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ORIGINAL ARTICLE

Prediction of Fetal Growth Restriction by Ultrasonography and Biochemical Markers in Zagazig University Hospital

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ABSTRACT

Objectives: To measure the efficiency of combining clinical, biochemical markers, and doppler studies (uterine and umbilical arteries) as values to predict fetal growth restriction.
Methods: This randomized clinical cross-sectional research has been carried out at the ultrasound unit in the Department of Obstetrics and Gynecology and the laboratory unit, Faculty of Medicine, Zagazig University between 2017 and 2021.
Results: One hundred twenty-four pregnant women who visited the antenatal clinic at the Department of Obstetrics and Gynecology with suspected clinical criteria for FGR were included. In our study, the incidence of positive FGR in high-risk patients was 24.5%. Abnormal biochemical markers (PAPPA≤0.42 + Homocysteine ≥6.3) were 42.3% sensitive, 88.0% specific, and 70.8% accurate in the prediction of FGR. Also, a statistically significant relationship between FGR and uterine artery doppler is noted. However, a combination of uterine artery doppler (PI>1.57 + diastolic notching) and biochemical markers was 46.2% sensitive, 58.8% specific, and 55.7% accurate in the prediction of FGR. Finally, there is a highly statistically significant relationship between both FGR and umbilical artery Doppler at 29th–31st weeks.
Conclusions: The incorporated model of screening in this study can be a beneficial method to identify patients at increased risk of FGR. The best finding in this study is that a combination of uterine artery and umbilical artery doppler was 88.5% sensitive, 96.3% specific and 94.3% accurate in the prediction of FGR.
Keywords: Fetal Growth Restriction, Homocysteine, Pregnancy Associated Plasma Protein -A, Pulsatility index

INTRODUCTION

Impaired fetal growth is associated with a higher risk of perinatal mortality and morbidity, and adverse long-term infant outcomes [1]. Growth-restricted fetuses have a greater rate of conditions associated with prematurity [2], a worse neurodevelopmental outcome, and are at increased risk of non-transmissible diseases in adulthood, such as systemic hypertension, metabolic syndrome, insulin resistance, type-2 diabetes mellitus, ischemic heart disease, and cerebrovascular stroke [3].
Recently, Nohuz et al. [4] stated that prenatal documentation of fetal growth restriction (FGR) is the main factor in preventing stillbirth, up to 30% of FGR cases are small-for-gestational-age (SGA) in the third trimester. According to Lees et al. [5], early FGR is discovered at or beyond 32 weeks of pregnancy and differs from late-onset FGR in clinical manifestations, according to hypertension [5], placental dysfunction severity, and worsening features [6]. FGR is a complex condition that affects fetal development and is the leading cause of unfavorable perinatal outcomes. It is also the leading cause of long-term neurological risks. To date, there has been no clear medical approach to altering the course of FGR other than delivery [6].

Medical and obstetric history, as well as uterine artery doppler and maternal serum parameters, are regarded as crucial screening techniques for the early prediction of FGR, according to Baschat's results [7]. The uteroplacental Doppler, on the other hand, is the most reliable predictor of clinical worsening and delivery. Uterine artery doppler is a predictor of FGR, according to a recent systematic review and meta-analysis, with a more precise prediction when acquired in the second trimester than in the first trimester [7].

Several studies have found that some maternal biochemical markers (e.g., inhibin A, pregnancy-associated plasma protein-A, alfa-fetoprotein, and human chorionic gonadotropin) are primarily related to both placental function and fetal growth, and their quantities are distorted in SGA and FGR pregnancies [8].

The combination of uterine artery doppler and biochemical markers might enhance SGA fetus prediction greatly, although the predictive values are still low. Sequence testing in the second trimester appears to be more effective than screening in the first trimester in predicting placental insufficiency and its associated deleterious effects [9].

Flood et al. [10] documented that both early- and late-onset FGR vary significantly in clinical evolution because they represent two distinctive clinical phenotypes of placental dysfunction. Early-onset FGR results in higher umbilical artery blood flow resistance when villous damage exceeds 30%, leading to high-resistance uteroplacental perfusion. Moreover, late-onset FGR is common and less severe where the umbilical artery doppler may be normal with mild or even absent placental abnormalities. However, fetuses may change with decreased middle cerebral artery (MCA) resistance because of significant hypoxemia, according to Figueras and Gratacos [11].

