionals.
4. Risk factors for antenatal depression:
    - Low socio-economic status, poor social and family support (1)
    - Preference to have a male child.
    - Multiple births and younger maternal age
    - Alcohol abuse by husband
    - Marital conflicts
    - Intimate partner violence
    - History of abortions
    - Pregnancy associated with obstetric complications.
    - Poor relationship with the husband/in-laws(1).
5. What are the symptoms of antenatal depression? (DSM-5 criteria)
    - Feelings of depressed/ irritable mood
    - Anhedonia (decreased interest in past pleasurable activities)
    - Significant weight loss or weight gain (change of >5% of body weight in a month)
    - Insomnia or hypersomnia
    - Psychomotor agitation or retardation
    - Fatigue or loss of energy
    - Feelings of worthlessness or excessive guilt
    - Diminished ability to think or concentrate.
    - Recurrent thoughts of death, suicidal ideation/suicidal attempt.
    - Depressive disorder can be diagnosed when 5 or more of the above symptoms are present for a 2-week period causing intense distress, dysfunction/ impairment in the functioning of the women.
6. Why is it important to address antenatal depression?

    Impact of untreated maternal depression on mother herself: (Maternal outcome)
    - Severe depression leads to suicidal behavior.
    - Nicotine dependence and other substance use

- Poor nutrition
- Poor weight gain
- Less compliant with pre-natal care
- Pre-eclampsia
- Increased risk of premature delivery, increased surgical delivery interventions (5).

Impact of untreated depression on fetus: (Neonatal outcome)

- Low-birth weight (6)
- Pre-term birth (6)
- Intra-uterine growth restriction (7)
- Low motor and cognitive attainment at 1 year of age (8)
- Poor pro-social behavior at 6 years of age (9).

7. How to screen for antenatal depression in busy Ops?

JAMA Psychiatry | Original Investigation | META-ANALYSIS

Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression
A Systematic Review and Meta-analysis

Alexander Jarde, PhD; Michelle Morais, MD; Dawn Kingston, PhD; Rebecca Giallo, PhD; Glenda M. MacQueen, MD; Lucy Giglia, MD; Joseph Beyene, PhD; Yi Wang, BHSc; Sarah D. McDonald, MD

IMPORTANCE Despite the prevalence of antenatal depression and the fact that only one-third of pregnant women with depression consider it acceptable to take antidepressants, the effect of untreated depression on neonatal outcomes remains to be addressed thoroughly.

OBJECTIVE To undertake a systematic review and meta-analysis to understand the effect of untreated depression on neonatal outcomes.

DATA SOURCES We executed our search strategy, with emphasis on its exhaustiveness, in MEDLINE, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials, and Web of Science. The search was conducted in July, 2015.

STUDY SELECTION We included randomized and nonrandomized studies that examined neonatal outcomes in women with depression receiving neither pharmacological nor nonpharmacological treatment compared with women without depression.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently screened titles and abstracts, assessed full-text articles, extracted data, and assessed their quality using a modified version of the Newcastle-Ottawa Scale. We pooled data using random-effects meta-analyses, quantified heterogeneity using the I^2 statistic, and explored it with subgroup analyses by type of assessment of depression, severity, reported conflicts of interest, and study quality.

MAIN OUTCOMES AND MEASURES Primary outcomes were preterm birth before 37 weeks and before 32 weeks, small and large for gestational age, low birth weight, and neonatal intensive care unit admission.

RESULTS Of the 6646 titles initially identified, 23 studies met inclusion criteria, all observational, with a total of 25 663 women. Untreated depression was associated with significantly increased risks of preterm birth (odds ratio [OR], 1.56; 95% CI, 1.25-1.94; 14 studies; I^2, 39%) and low birth weight (OR, 1.96; 95% CI, 1.24-3.10; 8 studies; I^2, 48%), with a trend toward higher risks for exposure to more severe depression. While the odds of preterm birth more than doubled in studies reporting conflicts of interest (OR, 2.50; 95% CI, 1.70-3.67; 5 studies; I^2, 0%), studies not reporting such conflicts showed more moderate results (OR, 1.34; 95% CI, 1.08-1.66; 9 studies; I^2, 30%).

CONCLUSIONS AND RELEVANCE Our results contrast with what is, to our knowledge, the only previous systematic review that examined the question of untreated depression because we found significant risks of 2 key perinatal outcomes, preterm birth and low birth weight. These are important results for pregnant women and clinicians to take into account in the decision-making process around depression treatment.

