

Maternal and fetal outcomes in Growth-Restricted pregnancies befor 32 weeks

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ABSTRACT

Introduction: The study aims to determine the fetal and maternal consequences of fetal growth restriction (FGR) and small for gestational age (SGA) pregnancies ≤ 32 weeks, referring to Imam Khomeini Hospital in Ahvaz City, Iran.

Materials and Methods: This study examines pregnant women with FGR and SGA ≤ 32 weeks (March 2021-2022) in Ahvaz, Iran. After obtaining consent forms from participants, 127 participants were included in the study. The study collected data from their medical records.

Results: The Study participant's average age was 29.13 years. Most participants had no previous pregnancy or abortion (n=95, 74.8%). Cesarean section was the most common delivery method (90.6%, n=115), and a significant number of participants had gestational diabetes (22%, n=28) and gestational hypertension (19.7%, n=25). Most participants were diagnosed with IUGR stage I (67.7%). Fetal distress was the most common cause of premature termination (n=39, 45.9%). Abnormal Doppler indices were found in 95.3% of participants (n=121). The first and second-trimester screening tests showed that 7.1% and 10.2% had abnormal results, respectively. Intrauterine fetal death rate was 7.9% (n=10).

Conclusion: The study found 7.9% Intrauterine fetal death (n=10). Additionally, overall infant mortality rates were found to be 14.2%, 16.5%, and 18.1% for Infants up to one, three, and six months of age, respectively. Abnormal Neurological health and movement status occurred in 3.9% (n=5) and 11% (n=14) of the infants at three months, 4.7% (n=6) and 11% (n=14) of the infants at six months, respectively.

Keywords: Fetal Growth Restriction, Small for Gestational Age, Fetal Diseases, Maternal-Fetal Relations, Fetus, Low birth weight

Introduction

Pregnancy induces changes in the social, psychological, and physiological realms. Research has demonstrated that maternal mental health concerns and stress exposure during pregnancy can detrimentally affect the well-being of both the mother and the fetus. Employing an appropriate methodology to assess fetal health in pregnancies at high risk effectively reduces mortality and complications. This approach facilitates continuous fetal monitoring within favorable intrauterine conditions, preventing premature birth—the previous recourse for salvaging fetuses in high-risk pregnancies. These pregnancies subject both the mother and the developing fetus to jeopardies concerning their survival, health, and comfort due to an array of conditions and factors. Etiologies contributing to high-risk pregnancies can be categorized into maternal and fetal factors. Maternal factors encompass ages below 18 and above 35 years, weights under 45 kg, heights shorter than 150 cm, histories of five or more

pregnancies, prior pregnancy complications, bleeding, genital irregularities, hypertension, RH incompatibility, infections, and chronic illnesses. Fetal factors encompass abnormalities, placenta-mediated conditions, and exposure to teratogenic or harmful drugs[1].

Approximately 500,000 of the 4 million births that occur annually in America are placed in the high-risk pregnancy group due to maternal and fetal complications. Fetal growth restriction (FGR) is associated with significant complications and mortality in the perinatal period, fetal death, asphyxia during delivery, meconium aspiration, hypoglycemia, and increased hypothermia of the newborn [2]. Furthermore, abnormal neurological development is more common in these babies. Many cases of reduced fetal growth are related to viral infections in the early stages of fetal development or genetic disorders in fetal development. The underlying problem's nature and severity dictate the long-term prognosis of these cases. However, in other cases, placental insufficiency-caused FGR in a healthy fetus can

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reduce the risk of adverse outcomes with timely diagnosis and appropriate obstetric and neonatal treatments [3].

Placental dysfunction is the most reported association with stillbirth, so placental disorders cause stillbirth in 11% to 56% of cases. Placental dysfunction may be clinically related to FGR and small for gestational age (SGA) infants. This condition can occur due to placental abruption or hypertensive disorders of pregnancy and many other disorders and factors. FGR and SGA are terms used interchangeably for fetuses that have not reached their appropriate growth potential. FGR is preferred to be applied in the American College of Obstetrics and Gynecology [4].

Research shows that FGR has a significant relationship with infant mortality, stillbirth, and increased vascular resistance of the umbilical and uterine arteries. In addition, growth restriction of unrelated fetuses that start later is associated with a birth weight less than the third centile of severe Oligohydramnios and premature separation of the placenta [5].

Diagnosing intrauterine FGR poses a formidable challenge. SGA refers to infants whose birth weight falls below 10% of the community's average weight for that gestational age. Perinatal mortality escalates markedly when birth weight dips below 3%. SGA often correlates with potential FGR; 30% of infants with birth weights below the 10th percentile are classified as having FGR, whereas 70% of those below the third percentile do not carry this classification. Accurate identification of SGA newborns is linked to diminished rates of perinatal mortality. However, prevailing methods like fundus height measurement exhibit limited sensitivity and specificity in detecting SGA [6].

FGR can have short-term consequences such as perinatal asphyxia, meconium aspiration, persistent pulmonary hypertension, hypothermia, hypoglycemia, hyperglycemia, hypocalcemia, polycythemia, jaundice, feeding problems, neurobehavioral disorders, ferritin deficiency, and long-term consequences include disorders Inhibition of neurocognitive deficits, psychological disorders, osteoporosis, poor performance during education. In adulthood, FGR is associated with high blood pressure, cardiovascular disease, obesity, diabetes, and metabolic diseases [7].

Research shows that daily monitoring in the early detection of intrauterine growth restriction and using aspirin and low molecular weight heparin during pregnancy can reduce the consequences during delivery. However, the result of the babies has not changed much despite these efforts, and the change in delivery time and management is still controversial. Late FGR starts in weeks 34 to 36 but may be detected late before birth. Discovering growth-restricted pregnancies using second-trimester tests, blood biomarkers, and imaging techniques can partially identify and improve perinatal outcomes. While these tests have limited effectiveness for early diagnosis, it is possible to identify late FGR by touching the abdomen serially and measuring the height of the uterus during care visits and velocimetry of the umbilical artery. Ultrasound diagnostic methods can also predict FGR in the third trimester, but research has shown that their use has not improved perinatal outcomes. With reduced intrauterine growth, children are at increased risk

of middle-aged diseases, including diabetes, stroke, and coronary artery disease deaths [8].

Many factors affect low birth weight, the most important of which are genetics, environmental, fetal, placental, and maternal factors. Maternal factors have the most critical and significant impact on infant birth weight based on research conducted. Maternal factors during pregnancy include age, body mass index, socioeconomic factors, medical activity, type of nutrition, smoking habits, unfavorable life situations, how to deal with stress, and how to use health therapy services. The results of some studies admit that these factors may be related to the birth of a low-birth-weight baby [9].

