# FOGSI FOCUS

Under ageis of Federation of Obstetrics & Gynecological Society of India

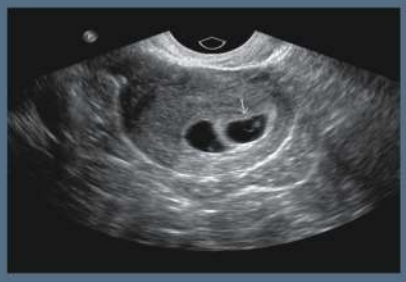
# Preconception & Antenatal Care

(Update)

Bridging Gaps in Women Healthcare

Preventing The Preventable

Editor : **Dr. Sadhana Gupta,** Vice President FOGSI (2016)



Core group meeting on GCPR for management of AUB at AIIMS on 26th Sep 15 under leadership of Prof. Alka Kriplani

Core Group meeting for general clinical practice recommendation on anemia management under leadership of Prof. Alka Kriplani FOGSI President 2016

Facilitation of facilities in-charge in Merck for Mothers Project for providing good quality obstetrical care in Jharkhand Society at Jamshedpur


FOGSI representation in Humman Rights for Law & Pryas for expansion of women reproductive right by strengthening law & legislation


FOGSI Jhipeigo Meeting on 10-11 Dec on Development of Tool Kit for quality obstetrical care

FIRST ANNOUNCEMENT 1st

NORTH ZONE

# YUVA FOGSI Conference 2016

Theme
"Preventing the Preventable
Faith in Every Footstep"

1st-3rd April 2016
**Hotel Country Inn**
Ghaziabad, Uttar Pradesh
Hosted by
**Ghaziabad Obstetric & Gynaecological Society**
under the aegis of FOGSI

**Thanks & Regards**

President FOGSI 2016
Dr. Alka Kriplani

Vice President in-charge
Dr. Sadhna Gupta

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Dr Archana Verma

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# SAVING MOTHERS - PREVENT THE PREVENTABLE

# SAVMA 2016

## 21st, 22nd & 23rd October 2016
## Allahabad.

Dr. Sadhana Gupta
Organising Chairperson

Dr. Alka Kriplani
President, FOGSI

Dr. Ranjana Khanna
Organising Secretary


Conference Secretariat - **RANJANA HOSPITAL**
13, D-Road; Behind Chandralok Cinema, Allahabad – 211 003, M. : +91 9335106867; +91 9721374104
E-mail : ranjanahospital@rediffmail.com; website : www.savma2016.com

**Dr. Prakash Trivedi**
President FOGSI 2015-2016

**FOGSI Theme : Minimal access Maximum care pregnancy in High risk patients.**

**Dr. Suchitra N Pandit**
President FOGSI 2014-2015

"There is nothing impossible … Hard work and true determination will give you success … so believe in yourself!!"

**FOGSI Theme : Empower women Empower India … Pledge for Excellence.**

**Dr. Hema Divakar**
President FOGSI 2013-2014

*"I believe in being optimistic – because there is not much use being anything else! We are working with a strong conviction that each one of us can make a difference to women's healthcare in India by building novel solutions – To innovate, implement & make an impact – that's the dream!"*

**FOGSI Theme : Innovation to Implementation**

**Dr. P.K. Shah**
President FOGSI 2012-2013

**FOGSI Theme : Life of every mother & neonate count**

**Dr. P.C. Mahapatra**
President FOGSI 2011-2012

*"If you have a vision for 1 year cultivate flowers*
*If you have a vision for 10 years cultivate trees*
*... But if you have a vision for eternity cultivate people !!*

**FOGSI Theme : FOGSI's Will and Your skill for Women's Health 2011**

**Dr. Sanjay Gupte**
President FOGSI 2010-2011

*"We should set the continuous momentum of the Federation towards reducing maternal mortality."*

**FOGSI Theme : Reaching the unreached**

# FOGSI
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Jt. Treasurer

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# President's message

It is indeed a matter of great privilege for me to release the first FOGSI FOCUS on the theme of

"Preconception and Antenatal Care Update" during my tenure as President of Federation of Obstetric & Gynaecological societies of India (FOGSI) : 2016.

It is even more momentous that the we happen to begin at the beginning : "THE PRECONCEPTION."

Keeping in spirit with the theme of the year "PREVENTING THE PREVENTABLE: BRIDGING THE GAP", with this debut issue we get straight to work with the preventive aspect of pregnancy.

As they say " A work well begun is half done". Planning and optimising the conditions before pregnancy can go a long way in begetting a favourable outcome. The care now starts in preconceptional period which may start from childhood and adolescence like Rubella Vaccination, achieving good Body Mass Index and preconceptional folate just to mention a few. Trimester wise focussed and dedicated antenatal care startifying optimal Clinical Examination, Imaging and Laboratory investigations sets the stage for a safe and healthy mother and newborn.

This FOGSI FOCUS has covered all aspects of preconception and antenatal care. A situational and clinical approach provides clear messages and roadmap for good clinical practice. When India is slow but steadily inching towards achieving the millenium development goals we envisage our contributions to make a dent and lay the path by empowering each and every gynaecologist and BRIDGING THE KNOWLEDGE GAPS along the way.

I am sure that this FOGSI FOCUS will be a landmark publication on the subject providing comprehensive information and a crisp message.

I congratulate my Vice President Dr. Sadhana Gupta for this initiative and her dedicated work. Dr. Sadhana Gupta has consistently proven her excellence as author and editor as recipient of Dr. D.C. Dutta Award for best FOGSI Publication three times in a row and I am sure that this issue will be well appreciated by readers and obstetrician working at levels of.

Wishing you all a very happy new year and happy learning,

**Prof. Alka Kriplani**
President FOGSI 2016

# President's message

Dear Colleagues,

It gives me great pleasure to know that the FOGSI FOCUS on, "Preconception & Antenatal Care" is being released at the All India Congress of Obstetrics and Gynaecology – AICOG 2016 at Agra.

Preconception care is often neglected and the relevant tests and nutrition management are usually not done in our country. Also the specific problems of the antenatal period are not taken care of by the patient and obstetrician. By focussing on this very important aspect, we can bring about significant improvement in maternal and newborn health.

I am sure that the FOGSI FOCUS will be of help to our fellow gynecologists to get updated on the subject of Preconception and Antenatal Care. I thank Dr. Sadhana Gupta for her efforts in bringing out the FOGSI FOCUS.

*"The will to win, the desire to succeed, the urge to reach your full potential*
*These are the keys that will unlock the door to personal excellence"*


**Dr. Rishma Dhillon Pai**
FOGSI President Elect – 2017
*Vice President* – ISAR

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# Editorial

## Changing Pyramid of Antenatal Care

It is a moment of pride and pleasure for me while I communicate to readers in capacity of Vice President FOGSI 2016 and Editor of FOGSI FOCUS 2016 which is on the theme of 'Preconception and Antenatal Care –Update'

Preconception and Antenatal care has been in some forms from ancient times in almost all cultures. In India which is place of spiritual search, takes life and birth as a precious moment in eternal journey of soul. Aurved as well Aristole describes antenatal care .However modern antenatal care has been evolved only in late 19th Century. In last two decade technology as well science has reached momentous development and Anteantal care is nowhere any routine palpation and prescribing iron and calcium supplement but a sub and super speciality. It includes diagnostic modality of imaging, Biochemical and Biophysical markers, promotive and preventive care in form of vaccination, Screening for medical and obstetric disorders and timely decision making for birth plan. It also takes concern of desire and expectation of women and their families as well.

In course of almost a century It was usually a traditional approach for high concentration of visit in third trimester of pregnancy, as most obstetric complications happen in third trimester and most adverse outcome were unpredictable during first and second trimester. WHO proposes four clinical antenatal visits which should be goal oriented and focussed, however women are less satisfied with this model and there can be 15% increase risk of perinatal complications.

Changing Pyramid of Antenatal care is concept of inversion of traditional pyramid with main emphasis on first trimester. The basis of this change is the fact and observation that we can detect and predict many maternal and fetal complications in first trimester around 11 week of gestation with focussed antenatal care. Tools for this paradigm change in Antenatal care are Ultrasound, Biochemical, and Biophysical Markers. Beside this minimum investigations which must be done for all is Hemogram, Blood Grouping and Rh typing, Blood Sugar 75 gm Glucose Challenge test, Hepatitis B, HIV screening, Urine complete analysis and preferably TSH.

Well done ultrasound at 11-12 week defines gestational age, number of fetus, chorionicity in case of multiple pregnancy and very importantly a good anatomical survey can detect 90% of all major congenital anomaly and markers for chromosomal aneuploidy. In India half a million children are born with congenital malformation and birth defect contribute to 6 % of all perinatal death. Detection of congenital anomalies, aneuploidy in first trimester gives parents safer option for pregnancy termination or birth preparedness at appropriate place.

It is also important fact to appreciate that Ultrasound with cervical length measurement and Doppler studies of uterine artery have good predictive value for Hypertensive Disorders of Pregnancy, Miscarriage, Intrauterine Growth Retardation, and Preterm Labor. In background of clinical profile of woman like age, co-morbidity, obstetric history, smoking habit, nature of conception like IVF pregnancies we now can have fairly objective risk stratification of obstetric patient and plan obstetric care accordingly. High risk patient should be in closer follow up with specialist care while low risk patient can have care with 4-5 routine antenatal visits. To achieve Millennium Developmental goal Health system calls women for Institutional delivery, yet there is scarce human and infrastructure resource. It is now need of time that we have objective documentation of risk stratification and focus specialised care on women who are in need of it.

There are many challenges for this approach. Availability of good Ultrasound specialist and machines, standardization of Laboratory values, report of Laboratory values and women availability at 11-13 weeks are few major concerns. Beside we have to take care of the fact that despite risk assessment in late first and second trimester there is possibility of third trimester complications and women should be counselled for that.

It is high time that technology should be used not as a last resort but at the earliest. At the same time it is imperative that we have to learn the basics and skills of the upcoming technology for best use of it in clinical practice. Optimum clinical decision making by obstetrician and family is the desired end point of medical care.

Present FOGSI FOCUS is planned and aimed for this. Experts from the field have contributed to its content. We have taken right from Preconception care, teratogenicity understanding, promotive and preventive obstetrics like Nutrition, Vaccination, Screening for maternal and fetal disorders and road map in diverse clinical situations like Rh negativity, Hepatitis B positive, HIV positive, Animal bite, Viral fever, etc. Quiz will help in your self assessment and knowledge of Garbh Sanskar will make you aware of childbirth environment. I owe a heartfelt thank and gratitude to all learned authors to contribute excellent chapters in due time, which has enabled us to release FOGSI FOCUS in time.

I owe big thanks for our FOGSI President Padmashree Prof. Alka Kriplani for giving her instant approval and valuable advice for planning this FOGSI FOCUS.

Knowledge is empowerment, Invest your time, treasure and talent in it.

Wishing you a happy and enjoyable reading and a great year ahead.

Sincerely yours

**Dr. Sadhana Gupta**
MS, MNAMS, FICMU, FICOG, FICMCH

*Vice-President* FOGSI (2016)
*Governing Council Member* ICOG (2015-17)
*Chairperson Safe Motherhood Committee* FOGSI (2011-2013)
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# PACTICAL 'PRECONCEPTION CARE'

**A K Debdas**
Rajkumari Foundation

## Definition of pre-conception care

"a set of interventions that aim to identify and modify biomedical, behavioral and social risks to a woman's health or pregnancy outcome through prevention and Management" (Centre for disease control and prevention, 2006).

## Necessity for pre-conception care

The current research and investigations have shown that a lot can be offered to women who are planning to embark on pregnancy which would greatly improve their obstetric outcome both for themselves and specially so for their offspring and, through these many pregnancy related dangers and mishaps can be avoided. However, unfortunately the awareness about this is grossly lacking and

Because we still see NTDs, uncontrolled diabetes and hypothyroidism, effects of gross obesity and also malnutrition and their deleterious effects on pregnant women and their fetuses inadvertently prescribed drug related fetal and neonatal anomaly and handicaps from inadvertently prescribed. Hence there is major necessity for awareness campaign on this vital issue. This is specially so because in India 50% pregnancies are unplanned and the average gestation of the first antenatal visit is $10^{th}$ week.

Besides, there is also a small growing group of educated, professional, quality conscious women who on their own drive make appointment with gynaecologist for advice for this very important aspect of reproduction. So, gynaecologists have to be equipped with all the latest information to crater for them.

## Candidates for pre-conception care

- All nulliparous women contemplating marriage and, if already married, contemplating pregnancy.
- Women who had a pregnancy mishap in the past..
- All women having some kind of medical, psychiatric, surgical and congenital disorder.
- Women having some familial disease.
- Ideally, all college going girls

## Ideal time for taking appointment for Pre-conception advice

Three months before the target month of trying. This lead time is required for conducting investigations and managing any abnormality found. Prophylactic vitamins

like Folic acid and other micro nutrients should be started about six weeks prior to the target month.

## Five basic components of pre-conception care

Past history in minute detail, through clinical examination, relevant investigation, appropriate treatment of any significant factor found including referral to appropriate specialist and relaxed counseling (see later).

### HISTORY

Various components of history –

- Age
- History of past illnesses
- History of present illness or disease, if any
- Drug history
- Past obstetric history
- Family history
- Occupational history
- Immunisation history
- Addiction history

### AGE

**Increased age -** specially age above 35 years. This is important for two reasons :

Firstly, because as is well known, the risk of chromosomal abnormalities increase with increasing age of the women e g while it is 1 in 1300 at age 24, it is 1in 100 at age 40 years, the common chromosomal anomalies being 21 trisomy (Downs syndrome), 18 trisomy (Edwards syndrome), 13 trisomy (Patau syndrome).

Secondly, the incidence of general and familial diseases like hypertension, diabetes etc. usually make their appearance as the age advances.

**Too young women –** For example, women in their teens. Their parents need counseling. They should be made aware of increased risks of pregnancy and delivery at this tender age e g high incidence of PIH &Eclampsia, prolonged and obstructed labor etc. The contributory factors here are their lack of mental maturity and education.

## History of past illness

It should be taken system by system as follows -

*Nervous system* - Any Neurological problem-congenital e g spina bifida or acquired e g operation for Prolactinoma etc..

*Respiratory system* – Asthma, Tuberculosisetc

*Cardio-vascular system* – Any kind of heart disease – congenital or acquired.

*Urinary system* – Recurrent Urinary tract infection, history of renal colick with or without stone.

*Reproductive system* – Any gynae disorder or specially any Gynaeoperation, anyhistory of Infertility.

*History of any mental illness* – Depression, Schizophrenia etc

*Endocrine system* – Thyroid disorder, Diabetes etc. These women should not try for pregnancy until they are euthyroid and euglycaemic.

*Skeletal system* – Specially deformity of pelvis and lower lower limbs. Any history of limping. Needs assessment of pelvic capacity and shape.

*Haematological system* – Thalassaemia, Sickle cell disease, Thrombocytopenia, history of petechial haemorrhageetc.Hb

Electrophoresis to be advised.

*GI system* – Chronic diarrhea, dyscentry, Ulcerative colitis etc.

*Hepato-billiary system* – Cholethiasis, Cholecystitis etc. Lapchole is to be done before embarking on pregnancy.

*History of any significant generlised disease* – like HIV.

HIV affected women should try for pregnancy only when the viral load is low. If she is on the antiviral drug Efavirenz she should be changed to other safer drug.

*History any auto-immune disease* – like SLE etc. To be referred to physician for the control of the disease

## PRESENT HISTORY

Enquire whether she is suffering from any kindly of illness presently – Medical, Surgical, Psychiatric or Gynaec and what drug is she on for that, and this leads to the current drug history.

## DRUG HISTORY and DRUG MANAGEMENT

This is vital.

Action plan

*Checking the 'Risk category' of drug in relation to pregnancy* - Patient should be advised to bring the wrapper of the drug so that its composition can be checked. Each drug should be checked in the CIMS for their advisability during pregnancy as to whether it falls under 'special precaution' category or 'contraindicated' category. Ideally, FDA category of the drug should also be found out. OK index by Debdas (2015) is an easy alternative to FDA risk category.

*If any drug is found to be contraindicated in pregnancy* - options are :

a) Stopping the drug if the particular disease condition permits this.

b) Change to some relatively safer drug specially up to the end of first trimester.

   The woman should be advised to go back to the specialist concerned for his advice on this.

c) The course of the concerned drug should be finished before embarking on pregnancy if that is possible. This is the best option for example Antitubercular drugs..

**The drugs that need special attention** – Oral anticoagulents, Oral antidiabetics, anti hypertensives, antiepileptics, antituberculars, antiasthmatic, psychotopic drugs etc. These women should be referred to concerned specialist.

An instant NO-NO drug list

Drugs which should be stopped or changed during pre-conception period

*Antihypertensive*

ACE Inhibitors, Atenelol, Guanethidine

*Anti Diabetic*

Oral Hypoglycaemic agents

*Anti-epileptic*

Sodium Valproate - No

Recommended one drug therapy-not multiple drug.

*Anti-psychiatric*

Lithium, Carbezepine, MAOIs,

*Anti-thyroid*

Methiazole, Pot Iodide, Radioactive

Iodine

*Anti-tubercular*

Capreomycin, Streptomycin, Ethionamide

*Hyper-prolactinaemia*

Cabergoline

*Analgesic & Anti-inflammatory*

Phenylbutazone, Indomethacin, Diclofenac, Penicillamine.

## PAST OBSTETRIC HISTORY

History of birth of congenitally malformed baby, even history of recurrent abortion needthrough investigation before embarking on next pregnancy.

## FAMILY HISTORY

History of the following diseases amongst the woman's *blood relations* has to be elicited –

Diabetes, Hypertension, Thalassaemia, Sickle Cell disease, Thrombocytopenia, Phnylketonuria, Tay-Sach's disease, Cystic fibrosis, Fragile X-syndrome etc or whether she previously had a congenitally abnormal child etc.

Thlassaemic couple may go for Pre-implantation Genetic Diagnosis (PGD).

These women.should be referred to Genetic counselor. Unmarried women may be advised eugenic marriage.

Phenylketonuric women should be advised Phenylalanine restricted diet.

## OCCUPATIONAL HISTORY

Whether her job entails exposure to radiation, extreme heat, high noise, heavy physical work, long travel with lot of change of transport etc.

The woman should be advised job rotation, job change and better transport arrangement.

## IMMUNISATION HISTORY

Whether she had all the usual immunizations like DTP, BCG and MMR.

*Rubella immunization* - If she has not had it she should be advised to get her immunized straightway and not to try for pregnancy until three months after that.

*The same applies for* – HPV andhepatitis B vaccine.

*Rhesus Negative women* – should be asked about any previous blood transfusion and the 'Rhesus type' of the blood that she was transfused. If she is not sure about the blood type she should be advised to get her blood tested for Rhesus antibody. If she had any abortion or MTP or ectopic in the past she should be asked whether she had Anti-D injection following that.

## ADDICTION HISTORY

If she has been a smoker or drinker or a drug addict – she must be completely completelywinned out of these before trying for pregnancy.

## CONTRACEPTIVE HISTORY

OCP and IUCD usage is best stopped two cycles before the proposed month so that there is no confusion on dating of pregnancy. Physical methods like condom or withdrawal may be used during this window period.

## PET KEEPING HISTORY

One has to be careful about cat specially about handling their litter to avoid contracting Toxoplasmosis. For the same

reason eating undercooked meat should be avoided.

### EXAMINATION

*Weight and Height*

BMI (Body mass index) isto be calculated from these by the use of the following formula – Weight in KG– divided by – square of Height in cm = BMI

*WHO guide on BMI*

| | | |
|---|---|---|
| Less than | 18.5 | - Under weight |
| | 18.5 – 24 | - Average weight |
| | 24 – 30 | - Obese |

Higher the BMI worse the risk.

## Pregnancy perils of overweight and obesity

Increases the propensity for - Gestational hypertension, Diabetes, Stillbirths, Congenital heart defects, DVT.

*Clinical problem* - Difficult examination during pregnancy, difficulty in clinical diagnosis, difficult for her to move about, chronic backache, pain in the legs.

### ADVICE

Physical methods -Brisk walk,jogging, yoga etc.May join Gym.

*Diet* - Avoid sweets, carbohydrate and fatty foods. May take the advice of Wellness consultant

*Chemical methods* - Cetilistat, Orlistat, Leucine & Pyridoxin combination, volume loading of stomach by some no calorie fibrous substance, fat burners etc.

Taking weight weekly to monitor the progress

NOTE : These women should be tested for diabetes (blood sugar – fasting & PP, HbA1C) and hypothyroidism (TSH) etc.

## Perils of underweight women

Higher incidence of– Stillbirths, Preterm birth, Low birth weight and Small-for-gestational-age babies and microcephaly.

### Advice

a) Refer her to a physician to spot any underlying cause of her being underweight

b) If none is found –she may be advised to take balanced but high calorie diet i e diet having high carbohydrate and fat.

c) If she is hyperactive by nature or overworked –she should be advised to arrange adequaterest.

d) Proprietary appetite stimulants (tonic) like Sioplex with lycine, CYP-L etc may be prescribed – to be taken 30 minutes before the main meals.

e) Vegetarians should be advised to take more of Cheese as a source of animal protein.

Note : Large Sea fish should be avoided for the possibility of contamination with Mercury- Mercury being Neurotoxin.

### GENERAL SURVEY

This should be done head to foot – Pallor, enlarged lymph nodes, BP, any enlargement of liver and spleen (to be referred to physician), any suprapubic lump, oedema, varicose veins etc

Women with high BP have should have their creatinine level estimated and also *ophthalmoscopy*.

## GYNAECOLOGICAL EXAMINATION

Bimanual and also Speculum examination –Apart from the routine any tenderness and presence of any septum or stricture or ulcer etc. to be looked for.

Pap smear-specially if she is aged above 30 years.

High vaginal swab- for microscopy and culture & sensitivity only if there is complaint of excessive vaginal discharge or foul smelling discharge or itching or burning.

Routine lower abdominal and transvaginal sonography- Should be done.

## INVESTIGATION

*Routine tests*

Hb, TC, DC, ESR, Platelet count, Blood sugar-fasting & PP, creatinine, TSH, VDRL, HIV, HBsag, HCV, TORCH test.

Urine routine, microscopy and Culture and sensitivity.

In case she is a case of Recurrent abortion– Anti Phospholipid, anti Cardiolipin and Anti Nuclear antibodies, PT, APTT, LA-1 & II.

If her mens was infrequent-PRL, AMH.

If there is family history of Diabetes – HbA1C

If there is family history of Haemolytic disease – Hb electrophoresis.

HVS – Smear and C & S (already mentioned)

Vitamin D estimation – Suddenly, there seem to be an epidemic of vitamin D deficiency in India !and papers have reported the association of a whole host of reproductive process handicap due to deficiency of this vitamin. So, an estimation of level of this is logical and any deficiency detected to be compensated in preconception period.

*Pap test* – if she is aged 30+ or has abnormal vaginal discharge or the cervix is abnormal looking or there is history of post coital bleeding.

*USS pelvis* – already mentioned above.

Liver function-if there is history of jaundice within last one year.

## THERAPEUTIC MANAGEMENT

Obviously, it will depend on the disease condition detected if any. For medical disorders she should be referred to the specialist physician for the change of drug or adjustment of dose in view of her contemplating pregnancy.

List of some common drugs that are contraindicated in pregnancy has already been given above.

There is no evidence that the use of Microwave oven or that of Cell phone cause any harm.

## COUNSELING

This is the vital concluding part. The result of each test should be explained to her report by report. The main idea is remove her fear and assure her about the treatability in case some abnormality is found. It is best that during counseling some close relation of the woman is present e g her parents or husband as would be chosen by her.

The woman should be informed about the increased chance occurrence of domestic violence during pregnancy and that she should cleverly arrange to prevent this

happening by exhibiting smoother interrelation with the husband..

## Counseling the husband

*Counseling points for husband*

Dangers of passive smoking, tobacco chewing and alcoholic drink and narcotic drugs taking.

He should be specially advised that he needs to take even greater care of the wife physically and *emotionally* during the whole pregnancy period because she needs it at this difficult and delicate period.

He also need to supervise his wife's diet, rest and activity habit and addiction, if any e g tobacco chewing, smoking, drinking etc. These should be stopped or at least moderated.

## FURTHER READING


1. Drug Handbook in Obstetrics, 3rdedition:Debdas AK :, Jaypee Medical Publishers, Delhi.p.337-358, 2015.
2. Principles & Practice of Obstetrics & Gynaecology for Postgraduates, 4th edition, Edited by Malhotra N, Shah PK and Divakar H, Jaypee Medical Publishers, Delhi., p.3-6, 2014.
3. William's Obstetrics, 23rd edition: Edited by Cunnigham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ,Spong CY, MC Graw Hill, New York, p. 174-190.

# PRE-CONCEPTIONAL CARE AND COUNSELING

**Pratima Mittal[1], Jyotsna Suri[2]**
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[1]President AOGD. [2]Editor AOGD 2015-16

Preconception care refers to the process of identifying social, behavioral, environmental, and biomedical risks to a woman's fertility and pregnancy outcome and then reducing these risks through education, counseling, and appropriate intervention before conception1. Preconception intervention is more important than antenatal intervention for prevention of congenital anomalies since as many as 30 percent of pregnant women begin traditional prenatal care in the second trimester (>13 weeks of gestation), which is after the primary period of organogenesis. The Preconception Care Work Group of the Centers for Disease Control USA recommends that preconception care should be an essential part of primary and preventive care 2-3.

The **three integral components** of pre-pregnancy counseling are:

- Identification of risk factors related to pregnancy (screening).
- Patient education regarding pregnancy risks, management options and reproductive alternatives (information and counseling).
- Initiation of interventions, when possible, to provide optimum pregnancy outcome (interventions).

## When and by whom should preconceptional counseling be done?

Local doctor (general practitioner or family physician), obstetricians and gynecologists, and health providers at maternity hospitals/clinic, preconception health clinics, family planning and community health centers.

Health care providers can dispense preconceptional care and counseling during any encounter involving contraception, infertility, pregnancy testing, evaluation for sexually transmitted disease or vaginal infection, or periodic health examination, especially if the woman has pre-existing medical problems. Addressing the preconceptional issues with the women in the reproductive age group at any point of their contact with the health care system is desirable because more than half the pregnancies are unplanned. Furthermore in our country, there are very few dedicated preconceptional counseling centres.

Factors which facilitate the process of counseling are preconceptional care checklists; patient information sheets in local and simple language; posters and video films in the patient waiting areas; and availability of dedicated health care providers.

## Check list for comprehensive preconceptional health package[4]

*Screening*

- Screening of the couple through a detailed medical and family history, including genetic history of patient, spouse and family (Table 1); followed by examination.
- Screening to detect haemoglobinopathies, e.g. sickle cell anemia, thalassemia if suspected by family history or examination.
- Screening to identify ABO and Rh(D) blood type to detect possibility of blood incompatibility between would-be couple.
- Screening to detect infectious diseases like HIV, hepatitis B, C and syphilis as suggested by history and examination.
- Screening to detect sexually transmitted diseases (other than syphilis, HIV and HBV) such as gonorrhea and chlamydia as indicated by history.
- Psychosocial and domestic issues should be identified and women with mental health issues should be referred to a psychiatrist.
- Screening to identify rubella immunity of females.
- Haemoglobin levels to identify anaemia.
- Screening for diabetes, hypertension etc. if directed by family history or examination.
- Screening for obesity/underweight

*Information and counseling*

- Timing of pregnancy - The optimum biological age for pregnancy is between 20-35 years of age. Pregnancy at an earlier or later age entails poor outcomes for both the mother and the child. There is a 3 times increased risk of hypertension in women with advanced maternal age, besides the risk of placenta praevia, gestational diabetes, preterm birth and increased cesarean section rate5. There is also an increased risk of poor fetal outcomes, in terms of increased still births, perinatal mortality, low birth weight and nursery admissions.Women should be counseled that advanced maternal age is also associated with an increased risk of conditions such as infertility, fetal aneuploidy miscarriage and the risk of fetal chromosomal anomalies, in particular Down's syndrome, which increases sharply with increasing maternal age.
- Imparting knowledge about reproductive biology and physiology of pregnancy.
- Information about different contraceptive options available for the couple.
- Counseling regarding safe sex practices and behavior.
- Counseling regarding ill effects of substance abuse, alcohol.
- Counseling about optimizing pre pregnancy weight.
- Counseling about healthy life style, nutritive diet and regular exercise.
- Information about effect of chronic diseases, genetic disorders and

teratogenic drugs on future child bearing if relevant to the patient.

- Genetic Counseling : genetic counseling is the process by which patients at risk of a genetic disorder (identified by taking the genetic history-Table 1) are informed about the consequences of the disorder; the probability of developing and transmitting it; and the means by which this risk can be reduced. It aims at empowering the couple to take the appropriate decision and course of action in view of the risk. The risk is assessed by taking detailed structured history of previous pregnancy outcomes, chromosomal disorders, genetic diseases in family and consanguinity. Consanguineous couples are counseled regarding increased risk of autosomal recessive disorders. A three generation pedigree chart is made in the cases with suggestive history. The genetic counseling allows patients planning pregnancy to make informed reproductive decisions about adoption, surrogacy, use of donor sperm, in vitro fertilization after preimplantation genetic diagnosis, avoidance of pregnancy, and prenatal diagnosis.

*Interventions*

- Confirmatory tests if any of the screening test is positive
- Live vaccines (varicella; measle, mumps, rubella) should be administered at least one month prior to pregnancy.
- Vaccination of eligible partners for hepatitis B. Individuals, whose partner is HBsAg positive, are given a booster dose of hepatitis B vaccine if they have been vaccinated before, and a full vaccination series if they have not been vaccinated before.
- Couples with a family history of haemoglobinopathy or any other genetic disease are referred to genetic specialist in the region for further evaluation.
- Referral of persons with chronic disorders to respective specialists so as to ensure good control of disease prior to marriage and pregnancy.
- Folic acid (400-800mcg daily) supplementation before pregnancy.
- Iron supplementation in iron deficiency anaemia.
- Treatment of STIs detected during screening.
- Cessation of smoking, alcohol and drugs before pregnancy.
- Limit caffeine consumption to less than 200 to 300 mg per day.
- Only cooked fish should be consumed and fish high in mercury content avoided.
- Multivitamin preparations containing more than 5000 international units of vitamin A should be avoided (increased risk of teratogenesis at >10,000 international units/day).
- Glycemic control in women with diabetes- the American Diabetes Association recommends aiming for an A1C <7 percent prior to conception[6].
- Optimizing weight in obese and lean.Obesity is associated with both infertility and several adverse pregnancy outcomes including birth defects. Underweight women

(especially those with eating disorders) have a 20 percent increase in risk for preterm birth and a 40 percent increase in risk of having a small for gestational age infant in one large cohort study[7].

- Replacement of teratogenic drugs like ACE inhibitors, ARBs, statins, lithium, valproic acid, streptomycin, tetracycline, methotrexate etc. by safer alternatives few months before pregnancy

## Preconceptional counseling for maternal medical conditions[8]

Various studies have shown improved outcome with preconceptional intervention in the following medical disorders

*Diabetes* - Preconceptional advice on diet, exercise and weight loss is crucial for good outcome. Women should be explained thatwith good glycaemic control the risks of miscarriage, congenital malformations, stillbirth and neonatal death is reduced. ADA recommends a A1C of < 7% before planning pregnancy. Women with higher levels are at an increased risk of miscarriage and teratogenesis. Self-monitoring of blood glucose and management of hypoglycemic symptoms should be should be explained.

*Hypertension* - The goal should be to control blood pressure prior to conception. ACE inhibitors should be stopped before pregnancy (fetal growth restriction, oligohydramnios, renal failure in fetus) and replaced by safer alternatives. Methyldopa or labetalol are the drugs of choice in pregnancy. Those with chronic hypertension should be assessed for end organ damage (heart, eye, kidney) and referred to the concerned specialist.

*Asthma* - Patients should be advised to use their peak flow meters regularly. Women with repeated asthmatic attacks or severe disease should be referred to a specialist in asthma therapy and not managed by the local doctor. If necessary, the use of steroids (inhaled and systemic) in pregnancy is generally safe as compared to the risk of maternal acid base disturbances and fetal hypoxaemia.

*Thyroid disorders* - Routine screening of thyroid function and antibodies in women planning a pregnancy is advisable. Severe and untreated thyrotoxicosis should prompt referral to an endocrinologist during the preconceptional period, as this condition can lead to anovulation, miscarriage, growth restriction and preterm delivery. In newly diagnosed hypothyroidism, specialist advice should be sought about the levothyroxine starting dose

*Cardiac disease* - Women with a history of cardiac problems should be referred to a cardiologist for baseline cardiac assessments and discussion of potential pregnancy risks. Women advised against pregnancy should be given appropriate contraception.

*Epilepsy* - Women should be referred to a neurologist for a thorough discussion of the risk of anticonvulsant medications, adjustment of drug regimen and close monitoring during pregnancy.

Polytherapy should be avoided to minimize the teratogenic effects of anticonvulsants.In particular, valproate should be discontinued if seizures can be adequately controlled with an alternative drug, since valproate appears to be a more potent teratogen than other antiepileptic drugs. Preconceptional folic acid (5 mg/day) is advised for women on anticonvulsants.

*Chronic renal disease* - Women should be informed that the outcome of pregnancy and any adverse effects on underlying renal disease are influenced by the presence and degree of renal impairment, hypertension (10% risk of fetal loss if pre-existing) and proteinuria. Renal disease during pregnancy is associated with risk of prematurity, growth restriction and deterioration in maternal renal function.

Women with renal transplants should be asked to avoid pregnancy for a minimum of 2 years until renal function is optimized on a reduced amount of immuno suppressants.

*Systemic lupus erythematosus* - the prognosis is best when the disease has been quiescent for at least six months prior to pregnancy and the patient's underlying renal function is stable and normal or near normal. Maternal medications may need to be changed because of potential fetal risks.

*Inherited thrombophilias* - These women are at higher risk of thromboembolic complications during pregnancy because of pregnancy-associated changes in several coagulation factors; in some cases, they are at increased risk of adverse pregnancy outcome, as well. Indications for, and management of, anticoagulation should be addressed with a thrombosis specialist.

*Dental caries* and other oral diseases (eg, periodontal disease)- are common and may be associated with pregnancy complications, such as preterm delivery; thus, referral to a dentist is essential.

