# Guidelines & Protocols in OBGY

## A Ready Reckoner

## Fetal Medicine Update - Part 2

Dr. Vaidehi Marathe
President

Dr. Rajasi Sengupta
Hon. Secretary

Volume 7

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# From The President's Desk ...

Dear Members,

It gives me immense pleasure to release the sixth volume our **"READY RECKONER - The Guidelines and Protocols in Ob-Gy"**.

In this era of evidence based medicine, it is expected that all treatment modalities be guidelines based. To have a quick access to the standard guidelines and have them well sorted out, we will be releasing this ready reckoner on various essential topics every month. This **first of its kind and unique attempt** is our small effort to simplify protocols.

With great pleasure we announce the release of its sixth volume : **"Fetal Medicine Update - Part 1 & Part 2".** I am sure, this release will be valuable in your clinical practice and help quick amending.

I will fail in my duty if, I don't acknowledge the tremendous efforts and contributors Dr. Unnati Shende, Dr. Neelam Chhajed, Dr. Neha Puniyani, Dr. Kunda Shahne, Dr. Amee Rahatekar. They have toiled very hard to compile these guidelines for your benefit.

Happy reading...Wishing you all Safe and Ethical Clinical Practice...

Academically yours,
**Dr. Vaidehi Marathe**
President NOGS-2020-21

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# FETO MATERNAL DOPPLER STUDY

-DR.NEELAM CHHAJED

- **OBJECTIVES**

**1.** To discuss the indications of obstetrical Doppler

Surveillance of growth restricted babies

predicting preeclampsia

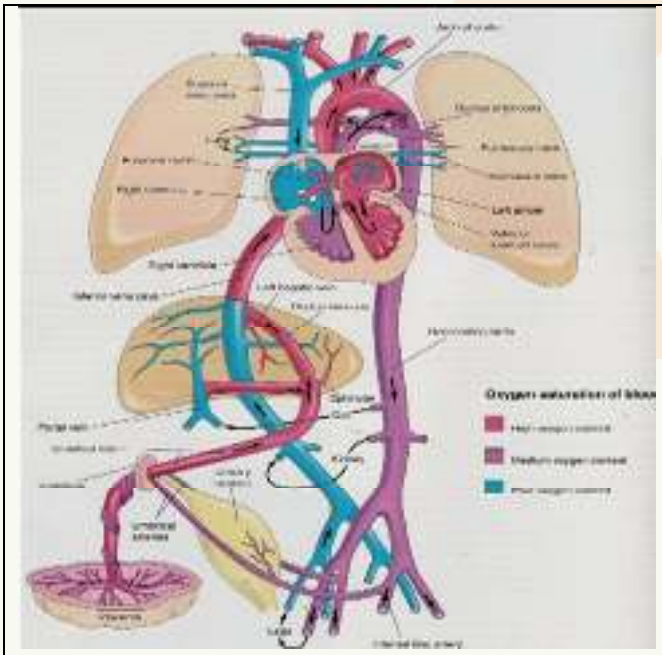
Monitoring Fetal anaemia

Monitoring monochorionic twins(TTTS And TRAP sequence)

2. To discuss the methods of Doppler evaluation (interrogating arteries and veins)

3 . To discuss the results and limitations of Doppler in screening in FGR & preeclampsia

## KEY CONCEPTS OF FETAL CIRCULATION



Pump : Fetal heart

Receiver : Placenta

Pipes:

Uterine artery

Umbilical artery

Middle cerebral artery

Aortic isthmus

Ductus venosus

umbilical vein

## SGA V/S FGR

The first step in the appropriate management of small-for-gestational age foetuses distinguish between "physiologically small" and "pathologically small" foetuses

Serial abdominal circumference or fetal weight estimates are the best screening tests for IUGR

EFW - <10%tile

Will follow a normal growth curve

Normal Uterine A ,UA doppler ,MCA Doppler, normal CPR

If infections and genetic causes are excluded then perinatal outcome is good

2 weekly growth and Doppler assessment is a standard practice.

## MAIN DIFFERENCE OF EARLY v/s LATE IUGR

| Early /PretermUGR | Late/ term IUGR |
|---|---|
| Problem--management | Problem – diagnosis |
| Placental disease- severe ,high association with PE | Placental disease – mild – UA doppler is normal ,low association with PE) |
| Hypoxia - ++ systemic cardiovascular adaptation | Hypoxia -+/-- central cvs adaptation |
| Immature fetus – higher tolerance to hypoxia | Mature fetus- Lower tolerance to hypoxia |
| High mortality and morbidity | Lower mortality ( but common cause of late still birth ) |
| Lower prevalence | Poor long term outcome |
| | Affects large fraction of population |

## SURVEILLANCE TESTS

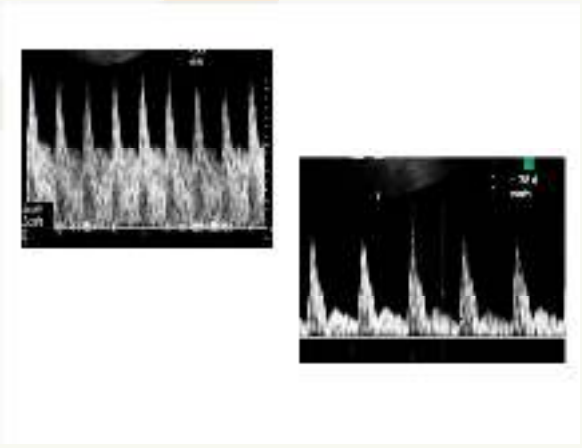
- **Doppler's**
    - ✓ Uterine artery
    - ✓ Umbilical artery
    - ✓ Middle cerebral artery
    - ✓ Cerebroplacental ratio
    - ✓ Ductus venosus
    - ✓ Aortic isthmus dopplers

- **BPP with Doppler's**
- **Computerised cardiotocography(CTG)**

## UTERINE ARTERIES

- Only vessel to be measured in all 3 trimesters.
- Mean of the left and right UT. A measured
- Notch is a characteristic of uterine artery and is normal in non pregnant status and during 1st trimester
- Impedance to blood decreases progressively throughout pregnancy
- Increased resistance in first trimester predictive of preeclampsia in future
- Interventions available to act on the early information available
- Aspirin 150 mg at bed time(ASPRE TRIAL)

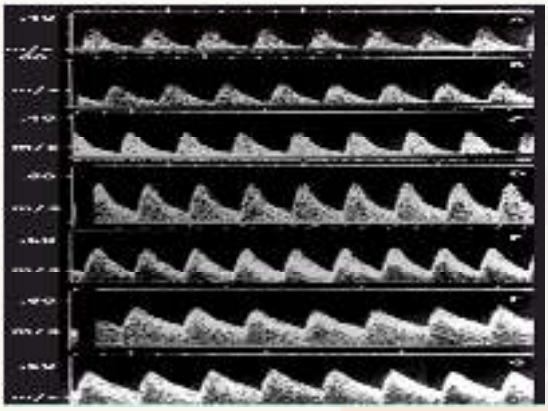
**Uterine artery waveform normal v/s abnormal**

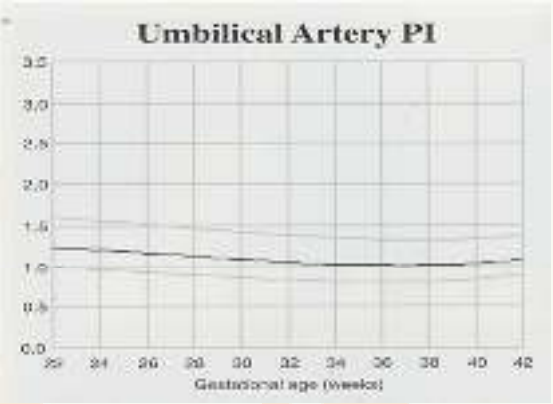


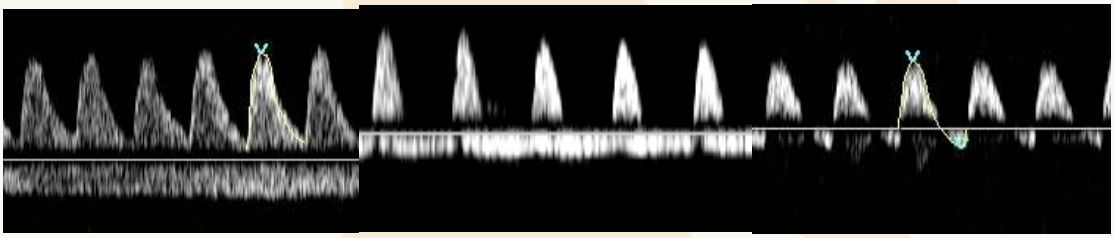
## UMBILICAL ARTERY DOPPLER

Umbilical artery doppler is measured in a free loop of umbilical cord.

PI decreases with increasing gestation.

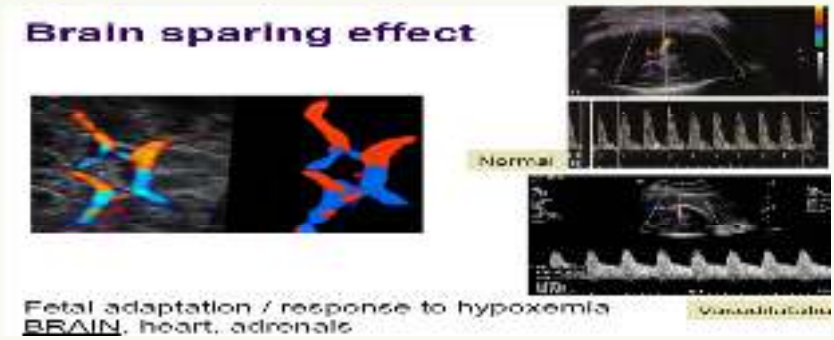




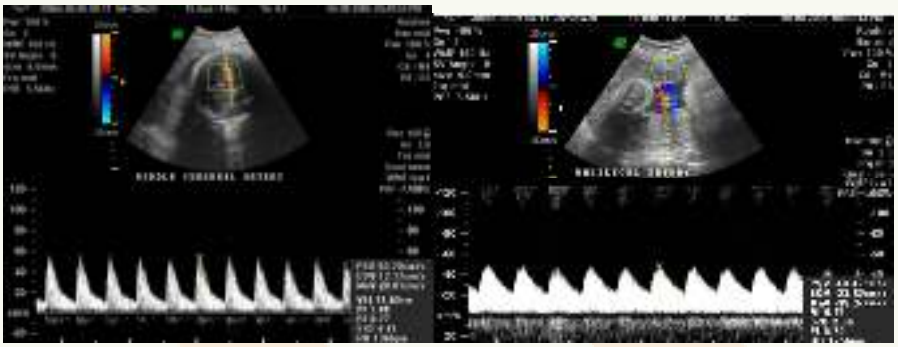
**NORMAL WAVE FORM** **ABSENT FLOW** **EVERSE END DIASTOLIC FLOW**

## MIDDLE CEREBRAL ARTERY

- High resistance bed – Brain
- Pipe – MCA
- Pump- left ventricle
- PI decreases with advancing gestation but not <5 % tile
- Brain sparing effect – profuse supply to brain –vascular bed – low resistance bed
- 

## CEREBROPLACENTAL RATIO

### ( CPR = MCA PI / UMB A PI)

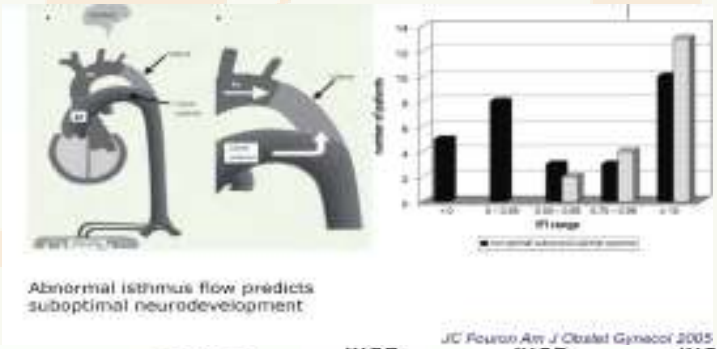


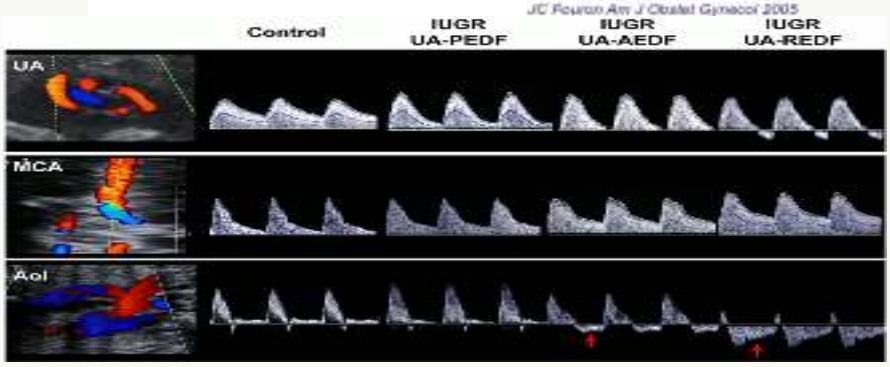
**CPR in normal pregnancy is always more than 1**

**CPR ≤ 1 means blood flow redistribution increasing.**

## AORTIC ISHMUS

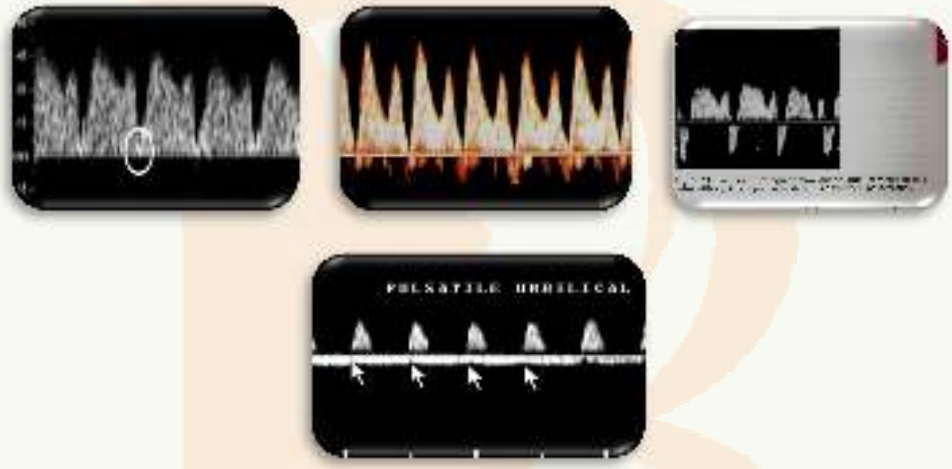
- ✓ section of the aorta located between origin of left subclavian artery and the ductus arteriosus.
- ✓ Reflects balance between the impedance of the brain and systemic circulation.
- ✓ Elevation or reversal of flow precedes abnormalities in the DV, often by approximately one week
- ✓ associated with adverse perinatal outcome
- Normal and abnormal waveforms in aortic isthmus



## DUCTUS VENOSUS

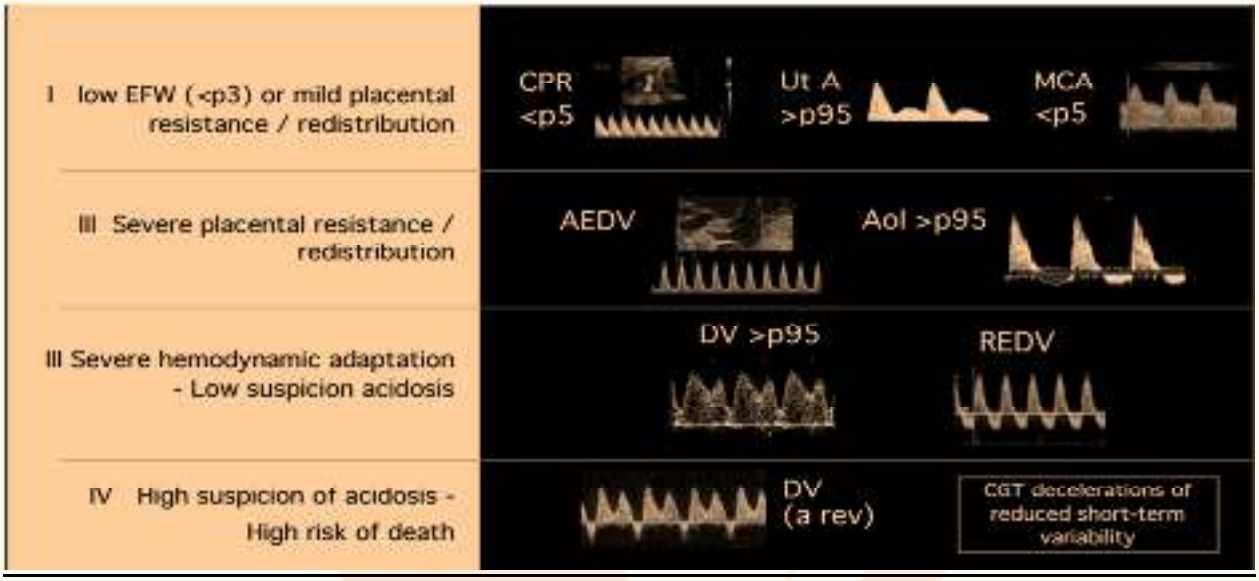
- One of the last vessels to be affected in fetal hypoxia.
- Only vessel to have forward flow throughout the car
- with advancing gestation PI reduces.
- Changes in ductus predict poor outcomes in fetus along with suboptimal neurodevelopment.
- Ductus venosus waveform progression cascade




## Apparent temporal sequence of progression in growth restricted fetuses

- Elevated umbilical artery S/D ratio(reduced diastolic fill)
- Middle cerebral artery PI < 5th percentile (brain-sparing)
- Umbilical artery - absent diastolic flow
- Umbilical artery - reversed diastolic flow
- Aortic isthmus and Ductus venosus - elevated pulsatility index
- Ductus venosus - reversed a-wave
- Ductus venosus - decreased IVR, reversed a-wave
- Umbilical vein double pulsations
- Umbilical vein triple pulsation with reversed a-wave flow
- Ctg and BPP abnormalities
- Fetal acidaemia and still birth

## Staging IUGR – *"THE BARCELONA PROTOCOL"*




**STAGE I :**

- Severe smallness or mild placental disease
- Criteria ( any of )
    - Efw - <3rd centile
    - Ua>p95
    - MCA <5
    - CPR <5
    - Uta>p95
- Weekly monitoring + BPP
- Ga at delivery – 37weeks ,
- Mode of delivery – labour induction

- **STAGE II**
    - Severe placental insufficiency
    - Criteria ( any of )

- Umb a-- aedf
- reverse Aoi flow

- Admission +biweekly monitoring + BPS
- Ga at delivery – 34weeks ,
- Mode of delivery – lscs

- **STAGE III :**
- Low-suspicion fetal acidosis
- Criteria ( any of )
  - Ua-- redf
  - DV PI >p95
- Admission + 1-2 days monitoring + bps+ daily cctg
- GA at delivery – 30weeks ( gratocos management,2014)
- GA at delivery – 32 weeks( baschat et al,obstet gyne 2016)
- (Reason for delivery at 32 weeks – delivery before 30 weeks carries a higher risk for adverse neurodevelopment at age 2 )
- Mode of delivery – LSCS
- **STAGE IV :**
- High-suspicion fetal acidosis
- Criteria ( any of )
  - DV reversal of flow
  - cCTG<3ms
  - FHR decelerations
- Admission + 12hrs monitoring + BPS+ cctg
- GA at delivery – 26weeks

( Gratocos management,2014)

(Lower GA threshold recommended acc to current literature- at least 50% survival. Tailor GA at delivery as per NICU statistics and parent's wishes)

Prepare for delivery ( baschat et al,obstet gyne 2016)

- Mode of delivery – LSCS

## SUMMARY

- FGR Fetuses between 24-32wks:
  - ✓ Give a course of antenatal steroids
  - ✓ Consider Mgso4 24hrs before Delivery imminent
- Deliver FGR fetuses with
  - ✓ RED≥32 weeks
  - ✓ AED at ≥34 weeks
  - ✓ decreased diastolic flow (pulsatility index >95$^{th}$%tile @37 to 38 wks
  - ✓ Normal Umb A Doppler @ 39 to 40 wks gestation.

## Take home message--

Doppler gold standard in management of IUGR

- ✓ Identify small for dates v/s growth restricted
- ✓ Distinguish early v/s late IUGR
- ✓ Follow objective stage based protocol to achieve optimum goals
- ✓ Biophysical score and ctg as adjuncts.
- ✓ Team work to optimise Fetus for delivery(counselling of parents, NICU and neonatologist, theatre staff)

## References


**1. Stage-based approach to the management of fetal growth restriction**

***Francesc figueras, Eduard gratacos***

**2. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens**

***AA Baschaat, U gembruch. CR harman***

**3. Fetal medicine foundation, uk website**

***www.fetalmedicine.org***

# INTRA UTERINE GROWTH RESTRICTION – THE ULTRASOUND PERSPECTIVE

-DR.NEHA PUNIYANI

## INTRODUCTION

- Intrauterine growth restriction is also known as fetal growth restriction (FGR).
- In FGR, the fetus does not reach its biological growth potential as a consequence of impaired placental function, which may be because of a variety of factors.
- FGR fetuses are at increased risk of perinatal morbidity & mortality.
- They may also have poor long- term implications like impaired neurological & cognitive development , cardiovascular & endocrine diseases in adulthood.
- FGR is the second most common cause of perinatal mortality after prematurity, accounting for 30% of all still births.
- Therefore, timely diagnosis & management goes a long way.

## DEFINITION

- Fetal growth restriction (FGR) is defined as a failure to achieve the endorsed growth potential
- The diagnosis of fetal 'smallness' is currently performed on the basis of an estimated fetal weight (EFW) below a given threshold, most commonly the 10th centile.
- This definition lacks sensitivity, such that it misses cases of growth restriction that do not fall below the 10th centile, but it identifies a subset of pregnancies at high risk of poorer perinatal outcome.
- FGR & SGA are two different entities

## DISTINCTION BETWEEN FGR & SGA(constitutionally) SMALL BABIES

| | |
|---|---|
| -FGR - refers to small fetuses with higher risk for fetal in utero deterioration, stillbirth & overall poorer perinatal outcome as compared with normally grown fetuses | - SGA – fetuses are just constitutionally small |
| -These fetuses are thought to have **'true' growth restriction** | - SGA refers to- subgroup of small fetuses that do not present the changes described in FGR babies, so there appears to be no fetal adaptation to an abnormal environment |
| - FGR is associated with Doppler signs suggesting hemodynamic redistributionas a reflection of fetal adaptation to undernutrition/hypoxia | - Therefore, perinatal outcomes are similar to those of normally grown fetuses.. |
| -It is reasonable to deliver electively FGR when lung maturation can be presumed, or earlier if signs of | - In SGA babies- active management or elective delivery before full term offers no |

| | |
|---|---|
| fetal deterioration | benefit ( as they have virtually normal perinatal outcome |

## BREAKING THE MYTH- USING UMBILICAL ARTERY AS A STAND ALONE PARAMETER

- For almost 2 decades, umbilical artery (UA) alone has been used to differentiate FGR from SGA.
- Umbilical artery is a surrogate marker of placental disease & changes in the UA Doppler are observed only with extensive placental damage/disease (50-60% of placenta is damaged)
- This led to consideration of small fetuses with normal UA Doppler as SGA with no placental disease
- Although UA identifies severe placental disease, it fails to pick up instances of mild placental disease which constitute a proportion of early-onset cases and virtually all instances of late onset FGR

## SCREENING FOR FGR

- FGR screening ideally should be done in all cases
- However, certains conditions where screening becomes mandatory are:
  - patients with pregnancy induce hypertension(PIH) in present pregnancy
  - low PAPP-A (<0.5 MoM) on double marker/ combined test
  -Uterine artery resistance – increased PI> 95$^{th}$ (2.35) centile on 11-13+6 weeks/ NT scan
  - patients with past history of IUGR/FGR & PIH in previous pregnancy
  - decreasing growth velocity on growth charts

## SCREENING PARAMETERS

- FGR screening starts in 1$^{st}$ trimester , various parameters are-
- **First trimester screening**:
  -Low PAPP-A : < 0.5 double marker/combined test
  - Increased Uterine artery PI: >95$^{th}$ centile on 11-13+6 weeks or PI > 2.35 (approx)
- **Second trimester screening** :
  - **serial biometric measurements** on ultrasound
  -plotting of fetal growth using growth chart over a period of time may help identify fetuses having **decreased growth velocity/falling growth**
  - **drop in the centiles of more than2 quartile** (50 centiles) should trigger

further monitoring

- growth curve for a SGA although will be along lower centile but will follow normal velocity

**- Uterine artery PI > 95$^{th}$ centile**

## ALGORITHM FOR APPROACHING A CASE OF IUGR

Once a diagnosis of IUGR is made (after correcting the dates by patient's h/o or from CRL taken in early scans)

↓

Do a detailed US examination to look for any associated structural anomaly, syndrome, any markers of aneuploidy & any signs of intrauterine infections

↓

After excluding all the above mentioned causes of IUGR , proceed with Doppler examination & assess true gestational age to classify it as early or late onset FGR

↓

Once the FGR is classified as early or late onset, determine the stage of FGR , monitor & manage accordingly

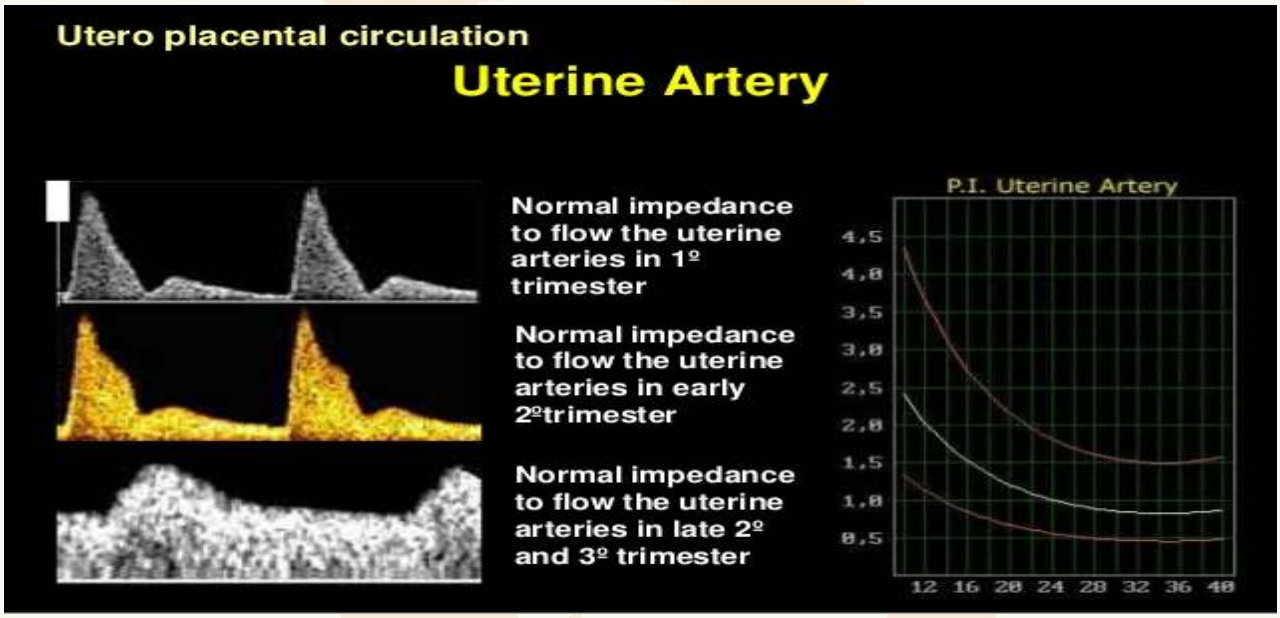
## DOPPLER INDICES COMMONLY USED IN FGR FETUSES

- **UTERINE ARTERY:**

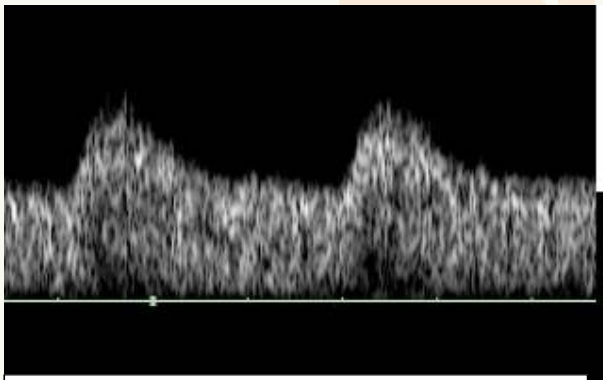
- Uterine artery (UtA) doppler reflects placental development.
- In early gestation, uterine artery has high resistance flow.
- With advancing gestation, resistance in both Uterine & Umbilical artery decreases.
- Uterine artery is essentially a diagnostic marker

- Once the UtA shows resistance/ PI>95$^{th}$ centile & a diagnosis of FGR is made then there is no need to look for UtA doppler in subsequent visits as it is not going to change the stage of disease or affect the outcome.
- Hence , once Uterine artery resistance has been documented then it is worth looking at other Doppler indices (UA,MCA,DV,CPR) to monitor the progression of disease.

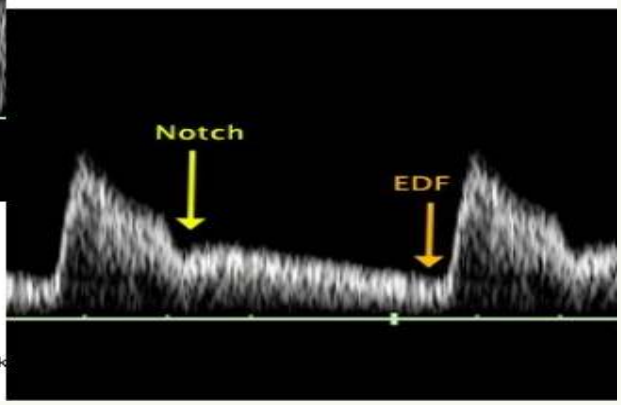
## NORMAL UTERINE ARTERY DOPPLER WAVEFORM




## ABNORMAL UTERINE ARTERY WAVEFORM



Above picture- showing normal Uterine artery waveform




Bottom picture – showing notching & reduced end diastolic flow ( increased resistance/ ↑ PI in Uterine artery

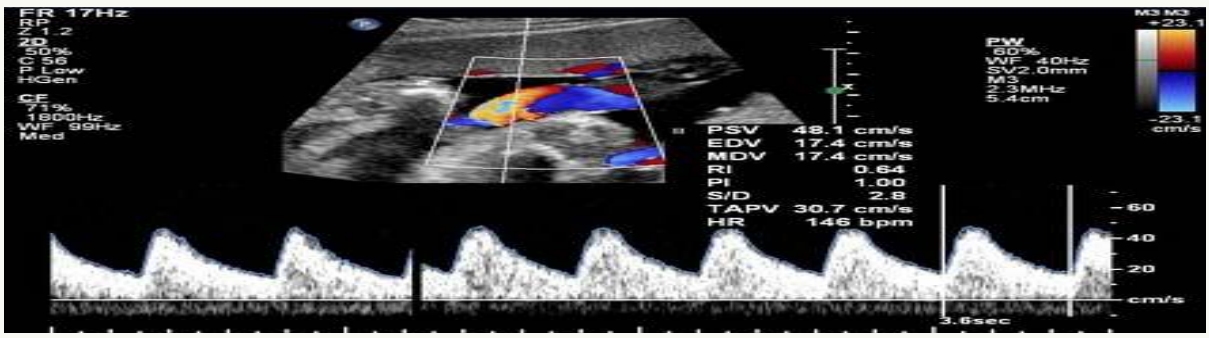
## UMBILICAL ARTERY

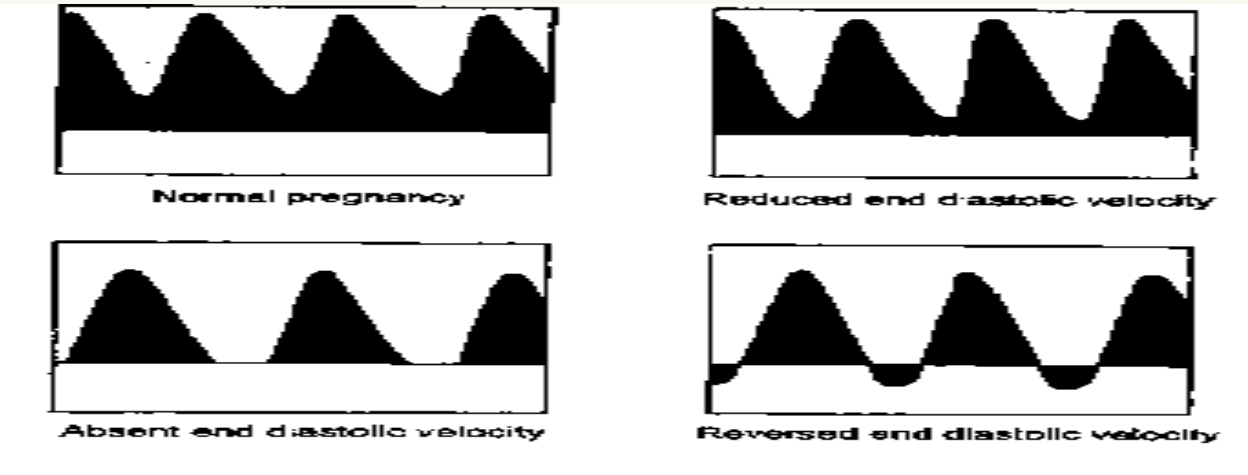
- **Umbilical artery (UA) Doppler –**

-Umbilical artery doppler reflects placental function & indicates the degree of placental insufficiency.

