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Fetal Growth Restriction (FGR)

Review

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Abstract – In recent years, there has been a growing amount of interest in the possibility that inadequate maternal hemodynamic adaptations to the pregnancy and adverse pregnancy outcomes (APOs) are connected. It has been suggested that "placental syndromes," such as preeclampsia (PE) and fetal growth restriction (FGR), may be linked to later maternal cardiovascular diseases (CVD). The two subtypes of FGR have distinct clinical and pathogenetic characteristics. It is thought that poor trophoblastic invasion of the maternal spiral arteries during placentation is a major factor in the development of early-onset PE and FGR. A pre-existing or subsequent cardiovascular impairment may play a significant role in the pathogenesis of early-onset FGR because placental functioning is dependent on the cardiovascular system of the mother. A primary abnormal placentation in the first trimester does not appear to be the factor that determines late FGR. A primary cardiovascular maladaptation in the mother may be the cause of the pathological pathway of late-onset FGR: The CV system displays a profile that is flat and remains comparable to that of non-pregnant women. A hypovolemic state could result in placental hypoperfusion, altered villous tree maturation, and altered fetal growth during the second trimester, when the placenta is already developed and has a higher functional demand. As a result, the focus of this review is on the possible connection between placentation and maternal cardiac function during pregnancy and the onset and progression of FGR. A superior comprehension of maternal hemodynamics in pregnancies confounded by FGR could get different advantages in clinical work, further developing screening and therapeutic tools.

Keywords – Fetal Growth Restriction, Maternal Hemodynamics, Cardiovascular Diseases, Abnormal Placentation, Cardiac Output.

I. INTRODUCTION

1. Systemic vascular resistance

Fetal growth restriction, also known as FGR, occurs when the fetus does not reach its biological growth potential [1]. FGR's etiology can range from congenital defects to infectious or genetic anomalies, but the majority of cases are described as the result of impaired placental function [2]. This review focuses on FGR, leaving out congenital defects, infectious conditions, and genetic anomalies. The diagnosis of FGR is based on biometric and Doppler criteria, according to the Delphi consensus, and there are two subtypes: based on the gestational age at presentation, with 32 weeks as the established cut off for early-onset FGR [3]. The pathogenetic and clinical characteristics of the two subtypes of FGR differ in addition to the gestational age at presentation. Preeclampsia (PE) and abnormal placentation are more frequently associated with early FGR (60–70%), making it a less common condition than late FGR. Poor fetal and neonatal outcomes, including perinatal mortality, frequently result. On the other hand, it appears that late FGR has fewer connections to PE and abnormal uterine circulation to the placenta [4].

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2. The Placenta's Contribution to FGR

The connection between fetal growth and placental development has been the subject of extensive research since the 19th century [5].The uterine maternal spiral arteries undergo extensive physiological changes related to the process of trophoblast migration, differentiation, and proliferation during the first half of pregnancy [6]: The spiral artery modification and subsequent placental development are determined by the extravillous trophoblast cells. During the early stages of pregnancy, when cytotrophoblast cells break away from the trophoblast columns of the anchoring villi and invade the maternal uterine tissues, extravillous trophoblast forms. Systemic and/or local-intrauterine oxygen levels are linked to the differentiation and migration of trophoblasts [7]. Endovascular trophoblasts, a subtype of extravillous trophoblasts, invade the uterine wall, destroying the vessels' lumens, the muscular vascular component, and vasomotor control. The process of arterial remodelling alters the anatomy and function of the uterine spiral arteries. Endovascular trophoblasts replace the arterial endothelium and muscle cells of the vascular wall, resulting in vascular changes. According to the demands of the fetus, the trophoblast replacement that results in dilatation induces low-pressure and low-velocity utero-placental perfusion and reduces maternal uteroplacental blood-flow resistance [8]. In point of fact, the ability of the villous tree to perfuse is determined by the velocity at which maternal blood enters the placental intervillous space. This is necessary to ensure that the placental villi develop appropriately and that the feto-maternal exchange travels sufficiently. Additionally, mechanical villous damage is prevented by the low pressure and velocity of flow obtained through spiral artery remodelling [9]. All of these things make it possible for the placenta to grow and work properly, which in turn makes it possible for the feto-maternal exchange to be adequate. Indeed, the fetal growth physiology is consistent with the placentation process's physiology. Normal spiral artery remodelling can also be seen in cases of FGR, but signs of abnormal spiral artery remodelling can also be seen in healthy pregnancies [10]. Consequently, a non-placentocentric perspective ought to be considered to completely comprehend the pathophysiology of FGR and the two unique aggregates. The theory that the placenta played a major role in the development of FGR is limited in that it considers the placenta as a single component. However, its functioning is contingent on adequate maternal systemic perfusion; Consequently, maternal cardiovascular function should be taken into consideration [11].

3. How do the maternal systemic cardiovascular systems and the placenta interact to help women adapt to pregnancy?

Spiral artery modification (got thanks to the trophoblast intrusion decreases the utero-placental stream opposition). The placental secretion of angiogenic factors like vascular endothelial growth factor VEGF and placental growth factor PlGF, which increase nitric oxide (NO) and other vasodilatory factors like prostacyclin (PGI2) and endothelium-derived hyperpolarizing factor (EDHF), is linked to these alterations in the arteries. During pregnancy, placental secreted factors and pregnancy hormone (human chorionic gonadotropin) and sodium from the kidney, expanding the plasma volume and diluting the blood. Additionally, relaxin plays a role in maternal hemodynamic adaptation by reducing renal artery resistance, and estrogens can indirectly influence NO pathway regulation. Reduced renal vascular resistance was also caused by the increased NO in renal arteries. As a result, maternal blood volume rises, cardiac output rises, and peripheral resistance decreases. Osol et al., recently conducted a comprehensive review of the maternal placental signaling [15] endothelial dysfunction, which results in decreased arterial compliance. Every one of these risk factors, along with unfortunate ways of behaving like inactive way of life, smoking, and poor eating, coordinate to increase the risk of CVD following an APO.This review focuses on the possible role of maternal cardiac function in the genesis of both early and late-onset FGR.

