Dr. Seham Abufraijeh

Normal fetal growth — The process of fetal growth comprises three consecutive and somewhat overlapping phases :

1)The first phase is the phase of cellular hyperplasia and encompasses the first 16 weeks of gestation.

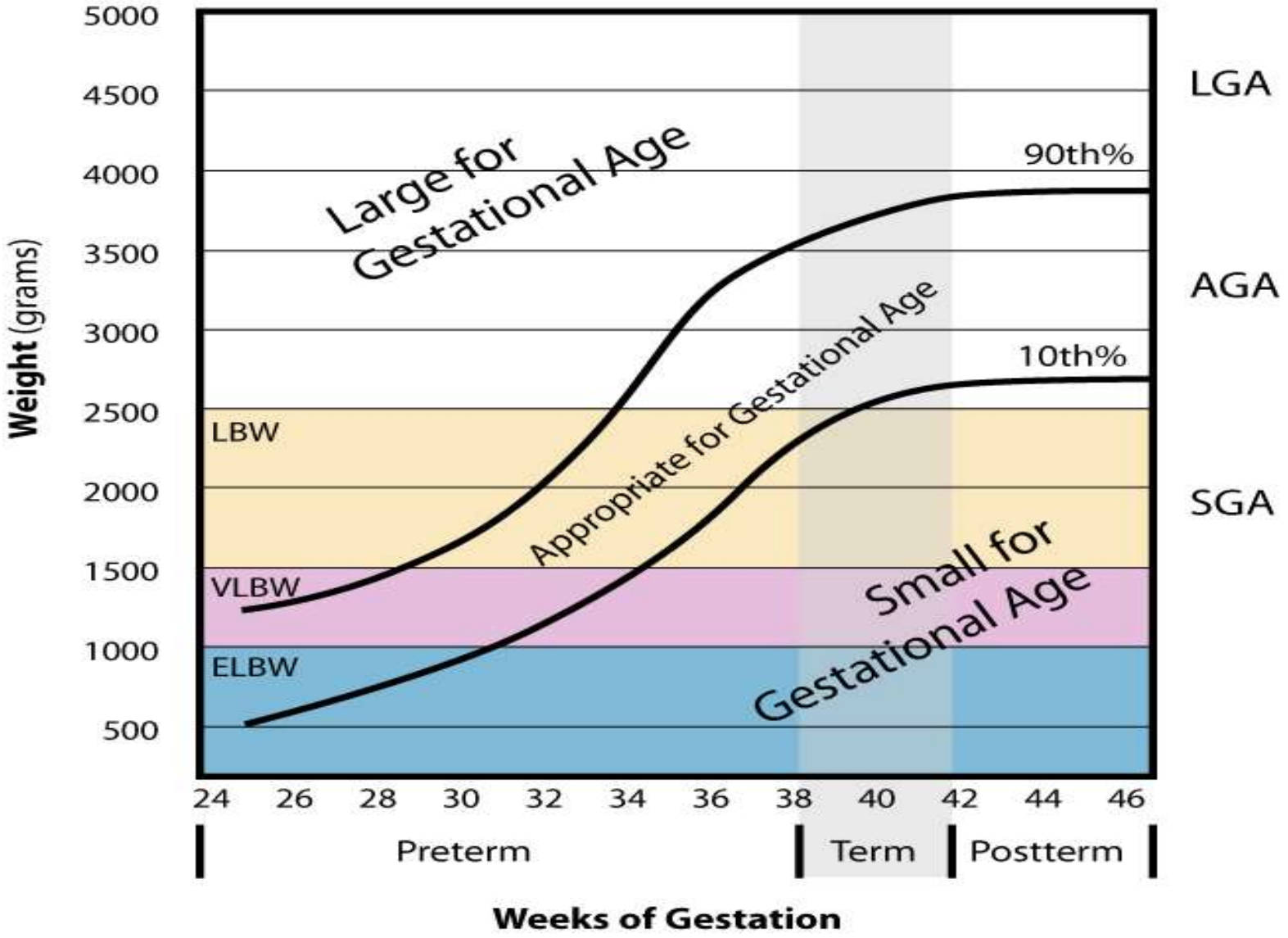
2)The second phase, known as the phase of concomitant hyperplasia and hypertrophy, occurs between the 16th and 32nd weeks and involves increases in cell size and number.

3) The third and final phase, called the phase of cellular hypertrophy, occurs between the 32nd week and term and is characterized by a rapid increase in cell size.

Quantitatively, normal singleton fetal growth increases from approximately **5 g/day at 14 to 15 weeks** of gestation to **10 g/day at 20 weeks** and **30 to 35 g/day at 32 to 34 weeks**, **after which the growth rate decreases**.

** The median growth rate in multiple gestations is lower than that of singletons during the third trimester.

Small for gestational age (SGA) : Refers to fetus who weighs below the 10th percentile for gestational age.



A small for gestational age (SGA) fetus may be either :

1) Constitutionally small (70%) : They are not at high risk of perinatal mortality and morbidity.

2) Growth restricted (30%) = Fetal growth restriction (FGR, also called intrauterine growth restriction [IUGR]): They are at high risk of perinatal mortality and morbidity and long term complications.