Although maternal and child health services have expanded extensively, women during pregnancy still face many health problems that put their lives at risk. In mothers who had intrauterine death along with SGA in a subsequent pregnancy, the probability of intrauterine death of the fetus is 1/2 times. Respiratory failure is also three times higher in babies with SGA than in AGA. Meconium aspiration, hypoglycemia, hypothermia, and polycythemia are common in these babies [10]. Risk factors for intrauterine growth disorder that causes low birth weight babies are small mothers, weight gain during pregnancy, low nutritional and socioeconomic status, fetal infections, fetal abnormalities, anticonvulsant drugs, smoking, alcohol, Narcotics, maternal high blood pressure, chronic kidney diseases, maternal anemia, multiple births, abnormalities of the placenta and umbilical cord [11].

Although very low birth weight babies have a high risk of mental illness and symptoms in adulthood, there is no risk for SGA babies. Academic grades in primary and secondary school babies with SGA are lower than in babies with AGA. Although it cannot be claimed that babies with SGA are entirely preventable, measures such as preventing high-risk pregnancies, the necessary care, and appropriate treatments can reduce the number of babies with SGA [12]. Sheibani and colleagues in a historical cohort study on 8460 consecutive pregnant women recruited for chromosomal abnormalities screening within the first trimester at the fertility infertility and perinatology research center in Ahvaz Joundishapor University of Medical Sciences between April 2014 and April 2015 showed that measuring the serum level of MOM PAPP-A during the first trimester can be a valuable marker for predicting adverse outcomes of pregnancy such as SGA and abortion. The best cutoff value for this marker to predict the outcome is 0.3 in pregnant Iranian women [13]. Considering what has been said and since the problems of the fetus during the fetal period will cause problems for him in the future, this study will be conducted to determine the fetal and maternal consequences of FGR and SGA pregnancy less than or equal to 32 weeks referring to Imam Khomeini Hospital in Ahwaz city, Iran.

Materials and Methods:

This retrospective cross-sectional descriptive study examined pregnant women with FGR and SGA less than or equal to 32

weeks, referring to the Imam Khomeini Hospital in Ahwaz, Iran, between March 2021 and 2022. After receiving informed consent from the participants and explaining the study method, 129 pregnant mothers were included. At the beginning of the diagnosis, two individuals diagnosed with IUGR were later found not to have IUGR at the time of termination and were excluded from the analysis. Finally, 127 participants were examined. All phases of this research took the Helsinki Declaration's ethical precepts and participant confidentiality into account.

According to ACOG's criteria, infants categorized as SGA (those with birth weights between 3 to 10 percentile) were considered IUGR Stage I. Moreover, the Delphi criteria were employed in this study. The inclusion criteria encompassed all singleton pregnancies attending Imam Khomeini Hospital in Ahwaz with SGA and FGR diagnoses equal to or less than 32 weeks. The study's exclusion criteria encompassed maternal dissatisfaction with study participation, multiple pregnancies, and maternal addiction.

A questionnaire that included demographic information about the participants (age, education level, parity, gravidity, number of abortions, delivery mode, pregnancy termination method, fetal sex) and underlying diseases (diabetes, high blood pressure, maternal fatty liver diseases, thyroid diseases) was received from the participants.

Maternal outcomes (preterm delivery, lupus, antiphospholipid syndrome, pre-eclampsia and its type, abortion, HELLP syndrome), access in ICU, the cause and amount of hospitalization in ICU, the reason of premature termination, gestational age at delivery/termination, stage IUGR at the first diagnosis and at the time of termination, gestational age at the time of diagnosis of IUGR, average age of pregnancy at birth/termination of pregnancy, diagnostic test results to determine the cause of IUGR, fetal outcomes (intrauterine fetal death, meconium, apgar score, infant death), birthweight at birth, 1 month, 3 months and 6 months, access in NICU and the

days of hospitalization in NICU, investigating neurological health and neonatal motion status at 3 and 6 months, and laboratory findings (Results of screening in the screening in the first and second trimester in the fetus, Cell Free DNA and amniocentesis, Echocardiography, fetal scanning anomaly, fetal anomaly, and abnormalities in accompanying ultrasound, Doppler Indexes) were extracted from their medical records. All of this data was then examined and analyzed.

Statistical analysis:

Continuous variables were described using mean \pm standard deviation (SD). The Kolmogorov-Smirnov test was used to check the normality of the data. Kruskal-Wallis was used to evaluate non-normally distributed data, and the chi-square statistical test was used for qualitative data. All analyses were performed by IBM SPSS software for Windows (version 22, SPSS Inc., Chicago, IL, USA). P-values less than 0.05 were considered significant.

Results:

In this study, the average age of the participants was 29.13 years. The minimum gestational age at birth or termination was 24 weeks, and the maximum was 38 weeks, with an average of 33.35 weeks. The average weight of the studied infants was 1555.91 grams, ranging from 500 to 3000 grams. Ten fetuses that died in utero were excluded from the analysis. The 500-gram infant was male and was born to a 22-year-old mother at 36 weeks of gestational age with Stage I IUGR. The delivery was performed by cesarean section (CS). The 3000-gram infant was female and was born to a 24-year-old mother at 38 weeks gestational age with Stage I IUGR. This delivery was also performed by CS. At 1, 3, and 6 months after birth, the average weight of the infants was 2048.65, 3414.04, and 5735.22 grams, respectively (Table 1).

Table 1. Quantitative variables in the studied subjects

Variable	N	Mean	Std. Deviation	Min	Max
Mother's age (year)	127	29.13	6.343	15	43
Mother ICU Admission (day)	19	2.26	0.733	1	4
Gestational age at birth/termination (weeks)	127	33.35	2.96	24	38
Weight of the baby at birth (gram)	117	1555.91	625.838	500	3000
Baby weight after one month (gram)	109	2048.65	776.180	700	4000
Baby weight after three months (gram)	106	3414.04	1184.709	1000	7000
Baby weight after six months (gram)	104	5735.22	1346.524	3000	9000

In this study, the majority of infants fell below the third weight centile at birth (n=59), one month (n=77), three months (n=67), and six months (n=44). At these same time points, 25, 15, 6, and 17 infants were in the third to tenth centile. 30, 11, 25, and 29 infants were in the tenth to 50th centile. 3, 2, 4, and 8 infants were in the 50th to 90th centile. Lastly, 2, 4, 4, and 6

infants were above the 90th centile (Figure 1). The study recorded 10 cases of Intrauterine fetal death (IUFD) (7.9%). Additionally, overall infant mortality rates were found to be 14.2% (n=18), 16.5% (n=21), and 18.1% (n=23) for Infants up to one, three, and six months of age, respectively. These deaths were not included in the analysis presented in Table 3.

