

Manual Removal versus Spontaneous Delivery of the Placenta at Cesarean Section: A Meta-Analysis of Randomized Controlled Trials

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Purpose: Several randomized clinical trials (RCTs) investigated the effects of the manual placental removal on hemorrhage or other hemorrhage-related complications compared with the spontaneous placental removal during cesarean section (CS), while the results remained controversial and were inconsistent. The purpose of this meta-analysis was to quantify the pooled effects of the methods of placental removal on hemorrhage during CS.

Patients and Methods: A systematic literature search was conducted using PubMed, EMBASE, Web of Science, and Google Scholar. Heterogeneity was tested by I^2 statistics and Q-statistic. The random-effects model or fixed-effects model were used to calculate the pooled effect for the included studies according to heterogeneity. And the term of standardized mean difference (SMD) with 95% confidence intervals (CI) was pooled and estimated the effects across all studies.

Results: A total of nine RCTs were included in this meta-analysis. Compared with spontaneous group, manual placental removal increased the amount of hemorrhage ($SMD = 0.53$, 95% CI [0.12, 0.94]; $Z = 2.54$, $P = 0.011$) and increased the risk of endometritis ($OR = 1.84$, 95% CI [1.31, 2.58]; $Z = 3.52$, $P < 0.0001$). In contrast, there was no significant difference concerning the operating time ($SMD = -0.30$, 95% CI [-0.85, 0.24]; $Z = 1.09$, $P = 0.276$), the length of hospital stays ($SMD = 0.11$, 95% CI [-0.08, 0.30]; $Z = 1.11$, $P = 0.265$), and blood transfusion requirement ($OR = 1.36$, 95% CI [0.91, 2.04]; $Z = 1.52$, $P = 0.129$), respectively.

Conclusion: Comparing with spontaneous placental removal, manual placental removal appeared to be less positive effect during CS. Because of the limitations of this meta-analysis, more high-quality RCTs are needed to confirm our findings.

Keywords: cesarean section, manual placental removal, spontaneous placenta removal, hemorrhage, meta-analysis

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Introduction

Cesarean section (CS) is a life-saving surgery when certain complications occur during pregnancy and childbirth.¹ CS rates have consistently increased in both developing and developed countries in the recent few decades.² Based on the recent data from 150 countries, currently, CS accounts for 18.6% of all births, and for the least and most developed regions ranged from 6% to 27.2%, respectively.¹ Despite advances in modern surgical equipment and postoperative care, related risks such as hemorrhage, iatrogenic tumors, thromboembolic events, and infection are still potential threats.³ Patients with malignant placenta may have influence on the blood loss and clinical outcomes of cesarean section. Additional therapeutic

methods can reduce blood loss during cesarean delivery and preserve fertility in pernicious placenta previa patients who are complicated with placenta accrete.⁴ Among them, hemorrhage is one of the most common complications of delivery and is considered to be the main cause of preventable maternal mortality in the world.⁵ Meanwhile, compared with vaginal delivery, cesarean delivery has a higher risk of hemorrhage.⁶ Estimating the amount of blood loss during CS is critical to reducing surgically induced morbidity.⁷ However, due to its extremely hard accuracy and poorly reproducible, it is usually underestimated.⁸ As complications of CS may cause life-threatening bleeding, appropriate procedures should be taken to reduce intraoperative and postoperative blood loss.⁹ The type of uterine incision and the method of placental removing are important factors in determining the outcomes during CS, such as the amount of blood loss. Compared with lower vertical incision or classic incision, lower transverse uterine incision has less operative blood loss. Patients with lower vertical and classic incision could increase operative blood loss.^{10–12}

The method of placental removing is one such procedure that can affect outcomes of cesarean delivery, such as the amount of bleeding during intraoperative and postoperative, the time of operation, the occurrence of postoperative endometritis^{13,14} and may contribute to an increase or decrease in the incidence of CS.³ But the ideal method of placental removal during CS is still a controversial issue.¹⁵ The choice mainly bases on the surgeon's preference. At present, the research of placenta resection technology mainly focus on "manual" or "spontaneous" removal.^{14,16} Manual placental removal remains a conflicting issue owing to the risk of postpartum hemorrhage, postpartum endometritis, and placental abnormalities in subsequent pregnancies.^{13,15,17}

