TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 16
Number 2 *Spring 2023*

23-29

2023

Improving the Prediction and Management of Intrauterine Growth Restriction

Shulamis Sadowsky

Improving the Prediction and Management of Intrauterine Growth Restriction

Shulamis Sadowsky

Shulamis Sadowsky will graduate with a Bachelor of Science degree in Honors Biology in June 2023

Abstract

Intrauterine growth restriction (IUGR) is a potentially fatal and often missed obstetric complication. The fetus is deprived of vital blood, oxygen, and nutrients due to faulty maternofetal circulation, leading to a severe lack of fetal growth. Since current prenatal testing is highly ineffective at diagnosing the condition, many babies with IUGR are negatively impacted before, during, and after birth. This paper assesses alternative and innovative detection and management methods of IUGR. Current routine prenatal care includes simple fundal height measurements to screen for IUGR. This analysis finds that other testing may increase the rate of detection of the disease. Maternal serum analytes, uterine artery dopplers, and fetal heart rate analysis all provide relatively small rates of detection. However, due to their non-invasive nature, they offer the option of taking a multipronged testing approach to increase the chance of an IUGR pregnancy being properly diagnosed and managed. Possible management includes aspirin and early delivery; however, this analysis does not find a consistently positive effect for either of these options, despite the pathology of the disease suggesting that these approaches would improve outcomes. More research is needed to find optimal diagnostic testing and treatment for intrauterine growth restriction.

Introduction

Intrauterine Growth Restriction (IUGR) is a condition in which there is abnormal or impaired growth of the fetus inside the uterus that is due to a pathological cause. The growth of the fetus in the womb is a significant predictor for the outcome of the pregnancy. Low-weight fetuses are at a greater risk of intrauterine injury and death. An astounding 50% of stillbirths have been found to fit the criteria for IUGR. For pregnancies that result in liveborn infants, the detection of fetal growth restriction is abysmal, with as many as 85% of IUGR cases going undetected until delivery (Albu et al., 2014).

Ideal fetal growth is allowed by placental ability to handle injury caused by outside stimuli. In IUGR, the placenta shows abnormal maternal spiral arterioles, dysregulated villous vasculogenesis, and profuse fibrin deposition. Regardless of the cause for these abnormalities, the villi of the trophoblasts show severe injury to the epithelium and stress to the endoplasmic reticulum, leading to a lack of regulation. The escalating stages of placental dysfunction that develop through the pregnancy, as the IUGR diagnosis surfaces, eventually leads to a reduction of blood flow and limitation of nutrient transfer to the fetus (Scifres and Nelson, 2009).

Currently, the main method of detection of IUGR includes fundal height measurements at prenatal visits, with abnormal findings indicating the need for biometric testing, which uses specific formulas to estimate fetal weight based on general fetal growth curves. Primary management of IUGR is limited to monitoring fetal well-being at specific intervals, and, when fetal risks are greater than neonatal risks, intervening by administering steroids and delivering the fetus at a hospital that is equipped to deal with a seriously ill neonate (Militello et al., 2009).

New research suggests other methods of predicting IUGR, potentially improving outcomes of pregnancies afflicted with fetal growth restriction. This paper will analyze the different approaches and explore their effectiveness in improving disease management.

Materials and Methods

Research on detection methods for intrauterine growth restriction was obtained from peer-reviewed scientific articles and academic journals. These were accessed via Touro University Library as well as Google Scholar, using various databases including PubMed, ProQuest, and Ebsco. The main keywords and phrases used to obtain research data for the paper include "IUGR pathology," "IUGR testing," "IUGR treatment," and "IUGR neonatal outcomes."

Placental Pathology

The most common cause of IUGR is dysfunctional maternal-fetal circulation (Vandenbosche and Kirchner, 1998). The development of the placenta to support and nourish the fetus throughout gestation is a complex process involving the formation of an entirely new uteroplacental circulation. A fetus's growth can be restricted due to faulty development of the uteroplacental circulation. The fetus is deprived of vital nutrients and oxygen, causing its failure to reach its growth potential (Albu et al., 2014).