The Royal College of Obstetricians and Gynecologists (RCOG) has recommended the use of umbilical artery Doppler in high-risk patients to demonstrate its value in reducing perinatal morbidity and mortality because it provides critical diagnostic and prognostic information for proper FGR management [12]**.** Because umbilical artery flow specifies distinct stages of compromised placental functioning, it might be the major surveillance method in fetuses with SGA. As a result, fetal deterioration with decreased blood flow is associated with absent or reversed end-diastolic flow (AEDF or REDF). Clinical emphasis should be done on EFW, gestational age, and fetal Doppler while assessing the FGR fetus. Theoretically, fetal can survive outside the uterus when EFW is above 500 grams. Moreover, EFW below the 3rd centile is considered predictive of adverse outcomes [12].

The aim of this study was to measure the efficiency of combining clinical, biochemical markers, and doppler studies (uterine and umbilical arteries) as values to predict fetal growth restriction.

METHODS

I. Technical Design:

Study design:

In the interval between 2017 and 2021, this cross-sectional study has been conducted in the ultrasound unit of the Department of Obstetrics and Gynecology in collaboration with the laboratory unit at the Faculty of Medicine at Zagazig University. The study protocol was approved by the research ethics committee of the Faculty of Medicine at Zagazig University. The study was done according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Sample size:

Assuming that the success rate of prediction of FGR by all parameters is 64%, the success rate of FGR by traditional methods is 5 %, using EPI-INFO version 6 (Atlanta, GA, USA), with power 80% and CI 95%. This study included 124 pregnant women, representing all cases attended during the period between 2017 and 2021, who met at least two of the inclusion criteria and visited the antenatal clinic in the Obstetrics and Gynecology Department. Eighteen cases were missed during follow-up, so the total number of cases is 106.

Patients:

This study finally included 106 pregnant women who attended the antenatal clinic of the Department of Obstetrics and Gynecology. Written informed consent was obtained from all participants. The patients were enrolled when at least two of the following clinical criteria for suspected FGR were present: The clinical criteria are maternal risk factors (maternal age >40 years, smokers, and dugs misuse), previous obstetric history (previous SGA: patients with baby birth weight of <10th centile, and previous stillbirth), and maternal medical history (chronic hypertension, diabetes mellitus, renal impairment, and antiphospholipid syndrome). Patients aged under 18 years and patients who refused to give informed consent were excluded from this study. Patients who have multiple pregnancies, known abnormal karyotype, or major fetal structural

abnormalities are known to be lethal at enrolment were also excluded.

II. Operational design:

Patients were subjected to four visits in this study.

1st visit: At their first antenatal care visit, patients who met at least two of the inclusion criteria were selected from the outpatient antenatal clinic at the Zagazig University Hospital**.** Participants were asked about their age, parity, and family history of chronic illnesses, and smoking status. The BMI was computed by dividing the weight in kilos by the height in meters squared. The day of the last menstrual cycle was used to determine gestational age (GA), which was validated by first-trimester ultrasonography.

Maternal serum markers [pregnancy-associated plasma protein-A (PAPPA) and homocysteine (Hcy)] were assessed at 11–14 weeks of gestation. Whole blood is collected via venipuncture, then it is allowed to be clotted for 10-20 minutes at room temperature, then it is centrifuged at 1200 xg for 10 minutes, and the serum is collected carefully. PAPPA and Hcy were measured by enzyme-linked immunosorbent assay (ELISA) kits (Figure 1). The standard curve was created from the concentrations of the standards and their corresponding OD values. The sample's OD value is then substituted to compute its concentration.

2nd visit: The initial obstetric ultrasound scan was done to document the gestational age and number of fetuses, in order to exclude multiple gestation and fetuses with malformations. Uterine artery doppler waveforms were done at 18 – 20 weeks. We used an abdominal probe on the lower lateral border of the uterus. The average of three consecutive waveforms was obtained for the pulsatility index (PI) for each uterine artery, then the mean PI from both uterine arteries was calculated. If the mean PI was more than 1.45, the flow velocity waveforms were deemed abnormal.

