ORIGINAL ARTICLE

Umbilical Artery and Middle Cerebral Artery and Cerebroplacental Ratio for Doppler Indices' Reference Ranges

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ABSTRACT

Aim: To investigate the reference values of Doppler indices for umbilical artery and Middle Cerebral Artery as well as Cerebro-placental Ratio and specifically, to evaluate the quality of methodology used on which these reference values are grounded, with the help of already established quality standards for research design, statistical analysis as well as methods of results reporting.

Methodology: The methodological quality of the full-text versions of eligible studies was assessed independently by the same reviewers and a medical statistician (E.S.U.). Disagreements were resolved by consensus or consultation with two other reviewers (A.T.P. and E.F.). Quality criteria for evaluation methodologies of the published articles was developed which was based on the already available research publication[25,36,37]. The methodology evaluation criteria was segregated into two levels, one is study design and the other one is statistics used as well as its reporting methods. Total no. of criteria of quality were 24 to be evaluated.

Results: Generally, methodological quality score was parallel for the research articles designed to evaluate umbilical artery range (median 42%; range 13.8–63.8%). For the studies focusing on middle cerebral artery range showed a median of 48% with a Class interval of 22.1–72.1% whereas the median score of cerebroplacental ratio was 47.1% with a Class interval of 34.6–55.5%.

Conclusion: Rigorous methodology of this review study is the major strength, which is consisted of a standard and well developed methodology of scoring the quality of studies according to their methodology selection as well as the statistical analysis and the level of its interpretation.

Keywords: Umbilical artery, Middle Cerebral Artery, Cerebro-placental Ratio, Doppler indices

INTRODUCTION

The assessment of small-for-gestational–age is done by using doppler velocimetry as this assessment helps in evaluating the prenatal risk factors which may results in negative outcome[1]. Diseases of placenta have been proved to be linked with umbilical artery anomalies as assessed by Doppler velocimetry[2]. Redistribution of blood flow, hypoxia, occurring in fetus depict the cardiovascular adaptations which could be assessed by evaluating alterations in the middle cerebral artery of fetus[3-5]. Therefore, in the intrauterine growth restriction context, it is important to consider declined pulsatility index to prevent brain damage in fetus[6-9]. Literature has proposed that the middle cerebral artery-pulsatility index to umbilical artery-Pulsatility index, and the cerebroplacental ratio independently predict the fetal anomalies[10] as well as C-section[11,12] along with the negative affects at perinatal level.[13-16] So, for the alterations in planning of antepartum investigations and compromised fetus delivery in few conditions, CPR and Doppler indices of middle cerebral artery as well as umbilical artery is currently in use[2,10]. At the same time as the standardization of fetal Doppler signals obtaining methods has been attained[17], numerous reference ranges have been stated as well as the characterization of Doppler progression patterns[18-22].

Hence, literature evident that indication of high risk of fetal demise has clearly been done by qualitative alterations in

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Doppler indices of umbilical artery, for example, the incidence, deficiency or reversal of end-diastolic velocity.[23–25] Whereas, the relationship among the quantitative alterations of doppler indices with regards to middle cerebral artery and umbilical artery, changes recorded using pulsatility index as well as perinatal results and future consequences are not standardized yet.[26–28] Moreover, appropriate or increased gestational age fetuses' Doppler indices as well as postterm pregnancy[29], problems in pregnancy being diabetic[30], and normal dichorionic twin pregnancy[31] are not yet explored[32]. So, it was hypothesized that this evidence lacking may be elucidated to some extent by various Doppler indices to investigate the normal or abnormal results, based on a latest systematic review of indices estimations for fetal biometry[33].

Current study aimed to investigate the reference values of Doppler indices for umbilical artery and Middle Cerebral Artery as well as Cerebro-placental Ratio and specifically, to evaluate the quality of methodology used on which these reference values are grounded, with the help of already established quality standards for research design, statistical analysis as well as methods of results reporting.

METHODS

The planning and conduction of current study was based in accordance with MOOSE group checklist and PRISMA statement for systematic review reporting after approval from Institutional Review Board.

Eligibility criteria, information sources and search strategy: After formulating search strategy with the help of

Professional information specialist. Google scholar, MEDLINE and Web of Science databases were targeted to explore the relevant studies reported from 2017 to 2020. For exploration of more relevant articles, bibliography of all the articles was examined. English language was consider as medium of selected published articles.

Inclusion criteria: Studies in which reference ranges were made for Doppler indices for middle cerebral artery, and umbilical artery as well as Cerebroplacental ratio were included based on observational research design.