Placental exchange is controlled by a complicated interaction between placental growth, rates of blood flow through the placenta, expression of transporter proteins, and metabolic needs of placental tissue. This interaction is regulated by hormones from the mother, fetus, and the placenta. When operating properly, this system allows for an adequate flow of blood, oxygen, and nutrients to the fetus. Humans have hemochorial placentas, with a limited cellular barrier separating the mother's blood from the blood of the fetus. The deep trophoblast invasion poses risks for developing placental complications during pregnancy, such as IUGR (Burton and Fowden, 2015).

A study of 69 placentas, with 45 of them from pregnancies complicated by IUGR (birth weight <10th percentile), and 24 of them from uncomplicated pregnancies with fetuses

who were average for gestational age (AGA), showed certain abnormalities in the placentas of IUGR fetuses. There was increased decidual vasculopathy, infarct, increased syncytial knots, villous fibrosis, and more extensive deposition of perivillous fibrin. Additionally, the placentas of IUGR-complicated pregnancies were considerably lower weights than the placentas from uncomplicated pregnancies. These findings suggest the main disease processes that are associated with placental pathology of intrauterine growth restriction. Included in those findings are chronic uteroplacental insufficiency and abnormal uteroplacental vasculature, coagulation pathologies of the fetoplacental, intervillous, and uteroplacental vasculature, as well as chronic inflammatory lesions. Ultimately, the fetus is deprived of adequate blood flow, causing the low birth weight that is characteristic of IUGR (Park et al., 2002).

Fundal Height Measurement

Current screening and surveillance protocols for intrauterine growth restriction in low-risk pregnancies include obtaining a thorough medical and obstetric history and measuring the fundal height at each prenatal visit after 24 weeks. The threshold determined by the American College of Obstetricians and Gynecologists as an indication of IUGR is a discrepancy of at least 3 between gestational age in weeks and measurement of fundal height in centimeters (ACOG practice bulletin).

The reliability of this measurement as a predictive tool is questionable, with research showing low effectiveness. A large study evaluated the efficacy of fundal height measurements as a predictive tool. There are two methods of using fundal height to predict IUGR. The first is looking at a single value of fundal height, however, this method is very inaccurate. In this study, they found that it has low sensitivity, ranging from 0 to 52% from weeks 22 to 35. The other option is to observe the measurements over a period of time during the pregnancy. This method also had low predictive value, detecting only 56% of IUGR pregnancies, even when looking at values through the full gestational period. The results also indicated an unacceptably high rate of false positives (Rosenberg et al., 1982). Therefore, this examination that is routinely performed at prenatal visits can easily miss a large percentage of IUGR cases, increasing the risk of neonatal morbidity and mortality.

Serum Markers

Maternal serum analytes have been examined to assess their role in the detection of IUGR. Two important analytes which have been studied in relation to IUGR and other pregnancy complications are free beta human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A) (Ong et al., 2000). Beta hCG has an important role in placental development by stimulating vasculogenesis and angiogenesis. These provide the placenta with sufficient blood flow from the mother and adequate nutrition for the embryo while the uterine endometrium is invaded (Gridelet et al., 2020). PAPP-A, a protein secreted by syncytial trophoblasts, enters circulation following implantation of the blastocyst. The protein releases insulin-like growth factor (IGF) by cleaving IGF binding protein. The released IGF participates in cell differentiation, multiplication, and trophoblast invasion. Therefore, it is important for the development of the placenta. Additionally, IGF also controls the absorption of amino acids and glucose, thus directly impacting the growth of the fetus (Shah et al., 2020).

Due to the important roles that β-hCG and PAPP-A play in placental and fetal development, it would be reasonable to suggest that a decrease in their levels may predict intrauterine growth restriction, even at an early stage. A screening study performed at antenatal clinics measured levels of both maternal serum analytes between 10 and 14 weeks gestation. The levels were then compared, based on the ultimate outcomes of the pregnancies. Approximately 20% of the pregnancies that resulted in complications including IUGR, had levels of PAPP-A that were below the 10th percentile of the reference range. About 15% of complicated pregnancies, including those which developed IUGR, showed □-hCG levels below the 10th percentile of the reference range (Ong et al., 2000).