3rd visit: Doppler waveforms of the umbilical artery were taken at 26-28 weeks. The umbilical artery doppler was taken at a free loop of the cord, and the velocimetry was measured in the absence of fetal movement or uterine contraction. The doppler parameters for both the uterine and umbilical arteries were generated by automatic/manual tracing of the waveforms. The average and mean of three successive waveform values were recorded. The systolic-diastolic ratio (S/D), the RI, the PI, and the end-diastolic velocity (EDV) were all recorded. Abnormal umbilical artery waveform signs were taken as any of the following criteria: reduction in end-diastolic flow [absent end-diastolic flow (AEDF) or reversal of end-diastolic flow (REDF)], raised RI > 0.72, raised PI > 1.42 above two standard deviations (SDs) above the mean for GA, and S/D ratio >4.52.

Lastly, at the 4th visit, fetal weight (EFBW) was measured and umbilical doppler done at 29–31 weeks to detect early onset FGR (according to EFBW, AC below the 3rd percentile).

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 15 for Windows® was used to gather and analyse data (SPSS Inc, Chicago, IL, USA). Numbers and percentages were used to portray qualitative data. The Kolmogrov-Smirnov test was used to check for normalcy in quantitative data. The mean and SD were used to represent normally distributed data. It was statistically significant if the p-value was less than 0.05.

RESULT

The incidence of positive FGR was 24.5% and negative in 75.5% of cases (Figure 2). Maternal risk factors among the study participants were evaluated. Figure 3 showed that the most frequent maternal risk factors among the study participants were hypertension (53.8%), diabetes mellitus (46.2%), and smoking (10.4%). There is a statistically significant association between FGR and some maternal risk factors in the study participants. Previous fetal growth retardation, kidney disease, and smoking were associated with increased FGR risk. A positive history of either previous FGR, kidney disease, or smoking was 76.9% sensitive, 85.4% specific, and 51.9% accurate in predicting FGR.

Figure 4 showed that the mean ± SD of PAPP-A was 0.61 ± 0.31 mmol/L. Our study shows that there is a statistically significant association between FGR and PAPP-A among participants. Abnormal PAPP-A (≤0.42) was associated with high FGR risk. Figure 5 showed that the mean ± SD of Hyc was 5.5 ± 1.4 mmol/L. Also, abnormal serum markers (PAPP-A≤0.42+ Hcy≥6.3) were 42.3% sensitive, 88.0% specific, and 70.8% accurate in the prediction of FGR.

Figure 6 showed that the mean ± SD of the pulsatility index of the uterine artery was 1.72 ± 0.48. However, abnormal uterine artery doppler (PI>1.57 + diastolic notching) was 34.6% sensitive, 58.8% specific, and 52.8% accurate in the prediction of FGR. But the combination of uterine artery doppler and serum markers improved the result with 46.2% sensitivity, 58.8% specificity, and 55.7% accuracy in the prediction of FGR. Our study shows that there is a highly statistically significant association between IUGR and umbilical artery doppler at 29–31 weeks of gestation in the study participants. Finally, a

combination of uterine artery doppler and umbilical artery doppler was 88.5% sensitive, 96.3% specific, and 94.3% accurate in the prediction of FGR.

