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SYSTEMATIC REVIEWS/META-ANALYSIS

Meta-analysis to Assess the Association of Lateral Location of Placenta on Ultrasound with Preeclampsia

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Abstract

Introduction Several studies have shown association between lateral placenta on ultrasound and preeclampsia (PE).This meta-analysis aims to review majority of the articles published between 1990 and 2020 and analyze the data extracted from them to find whether such an association really exists.

Objective To conduct a meta-analysis to determine the degree of the association of lateral placenta on ultrasound with preeclampsia.

Methods We searched electronic databases keeping filters for human studies and published in the English language, between the year 1990 and 2020. Studies were reviewed by reviewers and studies which were analytical in nature, having focused research question and where odds ratio could be derived were identified, and included in the metanalysis.

Result Out of 16 included studies, 15 studies showed positive association (OR > 1) out of which 13 were statistically significant and only one study showed negative association. Eight studies showed extremely significant statistical positive association. The meta-analysis points toward positive association with OR 3.48 and Mantel–Haenszel Chi square 325.82 with relatively narrow 95% confidence interval around OR as 3.03–3.99 which clearly indicates a positive association between laterally placed placenta and preeclampsia. The findings of the individual studies in terms of OR and 95% confidence interval were plotted as individual line for each study, one aggregate estimate with summary OR and its 95% confidence interval was plotted on the Forest Plot**.**

Conclusion The Forest plot revealed association between lateral placenta on ultrasound and preeclampsia (PE).Hence it can be concluded that there is an association between lateral placenta on ultrasound and preeclampsia.

Keywords Lateral location of placenta · Lateral placenta on ultrasound · Pregnancy induced hypertension · Hypertensive disorders of pregnancy · Preeclampsia

Introduction

Preeclampsia (PE) is the most common medical complication affecting about 7–15% of all pregnancies and is responsible for almost 25% of all the antenatal admissions [1]. A systematic review on maternal mortality was conducted worldwide by WHO and it was concluded that PE is a leading cause of maternal mortality. Along with hemorrhage and infection, hypertension forms the deadly triad that contributes to morbidity and mortality during pregnancy and childbirth [2]. In India 24% of all maternal deaths are due to PE [3]. It has been observed that hypertensive disorders have long-term complications and effect on the health of women in the form of chronic hypertension and increase in lifetime risk of cardiovascular diseases. PE is strongly associated with stillbirth, fetal growth restriction, low birth weight, spontaneous preterm delivery, respiratory distress syndrome and NICU admissions [4]. Thus it is necessary to protect mothers from hypertensive disorders by providing good antenatal care, early diagnosis, timely intervention, and having a high index of suspicion. In a developing country like India it is necessary to identify and evaluate woman at risk of developing PE with an accurate, sensitive, clinically acceptable and affordable investigation.

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For PE to occur the presence of placenta is needed [5]. The site on the uterine surface where the placenta implants is an important factor determining the placental blood flow [6]. Ultrasound (USG) has been the safest, easiest, readily available and the most accurate diagnostic tool for determining the placental location [7]. On USG when the placenta is equally distributed between the right and left side of the uterus irrespective of fundal, posterior or anterior position it is classified as central placenta. It is classified as unilateral right or left placenta, when more than 75% of the placenta is situated on one side of the midline (Figs. 1, 2).

In a centrally located placenta the blood flow in the uteroplacental bed kept in equilibrium by equal contribution from both uterine arteries, whereas in a laterally located placenta the blood flow in the uteroplacental bed is primarily from one of the uterine arteries with minimal contribution from the other via a collateral circulation [8]. This collateral circulation is deficient in some patients which facilitates the development of PE, FGR or both [9]. Doppler studies reveal that in a laterally located placenta the uterine artery close to the placenta has resistance lower than the opposite one while in centrally located placenta both uterine arteries have same resistance [10–12].

Literature search revealed several studies on association of lateral placenta on USG and prediction of PE. A systematic review of literature was done on all studies on lateral placenta and occurrence of PE; data was extracted and prevalence of PE as well as its association with lateral placenta was analyzed. PRISMA guideline was used to frame the meta-analysis. Till date there has not been a study that collected and systematically analyzed the association between lateral placenta on USG and PE.

