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Reference centile charts of first-trimester aneuploidy screening & Doppler parameters for Indian population

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***Background & objectives*: The risk estimation for foetal aneuploidies in the first trimester of pregnancy uses reference curves based on western data. The objective of this study was to construct the reference curves of first-trimester foetal aneuploidy screening parameters for the Indian women.**

***Methods*: Cross-sectional data were obtained from 1204 singleton pregnancies between the crown-rump length (CRL) of 40-84 mm. Linear regression models were constructed; the mean, median and standard deviation were derived as a function of CRL.**

***Results*: The mean value of CRL was 61.3 mm. The regression analysis showed a significant correlation between all variables and CRL ($P<0.001$). There was a positive correlation of CRL with nuchal translucency (NT) ($y=0.010x+0.629$, $R^2=0.116$) and pregnancy-associated plasma protein-A (PAPP-A) ($y=0.107x-1.079$, $R^2=0.173$), whereas inverse correlation was seen with free β-human chorionic gonadotropin (β-hCG) ($y=-0.409x+75.025$, $R^2=0.018$) and Doppler parameters pulsatility index (PI) ($y=-0.008x+1.924$ $R^2=0.053$). The centile charts of NT, PAPP-A, free β-hCG and uterine artery (Ut A) Doppler PI were constructed.**

***Interpretation & conclusions*: The reference centile charts of first trimester aneuploidy screening along with Doppler parameters were derived in Indian pregnant women. These centile charts may be used as a reference for clinical use in Indian population.**

Key words Down syndrome - first-trimester ultrasound - free β-human chorionic gonadotropin - nuchal translucency - pregnancy-associated plasma protein-A - uterine artery Doppler

The first-trimester screening for aneuploidy involves a combination of maternal age, foetal nuchal translucency (NT), maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11+0 to 13+6 wk of gestation. It has proved to be an important test in terms of timing and sensitivity in detecting foetuses at risk of aneuploidy. For a false-positive rate of five per cent, the detection rate of aneuploidy with this method is about 90 per cent, which is superior to 30 per cent achieved by maternal age alone or 65 per cent by maternal age and second-trimester

serum biochemistry[1]. Therefore, all pregnant women, regardless of age should be offered prenatal screening for foetal aneuploidies in the first trimester through an informed counselling process[1]. The first-trimester foetal biomarkers have been implicated in predicting adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction (IUGR) and intrauterine death (IUD)[2-5]. Uterine artery (Ut A) Doppler studies, shown to be significant in predicting preeclampsia[6], have been implicated in predicting adverse foetal outcome in Indian population as well[7].

In order to screen for aneuploidy and adverse perinatal outcome, normal levels of these parameters should be known. Although centile charts of all markers are available, studies have shown ethnic variation in foetal growth. Bottomley *et al*[8] showed that before 14 wk of gestation, foetuses of black women had a faster increase in crown-rump length (CRL) than those of white or Asian women. Thilaganathan *et al*[9] compared the overall average NT thickness among various ethnic groups and found an ethnic difference. Therefore, there is a need for region-specific centile charts for aneuploidy markers. The present study was thus aimed to find out the level of PAPP-A, free β-hCG and NT along with Ut A Doppler parameters between foetal CRL of 40-84 mm, in pregnant women in first trimester and to construct centile charts for the same.

Material & Methods

The study was carried out in the department of Obstetrics and Gynaecology, Lady Hardinge Medical College and Shrimati Sucheta Kriplani (SSK) Hospital, New Delhi, India, after ethical clearance from Institute's Ethical Committee. It was a prospective study conducted for four years (2012-2016). All consecutive pregnant women registering in antenatal Outpatient Department in the first trimester were enrolled. All women provided informed written consent. All live singleton pregnancy in the first trimester or early second trimester with foetal CRL between 40-84 mm were included. Women with multiple pregnancy and those who did not give consent were excluded. A total of 1204 women with normal outcome were included in the study. The transabdominal ultrasound was done using 3-5 MHz probe on machine Nemio XG (Toshiba, Japan). The CRL was taken in midsagittal section with the neck in neutral position and was measured up to the nearest mm. In the same position, NT was also measured; the measurement was done according to Fetal Medicine Foundation (FMF) criteria[10]. The Ut A Doppler was performed by visualizing the Ut A at internal OS, the resistance index (RI), pulsatility index (PI) and standard deviation (SD) ratio were noted. The ultrasound was done by the single observer, the intraobserver reliability for these yielded Cronbach's alpha values ranging from 0.913 to 0.978 for the various parameters which could be considered to be excellent in internal consistency.