The incidence of small for gestational age (SGA) varies among populations and increases with decreasing gestational age. Approximately **10 %** of term infants in developed countries are small for gestational age (SGA), compared with **23 %** of term infants in developing countries.

Fetal growth restriction (FGR) : a fetus that has not reached its growth potential because of genetic or environmental factors. The origin may be fetal, placental, or maternal, with significant overlap among these entities.

→ Most of the FGR fetuses are SGA. But sometimes the FGR fetuses have a weight slightly greater than the 10th percentile for gestational age.

→ Estimated fetal weight <3rd percentile is consistently associated with adverse outcome.

Symmetric and asymmetric growth restriction

- **Symmetric FGR** : Which comprises 20 to 30 % of growth restricted fetuses, refers to a growth pattern in which all fetal organs are decreased proportionally due to global impairment of early fetal cellular hyperplasia. Symmetric FGR begins early in gestation and usually is caused by intrinsic factors such as congenital infections or chromosomal abnormalities and inborn error of metabolism. However, decreased nutrient supply early in development can restrict growth of all organs.

- **Asymmetric FGR :** Is characterized by a relatively greater decrease in abdominal size (liver volume and subcutaneous fat tissue) than head circumference and is found in the remaining 70 to 80 % of the FGR population.

Asymmetric fetal growth is thought to result from the capacity of the fetus to adapt to a hostile environment by redistributing blood flow in favor of vital organs (brain, heart, adrenals) at the expense of non-vital fetal organs (abdominal viscera, lungs, skin, kidneys).

Abnormal growth typically begins in the late second or third trimesters and results from reductions in fetal nutrients that limit glycogen and fat storage yet allow continued brain growth(utero-placental insufficiency). Mechanisms that spare brain growth are uncertain, but may include increased cerebral blood flow.

ETIOLOGY

-Fetal growth restriction (FGR) may be caused by maternal, placental, or fetal factors.

-Approximately one-third of FGRs are due to genetic causes, and two-thirds are related to the fetal environment.

Maternal factors :

- Severe maternal starvation during pregnancy.
- Maternal hypoxemia.(chronic)
- Hematologic and immunologic disorders that cause thrombosis of the intervillous space and decrease uteroplacental perfusion.
- Maternal medical disorders (nephropathy, collagen vascular disease) and obstetrical complications (preeclampsia) associated with vasculopathy.
- Viruses and parasites (rubella, toxoplasmosis, cytomegalovirus, varicella-zoster, malaria) that gain access to the fetus transplacentally or across the intact fetal membranes.

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- Maternal substance abuse, including cigarette smoking, alcohol consumption, and illicit drug use.
- Toxic exposures, including various medications such as warfarin, anticonvulsants, antineoplastic agents, and folic acid antagonists.
- High altitude.
- Demographic variables including race, pregnancy at the extremes of reproductive life, maternal age at first childbirth, nulliparity or grand multiparity, and previous delivery of a SGA newborn, low prepregnancy weight.

Placental factors :

Any mismatch between fetal nutritional or respiratory demands and placental supply can result in impaired fetal growth. FGR results from an accumulation of placental injuries, such as abnormal uteroplacental vasculature, chronic inflammatory lesions, abruptio placenta, or thrombophilia-related uteroplacental pathology, and gross placental structural anomalies, such as single umbilical artery, velamentous umbilical cord insertion, and placental hemangioma.

Fetal factors :

- Karyotypic abnormalities, such as aneuploidy, autosomal deletions, ring chromosomes, uniparental disomy, and confined placental mosaicism. The presence of a chromosomal abnormality often results in the appearance of FGR early in pregnancy, most likely of the symmetric type.
- Genetic syndromes, such as Bloom syndrome, dwarfism, and Russell-Silver syndrome.
- Major congenital anomalies. In one study reviewing data from the National Birth Defects Prevention Study, infants with congenital heart disease, in particular conotruncal and septal defects, were twice as likely to be small for gestational age compared with those without a birth defect (15.2 versus 7.8 %).