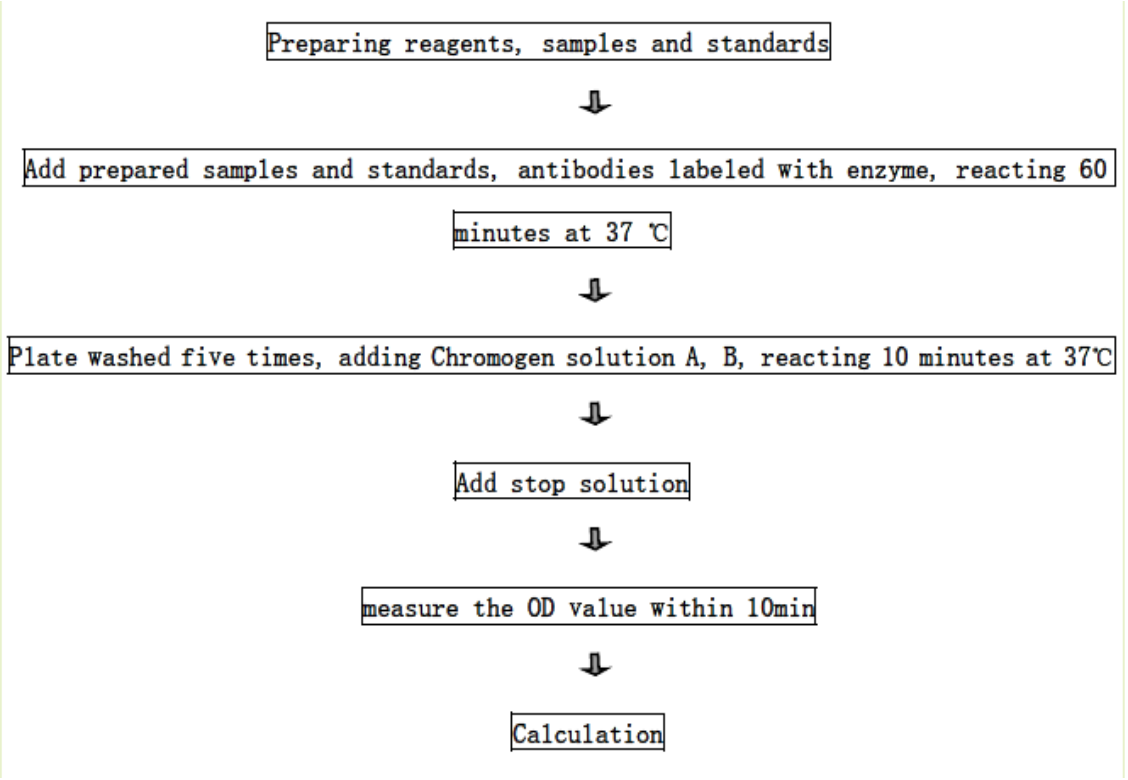

Figure 1: Summary of ELISA procedure

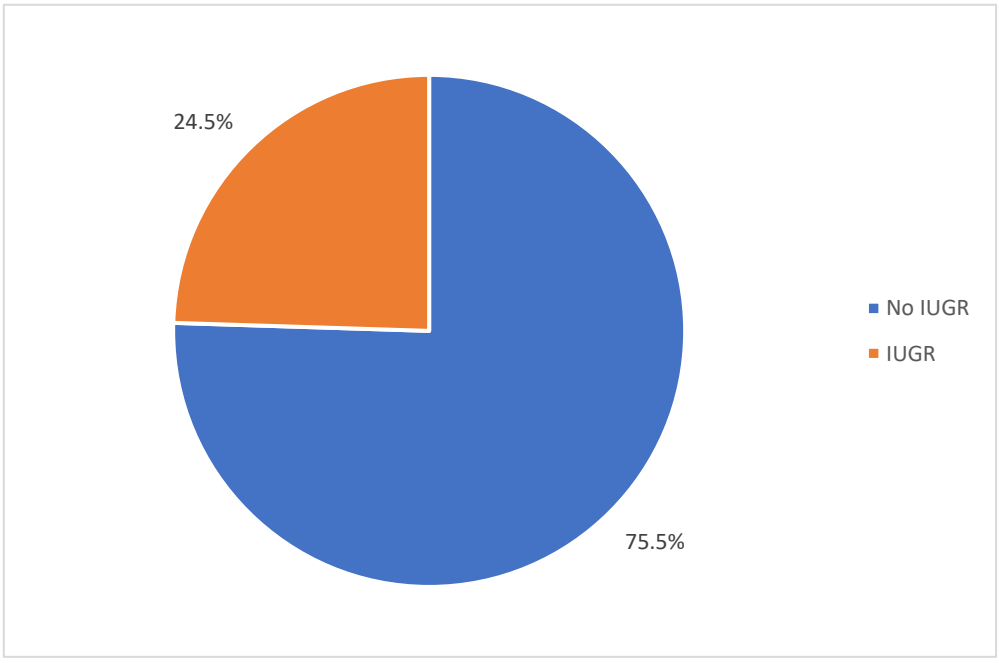

Figure 2: Incidence of IUGR in the study participants

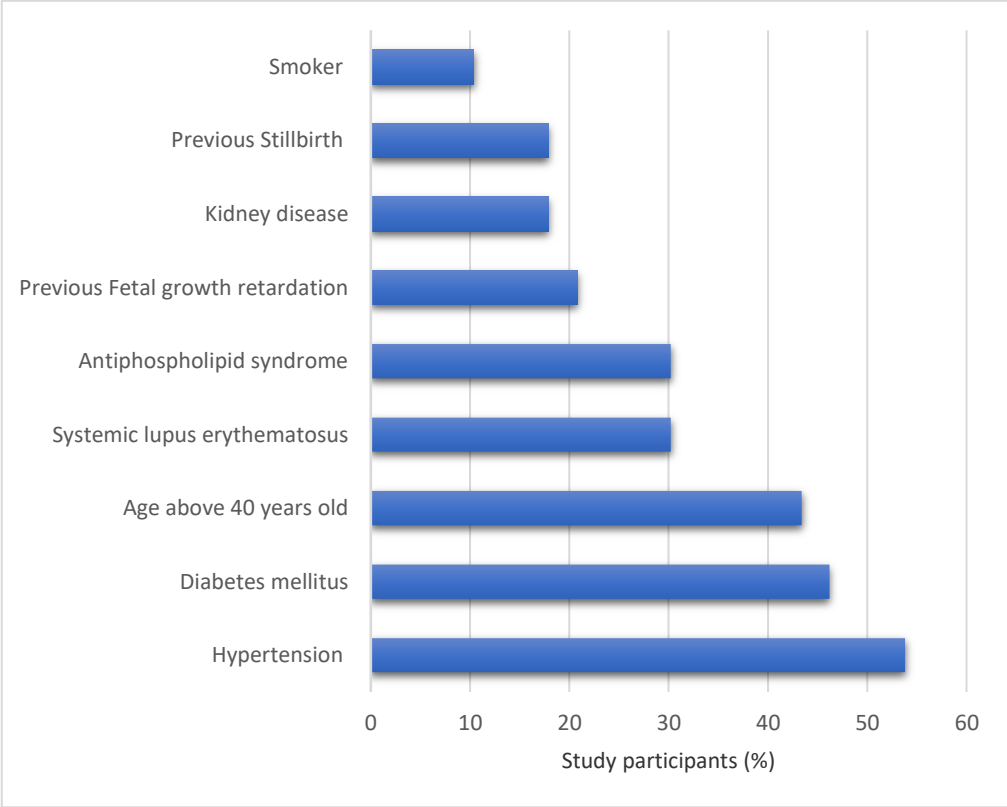

Figure 3: Maternal risk factors among the study participants

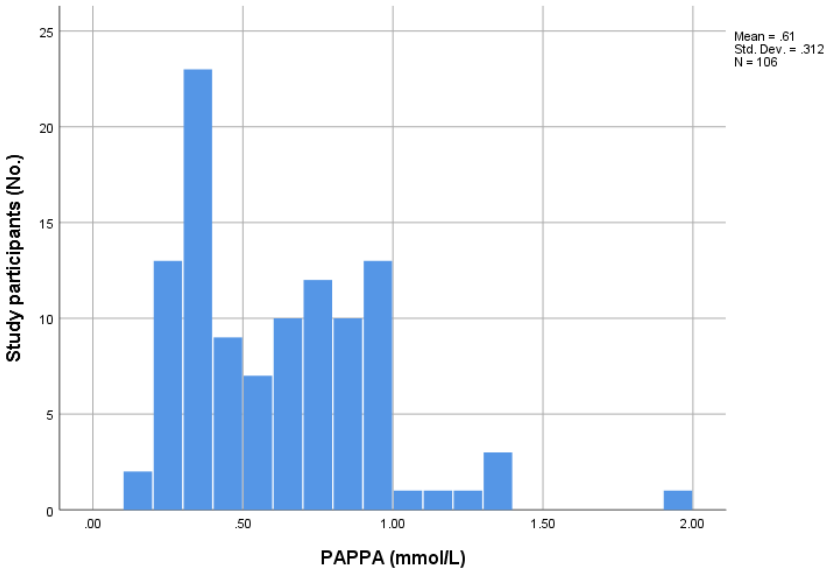

Figure 4: Serum PAPP-A in the study participants

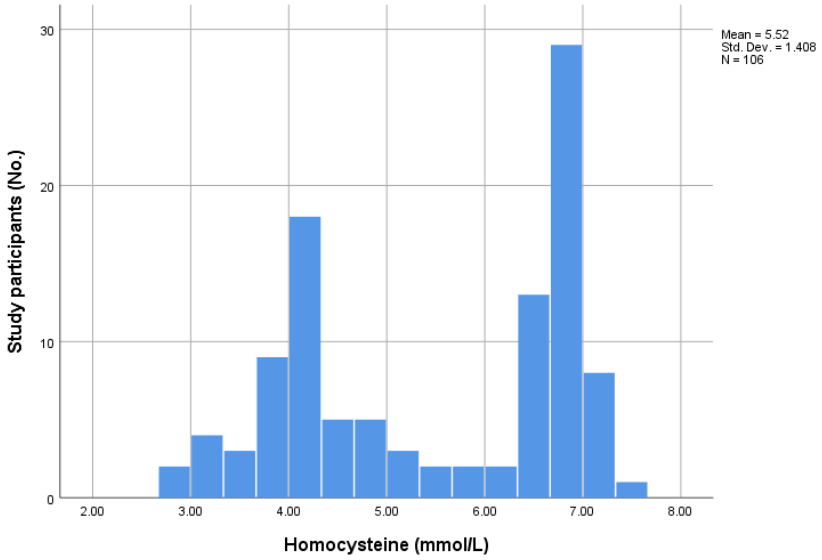

Figure 5: Serum homocysteine in the study participants

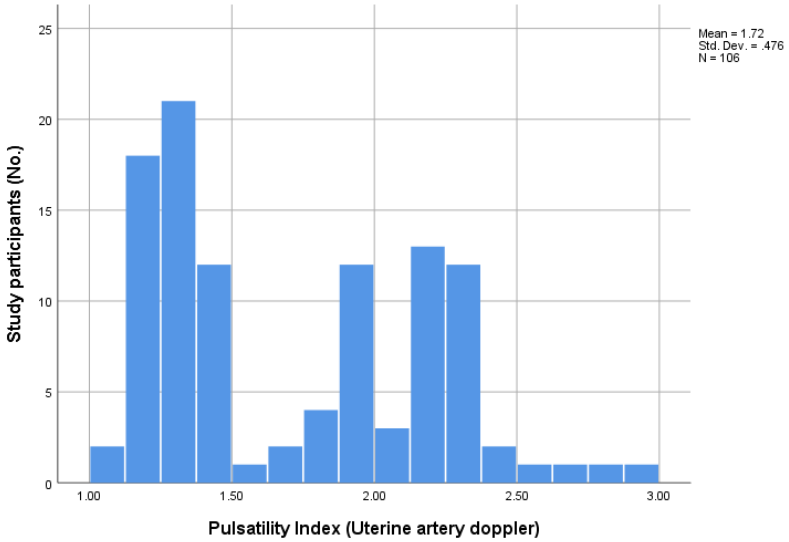

Figure 6: Uterine artery doppler in the study participants

DISCUSSION

It was pointed out that precise prediction of negative pregnancy outcomes is an important aspect of good obstetric care. Doppler indices have recently been identified as important strategies for predicting poor pregnancy outcomes in recent research. Our research aimed to determine elements of suspicion that could help