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4. Maternal Systemic Hemodynamic Adaptations in FGR

There has been a growing interest in the connection between FGR and inadequate maternal systemic hemodynamic alterations during pregnancy in recent years. It is common knowledge that pregnancy causes physiological changes in the cardiovascular

system of the mother. Increased cardiac output (CO), expanded blood volume, and decreased systemic vascular resistance (SVR) and blood pressure are the primary hemodynamic adaptations.[12] CO increases by about 20% at 8 weeks of gestation and continues to rise in a non-linear fashion, reaching the peak in the early third trimester (+ 50% at 30–32 weeks) [13]. The increased preload caused by the increase in blood volume, the increased maternal heart rate (HR) (10–30 bpm), and stroke volume (SV), as well as the decreased afterload caused by the decreased SVR, all contribute to the rise in CO [14].SVR progressively decreases from the first trimester and reaches its Placental development and maternal systemic adaptation to pregnancy interact tightly during physiological pregnancy [15]: Utero-placental resistances decrease simultaneously with SVR decreases; In fact, during the first and second trimesters, flow resistance in the uterine arteries gradually decreases [16,17].Pregnancy is really difficult for women' cardiovascular framework, going about as a clinical pressure test for the mother [18]. A significant increase in the mass and remodelling of the left ventricle were observed in echocardiographic examinations of straightforward pregnancies. This is linked to diastolic dysfunction in a small but significant number of women at term, but all of these women return to normal after delivery [19,20].

This is especially true for women who have obstetric complications that, even if they only last a short time while they are pregnant, could be seen as early signs of a high-risk path for CVD in the future [21]. (HCG, estrogen, progesterone, relaxin) perform a variety of functions. They are angiogenic factors and can activate the renin-angiotensin system, resulting in an increase in aldosterone and reabsorption of water the possible connection between impaired hemodynamic adaptation during gestation, adverse pregnancy outcomes (APOs), and maternal cardiovascular diseases (CVD) has been the subject of several studies. Among 75,380 women with placental syndromes (gestational hypertension, preeclampsia, placental abruption, or placental infarction), a retrospective population study (CHAMPS study) [22] found an increased risk of premature cardiovascular disease (HR 2.0, 95% CI 1.7–2.2) and a higher risk of intrauterine fetal death (HR 4.4, 95% CI 2.4–7.9) when a maternal placental syndrome. Lane-Cordova et al. recently conducted a review, summarized the role that APOs play in the development of subsequent CVD [23]. They thought of APOs as distinct syndromes with a similar pathogenesis of inadequate placentation, inflammation, and vascular dysfunction in the mother. APOs and CVD share a number of risk factors and pathophysiology mechanisms, according to them. In this scenario, placental vascular abnormalities that result in APOs may be more likely to occur if there are already cardiovascular risk factors in the mother. These, in turn, may be the cause of persistent postpartum inflammation as well as cardiovascular dysfunction.

4.1 Early FGR

Definition and Clinical Characteristics The diagnostic criteria for early FGR are fetal abdominal circumference (AC) or estimated fetal weight (EFW) < 3rd centile or umbilical artery absent end diastolic flow (UA-AEDF) detected before 32 weeks of gestation, according to Delphi consensus. Alternately, early FGR can be identified if two or more of the following three criteria are met: Uterine artery pulsatility index (UtA-PI) > 95th percentile, and AC/EFW 10th percentile [3] About 0.5–1 percent of cases of early FGR have been reported. Preeclampsia (PE) and abnormal placentation (60–70%) are frequently linked to this condition. Poor fetal/neonatal outcomes, including perinatal mortality, are frequently the result [4]. Placenta in Early FGR Early-onset PE and FGR are thought to be primarily caused by defective placentation caused by inadequate trophoblastic invasion of the maternal spiral arteries. FGR may result from abnormal placentation with altered trophoblast invasion, according to the "placental theory" [2].

A disappointment of the physiological change of the spiral arteries, with steadiness of a high-obstruction and high-speed stream in the uterine dissemination and intervillous space, is noticed. As a result, FGR may result from the effects of defective trophoblast invasion on the villous tree development, oxygen and nutrients transferred from the mother to the fetus, and the final size of the placenta. In these circumstances, the normal placental findings are lesions predictable with maternal vascular malperfusion (MVM) [24]. Placental infarcts, a small placenta, and the presence of histological abnormalities of the placental villous tree, such as distal villous hypoplasia, are all MVM symptoms. Spiral artery thrombosis, which may result in focal placental ischemia and infarction, may occur in poorly or incompletely recovering patients. FGR and abnormal uterine artery Doppler waveforms are linked to the loss of functional placental parenchyma caused by multiple placental infarcts [25]. Furthermore, abnormal umbilical artery Doppler velocimetry is frequently associated with the presence of hypoplastic, thin, and elongated villi [24, 26]. Distal villous hypoplasia is most common in pregnancies that last less than 32 weeks [24], which fits the definition of early FGR [27].

The placenta may experience a stress response as a result of the smooth muscular cells' retention in the spiral artery walls, which may also result in intermittent perfusion. As a result of the ischemia-reperfusion of the intervillous space, it is likely that the stress caused by placental malperfusion is an oxidative stress. It results in the dysfunction of the maternal endothelial cells, a systemic inflammatory response, and the clinical syndrome of PE [11, 28], which includes FGR. It also causes the release of a number of mediator factors into the maternal circulation, including pro-inflammatory cytokines, exosomes, and cell-free fetal DNA. In addition, the ischemia-reperfusion process is linked to the formation of syncytial knots in the placental villi and a shift in the ratio of angiogenetic agents: early-onset FGR is associated with abnormal maternal circulating levels of angiogenic ratios of sFlt-1/PlGF, as well as an excess in the production and secretion of the antiangiogenic protein soluble fms-like tyrosine kinase (sFlt)-1 in syncytial knots [29], and the suppression of the proangiogenic placenta's syncytiotrophoblast secretion.[30,31] This abnormality is correlated with placental MVM. [32]. The EVERREST Consortium's clinical trial protocol is based on abnormal placentation with abnormal angiogenesis and vasculogenesis. It aims to improve the outcome of maternal vascular endothelial growth factor (VEGF) gene therapy administered through maternal uterine arteries for severe early onset fetal growth restriction [33]. Extravillous and endovascular trophoblast, as well as villous cyto- and syncitiotrophoblast, express VEGF [34,35]. It is regularly discharged by the human placenta. Isoforms of secreted VEGF mediates the endothelial cell proliferation and endothelial tube formation, leading to branching angiogenesis [27]. A shift toward an antiangiogenic state with a decrease in maternal circulating VEGF, as well as the previously mentioned decrease in PlGF and increase in sFlt-1, affects the early-onset FGR [36,37]