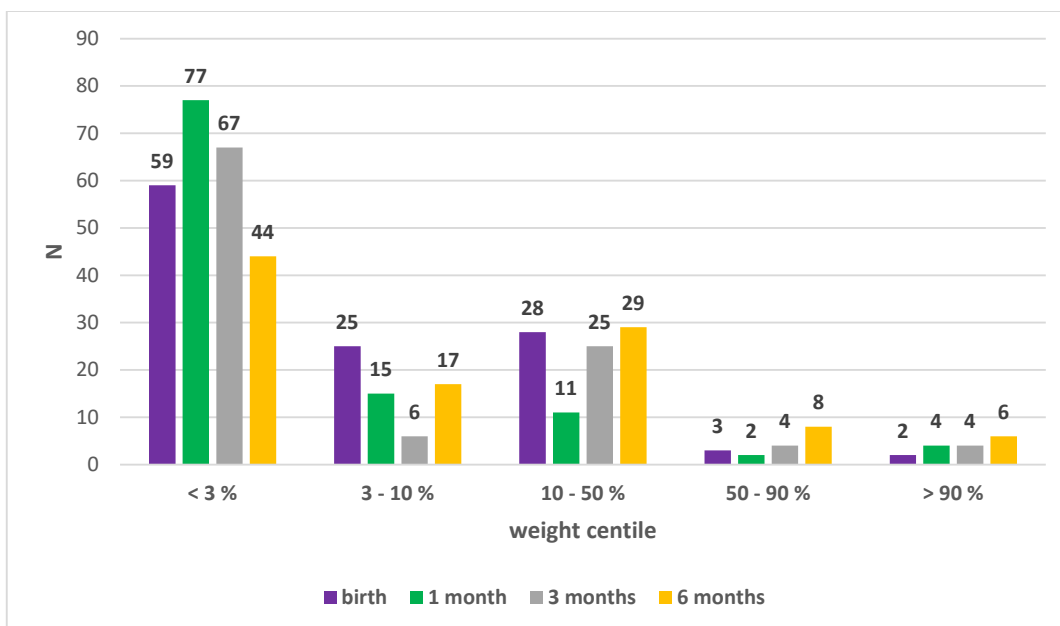


Figure 1. Weight centiles in infants studied at birth, 1, 3, and 6 months

In terms of the level of education, 33.9% (n=43) had attained a lower diploma. A diploma or bachelor's degree was held by 61.4% (n=78), and postgraduate degrees were held by 4.7% (n=6). The maximum gravity among the study subjects was 6 (n=2, 1.6%), and the minimum was 1 (n=61, 48%). In the study subjects, the maximum Parity was 4 (n=5, 3.9%). Also, most study subjects have zero Parity (n=76, 59.8%). The highest number of abortions among participants is 3 (n=2, 1.6%), and most participants are in their first pregnancy or have no previous abortions (n=95, 74.8%). Most of the participants, 115 (90.6%), underwent a CS for delivery, and vaginal delivery was performed in 12 (9.4%) cases. The study population included participants with various comorbidities. Overt diabetes was present in 3 individuals (2.4%), and gestational diabetes affected 28 (22%). Four (3.1%) had chronic hypertension, while gestational hypertension was diagnosed in 25 (19.7%). Additionally, lupus affected two individuals (1.6%), and the antiphospholipid syndrome was present in 1 (0.8%). Pre-eclampsia was diagnosed in 16 (12.6%), while hypothyroidism occurred in 25 (19.7%). 4% of the participants (n=5) had other diseases such as thalassemia minor, asthma, and rheumatism. None of the studied subjects had fatty liver or HELLP syndrome (Table 2).

In this study, 15% of the participants (n=19) had an average stay of 2.26 days in the ICU. Pre-eclampsia (early=12, late=4), DKA (n=2), and difficulty during operation (n=1) were observed as reasons for admission to the ICU in 12.6%, 1.6%, and 0.8% of participants, respectively. Regarding the stage of IUGR at the

first diagnosis, 67.7% were in stage I, 29.9% in stage II, and 2.4% in stage III. Stage I of IUGR at pregnancy termination was present in 59.1% of participants, stage II in 33.9%, and stage III in 7.1%. None of the participants was in IUGR stage IV at either the time of diagnosis or termination. Also, IUGR was diagnosed in 10 participants (7.9%) between 19 and 25 weeks of gestation. The other 117 participants (92.1%) received an IUGR diagnosis at 31 weeks and six days of gestation. During serial biometric and Doppler assessments, 12 individuals progressed from IUGR stage I to stage II, and 6 transitioned from stage II to stage III. No individuals advanced to IUGR Stage IV (Table 2).

Our research protocol was followed by 42 participants (33.1%) who terminated their pregnancy according to the protocol. The other 85 participants (66.9%) terminated prematurely. Among the premature terminations, CS was performed on 78 participants (61.4%), while 7 participants (5.5%) delivered vaginally. Of the protocol-compliant terminations, 37 participants (29.1%) had CSs, and 5 participants (3.9%) delivered vaginally (Figure 2).

The most common cause of premature termination was fetal distress (n=39, 45.9%). Other reasons included early labor pains (n=17, 20.0%), severe pre-eclampsia (n=16, 18.8%), intrauterine death of the fetus (n=10, 11.8%), water sac rupture (n = 2, 2.4%) and oligohydramnios (n=1, 1.2%). Regarding termination time, 43.3% (n=55) of mothers were under 32 weeks gestation. Also, 22% (n=28) were between 33 and 34 weeks, and 34.6% (n=44) were between 35 and 37 weeks gestation, as shown in Table 2.

