FETAL GROWTH RESTRICTION

Fetal growth restriction (FGR) or Intrauterine Growth Restriction (IUGR) constitutes one of the major complications of pregnancy associated with an increased risk of perinatal mortality and morbidity, and long-term adverse consequences extending into adult life. Fetal growth restriction therefore interests obstetricians, fetal medicine specialists, pediatricians and adult physicians as well.

It is an important clinical problem. The prevalence is about 8% in the general population. It has been shown that 52% of stillbirths are associated with IUGR and 10% of perinatal mortality is a consequence of IUGR. Up to 72% of unexplained fetal deaths are associated with SGA below the 10th percentile

The causes of fetal growth restriction are varied but the most significant of them is placental dysfunction that is more recently termed ischemic placental disease.

Many aspects of this complex problem still remain unclear. We still do not detect many fetuses who are growth restricted and we do not as yet have an effective therapy for preventing growth restriction or indeed correcting it. However, meaningful advances have been made in recent years both in our understanding of and in management of FGR.

Before discussing about growth restriction, it is important for us to understand the definitions of Gestational Age & Growth and understand the basic principles of fetal growth.

Gestational age: Means the "estimated age" of the fetus at any given point in the gestation. This is done by a biometric measurement such as the Crown Rump length (CRL) in the first trimester or an average of BPD, HC, AC & FL (composite gestational age) from the second trimester.

Fetal growth: Means how much the baby has grown over a period

of time and is usually expressed as percentiles. The assessment of fetal growth can only be done by serial measurements and plotting growth curves

Rules of fetal growth:

Fetuses increase in size over a period of time and the degree of increase in size varies between fetuses. The three basic rules of fetal growth are:

- Every fetus has its own growth rate
- Every fetus maintains its growth rate as long as it is growing normally
- Younger fetuses grow faster than older fetuses

From this it is understood that we need to identify the growth rate of each fetus which can only be done by plotting the growth curve. We will be more accurate if we start early in gestation as the variability in growth is lesser in a younger fetus.

What is Fetal Growth Restriction?

There have been many suggested definitions for fetal growth restriction. Some use fetal weight of 2nd, 3rd, 5th or 10th centiles for the given gestational age as cut off for calling a fetus growth restricted. Depending on the cut off we use, we are likely to either miss some of the growth restricted babies or include some normal babies as growth restricted.

A satisfactory definition of FGR has been suggested by the American College of Obstetricians and Gynecologists (ACOG) as describing ''a fetus that fails to reach its own potential growth''. This automatically means that we have to identify the growth potential of each fetus, as each fetus has a unique growth pattern.

What is an SGA baby?

SGA is defined as a birth weight (BW) below a given (usually the 10th) percentile for gestational age. If such a fetus is found to be growing along the lower percentile (10th or 5th), but maintaining it growth curve, it is called as "low growth potential" or "low profile fetus".

Not all small babies therefore are growth restricted. A fetus that is small may be growth restricted or may just be a constitutionally small baby. Further on we will answer the question "How do we distinguish these two?"

The Causes of FGR

About 50 – 60% of growth restriction is caused by placental dysfunction. 20% of fetuses have associated chromosomal abnormalities. About 10% have structural abnormalities and 6 – 8% of growth restricted fetuses result from intrauterine infections.

Ultrasound biometry and the use of growth charts therefore the mainstay for the diagnosis and subsequent management of fetal growth restriction.

The various causes of Growth restriction are:

Fetal factors
Infection
Heart disease
Malformations
Chromosomal abnormalities

Maternal factors
Cardiorespiratory disease
Renal disease
Anemia, Drugs
Smoking, Alcohol

Fetal
growth
defficiency

Placental factors
Abruption
Thrombosis, Infarction
Placentitis
Chorioamnionitis
Chorioangioma

Uterine factors
Dec. Uteroplacental flow
Chr. HTN
Preeclampsia
Diabetes mellitus
Connective tissue disorders
Morphological abnormalities

Types of FGR

Traditionally, growth restriction has been classified as

- Symmetric / early onset / proportionate
- Asymmetric / head sparing / late onset / disproportionate

It is compelling to relate the type of IUGR with the cause of FGR. Traditionally a symmetrically growth restricted fetus was thought to arise from chromosomal / fetal causes and a asymmetric fetus from placental causes.

We understand today that this is not necessarily true and there is considerable overlap of the causes and type of FGR.

What determines whether a fetus is symmetrically small or not is the timing of the insult or cause that is operational. Therefore if placental dysfunction begins early enough, a symmetrically small

fetus can result fairly early in the second trimester.

Management

The four important aspects of FGR management are

- Making the diagnosis
- Identifying the cause
- Follow up / monitoring the fetus
- Deciding timing of delivery

Ultrasound and doppler play a pivotal role in all of these.

a. Making a diagnosis

In both screening for and diagnosing of FGR, the importance of accurate gestational dating cannot be overemphasized. Although there are a number of methods for dating pregnancy, the use of early ultrasound measurements provides the most accurate estimation of gestational age. Once dating is done, the use of growth charts and centiles helps diagnose growth restriction.

Dating

Dating is best done in the first trimester and the measurements have to be taken properly according to prescribed techniques. In mid trimester, fetal Biometry is done to assess fetal age and "size for the age".

FIRST TRIMESTER BIOMETRY & DATING PREGNANCY

How to determine gestational age?