Previously, several longitudinal studies and randomized clinical trials have suggested that manual removal of the placenta increased risks of postpartum blood loss, postpartum endometritis, and placental abnormalities. A longitudinal linked national cohort study by Ruiter et al concluded that the incidence of hemorrhage was higher in women with manual placental removal compared to women have no history of manual placental removal.¹⁸ A randomized clinical trial by Baksu et al suggested that manual placental removal during CS could lead to more blood loss and a higher risk of postpartum endometritis,

compared with method of spontaneous.¹⁹ Dabashi et al reported that manual placental delivery increased the risk of blood loss and endometritis compared with the spontaneous way of placental removal.²⁰ Similarly, Hider et al observed that compared with the way of spontaneous, manual removal of the placenta during CS significantly increased perioperative hemorrhage and maternal infection rates.¹³ However, some other studies showed that it had no significant effect on blood loss. A randomized clinical trial by Gun et al concluded that there was no correlation between the way of removal of the placenta and hemorrhage in CS deliveries.³ Chandra et al also showed that both postoperative endometritis and bleeding were independent of the method of placental delivery.²¹ Gol et al found that compared with natural separation, manual placental removal without a significant relationship with increased bleeding; Also, in terms of the incidence of postoperative complications or postoperative hemoglobin levels, manual placental removal without influence.²² A prospective multicenter trial reported that manual removal of the placenta and intrauterine cleaning have no adverse effects on maternal blood loss and infectious morbidity after elective cesarean section.²³

All the studies above demonstrated that results from the randomized clinical trials or other type studies did not indicate a consistent conclusion. Whether manual removal of the placenta increases blood loss or other complications related to blood loss during CS remained a controversial issue. In the present study, we carried out a comprehensive search and meta-analysis to investigate the effect of manual removal of the placenta on blood loss and other complications compared with the spontaneous placenta removal during CS.

Materials and Methods

We developed this meta-analysis according to the Preferred Reporting Item for Systematic Review and Meta-Analysis Protocols statement.²⁴

Literature Search Strategy

A comprehensive and systemic retrieval was conducted in various databases, containing PubMed, EMBASE, and Web of Science We searched all published RCTs of manual and spontaneous placenta removal in CS. The latest search was updated on July 1, 2020. We used a combination of keywords for retrieval ("Manual

removal of placenta OR manual placental removal OR manual placental separation” and “spontaneous placental delivery OR spontaneous placental separation” OR “removal of the placenta OR placental separation OR placental removal” and “cesarean section OR cesarean delivery” and “hemorrhage OR bleeding OR blood loss” AND “Randomized Controlled Trial OR RCT”). To further find potentially relevant studies, we manually scanned the references of all selected articles, and read recent reviews. Two authors carefully reviewed each identified report.

Inclusion Criteria and Study Selection

Studies were included if they satisfied the following inclusion criteria: 1) the mode of delivery was cesarean section; 2) randomized clinical trials; 3) reporting at least one measurement and other complications related to blood loss; 4) two groups were treated with the manual placenta and spontaneous separation, respectively.

Studies were excluded if they met the following exclusion criteria: 1) the study involved only one form of placental separation; 2) the methods of placenta separation were a mixture of manual placenta and spontaneous separation and other factors; 3) studies have no full-text and conference abstracts; 4) case reports, cohort studies, and animal trails; 5) not written in English. Two authors separately selected titles and abstracts and subsequently full-text articles. Discuss the disagreement with the third author and adjust the inconsistent after reaching a consensus.

Data Extraction and Study Quality Assessment

Two authors carefully and independently read the full text of retrieved included articles. The extracted information of eligibility studies contained publication year, first author's name, sample size, blood loss in the spontaneous dissection group and manual group, the operating time, the length of postoperative hospital stay, postoperative complications (endometritis and), and conclusion. In order to assess the quality of the articles included in this analysis, we applied the modified Jadad scale ranging from 0 (minimum) to 8 (maximum) points. It contained eight quality criteria. The higher the score of the study, the better its quality.

Statistical Analysis

The data analysis was performed using stata 14.0 software. The pooled measure of the effect across the included studies was estimated by the term of standardized mean difference (SMD) and 95% confidence intervals (CI). When there were categorical variables, odds ratios (OR) were calculated for each study. The level of heterogeneity was explored using the I^2 statistic and Q-statistic. The I^2 index expresses the proportion of true heterogeneity in the observed variance. An I^2 value of 0% indicates that no heterogeneity is observed, and a larger value indicates an increase in heterogeneity. Therefore, percentages of about 25% ($I^2 = 25$), 50% ($I^2 = 50\%$), and 75% ($I^2 = 75\%$) would explain low, medium, and high heterogeneity, respectively. The Q-statistic is a measure of the real variance among studies. A significant Q-statistic demonstrates heterogeneity within studies. If there was no heterogeneity ($P \geq 0.05$, $I^2 < 50\%$), a fixed-effect meta-analysis was used, otherwise ($P < 0.05$) a random-effects meta-analysis was used. SMD, 95% CI, and the pooled effect sizes were expressed by forest plots. The Z-test examined the significance of the pooled effect. A P value below 0.05 was considered statistically significant.

