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ORIGINAL ARTICLE

Risk Assessment at 11–14-Week Antenatal Visit: A Tertiary Referral Center Experience from South India

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Abstract

Background Present study carried out in a tertiary referral hospital in South India attempts to determine the predictive value of integrated screening at 11–14-week antenatal visit. *Objectives* To determine the detection rate of fetal abnormalities at 11–14 weeks and also to predict the placental dysfunction disorders based on early integrated evaluation.

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Method Integrated screening performed on 440 women between 11 and 14 weeks, including detailed maternal history [medical history, bad obstetric history (BOH)], body mass index (BMI), mean arterial pressure (MAP), detailed ultrasound and maternal serum biochemistry as part of combined first-trimester screening for aneuploidy.
Results There were two proven Down's syndrome foetuses; both detected with combined screening test. There were 12 fetuses with major anomalies, out of whom 7 (58.3%) detected in 11–14-week scan. Among 440, 114 pregnancies (25.9%) developed complications in pregnancy, including 33 (7.5%) gestational hypertension, 8 (1.8%) pre-eclampsia, 41 (9.38%) SGA, 13 (2.9%) abortions, 22 (5%) indicated and 9 (2.04%) spontaneous preterm deliveries, 38 (8.63%) GDM and 3 (0.6%) stillbirth/IUD. Among the risk factors, age >35 years, BMI >23 kg/m^2, BOH, MAP >105 mmHg and PAPP-A <0.5 MoM correlated well with adverse outcome. Using early integrated screening, 78.9% of obstetric complications could be predicted although 306 (69.5%) were labeled high risk, among whom 90 (29.4%) developed adverse pregnancy outcomes.
Conclusions Majority of fetal abnormalities can be detected, and majority adverse pregnancy outcomes can be predicted at 11–14-week antenatal visit, although this study shows high screen positivity and low specificity in a tertiary referral unit.

Keywords Early integrated screening · 11-14 weeks screening · Pyramid of care · Placental dysfunction disorders · Serumbiochemistry · Pregnancy risk prediction

Introduction

Frequent antenatal visits in the last trimester are aimed at detecting pregnancy complications. Inverting the pyramid of care [1, 2] has long been a topic for research, wherein a detailed integrated evaluation in early pregnancy segregates pregnant women into low-risk and high-risk category. The literature on such strategy is scarce from developing countries, where this would be useful for better organization of healthcare delivery. Present study carried out in a tertiary referral hospital in South India attempts to determine the predictive value of 11–14-week antenatal visit, including detailed history, examination, a targeted early anomaly scan and serum biochemistry. First objective was to evaluate what proportion of fetal abnormalities can be detected at 11–14 weeks. Since obstetric complications arising from placental dysfunction disorders are commoner than fetal anomalies, we attempted to predict these obstetric complications based on the early integrated evaluation. Our aim was to know whether this risk prediction would be useful to organize early referral system among primary obstetric care givers.

Methods

This prospective observational study was done over 2 years in a tertiary care hospital, affiliated to a medical university. Study was approved by the Institutional Ethics Committee (IEC-449/2013). Sample size calculated using Breslow's formula, power of test being 80%. For anticipated sensitivity of 90% in predicting high-risk pregnancy, sample size was calculated to be 435. Study population consisted of 500 pregnant women booked between 11 and 14 weeks with singleton viable pregnancy, who chose to undergo combined screening for aneuploidy which included nuchal translucency and serum biochemistry. An informed consent about the patient's participation and consent for prospective data collection on the pregnancy outcome was taken from the patients. Integrated screening included detailed maternal history [medical history, history of any adverse outcome in previous pregnancy (bad obstetric history BOH)], maternal characteristics like body mass index (BMI), and mean arterial pressure (MAP), detailed ultrasound and maternal serum biochemistry.