For the measurement of biomarkers, 3 ml of venous blood was drawn by venipuncture into non-heparinized tubes. The serum was separated and aliquots were stored at −80°C until further use. The serum concentrations of PAPP-A and free β-hCG were analyzed by Immulite-1000 which is a chemiluminescent enzyme-linked immunosorbent assay-based analyzer (Siemens LTD, Germany). All women were followed by periodic check-up till delivery. The development of any maternal or foetal complications was noted. The normal outcome was defined as pregnancies with no adverse maternal complications such as pregnancy hypertension, diabetes, hypothyroidism or any other medical illness or foetal complications such as the presence of a congenital anomaly, IUGR and premature birth or stillbirth. Only those with normal outcome were included for analysis.

Statistical analysis: The estimation of NT, biomarkers and Ut A Doppler parameters were done based on the CRL measurements. The z scores were calculated to see if the parameters followed a normal distribution. The regression analysis was done with CRL as the independent variable and NT, PAPP-A, free hCG and Ut A Doppler parameters as the dependent variables. The variables were presented as mean, median and SD (σ). By definition of the standard normal distribution, the ±1σ limits incorporates 68.27 per cent of the total population, ±2σ limits incorporate 95.45 per cent and ±3σ limits comprise 99.73 per cent of the total population[11]. There were exactly 95 per cent observations between ±1.645σ limits and hence these points acted as the 5th and 95th percentiles and centile charts were constructed. The statistical analysis was performed using SPSS version 15.0 (IBM Corporation, New York, USA).

Results

Of the 1800 pregnant women, 175 (9.7%) were lost to follow up, 1625 cases were followed till delivery. During the course of the pregnancy and subsequent delivery, maternal complications comprising hypertension in pregnancy (167, 10.3%), gestational diabetes (16, 1%), hypothyroidism (4, 0.2%), hepatitis (1, 0.1%) and epilepsy (1, 0.1%) were observed in 189

(11.6%) women. Similarly, foetal adverse outcome was seen in 232 (14.2%) which encompassed abortions and stillbirth (51, 4.4%), foetal growth restriction (FGR) (90, 5.5%) and preterm birth (91, 4.3%). These women having adverse pregnancy outcome were excluded from the study. Total 1204 women with normal outcome were included for final analysis (Fig. 1). Almost all of them went into spontaneous labour; in 22 women, induction of labour was required. Lower segment caesarean section (LSCS) was done in 276 (23%). The mean gestational age at delivery was 40±1.2 wk. Regarding foetal outcome all were live births and had mean birth weight of 2.9±0.33 kg, the Apgar score was normal (>7 at 5 min) in 91 per cent, only 11 (0.9%) neonates required a brief nursery stay.

The mean maternal age was 24.4±3.57 (18-37) yr. The mean CRL was 61.3 mm (40.1-84.4 mm), corresponding to gestational age of 12 wk and four days (10 wk four days to 15 wk three days). Table I shows the distribution (5th, 50th and 95th centile) of women according to CRL of 40-84 mm divided into groups of 4.9 mm CRL each, the number varied from 93 to 170 in each group. For 80-84 mm CRL, the 50th centile was 13 wk and six days whereas the 95th centile was calculated as 15 wk and three days.

