Gestational hypertensive disease and birthweight discordance in twin pregnancies: a systematic review and meta-analysis

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Abstract

Background: For singletons, the relationship between gestational hypertensive disease (GHD) and fetal growth anomalies has been established. However, the association between GHD and birthweight discordance in twin pregnancies is inclusive. Objective: To explore the association between GHD and birthweight discordance in twin pregnancies. Search strategy: PubMed, Embase, Web of Science and Cochrane Library were systematically searched from establishment until July 2021. Selection criteria: Studies reporting the risk of birthweight discordance in twin pregnancies complicated by GHD compared with those not were included. Data collection and analysis: Odds ratios (OR) and 95% confidence intervals (CI) were extracted. Study heterogeneity was evaluated by I2 index. Sub-group analyses and stratification were performed. Risk of bias was assessed with the Newcastle-Ottawa Scale. Main results: Ten studies (304181 twin pregnancies) were included. GHD (OR 1.65, 95% CI 1.41-1.94) was a risk factor for intertwin birthweight discordance [preeclampsia (OR 1.66, 95% CI 1.32-2.08); chronic hypertension (OR 1.59, 95% CI 1.46-1.73)]. No evident association was observed between gestational hypertension (GH) and intertwin birthweight discordance (OR 1.24, 95% CI 0.96-1.60). After stratification, birthweight discordance was related to GHD (OR 2.51, 95% CI 2.01-3.14), GH (OR 2.08, 95% CI 1.33-3.25) and preeclampsia (OR 2.74, 95% CI 2.09-3.61) in dichorionic pregnancies, but no longer associated with GHD and preeclampsia in monochorionic group. Conclusions: Twin gestations complicated with GHD, especially in DC pregnancies, were at significantly higher risk of birthweight discordance. Funding: Science and Technology Program of Nantong City (MS12020036). Keywords: gestational hypertensive disease, birthweight discordance, twin pregnancies, chorionicity, systematic review

Introduction

During the past decade, the rate of twin pregnancies has remarkably increased, and this is mainly ascribed to the rise in maternal age and the improvements in fertility enhancing treatments.[1-3]A common adverse outcome for twin pregnancies is intertwin birthweight discordance, defined as the birthweight discrepancy divided by the birthweight of larger twin and multiplied by 100.[4] Birthweight discordance has been reported to be related to an increased incidence of fetal intrauterine death, neonatal neurological morbidities, respiratory distress, infection, abnormal acid-base status, or necrotizing enterocolitis.[4,5]

Though the cause and pathophysiology of rising birthweight discordance in twin pregnancies are not completely understood and mastered, recent studies ascribed it to chorionicity,[6] parental race,[7]maternal vitamin D levels,[8] total birthweight, maternal age, education, fetal sex,[9] weight gain during pregnancy[10] and GHD.

Gestational hypertensive disease (GHD), classified into gestational hypertension (GH), preeclampsia (PE), eclampsia and chronic hypertension (CH),[11,12] is one of the most common disorders in pregnancy and its incidence in twin pregnancies is at least double greater than in singletons.[13,14] The risk of PE was 2.3% in singletons, 8.1% in dichorionic (DC) twin pregnancies and 6.0% in monochorionic (MC) twin pregnancies. GHD is well recognized as a major risk factor for maternal morbidity, perinatal mortality and

preterm delivery.[14,15]For singletons, the relationship between GHD and fetal growth anomalies has been well established.[16] However, studies investigating the association between GHD and birthweight discordance in twin pregnancies have reported differing results. In spite of the previous negative findings that the risk of intertwin birthweight discordance was similar between pregnancies with GHD and normotensive ones,[17-19] some other reports have shown that the degree of intertwin birthweight discordance in twin pregnancies is directly correlated with the risk of GHD.[20-26]

It is crucial to clarify the impact of GHD on intertwin birthweight discordance, as increased risks of perinatal outcomes are associated not only with GHD itself, but also with intertwin birthweight discordance.[4,27-29]Therefore, the aim of this systematic review was to explore the association between GHD and birthweight discordance in twin pregnancies.

Material and methods

Protocol, eligibility criteria, information sources and search

This systematic review was performed and conducted following the PRISMA[30] and MOOSE[31] guidelines, which were recommended standards for systematic reviews and meta-analysis. PubMed, Embase, Web of Science and Cochrane Library were searched systematically for relevant studies from establishment until July 2021, combining relevant medical subject heading terms, key words and word variants for "hypertension" or "hypertensive" or "preeclampsia" or "preeclamptic" or "eclampsia" or "eclamptic" and "birthweight" and "discordance" or "discordant" and "twin pregnancies" (Appendix S1). The search and inclusion criteria were restricted to human data and English language. Additional reports were manually searched by two authors (YW, HYZ) according to the reference lists of selected articles and reviews.

