Fetal Growth and Doppler

FEMPO : Workshop Series

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Foreword

Dear Friends,

We have put together the content of the Fetal Growth and Doppler workshop as a handbook for your reference later.

These are practical points that you should understand in order to optimally manage fetal growth issues. We have simplified many of the topics so that it does not consume much time to get to the point of discussion. Therefore, for further reading, you are requested to refer to Textbooks.

The contributors for this booklet include Drs Manikandan, ES Usha, and Aarthi M Rangaraj. The sources are varied - from personal experience and understanding to published articles, guidelines and textbooks.

If you have any comment or clarification, please write back to us at mani@fetalclinic.in and we would be happy to address your concern.

Kind regards
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01 Doppler Physics for the Clinician

In B-mode ultrasound, B stands for brightness. We can see that only the 'amplitude' information of the returning echoes is used to differentiate the signals. We know, from Doppler principles, that there is a change in "frequency" of sound waves perceived by the observer when the signal source moves. Therefore when the transmitted ultrasound is reflected back by the moving red cells in vessels, the returning echoes have a different frequency than the original sound waves. This difference in frequency can be calculated and displayed on to the monitor. There are two basic ways of displaying this information: Color Flow Mapping (Color Doppler) and Spectral Wave Doppler (Pulsed Wave Doppler)

In "Color Doppler" mode, the computer analyses the frequency change in a specific number of scanning elements during a specific duration of listening. This active area is represented by the color box (or the region of interest box): the width of the color box correspond to the number of scanning elements detecting frequency change and the height of the box correspond to the listening window. Thus when the color box is activated, a group of crystals will start detecting "frequency change" for a particular period of time after the transmission of ultrasound waves. The returning echoes from flowing blood will have a different frequency and this change in frequency will be detected and displayed on the monitor. The computer, instead of assigning grey values, will now assign color values (hence, Color mode) to the signals: typically, if the frequency change is positive (the source is moving towards the probe) the color values assigned are in the red zone while the opposite is true for blue zone. However, it must be noted that this color assignment is arbitrary and by convention only. The machine can be set to assign different colors for different frequency change.

In "Pulse Wave" or "Spectral" mode, the probe 'listens' along a single line - insonation line (corresponding to a single scanning element) for frequency change at a specified depth (sample gate or sample volume). The change in frequency over time in that specified area is then displayed as a wave form: using the Doppler equation, the velocity of the source (i.e blood flow) can be derived from the frequency change (eqn 1)

Velocity of the blood = Frequency shift detected * speed of sound / 2 * transmitted frequency * cos ø

Angle of Insonation

The angle made by the insonation beam with the blood flow direction is called the angle of insonation. This angle is critical in obtaining accurate and optimal Doppler signals. As we can see from the Doppler equation, there is a direct relation between frequency shift detected and the cosine of the angle of insonation (θ in figure 1). Since cosine of 0 degrees is 1, the best Doppler signals are obtained when the insonation beam falls along the blood flow direction.

Region of Interest

The machine can be set to detect frequency shift along particular scanning elements for a particular depth of scanning. This region of interest appears as the color box on the screen when the color Doppler is switched on. If we keep the box wide, more scanning elements are set to detect frequency shift in addition to B mode imaging and hence the frame rate slows down. Ideally, the box must be as narrow as possible to correctly identify the vessel of interest. The height of the color box, does not have any significant impact on the frame rate.

Pulse Repetition Frequency

The transducer sends the original soundwaves in pulses and listens for the echoes between the pulses. If the pulsing frequency is set high, the machine detects only high frequency changes (ie high velocity flows). The maximum velocity that can be detected is half of the pulse repetition frequency (Nyquist Limit).

Aliasing

When the actual flow in the vessel is high but the pulse repetition frequency is set low, the Doppler signals are "confused" with respect to direction. In color Doppler, this is shown as mosaic pattern of color signals instead of blue or red; in spectral Doppler, this is shown as the waveform being wrapped around the baseline. The PRF (or velocity range or scale) should be adjusted such that there is no aliasing. In certain conditions such as valvular stenosis, aliasing on color Doppler is the first clue to the condition. While imaging the ductus venosus, the normal high-kinetic flow in the isthmic portion of DV is seen as aliasing and this is a pointer for its anatomical location

Sweep speed

The machine displays the waveforms of the spectral Doppler as a function of time; the speed at which the x-axis sweeps forward can be adjusted: faster sweeping will display fewer waveforms but well spread out; slower sweeping will display more waveforms but too crowded. Ideally, about 4 - 6 waveforms should be displayed on the monitor.

Wall-motion filter

The vessel walls also move during cardiac cycle and can produce 'noise' effect while detecting Doppler shift. This can be contained to a certain extent by adjusting the wall motion filter. However, the filter must be lowered such that the waveforms do not appear to be separated from the baseline by a black band.

Power output

The total acoustic output from the scanning elements can be increased or decreased to have an overall impact on the intensity of the returning echoes. However, attention should be paid to the safety indices that are displayed on the monitored while

increasing the acoustic power. Doppler modes tend to rise the mechanical and thermal indices to non-safe zone over prolonged usage.

Color (or Spectral) Gain

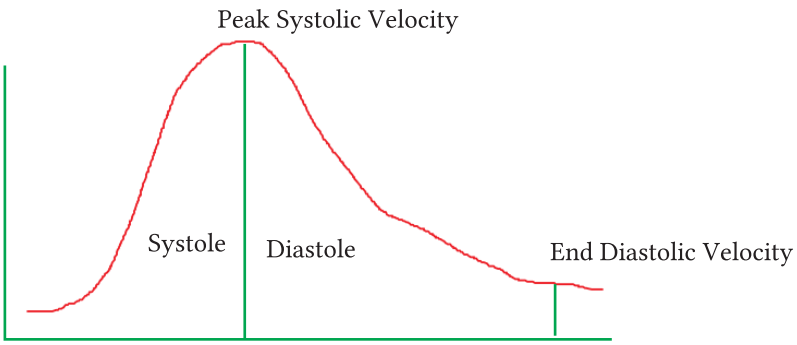
The returning echoes (or frequency shifts) can be amplified or dampened, and this refers to the Gain. This can be controlled to optimally display the image for clinical information. Gain can be increased when the vessel is small and has low flow. Overcompensation leads to noise artefacts.

Terminology

Terminology	Explanation	Clinical Application
Doppler Ultrasound		To study the flow characteristics in different vessels
Color Doppler	Type of Doppler Display: A region is sampled for frequency shift, and color coding is assigned as per the direction of frequency shift (or direction of movement). Usually red indicates movement towards and blue indicates movement away from the transducer	To map the vessels so that further quantification of velocities can be accurately done. To study the vascularity of a structure
Spectral Doppler	Type of Doppler Display: The frequency shift (or change in velocity) at a specified depth along a single scanning element's insonation line is displayed on a timeline.	To study the velocity of blood flow (and direction) over different phases of cardiac cycle. Quantification of velocity allows for calculation of downstream resistance
Angle of Insonation	Angle between the insonation beam and the direction of blood flow	Angle closer to zero degree provides the most accurate quantification of velocity
Pulse Repetition Frequency	Frequency at which the scanning elements sends sound in pulses. Higher frequency of pulses will detect higher velocity of flow; lower frequency of pulses will detect low flows.	Not to be confused with the frequency of the transducer.
Wall motion Filter	Noise reduction to cancel the frequency shift generated from the vessel wall movement	In general, low filter is to be used in most obstetrical Doppler measurement

Sweep speed	Speed at which the time axis sweeps forward in a spectral Doppler display Doppler display	Higher sweep speed displays fewer waveforms but well spread out. Generally 4-6 waveforms should be displayed.
Acoustic Power	Overall power output from the scanner.	Higher output gives better returning signals but increases the mechanical and thermal indices also
Gain	Dampening or amplification of the returning echoes	Too high settings will produce noise artefacts

02 Downstream Resistance: Central Concept in FGR Doppler



The concept of downstream resistance is central to the understanding of, and utilisation of Doppler studies in Obstetrics. Blood flows in any vessel with a characteristic flow velocity. In all arterial vessels, and in most pre-cordial venous vessels, this flow velocity changes according to the phase of the cardiac cycle. Thus, if we plot the flow velocity within an artery, it would be similar to fig 1.