predict early-onset FGR fetuses in high-risk pregnancy, which have serious problems during pregnancy and labour, by correlating patients' medical histories with biochemical markers (Hcy, and PAPP-A) and Doppler measurements detectable in the second trimester of pregnancy, either alone or in combination.

The aim of our study was to examine the role of Hcy, and PAPP-A detection in 11–14-week gestation (1st visit) in predicting FRG. Furthermore, we evaluated the ability of second-trimester uterine Doppler indices (2nd visit) to predict FGR among high-risk women. In addition, early evaluation of umbilical Doppler was performed in high-risk patients at both 26-28 weeks gestation (3rd visit) and follow-up at 29-31 weeks gestation (4th visit).

Interestingly, the current study revealed that the combination of both uterine artery doppler and biochemical markers was 46.2% sensitive, 58.8% specific, and 55.7% accurate in predicting FGR. Also, there was a highly statistically significant

association between FGR and umbilical artery doppler at 29-31 weeks. Of note, a combination of uterine and umbilical artery doppler indices was 88.5% sensitive, 96.3% specific, and 94.3% accurate in predicting FGR.

Generally, FGR affects 3% to 10% of normal pregnancies. However, in the present study, the prevalence of FGR in clinically suspected cases of FGR was documented in 24.5% of high-risk patients. In accordance with our study, using a similar research methodology as ours, Chanprapaph et al. [13] reported FGR prevalence of 50.9 percent. This greater incidence of FGR in the current study might be explained by the fact that the participants had previously been diagnosed as clinically suspected FGR cases, and a higher prevalence of FGR among these clinically suspected FGR patients is already known.