Guidelines for dating pregnancy in 1st trim

G. Sac+ [No YS, embryo or cardiac activity]	5.0
G. Sac + YS+ [No embryo or heartbeat]	5.5
G.Sac + YS+ Living embryo CRL<5mm(too small)	6.0
Embryo> 5mm in length	Age based on CRL

Between 5-11 weeks – GA in days = MSD (in mm) + 30

Gestational age calculation using CRL
CRL (in cms) + 6.5 = Gestational age in weeks
It is preferable to use CRL rather than gestational sac measurement for dating.

To ensure correct dating of pregnancy follow these steps. It is very useful to have the obstetric wheel while verifying dates.

Step 1: Ascertain menstrual age in weeks based on the 1st day of the LMP

Step 2: Ultrasound measurement of the gestational sac / CRL. CRL is the preferred measurement.

Step 3: Compare CRL age and menstrual age

Step 4:
- If difference is < 5 days assign MENSTRUAL AGE
- If difference is > 5 days assign CRL AGE (ULTRASOUND AGE) & Correct EDD

Note:
- In patients with irregular cycles assign CRL AGE.
- Once gestational age is assigned by CRL do not change dates in the subsequent scans

- Subsequent scans must be related to the corrected EDD only

SECOND TRIMESTER BIOMETRY

What do we measure?

Parameters used for establishing the gestational age are:

- Biparietal diameter (BPD)
- Head circumference (HC)
- Abdominal circumference (AC)
- Femur length (FL)

Other long bones that can be measured but not necessary during a routine scan are tibia, fibula, humerus, radius and ulna. It is also, wise to include transcerebellar diameter (TCD) in the biometric protocol.

Measurements should be taken in the correct plane.

Step 1: Assign menstrual age based on the first day of the last menstrual period

Step 2: Measure BPD, HC, AC and FL

Step 3: Assign gestational age for each parameter from the table. AC is not used for gestational age estimation, but should be compared with other parameters.

Step 4: Compare BPD, HC, FL ages
Step5: If the calculated gestational age by the above parameters is +/- 2 weeks of each other, calculate average ultrasound age. This is termed as "multiple parameter gestational age assessment".

Step 6: Compare USG Age and MENSTRUAL Age

- If difference between the individual parameters and menstrual age < 2 wks, assign menstrual age.
- If difference > 2 wks, assign GA by USG parameters

Two decisions are made at this stage
- To Correct EDD
- To re-check measurements with a repeat scan after at least 4 weeks or more

Re-scan may be done after 30 weeks in an otherwise normal pregnancy since a growth curve can be plotted and most growth disorders will be detectable at this stage.

Plotting Growth

Fetal growth profiles are best understood by plotting a growth curve using serial biometric measurements. This growth curve is compared with the normal curves for the population. To plot a curve, at least 2 points are needed and therefore there must be at least 2 biometric examinations to generate the curve. Ideally these examinations should at least be 3 weeks apart.

There are standardised centile charts available for each biometric measurement to be plotted against gestational age to assess growth.

How do we use the growth charts?

Growth charts have the gestational age in the x axis and the biometry parameter in the y axis.
The first time a scan is done in pregnancy, it is called as a dating scan. This is preferably done in the first trimester. In some cases if the first scan is done in the second trimester, this is considered as a dating scan.
The question we answer here is how old is the baby.

From the second scan onwards, all scans are considered as growth scans and is used to answer the question "how much the baby has grown?"

It is important to remember that the later the dating scan, lesser the accuracy of dating due to variability in fetal size.

Let us illustrate the use of growth charts with a few examples.

Scenario 1:
LMP known 10 weeks by dates, CRL 35mm corresponding to ten weeks. Hence we do not change the EDD and gestational age is fixed at ten weeks. If the CRL is 22 mm, we have a 9 week fetus and since there is a discrepancy of one week, dates would change and EDD corrected. It is extremely important to note that the dates once fixed should not be changed in subsequent scans.

As we follow up a fetus with subsequent scans, the plotting of the biometric measurements on the chart give a visual impression of growth and the growth curve generated is the fundamental basis on which growth disorders are diagnosed and managed.

Scenario 2:
Dating scan has been done at 11 weeks, the patient comes for a targeted scan at 21 weeks, it is obvious that 10 weeks has elapsed from the last scan. When we plot the growth curve,we should first go to the x axis, mark 21 weeks and then plot the biometry value for 21 weeks and see which centiles that falls on. We can then say that the AC of 151 cm is on the 20th centile for 21 weeks and BPD of 49 mm is on the 18th centile

Growth charts
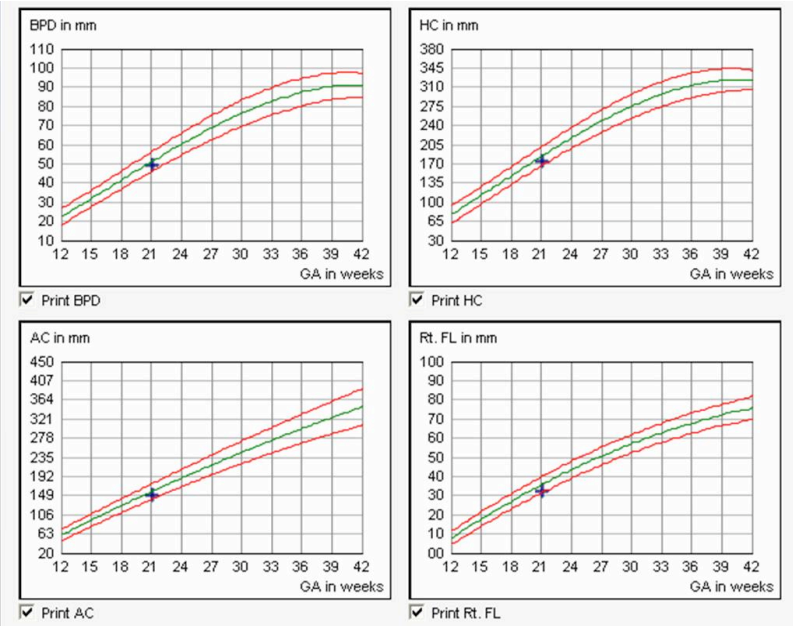
Caution: The common tendency is to print the interpretation of biometric values from the ultrasound machine. The machine will always give the 50th centile value for any parameter at any gestational age,as it has been programed in that fashion.