Exclusion criteria: Case control studies were excluded if the objective of those studies was other than construction of ranges for Doppler reference ranges as well as the studies were limited to the gestational period greater than 20 weeks or Less than 40 weeks.

Methodological quality assessment: The same medical statistician and reviewers assessed the methodological quality independently in terms of entire-text versions of appropriate research papers. With the mutual consensus or by taking second opinion from supervisor. Quality criteria for evaluation methodologies of the published articles was developed (Table 1 and Table 2)[38] which was based on the already available research publication. [25,36,37] The methodology evaluation criteria was segregated into two levels, one is study design and the other one is statistics used as well as its reporting methods. Total no. of criteria of quality were 22 to be evaluated.

Data extraction: After reviewing the research studies selected according to inclusion/exclusion criteria, data was entered in MS Excel 2013. Evaluation of studies was done by considering the quality assessment criteria for methodologies developed earlier and on that bases the score was assigned 0 or 1 whereas 0 mean higher risk of biasness and 1 means low risk of biasness. The scoring was by taking score of all the possible scores ranges between 0-24. Inter-rater reliability was assessed to make sure the data reliability which was 0.751 (75.1%) that means a good reliability of the evaluated data.

Data analysis: After entering data in SPSS version 23.0, Median score and frequency (percentages) were calculated.

Table 1: Domains based on study design and measurement criteria of risk bias[38]

Domain	Low Risk Bias	High Risk Bias
Design	Clearly described as either cross-sectional or Longitudinal	Not reported Mixture of cross-sectional and longitudinal data
Population	Women reported as coming from population of low risk of pregnancy complications	Women from unselected population; or selected; or at high risk of pregnancy complications; or not reported
Prospective data collection	Prospective study and ultrasound data collected specifically for purpose of constructing charts of fetal Doppler	Retrospective study, data not collected specifically for purpose of constructing charts of fetal Doppler, or unclear (e.g. use of routinely collected data)
Specific scan	Specific scan for research purposes	Routine scan in context of pregnancy assessment
Sample size	*A-priori* determination or calculation of sample size and justification	Lack of *a-priori* sample size determination or calculation and justification
Recruitment period	Reported	Not reported
Consecutive enrolment	Consecutively included patients	Did not include patients consecutively
Inclusion/exclusion criteria	Made clear that women at high risk of pregnancy complications were not included and that women with abnormal outcome were excluded, i.e. an effort was made to include as normal an outcome as possible. As a minimum, the study population should exclude: multiple pregnancy; fetuses with congenital, structural or chromosomal anomaly; fetal death/stillbirth; women with disorders that may affect fetal growth or Doppler (at least should specify exclusion of women with pre-existing hypertension, diabetes mellitus, renal disease and smokers); pregnancy complications (at least pre-eclampsia, SGA/IUGR, prematurity, diabetes mellitus); delivery prior to 37 weeks	Study population included both low- and high-risk pregnancies, or women with abnormal outcome were not excluded. Study population did not exclude fetuses or pregnancies with the characteristics described in the 'low risk' column Exclusions which would have a direct effect on the Doppler, such as fetuses found at birth to be small for dates
Method of dating pregnancy	Clearly described known LMP and sonogram before 14 weeks' gestation demonstrating crown–rump length that corroborates LMP dates (within how many days unspecified)	Not described clearly Gestational age assessment at >14 weeks or gestational age assessment not including ultrasonographic verification
Multicenter study	Study performed with more than one center collaborating	Performed at only one hospital

Table 2: Domains based on Statistical methods and reporting and measurement criteria of risk bias[38]

Domain	Low Risk Bias	High Risk Bias
Perinatal outcome	Collected and reported prospectively	Not reported
Gestational age range	Reported	Not reported
Ultrasound machines and probe type used	Clearly specified	Not clearly specified
Reported sonographers	Number of sonographers reported	Not clearly specified
Sonographer experience	Experienced or specifically trained sonographers clearly reported	Not clearly specified
Blinded measurements	Sonographers were blinded	Not clearly specified
Ultrasound machines quality control measures	Should include the following: assessment of intra-observer variability; assessment of inter-observer variability; image review; image scoring; image storage	Does not contain quality control measures
Protocol	Study described sufficient and unambiguous details of measurement techniques used for fetal Doppler parameters	Study did not describe sufficient and unambiguous details of measurement techniques used for fetal Doppler parameters
Number of measurements taken for each Doppler variable	At least three measures per fetus per scan	Single measure or not specified
Angle correction	Clearly specified	Not clearly specified