The average NT was 1.3±0.3 mm (0.2-5.2 mm), it was more than 2.5 mm in only four women. The mean PAPP-A level was 5.5±2.6 mIU/ml (0.1-10 mIU/ml), and free β-hCG level was 49.8±32.5 IU (2-200). Among Doppler parameters, the mean PI was 1.54±0.4 (0.3-3.97), the mean RI was 0.71±0.8 (0.29-2.17) and the mean SD ratio was 3.82±1.6 (1.1-17.23).

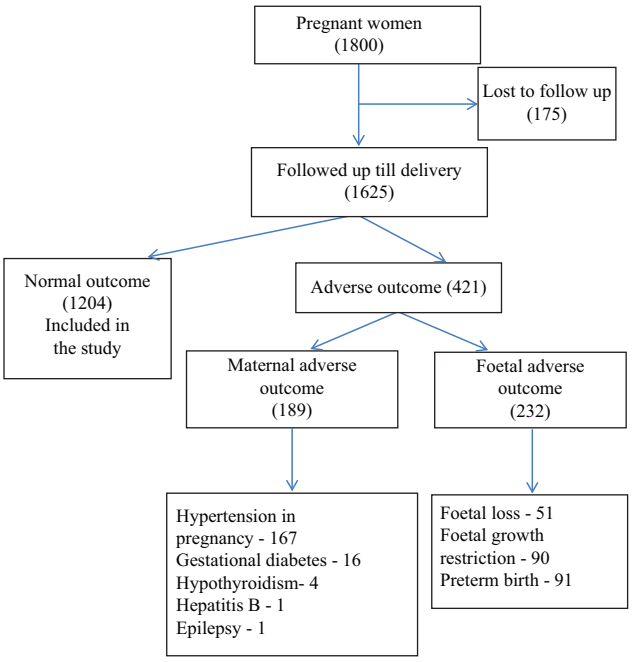

Fig. 1. Flow chart showing distribution of cases according to their outcome.

The z- score and histogram showed that the data were normally distributed as there was a minimal deviation from the straight line in the z-score and the histogram showed Gaussian distribution in observations. The maximum number of observations were in the centre, with decreasing observations away from midline. The regression analysis was done subsequently to see the relationship between CRL as an independent variable in relation to NT, PAPP-A, free β-hCG and uterine artery Doppler parameters PI, RI, SD ratio as the dependent variables. The coefficient of correlation of each variable along with significance is shown in Table II. There was a

Table I. Centile chart of crown rump length in mm in relation to the last menstrual period in weeks and days

Crown rump length (mm)	n=1204	Centile for last menstrual period in wk and days		
		5th	50th	95th
40-44.9	113	10+4	11+3	12+1
45-49.9	124	10+6	11+5	12+3
50-54.9	146	11+0	12+0	12+5
55-59.9	165	11+2	12+4	13+2
60-64.9	164	11+4	13+0	13+6
65-69.9	170	11+4	13+1	14+1
70-74.9	122	11+5	13+2	14+5
75-79.9	107	11+6	13+4	15+0
80-84	93	12+0	13+6	15+3

Table II. Correlation of crown rump length with aneuploidy markers and uterine artery Doppler parameters

Parameters	Coefficient of correlation (r)	*P*
NT	0.343	<0.001
PAPP-A (mlU/ml)	0.416	<0.001
Free β-hCG (ng/ml)	−0.129	<0.001
Uterine artery - pulsatility index	−0.228	<0.001
Uterine artery - resistance index	−0.193	<0.001
Uterine artery - mean systolic/ diastolic ratio	−0.211	<0.001