Detailed ultrasound using Philips HD 11XE machine was done at 11–14 weeks, in which CRL and complete fetal anatomical survey along with nuchal translucency measurement was done either by TAS or TVS. Serum biochemistry (PAPP-A and βhCG) was performed. Following this integrated screening, fetal anomalies were noted and the presence of following risk factors was considered significant—the presence of BOH, age >35 years, BMI >23 kg/m^2 (abnormal as per Asian standards), MAP >105 mmHg, PAPP-A levels <0.5 MoM for gestation, beta hCG <0.4 MoM.

Targeted scan was done routinely at 18–20 weeks. All detected fetal anomalies at the first- and second-trimester scans were confirmed after delivery/termination of

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pregnancy. Pregnancy outcomes were recorded by following them till delivery. Primary outcome measures were early detection of structural fetal anomalies and chromosomal abnormalities. The second objective was to assess the early prediction of other pregnancy complications like miscarriage, still birth, perinatal mortality, small for gestational age neonate (SGA), preterm delivery, gestational hypertension and pre-eclampsia.

Statistical analysis was done using Scientific Package for Social Sciences (SPSS version 16.0). For statistical analysis, Chi-square test was used when appropriate. Statistical significance was accepted at $p < 0.05$.

Results

Five hundred pregnant women booked at 11–14 weeks, who had ultrasound and serum biochemistry, were included in the study. Among them, 60 were lost to follow up, and 440 were followed up till delivery. Among 440 patients included in the study, 259 were primigravidae and 181 multigravidae. Preexisting medical disorders were seen in 63/440 (14.3%) of patients. BOH was seen in 54/181 multigravidae (29.8%) (Table 1).

Twenty-three foetuses were anomalous in this study (5.22%). Twelve were major anomalies, out of which, 7 were detected in first trimester, 3 could be detected in the 18–20-week scan and 2 could be detected only after birth. Therefore, 58.3% of major fetal anomalies could be detected in the first-trimester scan. Among 11 minor abnormalities, all were detected in the 18–20-week anomaly scan. Total antenatal detection rate of anomalies was (21/23) 91.3% (Tables 2, 3).

Combined aneuploidy screening reported low-risk results for 429 patients, all of whom were phenotypically normal at birth. Eleven (2.5%) had high-risk results, and 2 of them were confirmed to have Down's syndrome (Fig. 1).

Table 1 Demography

Characteristics	Mean ± S.D ($N = 440$)
Age (years)	28.45 ± 3.80
Mean arterial pressure (mm of Hg)	89.85 ± 5.09
Parity	
Primigravidae	259 (58.8%)
Multigravidae	181 (41.2%)
BMI (kg/m^2)	24.13 ± 2.14
Total no. of patients with preexisting medical disorders	63 (14.3%)
No. of pregnancies with bad obstetric history in multigravidae ($N = 181$)	54 (29.8%)

Among 440, 114 pregnancies (25.9%) developed complications. There were 33 (7.5%) gestational hypertension, 8 (1.8%) pre-eclampsia, 41 (9.38%) SGA, 13 (2.9%) abortions, 22 (5%) indicated and 9 (2.04%) spontaneous preterm deliveries, 38 (8.63%) GDM and 3 (0.6%) stillbirth/IUD.

Table 4 shows the prevalence of all the predictive factors that were considered high risk in our study, along with their association with various individual pregnancy complications.

A total of 10/440 patients had high MAP at 11–14-week visit. Among them, 6 (60%) developed hypertensive disorders later in pregnancy, three had gestational hypertension/SGA and three had pre-eclampsia.

There was a significant association between low PAPP-A and SGA, pre-eclampsia and overall adverse pregnancy outcomes. No statistically significant association was noted between low βhCG levels (<0.4 MoM) and development of adverse outcome.

For predicting hypertensive disorders of pregnancy, integrated test involved presence of any of the following risk factors—advanced age, presence of BOH, high BMI >23 kg/m^2, MAP >105 mm of hg, low PAPP-A <0.5 MoM and βhCG <0.4 MoM. For predicting all other adverse pregnancy complications, integrated test included any of the above-mentioned factors except MAP.

Figure 2 shows proportion of individual pregnancy complication which was successfully predicted by early integrated screening. Clearly, more than two-thirds of complications could be predicted.