Supplemental content at jamapsychiatry.com

Author Affiliations: Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada (Jarde, Morais, Wang, McDonald); Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada (Kingston); Healthy Mothers Healthy Families Group, Murdoch Childrens Research Institute, Parkville, Victoria, Australia (Giallo); Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada (MacQueen); Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada (Giglia); Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada (Beyene).

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BMC Public Health

RESEARCH ARTICLE Open Access

Global burden of antenatal depression and its association with adverse birth outcomes: an umbrella review

Abel Fekadu Dadi[1,2*], Emma R. Miller[1], Telake Azale Bisetegn[3] and Lillian Mwanri[1]

Abstract

Background: Women of childbearing age are at high risk of developing depression and antenatal depression is one of the most common mood disorders. Antenatal depression is also associated with a number of poor maternal and infant outcomes, however, there remains a lack of focus on mental issues in antenatal care, particularly in lower income countries. This systematic review of reviews provides useful evidence regarding the burden of antenatal depression which may provide guidance for health policy development and planning.

Methods: We searched CINAHL(EBSCO), MEDLINE (via Ovid), PsycINFO, Emcare, PubMed, Psychiatry Online, and Scopus databases for systematic reviews that based on observational studies that were published in between January 1st, 2007 and August 31st, 2018. We used the Assessment of Multiple Systematic Reviews (AMSTAR) checklist scores to assess the quality of the included reviews. We applied vote counting and narrative review to summarize the prevalence of antenatal depression and its associated factors, while statistical pooling was conducted for estimating the association of antenatal depression with low birth weight and preterm birth. This systematic review of reviews was registered on PROSPERO with protocol number CRD42018116267.

Results: We have included ten reviews (306 studies with 877,246 participants) on antenatal depression prevalence and six reviews (39 studies with 75,451 participants) conducted to identify the effect of antenatal depression on preterm and low birth weight. Globally, we found that antenatal depression prevalence ranged from 15 to 65%. We identified the following prominent risk factors based on their degree of influence: Current or previous exposure to different forms of abuse and violence (six reviews and 73 studies); lack of social and/or partner support (four reviews and 47 studies); personal or family history of any common mental disorder (three reviews and 34 studies). The risk of low birth weight and preterm birth was 1.49 (95%CI: 1.32, 1.68; $I^2 = 0.0\%$) and 1.40 (95%CI: 1.16, 1.69; $I^2 = 35.2\%$) times higher among infants born from depressed mothers.

Conclusions: Globally, antenatal depression prevalence was high and could be considered a common mental disorder during pregnancy. Though the association between antenatal depression and adverse birth outcomes appeared to be modest, its absolute impact would be significant in lower-income countries with a high prevalence of antenatal depression and poor access to quality mental health services.