Thus this study aims to systematically review the various studies on occurrence of PE in patients with lateral placenta and analyze the extracted data for prevalence and association of PE with placental laterality.

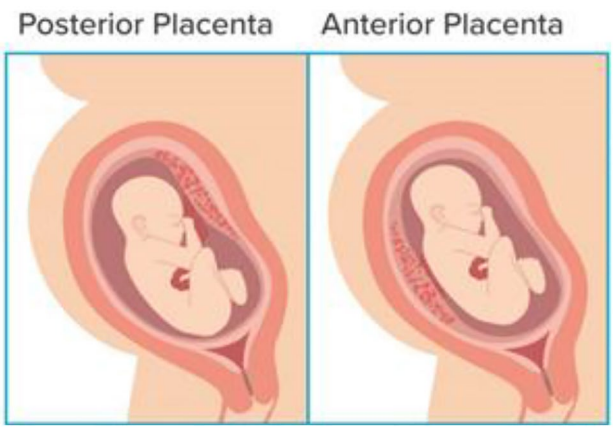

Fig. 1 Anterior and posterior location of placenta—schematic diagram

Methods

Eligibility Criteria

Inclusion Criteria

Human Studies conducted on lateral placenta on USG and PE, published in English between 1990 and 2020, having focused research question, analytical in nature, and where the Odds ratio, chi square and 95% confidence interval of Odd's ratio was either already calculated or could at least be derived from the table were selected for advanced meta-analysis.

Exclusion Criteria

Studies not having a focused research question.

Descriptive in nature.

Where Odds ratio could not be derived.

Information Source

Electronic databases like Google scholar and PubMed were used as search engines. Before beginning this Meta-analysis, we ensured that there is no systematic review or Meta-analysis done on similar topic by looking up the Cochrane Database and International Prospective Register of Systematic Reviews (PROSPERO).

Fig. 2 Lateral location of Placenta – USG image

Search Strategy

A systematic search was carried out using the selection criteria and the keywords, in the above-mentioned databases. The human studies published in English between the years 1990 and 2020 were searched for in the databases. The following keywords were used to perform the search review. *Keywords*-lateral placenta and pregnancy induced hypertension, lateral location of placenta, pregnancy induced hypertension, hypertensive disorders of pregnancy, preeclampsia.

Selection Criteria

Human studies done on lateral location of placenta on ultrasonography and its association with PE that were published between 1990 and 2020 in English, were retrieved and included in the systematic review and meta-analysis.

Selection and Data Collection Process and Assessment of Methodological Quality

Two independent reviewers (SN and AN) reviewed every article obtained by literature search done according to the selection, inclusion and exclusion criteria that were identified. The information given in the full texts of all the articles obtained through search were further assessed to see that they met the selection criteria and were eligible for inclusion in the meta-analysis. In case of any controversy an opinion was taken from a third reviewer (SP).

A critical appraisal skills programme (CASP) checklist for quantitative studies [13] was used to assess the quality of the included studies by the two independent reviewers. The studies were assessed based on the following points: clearly focused research question/objectives, appropriate method, clearly specified target population, adequate sampling techniques and sample size, adequate response rate, valid measurement tool, minimum selection bias, appropriate significance level and 95%confidence interval, Odds ratio and relevant findings applicable to our study. For any disagreement between the reviewers a third reviewer was approached to reach a consensus with proper discussion.

Around 23 articles published between 1990–2020 were found after searching the database. In certain studies the research question was not focused, while some studies were descriptive in nature; these were excluded from the analysis thus further decreasing the articles to 17. Outcome measures like Odds ratio and 95% confidence interval were not given nor could be derived from one study hence this too was excluded from the study (Fig. 3).