Table 2. Variables studied in participating mothers

Variable	Groups	N (%)
Education Level	Lower diploma	43 (33.9)
	Diploma or bachelor	78 (61.4)
	Postgraduate degree	6 (4.7)
Gravidity	1	61 (48.0)
	2-3	50 (39.4)

Variable	Groups	N (%)	
Parity	4-6	16 (12.6)	
	0	76 (59.8)	
	1-2	42 (33.1)	
	3-4	9 (7.1)	
Abortions	0	95 (74.8)	
	1-2	30 (23.6)	
	3	2 (1.6)	
Delivery Type	Vaginal Delivery	12 (9.4)	
	Cesarean section	115 (90.6)	
Admission to the ICU	-	19 (15.0)	
ICU admission reasons	Pre-eclampsia	16 (12.6)	
	DKA	2 (1.6)	
	difficulty during operation	1 (0.8)	
Maternal diseases	Overt diabetes	3 (2.4)	
	Gestational diabetes	28 (22.0)	
	chronic hypertension	4 (3.1)	
	gestational hypertension	25 (19.7)	
	lupus	2 (1.6)	
	antiphospholipid syndrome	1 (0.8)	
	pre-eclampsia	16 (12.6)	
	Hypothyroidism	25 (19.7)	
	IUGR at first diagnosis	I	86 (67.7)
		II	38 (29.9)
III		3 (2.4)	
IV		0 (0)	
IUGR at the time of termination	I	75 (59.1)	
	II	43 (33.9)	
	III	9 (7.1)	
	IV	0 (0)	
gestational age at the first diagnosis of IUGR	19w-25w	10 (7.9)	
	26w-31w6d	117 (92.1)	
pregnancy termination method	According to the protocol	85 (66.9)	
	Prematurely	42 (33.1)	
cause of premature termination (%)	fetal distress	39 (45.9)	
	early labor pains	17 (20.0)	
	severe pre-eclampsia	16 (18.8)	
	Intrauterine fetal death (IUFD)	10 (11.8)	
	sac rupture	2 (2.4)	
	Oligohydramnios	1 (1.2)	
termination time (%)	less than 32 weeks	55 (43.3)	
	33 to 34 weeks	28 (22.0)	
	35 to 37 weeks	44 (34.6)	

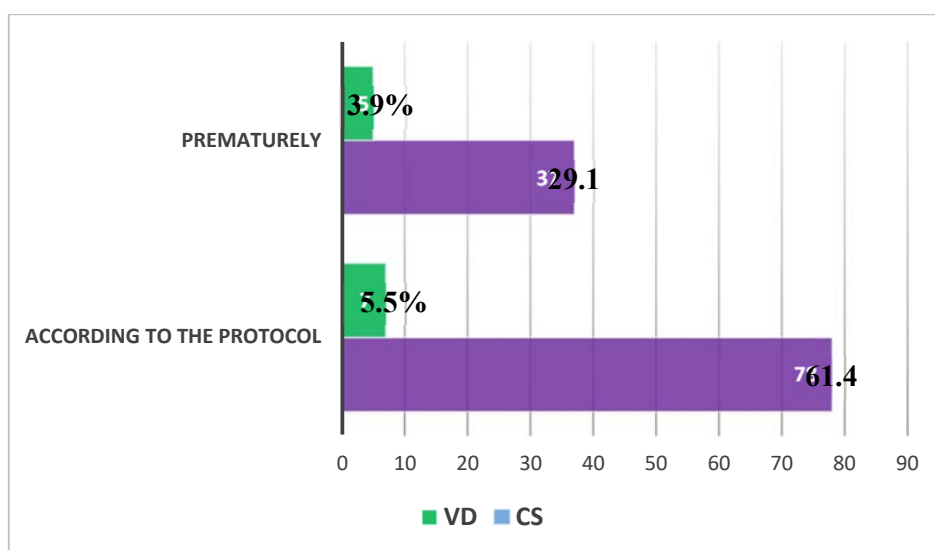


Figure 2. Pregnancy termination Methods

The gender distribution of the fetuses in this study was 57.5% (n=73) male and 40.2% (n=51) female. Also, 2.4% (n=3) had ambiguous gender. Most of the babies had an Apgar score of 7 or higher at birth (n=58, 49.6%) and the fifth minute (n=89, 76.1%) (Table 3). There was no significant difference between the Apgar score and the gender of the fetus (p-value = 0.482 and

0.482, respectively) (Figure 3). Meconium excretion was positive in 9 fetuses (7.1%) (Table 3). There was no significant difference between the Apgar score at birth and the fifth minute and meconium excretion (p-value = 0.094 and 0.132, respectively) (Figure 4). Ten fetuses died in utero and were excluded from the analysis.