PAPP-A, pregnancy-associated plasma protein-A; β-hCG, β-human chorionic gonadotropin; NT, nuchal translucency

significant correlation between all variables and CRL ($P<0.001$), the correlation was positive with NT and biomarker PAPP-A. The univariate equation was derived for NT (y=0.010x+0.629 R^2=0.116) and PAPP-A (y=0.107x-1.079 R^2=0.173) (Figs 2 and 3). There was a negative correlation with free β-hCG, Doppler parameters PI, RI, SD ratio. The regression analysis yielded the univariate equation for free β-hCG (y=-0 .409x+75.025 R^2=0.018), Doppler parameters PI (y=-0.008x+1.924 R^2=0.053), RI (y=-0.0023x+0.853 R^2=0.034,), SD ratio (y=0.0288x+5.728 R^2=0.046) (Figs 4-7). The correlation was found to be moderate for NT and PAPP-A (>0.3), but was low for Doppler parameters and free β-hCG (Table II). The centile chart for NT, PAPP-A, free β-hCG along with Ut A Doppler PI showing 5th, 50th and 95th centile along with SD values and extrapolated 2 multiples of median (MOM) were constructed for NT, free β-hCG, Ut A PI and 0.4 MOM value for PAPP-A for specific 5 mm CRL range were derived and shown in Tables III-VI.

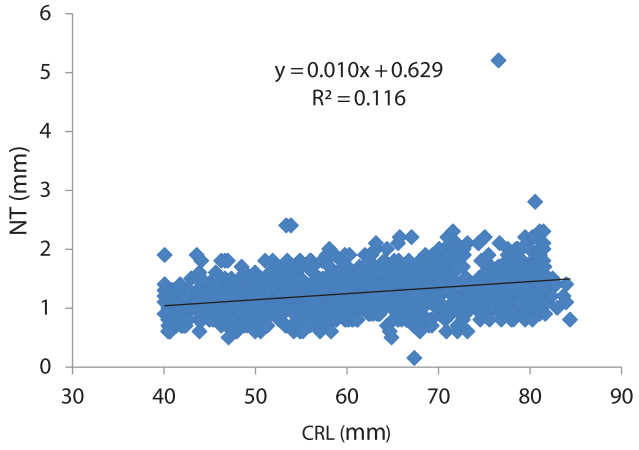

Fig. 2. Regression plot of nuchal translucency (NT) with crown rump length (CRL) along the X-axis.

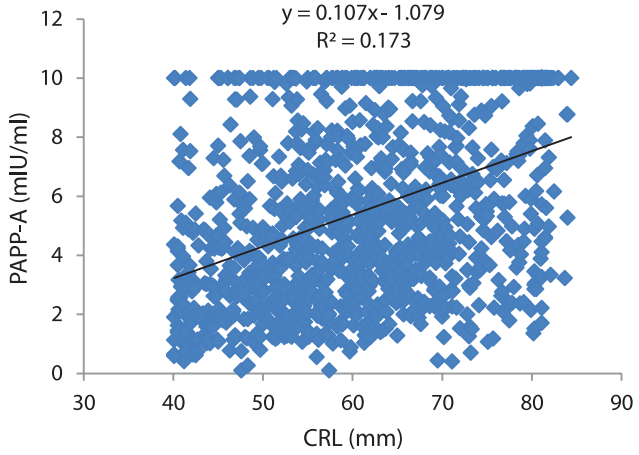

Fig. 3. Regression plot of pregnancy-associated plasma protein-A (PAPP-A) with crown rump length (CRL) along the X-axis.

Discussion

The study provided the first-trimester reference charts for NT, biomarkers and Ut A Doppler PI to be used for screening for adverse materno-foetal outcome in Indian women. It confirmed the feasibility of assessing uteroplacental circulation by transabdominal US in the first trimester of pregnancy (11-14 wk) and hence, incorporating Ut A Doppler during routine screening.