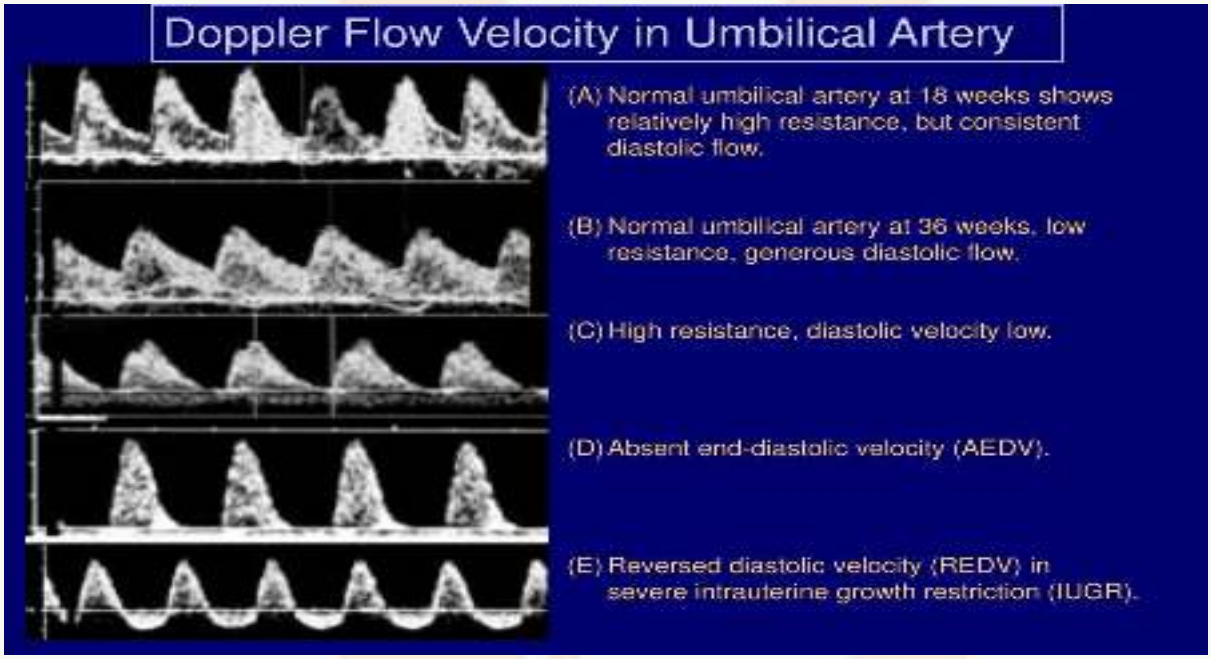
- UA acts as a surrogate marker for placental function.
- So whenever there is placental insufficiency, UA doppler becomes abnormal (resistance)
- However, UA doppler shows resistance ( becomes abnormal) when atleast 30-40% of placenta is damaged.
- In almost all the cases of early onset IUGR , placental damage occurs to a great extent & therefore UA doppler shows changes.
- Absent or reversal of end diastolic flow in UA occurs when atleast 60-70% of placental damage has occured.
- As placental involvement is very minimal in cases of late-onset IUGR, therefore UA doppler is virtually normal in all such cases
- UA Doppler provides both diagnostic & prognostic information for the management of FGR
- On one hand, increased UA Doppler PI helps in identification of FGR, alone or combined in the CPR ratio.
- On the other hand, the progression of UA Doppler patterns to absent or reverse end-diastolic flow relates with the risk of injury/death.
- There is an association between reversed end-diastolic flow in the UA & adverse perinatal outcome (with sensitivity and specificity of about 60%),independent of prematurity.
- Therefore, monitoring with UA doppler along with other methods like non-stress test, DFMC,BPP helps in improving outcome in such cases

## NORMAL & ABNORMAL UMBILICAL ARTERY DOPPLER WAVEFORM






## SEQUENTIAL CHANGES IN UA IN IUGR



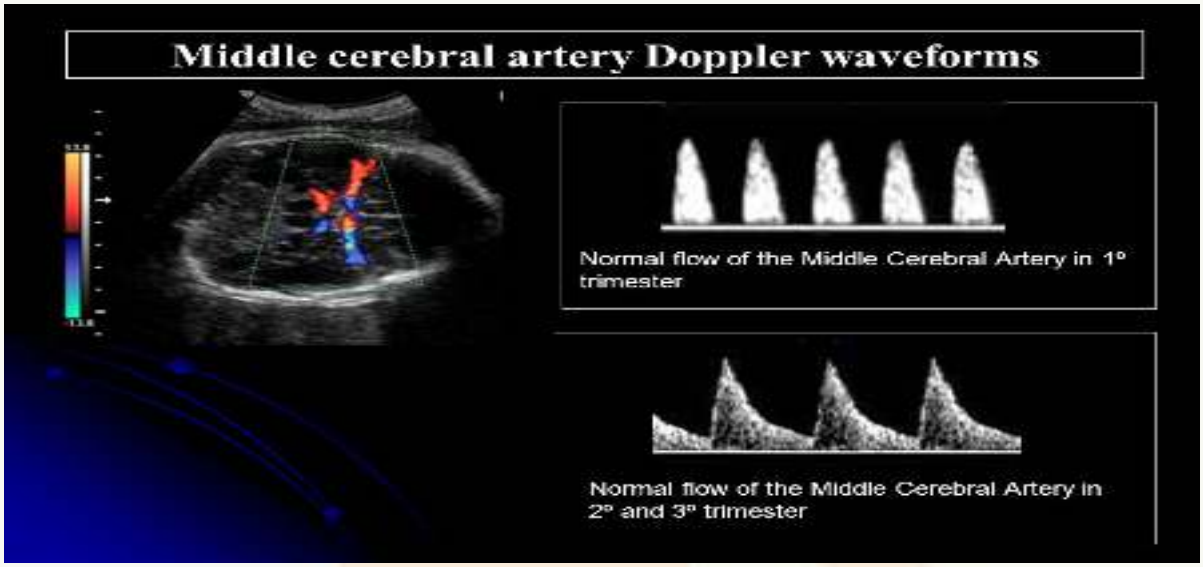

## MIDDLE CEREBRAL ARTERY DOPPLER

- MCA doppler is a surrogate marker for hypoxia & it tells about brain vasodilatation.
- In chronic hypoxic conditions , there is re – distribution of blood flow to vital organs ( brain, heart , etc ) leading to increased diastolic flow in the MCA .
- Increased diastolic flow in MCA is reflected as reduced MCA PI on Doppler
- However, changes in MCA doppler are observed only in cases of late-onset FGR while it may or may not be normal cases of early-onset FGR.
- This is because initially brain stem is tolerant to hypoxia & therefore it is generally not affected (early-onset FGR) but as gestation advances; tolerance

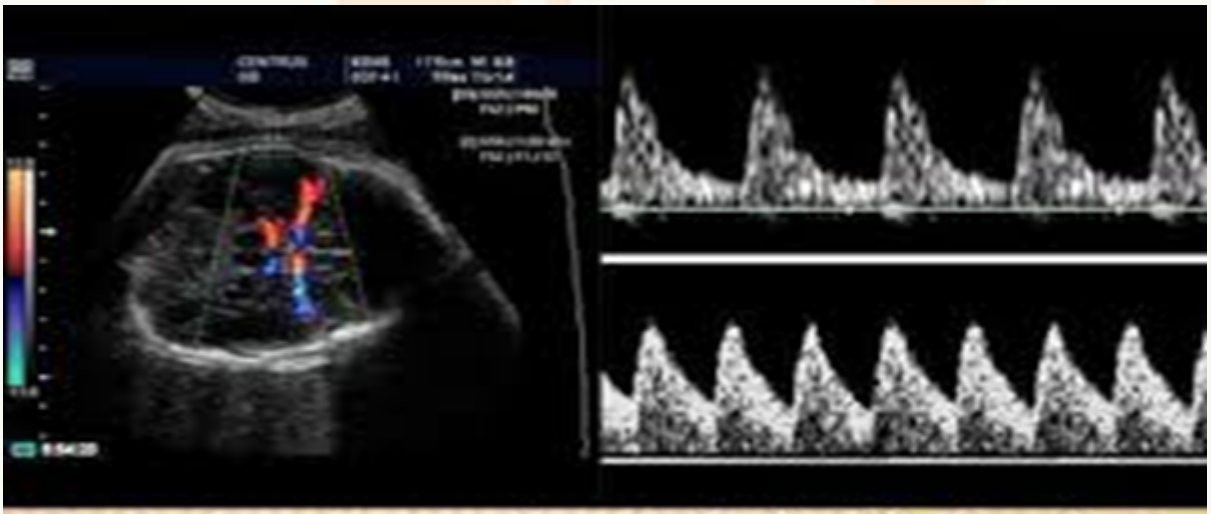
of brain stem to hypoxia decreases & it becomes abnormal ( vasodilatation- reduced PI).

- MCA is particularly valuable for the identification & prediction of adverse outcome among late-onset FGR, independently of the UA Doppler, which is often normal in these foetuses

## MCA DOPPLER NORMAL WAVEFORM




## MCA DOPPLER SHOWING INCREASED DIASTOLIC FLOW IN CASE OF IUGR (bottom picture)



*Color Doppler examination of the circle of Willis (left). Flow velocity waveforms from the middle cerebral artery in a normal fetus with low diastolic velocities (right, top) and in a growth-restricted fetus with high diastolic velocities (right, bottom)*

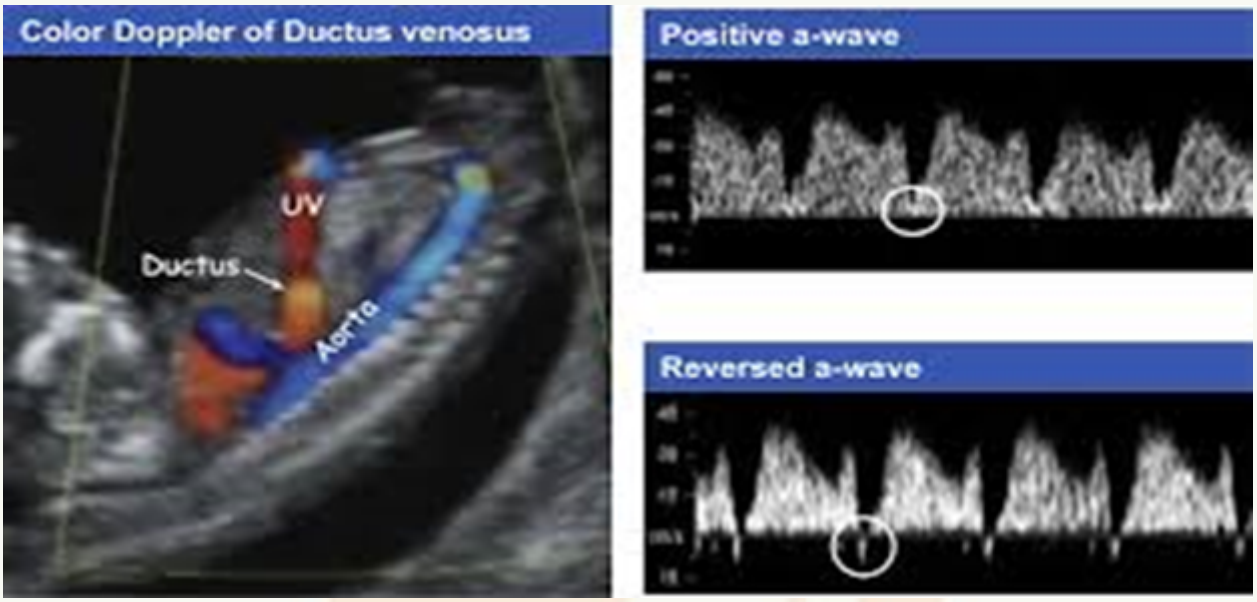
## CEREBROPLACENTAL RATIO (CPR)

- The CPR is essentially a diagnostic index.
- CPR is calculated by dividing the MCA PI by the UA Doppler PI.
- CPR improves remarkably the sensitivity of UA & MCA alone, because increased placental impedance (UA) is often combined with reduced cerebral resistance.
- Therefore, CPR is already decreased even when mild changes in MCA PI or UA PI occur but are still indiviudually within normal limits.
- In late FGR fetuses, abnormal CPR is present before delivery in 20–25% of the cases & is associated with a higher risk of adverse outcome at induction

## DUCTUS VENOSUS (DV) DOPPLER

- DV is essentially a prognostic marker.
- DV is the strongest single Doppler parameter to predict the short-term risk of fetal death in early-onset FGR.
- DV flow waveforms become abnormal only in advanced stages of fetal compromise.
- DV doppler changes are observed only in cases of early-onset FGR as in these cases there is systemic cardiovascular adaptation.
- There is no need of monitoring DV doppler in late - onset FGR cases due to absence of systemic cardiovascular adaptation.
- Consistently, there is a good correlation of abnormal DV waveform with late stage acidemia at cordocentesis
- Absent or reversed velocities in DV during atrial contraction are associated with perinatal mortality independent of the gestational age at delivery , with a risk ranging from 40 to 100% in early-onset FGR .
- Thus, this sign is normally considered sufficient to recommend delivery at any gestational age, after completion of steroids.
- In about 90% of cases , DV becomes abnormal 48–72 h before the biophysical profile (BPP).
- Hence, it provides a better window for delivering fetuses in critical conditions at very early gestational ages

## DV WAVEFORM- NORMAL & REVERSAL (in IUGR)




## RE- DEFINING FGR

- An international Delphi consensus was carried out to improve the definition of FGR.
- For the first time, consensus based definition for FGR that included both biometric as well as functional parameters was established.

## Consensus based definitions for early & late fetal growth restriction (FGR) in absence of congenital anomalies

| Early FGR: GA< 32 weeks, in the absence of congenital anomalies | Late FGR: GA> 32 weeks, in the absence of congenital anomalies |
|---|---|
| AC / EFW <3rd centile or UA-AEDF or<br>1. AC/EFW < 10th centile combined with<br>2. UtA PI > 95th centile and/or<br>3. UA PI > 95th centile | AC / EFW < 3rd centile<br>Or atleast two out of three of the following<br>1. AC / EFW < 10th centile<br>2. AC /EFW crossing centiles > 2 quartiles on growth centiles<br>3. CPR < 5th centile or UA PI > 95th centile |

## EARLY ONSET FGR

- Early-onset FGR represents 20–30% of all FGRs.
- Approximately 50% cases of early FGR show association with preeclampsia.
- Early FGR is highly associated with severe placental insufficiency & with chronic fetal hypoxia, which is why the UA doppler is abnormal in majority of these cases.
- If left untreated the fetal condition deteriorates with progression to decompensated hypoxia & acidosis, which is reflected by escalating abnormalities in the UA & increased PI in the Ductus venosus
- Sequential doppler changes follow a cascade of events thereby allowing to monitor the progress of fetal deterioration & tailor elective delivery .
- The latency of severe fetal deterioration can vary in individual cases, but it normally lasts weeks.
- Early severe FGR is associated with severe injury and/or fetal death before term in many cases.
- Diagnosis is easy but management is challenging & should be based on achieving the balance between risk of leaving the fetus in-utero versus the complications of prematurity

## LATE ONSET FGR

- Late-onset FGR represents 70–80 % of all FGR.
- Association with pre-eclampsia is low(10%)
- Placental disease is very mild in these cases & thus UA doppler is normal in almost all cases but there is high association with abnormal CPR.
- Cerebral vasodilatation occuring due to chronic hypoxia is reflected as low MCA PI < $5^{th}$ centile.
- Advanced signs of fetal deterioration with changes in DV are never observed.
- Hence, the cascade of sequential fetal deterioration as seen in early FGR cases does not occur in late FGR.
- Thus, late FGR lacks a ‘natural history’ & may undergo rapid deterioration as suggested by high contribution to late-pregnancy mortality , intra-partum fetal distress & neonatal acidosis leading to severe injury or death without observable late-stage signs as in early FGR .
- This could be explained by a combination of causes like the very low tolerance of term fetuses to hypoxia & increased uterine contractions near term.

- Therefore, although management of late FGR is easy ; diagnosis still remains challenging.

## MAIN DIFFERENCES BETWEEN EARLY & LATE ONSET FORMS OF FGR

| Early onset FGR (1-2%) | Late onset FGR (3-5 %) |
|---|---|
| Problem : management | Problem : diagnosis |
| Placental disease : severe (UA Doppler abnormal , high association with preeclampsia | Placental disease : mild ( UA Doppler normal, low association with pre-eclampsia) |
| Hypoxia ++ : systemic cardiovascular adaptation | Hypoxia +/ - : central cardiovascular adaptation |
| Immature fetus = higher tolerance to hypoxia = natural history | Mature fetus = lower tolerance to hypoxia = no (or very short natural history) |
| High mortality & morbidity ; lower prevalence | Lower mortality (but common cause of stillbirth) , poor long-term outcome; affects large fraction of pregnancies |

## METHODS OF FETAL SURVEILLANCE IN FGR

- **Cardiotocography (CTG**): CTG is a marker of fetal hypoxemia & should be incorporated in FGR surveillance. A silent FHR pattern and/or presence of spontaneous decelerations represent a very late event preceding fetal demise.
- **Daily fetal movement count (DFMC**): Patient should be asked to keep an account of daily fetal movements & report in case of decreased fetal movement.
- **Biophysical profile (BPP)/Modified biophysical profile**- may be used after 30 weeks for fetal surveillance . Fetal breathing must be assessed in every Doppler because respiratory centre is very sensitive & the first to get affected due to hypoxia.
- **Amniotic fluid index (AFI**)-Amniotic fluid index (AFI) is used essentially as part of BPP. Amniotic fluid volume is believed to be a chronic parameter. AFI progressively decreases . One week before acute deterioration, 20–30% of cases have oligohydramnios
- **Doppler –** Doppler monitoring of UA , MCA,CPR

## STAGE BASED CLASSIFICATION & MANAGEMENT OF FGR

| Stage | Pathophysiological correlate | Criteria( any of) | Monitoring | GA/Mode of delivery |
|---|---|---|---|---|
| 1. | Severe smallness or mild placental insufficiency | EFW < 3rd centile<br>CPR < p5<br>UA PI > p95<br>MCA PI < p5<br>UtA PI > p95 | Weekly | 37 weeks , labour induction |
| 2. | Severe placental insufficiency | UA AEDV<br>Reversal Aortic isthmus | Biweekly | 34 weeks<br>CS |
| 3. | Low – suspicion fetal acidosis | UA REDV<br>DV PI > p 95 | 1-2 days | 30 weeks<br>CS |
| 4. | High suspicion fetal acidosis | DV reversal<br>cCTG < 3 ms<br>FHR decelerations | 12 hours | 26 weeks<br>CS |

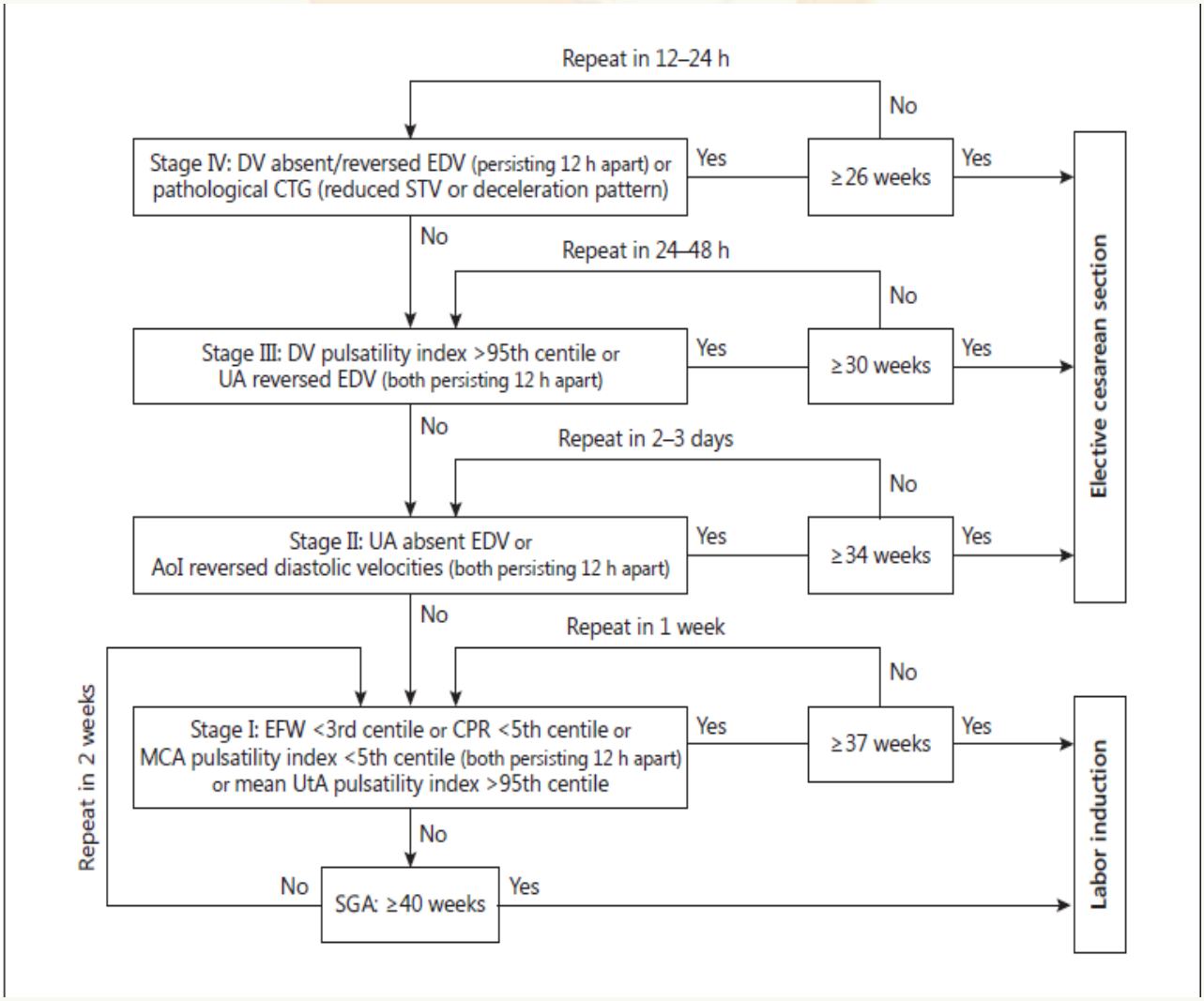
AEDV- absent end diastolic velocity, REDV- reverse end diastolic velocity, CS- cesarean section

## MANAGEMENT

- Stage 1 - Due to low risk of fetal deterioration before term. Labour induction beyond 37 weeks is acceptable, but the risk of intrapartum fetal distress is increased. Weekly monitoring seems reasonable.
- Stage 2- Delivery should be recommended after 34 weeks. As risk of emergency cesarean section is more after labour induction ,therefore elective cesarean section is a reasonable option.
  Monitoring twice a week is recommended
- Stage 3- There is an association with a higher risk of stillbirth and poorer neurological outcome. Delivery is recommended by cesarean section after 30 weeks. Monitoring every 24–48 h is recommended

- Stage 4 –Spontaneous FHR deceleration is an ominous sign and DV reversal is associated with very high risks of stillbirth within the next 3–7 days & disability. Deliver after 26 weeks by cesarean section at a tertiary care centre under steroid treatment for lung maturation. Intact survival exceeds 50% only after 26–28 weeks, and before this threshold parents should be counselled by multidisciplinary teams. Monitoring every 12-24 is recommended.
- However, in the presence of pre-eclampsia especially from the early gestational ages( not always possible to follow stage based management in such cases),the course of natural history is distorted requiring meticulous fetal monitoring & timely delivery to avoid complications.

## STAGE BASED DECISION ALGORITHM FOR MANAGEMENT OF FGR



# MANAGEMENT OF MULTIPLE PREGNANCY

- DR.UNNATI SHENDE

# MANAGEMENT OF MULTIPLE PREGNANCY

## MULTIPLE GESTATION

- Incidence- 2-3% (Increasing Trend in Assisted Reproduction)
- 2/3 Dichorionic (Non-Identical),1/3 Monochorionic (Identical)
- Perinatal Morbidity and Mortality Is Higher Than Singleton Pregnancy and Therefore Additional Support Is Required
- Risk of Pregnancy Complication Much Higher in Monochorionic Twins

## ANEUPLOIDY SCREENING

- Combined test (dual marker with NT scan) is recommended
- Multiple pregnancy with one vanishing twin – if the vanishing sac shows embryonic pole then biochemical screen is not reliable.
- In such case only ultrasound-based screening is recommended
- Second trimester screening by quadruple marker
- In monochorionic twins, pregnancy specific risk is calculated whereas in dichorionic fetus specific risk is calculated
- First trimester screening has high detection rate than second trimester screening

## NIPT

- Cell-free DNA testing can safely be offered in monochorionic twin pregnancies with expected performance of screening as high as in singleton pregnancies.
- The test can also be offered in dichorionic pregnancies, but parents should be warned that data on accuracy are inadequate

## PROTOCOL FOR ULTRASONOGRAPHY

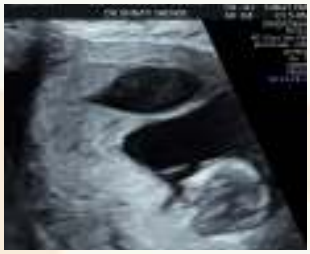
- Dating scan – spontaneous conception – use CRL crown rump length to confirm period of gestation

IVF CONCEPTION – use Embryo transfer (ET) date to calculate period of gestation

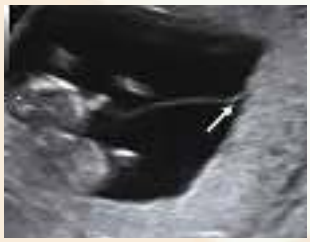
FOUNDATION STONE IN MULTIPLE GESTATION IS DETERMINING CHORIONICITY

## USG FEATURES-

- Lambda sign-/twin peak sign – projection of placental tissue suggests dichorinicity
- T sign indicates – monochorionic twin pregnancy
- Best seen in first trimester during NT scan
- Follow up in pregnancy is based on chronicity
- LAMBDA SIGN



- T SIGN



## PROTOCOL FOR DICHORIONIC TWINS

- NT scan- (11 -13 weeks 6 days)
- Anomaly scan (18 – 20 weeks) also measure cervical length, detailed fetal heart evaluation – refer to fetal medicine unit in case of any anomaly
- Growth scan 4 weekly – which includes biometry with fetal anatomical survey
- Colour doppler study in cases of suspected growth retardation
- Refer in cases of growth discrepancy

IF there is no complication, consider delivery at 37 weeks

## PROTOCOL FOR MONOCHORIONIC TWINS

- NT scan – (11 -13 weeks 6 days)
- Scan at 16 weeks then every 2 weeklies
- At 16 weeks – measure biometry, liquor, umbilical and ductus venosus doppler
- There after every 2 weekly scans to rule out complications associated with monochorionic twins- TTTS, selective growth restriction (sGR), TAPS

- Chances of developing TTTS is maximum till 26 weeks
- Selective growth restriction (> 20 % difference in EFW) is seen in around 15 % monochorionic twins without TTTS
- OTHER complications seen in monochorionic twins- TAPS (Twin anemia polycythemia sequence, TRAP Sequence,Siamese twins

## MONOCHORIONIC TWINS

- ANOMALY SCAN (20 WEEKS) – WITH fetal echocardiography
- Measure cervical length and colour doppler
- Refer to fetal medicine unit if there is any deviation from normal
- Growth and doppler study – 2 weeklies
- If there is no complication, plan delivery at 36 weeks

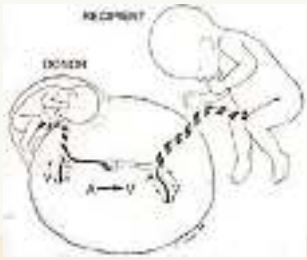
## TWIN TO TWIN TRANSFUSION SYNDROME

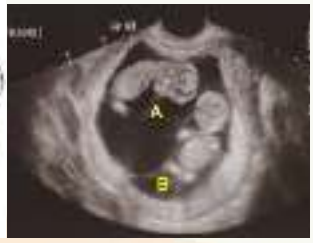
- Incidence – 15 % of monochorionic twins
- Prediction of TTTS-
- 1. intertwin membrane folding
- 2.liquor discrepancy of 3.1 cm and above

Quintero staging system in TTTS

| STAGE | OLIGO/POLY | ABSENT BLADDER IN DONOR | ABNORMAL DOPPLER | HYDROPS | DEMISE |
|---|---|---|---|---|---|
| I | + | - | - | - | - |
| II | + | + | - | - | - |
| III | + | + | + | - | - |
| IV | + | + | + | + | - |
| V | + | + | + | + | + |

## USG FINDINGS






- Quientero staging is good for prognosis but it is not very reliable as stage I can also have cardiac dysfunction
- A cardiovascular scoring system has been reported from Children's Hospital of Philadelphia (CHOP score), based on echocardiographic and peripheral doppler findings.

Management options –

- Fetoscopic laser coagulation
- Expectant
- Amnioreduction
- Septostomy
- Selective reduction


## MANAGEMENT OF TTTS

- Refer to fetal medicine unit after diagnosis
- Before 26 weeks – fetoscopic laser assisted equatorial dichorionization by Solomon technique is preferred over other other procedures
- After 26 weeks – amnioreduction should be planned till laser ablation is available
- After treatment – growth and doppler study should be performed on weekly basis
- Treated TTTS – DELIVERY should be planned between 34-36 weeks

## SELECTIVE GROWTH RESTRICTION(SGR)

- TYPE I- Growth discordance but positive diastolic velocities in both fetal umbilical arteries.
- TYPE II- Growth discordance with absent or reversed end-diastolic velocities (AREDV) in one or both fetuses.
- TYPE III -Growth discordance with cyclical umbilical artery diastolic waveforms (positive followed by absent then reversed end-diastolic flow in a cyclical pattern over several minutes [intermittent AREDV; iAREDV]).

## MANAGEMENT OF SELECTIVE GROWTH RESTRICTION

- In early onset IUGR, poor growth velocity – selective termination can be advised
- Suspected cases -Doppler – every 2 weeks
- Longer latency period between diagnosis and delivery as compared to singleton and dichorionic pregnancy
- Type I –with normal growth and doppler study, plan delivery at 34-36 weeks
- Type II and III – PLAN DELIVERY by 32 WEEKS

## SINGLE FETAL DEMISE IN TWINS

- There can be death of co twin with / without any complication.
- Risk in surviving twin –
- 1.risk of death I survivor – 15%
- 2.risk of neurological abnormality -26 %
- **USG advised to check** – growth, liquor biophysical profile and MCA PSV
- MCA PSV of survivor is indicated to rule out fetal anemia which may occur due to intertwin transfusion.
- Fetal anemia in the survivor twin indicates risk of CNS injury
- Fetal brain MRI – advised after 3-4 weeks or earlier in case of fetal anemia
- Procedures in case of complication –
- Transfusion in very preterm cases/ plan termination after counselling
-

## MULTIFETAL PREGNANCY REDUCTION AND SELECTIVE TERMINATION

- FETAL REDUCTION- Procedure that reduce the number of fetus in higher order multiple gestation
- usually done after NT SCAN, BY INJECTING INTRACARDIAC kcl IN DICHORIONIC TWINS
- SELECTIVE TERMINATION – reduction of anomalous fetus only
- Monitoring for DIC not required
- Complications -5-10 % depending on period of gestation

# CERVICAL ASSESSMENT- PREDICTION OF PRETERM BIRTH

-DR.NEELAM CHHAJED

## INDICATIONS FOR CERVICAL ASSESSMENT

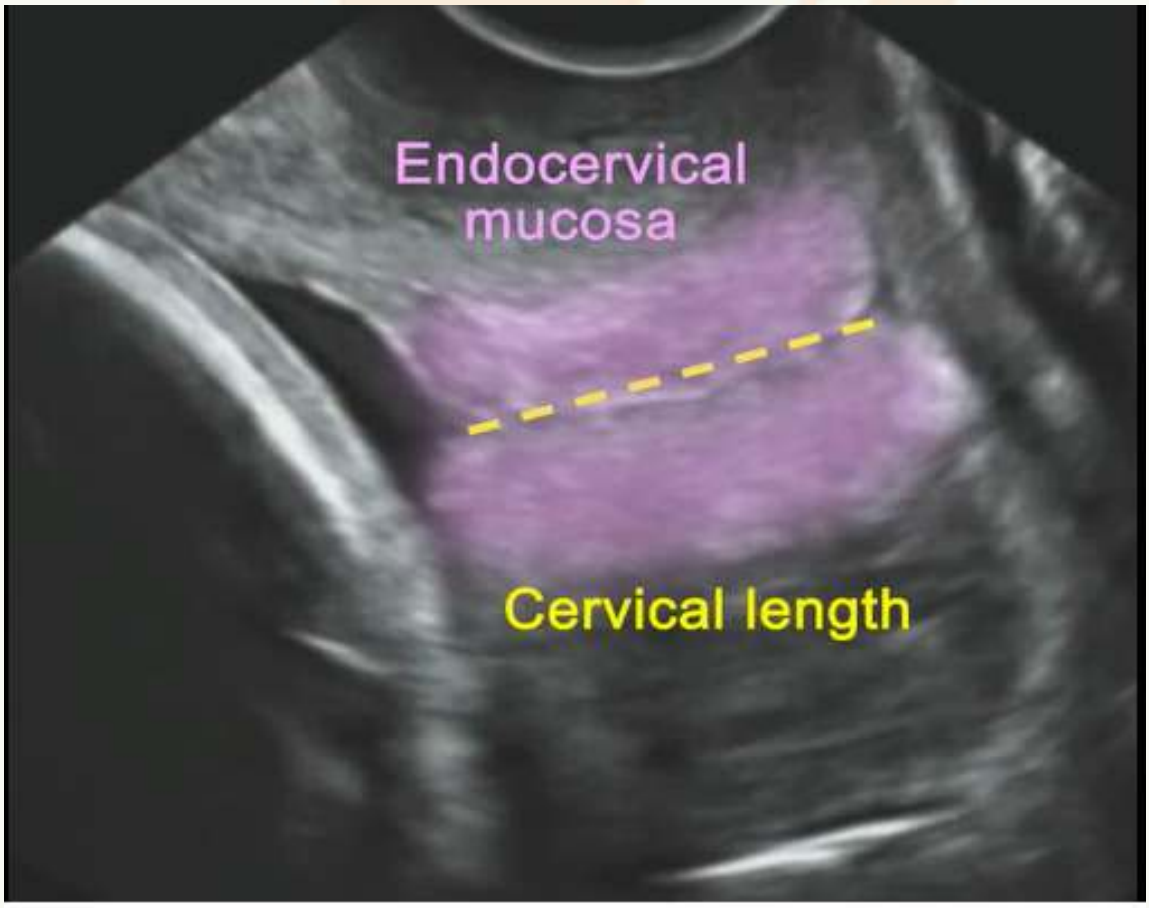
- Previous late miscarriage
- Previous spontaneous preterm birth
- Women with uterine anomalies
- Excisional cervical treatment for cervical intraepithelial neoplasia (LEETZ and cone biopsy
- Prior multiple dilatation and evacuation procedures (beyond 13 weeks of gestation

## MEASUREMENT OF CERVICAL LENGTH

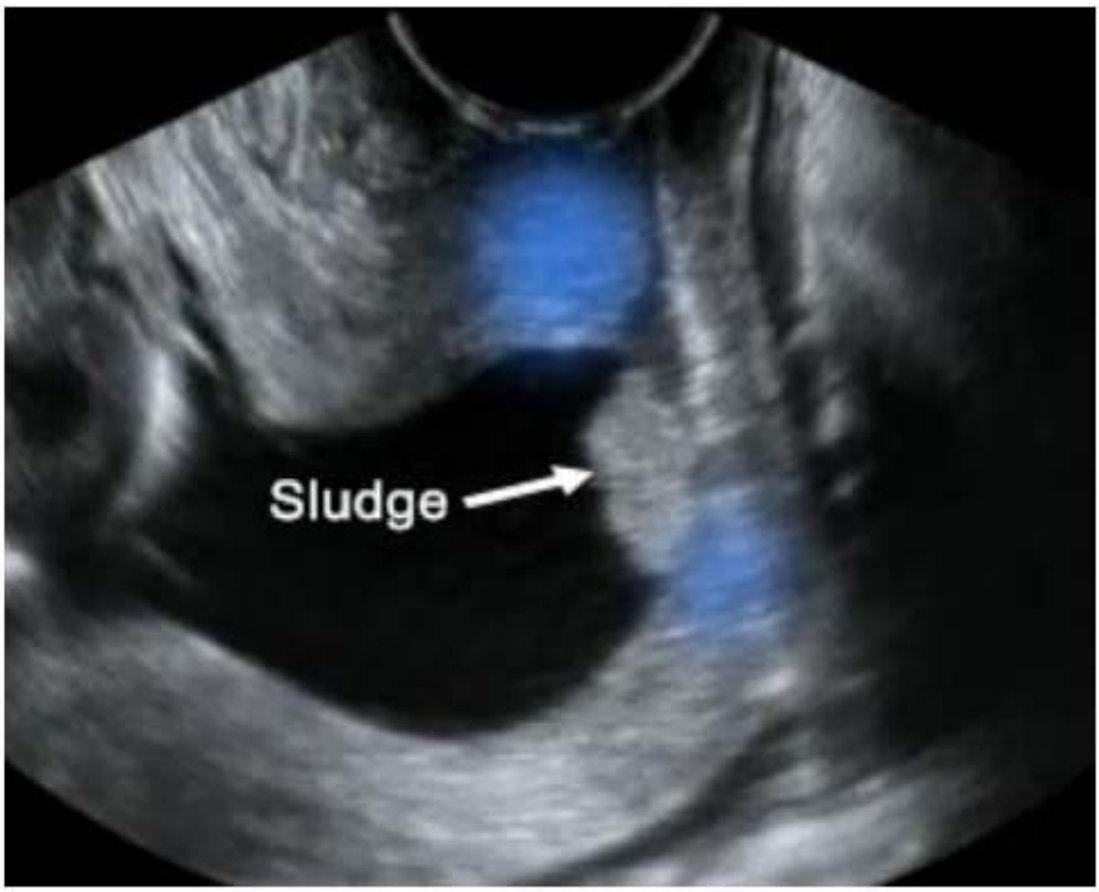
### ✓ Technique

- Transvaginal route (gold standard)
- Empty bladder
- Dorsal lithotomy position
- The ultrasound probe is introduced in the vagina, directed in the anterior fornix
- Avoid putting undue pressure as will artificially increase length
- A sagittal view of the cervix is obtained and the endocervical mucosa (which may be of increased or reduced echogenicity compared to the cervix) is used as a guide to the true position of the internal os, thereby avoiding confusion with the lower segment of the uterus.

