Vol. 9. No. 1. 2022

Contents available at:
http://www.crdeepjournal.org/category/journals/global-journal-of-current-reseach-gjcr/
DOI: https://doi-ds.org/doilink/10.2020-51948721/

Global Journal of Current Research (ISSN: 2320-2920) CIF: 3.269
A Quarterly Peer Reviewed Journal

Full Length Research Paper

Evaluation of Sex Specific Circulatory Differences in Cerebroplacental Doppler Measurements

Hanaa Ahmed Farouk Hussein [1], Alaa Eldin Mahmoud Megahed [2], Mahmoud Farouk Midan [3]
Department of Obstetrics and Gynecology, El-Zarka Central Hospital, Damietta, Egypt
Department of Obstetrics and Gynecology, Damietta Faculty of Medicine, Al-Azhar University, Egypt.

ARTICLE INFORMATION

Corresponding Author:
Hanaa A. F Hussein

Article history:
Received: 10-01-2022
Revised: 18-01-2022
Accepted: 25-01-2022
Published: 08-02-2022

Key words:
Doppler Ultrasound;
Umbilical Artery;
Middle Cerebral Artery;
Cerebroplacental;
Pulsatility Index

ABSTRACT

Background: *Ultrasound is a feasible, non-invasive, readily available tool for monitoring or diagnosis of pregnancy associated abnormal conditions. However, the normal values related to the sex of the fetus are not sufficiently examined yet.* ***Aim of the work:*** *The current study was designed to evaluate the association between fetal sex and different fetal Doppler indices in normal pregnancy.* ***Methodology:*** *The study included 200 pregnant females with normal singleton pregnancy, which completed their pregnancy normally (without the development of any medical conditions during their gestation) and all delivered a full-term neonate. All were clinically evaluated by full history taking, physical examination and ultrasound examination during their regular antenatal care visits. All data were documented after obtaining a full informed consent for participation. Values at 28, 32, 36 weeks of gestation were included in the statistical analysis. Also, values just before delivery were added.* ***Results:*** *The delivery mode was normal vaginal delivery among 68.0% of all participants. The placental weight showed significant increase in male's neonate than the female's neonate group (634.0±41.0 vs. 614.0±44.0 g). The umbilical artery pulsatility index (PI) was significantly increased in the female than male neonates groups at 28, 32, and 36 weeks of gestation (1.23±0.10, 0.94±0.12 and 0.88±0.09 vs. 1.10±0.08, 0.83±0.09, and 0.77±0.08 respectively) and before delivery. In addition, there was progressive reduction of umbilical artery PI from 28 weeks of gestations to values just before delivery. Umbilical artery resistance index (RI), middle cerebral PI and RI, systolic/diastolic ratio showed similar statistical results. Otherwise, cerebroplacental ratio (CPR) significantly increased in males than females neonate groups at 28, 32 and 36 weeks of gestation and just before delivery, and it was progressively increased with advanced pregnancy.* ***Conclusion:*** *There are sex-specific differences in fetal Doppler indices (umbilical and middle cerebral arteries) during the third trimester of normal pregnancy.*

Introduction

The practice of ultrasound examination is among the most principal tools of current obstetric evaluation. In particular, Doppler ultrasonography provides valuable data about fetal circulation and fetal hemodynamic conditions [(1)]. In the earlier literature, sex-related variances have been observed in fetal development regarding physical growth and adaptation to intrauterine circumstances [(2)]. Male gender is an independent risk factor for adverse perinatal outcomes, such as fetal stress during labor [(3)], prematurity [(4)], and unfavorable neonatal sequels [(5)], while the overall mortality from the conception to childbirth is higher in female gender [(6)]. Furthermore, the neonatal birth weight and placental weight were reported to be greater in males than in females. Sexual differentiations in the regulation and representation of genetic materials and signaling pathways [(7)], leads to variations in the functioning of the placenta and subsequently in the intrauterine conditions that may lead to sex disparities in the health condition in later years [(8)].