Pregnancy with any of the above-mentioned risk factors was labeled high risk. In our study group, 306 (69.5%) women were labeled high risk at 11–14 weeks. Among them, 90 (29.4%) had adverse pregnancy outcomes and 216 (70.58%) had normal outcome. The sensitivity of integrated test to pick up the overall adverse outcomes was 78.9%, specificity was 33.7%, positive predictive value was 29.4%, and negative predictive value was 82.08% at 95% confidence intervals.

Using multiple logistic regression analysis, a predictive model which includes advanced maternal age, BOH, high BMI, low PAPP-A and low βhcg was created in predicting adverse pregnancy outcomes. Among all the factors, statistically significant association was noted with advanced age, presence of BOH and low serum PAPP-A levels. The probability of having an adverse pregnancy outcome can be calculated using the prediction formula:

$$-1.349 + 1.095\,(\text{If PAPP A} < 0.5\ \text{MoM}) + 0.864\,(\text{If BOH is present}) + 0.856\,(\text{If age} > 35\ \text{years})$$

The odds ratio of advanced age was 2.35 (95% CI = 1.12, 4.95), bad obstetric history was 2.37 (95% CI 1.29, 4.37),

Table 2 Detection of anomalies

	Detection rate at 11–14-weeks scan		Detection rate at 18–20-weeks scan		Anomalies detected at birth
	N	Sensitivity %	*N*	Sensitivity %	*N*
Major anomalies (12)	7	58.3%	3[a]	83.3	2[c]
Minor abnormalities (11)	0	0	11[b]	100	

Total scans 440, total anomalies detected 23 (5.22%)

[a] Major anomalies detected in second trimester: congenital cystic adenomatoid malformation (CCAM), complex congenital heart disease (heterotaxy), bilateral polycystic kidney disease

[b] Minor abnormalities detected in second trimester: choroid plexus cyst (4) echogenic foci in heart (2), renal pyelectasis (4), myocardial hypertrophy (1)

[c] Anomalies detected at birth: (1) congenital rubella syndrome with mild VSD and congenital cataract, (2) moderate-sized VSD

Table 3 Major anomalies detected in this study

11–14-week scan	18–20-week scan	Anomalies detected at birth	Outcome
Early hydrops and mediastinal shift	Congenital Diaphragmatic Hernia.? Fryns syndrome	Polydactyly	IUD at 28 weeks
Isolated pericardial effusion		–	Missed abortion at 13 weeks
Hydrops + large ASD + hypoplastic nasal bone		–	MTP at 12 weeks
Early hydrops and NT4 mm		–	Missed abortion at 15 weeks
Cystic hygroma, suspected holoprosencephaly		–	MTP at 14 weeks
Hydrops + cystic hygroma		–	MTP at 13 weeks
Abdominal wall defect		–	MTP at 13 weeks
	Severe IUGR + oligohydramnios + mega cisterna magna + polycystic kidney disease	–	Poly cystic kidney disease, IUD
	Congenital cystic adenomatoid malformation	–	Respiratory distress at birth
	Complex congenital heart disease (heterotaxy)	–	MTP at 19 weeks
Normal study	Normal study	Congenital cataract + mild VSD	Congenital rubella syndrome
Normal study	Normal study	Moderate VSD	Awaiting for surgery

and low PAPP-A was 2.99 (95% CI = 1.40, 6.39) hence a fair statistical association.

Discussion

Integrated screening at 11–14 weeks is not commonly done in low-resource countries where majority of antenatal care is concentrated around the late second and third trimester. We attempted to test the value of this exercise, in a tertiary care center.

Limitations of early anomaly scan are known [3–5], including late evolution/detection, need of expertize/quality USG machine, woman's preexisting risks, abdominal versus vaginal probe, single versus multiple anomalies. Nevertheless, we could achieve a good detection rate for major anomalies comparable to published literature [4, 5], despite varying degrees of sonological expertize. Often in our country, structural fetal survey is done only in late second trimester, leading to late detection of anomalies and late terminations. Therefore, our study reemphasizes the need for widespread use of early anomaly scan in our country. However, 18–20-week scan remains to be very important for anatomical survey as well as a part of genetic sonogram.