Keywords: Antenatal depression, Adverse birth outcomes, Review of reviews

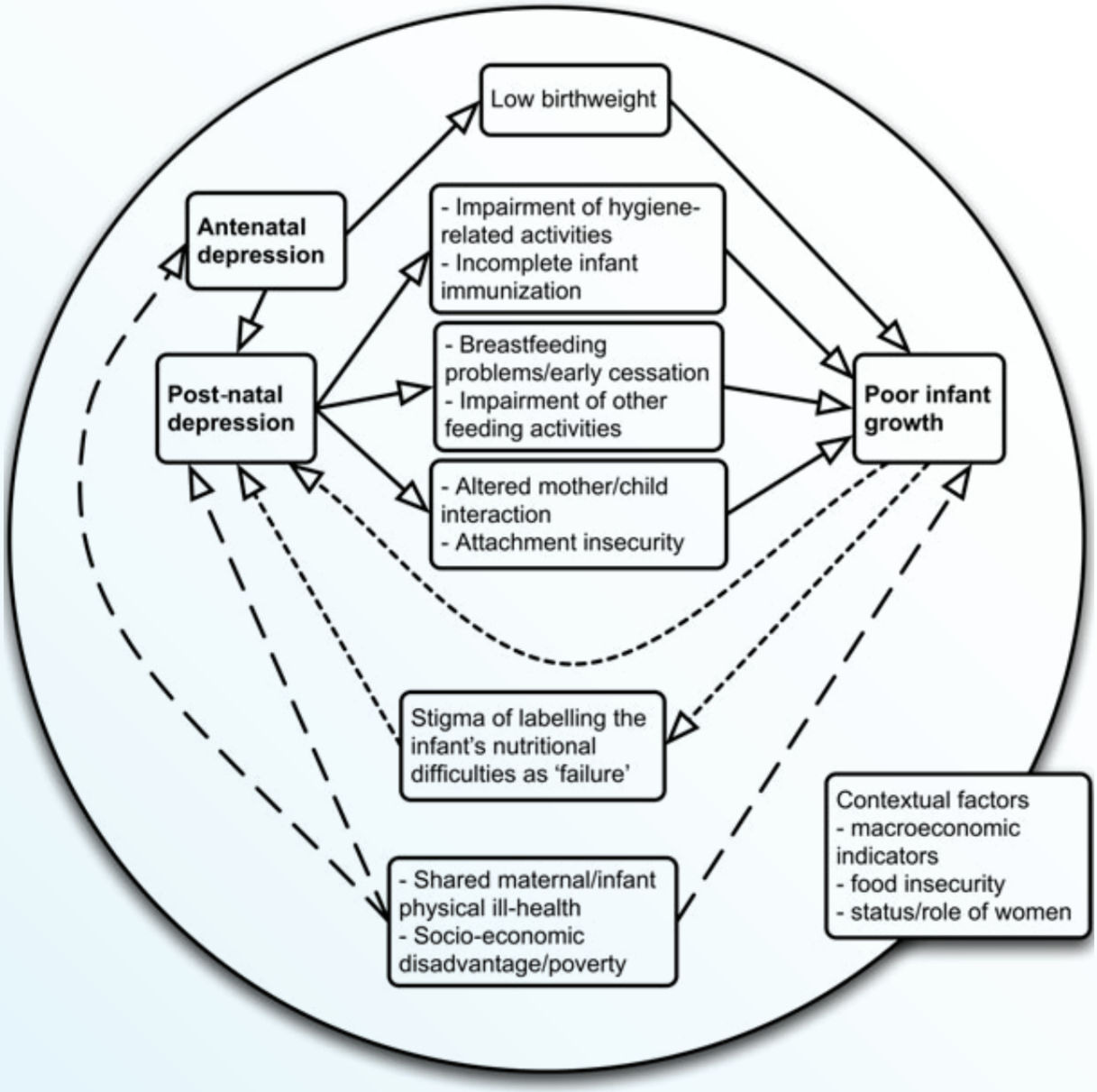


Fig. 1. Possible interactions between maternal depression and infant growth.

- PHQ-9 and EPDS are the screening tools that could be used in the busy Obstetric OPD.

Patient Health Questionnaire- 9 (PHQ-9):

- PHQ-9 screens for depressive symptoms in the last 2 weeks.
- It takes 5-10 min to be completed and could be easily administered by the ANM/ any support staff.
- For scores less than 10, brief psychological interventions can be offered by the lay counsellor.
- Score more than 10 must be referred to the Psychiatrist for interventions (10,11).
- Edinburg Postnatal Depression Scale (EDPS):

ID #: _____ **DATE:** _____

Over the last *2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+
		TOTAL:		

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

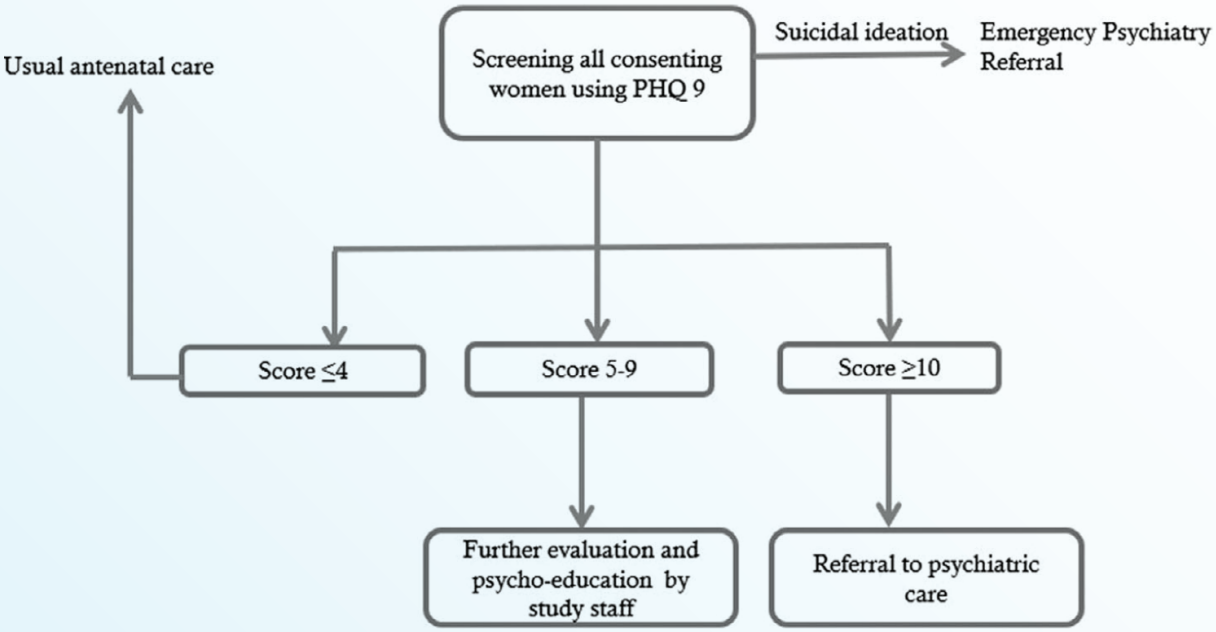
10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

