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


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 hemocrit (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 × 10¹²/L; 95% CI, −0.30 × 10¹²/L to −0.01 × 10¹²/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% to −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...
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) “section,” “obstetric,” “perinatal,” “peri-natal”; and (3) “placental transfusion,” “blood volume,” “red blood cell,” “erythrocyte,” “hemoglobin,” “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, ≥7 stars were deemed as a high quality study, 4 to 6 stars as medium, and ≤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 I2 statistics. If the I2 value was >50%, the WMD was calculated using a fixed effects model; if the I2 value was ≥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
718 subjects in developing countries. Seven studies were described as prospective studies, 2 as cross sectional studies, and 6 did not mention the type of study. In this review, we assessed the studies’ quality according to the NOS guidelines for cohort study, because the measurements of placental residual blood volume or iron-related hematological indices in cord/peripheral blood always take place after delivery. Overall, 10 studies were assessed to be high-quality and 5 medium-quality; no studies was deemed to be low-quality. Four studies measured the impact of delivery mode on placental residual blood volume. Eleven studies assessed the impact of delivery mode on iron-related hematological indices, among which 9 focused on cord blood, 1 on neonate’s peripheral blood (6 h after birth), and 1 on both cord and neonate’s peripheral blood (3 h after birth). The detailed characteristics for included studies are shown in Table 1.

3.2. Meta-analysis

3.2.1. Placental residual blood volume

Four studies [19,27,29,32] assessing placental residual blood volume involved a total of 1170 neonates. The WMD of placental residual blood volume for neonates delivered by cesarean section compared with those born vaginally was 8.87 ml (95%CI, 2.32 ml–15.43 ml; \( P = 0.008 \)) (Fig. 2). A moderate heterogeneity between individual studies was observed (\( I^2 = 51\% \), \( P = 0.11 \)). In order to assess whether the heterogeneity was caused by the timing when the placental residual blood volume was measured, we performed a subgroup analysis. The placental residual blood volume measured before placental delivery increased by 9.80 ml in cesarean section compared with vaginal delivery and by 7.92 ml after placental delivery (\( P \) for interaction = 0.69), indicating that the heterogeneity was not likely to be caused by the timing of the measurement.

3.2.2. Hematocrit

Seven studies [17,21,24,30,31,33,34] with 5098 neonates reported totally 11 MDs for hematocrit level. The WMD for neonates delivered by cesarean section compared with those born vaginally was 2.91% (95%CI, −4.16% to −1.65%; \( P < 0.001 \)) (Fig. 3). High heterogeneity between individual studies was observed (\( I^2 = 88\% \), \( P < 0.001 \)). In sensitivity analyses, the WMD was slightly increased when the analysis was restricted to high-quality studies (−3.25%; 95% CI, −4.64% to −1.85%; \( P < 0.001 \)) or when the study with the
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<td>VD:2692</td>
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<td>Farrar et al., 2010</td>
<td>UK; prospective observational study; high quality study</td>
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<td>Kleinberg, 1975b</td>
<td>USA; no mentation study type; high quality study</td>
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<td>VD:33</td>
<td>cord venous blood</td>
<td>PRBV (ml/Kg)</td>
<td>NO</td>
</tr>
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<td>Lee et al., 2009</td>
<td>Korea; no mentation study type; medium quality study</td>
<td>Term infants</td>
<td>VD: 39.7 ± 0.9</td>
<td>EICS:9</td>
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<td>Hb (g/dL)</td>
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<td>Lubetzky et al., 2000</td>
<td>Israel; prospective study; high quality study</td>
<td>Term neonates born by healthy nonsmoking mothers</td>
<td>VD: 39.7 ± 0.9</td>
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<td>Marwaha, 1992</td>
<td>India; no mentation study type; medium quality study</td>
<td>Term normal neonates</td>
<td>VD: 39.1 ± 0.9</td>
<td>EICS:38.8 ± 0.8</td>
<td>Peripheral blood at 6 ± 6 h</td>
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<td>CS vs. VD: 6.00 (-9.53, 2.47)</td>
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<tr>
<td>Mimouni et al., 2003</td>
<td>Israel; Prospective study; high quality study</td>
<td>Term infants</td>
<td>VD: 39.7 ± 0.9</td>
<td>EICS:38.8 ± 0.8</td>
<td>Peripheral blood at 6 ± 6 h</td>
<td>RBC (×10^12/L)</td>
<td>CS vs. VD: 6.00 (-9.53, 2.47)</td>
</tr>
<tr>
<td>Nikischin et al., 1997</td>
<td>Germany; prospective study; high quality study</td>
<td>Term infants</td>
<td>VD: 37–42 weeks gestation</td>
<td>EICS:38.8 ± 0.8</td>
<td>Peripheral blood at 6 ± 6 h</td>
<td>RBC (×10^12/L)</td>
<td>CS vs. VD: 6.00 (-9.53, 2.47)</td>
</tr>
<tr>
<td>Omori et al., 2010</td>
<td>Japan; no mentation study type; high quality study</td>
<td>Healthy singleton neonates</td>
<td>VD:37.9 ± 1.1</td>
<td>EICS:19</td>
<td>Cord venous blood</td>
<td>RBC (×10^12/L)</td>
<td>CS vs. VD: 6.00 (-9.53, 2.47)</td>
</tr>
<tr>
<td>Ozbek et al. 2000a</td>
<td>Turkey; no mentation study type; medium quality study</td>
<td>Healthy term neonates</td>
<td>38–41 weeks</td>
<td>EICS:21</td>
<td>Cord venous blood</td>
<td>RBC (×10^12/L)</td>
<td>CS vs. VD: 6.00 (-9.53, 2.47)</td>
</tr>
<tr>
<td>Pafumi et al., 2002</td>
<td>Italy; no mentation study type; medium quality study</td>
<td>Term uncomplicated infants</td>
<td>VD: 40.1 ± 1.0</td>
<td>EICS:40.1 ± 1.0</td>
<td>Cord venous blood</td>
<td>Hb (g/L)</td>
<td>CS vs. VD: 10.00 (6.65, 13.35)</td>
</tr>
<tr>
<td>Redzko et al., 2005</td>
<td>Poland; cohort study; high quality study</td>
<td>Live-born term normal infants</td>
<td>VD: 38–41 weeks of gestation</td>
<td>EICS:40.1 ± 1.0</td>
<td>Cord venous blood</td>
<td>Hb (g/L)</td>
<td>CS vs. VD: 10.00 (6.65, 13.35)</td>
</tr>
</tbody>
</table>
3.2.3. Hemoglobin and erythrocyte