Of note, a much larger study consisting of 4390 pregnancies showed conflicting results to the previous study. Between weeks 11 and 13 of these pregnancies, the mothers' PAPP-A and □-hCG markers were checked. In the 172 pregnancies which ultimately developed fetal growth restriction, their PAPP-A levels were significantly lower. However, their □-hCG levels were not significantly lower, making the results of the previous study questionable, particularly due to its small sample size (Spencer et al., 2005). Others also concluded that abnormal levels of □-hCG are not as reliable as PAPP-A in predicting adverse pregnancy outcomes, including IUGR (Gaccioli et al., 2018).

Other markers have been studied due to their roles in placentation, with varying results. Angiogenic factors are key elements in the uterus's vasculature remodeling during pregnancy. Certain placental products with proangiogenic and antiangiogenic properties are secreted and regulated to ensure ideal placentation and to allow for ideal development and growth of the fetus (Gaccioli et al., 2018). Placental growth factor (PlGF), an important proangiogenic protein that supports fetoplacental circulation, is secreted by the placenta throughout the entire

pregnancy. PlGF is detectable in maternal serum, where it affects the well-being of the endothelium. An increased risk of developing IUGR has been observed in pregnancies with low levels of this protein in the first trimester. (Romero et al., 2008, and Karagiannis et al., 2011). For antiangiogenic factors, there has not been consistent findings regarding their predictiveness of IUGR. When maternal serum levels of soluble endoglin (sENG) were high in the first trimester, it seemed to indicate an association with IUGR. However, for another antiangiogenic factor, soluble fms-like tyrosine kinase-1 (sFLT1), the opposite was true. Low levels of sFLT1 indicated a greater risk of developing FGR (Smith et al., 2007). Proangiogenic factors seem more promising than antiangiogenic factors in showing a consistent relationship with the presence of IUGR.

Ultrasound Markers

An alternate method of non-invasively surveying the development of the placenta and assessing blood flow to the fetus involves utilizing ultrasound technology. Maternal-fetal blood flow interactions are assessed by using uterine artery doppler (UAD). A study involving a large number of participants was conducted to assess the ability of UAD to predict the onset of IUGR. Included in the study were 3,010 singleton pregnancies. Of these pregnancies, 565 of them delivered SGA (small for gestational age) neonates (<10th percentile). They looked at resistance indices and the prevalence of bilateral notching in abnormal versus normal pregnancies during weeks 11 to 14. Both of these measurements can indicate resistance to blood flow which is an important factor in IUGR. In women whose pregnancies resulted in SGA neonates, their resistance indices were found to be considerably higher than what was seen in healthy pregnancies (median uterine artery RI, 0.74 vs. 0.70). Additionally, there was a higher incidence of bilateral notching in the abnormal pregnancies. The study discovered that the mean uterine artery resistance index decreased as gestational age at the time of delivery increased, with a statistical significance of P = 0.01. This study shows very promising results for using early ultrasound to predict the development of IUGR (Melchiorre et al., 2009).

Another study took a different approach to the utilization of uterine artery dopplers to predict the development of IUGR and other adverse outcomes. Rather than look at ultrasound findings from a single period, they examined trends in the dopplers and assessed their association with pregnancy outcomes. A cohort of 870 pregnancies underwent ultrasound evaluation during the first trimester (11-14 weeks), which was then followed in the second trimester (19-22 weeks) by repeat evaluation. The trend seen within the two intervals was a significant linear decrease of mean uterine artery pulsatility indices. A decrease in the prevalence of bilateral notching was only seen during weeks 11-13 of the first trimester. With continued follow-up, it was found that 37 (4.25%) of the pregnancies subsequently developed IUGR. When retroactively comparing these pregnancies UAD's with pregnancies that had normal outcomes, it was found that the complicated pregnancies had considerably higher average pulsatility indices and a greater occurrence of bilateral notching in both intervals studied. Further comparison showed that in complicated pregnancies more than in uncomplicated pregnancies, the bilateral notching persisted (30% vs. 8%), abnormal first-trimester pulsatility indices shifted to normal in the second trimester (14% vs. 4%), and normal first-trimester pulsatility indices became abnormal in the second trimester (13% vs. 4%). The study was able to find an association between these UAD findings and the level of risk for the development of adverse outcomes. Pregnancies with persistent notching and/or shifting pulsatility indices from the first to the second trimester were associated with an intermediate risk of developing hypertensive disorders including IUGR. Pregnancies that showed unrelenting abnormally high pulsatility indices had the greatest risk for IUGR and other negative pregnancy outcomes (Gomez et al., 2006).