Many Doppler indices are used to assess the fetal well-being among patients with high risk pregnancy, and to predict the outcome of those with intra-uterine growth restriction. Among these, the umbilical artery (UA) Doppler indices are frequently used. UA indices include the UA pulsatility index (UAPI), UA resistance index (UARI), and UA systolic to diastolic ratio (S/D). All these indices are computed from the recording of blood flow velocities. The increased UAPI is an indicator of elevated placental vascular resistance related to microvascular injuries and consistently decreased placental function [9]. Assessment of the fetal placental circulation and function of the cardiac system during 28-34 gestational weeks revealed that there was elevated preload and decreased afterload (significant decrease of UAPI) in male fetuses [10]. Another cross-sectional study examined maternal hemodynamics and placental circulation, determined significant decrease of UAPI in males than female fetuses at 22+0 to 24+0 weeks of gestation [11]. The fetal Doppler testing of the middle cerebral artery had a significant role in evaluating fetal cardiovascular disease, fetal anemia, or fetal hypoxia. In the proper condition, it is very useful as a complement to the Doppler assessment of the umbilical artery [12].

Aim of the work

The aim of this study was to assess the effect of fetal gender on umbilical artery and middle cerebral artery Doppler indices and to establish sex specific references for clinical use.

Patients and methods

This was prospective cohort study. It had been carried at the Department of Obstetrics and Gynecology, Al-Azhar University Hospital (Damietta Faculty of Medicine, Al-Azhar University). It included 200 females, as a convenient sample. Female was included if it had an uncomplicated singleton pregnancy, that completed with development of any complication and it had been participated at gestational age 28 weeks until delivery. On the other side, female was excluded if she had multiple pregnancy, fetal growth restriction, preeclampsia or gestational diabetes, prematurity or preterm labor, known fetal anomaly as chromosomal or structural anomalies in the current pregnancy, maternal age < 20 years, and chronic medical disease (e.g., diabetes mellitus, liver disease, renal diseases, connective tissue disease and other systemic disorders). Participants were divided into two groups according to fetal gender. The first group for male neonates (n=114) and the second for female neonates (n=86). All participants were submitted to clinical evaluation, ultrasound and Doppler examination. All Doppler measurements were performed by a single experienced (more than 10 years' experience) operator.

Technique of Doppler: Patient in supine position, semi-sitting and the Doppler was done in the absence of the fetal breathing movements starting from 28 weeks every 4 weeks until delivery. The setting of Doppler machine was adjusted to the following values: 50-100 Hz for high-pass filter in the modes of imaging and Doppler to avoid signals from slowly in-motion organs. The power was set to <50 mW/cm^2 spatial temporary average velocity in both modes and the sample volume was 2–3 mm for the MCA. The insonation angle always preserved below 10 degrees (close to 0), and correction of the angle was applied if it was not zero. To confirm the Doppler documentation of the longitudinal highest blood velocity, an extended sample gate of 5-12 mm is applied according to the gestational age. Images were frozen during periods of stopped fetal breathing and movements, and the waveforms were quantified. Unnecessary pressure on the fetal head was avoided and both thermal and mechanical and indices were always kept below 1. To measure Doppler indices for the MCA, an ultrasound scan of the fetal head was done to get a transverse view at the level used to measure BPD. The transducer was then moved parallel to this plane towards the skull base at the level of the sphenoid bone lesser wing to recognize the circle of Willis. At the level of the sphenoid bone lesser wing, the MCA was easily verified as a major branch of the circle of Willis. After MCA localization by color Doppler flow, velocity was measured from its proximal portion. At least three waveforms were measured by sonographer and the average value was used in analysis. Multiple waveforms recordings were obtained and resistance index (RI), pulsatility index (PI) and systolic/diastolic (S/D) ratio were calculated:

RI = Peak systolic velocity (PSV) - end diastolic velocity/PSV
PI = PSV - end diastolic velocity/mean velocity
S/D ratio = Peak systolic velocity/End diastolic velocity
Cerebroplacental ratio (CPR): MCA PI/ UA PI

Blood flow velocity waveforms of the umbilical artery were obtained from the free-floating loops of the umbilical cord using color Doppler. Spectral trace was get with a 4 mm sample volume from the free loop of the umbilical cord (UC). In difficult identification the free loop of the UC, the placental insertion of the cord was tracked along to help the identification of the free loop. PI and RI were measured in the automatic mode for three consecutive cardiac cycles. The measurements were repeated and two successive identical readings were finally documented and considered for the study.