The wave-form of the blood flow velocity has four components: **a steep rise** reaching a **peak velocity**, a **steady fall** reaching an **end velocity**. The peak velocity represents the end of systole and is also known as peak systolic velocity, while the end velocity represents the end of diastole and is also known as the end-diastolic velocity.

The peak systolic velocity is determined by the cardiac stroke volume and the blood viscosity. Consequently, when the stroke volume is relatively constant, changes in peak systolic velocity represents change in blood viscosity (e.g. increase in peak systolic velocity occurs in anemia)

The end diastolic velocity reflects the downstream resistance to blood flow. This in turn is determined by the vessel tone (or compliance), cross sectional area of the vessel or the number of branches, and for pre-cordial veins, the compliance of the heart.
Therefore, by measuring the velocity of the waveform in a given vessel, it is possible to accurately estimate the downstream resistance of that particular circulation. Knowledge of the pathological states and its relation to the downstream resistance then helps us in diagnosis and treatment (table 1).

In pathological states such as fetal growth restriction, there is an abnormally increased downstream resistance in the uterine arteries due to suboptimal transformation of the uterine spiral arteries into uteroplacental flaccid conduits; there is abnormally increased downstream resistance in the umbilical arteries due to obliteration of villus vascular tree; there is abnormally decreased downstream resistance in the middle cerebral arteries due to vasodilatation in the cerebral vessels secondary to ongoing hypoxemia; and finally there is abnormally increased downstream resistance in the ductus venosus due to cardiac dysfunction in the face of severe myocardial hypoxemia.

Table 1: Changes in Downstream Resistance in Fetal Growth Restriction

Vessel	Downstream Resistance	Remark
Uterine Artery	Increases	Suboptimal transformation of spiral arteries into uteroplacental flaccid conduits secondary to poor trophoblastic invasion
Umbilical Artery	Increases	Villus vascular obliteration leads to decreased cross sectional area of the placental circuit
Middle Cerebral Artery	Decreases	Hypoxemia induced vasodilatation in the cerebral circuit decreases resistance to flow
Ductus Venosus	Increases	Severe hypoxemia induced myocardial dysfunction causes increased resistance to DV flow

03 Placenta, uteroplacental and fetoplacental circulations.

Placenta

The placenta is the specialised thickening of the fetal membranes where maternal - fetal interdigitation occurs: this is true for all mammals. The variability between species accounts for the difference in gestational age, fetal maturity at birth, labor physiology, maternal complications during pregnancy, labor and birth. The human placenta is discoid and focal thickening of the fetal membranes: the vascularisation is derived from thevesical arteries and hence are referred to as chorioallantoic placenta. The thickened specialised area serves as the gas exchange (and nutrient exchange) membrane between the maternal circulation and fetal circulation. The maternal blood directly bathes the placental exchange units such that the fetal blood is separate from the maternal circulation by the layers of the placenta only and none of the maternal tissues - thereby earning the designation, hemochorial placenta.

Early development

The trophoblasts derived from the outer trophectoderm of the morula invades into the decidua all around the embryo. However, endovascular trophoblasts advance and plug out the maternal venules only over the region that underlies the embyronic attachment to the trophectoderm. Rest of the trophoblasts surrounding the embryo undergo "regression" to form fetal membranes (chorion laeve) under the deleterious effect of the free reactive oxygen radicals derived from maternal blood. The layer subjacent to the endovascular plugging proliferates and forms the scaffold for future placenta (Chorion Frondosum)

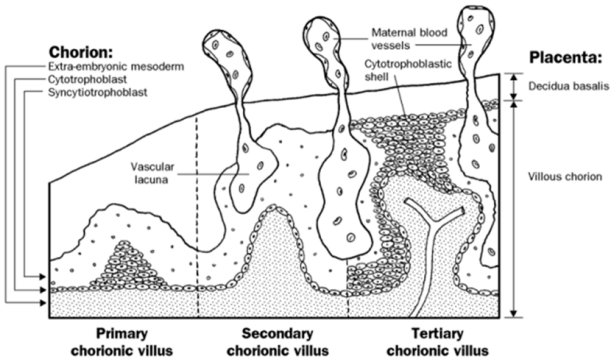
Uteroplacental artery transformation

The endovascular trophoblasts subsequently advance into the maternal spiral arteries reaching as far out as the inner 1/3rd of the myometrium, "eating away" the myometrial muscular coat and replacing it with a insensitive flaccid conduit lined by the trophoblasts: the process is referred to as transformation and the product as uteroplacental arteries.

Villus development

The trophoblastic shell in the chorion frondosum differentiates into a single layer of continuous fused trophoblast called the syncytiotrophoblast and multiple layers of individual cells called the cytotrophoblasts. Within the layers of the cytotrophoblasts multiple spaces open up and interconnect to form a lattice like network. The trophoblastic layers then protrude into this contiguous space (primary villus),

acquire a mesothelial core (secondary villus) and finally blood vessels (tertiary villus). Thus by the end of the first trimester, the chorion frondosum is thrown out into a number of vascularised villi that are bathed in the intervillus space into which the transformed uteroplacental arteries open up and infuse maternal blood.



Placental Exchange Efficiency

The efficiency of the placental membrane in gas and nutrient exchange is the central factor in the successful outcome of the pregnancy as far as the embryo is concerned. Simply put, there are two major mechanisms by which this efficiency keeps increasing through the gestation to keep up with the increasing demands put forth by the exponentially growing fetus.

The first is the primary mechanism which involves rapidly incrementing the vascularisation both on the uterine side and on the fetal side of the placenta. On the uterine side, continued transformation of the spiral arteries occur increasing both the number of transformed arteries and the depth of transformation. In effect, this leads to a steady drop in the downstream resistance to flow in the main uterine artery with advancing gestation resulting in increasing rate of blood flow into the intervillus space. On the fetal side, progressive formation, branching and vascularisation of the villi leads to a steady increase in the cross sectional area of villus capillary surface exposed to the intervillus space. Both these vascular changes reach a "ceiling" effect by the late second to early third trimester, from where the secondary mechanism start operating to keep the gas exchange efficiency to meet the demands of the third trimester. Suboptimal primary mechanism leads to the clinical phenotype of early onset fetal growth restriction with variable severity depending on the degree of derangement.

In the secondary mechanism, a number of ultrastructural changes occur in the villi that effectively increase the surface area as well as decrease the membrane thickness, of the gas exchange. Failure or suboptimal secondary mechanism leads to the clinical phenotype of late onset fetal growth restriction, where the uteroplacental downstream resistance is normal or near normal.

Placental dysfunction

Abnormal development of the villus vascular tree or inadequate transformation of the uteroplacental arteries leads to a state of placental dysfunction. Often, both abnormalities are seen together. Such affected pregnancies also show other evidences of damage or dysfunction: morphological changes include increased intervillus and subchorionic fibrin deposition, small area of implantation, and increased thickness; biochemical changes include decreased circulating levels of pregnancy associated plasma protein A (PAPP-A), decreased circulating levels of placental growth factor (PlGF), and increased circulating levels of soluble fms-like tyrosine kinase-1. The morphological changes are detectable by ultrasound to a large extend through the mid-second trimester and early third trimester.

Inadequate transformation of the uteroplacental arteries is associated with a failure to achieve a low resistance circulation in the downstream circuit of the uterine arteries and this can be readily observed by Doppler examination of the right and left uterine artery. Similarly, decreased villus vascular arborisation is associated with increasing resistance in the umbilical artery and can be observed by Doppler examination of the fetal umbilical artery.