## Key points

- Preconeptional counseling and screening is a very important intervention, which prepares a woman embarking into motherhood physically and emotionally and hence ensures a good maternal and fetal outcome
- The goals of preconceptional counseling are screening for risk factors, imparting relevant information and counseling and initiating interventions before conception.
- A structured form or check list aids in obtaining a thorough history and identifying the risk factors.
- Women with high risk history should undergo genetic counseling.
- Chronic medical ailments should be optimized before embarking on a pregnancy.
- Core preconception interventions that can reduce the occurrence of congenital disorders, fetal growth abnormalities, and pregnancy complications include: Folic acid supplementation and intake of fortified foods; glycemic control in women with diabetes; abstinence from alcohol and illicit drugs, smoking cessation; reduction of obesity; avoidance of teratogens; vaccinations; and behavioral changes to reduce the risk of acquiring infections like toxoplasmosis, cytomegalovirus and sexually transmitted infections.

**Table 1 :** Genetic history of patient, spouse and family

| **History of congenital abnormalities** |
|---|
| Neural tube defects |
| Heart defects |
| Cleft lip/palate |
| Any other |
| **Chromosomal abnormalities** |
| Downs syndrome |
| Mental retardation/learning disabilities (fragile X syndrome) |
| **Advanced maternal or paternal age** |
| **Inherited diseases** |
| Hemoglobinopathy |
| Muscular dystrophy |
| Thrombophilia |
| Cystic fibrosis |
| Huntington's chorea |
| Hemophilia |
| Metabolic disorders (eg, phenylketonuria, diabetes) |
| Kidney disease |
| Deafness |
| Marfan syndrome |
| Any other |
| **Ethnicity** |
| Eastern European (Ashkenazi) Jews (Tay-Sachs, Canavan risk, etc) |
| French Canadian or Cajun (Tay-Sachs risk) |
| Mediterranean region (hemoglobinopathy risk) |
| Asia, including Souteast Asia and Western Pacific (hemoglobinopathy risk) |
| Africa and Middle East (hemoglobinopathy risk) |
| South America and Caribbean (hemoglobinopathy risk) |
| Caucasian (cystic fibrosis) |
| **Consanguinity** |
| **Recurrent pregnancy loss, stillbirth, or early infant death** |
| **Maternal metabolic disorder** |

*Adapted from : The preconception office visit, Joyce A Sackey, Uptodate, 2015*

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# ANTENATAL CARE BEYOND MEDICINE : GARBHASANSKAAR

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"Birthing is not just about making babies. Birth is about making mothers strong, competent, capable mothers who trust themselves and know their inner strength"

*– Barbara Katz Rothman*

The aim of good antenatal care is to have a healthy mother as well as a healthy child. However if we go by the classical WHO definition of "health" — "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". This definition has not been amended since 1948 and as per this definition the conventional antenatal care is way behind providing support for mental and social well being of the developing fetus and this is where the concept of " Garbha Sanskaar" comes in.

The Sanskrit word "Garbh" means foetus in the womb and "Sanskar" means educating the mind. So, Garbh sanskar essentially means educating or training the mind of the foetus. As per the Indian tradition it is believed that a child's mental and behavioural development starts not after birth but in utero itself. The persona begins to take shape in the womb itself and all of this is greatly influenced by the mother's state of mind- her thoughts ,feelings and emotions during pregnancy.

The popularity of Garbh sanskar is gaining back as more and more researchers have proved its relevance and importance in the development of the child. There are scientific evidences that prove that a baby inside the mother's womb responds to the outside stimulus. Garbh sanskar not only educates the developing child but these practices have an impact on the health of the mother also. The positive thinking and attitude promotes physical well being of the mother. Garbha sanskar is about being in a good state emotionally, mentally, physically and spiritually for the sake of your growing baby. To do this, ancient scriptures supported by recent evidence suggest: listening to music, thinking positive, eating healthily, yoga, meditation and prayer, being creative and communicating with your unborn child

## Historical perspective :

Garbha sanskar can be traced back to ancient Hindu texts like the Vedas which date to 1500-500 BC. It also finds reference in the Mahabharata which was written roughly around 400 BC. It finds a place in traditional ayurvedic medicine as a guide for pregnant women in prenatal education.

One of the most famous and well-known tales is that of Abhimanyu from the Mahabharata. When Arjuna's wife was pregnant with their son Abhimanyu, he told her about how to penetrate the Chakravyuh, a particular war formation. When Abhimanyu became a young

man and a warrior in the Kurukshetra war, he remembered his father's story. He was able to employ the strategy that he had heard his father tell his mother while he was in her womb. The story of Prahlad is from the Puranas. Prahlad was born into a family of demons who were wreaking havoc on the Gods in heaven. His mother listened to devotional prayers and stories about Lord Vishnu while he was in her womb. As a result, he became a devotee of Lord Vishnu. He stood by good and renounced all evil. This led to the downfall of his demon father's evil empire. Lord Hanuman's mother Anjana was an ardent devotee of Lord Shiva. When she was pregnant she ate a blessed dessert meant to produce divine children. Lord Hanuman was thus born with divine powers. He dedicated his life to fighting evil and was loyal to Ram and Sita.

## Scientific evidence :

Evidence of an intelligent life in utero :

- By nine weeks, a developing fetus can hiccup and react to loud noises. By the end of the second trimester it can hear
- Just as adults do, the fetus experiences the rapid eye movement (REM) sleep of dreams.
- The fetus savors its mother's meals, first picking up the food tastes of a culture in the womb.
- The fetus can distinguish between the voice of the mother and that of a stranger, and respond to a familiar story read to it.
- Even a premature baby is aware, feels, responds, and adapts to its environment.

## Is their evidence of memory in utero?

Just as studies exploring memory in the newborn infant have used learning paradigms, similar paradigms have been applied to the fetus to explore its memory. Paradigms of "exposure learning", classical conditioning and habituation have been used to examine fetal learning and fetal memory.

Studies of classical conditioning of the fetus, although few, have a long history, dating back to the 1930s. Ray[1] paired a vibration (the CS) with a loud noise (the UCS). Although using only a single subject and reporting no data, Ray concludes the subject suffered "no ill effects from her prenatal education", suggesting the fetus was successfully conditioned. Using a similar procedure Spelt[2] paired a vibration (the CS) with a loud noise (the UCS). He reported that after 15-20 pairings, most fetuses, in the last 2 months of gestation, responded to the vibration (CS) alone. More recently Feijoo[3,4] paired maternal relaxation (the UCS) with music (the CS) and examined individuals as fetuses and after birth. After 24 pairings of the stimuli, when the music was played to the fetus in the last weeks of pregnancy, individuals began moving and when played to the new-born, these babies stopped crying, opened their eyes and exhibited fewer clonic movements. The final paradigm used to investigate fetal learning and memory is that of "exposure" learning. This

paradigm has the potential to be a powerful tool in the exploitation of fetal memory abilities given the control available to the experimenter over the presentation of the stimulus and subsequent testing.

One study looked at the ability of the fetus to learn a TV theme tune, "Neighbours", frequently heard by the mother during her pregnancy[5,6] In the first experiment newborn infants (2-4 days of age) of mothers who watched Neighbours during pregnancy (and heard the theme tune) became alert stopped moving and their heart rate decreased (orienting) upon hearing the tune. These same individuals showed no such reaction to other, unfamiliar tunes. Newborns of mothers who did not watch the TV programme during pregnancy showed no reaction to the tune. There was no exposure to the TV tune after birth, the last exposure occurring before birth. Hence individuals must have learned the information about the tune prenatally and retained it 2-4 days until tested postnatally. A second experiment examined when learning and memory could first be evidenced before birth. Individuals were observed using ultrasound and their response to the theme tune noted. Individuals exposed to the theme tune showed a significant increase in movements at 37 weeks of gestation but not at 30 weeks of gestation. Fetuses not previously exposed to the tune showed no response at either age. This suggests that the ability to recognise familiar stimuli commences between 30 and 37 weeks of gestation (although see comments above). A third experiment looked at the duration of this memory by examining the response of individuals, prenatally exposed to the tune, 21 days after birth. Whilst the previous study showed newborns at 2-4 days of age "recognized" the tune there was no response when individuals were tested at 21 days of age. This may indicate that any recognition of memory is lost by 21 day of age in the absence of any postnatal exposure. Despite making inroads into the development of fetal memory much remains unanswered. Exactly how this memory is acquired, simple exposure leading to recognition or some form of classical conditioning, is unknown. Similarly, prenatal exposure to stimuli in this study was relatively uncontrolled thus exactly how much exposure to establish a preference is yet to be determined. The study does indicate that the fetus is able to learn and remember familiar auditory stimuli in the womb, retain this information over the birth period and that this learning is specific to the familiar stimulus. Other studies have confirmed the ability of the fetus to learn familiar audtory stimuli in utero[7,8]

The above studies, using different paradigms, have all demonstrated successful learning and the presence of memory abilities in the fetus. The use of identical paradigms as used in newborns, infants and adults may suggest identical memory processes are used in solving these tasks. However great care must be exercised here. Similar learning abilities have been observed in a variety of fetal animal, including invertebrates[9-13]. Similar behavioural demonstrations of memory need not necessarily indicate similar memory processes or underlying neural mediation, or even continuity with the later memory processes of the individual.

## Function of fetal memory

Prenatal memory may be important for developing maternal recognition and attachment . Evidence has it that the fetus learns the speech characteristics of its mother prenatally and prefers its mother's voice to other female voices after birth[14,15, 16-18] It may be possible that by learning to recognise its mother prenatally the newborn infant has a "familiar" stimulus in its environment after birth to respond to. It is unlikely that the newborn recognizes this familiar stimulus as its mother, but rather a familiar auditory stimulus. However this prenatal priming may ensure and promote both the recognition of the individual's mother and the development of attachment. Although further evidence is required it may be that the individual learns about its mother's smell prenatally[19] and this too would similarly promote maternal recognition and attachment.

FETAL TASTE : By 13 to 15 weeks a fetus' taste buds already look like a mature adult's, and the amniotic fluid can smell strongly of curry,cumin, garlic, onion and other essences from a mother's diet. A memory in utero may be important for the establishment of breast feeding. The mother's diet flavours both the amniotic fluid and her breast milk[19-21]. The fetus may learn about the flavour of the amniotic fluid via its swallowing of this fluid which begins at 12 weeks of gestation[22]. When presented to the breast for the first time, the newborn recognises the colostrums as familiar due to the presence of the same tastes that have been present in the amniotic fluid. This may enhance the individual's willingness to suck and promote breast feeding. Prenatal familiarisation with the taste of milk would contribute to ensuring breastfeeding was successfully established. Recent evidence suggests the fetus can learn tastes experienced only prenatally[23] and through such learning acquires a preference for these tastes[24.] Furthermore, preliminary observations suggest that those mothers who experience the greatest change in diet between before and after birth have the greatest difficulty in establishing breast feeding.

FETAL HEARING : A very premature baby entering the world at 24 or 25 weeks responds to the sounds around it, so its auditory apparatus must already have been functioning in the womb. Many pregnant women report a fetal jerk or sudden kick just after a door slams or a car backfires. Fifer has found that fetal heart rate slows when the mother is speaking, suggesting that the fetus not only hears and recognizes the sound, but is calmed by it.

The fetus has the ability to learn its mother's voice[14,14, 16-18.] Recordings of the fetal uterine auditory environment, reveal the prosodic nature of speech can be clearly heard inside the womb[25,26.] Further, the fetus has been shown to be able to differentiate between different speech sounds in the womb[25,26.] Newborns also seem to have a preference for their mothers' native language[27.] It may be that experience of speech prenatally begins the process of acquiring language.

FETAL LEARNING : Along with the

ability to feel, see, and hear comes the capacity to learn and remember. These activities can be rudimentary, automatic, even biochemical. For example, a fetus, after an initial reaction of alarm, eventually stops responding to a repeated loud noise. The fetus displays the same kind of primitive learning, known as habituation, in response to its mother's voice. In the 1980s,psychology professor Anthony James DeCasper and colleagues at the University of North Carolina at Greensboro devised a feeding contraption that allows a baby to suck faster to hear one set of sounds through headphones and to suck slower to hear a different set. With this technique, DeCasper discovered that within hours of birth, a baby already prefers its mother's voice to a stranger's, suggesting it must have learned and remembered the voice, albeit not necessarily consciously, from its last months in the womb. More recently, he's found that a newborn prefers a story read to it repeatedly in the womb—in this case,The Cat in the Hat—over a new story introduced soon after birth.

By monitoring changes in fetal heart rate, psychologist JeanPierre Lecanuet and his colleagues in Paris have found that fetuses can even tell strangers' voices apart. They also seem to like certain stories more than others. The fetal heartbeat will slow down when a familiar French fairy tale such as "La Poulette" ("The Chick") or "Le Petit Crapaud" ("The Little Toad") is read near the mother's belly. When the same reader delivers another unfamiliar story, the fetal heartbeat stays steady. The fetus is likely responding to the cadence of voices and stories, not their actual words, observes Fifer, but the conclusion is the same: the fetus can listen, learn, and remember at some level, and, as with most babies and children, it likes the comfort and reassurance of the familiar.

FETAL PERSONALITY : It's no secret that babies are born with distinct differences and patterns of activity that suggest individual temperament. Just when and how the behavioral traits originate in the womb is now the subject of intense scrutiny. In the first formal study of fetal temperament in 1996, DiPietro and her colleagues recorded the heart rate and movements of 31 fetuses six times before birth and compared them to readings taken twice after birth. Fetuses that are very active in the womb tend to be more irritable infants. Those with irregular sleep/wake patterns in the womb sleep more poorly as young infants. And fetuses with high heart rates become unpredictable, inactive babies.

"Behavior doesn't begin at birth," declares DiPietro. "It begins before and develops in predictable ways." One of the most important influences on development is the fetal environment. As Harvard's Als observes, "The fetus gets an enormous amount of 'hormonal bathing' through the mother, so its chronobiological rhythms are influenced by the mother's sleep/wake cycles, her eating patterns, her movements."

STRESS AND MATERNAL EFFECTS: There is a significant effect of the hormonal secretions that are activated by the thoughts of a mother specially in response to stress on the unborn baby. DiPietro finds that highly pressured mothers-to-be tend to have more active fetuses—and more irritable infants.

Stress, diet, and toxins may combine to have

a harmful effect on intelligence. A recent study by biostatistician Bernie Devlin, of the University of Pittsburgh, suggests that genes may have less impact on IQ than previously thought and that the environment of the womb may account for much more. DiPietro insists. "There is an antenatal environment, too, that is provided by the mother."Parents-to-be who want to further their unborn child's mental development should start by assuring that the antenatal environment is wellnourished, low-stress, drug-free.

Gently talking to the fetus, however, seems to pose little risk. Fifer suggests that this kind of activity may help parents as much as the fetus. "Thinking about your fetus, talking to it, having your spouse talk to it, will all help prepare you for this new creature that's going to jump into your life and turn it upside down," he says—once it finally makes its anti-climactic entrance.

## How does one give garbha sanskaar?

Garbha sanskar is about being creative and communicating with your unborn.

Traditional Indian culture describes this theory as "Supraja janan" or eu-maternity This "Supraja janan", as conceptualised in Ayurveda, involves the preparation of the couple planning pregnancy, three months prior to conception.

The beginning is by pinda shuddhi or the purification of the gametes (sperm and ovum). If the couple is not in a state of mental stability and calmness, even if they are physically fit, they cannot give birth to a healthy child. This mental calmness and stability ("Satwa Guna") of mind is closely related to ones food habits and many other factors. Abstinence from spicy foods and addictive substances is advised.

Although it may sound strange and weird, bonding with one's child starts right from the time you conceive. The baby listens to you and feels your feelings even when it is developing in your womb. One can shape up your baby's first impressions by listening to good music, visualizing, massaging gently, meditating and of course, with the help of positive thinking. Meditation, chanting and mantras are most important during the process of Garbh Sanskar.

## Practical implementations

*Read Books :* Reading books that give positive feelings and thoughts and avoid books that are filled with horror or thrilling feelings. Garbhopnishada is an ancient Indian manuscript which describes in the daily routine to be followed.

*Positive Thinking :* Thinking positive always. Visualisation techniques are used wherin one remembers about good times in the past or beautiful scenery or landscape or anything that hives happiness .

*Talk to Your Child :* You can literally talk to your child when he or she is in your womb, reading out stories, discussing the daily routine

*Practice Yoga :* Prenatal yoga under supervision keeps both the body fit as

well as the mind relaxed. Women who do so are also able to tackle labour pains better.

*Meditation :* Breathing techniques and meditation also helps in developing positive thoughts and will make you feel good from within. If you want to get the best out of garbh sanskar, you must be very careful with your lifestyle during pregnancy. Avoid watching horror movies and also avoid very spicy or fermented food items during this period for better physical, emotional and spiritual health of the baby.

*Behavioural suggestions :* control of negative emotions like anger, stress, anxiety, loneliness, fear and replacing them with positive thoughts. A mother who remains depressed, nervous may lay the seed for the negative personality of the child in future

*Music :* The sound of the veena, flute and other musical instruments are pivotal in this. Music is also the ear for the baby's development as well as soothing and relaxing to de stress the mother. The use of healing music is the most important aspect of Garbha Sanskar. Music or sound vibration reaches the baby in the womb. "It has a soul and recognises values. The choice of music to be heard during pregnancy is also important. The Vedic mantras promote a healthy pregnancy, good growth of the parts of the body, and stimulate the development of the sense organs, respectively. After childbirth, the music serves to calm the child. Babies find it enjoyable and are able to sleep comfortably with its help.

In the "Garbha Uttejan", the baby's attention is attracted with the help of a particular sized resonant bell. This practice of wearing a small bell around the mother's abdomen is also found in the cultures of some Scandinavian countries.

The practice of "Garbha Chintan" involves visualization of the pregnancy goals as a whole, visualizing the outcomes at child birth as well as say 30 years later. Visualization techniques are also combined with chromotherapy.

The fetal brain grows new nerve cells and connections whose activities may be random initially but become synchronized gradually. Those cells that fail to develop synapses or relevant feedback mechanisms die out . this is the basis of early teaching… "Use it or lose it". Unless a child is exposed to stimulation about 450 trillion cells or half the brain cell connections may die off by 10 years of age. Moreover, early stimulation ensures that both the right (artistic functions) and the left brain (all studious functions) hemispheres develop well.

Garbha Sanskar is both a medical practice and a 'culture'. Just like a person brought up in a musician's house imbibes a musical culture, the child is conditioned within the womb. It may be worth talking to your baby, listening to music and reading educative books while you are pregnant. This baby may have better sleeping habits, be more alert and confident, more content, more active at birth, better at breast feeding and bond with parents better.

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## Key Points

- An intelligent life exists in utero itself- the fetus inside can growing sensations of taste, touch, hearing, learning and memory
- Unless a child is exposed to stimulation about 450 trillion cells or half the brain cell connections may die off by 10 years of age.
- As per the Indian tradition it is believed that a child's mental and behavioural development starts not after birth but in utero itself. The persona begins to take shape in the womb itself and all of this is greatly influenced by the mother's state of mind-her thoughts, feelings and emotions during pregnancy.
- Garbh sanskar not only educates the developing child but these practices have an impact on the health of the mother also. The positive thinking and attitude promotes physical well being of the mother.
- Garbha sanskar is about being in a good state emotionally, mentally, physically and spiritually for the sake of your growing baby. To do this, ancient scriptures supported by recent evidence suggest: listening to music, thinking positive, eating healthily, yoga, meditation and prayer, being creative and communicating with your unborn child

# TERATOGENESIS - PREVENTION IS BETTER

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An average Obstetrician and gynecologist is exposed to clinical cases dealing with teratogenicity in day to day life. Some of the clinical scenarios include-

1. A couple is planning a pregnancy and is being exposed to drugs/chemicals.
   *What is the risk? Should this exposure be changed or stopped?*
   *Does this exposure decrease fertility?*
2. A pregnant woman has taken a drug before she realises that she is pregnant.
   *What is the risk? Would recommending termination of pregnancy be justified?*
   *What prenatal diagnostic procedures can be offered?*
3. A drug has to be prescribed to a pregnant woman.
   *Is it safe? Is there a less toxic/teratogenic drug with comparable therapeutic efficacy to which the woman should be transferred?*
   *Is the risk of taking a drug greater than the risk of the disease for which the drug is taken? Are there risks acceptable to the patient when compared with the spontaneous risk of developmental disorders?*
4. A pregnant woman has attempted to commit suicide by taking an overdose of a drug.
   *What information should be given to the physician at the emergency department? Can the appropriate antidote be given to her*
5. A pregnant woman is addicted to drugs/alcohol.
   *Do they have an adverse effect on the course of pregnancy? What are the effects on fetal development? Can neonatal problems be expected or are there any long-term consequences for the child?*
6. A pregnant woman is exposed at work to certain chemicals.
   *What is the risk? Should she continue this work?*
7. A pregnant woman is exposed to an infectious agent.
   *What are the risks of a maternal infection for the fetus?*
   *Are techniques available for the diagnosis of a fetal infection and what are the management options?*
8. A pregnant woman has been exposed to...
   *What are the risks of certain physical exposures such as heat and radiation (especially x-rays and radioactive materials), vaccinations or environmental pollution?-*
9. A man has been exposed to chemicals or has been treated with drugs. *Are there any*

*paternally mediated risks for the fetus or baby?*

10. A baby is born with a birth defect or a neonatal disorder.
    *Can this be attributed to a drug or chemical to which the mother was exposed before or during pregnancy?*
11. A drug has to be prescribed to a mother while she is breast feeding. A mother uses a prescription drug or is exposed to an other exogenous agent, while breast feeding.
    *What is the (relative) dose the neonate (infant) is exposed to?*
    *Is this acceptable for its age?*
    *What is the treatment of choice during breast feeding?*

**Teratology** is the science that studies the causes, mechanisms, and patterns of abnormal development. Developmental disorders present at birth are called congenital anomalies, birth defect or congenital malformation. Congenital anomalies are of four clinically significant types: malformation, disruption, deformation and dysplasia.

**Congenital malformation** are structural defects present at birth. They may be gross or microscopic, on the surface of the body or within it, familiar or sporadic, hereditary or nonhereditary, single or multiple. A major congenital anomaly is one that is incompatible with survival, is life-threatening, or seriously compromises an individual´s capacity to function normally in society.

**Birth defects -** 3% of all live-born infants have an major anomaly. Additional anomalies are detected during postnatal life – about 6% at 2 year-olds, 8% in 5year-olds, other 2% later. Single minor anomalies are present in about 14% of newborns. Major anomalies are more common in early embryos (up to 15%) than they are in newborns (3%). Most severely malformed embryos are spontaneously aborted during first 6 to 8 weeks.

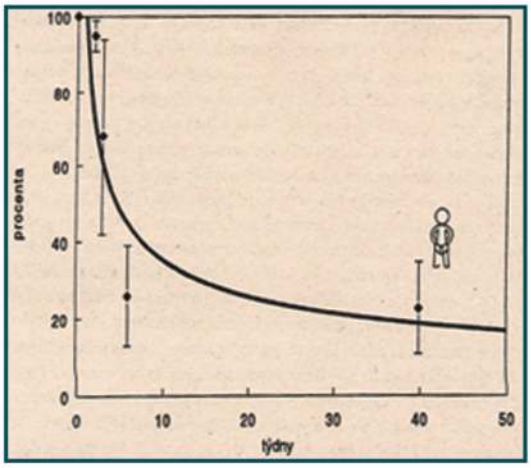



Figure-1 : Course of losses in pregnancy

## Teratology – terms

- Malformation is a primary structural defect resulting from a localized error of morphogenesis
- Disruption is specific abnormality that results from disruption of normal developmental processes It depends on time not on agent
- Deformation is an alteration in shape/ structure of previously normally formed part.
- Syndrome is a recognized pattern of malformations with a given etiology

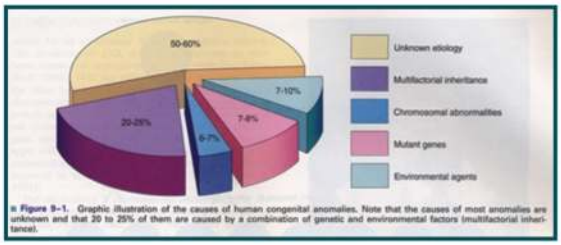



Figure 2 - Causes of congenital anomalies

**Anomalies caused by genetic factors** – Chromosomal aberrations are common and are present in 6 to 7% of zygotes – (result = abort)

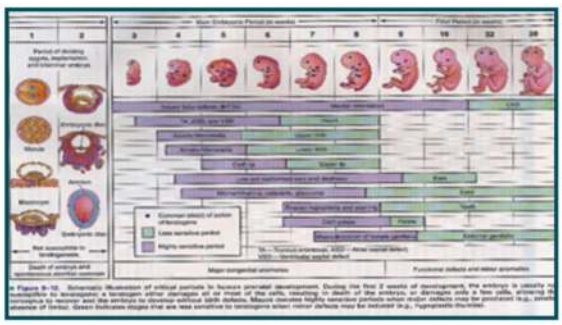
- *Numerical chromosomal abnormalities* – usually non-disjunction- error in cell division Down syndrom (21) Edwards (18) Patau (13) Turner (X0), Klinenfelter (XXY)
- *Structural chromosomal abnormalities* – chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion.
- *Mutant genes* – achondroplasia, fragile-X syndrome

**Anomalies caused by environmental factor s -** Teratogens are exogeneous agents that may cause developmental defects:

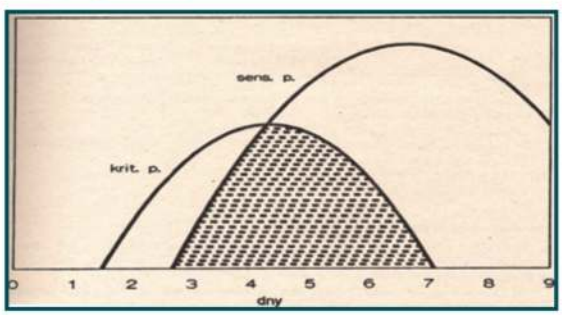
- *Drugs* (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, cytostatic drugs – cyclophosphamide, lithium carbonate)
- Chemicals (PCBs, methylmercury, alcohols)
- Infections (rubella, cytomegalovirus, herpes, toxoplasma, syphilis)
- Ionizing radiation (RTG)
- Maternal factors (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/ hypo-thyreosis)

**Basic principles in teratogenesis-**

- Critical periods of development
- Dosage of the drug or chemical
- Genotype (genetic constitution) of the embryo and mother



## Critical and sensitive periods of development




## The thalidomide disaster heralded modern teratogenicity testing

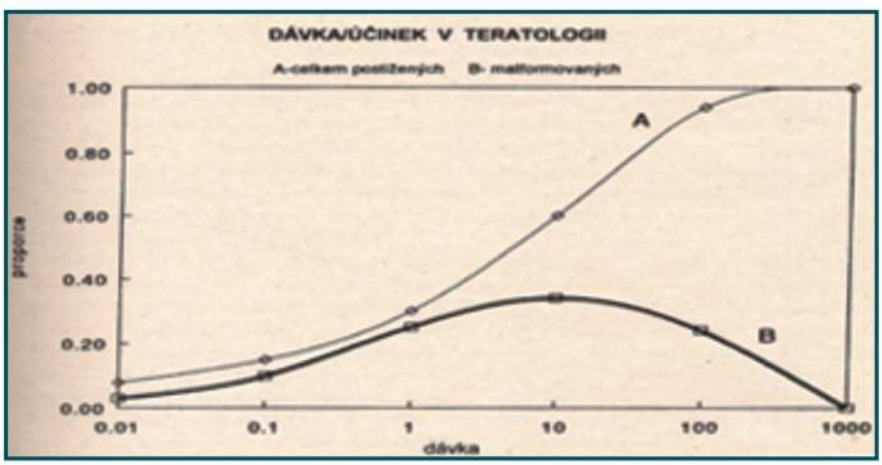
In 1950's- thalidomide was synthesized by the Grünenthal It was non-toxic at high doses in all animals species tested. In 1957 it was marketed throughout Europe in as Contergan a non-lethal hypnotic and sedative, recommended as an anti-emetic to treat morning sickness in pregnant women. In 1961, thalidomide was the best-selling sleeping pill in West Germany and the UK. However, thalidomide produced teratogenic effects in 100% of foetuses exposed between 3-6 weeks gestation. An estimated 8-12,000 infants were born with deformities

caused by thalidomide, and only about 5,000 of these survived beyond childhood. In 1968 - Contergan case was brought to trial, in 1970 - court dismissed the case due to only minor responsibility of Grünenthal and "minor importance to the public of the Federal Republic of Germany". In fact, thalidomide is a useful drug, used today to treat leprosy and multiple myeloma (probably due to inhibitory activity on tumour necrosis factor (TNF)-a production)

| Stage | Gestation period | Cellular process | Affected by |
|---|---|---|---|
| Blastocyte formation | 0-16 days | Cell division | Cytotoxic drugs<br>Alcohol |
| Organogenesis | ~ 17-60 days | Division<br>migration<br>differentiation<br>death | Teratogens<br>(thalidomide,<br>retinoids<br>antiepiletics<br>warfarin) |
| Maturation | > 60 days | As above | Alcohol<br>Nicotine<br>ACE inhibitors<br>Steroids |

Effects of drugs on fetal development

Teratogenesis is process with threshold-level effect.Every chemical substance may be teratogenic. This effect depends on quantity. In small amount is without any effect. Teratogen is factor that is present in environment in so high amount that it can increase occurrence of embryotoxicity manifestation up to basic frequency in non-exposed population Teratogenicity is a manifestation of developmental toxicity representing a particular case of embryo/fetotoxicity, by the induction or the increase of frequency of structural disorders in the progeny.




Dose response relation in teratology A – afflicted B – malformed

## Consequences of exposure to teratogens

- Death – abortion or miscarriage
- Malformation
- IUGR – intrauterine growth retardation
- Functional defects in the newborn
- Normal newborn

About 80% pregnant women use prescribed or over-the-counter drugs. The drugs should only be taken when essential thereby avoiding unnecessary and unknown risks. The same is obviously applied to social drugs like tobacco, alcohol and additive drugs

### PREGNANCY RISK CATEGORIES - RESPONSE

Labeling of some prescription drugs includes information about the level of risk for the fetus and the extent of caution necessary in their use. The FDA has established five categories (A, B, C, D, and X) to indicate a drug's potential for causing teratogenicity. This format was first announced in the September 1979 FDA Drug Bulletin. Because of labeling revisions, many products now use this format. A similar, but somewhat expanded, classification system was adopted by the Australian Drug Evaluation Committee (ADEC) in 1989. Germany set forth its own classification system.

## US FDA Pregnancy Category Definitions

- **A -** Adequate, well-controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first (second, third, or all) trimester(s), and the possibility of fetal harm appears remote.
- **B -** Animal studies do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect on the fetus but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the animal findings, the possibility of fetal harm appears remote, if used during pregnancy.
- **C -** Animal studies have shown that the drug exerts teratogenic or embryocidal effects, and there are no adequate, well-controlled studies in pregnant women, OR No studies are available in either animals or pregnant women.
- **D -** Positive evidence of human fetal risk exists, but benefits in certain situations (eg, life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.
- **X -** Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

## Testing for teratogenicity -

Standardized procedures for testing drugs for Teratogenic potential are used. They use at least two common mammalian laboratory species that are given several different doses of the test agent once or several successive days during organogenesis and early fetal period. Coventionally 3 doses are administered; the highest causing maternal

toxicity. Evaluation of human case reports and epidemiological investigation (retrospective and prospective) are carried out.

## Process of assessing reproductive or embryo/fetotoxic effect of drug

- A sudden increase in the prevalence of a specific malformation is observed
- An association is established between the introduction or an increased usage of a drug and an increased prevalence of a specific malformation
- Drug use must be taken place in the sensitive period for the introduction of that specific malformation
- Drug or its metabolite suspected of causing malformation has to be proved capable of reaching the embryo or fetus
- It must be established that the drug and not condition (disease) causes the specific malformation
- The finding have to be confirmed by another independent study
- The result of specific laboratory animal studies might support the epidemiological findings

## Stages of drug development

| | | |
|---|---|---|
| **Phase I** | 100 – 200 Healthy Subjects | • Does it seem safe in humans?<br>• What does the body do to the drug (pharmacokinetics)?<br>• What does the drug do to the body (pharmacodynamics)?<br>• Might it work in patients? |
| **Phase II** | 200 – 300 Patients | • Does it seem safe in patients?<br>• Does it seem to work in patients? |
| **Phase III** | 1,000 – 3,000 Patients | • Does it seem safe in patients?<br>• Does it really work? |
| **Phase III b** | Hundreds – Thousands Patients | • Does it seem safe in a different group of patients?<br>• Does it really work in a different group of patients? |
| **Phase IV** | Tens to many thousands Patients | • Is it truly safe?<br>• How does it compare with similar drugs? |

## Environmental factors –

- Radiation
- Chemical agents
- Maternal Diseases
- Hypoxia
- Infectious agents
- Hormones
- Nutritional deficiencies

Fetal Hydantoin Syndrome – This syndrome occurs in 5 to 10 percent of children born to mothers treated with phynetoins which are anticonvulsants. Microcephaly, wide anterior fontanelle, metopic ridging, ocular hypertelorism, broad depressed nasal bridge, short nose with bowed upper lip, cleft lip and cleft palate are the significant features.

Valproic acid, gestational diabetes, phenyl ketonuria, rubella, environmental drugs like mercury, antipsychotic drugs, antianxiety drugs, herpes simplex, anticoagulants, antihypertensives, isotroin, hormones, thalidomide are other widely studied and proved teratogens.

### Prevention of birth defects

- Good prenatal care
- Iodine supplementation eliminates mental retardation & bone deformities
  - Prevent cretinism
- Folate/Folic Acid supplementation
  - ⇓ incidence of neural tube defects
- Avoidance of alcohol & other drugs during all stages of pregnancy
  - ⇓ incidence of birth defects

## Conclusion

- Disease have to be treated in all cases! Disease without treatment is more risky than appropriate treatment.
- We should use drugs with well-known effect on pregnancy without signs of embryotoxicity. It is not recommended to change quickly a lot of drugs.
- It is not recommended to use combinations of various drugs. Undesirable effects may be multiplayed.
- Any woman in reproductive age may be pregnant !!

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# NUTRITION SUPPLIMENTS IN PREGNANCY-OPTIMAL USE

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Pregnant women should have a diet that consists of a variety foods including proteins, carbohydrates, vitamins, minerals and fats. From these she should get the right nutrients and vitamins for pregnancy health and her baby's development.

A balanced diet is the best way to receive nutrients, but vitamin supplements can also be beneficial. Pregnant women should only take vitamin supplements on a health care provider's recommendation. Supplements do not replace a healthy diet, but rather ensure that a woman is receiving enough daily nutrients. Vitamin supplements work best when taken as part of a healthy diet and not as a substitute for a healthy diet.

