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Intravenous fluid rate for reduction of cesarean delivery rate in nulliparous women: a systematic review and meta-analysis

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Key words

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. The National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, and Society for Maternal-Fetal Medicine have emphasized the need to promote vaginal delivery and have offered recommendations to safely prevent primary cesarean delivery. However, there has been limited discussion regarding management of intravenous fluids and other aspects of labor management that may influence mode of delivery. Therefore the aim of our study was to determine whether an intravenous fluid rate of 250 vs. 125 mL/h is associated with a difference in cesarean delivery rate. **Material and methods.** Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, Embase, Web of Science, and the Cochrane Library for randomized controlled trials. We included all randomized controlled trials comparing intravenous fluid rates of 250 vs. 125 mL/h in nulliparous women in spontaneous labor at term with singleton pregnancies at ≥ 36 weeks. Studies were included regardless of the type of intravenous fluids used and regardless of whether oral intake was restricted during labor. Studies including multiparous women or women whose labor was induced were excluded. The primary outcome was the incidence of cesarean delivery. We planned to assess a subgroup analysis according to type of fluids used and according to restriction of oral fluid intake. **Results.** Seven trials including 1215 nulliparous women in spontaneous labor at term were analyzed; 593 (48.8%) in the 250 mL/h group, and 622 (51.2%) in the 125 mL/h group. Five studies used lactated Ringer's solution, one used normal saline in dextrose water, and in one study it was unclear which intravenous fluid was used. Women who received intravenous fluids at 250 mL/h had a significantly lower incidence of cesarean delivery for any indication (12.5 vs. 18.1%; RR 0.70, 95% CI 0.53–0.92; seven studies, 1215 participants; $I^2 = 0\%$) and for dystocia (4.9 vs. 7.7%; RR 0.60, 95% CI 0.38–0.97; five studies, 1093 participants; $I^2 = 18\%$), a significantly shorter mean duration of labor of about one hour (mean difference -64.38 min, 95% CI -121.88 to -6.88 ; six studies, 1155 participants; $I^2 = 83\%$) and a significantly shorter mean length of second stage of labor (mean difference -2.80 min, 95% CI -4.49 to -1.10 ; 899 participants; $I^2 = 22\%$) compared with those who received intravenous fluid at 125 mL/h. No differences were found in the other secondary outcomes. There were no maternal or perinatal deaths and only one

woman, in the 125 mL/h group, developed pulmonary edema. The findings persisted regardless of the type of intravenous fluid used. No significant reduction in the incidence of cesarean delivery was demonstrated in women with unrestricted oral intake; however, this was limited to only two studies evaluating 254 women. *Conclusions.* Our findings provide evidence that the duration of labor in low-risk nulliparous women may be shortened by a policy of intravenous fluids at a rate of 250 mL/h rather than 125 mL/h. A rate of 250 mL/h seems to be associated with a reduction in the incidence of cesarean delivery compared to 125 mL/h. The number needed to treat to prevent one cesarean delivery is 18 women. Our data support increased hydration among nulliparous women in labor when oral intake is restricted. Further study is needed regarding risks and benefits of increased hydration among women with unrestricted oral intake, those undergoing induction of labor, and those with medical comorbidities.

Abbreviations: CI, confidence interval; IV, intravenous; RCT, randomized clinical trial; RR, relative risk.

Introduction

In the USA, approximately one of every three deliveries over the past decade has been via cesarean delivery (1). Safe prevention of primary cesarean delivery has been a focus of major medical organizations, and the USA Public Health Service Commissioned Corps and the Healthy People 2020 campaign have established a goal to decrease the rate of cesarean deliveries from 26.5% (baseline in 2007) to 23.9% in low-risk women without a prior cesarean section (2). The National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, and Society for Maternal-Fetal Medicine have emphasized the need to promote vaginal delivery and have offered recommendations to safely prevent primary cesarean delivery (2). The recommendations emphasize permitting appropriate time for labor to progress and training in operative vaginal delivery, and include guidance for management of fetal heart tracings and fetal occiput posterior, among other common scenarios (2). However, there has been no discussion regarding management of intravenous fluids and other aspects of labor management that may influence mode of delivery.