Results

Figure 1 displays the flow chart of the study systematic retrieve. The initial literature search discovered 1296 articles, including 894 duplicates which were deleted at first. Based on titles and abstracts 389 articles clearly did not meet our inclusion criteria and were eliminated then. For the remaining thirteen studies, the full texts were screened, and four studies did not satisfy our inclusion criteria. Finally, nine randomized controlled trials were included in this meta-analysis.

The baseline characteristics of the included articles are shown in Table 1. A total of nine RCTs containing 1248 cases of the manual group and 1252 cases of the spontaneous group were included in this meta-analysis. Five studies reported that all patients undergo transverse lower segment CS, one studies undergo low uterine vertical incisions, three studies did not mention the type of incision. Quality assessment results based on eight quality criteria as shown in Table 2. The Jadad scores of the five studies were above 5, with high quality.

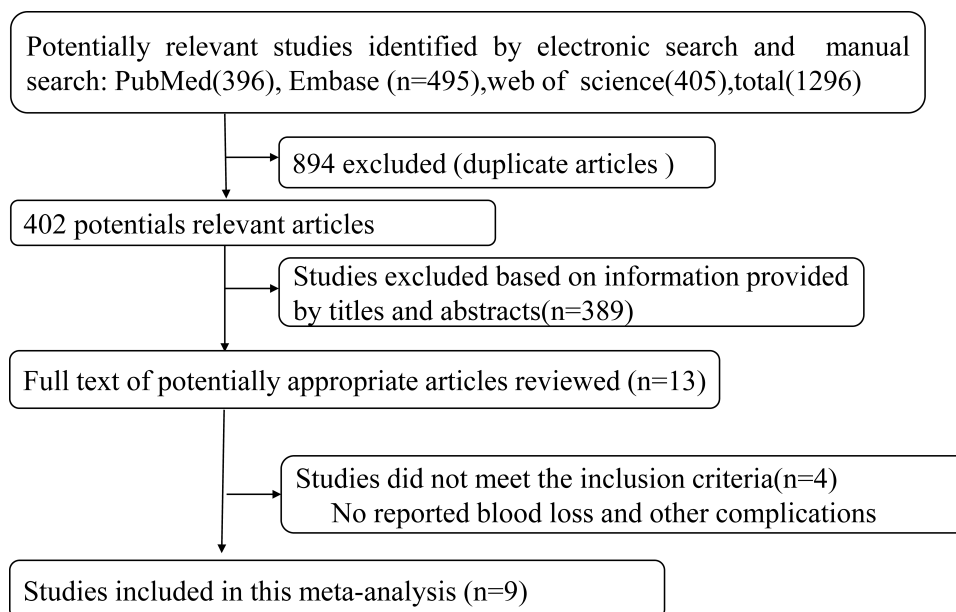


Figure 1 Flowchart of search and study selection.

Hemorrhage

Six studies reported the difference in blood loss between the manual group and spontaneous group. The heterogeneity test showed significant heterogeneity across these studies ($I^2=93.9\%$, $P < 0.001$; [Figure 2](#)), therefore the random-effects model was used. The pooled results indicated that statistical difference was found between the manual group and spontaneous group in terms of hemorrhage ($SMD = 0.53$, 95% CI [0.12, 0.94]; $Z = 2.54$, $P = 0.011$; [Figure 2](#)). The amount of bleeding with manual placental removal was more than with spontaneous placental delivery.

The Operating Time

A comparison of the operating time between the manual group and spontaneous group was obtainable in six studies. This random-effects meta-analysis showed that there was no statistical difference in the operating time between the two methods of placental removal ($SMD = -0.30$, 95% CI [-0.85, 0.24]; $Z = 1.09$, $P = 0.276$), with high evidence of the heterogeneity ($I^2=96.0\%$, $P < 0.001$; [Figure 3](#)).

The Length of Postoperative Hospital Stays

Five articles reported the comparison of the length of postoperative hospital stays between the manual group and spontaneous group. The pooled results revealed that

there was no significant difference in the length of post-operative hospital stay between the manual group and spontaneous group ($SMD = 0.11$, 95% CI [-0.08, 0.30]; $Z = 1.11$, $P = 0.265$), with medium evidence of the heterogeneity ($I^2=74.4\%$, $P < 0.001$; [Figure 4](#)).

Postoperative Complications

Seven articles reported the occurrence of endometritis and blood transfusion requirements after the cesarean section. Pooled effects by a fixed-effects model demonstrated there was a difference in the incidence of endometritis between cesarean section placental manual removal group and spontaneous removal group ($OR = 1.84$, 95% CI [1.31, 2.58]; $Z = 3.52$, $P < 0.0001$); in terms of blood transfusion requirement, there was no difference in the blood transfusion requirement between cesarean section placental manual removal group and spontaneous removal group ($OR=1.36$, 95% CI [0.91, 2.04]; $Z = 1.52$, $P = 0.129$), without significant heterogeneity ($I^2=0.0\%$, $P = 0.531$; [Figure 5](#)). The incidence of endometritis was higher in the manual removal group than in the spontaneous removal group.