The EVERREST trial's promising goal is to increase local VEGF availability and endothelial cell proliferation in the perivascular adventitia, thereby improving the vascular remodelling of the maternal spiral arteries [38]. However, the correlation between APOs and maternal cardiovascular diseases cannot be explained by the placental theory alone. In particular, the placental theory fails to explain why women with pre-pregnancy cardiovascular risk factors have a higher risk of PE and FGR in pregnancy [39] or why women with PE in their pregnancies have a higher cardiovascular risk later in life. A Model Based on Maladaptation of the Maternal Cardiovascular System and the Placenta. There are two unrelated hypotheses regarding the connection between abnormalities in the placenta and adaptation of the maternal cardiovascular system in early FGR. The first one puts the placenta at the center of the changes in hemodynamics. High placental vascular resistance raises the impedance of the mother's uterine arteries, which in turn raises the resistance of the mother's peripheral arteries. Maternal cardiac output is impeded by this rise in cardiac afterload [40].

As a result, reduced placental perfusion and the emergence of FGR may be attributed to the absence of an adequate maternal cardiovascular compensatory response to an abnormal trophoblastic invasion [41,42].The second hypothesis suggests that a low maternal CO and high SVR prior to pregnancy reduced placental perfusion. This impairs trophoblasts and causes problems on both the fetal and maternal sides of the placenta. The hypothesis that maternal cardiovascular dysfunction rather than primary placental dysfunction is the cause of complicated pregnancy is consistent with this sequence [17].

The fact that a hypovolemic state, which is frequently observed in FGR pregnancies, also exists prior to the onset of the disease in early pregnancy [43–45] and the preconception period lends credence to this hypothesis. Foo et al., most recent study starting from the time of conception, longitudinally assessed cardiovascular function in 356 spontaneously conceived pregnancies in women who appeared to be in good health [46]. Prior to pregnancy, women in this series who had FGR-complicated pregnancies (with or without PE) had lower CO and higher SVR, indicating a pre-existing hemodynamic dysfunction that predates any sequalae of placental disorder. As a result, women with poor cardiovascular function prior to pregnancy may be more likely to experience poor trophoblast development and reduced blood flow to the uterine arteries. However, it is impossible to draw the conclusion that poor maternal cardiovascular performance is the cause of poor trophoblastic invasion because the number of patients was so small (15, including 3 cases of PE, 8 cases of FGR, and 4 cases of PE with FGR), and the majority of FGR cases were late-onset [46].

A subclinical hypoxia could result from a maternal hemodynamic dysfunction. The process by which cytotrophoblasts differentiate into extravillous trophoblasts may be hindered by the maternal systemic hypoxic state. Endovascular trophoblast development and, consequently, spiral artery remodelling may be affected by this change. In fact, oxygen-dependent [7] phenotypic differentiation occurs during normal embryo and placenta development: first and foremost, differentiation toward the trophoblast lineage in the morula; second, the transformation into cytotrophoblasts and syncytiotrophoblast; Lastly, the differentiation into trophoblasts with and without villi [47]. The invasion of the maternal spiral arteries and subsequent vascular

remodelling are the two major outcomes of the cytotrophoblast differentiation into extravillous trophoblasts. The process of trophoblast differentiation may be hindered by maternal oxygen deprivation, which in turn may hinder the development of the utero-placental vessel and the remodelling of the spiral artery [7].

In point of fact, the two hypotheses most likely coexist. Low cardiac reserve and impaired placental development contribute to obstetric complications like PE and early FGR in the periconceptional cardiovascular status. These pregnancies are characterized by a high SVR, inadequate preload, CO increase, and reduced maternal intravascular space expansion [40,41,48]. Asymptomatic left ventricular diastolic dysfunction and impaired myocardial relaxation appear to be more common in pregnant women with early FGR than in controls, despite conflicting data on diastolic function [41]. These cardiovascular findings may continue even after delivery. In point of fact, there is increasing evidence that patients who have had an earlier early PE after delivery have prehypertension, left ventricular hypertrophy, and asymptomatic left ventricular systolic and diastolic dysfunction [49–51].

Notably, Scholten et al. [52], determined that the relationship between prepregnancy plasma volume and the risk of recurrent PE and FGR in a subsequent pregnancy is both inverse and linear. In addition, it has been extensively demonstrated [53,54] that chronic hypertension is a risk factor for the subsequent occurrence of placenta-mediated complications like FGR, superimposed PE, severe hypertension, and preterm birth (PTB). There are various types of chronic hypertension. The most prevalent type is "essential" hypertension, which has no known cause. The second type, "secondary," affects less than 15% of patients and is related to underlying conditions like renal, endocrine, and vascular disease. Both of these can have an effect on a pregnancy [55]. Pre-existing hypertension severity (severe versus mild) and inadequate pharmacological control are associated with an increased risk of superimposed pregnancy hypertension disorder [56]. Low-dose aspirin administration for the prevention of PE and FGR is recommended in patients with chronic hypertension and PE [57, 58]. Interestingly, the association between end-organ damage like maternal cardiac dysfunction and the incidence of adverse fetal outcomes appears to be related to the duration and severity of the pre-existing chronic hypertension [59]. The risk of abnormal fetal growth rises to 25–40% in women with severe chronic hypertension, end-organ disease, or secondary hypertension [60].

The relationship between spiral artery transformation and trophoblast development has been re-evaluated in light of other recent findings, with an emphasis on the role of maternal systemic hemodynamics rather than local placental development. It is common knowledge that a Doppler assessment of the blood flow in the uterine artery can be used to predict early-onset PE and FGR. The connection between uterine artery blood stream and trophoblast cell capability is viewed as an intermediary of trophoblast intrusion, showing that the persistence of high resistance in the uterine artery Doppler records reflects an impaired trophoblast invasion and inadequate spiral course. A modern perspective suggests that there is an inverse biological connection: Poor placental perfusion may result in impaired trophoblast invasion and function as a result of poor maternal hemodynamic adaptation to pregnancy [61].