- The callipers are used to measure the linear distance between the triangular area of echo density at the external os and the V-shaped notch at the internal os.
- Each examination should be performed over a period of 2-3 minutes. In about 1% of cases the cervical length may change due to uterine contractions and in such cases the shortest measurement should be recorded.



**Evaluate for presence of amniotic fluid “sludge” or debris – Associated with increased risk for PTB**




Open cervix

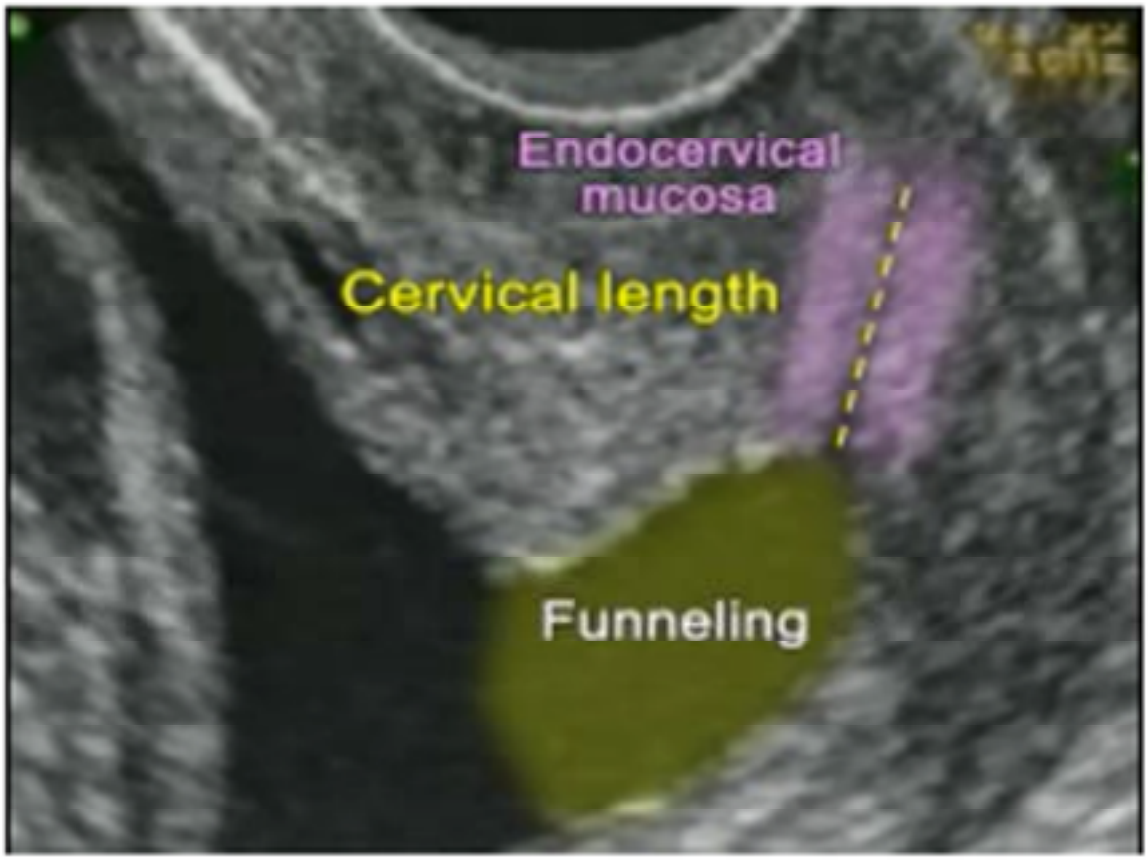
## CONCEPT OF SHORT CERVIX

- The cervix is often curved and in these cases the measurement of cervical length taken as a straight line between the internal and external os is inevitably shorter than the measurement taken along the endocervical canal.

From the clinical point of view the method of measurement is not important because when the cervix is short it is always straight.

## CONCEPT : CERVICAL FUNELLING

- Dilatation of the internal os, observed sonographic ally as funnelling, is no more than a simple reflection of the process of producing cervical shortening that will eventually result in preterm birth. Almost all women with a short cervix have funnelling of the internal os.
- Women with a long cervix and funnelling are not at increased risk of preterm delivery.




Short cervix with funneling

## PREDICTION OF PRETERM BIRTH

- There are essentially two strategies for identifying the high-risk group among women who are either in their first pregnancy or their previous pregnancies resulted in deliveries at term:
- Cervicovaginal fetal fibronectin at 22-24 weeks.
- Cervical length at 20-24 weeks

In women with a short cervix (<25 mm) diagnosed by routine transvaginal sonography at 20-24 weeks

- Sonographic measurement of cervical length is clinically useful in the prediction of PTB in the following situations:
- In asymptomatic women with previous history of PTB and in those with uterine abnormalities, such as unicorn ate uterus, the cervical length should be measured every two weeks at between 14 and 24 weeks of gestation.
- In asymptomatic women with no previous history of PTB measurement of cervical length should be carried out routinely at the time of the second trimester scan at 20-24 weeks.

## PREVENTION OF PRETERM BIRTH

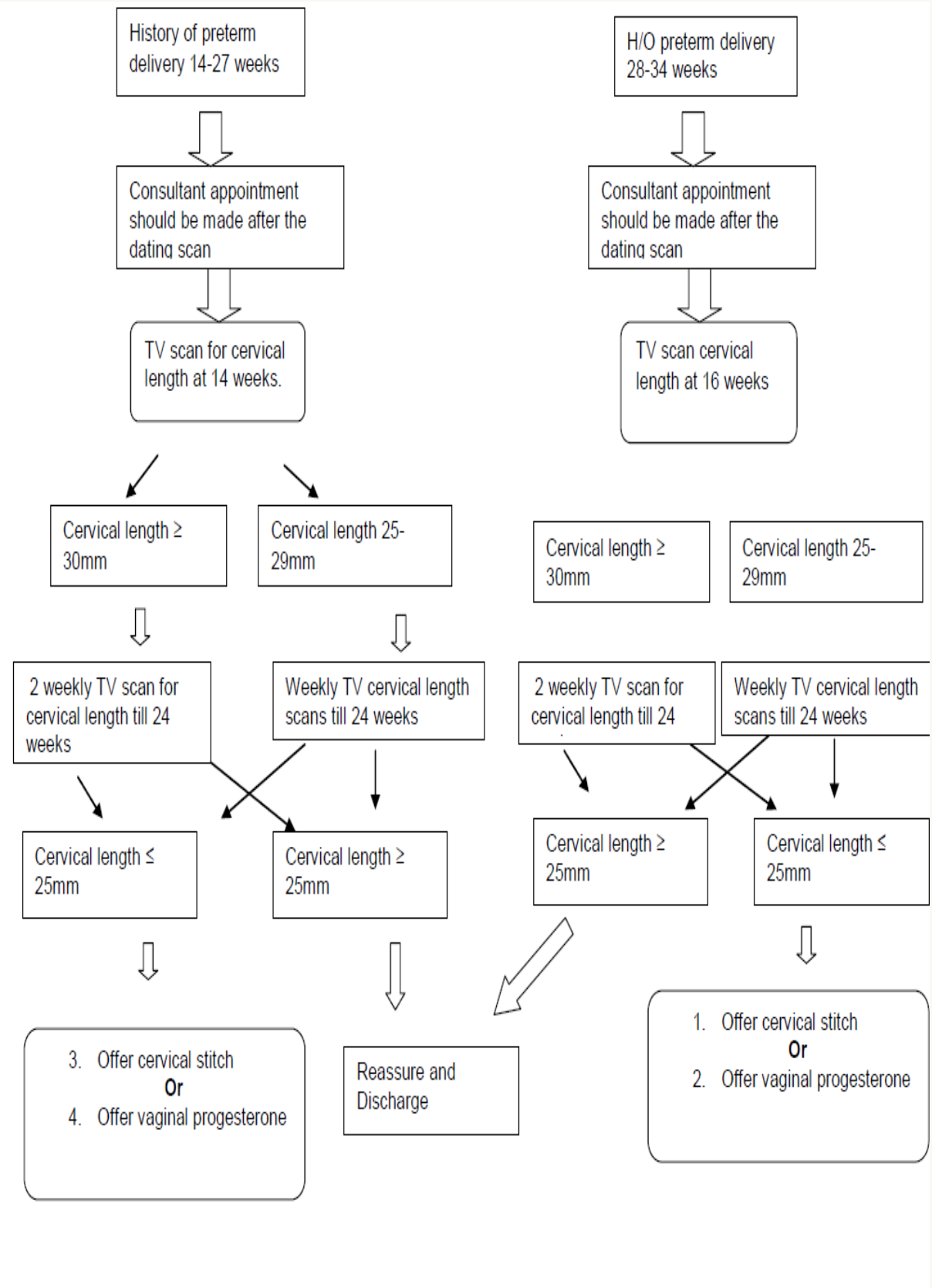
- Women with previous preterm birth
- No benefit from bed rest, prophylactic tocolytics or lifestyle interventions
- Vaginal progesterone every night from 20 to 34 weeks reduces PTB by 25%
- Measurement of cervical length every 2 weeks between 14 and 24 weeks and cervical cerclage if the cervix becomes less than 25 mm reduces PTB by 25%

## PREDICTION OF DELIVERY AT TERM

- Sonographic measurement of cervical length is clinically useful in the prediction of time of delivery at term
- The risk of respiratory morbidity in the neonate is halved with each completed week of gestation between 37 and 41 weeks.
- In women with planned cesarean section measurement of cervical length at 37 weeks can help in deciding whether to carry out the delivery at 37-38 weeks or delay this until 39-41 weeks.
- In women undergoing induction of labour the pre-induction cervical length gives useful prediction of the induction-to-delivery interval and the likelihood of vaginal delivery and caesarean section.

- Measurement of cervical length at 37 weeks is useful in predicting spontaneous onset of labour and delivery at term. This information can be utilized in individualizing the gestation for elective caesarean section:
- In women with cervical length of less than 20 mm there is a 95% chance of spontaneous onset of labour before 40 weeks. In such patient's elective caesarean section is best carried out at 37–38 weeks to avoid the increased risk of maternal mortality and morbidity from emergency as compared with elective surgery.
- In women with cervical length of more than 30 mm there is a 95% chance that spontaneous onset of labour will not occur before 40 weeks. In such patient's elective caesarean section could be delayed until 40 weeks to reduce neonatal respiratory morbidity.

## CERVICAL SCAN ALGORITHM IN PREVIOUS PRETERM BIRTH



## References


- Preterm labour and birth – NICE Quality standard QS135 (October 2016)
- Preterm labour and birth – NICE Guideline NG25 (November 20015
- Fetal medicine foundation  UK

# PLACENTAL ANOMALIES

- DR.UNNATI SHENDE

# PLACENTAL ANOMALIES

## INTRODUCTION

- Placenta is a vital and fascinating organ which provides primary support to the developing fetus.
- Placenta is primarily a fetal organ, its size and echogenicity are often a reflection of the fetal health
- Generally placental thickness corresponds to period of gestation (in millimeter)

## LIST OF ANOMALIES OF PLACENTA

- Placentomegaly
- Circumvallate placenta
- Succenturiate lobe
- Focal cystic /hypoechoic lesions
- Placental calcification
- Chorioangioma
- Abruptio placenta
- Placenta praevia
- Placenta accreta spectrum

## PLACENTOMEGALY

Placentomegaly is a term applied to an abnormally enlarged placenta

- Etiology

| Maternal | Fetal |
|---|---|
| Maternal anemia | Fetal high output failure |
| Diabetes | Congenital infections |
| Chronic intrauterine infections | Fetal malformations |
| Alpha thalassemia | Umbilical vein obstruction |

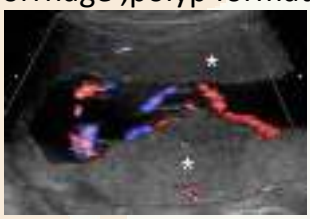
## CIRCUMVALLATE PLACENTA

- Circumvallate placenta is an abnormality of shape of placenta in which the membranes insert inward from the edge, towards center of the placenta
- It is characterized by thickened, rolled chorioamniotic membranes peripherally
- Clinical significance – it is associated with fetal growth restriction, oligohydramnios, preterm labour and abruption

## SUCCENTURIATE LOBE

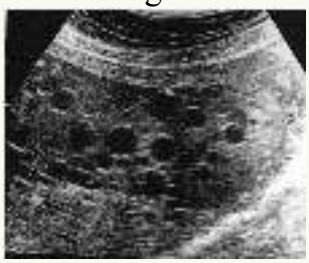
Incidence – up to 5 %

- One or more small accessory lobes develop in the membranes at a distance from the main placenta, to which they usually have vascular connections of fetal origin.
- Clinical significance – it is associated with retained placenta, subinvolution of uterus ,post partum hemorrhage ,polyp formation and sepsis



## FOCAL CYSTIC /HYPOECHOIC LESIONS

- These are venous lakes, commonly seen after 25 weeks
- They are more concerning if they are seen in early gestation, are large /are numerous and diffuse.
- Etiology-intervillous thrombus, decidual septal cysts, peri villous fibrin deposition
- Clinical significance – it is associated with placental insufficiency



## PLACENTAL CALCIFICATION

- It is regarded as a physiological aging process, seen near term.
- Accelerated placental calcification is associated with placental maturity, maternal thrombotic disorders, maternal hypertension, fetal growth restriction, cigarette smoking, maternal SLE.

## CHORIOANGIOMA

- Prevalence – 1: 5000 pregnancies
- Ultrasonography features– hyper/hypoechoic, well-circumscribed mass, which is usually located underneath the chorionic plate near the umbilical cord insertion, and often protrudes into the amniotic cavity.
- Color Doppler demonstrates large vascular channels around and within the tumor.
-

- Clinical significance – it is associated with fetal anemia, fetal thrombocytopenia, fetal heart failure, placentomegaly and polyhydramnios.
- Investigations – detailed evaluation with fetal echocardiography and MCV-PSV
- Follow-up scans every 2 to 3 weeks to monitor growth of the tumor, heart function, MCA PSV and amniotic fluid volume.
- PRENATAL THERAPY -Ultrasound guided laser coagulation of vessels within the tumor, fetal blood transfusions and amnioreduction may become necessary.

**DELIVERY IN CHORIOANGIOMA-** Patient should be referred to tertiary care center for delivery as good neonatal support is required

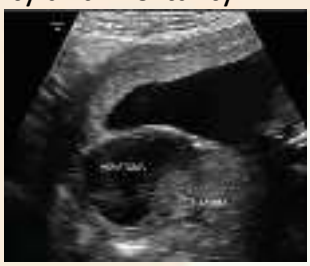
- Time of delivery –in case of fetal hypoxia, fetal hydrops, and fetal growth retardation preterm termination may be required
- Mode of delivery – as such vaginal delivery is not contraindicated

PROGNOSIS- Symptomatic chorioangiomas carry a high risk of perinatal mortality and morbidity.

- The neonate may have severe microangiopathic hemolytic anemia and thrombocytopenia.
- Recurrence – no risk of recurrence

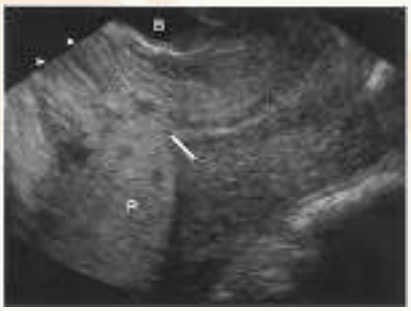
## ABRUPTIO PLACENTA

- Definition – premature separation of normally located placenta before term, before third stage of labour
- Incidence 3-5 %
- Clinical presentation – tense, tender, board like abdomen with/without bleeding per vaginum
- It is a fatal complication of pregnancy
- Major separation is associated with fetal growth retardation, fetal demise and maternal morbidity and mortality



## PLACENTA PRAEVIA

- It is referred to abnormally located placenta which is completely /partially covering internal os.
- Incidence – 1: 200 pregnancies
- Placenta previa can be a potentially life-threatening condition if not diagnosed antenatally.
- Clinical presentation – painless causeless bleeding per vaginum
- High fetal presenting part



- If diagnosed during second trimester, then repeated ultrasonography should be done at 32-34 weeks of gestation to confirm the location of placenta

- Antenatal steroids should be administered as these cases may require preterm caesarean section
- Delivery –at 37 -38 weeks of gestation

## PLACENTA ACCRETA SPECTRUM

- Incidence 1:400 pregnancies
- Mainly associated with previous caesarean section
- Placenta accreta – placenta attached to myometrium, absence of nitabuch membrane in between
- Placenta increta-placenta invading into the myometrium
- Placenta percreta –placenta penetrating through the placenta, attached to bladder or bowel.

- Investigations – 2D/3D with colour doppler

MRI if ultrasonography is inconclusive

- Patient should be referred to tertiary care center for termination of pregnancy.
- There is high risk of massive hemorrhage and cesarean hysterectomy
- Elective termination should be planned at 36 -37 weeks of pregnancy.
- Early diagnosis reduces mortality and morbidity by 50 %.

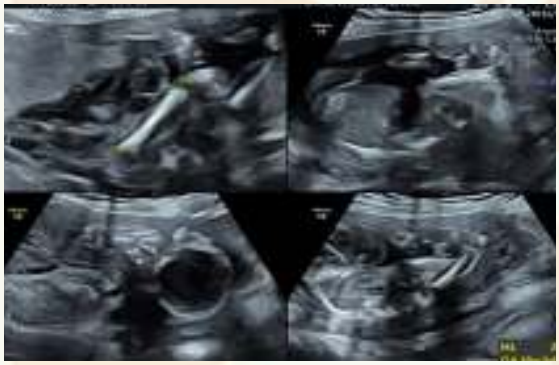
# AMNIOTIC FLUID DISORDERS

-DR.UNNATI SHENDE

# AMNIOTIC FLUID DISORDERS

## OLIGOHYDRAMNIOS

- Decreased in amniotic fluid volume
- Incidence – 1 to 8 % depending on different cut off
- USG criteria – single vertical pocket (SVP) less than 2 cm **OR** Amniotic fluid index AFI (sum of vertical pockets in four quadrunts) less than 5 cm



### ETIOLOGY

- Uteroplacental insufficiency  in fetal growth restriction(FGR)
- Preterm prelabour rupture of membranes (PPROM)
- Fetal chromosomal anomalies
- Fetal structural anomalies – bilateral renal agenesis, multicystic dysplastic kidneys, polycystic kidneys, urethral obstruction, Meckel gruber syndrome
- Maternal medication- prostaglandin synthetase inhibitor, ACE inhibitors
- Multiple pregnancy- TTTS twin to twin transfusion syndrome and selective growth restriction
- Idiopathic

- Post term pregnancy

## MANAGEMENT OF PREGNANCY

- History- hypertension ,chronic renal disease, use of medication NSAID'S like indomethacin
- Clinical evaluation – sterile speculum examination
- Rule out Dehydration
- Termination of pregnancy sos

## COMPLICATIONS

| Fetal | Maternal |
|---|---|
| • Abortion<br>• Intrauterine fetal death<br>• Prematurity<br>• Deformities- contracture,pulmonary hypoplasia,CTEV ,amputation<br>• Malpresentation<br>• Low APGAR score<br>• Fetal distress | • Increased morbidity<br>• Prolonged labour<br>• Increased operative interventions |

## INVESTIGATION

- Detailed ultrasound evaluation
- Invasive testing – karyotype for relevant fetal abnormalities
- Molecular analysis by chorionic villous sampling or amniocentesis for Meckel gruber syndrome and icthyosis

## FOLLOW UP

- Ultrasound evaluation every 1-3 week to assess amniotic fluid volume and to monitor fetal condition
- Uteroplacental insufficiency – growth and doppler studies
- Monitoring for chorioamnionitis in case of suspected PPROM

## FETAL INTERVENTION

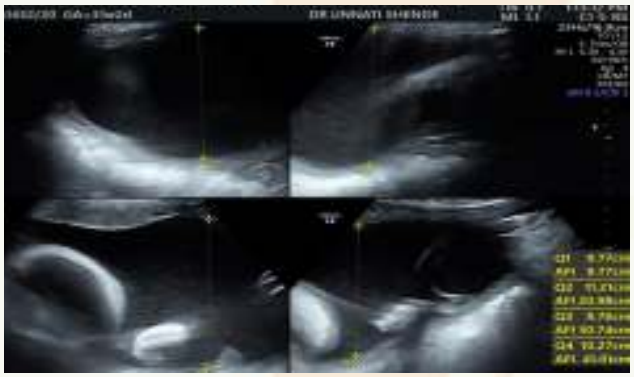
- Vesico-amniotic shunt in bladder outlet obstruction
- Amniotic membrane patching – more studies required
- Amnioinfusion – limited evidence

## PROGNOSIS

- Oligohydramnios below 24 weeks carries poor prognosis
- Bilateral renal agenesis, multicystic or polycystic kidneys are lethal anomalies
- Severe Uteroplacental insufficiency developing in second trimester carries poor prognosis
- Rupture of membranes in early gestation carries risk of chorioamnionitis and prematurity complications

## POLYHYDRAMNIOS

- Increase in the amniotic fluid volume
- Incidence- 1 in 100 pregnancies
- USG criteria – single vertical pocket (SVP) more than 8 cm OR Amniotic fluid index AFI (sum of vertical pockets in four quadrunts) more than 24 cm



## CLINICAL FEATURES

- Overdistended abdomen with discomfort
- Breathlessness and palpitation
- Indigestion
- Edema
- Varicosities

## ETIOLOGY OF POLYHYDRAMNIOS

| FETAL | MATERNAL |
|---|---|
| • CNS Anomalies (eg.anencephaly ,dandy walker malformation, open spina bifida )<br>• Fetal and placental tumours<br>• GI Obstruction<br>• Compressive pulmonary disorders<br>• Skeletal dysplasia<br>• Fetal akinesia<br>• Fetal anemia<br>• Twin to twin transfusion syndrome<br>• Bartter syndrome<br>• chromosomal abnormalities | • Maternal diabetes mellitus<br>• Maternal uraemia<br>• isoimmunization |

## INVESTIGATIONS

- Detailed anomaly scan with fetal echocardiography
- Invasive testing for karyotype or array if there are fetal anomalies
- DNA testing for myotonic dystrophy mutation in case of fetal abnormal posture of extremities
- Glucose tolerance test
- TORCH TEST if features suggestive of congenital infection

## PRENATAL INTERVENTIONS

- Maternal diabetes mellitus – good glycemic control
- Hydrops due to fetal arrythmia – antiarrhythmic medication
- Fetal anaemia – intrauterine blood transfusion
- Pleural effusion/ pulmonary cyst – thoracoamniotic shunting
- Fetal/placental tumours – laser occlusion of feeding vessel
- Twin to twin transfusion syndrome – laser occlusion of placental anastomosis
- Amnioreduction in selected cases
- Indomethacin – risk of closure of ductuc arteriosus

## COMPLICATIONS OF POLYHYDRAMNIOS

- Malpresentation and malposition
- Preterm labour
- Abruptio placenta
- Cord prolapse
- Postpartum haemorrhage

## PROGNOSIS

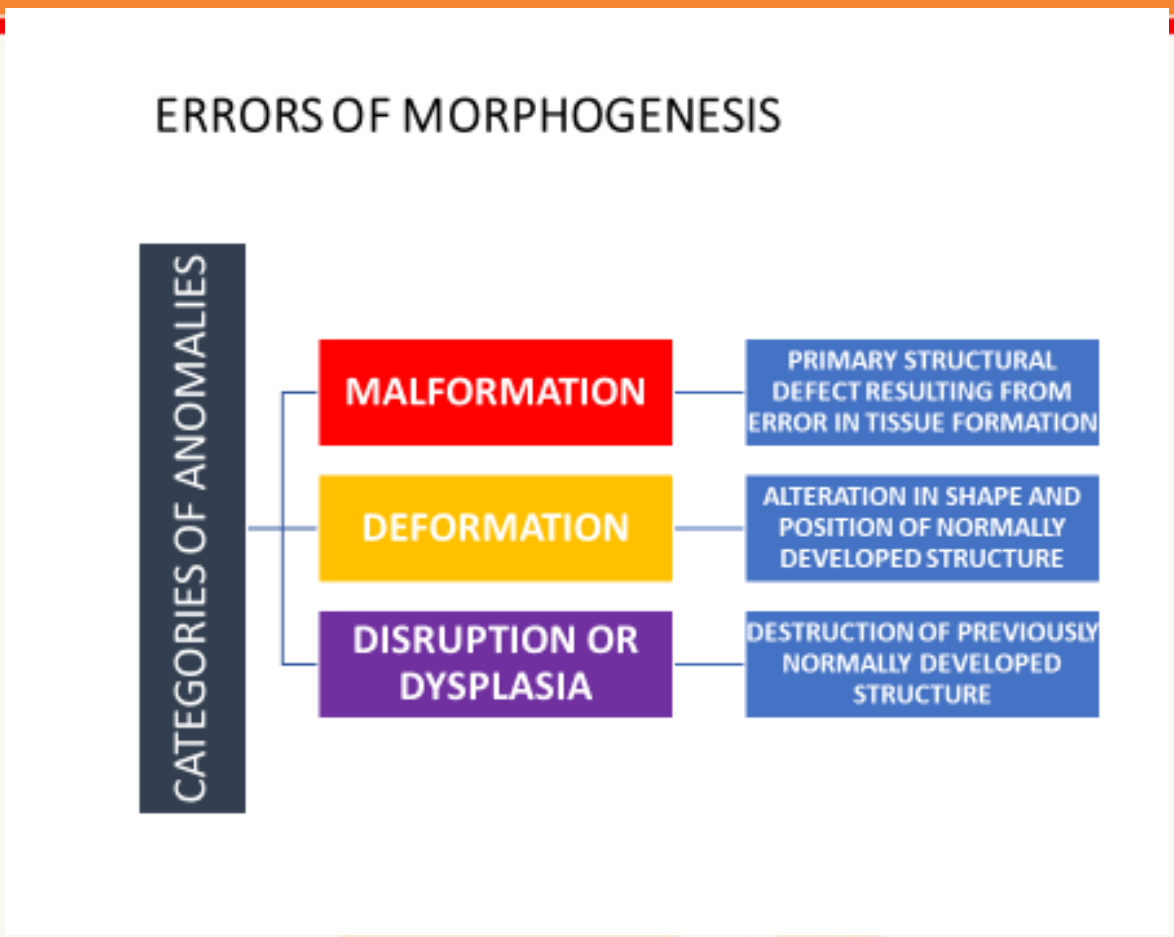
- Depends on the cause and gestational age at delivery

## RECURRANCE RISK

- Idiopathic :no increased risk
- Maternal and fetal condition : depending on the cause

# FETAL INFECTIONS

- DR AMEE RAHATEKAR



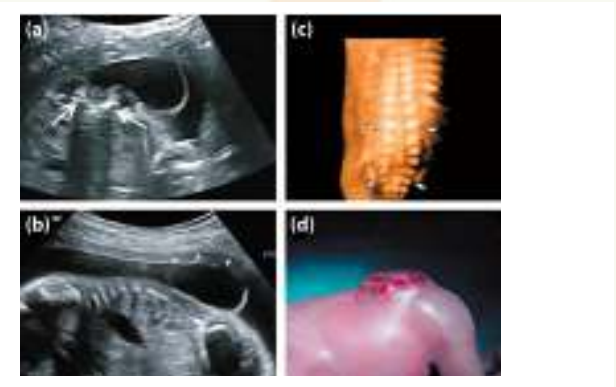

## MALFORMATION

Primary structural defect resulting from error in tissue formation.

**ETIOLOGY**

- Chromosomal
- Genetic
- Teratogenic

  (viral infection)
- Unknown



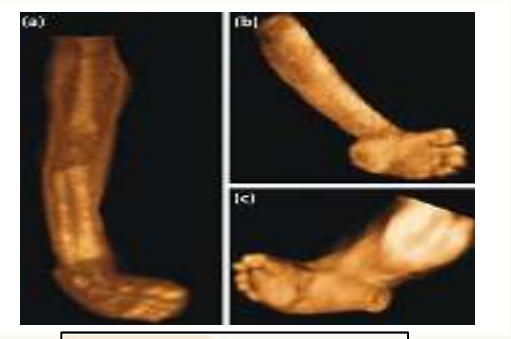

EXAMPLE: Myelomeningocele

## DEFORMATION

Alteration in shape and position of normally developed structure.

**ETIOLOGY**

- Extrinsic (fetal constraint)
- Intrinsic (fetal akinesia)



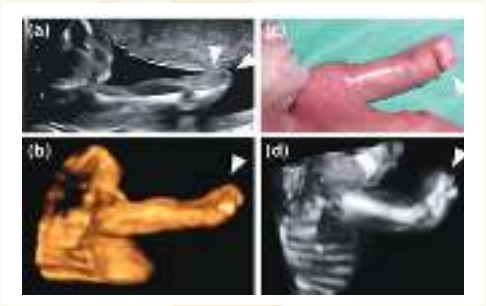
EXAMPLE: Club Foot

## DISRUPTION OR DYSPLASIA

Destruction of previously normally developed structure.

**ETIOLOGY**

- Vascular
- Compressive
- Tearing



EXAMPLE: Limb Reduction Deficit.