The American College of Sports Medicine has reported that dehydration of greater than 2% of body mass may compromise physiologic function, impairing exercise function (3). One can hypothesize that dehydration will also compromise the function of the contracting uterus. In the USA, general practice is to administer 125 mL/h of intravenous fluid to all laboring women, which is similar to what is often given to someone convalescing from surgery (4). However, the insensible fluid loss during labor is much greater, as are the body's requirements for

hydration (5). Oral intake is often restricted in laboring women due to concerns of aspiration in the event that general anesthesia is required (6).

Multiple randomized controlled trials (RCTs) have compared intravenous fluid rates of 125–250 mL/h in laboring nulliparous women (7–14). Many of these studies have demonstrated clinically significant reductions in the rate of cesarean delivery but others have not.

Thus, we sought to perform a systematic review and meta-analysis to determine whether increased hydration during labor is safe and associated with a reduction in the risk of cesarean delivery.

Material and methods

Sources

This review was performed according to a protocol designed a priori by the investigators (R.E., G.S.) and recommended for systematic review and meta-analysis (15). Searches were performed independently by authors (R.E., G.S.) in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, Embase, Web of Science, and the Cochrane Library with the use of a combination of keywords: “intravenous fluids,” “hydration,” “oral intake” “labor,”

Key Message

Incidence of cesarean delivery may be reduced by a policy of giving intravenous fluids in labor at a rate of 250 mL/h rather than 125 mL/h.

“intrapartum,” “duration of labor,” “labor dystocia,” “intrapartum management” “duration of labor,” “arrest of labor,” “caesarean” and “cesarean” from inception of each database to February 2017. No restrictions as to language or geographic location were applied. References from relevant research articles and reviews were also reviewed.

Study selection

All RCTs comparing intrapartum intravenous (IV) fluid rates of 250 vs. 125 mL/h in low-risk nulliparous women in spontaneous labor at ≥36 weeks with singleton pregnancies were included. The decision was made to include any study comparing intravenous fluid rates that were within 10% of these rates, since this is not likely a clinically significant difference. Studies of women with spontaneous onset of labor, including premature rupture of membranes, were included, and augmentation of labor with oxytocin was not considered a criterium for exclusion. Non-randomized or quasi-randomized trials (i.e. trials in which allocation was done on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation studies) were excluded. Studies which included high-risk pregnancy (for example women with preeclampsia, intrauterine growth restriction, maternal cardiac or renal disease) were also excluded.

Titles and abstracts for all identified studies were independently reviewed by two reviewers (R.E., G.S.). Any disagreements were resolved with discussion with a third reviewer (N.S.). However, RCTs that included women undergoing either elective or medical induction of labor were excluded, as were those that included multiparous women or multiple gestations, as we deemed that this would introduce substantial clinical heterogeneity in the women. Studies were included regardless of whether oral intake was restricted and irrespective of the type of intravenous fluids used. We planned to assess the primary outcome (i.e. incidence of cesarean delivery for any indication) with a subgroup analysis according to type of fluid used and according to restriction of oral fluid intake. Only the primary outcome was assessed in the sensitivity analysis (15).

Outcomes

The primary outcome was the incidence of cesarean delivery for any indication. Secondary outcomes were cesarean for labor dystocia, cesarean for fetal well-being, cesarean for other indications, spontaneous vaginal delivery, operative vaginal delivery (either vacuum or forceps), augmentation of labor, mean of duration of labor, mean of second stage of labor, pulmonary edema, chorioamnionitis, postpartum hemorrhage and neonatal outcomes