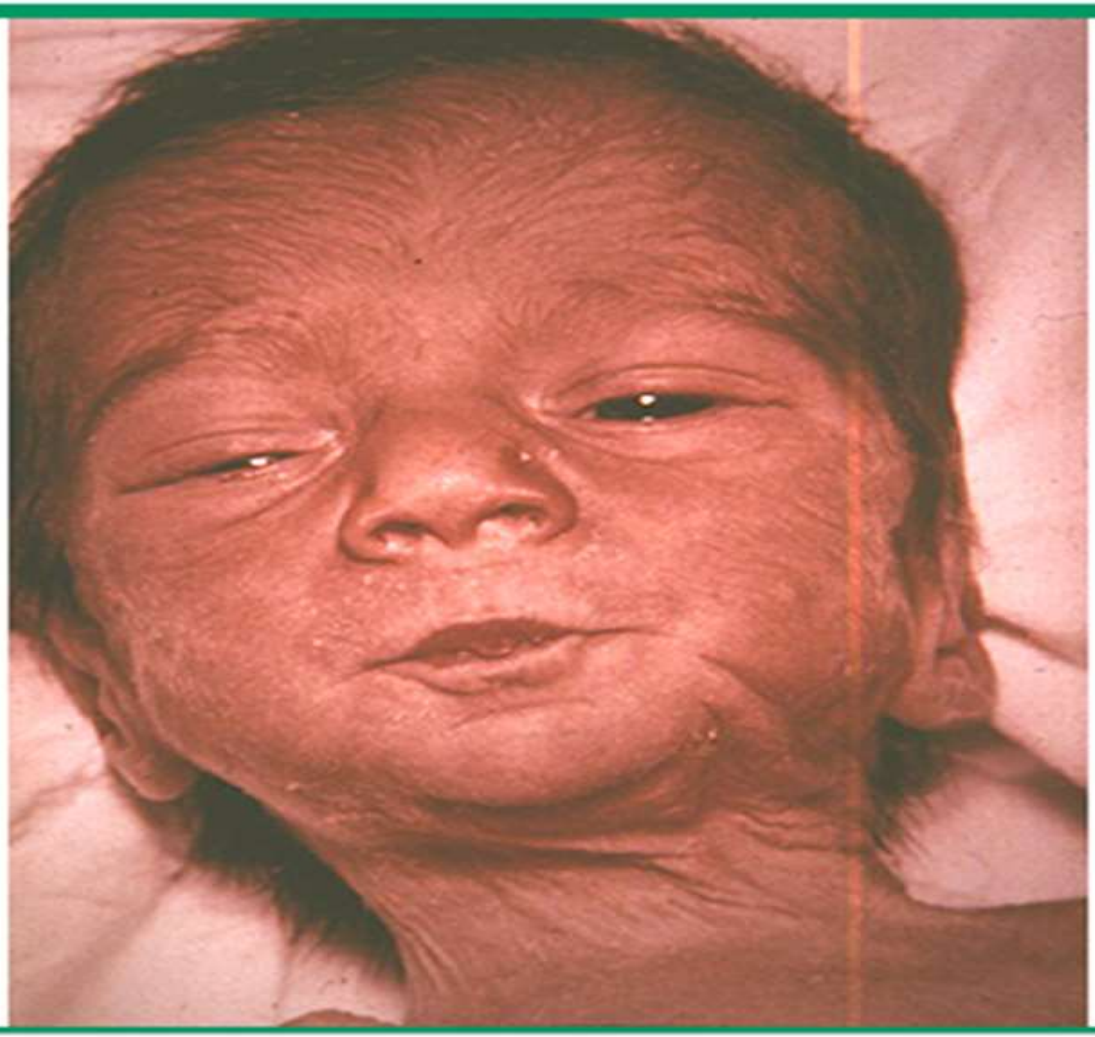
- Multiple gestation: fetal growth abnormalities in direct relationship to the number of fetuses present.
- Fetal infection (TORCH).

CLINICAL FEATURES

---FGR infants appear thin with loose, peeling skin and decreased skeletal muscle mass and subcutaneous fat tissue. The face has a typical shrunken or "wizened" appearance, and the umbilical cord often is thin. Meconium staining may be present.

---- In newborns with asymmetric FGR, the head appears relatively large compared with the size of the trunk and extremities.

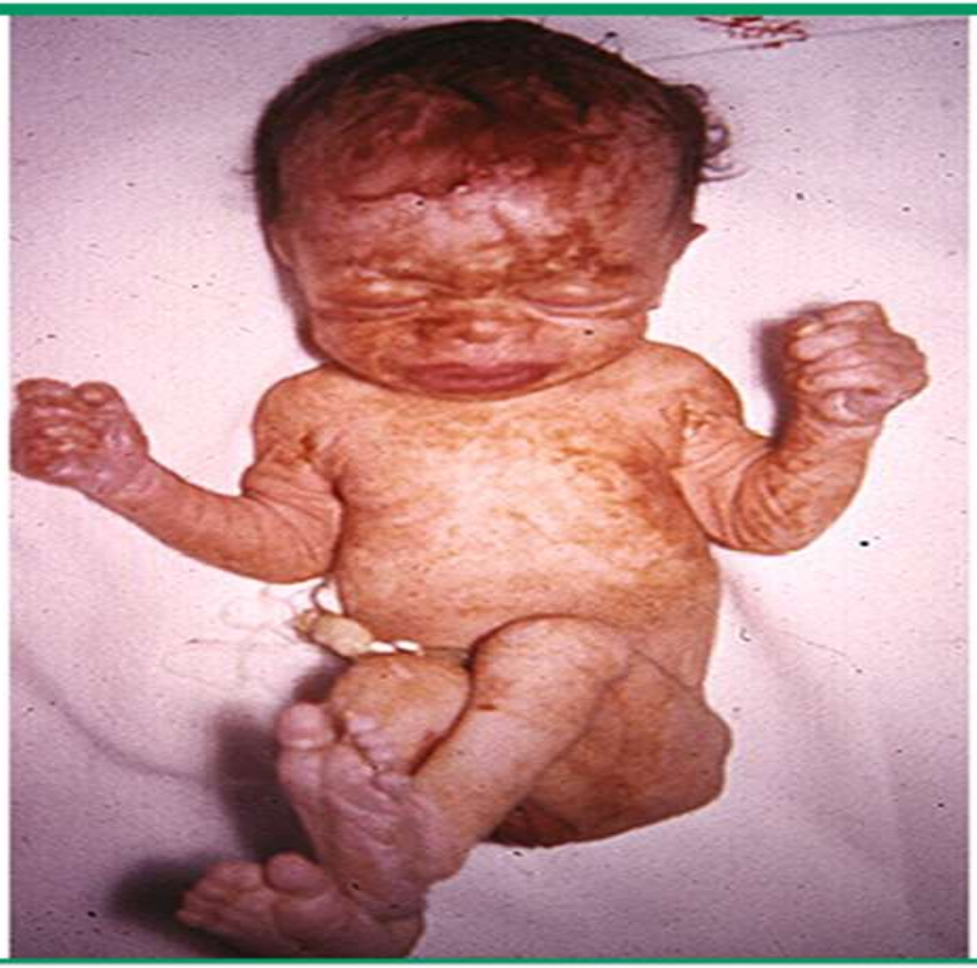
Infant with severe intrauterine growth restriction