## Nutrients and Vitamins for Pregnancy

| Essential Vitamin / Mineral | Why You Need It | Where You Find It |
|---|---|---|
| **Vitamin A & Beta Carotene** (770 mcg) | Helps bones and teeth grow | Liver, milk, eggs, carrots, spinach, green and yellow vegetables, broccoli, potatoes, pumpkin, yellow fruits, cantaloupe |
| **Vitamin D** (5 mcg) | Helps body use calcium and phosphorus; promotes strong teeth and bones | Milk, fatty fish, sunshine |
| **Vitamin E** (15 mg) | Helps body form and use red blood cells and muscles | Vegetable oil, wheat germ, nuts, spinach, fortified cereals |
| **Vitamin C** (80 – 85 mg) | An antioxidant that protects tissues from damage and helps body absorb iron; builds healthy immune system | Citrus fruits, bell peppers, green beans, strawberries, papaya, potatoes, broccoli, tomatoes |
| **Thiamin/B1** (1.4 mg) | Raises energy level and regulates nervous system | Whole grain, fortified cereals, wheat germ, organ meats, eggs, rice, pasta, berries, nuts, legumes, pork |

| | | |
|---|---|---|
| **Riboflavin/B2** (1.4 mg) | Maintains energy, good eyesight, healthy skin | Meats, poultry, fish, dairy products, fortified cereals, eggs |
| **Niacin/B3** (18 mg) | Promotes healthy skin, nerves and digestion | High-protein foods, fortified cereals and breads, meats, fish, milk, eggs, peanuts |
| **Pyridoxine/B6** (1.9 mg) | Helps form red blood cells; helps with morning sickness | Chicken, fish, liver, pork, eggs, soybeans, carrots, cabbage, cantaloupe, peas, spinach, wheat germ, sunflower seeds, bananas, beans, broccoli, brown rice, oats, bran, peanuts, walnuts |
| **Folic Acid/Folate** (600 mcg) | Helps support the placenta, and prevents spina bifida and other neural tube defects | Oranges, orange juice, strawberries, green leafy vegetables, spinach, beets, broccoli, cauliflower, fortified cereals, peas, pasta, beans, nuts |
| **Calcium** (1,000 – 1,300 mg) | Creates strong bones and teeth, helps prevent blood clots, helps muscles and nerves function | Yogurt, milk, cheddar cheese, calcium-fortified foods like soy milk, juices, breads, cereals, dark green leafy vegetables, canned fish with bones |
| **Iron** (27 mg) | Helps in the production of hemoglobin; prevents anemia, low birth weight, and premature delivery | Beef, pork, dried beans, spinach, dried fruits, wheat germ, oatmeal or grains fortified with iron |
| **Protein** (71 g) | Helps in the production of amino acids; repairs cells | Most animal foods, meat, poultry, eggs, dairy products, veggie burgers, beans, legumes, nuts |
| **Zinc** (11-12 mg) | Helps produce insulin and enzymes | Red meats, poultry, beans, nuts, whole grains, fortified cereals, oysters, dairy products |

In short, A good pregnancy/nursing diet includes :

- **Lots of high quality protein** from high quality sources like grass-fed beef, free-range poultry and eggs, and wild, caught, sustainable seafood (smaller fish preferable). Organ meats from grass fed sources are also wonderful for pregnancy and nursing and can help reduce the chance of anemia.
- **Large amounts of vegetables, especially green ones!** Green veggies have folic acid, which is important for fetal growth, and are also high in many other nutrients. They help prevent the constipation that can sometimes occur during pregnancy, and are great for making sure nursing moms are getting enough vitamins.
- **Healthy Fats galore!** Pregnancy and nursing are not times to skimp on healthy fats. Quality fats are absolutely vital for baby's brain development, organ and tissue growth, and good milk production for mom. Sources like healthy meats, coconut oil and coconut products, olive oil, avocados, and nuts are especially good during pregnancy (peanuts are not nuts!).
- Other high nutrient foods like

homemade bone broth, soups, fermented vegetables like homemade sauerkraut, fruit (especially berries) and green smoothies are also great for pregnancy and nursing.

1) **Vitamin A & Beta Carotene -** It is well known that vitamin A is an essential nutrient for normal cellular function, including reproduction and development. Vitamin A deficiency is a worldwide problem of great magnitude. It should be noted that "vitamin A" is a term used often ambiguously. The total indicated vitamin A content of foods usually includes vitamin A derived from carotene, a vitamin A precursor, as well as retinol. Carotene, e.g., beta-carotene, has not been associated with vitamin A toxic effects; accordingly the warning contained in a paper is intended for countries and their citizens that have high-potency vitamin A preparations (as retinol or retinyl esters) readily available. Supplements that contain 25,000 International Units (IU) or more of vitamin A per capsule are available as over-the-counter preparations in many areas. The risk of birth defects owing to synthetic vitamin A analogs has already been documented in humans, and recently the ingestion of excess vitamin A (25,000 IU or more) as retinol/retinyl esters during pregnancy has been associated with some birth defects in a small number of case reports, although it is not known that the relationship is causal. It is with this caution that the following recommendations concerning the use of vitamin A supplements as retinol/retinyl esters during pregnancy are presented to all interested individuals—parents, health care-providers, manufacturers, regulators, legislators, and scientists in our world community.

2) **Vitamin D -** The largest source of vitamin D in adults is synthesis from solar radiation; half an hour of sunlight delivers 50 000 iu of vitamin D with white-complexioned skin. Dietary intake of vitamin D makes a relatively small contribution to overall vitamin D status as there is little vitamin D that occurs naturally in the food supply. Melanin absorbs ultraviolet B (UVB) from sunlight and diminishes cholecalciferol production by at least 90%. 5 Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to a vitamin D binding protein. Pre-eclampsia and neonatal hypocalcaemia are the most prevalent complications of maternal hypocalcaemia and are clearly associated with substantial morbidity. A statistical association of glucose intolerance and hypovitaminosis D has been demonstrated. Maternal vitamin D is important to fetal bone development. Fetal lung development and neonatal immune conditions such as asthma may relate in part to maternal vitamin D levels. Although it is not clear whether maternal vitamin D supplementation will prevent these conditions, a strategy for supplementation and treatment of maternal vitamin D deficiency is proposed.

3) **Vitamin E -** Vitamin E helps to give

cells their structure.And with baby growing and developing at a rapid rate, it is an important nutrient to include in pregnancy diet.While a safe level supports to baby, too much can be harmful. One of its main functions is protecting cell membranes, which helps to maintain the structure of cells throughout the body. With your baby's cells multiplying at an astounding rate, vitamin E is an important nutrient to include in pregnancy diet. It is thought that vitamin E plays an important role in the development of baby's lungs.

4) **Vitamin C -** Vitamin C is likely safe for pregnant or breast-feeding women when taken in the recommended amount of 120 mg per day. Taking too muchvitamin C during pregnancy can cause problems for the newborn baby. Do not take vitamin C in doses greater than those found in basic multivitamins.

5) **Vitamine B1 -** Thiamin, also known as vitamin B1 or thiamine, enables mather & baby to convert carbohydrates into energy. It's essential for baby's brain development and aids the normal functioning of mother's nervous system, muscles, and heart.

6) **Vitamin B2 -** Riboflavin, sometimes referred to as vitamin B-2, is important for healthy skin, growth and good vision.

7) **Vitamin B6 -** Vitamin B6 is available in multivitamins, in suppliments containing other B complex vitamins, and as a stand-alone supplement. The most common vitamin B6 vitamer in supliments is pyridoxine(in the form of pyridoxine hydrochloride(HCL), although some supliments contain PLP.

Vitamin B6 supliments are available in oral capsules or tablets (Including sublingual and chewable tablets) and liquids. Absorption of vitamin B6 from supliments is similar to that from food sources and does not differ substancially among the various forms of supliments. Although the body absorbs large pharmacological doses of vitamin B6 well, it quickly eliminates most of the vitamin in the urine.

About 28%-36% of the general population uses supliments containing vitamin B6.Adults aged 51 years or older and children younger than 9 are more likely than members of other age groups to take supliments containing vitamin B6.

8) **Vitamin B12 -** Vitamin B12 crosses the placenta during pregnancy and is present in breast milk.

Exclusively breastfed infants of women who consume no animal products may have very limited reserves of vitamin B12 and can develop vitamin B12 deficiency within months of birth.

Undetected and untreated vitamin B12 deficiency in infants can result in severe and permanent neurological damage. Pregnant lactating women who follow strict vegetarian or vegan diets should consult with a pediatrician regarding vitamin B12 supliments for their infants and children.

9) **Zinc -** Zinc is an essential mineral known to be important for many biological functions including protein synthesis, cellular division and nucleic acid metabolism. Severe zinc deficiency is rare in humans, but mild to moderate deficiency may be common, especially

in populations with low consumption of zinc-rich animal-source foods and high intakes of foods rich in phytates, which inhibit zinc absorption. It is estimated that over 80% of pregnant women worldwide have inadequate zinc intake, consuming on average 9.6 mg zinc per day, well below the recommended minimum daily levels for the last two trimesters of pregnancy in settings of low zinc bioavailability.

It has been suggested that maternal zinc deficiency may compromise infant development and lead to poor birth outcomes. Low plasma zinc concentrations reduce placental zinc transport and may affect the supply of zinc to the fetus. Zinc deficiency also alters circulating levels of a number of hormones associated with the onset of labour, and because zinc is essential for normal immune function, deficiency may contribute to systemic and intra-uterine infections, both major causes of pre-term birth. Low birth weight and prematurity are significant risk factors for neonatal and infant morbidity and mortality. It has been hypothesized that zinc supplementation may improve pregnancy outcomes for mothers and infants.

10) **Omega 3s and Healthy Fats -** Omega-3 fatty acids have positive effects on the pregnancy itself. Increased intake of EPA and DHA has been shown to prevent pre-term labor and delivery, lower the risk of preeclampsia, and may increase birth weight. Omega-3 deficiency also increases the mother's risk for depression. This may explain whypostpartum mood disorders may become worse and begin earlier with subsequent pregnancies.

Omega-3s are also used after birth to make breast milk. With each subsequent pregnancy, mothers are further depleted. Research has confirmed that adding EPA and DHA to the diet of pregnant women has a positive effect on visual and cognitive development of the baby. Studies have also shown that higher consumption of omega-3s may reduce the risk of allergies in infants.

11) **Magnesium -** When pregnant, magnesium helps build and repair mother's body's tissues. A severe deficiency during pregnancy may lead to preeclampsia, poor fetal growth, and even infant mortality.

Magnesium and calcium work in combination: Magnesium relaxes muscles, while calcium stimulates muscles to contract. Research suggests that proper levels of magnesium during pregnancy can help keep the uterus from contracting prematurely.

Magnesium also helps build strong bones and teeth, regulates insulin and blood sugar levels, and helps certain enzymes function. Research indicates it may help control cholesterol and irregular heartbeats. Magnesium may also be helpful in reducing leg cramps.

12) **Protein - Promote growth**

Protein is crucial for your baby's growth, especially during the second

and third trimesters.

**How much her need :** 71 grams a day

**Good sources :** Lean meat, poultry, fish and eggs are great sources of protein. Other options include dried beans and peas, tofu, dairy products, and peanut butter.

| Food | Serving size | Protein content |
|---|---|---|
| *Source :* USDA National Nutrient Database for Standard Reference, Release 26 | | |
| Cottage cheese | 1 cup (226 g) low-fat, 1% milk cottage cheese | 28 g |
| Poultry | 3 oz. (86 g) boneless, skinless grilled chicken breast | 26 g |
| Fish | 3 oz. (85 g) canned pink salmon with bones | 16.8 g |
| Lentils | 1/2 cup (99 g) boiled lentils | 8.9 g |
| Milk | 1 cup (237 mL) skim milk | 8.3 g |
| Peanut butter | 2 T (32 g) smooth, vitamin-and mineral - fortified peanut butter | 8.2 g |
| Eggs | 1 large hard-boiled egg (50 g) | 6.3 g |

## Whey Protein Powder

Proteins are required for building and repair of the body's tissues. The amino acids that make up protein are the building blocks of the body's cells, including those of our baby. Protein is also an excellent source of energy. During pregnancy, a mother requires 70-90 grams of protein per day. Whey protein powder added to smoothies, soups, stews, etc., can help a woman to meet those requirements.

Whey contains 15 grams of protein per serving. It is derived from the milk of grass-fed cows that graze year round on natural pastures, is hormone-treatment-free, pesticide-free, chemical-free and does not contain GMOs.

If at all allergic to dairy, lactose intolerant or vegan, consider hemp protein powder instead.

## 13) Iron - Prevent anemia

Body uses iron to make hemoglobin, a protein in the red blood cells that carries oxygen to our tissues. During pregnancy her blood volume expands to accommodate changes in her body and help her baby make his or her entire blood supply — doubling her need for iron.

If shedon't get enough iron, she might become fatigued and more susceptible to infections. The risk of preterm delivery and low birth weight also might be higher.

**How much her need :** 27 milligrams a day

Good sources: Lean red meat, poultry and fish are good sources of iron. Other options include iron-fortified breakfast cereals, beans and vegetables.

| Food | Serving size | Iron content |
|---|---|---|
| Source : USDA National Nutrient Database for Standard Reference, Release 26 | | |
| Cereal | 3/4 cup (15 to 60 g) 100 percent iron-fortified quick oats | 29.7mg |
| Beans | 1/2 cup (88.5 g) boiled kidney beans | 2.9mg |
| Spinach | 1/2 cup (95 g) boiled spinach | 1.9mg |
| Meat | 3 oz. (85 g) roasted lean beef tenderloin | 2.6mg |
| Poultry | 3 oz. (85 g) roasted dark turkey | 0.9mg |

Prenatal vitamins typically contain iron. In

some cases, her health care provider might recommend a separate iron supplement.

The iron from animal products, such as meat, is most easily absorbed. To enhance the absorption of iron from plant sources and supplements, pair them with a food or drink high in vitamin C - such as orange juice, tomato juice or strawberries. If you take iron supplements with orange juice, avoid the calcium-fortified variety. Although calcium is an essential nutrient during pregnancy, calcium can decrease iron absorption.

## Folate and folic acid - Prevent birth defects

Folate is a B vitamin that helps prevent neural tube defects, serious abnormalities of the brain and spinal cord. The synthetic form of folate found in supplements and fortified foods is known as folic acid. Folic acid supplementation has been shown to decrease the risk of preterm delivery.

| Food | Serving size | Folate or Folic acid content |
|---|---|---|
| Source : USDA National Nutrient Database for Standard Reference, Release 26 | | |
| Cereal | 3/4 cup (15 to 60g) ready-to-eat cereal | 100 to 700 mcg - choose a cereal that's 100 percent fortified |
| Spinach | 1/2 cup (95g) boiled spinach | 115 mcg |
| Beans | 1/2 cup (88g) boiled Great Northern beans | 90 mcg |
| Asparagus | 4 boiled spears (60g) | 89 mcg |
| Oranges | 1 orange (154g) | 52 mcg |
| Peanuts | 1 ounce (28g) dry roasted | 41 mcg |

**How much her need :** 800 micrograms of folate or folic acid a day before conception and throughout pregnancy.

**Good sources :** Fortified cereals are great sources of folic acid. Leafy green vegetables, citrus fruits, and dried beans and peas are good sources of naturally occurring folate.

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# VACCINATION IN PREGNANCY

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Immunization programs are among the most cost beneficial health interventions. PREGNANCY provides a unique opportunity for vaccination, as majority of pregnant women makes contact with health care system. Immunization should be provided pre conceptionally, during pregnancy or immediately after if a particular product is contraindicated during pregnancy.

Maternal immunization may also effect fetal and neonatal well-being, as efficient placental transfer of maternal antibodies to the fetus starts at 32 weeks, conferring protection for first 6 months of life.

The objective of vaccination during pregnancy is therefore to protect the mother, the fetus, the neonate, and young infant. This can significantly reduce the occurrence of preventable diseases, benefiting not only the patient and her infant but also the rest of the population

As pregnancy is considered to be an immunologically competent status, a full and unaltered response to immunization is expected(1). However, given the theoretical risks to the fetus following administration of vaccines, it is essential to counsel the pregnant woman with respect to the risks and benefits of vaccines, as well as potential exposure to the diseases the vaccines are expected to prevent. Appropriate information and counselling must also be provided in cases of inadvertent vaccination in pregnancy.

If women comepericonceptionally a thorough immunization history should be taken. In many cases, women present for prenatal care having not had their immunization status reviewed since they completed the school-age vaccination schedule. Ideally, women should have their vaccination status optimized pre-pregnancy, so there would be no concern about coverage in pregnancy.

Immunizations can be either Active or Passive. Passive immunization is a process whereby the agent used has been obtained from serum from either a person or an animal already adequately immunized. From this process, antibodies can be obtained either as whole serum or as concentrated IgG and may be administered to the host to confer immediate protection. Active immunization relies on the

administration of antigens and results in a prompt but transient IgM response in the host. This is followed by a rise in IgG antibody production that will be more or less sustained, explaining why for some vaccines, booster doses may be required for long-term immune memory. Of note, oral vaccines will stimulate IgA initially as opposed to IgM (parenteral).

**The Centre for disease control (CDC) and Advisory committee on Immunization**

**practises (AICP) has established guiding principles for vaccine recommendation during breast feeding and pregnancy. The Table 1 provides recommendations as per AICP.**

## Live and Live-attenuated Vaccines

Live and/or live-attenuated virus vaccines are contraindicated during pregnancy – as they contain actual pathogen and plausible risk of fetal damage

Following vaccines are contraindicated – measles, mumps, rubella, varicella, live attenuated influenza and vaccinia (small pox), despite no evidence of fetal damage from vaccination during pregnancy except vaccinia.

### 1. Rubella

- Live-Attenuated Vaccine
- Rubella occurring in pregnancy can cause in CRS – congenital rubella syndrome. Greatest risk period for viremia & congenital defect is 1 week before to 4 weeks after conception. CRS may result in deafness, cataracts, cardiac defects, microcephaly, mental retardation, hepatosplenomegaly, bone damage, and thrombocytopenia.
- The rubella vaccine alone and in combination (MMR) is a live vaccine and therefore contraindicated during pregnancy. All susceptible women and women without adequate proof of immunization should be immunized before conception or postpartum. Women should delay pregnancy by one month following immunization.
- Inadvertent vaccination during pregnancy has not resulted in in fetal or neonatal disease & is not a reason for pregnancy termination.
- Safe in breast feeding
- Dosage – Single dose sc; preferably as MMR

### 2. Measles & Mumps

- Vaccination contraindicated in pregnancy.
- Can be given postpartum, breast feeding
- Measles occurring in pregnancy can lead to abortions, still birth, prematurity, & congenital malformation
- Dosage -Single dose sc as MMR

### 3. Varicella

Varicella (chickenpox) in the pregnant population can result in very significant maternal and fetal morbidity and mortality. Risk for congenital varicella syndrome is approximately 1-2% during first 20 weeks of gestation such as cerebral cortical atrophy, mental retardation, and dermatomal specific limb abnormalities[2]. Maternal varicella occurring five days before to two days after delivery is associated with severe neonatal varicella in 17% to 30% of infants and a case fatality rate as high as 31%.[3] Varicella in pregnancy can lead to serious maternal complications as pneumonia &can be a cause of maternal mortality.

- Non-pregnant women whose immunization status is not known

should be vaccinated before pregnancy and they should delay conception by one month.

- Vaccine is contraindicated during pregnancy.
- Can be given postpartum & in breast feeding.
- If women are inadvertently exposed to vaccine in pregnancy, then pregnancy should not be terminated as no of studies prove no cases of congenital varicella.

  Pregnant women with an uncertain or no previous history of chickenpox, or who come from tropical or subtropical countries, who have been exposed to infection should have a blood test to determine VZV immunity or non-immunity.
- **If the pregnant woman is not immune to VZV and she has had a significant exposure, she should be given varicella-zoster immunoglobulin (VZIG) as soon as possible.**
- **VZIG should be given within 96 hours of exposure but is effective even when given up to 10 days after contact[4].**
- **VZIG has no therapeutic benefit once chickenpox has developed and should therefore not be used in pregnant women who have developed a chickenpox rash.**
- VZIG – also indicated for women new-borns or women who developed varicella within 4 days before delivery or 2 days post delivery
- Vaccine Dosage: 2 doses (0, 4-8 weeks)
- VZIG – im one dose

### 4. Vaccinia (Small Pox)

- **Smallpox vaccine should not be administered in pregnant women.**

  Pregnant women who have had a definite exposure to smallpox virus (i.e., face to-face, household, or close-proximity contact with a smallpox patient) and are, therefore, at high risk for contracting the disease, should . . . be vaccinated. Smallpox infection among pregnant women has been reported to result in a more severe infection than among non-pregnant women. Therefore, the risks to the mother and fetus from experiencing clinical smallpox substantially outweigh any potential risks regarding vaccination[4].
- **Only vaccine known to cause fetal harm**
- Vaccine should not be given in postpartum & breast feeding mothers – Contraindicated
- Dosage – single dose sc

### 5. Yellow Fever

- Pregnancy is a precaution for YF vaccine administration, compared with most other live vaccines, which are contraindicated in pregnancy.
- If travel is unavoidable, and the risks for Yellow Fever exposure are felt to outweigh the vaccination risks, a pregnant woman should be vaccinated
- Postpartum& breast feeding –

precaution due to lack of data

- Dosage – single dose sc

### 6. Polio (IPV or Salk Vaccine)

- **Vaccination of pregnant women should be avoided**
- However, if a pregnant woman is at increased risk for infection and requires immediate protection /travel against polio, IPV can be administered as per dose schedule
- Susceptible women should be immunized postpartum
- Dosage : three dose (0,1,6 months)

### 7. Rabies

- Because of the potential consequences of inadequately managed rabies exposure, pregnancy is not considered a contraindication to postexposure prophylaxis.
- Postpartum & breast feeding – no restriction

### Inactivated Viral Vaccines, Bacterial Vaccines, and Toxoids

These vaccines are considered safe in pregnancy. As thereis no evidence to suggest a risk to the fetus or to the pregnancy from maternal immunization with these agents, the benefit of their use generally far outweighs the theoretical risks.

### 8. Influenza

Influenza is a highly contagious acute respiratory infection. It is manifested clinically as an abrupt onset of malaise, headache, and myalgia followed by a cough, fever, and sore throat.

Changes in the immune system, heart, and lungs during pregnancy make pregnant women more prone to severe illness from influenza as well as hospitalizations and even death. Pregnant women with influenza also have a greater chance for serious problems for their unborn babies, including premature labour and delivery.

- Current recommendations support immunization of pregnant women with the inactivated vaccine – FLU SHOT one dose
- Vaccination is highly recommended for women having comorbidities – cardiac or occupational
- Because vaccinating against influenza before the season begins is critical, and because predicting exactly when the season will begin is impossible, routine influenza vaccination is recommended for all women who are or will be pregnant (in any trimester) during influenza season, which is usually early October through late March.[8]

There is debate on immunization in which trimester? Canadian guidelines recommend in second trimester unless there is an immediate risk of transmission[9]

Immunization in pregnancy leads to protection of the new-born after birth, which can be accomplished with passive immunity (transfer of maternal antibodies). Studies have showed prenatal

maternal vaccination reduced infant influenza incidence in first six months of life by 63%. Moreover, it also reduced all febrile respiratory illness in infant by a third.[13]

CDC does not recommend any one type of flu vaccine. All influenza vaccines available Trivalent, Quadrivalent are recommended for use in pregnant women, with the exception of the live intranasal vaccine.

- **Live intranasal vaccine is contraindicated**

### 9. Rabies

- Killed virus vaccine.
- To be given in post exposure prophylaxis
- Rabies immune globulin – post exposure prophylaxis. Half dose at injury site, half dose in deltoid. Used in conjunction with rabies killed vaccine

### 10. Human Pappiloma Virus

- Recombinant vaccine
- **Not recommended for use in pregnant women.**
- If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed

### 11. Hepatitis A

- Inactivated vaccine
- To be used in pregnancy only if unavoidable travel to area where exposure likely to happen
- Hepatitis A immune globulin – used in post exposure prophylaxis & those at high risk. To be used along with vaccine.

### 12. Hepatitis B

- Recombinant inactivated
- Pregnancy is not a contraindication to vaccination
- Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., having more than one sex partner during the previous 6 months, been evaluated or treated for an STD, recent or current injection drug use, or having had an HBsAg-positive sex partner) should be vaccinated.
- Dosage – 3 doses (0,1 & 6 months)

  Hepatitis B immune globulin – post exposure prophylaxis.

  Exposed newborn to receive immediate prophylaxis and begin hepatitis B vaccine series

### 13. Typhoid

- Not recommended routinely. Except continued travel or exposure to endemic areas.
- Breast feeding not recommended due to lack of data

### 14. Meningococcal

- Inactivated.
- One dose, tetravalent vaccine
- Recommended for pregnant women at

risk & unusual outbreaks

### 15. Pneumococcal

- Inactivated polyvalent polysaccharide vaccine
- One dose
- Recommended for pregnant women at risk based on co morbidities

### 16. Tetanus, Diphtheria, and Pertussis (TAP); & Tetanus and Diphtheria (TD)

There have been dramatic and persistent increases in pertussis disease in the United States, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has updated its guidelines for the use of the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) for pregnant women

- **The revised Advisory Committee on Immunization Practices guidelines recommend administration a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap.** [10,11]

To maximize the maternal antibody response and passive antibody transfer and levels in the newborn, **optimal timing for Tdap administration is between 27 weeks and 36 weeks of gestation, although Tdap may be given at any time during pregnancy.**[10,11] However, there may be compelling reasons to vaccinate earlier in pregnancy. There is no evidence of adverse fetal effects from vaccinating pregnant women with an inactivated virus or bacterial vaccines or toxoids

- *For women who previously have not received Tdap* - if Tdap was not administered during pregnancy it should be administered immediately postpartum to the mother in order to reduce the risk of transmission to the newborn. Additionally, other family members and planned direct caregivers also should receive Tdap as previously recommended.
- *Wound Management :* If a Td booster is indicated for a pregnant woman, health-care providers should administer Tdap. (12)
- *Unknown or Incomplete Tetanus Vaccination :* To ensure protection against maternal and neonatal tetanus, pregnant women who never have been vaccinated against tetanus should receive three vaccinations containing tetanus and reduced diphtheria toxoids.
  - The recommended schedule is im 0, 4 weeks and third dose 6 - 12 months after 2nd. Tdap should replace 1 dose of Td, preferably between 27 and 36 weeks gestation . . . (12)

<u>Booster -</u>

- ✓ Single dose IM every 10 years,
- ✓ If as a part of wound care the booster should be given if >= 5 yrs has passed since last dose
- ✓ Or once in pregnancy

Table - 1

| Vaccine | Type of Vaccine | During Pregnancy | Breast Feeding & Postpartum | Dose |
|---|---|---|---|---|
| **MMR** | Live attenuated | contraindicated | Safe Can be given | Single dose; sc |
| **Varicella** | Live attenuated | contraindicated | Safe Can be given | 2 doses (0, 4-8 weeks) |
| **Vaccinia (Small Pox)** | Live attenuated | contraindicated | contraindicated | Single dose; sc |
| **Polio (IPV or Salk)** | Live attenuated | Precaution, given in women with increased risk of exposure | Safe Can be given | 3 dose (0,1,6 months) |
| **Yellow fever** | Live attenuated | Precaution, in women travel to high risk areas | Not advisable | Single dose; sc |
| **Rabies** | Killed virus | As Post exposure prophylaxis | Safe Can be given | As per schedule |
| **Influenza** | Inactivated | Recommended for all pregnant women regardless of trimester in flu season | Safe Can be given | One dose; im every year |
| **Hepatitis A** | Inactivated | Pre & Post exposure prophylaxis if needed | Safe Can be given | 2 doses 6 months apart; im |
| **Hepatitis B** | Recombinant Inactivated | Pre & Post exposure prophylaxis if infection | Safe can be given | 3 doses (0,1 & 6 months) |
| **HPV** | Recombinant | Not recommended | Immunize as per schedule | 3 doses (0,1 & 6 months); im |
| **Pneumococcus** | Inactivated | Recommended; only for high risk having comorbidities | Safe can be given | 2 doses (0, 4-8 wks.) |
| **Meningococcus** | Inactivated | Recommended; only for high risk having comorbidities | Safe can be given | 1 dose |
| **Tetanus Diphtheria Pertussis** | Inactivated | Recommended, in all pregnant women ideally between 27 and 36 weeks of gestation | Safe can be given | 3 doses (0, 4 weeks and third dose 6-12 months); im |

## Recommendations

1. All women of childbearing age should be evaluated for the possibility of pregnancy before immunization.
2. Immunization history should be obtained from all women planning pregnancy
3. In general, live and/or live-attenuated

virus vaccines are contraindicated during pregnancy, as there is a, largely theoretical, risk to the fetus.

4. Women who have by mistake received immunization with live or live-attenuated vaccines during pregnancy should not be counselled to terminate the pregnancy because of a teratogenic risk.
5. Non-pregnant women immunized with a live or live-attenuated vaccine should be counselled to delay pregnancy for at least four weeks.
6. Inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe in pregnancy.
7. Women who arepost-partum, breastfeeding should be immunizedif required
8. All pregnant women should be given influenza vaccine
9. Tdap should be given to pregnant women between 27 weeks and 36 weeks of gestation, although Tdap may be given at any time during pregnancy.
10. Breast feeding is not a contra-indication to avoid vaccination for all vaccines except vaccinia.
11. No evidence exists that suggests that any vaccine is associated with an increased risk of autism or adverse effects due to exposure to traces of the mercury-containing preservative thimerosal.

## Conclusion

Immunization is most important in disease prevention, evolving data demonstrate both maternal and neonatal protection against an increasing number of aggressive newborn pathogens through the use of maternal immunization programs, suggesting pregnancy is an optimal time to immunize for disease prevention in both mothers and newborns. And obstetrician-gynaecologists must play an active role in vaccine administration & advice thereby helping in development of healthy population.

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# OPTIMUM USE OF ULTRASOUND IN ANTENATAL CARE


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Women with an uncomplicated pregnancy should have a minimum of four visits, as outlined by WHO[1]. However, the protocol that is usually followed for antenatal care is that women is first seen at booking visit, then at 16 weeks, then at 20 and 28 weeks, fortnightly thereafter until 36 weeks and then weekly until delivery(fig 1). I could not find a rationale for this protocol but it is followed worldwide and may be we have adapted from NHS[2]. The high concentration of visits in the late third trimester occurs as most of the complications occur towards the end of pregnancy.

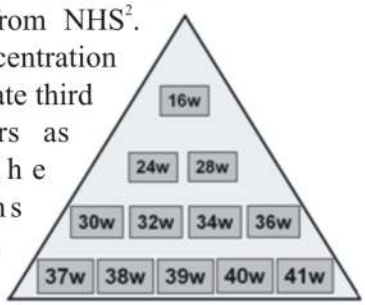



Fig 1

New research and advances in the last 20 years have raised the hope that many pregnancy complications are potentially detectable from at least as early as the 12th week of gestation.

Hence, a new concept of *"TURNING THE PYRAMID OF CARE"* (fig. 2) was introduced by Kypros Nicolaides[3].

According to this concept by doing a detailed first trimester scan at 11-13+6 weeks would provide early estimation of patient-specific risks for these pregnancy complications. A small proportion of women identified as being at high-risk for a variety of pregnancy complications can have close surveillance in specialist clinics.

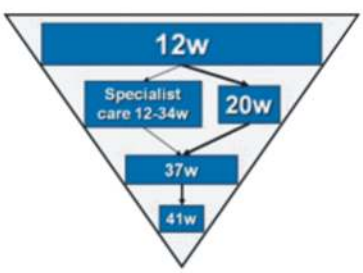



Figure 2. Turning the pyramid of care

Hence as a fetal and maternal medicine specialist, there are minimum 3 scans that are suggested in a normal pregnancy – 'as a part of optimum ultrasound care in antenatal care'.

1. **First trimester screening -11-13+6 weeks for screening for aneuploidy**
2. **Anomaly scan between 18-20 weeks**
3. **Growth scan between 32-34 weeks**

It is a good practice to perform an early viability scan between 6-10 weeks scan as it reassures the women as well as the obstetrician especially in IVF pregnancies, those with previous early pregnancy complications or failures or with risk factors for ectopic pregnancies.

## Early Viability Scan

- to confirm location to rule out ectopic pregnancies
- chorionicity
- to confirm the viability
- early pregnancy complications like bleeding per vaginum or pain lower abdomen.

Mesurements taken[6] are

1. *Mean sac diameter* - average of the three orthogonal measurements of the fluid-filled space within the gestational sac
2. *Crown Rump length* - In the presence of the embryo, the CRL provides a more accurate estimation of gestational age because MSD values show greater variability of age prediction[7,8]
3. Fetal cardiac activity - It is a good practice to mention about yolk sac, cervical length and adnexa and better if done, transvaginally.

Though majority of the guidelines[4,5] recommends scan at 11-13+6 weeks as the first scan because all these things can be done at 11-13+6 weeks scan and economically viable as well.

## First Trimester Screening -11-13+6 weeks -

I consider this as the most important scan as this in itself, is a complete scan, if done correctly by a trained person. Strict guidelines are laid down by Fetal Medicine foundation, UK and if done correctly, provides the maximum details.

### Who should be performing the scan ?

To achieve optimal results from routine ultrasound examinations it is suggested that scans should be performed by individuals who fulfill the following criteria[6]:

1. have completed training in the use of diagnostic ultrasonography and related safety issues;
2. participate in continuing medical education activities;
3. have established appropriate care pathways for suspicious or abnormal findings;
4. participate in established quality assurance programs.

### Safety

Keep the fetal exposure as minimum as possible. The principle of ALARA should be followed.

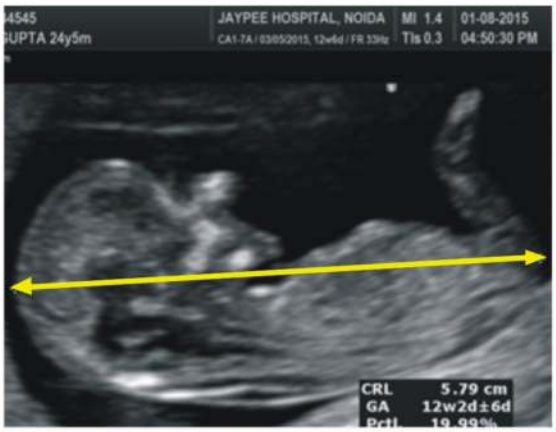
Use of B or M-Mode is advised as these asscociated with low power output. Dopplers have larger energy output, should be used if clinically indicated. When using Dopplers[9]-

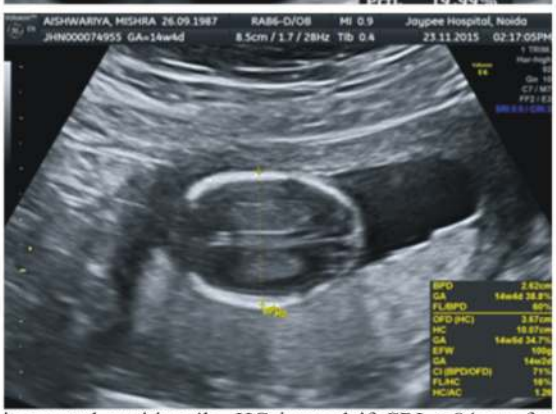
- avoid pulse wave
- keep thermal index <1
- time usually 5-10mins, not to exceed 60 mins.