An AC/EFW below the third centile or at least two of the following three criteria are required to diagnose late FGR after 32 weeks of gestation: AC/EFW < tenth centile, AC/EFW centile crossing two quartiles on growth curves, cerebroplacental proportion (CPR) < fifth centile, or UA-PI >95th centile [3]. A low perinatal mortality rate is linked to late FGR, which is rarely associated with other placental diseases like PE (15%). However, physicians still face difficulties in identifying and diagnosing this more common condition, with an estimated prevalence of 5 to 10%. As a result, fetal outcomes are significantly impacted clinically by late FGR [4]. Placenta in Late FGR in contrast to the early phenotype, it does not appear that abnormal placentation in the first trimester is primarily responsible for late FGR [4].

Be that as it may, histopathological assessments of placentas from FGR babies conveyed at term exhibit a higher pace of vascular injuries (particularly infarcts and thrombotic occasion) contrasted with ordinary term pregnancies. These histological findings are comparable to those of preterm FGR, indicating a quantitative rather than qualitative difference in the severity and extent of lesions. As indicated by Kim et al. [62], the failure of the maternal spiral arteries' physiological transformation is not an "all or nothing" event in every vessel; Consequently, varying degrees of abnormal remodelling may indicate varying degrees of disease severity and time of onset. In addition, previous research suggested that trophoblast invasion had a gradient of effect along the spiral arteries, with no remodelling in the decidual, myometrial, or both segments. In contrast to decidual cases, abnormal deep invasion results in more severe FGR [63]. Supporting this speculation, neither early appraisal of placental capability nor second-trimester uterine artery Doppler velocimetry separating everyone can anticipate late-beginning FGR. Doppler impedance of the uterine artery is typically thought to depict placental development via spiral artery invasion: Insufficient trophoblast invasion and

narrow spiral arteries are reflected in the high impedance. It is a good way to check for early-onset PE and FGR, but it doesn't look for late-onset phenotypes.

As a result, in 2016, a multicenter randomized trial involving 11,667 pregnant women found that routine second-trimester uterine artery Doppler ultrasound in a nonselected population has low sensitivity in detecting SGA fetuses (18%) and late FGR (24%) fetuses [64].In addition, it has been hypothesized that the hypoxic state of the late FGR placenta is mostly caused by intervillous malperfusion and decreased intraplacental oxygen concentration, not by defective trophoblast invasion [65–67]. Late FGR and normal umbilical artery Doppler waveforms may be associated with an increased abnormal development of the placental villous tree and accelerated villous maturation in these pregnancies [27]. Placental villi in those instances are short, small, and hypermature for the gestational period, which is linked to an increase in syncytial knots [24].

The majority of these cases of FGR have normal umbilical artery Doppler waveforms due to these characteristics, which help to reduce vascular impedance. With delayed villous maturation, the placenta of late-onset FGR may also exhibit completely distinct late-onset histological findings. This is a placental histopathological finding that typically occurs before 34 weeks of gestation [24] and can occur near the end of the pregnancy. It is clinically associated with FGR, as well as maternal metabolic disorder, intrauterine hypoxia, and obesity [68]. There are fewer vasculo-syncytial membranes, a continuous cytotrophoblast layer, a monotonous, unvarnished villous population, centrally placed capillaries, and an increased villous diameter in this condition [24].All things considered, it is difficult to find methods for early prediction of late-onset FGR, and there is no strong evidence for the most effective strategy for its detection and management [58].

4.2 Late FGR

As stated previously, the first-trimester Doppler velocimetry assessment of uterine arteries does not accurately predict the risk of late-onset FGR. In recent times, Binder et al. [69] used a longitudinal uterine Doppler assessment throughout the third trimester to evaluate 5887 pregnancies. One-third of patients who had previously had normal indices were found to have a de novo increase in uterine artery resistance in the late third trimester. Besides, this gathering had a higher commonness of SGA child and lower birthweight centile. These variations may indicate that pregnancy-related changes in maternal systemic and uterine vascular resistance occur independently of the effects of placental invasion. As a result, it appears that assessing maternal hemodynamic changes during pregnancy is a crucial step in identifying women who are more likely to have late FGR. Pregnancy has been suggested to reveal subclinical maternal cardiac dysfunction that was already present. As a result, failing to adapt the maternal cardiovascular system to the feto-placental demands, a subclinical impairment of maternal cardiac function that existed prior to pregnancy may emerge during the stress of pregnancy [70,71]. Therefore, a primary cardiovascular lack of adaptation with low CO, SV, and high SVR may be the primary cause of late-onset FGR's pathological pathway rather than the failure of angiogenesis and physiological low-resistance trophoblast invasion. These parameters do not change physiologically in late-FGR, maintaining a flat profile throughout the pregnancy and remaining comparable to those of non-pregnant women [72].

Stott et al., conducted a prospective observational cohort study [72] monitored the maternal hemodynamic parameters of 84 high-risk pregnant women on a regular basis. They discovered a longitudinal pattern of maternal hemodynamic variable that was in line with the known physiological changes that occur during pregnancy, in pregnancies with neonatal birthweights below the 10th percentile. On the other hand, the authors found a consistent pattern of lower CO, SV, and higher SVR in pregnancies with late-onset FGR. The abnormal placental villous tree development, also known as delayed villous maturation, which occurs in late FGR, may result from this primary and persistent failure of the maternal cardiovascular system to adapt to pregnancy. Therefore, in order to better identify women who are more likely to develop late FGR, assessment of maternal hemodynamics rather than uterine artery Doppler could be used in the second trimester. Roberts L.A. et al., used multivariate logistic regression analysis to assessed maternal hemodynamic function in conjunction with maternal demographics and history, fetal biometry, and Dopplers to improve birthweight prediction [73]. The combination of maternal anthropometric and hemodynamic parameters assessed early in the first trimester of pregnancy can provide a screening tool for late FGR, especially in high-risk pregnancies complicated by previous PE, chronic hypertension, or diabetes [74].The maternal hemodynamic factors, longitudinally surveyed in late FGR and adequate for gestational age (AGA) fetuses, contrasted from the first to the third trimester of growth. Additionally, the highest difference in cardiovascular parameters occurred at 25 weeks, indicating that a screening at this stage of the pregnancy may have even greater predictive power [75].