In this study, most of the fetal anomalies detected in 11–14 weeks are related to hydrops/cystic hygroma/NT >3.5 mm, which are very often associated with karyotypic abnormalities. However, couple opted for medical termination (MTP) without invasive testing, despite appropriate counseling. Possibility of genetic abnormality/

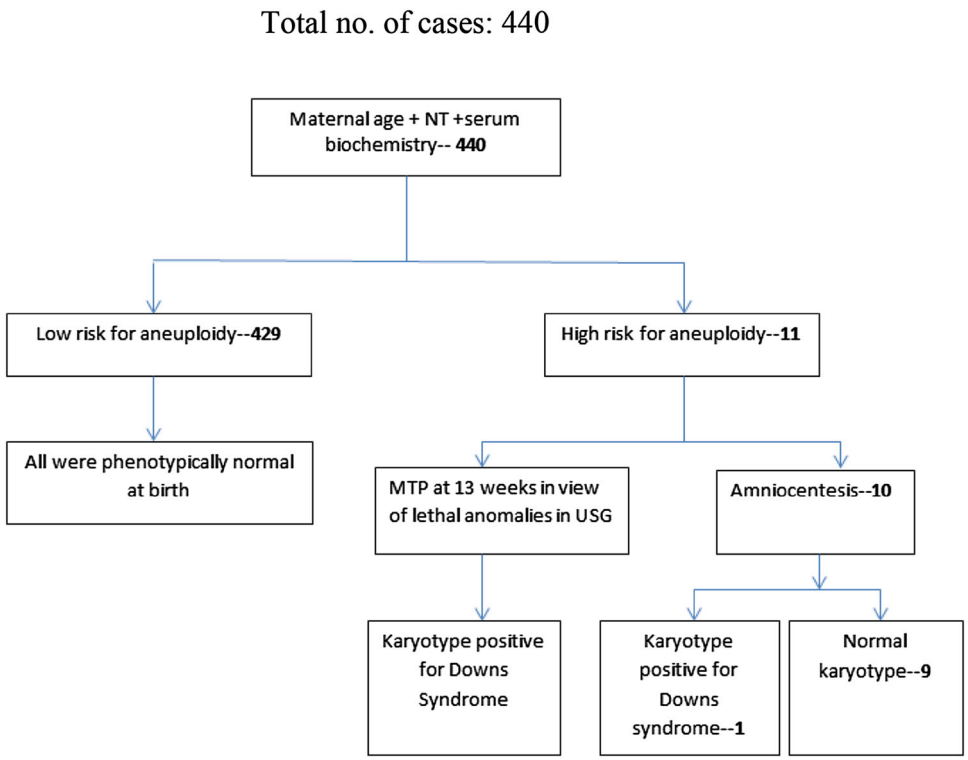

Fig. 1 Detection of aneuploidies

neurodevelopmental sequel in their child would inevitably lead to a decision on MTP.

Although aneuploidy detection rate in our study is comparable with other studies [6, 7], no conclusions can be drawn due to small sample size. Detection of chromosomal abnormalities is likely to be higher in our study as many pregnancies with third space fluid collection in fetuses directly went on to MTP. Significant proportion of obstetric population is deprived of good antenatal screening prior to 20 weeks among low-resource countries. No data are available on what proportion of Indian obstetric population has access to first-trimester aneuploidy screening. Incorporating this early integrated screening in primary-level public health sector would have major implications in reducing perinatal/maternal morbidity due to late detection of fetal abnormalities.

Overall burden of fetal abnormalities is much less than the burden caused by placental dysfunction disorders. Our study confirms that pregnancy complications can be predicted with fair degree of accuracy at early gestation, using simple prediction model. However, there were limitations in our risk prediction, namely small sample size, a high prevalence of preexisting risk factors and a high overall incidence of adverse pregnancy outcome (25%).