**MATERNAL INFECTIONS**

L E A D T O

**FETAL INFECTIONS**

## USG SIGNS OF FETAL INFECTIONS:

**Non-specific**

- **Intrauterine growth restriction (IUGR)**
- **Oligohydramnios**
- **Hyperplacentosis**
- **Hyperechoic ileus**

**Specific**

- **Brain lesions** (including calcifications)
- **Hydrops** (including ascites, pleural effusion, subcutaneous and prefrontal edema, and enlarged nuchal translucency)
- **Hepatomegaly, splenomegaly, and abdominal calcification**
- **Myocarditis**
- **Anemia**
- **Cataract**

### Most common fetal infections

**CYTOMEGALOVIRUS**

**RUBELLA VIRUS**

**TOXOPLASMOSIS**

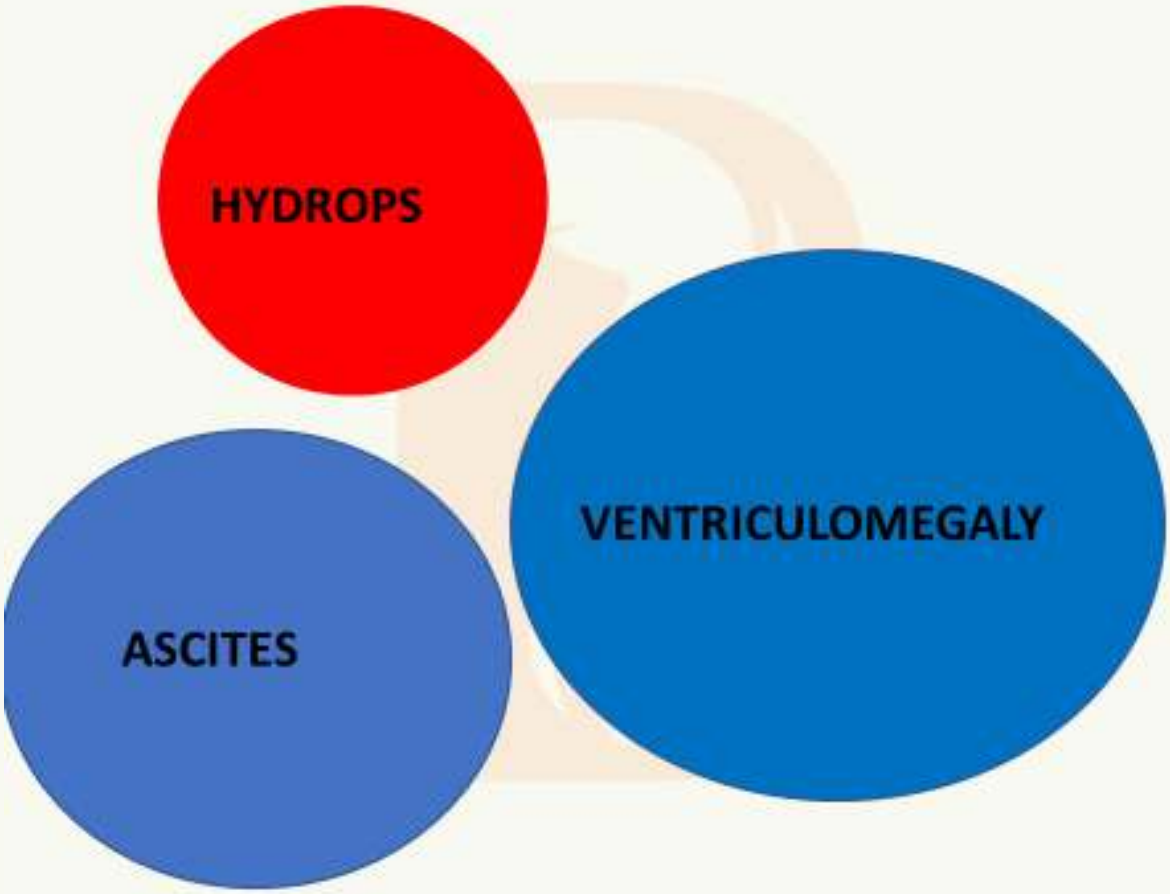
**PARVO VIRUS B19**

**VARICELLA ZOSTER VIRUS**

**SYPHILIS**

**HERPES SIMPLEX VIRUS**

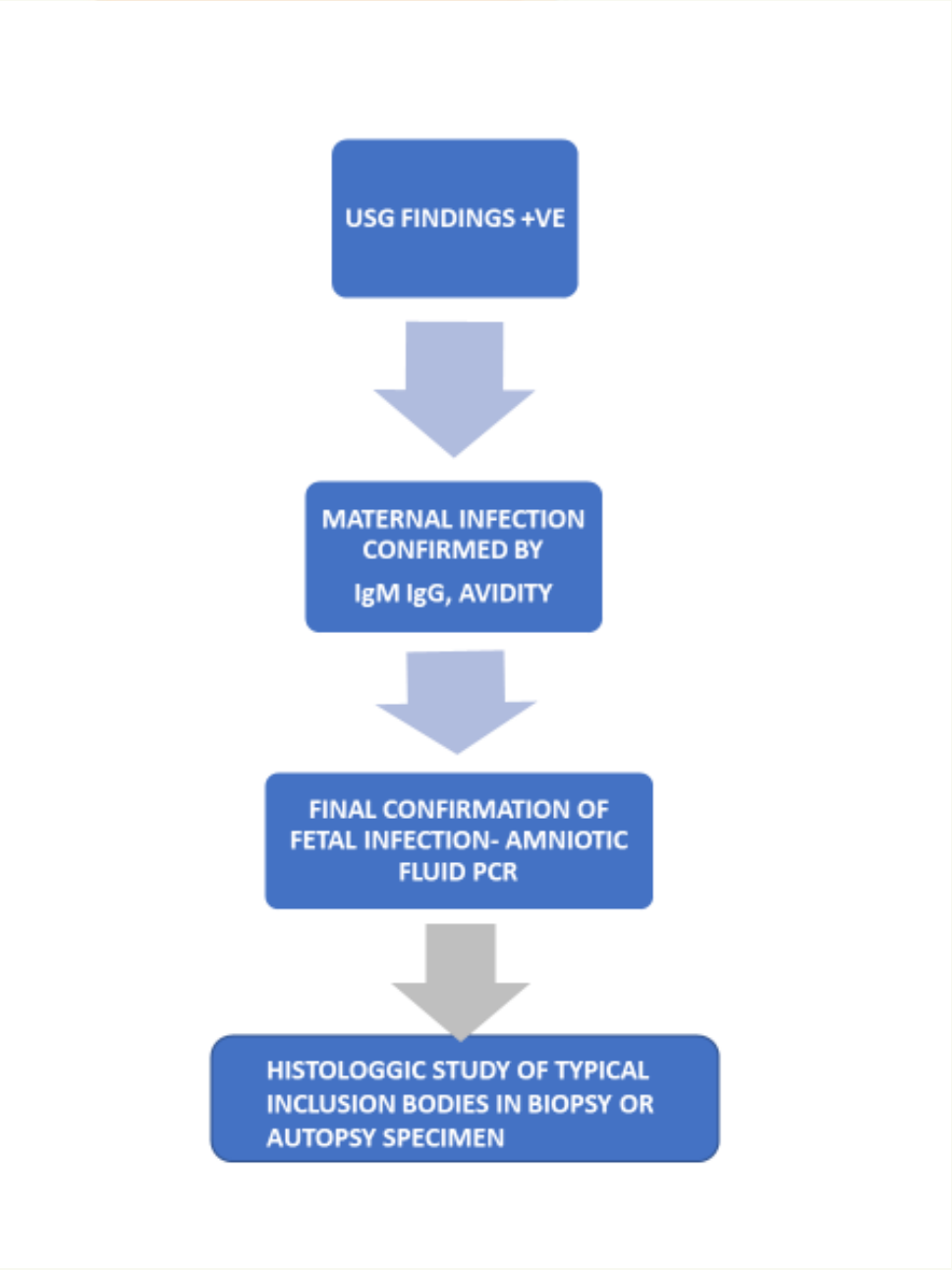
# CYTOMEGALOVIRUS




- DS DNA virus of the herpes family.
- Most common ( 1% all deliveries)
- vertical transmission rate is **40%,** with range of 24%–75%, as per time of infection and maternal serological status.
- **Timing of maternal infection** is linearly correlated with the chances of fetal infection and inversely correlated with the severity of feto-neonatal infection.

| Time of maternal CMV infection | Probability of vertical | Feto-neonatal infection |
|---|---|---|

| | transmission | |
|---|---|---|
| First trimester | 14% | Severe |
| Second trimester | 29% | Moderate |
| Third trimester | 60% | Mild |



## DIAGNOSIS OF MATERNAL INFECTION :

- Most women – asymptomatic .
- Less than 5% report non-specific signs and symptoms such as arthralgia, low fever, moderate lymph node swelling, and mononucleosis-like syndrome.
- preconceptional and early-pregnancy CMV screening not offered in most countries so OFTEN SUSPECTED when fetal signs of CMV are detected on USG.
- Serology- IgM, IgG
- Most reliable test to assess the possibility of CMV(in the absence of a formal maternal serology): **anti-IgG avidity test**.
- IgM may persist in maternal blood up to one year after the end of the acute phase of primary infection.
- **Maternal Serum or Urine PCR can also be done**

| Test result | Interpretation |
|---|---|
| High avidity | Past infection |
| IgM + & low avidity | Primary CMV infection |
| IgM+ & high avidity | Re-infection |

## DIAGNOSIS OF FETAL INFECTION :

- Vertical transmission - **hematogenous** (through infected maternal leucocytes that pass the placental barrier.)
- **Amniocentesis** : **more than 6 weeks** after the primary infection and, anyway, after 21 weeks of gestation.

**six–eight weeks** are needed after maternal infection for the virus to be excreted **in fetal urine**

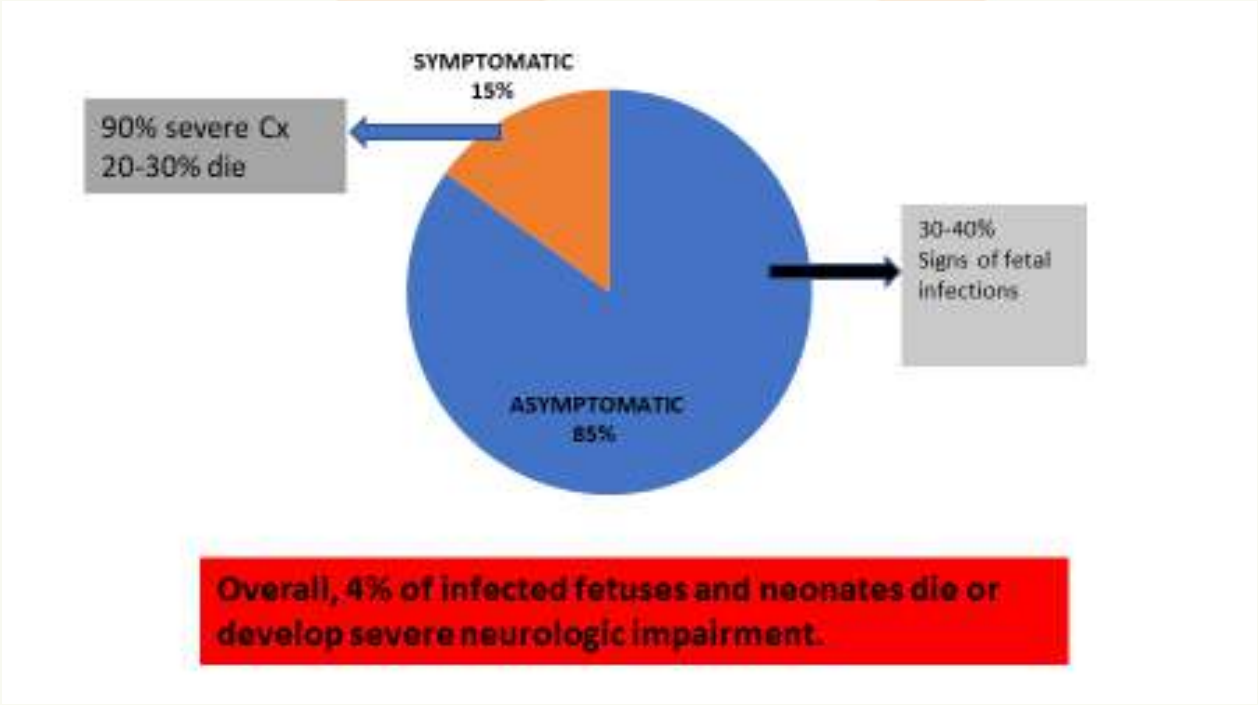
fetal disease is more likely to be **severe** if the infection is contracted **before the 16th week**

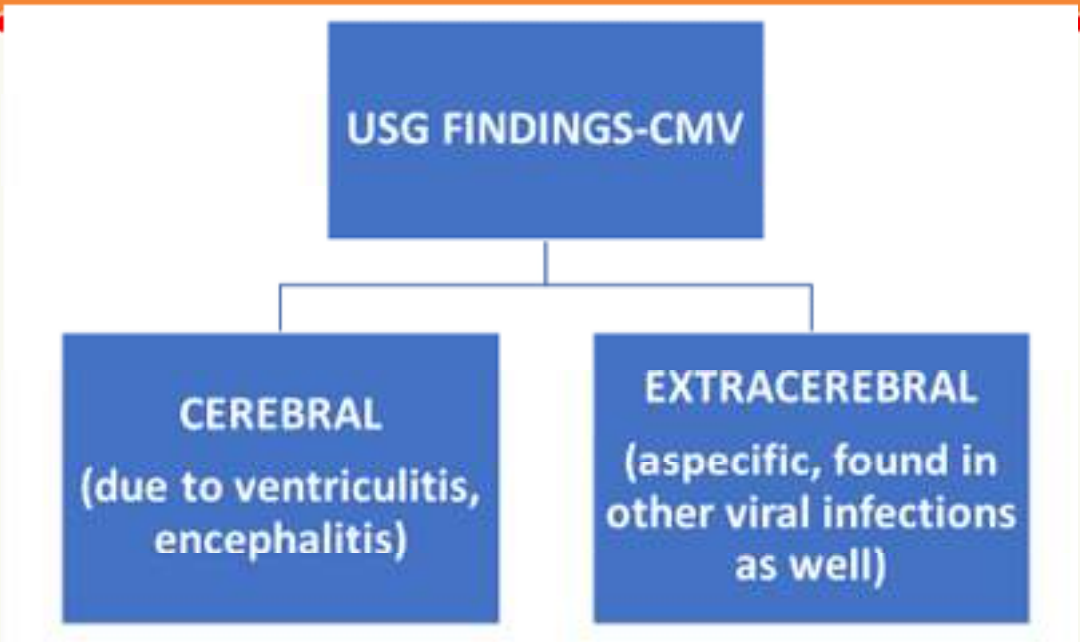
**Qualitative and Quantitative polymerase chain reaction (PCR) for viral DNA** - highly accurate (90%–98% sensitivity and 92%–98% specificity for qualitative PCR).

**Prognostic significance**: **viral load**

| Viral load | Prognosis |
|---|---|
| $<10^3$ copies/mL | **favorable** neonatal out-come<br>no severe damage |
| $>10^3$ copies/mL | **infected** fetuses |
| $>10^5$ copies/mL | **symptomatic** fetuses |

## NEONATAL OUTCOMES- after a primary maternal infection





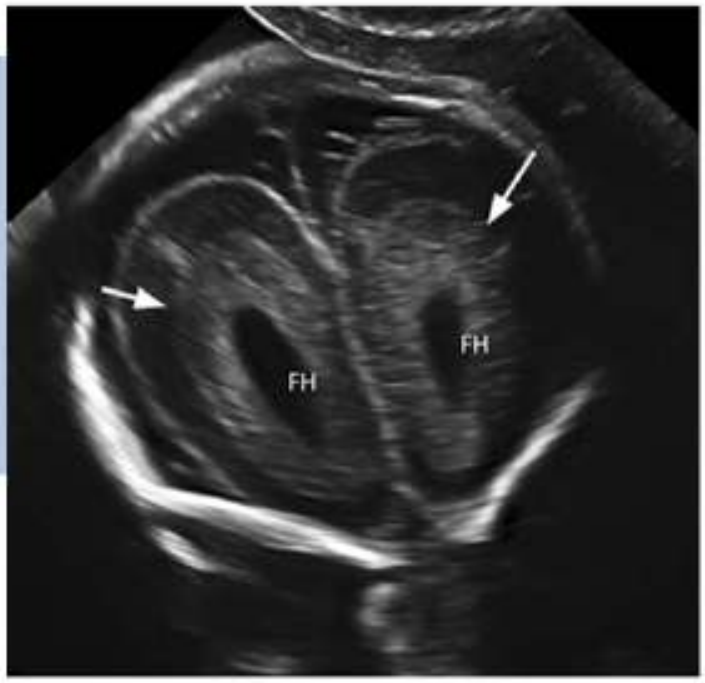

## CEREBRAL SIGNS :

Brain atrophy (microencephaly, microcephaly)

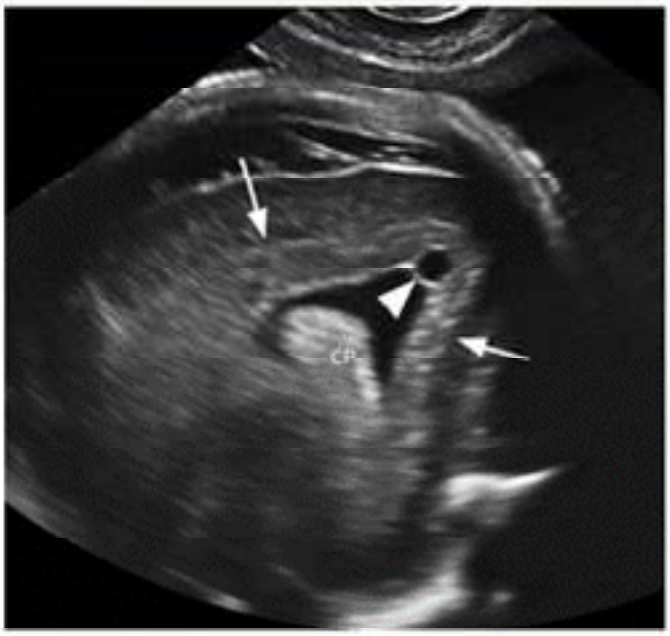
- **Secondary ventriculomegaly** (hemorrhage- thrombocytopenia)
- Obstructive hydrocephalus
- Cortical calcifications (along the vascular distribution)
- Candlestick calcifications of caudate nucleus
- Subependymal edema (halo)
- Fibrin strands in the occipital horn
- Subependymal cysts
- Periventricular focal pattern

  (hyperechogenicity + cysts)
- Hemorrhage (supra- or infratentorial)
- Destruction of corpus callosum

Cytomegalovirus infection at 22 weeks of gestation.
One of the cerebral signs is the presence of a **subependymal halo (arrows), due to inflammatory infiltration** and, on some occasions, cortical necrosis.

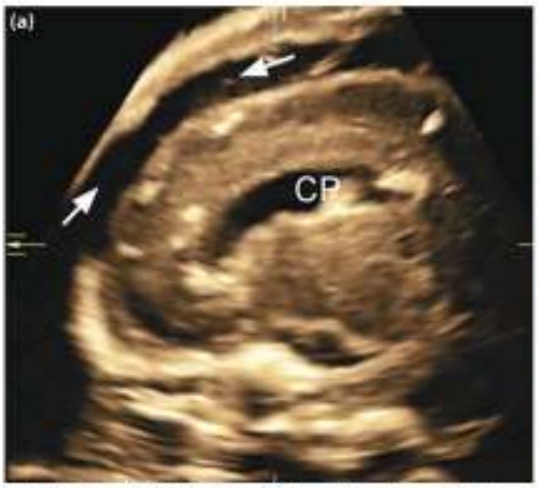



A coronal view at the level of the frontal horns (FH) showing the periventricular subependymal halo (arrows)

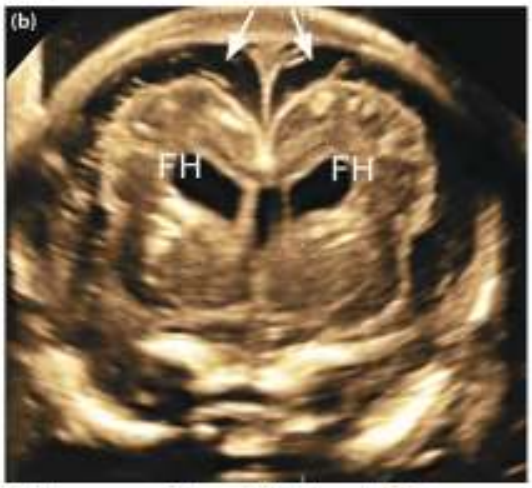



sagittal view of the occipital horn showing the same pattern (arrows) and, in addition, a fibrin strand (arrowhead) typical of the acute inflammatory process. CP: choroid plexus.

Cytomegalovirus infection at 22 weeks of gestation (a and b). **Diffuse calcifications** are seen and also **microencephaly** is evident.

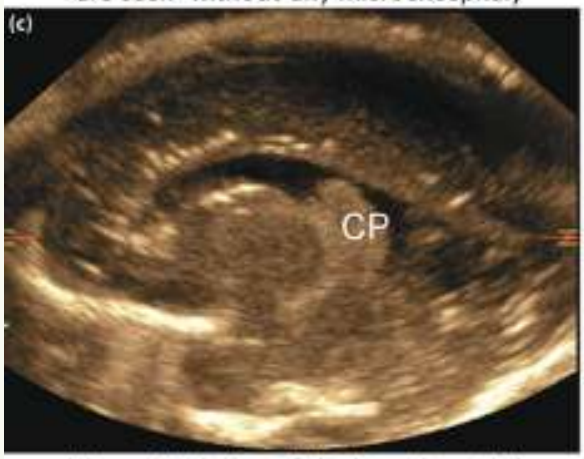



(a) **A sagittal view** of the lateral ventricle showing diffuse calcifications and **widened subdural spaces** (arrows);

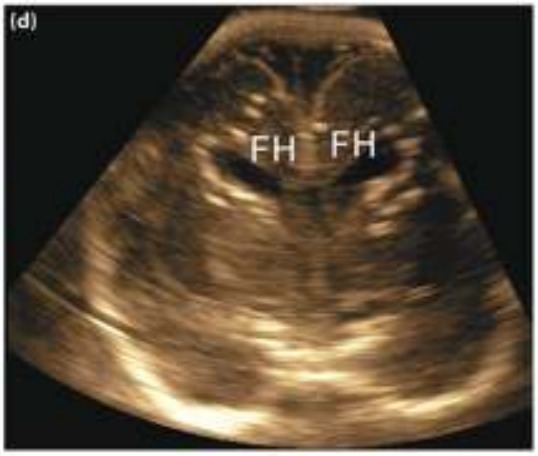



(b) **a coronal view** at the level of the frontal horns (FH) showing the same findings (note the large subdural spaces (arrows) due to the concurrent microencephaly; the **brain is small due to early neuronal loss from severe CMV infection**

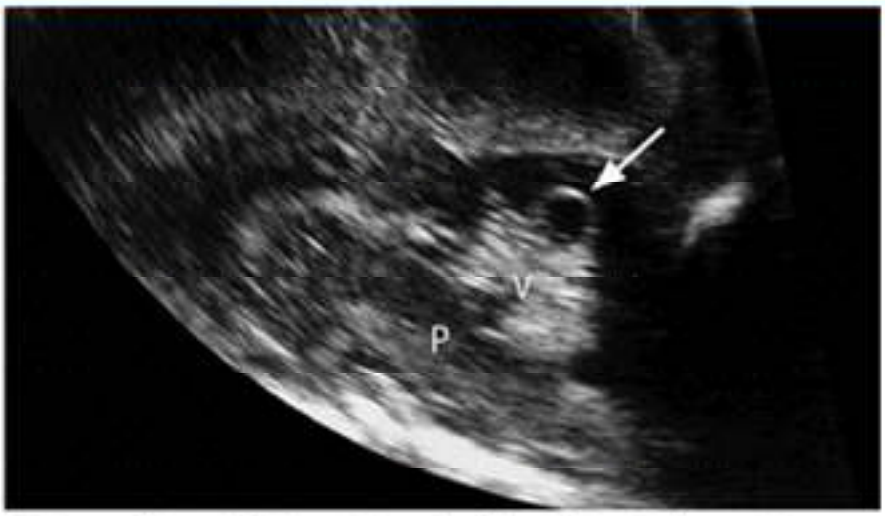
Cytomegalovirus infection at 32 weeks of gestation (c and d) . Diffuse calcifications are seen without any microencephaly



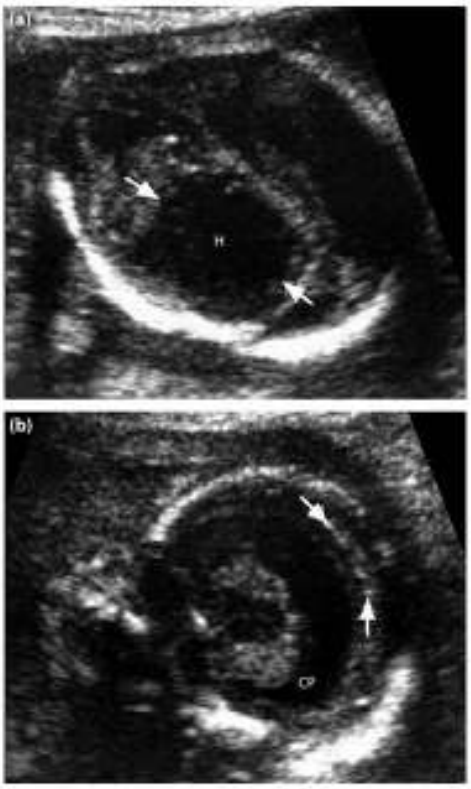

(c) a sagittal view of the lateral ventricle showing diffuse calcifications




(d) a coronal view at the level of the frontal horns(FH) showing diffuse calcification and a normal ratio between brain volume and subdural spaces.



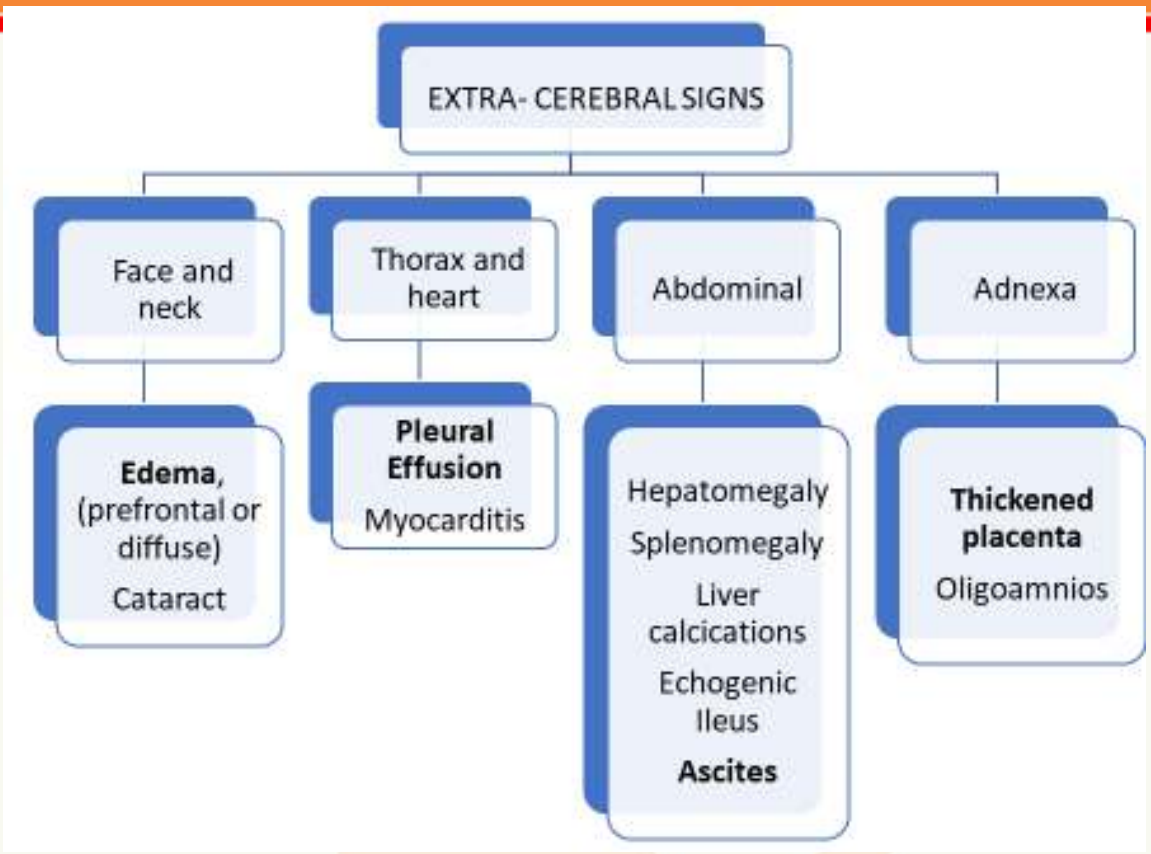

Cytomegalovirus infection at 32 weeks of gestation. In this case, in addition to diffuse cerebral calcification **a cerebellar cyst** also (arrow) was present.
P: pons; V: vermis.



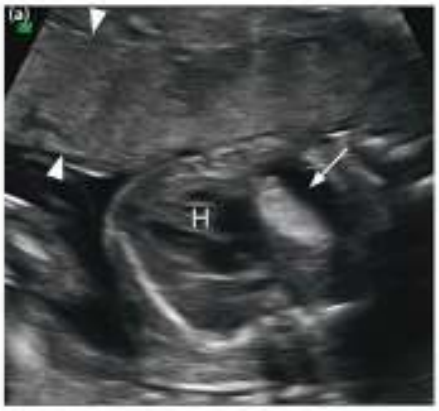

Cytomegalovirus infection at 24 weeks of gestation.

(a) The axial view of the brain shows severe parenchymal hemorrhage of the parietal lobe

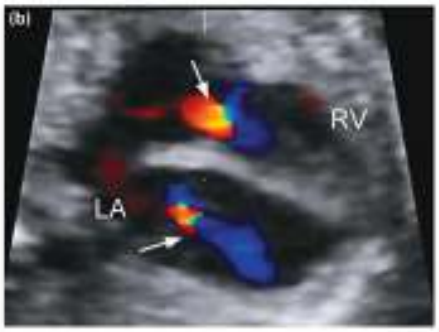
(b) the slightly parasagittal view of the brain demonstrates the associated calcifications.



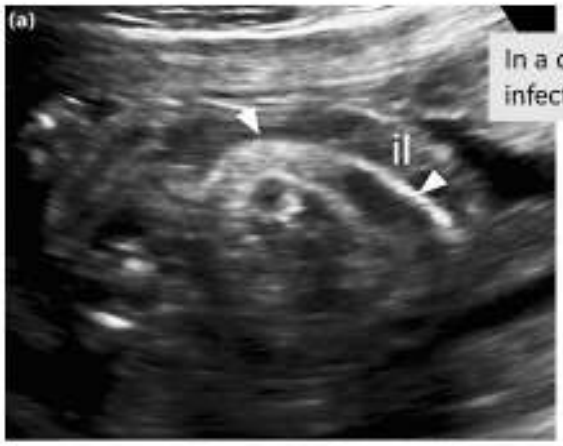

Cytomegalovirus infection at 24 weeks of gestation.




(a) The four-chamber view demonstrates **right pleural effusion** (arrow), associated with a **lung echogenic lesion**, and **thickened placenta** (arrowheads);

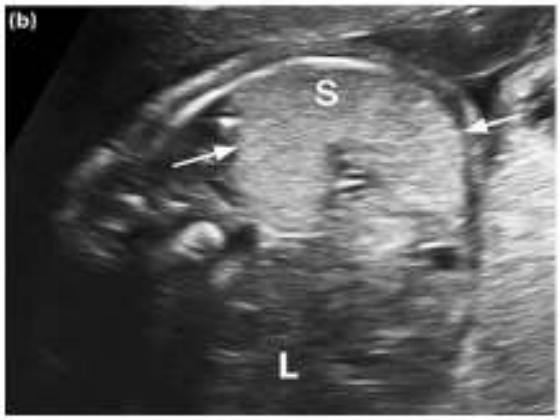



(b) the magnified color Doppler image shows **moderate cardiomegaly and bilateral atrioventricular regurgitation** (arrows), due to **viral myocarditis** (LA: left atrium; RV: right ventricle).

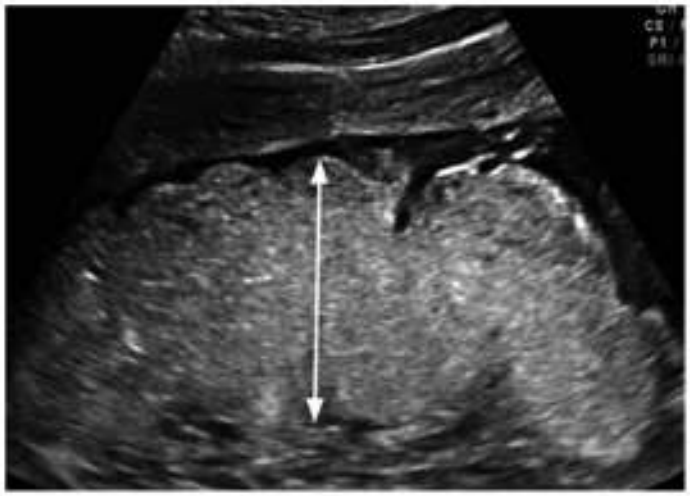



In a case of CMV infection

(a) echogenic ileus




(b) **splenomegaly** (S: arrows) and **hepatomegaly** (L), with the former prevailing on the latter.



Cytomegalovirus infection. Aspecific signs also include thickened placenta (arrows) and oligohydramnios.