Both studies on the role of ultrasonography in the prediction of IUGR show comparable results. UAD's were significantly different in complicated pregnancies when compared with uncomplicated pregnancies. These abnormalities were already apparent in early pregnancy, during the first trimester. However, with low predictabilities, the test does not recognize a high percentage of subsequent IUGR cases. Thus, the usage of UAD allows for a non-invasive but not consistently reliable prediction method for the development of IUGR.

Fetal Heart Rate Analysis

Fetal heart rate is an easily measured predictor of fetal well-being. Starting from 28 weeks of gestation, a healthy fetus goes through periods of active sleep and quiet sleep, with changes in heart rate reflecting the fetus's state of sleep. During active sleep, there is an increase in fetal movement and a high heart rate variability. During the quiet sleep period, there is little fetal movement and low heart rate variability. An indicator of fetal well-being is a period of active sleep. A study was performed to determine whether fetal heart rate can be used as an early predictor of IUGR. Because of the impact that restricted blood flow has on a fetus, they presumed that the cardiovascular system, or more specifically the heart

rate, would be affected, thereby providing a marker for the condition. They utilized cardiotocography (cCTG) to measure fetal heart rate, and they used the Dawes/Redman automated system of interpretation. Included in the research was a group of 1,630 IUGR pregnancies and a group of 1,630 same-sex and gestational age healthy pregnancies. Both groups showed increased periods of activity at more advanced gestational ages. However, they made an important finding specific to the IUGR group. Before 35 weeks gestation, the IUGR fetuses showed a significantly lower percentage of active sleep when compared to the healthy fetuses. They showed a delayed or compromised sleep state organization, indicating a lack of maturation for their gestational ages. Based on their results, it seems that the quality of this risk marker is better earlier in gestation (24-34 weeks), since the gap narrowed after that point. Of note, the AUC was only 0.76. However, the study does provide evidence of the effectiveness of fetal heart rate analysis in the detection of IUGR (Stroux et al., 2017).

IUGR Management

Once IUGR is detected and further testing determines the extent of placental dysfunction and stress on the fetus, treatment can be initiated. One treatment that has been researched repeatedly is the use of aspirin to prevent or treat IUGR. Aspirin has been found to affect placental vasculature. It works by inhibiting the production of thromboxane A2 without impacting prostacyclin levels. This results in vasodilation as well as a reduction in platelet aggregation. Since the placental pathology in IUGR includes increased syncytial knots at the terminal villi which impedes blood flow to the fetus, aspirin can reduce the damage by increasing perfusion to the placenta (Ali et al., 2018).

A randomized controlled trial in Egypt was conducted to determine the impact of aspirin on fetal weight in cases of idiopathic asymmetrical IUGR with abnormal UAD indices. One group of women with this complication was given 75 milligrams of Aspirin daily for a period of 4 weeks. The second group diagnosed with IUGR and abnormal dopplers received no intervention. Results showed significant improvement in the group taking aspirin, specifically in regard to fetal weight. The resistance index and pulsatility index decreased in the aspirin group, indicating an improvement of blood flow to the fetus. In terms of neonatal outcomes, the group that received aspirin had higher APGAR scores, although it is worth noting that the number of admissions to the NICU was similar in both groups (Ali et al., 2018). In contrast to this study, a clinical trial conducted on 90 pregnant women showed contradicting results. These women were at an increased risk of developing IUGR due to previous histories of pre-eclampsia. Half of the women were given 80 milligrams of aspirin daily and the other half were given a placebo. The results of the study indicated that there was no statistically significant difference in the pregnancy outcomes, with an IUGR rate of 27.9% in the aspirin group, and 25.6% in the control group (Abdi et al., 2020). Currently, the American College of Obstetricians and Gynecologists believes that there is not enough evidence to support the use of aspirin in the treatment of IUGR. Of note, the first study that found aspirin beneficial for the prevention and treatment of IUGR had a large overlap between the standard deviation error bars, suggesting the possibility that the results are not truly statistically significant. The results showed an increase in fetal weight in the aspirin group (1745±201 gm) when compared to the control group (1534±36gm). However, despite a p-value <0.05, there is a significant overlap in these results, making the results less likely to represent an actual clinical improvement in cases of IUGR.