A2663B 10-04-2005

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression



- Edinburg Postnatal Depression Scale (EPDS) screens for depressive symptoms in the last 1 week.
- It is widely used and validated for evaluating prenatal and post-natal depression (12).
- Any score more than or equal to 13 must be referred to the Psychiatrist for confirmation of the diagnosis and interventions.

Edinburgh Postnatal Depression Scale (EPDS)

Patient Label

Mother's OB or Doctor's Name:

_____

Doctor's Phone #: _____

Since you are either pregnant or have recently had a baby, we want to know how you feel. Please place a **CHECK MARK** (✔) on the blank by the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**—*not just how you feel today.* Complete all 10 items and find your score by adding each number that appears in parentheses (#) by your checked answer. This is a screening test; not a medical diagnosis. If something doesn't seem right, *call your health care provider regardless of your score.*

Below is an example already completed.

I have felt happy:
Yes, all of the time ____ (0)
Yes, most of the time ✔ (1)
No, not very often ____ (2)
No, not at all ____ (3)

This would mean: "I have felt happy most of the time" in the past week. Please complete the other questions in the same way.

1. I have been able to laugh and see the funny side of things:
   As much as I always could ____ (0)
   Not quite so much now ____ (1)
   Definitely not so much now ____ (2)
   Not at all ____ (3)

2. I have looked forward with enjoyment to things:
   As much as I ever did ____ (0)
   Rather less than I used to ____ (1)
   Definitely less than I used to ____ (2)
   Hardly at all ____ (3)

3. I have blamed myself unnecessarily when things went wrong:
   Yes, most of the time ____ (3)
   Yes, some of the time ____ (2)
   Not very often ____ (1)
   No, never ____ (0)

4. I have been anxious or worried for no good reason:
   No, not at all ____ (0)
   Hardly ever ____ (1)
   Yes, sometimes ____ (2)
   Yes, very often ____ (3)

5. I have felt scared or panicky for no good reason:
   Yes, quite a lot ____ (3)
   Yes, sometimes ____ (2)
   No, not much ____ (1)
   No, not at all ____ (0)

6. Things have been getting to me:
   Yes, most of the time I haven't been able to cope at all ____ (3)
   Yes, sometimes I haven't been coping as well as usual ____ (2)
   No, most of the time I have coped quite well ____ (1)
   No, I have been coping as well as ever ____ (0)

7. I have been so unhappy that I have had difficulty sleeping:
   Yes, most of the time ____ (3)
   Yes, sometimes ____ (2)
   No, not very often ____ (1)
   No, not at all ____ (0)

8. I have felt sad or miserable:
   Yes, most of the time ____ (3)
   Yes, quite often ____ (2)
   Not very often ____ (1)
   No, not at all ____ (0)

9. I have been so unhappy that I have been crying:
   Yes, most of the time ____ (3)
   Yes, quite often ____ (2)
   Only occasionally ____ (1)
   No, never ____ (0)

10. The thought of harming myself has occurred to me:*
    Yes, quite often ____ (3)
    Sometimes ____ (2)
    Hardly ever ____ (1)
    Never ____ (0)

TOTAL YOUR SCORE HERE ▶ ____

Thank you for completing this survey. Your doctor will score this survey and discuss the results with you.