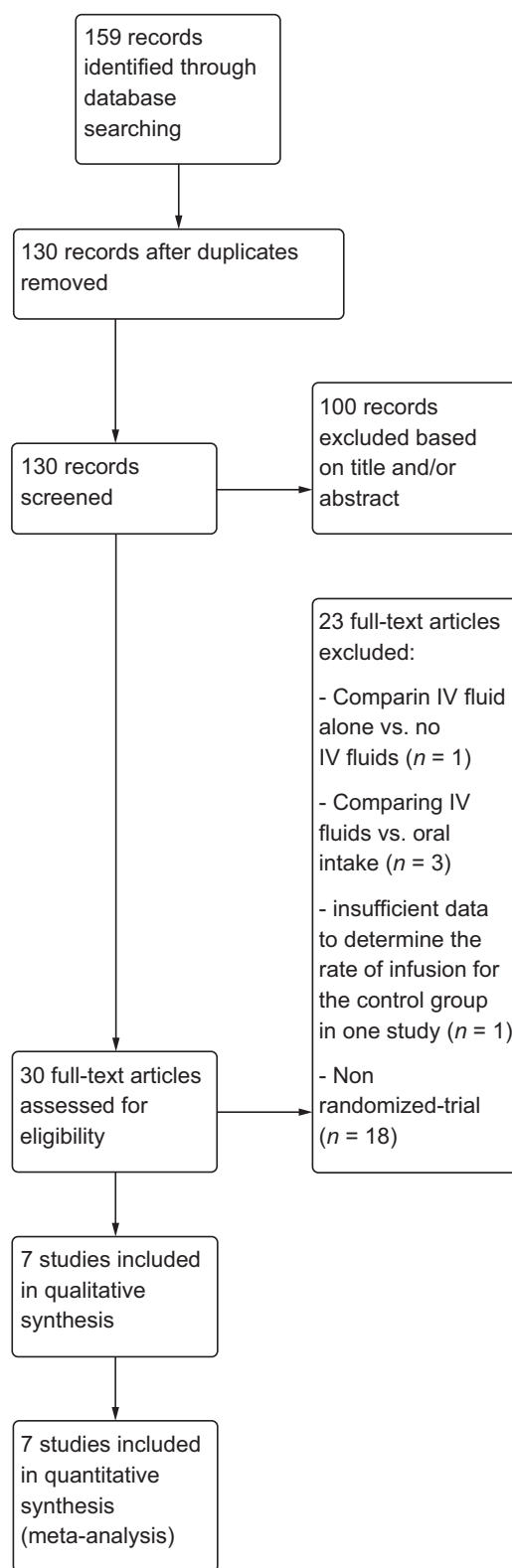


Figure 1. Flow diagram of studies identified in the systematic review [PRISMA template (Preferred Reporting Item for Systematic Reviews and Meta-analyses)]. IV, intravenous.