Analyzing individual risk factors, BOH alone could predict >50% of pregnancy complications among multigravidae. Adverse outcome was either similar to earlier pregnancy, or a new emerging problem, like cervical insufficiency among those with past history of induced abortion for an anomalous fetus. Only 7% of our study population were beyond 35 years of age, and among them, (16/34) 47% developed adverse pregnancy outcomes, attributable to associated medical disorders, obesity and BOH. However, all three stillbirths occurred in younger women, either due to structural anomaly or pre-eclampsia/IUGR. Advanced maternal age is strongly associated with pregnancy complications [8].

Obesity is now prevalent among south Indian pregnant women. Taking Asian-specific standards, normal BMI was noted in 184/440 (41.8%) and 58.2% (256/440) were overweight/obese. High BMI was strongly associated with gestational hypertension, indicated preterm deliveries and SGA babies. One-third (41 of 114 which is 35.9%) of those who developed pregnancy complications belonged to this category. High BMI predicts several pregnancy complications [9].

Although 6/10 (60%) patients with high MAP developed hypertensive disorders or SGA fetuses later, this number is very small for us to draw conclusions on the predictive power of this risk factor. But it remains a simple yet powerful tool in early pregnancy screening.

Many serum biochemical markers have been proposed to correlate with placental perfusion [10]. In our study, low PAPP-A levels predicted 62% of pre-eclampsia and 19.5% of SGA babies, which is a slightly low prediction rate compared to previously published reports [11]. Low specificity remains a problem. However, if serum biochemistry is performed on a large scale at primary care level, good proportion of at risk pregnancies can be given better perinatal outcome.

Table 4 Composite table: risk factors and prediction of adverse outcomes $N = 440$

Predictive factors	Outcome																	
	Abortions (13)		SGA (41)		Gestational hypertension (33)		Pre-eclampsia (8)		Still born/IUD (3)		Pre term (31)		GDM (38)		Obstetric complications (114)[a]	
	N	DR	*N*	DR	*N*	DR	*N*	DR	*N*	DR	*N*	DR	*N*	DR	*N*	DR
BOH 54/181	2/4	50%	12/19	63.15%	5/12	41.6%	4/6	66.67%	1/2	50%	9/16	56.2%	10/16	62.5%	25/43	57.14%
Age >35 years (34)	3	23.07%	5	12.19%	4	12.12%	3	37.5%	0	–	7	22.58%	6	15.78%	16	14.03%
BMI >23 kg/m^2 (256)	8	61.5%	30	73.17%	25	75.75%	3	37.5%	1	33.33%	7	22.58%	23	60.52%	41	35.96%
MAP >105 mm of Hg (10)	1	7.6%	1	2.4%	3	9.09%	3	37.5%	–	–	2	6.4%	–	–	8	7.07%
PAPP-A <0.5 MoM (32)	2	15.3%	8	19.5%	5	15.15%	5	62.5%	1	33.33%	4	12.9%	4	10.52%	17	14.91%
βhcg < 0.4 MoM (33)	–	–	4	9.7%	3	9.09%	1	12.5%	1	33.33%	2	6.4%	3	7.89%	9	7.89%
Integrated test	12	92.30%	34	82.92%	27	81.81%	7	87.5%	2	66.66%	27	87.09%	28	73.68%	90	78.94%