Verbal consent to contact above mentioned MD witnessed by:

_____

Edinburgh Postnatal Depression Scale (EPDS). Adapted from the *British Journal of Psychiatry*, June, 1987, vol. 150 by J.L. Cox, J.M. Holden, R. Segovsky.

SUMMARY :

- Antenatal depression is more prevalent among Indian women. Prevalence ranges from 3.8% - 65%.
- Untreated depression has poor obstetric and neonatal outcomes.
- LBW and pre-term birth are well-established outcomes of untreated antenatal depression.
- Prompt screening for depressive symptoms at each trimester offers protection against mental illness for both the mother and the fetus.
- PHQ-9 and EPDS are the brief screening tools that could be used in busy Obstetric OP.
- Collaboration with a mental health team offers benefit in navigating the complexities of peri-natal mental health issues.

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Dr E Aravindan, M.S DNB (Urology)
Consultant Urologist
Dharan Hospital, Salem

EMPIRICAL MEDICAL THERAPY OF MALE INFERTILITY

Introduction

- Infertility , the inability to conceive after one year of unprotected sexual intercourse is prevalent in 15% of couples worldwide
- Male factor contributes to about 50% of the cases
- In around 30 % no definite aetiology is identified in spite of extensive investigations . Hence termed Idiopathic.
- Specifically targeted treatment in hypogonadism with hCG and FSH has a specific role and attendant results is not to be confused with empirical therapy.
- This article is an attempt to summarise the present role and evidence for empirical treatment of men with Oligo Astheno Teratazoospermia (OAT)
- What is exactly is OAT and the parameters involved is beyond the scope of this review.

Oxidative Stress

- Reactive Oxygen Species (ROS) are oxygen containing chemically reactive molecules that are under normal physiologic conditions beneficial for sperm functions.
- They help in promotion of sperm capacitation , regulation of sperm maturation and enhancement of cellular signalling pathways .
- At higher levels they cause lipid peroxidation , sperm DNA damage and abortive apoptosis.
- Reduced membrane integrity occurs .
- Spermatozoa are particularly vulnerable to ROS since they lack the necessary cytoplasmic antioxidant repair systems.

- Sources of ROS - Leucocytes, Spermatozoa , Chemical and Bacterial Stimuli.
- 25-40 % of infertile men have higher levels of ROS in their semen when compared to fertile men,
- Significant negative correlation have been detected between OS and semen parameters , fertilisation rates , embryonic development and pregnancy rate.
- Hence reversal of OS could be considered a potential step in infertility management
- Antioxidant supplementation have been proposed as to increases the scavenging capacity of seminal plasma
- Actual clinical utility has not yet been proven beyond doubt.

AntiOxidants

- They are compounds that are acquired through a balanced diet or from oral supplements
- They exist in two types
- Enzymatic - Glutathione peroxidase , superoxide dismutase and catalase
- Non Enzymatic - All others that are available in food and supplements like vitamin E and C , Carnitine , N Acetyl Cysteine , Selenium and Zinc
- Scientifically acceptable evidence demonstrating benefit from antioxidant therapy in controlled human studies is scarce .
- The present usage is based on whatever evidence is available .

Arginine :

- Precursor of Nitric Oxide
- Helps is sperm motility , metabolism , capacitation and acrosome reaction.
- NO conclusive evidence that it increases pregnancy rates
- Available in Barley Brown Rice , Wheat , Chocolate , Dairy products and Nuts

Glutathione

- It forms an integral part of Glutathione Peroxidase / Reductase System (GPX)
- GPX provides main endogenous antioxidant protection against Lipid Peroxidation (LPO) in the epididymis and testes hence preserving sperm viability and motility
- Double blind study with 600 mg of GSH showed improvement in motility and morphology
- Disadvantage : Parental administration ; No concrete proof yet
- Naturally Found in fruits

Vitamin E

- Vitamin E (alpha tocopherol) is an organic fat soluble compound located mainly in the cell membrane
- Its s powerful chain breaking antioxidant reducing LPO initiated by ROS in plasma membrane
- Direct relationship has been demonstrated between levels of Vitamin E and the % of motile spermatozoa
- Sulaiman et al demonstrated improvement in oral use of 300 mg of Vitamin E with a 21 % pregnancy in the study group

Vitamin C

- Water soluble compound that exists in a concentration 10 x higher than in blood
- Has an ability to neutralise hydroxyl , superoxide and hydrogen peroxide radicals
- Lower levels have been found in seminal plasma of men with asthenospermia.
- Present evidence is related to studies where it has been combined with Vitamin E and has been found to increase pregnancy rates in patients undergoing ICSI.