Event	Explanation	Clinical Application
Chorion Frondosum Formation	Regression of chorion around the embryonic pole	Asymmetric regression leads to eccentric, marginal or velamentous cord insertion
Uteroplacental transformation	Eating up of the muscular coat of the spiral arteries in decidua and inner myometrium, converting them into flaccid conduits	Suboptimal transformation is associated with placental dysfunction syndromes - FGR and PE; Can be detected by Uterine artery Doppler study
Villus vascular arborisation	Progressive formation, branching and vascularisation of the villi in the placental substance	Suboptimal vascularisation or ongoing damage leads to increased resistance in umbilical artery blood flow
Placental Gas Exchange Efficiency	Primary mechanism is by vascular changes in uterine and umbilical artery circuits; secondary mechanism is by ultrastructural changes in the villi Increases through out gestation	Suboptimal primary mechanism manifests as early FGR while suboptimal secondary mechanism manifests as late FGR. Clinical phenotypes that have overlapping features of early and late have both mechanisms compromised to variable degrees

04 Optimising Doppler Imaging

The diagnostic potential of Doppler images is dependent on image quality.There are several factors and controls that affect the appearance of Doppler images. This section describes these factors and suggests ways to optimise images.

Colour flow imaging

Power : Color flow uses higher-intensity power than B-mode. Attention should be paid to safety indices. (Fig 1)

Mechanical index

The mechanical index is an estimate of the maximum amplitude of the pressure pulse in tissue. It gives an indication as to the relative risk of mechanical effects (streaming and cavitation).

Thermal index

The thermal index is the ratio of the power used to that required to cause a maximum temperature increase of 1°C The TI should be lower than 1.0 in the obstetrical setting. The exposure time should be kept as short as possible, usually no longer than 5–10 min and not exceeding 60 min.

The FDA regulations allow MI upto 1.9 to be used for all applications except ophthalmic.

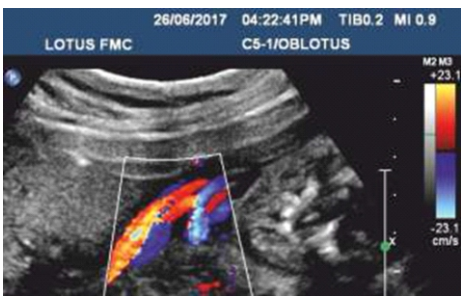


Fig 1: Pay attention to the safety indices: TI and MI while the Doppler is on

Gain: If the gain is too low then no colour is displayed, whereas if the gain is set too high, then noise may be displayed as a mosaic pattern throughout the image.

Frequency selection: High frequencies give better sensitivity to low flow and have better spatial resolution. Low frequencies have better penetration and are less susceptible to aliasing at high velocities. Velocity scale/pulse repetition frequency: The velocity scale or PRF should be adjusted to represent the real color velocity of the studied vessel. When the PRF is high, low-velocity vessels will not be displayed on the screen. When a low PRF is applied incorrectly, aliasing will present as contradictory color velocity codes and ambiguous flow direction. (Fig 2)

Region of interest: Because more pulses are needed to look at flow than for the B-mode image, reducing the width and maximum depth of the color flow area under investigation will usually improve frame rate and may allow a higher color scan line density with improved spatial resolution (Fig3)

Focus: The focus should be at the level of the area of interest. This can make a significant difference to the appearance and accuracy of the image

Color flow imaging: Practical guidelines

(1) Select the appropriate applications/set-up key. This optimizes parameters for specific examinations

(2) Set power to within fetal study limits.

(3) Ensure focus is at the region of interest and adjust gain to optimize color signal

(4) Use probe positioning to obtain satisfactory beam/vessel angle

(5) Adjust pulse repetition frequency/scale to suit the flow conditions.

(6) Set the color flow region to appropriate size. A smaller color flow 'box' results in a better frame rate and better color resolution/sensitivity

Spectral or pulse wave Doppler

Power and gain: Pulsed wave Doppler uses higher intensity power than Bmode. Attention should be paid to safety indices. Power and gain should be set so that clear signals are obtained. (Fig 4)

Velocity scale/pulse repetition frequency:
With pulsed ultrasound, there is an upper limit of the Doppler shift which can be displayed. This is known as the Nyquist limit and is defined as the pulse repetition frequency/2. With high velocity blood flow generating Doppler shifts above the Nyquist limit, aliasing occurs and results in the peak velocities being cut and wrapped around to the bottom half of the display below the baseline. (Fig 5)

This may be avoided by increasing the PRF or shifting the baseline. The waveform should fit at least 75% of the Doppler screen (Fig 6)

Gate size: If flow measurements are being attempted, the whole vessel should be insonated. In narrow vessels (eg Ductus venosus) a small gate must be used to avoid signals from adjacent vessels

Sweep speed: Doppler horizontal sweep speed should be fast enough to separate successive waveforms. Ideal is a display of four to six (but no more than eight to 10) complete cardiac cycles. For fetal heart rates of 110 – 150 bpm, a sweep speed of 50 – 100 mm/s is adequate (Fig 7)

Insonation angle The optimal insonation is complete alignment with the blood flow. This ensures the best conditions for assessing absolute velocities and waveforms. Small deviations in angle may occur. An insonation angle of 10◦corresponds to a 2% velocity error whilst a 20◦ angle corresponds to 6% error. When absolute velocity is the clinically important parameter (e.g. middle cerebral artery (MCA)) and an angle of >20◦ is obtained, angle correction may be used, but this in itself may lead to error. (Fig 8)
Calculation of indices are independent of angle of insonation.

Filter : Filter removes high amplitude lower Doppler frequencies from the slow-moving tissue such as the vessel walls. By convention, it should be set as low as possible (50 - 60 Hz) in order to eliminate the low-frequency noise from peripheral vessel walls. When using a higher filter, a spurious effect of absent EDV can be created .(Fig 9)
A higher wall filter is useful for structures like the aortic and pulmonary outflow tracts. A lower wall filter might cause noise, appearing as flow artefacts close to the baseline or after valve closures.

Spectral Doppler imaging: Practical guidelines

(1) Set power to within fetal study limits

(2) Position the pulsed wave Doppler cursor on the vessel to be investigated

(3) Set the sample volume to correct size. Correct the angle to obtain accurate velocities. Use the B-mode and color flow image of the vessel to make the angle correction

(4) Use probe positioning to obtain a satisfactory beam/vessel angle. Angles close to 90° will give ambiguous/unclear values. The beam/vessel angle should be 60° or less if velocity measurements are to be made

(5) Adjust gain so that the sonogram is clearly visible and free of noise

(6) Adjust the pulse repetition frequency/scale and baseline to suit flow conditions. The sonogram should be clear and not aliased

(7) Adjust sweep speed

(8) Recordings should be obtained during absence of fetal breathing and body movements, and if necessary during temporary maternal breath hold.

Which indices to use?

Commonly used indices available are: (Fig 10)

(1) Systolic/diastolic (S/D) ratio, sometimes called the A/B ratio; Peak systolic velocity/end diastolic velocity

(2) Resistance index (RI) (also called resistive index or Pourcelot's index); PSV-EDV/PSV

(3) Pulsatility index (PI) PSV-EDV/Mean

All three are highly correlated. PI shows a linear correlation with vascular resistance as opposed to both S/D ratio and RI, which show a parabolic relationship with increasing vascular resistance. Additionally, PI does not approach infinity when there are absent or reversed diastolic values. PI is the most commonly used index in current practice.