Based on these evidences, the maternal cardiovascular system in late-onset FGR is unable to respond to the increasing demands of pregnancy from the second trimester onwards, when the normally developed placenta increases its demands. A primary pump deficit may be the cause of the placenta's hypoperfusion and maladaptive response, which alters the villous tree's maturation and, consequently, fetal growth [72, 75].Maternal Cardiac Function Assessment to distinguish FGR from SGA Maternal hemodynamic indices are useful for both screening and diagnosing FGR, assisting in the identification of a growth-restricted fetus and a fetus that is too small for gestational age (SGA) [40, 45].At the time of diagnosis of FGR or SGA in normotensive pregnancies, a single hemodynamic investigation was conducted using a non-invasive device (USCOM-1A®) in a recent prospective study [76]. When compared to pregnancies with SGA fetuses or healthy control pregnancies, pregnancies complicated by FGR presented with worse maternal hemodynamic function, as evidenced by lower HR and CO as well as elevated SVR, uterine artery resistance, and mean arterial blood pressure. When compared to healthy control pregnancies or those with an SGA fetus, SV was similar in the FGR-complicated pregnancies. The authors hypothesized that the observed difference in maternal CO was caused by lower maternal HR because CO is calculated by multiplying SV and HR. Normally, relative tachycardia may be a physiological response to pregnancy's increased demands on the body's metabolism. In order to maintain CO against SVR and ensure adequate placental blood flow, an elevated HR helps. FGR develops when this adaptation fails to occur. The fact that there were no differences in the maternal hemodynamic indices of SGA pregnancies without FGR compared to healthy control pregnancies lends credence to the hypothesis that these fetuses have reached their full potential growth. A retrospective study of 51 pregnancies with FGR or SGA fetuses yields consistent results [77].

Compared to women with SGA fetuses and even controls, women with FGR had lower CO and higher SVR. On the other hand, the maternal hemodynamics of the SGA and control groups were identical. The authors used multivariate analysis to determine that CO at diagnosis was the primary independent predictor of new-borns' length of stay in the neonatal intensive care unit. Placenta and Cardiovascular System of the Mother: The Vicious Cycle The placenta's post-pregnancy cardiovascular state is linked to the placenta's pre-pregnancy cardiac function. An antiangiogenic state and endothelial and cardiac maternal dysfunction have been suggested to be characterized by defective placentation and the resulting proinflammatory state; This continues after birth and may be the cause of CVD later in life. In point of fact, non-pregnant women who had a history of PE and/or FGR were also found to have maternal cardiac dysfunction. Additionally, a new pregnancy may exacerbate an impaired hemodynamic environment, putting these women at risk for similar complications in the future [23].Valensise et al. in 2016 discovered systolic and diastolic dysfunction in the state before conception, which was followed by a second pregnancy that was complicated by recurrent early PE. In addition, previous early preeclamptic patients with non-recurrent PE exhibited intermediate left ventricular structural and functional characteristics in comparison to controls and patients with recurrent PE [51].An association between PE and the subsequent risk of major coronary events (OR 2.1, CI 1.73–2.65) was found in a large Norwegian register-based study [78].

When PE was combined with SGA fetuses (OR 3.3, CI 2.37–4.57) or PTB (Preterm Birth) (OR 5.4, CI 3.74–7.74), the risk was significantly increased. Women who had recurrent PE that complicated their first two pregnancies were found to have the highest risk of coronary events. Regardless of PE, gestational age at delivery and fetal growth appear to correlate with the risk of maternal cardiovascular disease, with a significantly increased risk of coronary heart disease in women with the most severe and early FGR cases [79].In addition, women who had previously experienced early-onset PE and FGR, but not late-onset PE, were found to have endothelial dysfunction in the postpartum state, as evidenced by decreased endothelium-dependent vasodilatation and increased arterial stiffness [80, 81]. A subset of women appears to be at higher risk for future endothelial dysfunction and cardiovascular disease (CVD) if they have a history of HELLP syndrome, FGR, or early-onset PE [82].Some FGR-linked histological lesions of decidual arteriopathy, which represent a systemic and local inflammatory milieu, share similarities with cardiovascular disease (CVD) from a clinical perspective. To regulate fetal growth and facilitate the implantation and placentation processes as well as to control fetal growth during pregnancy [83], the maternal immune system must be well-regulated. The cells of the decidual stroma, such as macrophages, T cells, and uterine natural killer cells, are encountered and interacted with by the extravillous trophoblast cells. Natural killer cells and extravillous trophoblast work together to release cytokines and proteases that cause the spiral artery to change [84, 85]. Fibrinoid necrosis and the accumulation of a subtype of macrophages known as foam cells, with or without a perivascular inflammatory infiltrate, predispose to abnormal spiral artery remodelling and acute atherosclerosis. Acute atherosis, like systemic and cardiac atherosclerosis during pregnancy, has been compared to an inflammatory lesion [86]. This is an example of a vicious circle: Poor placentation may be caused by pre-pregnancy cardiovascular risk factors, innate immune dysregulation, and genetic predisposition. Placental ischemia and the release of

antiangiogenic and proinflammatory factors cause cardiovascular damage during pregnancy and postpartum when placentation is incomplete [23].

5. Diagnosis of FGR

5.1 Uterine artery Doppler

Doppler Impaired placentation with abnormal trophoblastic spiral arterial invasion is linked to 46 FGR, pregnancy-induced hypertension, and PET [87]. Up to 65% of normal pregnancies in the first trimester have uterine artery Doppler notches. However, even persistent notching after 20 weeks has a lower positive predictive value for both PET and FGR in a high risk population than it does for women who are less likely to get these conditions [88] In contrast, in the high-risk population, its negative predictive value is high at 97%. Using uterine artery Doppler velocimetry and a variety of biochemical markers in the first trimester.

Fetal Medicine Foundation developed predictive models with variable detection rates of 52.3 percent and 73%, with a 10% false positive rate [88,89]. Uterine artery Doppler abnormalities are also better predictors of PET than FGR, according to a systematic review of 61 studies on FGR and 74 studies on PET [88,89]. 14.5% sensitivity was used to predict stillbirth. Therefore, risk prediction based on other risk factors is superior to risk prediction based on uterine artery Doppler screening. Due to the variable results of previous studies and the low reproducibility of first trimester Uterine artery Doppler, other impedance markers have been used as predictors of FGR rather than Uterine artery Doppler alone. According to a recent study [90], combining biochemical markers and Doppler flow studies of the uterine artery may improve FGR prediction. Doppler studies of the uterine artery in the second trimester outperform those of the first trimester [91,92], particularly for early onset PET and FGR [93]. Following a uterine artery Doppler assessment in the latter stages of the second trimester, the concept of individualized risk prediction based on maternal factors and uterine artery Doppler was first described. Doppler ultrasound of the uterine artery remains a useful technique for determining the cause of FGR during the second trimester [94].

