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The impact of lateral placenta on preeclampsia and small for gestational age neonates: a systematic review and meta-analysis

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Abstract

Objectives: We conducted a systematic review and meta-analysis to quantitatively summarize the present data on the association of prenatally identified lateral placenta in singleton pregnancies with small for gestational age (SGA) neonates, preeclampsia and other perinatal outcomes.

Methods: From inception to November 2021, we searched PubMed/Medline, Scopus and The Cochrane Library for papers comparing the risk of SGA and preeclampsia, as well as other perinatal outcomes in singleton pregnancies with a prenatally identified lateral placenta to those with non-lateral placentas. The revised Newcastle-Ottawa Scale was used to evaluate the quality of eligible papers. The I^2 test was employed to evaluate the heterogeneity of outcomes among the studies. To investigate the possibility of publication bias, funnel plots were constructed. Prospero RN: CRD42021251590.

Results: The search yielded 5,420 articles, of which 16 were chosen, comprising of 15 cohort studies and one case

control study with a total of 4,947 cases of lateral and 96,035 of non-lateral placenta (controls) reported. SGA neonates were more likely to be delivered in cases with a lateral placenta (OR: 1.74; 95% CI: 1.54–1.96; $p < 0.00001$; $I^2 = 47\%$). Likewise, placental laterality was linked to a higher risk of fetal growth restriction (OR: 2.18; 95% CI: 1.54–3.06; $p < 0.00001$; $I^2 = 0\%$), hypertensive disorders of pregnancy (OR: 2.39; 95% CI: 1.65–3.51; $p = 0.0001$; $I^2 = 80\%$), preeclampsia (OR: 2.92; 95% CI: 1.92–4.44; $p < 0.0001$; $I^2 = 82\%$) and preterm delivery (OR: 1.65; 95% CI: 1.46–1.87; $p < 0.00001$; $I^2 = 0\%$).

Conclusions: The prenatal diagnosis of a lateral placenta appears to be associated with a higher incidence of preeclampsia, fetal growth restriction, preterm delivery and SGA. This may prove useful in screening for these conditions at the second trimester anomaly scan.

Keywords: Apgar; birthweight; fetal growth restriction (FGR); hypertensive disorders; lateral placenta; NICU; outcome; preeclampsia; preterm delivery; small for gestational age (SGA).

Introduction

During pregnancy, about one in ten women will have a lateral placenta, with a reported incidence up to 12.6% [1]. Prenatal care in most countries includes a second trimester ultrasound scan to screen for fetal structural abnormalities and to determine the position of the placenta [2]. The identification of the location of the placenta is recommended, aiming primarily to exclude the possibility of placenta previa [3]. A lateral placenta is defined as a placenta positioned mainly on the right or left wall of the uterus. Notably, when the placenta implants in one of the lateral uterine walls, it is mainly supplied by blood flow from the ipsilateral uterine artery [4], a finding that could affect the current screening for preeclampsia [5].

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The majority of previous studies focused on the effect of low placental position and found a link with poor maternal and neonatal outcomes [6]. However, some other studies investigated a possible association between a lateral placental location and adverse obstetric outcomes, such as fetal growth restriction (FGR), preeclampsia, fetal distress, preterm delivery and low birthweight (BW), on the hypothesis of a less effective uterine blood supply [7, 8]. Regarding ischemic placental disease, FGR, which in turn leads to small for gestational age (SGA) neonates, has been associated with several perinatal complications [9]. Moreover, since the frequency of hypertensive disorders of pregnancy has risen over the last two decades affecting around 5–10% of all deliveries in the United States [10], research on the relationship between lateral position and these complications could be of interest.

Therefore, the aim of this meta-analysis was to critically evaluate and present the current data, in order to better understand the impact of lateral placenta on pregnancy outcomes, mainly small for gestational age neonates and preeclampsia.

Materials and methods

A pre-determined protocol with Registration No: CRD42021251590 was published in Prospero. The meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used to conduct and report this review [11].

Data sources and search strategy

From inception to 1/11/2021, two researchers (AS, PG) independently searched three electronic databases, including Scopus, PubMed/Medline and the Cochrane Central Register of Controlled Trials (CENTRAL), for literature reporting on placenta laterality and perinatal outcomes. Keywords included “placental laterality,” “lateral placenta,” “placental location,” “placental site,” “lateral localization,” and “laterally located placenta.” The bibliography of relevant primary studies and review articles were thoroughly examined, in order to distinguish applicable publications. In cases where we were unable to obtain access to publications of relevance, the authors were contacted. There were no limitations on publication year or language. We also searched PROSPERO, to identify similar meta-analyses and avoid duplication.