Discussion

In the current published studies, the mode of placental removal is still a conflicting issue because of the risk of

Table 1 The Baseline Characteristics of the Included Studies in this Meta-Analysis

Author (Year)	Group	Sample Size	Blood Loss	Operating Time	Length of Hospital Stays	Postoperative Complications		Conclusion	CS Incisions
						Endometritis	Blood Transfusion		
Hamza et al (2021)	Manual	106	NO	29.9±6	2.1±0.8	19	NO	No difference	Not mentioned
	Spontaneous	112	NO	29.9±5.8	2.1±0.8	13	NO		
Kamel et al (2018)	Manual	274	875.2±524.2	62.2±10.3	2±0.8	NO	48	Spontaneous delivery of placenta has advantage	Transverse lower segment
	Spontaneous	274	731.8±426.7	63±10.1	2±0.8	NO	31		
Gün et al (2013)	Manual	50	NO	25.5±2.7	NO	NO	NO	No difference	Transverse lower segment
	Spontaneous	50	NO	26.3±2	NO	NO	NO		
Ajay et al (2009)	Manual	50	100.9±22.52	NO	NO	NO	NO	Spontaneous delivery of placenta has advantage	Not mentioned
	Spontaneous	50	55.11±21.07	NO	NO	NO	NO		
Ramadani et al (2004)	Manual	200	713±240	40.2±3.2	4.2±1.2	9	5	Each has its advantages	Low transverse
	Spontaneous	200	669±253	45.5±3.9	4.3±1.1	9	6		
Gol et al (2004)	Manual	100	589±272	13.7±3.8	4.6±1.3	5	6	No difference	Low uterine vertical incisions
	Spontaneous	100	626±253	14.5±4.9	4.1±1.2	4	6		
Morales et al (2004)	Manual	237	546±279	NO	NO	NO	3	Spontaneous delivery of placenta has advantage	Not mentioned
	Spontaneous	235	550±378	NO	NO	NO	4		
Dehbashi et al (2004)	Manual	200	NO	NO	NO	68	NO	Spontaneous delivery of placenta has advantage	Low-segment transverse
	Spontaneous	200	NO	NO	NO	40	NO		
McCurdy et al (1992)	Manual	31	967±248	35.1±8.4	4.8±2.1	7	NO	Spontaneous delivery of placenta has advantage	Lower uterine segment
	Spontaneous	31	666±271	32.7±6.3	3.9±1.1	1	NO		

Note: no. indicators were not mentioned in the study.

Table 2 Modified Jadad Scores of the Included Studies

Corresponding Author	Was the Research Described as Randomized?#	Was the Approach of Randomization Appropriate?*	Was the Research Described as Blinding?#	Was the Approach of Blinding Appropriate?*	Was There a Presentation of Withdrawals and Dropouts?#	Was There a Presentation of the Inclusion/ Exclusion Criteria?#	Was the Approach Used to Assess Adverse Effects Described?#	Was the Approach of Statistical Analysis Described?#	Total
Hamza et al, 2021 ²³	0	0	0	0	1	1	1	1	4
Kamel et al, 2018 ³¹	1	1	0	0	1	1	0	1	5
Gün et al, 2013 ³	1	0	0	0	0	1	0	1	3
Ajay et al, 2009 ³⁰	1	0	0	0	0	1	0	1	3
Ramadani et al, 2005 ¹⁷	1	1	1	1	0	1	0	1	6
Gol et al, 2004 ²²	1	1	1	1	0	0	0	1	5
Morales et al, 2004 ²⁹	1	1	1	1	0	1	0	1	6
Dehbashi et al, 2004 ²⁰	1	0	0	0	0	0	1	1	3
McCurdy et al, 1992 ¹⁰	1	1	1	1	0	1	1	1	7

Notes: #The maximum score is 1; *The maximum score is 2.