Estimated fetal weight

The estimated fetal weight is calculated every interview by measuring the bi-parietal diameter (BPD), abdominal circumference (AC), and femur length (FL) built on the Hadlock 2 formula [13]. Briefly, BPD and HC were measured in an axial section, at the level of the thalami, preserving midline echo in the central position broken anteriorly by cavum septum pellucidum, provided that, orbitae and cerebellum were non-visible.

The BPD callipers were positioned on the proximal parietal bone outer margin, and the distal parietal bone inner margin. HC was measured by placing the callipers on the frontal and occipital outer borders, and the contours of the skull were traced. AC was measured in cross-section, provided that, it was in the abdominal circular view with visible stomach, the umbilical vein in the anterior abdominal third and the aorta and inferior vena cava anterior to the spine. Further, the majority of a rib must be seen, but not the heart or kidneys. AC was measured using the ellipse to follow the outer contours of the skin. FL was measured in a longitudinal section of the femur in 45°–90° angle of insonation, with placing of callipers on the outer edges of the femoral diaphysis [14].

Ethical consideration

The study protocol had been submitted and approved by the local research and ethics committee, Damietta Faculty of Medicine, Al-Azhar University, Egypt (IRB00012367-19-10-003). All females accept to participate and signed an informed consent, with preservation of all rights. The study had been completed according to Helsinki Declaration of Research Conduct and Reporting. The Research did not receive any fund and the research completed funded by him.

Statistical analysis of data

All documented measures were anonymized and fed to statistical computer packages for analysis. Data if categorical were explained by the calculation of the relative frequency and percentages, and if numerical, were expressed in the form of arithmetic mean and standard deviation. Groups were compared by Chi square or student "t) tests, for categorical and numerical variables, respectively. P value < 0.05 was set as the significant level.

Results

In the current work, the maternal age ranged between 18 and 40 years, and there was no significant difference between group 1 (male neonates) and 2 (female neonates), regarding maternal age (28.47±4.07 vs 29.07±4.59 years, respectively). The majority of participating females were Egyptians (81.0%), followed by Syrian (14.0%) and Yamani (5.0%), and there was no significant difference between study and control groups. The body mass index (BMI) of females at the beginning of pregnancy ranged between 22.76 and 28.04 kg/m^2 and there was no significant difference between groups 1 and 2 (24.74±1.15 vs. 24.97±1.28 kg/m^2, respectively) (Table 1).

Mode of delivery was normal vaginal delivery (NVD) among the majority of studied females (68.0%) followed by cesarean section (19.0%) and finally assisted NVD (13.0%). There was no significant difference between group 1 (male neonates) and 2 (female neonates) regarding the mode of delivery. Gestational age (GA) at delivery ranged between 37 and 42 weeks of gestation, and there was no significant difference between groups (39.21±1.1 vs. 39.06±1.16 weeks of gestation, in groups 1 and 2 respectively). Birth weight ranged from 2.38 to 3.65 kg and there was no significant difference between group 1 (male neonates) and 2 (female neonates) (3.000±0.208 vs 3.039± 0.211 respectively). Placental weight ranged between 530 and 720 g, and there was significant increase of placental weight in the first group (male neonates) when compared to group 2 (female neonates) (634.0±41.0 vs. 614.0±44.0 g, respectively) (Table 2).

The umbilical artery PI was significantly increased in the female than male neonates groups at 28, 32, and 36 weeks of gestation (1.23±0.10, 0.94±0.12, and 0.88±0.09 vs. 1.10±0.08, 0.83±0.09, and 0.77±0.08) respectively. Similar situation was documented such before delivery. In addition, there was progressive reduction of umbilical artery PI from 28 weeks of gestations to values just before delivery. RI showed similar situation (Detailed results are depicted table 3). Middle cerebral artery PI and RI were significantly increased in females than males at 28, 23, 36 weeks of gestation and just before delivery. In addition, there was progressive decrees in PI and RI with advancement of pregnancy (Table 3).

In the current study, S/D ratio was significantly increased in females than males at 28, 23, 36 weeks of gestation and just before delivery. In addition, there were progressive decrees in S/D ratio with advancement of pregnancy. However, fetal heart rate at 36 weeks of gestation did not differ significantly between groups. After that, it showed significant increase among females than males, at 32, and 36 weeks of gestation and just before delivery (Table 4). Estimated fetal weigh was reduced among males than females at 28 weeks of gestation and similar situation was documented for birth weight. However, at 32 and 36 weeks of gestation, estimated fetal weight was higher among males than females. For all times, the difference was statistically non-significant (Table 4).Cerebroplacental ratio (CPR) significantly increased in males than females neonate groups at 28, 32 and 36 weeks of gestation and just before delivery. From week 28 to the delivery in each group, the CPR progressively increased (Table 4).