Most of the previous studies have calculated the parameters with respect to the period of gestation in weeks[12,13], whereas in the present study the reference centile chart of the parameters was constructed in relation to CRL. The CRL was preferred over gestational age in weeks, as it was more precise and easier to take, and it could be used when the last menstrual period was not known. The 5th centile of the period of gestation for

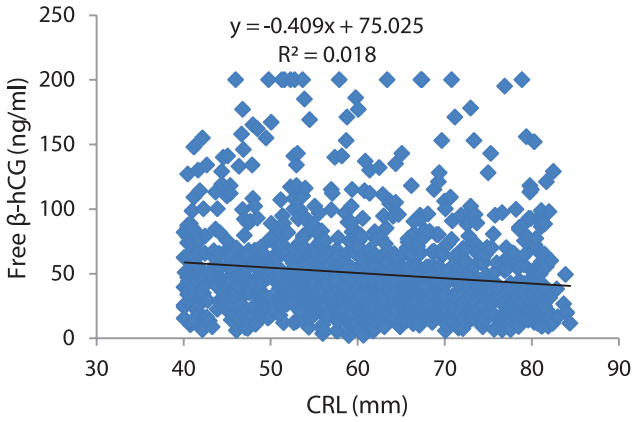

Fig. 4. The regression plot of β-human chorionic gonadotropin (β-hCG) with crown rump length (CRL) along the X-axis.

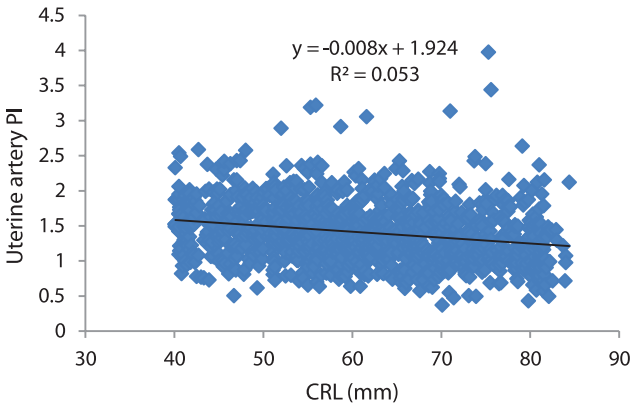

Fig. 5. Regression plot of uterine artery pulsatility index (PI) with crown rump length (CRL) along the X-axis.

Table III. The 5th, 50th and 95th centile, standard deviation and 2 multiples of median (MOM) value of nuchal translucency (NT) measurement in mm

CRL in mm	n=1204	NT in mm				2 MOM
		5th centile	50th centile (MOM)	95th centile	SD	
40-44.9	113	0.6	1.0	1.5	0.25	2.0
45-49.9	124	0.7	1.1	1.6	0.27	2.2
50-54.9	146	0.7	1.1	1.7	0.32	2.2
55-59.9	165	0.7	1.2	1.7	0.28	2.4
60-64.9	164	0.8	1.3	1.8	0.30	2.6
65-69.9	170	0.8	1.3	1.9	0.32	2.6
70-74.9	122	0.8	1.4	2.0	0.37	2.8
75-79.9	107	0.8	1.5	2.2	0.49	3.0
80-84	93	0.9	1.5	2.2	0.39	3.0

CRL, crown rump length; n, number of cases; SD, standard deviation

Table IV. The 5th, 50th and 95th centile, standard deviation and 0.4 multiples of median (MOM) value of pregnancy-associated plasma protein-A (PAPP-A) in mIU/ml in relation to crown rump length (CRL)

CRL in mm	n=1204	Serum PAPP-A in mIU/ml				
		5th centile	50th centile MOM	95th centile	SD	0.4 MOM
40-44.9	113	0.1	3.3	6.6	2.0	1.3
45-49.9	124	0.2	3.8	7.4	2.2	1.5
50-54.9	146	0.5	4.5	8.7	2.5	1.8
55-59.9	165	0.6	5.1	9.6	2.7	2.0
60-64.9	164	1.0	5.5	10.0	2.7	2.2
65-69.9	170	1.5	6.0	10.7	2.8	2.4
70-74.9	122	1.6	6.5	11.4	2.9	2.6
75-79.9	107	2.6	7.4	12.1	2.9	3.0
80-84	93	3.2	7.9	12.7	2.9	3.2

n, number of cases; SD, standard deviation

Table V. The 5th, 50th and 95th centile, standard deviation and 2 multiples of median (MOM) value of maternal serum-free beta human chorionic gonadotropin (β-hCG) measurement in ng/ml