In our study, the most frequent maternal risk factors among participants were hypertension (53.8%), followed by diabetes mellitus (46.2%), age above 40 years old (43.4%), systemic lupus erythematosus (30.2%), and antiphospholipid syndrome (30.2%). Moreover, our study documented a statistically significant association between FGR risk and some maternal risk factors such as previous FGR (total n. of cases 22) (FGR with previous FGR n. 12 → 59.1%), kidney disease (total n. of cases 19) (FGR with kidney disease n. 8 → 42.1%), and smoking (total n. of cases 11) (FGR with smoking n. 7 → 63.6%), where the positive history of either previous fetal growth retardation, kidney disease, or smoking was 76.9% sensitive, 85.4% specific, and 51.9% accurate in predicting FGR.

Similarly, in a recent population-based cohort study using data from the Swedish Medical Birth Register, Jacobsson et al. [14] found that, compared with women aged 20 to 29 years, those aged 40 to 44 and 45 years had ORs of 1.94 and 2.67 for FGR, respectively. Their analysis, however, failed to evaluate the risk of FGR in women between 35 and 40 years old.

As a result, a positive history of FGR risk factors might create the problem of intensified surveillance with the explicit purpose of early diagnosis of growth insufficiency, as mentioned by Conde-Agudelo et al. [15]. Furthermore, additional diagnostic tests may have a greater impact on a high-risk group. However, because efficient screening measures have not yet been established, these clinical characteristics have shown a distinct influence on each individual instance.

Our study showed that abnormal biochemical markers, PAPPA≤0.42 and Hcy ≥6.3, were 42.3% sensitive, 88.0% specific, and 70.8% accurate in predicting early-onset FGR. Similarly, a study conducted by Spencer et al. [16] concluded that lower levels of maternal serum PAPP-A in the absence of an abnormal karyotype were associated with an increased risk for FGR (16).

Also, in accordance with our study findings, a cohort study by Ranta et al. [17] on 2844 pregnant women found that the concentration of first-trimester serum markers was decreased in pregnancies with preeclampsia, small gestational age, and preterm delivery. Lower levels of PAPP-A were also revealed as predictors of FGR by Poon et al. [18] in a study on 2178 women (18).

Where PAPP-A as a single marker is an insufficient screening tool for FGR documentation, the sensitivity of identifying FGR for the first trimester PAPP-A level below the 5th percentile ranges only between 8% and 33%. However, Spencer et al. [16] observed that a lower level of maternal serum PAPP-A at 11-13 weeks of pregnancy was significantly related to worse pregnancy outcomes in 4390 women with singleton pregnancies.

The establishment of the uteroplacental circulation in the second trimester is not considered as a random phenomenon but somewhat a consequence of subsequent events in the first trimester. Evidence suggests that uterine artery Doppler is a useful, non-invasive method to measure uteroplacental perfusion in the second trimester. Thus, in line with our study, scientific interest is now focused on early pregnancy as identification of the at-risk population in the first trimester would lead to the investigation of different preventive strategies.

The gestational age of screening between 20 and 24 weeks has been suggested as the finest time for a screening of high-risk pregnancies for obstetric vasculopathies [19]. Accordingly, our study revealed a statistically significant association between FGR and uterine artery doppler at 18-20 weeks of gestation in the high-risk study participants. With a high pulsatility index (PI) of uterine artery doppler (>1.57), number of FGR cases is 17 (34.0%), and several FGR cases with absent diastolic notching 10 (17.0%).

Also, in the present study, abnormal uterine artery doppler (PI>1.57 + diastolic notching) was 34.6% sensitive, 58.8% specific, and 52.8% accurate in predicting early-onset FGR, with a positive predictive value of 21.4% and a negative predictive value of 73.4%. Furthermore, the combination of uterine artery doppler and serum markers was 46.2% sensitive, 58.8% specific, and 55.7% accurate in predicting early-onset FGR: in a high-risk group, with a positive predictive value

of 26.7% and a negative predictive value of 77.0%.

In line with the present study, Chan et al. [20] showed that the combination of a diastolic notch and an abnormal resistance index in both uterine arteries at 20 weeks of gestation is the most precise indicator for predicting severe pregnancy complications. These studies are almost eight times more likely to develop clinically significant hypertension, delivery prior to 32 weeks, perinatal demise, or an infant with a birth weight of less than 1500 gm.

Adefisan et al. [21] found that RI and PI had limited sensitivity for predicting FGR, with 23.1 percent and 0 percent, respectively. In a low-risk pregnancy, it also demonstrated that PI in the second trimester had no effect on later FGR. The sensitivity of RI (23%) is within the range of 11–53 percent when employing identical RI cut-offs in a low-risk group. This research backs up a meta-analysis that found uterine Doppler ultrasonography is a poor predictor of FGR and neonatal mortality in low-risk mothers.