Hence, biometric interpretation must always be done off line.

Scenario 3:

If a patient presents late, say 26 weeks for the first time and we find all parameters are on the 5th centile or if the discrepancy between ultrasound age and menstrual age is more than 2 weeks, then the following possibilities could exist

- Wrong dates
- Growth restriction
- Low growth profile fetus

The transcerebellar diameter may help in such situations. If the liqour is normal, fetus is active and is structurally normal, and if doppler is also normal, this is unlikely to be placental dysfunction.

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In such cases a repeat scan after 2 - 3 weeks needs to be done to plot a growth curve and tell us if the fetus is maintaining its growth.

b. Identifying the cause

Once we see growth restriction, we need to determine the cause. This involves

- Ruling out structural abnormalities
- Ruling out chromosomal problems and infections
- Looking for indicators of placental dysfunction

A detailed targeted scan will help identify most significant structural anomalies.

Many of the chromosomal problems and some of the fetal infections have typical structural abnormalities that can be picked up on scan.

Placental dysfunction can be monitored by fetal biometry and doppler study.

When we have very early onset growth restriction, in order to confirm or rule out chromosomal problems and infections, invasive testing is offered. Amniocentesis will help both for karyotyping and getting immunology / PCR for fetal infections such as CMV.

c. Monitoring the fetus

Monitoring a growth restricted fetus includes monitoring its growth and its environment. While carefully watching the fetus, it is important not to loose sight of the mother as medical conditions such as preeclampsia / APLA may suddenly cause deterioration of maternal and fetal condition, shift the balance and influence decision making.

What to monitor?

Biometry and Growth
Doppler
Biophysical profile / CTG + AFI

How often to monitor?

The frequency of monitoring is dictated by the severity of the growth restriction and the gestational age of the fetus.
To monitor growth, biometry is done every 2 – 4 weeks depending on the clinical situation. There is no advantage in doing biometry in less than 2 week intervals.

Doppler

Doppler plays a vital role in management of growth restriction that is of placental origin. Placental dysfunction starts with abnormal tertiary villous vessels and ends with characteristic fetal multi-vessel cardiovascular manifestations. These effects can be documented with Doppler ultrasound examination of a number of vessels: the fetal umbilical arteries for the placenta; middle cerebral artery (MCA) for preferential brain perfusion; and ductus venosus for the cardiac effects of placental dysfunction. As growth restriction progresses, Doppler abnormalities in these vascular territories also deteriorate, suggesting a sequential pattern of disease progression.
Doppler changes in the MCA and venous dopplers have also been shown to correlate with fetal hypoxemia and acidemia. This presumed sequence and the anticipation of fetal deterioration form the basis for Doppler surveillance in FGR. The sequence of changes tends to follow a pattern in most cases. When there is maternal disease though there can be sudden deterioration in this sequence

- Increased placental blood flow resistance indicates placental dysfunction as the underlying cause
- Increased diastolic blood flow in the cerebral circulation

indicates redistribution
- As more placental vasculature is damaged, there is loss of diastolic flow in umbilical artery progressing to reversal
- Progressive elevation in venous doppler indices indicates alterations in cardiac function that precede deterioration of biophysical parameters in the fetus

'Who' to monitor is indicated by the constellation of maternal and fetal factors

'When' to monitor begins with the onset of intact survivability and monitoring frequency depends on the anticipated speed of clinical deterioration

'What' to monitor is the combination of arterial and venous Doppler, with input from biophysical variables in compromised FGR.

Abnormal umbilical artery		F
Brain sparing — Loss of brain sparing		E
Abnormal precordial veins		T
Umb vein pulsation		A
		L
Decreased AFV		D
Decreasing foetal activity		E
		A
Loss of FH variation		T
Late decels		H
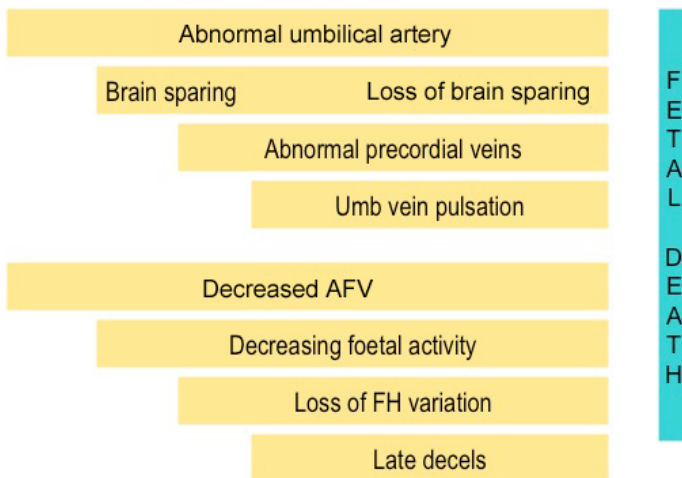
Fig: Sequence of change in a growth restricted fetus