Carnitines :

- Water Soluble anti oxidant that acts as a fuel source for sperm motility
- Regulates intra cellular metabolism through beta oxidation
- Men with iOAT have low levels of carnitine in their semen
- Available in two forms : L- Carnitine and L - acetyl carnitine
- Studies involving carnitine have showed improvement in sperm parameters but not consistently
- Naturally found in Red meat , fish and dairy products

Coenzyme Q10

- Ubiquitous antioxidant to almost all body tissues . Found in high concentration in sperm mitochondria
- Transports electrons in mitochondrial respiratory chain
- Inhibits hyper oxide formation
- Linear correlation with sperm count and motility
- Several studies have sensed the impact of CoQ on sperm parameters
- MetaAnalysis by Lafuente reported improvement in sperm motility and concentration
- Found in Whole grain , bran , soya , nuts and fish

N Acetyl Cysteine

- Amino Acid that exhibits antioxidant properties after being converted to cysteine which is a precursor of glutathione
- Also has direct antioxidant properties
- Multiple studies have proven the ability of NAC to improve semen parameters but not the pregnancy rates

Selenium

- Essential Trace element that provides protection against OS -Mechanism not fully understood
- Augments the function of biologic glutathione
- Mainly studied in combination with Vitamin E
- Evidence points to a favourable influence on viability of spermatozoa

Zinc

- Essential mineral involved in metabolism of DNA and RNA
- It has antiapoptotic and antioxidant properties .
- Found in higher levels in fertile men
- Sperm flagella abnormalities is associated with Zinc deficiency
- Studies show beneficial effect but it was limited to a small study

Folic Acid

- It plays a vital role in amino acid synthesis and metabolism
- Folic Acid reduced the risk of disomy X and DNA aneuploidy
- At a dose of 400 mcg , there are few studies that show improvement in sperm parameters but the evidence is scarce .

Lycopene

- Naturally synthesised carotenoid present in fruits and vegetables
- Major role in dox defence system as it has the highest quenching ability against the singlet oxygen , a high energy form of oxygen.
- Studies show improvement in motility at a dose of 2000 mcg but evidence is scarce

SUMMARY OF EVIDENCE

Following are the facts and limitations of the present evidence on antioxidants

- A Cochrane systematic review and meta analysis including 34 RCTS and 2876 couples found that antioxidant therapy had a positive impact on live birth and pregnancy rates in sub fertile couples undergoing ART cycles

LIMITATIONS :

- Low quality RCTs
- Serious risk of bias due to poor methods of reporting randomisation
- Failure to report in the clinical outcomes especially live birth and clinical pregnancy rates
- High attrition rates
- Small sample sizes in many studies

Selective Estrogen Receptor Modulator

- SERM have been long proposed as empirical treatment of iOAT
- Proposed mechanism is that they block oestrogen receptors at the level of hypothalamus which results in the stimulation of GnRH secretion leading to an increase in pituitary gonadotrophin release thereby stimulating spermatogenesis
- Commonly used agents are Tamoxifen and Clomiphene
- Meta Analysis by Chua et al showed that SERM increased pregnancy rates along with improved sperm parameters .
- No conclusive recommendations due to the poor quality of available evidence

Aromatase Inhibitors

- Aromatase is a cytochrome p450 enzyme .It is present in the testes , prostate , brain , bone and adipose tissue of men
- It converts testosterone and androstenedione to oestradiol and oesterone respectively
- AIs block the conversion of testosterone to estradiol , the main source of estrogen in men, This causes feedback inhibition of HPG axis and causes pulsatile FSH.
- Common AIs used are Letrozole and Anastrazole.
- Best used in men with hypogonadism with low T/E ratios.
- However there is no conclusive evidence to recommend the sue of AIs in idiopathic OAT and is not recommended routinely .
- AIs are potentially useful in iOAT with low testosterone and elevated estradiol levels .
- There is a shortage of good studies for recommending aromatase inhibitors in OAT.

Dr.jayanthi
D.G.O,D.NB(OBS), FRM

Approach to Recurrent pregnancy loss

Recurrent pregnancy loss (RPL) is one of the most frustrating and difficult areas in reproductive medicine. Due to the changing gestation of viability The definition of RPL varies, which makes . clinicians studying the phenomenon, and determining which couples to counsel or treat, more challenging .