5.2 Umbilical artery Doppler

There is clear evidence that measuring the umbilical artery with a Doppler device reduces the number of perinatal deaths by as much as 29% in high-risk pregnancies [95]. Reversed flow can be linked to neonatal mortality, but increased resistance to umbilical artery flow aids in the diagnosis of FGR [96]. Umbilical artery Doppler is essential for the diagnosis of early onset FGR [97] because CTG findings in fetuses younger than 28 weeks of gestation are difficult to interpret. Tragically, in normal clinical practice there is still weighty dependence on CTG discoveries past 28 weeks of growth and, when the following becomes pathological, up to 80% of embryos are as of now hypoxic [98]. Nine randomised trials show that combining CTG tracings with umbilical artery Doppler monitoring reduces perinatal mortality and length of hospital stay [99]. Furthermore, a positive correlation between deteriorating changes in the umbilical artery Doppler velocimetry and perinatal outcomes was found in a European trial [100]. Umbilical artery Doppler velocimetry changes started around 15 days before the condition started to deteriorate, and the most severe abnormalities, such as reversed flow, started about 4-5 days before the baby was born [101]. Although abnormal changes in the umbilical artery Doppler can progress quickly in early-onset FGR [102], it has been demonstrated that absence or reversed flow after weeks of gestation has an independent impact on neuro development [103]. At the age of two, children with these abnormalities have been found to have impaired motor and cognitive development [104]. While umbilical artery Doppler indicates a fetus that is "at risk," it is not good at predicting or providing information regarding the timing of delivery in early onset FGR.

5.3 Middle cerebral artery (MCA) Doppler

In contrast to the Doppler scan of the umbilical artery, the MCA Doppler scan is a proxy for hypoxia and may be abnormal for many weeks in early onset FGR. Due to an association with adverse perinatal outcomes [105], the MCA Doppler may be useful in tracking late-onset FGR independently of umbilical artery Doppler findings. Additionally, it can be used to anticipate an emergency Caesarean section; When compared to MCA with a normal PI, MCA with a lower pulsatility index (PI) and a cerebro-placental ratio is associated with an increased risk of abdominal delivery by a factor of 6 [106]. These children have additionally been displayed to have hindered neurodevelopment at 2 years old [107]. The interpretation of the MCA Doppler findings is unclear, particularly in relation to the timing of delivery. Brain sparing is linked to early onset FGR. Nevertheless, cerebral vasodilatation can be evaluated by MCA PI below the 5th centile, and a recent study found that CPR is linked to a worse perinatal

outcome [108]. In a similar vein, the cerebroplacental ratio (CPR), which is the ratio of the umbilical artery PI to the MCA PI, is more useful in late-onset FGR. Impaired CPR is found in up to 25% of late-onset FGR [109] and is linked to a worse delivery outcome than MCA Doppler alone [106]. Even though one recent study found a correlation between CPR and adverse perinatal outcomes, even in cases of early onset FGR [110], CPR on its own may not be able to predict adverse outcomes or provide information about the best time to deliver, leaving it unclear which factors should trigger delivery in cases of late onset FGR [111,100].

5.4Ductus venosus (DV) Doppler

There is strong evidence that (DV) Doppler can predict the risk of fetal death in early onset FGR [112,113,114] and that absent or reversed "a" waves are linked to perinatal mortality regardless of gestational age, with a risk of up to 100% in early onset FGR [115-117]. The significance of DV Doppler velocimetry in predicting perinatal mortality has also been demonstrated by a systematic review of 18 observational studies [118]. Computerized CTG changes are preceded by DV abnormalities in 50% of cases [112] and by up to 3 days [119] before abnormal biophysical profile (BPP). As a result, it is thought to be a better study for figuring out when fetuses will give birth, especially after taking steroids. GRIT and TRUFFLE are two multicenter randomized controlled 7 trials (RCTs) that investigated the timing of delivery in early onset FGR [120,121]. The growth restriction intervention trial (GRIT) included women who were pregnant before and after the 30th week of their gestation; however, the trial has been criticized for selecting the delivery date based on the judgment of the clinician rather than on objective signs [120]. It didn't look at the Doppler results in particular. At two years of age, the outcomes of the 11 groups were the same—immediate or delayed delivery following signs of fetal distress—and the best time to deliver was unknown. The women in the more recent TRUFFLE trial were randomly assigned to the reduced CTG short term variation (STV), early, or late DV changes groups, with the average entry age being 29 weeks. They discovered that, despite the fact that survival without neurological impairment was the same in all three groups, an improvement in developmental outcomes at two years of age was linked to the timing of delivery based on late changes in DV [121]. This study reaffirms the significance of abnormal DV changes in the treatment of FGR with early onset.

5.5 Aortic isthmus

Doppler of the aortic isthmus The deoxygenated blood from the placenta enters the right atrium through the inferior and superior vena cava, while the oxygenated blood from the placenta enters the left atrium through the DV, left hepatic vein, inferior vena cava, right atrium, and foramen ovale. It then enters the right ventricle and is pumped out via the pulmonary artery from there. To reach the aorta at the aortic isthmuses, it travels through the ductus arteriosus. In this way, these two streams, the oxygenated and deoxygenated blood, meet meaningfully without precedent for the aortic isthmus. As a result, the aortic isthmus (AI) is very important because it connects the oxygenated and deoxygenated circulations [122]. Animal studies have shown that AI blood flow goes backwards before cerebral blood flow goes down [123], and that AI flow changes are even more obvious before umbilical artery velocimetry changes [124]. A correlation between neonatal mortality and neurological morbidity in early-onset FGR and abnormal changes in AI velocimetry has also been found in human studies [125]. AI flow abnormalities have also been found in some cases of late-onset FGR, although reversed AI flow can be seen as a late step in the spectrum of Doppler abnormalities [73]. In addition, abnormal AI flow occurs one week before abnormal DV flow, making it unsuitable as a marker for predicting fetal death in early-onset FGR [117,126,127]. Abnormal AI flow in early-onset FGR may be useful for predicting neurological injury [66], but clinical application will require additional research and education.