Eligibility criteria

The following inclusion criteria were used: (a) singleton pregnancies in randomized-controlled trials, cohort studies, or case-control studies reporting on neonatal outcomes in lateral and non-lateral placenta sites, regardless of blinding, publication year, or language (b) prenatal targeted sonographic detection of placental position and (c) control group of singletons with non-lateral placenta. Studies on

multiple pregnancies and cases with placenta previa or vasa previa were excluded.

Main outcomes

SGA, defined as BW<10th centile and preeclampsia, were our primary outcomes. Fetal growth restriction (FGR) preterm delivery (PTD), birthweight (BW), low Apgar score (<7 at 5 min) and neonatal intensive care unit (NICU) admission rates were the secondary outcomes.

Study selection and data extraction

We imported all the references identified after the preliminary search into two reference software programs (EndNote, Mendeley). All the duplicates were identified and eliminated. Two separate reviewers utilized an internet software (Rayyan) to screen the remaining studies for title and abstract, then full-text screening (AS, PG – doctors). A third reviewer settled any differences (IT – biostatistician).

A standard pre-determined data extraction form was used to extract the data. From the eligible studies, the year of publication, first author, study population, numbers of participants in study, outcomes of interest and the control groups were collected. Authors were contacted in case of missing data in any of the eligible studies.

Two independent reviewers (both of them doctors) assessed the quality of eligible papers using the improved Newcastle-Ottawa Scale (NOS) (AS, AA). This tool evaluates the study groups' selection, comparability, and identification of lateral placenta and outcomes. Each section includes its own set of questions.

Statistical analysis

We estimated the effect sizes by employing the Review Manager ver. 5.0. For continuous variables, measures of effects were the mean differences (MD) presented with 95% confidence intervals (CI), whereas for categorical data, odds ratios (OR) and 95% CI were used. The I^2 test was used to analyze the heterogeneity of outcomes across studies. In all analyses, the Mantel-Haenszel random-effects model was used. Funnel plots were constructed to test for publication bias.

Results

General characteristics of the studies

Our search initially yielded 5,420 studies, of which duplicates (1,486 studies) were removed. Subsequently, 3,887 publications were discarded after an assessment of both the title and abstract because they were reviews, case reports, or did not fulfill the inclusion criteria; 47 papers were chosen for full-text evaluation. Furthermore, two papers were deemed eligible after reviewing the reference lists of review articles and eligible primary studies [12, 13]. The following factors led to the exclusion of 33 of these studies: 15 studies did not report on the relevant control group as

specified, 12 did not include outcomes of interest, three studies included multiple pregnancies, two were reviews and one was a case report. As a result, the final analysis included 16 papers [1, 7, 8, 12–24], with a total of 4,947 cases of lateral and 96,035 cases of non-lateral placenta (Figure 1).

The included articles were published between 1989 and 2021. Of these, 15 (94%) were cohort studies [1, 7, 12–24], and one (6%) was a case-control study [8]. The characteristics of the included studies are shown in Supplementary Table S1 and the associated outcomes in Table 1.

Regarding the definition of a lateral placenta most of the studies [1, 7, 12, 13, 16, 17, 20, 22, 24] used a cut off ranging from 66 to 75% for the percentage of placental

mass on one side of the midline. However, six studies [8, 14, 15, 18, 19, 23] did not provide a definition.

Regarding the incidence of a lateral placenta in the included studies, it was 2.5 and 6.6% in the two studies with the biggest sample size [14, 15].

All of the included cohort studies met the following NOS quality criteria in the selection section: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the beginning of the study, thus scoring perfectly in the group selection. Regarding the outcomes' section, two cohort studies [17, 21] did not receive a perfect score due to the lack of description of the assessment of outcome; nonetheless, the rest of the studies received the highest possible score in