RESULTS

Total number of articles found were 152 published articles among which only 35 articles were deliberated for inclusion. A total of 10 articles met the inclusion criteria which were used to assess the methodological quality at predefined criteria.[39-48]
Mean score of all the research articles included in the current study was 49.7% (95%, CI, 45.1-54.1%). For the study design along with statistics used and the way of reporting, the quality assessment mean scores were 45.7 (95% CI, 40.9–50.4%) and 52.6% (95% CI, 47.1–58%), respectively. The most primitive research was published in 2017[48] and the latest in 2020.[48]

Sample size median score was 156 women. On the other hand, the ultrasound examination's median score was 258. Umbilical artery reference ranges were mentioned in 4 studies, reference ranges for Doppler of Middle cerebral artery was reported in 3 studies. In 3 studies, both Umbilical and middle cerebral artery Doppler reference ranges were reported, whereas only 2 studies reported cerebroplacental ratio. Pulse index was given in 4 studies. Generally, methodological quality score was parallel for the research articles designed to evaluate umbilical artery range (median 42.0%; range 13.8–63.8%). For the studies focusing on middle cerebral artery range showed a median of 48.0% with a Class interval of 22.1–72.1% whereas the median score of cerebroplacental ratio was 47.1% with a Class interval of 34.6–55.5%.

Prospective research studies were 8. 1 study was longitudinal in nature, whereas 7 studies were crossectional in nature. 5(50%) studies included low risk pregnancies, whereas about 60% of the total included studies, dating method was used which was considered in low risk of biasness.

In studies focused on umbilical artery, Doppler ranges of middle cerebral artery and cerebroplacental ratio were parallel with each other in terms of highest risk of bias. It was noted that studies were lacking "multicenter study" in which only 2 studies were conducted in more than one center, quality control measures for ultrasound; only 1 study reported a proper strategy for quality control. Sonographic experience was not mentioned in even a single study. The training or experience of sonographer was clearly mentioned in five studies. no study has mentioned the blinded measurements in which sonographer was not known about the recorded measurements at the time of ultrasound examination and only 4 studies mentioned number of measurements taken. Recruitment method was not clear in most of the studies.
Even though few separate 'inclusion/exclusion criteria' of subjects (item 1.08) were utilized in studies, but no research study was having a systematic use of these criteria. Along with this, only 3(30%) studies mention 'sample size' calculation.
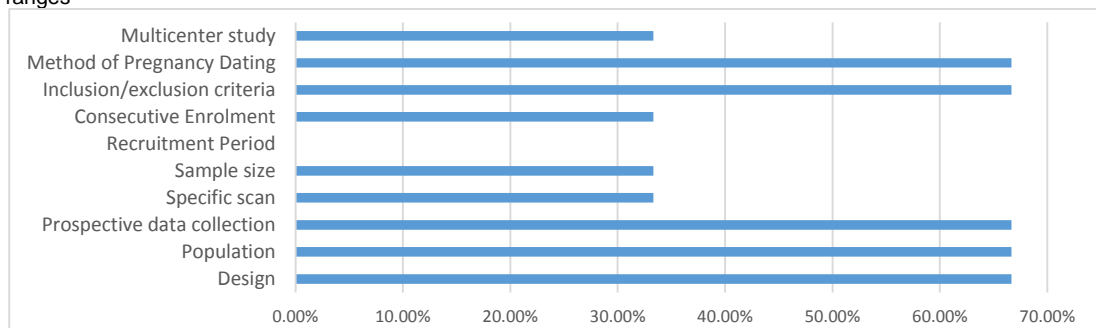
Graph 1: Methodological quality assessment score percentage extracted from 4 studies reported umbilical artery reference ranges
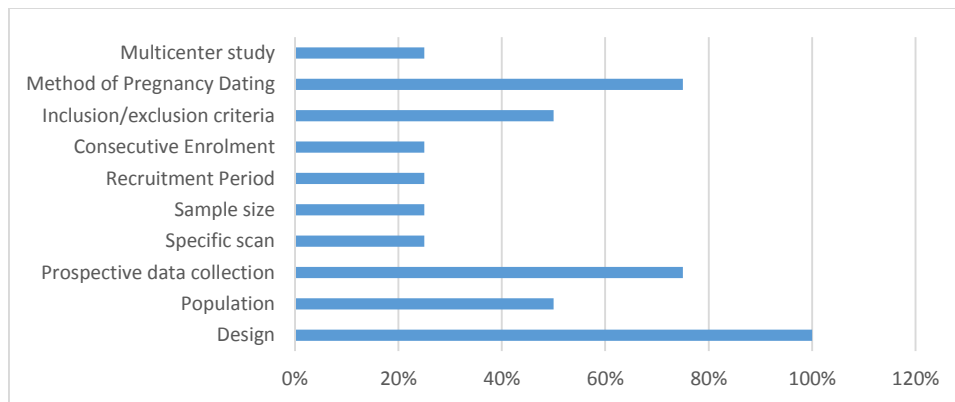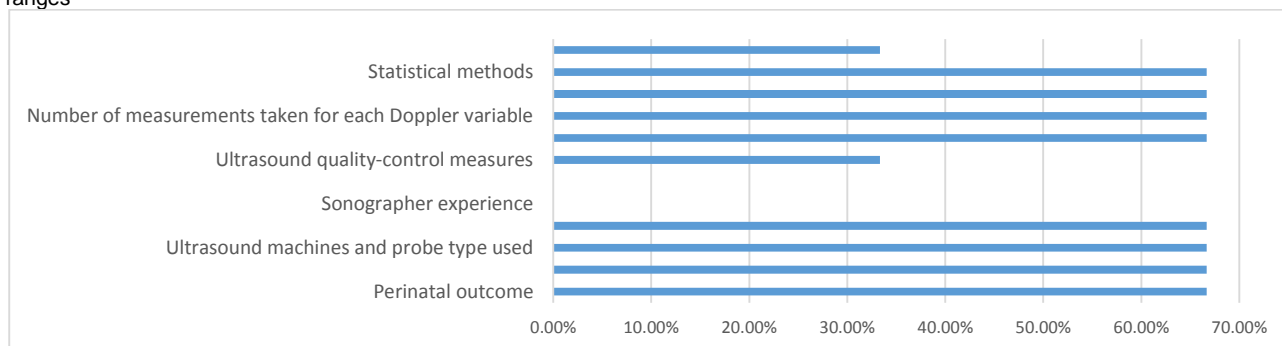