The study conducted by Turk et al. [22] who e selected 100 pregnant females with an average age of 23.2 years and from 11 to 14 and 21 to 24 gestational weeks, found that a notch in uterine artery doppler was functioning in the diagnosis of adverse pregnancy outcomes, and our study also revealed this finding, which is valuable in predicting FGR.

For the avoidance of high-risk pregnancy-related complications such as FGR, intrauterine fetal deaths, and PE, uterine artery doppler, which is performed at 18 and 22 weeks of gestation, might be helpful as an applicable method for diagnosis.

Furthermore, Llurba et al. [23] demonstrated that uterine artery PI measurement at 20 weeks predicts 70.6 percent of early onset PE and 73.3 percent of early-onset FGR, with a 10% false-positive rate. Uterine doppler screening has also been proven to be more accurate in predicting severe early-onset disease, or PE linked with FGR, with sensitivities of 80 to 90%.

Our study shows that the number of FGR cases with a high S/D ratio of umbilical artery doppler (>4.54) at 26-28 w: 3 cases (100%), abnormal end diastolic velocity (EDV): 3 case FGR (42.9%), high (>1.37) Pulsatility Index (PI): 3 cases FGR (13%), high (>0.76) Resistance Index (RI): 1 case FGR (9.1%). Our study shows that the number of FGR cases with a high S/D Ratio of Umbilical artery doppler (>4.54) at 29-31 w: 23 cases (88.5%), Abnormal EDV: 23 case IUGR (46.9%), high (>1.37) PI: 26 cases FGR (34.2%), high (>0.76) RI: 23 case FGR (37.1%).

The present study showed a highly statistically significant association between FGR and umbilical artery doppler at 29-31 weeks of gestation. Also, it was reported that a combination of uterine artery doppler and umbilical artery doppler was 88.5% sensitive, 96.3% specific, and 94.3% accurate in predicting FGR.

Khanduri et al. [24] measured both PI and RI in the umbilical artery at the first (23-27 weeks), second (28-32 weeks), and third (32-36 weeks) visits of pregnancy. The sensitivity indices for umbilical artery PI>1.42 were (61.5 percent, 74.4 percent, and 82.1 percent, respectively), specificity indices were (73.9 percent, 78.3 percent, and 87.0 percent), positive predictive values were (80.0 percent, 85.3 percent, and 91.4 percent, respectively), negative predictive values were (53.1 percent, 64.3 percent, and 74.1 percent, respectively), and accuracy indices were (66.1 percent, 75 percent, and 75 percent, respectively).

However, according to Dhand et al. [25] the umbilical artery PI was 44 percent sensitive and 61.5 percent specific in predicting FGR. In comparison to this investigation, we were able to improve the performance of these factors. This was since we only had a prospective case sequence of high FGR risk pregnancies. Dhand et al. [25] on the other hand, conducted their research as a case-control study.

It's worth noting that the umbilical artery PI has a higher specificity than sensitivity. Khanduri et al. [24] found that sensitivity increased from 61.5 percent on the first visit to 82.1 percent on the third visit, with a comparable increase in specificity from 73.9 percent to 87.0 percent. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) had all risen by the third visit.

Umbilical artery RI had poor sensitivity and high specificity in our study. In comparison, Lakhkar et al. [26] found that RI sensitivity in the umbilical artery is 58 percent, specificity is 71.7 percent, PPV is 35 percent, and NPV is 86.8%. As a result, it has a diagnostic accuracy of 56.8% for severe adverse outcomes in suspected FGR cases, and 44.4 percent sensitivity, specificity, PPV, and NPV for mild adverse effects of 44.4 percent, 81.8 percent, 80 percent, and 47.3 percent, respectively.

CONCLUSIONS

The combined model of screening identified in our study can be a beneficial method to identify patients at increased risk of FGR. The ability to predict the incidence of FGR in early pregnancy would allow maternal and fetal morbidity to be decreased through the introduction of strict

obstetric surveillance as well as scheduled delivery in a qualified center. The best result in our study is that the combination of uterine artery and umbilical artery doppler was 88.5% sensitive, 96.3% specific, and 94.3% accurate in the prediction of FGR.

While a combination of uterine artery doppler and biochemical markers was 46.2% sensitive, 58.8% specific, and 55.7% accurate in the prediction of FGR..

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