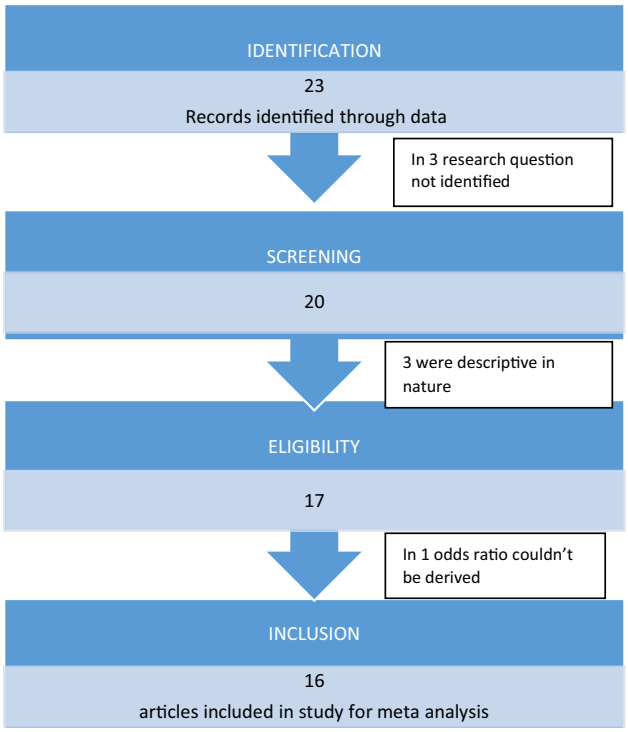

Fig. 3 Selection process of the articles for the meta-analysis

Synthesis Methods

Sixteen studies were found to be eligible and were included in the meta-analysis. In some of the studies the Odd's ratio was already calculated and was scrutinized but in none of the studies the Mantel–Haenszel Chi square was calculated. This was calculated manually for all these studies by applying the appropriate formulae and were rechecked using medical calculator, for confirmation. Analysis was done in terms of summary Odds ratio, summary Mantel–Haenszel Chi square test and 95% confidence interval of summary Odd's ratio and plotted in the forest plot representation.

Using the PRISMA expanded checklist of 2020, the manuscript of the meta-analysis was written by the reviewers (SN & AN) and was then peer reviewed evenly by all the three authors.

Results

Study Characteristics

The individual studies were reviewed using full text articles and using the CASP checklist by the two reviewers (SN &AN). While reviewing these articles individually it was observed that all the studies defined PE according to the American College of Obstetricians and gynecologists

(ACOG) classification of Hypertensive disorders of pregnancy. The location of placenta on USG was also defined as per the norms mentioned in the introduction above.

All the studies included in the meta-analysis had a sample size of more than 100 and were from different geographical locations in India. Only one study from Iran met the eligibility criteria of our study.

Table 1 summarizes the list of the various studies selected after thorough review by the reviewers with their reference numbers and also outlines the various features of the included studies.

Table 2 summarizes the data extracted from the individual studies like OR, chi square, etc., and also indicates the degree of association of individual studies.

The composite OR of all the studies was calculated and included in Table 2 as Composite estimate.

From the above table it can be observed that the composite estimate summary OR is 3.48, chi square MH is 325.82 and 95%CI of all the ORs is 3.03–3.99 thus giving *p* value = 0.000000…) this is an extremely significant result. So we can conclusively say that laterally placed placenta is very strongly associated with PE.

The below figure (Fig. 4) shows the distribution of studies with reference to type of association/ statistical significance.

This meta-analysis points toward positive association with OR 3.48 and Mantel–Haenszel Chi square [29] 325.82 with relatively narrow 95% confidence interval OR as 3.03–3.99 which clearly indicates positive association between laterally placed placenta and pregnancy induced hypertension. The findings of the individual studies in terms of OR and 95% confidence interval were plotted as individual line for each study one aggregate estimate with summary OR and it's 95% confidence interval on the Forest Plot [30] (Fig. 5).

The left side of the forest plot shows the names of each study included in the meta-analysis. A graphical representation of the observed data is provided in the center of the plot. The OR of the individual study is visualized as a point estimate on the on the x-axis. This point estimate is supplemented by a line, which represents the range of the confidence interval calculated for the observed data. Usually, the point estimate is surrounded by a square.