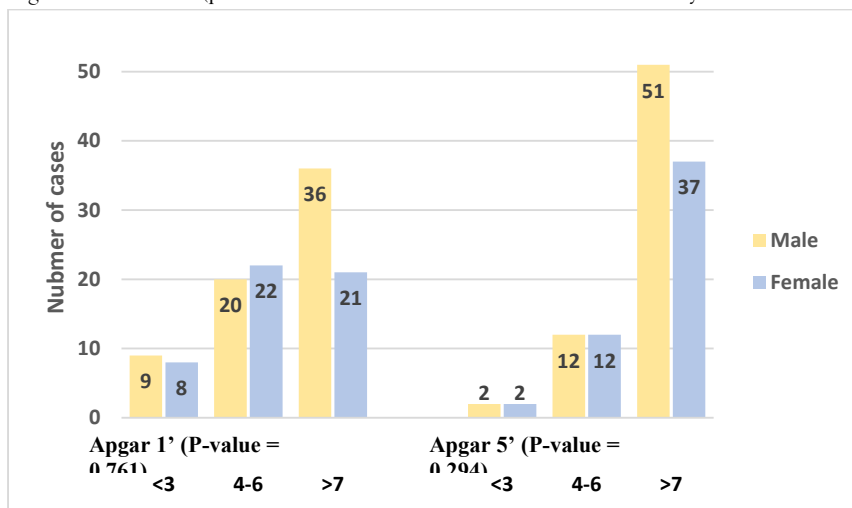


Figure 3. The Apgar score (1' and 5') and the gender of the fetus

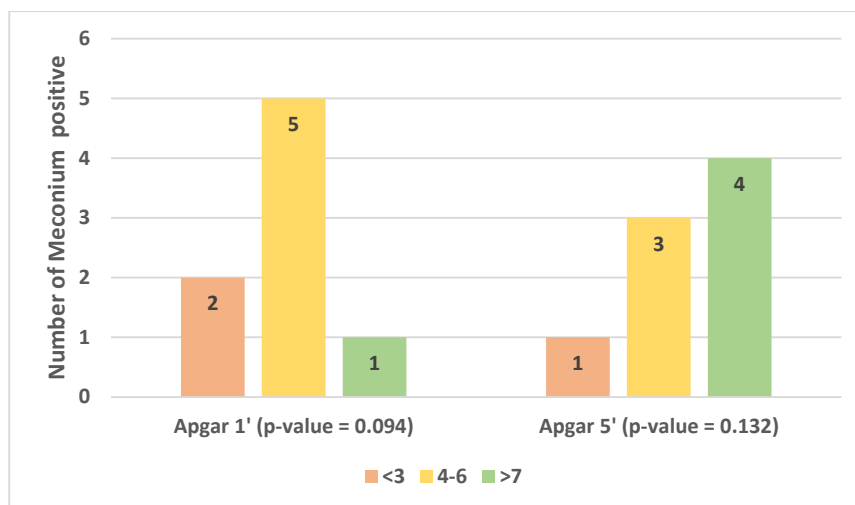


Figure 4. Apgar score (1' and 5') and meconium excretion

Abnormal Doppler indices were observed in 121 study population participants (95.3%). Of these, 113 subjects (89%) had an AC below the third centile, while 74 subjects (58.3%) had an EFW below the third centile. The CP ratio was below the fifth centile in 93 subjects (73.2%), and the MCA was below the fifth centile in 58 subjects (45.7%). The umbilical PI and the mean uterine artery PI were above the 95th centile in 93 subjects (73.2%) and 84 subjects (66.1%), respectively (Table 3). Most neonates admitted to the NICU stayed below 30 days (n=74, 63.2%), while 23 neonates (19.7%) remained in the unit

for 30 to 119 days. Only one neonate (0.9%) had a prolonged hospitalization exceeding 120 days. Nineteen infants (16.2%) were not admitted to the NICU. Notably, ten studied fetuses died in utero and were excluded from this analysis.

Neurological health and movement status were evaluated at three and six months. At these time points, 79.5% (n=101) and 72.4% (n=92) of the infants had healthy outcomes, respectively. On the other hand, abnormal outcomes occurred in 3.9% (n=5) and 11% (n=14) of the infants at three months, 4.7% (n=6) and 11% (n=14) of the infants at six months (Table 3).

Table 3. Variables studied in participating fetuses and infants

Variable	Groups	N (%)
Gender	Male	73 (57.5)
	Female	51 (40.2)

Variable	Groups	N (%)
Meconium excretion hospitalized in the NICU	Ambiguous	3 (2.4)
	-	9 (7.1)
	less than 30 days	74 (63.2)
	30 to 119 days	23 (19.7)
Abnormal neurological status	more than 120 days	1 (0.9)
	Three months	5 (3.9)
	Six months	6 (4.7)
Abnormal Movement Condition	Three months	14 (11.0)
	Six months	14 (11.0)
Ultrasound examination at diagnosis	Abnormal Doppler index	121 (95.3)
	AC <3 rd centile	14 (11.0)
	EFW <3 rd centile	74 (58.3)
	CPR <5 th centile	34 (26.8)
	MCA-PI <5 th centile	69 (54.3)
	UA-PI >95 th centile	34 (26.8)
	UtA-PI >95 th centile	43 (33.9)
	IUFD	10 (7.9)
Fetal/Infant Death	Up to 1 month	18 (14.2)
	Up to 3 months	21 (16.5)
	Up to 6 months	23 (18.1)

According to the Kruskal-Wallis statistical test, there is a significant relationship between the groups concerning the Apgar score (at birth and fifth minute) and gestational age at termination/birth (p-value=0.001). The table's average ranks (Mean rank) suggest that the gestational age at termination is also higher in individuals with higher Apgar scores (at birth and the fifth minute). Participants with Apgar scores of 3 or lower exhibit the lowest gestational age. Conversely, those with an Apgar score of 7 or higher display the highest gestational age (Table 4). Participants with Apgar scores of 3 or lower exhibit the lowest gestational age. Conversely, those with an Apgar score

of 7 or higher display the highest gestational age (Table 4). A meaningful association has been observed between an infant's Apgar score and weight at birth (p-value=0.001).

Furthermore, referring to the mean ranks in the table, it can be said that in individuals with higher Apgar scores at birth, the weight of the fetus at birth is also higher. The lowest birth weight was observed in individuals with Apgar scores lower / equal to 3 at birth, and the highest was in individuals with Apgar scores of 7 or higher. However, no significant correlation was found between the Apgar score in the fifth minute and birth weight (p-value=0.142) (Table 4).

Table 4. The results of the Kruskal-Wallis analysis on the variables studied

Variable	<=3			4-6			7			p-value	
	N	%	Mean rank	N	%	Mean rank	N	%	Mean rank		
gestational age at termination/birth	Apgar at birth	17	14.5	41.44	42	35.9	46.92	58	49.6	72.90	0.001*
	Apgar fifth minutes	4	3.4	36.75	24	20.5	38.71	89	76.1	65.47	0.001*
weight of the fetus at birth	Apgar at birth	17	14.5	35.59	42	35.9	52.19	58	49.6	70.79	0.001*
	Apgar fifth minutes	4	3.4	46.00	24	20.5	48.31	89	76.1	62.47	0.142

Of the individuals examined for TORCH and APS diseases, 101 did not undergo this test, and 26 had negative results (20.5%). During the first-trimester screening tests in fetuses, 102 participants (80.3%) had low-risk results, 9 participants (7.1%) had abnormal results, and the results were unavailable for 16 participants (12.2%). The results of genetic tests (amniocentesis) were also checked, with 1 participant (0.8%) having abnormal results, 16 participants (12.6%) having low-risk test results, and the results were not available for 110 participants (86.6%). The results of the Cell-Free DNA test from the mother's blood

showed that 23 participants (18.1%) had Low-Risk test results, while the test was not conducted for 104 participants (81.9%). During the second trimester screenings in fetuses, 110 participants (86.6%) had low-risk test results, 13 participants (10.2%) had abnormal results, and the results were unavailable for 4 participants (3.1) (Table 5).

Regarding the echocardiography of the fetuses, 19 participants (15%) had abnormal results. The fetal scan anomaly showed that 14 participants (11%) had abnormal results, and 21 (16.5%) had fetal anomalies. In the accompanying ultrasound, 47 participants

(37%) had abnormal points (Table 5). Reported anomalies in newborns included cleft lip and palate, agenesis or hypoplasia of kidneys, gastrointestinal disorders (intestinal atresia), echogenic bowel, hepatic disorders, cardiac anomalies and diseases,

musculoskeletal disorders (limb anomalies), skeletal dysplasia, short femur and humerus, ocular anomalies, short tongue, and patent ductus arteriosus (PDA).