d. Decision to deliver

Delivery is indicated when the risk for fetal acidemia and/or stillbirth outweigh the likelihood of meaningful extension of pregnancy. This decision is made taking into consideration the gestational age of the baby and its condition based on the results of
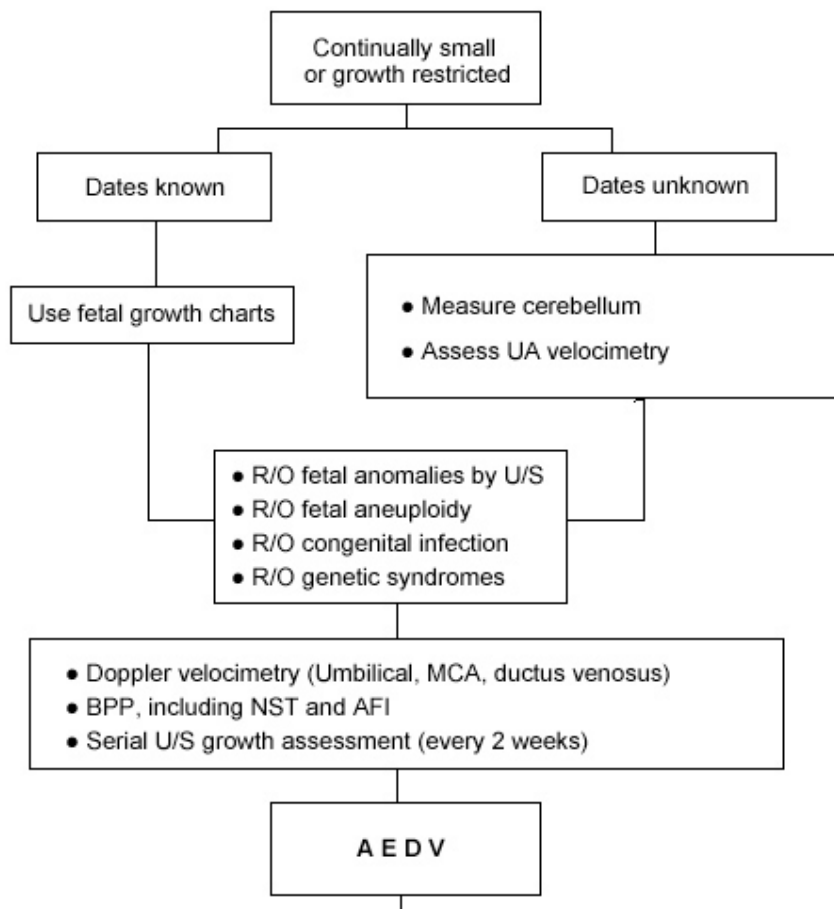
Doppler findings, CTG and AFI.

Finding the balance between delivering a premature baby needing neonatal care and an intrauterine loss can sometimes be tricky. It depends on neonatal viability and local neonatal survival rates. All FGRs where premature delivery is likely, will benefit from antenatal steroids.

End diastolic component of umbilical artery Doppler is very important in fetal prognostication. Absent or reversed end diastolic flow associated with very high perinatal mortality (40%)

If the baby is 32 - 34 weeks or more and there are absent or reversed EDV it is best to deliver. If the baby is < 32 weeks, then every day gained is a benefit – so here venous dopplers may play a role.

Doppler deterioration may antedate CTG changes – and so it is important to look at the whole picture and not monitor FGR babies with CTG alone.

Severe oligohydramnios in its own merit, even with reasonable dopplers may dictate need to deliver.

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        ┌─────────────────────┐
        │  Continually small  │
        │  or growth restricted│
        └─────────────────────┘
         │                    │
┌──────────────┐      ┌──────────────┐
│  Dates known │      │ Dates unknown│
└──────────────┘      └──────────────┘
       │                      │
┌──────────────────┐  ┌──────────────────────────┐
│ Use fetal growth │  │ • Measure cerebellum     │
│ charts           │  │                          │
└──────────────────┘  │ • Assess UA velocimetry  │
       │              └──────────────────────────┘
       │                      │
     ┌──────────────────────────────┐
     │ • R/O fetal anomalies by U/S │
     │ • R/O fetal aneuploidy       │
     │ • R/O congenital infection   │
     │ • R/O genetic syndromes      │
     └──────────────────────────────┘
                  │
 ┌────────────────────────────────────────────────────┐
 │ • Doppler velocimetry (Umbilical, MCA, ductus venosus)│
 │ • BPP, including NST and AFI                        │
 │ • Serial U/S growth assessment (every 2 weeks)     │
 └────────────────────────────────────────────────────┘
                  │
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         │     A E D V      │
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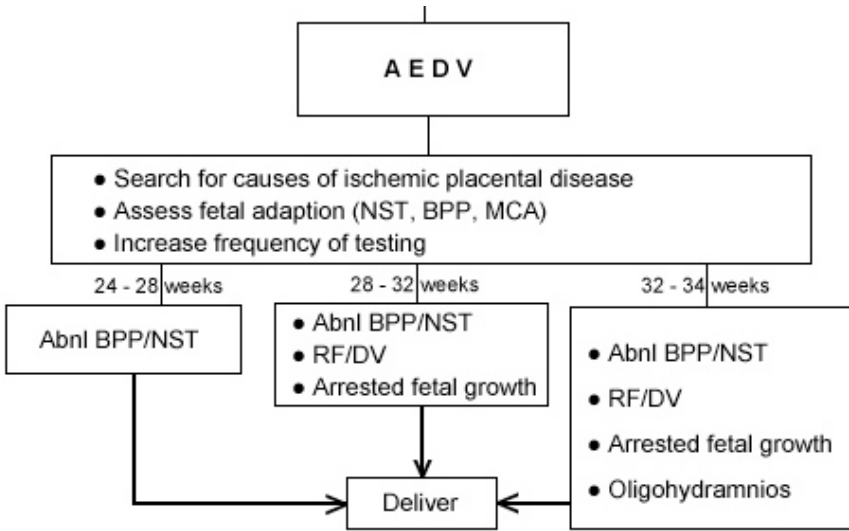
Fig: AEDV absent-end diastolic velocity; AFI amniotic fluid index; BPP, biophysical profile; FL/AC, femur length / abdominal circumference; L/S, lecithin / sphingomyelin; MCA, middle cerebral artery; NST, non-stress test; RF-DV, reverse flow in the ductus venosous; R/O, rule out; UA, umbilical artery; U/S, ultrasound