### What is done in this scan ?

1. Confirm viability

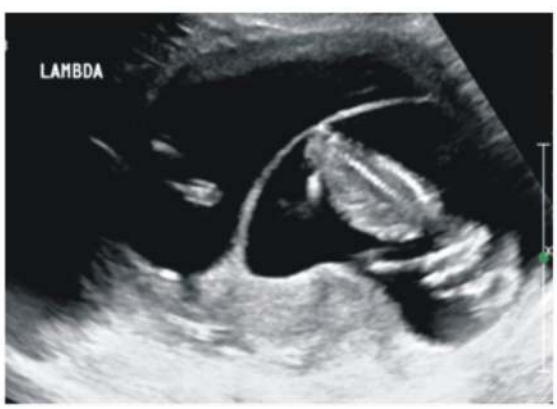
2. *Dating* – CRL is used for dating. If CRL > 84mm then HC is used[6] (fig. 4a,b).

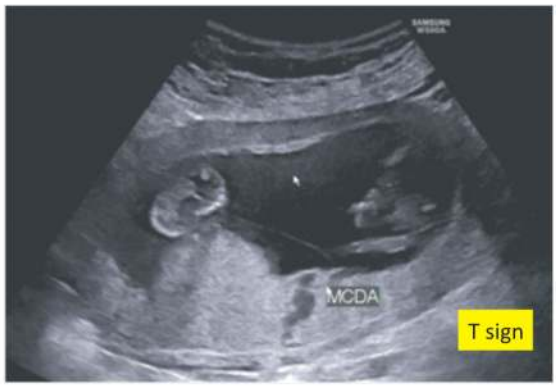



in neutral position.4b HC is used if CRL >84mm for dating.

3. *Number of fetuses and chorionicity*- assessment of lambda (dichorionic)and T (monochorionic) sign (figure 5a,b).




membrane. 5b monochorionic (MC) twins there is no chorionic layer present

4. *Screening for aneuploidy* - minimum nuchal translucency and nasal bone (Fig. 6) should be seen and correlated with CRL for aneuploidy risks[4,6]along with dual marker. (detection rate 87%, false positive rate of 5%)[12]

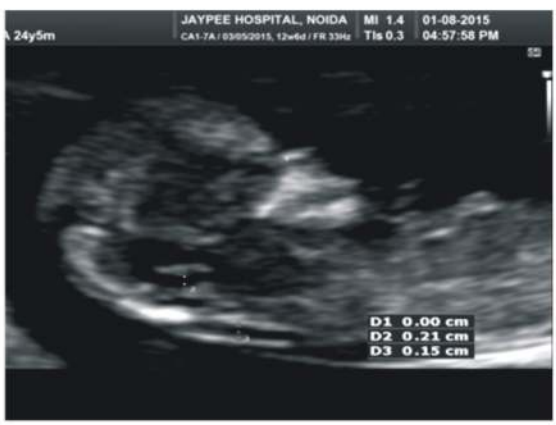


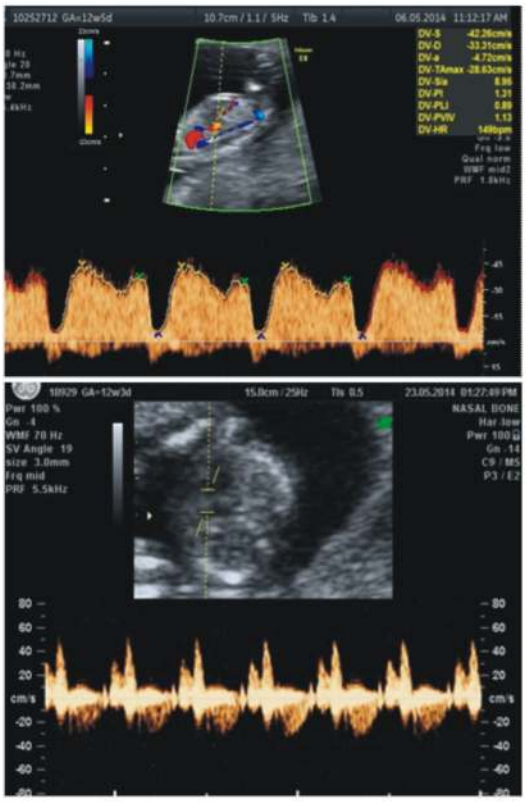

Fig 6 Nuchal translucency- magnify-the fetal head and upper thorax occupy the whole screen
mid sagittal section of the fetus must be obtained
- neutral position, with the head in line with the spine.
- Measurements should be taken with the inner border of the horizontal line of the callipers placed ON

The aneuploidy risk assessment to date with the highest sensitivity of 92% with a false positive rate of 3% - is by the combined first trimester risk assessment[10] in accordance with FMF,UK guidelines[11] which includes-

1. Ultrasound factors[12]-nuchal

translucency, nasal bone, ductus venosus (fig 7a), tricuspid regurgitation and fetal heart rate (fig 7b).

2. Maternal serum bio-chemistry- PAPP-A and serum B HCG Mom values (Fig 9)



Additional markers- 7a Ductus venosus PI. 7b 4 chamber view of the heart for tricuspid regurgitation and measuring fetal heart rate.

5. Screening for structural problems at the time of first trimester scan by ISUOG statement[6]-

| Organ / Anatomical area | Present and/or normal? |
|---|---|
| **Head** | Present<br>Cardinal Bones<br>Midline falx<br>Choroid-plexus-filled ventricles |
| **Neck** | Normal appearance<br>Nuchal translucency thickness (if accepted after informed consent and trained/certified operator available)* |
| **Face** | Eyes with lens*<br>Nasal bone*<br>Normal profile/ mandible*<br>Intact lips* |
| **Spine** | Vertebrae (longitudinal and axial)*<br>Intact overlying skin* |
| **Chest** | Symmetrical lung fields<br>No effusions or masses |
| **Heart** | Cardiac regular activity<br>Four symmetrical chambers* |
| **Abdomen** | Stomach present in left upper quadrant<br>Bladder*<br>Kidneys* |
| **Abdominal wall** | Normal cord insertion<br>No umbilical defects |
| **Extremities** | Four limbs each with three segments<br>Hands and feet with normal orientation* |
| **Placenta** | Size and texture |
| **Cord** | Three-vessel cord* |

*optional structures

6. Screening for pre-eclampsia

The patient-specific risk of developing PE can be predicted by a combination of factors in the maternal history, including Black racial origin, high body mass index and prior or family history of PE, and the following measurements taken at 11-13 weeks:

- maternal blood pressure
- uterine artery pulsatility index (PI)-hence should be taken at the time of first trimester scan(fig 8)
- maternal serum level of PAPP-A
- maternal serum level of PLGF

Screening by this combined approach could identify about 90% and 45% of patients developing early-PE and late-PE, respectively, at a false positive rate of 5%.

If the patient is screen positive or uterine artery PI is greater than 95$^{th}$ centile, low dose aspirin can be started. Administration of anti-platelet agents to women at risk of pre-eclampsia can lead to a 17% reduction in the risk of developing pre-eclampsia[14], especially when started prior to 16 weeks[15]. Hence, uterine artery PI should be measured at the time of first trimester scan.

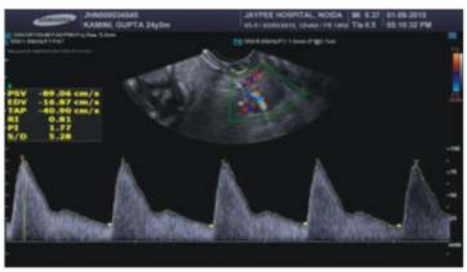


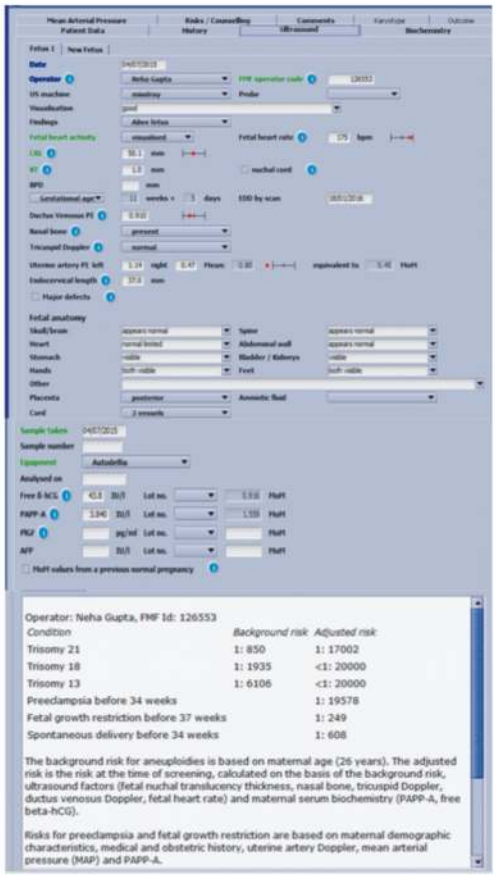
Fig8 Uterine artery PI-is used.-11+0-13+6 weeks –at CRL 45-84 mm

- Sagittal section of the uterus - cervical canal and internal cervical os identified. identify each uterine artery along the side of the cervix and uterus at the level of the internal os by colour flow Doppler
- gate size 2mm, angle of insonation<0
- When three similar consecutive waveforms are obtained the uterine artery PI should be measured and the mean uterine artery PI of the left and right arteries calculated

## Second Trimester Scan – 18-20 weeks

The 18-20 weeks scan aims to assess the fetal anatomy and growth, the amount of amniotic fluid and the position of the placenta. There is good evidence that in this scan the cervical length (for assessment of

A sample report (fig 9):



Operator: Neha Gupta, FMF Id: 126553

| Condition | Background risk | Adjusted risk |
|---|---|---|
| Trisomy 21 | 1: 850 | 1: 17002 |
| Trisomy 18 | 1: 1935 | <1: 20000 |
| Trisomy 13 | 1: 6106 | <1: 20000 |
| Preeclampsia before 34 weeks | | 1: 19578 |
| Fetal growth restriction before 37 weeks | | 1: 249 |
| Spontaneous delivery before 34 weeks | | 1: 608 |

The background risk for aneuploidies is based on maternal age (26 years). The adjusted risk is the risk at the time of screening, calculated on the basis of the background risk, ultrasound factors (fetal nuchal translucency thickness, nasal bone, tricuspid Doppler, ductus venosus Doppler, fetal heart rate) and maternal serum biochemistry (PAPP-A, free beta-hCG).

Risks for preeclampsia and fetal growth restriction are based on maternal demographic characteristics, medical and obstetric history, uterine artery Doppler, mean arterial pressure (MAP) and PAPP-A.

risk for preterm birth) and uterine artery pulsatility index (for assessment of risk for preeclampsia and fetal growth restriction) should also be measured.

The Eurofetus study[16], a multicenter project, examined the accuracy of routine mid-trimester ultrasonographic examination in unselected populations. Over one half (56%) of 4615 malformations were detected and 55% of major anomalies were identified before 24 weeks of gestation.

As a person affiliated with Fetal Medicine Foundation, UK, we follow their guideline which require following images to be taken at the time of an anomaly[17] scan-

1. Transverse view of the head at the level of the septum cavum pellucidum for

measurement of biparietal diameter, head circumference, hemisphere and cerebral ventricles (Fig 10. 1)

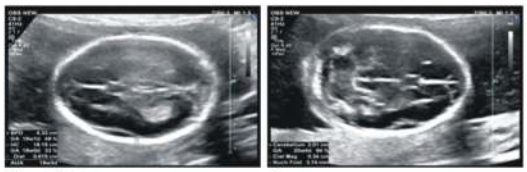


Fig-10.1 2

2. Suboccipital-bregmatic view of the head for measurement of cerebellum and cisterna magna (Fig 10.2)
3. Transverse views of the face through the orbits (fig 11a), lips (fig 11b) and maxilla (fig11 c).

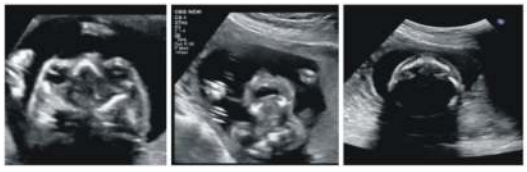
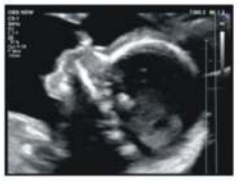


Fig11a b c

4. Sagital view of the face (profile) demonstrating the nasal bone (fig 12)



(fig 12)

5. Four-chamber view of the heart (Fig 13a)
6. Views demonstrating the outflow tracks of the heart- (fig 13b) left ventricular outflow tract and (fig 13c) right ventricular outflow tract

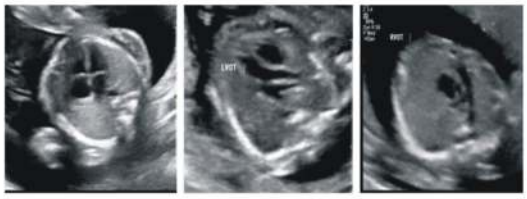


Fig 13a b c

7. Transverse view of the abdomen at the level of the stomach and umbilical vein for measurement of the abdominal circumference (fig 14a)

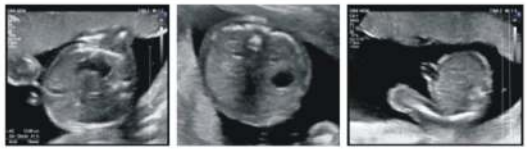


Fig14a b c

8. Transverse views of the abdomen to demonstrate the kidneys (Fig 14 b)
9. Transverse or longitudinal view to demonstrate the umbilicus (Fig 14 c)
10. Transverse or longitudinal view to demonstrate the bladder
11. Longitudinal view to demonstrate measurement of the femur (fig15a)

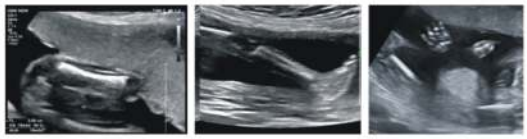


Fig 15

12. Longitudinal view to demonstrate the leg and foot (fig15b)
13. View of the open hand (fig15c)
14. One or two longitudinal views demonstrating the whole spine (Fig 16a)

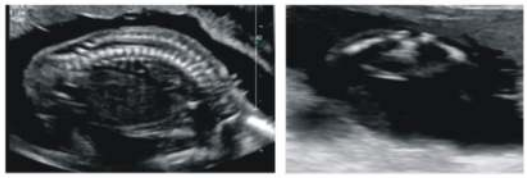


Fig 16a b

15. Transverse view of the sacral spine (Fig 16b)
16. Longitudinal view demonstrating the

relation between the lower end of the placenta and thecervix

The second trimester scan is also called genetic sonogram when we look at markers of aneuploidy as well. We look for ventriculomegaly, nuchal fold thickness, absent or hypoplastic nasal bone, intra-cardiac echogenic focus, short long bones, echogenic bowel[19] in order to provide risks for aneuploidy +/- biochemistry (depending on the situation). Well, there is another guideline for second trimester scan issued by ISUOG which is available free online, can also be consulted[18].

Then, there is an early anomaly scan done between 16-17 weeks- an assessment of the anatomy can be done. Usually done in cases which have no previous scan or missed first trimester screening or when there were problems in first trimester scan like increased nuchal translucency with normal risk in combined first trimester risk or tricuspid regurgitation.

## Growth Scan – 32-34 weeks

The aim of this scan is to detect fetal well being. Assessment of lie, growth and amniotic fluid is mainly done. What is more important to look at it is the centiles of the parameters, growth and amniotic fluid and where they lie on the charts and trend is what is more important than the absolute values (fig 17). The Dopplers are not advised to be done routinely in low risk cases.

RCOG guidelines also states that the Umbilical artery Doppler should be the primary surveillance tool in the SGA fetus[15].

But as a fetal medicine specialist, I believe it is a good practice to switch on the Dopplers, if the facility is available even if the

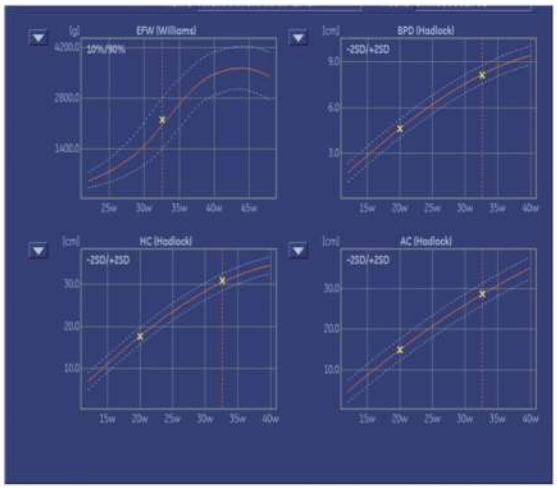



Fig 17

pregnancy is deemed low risk. By doing so,atleast umbilical artery Doppler, 30% of stillbirths due to unidentified causes can be avoided asthey are mainly due to uteroplacental insufficiency.

## Conclusions

WHO Study Group[20] stated in 1998 that 'worldwide, it is likely that much of the ultrasonography currently performed is carried out by individuals with in fact little or no formal training.' However, the sad part is it is still the same in developing countries.

It is very important that the 11-13+6 weeks scan is performed by a professional with necessary expertise as the major problems of dating and IUGR are sorted out. It is unfortunate that we still see anencephaly and neural tube defects late in second and third trimesters which could have been detected in the first trimester as well, hence we need people who have proper training and their work should be regularly audited so that the quality is ensured.

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# GESTATIONAL DIABETES MELLITUS

## FOGSI DIPSI GUIDELINES for screening

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The pregnancy related diabetes, GDM is steadily increasing in India from 2 per cent in 1982 to 7.2 per cent in 1991 and it had doubled to 16.55 per cent in 2002, which is a dangerous phenomenon. Unless, we tackle this problem on a war-footing, we will be adding more number of people to the diabetic population, which is not a good health indicator for a developing country like ours.

Diabetes is often diagnosed in women during their childbearing years and can affect the health of both the mother and her unborn child. Proper health care before and during pregnancy can help prevent birth defects and other poor outcomes.

Gestational Diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[1] In developing countries such as India, particularly in rural areas, there are several challenges to screening for GDM. Some of these challenges include lack of trained phlebotomists, lack of standardized laboratories to do blood glucose estimations, and the problem in getting all women to visit in a fasting state. Due to these challenges, the WHO 1999 criteria, which require only a single sample (compared to three samples with the IADPSG and four samples with the Carpenter and Coustan criteria), became very popular in India. [2]

DIPSI also endorsed the 1999 WHO criteria and recommended universal screening at first contact, second at 16-18wks again at 28-32 weeks using this single-step 2-h value, which the WHO (1999) criteria proposed.[3] Because there are difficulties in getting women to visit in a fasting state for the OGTT, Anjalakshiet al.[4] conducted a study comparing the GTT done in the fasting and the non-fasting states. They found that the non-fasting OGTT had 100% specificity and sensitivity when compared to the fasting test taken as a "gold standard." Based on this study, DIPSI adopted the non-fasting OGTT as a single-step screening and diagnostic test for GDM in India. The DIPSI guidelines recommend using 75 g glucose load, which can be given in either a non-fasting or a fasting state, and one blood sample to be drawn 2 h after glucose load, and a cut-point of 140 mg/dL as the diagnostic cut-point for GDM irrespective of whether the GTT is done in the fasting or non-fasting state.[3,4] FOGSI endorses Single step screening and Diagnostic test with 75gm glucose load for diagnosis of Gestational Diabetes in our country and should be implemented in all centres across India.

## FOLLWUPOFGDM

GDM may be viewed as an unidentified preexisting disease, or the unmasking of a compensated metabolic abnormality by the added stress of pregnancy, or a direct consequence of the altered maternal metabolism stemming from the changing hormonal milieu.

Glucose tolerance test with 75g oral glucose is performed after 6 weeks of delivery and if necessary repeated after 6 months and every year to determine whether the glucose tolerance has returned to normal or progressed.

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# SCREENING AND CLINICAL MANAGEMENT GUIDELINES FOR THYROID DISORDERS IN PREGNANCY

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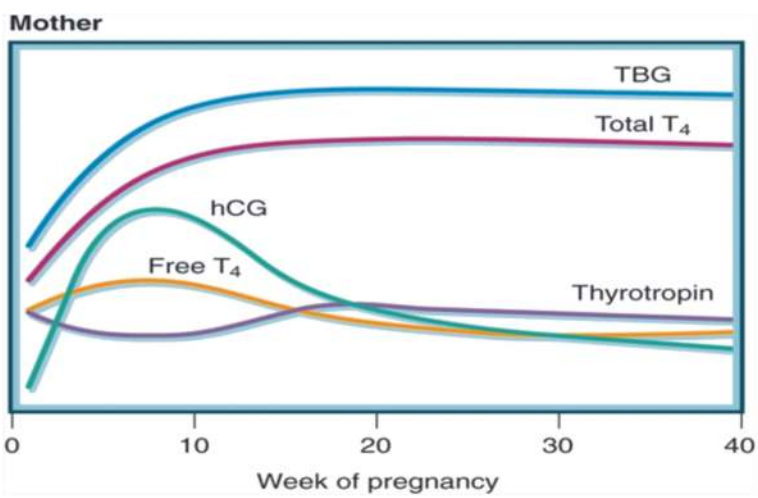
***"Amongst the most important freedoms one can have is the freedom from avoidable ill-health and escapable mortality"***
***- Amartya Sen, Nobel Prize Laureate***

There has been a paradigm shift in the approach to health care, more so in perinatal medicine with a focus on early detection and prevention. Women are more prone to thyroid disease in general and pregnancy has a profound impact on thyroid function. Thyroid disease is the most common preexisting endocrine disorder in pregnant women and affects approximately 3-7% of pregnant women.[1]

## Thyroid hormone physiology during Pregnancy:

- Human chorionic gonadotropin (hCG) and Estrogen, the hormones of pregnancy increase thyroid hormone levels in the blood.
- HCG, produced by placenta, is structurally similar to TSH (common alpha subunit) and mildly stimulates the thyroid to produce more thyroid hormone.
- Increased estrogen produces higher levels of thyroxine-binding globulin, a protein that transports thyroid hormone in the blood.
- As a result, there is increase in both serum total T4 and T3 levels. Normal T4 and T3 levels are 1.5 times the non pregnant reference range.
- In pregnancy, there is placental conversion of T4 to T3.



| Physiologic Change | Thyroid-Related Consequences |
|---|---|
| '↑ Serum thyroxine-binding globulin '↑ Total $T_4$ and $T_3$; | '↑ $T_4$ production, reduced hepatic clearance, estrogenic stimulation |
| '↑ Plasma volume | '↑ $T_4$ and $T_3$ pool size; '↑ $T_4$ production; '↑ cardiac output |
| First trimester '↑ in Hcg | '↑ Free $T_4$; "↑ basal thyrotropin; '↑ $T_4$ production |
| '↑ Renal Iodine clearance | '↑ Iodine requirements |
| '↑ Oxygen consumption by fetoplacental unit, gravid uterus, and mother | '↑ Basal metabolic rate; '↑ cardiac output |

## Sources of Thyroid Hormone for The Fetus :

Thyroid hormone is critical to normal development of the fetal brain and nervous system.

- During the first trimester, the fetus depends on maternal T4, which comes through the placenta.
- At around 10-12 weeks, fetal thyroid begins to function on its own.

The fetus is affected either directly by trans-placental passage of hormones, antibodies or drugs or indirectly influences on maternal physiology.

## Screening Recommendations :

Measurement of Serum TSH is the most simple, practical and economical screening test for thyroid dysfunction. A value of 2.5 mU/L is presently accepted as the upper limit of serum TSH for the first trimester of pregnancy.

Wherever available, use laboratory-specific and trimester-specific reference ranges in pregnancy. When not available, aim for[2] :-

| STAGE | TSH |
|---|---|
| Pre-conception | 0.3-2.5mIU/L |
| 1st trimester | 0.1-2.5mIU/L |
| 2nd trimester | 0.3-3.0mIU/L |
| 3rd trimester | 0.3-3.0mIU/L |

## Indications for Screening :

ACOG does not recommend universal screening for thyroid disorders in pregnancy.[3]

Screening is recommended for the following indications :

- Family h/o autoimmune thyroid disease
- Women on thyroid therapy
- Presence of goiter or thyroid nodules
- History of thyroid surgery
- Infertility
- Unexplained anemia or hyponatremia or high cholesterol level
- Previous History of
  - neck radiation
  - postpartum thyroid dysfunction
  - previous birth of infant with thyroid disorder
- Other autoimmune chronic conditions : Type 1 DM

## Screen or not to screen ?

The cost effectiveness of routine screening of all pregnant women is not

yet proven however many authors have suggested that screening for subclinical hypothyroidism in pregnancy will be a cost-effective strategy under a wide range of circumstances, as listed above.

Published Indian data are limited but a prospective study by Misra et al from Orissa reported a 5.3% prevalence of subclinical hypothyroidism. Data from a 5 year multicenter study by ICMR had reported an incidence of 1 in 900 for congenital hypothyroidism in newborns.

In our set-up we feel that screening of all pregnant patients is a cost effective strategy although it is not yet available free of cost through government programs everywhere. Pregnant women are offered screening at booking visit and most of them opt to do so.

**NEWBORN SCREENING RECOMMENDATIONS** through Perinatology Committee FOGSI

- Obstetric Care providers to make resources regarding newborn screening available to patients through informational brochures, electronic sources or through discussion during prenatal visits.
- Every baby should be screened for Congenital Hypothyroidism anytime after 24hrs of birth.
- Make available Basic and Expanded Newborn Screening for all who request it.
- There are no indications to not perform a Newborn Screening Test

## Hypothyroidism

Overt hypothyroidism is reported in 1 in 1600 pregnancies4. However, the prevalence of subclinical hypothyroidism is significantly higher, 2-3%.

**Causes :**

- Hashimoto's thyroiditis, most common cause.
- Prior radiation or surgical treatment of Grave's disease.
- Iodine deficiency

Hashimoto's disease is a form of chronic inflammation of the thyroid gland which like Graves' disease, is an autoimmune disorder.

**Effect of Hypothyroidism on Pregnancy :**

Overt maternal hypothyroidism is associated with pregnancy complications like preeclampsia, placental abruption, preterm birth, low birth weight, and fetal death & intellectual impairment during childhood. The effects of mild maternal thyroid deficiency with a normally functioning fetal thyroid gland are less clear & less studied. This is important because the spectrum of thyroid deficiency begins with subclinical hypothyroidism characterized by an elevated serum thyrotropin (TSH) concentration but a normal serum free thyroxine level till overt hypothyroidism.

Uncontrolled hypothyroidism during pregnancy can lead to

- spontaneous abortion
- preeclampsia
- abruption
- still births
- anemia
- low birth weight
- postpartum haemorrhage

**Diagnosis :**

Symptoms of hypothyroidism in pregnancy include:

- extreme fatigue
- cold intolerance
- muscle cramps
- constipation and
- problems with memory or concentration.

| | Clinical Hypothyroidism | Subclinical Hypothyroidism |
|---|---|---|
| TSH | High | High |
| Free T4 | Low | Normal |
| FreeT3 | Normal or low | Normal |

**Case Scenario :**

A 32 year old fourth gravida with previous intrauterine fetal death and 2 spontaneous abortions came for the first time at 9 months of gestation with physical appearances as below and with a pulse rate of 60/minute and BP=120/70 mmhg .

Her laboratory investigations were as follows :-

- TSH level of 21.24 micro IU/ml.
- Free T3 4.41 pg/ml,
- Free T4 26.61Pmol/l
- With ECG showing low QRS voltages with widespread T-wave inversions & heart rate of 60/minute

She had not been tested in the past and presented to us late in pregnancy with classical features of overt hypothyroidism (Figs 1 and 2).

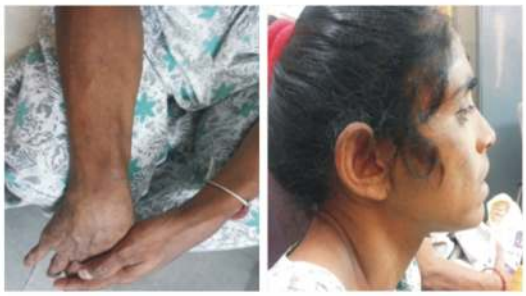


Fig. 1. Skin changes in pregnant gravid woman with bad obstetric history (G4P1A2L0) presenting with TSH of 21.2 in third trimester

Fig. 2. Fullterm growth restricted newborn of case shown in Fig 1

**Treatment** :

Guidelines for clinical management of maternal hypothyroidism in pregnancy:[5]

- Optimize levothyroxine doses prior to pregnancy (TSH 0.5-2.5 mIU/L)
- Check TSH levels as soon as pregnancy is confirmed
- Treatment is with synthetic thyroid hormone thyroxine which is identical to T4 made by the thyroid.
- Daily dose of 2mcg/kg/day should be started in TSH levels > 10 mIU/L, for TSH levels < 10, dose of 100 mcg/day should be started.
- Adjust levothyroxine doses to maintain TSH levels < 2.5 mIU/L.

- Dose incremented by 4–6 wk gestation and 30–50% increase in dosage.
- TSH should be monitored every 4-6 weeks in first half of pregnancy.
- Subsequently, repeat TSH every 8 weeks unless a dose adjustment is made.
- Separate levothyroxine ingestion and prenatal intake of vitamins, iron or calcium supplements.
- After delivery, levothyroxine dose should be reduced to pre pregnancy levels and serum TSH to be measured 6 weeks postpartum.
- Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored for elevation of TSH above the normal range.
- Recommends T4 replacement in women with subclinical hypothyroidism.

## Hyperthyroidism :

Hyperthyroidism affects about one of every 500 pregnancies.[6]

**Causes :**

- Graves' disease, most common cause affecting 85-90% cases
- Toxic nodular disease (10%)
- Thyroiditis (1-2%).

In Graves' disease, an antibody called thyroid-stimulating immunoglobulin (TSI) or TSH receptor antibody (TRAb) is produced, which mimics TSH and stimulates the thyroid to produce excess thyroid hormone.

Although Graves' disease may first appear during pregnancy, a woman with preexisting Graves' disease could actually see an improvement in her symptoms in her second and third trimesters. Remission of Graves' disease in later pregnancy may result from the generalized suppression of the immune system that occurs during pregnancy. The disease usually worsens again in the first few months after delivery.

Rarely, gestational tyrotoxicosis[7] is caused by a spectrum of HCG induced hyperthyroidism and hyperemesis gravidarum. This extreme nausea and vomiting is believed to be triggered by high levels of hCG that activates the TSH receptor by a spillover mechanism because of molecular similarity between the two glycoproteins.

## Signs and Symptoms of Hyperthyroidism : (fig 3 & 4)

- Nervousness
- Tremor
- Tachycardia
- Frequent stools
- Sweating
- Heat intolerance
- Weight loss
- Goiter
- Insomnia
- Palpitations
- Hypertension
- Lid lag/lid retraction
- Pretibial myxedema

Uncontrolled hyperthyroidism during pregnancy can lead to

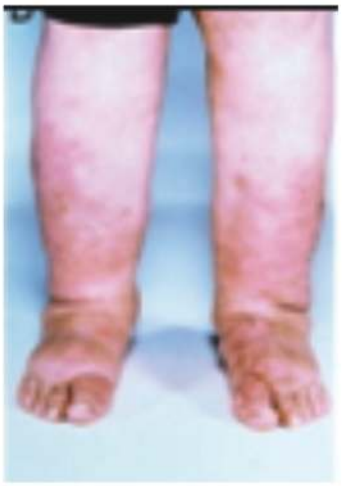


Fig. 3. Pretibial Myxedema

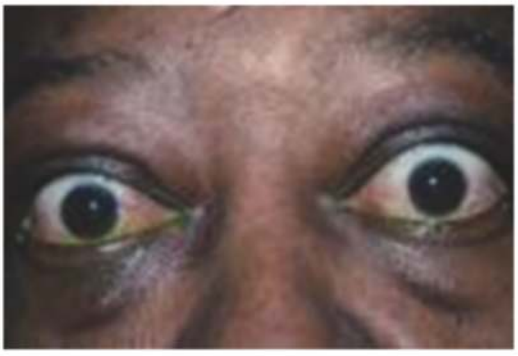


Fig. 4. Ocular changes in hyperthyroidism

- congestive heart failure
- preeclampsia
- thyroid storm - a sudden, severe worsening of symptoms
- miscarriage
- premature birth
- low birth weight

**Fetal & Neonatal Effects of Hyperthyroidism :**

- Associated with preterm delivery, low birth weight, fetal loss
- Fetal thyrotoxicosis (related to disease itself or treatment)
- Risk of immune-mediated hypo/hyperthyroidism (due to antibodies crossing the placenta, esp. in Graves or chronic autoimmune thyroiditis)
- Antibodies in Graves' disease can be either stimulatory or inhibitory
- Neonates of women with Graves' who have been surgically/ radioactively treated are at higher risk, as they are not taking suppression.

If a woman has Graves' disease or was treated for Graves' disease in the past with surgery or radioactive iodine, the TSI antibodies can still be present in the blood, even when thyroid levels are normal. The TSI antibodies she produces may travel across the placenta to the baby's bloodstream and stimulate the fetal thyroid. If the mother is being treated with antithyroid medications, hyperthyroidism in the baby is less likely because these medications also cross the placenta.

**Diagnosis :**

- Clinical diagnosis of hyperthyroidism is difficult because some of the symptoms (palpitations, decreased exercise tolerance, fatigue, heat intolerance) overlap with those of pregnancy.
- Low TSH levels may also occur in a normal pregnancy, especially in the first trimester, due to the small increase in thyroid hormones from HCG.
- Document elevated FT3 or elevated FTI with suppressed TSH (< trimester specific 95% lower

confidence limit), with or without diffuse goiter sometimes with a bruit.

- TSH receptor antibodies - TSI, antimicrosomal, antithyroid peroxidase antibodies are usually detectable and are of diagnositic utility
- Thyroid antibodies are linked with miscarriage, but universal screening for antithyroid antibodies is not recommended.