Study selection, data collection and data items

All studies (cohort studies and case-control studies) reporting data on the birthweight discordance affected by GHD in twin pregnancies were included. This review included all women in both DC and MC twin pregnancies complicated with gestational hypertension, chronic hypertension, preeclampsia and eclampsia. We excluded pregnancies with intrauterine death of one or both twins.

The outcome was the intertwin birthweight discordance, which was calculated utilizing the following equation: birthweight discordance (%) = (larger twin's birthweight - smaller twin's birthweight)/larger twin's birthweight) $\times$ 100. We performed the review according to one of the most common cut-offs of birthweight discordance ([?]15%).[4]

Furthermore, according to the classification of GHD, we planned to perform sub-group analyses reporting cases with GH, PE, eclampsia and CH separately. According to the criteria outlined by ACOG,[32,33] concretely, GH was defined as systolic blood pressure (BP) [?]140 mmHg or [?] 90 diastolic mmHg after 20 weeks of gestation, PE met the same criteria as GH with either proteinuria or end-organ dysfunction (liver dysfunction, renal dysfunction, central nervous system disturbances, thrombocytopenia, or pulmonary edema). Eclampsia was defined as a new onset of seizures in women with PE, who showed a convulsive episode or other sign of altered consciousness. CH was diagnosed as a pre-existing hypertensive disease or BP [?]140 mmHg systolic or [?] 90 mmHg diastolic preceding 20 weeks gestation.

In order to ascertain whether the association between GHD and intertwin birthweight discordance differs according to chorionicity, stratification by twin chorionicity (DC and MC) was performed. The assessment of chorionicity was clinically based on the ultrasound evaluation, including the number of gestational sacs, placenta and embryos at early pregnancy, τ-sign or λ-sign, the fetal sex,[34] and after delivery it was confirmed by examining the placenta.

Two authors (YW, HYZ) screened all studies independently in view of the inclusion and exclusion standards. Where there were inconsistencies, consensus was reached by discussion with another reviewer (FZ). With full text copies of included studies obtained, the same two reviewers extracted relevant data in regard to study characteristics and pregnancy outcomes independently. In case over one study was published based on the

identical cohort with uniform endpoints, the report demonstrating the most comprehensive information was included.

Quality assessment was performed with the Newcastle-Ottawa Scale (NOS) adapted for cohort and case-control studies. Each study is evaluated from three broad aspects: selection of patients, comparability of study groups and ascertainment outcome of interest. The scores of the NOS range from 0 to 9. The included studies were interpreted to be of high risk of bias (for scores [?] 4), medium risk of bias (for scores 5-7), or low risk of bias (for scores [?] 7).[35] Articles with low risk of bias were included in the analysis.

Statistical analyses

Data analysis was carried out using Review Manager (version 5.3) software. Heterogeneity between studies was explored using the Higgins I^2 statistics. When there was substantial heterogeneity (I^2 [?] 50%), the random effect model was used to estimate the pooled risk ratio, otherwise the fixed effect model was used. Subgroup analyses were employed to evaluate the sources of heterogeneity, and stratification by twin chorionicity (DC and MC) was performed to exclude the impact of chorionicity on the outcome. The odds ratio (OR) and 95% confidence interval (CI) were the summary measures applied to assess each endpoint. Potential publication biases were statistically examined by Egger's test and visually by funnel plots (Figure S2).

Results

General characteristics

A total of 2532 articles were identified, 57 were assessed with respect to their eligibility for inclusion, and 10 studies[17-26] were deemed suitable to be included in this systematic review (Table S1; Figure S1). These 10 studies (including 304181 twin pregnancies) reported the occurrence of birthweight discordance in twin pregnancies complicated by GHD compared with those not. Eight of these included papers were cohort studies, whereas two were case-control studies[17,19]. Three of them were conducted in China[19,24,26], two in the USA[21,22], two in the UK[17,25], two in Rome[18,20] and one in Ireland[23]. Among the selected studies, four reported the intertwin birthweight discordance affected by GH[17,18,24,26], three affected by CH[17,21,22] and five affected by PE[19-21,24,26] in detail. Only three of the included studies[24-26] conducted stratification by twin chorionicity.

Quality assessment of the selected studies performed using NOS is presented in Table S2. Most of the studies scored well in terms of selection, comparability and outcome. The main weaknesses of these studies were their retrospective design, small sample size, lack of information on the follow-up outcome, different gestational ages at scan and heterogeneity in the cut-off of birthweight discordance adopted.