The infant has the typical shrunken or "wizened" appearance of an infant with intrauterine growth restriction.

Courtesy of George T Mandy, MD.

Meconium-stained infant with severe intrauterine growth restriction



The infant has the characteristic appearance of an infant with intrauterine growth restriction. Note the loose, peeling skin, decreased subcutaneous tissue and muscle mass, and meconium staining.

Courtesy of George T Mandy, MD.

FETAL GROWTH RESTRICTION

COMPLICATIONS

1)Premature infants : Had significantly greater rates of neonatal death, necrotizing enterocolitis, and respiratory distress syndrome (RDS).

2)Impaired thermoregulation : Because of increased heat loss and reduced heat production. The former is caused by reduced subcutaneous fat, whereas the latter results from both depletion of catecholamines (needed for thermogenesis by brown fat) by intrauterine stress and reduced availability of nutrient substrates. Affected infants should be cared for in a neutral thermal environment so that oxygen consumption is minimized.

3)Hypoglycemia : Glucose must be monitored in FGR infants because hypoglycemia is common. The risk of hypoglycemia correlates with the severity of growth restriction. FGR infants become predisposed to hypoglycemia in utero as low intrauterine insulin concentrations result in decreased glycogen synthesis and reduced glycogen stores. After delivery, a poorly coordinated response of counter-regulatory hormones and peripheral insensitivity to these hormones may contribute to hypoglycemia in some infants. Hypoglycemia typically occurs within the first 10 hours after birth.

4)Polycythemia and hyperviscosity : Polycythemia and hyperviscosity occur more frequently in FGR infants. In one study, hyperviscosity was detected with a microviscometer in 18 % of FGR infants; most had hematocrits greater than 64 %.

*** The risk of polycythemia : increases with the severity of growth restriction. Increased erythropoietin production resulting from fetal hypoxia is thought to be responsible.

5) Impaired immune function : Cellular immunity can be impaired in FGR infants in the newborn period and through childhood. Approximately 50 % of infants born to mothers with severe hypertension (a common cause of FGR) have neutropenia that may increase their risk of infection. In one study, nosocomial infection occurred more often in neutropenic than in nonneutropenic infants (55 versus 12 %).

6) Mortality : Fetal, neonatal, and perinatal mortality are increased in FGR fetuses.

Long term complications

1)Impaired Physical growth : Severely affected FGR infants frequently weigh less and are shorter than AGA infants throughout childhood and adolescence.

2)Impaired Neurodevelopment : FGR infants appear to be at increased risk for neurodevelopmental abnormalities and decreased cognitive performance (Lower scores on cognitive testing, School difficulties or require special education, Gross motor and minor neurologic dysfunction and Behavioral problems (attention deficit hyperactivity syndrome)).

3)Cerebral Palsy (4-6 times higher).

4) Increased risk for ischemic heart disease, hypertension and chronic kidney disease.

Barker hypothesis : Fetal origins of adult disease.

DIAGNOSIS

-A major focus of prenatal care is to determine whether a fetus is at risk for growth restriction and to identify the growth restricted fetus.

- Diagnosis by **ultrasound.**

Screening :

After detailed history :

- ●High risk pregnancy for FGR : Sonographic screening should be done.
- ●Low risk pregnancy for FGR : Symphysis-fundal height measurement **(SFH)**---a simple, inexpensive, and widespread procedure performed during antenatal care to detect fetuses that are poorly grown.

The first suspicion of FGR often arises when this length is noted to be discordant with the expected size for dates.

***Discordancy has been defined in various ways, the most common fundal height in centimeters that is at least three centimeters below the GA in weeks (fundal height 32 cm at 36 weeks of gestation).

→ The routine use of ultrasound in the third trimester to screen for fetal growth disturbance in low risk women has not been recommended.

SONOGRAPHIC DIAGNOSIS

1) Abdominal circumference (**AC**) : When fetal growth is compromised, the fetal AC is smaller than expected because of depletion of abdominal adipose tissue and decreased hepatic size related to reduced glycogen storage in the liver.

AC is the most sensitive single morphometric indicator of FGR.

2) Estimated fetal weight (**EFW**) : Is the single best morphometric test to screen for and diagnose FGR.

3) Growth velocity : Serial sonographic examinations at two-week intervals, there is a significantly lower rate of change over time of AC or EFW in FGR fetuses compared with those fetuses whose growth is appropriate for GA.