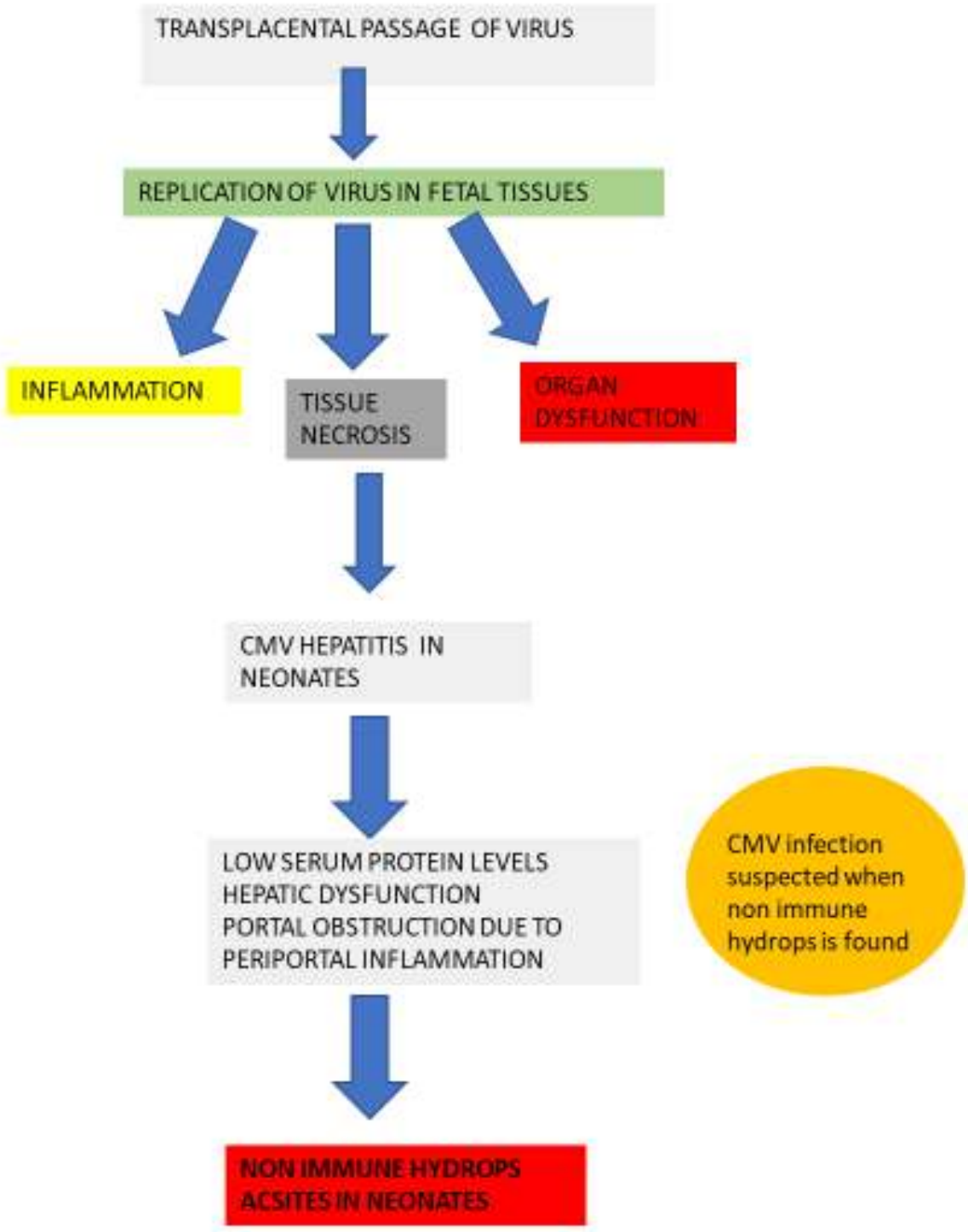
Placental thickness at any stage >4cm placentomegaly

- **USG** - suboptimal accuracy in the prediction of symptomatic and severe infection at birth
- **MRI**: addition of MRI to US increases the positive predictive value but cannot replace USG
- Majority of studies concluded that fetuses with negative US and negative MRI are highly likely to be asymptomatic and well after birth
- But most of these studies were carried out between 28 and 34 weeks, use of mid trimester MRI would be debatable in countries like India where Abortion Law Limit is 20 weeks of gestation

## THERAPY- UNDER TRIAL

- Ganciclovir, Foscarnet, Cidofovir- treatment in adult
- Not proven in fetal infection
- Most promising – Hyperimmune globulin – under trial

# PATHOGENESIS



# DIFFERENTIAL DIAGNOSIS

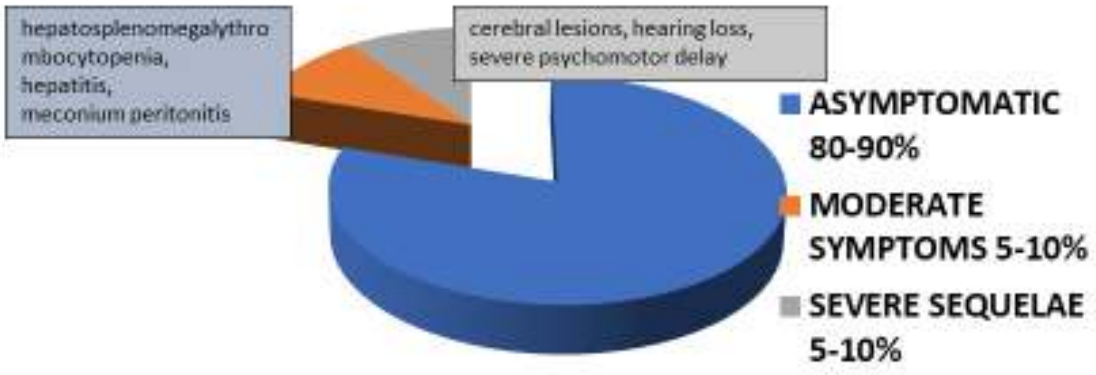
**ASCITES AND HYDROPS:**
- OTHER CONGENITAL INFECTIONS
- IMMUNE HYDROPS
- FETAL ANEMIA

**INTRACRANIAL CALCIFICATIONS:**
- TOXOPLASMOSIS
- TUBEROUS SCLEROSIS
- HEMORRHAGE

**ECHOGENIC BOWEL**
- CYSTIC FIBROSIS
- DOWNS SYNDROME
- IUGR
- BLOOD SWALLOWED BY FETUS

**HEPATOMEGALY:**
- PRIMARY LIVER DZ
- EXTRAMEDULLARY HEMATOPOESIS

# OUTCOME OF FETAL CMV INFECTION



## PROGNOSIS

NEONATES WITH SYMPTOMATIC CMV:

- POOR PROGNOSIS
- MORTALITY RATE : 5%
- SEVERE MORBIDITY ( NEUROLOGICAL) : 50-60%

CMV HEPATITIS : REVERSIBLE

INTELLECTUAL DISABILITY
MOTOR DEFICIT
HEARING LOSS
} IRREVERSIBLE

NEUROLOGIC MORBIDITY PROPORTIONAL TO ANTENATAL VENTRICULOMEGALY (>15mm)

ASYMTOMATIC CMV –
10%-15% - LATE SEQUALE
SENSORINEURAL HEARING LOSS AND NEURO DEVELOPMENTAL DISORDER

A NORMAL USG – DOESNOT EXCLUDE
POSSIBILITY OF SYMPTOMS IN NEWBORN
OR
LONG TERM COMPLICATIONS

**RECURRENCE RISK :**

- VERY LOW
- Immunity in most patients (post primary infection)
- A small theoritical risk of infection in another pregnancy

# MANAGEMENT

1. Termination can be offered before viability

2. If continuation is chosen: follow up **USG 2-4 weekly** to look for

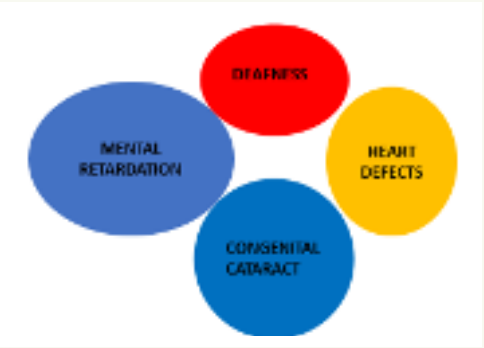
**Growth restriction**
**Hydrops**
**Fetal manifestations**

3. ANTI VIRAL MEDICATIONS: not shown to decrease perinatal transmission

4. HYPER IMMUNOGLOBIN THERAPY : Under trials

## RUBELLA :

- Togaviridae family- RNA virus
- In children- **mild disease** - classic non confluent **maculopapular rash**, which appears on the face first and then disseminates to the trunk and limbs.




- In the adult- **more severe disease-** significant arthralgia, cough, conjunctivitis, and headache.

| Gestation age | Risk of transmission of Rubella |
|---|---|
| **Till 12 weeks** | **90%** |
| **13-17 weeks** | **60%** |
| **18-24 weeks** | **25%** |
| **Last trimester (>30weeks)** | **Increases again to 60%** |

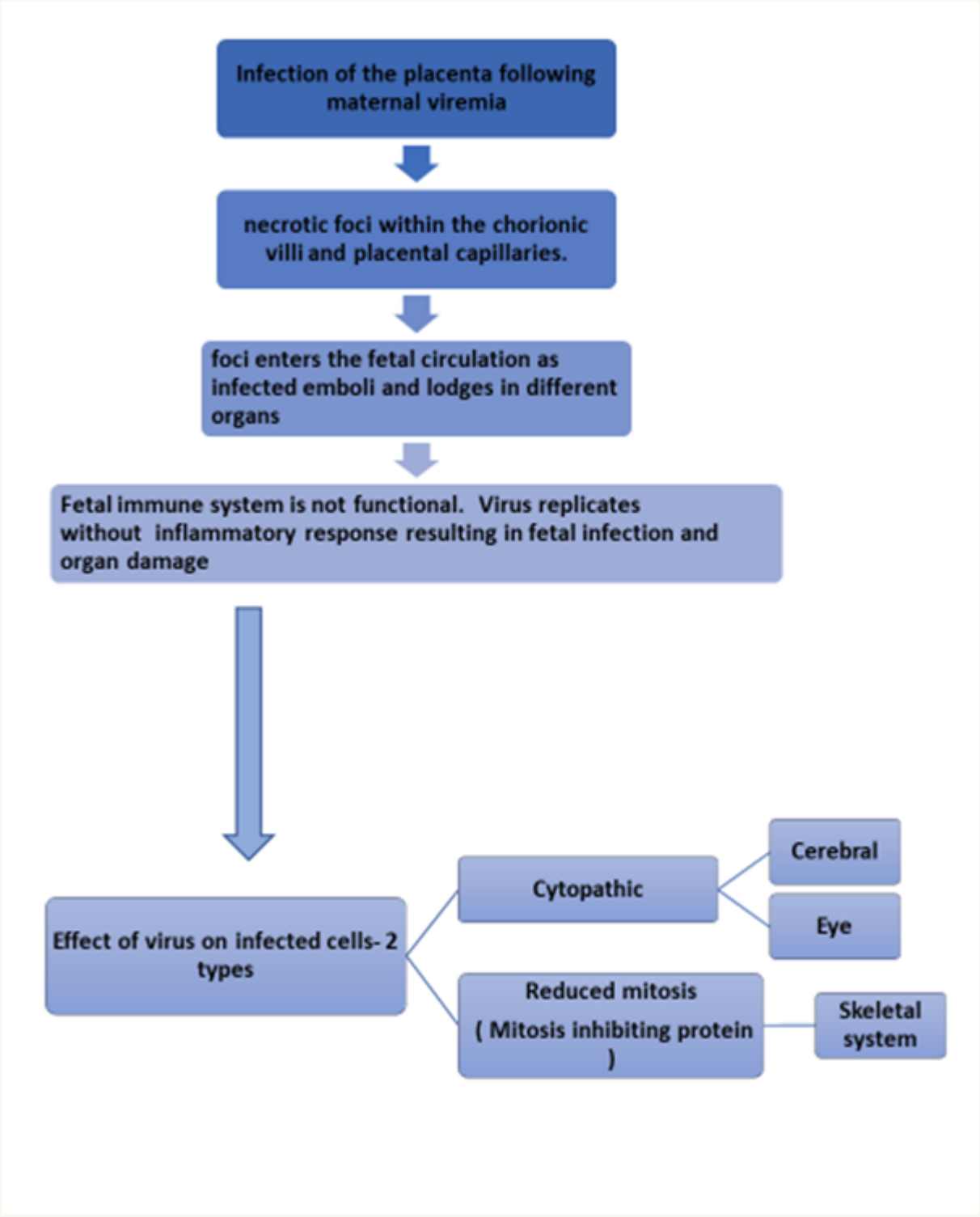
The risk of transmission is up to 90% if the infection is acquired in the first trimester, with 85% of the infected fetuses developing severe infection and/or malformations.

Multiple defects are more common for infections acquired in the first eight weeks of pregnancy.

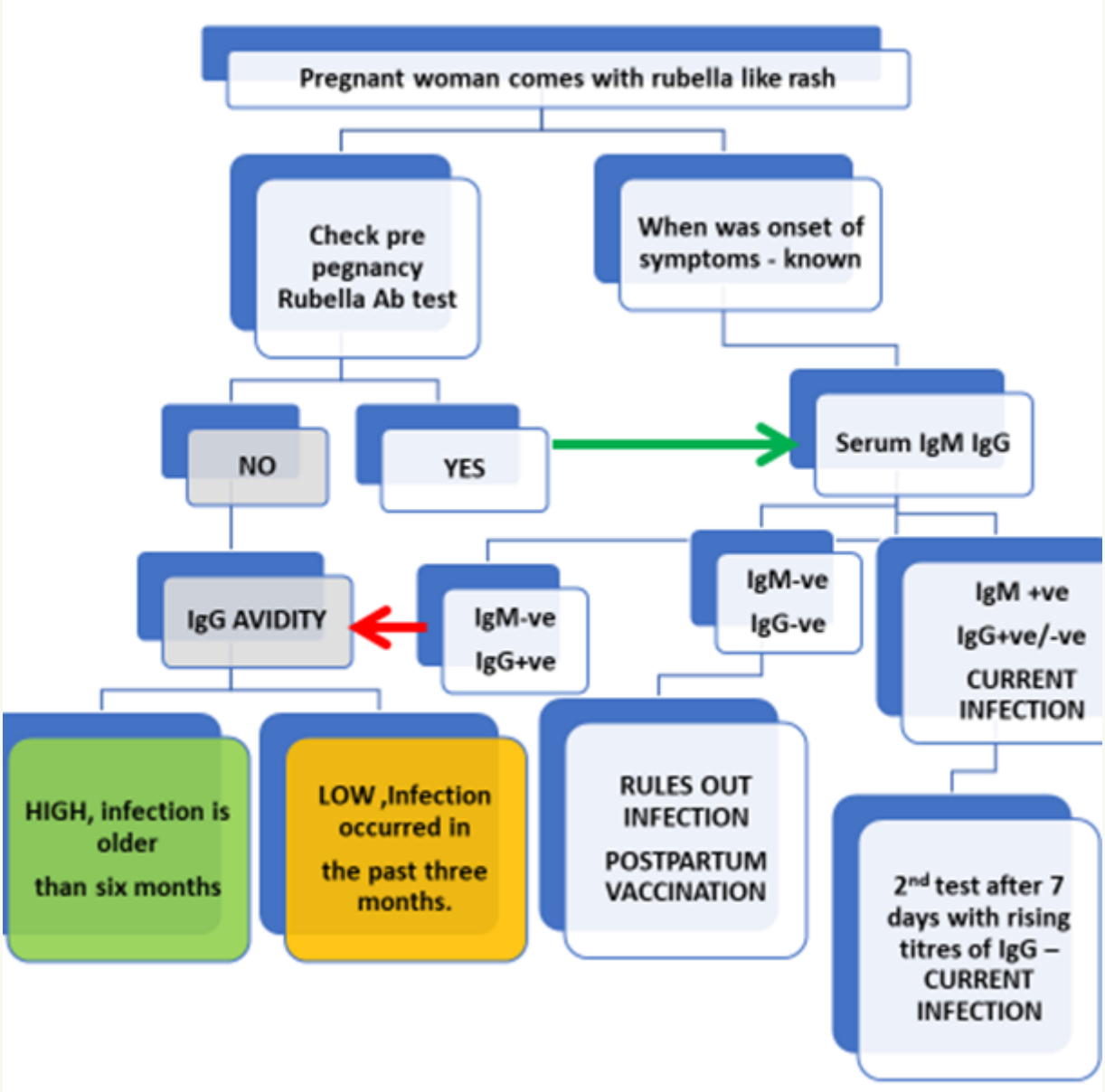
**RISK OF CONGENITAL DEFECTS IS LIMITED TO MATERNAL INFECTION DURING FIRST 16 WEEKS**

**INCIDENCE : VERY LOW – DUE TO COMPREHENSIVE VACCINATION**

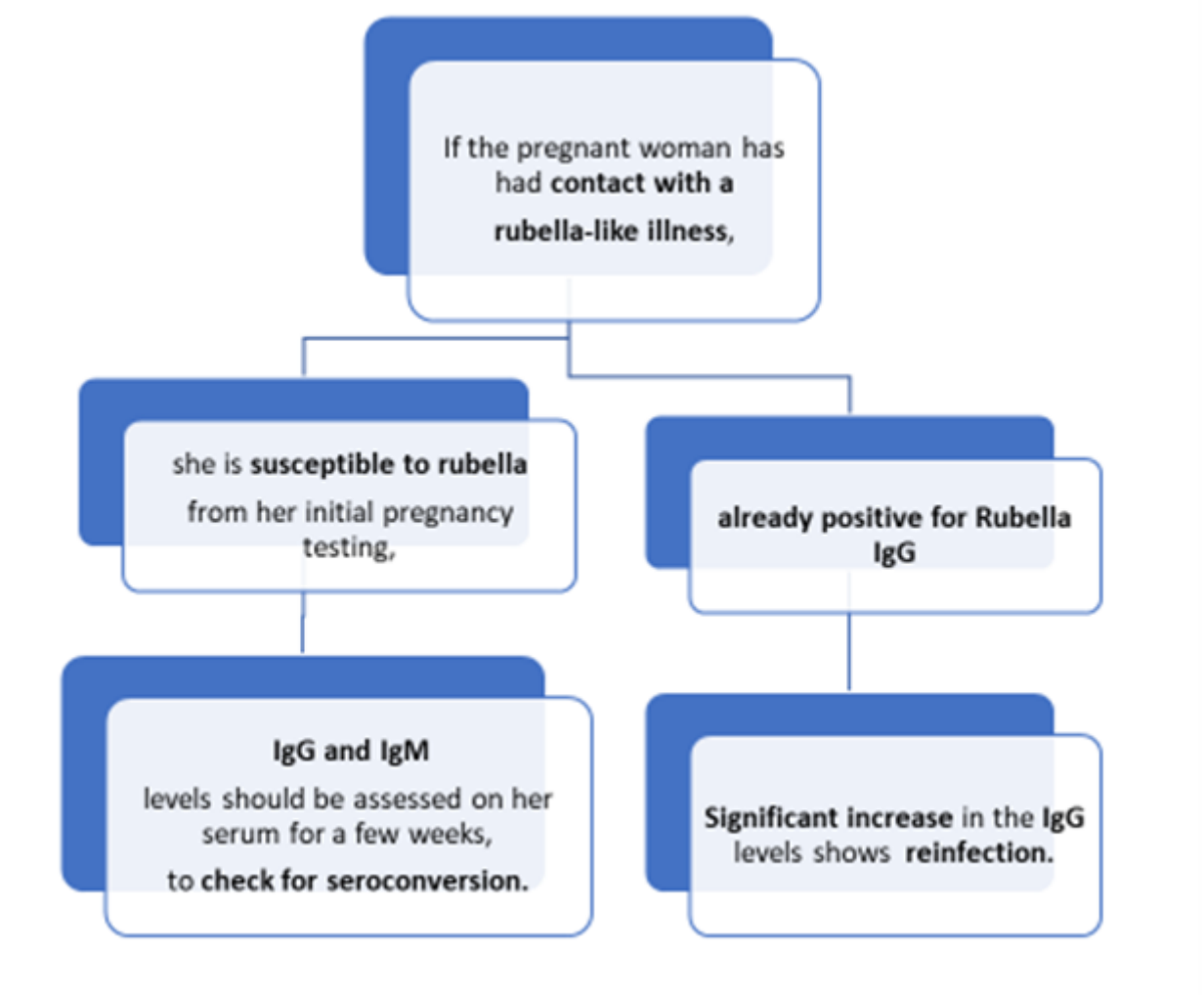
## PATHOGENESIS



## DIAGNOSIS OF MATERNAL INFECTION



## DIAGNOSIS OF MATERNAL INFECTION



## DIAGNOSIS OF FETAL INFECTION :

There are **two issues** that make prenatal diagnosis and US in rubella infection different from other fetal infections :

1. An **initial pregnancy rubeo-test is available** in the

overwhelming majority of cases.

2. most cases are referred because of **maternal rubella or contact with a rubella-like illness**

Therefore, in this case both –
**prenatal diagnosis and US** are carried out in a fetus **known to be at risk for the disease.**

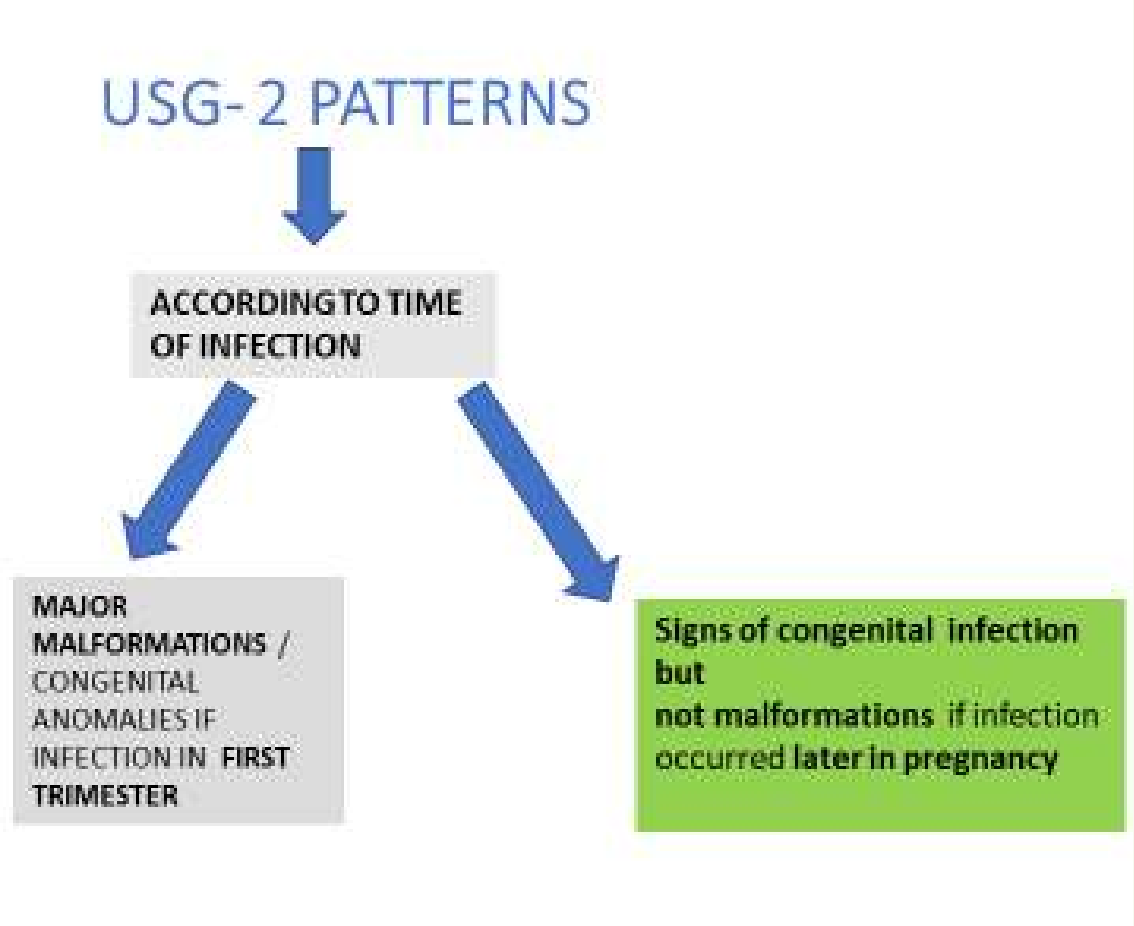
3. Prenatal diagnosis is carried out by checking the **presence of the viral DNA by PCR** on the **amniotic fluid**

**4. more than 7–8 weeks after maternal infection** and anyway after the 21st week of gestation.

**5. Reverse transcription PCR (RT-PCR)** on multiple samples should be used.

## Main Indications for prenatal testing are:

1. **Equivocal IgM results in the first trimester**, which do not allow one to rule out maternal infection
2. When, more frequently, maternal rubella **infection** is confirmed by the lab to have occurred in the **first 12 weeks** of pregnancy
3. When rubella **reinfection** is confirmed to have occurred in the **first 12 weeks** of pregnancy.


USG- 2 PATTERNS
ACCORDING TO TIME OF INFECTION
MAJOR MALFORMATIONS / CONGENITAL ANOMALIES IF INFECTION IN FIRST TRIMESTER
Signs of congenital infection but not malformations if infection occurred later in pregnancy

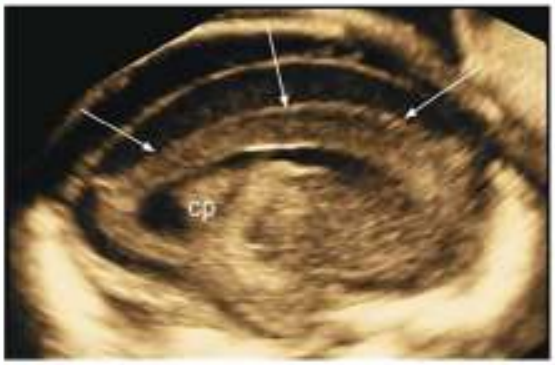
## MAJOR MALFORMATIONS / CONGENITAL ANOMALIES IF INFECTION OCCURS IN 1st TRIMESTER

| ORGAN | MALFORMATION | EFFECTS |
|---|---|---|
| **CEREBRAL** | Microcephaly,<br>Leukoencephalopathy<br>Basal ganglia calcifications<br>periventricular halo | Neuronal loss<br>Severe mental retardation<br>Central or neurosensory hearing loss |
| **EYE** | Microphthalmos<br>Cataract | Blindness |
| **CARDIAC** | patent ductus arteriosus (Most common)<br>pulmonary artery stenosis or atresia (2nd Most common), septal defects | PDA - represents 30% of all<br>cardiac defects seen in congenital rubella.<br>Not detectable in utero. |
| **SKELETAL** | Celery stalk metaphysis in<br>Long bones and clavicle | No residual effects |
| **OTHERS** | Hepatomegaly<br>Splenomegaly<br>Growth restriction | |

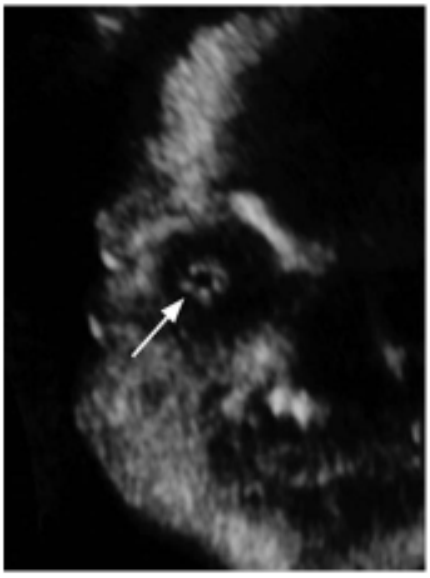
## USG DIAGNOSIS :

Signs of cerebral involvement are similar to those seen with CMV infection:

- periventricular halo
- basal ganglia calcifications (candlestick aspect)
- microcephaly (late onset).




case of confirmed rubella infection at 28 weeks, the parasagittal view of the cerebral hemisphere demonstrates the periventricular halo (arrows).

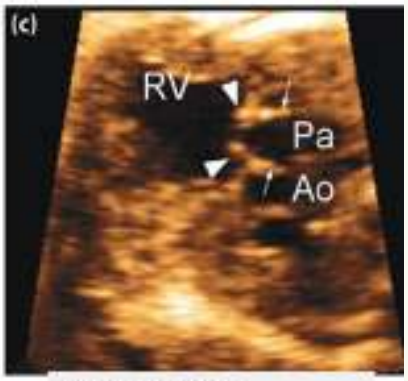


coronal view of the fetal face demonstrates the opacity of the lens (cataract: arrow)

**Fetal echocardiography demonstrates the presence of moderately severe pulmonary stenosis, due to a inflammatory process**


(a) on color Doppler, during systole, the incompletely open cusps are visible and determine significant stenosis of the lumen. Aliasing and turbulence, due to high velocity of the jet across the valve, are also visible (arrow).

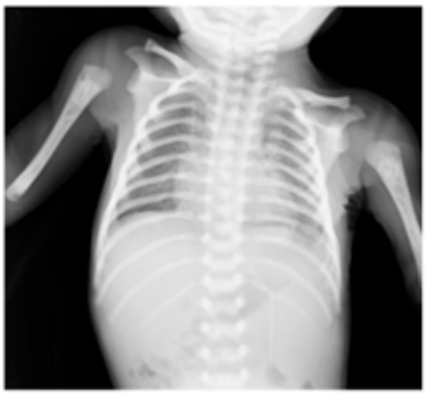

(b) During diastole, a regurgitant jet across the hypomobile valve is visible (arrow)




(c) on three-dimensional surface rendering, the restricted valvar orifice (arrowheads) and the poststenotic moderate dilatation (arrows) of the main pulmonary artery are visible.

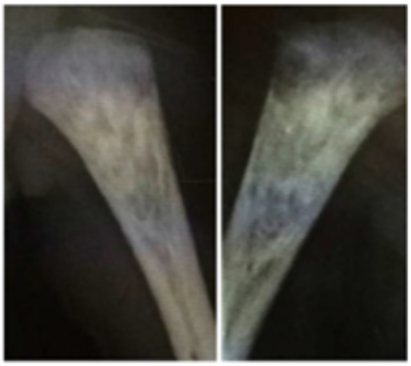
## RUBELLA :

Chest Xray of a neonate having osseous manifestation of CRS



proximal humeral metaphyses revealed the classical radiological appearance of metaphyseal radiolucent bands commonly described as the 'celery stalk metaphysis

focal osteoporosis is responsible for the radiological appearance of radiolucent metaphyseal bands



These bony lesions are only seen in the first few weeks of life, do not recur and are generally not associated with any permanent residual effects

## ASSOCIATED ANOMALIES :

- ❑ Renal disorders
- ❑ Hypospadias
- ❑ Cryptorchidism
- ❑ Meningocele
- ❑ Glaucoma

## OUTCOME :

The outcome of rubella infection is POOR, especially if contracted in the first 12 weeks of gestation - an 80% vertical transmission rate with 85% of malformations in infected fetuses.

This is why termination of pregnancy is often chosen on confirmation of fetal infection.

## PROGNOSIS :

- Risk of spontaneous abortion and IUD
- Postnatal impact varies from- absence of any defect--- to---all anomalies mentioned earlier
- Rubella virus may remain for years in body tissue leading to complications of **chronic infection** like **Chronic viropathy of pancreas – Diabetes Mellitus**

## RECURRENCE RISK :

**NO RECURRENCE RISK OF FETAL RUBELLA SYNDROME**

## MANAGEMENT :

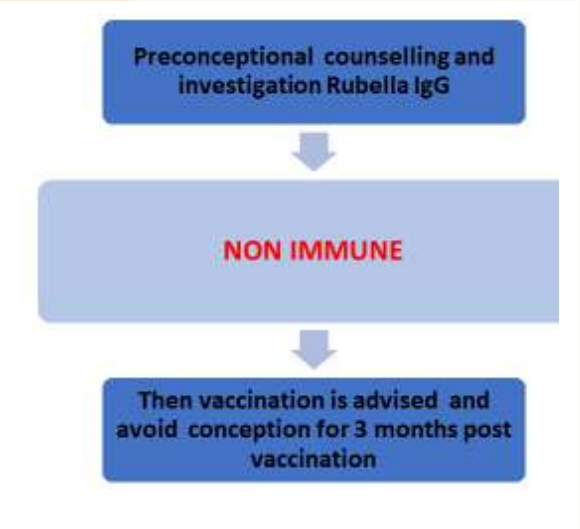
**Termination** should be discussed if fetal infection detected during first trimester

After viability monthly USG for growth and follow up of anomalies is recommended

## PREVENTION :

- Women found NON IMMUNE during pregnancy should be offered vaccination post partum prior to discharge from hospital

- BREAST FEEDING is NOT a CONTRAINDICATION to vaccination



## CONGENITAL TOXOPLASMOSIS :


- Caused By : Protozoan Parasite- *Toxoplasma gondii*
- Immunocompetent individuals- ASYMPTOMATIC
- Acute Infection in pregnancy – may lead to SEVERE ILLNESS in fetus- Blindness, Epilepsy, Mental Retardation
- Transmitted by eating contaminated MEAT
- Incidence of toxoplasmosis during pregnancy : 1-4 /10000

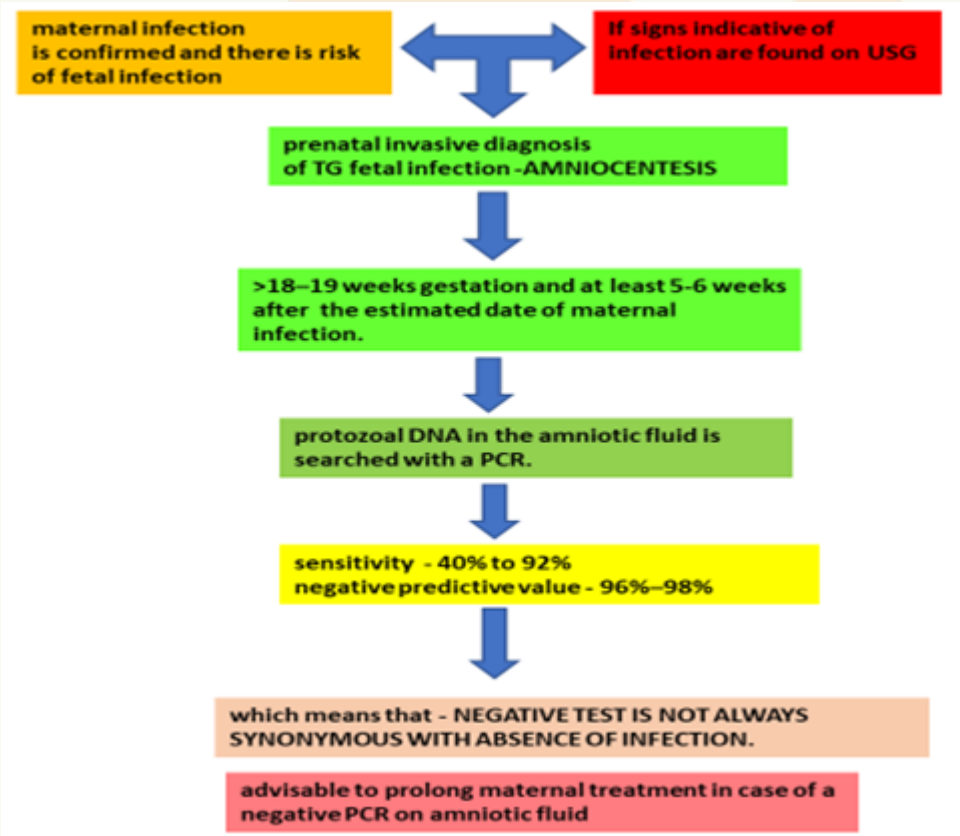
**Transplacental transmission following maternal primary infection**

| Time of maternal infection | Probability of vertical transmission | Feto-neonatal infection |
|---|---|---|
| First trimester | 15% | Severe |
| Second trimester | 30% | Moderate |
| Third trimester | 60% | Mild (Asymptomatic sometimes) |

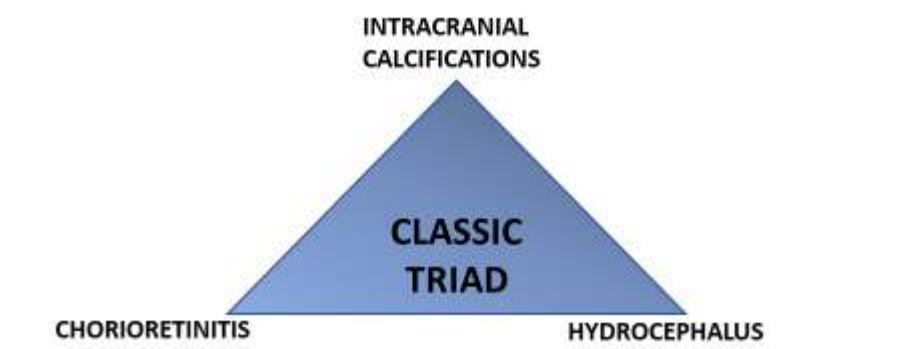
## DIAGNOSIS OF MATERNAL INFECTION :

- In adults, TG infection is asymptomatic in more than 90% of cases.
- The remaining 10% complain of fatigue, fever, malaise and laterocervical lymphadenopathy (typical of TG infection).
- Primary infection leads to lifelong immunity, with the presence of IgG.
- As for the IgM, it has been demonstrated that these antibodies may persist years after the end of the primary infection, making the ascertainment of the exact time of infection sometimes challenging.
- Care should be made in diagnosing a recent infection if both IgG and IgM are positive, because, IgM may persist for years after the end of the primary infection.
- If a former negative Toxo-test (IgG and IgM negative) is not available, then to ascertain whether the infection is recent or not, the IgG avidity should be performed.
- A high avidity indicates an old infection (usually older than six months), whereas a low avidity indicates an infection in the last three months.