CRL in mm	n	Maternal serum-free β-hCG measurement in ng/ml				
		5th centile	50th centile MOM	95th centile	SD	2 MOM
40-44.9	113	21.4	68.7	110.0	32.4	137.4
45-49.9	124	18.1	55.2	123.6	30.9	110.4
50-54.9	146	11.2	50.6	128.9	31.5	101.2
55-59.9	165	11.0	47.7	102.2	33.1	95.4
60-64.9	164	10.6	47.2	99.9	32.0	94.4
65-69.9	170	14.3	45.4	96.0	30.8	90.8
70-74.9	122	10.3	45.4	101.9	34.6	90.8
75-79.9	107	10.1	46.8	106.0	36.4	93.6
80-84	93	9.4	42.1	93.3	31.1	84.2

CRL, crown rump length; n, number of cases; SD, standard deviation

Table VI. The 5th, 50th and 95th centile, standard deviation and 2 multiples of median value of maternal uterine artery pulsatility index

CRL in mm	n	Maternal uterine artery pulsatility index				
		5th centile	50th (median)	95th centile	SD	2 MOM
40-44.9	113	0.9	1.6	2.2	0.4	3.2
45-49.9	124	0.9	1.5	2.2	0.4	3.0
50-54.9	146	0.9	1.5	2.1	0.4	3.0
55-59.9	165	0.8	1.4	2.1	0.4	2.8
60-64.9	164	0.8	1.4	2.0	0.4	2.8
65-69.9	170	0.7	1.3	2.0	0.4	2.6
70-74.9	122	0.6	1.3	1.9	0.4	2.6
75-79.9	107	0.6	1.2	1.9	0.4	2.4
80-84	93	0.5	1.2	1.9	0.4	2.4

CRL, crown rump length; n, number of cases; SD, standard deviation; MOM, multiples of median

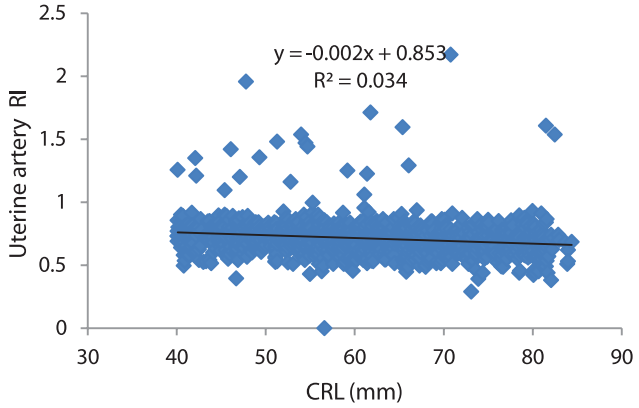

Fig. 6. Regression plot of uterine artery resistance index (RI) with crown rump length (CRL) along the X-axis.

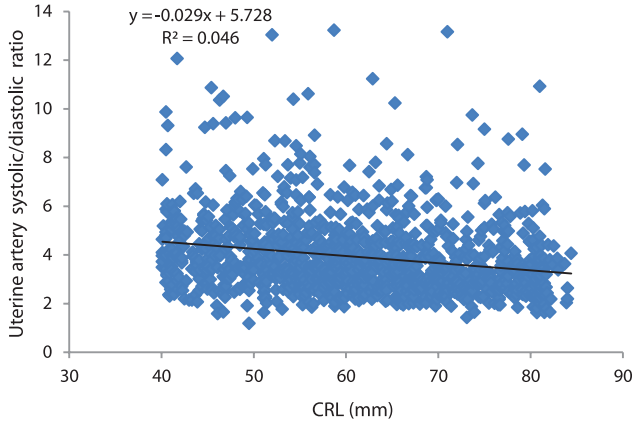

Fig. 7. Regression plot of uterine artery systolic/diastolic ratio (standard deviation) with crown rump length (CRL) along the X-axis.