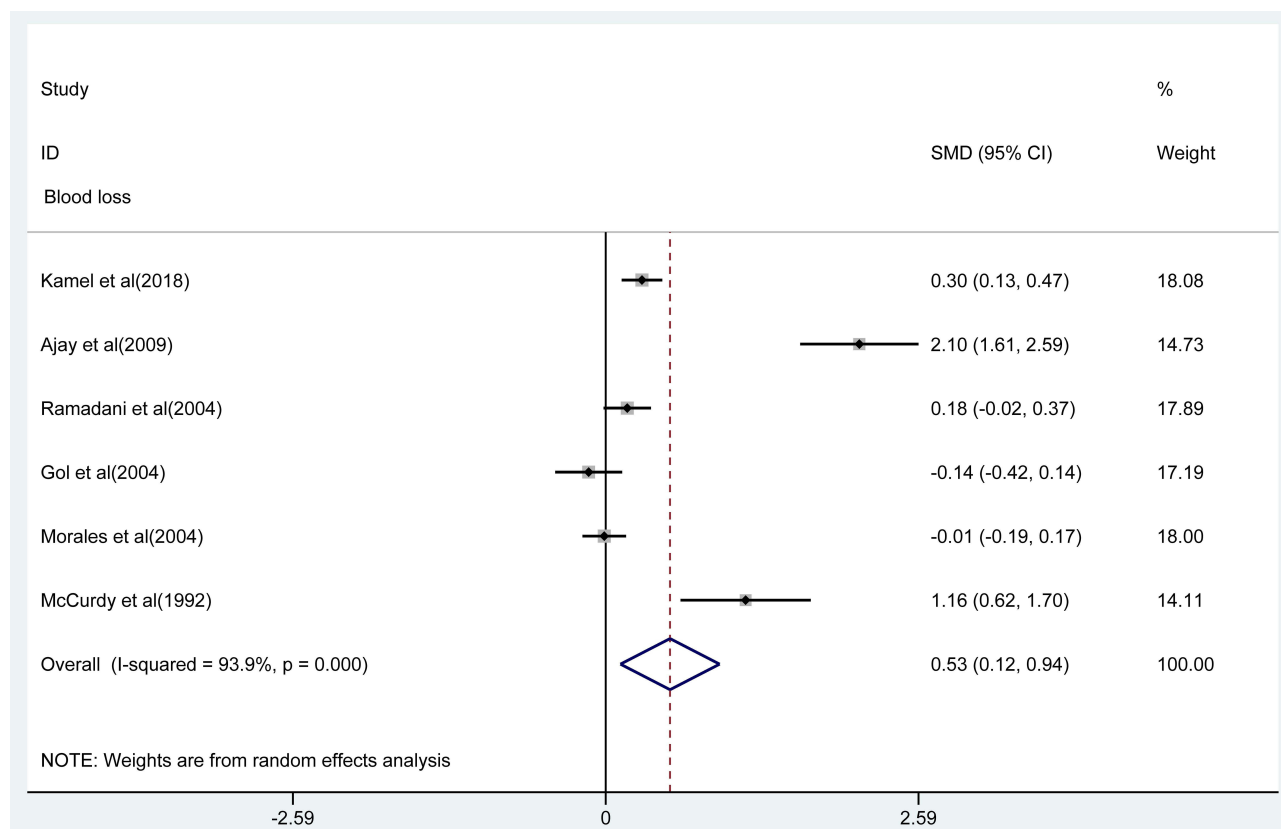


Figure 2 Forest plot of hemorrhage when using manual and spontaneous.

hemorrhage, and other complications related to hemorrhage. This meta-analysis explored whether the manual placental removal during CS affects hemorrhage and other complications compared with spontaneous placental removal. Nine RCTs published were included in this analysis. The results of this study demonstrated that the risks of hemorrhage and endometritis in CS were increased by the manual method of placental removal compared with the spontaneous placental delivery. In contrast, this way failed to reduce operative time, the length of hospital stays, and the blood transfusion requirement. Manual method of placental removal may put women at undue risk with no added benefit.

We found significant hemorrhage in the manual method of placental removal group. This was consistent with other authors' findings.^{10,12} The current results were comparable with a published review of Anorlu et al, who reported that Manual placenta removal was associated with more hemorrhage (weighted mean difference

[WMD] 94.42, 95% CI [17.19, 171.64]).²⁵ From a mechanistic view, after the fetal is removed, the uterine muscles begin to contraction and retraction immediately, thereby lessening the size of the uterus; As the uterus becomes smaller, the size of the placental bed is significantly smaller than that of the incompressible placenta; This causes shear movement, which results in separation of the placenta and compression of the new exfoliated vessels supplying the placental bed, thereby reducing blood loss; This mechanism may explain why spontaneous placental separation causes less blood loss than manual placental dissection.²⁵ Manual placental dissection could cause the problem of fetal membrane residue and affect the contractile function of uterus, which is an important factor in the increase of bleeding. Abnormal placental attachment, placental adhesion or retention are the most common placental factors of bleeding during manual separation of the placenta. In contrast, some authors found no difference between either method.^{11,21,22} Gol