## DIAGNOSIS OF FETAL IINFECTION :



## DIAGNOSTIC TRIAD




**CEREBRAL –**
- VENTRICULOMEGALY
- CALCIFICATIONS
- MICROCEPHALY

**MOST INFECTED NEONATES HAVE NO OBVIOUS SIGNS ON EXAMINATION – BUT– MAY DEVELOP LEARNING AND VISUAL DISABILITIES, SEIZURES LATER**

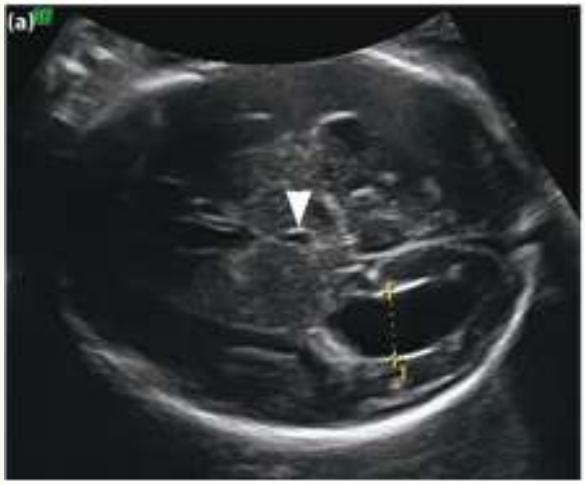
**EXTRA CEREBRAL**

- CATARACT
- ASCITES
- PERICARDIAL EFFUSION
- PLEURAL EFFUSION
- INTRAHEPATIC DENSITIES
- HEPATOSPLENOMEGALY
- ECHOGENIC ILEUS

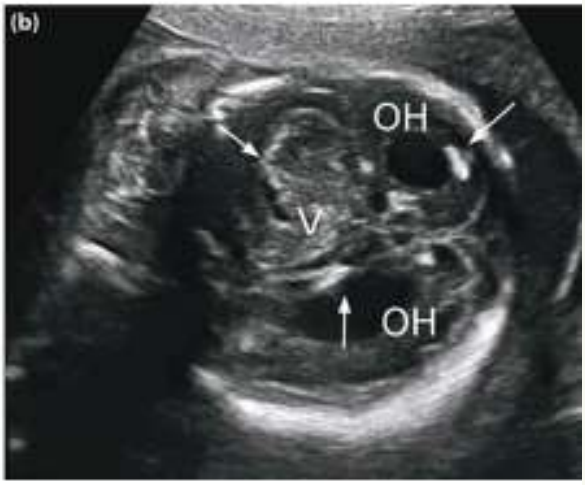
**IF LEFT UNTREATED**

↓

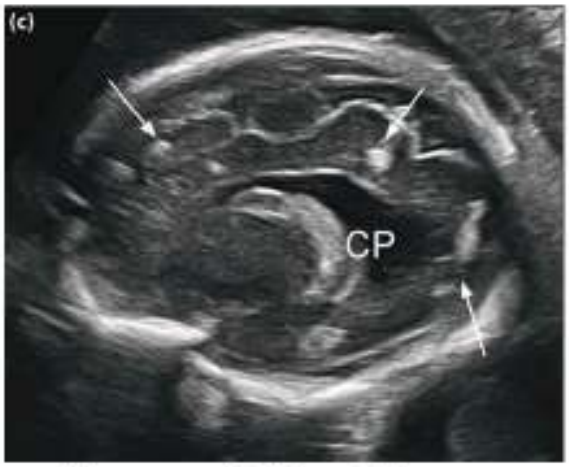
**SEVERE -- FATAL**



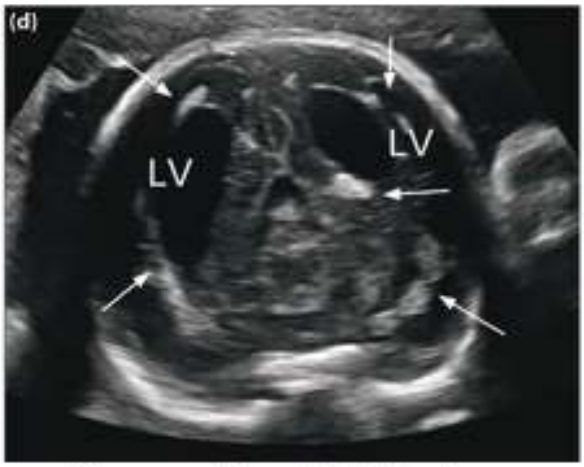
a) Mild ventriculomegaly




b) diffuse calcifications (a coronal view of the occipital horns (OH))

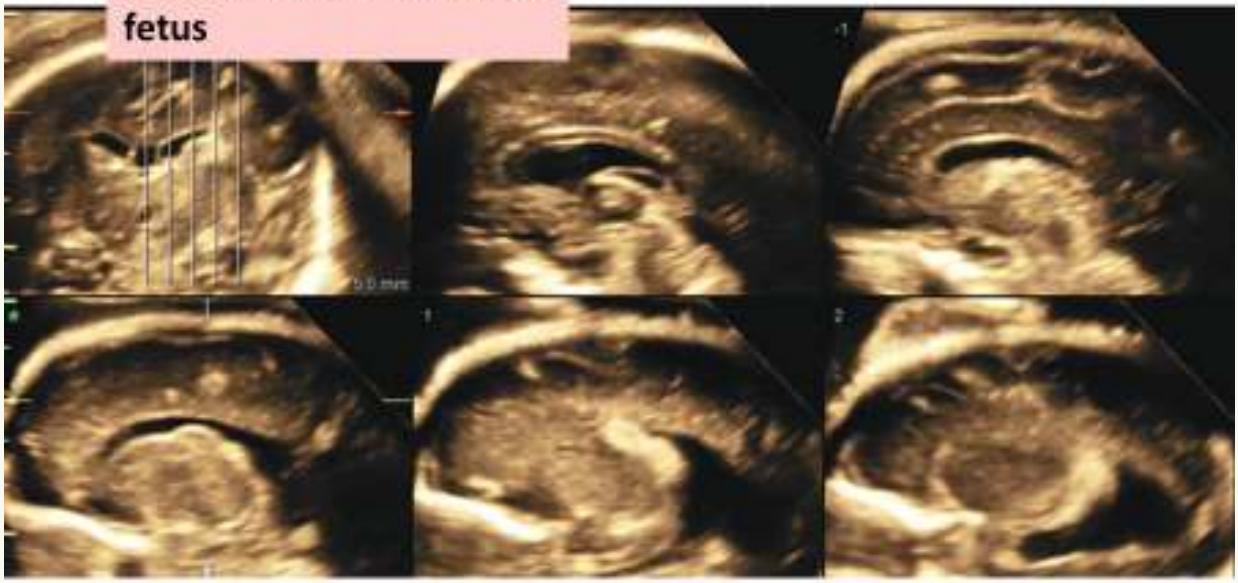



(c) a parasagittal view of the hemisphere and the lateral ventricle showing calcifications(CP: choroid plexus)

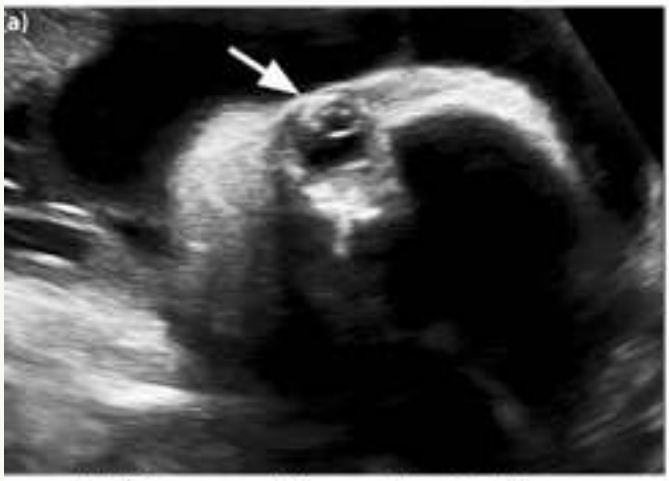



d) a coronal view of the lateral ventricles with calcifications

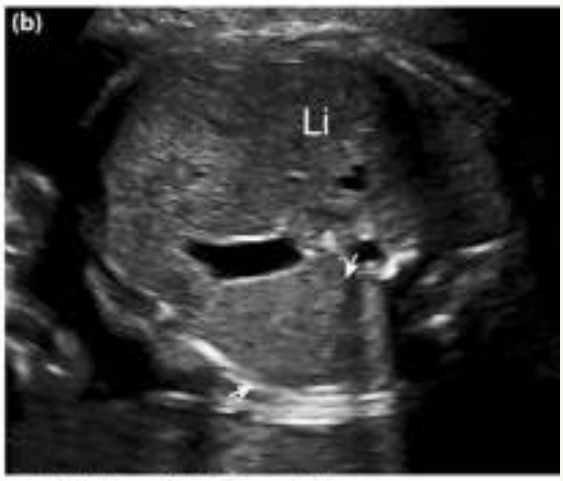
## TG infection in 28 weeks fetus



three-dimensional tomographic ultrasound imaging (TUI) demonstrates strikingly similar findings, with diffuse macrocalcifications. The top-left panel is the reference image showing the positions of the planes displayed in the other five panels (−2, −1, *, +1, and +2).




(a) The coronal view of the fetal face demonstrates a hyperechoic and irregular rim of the lens, consistent with a cataract (arrow)




(b) the axial view of the upper abdomen demonstrates enlarged liver (Li) and spleen (small arrows)

## DIFFERENTIAL DIAGNOSIS :

US signs of TG infection overlap significantly with those of CMV infection .

- Overall, abdominal signs are more frequent in TG than in CMV fetal infection
- Among noncerebral signs, liver calcifications are more likely to be associated with TG, while intestinal dilatation is more frequent in CMV infection.

## PROGNOSIS :

Approximately 75% of congenitally infected newborns are asymptomatic

## RECURRENCE RISK :

There is no recurrence risk

## MANAGEMENT :

1. Antibiotic –Spiramycin is used for prevention of vertical transmission
2. Sulfadiazine alone or as a combination with pyrimethamine – used for treatment.
3. Treatment of acute infection in pregnancy

approximately 50% reduction in fetal infection

If maternal infection occurs up to the **18th week of gestation**

**Administration of oral Spiramycin (1 g every 8 h)** has been shown to **prevent transmission** of the infection to the fetus.

1. Spiramycin is a macrolide antibiotic that **does not cross the placenta, so it cannot be used for fetal treatment** in case of confirmed fetal infection.
2. In the **absence of signs of fetal infection, Spiramycin should be continued until delivery**.
3. It is **safe** for the fetus and may cause only mild gastrointestinal side effects.

## If seroconversion occurs after 18 weeks or fetal infection is confirmed by PCR or US findings

**Pyrimethamine** 50 mg twice daily for two days followed by 50 mg per day

+

**Sulfadiazine** 75 mg/kg per day in two divided doses for two days followed by 50 mg/kg twice daily

+

**Folinic acid** 10 to 20 mg per day.

This schedule has been shown effective in preventing congenital infection and also treating the fetus.

## CAUTION :

**Caution should be used in administering pyrimethamine, because this drug is a folic acid antagonist and, as such, is teratogenic during the first weeks of pregnancy.**

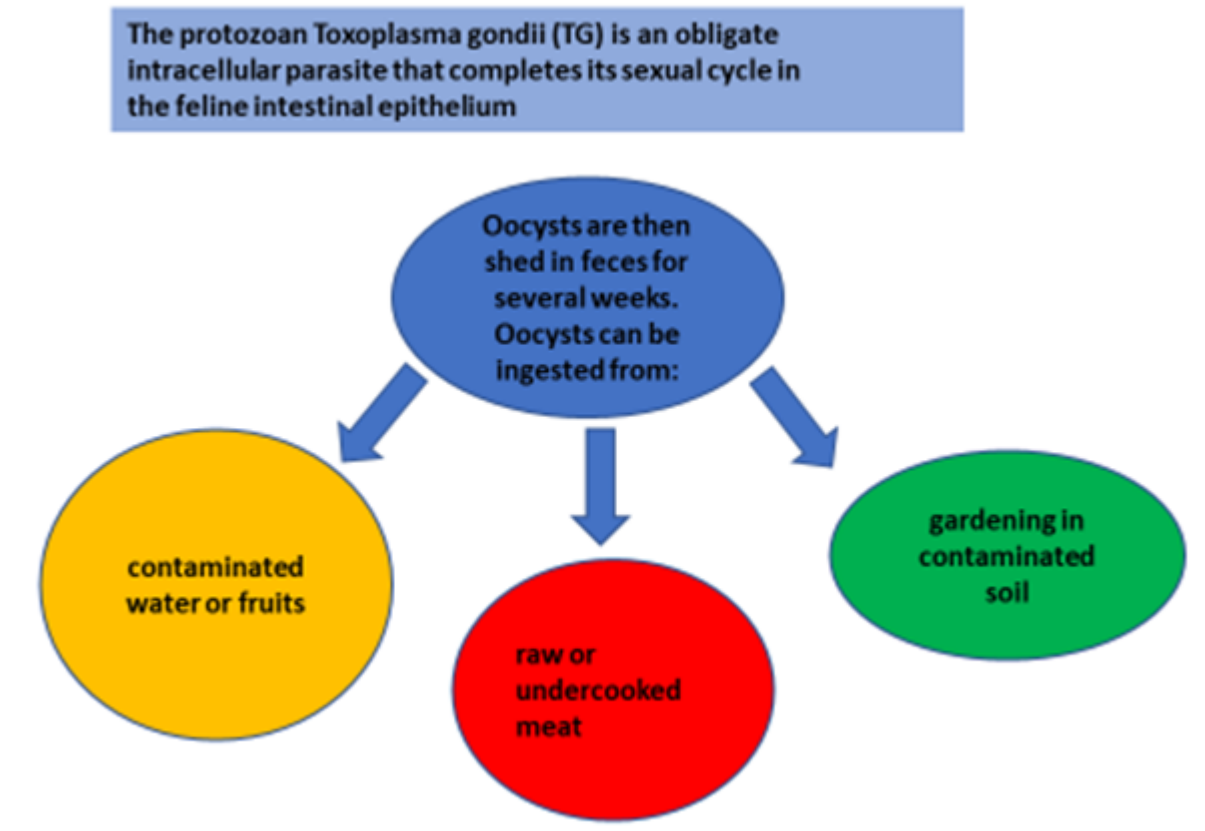
**Since it may cause significant bone marrow depression, repeated red blood cell counts should be scheduled during treatment.**

**The concurrent administration of folinic acid is meant to**

**prevent hematologic toxicity.**

## PREVENTION :

1. Cooking meat to a safe temperature
2. Peeling or thoroughly washing fruits and vegetables before eating
3. Pregnant women should avoid changing CAT litter ( CATS – Primary host)



## OUTCOME :

- The overall risk of vertical transmission is 10%.
- 30% percent of untreated infected infants develop serious lesions after birth, including chorioretinitis, seizures, encephalitis, and hydro-cephalus; and
- a significant number of neonates who are asymptomatic at birth develop chorioretinitis by adulthood, leading to severe visual impairment in half of them.
- On the contrary, if long-term antibiotic therapy is administered just after birth, most remain asymptomatic (74%) and the rate of chorioretinitis halves (26%).
- Only 1% of cases are expected to have serious brain damage.
- **The evidence that prenatal treatment decreases serious neurological consequences is high.**

## POINTS TO REMEMBER :

### CMV

1. The timing of maternal infection is linearly correlated with the chances of fetal infection and inversely correlated with a poor outcome (highest risk in first-trimester infections)

2. The method of choice for diagnosing fetal infection is an amniocentesis performed after 21 completed gestational weeks, on which both a quantitative PCR for the viral DNA and an amniotic fluid culture are done.

3. 80 to 90% of infected neonates are asymptomatic at birth, with only 10%–15% showing mental retardation or hearing loss.

4. If brain lesions are demonstrated by US and/or MRI in a fetus known to be infected (or at high risk of being infected) with CMV, the outcome is likely to be poor and the neonate highly symptomatic.

5. In contrast, if both US and MRI are normal, the outcome is highly likely to be good, with an asymptomatic infection in the neonate and a normal outcome.

6. However, hearing loss and mental retardation also have been found in cases with isolated abdominal signs (echogenic ileus and/or hepatosplenomegaly) and no brain lesions.

7. An early prediction of outcome—in the course

of the second trimester—remains a major challenge.

### RUBELLA

1. Rubella infection in the first trimester is associated with an 80% rate of vertical transmission and 85% incidence of severe malformations in infected fetuses.
2. Unlike other infections, an early rubeo-test (IgG and IgM levels) is available in most cases, which allows adequate assessment of the timing of infection and likelihood of fetal infection.
3. If needed, amniocentesis with an RT-PCR search of viral DNA should be performed after seven–eight weeks from primary infection and after 21–22 weeks of gestation.

4. In consideration of the extremely high risk of severe sequelae, the termination of pregnancy may be offered if the fetus is shown to be infected on amniocentesis, or if major malformations are already evident at US.

## TOXOPLASMOSIS

The timing of maternal infection is linearly correlated with the chances of fetal infection (15, 30, and 60% in the first, second, and third trimesters, respectively) and inversely correlated with a poor outcome (highest risk is in first-trimester infections).

2. Diagnosis of maternal infection is based on seroconversion or positive IgM and IgG, with low IgG avidity due to the sometimes long persistence of IgM in the maternal blood.

3. The method of choice for diagnosing fetal infection is an amniocentesis performed at after 18–19 weeks of gestation, and at least 5–6 weeks after the estimated date of maternal infection.

4. The accuracy of the PCR is highly dependent upon

the quality of local laboratories, and therefore reatment should not be discontinued after a negative result.

. Sonographically detectable brain lesions overlap significantly with CMV ones, but liver calcifications are much more common in TG than in CMV infection.

6. Antibiotic treatment has repeatedly been shown to significantly reduce the risk of severe neurological sequelae in neonates and therefore is mandatory.

7. The antibiotic treatment regimen consists of :

**Spiramycin** in low-risk cases and before 18 weeks, and

**pyrimethamine + sulfadiazine** after 18 weeks,

although no difference in the prevention of severe neurological sequelae has been demonstrated between the two.

**BIBLIOGRAPHY**


- CALLEN'S Ultrasonography In Obstetrics And Gynaecology 6th Edition
- PALADINI and VOLPE Ultrasound of congenital fetal anomalies 2nd Edition
- Arias' Practical guide to HIGH RISK PREGNANCY and DELIVERY – 4th Ediition
- GTG 13 RCOG guideline

# IMMUNE HYDROPS – RH NEGATIVE PREGNANCY

-DR. AMEE RAHATEKAR

**CDE (Rhesus system) – discovered in Rhesus monkey**

- **RBC antigens - c, C, D, e, E**
- **D antigen – its presence determines Rh positivity**
- **Absence of D antigen- Rh negative**

Minor RBC Antigens – Kell, Duffy, MNS, Kidd

## INCIDENCE and PREVALENCE

**RH -VE** **5%**

- Caucasian 15%
- Afro- carribean 7-8%
- Asian 5%
- Chinese and Japnese 1%

**India-**
**North India – 10%**
**South India- 5%**

# LANDMARKS IN RH ISOIMMUNISATION

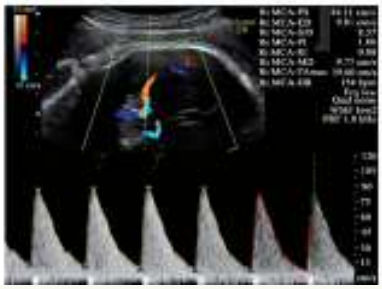
Existence of Rh factor
**Philip Levine 1939**
**Landsteiner 1940**

Liley's Chart for Optical Density on Spectrophotometry of Amniotic Fluid
**Sir William Liley 1963**

First Direct Intravascular transfusion
**Charles Rodeck 1981**


Development of Anti D immune globulin
**William Pollack 1968**

Non Invasive Assessment of fetal anemia
**Mari et al – year 1995**

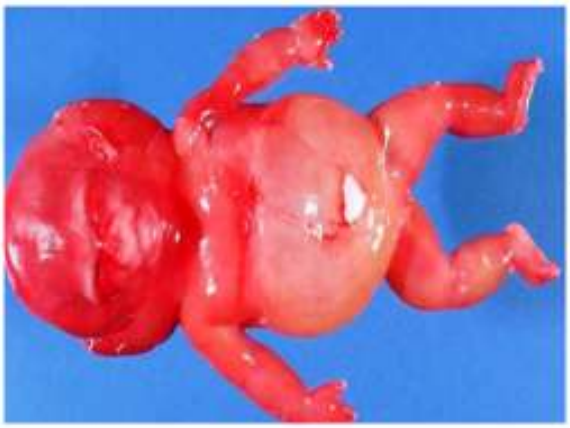


RH NEGATIVE – HIGH RISK

↓

RH ISOIMMUNISATION

**HIGHLY DREADED COMPLICATION- HYDROPS FETALIS**



- **EDEMATOUS FETUS**
- **SEVERE ANEMIA**
- **CARDIAC FAILURE**
- **HIGH RECURRENCE IN FUTURE PREGNANCIES**

RH ISOIMMUNISATION CAN BE PREVENTED

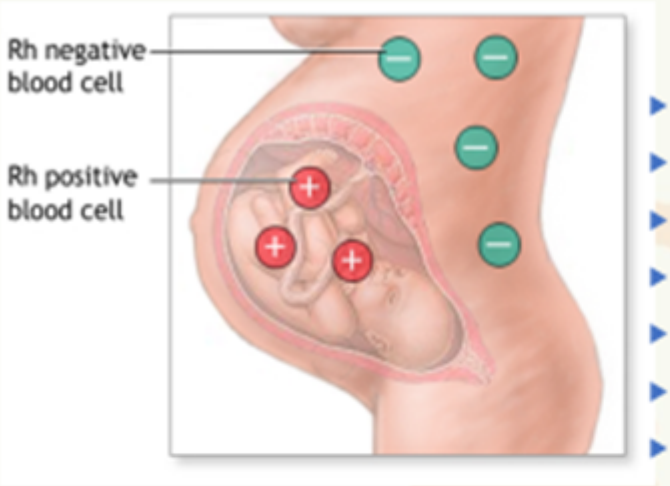
The widespread use of Anti D has lead to decrease in overall incidence of immune hydrops

| YEAR 1970 | YEAR 2000 |
| --- | --- |
| **82%** CASES OF HYDROPS WERE IMMUNE HYDROPS | **10%** CASES OF HYDROPS ARE IMMUNE HYDROPS |

**SUCCESS OF ANTI D**

## PATHOPHYSIOLOGY OF RH INCOMPATIBILITY :

Rh negative mother carrying a Rh positive fetus



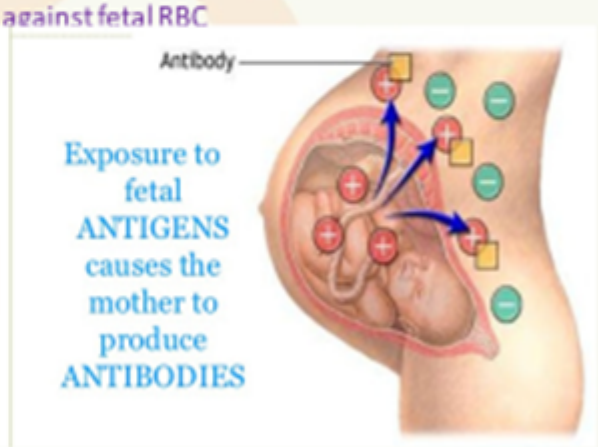

**BREACH IN THIS BARRIER**

- Abortion/ectopic pregnancy
- Antepartum hemorrhage
- Amniocentesis/CVS/Invasive fetal procedure
- External cephalic version
- Abdominal trauma
- Delivery
- Inadvertent transfusion of Rh positive blood

**During pregnancy placenta acts as a BARRIER to fetal blood cells**

Sensitisation- production of IgG antibodies against fetal RBC

- Sensitisation takes time- doesnot affect the first pregnancy usually
- Antibodies once formed remain in maternal circulation throughout life.
- SENSITIZED MOTHER - FOREVER




**1% mothers are sensitized in antenatal period**

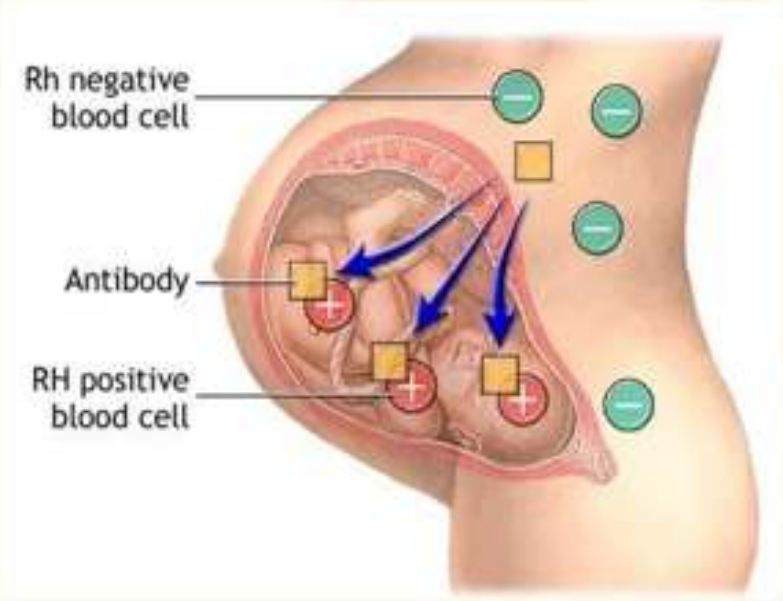
**10-15% sensitized at time of delivery**

**0.25 ml of fetal blood** is the minimum amount required to lead to alloimmunisation

Delivery poses the greatest risk for Rh sensitisation

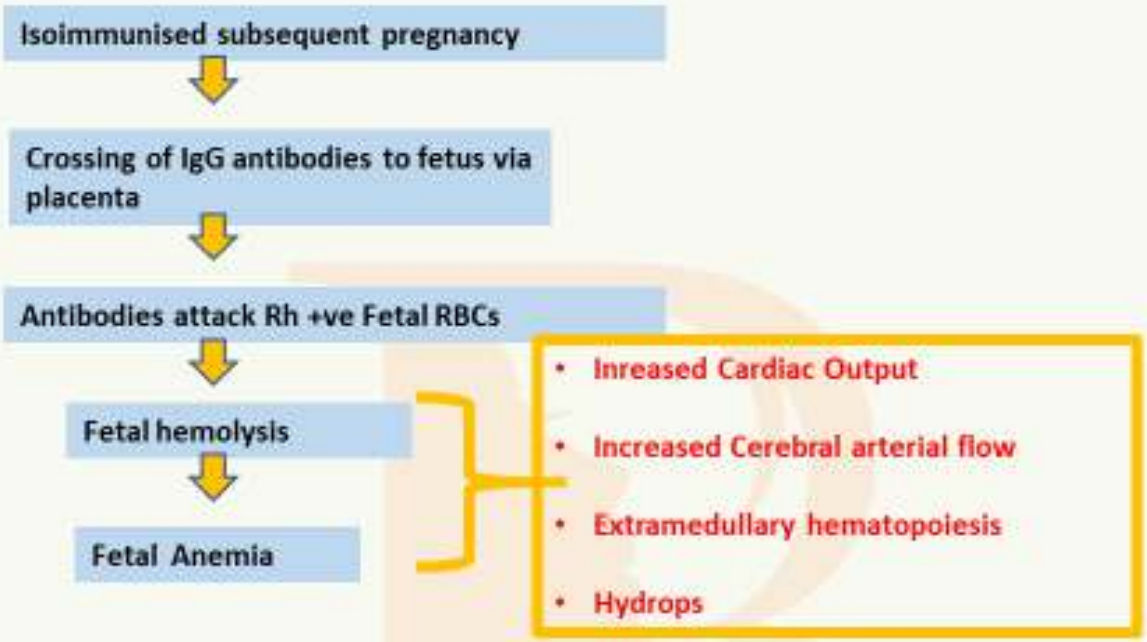
Transfusion of incompatible blood can also lead to maternal sensitisation

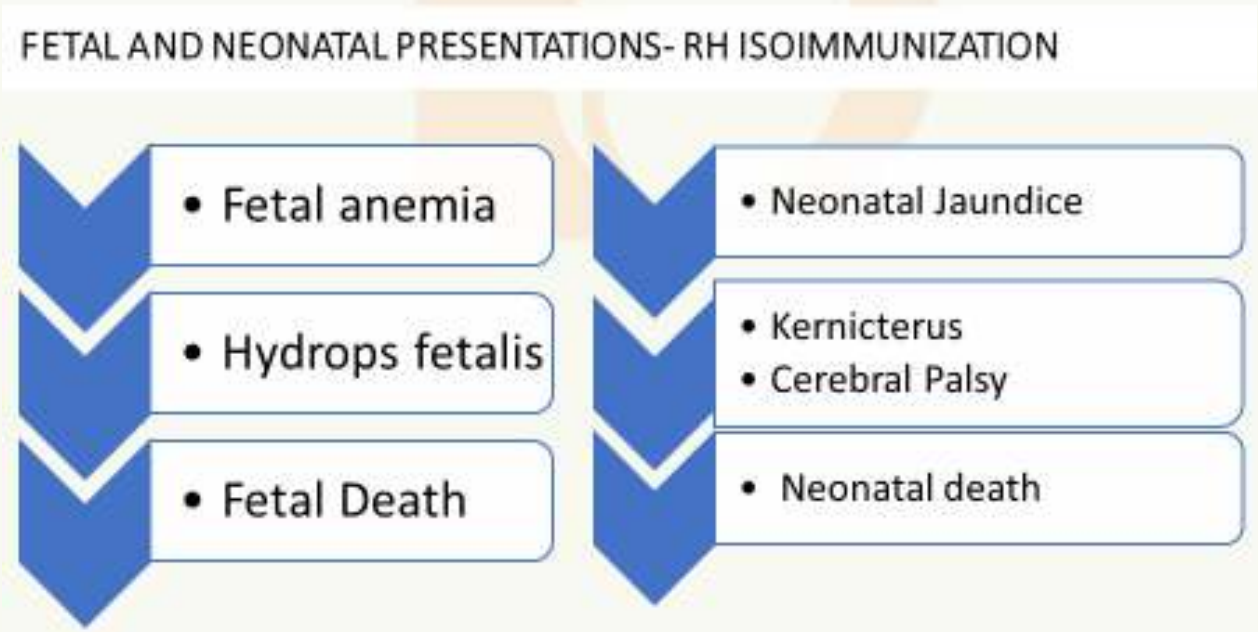
INDIRECT COOMBS TEST - POSITIVE




In the next pregnancy, these Anti D antibodies cross placenta and cause hemolysis of fetal cells leading to a spectrum clinical presentations of Rh isommunisation

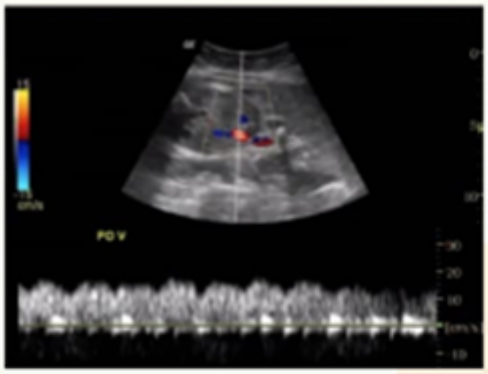
## PATHOPHYSIOLOGY AND ITS CORRELATION WITH ULTRASOUND :

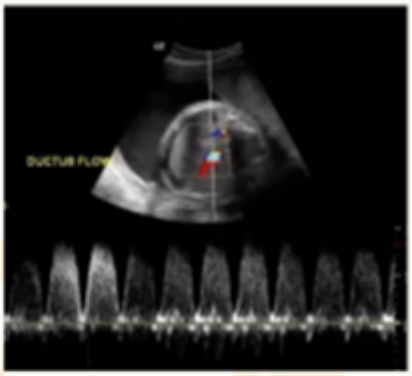


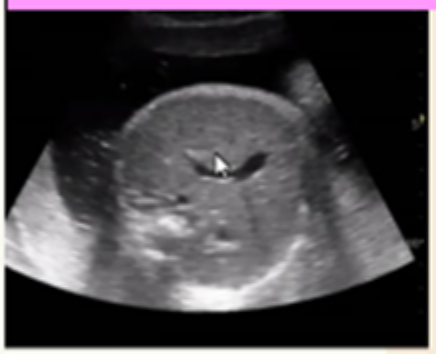
## USG SIGNS OF FETAL ANEMIA :