Definition:

The American Society for Reproductive Medicine (ASRM)

Recommend clinical evalu ation after two first trimester clinical pregnancy losses (i.e. those documented by ultrasonography or histopathological examination). However, they have recommended a threshold of three or more losses for epidemiological studies.

The European Society for Human Reproduction and Embryology (ESHRE) 2017 &2022 -concluded with a definition of two or more pregnancy losses. Confirmation by serum or urinary chronic gonadothropin will be enough. Do not include ectopic and molar pregnancies

RCOG – COG, in their Green-top Guideline No. 17, says that RPL is a miscarriage of three or more pregnancies. Do not have to be consecutive .Clinical pregnancy, also includes biochemical pregnancy

The most recent international 'consensus' on the definition of recurrent pregnancy loss (RPL) is two or more pregnancy losses prior to 24 weeks gestation with the same partner. It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more.

TYPES

A. Depending on previous viable pregnancy

Primary RPL- multiple losses in a woman with no previous viable infants

secondary RPL- multiple losses in a woman who has already had a pregnancy beyond 20 gestational weeks.

B. Depending on gestational age

Early pregnancy loss- loss before 13 weeks.

Mid trimester loss- loss between 13-24 weeks.

In early pregnancy loss it is must to document whether fetal heart pulsations were seen or not.

Etiology:

Age: The risk of a chromosomal abnormality of the fetus is higher in women older than 35 years of age, which supports the association of aneuploidy and increasing maternal age. Age of the father has greater impact than maternal age, on cases of sporadic autosomal dominant congenital diseases such as Apert, Crouzon, Pfeiffer, Noonan and Costello syndromes, multiple endocrine neoplasia (types 2A and 2B) and achondroplasia.Thus both maternal and paternal age plays an important role.

BMI : A case control study of 4932 women reported that repeated episodes of miscarriages were more common in the obese group compared to those with a normal. Centre for Maternal and Child Health Enquiry (CMACE), indicated that 30% of mothers who had a stillbirth or a neonatal death were obese. Observational studies have reported that obesity increases the risk of sporadic miscarriage.28–30 In the meta-analysis of Ng et al. (2021) women with a BMI below 19 and above 25 were at higher odds of recurrent miscarriage.

Cavity abnormalities/anatomical factors: Congenital uterine anomalies (CUAs) are frequently associated with RPL patients, with a prevalence of 13.3% in those with a history of miscarriage compared with 5.5% in an unselected population. In high-risk populations, uterine septae are commonest. Although some acquired uterine malformations such as fibroids, polyps and uterine adhesions have been found in people with RPL there is a lack of evidence of a direct association. Cervical insufficiency is associated with RPL more commonly in the second trimester.

Drugs: Certain medications taken while pregnant are associated with pregnancy loss. The risk is highest with FDA Pregnancy Category D or X medications.ex.,-. Retinoids, warfarin, and certain blood pressure medication, nonsteroidal anti-inflammatory drugs (NSAIDs), certain antibiotics, and benzodiazepines can also harm a developing fetus.

Endocrinological abnormalities: thyroid-while overt hypothyroidism, Hyperthyroidism, Autoimmune thyroid disease are assosciated with increased risk of RPL the possible role of subclinical hypothyroidism cannot be correlated unless it is assosciated with throid antibodies.

- LPD- A typical luteal phase length is relatively fixed at 12–14 days but may range from 11–17 days. Luteal phase deficiency (LPD) is defined as an inability of the corpus luteum to secrete progesterone in high enough amounts or for too short a duration.

PCOS-may contribute because of confounding obesity, altered glycemic status, hyperandrogenemia.

Hyperprolactinaemia- its assosciation is controversial in human studies but it is indirectly assosciated with defective corpus luteal function.

Diabetic-Patients with poorly controlled diabetes are known to have an increased risk of spontaneous miscarriage, which is reduced to normal spontaneous loss rates when women are euglycemic preconceptually. Testing for fasting insulin and glucose is simple and treatment with insulin-sensitizing agents can reduce the risk of recurrent miscarriage.

Fertility There is still insufficient evidence for a link between the ovarian reserve and recurrent pregnancy loss. some studies have found the association between abnormal sperm DNA parameters such as sperm DNA fragmentation, nuclear chromatin decondensation, and sperm aneuploidy and miscarriage.