5.6 Cardiotocography

Routine CTG has been shown to have a high false positive rate (50 percent) in FGR fetuses [128]. Furthermore, it is difficult to interpret the fetal heart rate (FHR), particularly in extremely small foetuses . However, unprovoked decelerations or significantly reduced and prolonged variability are considered preterminal events and are not useful for early identification [96]. According to Bracero et al. [129], computerized CTG (cCTG) could result in five times fewer interventions than non-cCTG use (9% vs. 49%). In addition, patients in the cCTG group spent less time on each test than in the visual interpretation group, despite the fact that the perinatal outcome was the same in both groups. The cCTG group had a slightly shorter NICU stay than the visual CTG group, but this difference could be due to chance. Short-term variability (STV), which is evaluated late changes in DV, appears to have a similar ability to predict fetal death, according to evidence [96]. A longitudinal study has confirmed its role as a marker of acute compromise, which coincides with abnormal DV flow velocimetry [112], and a Cochrane database review [77] suggested that

STV correlates with acidosis and severe hypoxia. In a meta-analysis of 18 RCTs, Oligohydramnios, the amniotic fluid index, was found to be correlated with a low Apgar score [132]. Reduced amniotic fluid index (AFI) is not strongly associated with acidosis [112, 113], so its role in the treatment of early onset FGR is unknown. Evidence of the significance of abnormal DV velocimetry in the prediction of fetal death and academia. As a result, DV velocimetry and umbilical artery Doppler analysis should be routine tools for monitoring these compromised fetuses [121,132,133].

Observing ought to begin from 24 weeks in women recognized as high gamble during screening at booking with early multidisciplinary input from the neonatal group. There is a likelihood that infection and hemorrhage will be greater following a classical incision than following a lower segment Caesarean section, but there are insufficient data to inform either the patient or the physician. There are no tested treatments for FGR that can boost fetal growth during pregnancy. After administering maternal corticosteroids and magnesium sulfate to improve neonatal outcome, the only effective treatment option is timely iatrogenic PTB [87].According to a number of studies [135, 136], the use of low-dose aspirin as a preventative measure in women who are at high risk of developing PE and FGR may reduce the incidence of these complications. Several vascular and coagulation effects of aspirin support FGR prevention: it smothers the creation of prostaglandins and thromboxane, repressing platelet aggregation; enables the release of nitric oxide from the vascular endothelium [137]; decreases oxidative release, injury, and inflammation by increasing the activity of heme oxygenase-1 in endothelial cells to catabolize heme [138]. For women at high risk of FGR, the majority of national and international guidelines recommend taking 100–150 milligrams of aspirin daily before 16 weeks [108].

6. Future Prospective

NO donors appear to increase uterine and umbilical blood flow, according to extensive research on their use in PE and FGR prevention and management [139-141]. The family of calcium-calmodulin-dependent enzymes known as nitric oxide synthases (NOS) synthesize NO, an autocrine and paracrine signaling molecule, from L-arginine. NO is produced by NOS. It has a physiological vasodilating effect when released by endothelial cells, increasing blood flow. Besides, it instigates a diminished responsiveness to vasopressors and restraint of platelet capability [142]. As was mentioned earlier, the trophoblast produces NO during a normal pregnancy. This appears to play a significant role in the normal development of the placenta, resulting in a decrease in the SVR of the fetoplacental and uterine circulations. On the other hand, decreased NO release is linked to endothelial dysfunction and placental hypoxia in PE or FGR-complicated pregnancies [44]. The different ways that NO donors affect the maternal hemodynamics are a decrease in blood pressure, an increase in heart rate, and dilatation of capacitance vessels. The latter effect on the venous bed increases venous pooling and decreases preload, both of which are defects that are already present in mothers of FGR fetuses. The administration of a plasma volume expander (PVE) simultaneously appears to be a reasonable strategy in order to steer clear of this potential side effect. In point of fact, fluid management results in an increase in preload, whereas NO donors improve SV and CO by reducing afterload and SVR. Valensise et al,[143]. PVE and NO donors were found to prolong gestation in hypertensive mothers of severely growth-restricted fetuses by reducing fetal-placental impedance (reappearance of end diastolic flow in the UA) and improving maternal hemodynamic parameters (resulting in a decrease in SVR and an increase in CO). Tiralongo et al., conducted a subsequent cohort study on FGR pregnancies, reported a significant increase in CO, SV, and a decrease in SVR following therapy with NO donors and PVE, which confirmed these findings. Additionally, the treated group demonstrated an improvement in fetal growth. In contrast, the untreated group lacked any differences [144].

The administration of statins has recently produced promising results. Generally, statins are used to prevent atherosclerotic cardiovascular diseases and inhibit cholesterol biosynthesis. Pregnancies with early-onset FGR treated with pravastatin 40 mg/die had a significantly improved angiogenic profile, which improved the sFlit1/PlGf ratio [145]. This outcome could be connected with the relationship between pleiotropic impact of statins and the NO motioning, as seen in animal models [146]. Even though the Doppler progression did not change in human pregnancies treated with pravastatin, there was an increase in the time it took to deliver the baby and a higher newborn birthweight [145].

A phosphodiesterase type 5 inhibitor known as sildenafil has recently been proposed as a treatment for FGR [147, 148]. The actions mediated by NO are enhanced by sildenafil, possibly enhancing placental perfusion. For a situation control concentrate by von Dadelszen et al. [149], a significant increase in AC was linked to the use of sildenafil citrate during pregnancies complicated by severe FGR. However, the authors did not examine the hemodynamic changes in the circulation of the mother and the fetus. Sildenafil has been shown to lower UtA- and UA-PI levels in FGR fetuses in subsequent studies [150–152]. Khalil et al., [153] found that this molecule expanded maternal HR and decreased circulatory strain and blood vessel firmness in pregnancies muddled by extreme beginning stage FGR. However, these CV effects were temporary and mild. In addition, when tested in a

sufficiently powered multicenter randomized controlled trial, sildenafil did not improve pregnancy outcomes or extend the duration of the pregnancy in severe early-onset FGR [147]. In addition, the Dutch STRIDER trial was terminated prematurely due to excessive neonatal mortality caused by pulmonary hypertension, which may have been related to the treatment [148].

Because of the underlying cardiovascular phenotype, determining the most effective treatment for women with hypertension and FGR should be made easier by determining the maternal hemodynamic status. Drugs with beta blocking activity reduce CO and have a negative chronotropic effect in those instances. As a result, women with FGR, in which the uteroplacental circulation is already impaired, may suffer harm from them. Calcium antagonists, on the other hand, are likely to be more effective in the high SVR state of hypertensive women with FGR [154].