Seven studies [15–17,21,23,31,34] involving a total of 6563 neonates evaluated hemoglobin concentration in cord blood, and 8 MDs were extracted. The WMD for neonates delivered by cesarean section compared with those born vaginally was \(-0.51\) g/dL (95% CI, \(-0.74\) g/dL to \(-0.27\) g/dL; \(P < 0.001\)) (Fig. 4). In sensitivity analysis, the WMD was slightly increased when medium-quality studies were removed (\(-0.57\) g/dL; 95% CI, \(-0.93\) g/dL to \(-0.22\) g/dL; \(P = 0.001\)) or when the study with the largest weight was excluded (\(-0.57\) g/dL; 95% CI, \(-0.93\) g/dL to \(-0.22\) g/dL; \(P = 0.001\)) (Fig. 4). In subgroup analyses, the WMDs for cord blood (8 MDs) and neonate’s peripheral blood (3 MDs) were \(-1.72\%\) (95% CI, \(-1.76\%\) to \(-1.72\%\); \(P = 0.001\)) and \(-6.94\%\) (95% CI, \(-9.15\%\) to \(-4.73\%\); \(P < 0.001\), respectively (\(P\) for interaction = \(0.001\)). Of the 11 MDs, only 5 were reported by elective/emergency cesarean section [24,30,31]. The WMD for elective cesarean section (3 MDs) was \(-4.72\%\) (95% CI, \(-8.16\%\) to \(-1.27\%\); \(P = 0.007\)) and \(-3.45\%\) (95% CI, \(-9.46\%\), 2.56%); \(P = 0.26\)) for emergency cesarean section (2 MDs) (\(P\) for interaction = \(0.72\)).

3.2.4. Publication bias

The funnel plot for hematocrit showed somewhat asymmetry, despite the Begg’s test not being significant (\(P = 0.36\)) (Fig. 5). The trim-and-fill analysis showed that the WMD for cesarean section compared with vaginal delivery was still statistically significant (WMD = \(-1.72\%\), 95% CI \(-2.99\%, -0.46\%; \(P < 0.01\)), indicating the pooled results were not likely affected by potential publication bias. The publication bias for other outcome measures was not assessed due to the limited number of studies.

4. Discussion

In this systematic review and meta-analysis, we found that cesarean section, compared with vaginal delivery, was associated with an increased placental residual blood volume and a decreased level of several iron-related hematological indices including hematocrit, hemoglobin, and erythrocyte in both cord and peripheral blood in term neonates. The magnitude of reduction in hematocrit level was more pronounced in elective cesarean section than in emergency cesarean section, and in peripheral blood than in cord blood.