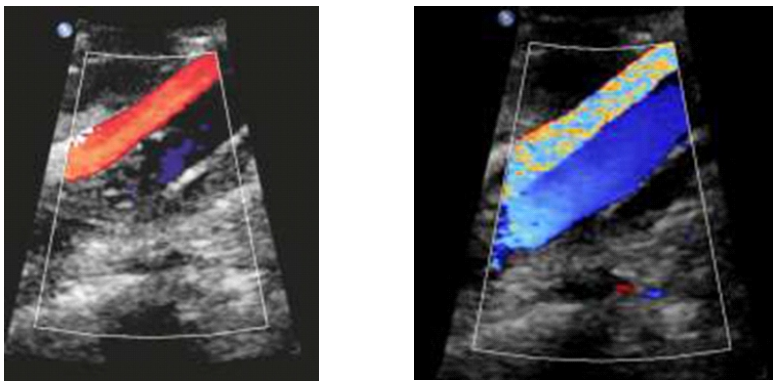


Fig 2: Effect of PRF (velocity scale): The PRF is set high in the left hand image - the vein is not imaged satisfactorily; lowering the PRF in the right hand image, brings out the venous flow. Aliasing (mosaic pattern) occurs in the arterial signal as a result

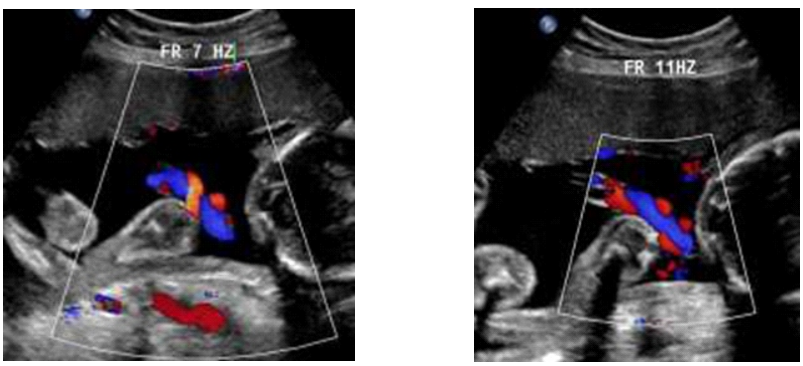


Fig 3: Effect of color box width on Frame rate: Narrow color box on the right hand image improves the frame rate

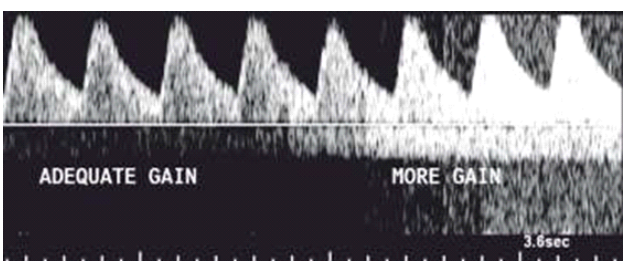


Fig 4: Effect of Doppler Gain on waveform: Increasing gain increases background noise artefact

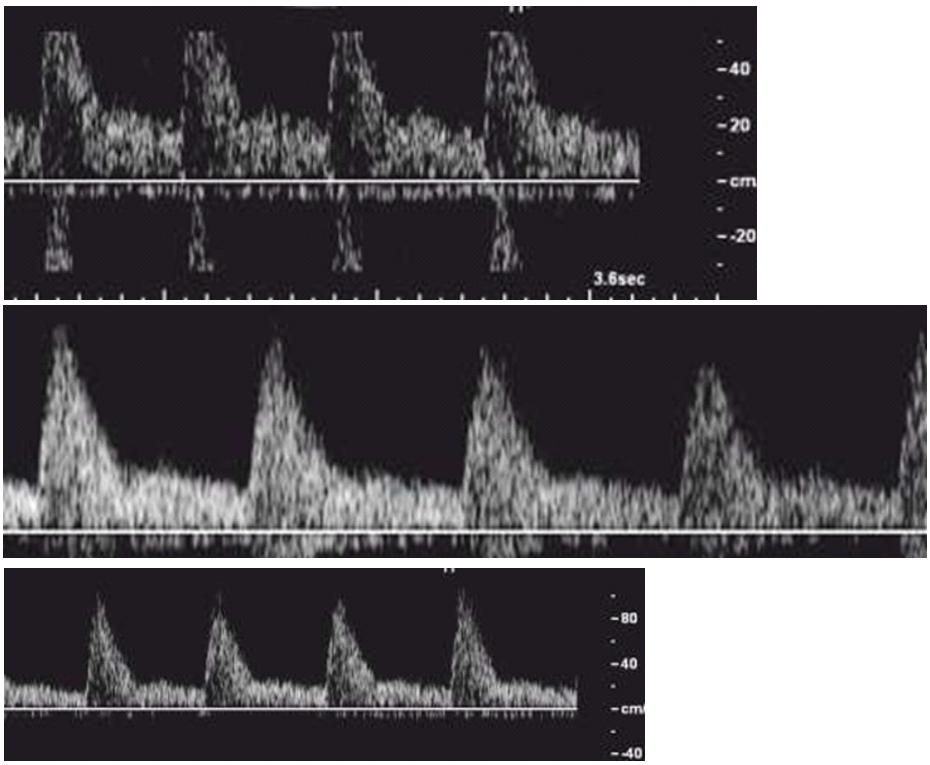


Fig 5: Aliasing in Spectral Wave and rectification by adjusting the baseline (top Fig) and by adjusting the PRF (bottom Fig)

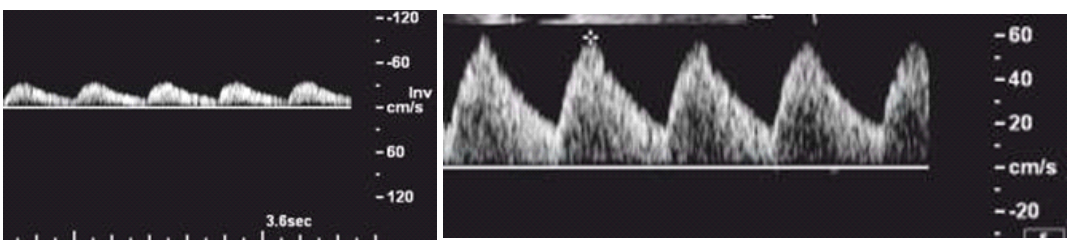


Fig 6: Waveform height adjustment by altering the PRF (optimal height in right hand image)

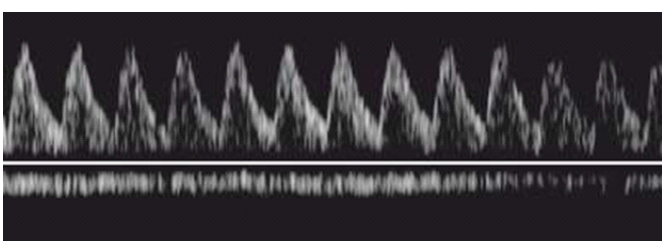


Fig 7: Too many waves seen: sweep speed is too low

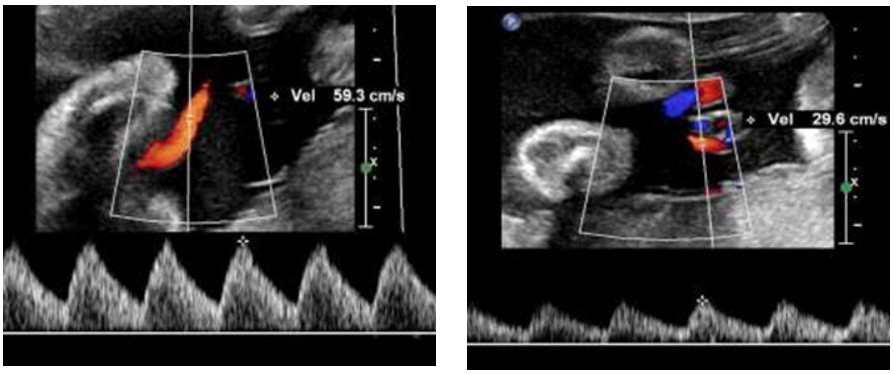


Fig 8: Effect of Insonation ange and angle correction on calculated velocity: LH image showing acceptable insonation angle, calculated velocity 59 cm/s; RH image insonating at nearly 90deg, calculated velocity 30cm/s