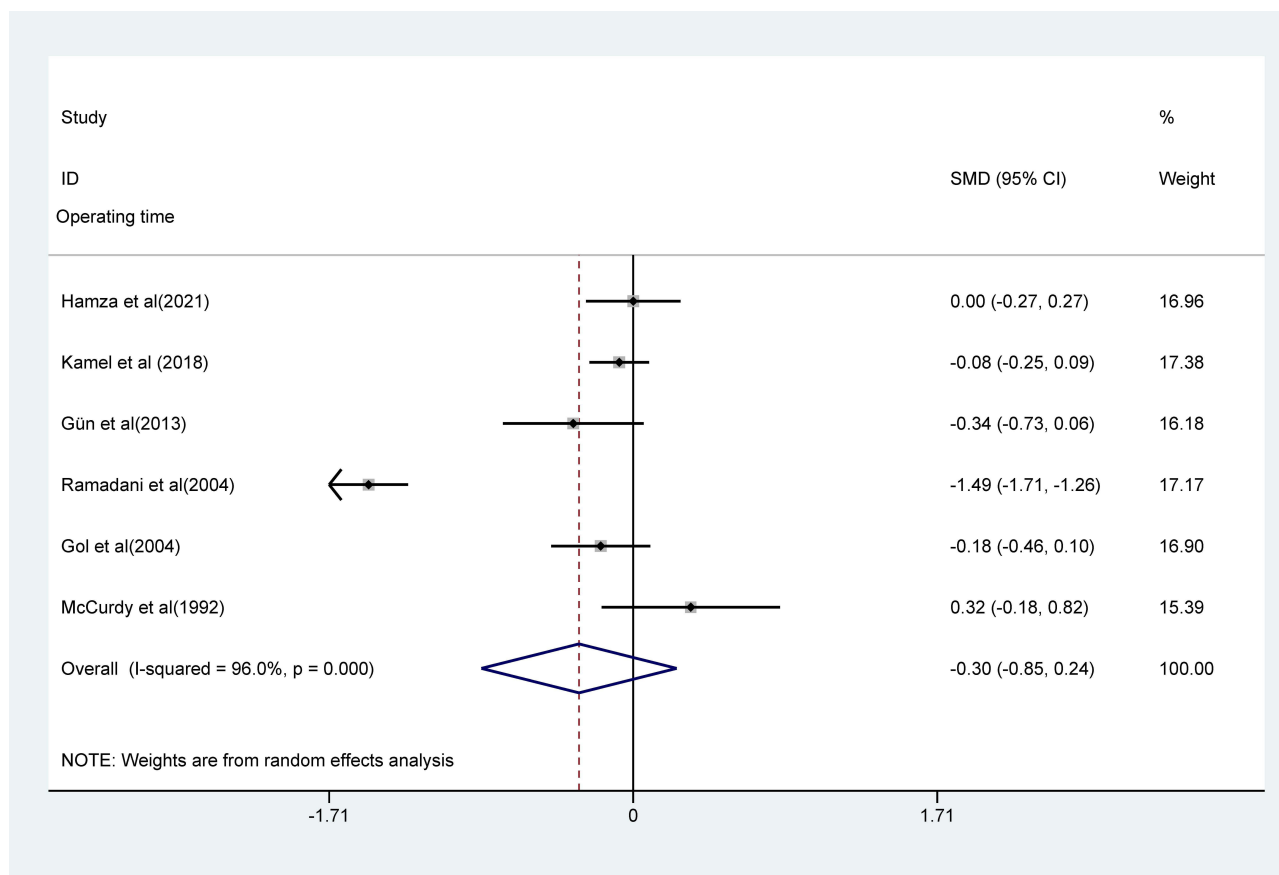


Figure 3 Forest plot of operating time when using manual and spontaneous.

et al²² reported that manual removal of the placenta was not connected with any significant risk of bleeding, this may be due to the clamping of the incision and the use of oxytocin, which is the most crucial factors in preventing excessive hemorrhage during CS. An additional important factor that affects the amount of bleeding during CS was the type of uterine incision.²² Patients with vertical lower segment incision or classical upper segment incision are known for more blood loss than the transverse lower segment incision.^{17,19,22}

In regard to endometritis, endometritis is the most common complication of cesarean section, with an incidence of between 5% and 85%, depending on the patient population investigated.²⁶ In our study, pooled results showed that the risks of endometritis in CS was increased by the manual method of placental removal compared with the spontaneous placental delivery. Meanwhile, some studies have claimed that higher risks of endometritis.^{10,27} In the study of Anorlu et al, following manual placental removal, an increase in the

risk of endometritis has been shown.²⁵ It was speculated that manual placental removal will damage the local host's defense ability, and may bring bacteria into the endometrial cavity, leading to endometritis. However, in the study of Gol et al, the incidence of endometritis was no significant difference.²² The study of Chandra et al studies found no difference in postoperative endometritis.²¹ Even in the spontaneous placental group, entering of foreign microbes (for example, through curettage or gauze used by a surgeon to remove clots and placental debris in the uterine cavity) can lead to endometritis. In theory, any foreign body entering the uterine cavity will cause a large number of microorganisms to enter the uterine cavity, even if the foreign body is a sterilized surgical glove.²⁰ Therefore, if the patient's condition is stable, we think that it is better to allow the placenta to deliver naturally, which is consistent with Atkinson's finding that the risk of endometritis after artificial placenta extraction in cesarean section is significantly higher than that after assisted spontaneous placenta delivery.²⁸