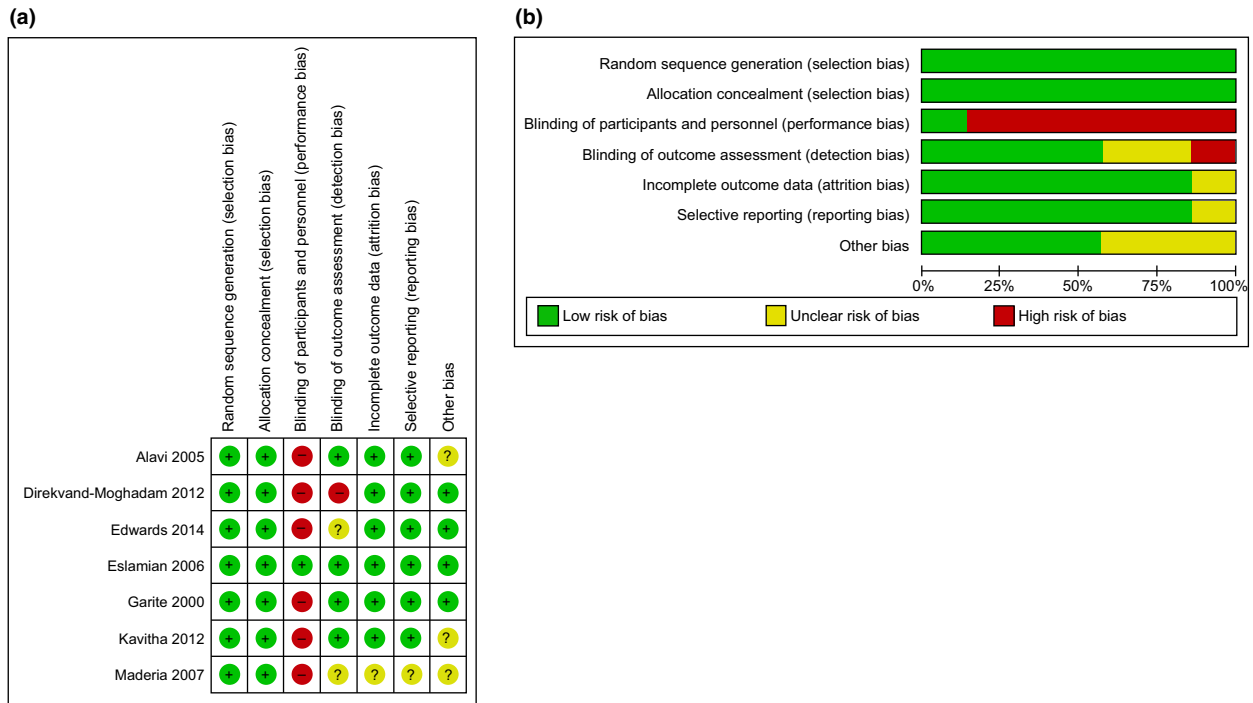


Figure 2. Assessment of risk of bias. (a) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (b) Risk of bias graph about each risk of bias item presented as percentages across all included studies. [Color figure can be viewed at wileyonlinelibrary.com]

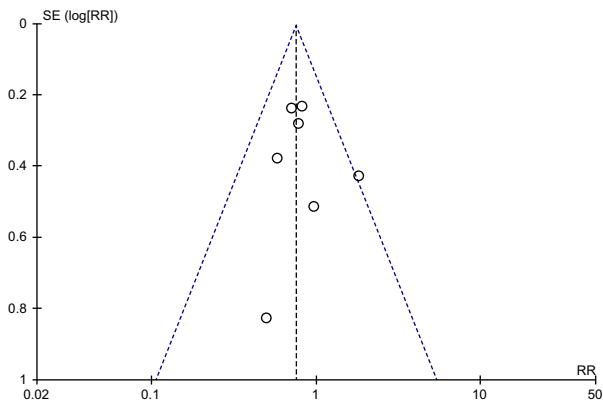


Figure 3. Funnel plot for assessing publication bias. RR, relative risk. [Color figure can be viewed at wileyonlinelibrary.com]

including admission to neonatal intensive care unit and 5-minute APGAR <7.

Quality of the studies

The risk of bias in each included RCT was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with

biased estimates of treatment effect: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors’ judgments were categorized as “low risk,” “high risk” or “unclear risk” of bias (15).

Statistical analyses

The data analysis was completed independently by two authors (N.S., G.S.) using REVIEW MANAGER 5.3 (Copenhagen: The Nordic Cochrane Center, Cochrane Collaboration, 2014). Heterogeneity across studies was assessed using the Higgins I^2 -test. In case of statistically significant heterogeneity ($I^2 \geq 50\%$) the random effects model of DerSimonian and Laird was used, otherwise ($I^2 < 50\%$) a fixed effect model was managed. The pooled results were reported as relative risk (RR) or as mean difference with 95% confidence interval (CI). Potential publication biases were assessed graphically using funnel plot and statistically using Begg’s and Egger’s tests (15). A p -value <0.1 was considered statistically significant.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement (16).

Table 1. Characteristics of the included trials.