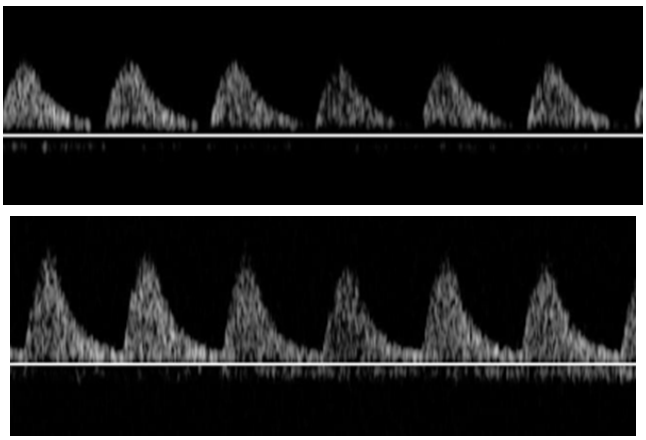


Fig 9: Effect of wall motion filter on waveforms: Top image - too high WMF resulting in pseudo absent end diastolic flow; lowering the WMF reveals the true picture in bottom image

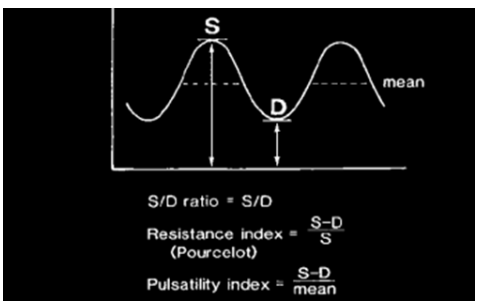


Fig 10: The indices reflect downstream resistance and eliminate the error of insonation angle; the preferred index to infer downstream resistance in obstetric Doppler is pulsatility index

05 Protocols: Obstetric Doppler Examination

Uterine artery

First-trimester uterine artery evaluation

1. Transabdominal Technique

Transabdominally, a midsagittal section of the uterus is obtained and the cervical canal is identified. An partially empty maternal bladder is preferable. The probe is then moved laterally until the paracervical vascular plexus is seen.

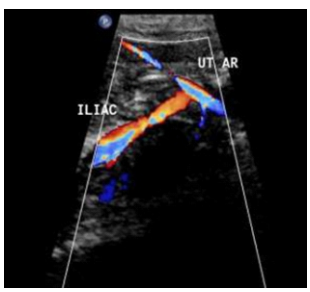
Color Doppler is turned on and the uterine artery is identified as it turns cranially to make its ascent to the uterine body.

Measurements are taken at this point, before the uterine artery branches into the arcuate arteries.

The same process is repeated on the contralateral side.

2. Transvaginal Technique

Transvaginally, the probe is placed in the anterior fornix. Similar to the transabdominal technique, the probe is moved laterally to visualize the paracervical vascular plexus, and the above steps are carried out in the same sequence as for the transabdominal technique. Care should be taken not to insonate the cervicovaginal artery (which runs from cephalad to caudad) or the arcuate arteries. Velocities over 50 cm/s are typical of uterine arteries, which can be used to differentiate this vessel from arcuate arteries.



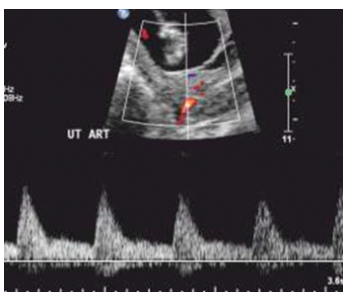


Fig 1: Identifying Uterine Artery: apparent cross-over of external iliac artery
Fig 2: Sample gate placement

Second-trimester uterine artery evaluation

1. Transabdominal Technique

Transabdominally, the probe is placed longitudinally in the lower lateral quadrant of the abdomen, angled medially. Color flow mapping is useful to identify the uterine artery as it is seen crossing the external iliac artery.(Fig 1)

The sample volume is placed 1 cm downstream from this crossover point.(Fig 2)

In a small proportion of cases if the uterine artery branches before the intersection of the external iliac artery, the sample volume should be placed on the artery just before the uterine artery bifurcation. The same process is repeated for the contralateral uterine artery.

2. Transvaginal Technique

Women should be asked to empty their bladder and should be placed in the dorsal lithotomy position.

The probe should be placed into the lateral fornix and the uterine artery identified, using color Doppler, at the level of the internal cervical os. The same should then be repeated for the contralateral uterine artery.

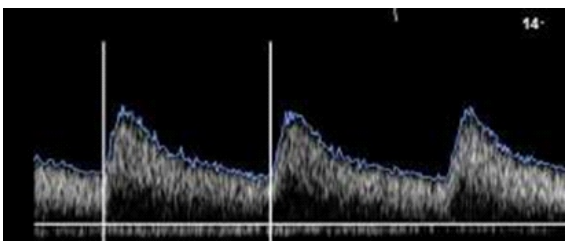


Fig 3: Normal Ut A waveform

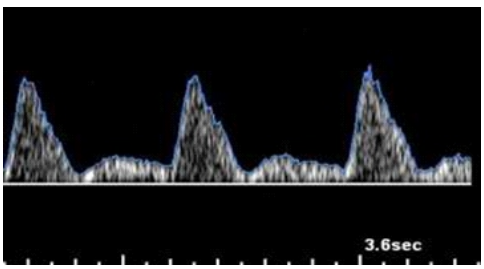


Fig 4: High resistance Ut A waveform with early diastolic notch

Umbilical artery

There is a significant difference in Doppler indices measured at the fetal end, the free loop and the placental end of the umbilical cord. The impedance is highest at the fetal end. For the sake of simplicity and consistency, measurements should be made in a free cord loop. However, in multiple pregnancies, and/or when comparing repeated measurements longitudinally, recordings from fixed sites, i.e. fetal end, placental end or intraabdominal portion, may be more reliable.(Fig 5)

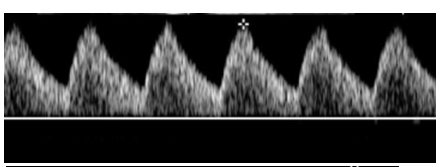


Fig 5: Normal waveform in Umbilical artery

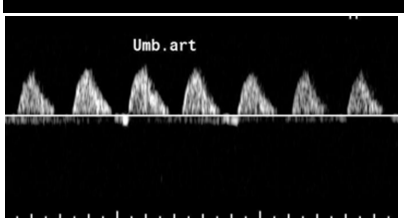


Fig 6: Absent End Diastolic Flow in Umbilical Artery

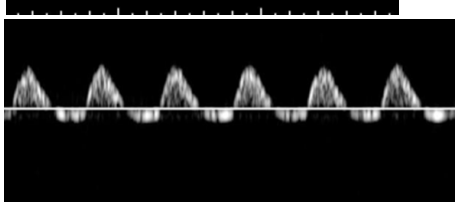


Fig 7: Reversed End Diastolic Flow in Umbilical Artery

Middle cerebral artery

The middle cerebral artery (MCA) is a branch of the circle of Willis in the base of the skull A transverse section of the fetal head is obtained and color flow mapping is used to identify the circle of Willis and the MCA.(Fig 8) The pulsed wave Doppler gate is then placed on the proximal one-third of the MCA. The angle of insonation should be zero degrees. (Fig 9)Attention should be taken to avoid any unnecessary pressure on the fetal head because this increases both the peak systolic velocity (PSV) and pulsatility index (PI).