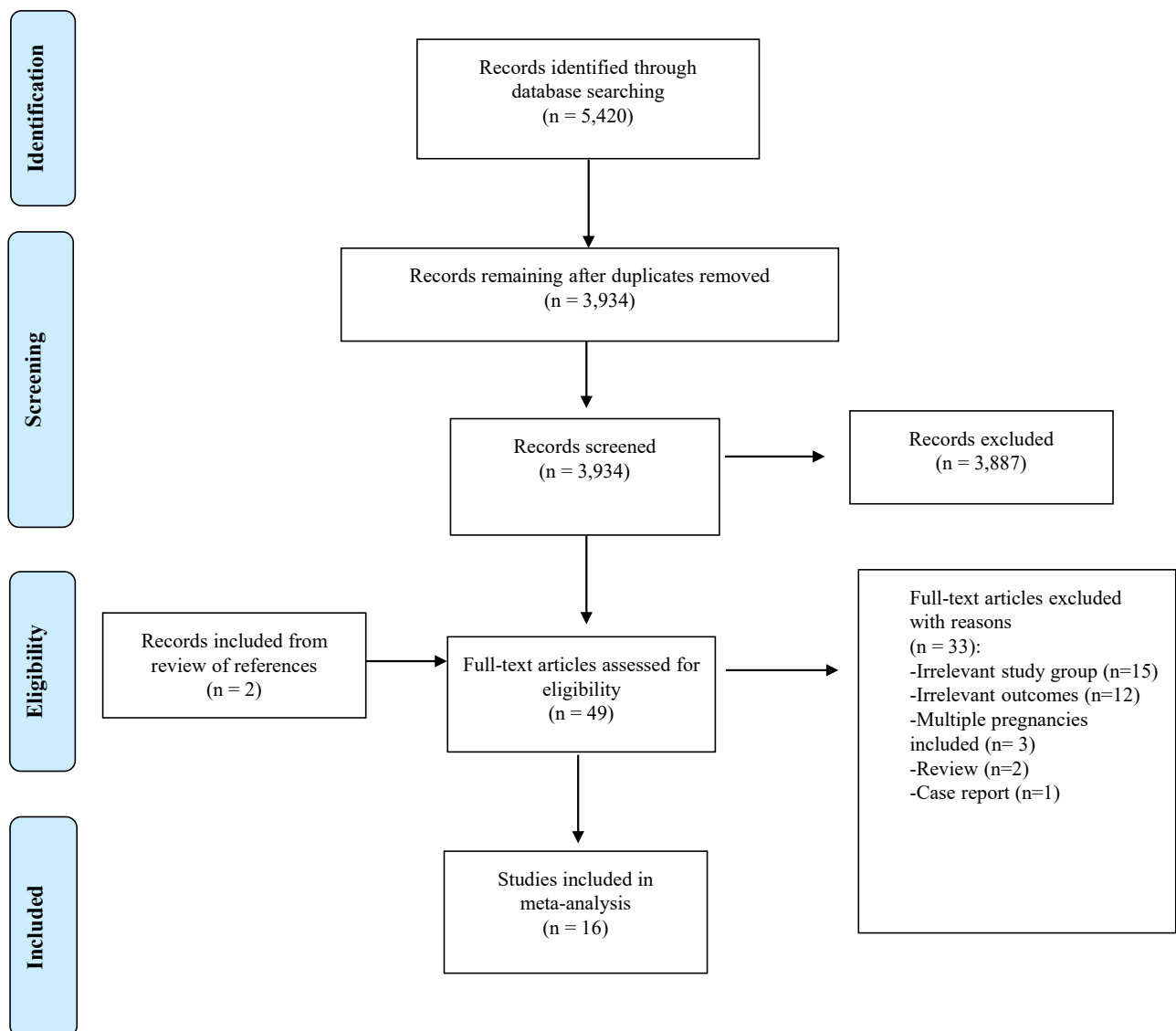


Figure 1: Study selection flow diagram according to the PRISMA statement.

Table 1: Results presented for each outcome.

Outcome	Number of studies	Number of participants (cases/controls)	Heterogeneity % – p-value	OR or MD (95% CI)	p-Value
SGA	7	3,748/94,445	47%, p=0.08	1.74 (1.54–1.96)	<0.00001
Birthweight	3	717/6,637	0%, p=0.57	–103.80 (–148.14 to –59.45)	<0.00001
FGR	4	430/673	7%, p=0.36	2.4 (1.54–3.74)	0.0001
Hypertensive disorders	15	4,923/95,802	80%, p<0.00001	2.39 (1.63–3.51)	<0.00001
Preeclampsia	12	4,247/94,475	82%, p<0.00001	2.92(1.92–4.44)	<0.0001
Preterm delivery	4	3,072/92,605	0%, p=0.84	1.65 (1.46–1.87)	<0.00001
5-min Apgar score	4	2,826/88,197	64%, p=0.04	1.30 (0.72–2.33)	0.39
NICU admission	4	1,099/16,773	45%, p=0.14	1.08 (0.92–1.25)	0.35