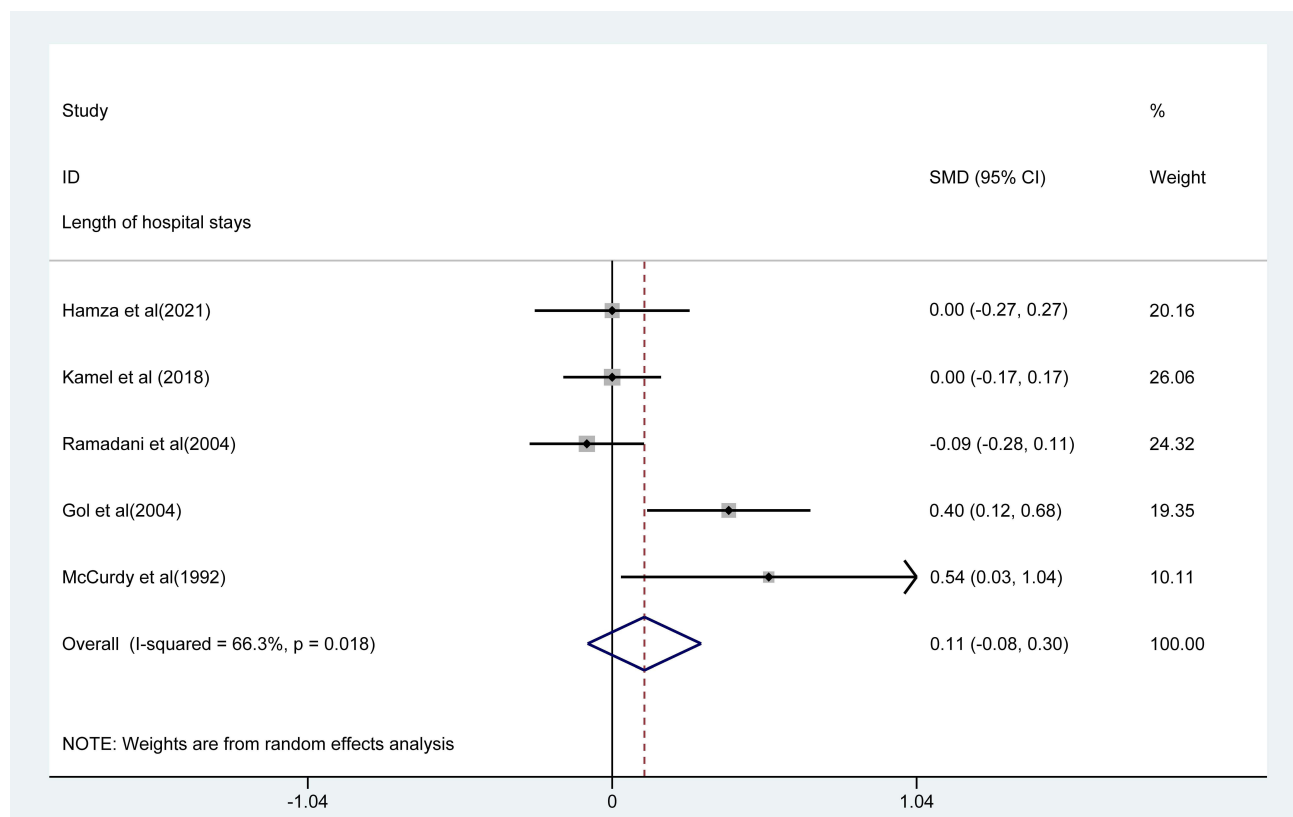


Figure 4 Forest plot of hospital stays when using manual and spontaneous.

In terms of the operating time, hospital stays, and the blood transfusion, without significant difference between two groups. McCurdy et al reported that the duration of the operating time, duration of operative stage III were not decreased by the methods of placental delivery.¹⁰ Ajay et al showed that the duration of surgery was not changed by the methods of placental separation.³⁰ The study found no significant difference in blood transfusions between the two methods (there are very few of such studies).

There were some limitations in this meta-analysis. First, the limited number of studies satisfied our searching criteria, not all related randomized trials were included mainly because of publication bias or selection bias, and this might affect the robust of the results. Also, the considerable heterogeneity existed in the included studies, because of the differences in the type of incision, publication year and study quality. Subgroup analysis of different incision types cannot be carried out due to the limitation of the number of included studies. In our future study, the effect of incision type on bleeding should be considered. Second, even if we have used the random

effect model, the combination of results may not be suitable for all outcome measurements. Finally, we did not assess the publication bias by funnel plot of the included studies, because each of the analysis indicators corresponds to a smaller than six included studies.