On observing the forest plot it can be noted that maximum number of studies have OR more than one, evident by being present on the right side of the line represented by OR = 1 in the forest plot. Out of the 16 included studies, 15 showed positive association (OR > 1), out of which 13 studies are statistically significant as evident by being far from the line of OR = 1. 13 studies showed positive association which were extremely significant statistically as evident by being farther away from the line of OR = 1.

Only 1 study showed negative association with OR < 1 as seen on the left of the line of OR = 1 but it is not statistically significant as can be observed in the forest plot. Studies were nonsignificant in terms of either positive or negative

Table 1 Table outlining the features of the included studies with reference numbers:

Name of study	Study type	Sample size	PE	LP	LP + PE	LP + PE %	Association	other tests
Kadium [14]	Case control	162	81	77	56	69.10%	Yes	Sen-78%, Sp-74%, PPV-73%, NPV-70%
Sandhya et al. [7]	Prospective observational	300	160	168	112	66.60%	Yes	
Rai et al. [15]	Prospective observational	106	17	37	12	70.16	Yes	
Kaku et al. [16]	Prospective observational	350	187	196	131	70%	Yes	
Ambastha et al. [17]	Prospective observational	250	48	102	40	39.22%	Yes	Sen-84%, Sp-70%, PPV-39%, NPV-94%
Rajoriya and Bagde [18]	Prospective observational	320	111	163	52	31.90%	No	
Keshavarz et al. [19]	Retrospective case control	454	177	42	20	47.50%	Yes	
Kakkar et al. [20]	Prospective observational	150		84	56	66.60%	Yes	
Kannamani and Narasimhan [21]	Prospective case control	300	42	72	38	80.90%	Yes	Sen-81%, Sp-85%, PPV-47%, NPV-96%
Dondapati and Bharathi [22]	Retrospective case control	400	200	206	112	56%	Yes	
Bhattacharjee et al. [23]	Prospective observational	200	98	100	66	66	yes	
Kaur et al. [24]	Prospective observational	100	12	13	12		Yes	
Naik et al. [25]	Prospective	100		83	63		Yes	Sen-75.9%, Sp-96%
Divya and Sumathy [26]	Prospective observational	120		80	52		Yes	
Chandra and Maheshwari [27]	Prospective	100	51	50	33	66%	Yes	
Jani et al. [28]	Prospective observational	400		80	28	35%	Yes	

PE preeclampsia, *LP* lateral placenta

Table 2 Details of individual study in terms of OR, chi square, *p* value and composite estimate of meta-analysis as well degree of association

Serial number	References	Odd's ratio	Chi square (MH)	95% CI of OR	*p* Value	Remarks
1	Kadium [14]	6.4	30.13	3.28–12.49	0.000	*** (pa)
2	Sandhya et al. [7]	3.5	27.18	2.17–5.63	0.000	*** (pa)
3	Rai et al. [15]	6.14	11.24	2.1–17.91	0.000	*** (pa)
4	Kaku et al. [16]	3.53	32.09	2.27–5.49	0.000	*** (pa)
5	Ambastha et al. [17]	11.29	44.32	5.59–22.8	0.0000	**** (pa)
6	Keshavarz et al. [19]	1.69	2.48	0.88–3.24	> 0.05	ns (pa)
7	Kakkar et al. [20]	3.5	13.55	1.8–6.8	0.00	** (pa)
8	Rajoriya and Bagde [18]	0.78	1.13	0.5–1.23	> 0.05	ns (na)
9	Naik et al. [25]	78.75	280.38	46.63–132.98	0.000000	****** (pa)
10	Kannamani and Narasimhan [21]	24.61	86.56	12.56–48.22	0.0000	**** (pa)
11	Chandra and Maheshwari [26]	6.4	19.11	2.78–14.76	0.00	** (pa)
12	Chandra and Maheshwari [27]	3.45	8.91	1.52–7.81	0.00	** (pa)
13	Bhattacharjee et al. [23]	3.45	17.92	1.95–6.1	0.00	** (pa)
14	Kaur et al. [24]	4.39	4.94	1.19–16.14	0.0	* (pa)
15	Jani et al. [28]	4.25	26.79	2.45–7.37	0.000	*** (pa)
16	Dondapati and Bharathi [22]	1.44	3.23	0.9–11.59	> 0.05	ns (pa)
17	Composite estimate	3.48	325.82	3.03–3.99	0.0000000	******* (pa)