SGA, small for gestational age; FGR, fetal growth restriction; NICU, neonatal intensive care unit.

the outcome segment. Three cohort studies [1, 14, 25] received two stars in the comparability segment, while the rest [7, 12, 13, 15–18, 20–24] received none. The case-control study [8] scored perfect in all three sections and received all 10 stars (Supplementary Table S2).

Quantitative synthesis of the results

Small for gestational age – birthweight – fetal growth restriction

We evaluated data from 7 retrospective cohort studies [1, 14–16, 18, 19, 22] and found that 378 (10%) out of 3,748 cases of lateral placenta resulted in SGA neonates compared to 4,663 (4.9%) out of 94,445 cases of non-lateral placenta, indicating a statistically significant link between lateral placenta and SGA (OR: 1.74; 95% CI: 1.54–1.96; p<0.00001). Among the included studies, there was high heterogeneity ($I^2=47\%$, $\text{Chi}^2=11.23$; p=0.08) (Figure 2).

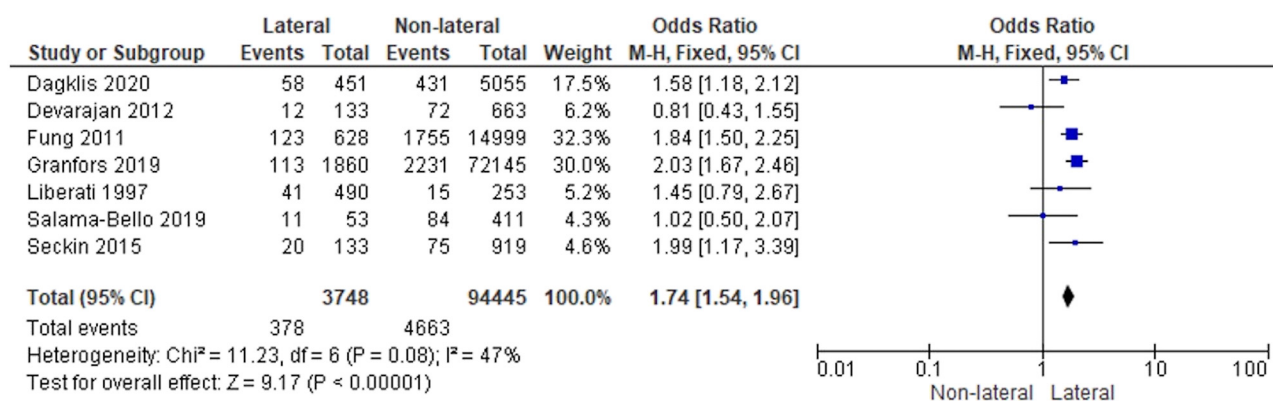
Three studies [1, 16, 19], including 717 cases with lateral placenta, reported on BW and showed that lateral position

of the placenta is associated with lower BW (MD: –103.8; 95% CI: –148.14 to –59.45; p<0.0001) (Figure 3).

Moreover, five studies [1, 8, 13, 23, 24] with data on FGR were analyzed, including 563 cases in the study group and 1,592 cases in the control group; FGR was detected in 14% (n=78) vs. 9.4% (n=150) of the cases, respectively. Therefore, a significant correlation between lateral placental localization and FGR was observed (OR: 2.18; 95% CI: 1.54–3.06; p<0.00001). The heterogeneity was low ($I^2=0\%$, $\text{Chi}^2=3.92$, p=0.42) (Supplementary Figure S1).

Hypertensive disorders of pregnancy – preeclampsia

The meta-analysis of 15 cohort studies [1, 7, 12–24] showed that 398 (8.1%) out of 4,923 pregnancies with lateral placenta were complicated by hypertensive disorders of pregnancy compared to 3.4% (n=3,236) in the control group of 95,802 cases. A statistically significant association (OR: 2.39; 95% CI: 1.63–3.51; p<0.0001) was found. The heterogeneity was significant ($I^2=80\%$, $\text{Chi}^2=69.96$, p<0.00001) (Figure 4).