Conclusion

In summary, this meta-analysis demonstrated that manual placental removal has testified to increase blood loss during CS, with an increased incidence of endometritis. Manual placental removal failed to diminish the operative time, the length of hospital stays, and the blood transfusion requirement. As a result, such obstetric surgery puts women at inappropriate risk without additional benefit. The placenta can be spontaneous placental delivery after the maternal delivery of the fetus during cesarean section. If the amount of bleeding increases and there is no indication of spontaneous delivery of the placenta, manual placental removal can be considered. To effectively compare the two methods, further studies are recommended with a more standardized estimation of

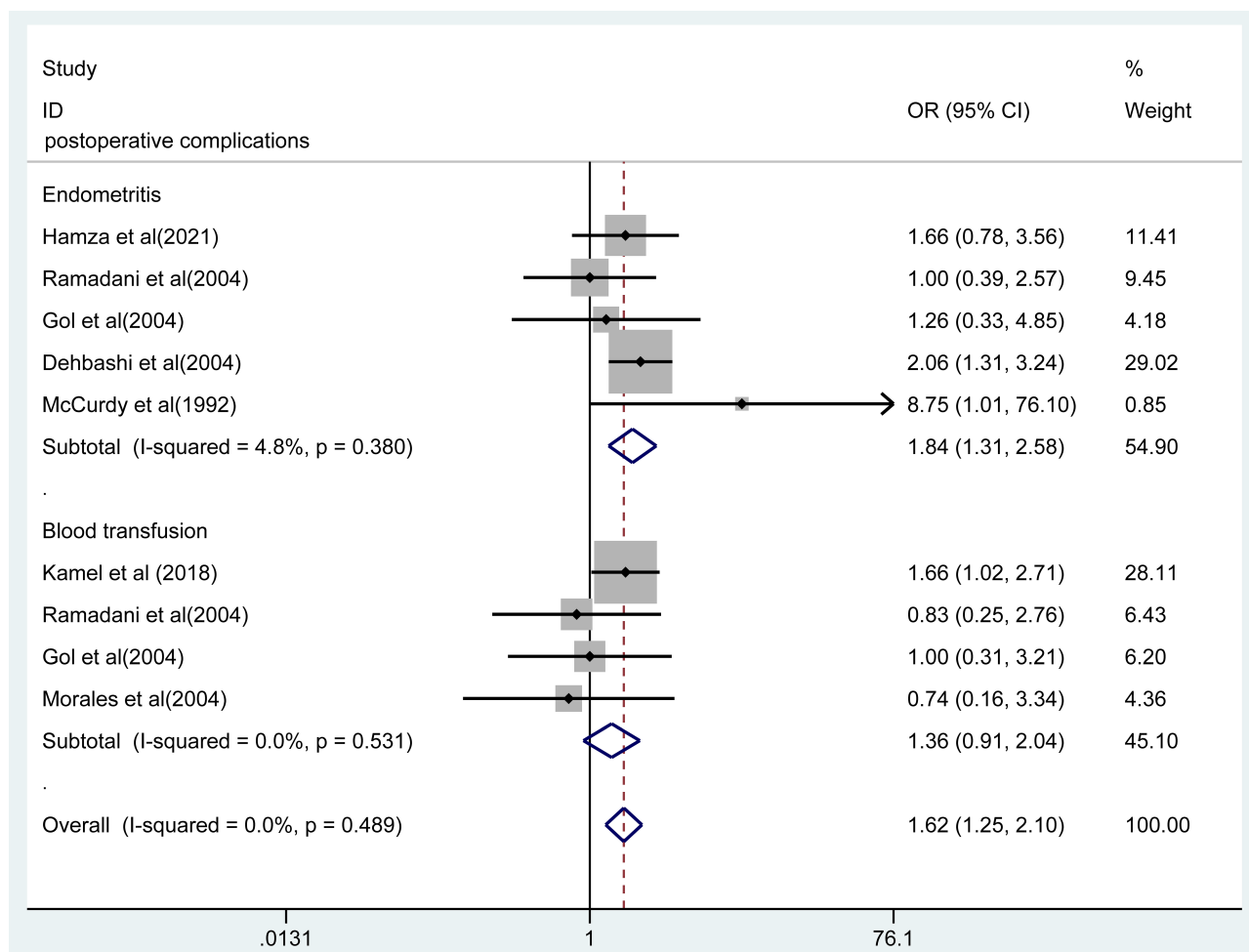


Figure 5 Forest plot of endometritis and blood transfusion when using manual and spontaneous.

blood loss. And large-scale randomized clinical trials are needed to further confirm our findings.

Compliance with Ethical Standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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Meng-Chang Yang and Peng Li are co-first authors for this study.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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