ACOG also does not recommend bed rest as a means to treat IUGR (ACOG Practice bulletin). This is in agreement with a study of 107 women with suspected fetal growth restriction who were split into a bed rest group and an ambulatory group. There was no evidence of improvement in the growth restriction or neonatal outcomes in the bed-rest group (Gulmezoglu & Hofmeyr, 2000).

Ultimately, the management of IUGR comes down to proper delivery timing to optimize neonatal outcomes. When the risk of a compromised uterine environment outweighs the risk of prematurity, delivery is indicated (ACOG Practice Bulletin). The Growth Restriction Intervention Trial assessed delivery timing for IUGR fetuses at gestational ages of less than 34 weeks. The study population included women carrying fetuses who had restricted growth, and their physicians were unsure whether early delivery would improve outcomes. They were divided randomly into 2 groups; the early delivery group delivered their babies within 48 hours of diagnosis, and the expectant management group underwent continued fetal monitoring until delivery couldn't be delayed anymore. There were equal rates of corticosteroid administration for fetal lung development in both groups. Both groups showed similar rates of death perinatally, as well as equal cognitive, behavior, motor, and language abilities seen in follow-up at 6 to 12 years. Preterm delivery did not significantly improve short and long-term outcomes in cases of IUGR (Walker et al., 2011). Another similar study was performed, but this study population included

women who were past 36 weeks gestation. The results were the same, with no benefit seen in early delivery when compared to the expectant management group (Boers et al., 2010).

Despite these findings, two suggestions are made by ACOG in cases of diagnosed IUGR: 1) in cases of isolated FGR, the fetus should be delivered at 38 0/7–39 6/7 weeks and 2) in cases of FGR complicated by other risk factors including abnormal dopplers and maternal risk factors, delivery should occur at 34 0/7–37 6/7 weeks (ACOG Practice Bulletin). Although the studies on delivery timing did not show significant improvement in outcomes with early delivery, the risk of stillbirth in IUGR fetuses, especially those with abnormal dopplers, is high. Therefore, the risk to the growth-restricted fetus in utero is considered higher than the risk of late prematurity.

If a growth-restricted fetus is at severe risk of negative outcomes prior to 34 weeks gestation, indicating the need for preterm delivery, certain steps can be taken to provide the best chance of a positive outcome. Firstly, the delivery should take place in a center that has a NICU, and a maternal-fetal medicine specialist should be consulted to ensure proper planning. Additionally, if IUGR has been diagnosed and subsequent fetal monitoring indicated the need for early delivery, corticosteroids should be given to the mother prior to delivery since it aids in fetal lung maturation, thereby improving neonatal outcomes (Roberts & Dalziel, 2006). If IUGR is not detected until the fetus is in distress, there may not be sufficient time to administer the corticosteroids, leading to an increased risk of neonatal respiratory distress.

Conclusion

The detection of intrauterine growth restriction at a point in pregnancy when proper management can still be initiated is low. Data suggests that aside from current methods, including fundal height measurements, there are other approaches which can improve the detection rate. Implementing a multipronged approach, including analyzing maternal serum analytes, observing uterine artery dopplers, and assessing fetal heart rate trends, can potentially improve the rate of early diagnosis of IUGR by a significant amount. Each method alone did not surpass current detection rates from fundal height measurements. However, by combining the three approaches along with current practices, more cases of IUGR can be detected, thus avoiding neonatal morbidity and mortality caused by late or missed diagnoses. None of the testing discussed in the paper poses any risk to the mother or fetus since they are non-invasive tests. Therefore, it may be a reasonable option to add testing during prenatal care to better predict cases of IUGR. If IUGR is detected, some research has shown that the administration of aspirin can improve outcomes. This would be expected based on the vascular pathology of IUGR and the mechanism of action of aspirin. However, due to conflicting data from reliable sources, more research is required to determine aspirin's effect on uteroplacental circulation. Finally, results of various studies have not shown expected improvement in outcomes with early delivery, yet ACOG continues to recommend the delivery of a high-risk IUGR fetus prematurely. It is reasonable to suggest that this is based on the assumption that the risk of prolonged impaired blood flow is too high, outweighing the relatively mild risks of late prematurity. However, more research must be conducted to ascertain the effectiveness of early detection methods and management protocols.