Table 5. Laboratory investigations in the fetus studied

Variable	Groups	N (%)
First-trimester screening tests	Low-risk	102 (80.3)
	Abnormal	9 (7.1)
	Not done	16 (12.2)
Cell-Free DNA	Low-risk	23 (18.1)
	Abnormal	0 (0)
	Not done	104 (81.9)
Genetic tests (amniocentesis)	Low-risk	16 (12.6)
	Abnormal	1 (0.8)
	Not done	110 (86.6)
Second-trimester screening tests	Low-risk	110 (86.6)
	Abnormal	13 (10.2)
	Not done	4 (3.1)
Abnormal accompanying ultrasound	-	47 (37)
echocardiography	-	19 (15)
Abnormal Fetal Anomaly Scanning	-	14 (11)
Fetal Anomaly	-	21 (16.5)

Discussion:

This study examined 129 pregnant mothers with FGR and SGA less than or equal to 32 weeks, referring to the Imam Khomeini Hospital in Ahwaz, Iran, between March 2021 and 2022. At the beginning of the diagnosis, two individuals diagnosed with IUGR were later found not to have IUGR at the time of termination and were excluded from the analysis.

In the present study, ten fetuses were IUFD (7.9%), and 21 infants had anomalies (16.5%). In the accompanying ultrasound, the most observed point was the oligohydramnios. Furthermore, in general, 13 infants died before six months of age (10.2%). Therefore, in general, the death rate of the examined infants was 23 of 127 cases (18%), which is inconsistent with the study by Monier *et al.*, who reported a higher mortality rate (25%) [14]. However, the rates in the present study are higher than those of Rodriguez *et al.* (2%) [15], the European Umbilical and Fetal Flow Trial (TRUFFLE) (6%) [16], and the Multicenter Growth Restricted Intervention Trial (GRIT) (7%) [17], due to poorer management of these mothers in terms of proper prenatal diagnosis, follow-up, and planned delivery. However, in the study by Pels *et al.*, the mortality rate was 12% in the fetal period and 8% in the neonatal period [18], which is higher and lower than our study in terms of fetal and neonatal mortality, respectively. It should be noted that babies with SGA often suffer from asphyxia at birth because they do not tolerate the stress of birth well. SGA accounts for many stillbirths with hypoxia in

utero [19]. Depending on the severity of FGR, the risk of stillbirth may increase 5- to 10-fold [20]. A population-based study in the United States also reported a significantly increased risk of stillbirth in complicated SGA pregnancies when delivery occurred after 37 weeks of gestation.

In the present study, 85 mothers (66.9%) had premature termination, of which 78 had a CS, and seven were performed naturally. Furthermore, fetal stress was the most important cause of premature termination in the current study. Michaeli *et al.*'s study also reported an increase in CS (70%) compared to natural delivery in FGR babies, which is consistent with our research. They also concluded that the increase in CS is related to FGR, and the decrease in the Apgar score of newborns is associated with SGA [21].

In the current study, 98 babies were admitted to the NICU (83.8%), and the maximum hospitalization rate was 30 to 119 days. Few studies have evaluated outcomes when growth restriction is diagnosed before 24 weeks. An extensive, population-based survey by Nakling *et al.* showed that growth delay at 18-week fetal anatomy ultrasound was associated with an increased risk of preterm birth, perinatal death, low birth weight, and SGA [22]. A study by Fox *et al.* [23] compared the outcomes between 252 patients with an estimated fetal weight less than the 25th centile with controls with average growth between 18 and 24 weeks of gestation and showed increased rates of stillbirth, neonatal death, preterm delivery, SGA, and hospitalization in NICU, which is consistent with the results of the present studies. SGA babies have worse oxygenation and acid-base balance at birth. Also, the risks of adverse neonatal outcomes are significantly higher in

FGR babies, which causes more need for NICU and days of hospitalization [24]. However, in the present study, most of the babies have Apgar at birth and at the fifth minute greater than 7 (49.6% and 76.1%, respectively), which is not consistent with other studies, so in Lubrano *et al.*'s study, the percentage of FGR subjects with Apgar less than 7 in the first and fifth minutes is significantly higher than normal babies [25].

In this study, 31 mothers had diabetes, 29 had hypertension, 2 had lupus, 1 had antiphospholipid syndrome, 16 had pre-eclampsia, and 25 had hypothyroidism. In the study by Rocha *et al.*, singleton pregnancy, full cycle of prenatal steroids, CS, maternal chronic arterial hypertension, gestational hypertension, PE, HELLP syndrome, and chronic arterial hypertension with PE were identified as prenatal factors associated with SGA, which is in complete agreement with our study and other studies [26, 27]. Maternal disorders such as PE/eclampsia, chronic renal vascular disease, and hypertensive chronic vascular disease often lead to decreased uteroplacental blood flow and are associated with SGA and/or FGR. Pre-eclampsia, both in a previous and current pregnancy, is more common in FGR cases, possibly reflecting a higher background risk of developing placental disease-related complications [15].

Marconi *et al.* recently evaluated the outcome of FGR infants with umbilical artery pulsatility index based on infant birth weight/gestational age standards and intrauterine growth charts. They found that 47% of FGR pregnancies had a birth weight above the 10th centile (FGR/appropriate for gestational age) compared to 53% with a birth weight below the 10th centile (FGR/SGA) [28]. In the present study, 66.2% of babies with a birth weight below the tenth centile and other babies above the tenth centile, consistent with the above research. Furthermore, Monier *et al.* found that birth weight is a growth parameter more related to poor neonatal outcomes [29].

Maternal history helps identify individual risk factors for FGR. High-risk populations include women with poor lifestyles, low pre-pregnancy weight, weight gain during pregnancy, previous preterm delivery, and pregnancy affected by FGR [30]. In the present study, only 61 participants (48%) were in their first pregnancy (48%), and the other women studied were in their second to sixth pregnancies.

A study has shown that fetuses with SGA and FGR have unfavorable cognitive development compared to normal fetuses [31]. In this study, 3.9% of infants at three months and 4.7% at six months are abnormal regarding neurological health. However, during this period, a higher percentage of babies have abnormal movement conditions (11% at three months and six months). The small size of the fetus does not necessarily indicate harm, but it does place the fetus at greater risk for adverse outcomes. While there is agreement on the clinical management of early and late FGR, diagnosing SGA in the preterm weeks is still challenging [32]. There is no gold standard for diagnosing SGA fetuses.