Table (1): Comparison between groups regarding data of participating females

		Males (n=114)	Female (n=86)	Test	p
Maternal age (years)	Mean±SD,	28.47±4.07;	29.07±4.59;	0.97	0.33
	min.-max.	19-36	18-40		
Nationality (n,%)	Egyptian	93(81.6%)	69(80.2%)	1.34	0.51
	Syrian	17(14.9%)	11(12.8%)		
	Yamani	4(3.5%)	6(7.0%)		
BMI (kg/m^2)	Mean±SD,	24.74±1.15;	27.97±1.28;	1.31	0.19
	min.-max.	23.23-28.03	22.76-28.04		

Table (2): Comparison between groups regarding data of delivery

		Males (n=114)	Female (n=86)	Test	p
Mode of	NVD	73(64.0%)	63(73.3%)	2.39	0.30
Delivery (n,%)	Assisted NVD	18(15.8%)	8(9.3%)		

	CS	23(20.2%)	15(17.4%)		
Gestational age at delivery (week)	Mean±SD, min.-max.	39.21±1.1; 37-41	39.06±1.16 37-42	0.96	0.33
Birth weight (kg)	Mean±SD, min.-max.	3.005±0.20872, 2.39-3.65	3.0392±0.21112, 2.38-3.65	1.33	0.18
Placental weight (g)	Mean±SD, min.-max.	634.0±41.0, 550-720	614.0±44.0, 530-720	***3.31***	***<0.001****

Table (3): Comparison between groups regarding umbilical and middle cerebral arteries Doppler indices

		Male (n=114)	**Female (n=86)**	***Test***	***p***
UA PI	28 weeks	1.10±0.08	1.23±0.10	***10.19***	***<0.001****
	32 weeks	0.83±0.09	0.94±0.12	***6.55***	***<0.001****
	36 weeks	0.77±0.08	0.88±0.09	***8.19***	***<0.001****
	Before delivery	0.71±0.08	0.81±0.09	***8.57***	***<0.001****
UA RI	28 weeks	0.61±0.06	0.70±0.05	***11.50***	***<0.001****
	32 weeks	0.59±0.06	0.68±0.05	***11.68***	***<0.001****
	36 weeks	0.57±0.05	0.67±0.06	***11.83***	***<0.001****
	Before delivery	0.56±0.06	0.66±0.05	***12.23***	***<0.001****
MCA PI	28 weeks	1.79±0.20	1.84±0.16	***1.99***	***0.048****
	32 weeks	1.75±0.18	1.82±0.15	***2.89***	***0.004****
	36 weeks	1.69±0.18	1.78±0.14	***3.77***	***<0.001****
	Before delivery	1.68±0.17	1.76±0.14	***3.83***	***<0.001****
MCA RI	28 weeks	0.72±0.04	0.79±0.02	***10.46***	***<0.001****
	32 weeks	0.67±0.04	0.72±0.02	***10.42***	***<0.001****
	36 weeks	0.61±0.04	0.67±0.02	***11.83***	***<0.001****
	Before delivery	0.56±0.04	0.62±0.03	***11.05***	***<0.001****

Table (4): Comparison between groups' regarding S/D ratio and fetal heart rate overtime

		Male (n=114)	**Female (n=86)**	***Test***	***p***
S/D ratio	28 weeks	3.56±0.21	4.07±0.23	***15.79***	***<0.001****
	32 weeks	2.76±0.19	3.30±0.22	***18.56***	***<0.001****
	36 weeks	2.51±0.21	3.08±0.24	***18.24***	***<0.001****
	Before delivery	2.34±0.23	2.98±0.24	***19.07***	***<0.001****
Fetal heart rate	28 weeks	143.18±4.69	144.33±4.05	***1.80***	***0.07***
	32 weeks	141.48±4.89	143.19±3.50	***2.74***	***0.007****
	36 weeks	140.18±4.69	141.64±4.01	***3.11***	***0.022****
	Before delivery	139.18±4.69	140.73±3.77	***2.51***	***0.013****
Estimated fetal weight (g)	28 weeks	1170.86±102.32	1188.54±81.25	1.32	0.19
	32 weeks	1965.79±28.24	1961.39±67.0	0.63	0.53
	36 weeks	2506.62±227.52	2472.65±190.76	1.12	0.26
	Birth weight	3000.50±208.72	3040.6±211.12	1.34	0.18
Cerebroplacental ratio	28 weeks	1.63±0.19	1.50±0.18	***4.77***	***<0.001****
	32 weeks	2.12±0.34	1.97±0.31	***3.13***	***0.002****
	36 weeks	2.21±0.32	2.06±0.28	***3.40***	***0.001****
	Before delivery	2.40±0.36	2.21±0.31	***3.90***	***<0.001****