CASE 1
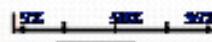
- Mrs SA, 22 year old Primi, Rh +ve Ht 162, Wt 47 kg
- Irregular cycles once in 3 months
- LMP was 12.2.09.
- Gestational age by dates – 16 weeks. EDC is 19.11.2009
- Dating scan on 13.4.2009 - dates were corrected as per CRL to EDC of 26.11.09.
- She did not undergo a First trimester screening
- At 19 weeks she was referred for a targeted scan.

BPD	37	1st centile
HC	136	2nd centile
AC	124	5th centile
FL	20	1st centile

16
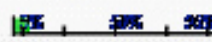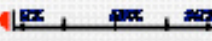
Biometry (mm)

☐ BPD	37		5%	50%	95%	16 W 3 D (1%ile)
OFD	49	CI	76	Range 75-85%	☑ To print	
☐ HC	135		5%	50%	95%	16 W 6 D (2%ile)
APD	39	TBD	40			
☐ AC	124		5%	50%	95%	17 W 6 D (6%ile)
☐ FL-Rt	20	◄	5%	50%	95%	16 W 6 D (<1%ile)
☐ FL-Lt						

Special Biometry (mm)

TCD	19	Nasal Bone	▼
Foot Length		Nuchal Fold	2.3	▼

GA Details

LMP : 12/02/2009

LMP GA: 20 W

LMP EDD: 19-11-2009

Biometry GA

GA : 19 W
US EDD 26-11-2009
Previous scan on 13/04/2009 (External)