pa positive association, *ns* not significant

*Indicates degree of association

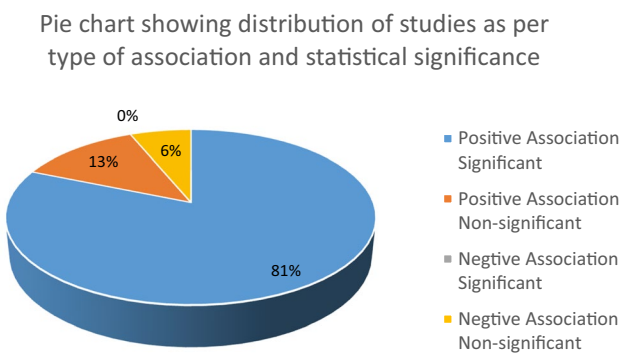

Fig. 4- Pie chart showing distribution of studies in % as per type of association and statistical significance

association where the 95% confidence interval around OR was crossing 1 as observed in the forest plot where 3 studies are seen crossing the line of OR = 1.

At the end of the forest plot the composite estimate OR can be seen on the right side of the line of OR = 1 thus stating statistical significance of positive association.

To summarize the forest plot interpretation, in individual studies having OR greater than 1 it was observed that there is possible positive association between the lateral location of placenta and PE. In the studies where OR was lesser than 1, the possible association between lateral placenta and PE was negative. Studies were nonsignificant in terms of either positive or negative association where the 95% confidence interval around OR was crossing 1.

Discussion

Sixteen observational analytical studies (cross sectional/case control studies) done at different geographical locations in India (1 study from Tehran, Iran) were filtered for processing for meta-analysis as per the inclusion criteria. All the studies were having sample size more than 100.

Kadium et al. [14] studied maternal and fetal outcome in the form of severity and complications of PE like development of late onset PE, abruptio placenta, preterm labor, fetal growth restriction and intrauterine death in lateral placenta. This study also revealed deteriorating Doppler changes with lateral placenta on ultrasound. Kaur et al. [24] also studied Doppler changes in cases of lateral location of placenta and development of PE along with maternal and fetal outcome with similar results.

Ambastha et al. [17] and Kakkar et al. [20] studied the maternal and fetal outcome in laterally located placenta in the form of severity of PE, fetal growth restriction, preterm premature rupture of membranes. Their results were consistent in showing all parameters to be worsening with lateral placenta. Fetal and maternal outcome according to placental location was also observed to be poor with lateral placenta in study by Keshavarz et al. [19], Sandhya et al. [7] and Kaku et al. [16] studied the severity of PE based on diastolic BP