**Treatment :**

Guidelines for clinical management of maternal hyperthyroidism in pregnancy:[5,8]

- Mild hyperthyroidism, in which TSH is low but free T4 is normal, does not require treatment.
- More severe hyperthyroidism is treated with antithyroid medications, which act by interfering with thyroid hormone production.
- Antithyroid drugs form the mainstay of treatment of Grave's disease during pregnancy. They decrease thyroid hormone synthesis by blocking organification of iodide and iodotyrosine coupling. PTU also reduces T4->T3 and may work more quickly.
- Antithyroid medications cross the placenta in small amounts and can decrease fetal thyroid hormone production, so the lowest possible dose should be used to avoid hypothyroidism.
- For hyperthyroidism, the first-line treatment in the first-trimester is Propylthiouracil (PTU), and Methimazole (MMI) after the first trimester:
  - o MMI is possibly linked with congenital anomalies, but can be used if PTU is unavailable or not tolerated.
  - o PTU is rarely associated with severe liver toxicity.
- In women with TRAb or thyroid-stimulating Ig elevated 2-fold to 3-fold or more, and in women treated with an antithyroid drugs ((PTU >450mg/day, MMI > 30mg/day) at 26-28 weeks.), maternal free T4 and fetal thyroid dysfunction should be assessed on the fetal anatomy ultrasound in the 18th to the 22nd week and every 4 to 6 weeks or as clinically indicated:
  - o Fetal thyroid dysfunction findings include thyroid enlargement, growth restriction, hydrops, goiter, advanced bone age, tachycardia, and cardiac failure.
  - o Fetal hyperthyroidism that might endanger the pregnancy can be treated with MMI or PTU with frequent clinical, laboratory, and ultrasound monitoring.
- Aim is to maintain maternal serum FT4 levels at or about 10% above the normal limit of non pregnant reference range or maternal total T4 at the upper limit of pregnancy (1.5 times the normal pre pregnant range) using lowest possible dose.
- Measure FT4/FTI every 2-4 weeks and titrate.
- Antithyroid medications can cause side effects
  - o allergic reactions such as rashes and itching
  - o leukopenia, which can lower

resistance to infection

o rarely, liver failure

- Beta adrenergic blocking agents (propranalol) may be used transiently to control adrenergic symptoms until antithyroid drug therapy decreases thyroid hormone levels.
- Iodine intake during pregnancy and breast-feeding should not exceed 500 µg/day.
- Radioactive iodine treatment is not an option for pregnant women because it can damage the fetal thyroid gland.
- Rarely, surgery to remove all or part of the thyroid gland is considered for women who cannot tolerate antithyroid medications.
- Studies have shown that mothers taking antithyroid medications may safely breastfeed.
- All newborns of mothers with Graves' disease should be evaluated for thyroid dysfunction.

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# SCREENING GUIDELINES FOR FETAL ANEUPLOIDIES

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## Outline

- Aneuploidies - do all of them make it to birth?
- Aneuploidy screening: Evolution and timeline
- Screening versus diagnosis
- 1st trimester aneuploidy screening
- 2nd trimester aneuploidy screening
- Is Down syndrome screening different for ART conceptions?
- Is the future here? – cell free fetal DNA (Non Invasive Prenatal testing; NIPT)
- Summary- guidelines
- Down Trivia!

'We have had 10-12 children, but have never undergone a sonography during pregnancy'. 'Are the ultrasound rays not harmful to the baby'? – are questions often asked by parents and in-laws of the expecting couple.

Over the past few decades, there has been an adjustment to a lower number of children or to a '1-child family' or at the most to a '2-child family'. Career planning, late marriages, advanced maternal age at conception, have led to this tendency of wanting fewer children and smaller families. But in this only pregnancy that the couple has, they want to do the most that they can, and they have the right to know all that is available for them.

On October 5th, 2010, President Obama signed a legislation requiring the federal government to replace the term "mental retardation" with "intellectual disability".

This measure, known as the Rosa's Law stripes the terms "mental retardation" and "mentally retarded" from federal health, education and labor policy.

Prenatal screening over the last three decades has become an integral part of antenatal care. Advances in biochemical screening combined with the excellent display of fetal dysmorphology by the technological advances in ultrasound equipment have opened up new horizons in the non invasive prenatal screening.


Figure 1 : President Obama signs Rosa's Law

As clinicians, it is our duty to provide a non-directive, but a thorough counseling regarding options available for antenatal aneuploidy screening, and decision making in diagnosis.

## Aneuploidies - do all of them make it to birth?

Aneuploidy means abnormality involving the chromosomal number. They occur in 0.1% to 0.2% of live births; Trisomy 21 (Down syndrome) is the most common karyotype abnormality in live-born infants (1 per 800 live births. Trisomy 21 is the most common genetic cause of mental retardation and one of the few aneuploidies compatible with post-natal survival, due to which a lot of emphasis is given on Down syndrome screening rather than other aneuploidies.

Screening for aneuploidies and open neural tube defects should be a part of standard antenatal care, but has unfortunately not been incorporated into any national screening guideline. Due to this, there is diversity in the offering and uptake of prenatal aneuploidy screening tests and most of the rural India continues to be devoid of a standard antenatal care.

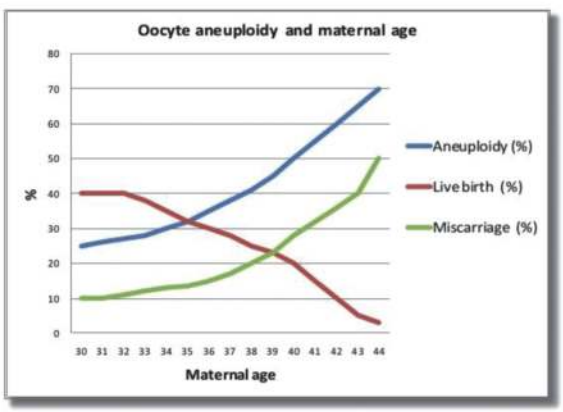


Figure 2 : Maternal age and aneuploidies

The risk for many aneuploidies increases with maternal age. Additionally, because aneuploid fetuses are more likely to die in utero than euploid fetuses, the risk decreases with gestation. More than 65% of first trimester miscarriages are aneuploidies.

The frequency of aneuploidy in embryos is much higher than what would be expected looking only at affected live borns.

For women between the ages of 35 to 39 years approximately 40% to 50% embryos are abnormal. For women 40 years and older, on average, greater than 50% of embryos are abnormal.

This difference in percentages in embryos versus live born is due to the fact that a pregnancy with aneuploidy is less likely to implant to the uterus or go to term. Most will be miscarried. As such, the percentage of affected pregnancies is reduced over the course of the pregnancy due to the affected pregnancies that are lost. Any embryo with a missing chromosome (monosomy) will cease to grow before implantation (except monosomy X and 21), and only few of those carrying an extra chromosome (trisomy) will go to term. The rate of fetal death between 12 weeks (when first trimester screening is performed) and term is about 30% for trisomy 21 and 80% for trisomies 18 and 13.

As mentioned above, most aneuploidies miscarry within 12 weeks; the common ones that can carry on beyond 12 weeks are Trisomy 21, 18 and 13, Turners syndrome. Trisomy 13 and 18 are easier to diagnose on ultrasound, as the affected fetus present

with obvious structural defects. Fetuses affected with Trisomy 21 usually show subtle markers on ultrasound, making prenatal diagnosis more difficult that the other aneuploidies.

*Therefore, the article further shall focus mainly on Trisomy 21 screening and diagnosis.*

## Aneuploidy screening : Evolution and timeline

Over the past decades, a lot has improved in the field of prenatal aneuploidy screening. From an era where all women more than 35 years of age were subjected to amniocentesis, we have reached a time where Down syndrome can be diagnosed by a maternal blood test, with a precision of 99.9%.

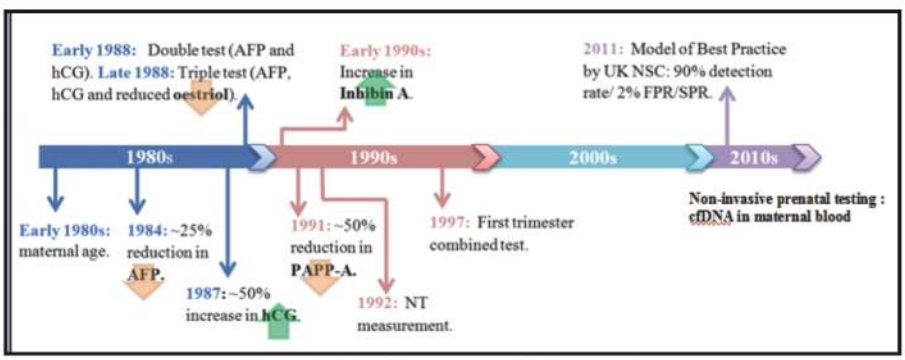


Figure 3 : Timeline of aneuploidy screening

There has been a shift to lesser invasive and more accurate screening tests. Following table shows the detection rates for various modes of aneuploidy screening, at a fixed false positive rate.

## Aneuploidy screening principles

*Whom to offer?*

ALL women, irrespective of their geographical location, resources or chosen

| METHOD | Detection Rate (%) | False Positive Rate (%) |
|---|---|---|
| Maternal Age | 30 | 5 |
| FIRST TRIMESTER | | |
| Maternal Age + Nuchal Translucency | 75-80 | 5 |
| Maternal Age + Double Marker (PAPP-A + Free β hCG) | 60-70 | 5 |
| Maternal Age + Nuchal Translucency + Double Marker (Combined Test) | 85-95 | 5 |
| Combined Test + Nasal Bone / Ductus Venosus flow / Tricuspid Regurgitation | 93-96 | 2.5 |
| SECOND TRIMESTER | | |
| Maternal Age + Triple Test (serum AFP, free β-hCG, uE3) | 65-70 | 5 |
| Maternal Age + Quadruple Test (serum AFP, free β-hCG, uE3, Inhibin A) | 70-75 | 5 |
| INTEGRATED 1ST & 2ND TRIMESTER | | |
| Maternal Age + [NT + Double Marker] + [Quadruple Marker] | 90-94 | 5 |

Figure 4: Detection rate and performance of screening tests for Trisomy 21

model of antenatal care, are entitled to informed prenatal screening and diagnostic testing for fetal abnormalities or genetic conditions that may impact on the future life and health of their baby.

*Should it be offered to 'elderly' women (> 35 years age) only?*

20 % of pregnant women are 35 years or older, and this group constitutes 50% of Trisomy 21 fetuses. Hence, half of the Down Syndromes still occur in the younger age group women. Therefore, the standard of care is to perform detailed combined first trimester screening for all pregnant women irrespective of the maternal age, and achieve a detection rate of 95% with a false-positive rate of less than 3%.

*When?*

There are various modes of prenatal screening, beginning from as early as 9

weeks (cell free fetal DNA, integrated first trimester screening at 12 weeks, and quadruple screening and genetic sonogram in the 2nd trimester). Indian prenatal screening nesicitates that the screening strategy be as stringent as possible in the first half of pregnancy, as termination beyond 20 weeks is not legally allowed even if a diagnosis of Down syndrome is confirmed after 20 weeks. Also, fortunately, the sensitivity and specificity of Down syndrome screening decreases with increasing age.

*Screening versus diagnostic testing : What to offer?*

Screening tests are applied to the whole population, and 'high risk' and 'low risk' cohorts are formed depending on the screening test results. The aim of screening test is to identify the 'at risk' population, and not to confirm the diagnosis.

The 'high risk' cohort is then offered diagnostic testing. Diagnostic tests are gold standard and confirm the problem.

Theoretically, there are various modes of prenatal screening for aneuploidies such as contingent testing, independent sequential screening, step-wise sequential screening, serum integrated screening and fully integrated screening. Going into details of them all, shall add to further confusion, without benefit in treatment and counselling.

Integrated testing has been considered simple, efficient and patient-friendly, whereas contingent testing has been proven to be complicated and less acceptable.

**As seen from the table above, integrated first trimester screening yields the best detection rate (93-96%), at the lowest false positive rate (2.5%).**

Every year approximately 23,000 to 29,000 children are born in India with Down's syndrome in India. Around 85-90% of such cases can be detected if pregnant mothers opt for genetic screening. Local needs should drive the methodology, and hence, the article further discusses only modes of screening feasible and practically possible in the Indian scenario.

## Tests for aneuploidy SCREENING:

*1st trimester combined aneuploidy screening :*

First trimester combined screening (sonographic nuchal translucency combined with serum markers pregnancy-associated plasma protein A and the free beta subunit of human chorionic gonadotrophin) has superseded second trimester serum screening (alpha-fetoprotein, total human chorionic gonadotrophin, unconjugated estriol with

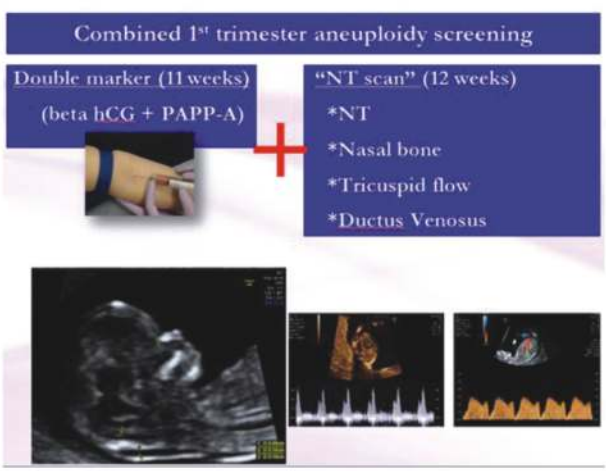


Figure 5: Components of combined first trimester aneuploidy screening

or without inhibin-A) as a screening paradigm for the detection of trisomy 21. This move is attributed to the recognition of superior detection rates, lower false-positive rates and earlier results associated with the former strategy.

*1st trimester maternal biochemistry :* The maternal biochemistry in 1st trimester is the 'double marker' and it comprises of beta hCG and PAPP-A. It can be done between 10-13+6 weeks. The sensitivity is highest when done early than late, and 11 weeks is an optimal time to do the double marker.

*Ultrasound in 1st trimester :* The 'NT' scan looks for much more than just the nuchal translucency. Although NT continues to be the most important maker for Down syndrome, its evaluation alone does not suffice the comprehensive 1st trimester scan.

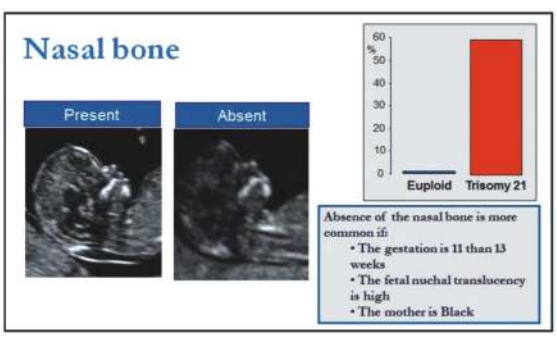


Figure 6 : Nasal bone

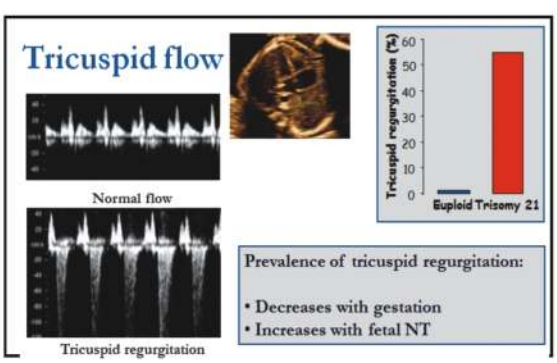


Figure 7 : Ductus Venosus

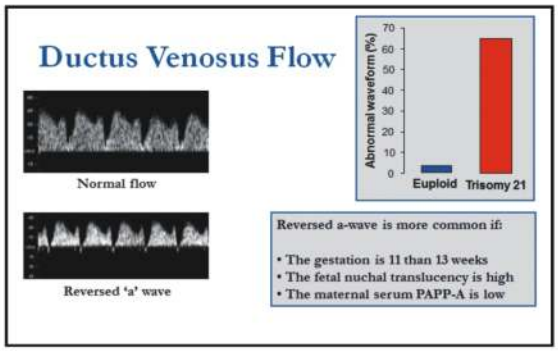


Figure 8 : Tricuspid flow

The 'NT scan' (done optimally at 12 weeks) should evaluate the following –

1. **Crown Rump Length (CRL) –** CRL at 12 weeks is the best time to date the pregnancy, unless it is an conception by IVF/ICSI. (Pregnancies conceived by assisted reproductive techniques are dated by embryo transfer date)
2. **Nuchal translucency –** NT continues to be the mainstay for aneuploidy diagnosis. Chromosomally normal fetuses with an increased nuchal translucency have a higher risk for fetal cardiac defects, skeletal dysplaisas, genetic syndromes.
3. **Assessment of nasal bone, ductus venosus and tricuspid regurgitation** should be included in the 12 weeks scan, as inclusion of these markers improves aneuploidy detection rates. Details are given in the figures.
4. **Screening for pre-eclampsia and fetal growth restriction (FGR) –** Maternal age, uterine artery pulsatality index, low PAPP-A on double marker, history of pre-eclampsia/hypertensive disorders, and previous pregnancy with FGR are good predictors for pre-eclampsia and FGR. Starting low dose aspiring and/or low molecular weight heparin may be

beneficial in tailor-made protocols.

5. **Screening for preterm birth** – Short cervical length, extremely high/low beta hCG values on double marker, history of previous preterm birth increase the risk of preterm birth in this pregnancy.

6. **Mini anomaly scan** – Structural defects are diagnosable at the NT scan, if a thorough structural check is done. The figure depicts various structural defects which can be diagnosed, may be diagnosed and cannot be diagnosed at the NT scan.

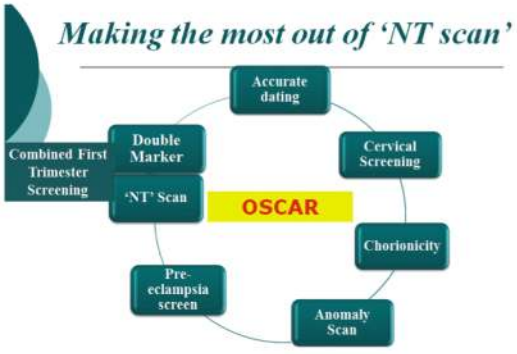


Figure 9: OSCAR – One Stop Clinic for Assessment of Risks

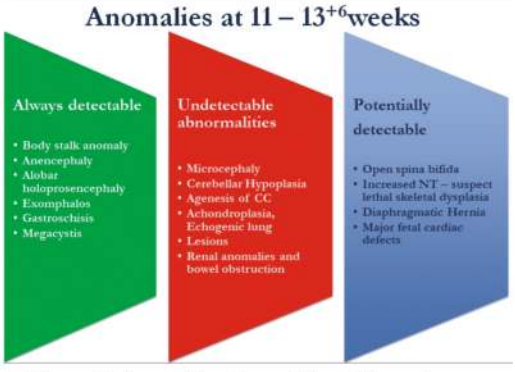


Figure 9: Anomalies detectable at 12 weeks scan

The double marker at 11 weeks is combined with the NT, nasal bone, ductus venosus flow, tricuspid flow – entered in a validated software (Fetal medicine Foundation recognized softwares – Astraia, Viewpoint), and combined 1st trimester risks are calculated.

**Individual risk assessment using double marker alone, or NT alone should be discouraged as they lead to confusing risks, multiple numbers and difficulty in decision making.**

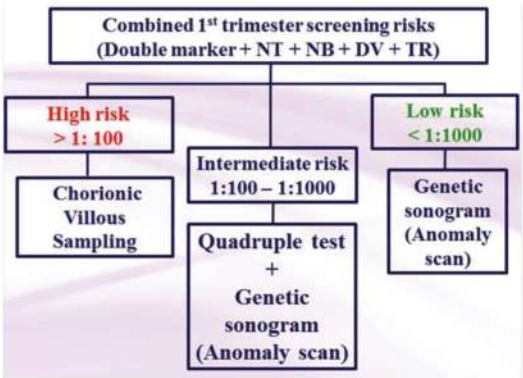


Figure 10 : Algorithm for prenatal aneuploidy screening: 1st trimester

A quadruple marker along with an anomaly scan is recommended for women with intermediate risks on combined first trimester screening. For women who are low risk (<1:1000), doing an anomaly scan in the second trimester suffices, and quadruple marker is not required.

## 2nd trimester aneuploidy screening:

***If first trimester screening is so good, then why the second trimester screening?***

A significant breakthrough was achieved when meta-analyses and randomized controlled trials globally proved the effectiveness of combined first trimester screening. First trimester combined screening is well established mainly in urban private centers. There is a great discrepancy in screening uptake between the private and public health care systems

and many parts of India continue to receive patients who seek health care in the second trimester directly. Second trimester aneuploidy screening (quadruple test + genetic sonogram) plays a vital role in such women and gives them re-assurance.

Genetic sonogram is the fetal anatomical survey between 15 and 20 weeks' gestation, optimal at 19 weeks, and it has emerged as one of the most widely utilized genetic screening tools in clinical practice in the Indian scenario.

*2nd trimester maternal biochemistry :* The 2nd trimester triple marker has been widely replaced by the quadruple marker, due to increased sensitivity and similar cost.

The triple test measures maternal serum alpha-feto protein (MSAFP), unconjugated estriol, free beta hCG. The quadruple marker adds estimation of inhibin to the triple marker. Current data suggest that with a fixed screen-positive rate of 5 percent, the detection rate for Down syndrome is 67 percent for the triple screen and 81 percent for the quadruple screen, wen either is combined with an anomaly scan.

Quadruple marker can be performed between 16 – 20 weeks, sensitivity is better at 16 weeks than 20. Where available, quadruple marker should be performed and triple marker is now considered obsolete.

*Ultrasound in 2nd trimester :* The ability of genetic sonogram to detect abnormalities relies on identification of either major structural malformations associated with aneuploidy or the "soft markers" for chromosomal abnormalities. This leads to two related conclusions: 1) detection of certain ultrasound findings must increase the risk for fetal aneuploidy by a constant proportion (Likelihood Ratio, LR) and 2) the absence of such findings must lower the risk (Negative Predictive Value, NPV).

| | Nuchal edema | Choroid plexus cyst | Echogenic intracardiac foci |
|---|---|---|---|
| Soft markers | Ventriculomegaly | Enlarged cisterna magna | Enlarged cisterna magna |
| | Short femur/humerus | Ventriculomegaly | Ventriculomegaly |
| | Hypoplastic/absent nasal bone | Short femur/humerus | Pyelectasis |
| | Echogenic bowel | Hypoplastic/absent nasal bone | Single umbilical artery |
| | Pyelectasis | Echogenic bowel | |
| | Sandal gap toes | Pyelectasis | |
| | | Single umbilical artery | |

Figure 11: Aneuploidy markers in 2nd trimester

Ultrasound detection of fetal aneuploidy depends on both major or structural defects, and nonstructural or minor markers. Major markers like increased nuchal fold and structural malformations (major cardiac defects, absent nasal bone) can be used in a low risk population too. Minor or "soft" markers are more common than major or structural abnormalities in fetuses with aneuploidies. These are anatomical findings which are present in a minority of normal fetuses, but more frequently in aneuploidy and therefore convey a statistically increased risk for chromosomal abnormality.

**A list of pooled likelihood ratio of various aneuploidy markers has been given in the**

| SOFT MARKER | Pooled Likelihood Ratio |
|---|---|
| HYPOPLASTIC NASAL BONE | 6.5 |
| ARSA | 3.9 |
| VENTRICULOMEGALY | 3.8 |
| INCREASED NUCHAL FOLD | 3.8 |
| ECHOGENIC BOWEL | 1.6 |
| MILD HYDRONEPHROSIS | 1.1 |
| INTRACARDIAC ECHOGENIC FOCUS | 0.9 |
| SHORT LONG BONES | 0.6 |

Figure 12: Pooled likelihood ratios of aneuploidy markers

**table. For eg., Pooled LR of ventriculomegaly is 3.8. This means, a fetus with ventriculomegaly on scan is 3.8 times more likely to have Down syndrome than a fetus without ventriculomegaly.**

**A simple free calculator of LR and risks is available at http://onlinelibrary.wiley.com/doi/10.1002/uog.12364/suppinfo**

Likelihood Ratios which have been assigned to the markers are used in conjunction to improve their accuracy in predicting risks for aneuploidies. This is then combined with the second trimester serum screening in the certified software, and combined risks are given.

The combination of serum biochemistry and genetic sonogram with a scoring system (in the second trimester) gives a detection rate of about 80% ,which makes it the next best option after combined first trimester screening.

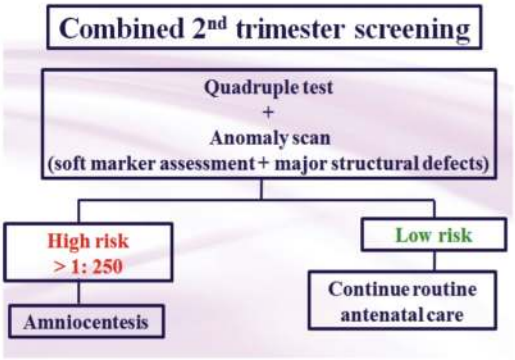


Figure 13: Algorithm for prenatal 4 aneuploidy screening: 2nd trimester

The presence of soft marker increases the likelihood of aneuploidy.

As the number of soft markers increases in a fetus, the likelihood ratio for aneuploidy increases.

| | Trisomy-21 | Normal | Likelihood Ratio (LR) |
|---|---|---|---|
| No markers | 31% | 87% | 0.4 |
| One marker | 23% | 11% | 2 |
| Two markers | 15% | 2% | 10 |
| > Two markers | 15% | 0.1% | 115 |

Figure 14 : Likelihood ratio of increasing number of aneuploidy markers

It is essential that risks from first trimester screening test and the 2nd trimester screening test are interpreted in combination and not separately as a separate interpretation of the two results is associated with a significantly higher overall false positive results and difficulty in counselling using two separate risk estimates.

Following is a composite algorithm which can be used for aneuploidy screening in pregnancy-

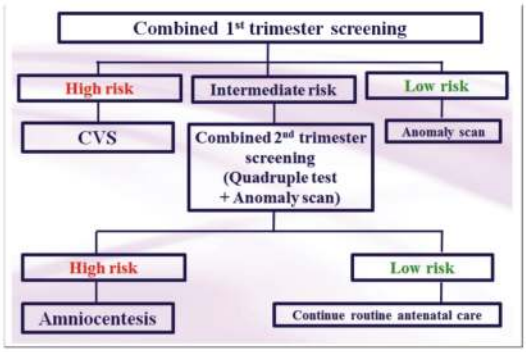


Figure 15: Composite algorithm for aneuploidy screening

It is of utmost importance that the referring obstetrician makes sure that the laboratory doing maternal biochemistry and prenatal genetic tests is certified by an authentic body such as Fetal Medicine Foundation. More importantly, a certified

fetal medicine specialist should perform the detailed prenatal ultrasounds, and accredited software should be used for generation of aneuploidy risks.

## How is aneuploidy screening different in ART pregnancies than spontaneous conceptions?

Although all pregnancies are 'precious', pregnancies conceived via assisted reproductive technologies (ART) are specifically considered 'precious' because of related difficulty in conception and increased pregnancy complications. The implications of first trimester screening are different in ART pregnancies as compared to the spontaneous conceptions. Following may be few influencing factors –

- It can be hypothesized that women carrying pregnancies conceived via ART would be less likely to proceed to a diagnostic test because of the 'precious' nature of these pregnancies and the risk of miscarriage associated with an invasive procedure. Therefore, it is of utmost importance that women conceived with ART undergo an effective non-invasive first trimester screening with a very low false positive rate, as the false positive rate translates into invasive testing (Chorionic Villous Sampling/ Amniocentesis).
- The median age in women with ART conceptions is higher than that in a population of spontaneously conceived women. This also increases the anxiety among women and obstetricians, of being at an increased risk for chromosomal abnormalities due to a higher maternal age. But it is important to note that advanced maternal age per se is not an indication for CVS or amniocentesis. Infact, the combined first trimester screening (NT scan + Double Marker) performs better in the advanced maternal age group as compared to the younger women.
- Determination of a correct gestational age is an important pre-requisite for interpretation of first trimester screening. The exact day of conception is known in pregnancies conceived after in-vitro fertilization (IVF), but whether the early growth and development of the fetus and/or placenta in these pregnancies differ from those in spontaneously conceived pregnancies is unknown.
- ART pregnancies being 'precious', there is a tendency of early withdrawal of blood sample for double marker. This remains a bias and may result in differences between the median values of double marker between ART and spontaneously conceived pregnancies.
- The higher incidence of twin/higher order pregnancies further complicates the interpretation of prenatal testing in women with ART pregnancies. ART increases the chances of dichorionic diamniotic pregnancies, due to the possibility of more than one embryo being implanted after embryo transfer. Because the overall incidence of twining in increased after ART, monochorionic twin pregnancies are also more commonly found in women conceived with ART.
- Rarely, the sample for double marker may be withdrawn immediately after the woman receives hCG injection (as a part of luteal support in some ART

Units). This can give a high value of free $^{2}$-hCG and a false positive double marker for Down syndrome, and trigger off a panic, may even lead to unnecessary invasive testing. Avoid hCG injections 2-3 days prior to giving the double marker test.

- Vanishing twin prior to double marker may cause confusion in interpretation of the combined first trimester screening. Doing a double marker should be avoided when there has been a recent vanishing twin/ if the fetal tissue of the vanishing twin is still visible. A detailed 12 week scan would suffice, and doing double marker may elicit false positive results.
- Although it is technically more difficult to perform selective embryo reduction at 12 weeks than at 7-9 weeks, it has an advantage of being able to differentiate the chromosomally normal fetus from the abnormal one before reduction. Also, when the first trimester screening ultrasound is performed before reduction, the fetus is big enough to diagnose major structural abnormalities, which may be missed if reduced at an earlier gestation (7-9 weeks). Hence, to optimize the results of 'selective' embryo reduction, it is very important to carefully select a structurally and chromosomally normal embryo before the reduction.
- More number of ART conceived women are now availing the benefit of NIPT (non invasive prenatal testing). Women conceived by ART are more likely to be elderly, and hence are more likely to get false positive risks for aneuploidies. The uptake of invasive tests in this grow up of women is low; as the conception has been long awaited and a difficult one, after ART. NIPT is a safe and accurate screening tool for such anxious women, and it avoids invasive testing.

### *Non-invasive Prenatal Testing for Chromosomal Abnormality using cell free fetal DNA in maternal plasma – Practical considerations in India*

Fetal genetic testing and aneuploidy diagnosis have until recently both needed invasive diagnostic sampling procedures carrying a small but significant risk of miscarriage. Over the last decade, the presence of cell-free fetal DNA (cffDNA) in the maternal circulation, and its utilization for aneuploidy screening has been widely studied. Fetal DNA comes from the placenta,2 can be detected from the first trimester of pregnancy onwards and is rapidly cleared from the maternal circulation after delivery. Maternal blood is therefore a reliable source of material for prenatal diagnosis.

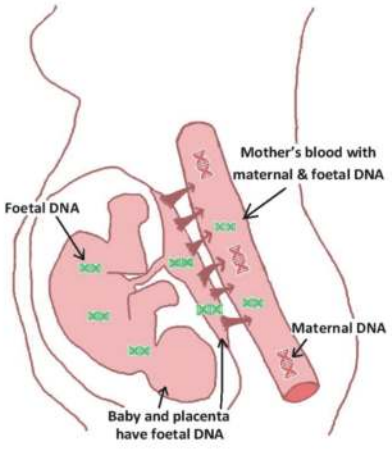


Figure 16: Cell free fetal DNA (cfDNA) in maternal blood

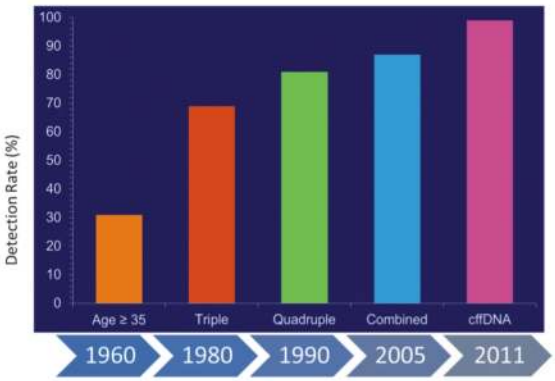


Figure 17: Improving trend of aneuploidy detection rates over the years

In 1999, it was shown that pregnancies with Down syndrome fetuses had higher absolute concentrations of fetal DNA in maternal plasma and, since then, a number of methods have been described for measuring fetal chromosome dosage using maternal plasma.

***Non Invasive Prenatal Testing (NIPT): What we need to know***

- Most accurate screening test for Trisomy 21, Trisomy 18 and Trisomy 13
- Not a diagnostic test
- The test is safe and does not pose any risk to mother or baby (done on 15 ml maternal blood)
- Currently only offered through specialist centres at a cost to the patient
- The gold standard for confirmation of aneuploidy is invasive testing - CVS or amniocentesis
- NIPT cannot replace ultrasound/ conventional modes of screening. It is an adjunct and can be utilized complimentary to conventional screening methods, to reduce the invasive testing rate.

***Management decisions, including termination of the pregnancy, should not be based on the results of the NIPT alone.***

***NIPT is a screening test and 'predicted to be affected' (high risk on NIPT) results should be confirmed by invasive testing.***

*At what gestation can NIPT be performed?*

NIPT can be performed from 9 weeks onwards, till advanced gestation. With the Indian law not allowing termination after 20 weeks even for an affected Down syndrome fetus, NIPT should be done as early as feasible in the particular patient scenario.

*What does NIPT test for?*

As of now, in India, NIPT tests for Down syndrome, Trisomy 13 and Trisomy 18. Microdeletions have also started being detected by few Indian genetic labs.

*How good is NIPT?*

NIPT is not a diagnostic test, but it is undoubtedly the most accurate screening test available. The test identifies more than 99% of fetuses with trisomy 21, 98% of fetuses with trisomy 18, and 80% of fetuses with trisomy 13. Performance of NIPT for detection of trisomy 13 and 18 is not as good as that for trisomy 21, but fortunately trisomy 13 and 18 are more obvious and easily detectable on ultrasound screening than trisomy 21 (which shows relatively subtle markers on ultrasound).

After the test, the number of women required to have a CVS or an amniocentesis is less than 1%.

*To whom should NIPT be offered?*

The 2012 ACOG Committee Opinion on Noninvasive Prenatal Testing for Fetal

Aneuploidy cautioned that the use of cfDNA testing should be an active, informed choice and not part of routine prenatal laboratory testing. Indian obstetricians and fetal medicine specialists have been sending NIPT samples since last 2 years, and the numbers are ever increasing.