4) Body proportions : The HC/AC ratio, FL/AC ratio, and ponderal index have also been used to identify the growth restricted fetus, particularly in the setting of asymmetric FGR.

5) Amniotic fluid volume : Oligohydramnios is one of the sequelae of FGR.

Oligohydramnios is a poor screening modality for suboptimal growth: a significant proportion (approximately 15 to 80 %) of fetuses with FGR do not have decreased amniotic fluid volume.

However, if it is present in the absence of ruptured membranes, congenital genitourinary anomalies, or prolonged pregnancy, FGR is the most likely etiology.

6) Doppler velocimetry : FGR is associated with diminished flow and abnormal Doppler waveforms in both maternal and fetal vessels.

-**Arteries**, particularly the umbilical artery, are the vessels most commonly insonated.

Venous Doppler assessment has been studied less extensively, and is used for monitoring, rather than diagnosis, of FGR.

-**The middle cerebral artery :**increases in diastolic flow represent compensation for in an increasing hypoxic state (brain sparing).

- MCA pulsatility index (PI) is combined with the umbilical artery PI, expressed as the cerebroplacental ratio (CPR) (MCA Doppler PI / UA PI), the relationship has a higher association with adverse pregnancy outcome than an abnormal UA doppler alone.

7) 3D ultrasonography : It appears to be highly promising in the clinical setting of FGR because it appears to provide more precise information regarding structural abnormality, organ volumetry, EFW and oligohydramnios.

After confirmation of the diagnosis we should to Determine the cause :

1-Fetal survey : A detailed fetal anatomic survey should be performed in all cases since approximately 10% of FGR is accompanied by congenital anomalies and 20 to 60% of malformed infants are small for gestational age.
Anomalies associated with FGR include omphalocele, diaphragmatic hernia, skeletal dysplasia, and some congenital heart defects.

2-Fetal genetic studies : A fetal karyotype/microarray is indicated in any of the following settings because of the increased risk of an abnormality:
•Early (<24 weeks), severe (<5th percentile), symmetrical FGR.
•Major fetal structural abnormalities.
•Ultrasound markers associated with aneuploidy, such as increased nuchal fold and abnormal hand positioning.

3-Work-up for infection : When infection is suspected clinically because of maternal history or physical examination or fetal ultrasound findings, maternal serum should be examined for seroconversion.
Infections associated with FGR include cytomegalovirus, toxoplasmosis, rubella, and varicella.
Amniotic fluid DNA testing can also be performed for specific infections, when indicated by the clinical setting. Sonographic markers for fetal infection are often nonspecific, but include echogenicity and calcification of the brain and/or liver, and hydrops.

→ Assessment for congenital and acquired thrombophilic disorders is not recommended, as evidence for an association between the inherited thrombophilias and FGR is weak.

PREGNANCY MANAGEMENT

● Management of FGR associated with congenital or chromosomal anomalies depends on the specific abnormality.

● In FGR fetuses due to uteroplacental insufficiency :
Serial ultrasound evaluation of :
(1) fetal growth,
(2) fetal behavior (biophysical profile [BPP]), and
(3) impedance to blood flow in fetal arterial and venous vessels (Doppler velocimetry)

represent the key elements of fetal assessment and guide pregnancy management decisions.

Doppler velocimetry of the umbilical artery

- Is the primary surveillance tool for monitoring pregnancies in which FGR is diagnosed.
- Normal diastolic flow is infrequently associated with significant perinatal morbidity or mortality and is strong evidence of fetal well-being, thus this finding provides support for delaying delivery when it is important to achieve further fetal maturity.
- When 30 % of the villous vasculature ceases to function, an increase in umbilical artery resistance leading to reduced end diastolic flow is consistently seen.
- When 60 to 70 % of the villous vasculature is obliterated, umbilical artery diastolic flow is absent or reversed and fetal prognosis is poor.
- Reversed diastolic flow is associated with poorer neonatal outcomes than absent diastolic flow.
- Perform weekly Doppler velocimetry of the umbilical artery upon diagnosis of FGR.