Genetic factors : With the development of reproductive genetics genetic abnormalities that may predispose to pregnancy loss include chromosomal aneuploidy, copy number variants, single-gene changes and genetic polymorphisms. Gene polymorphism means that the structure or nucleotide arrangement of the same gene may vary between individuals. It is an allelic variation that does not necessarily affect the function of the gene. Ex.,- genes assosciated with angiogenesis,immune regulation ,estrogen receptor,thrombogenic factors.

Hematological : Thrombophilia is a common cause of RPL and may be seen in 40–50% of cases Thrombophilia by affecting syncytiotrophoblast invasion of the maternal blood vessels, leads to the formation of microthrombosis at the site of implantation, resulting in implantation failure and RPL. .Thrombophilia is either inherited, acquired or a combination of both.

Congenital thrombophilias- Factor V Leiden (FVL) mutation (C677T), a hyperhomocysteinaemia mutation (A506G), a prothrombin mutation (G20210A) or prothrombin II (PTII) mutation, or a protein S and/or C deficiency.

Acquired thrombophilia: Antiphospholipid syndrome (APS) is the most important casuse for acquired thrombophilia.About 5 to 20% of patients suffering from RPL have positive antiphospholipid antibodies. This concerns the association between antiphospholipid antibodies—lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-B2 lycoprotein-I—and adverse pregnancy outcomes or vascular thrombosis.

Immunology : Cytokines-An imbalance in Th1/Th2 cytokines has been implicated in adverse pregnancy outcomes including recurrent mis-carriage.HLA- an increased risk of recurrent miscarriage in mothers carrying a HLA-DRB1*4, HLA-DRB1*15 ,or a HLA-E*01:01 allele and a decreased risk with HLA-DRB1*13.Natural killer (NK) cells- Several studies reported that uterine NK cell density in the endometrium around the time of implantation was increased and also women

with recurrent miscarriage versus controls had higher peripheral NK cell percentage.however their role in RPL is inconclusive.

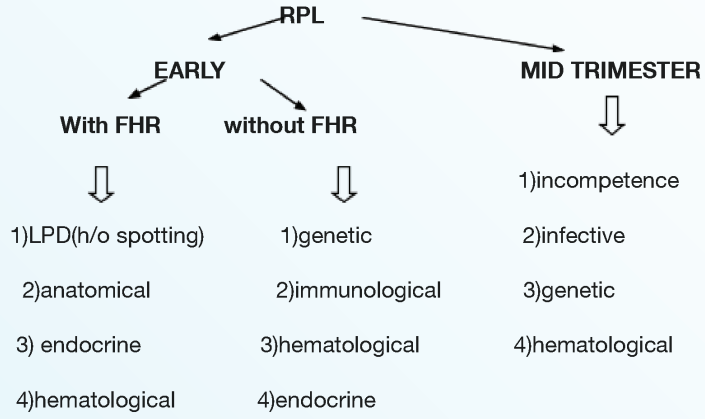
Infective factors: A whole range of organisms have been implicated in first and second trimester miscarriage, including ureaplasma/ mycoplasma, organisms causing bacterial vaginosis and chlamydia trachomatis. Chronic endometritis has also been implicated in recurrent miscarriage, although the diagnostic criteria remain controversial.

(J-K)

Lifestyle : Smoking has been shown to increase the risk of sporadic miscarriage.An observational database study found an increased risk of spontaneous miscarriage in the first trimester for women consuming five or more alcoholic drinks/week (approximately 10 units/week). Similarly, there is some evidence for an association between increased caffeine intake and sporadic miscarriage. The association between environmental risk factors (such as air pollution and household chemicals) and pregnancy loss is based mainly on women with sporadic rather than recurrent miscarriage.

EVALUATION

Based on gestational age



FACTOR	INVESTIGATION	MANAGEMENT
Age	Prenatal screenig	Social egg freezing
BMI		weight loss/weight gain
anatomical factors:	Lap+/-hystero, USG,MRI	anatomical correction,cervical stitch
Drugs	Proper evaluation and counselling	Convert to pregnancy safe medication
Endocrinological	FT4,TSH,75 gm GTT,prolactin,anti TPO abs	thyroid/antithyroid medication.insulin /hypoglycemic agents,P4 suplement
Fertility	Sperm DNA assays	antioxidants
Genetic factors	Karyotyping of couple/POC,advanced genetic testing –FISH, microarray,genome sequencing ,	PGD/CVS,Amniocentesis, detailed anatomy scan
Hematological	Thrombocheck panel	Heparin,aspirin
Immunological		Immunomodulators,LIT
Infective	Vaginal culture	Antibiotics/probiotics
lifestyle		Lifestyle modification