The indications for NIPT are –

- Maternal age of 35 years or older at delivery
- Fetal ultrasonography findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive test results for aneuploidy, including first trimester or integrated screen or quadruple screen
- ? previous pregnancies with high/ intermediate risks (ART conceptions, h/o RPL etc)

*Turnaround time for NIPT results*

The results of NIPT are available in 10-14 working days.

Rarely, a resampling may be required, if the fetal fraction was low in the previous sample.

*When not to do NIPT?*

- As a primary routine screening test in low risk population
- Fetal structural defect on ultrasound (karyotyping recommended)
- Suspicion of problems other than Downs
- Multiple pregnancy, Vanishing twins
- Co-existing single gene defect (not diagnosable by NIPT)

*PCPNDT and NIPT*

As for karyotype, NIPT can also detect the sex of the fetus. But the genetic labs in India, which are certified for NIPT testing, do NOT disclose the fetal sex. Also, these certified genetic labs should have taken permission for the local authorities and PCPNDT officials for performing the test. Hence, it is important for clinicians to send samples to an authentic lab. Appropriate referral form, and documentation is a pre-requisite as for any prenatal testing in India.

According to statistics by Indian National Family Health Survey 3, 63% of urban women and 36% of rural women receive any kind of antenatal care. Out of a total of 43% Indian women who receive antenatal care, only 56% avail first trimester care. Statistics look scary, but are true, necessitating a basic national antenatal care health programme.

*Although addressing basic antenatal care is the need of the hour, India awaits an era when trying to establish a National Down Syndrome Screening Programme is no more a distant dream.*

## Key points

- Prenatal aneuploidy screening – 'Screening for all' should be the dictum, irrespective of maternal age
- Follow informed, non-directive genetic counselling. Offer all options, guide the decisions, but leave the decision making to the expecting couple

- First trimester nuchal translucency should be interpreted for risk assessment only when measured by sonographers or sonologists trained and accredited for this service and when there is ongoing quality assurance
- Aneuploidy markers on 1st trimester scan are nuchal translucency, nasal bone, tricuspid regurgitation and Ductus Venosus.
- Quadruple screening is recommended over triple test for second-trimester serum screening
- Abnormal maternal serum biochemistry (double/triple/quadruple marker analytes) in a chromosomally normal fetus serve as surrogate markers and predictors for adverse obstetric outcomes
- Women who have had a low risk on combined 1st trimester screening (double marker + NT, NB, DV, TR) do not need to undergo quadruple/triple test.
- Anomaly scan is recommended irrespective of the 1st trimester risks.
- Interpretation of soft markers on anomaly scan becomes easier with use of likelihood rations, and counselling is also simplified, aiding decision making.
- NIPT, when ordered for indicated women, decreases rate of invasive testing.
- NIPT is not a diagnostic test, and it is nor a replacement for any mode of screening. In India, its uptake continues to be secondary and as an adjunct to the conventional screening methods.

## Down trivia!

- Hitler murdered an estimated 200,000 people with intellectual and developmental disabilities, a large number being people with Down syndrome.
- Down syndrome affected people were a key target in the eugenics movement in the United States - which influenced Hitler's first mass murders under the Aktion-T4 program in 1939
- Down used the term mongoloid, "mongoloid" (also "mongol" or "mongoloid idiot") continued to be used until the early 1970s, it is now considered pejorative and inaccurate and is no longer in common use
- There still are doctors who categorize feeding a baby with Down syndrome as a "lifesaving procedure" and proceed to starve babies to death
- In 1983, the average life expectancy of a child with Down syndrome was 25 years, now it is 60.
- 97% of people with Down syndrome like who they are, versus 63% of us!

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# SCREENING GUIDELINES FOR HAEMOGLOBINOPATHIES IN ANTENATAL CARE

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Hemoglobinopathies are inherited disorders of haemoglobin structure or synthesis that may lead to severe transfusion dependent anemia usually starting in infancy. These include alpha and beta-thalassemias as well as structural abnormalities in Hb which include HbS, HbC, and HbE. Although great advancement has occurred in the management of these otherwise burdensome disorders, they remain a major cause of morbidity and concern to our Indian society at large. The purpose of prenatal hemoglobinopathy screening is to identify and counsel asymptomatic individuals who may be at risk of an inherited hemoglobinopathy in their offsprings.

## Aims :

1. To identify and screen women and their partners at risk for haemoglobinopathies.
2. To offer genetic counseling to women and their partners who test positive for carrier status for thalassaemia or sickle cell disease.
3. Provide referral for women to the Maternal Fetal Medicine for specialised multidisciplinary obstetric management when there is a confirmed haemoglobinopathy which carries risk for the woman or fetus.

## Background Information

Haemoglobinopathies are autosomal recessive disorders which imply that they must be inherited through both parents who may have the disorder themselves, or be carriers. Haemoglobin contains a haem molecule that combines with four globin chains; two of which are alpha and two are beta chains.[1] The World Health Organisation estimates that approximately 5% of the world's population are carriers for haemoglobinopathies.[2]

The haemoglobinopathies can be categorised into two general types: the thalassemias (which are disorders of decreased globin chain production) and the hemoglobin structural variants (eg, hemoglobin S, hemoglobin C and E); a combination of the two is also possible.

## Prevalence

*Gene Frequency* - Thalassemia and Sickle cell disease are among the most common genetic diseases worldwide. Over 1 percent of couples are at risk for having an affected newborn. (3) The incidence of hemoglobinopathy varies worldwide and may be underreported in resource-limited countries where technologically sophisticated diagnostic laboratory tests are not available.

*Thalassemia* - Thalassemias occur in higher frequency in the Mediterranean area, the Middle East, Southeast Asia, Africa, and the Indian subcontinent. The prevalence of β-thalassemia carriers in the Indian population is 3-4%.[4] Some ethnic groups like Sindhis, Kutchis, Lohanas, Punjabis, few Muslim groups as well as few tribal populations have a higher prevalence (5-17%).[5,6] Extensive screening programs and prenatal diagnosis have resulted in a consistent decline in the birth of infants with beta-thalassemia in Mediterranean at-risk populations.[7] This article will be focussing on beta-thalassemia and not alpha-thalassemia as alpha-thalassemia is not seen as a major health hazard in our country, as most of the carriers are -/+, -/+ on each allele, and thus not likely to give rise to the more severe Hb Bart (complete absence of alpha chain or -/-,-/-) or HbFH (-/+,-/-) conditions.

Hemoglobin S, C, E — The structural hemoglobin variants S and C are most common in tropical Africa.[3] Hb S is prevalent in the central belt in India, mostly in tribal population with frequency varying from 5 to 40%. Hemoglobin E is found most commonly in Southeast Asia. It is estimated that 30 million Southeast Asians are carriers for hemoglobin E and one million have homozygous EE disease. In India, Hb E is very frequent in the North-East and the prevalence of carriers varies between 3% and 64%. Hb D Punjab is mainly seen in the North-Western region with a prevalence of 3-4%. [4]

## Identifying At-risk Parents

*Candidates for screening* - As beta – thalassemia is the most common single gene disorder in India, with high prevalence of carriers, a universal screening is required to detect more hemoglobinopathy carriers than selective screening based on race and ethnicity. (8) Carrier screening will help in detecting couples who would be at risk of having children with major thalassemia or hemoglobinopathy.

*Timing* - If not performed before pregnancy, hemoglobinopathy screening is most useful when performed early in pregnancy so that prenatal diagnosis, if indicated and desired, can be performed when couples have the option of terminating the pregnancy.

*Laboratory* - Laboratory testing is the cornerstone of prenatal screening for hemoglobinopathy

## Screening for thalassemia

i) Red Cell Indices: A complete blood count (CBC) with red blood cell indices is a common initial screening test for thalassemia. A mean corpuscular volume (MCV) <80 femtoliters (fL) in the absence of iron deficiency suggests alpha or beta thalassemia minor and further testing with hemoglobin analysis is indicated to establish a diagnosis. [8]

ii) HPLC / Hb Electrophoresis/ Isoelectric focussing (for Hb types): Pregnant woman's hemoglobin analysis can be performed either by high-performance liquid chromatography (HPLC) or isoelectric focusing (IEF) to identify abnormal hemoglobins associated with thalassemia (eg, hemoglobin F, hemoglobin A2, hemoglobin H). In case of beta – thalassemia carrier or trait or minor, an elevated HbA2 level ( >3.5 - 4 %) is considered a gold standard.

iii) NESTROFT : If no other facilities are available, Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT) can be used for preliminary screening for β-thalassemia carriers. However, since iron deficiency anemia is common in our population, many individuals who are screened would give a false positive result.

## Screening for sickle cell trait

Prenatal screening for sickle cell trait is performed with HPLC or IEF; hemoglobin electrophoresis is acceptable if these tests are not available. Sickle cell trait (rather than sickle cell disease) is established by finding both hemoglobin A and hemoglobin S, with the amount of hemoglobin A greater than hemoglobin S. These tests will also detect hemoglobin C and E carriers.

Once the pregnant lady is detected to be a carrier, as a next step, the husband should be evaluated for carrier status assesses fetal risk. In cases of advanced pregnancy (beyond first trimester), both husband and wife should be screened simultaneously to save time.

Pregnant women should be screened in all antenatal clinics irrespective of the gestational age. The women in the second trimester should also be screened as knowing the carrier status will help in controlling these disorders in subsequent pregnancies if required.[4] Husbands of carrier women with the following Hb abnormalities need to be screened:

- β thalassemia trait
- δβ thalassemia trait
- Hb S trait
- Hb E trait
- Hb D trait
- Hb Lepore trait
- Hb D–β thalassemia
- Hb $Q^{India}$- β thalassemia.

Prenatal diagnosis should be advised if the fetus is at risk for the following conditions:

- β thalassemia major
- δβ thalassemia major
- β–δβ thalassemia
- Hb S–β thalassemia
- Hb E–β thalassemia
- Sickle cell anemia

- Hb SD disease
- Hb Lepore–β thalassemia
- Hb SE disease.

Screening of antenatal women even later in pregnancy helps to identify couples at risk who could get their babies' blood checked at birth and opt for prenatal diagnosis in subsequent pregnancies.

## Prenatal Diagnosis

All hemoglobinopathies are inherited as autosomal recessive disorders, thus there is a 25% risk of having an offspring with the disorder in case couples who are both carriers (whether it is beta-thalassemia or HbS/C or E or combination of these), and this risk holds true for each pregnancy for the couple. It is estimated that 50 to 70 percent of couples with sickle cell trait or thalassemia minor who have received genetic counseling would request prenatal testing.[9], [10]

The process of prenatal diagnosis involves firstly a procedure to take fetal sample, followed by laboratory test which detects the genetic status of the fetus. For prenatal diagnostic procedure, chorionic villous sampling (CVS) is the most preferred technique, offered at or after 10-11 weeks of gestation. This can be performed either per abdomen or per vaginal depending upon the expertise of the fetal medicine specialist. In the second trimester, a placental biopsy would be preferred (if position of fetus is conducive) over amniocentesis because of the better availability of fetal DNA in a placental biopsy as compared to DNA extracted from amniocytes which would be far less. Beyond 18 weeks of gestation, depending on facilities and expertise available, a fetal cord blood sampling would be the procedure of choice to access fetal sample. The advantage of fetal cord blood is that a direct HPLC can be done in fetal blood to look for peak of HbA (adult Hb) to detect whether fetus would be likely to be affected with beta-thalassaemia or other hemoglobinopathy. This haematological method is however not 100% accurate and requires to be followed up by DNA based mutation studies for confirmation.

*Non-invasive testing* - Methods for noninvasive prenatal diagnosis of hemoglobinopathy are being developed, but remain investigational.

## Molecular genetic Analysis and prenatal diagnosis of b-thalassemia

Prenatal diagnosis is performed on a fetal sample i.e. DNA extracted either from CVS or amniotic cells or fetal cord blood, using molecular methods to provide the most accurate diagnosis. Mutation or 'disease –causing variation' in the beta-globin gene can be situated in any part of the gene. However, in India, five common mutations accounted for 85% of mutations while rare mutations and variants like HbE, HbD and HbS accounted for 10%. The common mutations observed are IVS1-5 G->C, IVS1-1 G->T, frameshift 8/9 +G, frame-shift 41/42 -CTTT and 619bp deletion, along with low frequency of rare mutations codon 16 -C, cap site +1 A->C, codon 15 G->A, -88 C->T, codon 30 G->A, codon 30 G->C, codon 5 –CT and frameshift 47/48 +ATCT. About five percent of chromosomes were uncharacterized and need to be sequenced

for molecular delineation.

*Methodology :* After DNA is extracted from fetal sample, it is subjected to either a PCR specific for the mutation identified in the couple at risk, or sequencing by Sanger method to identify mutation. The results are provided in terms of whether fetus is carrying none, one or two mutations according to which the thalassemia status is deduced. In case the fetus is detected to be carrying both mutations (i.e. maternal as well as paternal mutation), then it is termed as 'affected' with beta-thalassemia major. In case fetus is detected to carry no mutation or one mutation, then the fetus is termed unaffected or 'carrier'. In such situations, it is important to rule out a maternal contamination to avoid errors in testing. The results are followed by genetic counseling of the couple to explain the consequences. An option of termination of pregnancy is provided to couple in cases where an affected fetus is detected on prenatal diagnosis, as a preventive measure to avoid the burden of the disease on the family.

Over 3500 prenatal diagnoses of beta thalassemia and other hemoglobinopathies have been performed since 1997 at Sir Ganga Ram hospital. The trend in earlier years was of families with an affected proband desiring PND. However, in the last 10 years this has considerably changed with majority of PND being offered to couples who have had no family history and who have been identified as carriers by antenatal screening. Hopefully this trend would eventually reduce the burden of this dreaded yet common disease in India, and lead to its control.

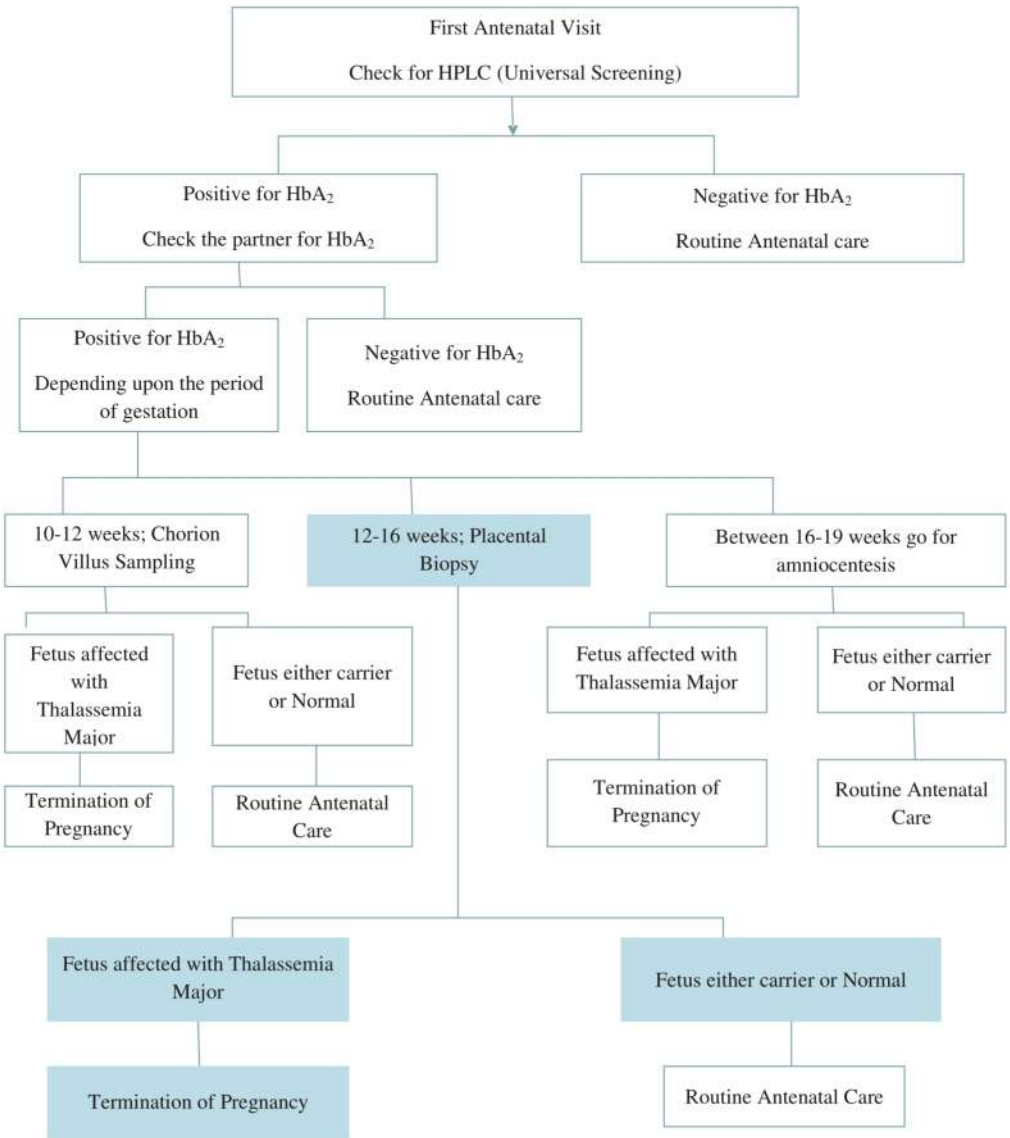
*Prior to implantation* - Some couples may prefer preimplantation genetic diagnosis because at-risk embryos can be identified before embryo transfer, thereby avoiding the need to consider termination of an affected pregnancy. However, this procedure can only be performed in conjunction with in vitro fertilization (IVF), which is a major disadvantage in couples who do not require IVF for treatment of subfertility.

## Summary and Recommendations

- Hemoglobinopathies are divided into disorders of decreased globin chain production (thalassemia) and hemoglobin structural variants (S, C, and E being most common).
- The purpose of preconceptional counseling and prenatal hemoglobinopathy screening is to identify couples whose future offspring or current pregnancy is at high risk of an inherited hemoglobinopathy. All pregnant women should be screened. After identification of couples at risk for having an offspring with an inherited hemoglobinopathy, prenatal diagnosis is offered to determine whether the fetus is affected.
- The purpose of prenatal diagnosis is to allow couples to make reproductive choices based on this information and, in the case of alpha-thalassemia major, to monitor the pregnancy for nonimmune hydrops fetalis and potentially intervene. The clinical sequelae of other hemoglobinopathies manifest later in life and have no adverse effects on the fetus, mother, or neonate.
- If prenatal screening by history or laboratory findings suggests an increased risk of hemoglobinopathy, hemoglobin analysis by HPLC is

indicated to establish a diagnosis.

- DNA-based testing for fetal hemoglobinopathies can be performed during the first trimester of pregnancy on cells obtained by chorionic villus sampling (typically performed at 10 to 12 weeks of gestation) or on cultured amniotic fluid cells obtained by amniocentesis (typically performed after 16 weeks of gestation), if the couple desires.
- If prenatal diagnosis results in diagnosis of fetal hemoglobinopathy, couples should be thoroughly counseled by a hematologist or expert in the management of hemoglobinopathies about the natural history of the specific disorder, how it may affect their child, and treatment approaches, as well as their reproductive options.



- A workflow chart is provided for guidance for screening and diagnosis of hemoglobinopathy in pregnancy.

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# DILEMMAS IN NEWER DRUGS IN OBSTETRICS

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Pregnancy places increased demands on the mother to provide adequate nutrition to the growing conceptus. A number of micronutrients function as essential cofactors for or themselves acting as antioxidants. Insufficient supplies of essential vitamins and micronutrients can lead to a state of biological competition between the mother and conceptus, which can be detrimental to the health status of both.Thus certain drugs are currently used in obstetric practices to improve the maternal and fetal outcomes but whether it is an evidence based practice or not is a question that need to be answered.

## L Arginine

L arginine forms the substrate to produce nitric oxide. The increased NO levels lead to increase in vasodilatation of the arterioles & increased blood supply to the placenta and improved fetal outcome. It also helps in reducing oxidative stress. Various claims are made about the increase in volumes of amniotic fluid in cases of oligohydramnios. One thing has been noted that in cases of Oligohydramnios, it keeps the volume of liquor to be static & does not let it reduce drastically in a very short time.The dosage is three grams per day & has been given safely without any compliance issues in most of the cases. (J mat Fetal Neonatal Med 2007, Aug.), (Int J Reprod Contrac Obst Gynecol 2013.) & (Archives of Perinatal Medicine 2007). The use of l-arginine in pre-eclampsia and intrauterine growth restriction can be seen only as one more intervention in the prevention/management of these conditions. Several existing confounding factors in the treatment of these conditions like the use of antihypertensives, antioxidants, nutrients, diet etc. may make it impossible to ascertain the extent of the role l-arginine may play in the mitigation if any, of these conditions. As is noted in several reviews more sustained studies would be required in well selected cases to reach conclusions as to the role of l-arginine in the prevention/management of pre-eclampsia and intrauterine growth restriction. It would be incorrect therefore at this point in time to view l-arginine as panacea for the prevention and management of pre-eclampsia and intrauterine growth restriction. J Obstet Gynaecol India. 2012 Feb; 62(1): 1–2

## Sildenafil citrate

When given in the dose of 25 mg thrice a day it helps improve fetal growth in women with severe early onset IUGR. (BJOG 2011). It augments vasodilatatory effects of nitric oxide by preventing the degradation of cGMP. It also has a selective effect on the uteroplacentalcirculation. It can reduce the placental bed vascular resistance & has been proved on Doppler studies & ultimately improves the fetoplacental perfusion in pregnancies complicated by pregnancies. (JResp Med Sciences July 2012& JCEM, July, 2013 JSildenafil, as a vasodilator has emerged as a potential management option in the treatment of Intra Uterine Growth Retardation (IUGR) and preeclampsia by later normalization in velocimetric profile. (J ReprodInfertil. 2014 Jul-Sep; 15(3): 168–169).

Sildenafil Citrate Therapy for Oligohydramnios (U.S. National Institutes of Health 2015 ongoing expected to complete in Feb2016)The aim of this randomized trial is to detect whether or not the use of Sildenafil citrate therapy will increase the amniotic fluid volume expressed in term of amniotic fluid index measured via ultrasound for fetuses of pregnancies complicated by oligohydramnios, and to compare the outcomes of Sildenafil-treated pregnancies with similar pregnancies that will remain Sildenafil-naïve. Thus the use of sildenafil in growth retardation is still questionable, if at all used it will be off label use in such conditions.

## Lycopene and other Antioxidants

There is imbalance between lipid peroxidation and antioxidant defenses leading on to endothelial dysfunction and free radical mediated endothelial cell injury in pre-eclampsia . There is some evidence that protective antioxidant systems are deficient in pre-eclampsia as lower placental tissue and maternal serum carot- enoid levels such as b-carotene, lycopene, and canthaxanthin have been observed in pre-eclampsia However, Several studies could not find any evidence of low vitamin E concentration and lycopene in pre-eclamptic patients. Am J ObstetGynecol 1996;175(4):1024 – 1028., Lancet (1999) The available evidence reviews does not support the use of antioxidants during pregnancy for the prevention of preeclampsia and other outcomes. (Scientific World Journal. 2012). Several randomized controlled trials that had compared antioxidants (vitamin C and/or E, selenium, lycopene or red palm oil) with no antioxidants or placebo and reported on clinical outcomes, namely pre-eclampsia, hypertension, preterm delivery, small-for-gestational age, perinatal mortality, birth weight and gestational age at birth.

The main results suggest that the risk of pre-eclampsia is not reduced when antioxidants are administered during pregnancy. Many pre-specified subgroup analyses are presented in the review according to women's risk status, trial quality, gestational age at entry, and dose level. All subgroup analyses are consistent with the main analysis, which further suggest that antioxidants are not beneficial for the prevention of pre-eclampsia and other unfavorable pregnancy outcomes. At the present time large randomized controlled trials on the prevention of pre-eclampsia with antioxidants are recruiting or are in the analysis phase.

Rumbold A, Duley L, Crowther CA, Haslam RR. Antioxidants for preventing pre-eclampsia. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004227; DOI: 10.1002/1465185

## Vaccination in Pregnancy

*.Influenzay.*

The vaccination for prevention of influenza during pregnancy & avoiding its complications on the maternal & child health is well established now. The safety of influenza vaccine is now well established. It can be given safely during any trimester of pregnancy but very safely administered during second and third trimesters of pregnancy. The most recently available vaccine is a third generation (SUBUNIT Vaccine).It has protection rates upto (96.55 to 96.66%) & has the least adverse effects. It comes in a prefilled syringe as a clear, colourless liquid & is to be stored at 2 to 8 degree temp. Adult dose is 0.5ml intramuscular or deep SC as a single dose to be repeated every year. The child from 6 months till 35 months will need a dose of 0.25 ml & has to be repeated after one month if the vaccination has happened for the first time. Vaccination is not indicated in less than six months of age. 1 The organizations like CDC, WHO, AAP, FOGSI, IAP, ACIP, NIH, ACOG etc have endorsed the use of influenza vaccine

## Progesterones current status

Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with a history of unexplained recurrent miscarriages. (Funded by the United Kingdom National Institute of Health Research; PROMISE Current Controlled Trials number) N Engl J Med 2015;373:2141-8.

Oral Progestogens result in statistically significant reduction in threatened miscarriages. (Cochrane database 2011). Clinical diagnosis of threatened miscarriages, there is now data from meta-analysis of several studies suggest that the progestogens is better than placebo or no therapy inreducing the rate of spontaneous miscarriages (European Progestin club guidelines 2015)

In a 2012 practice bulletin, the American College of Obstetricians and Gynecologists (ACOG) recommends that women with a prior spontaneous preterm birth should be offered progesterone supplementation (ie, weekly 17-alpha-hydroxyprogesterone caproate), starting at 16-24 weeks' gestation and continuing up to 36 weeks' gestation,

Cerclage, vaginal progesterone, or pessary are equally efficacious in the prevention of preterm birth in women with a short cervix detected on sonogrphy at the midtrimester in singleton gestation (Evidence level II). J Hum Reprod Sci. 2014 Jul-Sep; 7(3): 159–169..

# RH NEGATIVE IN PREGNANT MOTHER-MANAGEMENT UPDATE

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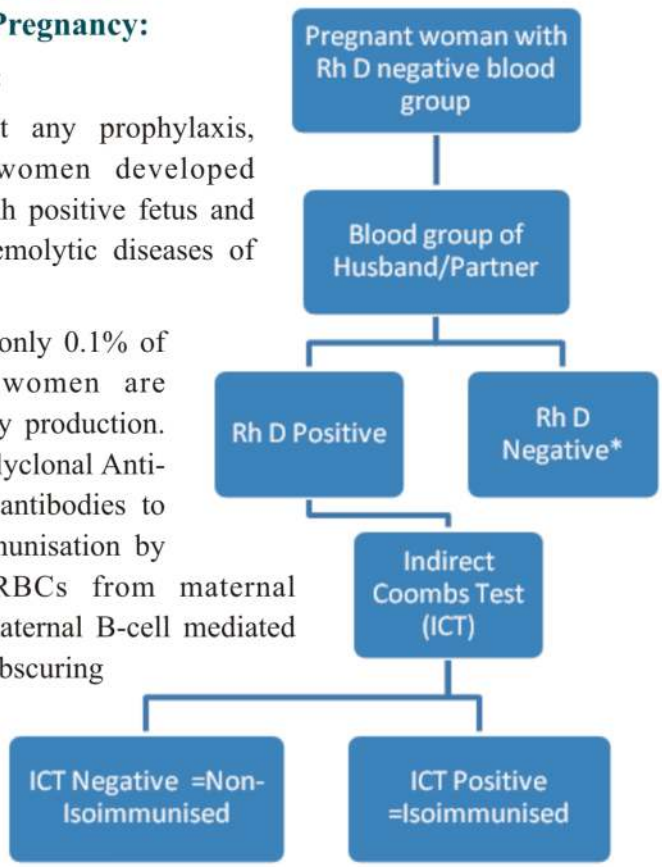
## Introduction :

Apart from ABO blood group, RhD blood group positive or negative signifying the presence (+) or absence (-) of the Rh D antigen; on the surface of the red blood cell. The prevalence of Rh negative blood group in different populations varies ranging from 1% in Native Americans to 30% in Spanish Basque. In India, it has been reported to be 3-5%.

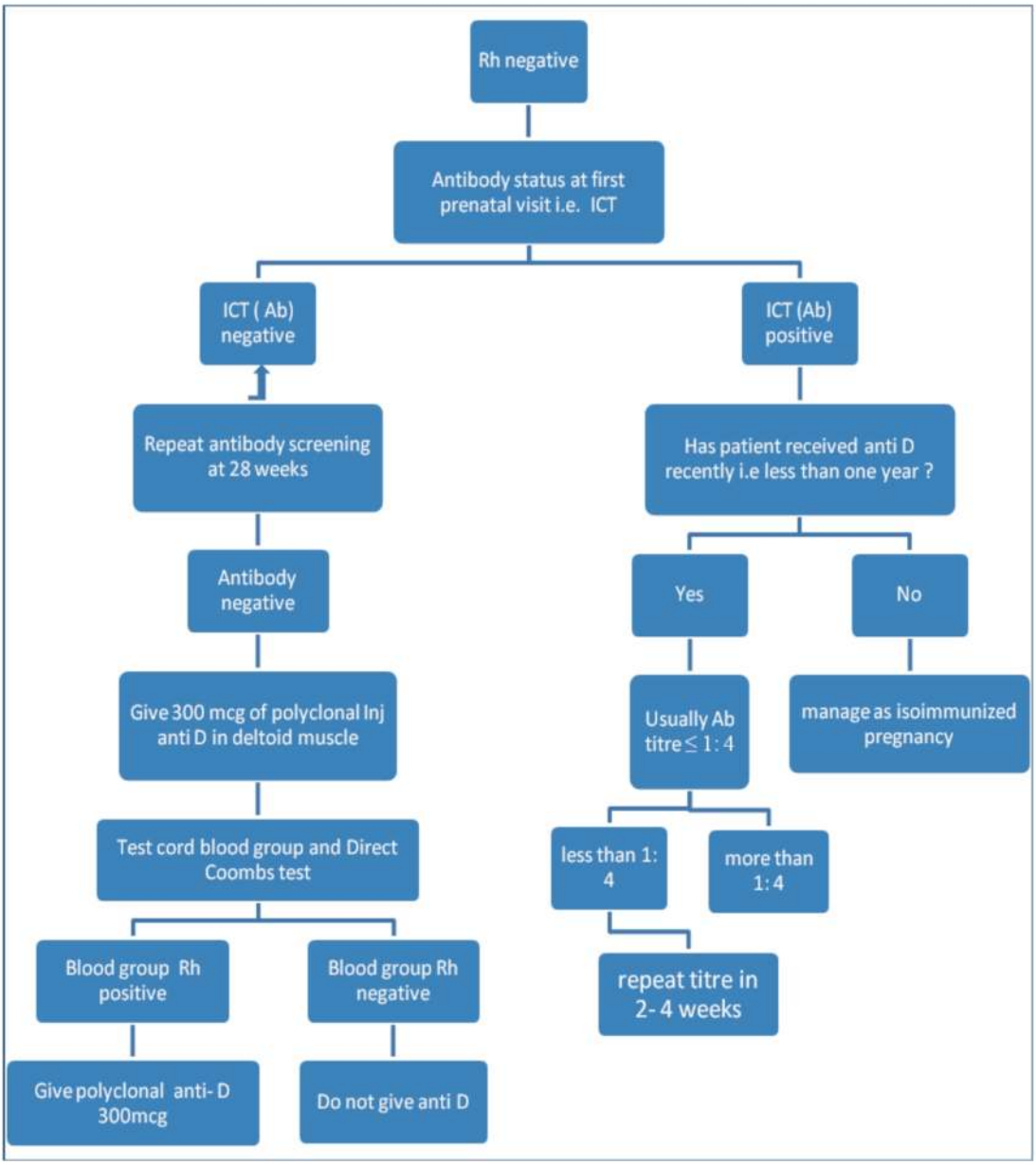
## Management of Rh Negative Pregnancy:

**Summary :**

- Without any prophylaxis, 17% women developed antibodies following delivery of Rh positive fetus and 10% of them are affected by haemolytic diseases of fetus or newborn.
- With use of preventive measures, only 0.1% of pregnancies in Rh negative women are complicated by anti-Rh D antibody production. Preventive measure is by use of polyclonal Anti-D i.e. pooled sterile human IgG antibodies to RhD antigens. It prevents alloimmunisation by clearing RhD positive fetal RBCs from maternal circulation, down-regulating the maternal B-cell mediated immune response and possibly obscuring antigen sites on fetal RBCs.
- The standard dose of polyclonal Anti-D is 300 µg IM given in the deltoid muscle (not to be given in the buttock) and that can neutralise 30ml of fetal Rh positive RBCs. Additional dosing of Anti-D especially in multiple pregnancy, severe abruption

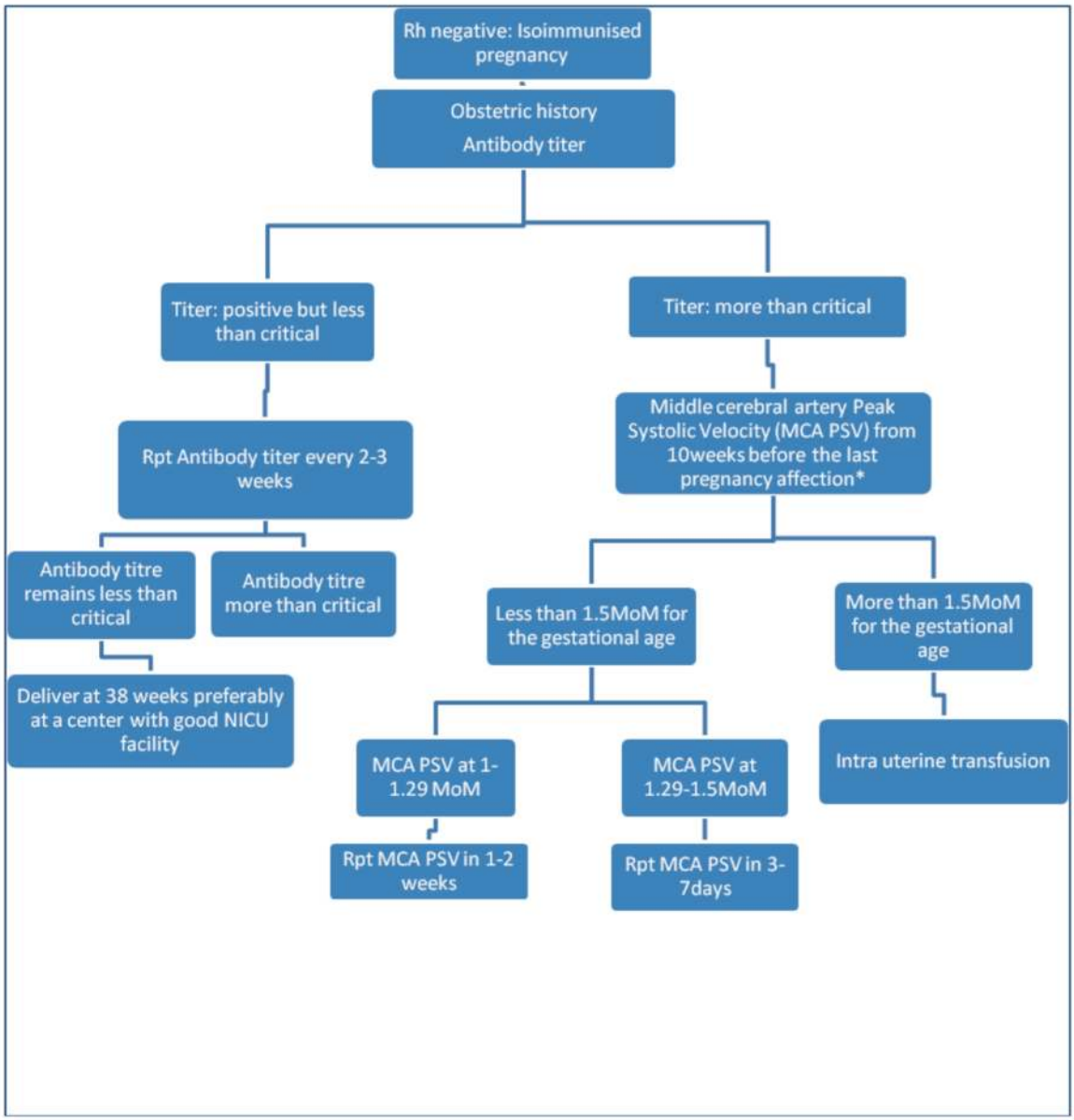



*Risk of isoimmunisation needs to be ket in mind due to previous blood or blood products transfusion, uncertain paternity, previous pregnancy termination, Grandma syndrome. Hence, ICT should be done at first antenatal visit even if husband's blood group is Rh D Negative.




placentae leading to fetal death is guided by quantification of feto maternal hemorrhage (FMH) with Kleihauer-Betke test.