Fetuses underdeveloped due to uteroplacental insufficiency are at increased risk of adverse outcomes ranging from poor perinatal outcomes to abnormal neurodevelopment and long-term

cardiovascular risk [33]. FGR is suspected when the estimated fetal weight by ultrasound (EFW) or abdominal circumference (AC) is less than the 10th centile or serial ultrasound examinations show a decrease in growth rate. Doppler studies of the umbilical artery (UA) are performed routinely in fetuses with SGA (SGA, EFW <10th centile), but in late SGA (>32 weeks), Doppler of UA is usually normal [34]. However, additional Doppler studies of cerebrovascular resistance and maternal uterine artery (UtA) can identify late SGA pregnancies at risk of adverse perinatal outcomes. These include fetuses with increased fetal cerebral blood flow (including decreased Doppler indices of the cerebral artery to the umbilical artery, that is, low cerebral-to-placental ratio, CPR) and pregnancies with high UtA vascular resistance [35]. There is also a higher risk of adverse perinatal outcomes with EFW below the third centile [36]. In the present study, 58.3% of the examined fetuses had EFW below the third centile. Additionally, 89% of examined babies have AC below the 3rd centile, a 73.2% CP ratio below the 5th centile, 45.7% MCA below the 5th centile, 73.2% umbilical PI above the 95th centile, and 66.1% uterine artery PI above the 95th centile. In general, low CPR is one of the crucial predictors of perinatal death, along with growth reduction, gestational age at birth, and maternal characteristics [37]. Individuals with early FGR (<32 weeks) show a determinant factor: a significant change in placental implantation, often resulting in increased resistance to the uterine artery (UA) and an increased risk of pre-eclampsia [38]. Early-onset FGR can also be classified and diagnosed when two of the following three parameters are present: (1) estimated fetal weight and/or AC <10th centile, (2) uterine artery pulsatility index (PI) > 95th centile, and (3) umbilical artery >95th centile. Follow-up of umbilical artery Doppler is vital in the early onset of FGR. In general, AC measurement is the most sensitive parameter for diagnosing FGR. The specificity (89.8%) and the negative predictive value (90.7%) of measuring AC above estimated fetal weight to diagnose FGR are high, indicating that when AC measurements are within the normal range, the presence of FGR is doubtful [39]. Doppler examination allows for non-invasive diagnosis of signs of placental insufficiency and fetal hemodynamic changes that occur during oxygen deprivation. Figueras *et al.* believe that the only measurement that provides diagnostic and prognostic information for managing fetuses with FGR is the Doppler examination of the umbilical artery (UA), alone or in combination with CPR. Furthermore, various abnormal CPR, UtA-PI, and very low EFW centile are the best predictive models to identify the subset of small fetuses with the worst perinatal outcome [40].

In the present study, there is a significant relationship between Apgar (first and fifth) and gestational age at termination (p-value <0.005), which shows that the higher the gestational age at termination, the higher the Apgar of newborns in the first and fifth minutes. Also, a significant relationship was found between the Apgar score at birth and the weight of the fetus at birth (p-value <0.005), which shows that babies with a higher Apgar weight have a higher birth weight; however, a significant relationship was not found between the Apgar score of the fifth

minute and the birthweight of the fetus (p-value >0.005). These results show that babies with higher weight or whose gestational age is higher suffered less from hypoxia.

Identifying babies with FGR and SGA is of great importance. In a UK study, 92,218 normal-form singletons (389 of whom were stillborn) were analyzed, and the stillbirth rate was reduced by 9.7 per 1,000 births with a prenatal diagnosis of FGR compared with 19.8 when FGR was not diagnosed [41].

One of the study's limitations was the failure to perform all the screening tests by the subjects, which affected the results of this study. Many mothers did not complete the first and second trimester screenings. Collecting information from patients who had lost their babies was also challenging.

Conclusions

This study showed that most of the mothers studied were in their first pregnancy and were in IUGR Stage I, gave birth to their babies by CS, and had premature termination. Most infants with FGR and SGA were admitted to the NICU and had Apgar 1st and 5th minutes greater than 7, significantly related to gestational age at the time of termination. In this study, various abnormalities were found in babies with IUGR. The study revealed that at the age of three and six months, 3.9% and 4.7% of infants, respectively, exhibited abnormal neurological health status. In addition, 11% of infants displayed abnormal movement at both time points.

The study further documented 10 cases of intrauterine fetal death (7.9%). The overall infant mortality rate reached 14.2%, 16.5%, and 18.1% at one, three, and six months, respectively. To advance our knowledge of FGR in the highly premature SGA population, it is imperative to conduct further research to identify the underlying factors contributing to the failure to detect FGR in this cohort. Moreover, the effects of antenatal and postnatal growth assessment on long-term outcomes should be thoroughly examined. These investigations will yield valuable insights into the efficacy of existing assessment techniques and facilitate the development of more efficacious strategies to improve the outcomes of these vulnerable neonates.

Author's Contributions:

Conflicts of interest:

There is no conflict of interest.

Ethical Issues:

This study is experimental research approved as a thesis with an

Ethical:

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References:

1. Majella, M.G., et al., *A longitudinal study on high risk pregnancy and its outcome among antenatal women attending rural primary health centre in Puducherry, South India*. Journal of education and health promotion, 2019. **8**.
2. Jaideep, K., D. Prashant, and A. Girija, *Prevalence of high risk among pregnant women attending antenatal clinic in rural field practice area of Jawaharlal Nehru Medical College, Belgavi, Karnataka, India*. Int J Community Med Public Health, 2017. **4**(4): p. 1257-9.
3. Kumar, M., N. Gnanadeep, U. Dixit, and P. Patil, *Prevalence of high risk pregnancy in rural Dharwad*. J Dent Med Sci, 2015. **14**: p. 29-32.
4. Zareen, N., S. Naqvi, N. Majid, and H. Fatima, *Perinatal outcome in high risk pregnancies*. J Coll Physicians Surg Pak, 2009. **19**(7): p. 432-5.
5. Burmeister, B., C. Zaleski, C. Cold, and E. McPherson, *Wisconsin Stillbirth Service Program: analysis of large for gestational age cases*. American journal of medical genetics Part A, 2012. **158**(10): p. 2493-2498.
6. Lassi, Z.S., et al., *Essential pre-pregnancy and pregnancy interventions for improved maternal, newborn and child health*. Reproductive health, 2014. **11**(1): p. 1-19.
7. Kozuki, N., et al., *The associations of birth intervals with small-for-gestational-age, preterm, and neonatal and infant mortality: a meta-analysis*. BMC public health, 2013. **13**(3): p. 1-9.
8. Hofmeyr, G.J., T.A. Lawrie, Á.N. Atallah, and M.R. Torloni, *Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems*. Cochrane database of systematic reviews, 2018(10).
9. Sharma, D., S. Shastri, and P. Sharma, *Intrauterine growth restriction: antenatal and postnatal aspects*. Clinical Medicine Insights: Pediatrics, 2016. **10**: p. CMPed. S40070.
10. Kramer, M.S., et al., *Is restricted fetal growth associated with later adiposity? Observational analysis of a randomized trial*. The American journal of clinical nutrition, 2014. **100**(1): p. 176-181.
11. Teixeira, M.P.C., T.P.R. Queiroga, and M.d.A. Mesquita, *Frequency and risk factors for the birth of small-for-gestational-age newborns in a public maternity hospital*. Einstein (Sao Paulo), 2016. **14**: p. 317-323.
12. Fujita, K., et al., *Prevalence of small for gestational age (SGA) and short stature in children born SGA who qualify for growth hormone treatment at 3 years of age: Population-based study*. Pediatrics International, 2016. **58**(5): p. 372-376.
13. Jafari, R.M., et al., *Value of pregnancy-associated plasma protein-A for predicting adverse pregnancy outcome*. Archives of Iranian Medicine, 2019. **22**(10): p. 584-587.
14. Monier, I., et al., *Gestational age at diagnosis of early-onset fetal growth restriction and impact on management and survival: a*

