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Impact of cesarean section on placental transfusion and iron-related hematological indices in term neonates: A systematic review and meta-analysis

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ABSTRACT

Evidence suggests that cesarean section is likely associated with a reduced placental transfusion and poor hematological status in neonates. However, clinical studies have reported somewhat inconsistent results. We conducted a systematic review and meta-analysis to examine whether cesarean section affects placental transfusion and iron-related hematological indices. Pubmed, Web of Science, ScienceDirect, and Ovid Databases were searched for relevant studies published before April 9, 2013. Mean differences between cesarean section and vaginal delivery in outcomes of interests (placental residual blood volume; hematocrit level, hemoglobin concentration, and erythrocyte count in cord/peripheral blood) were extracted and pooled using a random effects model. We identified 15 studies ($n = 8477$) eligible for the meta-analysis. Compared with neonates born vaginally, those born by cesarean section had a higher placental residual blood volume [weighted mean difference (WMD), 8.87 ml; 95% confidence interval (CI), 2.32 ml–15.43 ml]; a lower level of hematocrit (WMD, −2.91%; 95% CI, −4.16% to −1.65%), hemoglobin (WMD, −0.51 g/dL; 95% CI, −0.74 g/dL to −0.27 g/dL) and erythrocyte (WMD, -0.16×10^{12}/L; 95% CI, -0.30×10^{12}/L to -0.01×10^{12}/L). Subgroup analysis showed that the WMD for hematocrit in neonate's peripheral blood (−6.94%; 95% CI, −9.15% to −4.73%) was substantially lower than that in cord blood (−1.75%; 95% CI, −2.82%, −0.68%) (*P* value for testing subgroup differences <0.001). In conclusion, cesarean section compared with vaginal delivery is associated with a reduced placental transfusion and poor iron-related hematologic indices in both cord and peripheral blood, indicating that neonates delivered by cesarean section might be more likely affected by iron-deficiency anemia in infancy.

1. Introduction

Iron deficiency anemia, affecting both physical growth and mental development [1–3], is prevalent in developing countries, with an estimated prevalence of 30% in children under 4 years in 2005 [4]. Iron deficiency prevalence in some settings was up to 80% in children younger than 2 years [5]. In addition to maternal anemia status [6] and inadequate iron intake [7], a reduced placental transfusion at birth has been suggested to increase the risk of early-life iron deficiency [8,9]. Compared with vaginal delivery, cesarean section is often associated with a shorter period of placental transfusion due to immediate cord clamping [10] and with a weaker placental transfusion force, primarily related to uterine contraction [11], maternal blood pressure [12], delayed onset of respiration [13], and gravity [14]. It is likely that cesarean section is also associated with a reduced placental transfusion and an increased early-life iron deficiency risk.

Since the 1970s, the impact of cesarean section on placental transfusion and iron deficiency has been assessed in many clinical studies using various outcome measures including placental residual blood volume or some iron-related hematological indices (i.e. hematocrit level, hemoglobin concentration, and erythrocyte count) in cord blood or neonate's peripheral blood [15–34]. These

Abbreviations: CI, confidence interval; MD, mean difference; MOOSE, meta-analyses of observational studies in epidemiology; NOS, Newcastle-Ottawa scale; SD, standard deviation; WMD, weighted mean difference.

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studies have reported somewhat inconclusive or contradictory results, possibly due to small sample size, variations in study design or participant selection. Given the potential health burden of early-life iron deficiency and the widespread increase in the number of cesarean births [35], especially non-medically indicated elective cesarean births [36], it is of particular public health significance to clarify the association of cesarean section with placental transfusion and various iron-related hematological indices by performing a systematic review and meta-analysis.

2. Methods

The review and meta-analysis were conducted and reported according to the proposal for conducting and reporting Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [37].

2.1. Literature search and study selection

We searched Pubmed, Web of Science, ScienceDirect, and Ovid databases to identify relevant articles that were published before April 9, 2013 using combinations of three groups of search terms: (1) "cesarean", "caesarean", "cesarian", "caesarian"; (2) "c*section", "obstetric*", "perinatal", "peri*natal"; and (3) "placental transfusion", "blood volume", "red blood cell", "erythrocyte", "hemoglobin", "haemoglobin", "Hb", "hematocrit", "hematocrite", "haematocrit" or "Hct". In study selection, we first removed duplicate records identified from different databases, then assessed the relevance of the remaining records by reviewing their titles and/or abstracts, and finally retrieved full texts of potentially relevant publications for eligibility assessment. We also hand searched the references of eligible publications for additional relevant studies. This search strategy was initially determined based on a consensus discussion among the four reviewers, and subsequently updated several times for its accuracy and completeness. The literature search and study selection were done separately by two reviewers (YZ and HL). Any discrepancies regarding study selection were resolved by a consensus discussion between the two reviewers or with the third reviewer (JL).