- Most societies world over recommend giving Anti-D at 28 weeks and again postpartum after neonatal Rh positive status is confirmed. Smaller dose of 50µg IM is recommended for first trimester event. If not available, then giving 300µg which is safer than not giving anything.
- The half life of Anti-D is 24 days but can be detected in maternal circulation for upto 12 weeks and




maximum upto one year. Indirect Coombs test (ICT) done within one year of receiving Anti-D may indicate presence of antibody in low titer and should not be interpreted as alloimmunisation.

# HEPATITIS B – MANAGEMENT IN PREGNANCY

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## Introduction

The World Health Organization (WHO) estimates that approximately one-third of the world population is infected with Hepatitis B Virus (HBV) with serological evidence of past or present infection with HBV. Of these 2 billion people, more than 350 million suffer from chronic HBV infection. Approximately 15–40% of patients infected with HBV develop life-threatening liver consequences (including cirrhosis, liver failure and hepatocellular carcinoma) resulting in 600,000 to 1.2 million deaths per year.[1-4]

The risk for acute to chronic progression is highest among individuals with perinatally acquired HBV infection. Approximately 10% of adults and more than 90% of infants that are infected will go on to develop chronic disease.[5]

## Pathophysiology

Hepatitis B disease is caused by HBV, an enveloped virus containing a partially double-stranded, circular DNA genome.[6,7] HBV interferes with the functions of the liver while replicating in hepatocytes. The HBV DNA encodes for[8]

- HBV polymerase
- Hepatitis B nucleocapsid core antigen (HBcAg),
- Pre-core protein cleaved in the endoplasmic reticulum of the infected cell and secreted as hepatitis B e antigen (HBeAg)
- Large, middle, and small surface antigens (HBsAg)

## Transmission

*Perinatal transmission* from the mother to her newborn baby is the most important

mode of infection, particularly in areas with a high prevalence of disease and lack of identification of infected women. HBV does not cross the placenta because of its size, and usually does not infect the fetus unless there have been breaks in the maternal-fetal barrier. Women who are infected can transmit HBV to the infant during delivery.5

Infants born to mothers positive for hepatitis B surface antigen (HBsAg) and hepatitis B "e" antigen (HBeAg) have a 70%-90% chance of acquiring perinatal HBV infection, and 85%-90% of infected infants will become chronic HBV carriers.[9,10] The rate of transmission is approximately 10% in women with antibody to e antigen (AntiHBe).

In regions with widespread perinatal screening and adequate newborn prophylaxis, horizontal transmission secondary to percutaneous or parenteral exposure to contaminated blood products, body fluids, or sexual contact become the primary modes of transmission of HBV in the young adult population.[1] A break in the skin or mucosal barrier is required for transmission.[11]

## Effect on pregnancy

During pregnancy, viral hepatitis is associated with a lower risk of obstetric complications when compared with other potential hepatic complications, like HELLP and acute fatty liver of pregnancy. Most published data suggest possible associations between hepatitis B and gestational diabetes mellitus, antepartum hemorrhage, increased risk of prematurity and lower birth weight. There is possibility of intrapartum or postpartum haemorrhage if prothrombin time is prolonged. [12]

## Effect of pregnancy on Hepatitis B

Progression from acute to chronic carrier state is usually not influenced by pregnancy. Women with chronic infection generally do well during pregnancy. Studies have shown that although no significant difference was seen in viral levels during pregnancy, alanine aminotransferase (ALT) had a tendency to increase late in pregnancy and postpartum. The expected but sudden decrease in levels of corticosteroids during the postpartum period may result in hepatitis flares. Mothers with chronic hepatitis B should be monitored for hepatitis flare and exacerbation during the postpartum period [12]

## Clinical picture

Most infections during pregnancy are chronic and asymptomatic. Acute hepatitis may be asymptomatic in 50% women. Patient may sometimes present with fever, malaise, anorexia, nausea, abdominal discomfort and jaundice.

## Laboratory Markers

Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient is immune or

susceptible to HBV. (Table 1)

| Test | Result | Interpretation |
|---|---|---|
| HBsAg | Negative | Susceptible |
| anti-HBc | Negative | |
| anti-HBs | Negative | |
| HBsAg | negative | Immune due to natural infection |
| anti-HBc | Positive | |
| anti-HBs | Positive | |
| HBsAg | negative | Immune due to hepatitis B vaccination |
| anti-HBc | Negative | |
| anti-HBs | Positive | |
| HBsAg | positive | Acutely infected |
| Total anti-HBc | Positive | |
| IgM anti-HBc | Positive | |
| anti-HBs | Negative | |
| HBsAg | positive | Chronically infected |
| Total anti-HBc | Positive | |
| IgM anti-HBc | Negative | |
| anti-HBs | Negative | |
| HBsAg | negative | Interpretation unclear; four possibilities:<br>1. Resolved infection (most common)<br>2. False-positive anti-HBc, thus susceptible<br>3. "Low level" chronic infection<br>4. Resolving acute infection |
| anti-HBc | positive | |
| anti-HBs | negative | |

***Source :*** *Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03): 1-137.*[13]

- *Hepatitis B surface antigen (HBsAg):* can be detected in high levels in serum during acute or chronic hepatitis B virus infection. HBsAg is the antigen used to make hepatitis B vaccine. The presence of HBsAg indicates that the woman is potentially infectious.[5,7,11]
- *Hepatitis B surface antibody (anti-HBs):* indicates recovery and immunity from hepatitis B virus infection. It also develops in a person successfully vaccinated against hepatitis B.
- *Hepatitis B core antibody (anti-HBc):* Appears at the onset of symptoms in acute hepatitis B and persists for life. IgM anti-HBc appears early during the acute phase and usually disappears by 6 months; its presence indicates a recent infection. Anti-HBc IgG appears during convalescence and generally remains detectable for a lifetime.[7]
- Other antigens present during the acute phase include virions, HBV DNA (indicates viral load), HBV DNA polymerase, and HBeAg (marker of active replication). The presence of HBeAg is indicative of infectivity and disease severity.[7,11]
- HbsAg, HBeAg, and viral DNA are transiently present for about 6 months before clearing; then, they are replaced by anti-HBs and anti-HBe.

- Anti-HBe appears after anti-HBc and reflects decreased infectivity.

## Antenatal Management

- *ACOG, CDC and the US Preventive Services Task Force (USPSTF)* recommend routine prenatal screening for hepatitis B surface antigen (HBsAg) in all pregnant women—during every pregnancy—regardless of previous test results or vaccinations.[13-15]
- If not available, HBsAg status should be established at the time of admission. This will allow at-risk newborns to be appropriately immunized after birth.
- *RCOG[16] and NICE[17] Guidelines* recommend a second blood sample to confirm a hepatitis B positive result.
- Women with two screen positive results should be effectively managed by a multidisciplinary team (appropriate specialist, obstetric consultant and paediatric consultant) in the appropriate environment.
- Household members and sexual partners of HBV positive women should be tested to determine susceptibility to HBV infection and, if susceptible, should receive Hepatitis B vaccine.
- The risk of transmission to fetus associated with invasive diagnostic tests is low.

HBsAg positive pregnant women should have the following tests[17]:

- Complete blood count, Baseline liver function tests and prothrombin time
- Hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
- HBV DNA level - can be deferred until the third trimester, especially if the initial LFT results are normal or results prior to pregnancy are available.[18]
- Anti-HBc lgM
- hepatitis C virus antibody (anti-HCV), HIV, lgG-hepatitis A virus (anti-HAV)

The management of chronic hepatitis B (CHB) during pregnancy remains a challenge. Despite the standard immunoprophylaxis, a significant portion of infants born to highly viremic mothers remain infected with hepatitis B virus (HBV). Several authorities and organizations recommend HBV-targeted maternal antiviral therapy in the third trimester for the purpose of decreasing the risk of intrauterine fetal infection and adding to the effectiveness of HBIg and vaccination in women with high viral loads during pregnancy.9,14,16

- Pan CQ et. al.19 and Society for Maternal-Fetal Medicine (SMFM) 18 recommend antiviral therapy for women with a viral HBV DNA > 106 copies/mL (200,000 IU/mL), women with a previous child who failed HBIG and vaccine immunoprophylaxis, and in some cases of HBV positive women with threatened preterm labor.[19]

*Antiviral Therapy*

- Mothers with chronic hepatitis B infection are often treated in the third trimester(28-32 weeks) if the serum HBV DNA level is greater than 106 - 108 copies/mL, especially if she is positive for HBeAg.18-20
- The risks and benefits and the limited evidence for this approach should be discussed with the patient.

The most commonly used Nucleos(t)ide analogues are :

- Lamivudine *(Category C)* 100 to 150 mg orally per day
- Telbivudine *(Category B)* 600 mg orally per day
- Tenofovir *(Category B)* 300 mg orally per day

Tenofovir is the preferred antiviral by several studies because of its better resistance profile and more extensive safety data in pregnant, HBV positive women [18,20.]

Fig 1 and 2 show an algorithm for management of hepatitis B in pregnant women without and with active infection

Pregnant / Lactating women at high risk for hepatitis B infections should be specifically targeted for vaccination[14]

- Husband infected with hepatitis B, multiple sexual partners
- Household contact of people infected with hepatitis B
- I/V drug abusers

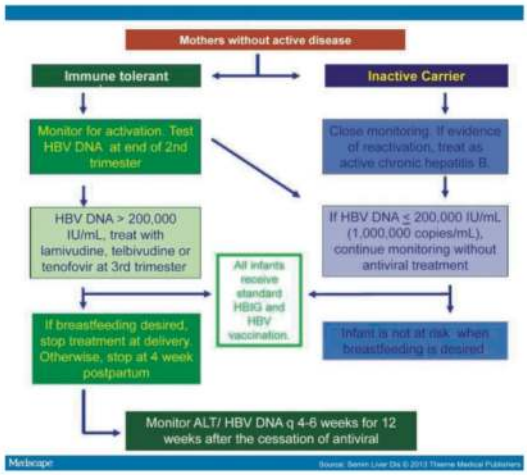


Fig. 1 : Algorithm for management of hepatitis B in pregnant women without active disease[12]

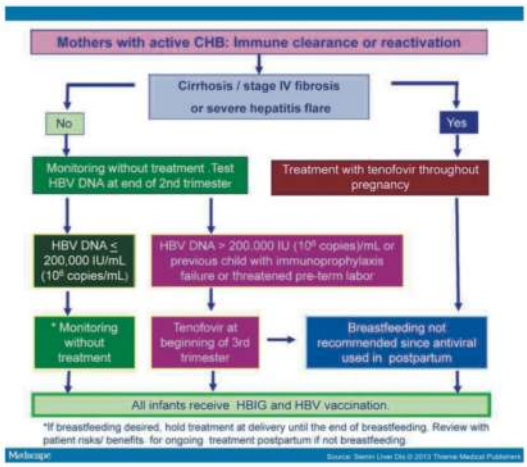


Fig. 2 : Algorithm for management of pregnant women with active chronic hepatitis B[12]

- Jobs that expose them to human blood or other body fluids
- Travel to countries where hepatitis B is common
- Chronic liver or kidney disease, kidney dialysis patients
- Diabetes, HIV infection

**Postexposure prophylaxis** of susceptible pregnant women[21]:

Management of the exposed person

depends on the HBsAg status of the source and the vaccination and anti-HBs response status of the exposed person.

*After Exposure to Persons Who Have Acute Hepatitis B*

When exposure has occurred as a result of sexual contact within 14 days, administer :

- A course of HBV vaccine IM.
- Hepatitis B immune globulin (HBIG) 0.06 mL/kg IM on contralateral side.

For prophylaxis after percutaneous or mucous membrane injury, a second dose of HBIG should be given 1 month later.

*After exposure to persons who have chronic hepatitis B*

- Active post exposure prophylaxis with hepatitis B vaccine alone.

**Hepatitis B vaccine** is a recombinant DNA type vaccine which provides protective antibody in 95% adults.1 It is given in 3 doses of 1ml in adults and 0.5ml in neonates intramuscularly at 0, 1 and 6 months.

An anti-HBs titer greater than 10 IU/L after 2-3 months is regarded as being protective.5, 11 The vaccine-induced immunity has been demonstrated to last at least 15 years, if not longer. Booster doses are not recommended.5,7,11

## Intrapartum Management

- Evidence is not conclusive to indicate that mode of delivery influences the likelihood of HBV transmission regardless of viraemia. Delivery by cesarean section for the purpose of reducing vertical transmission of HBV is not presently recommended by either the CDC9 or ACOG14
- Delivery should be managed to minimise the risk of vertical transmission, by avoiding fetal blood sampling and fetal scalp electrodes.
- Universal precautions with blood and body secretions should be implemented.

## Neonatal Management - Immunoprophylaxis

- Universal precautions related to disposal of blood / secretions should be observed.
- Infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin (HBIG) 0.5 mL intramuscularly (IM) once they are physiologically stable, preferably within 12 hours- after birth. Hepatitis B vaccine should be administered IM in three doses of 0.5 mL each. The first dose should be given concurrently with HBIG but at a different site.[9]
- Arrangements to complete the vaccination schedule need to be made when mother and baby are transferred to primary care.
- The vertical transmission rate is dramatically decreased when HBIG is given with the first dose of HBV vaccine, particularly when the mother is both HBsAg and HBeAg positive.[5,7]
- When administered within 24 hours after birth, HBIG and vaccination are 85-95% effective in preventing HBV infection and the chronic carrier state. Some studies have shown that when HBIG is unavailable or there are financial constraints, the HBV vaccine alone is 70-90% effective.[5]
- Testing the infant for HBsAg and its

antibody (anti-HBs) is recommended at 12-15 months of age to monitor the effectiveness of therapy. If HBsAg is not detectable and anti-HBs is present, the child can be considered protected.

- Testing for anti-HBc is not useful, since maternal anti-HBc can persist for more than a year. HBIG and HB vaccination do not interfere with the routine childhood immunizations.

## Breast-feeding

Breast feeding is not contraindicated in women chronically infected with hepatitis B if the infant receives HBIG and vaccine prophylaxis.[14]

*Recommendations for HBV-Infected Women Who Desire Pregnancy*[22]

| Liver Disease | Management |
|---|---|
| Advanced | Treatment before and during pregnancy; continue treatment after delivery |
| Moderate, no cirrhosis | Treatment before pregnancy; if response, stop treatment before pregnancy |
| Mild, very high viraemia | Treatment in last trimester with 'B' category drug with postpartum discontinuation |
| Mild, low viraemia | Pregnancy before treatment |

Programs to educate and coordinate the activities of those providing prenatal care, hospital- based obstetrical services, and paediatric well-baby care must be established to assure proper follow-up and treatment of infants born to HBsAg-positive mothers and other susceptible household and sexual contacts.

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# MANAGEMENT GUIDELINES IN CASE OF HIV POSITIVITY IN ANY PARTNER

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India has the third largest HIV epidemic in the world. The 2013 statistics reveal HIV prevalence in India to be approximately 0.02%. Owing to our huge population (1.2 billion) this small figure equates to approximately 2.1 million people living with HIV.[1] In the same year, an estimated 130,000 died from HIV related illness. With increasing awareness and government's strategies, There has been a gradual slowing down of India's HIV epidemic, with 19% decline in new HIV infections (130,000 in 2013) but there is still a long way to go.

## HIV testing and counselling in India

By 2014, we had nearly 15,000 health care facilities offering HCT (HIV testing and counselling). Despite of this only 13% patients of India are aware of this. The National Aids Control Organization (NACO) is the body responsible for formulating the policy and implementing programs for prevention and control of HIV in India. The current program, NACP-IV (National AIDS Control Programs-IV), 2012-2017, aims to reduce annually new HIV infections by 50% by providing comprehensive HIV treatment, education, care and support of the population.

HIV spreads via four modes-unsafe sexual practices, intravenous drug abuse, blood transfusions and MTCT (mother to child transmission). Amongst these, Prevention of Mother To Child Transmission(PMTCT)is our main aim and the Indian government is committed to eliminate new HIV infections among children by 2015. Based on 2013 WHO guidelines, the program aims to initiate anti retroviral treatment for all pregnant and breast feeding women living with HIV regardless of CD4 count or stage of HIV infection. However in 2013 only 18% received PMTCT treatment. As a result, 13,000 children were born with HIV.

The success of our government programmes will begin from 'womb to tomb'. Therefore it will require management at all levels i.e. from childhood to adolescence to reproductive age group to the entire life. Management in the reproductive age group begins from pre-conceptional counselling.

## Preconceptional counselling

All women of childbearing age should be educated regarding-

- Safer Sexual practices
- Effective and appropriate contraceptive method to reduce the likely hood of unwanted pregnancies.

- Elimination of alcohol, illicit drugs and smoking
- Above all, the couple should be counselled for HIV testing

Table 1. Depicts the panel recommendation regarding preconceptional counselling of HIV concordant and discordant couples.[2]

**Table 1.** Reproductive Options for HIV-Concordant and Serodiscordant Couples (Last updated August 6, 2015; last reviewed August 6, 2015)

| **Panel's Recommendations For Couples Who Want to Conceive** |
|---|
| *For Concordant (Both Partners are HIV-Infected) and Discordant Couples:* |
| • Expert consultation is recommended so that approaches can be tailored to couples' specific needs. |
| • Partners should be screened and treated for genital tract infections before attempting to conceive. |
| • The HIV-infected partner(s) should attain maximum viral suppression before attempting conception. |
| *For Discordant Couples:* |
| • The HIV-infected partner should be receiving combination antiretroviral therapy and demonstrate sustained suppression of plasma viral load below the limits of detection. |
| • Periconception administration of antiretroviral pre-exposure prophylaxis for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission. The utility of pre-exposure prophylaxis for the uninfected partner when the infected partner is receiving combination antiretroviral therapy with maximal viral suppression has not been studied. |
| *Discordant Couples with HIV-Infected Women :* |
| • The safest conception option is artificial insemination, including the option of self-insemination with a partner's sperm during the peri-ovulatory period. |
| *Discordant Couples with HIV-Infected Men :* |
| • The use of donor sperm from an HIV-uninfected man with artificial insemination is the safest option. |
| • When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or in vitro fertilization should be considered. |
| • Semen analysis is recommended for HIV-infected men before conception is attempted to prevent unnecessary exposure to infectious genital fluid when the likelihood of conception is low because of semen abnormalities. |

## Peri-conception pre-exposure prophylaxis (PrEP)

**PrEP** may offer an additional option to minimise the risk of transmission of HIV within discordant couples. PrEP, is the use of ARV (anti-retroviral) medications, by an HIV uninfected individuals, to prevent acquisition of HIV.

Once daily dosing of combination tenofovir and emtricitabine is currently FDA approved for use as PrEP. Pregnancy as well as breast feeding are no contraindications to it.

## National Prevention of Parent to Child Transmission (PPTCT) Programme

In accordance with WHO, the PPTCT programme aims at providing access to all pregnant women for HIV diagnostic, prevention, care and treatment services. The goal is to ensure safe delivery services within existing Reproductive& Child Health (RCH) programme.

The first and foremost important step for all pregnant women attending health services is to know their HIV status as part of the routine ante natal screening blood tests.

Following measures should be followed:

- Counselling to inform all pregnant women about routine ante-natal screening tests to be done.
- HIV counselling and testing should be offered to all pregnant women attending antenatal clinic with 'opt – out' option. However an informed consent to be taken as per guidelines.
- Pregnant Women who opt-out of HIV testing should be offered repeat counselling to explore the reasons for opting out and should be offered routine HIV testing at each subsequent clinic visit.
- Pre and post test counselling is equally important
- Disclosure of HIV status is to be done at only at stand – alone ICTC's (integrated counselling and testing centre) after confirmatory testing.
- Partner /spouse and family testing to be done as per ICTC's guidelines.

## Assessment and care of HIV Negative Pregnant Women

All women tested HIV negative, should be offered -

- Safe sex counselling
- Given couple counselling.
- Linked to family planning services.
- Counselled about the need of repeat HIV testing, considering window period if spouse is positive.
- Infant feeding and nutrition counselling also to be discussed.

## Assessment and care of HIV positive pregnant women

Initial and Follow-up Antenatal Assessment :

All HIV infected women should have routine antenatal care for the wellbeing of her baby including-

- At least four ANC check-ups,
- Routine antenatal blood screening,
- Two doses of tetanus toxoid,
- Nutritional counselling for the mother : good food, rest and exercise.
- Adherence to iron-folate and vitamin/mineral supplements.
- Screening for TB, STI's and other opportunistic infections at each visit
- Counsel for regular ante natal check-ups and institutional delivery.
- Link the couple to ART service
- Safe sex counselling and HIV testing of spouse and other living children
- Planned institutional delivery

## Criteria for ART initiation

- Initial assessment follows standard adult ART guidelines -The dictum should be "do not delay ART initiation" and it should be regardless of WHO clinical stage or CD4 cell count.[3]
- Once daily, fixed dose, combined ART(cART) to be started in all pregnant and breast feeding women

even when seen in first trimester or late in pregnancy(after 36 weeks)

## ART eligibility in pregnant women

- Initiate ART lifelong in all pregnant women with confirmed HIV infection
- It should be regardless of WHO clinical stage or CD4 cell count.
- Initiation of ART for pregnant women should not be withheld for the want of CD4 count and clinical staging.
- TDF (300mg)+ 3TC(300mg) + EFV(600mg)is recommended as first-line ART in pregnant and breastfeeding women.
- ART shall be initiated only at ART centre.

## Indication for cotrimoxazole prophylactic therapy (CPT)

Indication of CPT is when CD4 d" 250 cells/cmm. This helps in preventing opportunistic infections.

*Starting Co-trimoxazole in pregnancy*

- Co-trimoxazole should be started if CD4 count is d" 250 cells/mm3 and continued throughout pregnancy, delivery and breast feeding as per national guidelines (Dose: Double strength tablet – 1 tab daily)
- Pregnant women should take their folate supplements regularly

## Alternative First Line ART's in HIV positive pregnant women-

1. AZT (Zidovudine–NRTI) + 3TC (Lamivudine- NRTI) + EFV (Efavirenz - NNRTI)
2. AZT (Zidovudine-NRTI) + 3TC (Lamivudine–NRTI)+NVP (Nevirapine - NNRTI)
3. TDF (Tenofovir–NRTI)+3TC (Lamivudine–NRTI+NVP (Nevirapine – NNRTI )

NRTI – Nucleoside Reverse Transcriptase Inhibitor ,

NNRTI – Non – Nucleoside Reverse Transcriptase Inhibitor

## Pregnant women receiving ART prior to pregnancy :

- She must continue the regimen she is stabilized on.
- The same regimen should be followed throughout pregnancy,labour,breast feeding and lifelong.
- If the preferred regimen (TDF+3TC+ EFV) is not fully effective then these women will require – TDF+3TC+LPV/r (lopinavir/ritonavir), LPV/r being Protease Inhibitor.

## Mode of Delivery in known HIV Positive on Art

- Scheduled caesarean section at 38 weeks to minimise perinatal transmission of HIV is recommended for women with HIV RNA levels >1000 copies/ml.[4]
- In women who are already receiving combined ART and having HIV RNA d" 1000 copies/ml, caesarean section is not routinely recommended. In such women, Caesarean section should be perfomed for standard obstetrical indications at 39 weeks.
- The patient should be counselled that HIV infection may put them at higher risk of surgical complications

- When the viral load >1000 copies/ml and scheduled caesarean section is planned, then 1 hour loading dose followed by continuous intravenous Zidovudine infusion for 2 hours(total 3 hours) should be given before caesarean.
- For unscheduled caesarean in a patient with >1000 copies /ml, consideration can be given to shorten the duration between initiation of IV zidovudine administration and delivery by administering 1 hour loading dose only.
- If patient's HIV status is known late during pregnancy and ART is started late, then it is unlikely for patient to have HIV RNA copies d" 1000/ml. In such cases, scheduled caesarean delivery is likely to provide additional help in reducing MTCT and intravenous Zidovudine should be given prior to caesarean section.
- Once woman passes into labour or rupture of membranes occur (especially for over 4 hours), scheduled caesarean section may not reduce the risk of MTCT. In such cases, C.S. is performed for obstetrical indications only.[5]
- Administration of perioperative antimicrobial prophylaxis is recommended for all women to reduce infectious morbidity.

## Pregnant Women Screened HIV Positive During Labour Orimmediate Postpartum

- Initiate ART (TDF + 3TC + EFV ) immediately.[6]
- Such women should also receive intravenous Zidovudine during childbirth.
- Counsellor should visit post-natal ward the next day.But this should not delay ART initiation.
- After pre-test counselling, lab technician confirms HIV status by 3 rapid antibody tests and blood samples withdrawn for CD4 Testing.
- Samples are personally taken to the lab and reports are delivered to the patient's attendant. Along with the reports , one month treatment course of ART is also given.
- If patient has already started breast feeding, she is advised for exclusive breast feeding for 6 months.
- If patient has not started breast feeding, she must be counselled on option for breast vs replacement feeding but must adhere to either exclusive breast feeding or exclusive replacement feeding for 6 months.
- Patient should be motivated to report to ART Centre within 30 days.

## Safer Delivery Techniques

- Pregnant women on ART should continue to use their HIV medications during labour
- Universal work precautions to be followed by the medical and paramedical staff.
- Any HIV stickers NOT to be put outside or inside the file.
- Avoid repeated per vaginal examinations
- Do not rupture membranes artificially, unless there is delay in progress of labour or indication of foetal distress.

- Avoid invasive procedures like foetal blood sampling.
- Avoid instrumental delivery as much as possible.
- Avoid routine episiotomy as much as possible.
- Suctioning in new-born to be avoided unless there is meconium staining of liquor.
- Safer surgical techniques to be practised – use round tip needles, do not use fingers to hold the needle but instead forceps to be used to fish out or to handle the needle.
- During caesarean, try to keep membranes intact until head is delivered and also early cord clamping is indicated.
- Standard waste disposal management guidelines should be followed for waste disposal – specimens/waste to be doubly bagged and sent to lab following Ministry of Health policy procedure for hazardous waste.

## Post-partum Care

- Infants to be put on mothers abdomen for bonding
- Infants born to HIV mothers should receive Nevirapine (NVP) prophylaxis immediately after birth (within 1 hour of birth)
- Infants to be given exclusive breast feeding for atleast 6 months. However exclusive replacement feeding to be given if mother has died or decides not to breast feed the baby.
- Assessment and evaluation for post-partum infections.
- Not only the patient needs counselling and support, but same is required for family members.
- Offer dual contraception in the form of PP-IUD and condoms or IUCD are widely accepted.

## Care of HIV Exosed Infants

*Infants born to Women already receiving ART during pregnancy*

All infants born to HIV –positive mothers should receive a course of medication depending on ARV drug regimen that mother is taking and the infants feeding method.[7]

- If woman is exclusively BREAST-FEEDING:Infants should receive once – daily Syrup Nevirapine (NVP) from birth to six weeks in a dose of 2mg/kg/day.
- If infant on exclusive REPLACEMENT FEEDING : Infants should receive once daily NVP (or twice daily zidovudine ) from birth to 4-6weeks.
- Early infant diagnosis (EID) to be made at 6weeks of age, repeat testing at 6 months, 12 months & 6weeks after cessation of feeds.
- Pediatric ART for infants and children diagnosed as HIV positive by EID
- Co-trimoxazole prophylaxis from 6weeks
- Routine immunization
- Growth and nutrition monitoring.
- Gradual weaning after 6 months and introduction of complementary feeds from 6 months onwards along with continuation of breast feeding for at least 1 year
- Conformation of HIV status of all

babies at 18 months using all 3 antibody (rapid) testing, regardless of earlier diagnosis.[8]

## Infants born to women not on prior ART

- Infants to be started on daily Syrup Nevrapine (NVP) prophylaxis at their first contact with health services.[9]
- Daily infant NVP prophylaxis can be started even if more than 72 hours have passed since birth.
- Daily NVP to continue for at least 12 weeks and mother linked to ART SERVICES
- Do not stop NVP prophylaxis at 6 weeks as mother has not received ART for sufficient duration.
- Co-trimoxazole prophylactic therapy to be initiated at 6weeks and continued until is 18months old or longer if baby is confirmed HIV positive.
- Re-inforce Exclusive breast feeding
- Routine immunization
- Make Early Infant Diagnosis (EID)
- Conformation of HIV status of all babies at 18 months using all 3 antibody (rapid) testing.

## Family planning and birth spacing

- Inform about effective contraceptive measures to prevent unwanted pregnancies and dual protection[10]
- Importance of family planning and birth spacing
- Risk of transmission to an uninfected partner while having unprotected intercourse
- Risk of HIV transmission to infant and risks and benefit of ART
- Contraception should be dual contraception –condoms along with another method of contraception like oral contraceptives, depot medroxyprogester one acetate and IUCD's.

Therefore, it is our duty as a health provider to counsel women to have routine antenatal antenatal care, counsel her for routine HIV testing as well as encourage them to use of ICTC's and ART services. This will not only reduce the burden of HIV in India but globally as well and put brakes on this epidemic .

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# ROAD MAP TO VIRAL FEVER WITH RASH & ANIMAL BITE IN PREGNANCY

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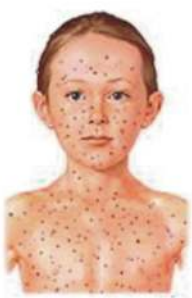
Viruses are simplest of living organisms and are an important causative factor for infectious disease. Viral infection ranges from asymptomatic and / or subclinical to overwhelming and highly lethal disease posing problem both for the mother and the fetus. Viral pathogenesis is mediated via several mechanisms. These include direct effect on infected host cell which may result in cell death via lysis or apoptosis. Infected cells can also be killed by antiviral antibody and complement or by cell mediated immune mechanisms. Host immune response to viral infection is by release of cytokines, chemokines and antibodies. Which may give rise to fever, rash, arthralgias and myalgia.

This article deals with important viral infections with rash during pregnancy.

## Chicken pox in Pregnancy



Varicella or chicken pox is caused by varicella zoster virus. It is highly contagious. It spreads by respiratory droplets or close contact.

Incubation period is about 14 days. Patients are infectious from 1 day prior to rash until lesions are crusted. Immunity is usually life long.

Infected patients classically present with a centripetal rash characterized by erythmatous macules, papules and vesicles that are highly pruritic appearing in crops. The rash spreads to extremities and is associated with fever, mylagia, arthralgias and headache. Secondary streptococcal or staphylococcal skin infection is the most common complication. Varicella pneumonia affect 20% of pregnancy. Hepatitis and encephalitis may also occur.

Following primary infection the virus remains dormant in sensory nerve root ganglia. Reactivation or latent VZV infection causes herpes zoster or shingle occurring primarily in the elderly and immunocompromised women. Shingles is characterized by rash within a segmental distribution. Pain, itching, paraestheseia can occur as a prodrome or with the appearance of the rash. Patients are infectious.

The classical congenital varicella syndrome results from a transplacental infection of the fetus in first half of pregnancy. The features of the syndrome include chorioretenitis, cerebral cortical atrophy, hydronephrosis, cutaneous and bony leg defect. In some studies congenital varicella occurred in 0.4% neonates when maternal infection occured before 13 wks. The highest risk to the fetus was 2% between 13–20 wks. Beyond 20 wks there was no evidence

of infection.

**Management of Varicella during pregnancy :** Affected pregnant women should be isolated and offered supportive care including calamine lotion, anti pruritic cream and if necessary systemic anti pruritics. Women with severe chicken pox should be hospitalized. Oral acyclovir 800 mg 5 times a day or valecyclovir 1 gm three times a day are safe in pregnancy, decrease duration of illness if instituted within 24 hours of rash and should be given to all infected women. IV acyclovir should be given to all pregnant women with severe chicken pox.

Amniocentesis has a strong negative predictive value but a poor positive predictive value in detecting fetal damage that can not be detected by non invasive method, women who develop varicella infection during pregnancy should be counseled about the risks versus benefit of amniocentesis to detect varicella DNA by PCR.

Amniocentesis should not be performed before skin lesions have completely healed. USG may detect congenital anamolies. Fetal MRI imaging may provide additional information.

Timing and mode of delivery of pregnant women with chicken pox must be individualized. General anaesthesia may exacerbate the respiratory comprise associated with varicella pneumonia. When epidural or spinal anaesthesia is undertaken in women with chicken pox a site away from cutaneous lesion should be chosen for needle placement. There is theoretical risk of transfer of infection from skin to CNS. Delivery may precipitate PPH due to thrombocytopenia or hepatitis.