References

Abdi, N., Rozrokh, A., Alavi, A., Zare, S., Vafaei, H., Asadi, N., Kasraeian, M., & Hessami, K. (2020). The effect of aspirin on preeclampsia, intrauterine growth restriction and preterm delivery among healthy pregnancies with a history of preeclampsia. Journal of the Chinese Medical Association, 83(9), 852-857. 10.1097/JCMA.0000000000000400

ACOG Practice bulletin no. 134: fetal growth restriction. (2013). Obstetrics and Gynecology (New York. 1953), 121(5), 1122-1133. 10.1097/01.AOG.0000429658.85846.f9

Albu, A. R., Anca, A. F., Horhoianu, V. V., & Horhoianu, I. A. (2014). Predictive factors for intrauterine growth restriction. Journal of Medicine and Life, 7(2), 165-171. https://www.ncbi.nlm.nih.gov/pubmed/25408721

Ali, M. K., Abbas, A. M., Yosef, A. H., & Bahloul, M. (2018). The effect of low-dose aspirin on fetal weight of idiopathic asymmetrically intrauterine growth restricted fetuses with abnormal umbilical artery Doppler indices: a randomized clinical trial. The Journal of Maternal-Fetal & Neonatal Medicine, 31(19), 2611-2616. 10.1080/14767058.2017.1350160

Boers, K. E., Vijgen, S. M. C., Bijlenga, D., van der Post, J A M, Bekedam, D. J., Kwee, A., van der Salm, P C M, van Pampus, M. G., Spaanderman, M. E. A., de Boer, K., Duvekot, J. J., Bremer, H. A., Hasaart, T. H. M., Delemarre, F. M. C., Bloemenkamp, K. W. M., van Meir, C. A., Willekes, C., Wijnen, E. J., Rijken, M., . . . Scherjon, S. A. (2010). Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). Bmj, 341(7787), 35. 10.1136/bmj.c7087

Burton, G. J., & Fowden, A. L. (2015). The placenta: a multifaceted, transient organ. Philosophical Transactions of the Royal Society B: Biological Sciences, 370(1663)10.1098/rstb.2014.0066

Gaccioli, F., Aye, I. L. M. H., Sovio, U., Charnock-Jones, D. S., & Smith, G. C. S. (2018). Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. American Journal of Obstetrics and Gynecology, 218(2), S725-S737. 10.1016/j.ajog.2017.12.002

Gómez, O., Figueras, F., Martínez, J. M., del Río, M., Palacio, M., Eixarch, E., Puerto, B., Coll, O., Cararach, V., & Vanrell, J. A. (2006). Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. Ultrasound in Obstetrics & Gynecology, 28(6), 802-808. 10.1002/uog.2814

Gridelet, V., Perrier d'Hauterive, S., Polese, B., Foidart, J., Nisolle, M., & Geenen, V. (2020). Human Chorionic Gonadotrophin: New Pleiotropic Functions for an "Old" Hormone During Pregnancy. Frontiers in Immunology, 11, 343. 10.3389/fimmu.2020.00343

Gulmezoglu, A. M., & Hofmeyr, G. J. (2000). Bed rest in hospital for suspected impaired fetal growth. The Cochrane database of systematic reviews. Retrieved from https://pubmed.ncbi.nlm.nih.gov/10796093/

Karagiannis, G., Akolekar, R., Sarquis, R., Wright, D., & Nicolaides, K. H. (2011). Prediction of Small-for-Gestation Neonates from Biophysical and Biochemical Markers at 11–13 Weeks. Fetal Diagnosis and Therapy, 29(2), 148-154. 10.1159/000321694

Melchiorre, K., Leslie, K., Prefumo, F., Bhide, A., & Thilaganathan, B. (2009). First-trimester uterine artery Doppler indices in the prediction of small-for-gestational age pregnancy and intrauterine growth restriction. Ultrasound in Obstetrics & Gynecology, 33(5), 524-529. 10.1002/uog.6368