Hyperdynamic circulation leading to increased flow velocity

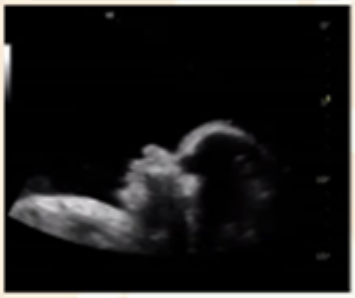




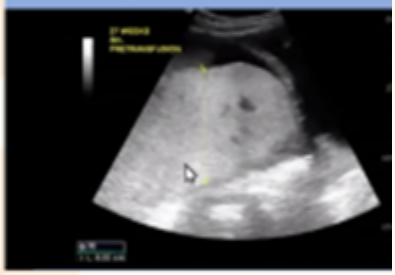
Portal vein diameter >5mm



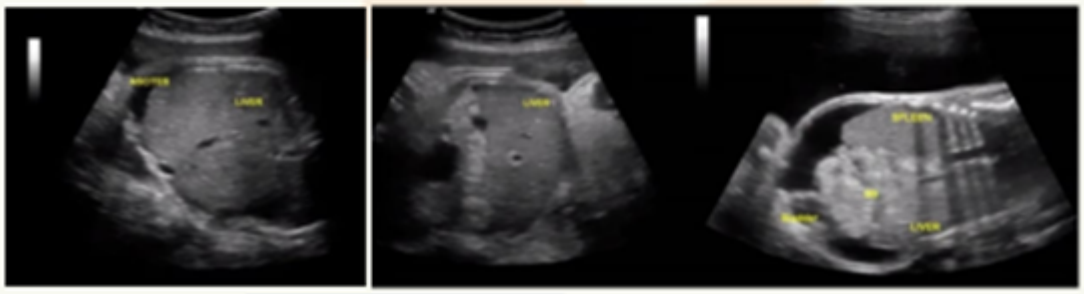
Polyhydramnios



Placentomegaly
Ground glass appearance



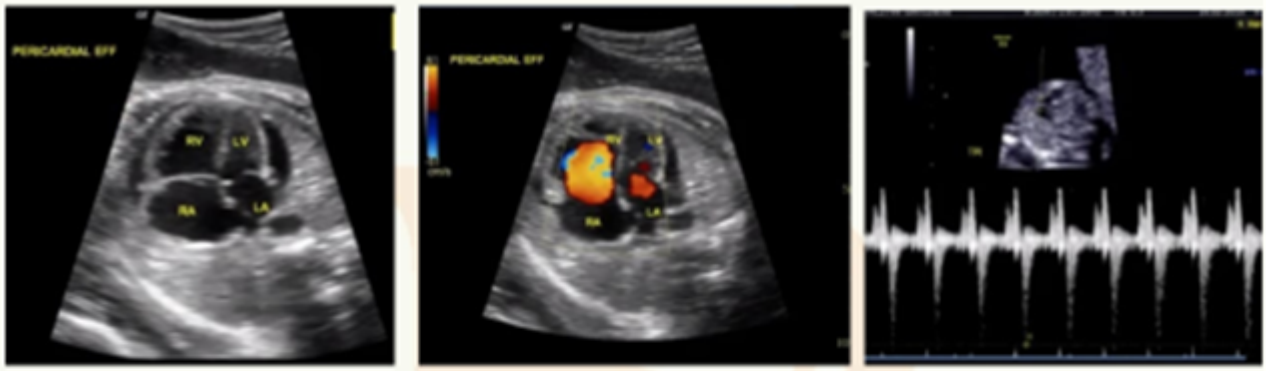
Extramedullary hematopoesis



hepatosplenomegaly

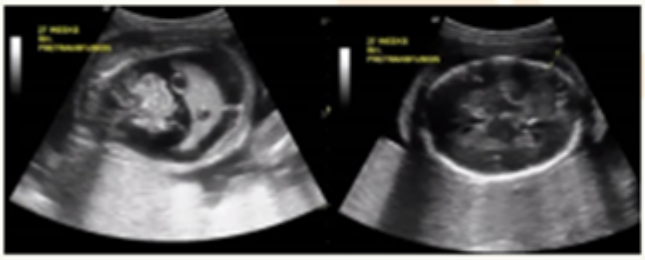
## USG SIGNS OF FETAL ANEMIA :

Increased Cardiac Output

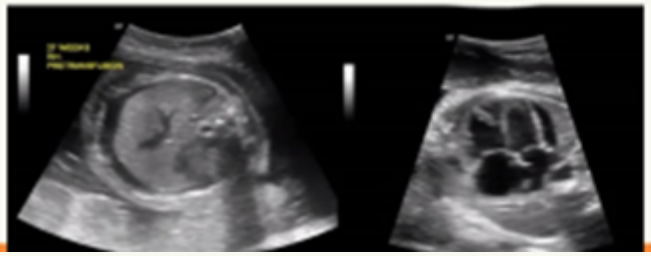


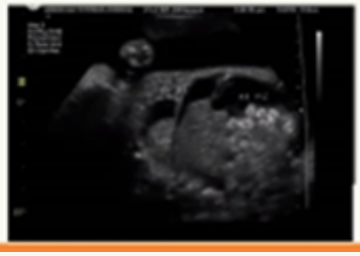
Cardiomegaly
CT ratio >50%
Right Atrial enlargement
Tricuspid Regurgitation
Pericardial effusion

Hydrops is pathologic accumulation of excessive fluid within two or more fetal compartments- scalp edema, bodywall edema, ascites, pleural effusion, pericardial effusion, polyhydramnios and placental thickening



- High output cardiac failure
- End stage sign of fetal anemia
- Appears at Hb<5gm%

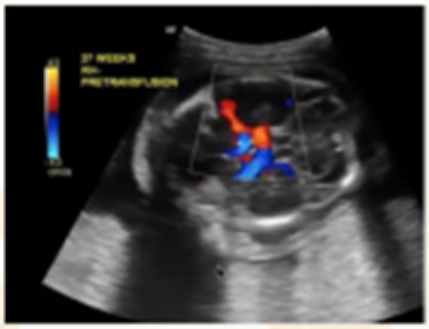




## USG SIGNS OF FETAL ANEMIA :

### Middle Cerebral Artery Peak Systolic Velocity

MCA PSV increases due to decreased viscosity of blood as a result of anemia

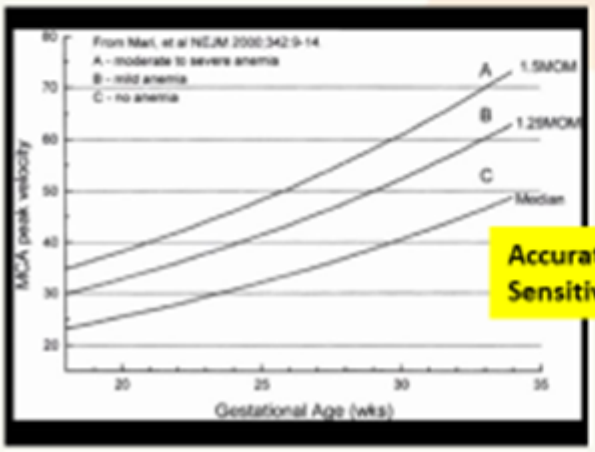



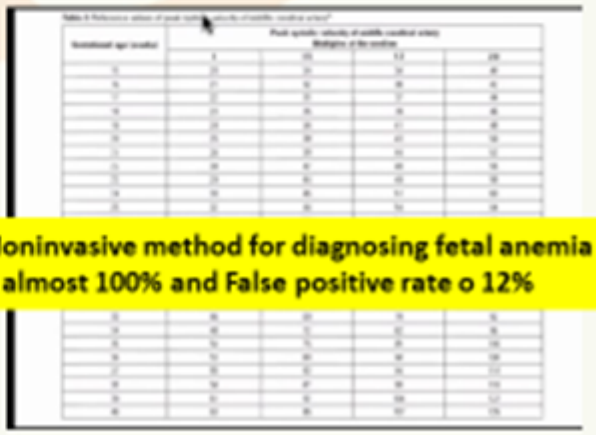
Hyperdynamic circulation leading to increased flow velocity

Use of Middle cerebral artery peak systolic velocity as noninvasive method to detect fetal anemia – by *Mari et al 1995- MOST IMPORTANT PRACTICE CHANGING DISCOVERY*

- MCA close to the probe
- Near its origin from internal carotid artery
- Angle <15 degree (velocity is angle dependent)
- Absence of fetal movement
- Can be evaluated from 18 weeks
- Less reliable after 35 weeks

MCA PSV Threshold for diagnosis of severe anemia is 1.5 MoM



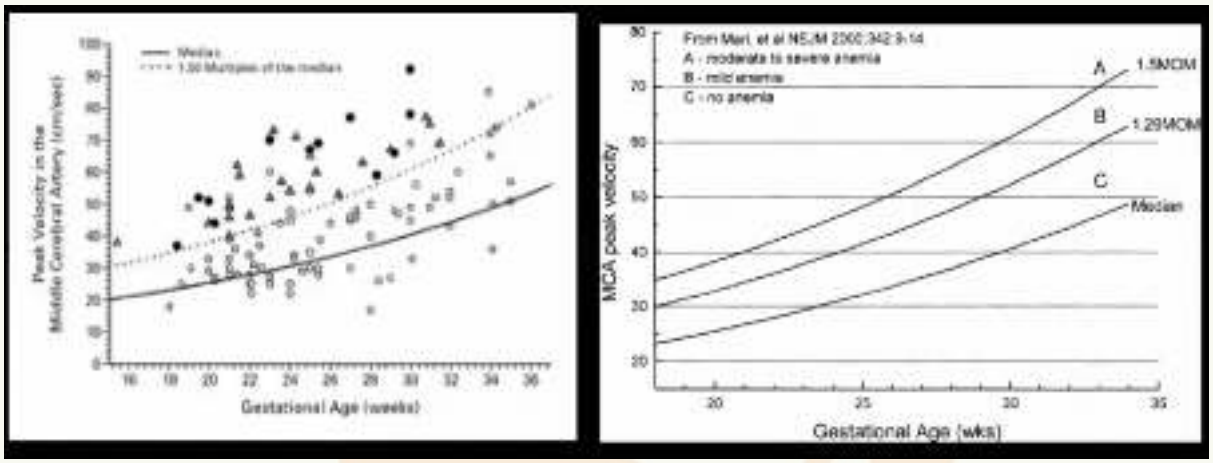



Accurate Noninvasive method for diagnosing fetal anemia
Sensitivity almost 100% and False positive rate o 12%

MCA PSV has safely replace invasive testing in management of Rh isoimmunised pregnancy

MCA PSV correlates well with the degree of fetal anemia

Identifies fetuses with moderate to severe anemia prior to hydrops which require intrauterine transfusion

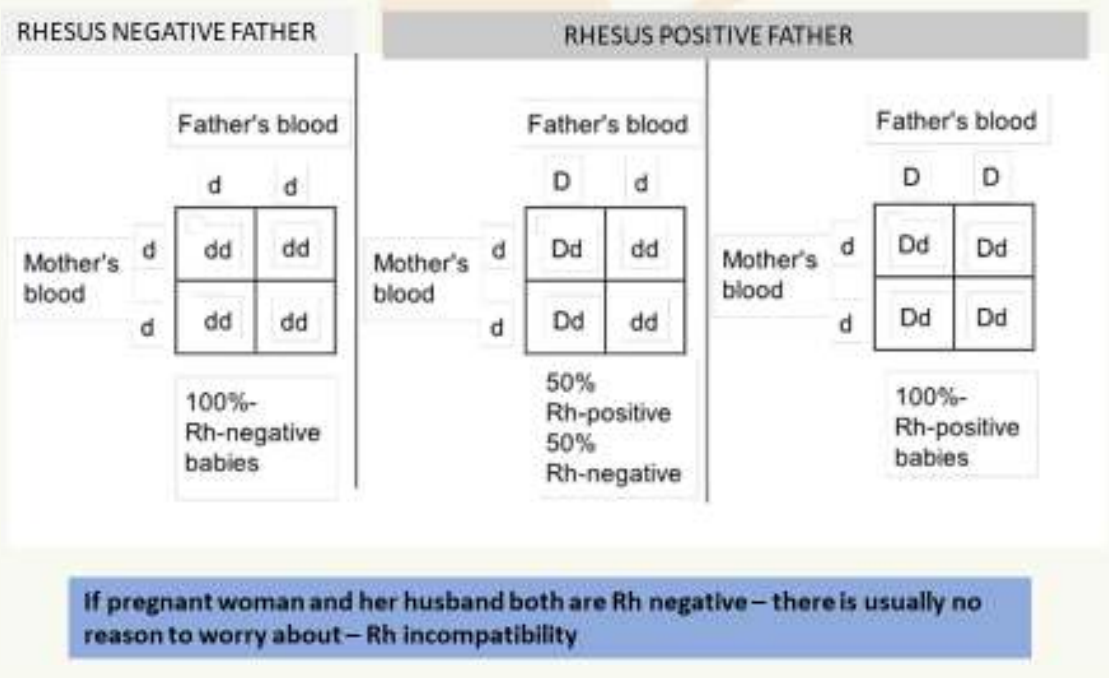



70% reduction in number of invasive procedures

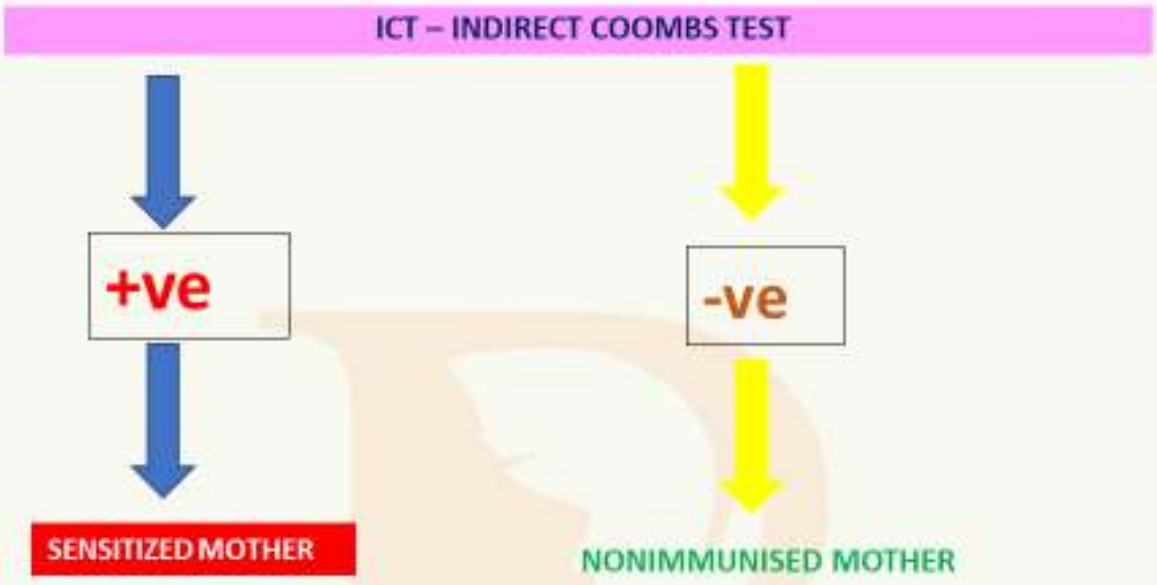
# HISTORY OF PATIENT

- Obstetric History- previous abortions/ectopic/ hydrops /fetal or neonatal death
- History of blood transfusion
- Whether Anti-D received in previous pregnancy (normal/abnormal)
- Husbands Blood group and Rh factor

HUSBAND BLOOD GROUP




**If pregnant woman and her husband both are Rh negative – there is usually no reason to worry about – Rh incompatibility**




RH NEGATIVE AND NONIMMUNISED MOTHER

ICT at Booking visit and 28 weeks

If ICT negative- give Inj Anti D 300mcg at 28 weeks

Anti D 300 mcg post delivery within 72 hrs

## PROPHYLAXIS

### Anti D - ICT NEGATIVE

- At 28 weeks
- Post delivery within 72 hrs
- Following an episode of antepartum hemorrhage
- Spontaneous / Threatened abortion/ectopic pregnancy
- External cephalic version
- Blunt trauma abdomen
- Post invasive fetal procedure

**RISK OF FETOMATERNAL HEMORRHAGE**

### HOW DOES IT WORK ?

The Antigen on Fetal RBC is not allowed to be presented to maternal immune system

**PREVENTS SENSITIZATION**

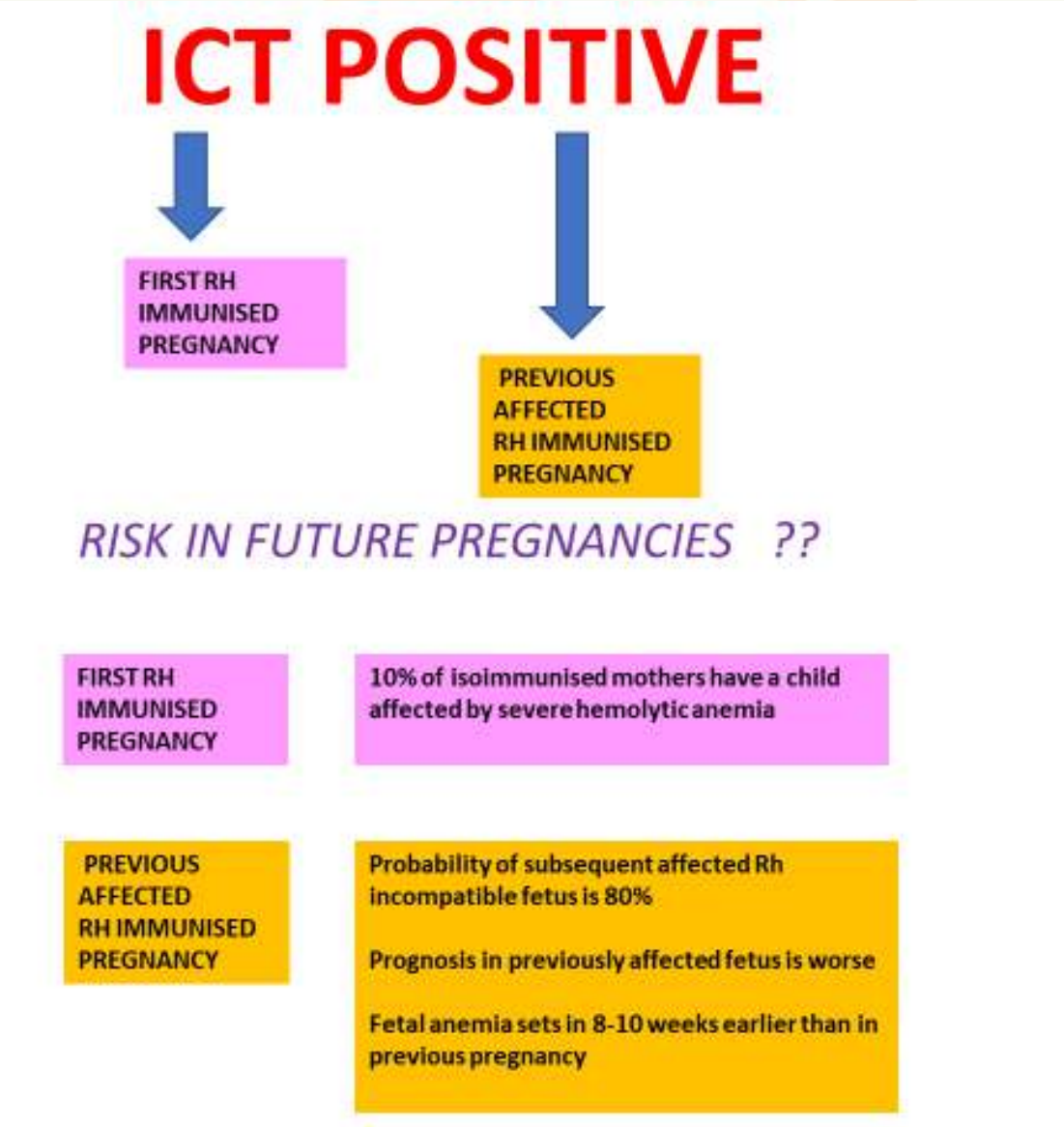
**300mcg of Anti D is enough to prevent exposure produced by 30 ml of RhD positive blood**

## PRECAUTIONS AT DELIVERY :

- No Methergin
- No Manual removal of placenta
- Early cord clamping
- Cord Blood sample – Hb , Direct Coombs test, blood group, serum Bilirubin

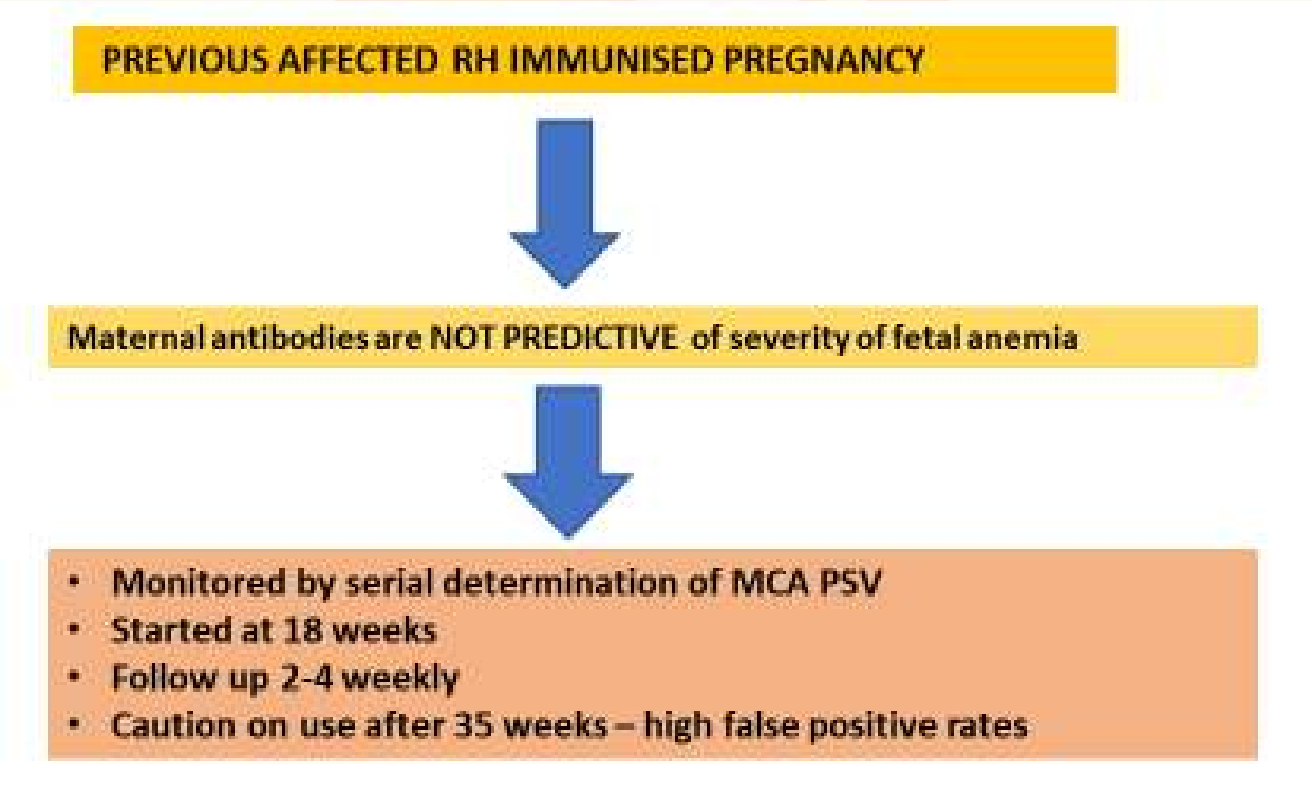
**Overall risk of isoimmunisation of Rh negative mother with Rh positive fetus is – 16%**

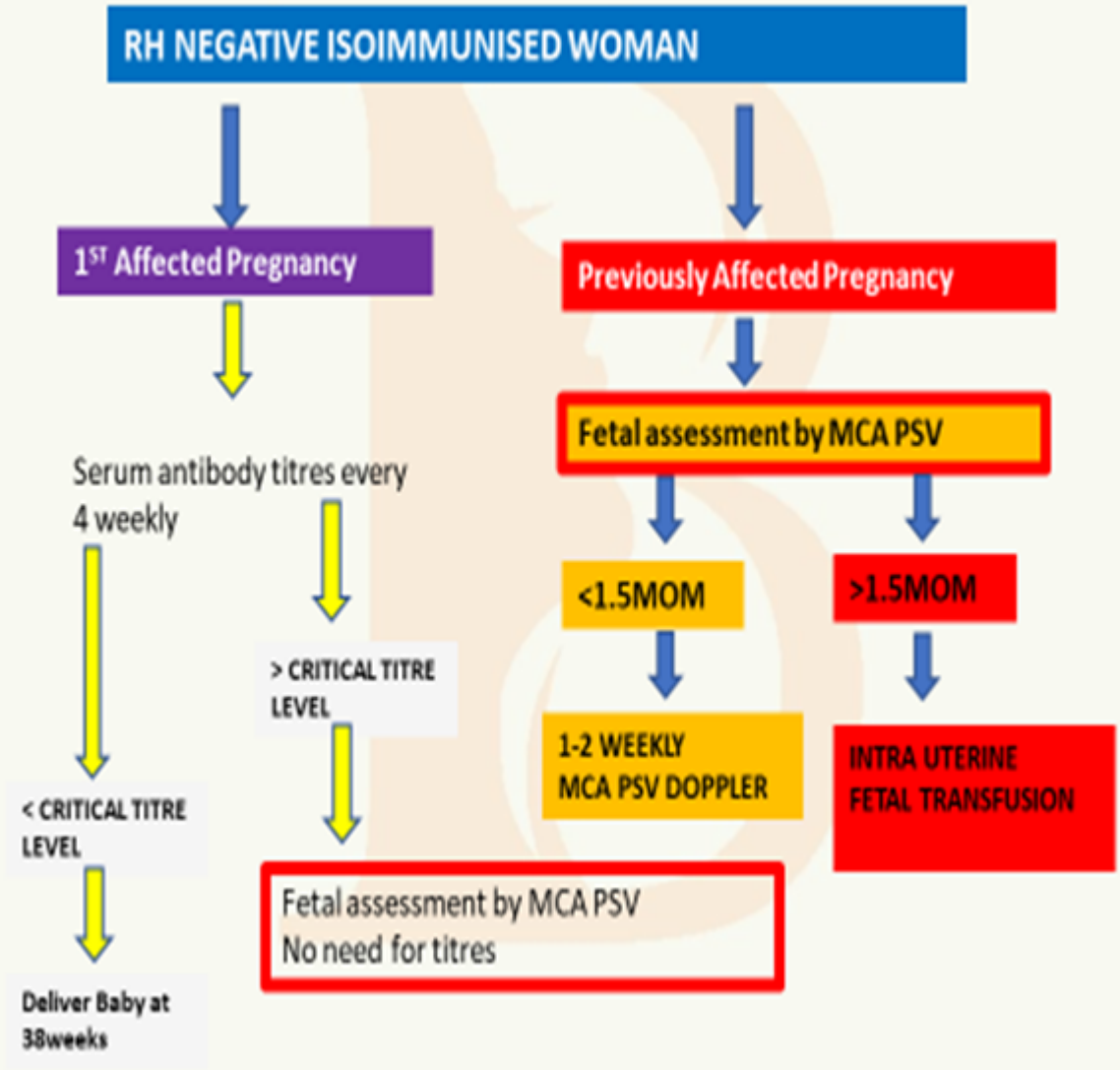
**This risk is reduced after Anti D administration to 1%**



## RH ANTIBODY TITRES :

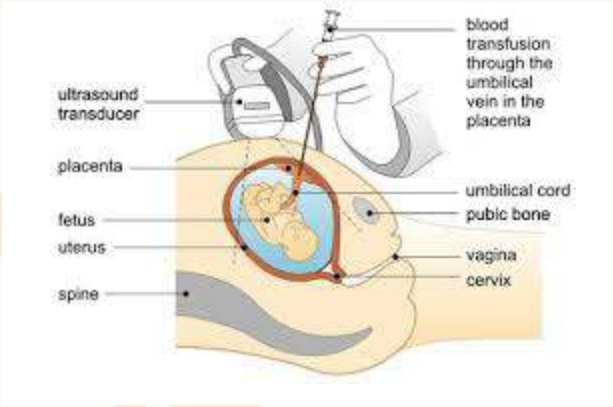
- Correlate well with severity of disease
- **Critical titre : Defined as titres below which there is no death due to hemolytic disease within one week and no association with hydrops**
- **(1:8 to 1:32 – avg 1:16)**
- **Once ICT poistive – titres are monitored 4 weekly**
- **If they remain below critical level then delivery planned at term**
- **If the levels go above critical titre level , then follow up as affected pregnancy**




RH NEGATIVE ISOIMMUNISED WOMAN
1ST Affected Pregnancy
Previously Affected Pregnancy
Fetal assessment by MCA PSV
Serum antibody titres every 4 weekly
<1.5MOM
>1.5MOM
> CRITICAL TITRE LEVEL
1-2 WEEKLY MCA PSV DOPPLER
INTRA UTERINE FETAL TRANSFUSION
< CRITICAL TITRE LEVEL
Fetal assessment by MCA PSV
No need for titres
Deliver Baby at 38weeks

## INTRA UTERINE TRANSFUSION :

- **MCA PSV > 1.5 MOM**
- **HYDROPS**




Fetal intervention is more effective if started prior to hydrops

For every 100 affected Rh isoimmunised patients, nine fetuses require intrauterine transfusion

TYPES:-

- **Intravascular**
- **Intraperitoneal**
- **Intracardiac**

**IUT CORRECTS FETAL ANEMIA AND PREVENT ITS SEQUELAE**

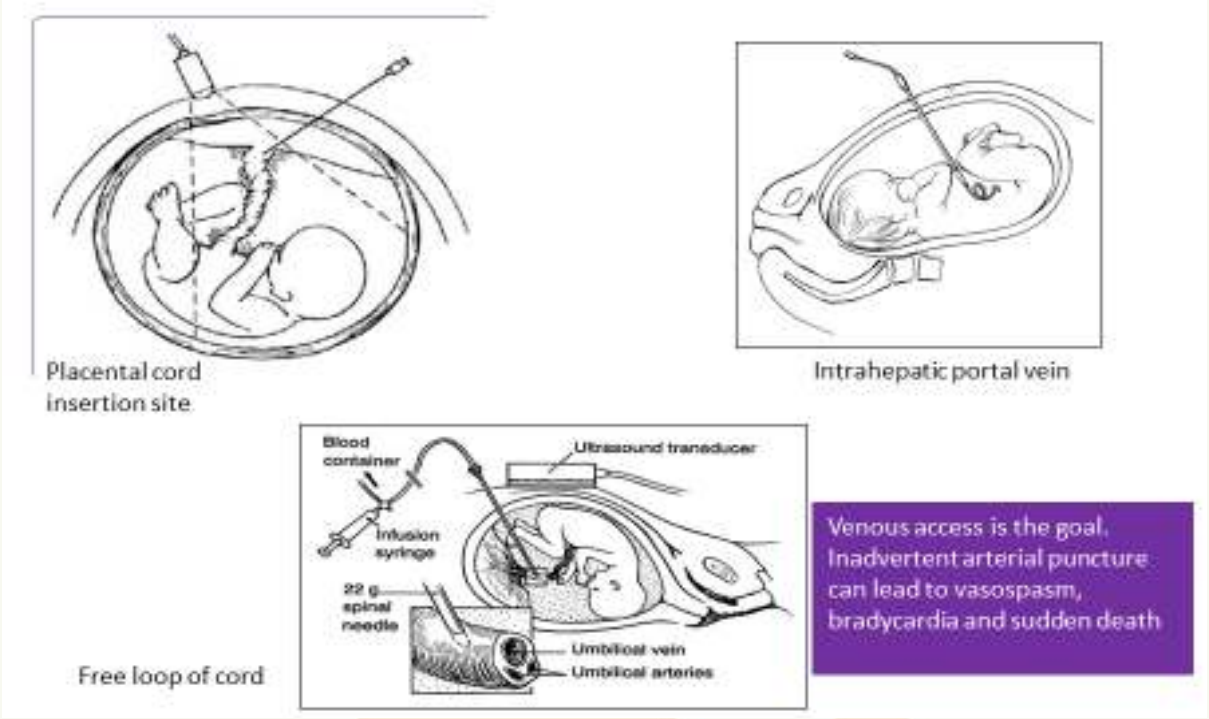
**AIM IS TO BUY TIME TILL THE BABY IS MATURE ENOUGH TO BE DELIVERED**

### INTRAPERITONEAL

- Need for Transfusion <18 weeks
- Direct Access to cord not feasible
- Sometimes combined with intravascular to allow longer interval between procedures