**Figure 2:** Forest plot for the outcome small for gestational age neonates in lateral vs. non-lateral placentas (control).

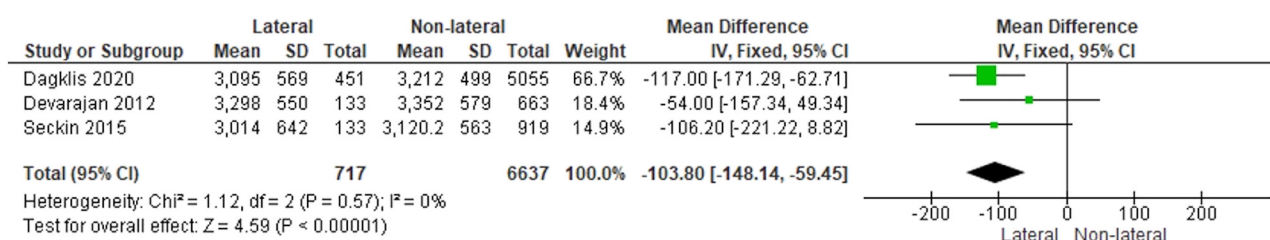


Figure 3: Forest plot for the outcome birthweight between lateral and non-lateral placentas (control).

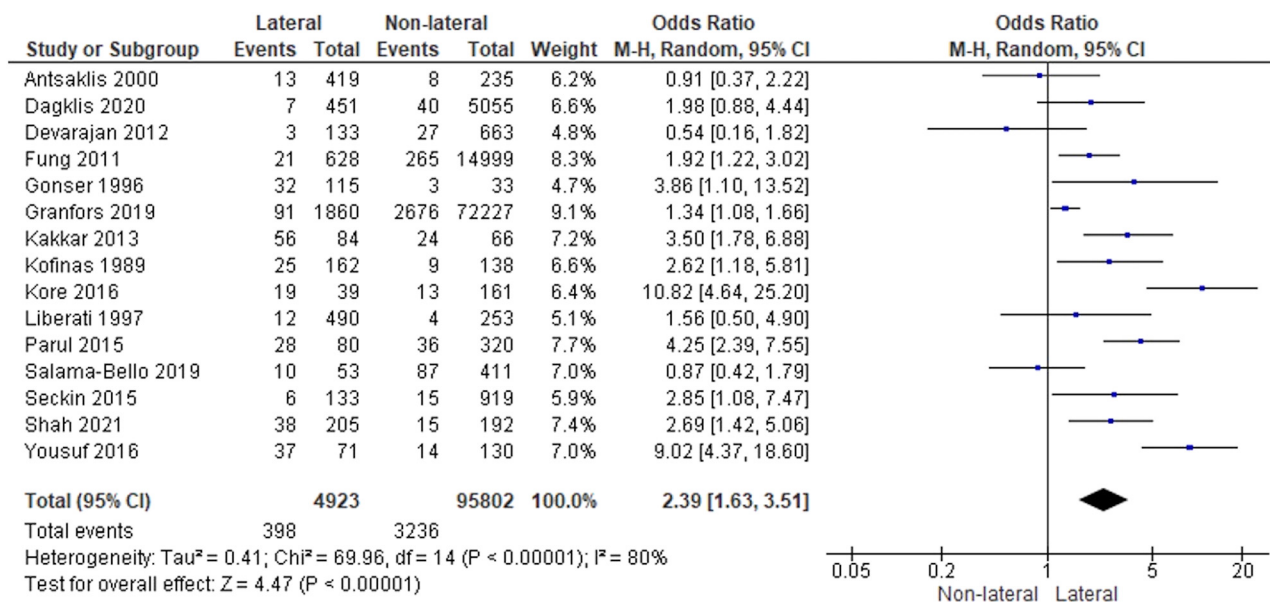


Figure 4: Forest plot for the outcome hypertensive disorders in pregnancy in lateral vs. non-lateral placentas (control).

Moreover, 12 studies [1, 7, 12–17, 20, 21, 23, 24], including 4,247 pregnancies with lateral placenta, reported on the incidence of preeclampsia. Preeclampsia was diagnosed in 8.8% ($n=373$) of cases in the study group compared to 3.3% ($n=3,118$) in the control group of 94,475 cases. The analysis showed statistically significant association (OR: 2.92; 95% CI: 1.92–4.44; $p < 0.00001$). The heterogeneity was high ($I^2=82\%$, $\chi^2=60.56$, $p < 0.00001$) (Figure 5).