Militello, M., Pappalardo, E. M., Ermito, S., Dinatale, A., Cavaliere, A., & Carrara, S. (2009). Obstetric management of IUGR. Journal of Prenatal Medicine, 3(1), 6-9. https://www.ncbi.nlm.nih.gov/pubmed/22439031

Ong, C. Y. T., Liao, A. W., Spencer, K., Munim, S., & Nicolaides, K. H. (2000). First trimester maternal serum free β human chorionic gonadotrophin and pregnancy associated plasma protein A as predictors of pregnancy complications. BJOG : An International Journal of Obstetrics and Gynaecology, 107(10), 1265-1270. 10.1111/j.1471-0528.2000.tb11618.x

Park, S.-Y., Kim, M. Y., Kim, Y. J., Chun, Y. K., Kim, H. S., Kim, H. S., & Hung, S. R. (2002, January 28). Placental pathology in intrauterine growth retardation. Retrieved from https://jpatholtm.org/upload/pdf/kjp-36-1-30.pdf

Roberts, D., & Dalziel, S. (2006). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database of Systematic Reviews, (3)10.1002/14651858.CD004454.pub2

Romero, R., Nien, J. K., Espinoza, J., Todem, D., Fu, W., Chung, H., Kusanovic, J. P., Gotsch, F., Erez, O., Mazaki-Tovi, S., Gomez, R., Edwin, S., Chaiworapongsa, T., Levine, R. J., & Karumanchi, S. A. (2008). A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. The Journal of Maternal-Fetal & Neonatal Medicine, 21(1), 9-23. 10.1080/14767050701830480

Rosenberg, K., Grant, J. M., Tweedie, I., Aitchison, T., & Gallagher, F. (1982). Measurement of fundal height as a screening test for fetal growth retardation. BJOG : An International Journal of Obstetrics and Gynaecology, 89(6), 447-450. 10.1111/j.1471-0528.1982.tb03634.x

Scifres, C. M., & Nelson, D. M. (2009). Intrauterine growth restriction, human placental development and trophoblast cell death. The Journal of Physiology, 587(14), 3453-3458. 10.1113/jphysiol.2009.173252

Shah, K. H., Anjum, A., Nair, P., Bhat, P., Bhat, R. G., & Bhat, S. (2020). Pregnancy associated plasma protein A: An indicator of adverse obstetric outcomes in a South India population. Journal of Turkish Society of Obstetric and Gynecology, 17(1), 40-45. 10.4274/tjod.galenos.2020.05695

Smith, G. C. S., Crossley, J. A., Aitken, D. A., Jenkins, N., Lyall, F., Cameron, A. D., Connor, J. M., & Dobbie, R. (2007). Circulating Angiogenic Factors in Early Pregnancy and the Risk of Preeclampsia, Intrauterine Growth Restriction, Spontaneous Preterm Birth, and Stillbirth. Obstetrics and Gynecology (New York. 1953), 109(6), 1316-1324. 10.1097/01.AOG.0000265804.09161.0d

Spencer, K., Yu, C. K. H., Cowans, N. J., Otigbah, C., & Nicolaides, K. H. (2005). Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free β-hCG and with second-trimester uterine artery Doppler. Prenatal Diagnosis, 25(10), 949-953. 10.1002/pd.1251

Stroux, L., Redman, C. W., Georgieva, A., Payne, S. J., & Clifford, G. D. (2017). Doppler-based fetal heart rate analysis markers for the detection of early intrauterine growth restriction. Acta Obstetricia Et Gynecologica Scandinavica, 96(11), 1322-1329. 10.1111/aogs.13228

Vandenbosche, R. C., & Kirchner, J. T. (1998). Intrauterine Growth Retardation. American Family Physician, 58(6), 1384-1390. https://www.aafp.org/pubs/afp/issues/1998/1015/p1384.html#:~:text=The%20condition%20is%20most%20commonly,trisomy%2021%20and%20trisomy%2018

Walker, D., Marlow, N., Upstone, L., Gross, H., Dr, Hornbuckle, J., Vail, A., Wolke, D., & Thornton, J. (. G.). (2011). The growth restriction intervention trial : long-term outcomes in a randomized trial of timing of delivery in fetal growth restriction. American Journal of Obstetrics and Gynecology, http://wrap.warwick.ac.uk/4569/