Some patients had >1 predictive factors

N number of pregnant women, *DR* detection rate for that adverse outcome

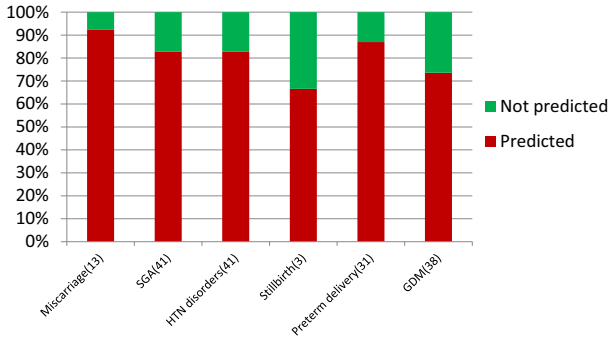

Fig. 2 Predictive power of early integrated screening

Integrated test was considered positive when single risk factor for the respective adverse outcome was present in a given patient. Using this prediction, 81.8% of gestational hypertension and 87.5% of pre-eclampsia could be predicted, which is comparable with other studies [12]. This excellent sensitivity to identify at risk pregnancies would have major impact on maternal mortality/morbidity as well as perinatal mortality in our country. Fetal Medicine Foundation included parameters like maternal factors, MAP, PAPP-A, PlGF and uterine artery Doppler in first-trimester screening. Among 7797 women, for a false-positive rate of 5%, overall detection rate was 93.1% for early-onset pre-eclampsia, 35.7% for late-onset pre-eclampsia and 18.3% for gestational hypertension [1]. A retrospective cross-sectional study [13] on 4702 singleton pregnancies concluded that prediction for birthweight deviations is feasible using multiple data available at the routine 11–14 weeks, achieving a sensitivity of 55% for SGA, for 20% screen positivity. Our study achieved higher sensitivity for SGA prediction (82.9%), although at the cost of high (69%) screen positivity and high false positivity, probably due to higher prevalence of risk factors.

Several studies have examined an integrated model for first-trimester prediction of ischemic placental diseases [14] necessitating indicated preterm delivery. These studies showed that first-trimester predictions are much stronger for the pregnancies necessitating preterm delivery as compared to near-term gestation. Currently, the predictive factors used are a combination of maternal characteristics, uterine artery PI, MAP, maternal serum PAPP-A and placental growth factor (PlGF). For severe pre-eclampsia and SGA prior to 34 weeks, detection rates are 95 and 55%, respectively, for a low false-positive rate of 5–10%. However, we have not included uterine artery PI/PIGF, and we have studied a wide spectrum of placental dysfunction disorders including miscarriage, spontaneous preterm delivery and GDM. Nevertheless, our integrated screening achieved 78% detection rate for obstetric complications, although at a cost of high false positivity.

Three hundred and six women (69%) were deemed high risk in early pregnancy in our study. High screen positivity is due to the nature of obstetric bookings in a tertiary center. This cannot reflect a low-risk obstetric setup, where a much smaller proportion would be deemed high risk. Out of those deemed high risk, one-third had some adverse pregnancy outcome. Out of the 134 women deemed low risk, 83% resulted in good outcome. Intense surveillance would be needed on a large population in order to achieve better outcome in a small proportion. Further research question would be to know whether such measures would be beneficial in terms of cost–benefit analysis and improved pregnancy outcome. The true value of this test would be the high negative predictive value which means that those labeled as low risk at 11–14 week could be offered less intense monitoring and lesser interventions, thus reducing burden on healthcare resources in low-resource setup. Strategies to test the value of this integrated early pregnancy screening in primary healthcare level in our public health sector are the need of the hour, in order to streamline our healthcare resources.

Nuchal translucency (NT) measurement and uterine artery Doppler require specialized training. In low-resource countries, such expertize is not available to all pregnant women. Until the time all sonographers obtain this training, prevailing situation of 11–14-week screening would remain the same. Due to small sample size, some adverse pregnancy outcomes were small in number; thus, predictive power of screening would be low in this study. Improving these limitations would be very useful to improve the predictive value of this integrated screening and also help in generalizing the results to our obstetric population.

Conclusions

A detailed 11–14-week scan along with serum biochemistry should be widely implemented in the public health sector among low-resource countries, as a good proportion of fetal abnormalities can be picked up with this strategy, with prevailing standards of sonological expertize. However, an integrated pregnancy risk prediction model at 11–14 weeks seems to have a high screen positivity and low specificity in an obstetric population of a tertiary referral unit, although a large majority of placental dysfunction disorders can be predicted. Value of such an integrated early pregnancy risk prediction should be tested in the primary-level public health sector among low-resource countries .

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interests for any author (financial or otherwise).

Ethical Standards Institutional ethical committee clearance has been obtained for the study.

Informed Consent Written informed consent has been taken from all patients for prospective data collection about their pregnancy details and delivery.

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