Discussion

There is a growing body of evidence that the fetal sex lead to different placental development. Thus, fetal sex must be included as a biological parameter in the study designs and in clinical decision-making [15]. This confirmed by a recent meta-analysis, which concluded that fetal sex is associated with multiple complications of pregnancy (e.g., preeclampsia at term and diabetes of pregnancy) [16]. In addition, there was a specific sex-related difference in hemodynamic Doppler indicators of placental and fetal maturation. The sex associated differences in healthy pregnant mothers during the second half of pregnancy had been reported for different Doppler indicators (for example, umbilical artery pulsatility index and cerebroplacental ratio. In addition, the MCA pulsatility index was found to be dependent on the fetal sex, immediately before active labor [17, 18]. Ultrasound is the standard-of-care method to assess fetal well-being during pregnancy. The reference ranges for ultrasound-originated indices of placental and fetal wellbeing are already established [19-21]; however, the fetal sex differences did not considered. Thus, the current study had been designed to evaluate the association between fetal gender and different Doppler indices in normal pregnancy. The value of the study is based on the suggestion that, if

Doppler indices are different between males and females, fetal sex must be considered in all future studies examine the value of Doppler indices to assess disorders of pregnancy.
Results of the current study revealed that, pulsatility indices of umbilical and middle cerebral arteries were significantly different between males and females. In addition, S/D and cerebroplacental ratio were significantly different based on the fetal sex. However, the estimated fetal and birth weights did not differ significantly between fetal males and females. Fetal heart rate increased significantly among females than males, except at 28 weeks of gestation. All Doppler indices showed progressive change over time (with advancement of pregnancy).

The umbilical artery PI was regularly used as an indicator of placental vascular resistance, aiming to recognize or predict fetal growth restriction that requires additional evaluation and early intervention [(22, 23)]. The differences of UA PI specific to fetal sex, observed in the current work, agree with that reported by Widnes *et al*. [(17)]. This study was carried for healthy pregnant females, as the current one. They also reported significant increase of PI in females than males (at 20-33 weeks of gestation). However, this difference was abolished at the end of pregnancy, which contradicts to the current work, where the differences continued till the end of pregnancy.
Jagota *et al*. [(15)] however, reported significant increase of UAPI among females than females from 28 weeks of gestation to the end of the pregnancy, as in the current study.

The possible explanation of such controversy may be attributed to different location of UAPI measurement (placental end vs. free loop) [(17)]. UA PI increased at the placental end [(24)]. Thus, International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommended the use of a fixed site (placental end) when measure UAPI in their recent guidelines [(14, 25)].

Birth weight and estimated fetal weight did not differ significantly between males and females in the current study. This is against the usual expectation reported and confirmed by Jagota *et al*. [(15)]. On the other side and in agreement with the current work, Widnes *et al*. [(17)] did not find any significant differences in birth weight between males and females. Owen *et al*. [(26)] reported that, UA pulsatility index did not depend on the fetal weight. These and our results confirm the effect of fetal sex on the Doppler indices. However, our results could not confirm the sex specific variances in estimated fetal weight and fetal weight [(27)], but confirmed the difference in placental weight [(28)].

Another study reported significant differences between male and female fetuses regarding estimated fetal weight [(29)]. These results contradict to our findings; however, these results could be explained in the light of different sample size. Anyway, the current results confirm that the differences observed in Doppler indices are due to fetal sex and estimated fetal weight did not play a role in such changes.