In our overall analyses, cesarean section compared with vaginal delivery increased placental residual blood volume by 8.87 ml. Previous study reported that a placental transfusion of 20–30 ml per kilogram birth weight endows about 30–50 mg of iron to newborn [43]. It is estimated that 3.0–7.0 mg iron would be deprived from a cesarean-delivered term neonate with an average birth weight of 3.3 kg. Our analyses also showed that cesarean section reduced hematocrit level by 2.91% (95% CI, 2.58% to 3.25%) and in cord blood, respectively (or when the study with the largest weight was excluded (WMD = \(-3.28\%\) and \(-0.57\) g/dL, respectively). We performed subgroup analyses only for hematocrit according to type of blood sample and types of cesarean section, but not for other outcome measures due to the limited available
studies. The significant reduction effect was observed not only in cord blood (WMD = -1.75%), but also in neonate’s peripheral blood (WMD = -6.94%); the magnitude of the effect in the latter was even larger than in the former (P for interaction < 0.001), indicating that the reduction effect lasted and became much stronger after birth. The reduction effect for elective cesarean section (WMD = -4.72%, P = 0.007) was slightly larger than that for emergency cesarean section (WMD = -3.45%, P = 0.26), although the test for subgroup differences was not statistically significant (P = 0.72). Notably, there were two studies that directly compared...
the impact of elective versus emergency cesarean section on hematocrit, and both showed that elective cesarean section had stronger reduction effect [24,30].

The reduction effect of cesarean section on placental transfusion is likely attributable to a weaker transfusion force and a shorter transfusion period. During cesarean section, a newborn is usually placed on the mother’s abdomen after delivery; therefore, the newborn’s position is often higher than the placenta before cutting the cord, which may prevent cord blood flowing from the placenta to newborn due to a gravity effect [14]. Compared with newborns delivered vaginally, those delivered by cesarean section often lack uterine or vaginal squeeze and thus newborns’ lung fluid is not likely squeezed out during the process of delivery, which might delay the onset of respiration and impede the placental transfusion [13,44]. In addition, maternal hypotension [45] and an insufficient uterine contraction [11,38] are often more common among women who experience cesarean sections due to anesthesia and uterine incision. On another hand, the duration of placental transfusion for a newborn delivered by cesarean section is shorter, since an immediate cord clamping is often performed to avoid maternal bleeding, infections or other surgery-related complications [10]. Obviously, an inadequate placental transfusion would lead to a decreased level of iron-related hematological indices both in cord and in neonate’s peripheral blood after delivery. Besides an inadequate placental transfusion, neonates born by cesarean section are already likely to have a decreased level of iron-related hematologic indices in utero, since fluid transfusion from intravascular to extravascular is less for a cesarean-delivered fetus compared with a vaginal-delivered fetus due to the lack of utero squeezing [24].

To the best of our knowledge, this is the first systematic review and meta-analysis to synthesize currently available observational studies investigating the impact of cesarean section on placental transfusion or iron-related hematological indices in term neonates. Our study has limitations. First, we might have missed some studies published in the non-English language and without an English abstract. Second, high heterogeneity was observed for hematocrit, hemoglobin and erythrocyte. We performed subgroup analyses for hematocrit to explore the sources of heterogeneity, and observed significant differences in hematocrit level both between cord and peripheral blood, and between elective and elective cesarean section. However, moderate- or high-heterogeneity within subgroups still remained, possibly attributable to other factors (such as maternal use of oxytocin, cord clamp timing or gravity) that we were unable to explore in the absence of data. Third, the instruments used for measuring hematological indices were different among studies. However, instrument-related bias, if any, would not materially affect the mean differences in hematological indices between cesarean section and vaginal delivery. Despite above-mentioned methodological concerns, our pooled results consistently showed that cesarean section was associated with a decreased placental transfusion and poor iron-related hematologic indices in term neonates.

In conclusion, cesarean section is associated with a reduced placental transfusion and a decreased level of iron-related hematologic indices in both cord and neonate’s peripheral blood, which may be of important public health implications given the high prevalence of cesarean births and the high prevalence of infantile iron-deficiency anemia particularly in developing communities. Our findings indicate potential benefits to increase placental transfusion during cesarean section and support efforts to reduce cesarean births, particularly non-medically indicated elective cesarean births. Future studies are warranted to further assess the longer-term impacts of cesarean section on anemic status in offspring.

Conflict of interest

None of the authors declared a conflict of interest.

Author contributions

YZ designed the study, did the analysis, interpreted the data, drafted and revised the manuscript. HL designed the study, did the analysis, interpreted the data and revised the manuscript. LZ interpreted the data and revised the manuscript. JL conceived and designed the study, did the analysis, interpreted the data, drafted and revised the manuscript.

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