Graph 2: Statistical analysis and reporting Quality score percentage extracted from 4 studies reported umbilical artery reference ranges
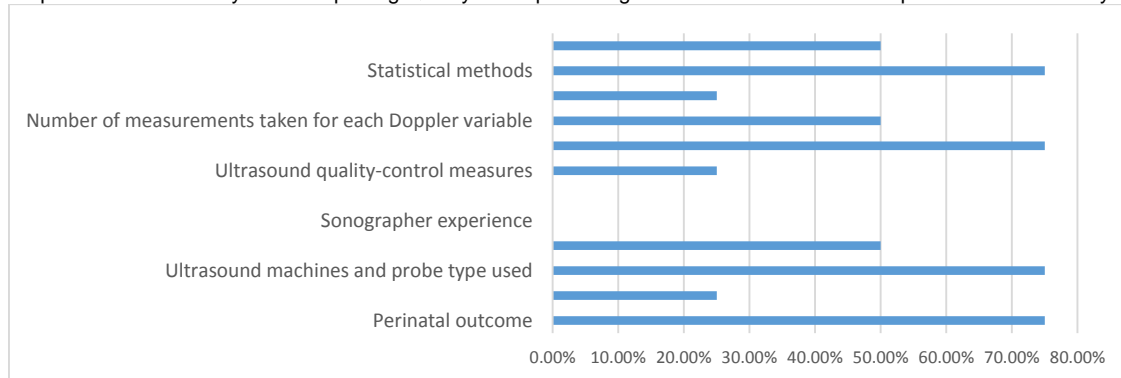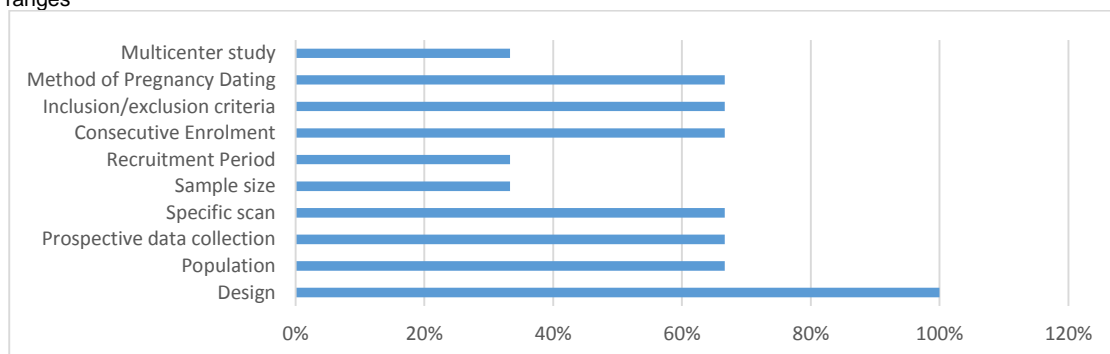
Graph 3: Methodological quality assessment score percentage extracted from 3 studies reported fetal middle cerebral artery reference ranges