Preterm delivery

The correlation between lateral placenta and PTD was investigated in four studies [1, 14–16] including 3,072 cases of lateral placenta with 300 cases of PTD (9.7%) comparing to 5.5% ($n=5,099$) in the control group of 92,605 cases. A statistically significant association was identified (OR: 1.65; 95% CI: 1.46–1.87; $p < 0.00001$). The heterogeneity was low ($I^2=0\%$, $\chi^2=0.83$; $p=0.84$) (Figure 6).

5-min Apgar score

Four studies [1, 14, 15, 24] were analyzed, including 2,826 pregnancies with lateral placenta; no statistically significant correlation was found with low Apgar score (<7 at 5 min) (OR: 1.30; 95% CI: 0.72–2.33; $p=0.39$). The heterogeneity was high ($I^2=64\%$, $\chi^2=8.38$, $p=0.04$) (Figure 7).

Neonatal intensive care unit admission

Based on data from four studies [1, 15, 19, 24] (1,099 pregnancies with lateral placenta), we found that there were 256 (23.2%) cases of NICU admission. The association between laterality of placenta and admission to NICU was not statistically significant (OR: 1.08; 95% CI: 0.92–1.25; $p=0.35$). There was high heterogeneity among the included studies ($I^2=45\%$, $\chi^2=5.45$, $p=0.14$) (Supplementary Figure S2).

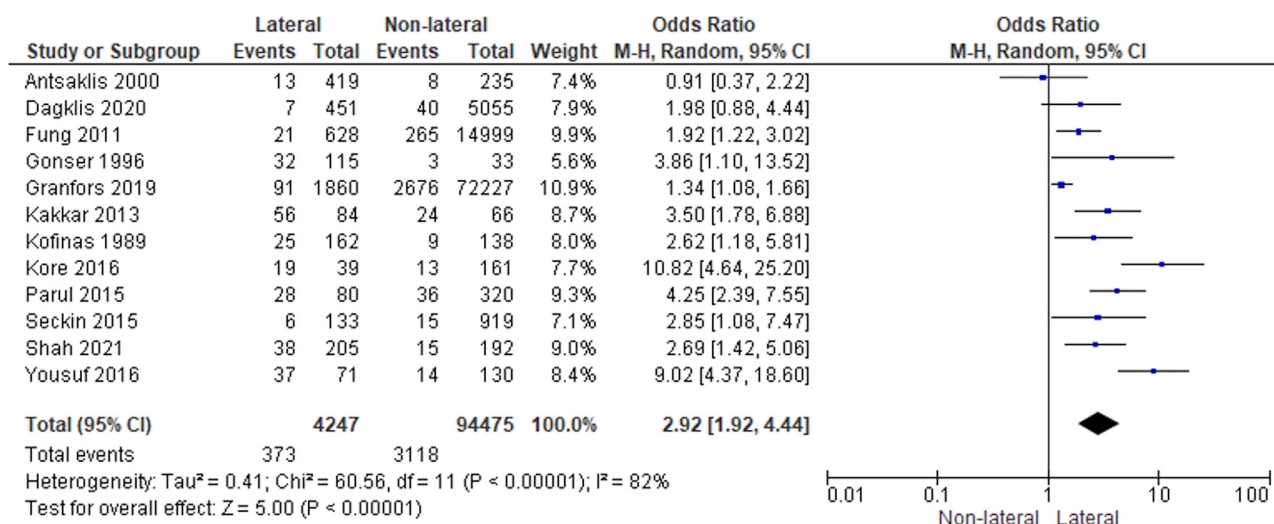


Figure 5: Forest plot for the outcome preeclampsia in lateral vs. non-lateral placentas (control).