In the line with the results of the current work, Prior *et al*. [(30)] reported a significant elevation of MCA PI in healthy females then healthy male fetuses immediately prior to active labor. All pregnancies in current study were normal and not complicated (as per inclusion and exclusion criteria). The significant differences in Doppler indices did not reflect a pathological condition in the female placenta. However, it may reflect a specific pattern in placental vascular impendence, which could be associated with sex-specific outcome of pregnancy. For instance, the early onset preeclampsia (developed before the 34 weeks of gestation) was highly reported in pregnancies of female fetuses [(31, 32)] and had an increased resistance of umbilical arteries [(33, 34)].

In addition, Clifton *et al*. [(7)] observed that, the placenta of female fetus responds to adverse environmental conditions with more gene alterations than the male fetus placenta. Furthermore, they observed that, in maternal asthma during pregnancy, the female fetus growth was decreased than that of the male fetus. However, during acute asthma exacerbations, the male fetus is at a higher risk of restricted growth.

Another important finding from this study was that females had higher HR than male fetuses after 28 weeks gestation that continued toward delivery. These results had been also been reported in previous works of Amorim-Costa *et al*. [(35)] and Schalekamp-Timmermans *et al*. [(10)]. In an interesting study, Widnes *et al*. [(17)] reported that, male and female fetuses in normal pregnancy showed non-significant difference regard fetal heart rate from 20 to 26 weeks of gestation, but after that, females had significantly higher HR than males. These results are consistent with the current work regarding values from 32 weeks to just before delivery. A plausible explanation of higher heart rate among females could be related to different levels of hormones and autonomic nervous system rate of maturation. Higher variability of the fetal heart rate [(36)], more complex patterns of fetal heart rate [(37)], and higher levels of catecholamine observed in female than male fetuses. The current work also confirms the results reported by Schalekamp-Timmermans *et al*. [(10)] and Widnes *et al*. [(11)]. They reported sex-specific differences in UA Doppler indicators during the second half of pregnancy that tapered off with pregnancy advancement towards delivery.

The association of male gender is already established and the current work adds to the known literature. For example, the male sex was associated with increased fetal distress during delivery [(3)], prematurity [(4)], and early neonatal death [(2, 38)].

In short, results of the current work highlighted the sex-specific differences in umbilical and middle cerebral arteries Doppler indices during the third trimester of normal pregnancy. These differences could participate, work as a potential predictor and monitor high risk pregnancies. The main advantages lie behind non-invasive examination, simplicity and incorporation in clinical practice. The strict inclusion and exclusion criteria of the current study add to the value of the obtained results. However, results should be treated cautiously till a larger future studies will be performed, and globalization of results will be obtained.

On the basis of the current results, it is recommended to
1-Take fetal gender into account in all clinical evaluations of pregnant mothers
2-Consider fetal sex as a biological variable in all future studies dealing with any abnormal conditions associated with pregnancy.
3-Design future studies to discover other aspects and roles the fetal gender could affect in the pregnant mothers
4-Examine – in the future studies- the role of fetal sex (if it had a role or not and to what extent) in pregnancy-associated medical diseases.