7. Planning of delivery

TRUFFLE data provide evidence that management of pregnancies in which there is early-onset FGR in a tertiary-level perinatal center and DV Doppler measurement in conjunction with cCTG improves long-term infant outcome; a flowchart explaining the recommended protocol is shown in (Figure1). DV measurement is not very time-consuming. Our advice, therefore, is to include DV Doppler measurement with cCTG for the monitoring of women with early-onset FGR. [121]

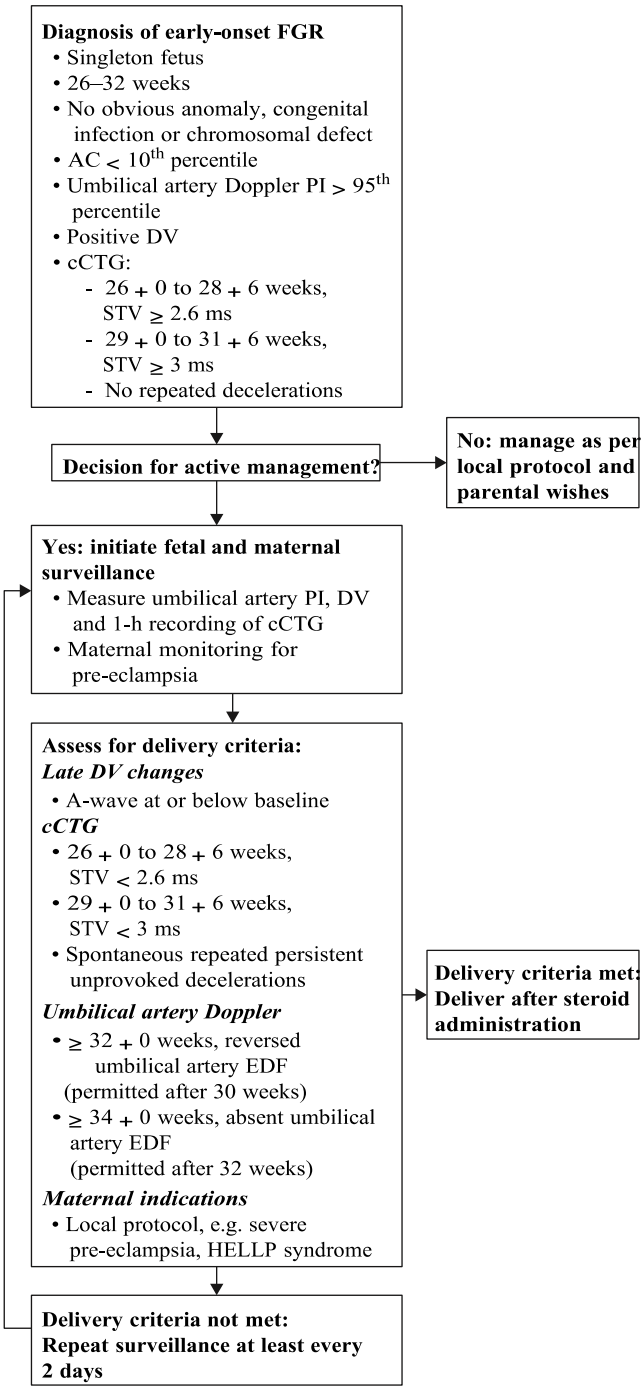

Figure 1

II. Conclusion

A better understanding of the maternal hemodynamics of FGR-complicated pregnancies could have a number of positive effects on clinical practice. As a matter of fact, it could have likely restorative ramifications, further develop screening instruments, assist with recognizing SGA from FGR, and forestall future CVD in these women. However, additional research is required to determine whether FGR women already experience changes in their hemodynamic parameters during the pre-gestational period and to investigate the possibility of manipulating maternal hemodynamics to improve pregnancy outcomes.

Neonatal morbidity and mortality are much lower in early onset FGR than is typically assumed, with over 80% of those presenting between 26 and 32 weeks surviving intact at 2 years [121]. On the other hand, there is evidence that, when compared to appropriately grown neonates born at that gestation and those with abnormal Doppler flow before 30 weeks' gestation, neonates with abnormal Doppler flow have higher rates of chronic lung disease, retinopathy, gastrointestinal disturbances, severe motor impairment, and increased cognitive impairment at school age [104,135,155]. Delivery may not be recommended earlier than 26 weeks of gestation unless directed by informed parental choice, as evidence suggests that outcomes for FGR neonates are comparable to those of appropriately grown neonates born two weeks earlier [156]. In addition, the fact that cerebral palsy is not more common in FGR preterm infants than it is in appropriately grown preterm infants [134,136,137] and about 1 percent in early onset FGR (TRUFFLE) emphasizes the significance of allowing gestational maturity despite the risk of intrauterine death and waiting to determine the timing of delivery. The evidence indicating a better outcome in subsequent pregnancies [138,157], particularly when treated with aspirin in early pregnancy, lends credence to this management plan. There is no evidence that corticosteroids are beneficial for FGR infants, despite the fact that they are recommended for use between 24 and 34 weeks of gestation if delivery is anticipated [158]. This is supported by the fact that, despite having accelerated indices of fetal lung maturation, FGR neonates have significant lung problems [159]. Understanding the pathogenesis of early onset FGR, its evolving phenotype with corresponding changes in Doppler velocities, the perinatal risks associated with delivering at various gestational ages, the active involvement of the neonatal team, and taking patient choice into consideration are the main components of the management of this condition.

Clinical points

- Early onset FGR and late onset FGR have different patterns of placental and maternal cardiovascular pathologies
- Umbilical artery and ductus venosus Doppler velocimetries play an important role in diagnosis and prognosis of early onset FGR
- Delivery of FGR babies at very preterm gestational ages is associated with higher morbidity but not significantly different risk of mortality compared to appropriately grown fetuses
- Delivery in early onset FGR should be in tertiary care centre given the high perinatal morbidity
- The trigger for delivery in early onset FGR should be based on late ductus venosus changes or abnormal CTG
- Identification and monitoring of late onset FGR is less clearly defined however given the much lower morbidity after 32weeks, a lower threshold for delivery applies should any of the Doppler, CTG or biophysical tests become abnormal.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

Authors have equally participated and shared every item of the work.

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