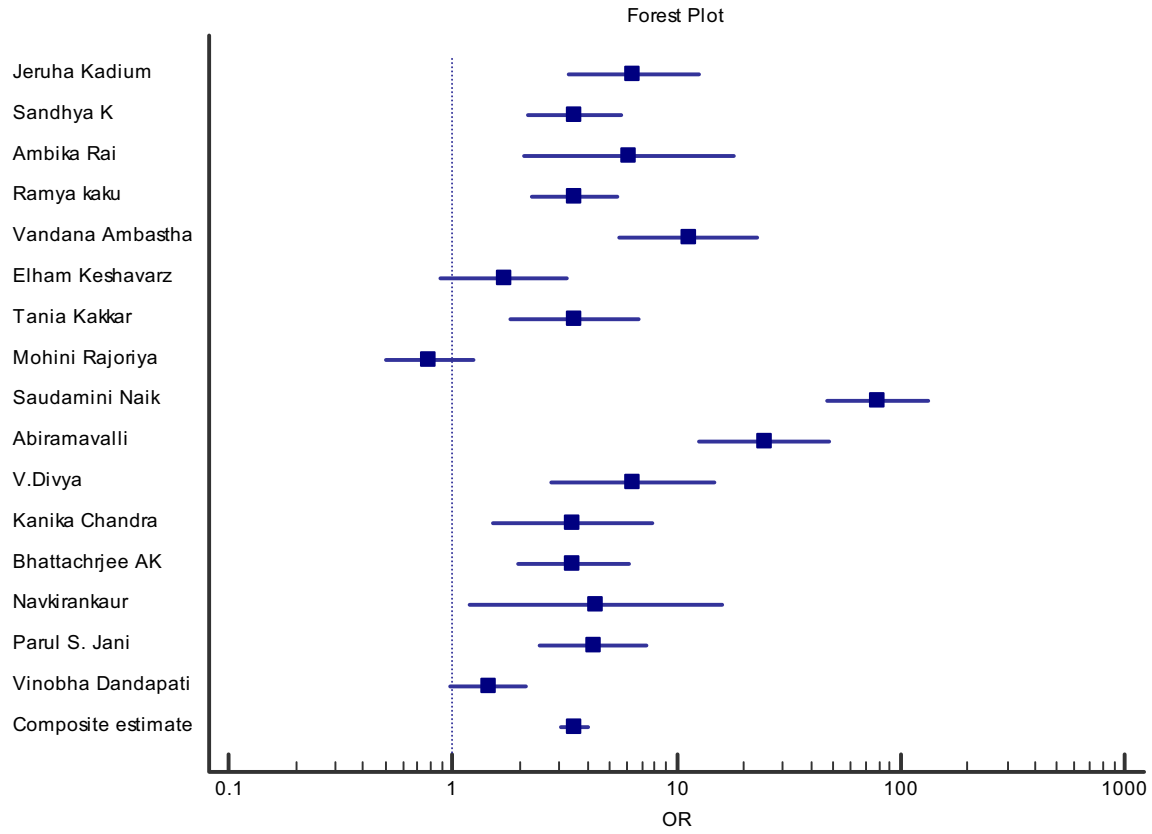

Fig. 5 Forest plot showing individual study OR and composite summary OR distribution (95% confidence interval)

in laterally located placenta. They concluded more severe PE with significant rise in diastolic BP in laterally located placenta.

The development of PE in lateral and central location of placenta was studied in all 16 studies. After plotting a 2 by 2 table the odds ratio was calculated in all the above studies with 95% confidence interval and statistical significance if any was noted in all the 16 studies.

13 out of 16 studies showed statistically significant positive association between laterally placed placenta and preeclampsia with Odd's ratio ranging from 0.78 to 78.75. Two studies showing positive association were not statistically significant. Only one study showed negative association but was not statistically significant. An apparent aggregate positive association cannot be considered unless we do the statistical synthesis of these studies in terms of meta-analysis.

The summary Odd's Ratio of our meta-analysis is 3.48 with 95% confidence interval from 3.03 to 3.99 which clearly indicates that there is a strong positive association and relatively narrow 95% confidence interval suggests that this association is extremely statistically significant with Mantel–Haenszel Chi square value of 325.82. Forest plot also clearly indicates a strongly positive association between lateral location of placenta and PE.

Conclusion

This meta-analysis thus shows significant association between lateral placenta on ultrasound and preeclampsia.

Take Home Message

A high index of suspicion for risk of developing PIH to be kept in mothers with lateral location of placenta on antenatal ultrasound.

Recommendations

Lateral location of placenta is an observation on USG and role of RCT's in predicting PE with location of placenta can be another area of research where a prospective study can be done with proper follow-up, along with use of color Doppler to assess the earliest change in flow indices and study the maternal fetal outcome, which can be statistically analyzed. No other systematic review or meta-analysis on the same topic appeared on searching the database.

Limitations

We have selected observational studies which were available to us through literature search and our conclusion is a synthesis of these. We are not extrapolating beyond these.

Bias

Since it is a qualitative study we have not estimated publication bias and heterogeneity was not calculated.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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