Graph 4: Statistical analysis and reporting Quality score percentage extracted from 3 studies reported fetal middle cerebral artery reference ranges

Graph 5: Methodological quality assessment score percentage extracted from 3 studies reported fetal middle cerebral artery reference ranges
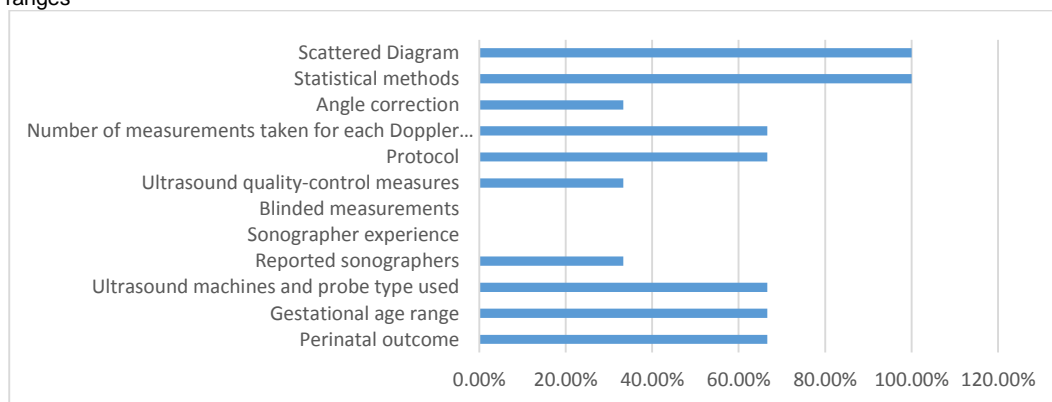

Graph 6: Statistical analysis and reporting Quality score percentage extracted from 3 studies reported fetal middle cerebral artery reference ranges

DISCUSSION

The aim of the study was to investigate the reference values of Doppler indices for umbilical artery and Middle Cerebral Artery as well as Cerebro-placental Ratio and specifically, to evaluate the quality of methodology used on which these reference values are grounded, with the help of already established quality standards for research design, statistical analysis as well as methods of results reporting. The results found are considerably heterogenetic in terms of quality scoring of methodology in sonographic studies based on Doppler reference values of umbilical artery, and middle cerebroplacental artery. These variations could be due to the reference ranges reporting ways whereas these alterations in reporting also clarify few changes observed in the prenatal examination in terms of Doppler[19-21,49] which also affects at perennial level.[15,26]

The current study has explored the potential risk of bias established on study design of the research publication and suitability of statistical analysis as well as its method of interpretation with the help of a predeveloped scoring sheet to rate quality of the research study methodology quality-scoring sheet of 22 standards to conclude the clinical management relevance of the study.

Eighty percent of the data was from prospective studies which was collected via clinical information collected regularly to make a reference might be significant cause of biasness, with higher depiction of cases which are at risk. Five research articles were conducted on unchecked populations. Population which is not predefined certifies a better demonstration of primary population. It was deliberated that the purpose of fetal Doppler chart should show that what are the optimal conditions as well as risk conditions of fetal hemodynamics[50]. All the studies were performed by one sonographer per study whereas two or more than two sonographer studies enhance the external validity of the results and consistency in data could be obtained by piloting before data collection[51]. Unavailability of blinding of researchers which was not present in any of the studies increase the risk of biasness whereas blinding is recommended by STROBE to reduce the biasness[52]. Data quality of ultrasound should be monitored via standard quality control strategy to reduce the risk of biasness while ensuring better quality and should preferably contain the usage of method of image scoring and the evaluation of intra-rater as well as inter-rater reliability of measurement[53]. Gestational age assessment should be precise as it a basic requirement for developing any fetal criteria[54,55,57].

CONCLUSION

Rigorous methodology of this review study is the major strength, which is consisted of a standard and well developed methodology of scoring the quality of studies according to their methodology selection as well as the statistical analysis and the level of its interpretation. The quality assessment in percentages makes results interpretation more objective.

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