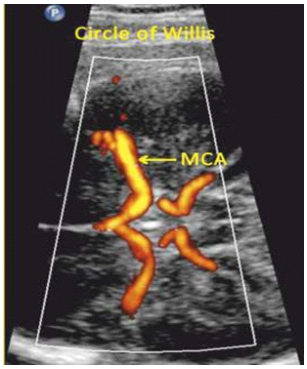


Fig 8: Color Mapping of Circle of Willis

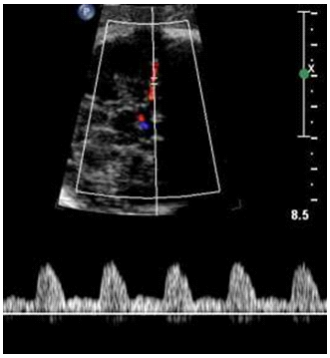
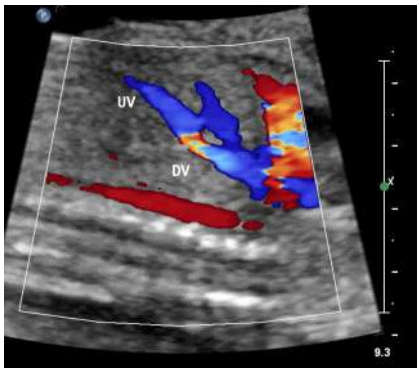


Fig 9: Normal high resistance flow in MCA

Ductus venosus

The ductus venosus (DV) connects the intra-abdominal portion of the umbilical vein to the left portion of the inferior vena cava just below the diaphragm First trimester The gestation should be 11+0-13+6 weeks and the CRL 45-84 mm The fetus should not be moving The magnification of the image should be such that the fetal thorax and abdomen occupy the whole screen A right ventral mid-sagittal view of the fetal trunk should be obtained Colour flow mapping should be used to demonstrate the umbilical vein, ductus venosus and fetal heart The pulsed Doppler sample should be small (0.5-1.0 mm) to avoid contamination from the adjacent veins and it should be placed in the yellowish aliasing areas The insonation angle should be less than 30 degrees The filter should be set at a low frequency (50-70 Hz) to allow visualization of the whole waveform The sweep speed should be high (2-3 cm/s) so that the waveforms are widely spread for better assessment of the a-wave (Fig 10 and 11) Color flow mapping demonstrating the high velocity at the narrow entrance of the DV confirms its identification and indicates the standard sampling site for Doppler measurements. Fig 12 shows correct placement of sample gate to avoid contamination. Normal and abnormal (reversal of a wave) waveforms are shown in fig 13.



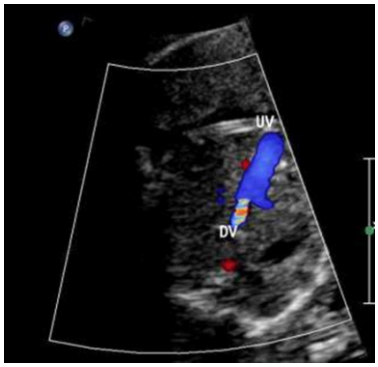


Fig 10: Mapping Ductus Venosus - Sagittal plane
Fig 11: Mapping Ductus Venosus - Oblique axial plane

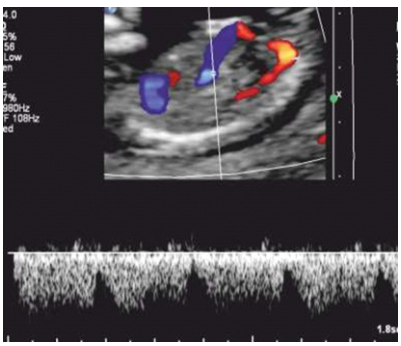


Fig 12: Sample gate placement in DV: adjust size to avoid contamination

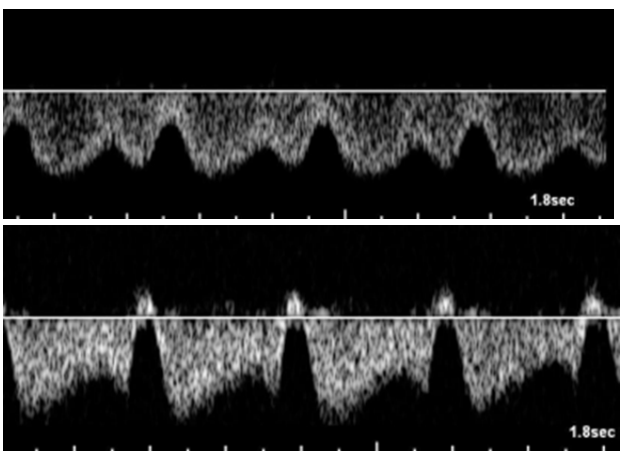


Fig 13: Normal and abnormal waveform in DV

06 Fundamental concepts in Fetal Growth

The three arms of in-utero progression of the embryo are growth, development and maturation. Growth refers to the increment in size of the fetus and its organs; development refers to the process of organogenesis; and maturation refers to the functional maturity of the various organs to meet the viability ex-utero.

In normal pregnancies, the three arms progress in a parallel, inter-linked but independent manner. While growth can become restricted due to various reasons, development and maturation may progress as expected.

Fetal Size

The fetal size is related to the gestational age and steadily increases with gestational age. The fetal size is usually assessed by the estimated fetal weight (EFW) calculated by one of the several equations that includes the fetal biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femoral length(FL). It is obvious that variability in any of these of components can affect the estimated fetal weight and thus the perceived fetal size.

BPD and HC can vary due to a variety of reasons: in the first half of pregnancy, abnormalities of the fetal head size and shape may point to malformations of the CNS and a diligent examination is warranted. Variations in the third trimester is usually due to familial head shape and sizes and this has to be taken into consideration.

FL, especially when short during the mid-trimester scan, may point towards skeletal problem, chromosomal problem, or growth restriction. Each of these possibilities will have other features to support. Late in gestation, femoral length is greatly influenced by the parental height.

AC is the most accurate estimator of fetal nutritional status and has the highest weightage in the EFW equation. It is also the most sensitive biometric parameter to change when there is placental insufficiency.

In summary, when the parameters are symmetric, EFW is a good indicator of fetal size and nutrition; when there is variability in individual parameters, these should be interpreted accordingly.

Fetal Size Classification

A fetus can be classified, based on its size (usually EFW) as follows:

AGA (Appropriate for Gestational Age): When the EFW falls within the 10th to 90th centile for the gestational age

LGA (Large for Gestational Age): When the EFW falls above the 90th centile for the gestational age

SGA (Small for Gestational Age): When the EFW falls below the 10th centile for the gestational age

SGA fetuses represents a heterogenous group comprising of normal, small fetuses (60 - 70%, constitutionally small), abnormal small fetuses (less than 2%), and starving small fetuses (20 - 30%). The subset that is small due to placental insufficiency is referred to as IUGR (Intrauterine Growth Restricted) fetuses.

Growth Velocity

The rate of increase in size of the fetus (BPD, HC, AC, FL and EFW) is described as the growth velocity and is related to the gestational age in a sigmoid fashion. Growth velocity of different biometric parameters can be used to distinguish the growth restricted fetus from the constitutionally small fetus and the fetus with wrongly assigned gestational age.

At least 2 biometric measurement sets, separated by at least 2 weeks after 20 weeks is necessary to accurately calculate growth velocity. Longer intervals show more accuracy than shorter intervals.

Typically, FGR fetuses show drop in growth velocity that is more pronounced in abdominal circumference than in the head circumference. Constitutionally small fetuses show drop in growth velocity that is symmetrical in all biometric parameters. Fetuses with wrongly assigned dates will show a normal growth velocity but the size will be consistently smaller.

Growth chart

Growth charts provide a visual assessment of fetal growth velocity. At present, there are more than 100 published population based and customised growth charts available. Customised growth charts (based on maternal characteristics and fetal sex), are no longer recommended as they do not improve prediction of adverse perinatal outcomes. While population–based charts are in wide use; recently, the INTERGROWTH-21st project has challenged the assumption that fetal growth variation is influenced by ethnicity and has provided international reference standards for fetal growth.