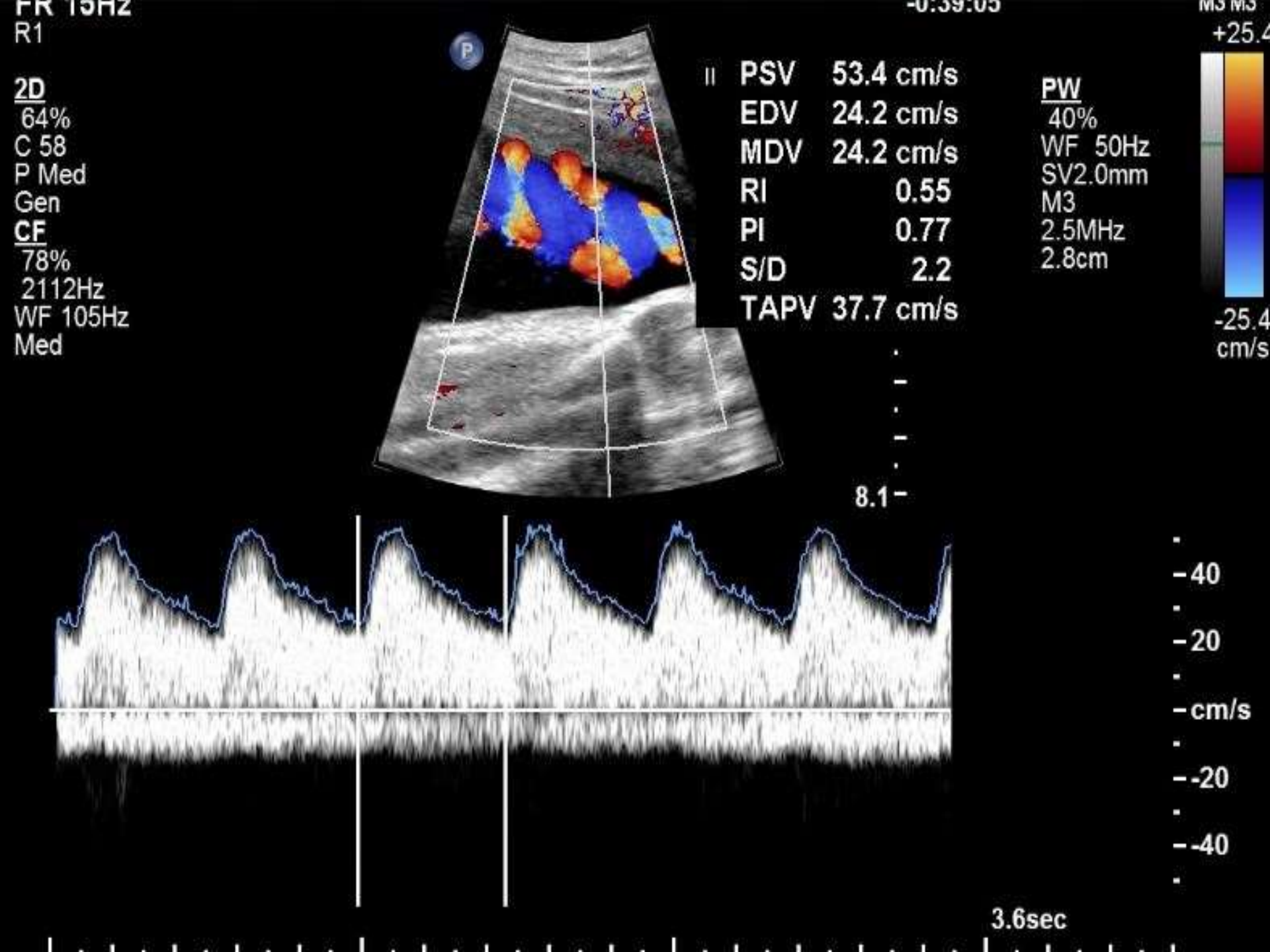
● Absent or reversed end diastolic flow in the umbilical artery can be a sign of impending fetal cardiovascular and metabolic deterioration. If either of these abnormal patterns is identified, delivery should be considered.

-Time of delivery of the growth restricted fetus based on a combination of factors, including:
gestational age, Doppler ultrasound of the umbilical artery, BPP score (or nonstress test), and the presence or absence of risk factors for, or signs of, uteroplacental insufficiency. The goal is to maximize fetal maturity and growth while minimizing the risks of fetal or neonatal mortality and short-term and long-term morbidity.

- deliver any fetus past 32 weeks with reversed umbilical artery flow, and any past 34 weeks with absent umbilical artery flow
-One course of antenatal corticosteroids is given between 24 and 34 weeks of gestation in the week before delivery is expected.

-In smokers, an intensive smoking cessation program may be of value and has other pregnancy and health benefits.