References
1. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017 Jun 13;6(6):CD007529. doi: 10.1002/14651858.
2. Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? Gend Med. 2007 Mar;4(1):19-30. doi: 10.1016/s1550-8579(07)80004-0.
3. Dunn L, Prior T, Greer R, Kumar S. Gender specific intrapartum and neonatal outcomes for term babies. Eur J Obstet Gynecol Reprod Biol. 2015 Feb; 185:19-22. doi: 10.1016/j.ejogrb.2014.11.035.
4. Peelen MJ, Kazemier BM, Ravelli AC, De Groot CJ, Van Der Post JA, Mol BW, Hajenius PJ, Kok M. Impact of fetal gender on the risk of preterm birth, a national cohort study. Acta Obstet Gynecol Scand. 2016 Sep;95(9):1034-41. doi: 10.1111/aogs.12929.
5. Peacock JL, Marston L, Marlow N, Calvert SA, Greenough A. Neonatal and infant outcome in boys and girls born very prematurely. Pediatr Res. 2012 Mar;71(3):305-10. doi: 10.1038/pr.2011.50.
6. Orzack SH, Stubblefield JW, Akmaev VR, Colls P, Munné S, Scholl T, Steinsaltz D, Zuckerman JE. The human sex ratio from conception to birth. Proc Natl Acad Sci U S A. 2015 Apr 21;112(16): E2102-11. doi: 10.1073/pnas.1416546112.
7. Clifton VL. Review: Sex and the human placenta: mediating differential strategies of fetal growth and survival. Placenta. 2010 Mar;31 Suppl: S33-9. doi: 10.1016/j.placenta.2009.11.010.
8. Gabory A, Roseboom TJ, Moore T, Moore LG, Junien C. Placental contribution to the origins of sexual dimorphism in health and diseases: sex chromosomes and epigenetics. Biol Sex Differ. 2013 Mar 21;4(1):5. doi: 10.1186/2042-6410-4-5.
9. Narendran N, Yusuf K. Fetal Doppler Assessment in Neonatal Care: Analysis of Fetal Doppler Abnormalities and Neonatal Outcomes. Neoreviews. 2019 Oct;20(10): e575-e583. doi: 10.1542/neo.20-10-e575. PMID: 31575779.
10. Schalekamp-Timmermans S, Cornette J, Hofman A, Helbing WA, Jaddoe VW, Steegers EA, Verburg BO. In utero origin of sex-related differences in future cardiovascular disease. Biol Sex Differ. 2016 Oct 13; 7:55. doi: 10.1186/s13293-016-0108-4.
11. Widnes C, Flo K, Acharya G. Exploring sexual dimorphism in placental circulation at 22-24 weeks of gestation: A cross-sectional observational study. Placenta. 2017 Jan; 49:16-22. doi: 10.1016/j.placenta.2016.11.005.
12. Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoonmade LJ, Bossuyt PMM, Mol BWJ, De Groot CJM, Bax CJ. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018 Mar;51(3):313-322. doi: 10.1002/uog.18809.
13. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985 Feb 1;151(3):333-7. doi: 10.1016/0002-9378(85)90298-4.
14. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, Glanc P, et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol. 2019 Jun; 53(6):715-723. doi: 10.1002/uog.20272.
15. Jagota D, George H, Walker M, Ravi Chandran A, Milligan N, Shinar S, Whitehead CL, Hobson SR, Serghides L, Parks WT, Baschat AA, Macgowan CK, Sled JG, Kingdom JC, Cahill LS. Sex differences in fetal Doppler parameters during gestation. Biol Sex Differ. 2021 Mar 10;12(1):26. doi: 10.1186/s13293-021-00370-7.
16. Broere-Brown ZA, Adank MC, Benschop L, Tielemans M, Muka T, Gonçalves R, Bramer WM, Schoufour JD, Voortman T, Steegers EAP, Franco OH, Schalekamp-Timmermans S. Fetal sex and maternal pregnancy outcomes: a systematic review and meta-analysis. Biol Sex Differ. 2020 May 11;11(1):26. doi: 10.1186/s13293-020-00299-3.
17. Widnes C, Flo K, Wilsgaard T, Kiserud T, Acharya G. Sex differences in umbilical artery Doppler indices: a longitudinal study. Biol Sex Differ. 2018 Apr 18;9(1):16. doi: 10.1186/s13293-018-0174-x.
18. Acharya G, Ebbing C, Karlsen HO, Kiserud T, Rasmussen S. Sex-specific reference ranges of cerebroplacental and umbilicocerebral ratios: longitudinal study. Ultrasound Obstet Gynecol. 2020 Aug;56(2):187-195. doi: 10.1002/uog.21870.
19. Guedes-Martins L, Cunha A, Saraiva J, Rita-Gaio A, Cerdeira AS, Macedo F, Almeida H. Foetal aortic flow velocity waveforms in healthy and hypertensive pregnant women. Cardiovasc Ultrasound. 2014 Jan 27; 12:1. doi: 10.1186/1476-7120-12-1.
20. Turan OM, Turan S, Sanapo L, Willruth A, Berg C, Gembruch U, Harman CR, Baschat AA. Reference ranges for ductus venosus velocity ratios in pregnancies with normal outcomes. J Ultrasound Med. 2014 Feb; 33(2):329-36. doi: 10.7863/ultra.33.2.329.
21. Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebro-placental ratio: systematic review. Ultrasound Obstet Gynecol. 2019 Apr;53(4):454-464. doi: 10.1002/uog.20102.
22. Salavati N, Smies M, Ganzevoort W, Charles AK, Erwich JJ, Plösch T, Gordijn SJ. The Possible Role of Placental Morphometry in the Detection of Fetal Growth Restriction. Front Physiol. 2019 Jan 8; 9:1884. doi: 10.3389/fphys.2018.01884.