Terminology

Growth	Increment in fetal Size	Dependent on placental gas exchange efficiency
Development	Systematic and Sequential organogenesis	Gestational age dependent
Maturity	Functional Maturation of Organs	Gestational age dependent
Fetal Size	Estimated Fetal Weight and a combination of the size of the head (BPD, HC), trunk (AC), limb (FL)	AC is the most sensitive indicator of fetal nutritional status and has the most weightage in the calculation of EFW
	AGA (Appropriate for Gestational Age)	EFW between 10th and 90th centile for gestational age
	LGA (Large for Gestational Age)	EFW above the 90th centile for gestational age
	SGA (Small for Gestational Age)	EFW below the 10th centile for gestational age
	FGR	A subset of SGA that shows features of placental insufficiency: Growth velocity drop more pronounced in AC, Increased downstream resistance in Umbilical or Uterine arteriesDecrease in the Cerebro-Placental Ratio
Growth Velocity	Rate of increase in fetal size	Good discriminator of subcategories of SGA (Constitutionally small, wrong dates, and FGR)

07 Risk factors for Placental Insufficiency

The risk factors for placenta based complications apply with similar effect to the development of FGR as well as pre-eclampsia. In the fact the pathogenetic pathway for the two syndromes is shared. In most instances, early FGR and PE go hand in hand.

Risk factors for Placental dysfunction

Category	Factor	Remarks
Previous Obstetric Outcome	FGR	Risk of recurrence is proportional to the severity and inversely related to the gestational age at diagnosis in previous pregnancy
	PE	
	Abruptio	
Maternal Medical History	Chronic HT	Risk depends on the severity and clinical activity of the disease at the time of, and preceding pregnancy
	Renal Disease	
	Pre-existing Diabetes	
	Collagen-vascular diseases	
	Cardiac or Pulmonary diseases	
	Hypothyroidism	
Maternal Clinical Findings	Malnourished (BMI <18 or >30)	
	Severe Anemia	
	Fundal height lag	
Ultrasound Findings	Extensive Subchorionic Fibrin Deposition	Findings at the 18 - 23 weeks morphology scan
	Small, thick placenta	
	Single Umbilical Artery	
	High Resistance Flow in Uterine Artery	
Maternal Serum Findings	PAPP-A < 0.4 MoM	Findings at 11 - 14 weeks FTS
	Low PlGF	
	AFP > 2.0 MoM or < 0.25 MoM hCG > 3.0 MoM DIA > 2 MoM uE3 < 0.5 MoM	Findings at 16 - 21 weeks QST

08 Diagnosis and management of fetal growth restriction

SGA is defined as EFW < 10th Centile for the gestational age and comprises a heterogeneous group. Fetal growth restriction (FGR), which is a subset of SGA is defined as failure to achieve the endorsed growth potential, consequent to placental insufficiency. FGR fetuses are at increased risk of perinatal mortality, morbidity and long-term adverse neurological outcomes. In the clinical management of SGA, it is therefore vital to try and distinguish the 'normal small' (constitutional SGA) fetus from the 'starving small' (FGR) fetus.

Early and late onset FGR

The gestational age cut-off to differentiate early and late-onset FGR has been set at 32 weeks (Delphi consensus). The key features of the two clinical phenotypes are as follows:

	Early-onset FGR (< 32 weeks)	Late-onset FGR (>/= 32 weeks)
Proportion of the total FGR cases	20-30%	70-80%
Association with pre-eclampsia	50%	10%
Degree of placental insufficiency/ pathogenesis	Severe; develops due to abnormal early implantation	Mild; secondary damage to placenta in the latter half of pregnancy
Natural history	Chronic under-nutrition/ hypoxia leads to a classical sequence of hemodynamic, metabolic and endocrine adaptations in the fetus (reflected by the worsening Doppler parameters); with progressive deprivation resulting in decompensation and severe fetal injury/ death.	No typical natural history. Mild placental disease leads to deceleration of fetal growth and mild hypoxia. However, these fetuses are at risk of sudden deterioration before labour without any warning signs; possibly due to intolerance of the term fetus to hypoxia or rapid placental failure.
Clinical outcomes	Higher incidence of IUFD, stillbirth, preterm birth with its attendant complications, neonatal death and long term adverse neurological outcomes.	Comparatively benign; but higher risk of sudden IUFD, term stillbirth, intra-partum fetal distress and poor long-term neurological outcome.

Diagnosis of FGR

Traditionally FGR was diagnosed when the EFW was < 10 th % and the Umbilical artery (UA) Doppler was abnormal. Using the above criteria would lead to an under diagnosis of FGR, as milder cases of placental insufficiency may not manifest Doppler abnormalities. (Perfusion Diffusion mismatch)

The most recent expert consensus based criteria (reached through Delphi procedure) for diagnosis of FGR is as follows:

	Early-onset FGR	Late-onset FGR
Stand-alone criteria	EFW/ AC < 3 rd centile OR UA-AEDF	EFW / AC < 3 rd centile
Combination	EFW / AC < 10th centile WITH 1.Uterine artery PI > 95th centile and / or 2.Umbilical artery PI > 95th centile	Any 2 out of the following 3: 1.EFW / AC < 10 th centile 2.CPR < 5 th % or UA > 95 th centile EFW / AC crossing centiles by > 2 quartiles (50%) on the growth chart.

Accurate dating of pregnancy and detailed anatomical evaluation to exclude anomalies are important pre-requisites for the correct diagnosis of FGR.

Fetal cardio-vascular response to placental dysfunction

Placental dysfunction results in impaired nutrition and oxygen supply to the fetus. The starving fetus attempts to cope, by evoking a number of compensatory mechanisms. These compensatory responses are responsible for the short/ long-term morbidity and altered fetal programming seen in these fetuses.

Summary of cascade of cardiovascular adaptations in FGR

The first true 'fetal' adaptation that is measurable is a fall in MCA downstream resistance: the MCA PI decreases. This is to increase the oxygen delivery to the cerebral circulation in the face of suboptimal oxygen delivery from the placenta. The placental efficiency (or lack of it) is reflected by the increased downstream resistance to the umbilical artery blood flow. Thus, although not a fetal adaptation, increase in umbilical artery PI precedes MCA PI fall in most cases of FGR as the temporal relation is cause-effect. In a good proportion of cases, the suboptimal placenta is associated with a suboptimal uteroplacental transformation also, and hence an increased downstream resistance in the uterine arteries:

The sequence of fetal adaptive response is as follows:

1. Venous re-distribution: (Pre-clinical)

Early placental dysfunction leads to reduced flow in Umbilical vein and increase shunting through Ductus venosus (hepatic bypass). This down-regulates Insulin-like growth factor pathway and causes depletion of liver glycogen stores resulting in lagging of fetal abdominal circumference and later in a fall of EFW.

In addition, the fetus re-directs much of the right ventricular output into the umbilical artery by "hind-limb reflex" - an adaptive vasoconstriction of the lower limb arterial vessels.

2. Arterial re-distribution: (early signs)

Obliteration of villous vasculature causes sub-clinical increase in placental blood flow resistance and relative hypoxia which can be evidenced by a decrease in Cerebro-Placental Ratio (CPR).

When > 1/3 rd of the placenta gets affected, the resistance increases sufficiently to cause reduced diastolic flow in UA and an increased Pulsatility Index (PI).

Further, as the cerebral auto-regulatory mechanism kicks in secondary to hypoxia, there is cerebral vasodilatation and Middle cerebral artery PI decreases – 'Brain sparing'.

Progressive obliteration of the villous vascular tree results in increasing resistance to UA flow and manifests as absent end diastolic flow (AEDF; when > 50% of the gas exchange area) or Reversed End Diastolic Flow (REDF; with loss > 70% of the gas exchange area).

Also, there is peripheral arterial vasoconstriction in the trunk to divert the nutrient rich blood to the vital circulations (brain and heart). Both the above mechanisms cause a marked increase in systemic blood pressure (increase in right ventricular afterload). Whereas, the pressure in the cerebral circulation is remarkably lowered (reduced left ventricular afterload) due to cerebral adaptation (brain sparing). The progressive imbalance in the right vs left ventricular afterload (indicating increasing hypoxemia) results in decreasing CPR, decreasing Aortic isthmic Index, and finally, reversal of diastolic flow in aortic isthmus.

3.Venous flow alterations: (late /critical signs)

Finally, ongoing fetal hypoxemia and resulting acidosis cause decline in fetal cardiac function, as evidenced by worsening of venous Doppler indices – increase in DV-PI followed by DV- 'a' wave reversal and UV pulsations (pre-terminal signs).