40 mm CRL was 10 wk four days, and the 95th centile for the CRL of 84 mm was 15 wk three days; similar findings have been observed in the centile charts by Papageorghiou *et al*[14].

The values of biomarkers have been expressed as MOM because it has been seen that, although the value of the parameters differs in various regions of the world, their degree of rise or fall above normal is almost constant, therefore when the values are expressed as MOM, the racial difference is eliminated[15]. In this study the normal range of values (5th-95th centile) and the median (1MOM) of different variables according to CRL was derived, which would act as a reference for Indian women. For NT and free β-hCG, 2 MOM and for PAPP-A 0.4 MOM are taken as cut-off[16,17].

In the present study, there was not much difference between the mean and median value of NT, indicating a normal distribution pattern. The mean NT in the present study was 1.3 mm which was lower than 1.7 mm reported in the Australian population and 1.6 mm in Taiwanese population[9,18]. Various other studies have also found that the NT values differ among populations. NT MOM values were lower in Africans and Asians, but higher in Orientals (P<0.05; in each case) in the study by Ardawi *et al*[19]. There was the difference in NT measurements between different regions of the Asian population, the NT of more than 2.5 mm was seen in six per cent Taiwanese women, and four per cent Korean population but was seen in only 0.3 per cent women in the present study[9,20]. Apart from ethnic variation, the discrepancy may have been due to exclusion of adverse outcomes such as IUGR, IUD or foetal anomaly and inclusion of only normal outcome cases in the present study. One previous study has also shown lower NT measurements compared to previous literature, with values similar to the present study[21].

The value of PAPP-A increased with gestation, suggesting its association with growing placenta. The

level of free β-hCG however, showed a decrease with increasing gestation. The β-hCG in maternal serum is derived from the placenta, and as the placenta becomes mature the concentration declines[22]. Ardawi *et al*[19] found a significant difference in the levels of biomarkers between different ethnic groups. Spencer *et al*[12] found that the median values of free β-hCG and PAPP-A were higher in Afro-Caribbean women and Asian women, compared to Caucasian women. It was estimated that correcting for maternal weight and ethnicity would increase the detection rate by a modest 1.4 per cent. However, it would lead to as much as two-fold increase in the patient-specific risk for trisomy 21. They concluded that larger studies were required to develop robust algorithms for correcting for ethnic origin in the first trimester[12]. In our previous study[23], it was found that taking 0.4 MOM as cut-off for PAPP-A and 2 MOM for Ut A PI gave sensitivity and specificity of 73 and 70 per cent, respectively, this supported the validity of the observations of the present study [24].

The U-RI and U-PI values decreased with advancing gestation from 11 to 14 wk. The trophoblastic invasion increases with gestation, leading to decrease in impedance in uterine vessels thus causing a decrease in Doppler parameters[22]. In our study, the mean UtA-PI was 1.54±0.4 which was similar to a study by Alves *et al*[24] on the Brazilian population (1.5±0.6 at 12 wk). The mean Ut A-PI values in the study by Gómez *et al*[25] was 1.75, which was higher than the present study. The values may have been higher due to use of transvaginal US as other studies have found significant differences in Ut A-PI measurements between the transvaginal and the transabdominal routes, the values being lower when obtained transabdominally.

In the present study, although the correlation of the markers with CRL was significant, the observations were scattered around the mean, and therefore, the correlation coefficient was low for Doppler parameters and free β-hCG whereas it was moderate for NT and PAPP-A. This could be one major limitation of the study. The strength of the study was that the normal ranges of aneuploidy screening and Doppler parameters were determined in a large number of Indian pregnant women with normal outcome. Although studies for preeclampsia and other adverse pregnancy outcome using these values have been done[7,23], its validity in aneuploidy screening is yet to be determined, and more studies are required for this purpose[26].

In conclusion, the normal range of values of different variables depending on the gestation (CRL) was derived, which would act as a reference for our population and would be beneficial in calculating the risk of an adverse materno-foetal outcome.

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***Conflicts of Interest*:** None.

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