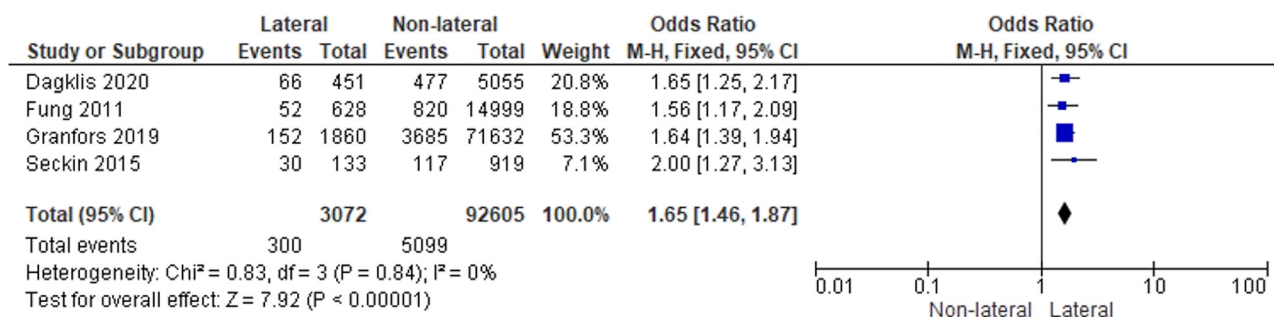


Figure 6: Forest plot for the outcome preterm delivery in lateral vs. non-lateral placentas (control).

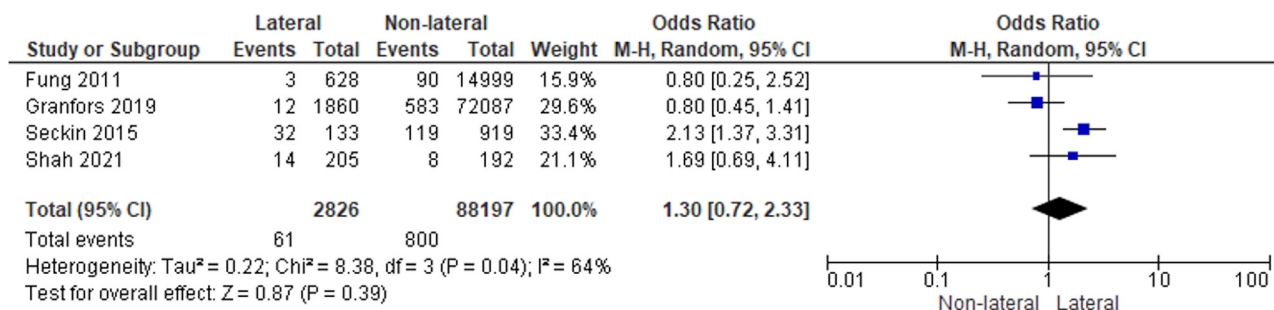


Figure 7: Forest plot for the outcome low 5-min Apgar score in lateral vs. non-lateral placentas (control).

Qualitative synthesis

Intrauterine/neonatal death

Two studies included data regarding perinatal death; Devarajan et al. [19] studied the incidence of perinatal death and found an adjusted (OR: 1.79; 95% CI: 0.18–17.67) indicating a higher incidence among the pregnancies with lateral placenta. On the contrary, Fung et al. [15] reported

no significant difference between the lateral and non-lateral pregnancies regarding stillbirth and neonatal death.

Publication bias

We were able to assess the probability of publication bias only for the outcomes of hypertensive disorders of pregnancy and preeclampsia, since less than 10 studies were

included for the other outcomes. The funnel plots for these outcomes were symmetric, thus indicating absence of significant publication bias (Supplementary Figures S3, 4).

Discussion

Main findings

This meta-analysis of 16 studies, which included 4,947 cases with lateral placenta, found an approximately three-fold rise in the incidence of preeclampsia and an almost two-fold increase in the incidence of SGA in the lateral placenta group. FGR, hypertensive disorders and PTD were also increased in the lateral group, whereas no effect was found on the 5-min Apgar score and admission to NICU.

Interpretation of the findings

The basis for investigating the associations between lateral placenta and hypertensive disorders and SGA is that different parts of the uterus may have different anatomical aspects, both in terms of cavity form and blood supply [23]. In particular, the anterior and posterior parts of the uterine cavity are more flattened, whereas the fundal and lateral parts are more curved, which may affect implanted placental function; it is the placenta, rather than the fetus, that is considered to be responsible for the development of preeclampsia [26]. Moreover, according to data from Sweden, a lateral placental location is linked to preeclampsia (OR: 1.30; 95% CI: 1.03–1.65), SGA (OR: 1.77; 95% CI: 1.39–2.25) and PTD (OR: 1.62; 95% CI: 1.32–2.00) [14].