Biophysical parameters are the last to be affected and show a rapid sequential decline (loss of FHR variability precedes loss of fetal respiratory and body movements) once venous doppler abnormalities set in. However, alteration of the venous indices and FHR changes may sometimes happen in parallel and CTG abnormalities may even precede abnormal DV doppler in 50% of cases.

Management of early-onset FGR:

Currently there are no known interventions to improve placental function. The 'starving fetus' can either be delivered and exposed to the risks of prematurity or allowed more time in-utero for functional maturity, while accepting the risk of stillbirth due to fetal acidemia.

Studies on FGR have shown that,

· Gestational age is the single most important variable determining survival at < 27 weeks and 'intact' survival at < 29 weeks.

· Between 27 and 32 weeks, each day in-utero increases survival rate by 1-2%

· Morbidity free survival exceeds 50% consistently only after 28 weeks.

Therefore, prolongation of pregnancy with the fetus under rigorous surveillance for signs of deterioration is the current standard of care in early-onset FGR.

Surveillance in early FGR:

Surveillance traditionally was done by serial Doppler examinations with the aim of optimizing the time of delivery. As mentioned earlier, the temporal sequence of Doppler changes is well established for the arterial and venous circulations, but not for the venous system and biophysical parameters. Therefore, optimally these fetuses should be followed up using both Doppler and CTG; as highlighted by the recent TRUFFLE study.

Frequency of monitoring early FGR:

· UA normal – weekly monitoring (atleast for the initial 2 weeks)

· UA with PI > 95 th % - twice or thrice weekly

· UA-AEDF/ REDF – daily

The monitoring frequency given here is arbitrary and should be dictated by severity of disease, rate of progression and maternal clinical condition and the NICU set-up.

Delivery thresholds:

The basic principle in the management of FGR is to deliver the fetus when the risks of ongoing hypoxemia outweigh the risks of prematurity (ie, in-utero hostility exceeds ex-utero threat): thus, timing of delivery is the crux in the management. In general, earlier the gestation, higher is the threshold to deliver.

· > 28 weeks – DV absent 'a' wave

· > 30 weeks – UA-REDF

· > 34 weeks – UA-AEDF

· CTG – unprovoked FHR decelerations, reduced short term variability (assessed using computerized CTG)

Variables that influence management:

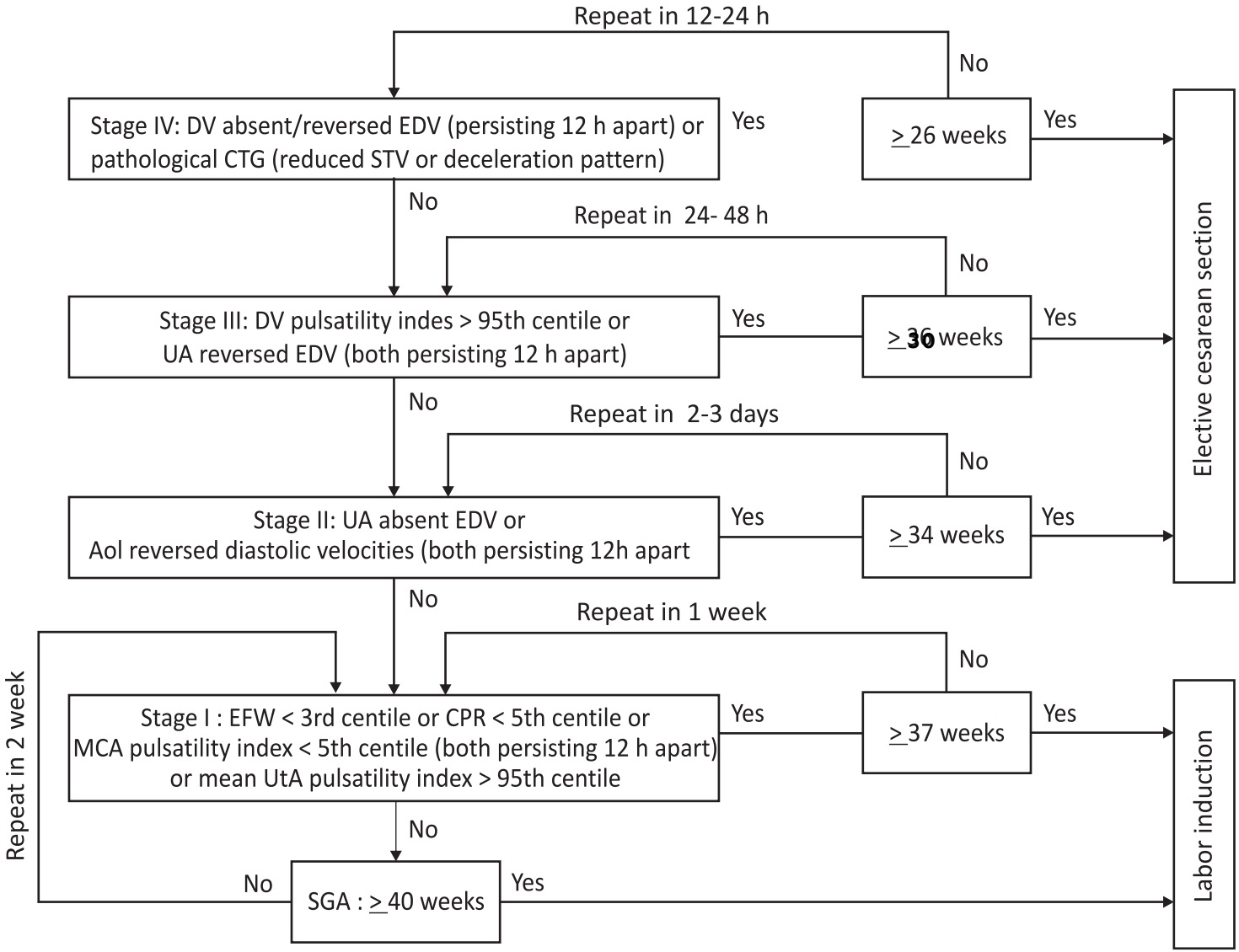
· Gestational age

· Birth weight

· Co-morbidities in the mother

· Doppler / CTG parameters

· NICU back up



Figueras F, Gratacós E: Update on the Diagnosis and Classification of Fetal Growth Restriction and Proposal of a Stage-Based Management Protocol. Fetal Diagn Ther 2014;36:86-98. doi: 10.1159/000357592

Expected outcome with above protocol; as per TRUFFLE study: (for counseling)

GA @ Delivery	26-27 w	28-29w	30-31w	32-33w	Overall
Survival at discharge (%)	81	91	97	99	94
Severe short term Morbidity (%)	51	35	20	12	24
Severe –morbidity free survival at discharge(%)	30	56	78	87	70

Unanticipated stillbirth rate – 2%
Perinatal mortality rate – 8%
Survival at 2 years – 92%
Survival without neuro-impairment at 2 years – 82%

Mode of Delivery:

In most instances, when Umbilical artery end diastolic flow is absent or reversed, the preferred route of delivery is prelabour cesarean; in fetuses with high resistance forward flow in umbilical artery or normal flow in umbilical artery, vaginal delivery may be attempted with intensive intrapartum monitoring. The risk of cesarean delivery due to fetal distress is high when the CPR is low.

Management of Late FGR

The principles of management remains the same with the caveat that fetal deteoration may happen without the above mentioned sequential Doppler changes. Hence the delivery threshold is low in late FGR compared to early FGR. Also, hasty decision based on only MCA alteration without considering the growth velocity would lead to overdiagnosis or unnecessary interventions. Therefore, the most important element in the management of the late FGR is the growth velocity and its trend. Doppler measurements, especially MCA (and therefore CPR) should be repeated to understand the trend. Decision to deliver before 37 weeks should be made on observations that consistently point towards late FGR. Unlike early FGR, vaginal route is the first choice as the route of delivery.

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