Assign gestational age

○ By LMP
◉ By Biometry
○ By User

Assign GA
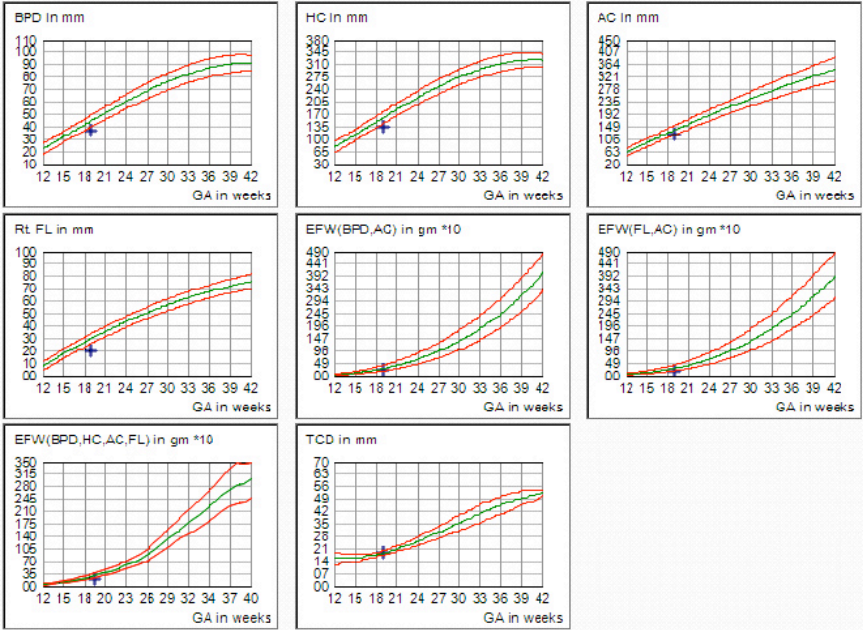
Her ultrasound showed-

- Placental appeared enlarged and thickness 4.8cm.
- Inferior vermis agenesis was seen with
- echogenic intra cardiac foci in LV,
- echogenic bowel.
- Doppler was normal.
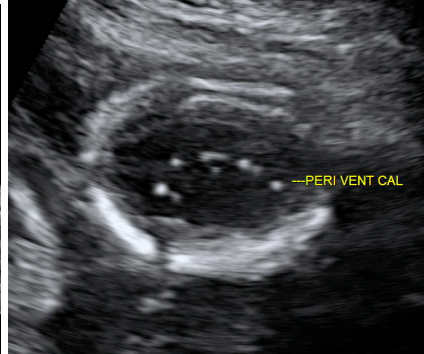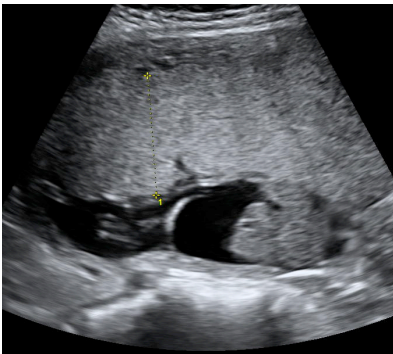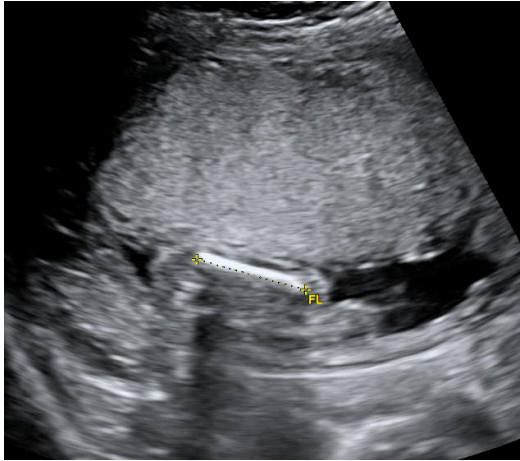
This patient has an early scan establishing dates. Now the scan shows severe growth restriction at 19 weeks, with placentomegaly and markers such as echogenic bowel.

In the light of this, the possibilities are
   a. Chromosomal abnormalities or
   b. Fetal infections.
   c. The normal dopplers suggests that placental dysfunction is not the operational cause here.

The patient must be offered for an amniocentesis for KT and infection screen. Poor prognosis has to be explained and decision of continuation and prognosis reassessed with the results.
Even if the couple is keen to consider termination of the pregnancy, it is important to perform tests to establish KT and rule out infections as the results will confirm the cause and be of value to counsel and manage a subsequent pregnancy.

Amniocentesis was done and KT was normal. Infection screen was **positive** for CMV and maternal CMV IgM titres were raised. Pregnancy termination was done and placenta and fetus sent for autopsy, which confirmed CMV infection.

Lessons learned

The final etiology of the growth restriction was intrauterine infection in this case.
In the early pregnancy the possibility of discrepancy in CRL due to an early growth delay cannot be ruled out.

CASE 2

- LB, a 32 year G2P0L0A1, conceived on ovulation induction.
- LMP was 22.10.2008. EDC by dates 29.7.2009
- Dating scan at 7 weeks - corresponded to dates – gestational age assigned as per LMP
- Her booking labs and BP were normal.
- *1st visit 20.1.08, FTS done –*
  - o CRL 66 corresponds to period of gestation (12wks 6 days)
  - o FTS screen negative 1:3100

Biometry (mm)

□ CRL	66	[graph]	13 W 1 D (60%ile)	
□ BPD	23	[graph]	12 W (26%ile)	
OFD	30	CI 77	□ To print	
□ HC	83	[graph]	12 W 4 D (39%ile)	
APD	19	TBD 21		
□ AC	63	[graph]	12 W 1 D (26%ile)	
□ FL	6	[graph]	12 W (16%ile)	

TCD		NT	1.7	▾
Heart rate	162	Nasal bone		Nasal bone seen ▾
		Ductus venosus	Normal flow	▾
		Tricuspid regurgitation		▾

GA Details

LMP : 22/10/2008
LMP GA: 12 W 6 D
LMP EDD: 29-07-2009

Assign gestational age

- ⦿ By LMP
- ○ By Biometry
- ○ By User

[Assign GA]

CRL in mm — GA in weeks

BPD in mm — GA in weeks

HC in mm — GA in weeks

AC in mm — GA in weeks

Rt. FL in mm — GA in weeks
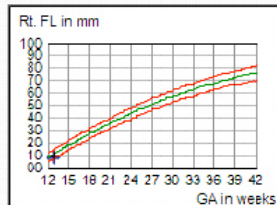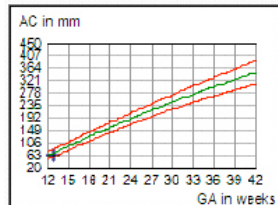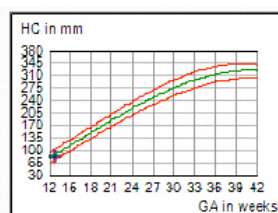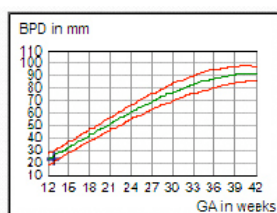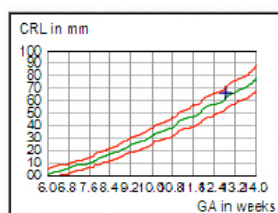
- *2nd scan done outside - 23.3.09* – all parameters on the 20th centile
- Doppler Rt Ut A 67.6 24.6
- Lt UA 62.6 7.12 with diastolic notch

A detailed scan showed no abnormality. One needs to consider placental insufficiency and watch the growth by serial scans.