Synthesis of the results

GHD VS Normotensive

Ten studies (304181 twin pregnancies) explored the risk of birthweight discordance ([?]15%) in twin pregnancies complicated by GHD compared with Normotensive group. Considering all twin pregnancies, the risk of birthweight discordance was significantly higher in twin pregnancies with GHD (OR 1.65, 95% CI 1.41-1.94; I^2 =57%). After stratified by twin chorionicity, birthweight discordance was associated with an increased risk for GHD (OR 2.51, 95% CI 2.01-3.14; I^2 =0%) in DC twin pregnancies. However, no significant association was observed in MC group (OR 1.14, 95% CI 0.76-1.72; I^2 =0%). (Figure 1)

GH VS Normotensive

Four studies (5216 twin pregnancies) explored the risk of birthweight discordance ([?]15%) in twin pregnancies with GH compared to Normotensive group. In all, no evident association was observed between GH and the incidence of intertwin birthweight discordance (OR 1.24, 95% CI 0.96-1.60; I^2 =0%). According to the stratified sampling, GH was a risk factor for birthweight discordance in DC group (OR 2.08, 95% CI 1.33-3.25; I^2 =0%), but a protective factor in MC group (OR 0.37, 95% CI 0.16-0.82; I^2 =0%). (Figure 2)

PE VS Normotensive

Five studies (293612 twin pregnancies) explored the risk of birthweight discordance ([?]15%) in twin pregnancies with PE compared to Normotensive group. It turned out that the risk of birthweight discordance was significantly higher in twin pregnancies with PE (OR 1.66, 95% CI 1.32-2.08; I^2 =64%). Birthweight discordance was associated was PE in DC (OR 2.74, 95% CI 2.09-3.61; I^2 =40%) but not in MC (OR 1.21, 95% CI 0.68-2.15; I^2 =0%) twin pregnancies based on the stratification by chorionicity. (Figure 3)

CH VS Normotensive

Three studies (269259 twin pregnancies) explored the risk of birthweight discordance ([?]15%) in twin pregnancies affected by CH compared with Normotensive group. Overall, twin pregnancies affected by CH were at a higher risk of birthweight discordance (OR 1.59, 95% CI 1.46-1.73; I^2 =3%). (Figure 4)

Discussion

Main Findings

This systematic review demonstrated that birthweight discordance was associated with GHD in twin pregnancies. The risk of birthweight discordance increases in parallel to the incidence of GHD. After stratification, birthweight discordance was related to GHD, GH and PE in DC pregnancies, but no longer associated with GHD and PE in MC group.

Strengths and Limitations

To the best of our knowledge, few systematic reviews explored the association between GHD and birthweight discordance in twin pregnancies. The main strengths are an inclusive and accurate literature search strategy, multitude of explored outcomes, sub-group analyses performed according to the classification of GHD and stratified sampling conducted based on twin chorionicity.

However, some limitations needed to be acknowledged were small number of selected studies, different inclusion criteria for the included population, and different approach towards the antenatal management of twin pregnancies. The reliability of the systematic review was strongly limited by the small sample size of individual studies. Furthermore, the findings were subject to the differences in the cut-off of birthweight discordance adopted by each study. Another major limitation of our present systematic review was that as only one of the included studies[21] reported twin pregnancies with eclampsia, lack of related data made it a challenge to report the association between the incidence of eclampsia and the risk of intertwin birthweight discordance.

In spite of these limitations, this study represents the newest and most comprehensive published assessment of the association between GHD and birthweight discordance in twin pregnancies.

Interpretation

GHD, particularly PE and CH, is a significant risk factor for intertwin birthweight discordance. Though the reason for the existence of this association remains unclear and may be in connection with the multifactorial aspect of GHD, there are some possible explanations for this association. Findings such as retroplacental hematomas, thrombotic lesions, fibrin deposition and more velamentous cord insertions were observed in the placentas of discordant twins.[36,37]

In discordant twins complicated with PE, the placental mass hypothesis might further explain the histological findings observed in the placentas. In twin pregnancies, an increased release of some antiangiogenic molecules may be related to lager placental mass. Soluble fms-like tyrosine kinase-1 (sFlt-1) turned out to play a crucial part in the pathogenesis of PE,[38,39] which possibly causes placental ischemia/hypoxia, supposing the placentas contract diseases, the smaller one in the twins might fail to achieve the growth potential because of the placental vascular dysfunction.[40,41]

Moreover, the genetic incompatibility and/or increased immunologic response theory maybe another explanation. Some studies revealed higher levels of syncytiotrophoblast microparticles and fetal nucleic acids in the maternal blood in twin pregnancies complicated by PE.[42-44] Other studies showed that the interactions between paternal antigens of leukocytes and maternal natural killer cell, and cytotoxic T-cell response to those antigens were mechanisms contributing to the development of PE.[45] Exposed to increased levels of placental microparticles or fetal antigens which can trigger in appropriate immune responses, women will possibly deliver twins with birthweight discordance.