23. Schwartz N, Sammel MD, Leite R, Parry S. First-trimester placental ultrasound and maternal serum markers as predictors of small-for-gestational-age infants. Am J Obstet Gynecol. 2014 Sep;211(3): 253.e1-8. doi: 10.1016/j.ajog.2014.02.033.
24. Bhide A, Badade A, Khatal K. The effect of sampling site on the variability of Umbilical artery PI. Eur J Obstet Gynecol Reprod Biol. 2019 Apr; 235:102-105. doi: 10.1016/j.ejogrb.2018.12.026.
25. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013 Feb;41(2):233-39. doi: 10.1002/uog.12371.
26. Owen P, Murphy J, Farrell T. Is there a relationship between estimated fetal weight and umbilical artery Doppler impedance indices? Ultrasound Obstet Gynecol. 2003 Aug;22(2):157-9. doi: 10.1002/uog.188. PMID: 12905510.
27. Johnsen SL, Rasmussen S, Wilsgaard T, Sollien R, Kiserud T. Longitudinal reference ranges for estimated fetal weight. Acta Obstet Gynecol Scand. 2006; 85:286–97.
28. Wallace JM, Bhattacharya S, Horgan GW. Gestational age, gender and parity specific centile charts for placental weight for singleton deliveries in Aberdeen, UK. Placenta. 2013 Mar;34(3):269-74. doi: 10.1016/j.placenta.2012.12.007.
29. Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, Giordano D, Cecatti JG, Abdel Aleem H, Talegawkar SA, *et al*. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med. 2017;14: e1002220.
30. Prior T, Wild M, Mullins E, Bennett P, Kumar S. Sex specific differences in fetal middle cerebral artery and umbilical venous Doppler. PLoS One. 2013;8(2):e56933. doi: 10.1371/journal. pone.0056933.
31. Taylor BD, Ness RB, Klebanoff MA, Tang G, Roberts JM, Hougaard DM, Skogstrand K, Haggerty CL. The impact of female fetal sex on preeclampsia and the maternal immune milieu. Pregnancy Hypertens. 2018 Apr; 12:53-57. doi: 10.1016/j.preghy.2018.02.009.
32. Paranavitana L, Walker M, Chandran AR, Milligan N, Shinar S, Whitehead CL, Hobson SR, Serghides L, Parks WT, Baschat AA, Macgowan CK, Sled JG, Kingdom JC, Cahill LS. Sex differences in uterine artery Doppler during gestation in pregnancies complicated by placental dysfunction. Biol Sex Differ. 2021 Feb 2;12(1):19. doi: 10.1186/s13293-021-00362-7.
33. Hu X, Zhang L. Uteroplacental Circulation in Normal Pregnancy and Preeclampsia: Functional Adaptation and Maladaptation. Int J Mol Sci. 2021 Aug 11; 22(16):8622. doi: 10.3390/ijms22168622.
34. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension. 2008 Apr;51(4):970-5. doi: 10.1161/HYPERTENSIONAHA.107.107607.
35. Amorim-Costa C, Cruz J, Ayres-de-Campos D, Bernardes J. Gender-specific reference charts for cardiotocographic parameters throughout normal pregnancy: a retrospective cross-sectional study of 9701 fetuses. Eur J Obstet Gynecol Reprod Biol. 2016; 199:102-7. doi: 10.1016/j.ejogrb.2016.01.036.
36. Bernardes J, Gonçalves H, Ayres-de-Campos D, Rocha AP. Linear and complex heart rate dynamics vary with sex in relation to fetal behavioral states. Early Hum Dev. 2008 Jul;84(7):433-9. doi: 10.1016/j.earlhumdev.2007.12.001.
37. Kim KN, Park YS, Hoh JK. Sex-related differences in the development of fetal heart rate dynamics. Early Hum Dev. 2016 Feb; 93:47-55. doi: 10.1016/j.earlhumdev.2015.12.005.
38. Inkster AM, Fernández-Boyano I, Robinson WP. Sex Differences Are Here to Stay: Relevance to Prenatal Care. J Clin Med. 2021 Jul 5;10(13):3000. Doi: 10.3390/jcm10133000.