- Patient continued regular antenatal visits. BP was normal
- *3rd scan - 27.4.2009.*

BPD	62	5th centile
HC	214	2nd centile
AC	185	2nd centile
FL	39	Below 1st centile

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Impression

All fetal parameters falls less than 5th %tile for 26-27 weeks of gestation.
As compared to the previous scan there is a drop in the growth rate of head circumference, abdominal circumference and femur length - SYMMETRIC IUGR.
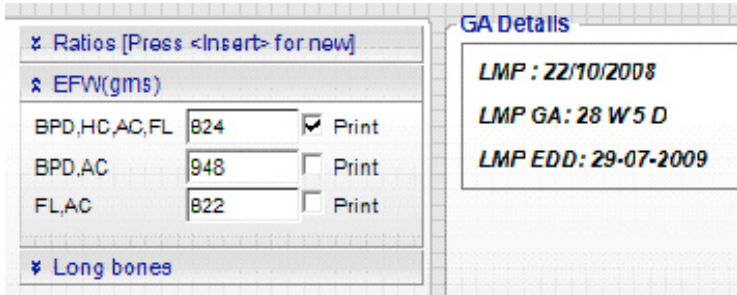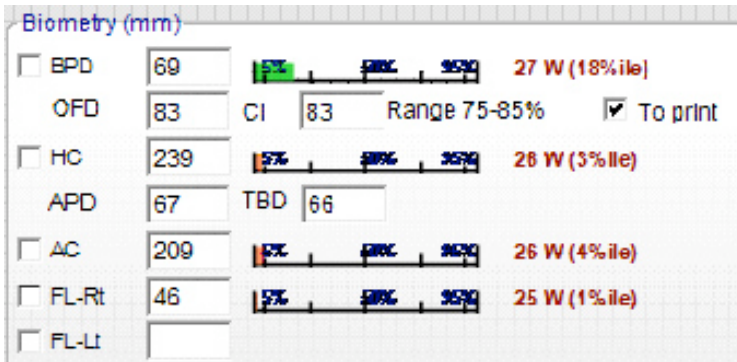
Doppler study
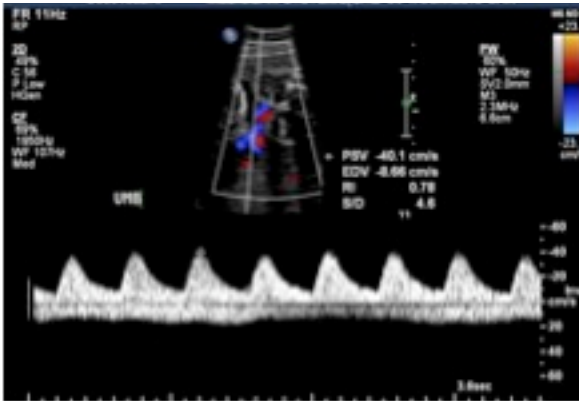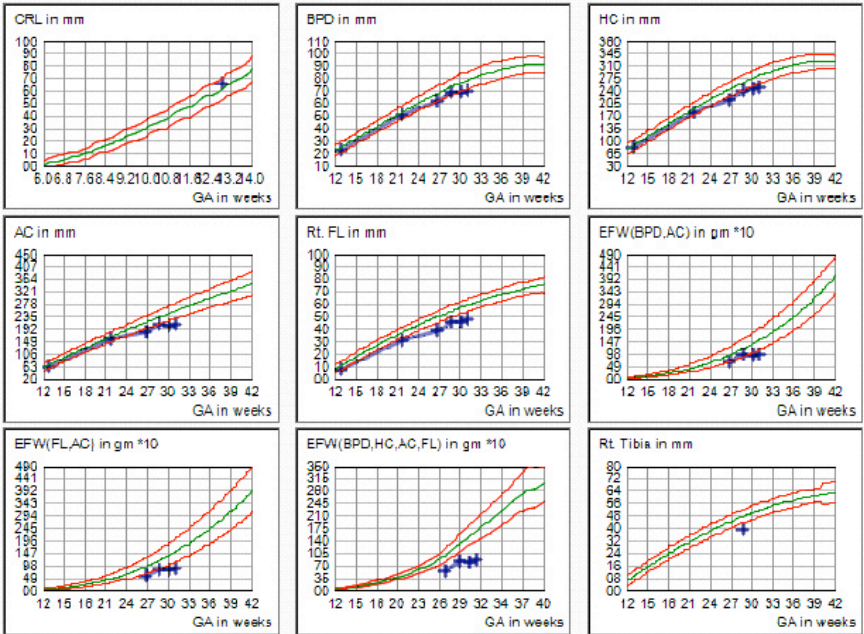
- Diastolic notch with high resistance type of flow seen in both uterine arteries.
- High resistance type of flow seen in umbilical artery.
- Normal flow seen in middle cerebral artery.
- Cerebro placental ratio - 0.96 (normal $> / = 1$).

A follow up scan and Doppler is needed in 2 weeks. Since it is likely that this baby may be delivered preterm, one needs to give steroids at about 28 weeks.