If maternal varicella occurs within 5 days before and 2 days following delivery varicella zoster immunoglobulin should be given to new born to reduce the incidence of neonatal varicella. The infant should be isolated from mother until all vesicles have crusted to prevent VZV transmission. If possible, delivery should be delayed 5-7 days following onset of maternal illness to allow passive transfer of antibodies from mother to child. Neonatal VZV has 20-30% mortality. Breast feeding can be done.

Prevention is by ascertaining the VZV status prior to pregnancy in women without a clinical history of infection and offering live attenuated VZV vaccine – 2 subcutaneous doses 4-8 weeks apart. Varicella vaccination pre-pregnancy or post partum is an option that should be considered for women who are seronegative. This live vaccine is contraindicated in pregnancy and pregnancy should be deferred for 3 months following vaccination.

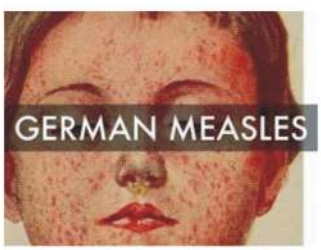
If a pregnant women without a clinical history of VZV infection or vaccination is exposed to varicella serology should be performed within 96 hours of exposure.

Most patients will be sero positive for Varicella IgG and not at risk for acute infection. If VZV susceptibility is confirmed or serology can not be obtained in a timely fashion the preferred prophylaxis is high titer Varicella zoster immune globulin intramuscular. Recommended dose is 125 units per 10 kg of body weight upto a maximum of 625 units.

VZIG is effective when given upto 10 days after contact. Non immune pregnant women who have been exposed to chicken pox should be managed as potentially infectious from 8–28 days after exposure if they receive VZIG and from 8-21 days after exposure if they do not receive VZIG. Second dose of VZIG may be required if further exposure is reported and 3 wks have elapsed since the last dose.

In the absence of VZIG, IV immune globulin can be substituted at a dose of 400 mg per kg. Prophylactic acyclovir 800 mg five times daily for 5-7 days beginning within 9 days of exposure is effective at preventing VZV infection in children with 85% reduction in infection. VZIG has no therapeutic benefit once chicken pox have developed and should not be used in pregnant women who have developed chicken pox rash.

## Rubella




Rubella is a small spherical enveloped single stranded RNA virus which spreads by droplet infection and close personal contacts. Incubation period is 12-19 days. 20-50% infection are asymptomatic and there is no associated prodromal illness.

Symptomatic infected patients present with rash, malaise, fever, conjunctivitis and generalized lymphadenopathy. The rash is non pruritic, begins on the face and neck as a faint macular erythema and spreads rapidly to trunk and extremities. The rash last approximately three days and blanches with pressure. Transient polyarthralgia or polyarthritis lasting 5-10 days may appear in adolescent and adults following the rash. Rare complications include thrombocytopenic purpura, encephalitis and neuritis.

Congenital rubella infection–80% of pregnant women with rubella infection and a rash during first 12 wks have a fetus with congenital infection. At 13-14 wks this incidence is 54% and by the end of second trimester it is 25%. As the period of gestation increases fetal infections are less likely to cause congenital infection. Congenital rubella syndrome includes one or more of the following.

*Eye defects* – Cataracts, congenital glaucoma and retinopathy.

*Heart disease* – patent ductus arteriousus and pulmonary artery stenosis.

## Sensorineural deafness

CNS defects include microcephaly, developmental delay, mental retardation, meningo encephalitis.

Purpura, hepatosplenomegaly and jaundice may be associated.

The extended rubella syndrome with progressive panencephalitis and type 1 diabetes may not develop clinically until the 2nd or 3rd decade of life.

*Diagnosis :* Enzyme linked immunoassay can detect IGM antibody which appears from 4-5 days after onset of clinical disease and can persist for 6 wks after onset of rash. Non immune persons demonstrate peak IgG antibody titers 1-2 wks after onset of rash.

Fetal infection can be confirmed by PCR or viral culture of chorionic villi, amniotic fluid or fetal blood. No treatment is available for maternal or fetal rubella

infection. Termination of pregnancy is the only available option in confirmed maternal infection in early pregnancy.

Prevention can be done by immunizing susceptible women with MMR vaccine. Pregnancy after vaccine should be avoided for one month as it contains live attenuated vaccine.

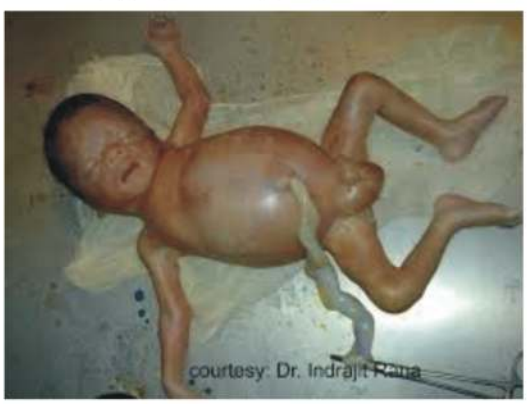
Any pregnant susceptible women should be immunized with vaccine in post partum period.

## Parvovirus

It is a small non enveloped virus containing negative stranded DNA. It preferentially invades rapidly dividing cells. It spreads by respiratory droplets, infected blood products, perinatally and hand to mouth contact.

The incubation period is 4-20 days following exposure. 65% pregnant women have evidence of prior infection and are immune.

*Clinical manifestation* – 20% women are asymptomatic. Most common presentation is facial rash consistent with a slapped cheek appearance and a lace like rash on trunk and extremities. This rash may be accompanied by fever, malaise, lymphadenopathy.




The fetus may be asymptomatic or may suffer from aplastic anaemia, high output congestive cardiac failure and non immune hydrops.

Diagnosis is by ELISA testing. PCR is a more sensitive method.

*Management* – The presence of IgG antibody is consistent with prior exposure / infection and further workup is needed. Susceptible women should be retested in three wks.

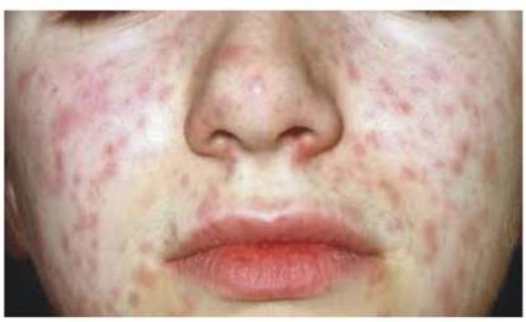
Pregnant women with confirmed infection should be followed up with serial USG for 8-10 wks after maternal illness. 19% of fetuses are severely affected if the gestational age is less than 12 wks and the 15% if the gestational age is between 13-20 wks.

Measurement of fetal middle cerebral artery peak systolic velocity can be useful in documenting fetal anaemia prior to development of hydrops.

Fetal mortality is 11% when maternal B 19 infection occurs during first 20 wks of pregnancy. Cordocentesis and intra uterine transfusion are recommended when fetal hydrops is present.

## Measles :

Measles or rubeolla is an enveloped negative stranded RNA virus. It is one of the most infectious viruses and spreads



primarily via respiratory droplets. With exposure 75-90% of susceptible contact become infected. The incubation period is 10-14 days.

Infected individuals first manifest prodromal symptoms which may includes myalgia, fever, malaise and headache. These are followed by photophobia and conjunctivitis. Koplis spots – white spots on a red base on the buccal mucosa lateral to molar teeth are pathognomic. The rash of measles appears between 2-7 days following to prodrome and is initially present behind the ears or face as blotchy erythema. The rash then spreads to the trunk followed by extremities. The hands and feet may be spared. The rash is initially macular and blanches with pressure, but becomes papular and coalescent with a red, non blanching component. The rash tends to fade after 5 days. Fever is accompanied with lymphadenopathy. Complications include laryngitis, bronchiolitis, pneumonia and otitis media. There is high rate of maternal morbidity and mortality therefore secondary bacterial infection should be treated promptly. There is 20-60% increased risk of spontaneous abortion, preterm delivery, IUGR, oligohydramnios and microcephaly.

Diagnosis : Clinical features and kopliks spots are pathognomic. An increase in antibody titer may be detected on 1st or 2nd day of rash. Assays for detection of IGM and viral RNA are also available.

The most effective way to prevent measles infection in pregnancy is to vaccinate prior to pregnancy. This live attenuated vaccine should not be given to pregnant women and women are recommended to use effective contraception for three months post vaccination. Any pregnant woman exposed to measles should have an IgG titer drawn. Sero negative woman should be treated with 0.25 ml/kg of immune globulin within 6 days of exposure. Neonates delivered to women who develop measles within 7-10 days after delivery should receive intra muscular immune globulin at a dose of 0.25 mg/kg. These children should receive MMR vaccine at 12-15 months of age. Infected women should receive supportive care and close observation.

## Animal bite in Pregnancy :

Rabies has plagued man since ancient times and is believed to be as old as our civilization. It is perhaps the most gruesome and dreadful of all human communicable diseases and continues to persist as a major public health problem.

Rabies is an acute viral disease which causes encephalomyelitis in virtually all the warm blooded animals including man. The causative agent is found in wild and some domestic animals, and is transmitted to other animals and to humans through close contact with their saliva (i.e. bites, scratches, licks on broken skin mucous membranes). In urban areas, the disease is mainly transmitted by dogs, being responsible for about 95% of animal bite cases.

Fortunately, animal bites, if managed appropriately and timely the disease is preventable to a large extent. In this regard the post exposure treatment of animal bite cases is of prime importance.

## Post – Exposure Treatment

Because of long incubation period, which is typical of most cases of human rabies, it is possible to institute prophylactic post exposure treatment. This must be started at

the earliest to ensure that the individual will be protected before the rabies virus reaches the Central Nervous System.

In rabies endemic country like India where every animal bite is potentially suspected as a rabid animal bite, the treatment should be started immediately. To bring out uniformity globally, the WHO recommended classification of animal bite fore post-exposure treatment should be followed (Table – 1).

**Table - 1 :** WHO Guide for post-exposure treatment against rabies

| Category - Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for observation | Recommended treatment |
|---|---|
| 1. Touching or feeding of animals Licks on intact skin | None, if reliable case history is available |
| 2. Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin | Administer vaccine immediately. Stop treatment if animal remains healthy throughout an observation period of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques |
| 3. Single or multiple transdermal bites or scratches Coniamination of mucous membrane with saliva (i.e. licks) | Administer rabies immunoglobulin and vaccine immediately Stop treatment if animal remains healthy throughout an observation period' of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques. |

A) Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies treatment
B) If an apparently healthy dog or cat in or from a low-risk area is placed under observation, the situation may warrant delaying initiation of treatment
C) This observation period applies only to dogs and cats. Except in the case of threatened or 'endangered species, other domestic and wild animals suspected as rabid should be killed humanely and their tissues examined using appropriate laboratory techniques

***Source :*** Guidelines for post-exposure treatment in 8th Report of the WHO Expert Committee on Rabies, WHO Technical report Series 824, 1992

Although unvaccinated animals are more likely to transmit rabies, vaccinated animals can also do so if the vaccination of the biting animal was ineffective for any reason. The risk of dog being infected with rabies is greatly reduced when it appears healthy and there is confirmed history of vaccination with minimum of two immunizations with potent rabies vaccine in last two years.

The post-exposure treatment comprises of :

- Management of wound
- Passive immunization
- Active immunization

## Management of animal bite wound

*Wound Toilet :* Since the rabies virus enters the human body through a bite or scratch, it

is imperative to remove as much saliva, and thereby the virus, from the wound as is possible by an efficient wound toilet that should not involve additional trauma. Since the rabies virus can persist and even multiply at the site of bite for a long time, wound toilet must be performed even if the patient reports late.

This can be done by prompt and gentle thorough washing with soap or detergent and flushing the wound with running water for 10 minutes.

Suturing of wound should be avoided as far as possible. If unavoidable, minimum loose sutures should be applied after adequate local treatment along with proper infiltration of anti rabies serum.

Cauterization of wound is no longer recommended as it leaves a very bad scar, and does not confer any additional advantage over washing the wound with water and soap. Inj. tetanus toxoid should be given to the unimmunized individual. To prevent sepsis in the wound, a suitable course of an antibiotic may be recommended.

## Application of antiseptic

After thorough washing and drying of the wound, any antiseptic should be applied: Savlon (in appropriate recommended dilution), Dettol (in appropriate recommended dilution), povidone iodine, alcohol etc.

## Local infiltration of rabies immunoglobulin

In Category III bites, rabies immunoglobulin should be infiltrated in the depth and around the wound to inactivate the locally present virus.

## Passive Immunization by rabies Immunoglobulin

*Antirabies serum/ERIG :* The antirabies serum provides passive immunity in the form of ready-made antirabies antibody to tide over the initial phase of the infection. Antirabies serum (ARS) has the property of binding with the rabies virus, thereby resulting in the loss of infectivity of the virus. A purified version of this antirabies serum called as equine rabies immunoglobulins (ERIG) is also now available.

*Human Rabies Immunoglobulin (HRIG) :* HRIG is free from the side effects encountered in a serum of heterologous origin, and because of its longer half life, is given in half the dose of equine antirabies serum. The antirabies sera should always be brought to room temperature (20-25°C) before use.

*Dose of rabies Immunoglobulin :* The dose of equine anti rabies serum is 40 i.u. per kg body weight of patient and is given after testing of sensitivity, upto a maximum of 3000 i.u. The ARS produced in India contains 300 i.u, per ml. The dose of the human rabies immunoglobulins (HRIG) is 20 i.u. per kg body weigh! (maximum 1500 i.u.). HRIG does not require any prior sensitivity testing. HRIG preparation is available in concentration of 150 i.u. per ml.

*Tolerance and side effects :* With HRIG, there may be transient tenderness at the injection site and a brief rise in body temperature which do not require any treatment. Skin reactions are extremely rare. Sensitivity testing is mandatory before giving ERIG. Skin test may be performed as

per the manufacturers instructions given in the product insert.

The total recommended dose of immunoglobulin must not be exceeded as it may reduce the efficacy of the vaccine. If the calculated dose of immunoglobulin is insufficient to cover infiltration in all wounds, sterile saline can be used to dilute 2 or 3 fold to permit thorough infiltration.

If immunoglobulin was not administered when vaccination was begun, it can be administered upto the seventh day after the administration of the first dose of vaccine. Beyond the seventh day, Rabies Immunoglobulin (RIG) is not indicated since an antibody response to anti rabies vaccine is presumed to have occurred.

Immunoglobulin should never be administered in the same syringe or at the same anatomical site as vaccine.

## Tissue Culture Vaccines (TCVs)

There has been a growing use of Tissue Culture Vaccines (TCVs) in India. Three type of vaccines that are currently available are :

- Human diploid cell strain vaccine (HDCV)
- Purifed chick embryo cell vaccine (PCEC)
- Purified Vero cell vaccine (PVRV)

As recommended by the WHO Expert Committee on Rabies (1992), the course for postexposure prophylaxis should consist of five injections (Day 0, 3, 7, 14 and 28). The sixth injection (D90) should be considered as optional, but should be considered for those individuals who are immunologically deficient, and are at the extremes of age and on steroid therapy. Day 0 indicates day of first injection.

The dose of the vaccine per injection is 1 ml for HDCV and PCEC vaccines and 0.5 ml for PVRV irrespective of age and weight of vaccine. The dose of PVRV produced by Pasteur Institute of India, Coonoor is 1 ml per injection.

*Indications :* All cases of animal bites, irrespective of severity of exposure, require the same number of injections and dose per injection. The Category III requires administration of rabies immunoglobulins as discussed earlier. The general indications remain same as discussed under neural tissue vaccines.

*Site of inoculation :* The deltoid region is ideal for the inoculation of these vaccines. Gluteal region is not recommended because the fat present in this region retards the absorption of antigen and hence impairs the generation of optimal immune response.

*Storage and transportation :* Though tissue culture vaccines are marketed in freeze dried (lyophilized) form which is more tolerant of vagaries of temperature, yet it is recommended that these vaccines should be kept and transported at a temperature range of +2°C to +8°C. Freezing does not damage the vaccine but there are chances of breakage of ampoule containing the diluent.

*Reconstitution and storage :* The lyophilised vaccine should be reconstituted with the diluent provided with the vaccine immediately prior to use. However, in case of unforeseen delay it should not be used after 6-8 hours of reconstitution.

*Protective level of antirabies antibody :* Humoral antibodies are believed to play important role in protection against rabies and a titre of 0.5 i.u./ml or more in serum is considered as protective.

*Adverse effects with tissue culture vaccines :* The tissue culture vaccines are widely accepted as the least reactogenic rabies vaccines available today. Various studies have now shown that adverse effects can be either general in nature or allergic in origin. The general adverse reactions include sore arm, headache, malaise, nausea, fever and localised oedema at the site of injection. Symptomatic treatment may be needed.

Switch over from one vaccine to the other Shifting from one brand of TCV to other brand also should nol be encouraged as literature supports that good immunity is best achieved with same brand.

## Post exposure therapy for previously vaccinated persons

If re-exposed, persons who have previously received full post-exposure treatment with a potent cell-culture vaccine should be given only two booster doses, intramuscularly on days 0 and 3, but no rabies immunoglobulin.

## Managing exposure following pre-exposure prophylaxis with TCV

If after recommended pre-exposure prophylaxis, a vaccinated person is exposed to rabies, a proper wound toileting should be done and two !M doses of Tissue Culture Vaccine be given on days 0 and 3. Treatment with RIG is not necessary.

Pre-exposure prophylaxis may be offered to high risk groups like laboratory staff handling the virus and infected material, clinicians and para-medicals attending to hydrophobia cases, veterinarians, animal handlers and catchers, wildlife wardens, quarantine officers and travellers from rabies free areas to rabies endemic areas. Pre-exposure immunization should be three full IM doses of TCV given on day 0, 7 and 28 or 0, 28 and 56 followed by booster at one year and then a booster every three years.

Laboratory staff and others at high continuing risk of exposure should have their neutralizing antibody titres checked every 6 months. If it is less than 0.5 i.u./ml a booster dose of vaccine should be given. Such individuals on getting exposed to rabies virus after successful pre-exposure immunization require only two booster injections of vaccine given on days 0 and 3 without any anti rabies serum.

## Management of animal bite exposure in pregnant women and lactating mothers

Pregnancy and lactation are no contraindications for rabies vaccination Post-exposure prophylaxis against rabies takes preference over any other consideration since it is a life saving procedure. Moreover, rabies vaccine does not have any adverse effect on fetus, mother-to-be and the course of pregnancy. Hence complete post-exposure treatment should be given depending on the category of the exposure.

# QUIZ ON PRECONCEPTINAL & ANTENATAL CARE

**Dr. Abha Rani Sinha**
Associate professor OB/GY Patna Medical College
Chairperson Quiz Committee FOGSI (2015-2017)
Vice President, Patna OB/GY society (2015-2016)
Joint Organising Secretary, AICOG 2014
Master Trainer, FOGSI-EMOC
UG & PG examiner
Published articles in State and National journals
Contributed Chapters in FOGSI Publications

**Dr. Sneh Kiran**
Junior Resident
Department of Obst & Gynae
Patna Medical College

## Preconceptional Care

1) In diabetic women, what should be the targeted prepregnancy HbA1c level?
2) In renal transplant patient, when the patient can safely conceive and at what serum creatinine value?
3) After rubella vaccination, patients should avoid pregnancy upto how many weeks?
4) What counselling is done in women with marfan syndrome planning for pregnancy?

## Confirmation of pregnancy

5) How many days after ovulation a sensitive test can detect HCG in maternal serum or urine?
   a) 4-5 days b) 8-9 days c) 14-15 days d) 21 days
6) When is the peak level of HCG detected in the serum?
   a) 20-30 days b) 40-45 days c) 60-70 days d) 100-110 days
7) HCG plateau is reached at?
   a) 12 weeks b) 16 weeks c) 20 weeks d) 24 weeks
8) The sandwich type immunoassay can detect HCG at the level of?
   a) 1 miu/ml b) 10 miu/ml c) 100 miu/ml d) 1000miu/ml

## Ultrasonography in Pregnancy

9) What confirms the certainty of an intrauterine pregnancy in early weeks?
10) Difference between gestational sac and pseudo gestational sac?
11) At which CRL value 1st trimester screening for aneuploidy is carried out?
12) Indicators of early intrauterine pregnancy?

## Vaccinations in pregnancy

13) MMR vaccine is contraindicated during pregnancy. True/False

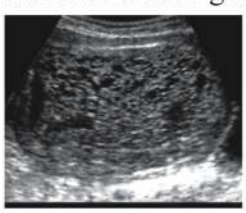
14) Influenza vaccine should be offered regardless of gestational age. True/False

15) Tdap vaccine should be given during each pregnancy optimally between 27-36 weeks. True/False

16) Influenza vaccine is contraindicated during pregnancy. True/False

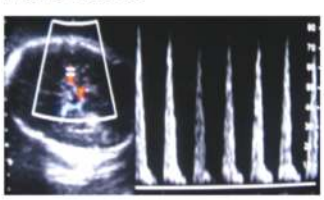
## Clinical Scenario

17) Mrs Rekha Devi, 20 yrs, G3P2+0, both full term vaginally delivered, came to ANC clinic with 12 weeks pregnancy and complain of nausea & severe vomiting. Her BHCG level is 2, 99,000 miu/ml. following is her USG report



a) What is your diagnosis?
b) How will you manage this case?

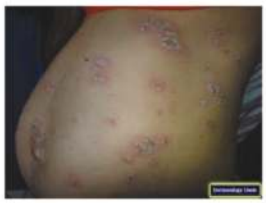
18) Mrs R, 23 yrs, G1, 20 wks, on routine checkup, Rh –ve, Husband A +ve, ICT+ve, Titres 1:8, no prior abortion or antenatal bleed. At 36 wks when the Rh Ab titre reached 1:32, and middle cerebral artery PSV showing following wave forms-



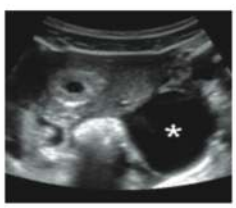
What is the reason for sensitisation in first pregnancy?

## How will you manage this case?

19) Sunita Devi, 29 yrs, G1, came to ANC clinic with 36 weeks pregnancy & multiple skin lesions. Diagnose the condition?



20) Rekha Devi, 30 yrs, came to ANC clinic with 2 months amenorrhoea & pain abdomen since last night. Her blood investigations was done, which was within normal limits. Her USG report is attached below-




Diagnose the condition?

## Recommendations

***Mcq- mark the correct answer***

21) According to ACOG 2013, what amount of caffeine intake doesn't appear to be associated with miscarriage or preterm birth?
a) 150 mg/day
b) 275 mg/day
c) 350 mg/day
d) 450 mg/day

22) According to ACOG 2013, pregnant women can fly safely upto?
a) 28 wks
b) 32wks
c) 34 wks
d) 36 wks

23) According to IADPSG 2011, threshold value for diagnosis of overt diabetes?
   a) 5.7%
   b) 6.5%
   c) 7.0%
   d) 9.2%

24) According to ACOG 2012, daily elemental iron supplementation in pregnant women?
   a) 12 mg
   b) 21 mg
   c) 27 mg
   d) 36 mg

## Miscellaneous

25) Name conditions in which maternal perception of fetal movements are reduced?

26) What is Barker Hypothesis?

27) By what percent in Trisomy 21, serum AFP levels are reduced ?

28) Cell free fetal DNA is released by which cells and detected at how many weeks of gestation?


1) Less than 6.1%, (NICE 2008)
2) After 1 year, serum creatinine- <1.5( fernando arias 24th edition , page 305)
3) After 4 weeks (CDC 2014)
4) 50% inheritance risk to the fetus irrespective of the gender of the affected parent. (Ian Donald's 7th edition, page 181)
5) B
6) C
7) B
8) A

   William's 24th edition, page no 169-170

9) V isualisation of a yolk sac- a brightly echogenic ring with an anechoic centre, seen by middle of 5th week. (William's 24th edition, page no-170)
10) Normal G-sac- implants eccentrally in the endometrium. Pseudosac – implants in the midline of the endometrial cavity.
11) 45-84 mm (Fernando arias 24th edition , page 2)
12) Intradecidual sign - anaehoeic centre surrounded by single echogenic ring. Double decidual sign - Two echogenic ring surrounded the gestational sac (William's 24th edition, page no-170)
13) False
14) True
15) True
16) False

   William's 24th edition, page no 184-186

17) H. Mole, suction evacuation
18) Undiagnosed or concealed abortion, unrecognized sensitizing event earlier in pregnancy, Mismatched blood or platelet transfusion, Grandmother Theory. Advice betamethsone, and elective LSCS done at 36 wks
19) Herpes gestinosis
20) Early intrauterine pregnancy with ovarian cyst
21) A (William's 24th edition, page no 187)
22) D (William's 24th edition, page no 183)
23) B (Fernando arias 4th edition, page 256)
24) C (William's 24th edition, page no 179)
25) a) Fetal sleep b) fetal anomaly c)anterior placenta d)hydramnios, e)obesity f)narcotics g) chronic hypoxia h) smoking
26) Concept of fetal programming by which adult morbidity and mortality are related to fetal health(William's 24th edition, page no 178)
27) 25% (FERNANDO ARIAS 4th edition, page 5)
28) Apoptotic placental trophoblast & detect after 7 weeks (William's 24th edition, page no-279)

# FIGO INITIATIVE ON GESTATIONAL DIABETES

**Dr. Hema Divakar**
Sr. Consultant Obs & Gyn
Divakar Hospital, Bangalore

## *FIGO recommends that hyperglycemia/ Gestational Diabetes Mellitus (GDM) be considered a global health priority*

Hyperglycemia is one of the **most common medical conditions women encounter during pregnancy**

**1 in 6** live births occur to women with some form of hyperglycemia

**84%** *of which are due to GDM*

### HYPERGLYCEMIA/GDM IS ASSOCIATED WITH:

- Leading causes of **maternal mortality**
- Higher incidence of **maternal morbidity**
- Higher incidence of **perinatal and neonatal morbidity**
- **Later long term consequences** for both mother and child

GDM IS ON THE RISE GLOBALLY

### Low and middle income countries account for:

**85%** of the annual **global deliveries**

**80%** of the **global diabetes** burden

**90%** of all **cases of maternal and perinatal deaths** and **poor pregnancy outcomes**

### PREGNANCY OFFERS A WINDOW OF OPPORTUNITY TO:

- **4 Establish** services
- **4 Improve** health
- **4 Prevent** intergenerational transmission of non-communicable diseases

**TO WORK TOWARDS ACHIEVING SUSTAINABLE DEVELOPMENT GOAL (SDG) 3**

Given the link between hyperglycemia in pregnancy, poor pregnancy outcome, and future risk of diabetes in both mother and offspring, a focus on **prevention**, **screening, early diagnosis** and **managing hyperglycemia** in pregnancy is needed globally

FIGO
INTERNATIONAL FEDERATION OF GYNECOLOGY & OBSTETRICS

# *FIGO recommends universal testing—all pregnant women should be tested for hyperglycemia during pregnancy using a one-step procedure*

## WHY TEST DURING PREGNANCY?

- **Maternal and newborn outcomes** depend on maternal glycemic control
- Testing is the **only route to diagnosis** and management
- Testing only women with 'risk factors' will **miss half of the women** with GDM
- Accounting for long term benefits and outcomes show that universal testing is **cost effective**

## SUCCESSFUL DIAGNOSIS

Diagnosis is best using lab results of **VENOUS PLASMA SAMPLES** but using a plasma calibrated **HAND HELD GLUCOMETER** is also acceptable

Use **WHO** diagnosis criteria

Pragmatic guides for **testing**, **diagnosis** and **management** must be based on each country's available:

- **Finances**
- **Human Resources**
- **Infrastructure Resources**

All countries have an obligation to implement the best testing and management practices they can!

**PRIORITY COUNTRIES:**
India, China, Nigeria, Pakistan, Indonesia, Bangladesh, Brazil and Mexico

These **8 countries** account for **55% of global live births** and **55% of the global burden of diabetes**

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INTERNATIONAL FEDERATION OF GYNAECOLOGY & OBSTETRICS

## *FIGO recommends that all countries provide the best GDM management possible given available resources*

### Aims:

- **ANTENATAL CARE** with a GDM trained healthcare provider
- Frequent **FOLLOW UP**
- **SELF-MONITORING BLOOD GLUCOSE** for all pregnant women with diabetes

### LIFESTYLE MANAGEMENT

**Nutrition counselling** and **physical activity** are KEY to reduce risk of future obesity, type 2 diabetes, and cardiovascular diseases

### PHARMACOLOGICAL MANAGEMENT

If lifestyle modification alone fails to achieve glucose control, **metformin**, **glyburide**, or **insulin** are safe and effective treatment options

**Fetal sonographic assessment** can help determine size of the baby and diagnose fetal macrosomia (the most frequent complication of GDM)

**Baby well-being** should be assessed through a simple **fetal kick count** technique or when resources are available through **biophysical profile** including cardiotocography

**Pregnancy** with good glycemic control and appropriate size fetus **can continue** until **40-41 *weeks***

**Elective cesarean delivery** may be recommended if fetal weight exceeds **4000 *grams***

Post-delivery the newborn must be **carefully observed** for respiratory distress and hypoglycemia

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# *FIGO recommends using the postpartum period for increased engagement to improve health for mother and child*

## POSTPARTUM AIMS

- Early **DETECTION** of infections
- **SUPPORT** of breastfeeding
- **ADVICE** on pregnancy spacing
- **RETEST** all women with GDM at 6-12 weeks postpartum
- Future blood glucose **TESTS**

The postpartum period is an important platform to **initiate early preventive health** for both the mother and the child who are both at higher risk of:

- **Future Obesity**
- **Metabolic Syndrome**
- **Diabetes**
- **Hypertension**
- **Cardiovascular Disorders**

Both **lifestyle intervention** and **metformin** can be effective in **delaying** or **preventing diabetes** in women with impaired glucose tolerance and a history of GDM

Obstetricians to link with other healthcare providers to support postpartum follow-up through **child vaccination/ regular health visits**

## AIMS FOR PRECONCEPTION & INTER-PREGNANCY INTERVALS

Increase acceptance and access to **preconception services**

**Universal pre-conception screening** for malnutrition, anemia, overweight and obesity, hypertension, diabetes and thyroid dysfunction

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Taken from The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care. Int J Gynecol Obstet 2015;131(Suppl 3):S173-212. The FIGO GDM Initiative (Phase 1) was funded with an unrestricted educational grant from Novo Nordisk.

# Femina Range

## Flourishing women's healthcare

**Lupigest**
Natural Micronised Progesterone Capsules/Injections

**Lupigest® SR** 200 300 400
Progesterone Sustained release tablets

**CORCIUM**
Coral Calcium

**CORCIUM D$_3$**
Coral Calcium 500 mg + Cholecalciferol 500 IU

**Faa 20** TABLETS/SYRUP
Iron Amino Acid Chelate

**Yamini**

**Fheal** Pessaries/Cream

**Grafyrec Inj** ™ 300 900 1200
Recombinant Human Follicle Stimulating Hormone

**Lupi-FSH**
Follicle Stimulating Hormone 75/150 IU

**Lupi-HCG**
Human Chorionic Gonadotrophin Injection I.P.

**Lupi-HMG**
Human Menopausal Gonadotrophin Injection I.P.

**Revofer®**
ferric carboxymaltose

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Available in Liquid & Wipes
Lactic acid

LUPIN

In PCOS

# NORMOZ

Myo-inositol, D-Chiro-inositol, Chromium and Vitamin $D_3$ tablets

**Right Ratio (40:1) for Quicker Action in PCOS**

- Improves menstrual frequency in oligo & amenorrhoeic PCOS women[1]
- Striking improvement in ovulatory function[2]
- Improves oocyte quality in PCOS women undergoing ART[3]
- Improves metabolic profile of obese PCOS women[4]
- Chromium picolinate ensures higher ovulation rate than Metformin[5]


Reference :
1. J. Endocrinol. Invest 2011; 34:757-763
2. Eur Rev Med Pharmacol Sci 2012;16:575-581
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4. Eur Rev Med Pharmacol Sci 2013; 17: 537-540
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In Female Infertility

# OVARES PLUS

With Cutting edge Superior Technology

Melatonin 3 mg + CoQ10 100 mg + Micronized DHEA 75 mg SR

**Rejuvenates, Protects & Energizes Oocytes**

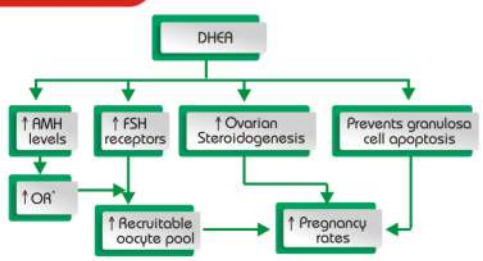
## Melatonin

- Powerful free radical scavenger and protects the oocyte from oxidative stress[1]
- Reduces intrafollicular oxidative damage[2]
- Is involved in folliculogenesis and follicle selection[6]

## CoQ10 - Energizes

- Restores normal energy production in the ovary[3]
- Significantly improved mitochondrial function and ATP production[4]
- Improves oocyte and embryo quality[5*]

## DHEA - Rejuvenates

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*Animal Study


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# CALENDER OF
# FOGSI EVENTS-2016

**13-17th January' 16**
AICOG
Agra

**12-14th Feb' 16**
Delhi

**4-6th March' 16**
YUVA FOGSI,
West Zone,
Rajkot

**18-20th March' 16**
High Risk Pregnancy, Obstetrics Sonography Modern Technology,
Aurangabad

**1-3rd April' 16**
YUVA FOGSI,
North Zone,
Ghaziabad

**9-10th April' 16**
GOAL
Delhi

**15-17th April' 16**
SAFOG with FOGSI
Mumbai

**22-24th April' 16**
High Risk Pregnancy,
Kolkata

**30th April, 1st May' 16,**
Managing Committee Meeting,
Gurgaon

**20-22nd May' 16**
YUVA FOGSI South Zone
Kodaikanal

**24-26th June' 16**
International FOGSI FIGO Conference (IFFC),
Pune

**8-10th July' 16**
FABCON
Jaipur

**27-28th Aug' 16**
Hyderabad

**2-4th Sep' 16**
Ahmedabad

**17-18th Sep' 16**
Managing Committee 2016,
Mumbai

**7-9th October' 16**
Core Committee Meeting,
Goa

**21-23rd Oct' 16**
National Conference
Allahabad

**16-18th Dec' 16**
YUVA FOGSI, East Zone,
Bardhaman