Additionally, as common umbilical cord abnormalities, velamentous cord insertions are risk factors for PE.[46] It was found that velamentous cord insertion is a crucial indicator of intertwin birthweight discordance.[47] It was speculated that the high incidence of velamentous insertions in twin pregnancies complicated with PE leads to an increased risk of birthweight discordance.

When it comes to twin pregnancies complicated with CH, Sparks et al.[22] pointed out that the chronic hypertension environment may further impose much more stress on twins with pre-existing differences regarding growth potential. However, whether related to potential genetic differences or not, abnormal placentation itself might lead to the development of fetal growth abnormalities. Therefore, the mechanism of the correlation between CH and intertwin birthweight discordance deserves further investigation.

However, GH might play an unknown beneficial role in MC pregnancies according to the stratified analysis, which was reflected by Ferrazzani S et al.[18] that GH could be a paraphysiological phenomenon in twin pregnancies ensuring a better placental perfusion. More studies are necessary to explain the pathogenesis of this finding.

According to the subgroup and stratified analyses, the risk of intertwin birthweight discordance differed based on chorionicity. DC twins are mostly fraternal twin pregnancies, either due to two separate placentas or pre-existing genetic differences between twins in growth potential.[40] The potential genetic differences between the twins might probably interact with hypertensive environments, leading to discordant uteroplacental blood flow, placental changes, and growth in DC group. The placental anatomy is unique in MC twin pregnancies, and the fetal circulations were conjoined in a single placenta. Among MC twins, birthweight discordance is related to placental territory discordance between the fetuses, velamentous cord insertions, and the type and number of vascular anastomoses.[48-50]

So as to why birthweight seemed to be less affected by GHD in MC twin pregnancies. It could be attributed to an earlier gestational age at delivery and before the occurrence of PE in MC twin pregnancies,[51] otherwise the true risk of birthweight discordance in MC twin pregnancies with PE might actually be higher. In addition, compared to DC ones, the circulating blood volume is lower in MC twin pregnancies, which brings about better cardiovascular adaptation to pregnancy.[52]

However, the findings of our study should be elucidated carefully due to small number and sample size of selected studies, more fundamental and clinical studies are warranted to focus on the effect of GHD on intertwin birthweight discordance.

Conclusion

We collected evidence suggesting the association between GHD and birthweight discordance in twin pregnancies. Twin gestations complicated with GHD, especially CH and PE, were at significantly higher risk of birthweight discordance. The influence of GHD on intertwin birthweight discordance differed based on chorionicity. GHD had greater effect on the risk of birthweight discordance of DC twins. The findings from the present review suggest that better clinical assessments and evaluations of prognosis, and increased maternal and fetal monitoring in twin pregnancies are justified, which can assist in providing better individualized counseling and optimal pregnancy management for twin gestations complicated by GHD.

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Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as

supporting information.

Contribution to authorship

YW and HYZ contributed to planning the review, screening all titles and abstracts, reviewing full articles, and performing data extraction. FZ was a third reviewer in case where there were inconsistencies. YW performed the data analysis and drafted the initial manuscript. JL assisted with the study design and data analysis. FZ contributed to interpreting the data and revising the manuscript. All authors approved the final version of this manuscript.

Details of ethics approval

Not applicable.

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Conflicts of interest

None

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Figure legends

Figure 1. Forest plots showing the risk of birthweight discordance in twin pregnancies with GHD. Strat-

ification by twin chorionicity (DC and MC) was performed. GHD, gestational hypertensive disease; DC, dichorionic; MC, monochorionic.

Figure 2. Forest plots showing the risk of birthweight discordance in twin pregnancies with GH. Stratification by twin chorionicity (DC and MC) was performed. GH, gestational hypertension; DC, dichorionic; MC, monochorionic.

Figure 3. Forest plots showing the risk of birthweight discordance in twin pregnancies with PE. Stratification by twin chorionicity (DC and MC) was performed. PE, preeclampsia; DC, dichorionic; MC, monochorionic.

Figure 4. Forest plots showing the risk of birthweight discordance in twin pregnancies with CH. CH, chronic hypertension.

Online Supporting Information

Appendix S1. Search strategy.

Table S1. General characteristics of the studies included in the meta-analysis.

Table S2. Risk of bias assessment cohort studies (Newcastle-Ottawa Quality Assessment Scale criteria).

Figure S1. Flowchart showing the selection process of the included studies.

Figure S2. Funnel Plot of the studies included.

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`Figure1-4.docx` available at https://authorea.com/users/734972/articles/711624-gestational-hypertensive-disease-and-birthweight-discordance-in-twin-pregnancies-a-systematic-review-and-meta-analysis