- Steroids given 6/5 and 7/5
- Follow up scan done in 2 weeks
- *4th scan 21.5.09*
- Single pocket 5.3

BPD	69	18th centile
HC	239	3rd centile
AC	209	4th centile
FL	46	1st centile

Biometry (mm)

BPD	69		27 W (18%ile)
OFD	83	CI 83 Range 75-85%	☑ To print
HC	239		28 W (3%ile)
APD	67	TBD 66	
AC	209		26 W (4%ile)
FL-Rt	46		25 W (1%ile)
FL-Lt			

Ratios [Press <Insert> for new]

EFW(gms)

BPD,HC,AC,FL	824	☑ Print
BPD,AC	948	☐ Print
FL,AC	822	☐ Print

Long bones

GA Details

LMP : 22/10/2008

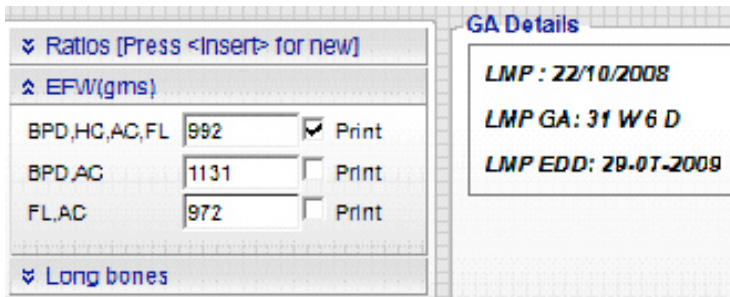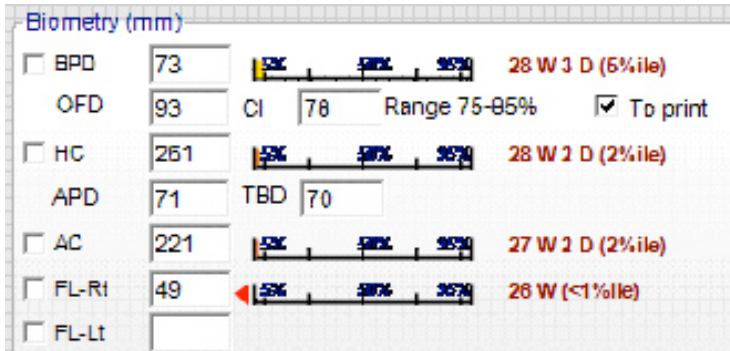LMP GA: 28 W 5 D

LMP EDD: 29-07-2009

- ***On 30.5.09, maternal BP increased to 140/94 with + alb***

Given the development of preeclampsia, the mother was admitted, started on antihypertensives and BP was monitored. 24 hr urine protein was elevated (459 mg/dl).

CTG and AFI were checked every 3 days and Doppler was repeated on 2.6.09

- ***5th visit 02.06.2009***

Biometry (mm)

BPD	73			28 W 3 D (5%ile)
OFD	93	CI 78	Range 75-85%	☑ To print
HC	261			28 W 2 D (2%ile)
APD	71	TBD 70		
AC	221			27 W 2 D (2%ile)
FL-Rt	49	◄		26 W (<1%ile)
FL-Lt				

˅ Ratios [Press <Insert> for new]

˄ EFW(gms)

BPD,HC,AC,FL	992	☑ Print
BPD,AC	1131	☐ Print
FL,AC	972	☐ Print

˅ Long bones

GA Details

LMP : 22/10/2008

LMP GA: 31 W 6 D

LMP EDD: 29-07-2009

Impression

Fetal head circumference, abdominal circumference falls at 2nd %tile and femur length falls less than 1st %tile for 31-32 weeks of gestation - suggestive of IUGR.

Doppler fetaures suggestive of cerebral redistribution due to utero placental dysfunction.

In the light of this, need to deliver if Doppler further deteriorates was discussed and review Doppler planned in 3 days.
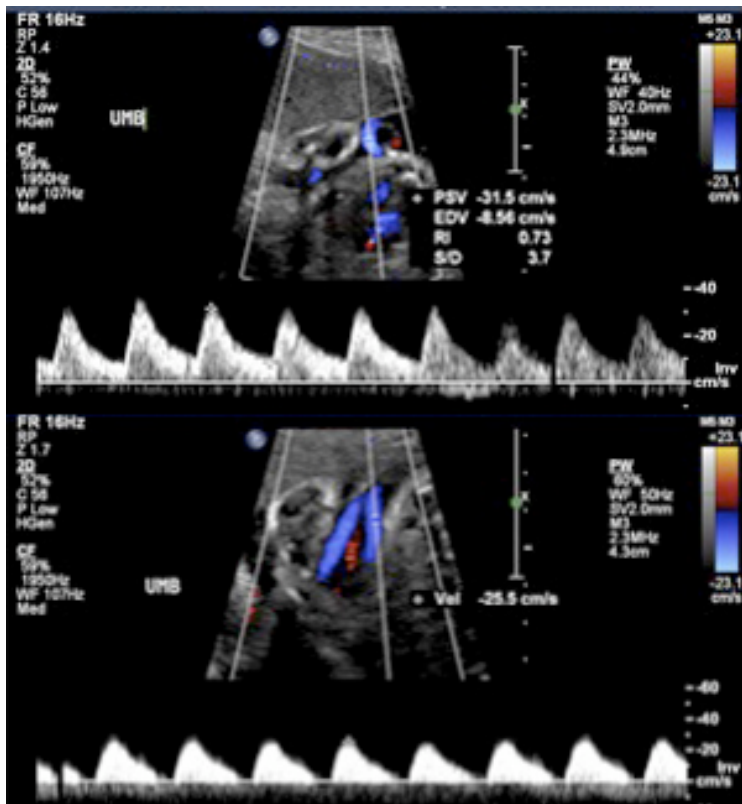
The following day, maternal BP went up to 150/100 with 2+ protein and headache.

In view of worsening preeclampsia, decision was made to deliver. LSCS was done and a 1.02 kg male baby was delivered. Baby needed NICU admission but did not need ventilation. Baby was in the NICU for 2 weeks, but course was uneventful. Baby is doing well now.

Lessons learned

The final etiology of the growth restriction was placental insufficiency due to PIH.