- population-based cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2017. **124**(12): p. 1899-1906.
15. Fernandez-Rodriguez, B., et al., *Obstetric and pediatric growth charts for the detection of fetal growth restriction and neonatal adverse outcomes in preterm newborns before 34 weeks of gestation*. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2021. **34**(7): p. 1112-1119.
 16. Lees, C., et al., *Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)*. *Ultrasound in obstetrics & gynecology*, 2013. **42**(4): p. 400-408.
 17. Group, G.S., *A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation*. *BJOG: an international journal of obstetrics and gynaecology*, 2003. **110**(1): p. 27-32.
 18. Pels, A., et al., *Early-onset fetal growth restriction: A systematic review on mortality and morbidity*. *Acta obstetrica et gynecologica Scandinavica*, 2020. **99**(2): p. 153-166.
 19. Gomella, T.L., M.D. Cunningham, F.G. Eyal, and D.J. Tuttle, *Neonatology: management, procedures, on-call problems, diseases, and drugs*. 2013: McGraw-Hill Education Medical New York, NY.
 20. Clausson, B., J. Gardosi, A. Francis, and S. Cnattingius, *Perinatal outcome in SGA births defined by customised versus population-based birthweight standards*. *British Journal of Obstetrics and Gynaecology*, 2001. **108**(8): p. 830-834.
 21. Michaeli, J., et al., *Application of Prospect Theory in Obstetrics by Evaluating Mode of Delivery and Outcomes in Neonates Born Small or Appropriate for Gestational Age*. *JAMA Network Open*, 2022. **5**(3): p. e222177-e222177.
 22. Nakling, J. and B. Backe, *Adverse obstetric outcome in fetuses that are smaller than expected at second trimester routine ultrasound examination*. *Acta obstetrica et gynecologica Scandinavica*, 2002. **81**(9): p. 846-851.
 23. Fox, N., M. Huang, and S. Chasen, *Second-trimester fetal growth and the risk of poor obstetric and neonatal outcomes*. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 2008. **32**(1): p. 61-65.
 24. Larkin, J.C., S.P. Chauhan, and H.N. Simhan, *Small for gestational age: the differential mortality when detected versus undetected antenatally*. *American Journal of Perinatology*, 2017. **34**(04): p. 409-414.
 25. Lubrano, C., et al., *Perinatal and Neonatal Outcomes in Fetal Growth Restriction and Small for Gestational Age*. *Journal of Clinical Medicine*, 2022. **11**(10): p. 2729.
 26. Rocha, G., et al., *Small for gestational age very preterm infants present a higher risk of developing bronchopulmonary dysplasia*. *Journal of neonatal-perinatal medicine*, 2019. **12**(4): p. 419-427.
 27. Kovo, M., et al., *Pregnancy outcome and placental findings in pregnancies complicated by fetal growth restriction with and without preeclampsia*. *Reproductive Sciences*, 2015. **22**(3): p. 316-321.
 28. Marconi, A.M., et al., *Comparison of fetal and neonatal growth curves in detecting growth restriction*. *Obstetrics and gynecology*, 2008. **112**(6): p. 1227.
 29. Monier, I., et al., *Fetal and neonatal outcomes of preterm infants born before 32 weeks of gestation according to antenatal vs postnatal assessments of restricted growth*. *American journal of obstetrics and gynecology*, 2017. **216**(5): p. 516. e1-516. e10.
 30. Cooke, R.W., *Conventional birth weight standards obscure fetal growth restriction in preterm infants*. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 2007. **92**(3): p. F189-F192.
 31. Sacchi, C., et al., *Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis*. *JAMA pediatrics*, 2020. **174**(8): p. 772-781.
 32. Lees, C., et al., *Clinical Opinion: the diagnosis and management of suspected fetal growth restriction: an evidence-based approach*. *American journal of obstetrics and gynecology*, 2022.
 33. Meher, S., E. Hernandez-Andrade, S. Basheer, and C. Lees, *Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review*. *Ultrasound in Obstetrics & Gynecology*, 2015. **46**(4): p. 398-404.
 34. Bullough, S., K. Navaratnam, and A. Sharp, *Investigation and management of the small for gestational age fetus*. *Obstetrics, Gynaecology & Reproductive Medicine*, 2021. **31**(1): p. 1-7.
 35. Oros, D., et al., *Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses*. *Ultrasound in obstetrics & gynecology*, 2011. **37**(2): p. 191-195.
 36. Savchev, S., et al., *Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices*. *Ultrasound in Obstetrics & Gynecology*, 2012. **39**(3): p. 299-303.
 37. Chatzakis, C., et al., *Perinatal outcome of appropriate-weight fetuses with decelerating growth*. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2021. **34**(20): p. 3362-3369.
 38. Figueras, F. and E. Gratacos, *Stage-based approach to the management of fetal growth restriction*. *Prenatal diagnosis*, 2014. **34**(7): p. 655-659.
 39. Ott, W.J., *Sonographic diagnosis of fetal growth restriction*. *Clinical obstetrics and gynecology*, 2006. **49**(2): p. 295-307.
 40. Figueras, F. and E. Gratacós, *Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol*. *Fetal diagnosis and therapy*, 2014. **36**(2): p. 86-98.
 41. Gardosi, J., et al., *Maternal and fetal risk factors for stillbirth: population based study*. *Bmj*, 2013. **346**.