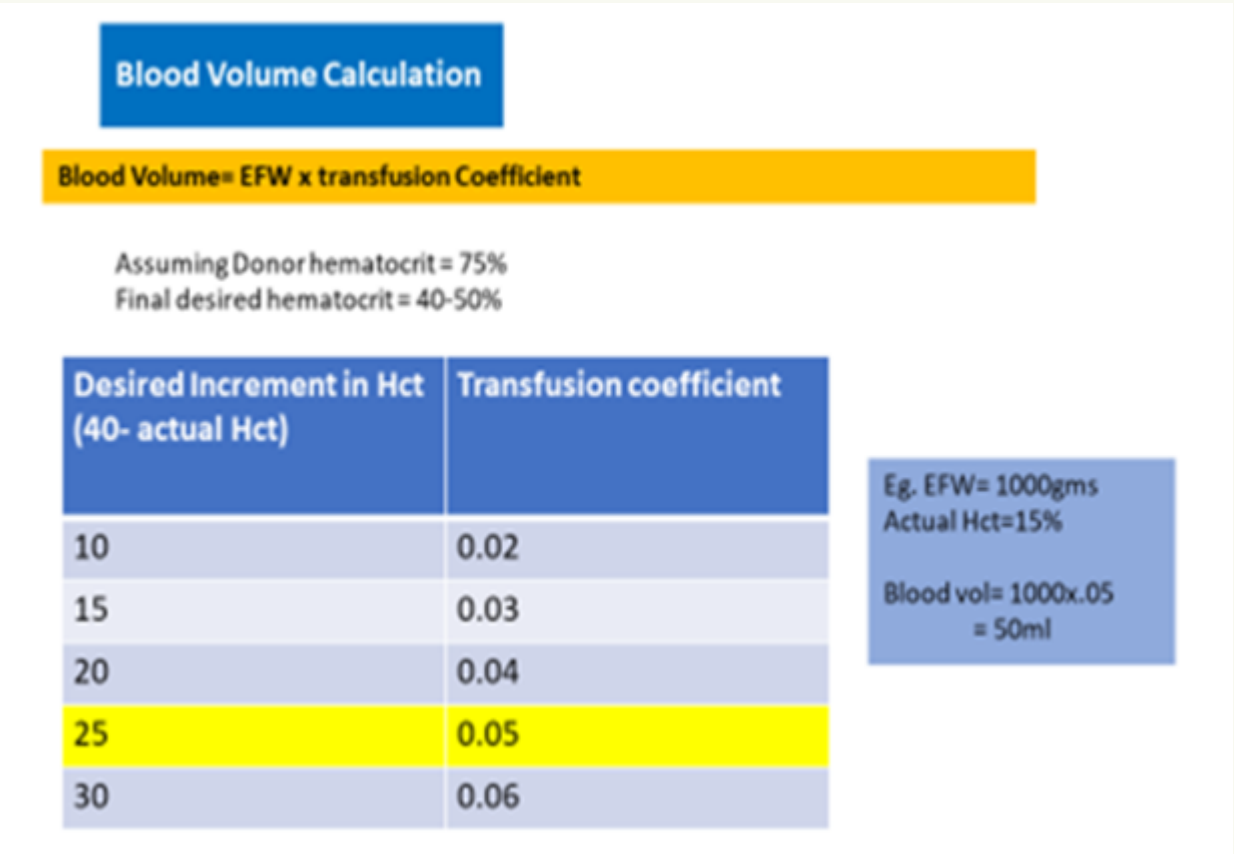
Mechanism : **Transport of Injected red cells through lymphatic system to the fetal circulation**
Absorption is slower in hydropic fetus- **less effective in hydrops**

## INTRAVASCULAR (Umbilical vein)




## WHAT TO TRANSFUSE :

- **O negative**
- **Hematocrit :75-80%**
- **Leucocyte depleted**
- **Gamma irradiated**
- **CMV negative**
- **Crossmatched with the mother**
- **Double packed cells**
- **Freshly collected within 72 hrs**




## PRE PROCEDURE COUNSELLING :

- Severe anemia in fetus may lead to intra uterine death if not corrected.
- Risks and acute complications of intra uterine transfusion-preterm labour, pprom , sudden bradycardia, cord hematoma, chorioamnionitis, bleeding from needle site, cardiac overload & sudden fetal death.
- Neonatologist counseling for need for postnatal exchange transfusions
- Overall fetal loss rate is 1-3% (Higher with earlier gestation and hydrops)

## PROCEDURE :

FETAL PARALYSIS

- Pancuronium/Vecuronium
- IM in thigh/ buttocks OR IV in Portal Vein
- Dose :0.2mg/Kg
- Effect lasts for 1-2hrs

Once Intravenous entry achieved-

Fetal Blood sample sent for – Blood group, Hct, Hb, DCT

Transfusion started at 5-10 ml/min rate

Continuous monitoring of FHR

Visible echogenic turbulence in the vein (reassuring)

Final sample collected for post transfusion hematocrit

Post transfusion hematocrit falls by 1% per day

Next transfusion is planned accordingly

**Patients who develop severe Rh isoimmunisation prior to 20 weeks**

May not always be treated with intravascular transfusion

Small size of fetal vessels mass it technically difficult

- Intraperitoneal transfusion
- SUPPRESIVE THERAPY: Maternal administration of IVIG suppresses maternal anti D ab synthesis
- Plasma Exchange- expensive

## TAKE HOME MESSAGES

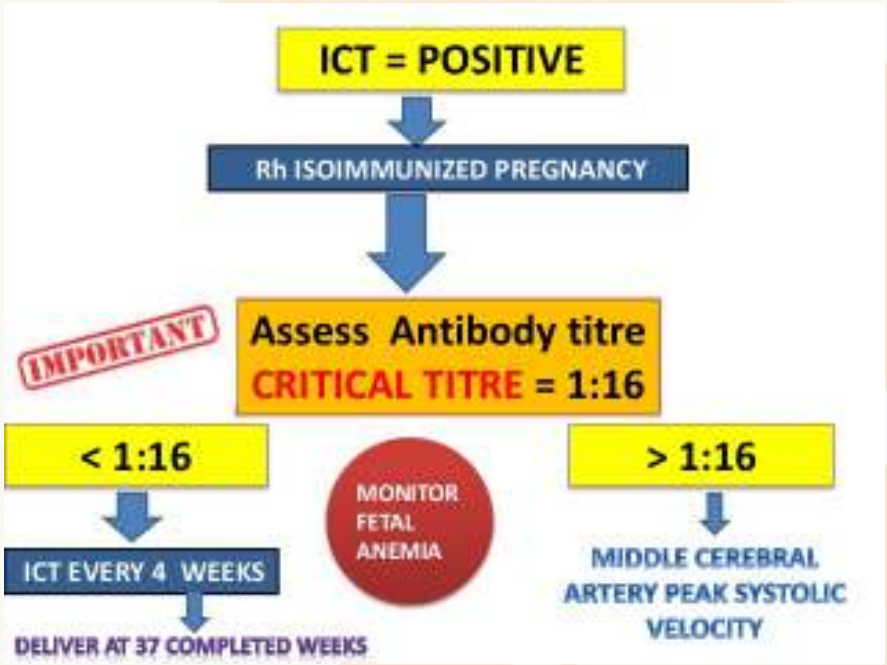
- **PREPREGNANCY COUNSELLING** with a clinician with knowledge and expertise of this condition.
- All women should have their **BLOOD GROUP AND ANTIBODY STATUS** determined at booking and at 28 weeks of gestation.
- **NON-INVASIVE FETAL GENOTYPING USING MATERNAL BLOOD** is now possible for D, C, c, E, e and K antigens. This should be performed in the first instance for the relevant antigen when maternal red cell antibodies are present.
- **ANTI-D PROPHYLAXIS** should be given to cover invasive testing if the mother is rhesus D (RhD) negative and is not sensitised.
- If immune anti-D is detected, prophylaxis is no longer necessary.

## REFERRAL TO A FETAL MEDICINE SPECIALIST SHOULD OCCUR WHEN -

- there are rising antibody levels/titres,
- A level/titre above a specific threshold (1:16)
- Ultrasound features suggestive of fetal anemia.
- There is a history of unexplained severe neonatal jaundice, neonatal anaemia requiring transfusion or exchange transfusion, in order to exclude haemolytic disease of the fetus and newborn (HDFN) as the cause.

## TAKE HOME MESSAGES

- Rh negative pregnancy should be thoroughly investigated
- Serial surveillance of fetus for signs of anemia
- Neonatal ICU care postnatally




**PREVENTION IS BETTER THAN CURE**

**Anti D Injection**

**Close collaboration and TEAM WORK of**

**Multidisciplinary teams – Obstetrician , Neonatologist, Haematologist and Fetal Medicine specialist is required to improve outcmes in Rh negative pregnancies!!**

## BIBLIOGRAPHY


- Callen's Ultrasonography in Obstetrics and Gynaecology 6th Edition
- GTG 65
- PALADINI VOLPE 2ND EDITION

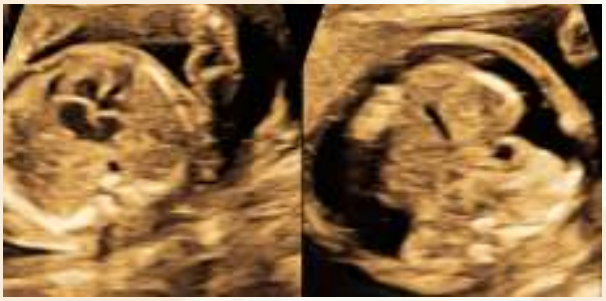
# NON IMMUNE HYDROPS

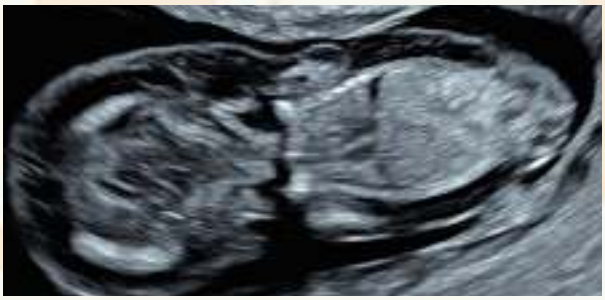
- DR.UNNATI SHENDE

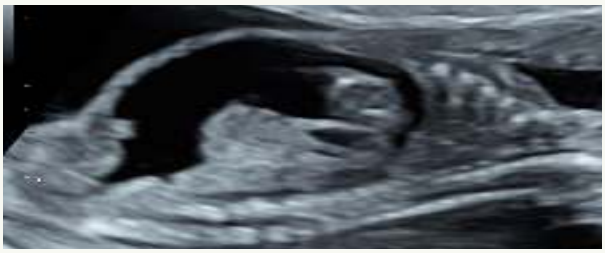
## INTRODUCTION

- Ultrasonography criteria - Abnormal accumulation of serous fluid in at least two of the following: body cavities (pleural effusion /pericardial effusion/ ascites) and skin edema.
- Placentomegaly and polyhydramnios are usually seen in cases of hydrops fetalis
- Because antenatal ultrasonography has become a routine examination, more and more cases are diagnosed before birth.
- Incidence – 1: 2000 births

## USG FINDINGS







## ETIOLOGY OF NON IMMUNE HYDROPS

| **Idiopathic** | **In 17-18 % cases of non immune hydrops etiology remains unknown** |
|---|---|
| Fetal cardiac anomalies ( 20-22%) | Hypoplastic left heart, pulmonary valve insufficiency,Ebsteins anomaly, subaortic stenosis, A-V canal defect, single ventricle, Fallot tetralogy, premature closure of foramen ovale, subendocardial fibroelastosis,heterotaxy syndrome |
| Chromosomal abnormalities (13-14 %) | Trisomy 21,13,18 and tuner syndrome,triploidy,tetraploidy |
| Fetal anemia (other than alloimmunization) (10-11%) | Alpha-thalassemia major 1 , Parvovirus B19, Erythroleukemia,Congenital erythropoietic porphyria(Gunther's disease) |
| Congenital infection | Parvovirus (either by anaemia, myocarditis, or hepatitis) Syphilis, Cytomegalovirus (primary & secondary; adenovirus; coxsackievirus) ,rubella ,Toxoplasmosis ,Herpes simplex, Leptospirosis Chagas' disease |
| Thoracic | Thoracic Diaphragmatic hernia, cystic adenomatous malformation, pulmonary hypoplasia, lung |
| Gastrointestinal anomalies | Jejunal atresia, midgut volvulus, intestinal malrotation or duplication, meconium peritonitis |
| Urological | Urethral stenosis or atresia, posterior bladder neck obstruction, bladder perforation, prune belly, neurogenic bladder, ureterocele |
| Skeletal anomalies | Thanatophoric dwarfism, arthrogryposis multiplex congenita, asphyxiating thoracic dystrophy, hypophosphatasia, osteogenesis imperfecta, achondroplasia, achondrogenesis, recessive cystic hygroma, and Neu-Laxova, Saldino-Noonan, and Pena-Shokeir type I syndromes |
| Conduction defects | Supraventricular tachycardias, heart block (including with maternal |

| | |
|---|---|
| | lupus erythematosus) |
| Neurological disorder | Encephalocele; Fetal intracranial hemorrhage; Vein of Galen aneurysm; Porencephaly with absent corpus callosum |
| Vascular | A-V shunts, large vessel thromboses (cava, portal, or femoral vein), Kasabach-Merritt syndrome |
| Neuromuscular | Fetal akinesia deformation sequence |
| Inborn errors of metabolism | Congenital disorder of glycosylation, Lysosmal storage diseases, Gaucher's disease, GM1 gangliosidosis ,MPS types VIa and VII Iron-storage disease |
| Miscellaneous | Nonaneuploid cystic hygroma , Meconium peritonitis, Fetal neuroblastosis ,Small bowel volvulus , Amniotic band syndrome Torsion of ovarian cyst, Polysplenia syndrome |
| Multifetal pregnancy | Twin-twin transfusion syndrome, twin reverse-arterial perfusion (TRAP) syndrome |
| Tumors | Sacrococcygeal teratoma ,Tuberous sclerosis |
| Placental causes | Chorioangioma, fetomaternal hemorrhage, A-V shunts, placenta trauma with fetal hemorrhage, twin-twin transfusion syndrome |
| Maternal causes | Medication like indomethacin , Diabetes mellitus , Thyroid disease ,Preeclampsia ,Severe anemia ,Hypoalbuminemia |

## MANAGEMENT OF PREGNANCY

- Following the sonographic detection of non immune hydrops, the pregnant woman should be promptly referred to a tertiary care facility, with availability of a multidisciplinary team consisting of fetal medicine specialist, neonatologists, and clinical geneticists.
- Detailed history taking to find any etiological correlation
- Investigations – as mentioned below

## FETAL PRENATAL INVESTIGATIONS

- Non invasive ultrasonography- a detailed real time evaluation for congenital anomalies, placental and umbilical cord abnormalities, fetal echocardiography and colour doppler
- Invasive tests- karyotype and array, hematologic test (full blood count ,Hb electrophoresis, group and coombs test),PCR and culture for fetal infection, enzyme analysis

## MATERNAL INVESTIGATIONS FOR HYDROPS

- Blood group and antibodies
- Infection (TORCH)
- GTT Glucose tolerance test
- SLE, especially anti-Ro/SSA or anti-La/SSB antigens, if bradycardia/ heart block
- Thyroid function tests including antibodies: TSH and TSH-binding inhibitor IgG
- Electrophoresis (depending upon blood count result and ethnic background)

## FETAL THERAPY

- Fetal anemia: Intrauterine blood transfusions.
- Pleural effusions or large pulmonary cyst: insertion of thoracoamniotic shunts.
- Fetal tachyarrhythmias: transplacental or direct fetal administration of antiarrhythmic drugs.
- Teratomas, chorioangiomas, pulmonary sequestration: ultrasound-guided laser coagulation of feeding vessel.
- Recipient fetus in twin-to-twin transfusion syndrome: endoscopic laser coagulation of the communicating placental vessels.
- Open fetal surgery in utero- eg .sacrococcygeal teratoma

## MATERNAL RISK

- Antenatal direct consequences – due to hyperplacentosis and hydramnios .This include Mirror syndrome, malpresentation, preterm labor, and preterm rupture of membranes (PROM) with the associated risk of placental abruption and chorioamnionitis.
- Antenatal indirect consequences-include the complications of intrauterine investigations and therapy, namely, PROM, chorioamnionitis, abruption (associated with amnioreduction), anemia, and maternal red blood cell alloimmunization.
- During labor and delivery: Hydrops may be associated with preterm labor, the side effects of tocolysis, dystocia (e.g., large tumors), cesarean delivery (e.g., associated with malpresentation, cord prolapse), abruption associated with membrane rupture in cases with hydramnios, postpartum hemorrhage (primary and secondary), and retained placenta.

## FETAL RISK

- Intrauterine fetal death
- Infant morbidity and mortality

## ANTENATAL FOLLOW UP AND MONITORING

- Scans every 2-3 weeks to monitor the evolution of hydrops.
- Maternal monitoring -There is a risk of maternal morbidity due to the 'mirror syndrome' (combination of fetal hydrops with generalized fluid overload and a preeclamptic state in the mother).

## DELIVERY

- Timing and method of delivery depends on the cause of hydrops

  Treatment of newborn

- Delivery should be planned at tertiary care center with immediate availability of a multidisciplinary neonatal resuscitation team.
- Often immediate neonatal endotracheal intubation is required and such intubations can be technically difficult.
- Paracentesis and thoracentesis, with placement of bilateral chest tubes, may also be needed to allow adequate ventilation and effective gas exchange.
- Use of blood products, albumin, and diuretics may be needed to effectively maintain adequate intravascular volume without significant fluid overload or soft-tissue edema

## PROGNOSIS

- Depends on the etiology of hydrops.
- Progressive unexplained hydrops is often lethal before or soon after birth.
- Often the abnormality remains unexplained even after expert post mortem examination of fetus.

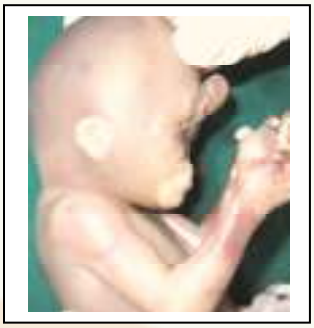
## RECURRENCE RISK

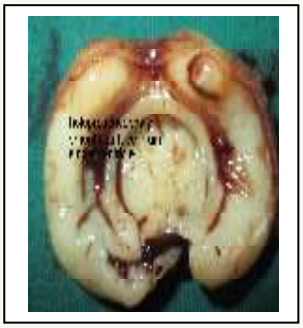
- Fetal defects: usually sporadic
- Congenital infections – no recurrence
- Part of trisomies: 1%
- Congenital heart block in SLE – 16 %
- Metabolic disorders: 25%

# FETAL AUTOPSY

-DR.KUNDA SHAHNE

# Fetal Autopsy





## INTRODUCTION

Post-mortem examination of a baby following spontaneous or missed miscarriage in the second trimester (11+0–23+6 weeks gestation) may provide a complete or partial explanation of the pregnancy loss, whilst following termination of pregnancy for fetal abnormality a postmortem examination may provide a specific diagnosis. In all situations post-mortem may provide information relevant to the management of subsequent pregnancies. The output from the autopsy should be sufficient to provide useful feedback to the family, to the clinicians involved in the case . The role of the autopsy is to:

1. Provide information regarding the baby to the bereaved family

2. Establish the immediate cause of second trimester miscarriage or factors that may have contributed to the pregnancy loss

3. Identify the immediate cause of second trimester intrauterine death (missed miscarriage)

4. Identify concomitant diseases, particularly those with implications for subsequent pregnancies (e.g. growth restriction, malformation, maternal diabetes)

5. Identify evidence of genetic disease and to allow determination of the likely recurrence risk

6. Pathology encountered at autopsy : Amniotic infection sequence ,Oligohydramnios , Growth restriction: symmetric, asymmetric (nutritional) ,Viral/protozoal infection (CMV, Parvovirus, toxoplasmosis, other) , Congenital malformation (all systems) , Hydrops fetalis , Fetal akinesia sequence ,Placental and umbilical cord disease .

9 .Changes in the baby and placenta secondary to intrauterine death.

## SPECIFIC HEALTH & SAFETY ASPECTS

The doctor needs to know the results of the antenatal infection screens. In regions of high maternal HIV prevalence, autopsy practice using universal precautions will significantly protect against accidental transmission.

## CONSENT :

Regardless of the gestation, post-mortem examination may only be performed if informed consent has been given, typically by the mother or both of the parents. Fetal tissue is considered in law to be the mother's tissue, and therefore tissue from the living.

Consent is an essential part of fetal autopsy. Loss of fetus comes as a great shock to the couple and the family. Consent has to be obtained in this atmosphere of grief. Therefore the process of autopsy audits benefits should be explained in most sensitive manner. Parents are concerned regarding the dissection and the later disposal of the body and organs. These aspects should be clearly explained to them. Many countries require it to be specifically mentioned in consent if the organs are to be retained for studies .ICMR mandates that process of autopsy, disposal of the fetus and genetic counseling should be covered in consent for fetal autopsy. While obtaining the consent the parents should be assured that the fetus will be treated with consideration and respect at all times.

Sometimes parents do not agree to dissection. Partial autopsy regarding in particular cavity or just external examination is sometimes agreed to by the parents. In such situation parent's wishes should be respected. At the same time it should be explained to them about limitations of such evaluation and it being inferior to the complete autopsy in diagnostic yield .Their choice for the partial autopsy should be mentioned in the consent. Sometimes parents wish the fetus to be returned to them for the later rites. Otherwise fetus and placental tissues should be disposed as per the prevailing law.

## Clinical information relevant to the autopsy

## HISTORY AND INVESTIGATIONS IN PREGNANCY:

Fetal loss/termination is end event of a pregnancy. Therefore all angles relating to the present pregnancy should be covered in history. This includes preconception history, conception, and pregnancy course. Past obstetric history and family history should be recorded. Particular attention should be given to pedigree charting as most fetal losses require looking into genetic etiology. Ultrasonography reports and investigation copies should accompany the consent and pregnancy record. Autopsy findings and evaluation with the help of the pregnancy history and record when considered together will achieve accurate diagnosis.

-Patient identification details, Maternal age/date of birth,Maternal height, weight and BMI.

- Relevant medical and family history, including consanguinity

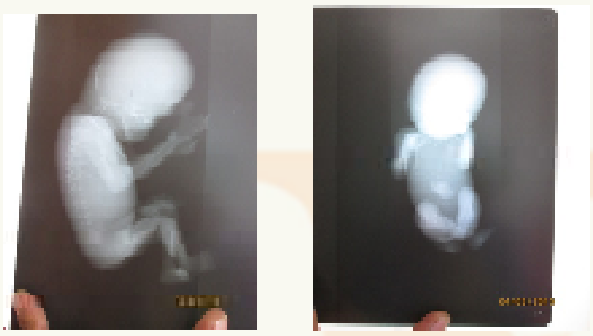
- Obstetric history, previous pregnancies/deliveries, including previous fetal and neonatal losses (and if post-mortem examination had been carried out), malformation and growth restriction and other complications

-History of current pregnancy, including – estimated delivery date – antenatal infection screen, including HIV – abnormal findings from ultrasound or other antenatal investigations (copies of reports are helpful) – hypertension/bleeding/pyrexia/membrane rupture – events leading up to delivery – for late miscarriages, live born or stillborn.

## AUTOPSY PROCEDURE :

Requires availability of appropriately sized instruments for small and very small fetuses; balances for weighing babies and organs ,charts of normal values (baby weight and measurements, organ weights and placenta weight)

## RADIOGRAPHY:



X.rays of fetus is informative in many ways. They are understandably very important in skeletal dysplasias and can be diagnostic. They also give information regarding osseous maturation. They may provide evidence of infection e.g. metaphysites in congenital syphilis or intracranial calcifications in congenital toxoplasmosis

Abdominal calcifications are evident in venous or arterial thrombosis. Both front view as well as lateral view of the fetus should be obtained. It is reported in literature that X-rays are informative in 10 to 30 % of autopsies .X rays of Meckel- Gruber Syndrome Fetus

Whole body X-ray for gestational assessment, malformation, etc. Recommended in all cases; mandatory for suspected skeletal dysplasia. Other imaging modalities may be appropriate in some circumstances and if available.

## CLINICAL PHOTOGRAPHS :

Clinical photographs are now made very easy with digital photography. Care should be taken that proper resolution photographs are obtained. At least a front and lateral view is taken. Posterior view should also be captured If any malformation is present it is captured in detail. It is always helpful to take images of placenta and cord especially in intrauterine fetal demise. Photographs make the documentation complete. They can be revisited if diagnosis is to be revised and help in genotype phenotype correlation Research publications. Always insist on good quality photographs of dysmorphic syndromes.

Photography recommended in all cases, essential to document external and internal abnormalities. Digital photography and secure storage preferred.

## MORPHOMETRY :

Morphometry means measurements of fetus, cord as well as placenta. This involves measurement of weight of fetus. Essential fetal measurements comprise, head circumference, chest circumference, abdominal circumference, crown rump length, rump heel length, and foot length. Foot length is important correlate of gestational age even in macerated fetuses when other measurements may be distorted .Inner and outer canthal distances have been given importance but impression regarding hyper or hypoteleorism is also useful. Various limb length measurements carry importance especially when skeletal dysplasia is suspected. Umbilical cord length should be measured and number of colis should be noted. Usually one coil is present per 5 cm cord length. Placenta also should be weighed and its shape and dimensions noted.

## EXTERNAL EXAMINATION:

External examination comprises checking all body as well as placenta and cord and noting down the findings. A checklist ensures that a thorough examination is performed. Careful attention is given to noting state of maceration of the fetus also as it helps in deciding the timing of the fetal demise. Brief description of salient features of external examination is given here.

**Head**: Size and shape of the head should be noted.Fontanelles should be examined for size as well as number. Presence of encephalocele may be a sign of Meckel syndrome. Trauma during instrumental delivery may be present in the form of abrasions or hematomas. Bulging sutures may indicate hydrocephalus while prominent sutures and abnormal skull shape is present in craniosynostosis syndromes .Defects in scalp skin are present in Thisomy 18

**Face**: Overall impression of face is important for a dysmorphologist. The clefts of lip and palate should be looked for and noted. The lips ,mouth,nose and cheeks are seen noted for their normalcy. The ears are examined for their size, position and disposition as well as presence of creases or pits. Presence of such pits and macroglossia is indicative of Beckewith Wiedeman syndrome. Presence of micrognathia and retrognathia is noted

and correlated with U shaped cleft palate. Eyes are examined for external features of slant epicanthic folds as well as internal features like presence of cataracts or globe abnormalities.

**Neck and Back**: Shortness of neck should be noted. Webbing of neck may be present in Turner syndromes. Cystic hygroma is associated with many single gene syndromes .Back should be examined for presence of neural tube defects as well as presence of kyphosis or scoliosis indicating vertebral abnormalites.

**Abdomen**: Distension of the abdomen can be because of fluid , megacysts, organomegaly, tumor or intestinal obstruction. Omphalocoele can be present in varying size .It is accompanied by spinal defects and extrophy of bladder and imperforate anus it forms OEIS association.

**Genitalia**: External genitalia Indicate sex of the fetus but can be ambiguous sometimes because of endocrine disturbances, or may be associated with renal or cloacal anomalies Presence of anus should be noted.

**Extremities:**Different segments of upper and lower arms can be affected in skeletal dysplasias and there measurements are essential as well as a good X.ray. Number of digits should be noted. Oligodactyly as well as poydatyly are very good handles for diagnosis of syndromes. Presence of simian crease and length of fingers and phalanges should be noted. Pterigia if present at joints are part of multiple pterigum syndrome or Barsocas Pappas syndrome.

**Skin**: Skin should be examined for degree of maceration. Hemangiomas,angiomas, café-au-lait spots lprovide clues regarding neurocutaneous syndromes while blue berry multiple lesions indicate hematological disorders lchthyotic lesions may indicate a storage disorder like Gaucher disease

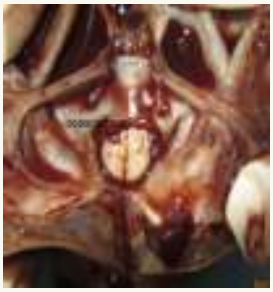
## PLACENTA MEMBRANES AND CORD:

Cord length should be measured. Number of coils should be noted Usually one coil present per 5 cm length. Hypercoiled cord is associated with IUDs. Number of vessels in the Cord should be noted as well as the diameter of the cord. Fetal end of the cord should be observed for constrictions as well as the placental end for the type of insertion. Placental external appearance should be noted. The external surface should be observed for its vessels congestion and hemorrhages.

## DISSECTION:

Dissection is performed to approach various internal cavities and the organs situated in them. Standard textbooks describe number of dissection techniques. T- or Y-shaped skin incision on body preferably used. Position of various organs and their relationship to each other should be noted. Photographs are needed to document this. Organ like heart requires special dissection technique along the direction of the blood flow. In majority of cases dissection confirms the sonographic diagnosis. Standard protocols are available for interpretation of placental pathology.

**Central nervous system (CNS) examination**: – median posterior or transverse posterior parietal scalp incision – observation of maturity to assist gestational assessment – consider removal under water – if suspected CNS malformation (including ventriculomegaly), examination of posterior fossa structures by posterior approach.



Posterior fossa

Brain Stem

This may include sampling peripheral nervous tissue (nerve root, peripheral nerve, muscle etc). Consulting the neuropathology team may be helpful if there is doubt about sampling.

Detailed systematic examination of other internal organs, including: – umbilical arteries and vein, ductus venosus – in situ examination of the heart and great vessels with sequential segmental analysis of malformations – in situ examination of thoracic and abdominal organs; consider removing in continuity to assess abnormal structures crossing diaphragm – weights of internal organs (minimum: brain, heart, lungs, liver, kidneys, thymus, adrenals, spleen) – apply special dissection techniques where appropriate.

Detailed examination of placenta and umbilical cord, including: – trimmed weight (after extraplacental membranes and cord detached) – dimensions of placenta (width in two planes and thickness) – umbilical cord: length, diameter, insertion into placental disc, number of vessels, coiling, lesions – membranes: appearance – fetal surface/chorionic vessels: appearance, infection – maternal surface: completeness, craters – slicing at approximately 1 cm intervals to evaluate parenchyma for colour and focal abnormalities.

## LIMITED AUTOPSY:

Where consent for a full autopsy is not given, limited examination may be of value. Forms of limited examination include autopsy limited to one or more body cavities · open or needle biopsy of specific internal organs (if feasible) · external examination of the body with X-ray, photography and genetics (if indicated) · placental examination only (with genetic testing if indicated), imaging (CT, MRI – if available) alone or with targeted biopsies.

## ORGAN RETENTION:

Short-term retention of organs to allow fixation does not require specific consent, provided they are reunited with the body before release for burial/cremation. · Specific consent should be sought for long-term retention beyond the release of the body, for the purpose of examining the organs. Consider for extra-cranial organs with congenital malformations (particularly heart) if input not available from a perinatal doctor or cardiac morphologist on site at the time of examination, and the abnormality cannot be satisfactorily recorded by photography. · Brain for macroscopic and histological assessment.

In practice, submersion for a minimum of 2–3 days in 20% formalin (±5% acetic acid) will usually produce sufficient fixation to allow adequate sectioning and block sampling to allow the brain to be returned to the body before release for funeral. If there is doubt consult the local neuropathology team.

## HISTOLOGICAL EXAMINATION:

Recommended blocks required at full autopsy:

thymus ,heart (septum and free walls) , lungs (right and left – each lobe) ,liver (both major lobes) ,pancreas , spleen , adrenal glands ,kidneys , muscle and diaphragm ,stomach, small and large bowels , larynx/trachea and thyroid ,

Bone: rib including growth plate in stillbirth; long bone (including growth plate), vertebral body and skull mandatory for suspected skeletal dysplasia

Brain: if preservation allows include cerebral cortex and periventricular white matter (frontal, parietal, temporal and occipital), deep grey matter (caudate, striatum, thalamus), hippocampus, midbrain (inferior colliculi), pons, medulla (inferior olives), cerebellum with dentate nucleus.

## FETAL TISSUE SAMPLING FOR SPECIAL INVESTIGATIONS :

Fetal autopsy is opportune time to sample tissues for further laboratory investigations. Formalin can interfere with DNA analysis and fixed tissues cannot be used for karyotyping as they are not viable .Therefore ideally samples should be obtained for laboratory investigations immediately after delivery Umbilical cord blood or intracardiac blood can be collected in Heparin vaccutainer for karyotyping studies and EDTA for DNA studies.

Skin tissue can also be used to obtain DNA or set up karyotyping on Fibroblast culture. For this piece of skin along with muscle tissue can be obtained from untouched part like axilla. Fascia, lungs, Achilles tendon are other tissues that can be used as sample. In a macerated fetus placenta is usually well preserved and is used for sampling In (Genomic testing presently has established itself in clinical practice e.g. chromosomal microarrays have better diagnostic yield in fetuses with multiple congenital anomalies.

Similarly targeted NGS panels are very useful n diagnosing broad entity like skeletal dysplasias. However for specific conditions such investigations are not required. When trisomy 18 is evident simple and less costly karyotype should suffice for confirmation of diagnosis and will also confirm whether it is pure trisomic in nature or translocation is present. .

Similarly for isolated condition like meningomyelocoele where presence of other malformation is ruled out microarray studies are not necessary. Appropriate genetic or genomic investigation should be ordered after considering

differential diagnosis. Database search is useful in this exercise. This helps in genotype-phenotype correlation in case of unexpected results in genomic testing. Presence of Congenital infection can be confirmed by molecular studies on fetal tissues.

## DATABASE SEARCH:

Genetic Disorders and syndromes are rare disorders and no geneticist, even a very experienced one, can claim to have seen all of them. Therefore a database search is helpful to arrive at a differential diagnosis. Excellent databases that available online free of cost include OMIM Online Mendelian Inheritance In Man) Ophranet, Genereviews etc. London Dlysmorphology and Neurogenetics and Possum are Exellent databases for syndrome search but require subscription.

## SUMMARY :

Fetal autopsy is a rewarding diagnostic exercise and helps in reaching the exact cause of congenital abnormalities, genetic disorders or fetal demise in most of the instances. Various studies in India and western countries have shown that it adds more information to ultrasonography and other findings in 30 to 50% of instances. It is important to counsel the couple in a sensitive manner so that they opt for it . Investigating for the cause is important at it helps in counseling and timely prenatal diagnosis in future. In some instances the couple may not opt for full autopsy. In such situations photographs, X-rays and other documentation along with fetal DNA storage should be performed as the next best thing. In our experience it is difficult to offer prenatal diagnosis on time in couples who come ultrasonography diagnosis of an abnormal outcome in previous pregnancy. Therefore fetal autopsy should be a part of every gynecologists practice.

## TO REMEMBER:

**<u>The report should include the following sections:</u>**

-Demographic and identification data ·

-Details of autopsy consent and limitations

-Body weight and appropriateness for gestation

-Body measurements

- List of main findings

clinicopathological summary (final report)

1. Summary of clinical history

2. Systematic description of external and internal findings and placental examination

3. Organ weights with relevant reference values and ratios

3. Details of ancillary tests taken

4. List of histology tissue blocks

Components of Fetal Autopsy

1.Consent

2.History and pregnancy timeline

3.Clinical Photographs

4. Radiography

5.External Examination

6.Dissection

7.Tssue sampling and Histopathology

8. Database Search

9. provisional dhagnosis

10 .Final Diagnosis

11. Counseling and Management