- Mode of delivery :the clinician should proceed to cesarean delivery if there is evidence of deteriorating fetal status, an unripe cervix, or any indication of additional fetal compromise during labor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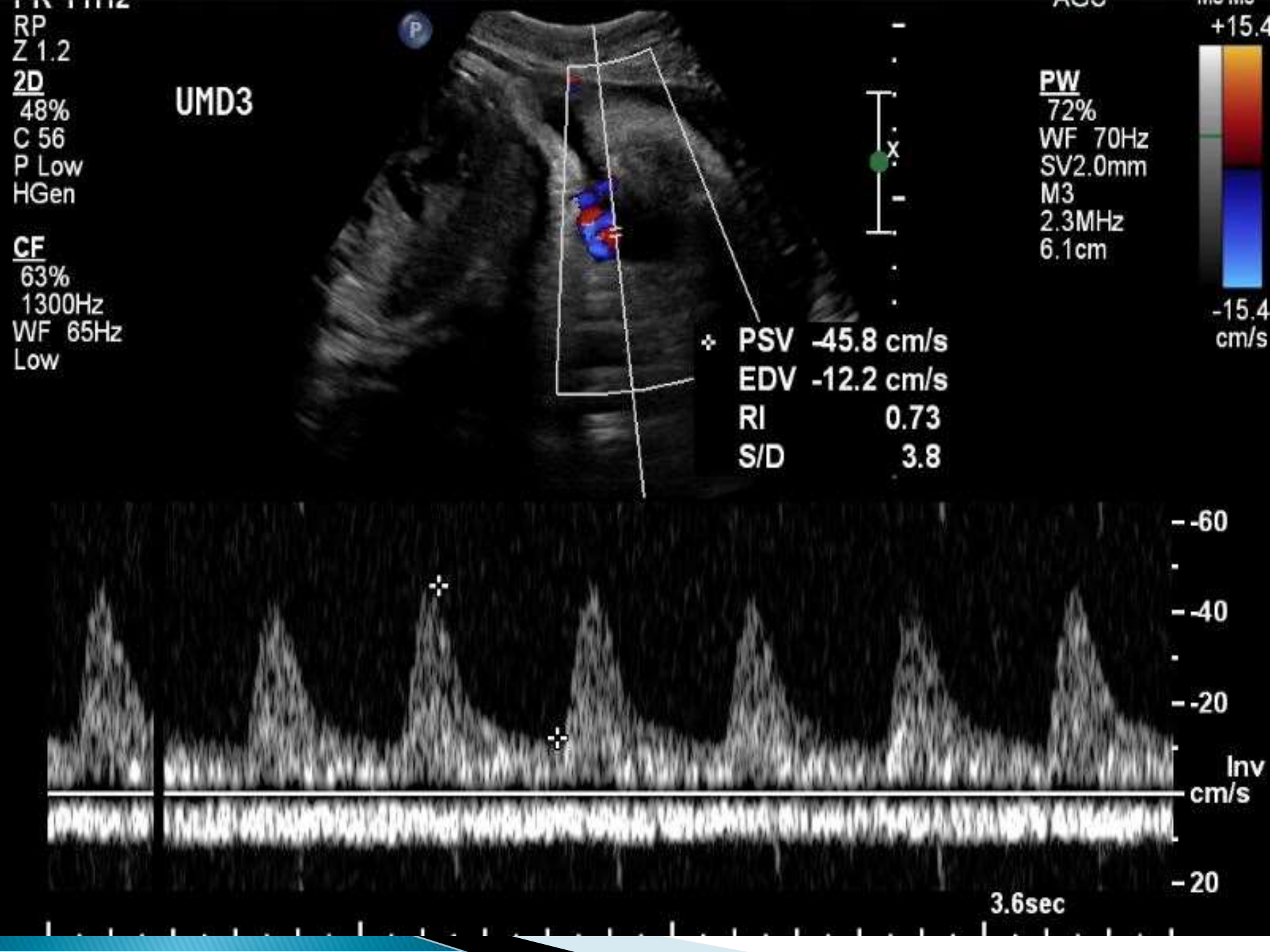