Similarly, regarding hypertension in pregnancy, we found that cases with lateral placentas had a 3-fold and 2.4-fold greater risk of having preeclampsia and hypertensive disorders respectively, as compared to those with non-lateral placental localization. Our findings are consistent with those by Kofinas et al. [23], who found that women with a lateral placenta had a 2.8-fold higher risk of preeclampsia than those with a centrally positioned placenta. Of note, five [16, 18, 19, 21, 22] of the included studies found no increased risk of hypertensive disorders in women with lateral placenta. Thus, Liberati et al. [22] and Dagklis et al. [16] reported a non-significantly higher incidence of gestational hypertension in patients with lateral placentas; notably, in the first study [22] the lateral placenta group comprised 65% of their study sample. Magann et al. in a study of 3,336 women, reported no link between FGR, preeclampsia, PTD or other perinatal complications and high lateral placental location, but they

identified an increased incidence of low 5-min Apgar score (<7) [27].

Preeclampsia is likely caused by impaired trophoblastic invasion of the spiral arteries, while a persistent high resistance in the uterine arteries (UtA) probably explains the pathophysiology [28]. The latter finding has been utilized as the basis for the recommended preeclampsia screening technique involving Doppler examination of both uterine arteries in the first and second trimesters of pregnancy [5]. Interestingly, a study from Greece found that cases with lateral placenta have a higher proportion of increased mean UtA pulsatility index (16.6 vs. 6.7%), which may offer a further insight to the pathophysiology of preeclampsia [16]; a lateral placenta is associated with a higher mean UtA pulsatility index, which in turn is associated with a higher risk of preeclampsia.

Regarding SGA, the site of implantation and the placenta's subsequent location may play a role in the association of a lateral placenta with the uterine blood supply, in a similar way to preeclampsia. Indeed, evidence from several studies exploring the relationship between placental attachment to the uterus and UtA Doppler support the concept that placental attachment to the uterus is a key driver of placental blood flow [4, 23, 29]. According to our findings, the lateral group had a lower BW, with a mean difference of 100 g and a 1.7-fold higher risk for SGA. Regarding FGR, the data have been contradictory; Magann et al. [27] did not find a difference in their study. On the contrary, in three other studies [1, 8, 23], a statistically significant correlation between FGR and lateral localization was found. Of note, preeclampsia and FGR share the same pathophysiology defined as ischemic placental disease, so the lateral position of the placenta could lead to both of these complications in a similar mechanism.

Strengths and limitations

This is the first meta-analysis examining the relationship between prenatally diagnosed lateral placenta and perinatal outcomes. It was conducted in compliance with the MOOSE standards. A broad literature search was conducted, with no language constraints, as well as a manual search of the references, enhancing the probability of retrieving all relevant research.

An important limitation of our study is that most of the included studies were retrospective. Furthermore, the lack of a precise definition of the placental position is a fundamental constraint in our research. The placenta typically occupies a portion of the lateral uterine wall, with its major mass on the anterior or posterior wall; the location

of the placenta is not always well-defined, and it may occasionally temporarily change due to uterine wall contractions. There is also no consensus on the classification for placental location. However, since the data on placenta location were collected prior to the analyses in the majority of studies, this possible source of misclassification can be assumed to be non-significant. Notably, some of the outcomes studied could be related to each other e.g., FGR is usually associated with PTD, so there is probably an indirect association between lateral placenta and such outcomes. Moreover, the number of studies on specific outcomes, such as stillbirth, was restricted. Additionally, for several of the outcomes studied, heterogeneity was significant that can lead to erroneous conclusions. Finally, the possibility of publication bias cannot be ruled completely out, according to the findings of our analyses.

Conclusions

Preeclampsia and SGA were found to be more common in lateral than in non-lateral placentas. This finding should be further investigated to determine the pathophysiological basis of this association and to clarify if this may be an independent predictor that could be implemented in the second trimester screening for ischemic placental disease. Furthermore, larger prospective observational studies may help elucidate a possible association with other perinatal outcomes that were not adequately addressed by the studies included in this meta-analysis.

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Author contributions: Themistoklis Dagklis developed the project, participated in data collection/analysis and the manuscript writing. Antonios Siargkas and Petros Grammenos designed, coordinated, implemented the project, evaluated the results and participated in manuscript writing. Ioannis Tsakiridis coordinated the project and participated in manuscript writing/editing. Aikaterini Apostolopoulou and Sonia Giouleka participated in data analysis and manuscript writing. Apostolos Mamopoulos and Apostolos Athanasiadis participated in manuscript editing. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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