The original study (i.e. not review articles, letters, commentaries, etc.) was considered eligible for the literature review if 1) the study assessed the association of cesarean section versus vaginal delivery with one or more of following outcome measures in term neonates: placental residual blood volume; hematocrit level, hemoglobin concentration, and erythrocyte count in cord/peripheral blood; 2) the study was limited to a human study; and 3) the study was published in English or with an English abstract. In the case of multiple publications from the same study population, we included the one that provided the most completed information. We did not include studies conducted in preterm neonates, since the hematological parameters between term and preterm neonates were materially different [38].

2.2. Data extraction and quality assessment

Two reviewers (YZ and HL) independently extracted study information using a pre-tested structured form. The extracted information included study setting, study type and study quality, participant selection, gestational age, sample size, types of blood sample (cord/neonate's peripheral blood), outcomes of interests, and effect estimates. The mean difference (MD) with 95% confidence interval (CI) between cesarean section and vaginal delivery was of primary interest. If MD was not provided, the mean and standard deviation (SD) were used to calculate a MD and 95% CI. Whenever possible, we extracted or calculated the MD for both total cesarean section and subtypes of cesarean section (elective/emergency cesarean section). For iron-related hematological indices, we extracted the MDs for both cord blood and neonate's peripheral blood if they were separately reported. If separate MDs were reported for different types of cord clamping (early/delayed cord clamping), we extracted all data. If separate MDs were reported for both umbilical artery and venous blood, we extracted those only for umbilical venous blood.

The quality of each study included in the meta-analysis was independently assessed by two reviewers (YZ and HL) according to the Newcastle-Ottawa scale (NOS) [39]. The NOS awards a maximum of 9 stars to each study: 4 stars for the study group selection, 2 for the comparability between study groups, and 3 for the ascertainment of outcome measures. In this review, $\geq$7 stars were deemed as a high quality study, 4 to 6 stars as medium, and $\leq$3 stars as low. Any disagreements in studies' quality assessment were resolved by a consensus discussion between the two reviewers or with the third reviewer (JL).

2.3. Data synthesis

The weighted mean difference (WMD) with 95% confidence interval (CI) was calculated for all interested outcome measures. We assessed statistical heterogeneity between studies using the I^2 statistics. If the I^2 value was <50%, the WMD was calculated using a fixed effects model; If the I^2 value was $\geq$50%, the WMD was calculated using a random effects model [40]. Whenever possible (i.e. with adequate number of studies), we further conducted sensitivity analyses by removing medium- and low-quality studies or by removing the study with the largest weight to assess the robustness of the pooled results and conducted subgroup analyses by types of blood sample (cord/neonate's peripheral blood) and types of cesarean section (elective/emergency).

Publication bias was assessed using a funnel plot and the Begg's rank correlation test [41]. The influence of potential publication bias on pooled results was assessed using the trim-and-fill method. The Begg's test and trim-and-fill analysis were performed using R statistical software (version 2.15.1) with the Metafor package (version 1.6-0) [42]. All other data syntheses were performed using Revman (version 5.1). *P* values were two-sided with a significance level of 0.05.

3. Results

A total of 18,655 non-duplicate records were retrieved (Fig. 1). Forty-one potential relevant studies were identified after reviewing titles, abstracts and full texts. Twenty-one studies were further excluded after detailed evaluation and 20 remained in the systematic review. Of these 20 studies, 5 were not eligible for the meta-analysis due to the MDs' unavailability and 15 remained in the meta-analysis.

3.1. Literature review

Of the 5 studies not eligible for the meta-analysis, one reported that cesarean section versus vaginal delivery increased placental residual blood volume only in late cord clamped group but the difference was not found in early cord clamped group [22]; of the remaining 4 studies that focused on iron-related hematological indices, 2 reported that cesarean section decreased hemoglobin concentration/hematocrit level in cord blood [20,25], whereas the other 2 studies showed that delivery mode had no significant impacts on hemoglobin concentration, hematocrit level, and erythrocyte count [18,28].

Of the 15 studies included in the meta-analysis, 11 studies with 7759 subjects were conducted in developed countries, and 4 with