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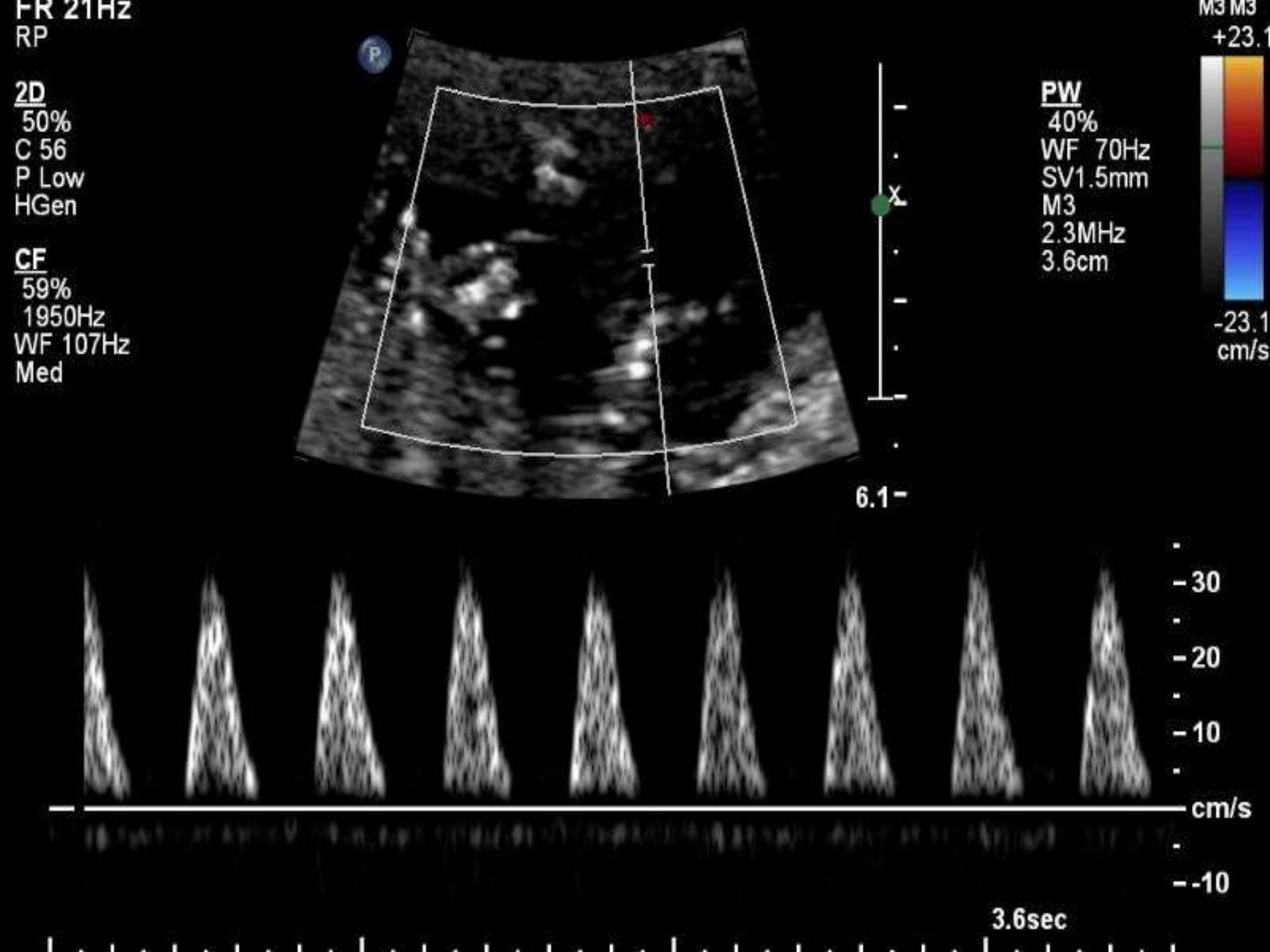
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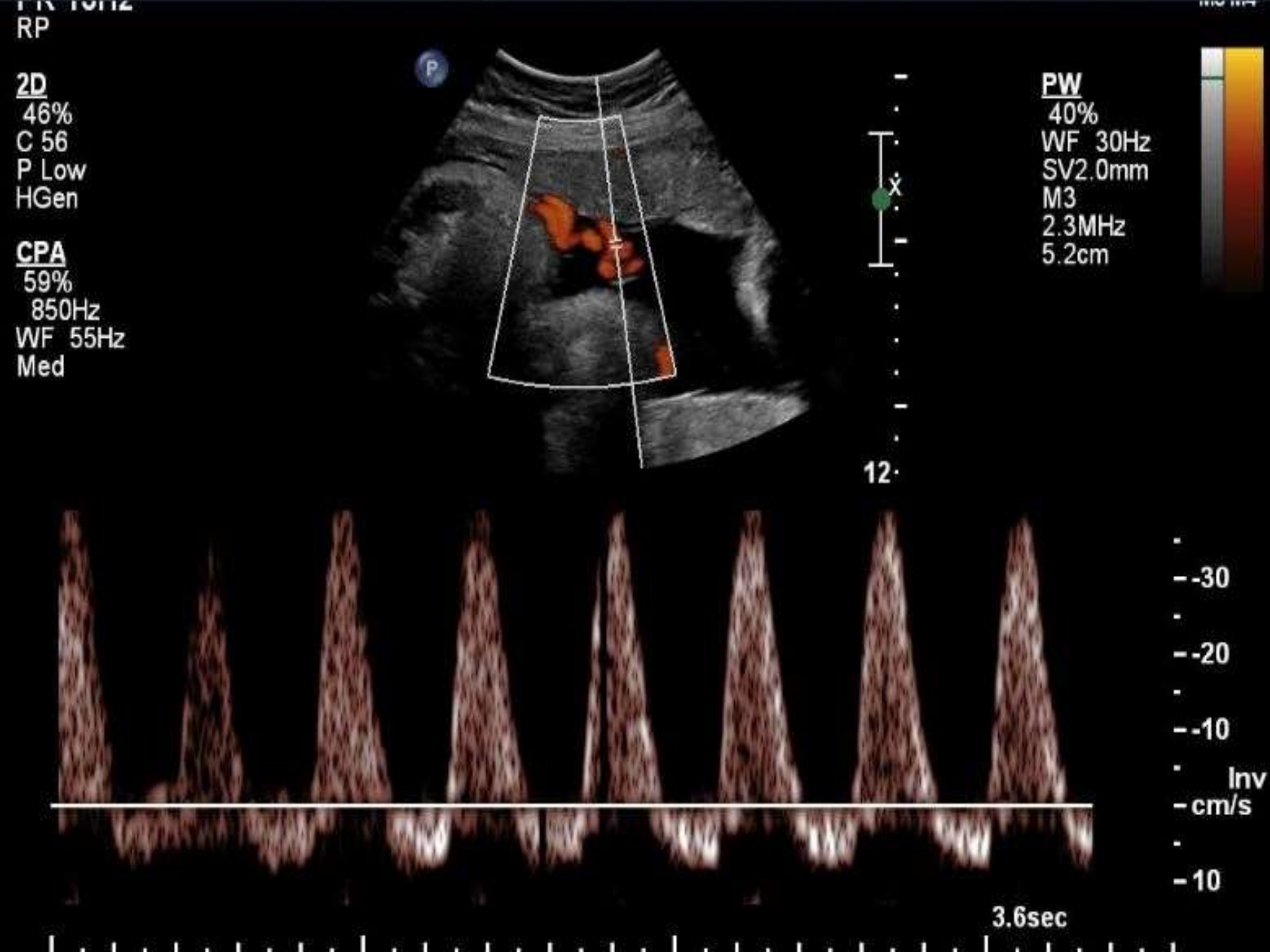
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