Reference	Study location	Number of participants 250 mL/h	Number of participants 125 mL/h	Intravenous fluid type	Oral intake	Primary outcome
Garite et al. (12)	USA	101	94	Lactated Ringer's solution	Restricted: Sips, ice chips	Duration of labor
Alavi et al. (10)	Iran	82	112	Normal saline in dextrose water	Restricted: NPO	Cesarean
Eslamian et al. (11)	Iran	147	153	Lactated Ringer's solution	Restricted: NPO	Cesarean
Maderia et al. (13)	USA	32	30	Unknown	Restricted: Ice chips or NPO	Cesarean
Direkvand-Moghadam et al. (7)	Iran	30	30	Lactated Ringer's solution	Unrestricted	Duration of labor
Kavitha et al. (9)	India	96	98	Lactated Ringer's solution	Unrestricted	Cesarean
Edwards et al. (8)	USA	105	105	Lactated Ringer's solution	Restricted: Ice chips, popsicles, and hard candy	Cesarean

NPO, taking nothing by mouth.

The was reported following the PRISMA guidelines for protocols (PRISMA-P) (16). The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (Registration Number: CRD42016048068).

Results

The flow of study identification is shown in Figure 1. Seven trials including 1215 nulliparous women in spontaneous labor at term were analyzed (7–13).

The overall risk of bias was low (Figure 2). All of the included studies had a low risk of bias in random sequence generation. Adequate methods for allocation of women were used in all seven trials. In all included studies, all women were accounted for in the analysis. Blinding was considered not feasible methodologically given the intervention; however, in Eslamian et al. (11) it was stated that infusion rates were masked. Figure 3 shows the funnel plot for assessing publication bias; the symmetric plot suggests no publication bias. Publication bias, assessed using Begg's and Egger's tests, showed no significant bias ($p = 0.59$ and $p = 0.44$, respectively).

Statistically, heterogeneity within the studies was low, with no inconsistency in risk estimates ($I^2 = 0\%$) for the primary and most of the secondary outcomes.

Table 1 shows the characteristics of the included trials. All RCTs included only low-risk singleton gestations with vertex presentation. Of the 1215 women included, 593 (48.8%) were in the 250 mL/h group (i.e. intervention group), and 622 (51.2%) in the 125 mL/h group (i.e. control group). Five studies used lactated Ringer's solution, one used normal saline in dextrose water (10), and in one study it was unclear which IV fluid was used (13).

All studies reported the incidence of cesarean delivery, and this was the primary outcome for five of the seven studies (8–11,13).

Table 2 shows pooled results for the primary and the secondary outcomes. Women who received IV fluids at 250 mL/h had a significantly lower incidence of cesarean delivery for any indication (12.5 vs. 18.1%; RR 0.70, 95% CI 0.53–0.92; Figure 4; seven studies, 1215 participants; $I^2 = 0\%$) and for dystocia (4.9 vs. 7.7%; RR 0.60, 95% CI 0.38–0.97; five studies, 1093 participants; $I^2 = 18\%$) and a significantly shorter mean duration of labor of about one hour (mean difference -64.38 min, 95% CI -121.88 to -6.88 ; six studies, 1155 participants; $I^2 = 83\%$) and length of second stage of labor (mean difference -2.80 min, 95% CI -4.49 to -1.10 ; 899 participants; $I^2 = 22\%$) compared with those who received IV fluid at 125 mL/h. No differences were found in the other secondary outcomes.

There were no maternal or perinatal deaths and only one woman, in the 125 mL/h group, developed pulmonary edema.

For the primary outcome of cesarean delivery, pre-planned sensitivity analyses were performed for both restriction of oral intake and intravenous fluid type.

In the one study (10) using normal saline with dextrose water, the incidence of cesarean delivery was 4.9 vs. 13.4% in the 250 vs. 125 mL/h group, respectively (RR 0.36, 95% CI 0.13–0.95). For the five studies (7–9,11,12) using lactated Ringers, an intravenous fluid rate of 250 mL/h was associated with a lower incidence of cesarean delivery (13.4 vs. 18.3%; RR 0.73, 95% CI 0.55–0.98; five studies, 959 participants; $I^2 = 0\%$) compared with 125 mL/h.

For the five studies with restricted oral intake (8,10–13), the incidence of cesarean delivery for any indication

Table 2. Primary and secondary outcomes.

	Garite et al. (12)	Alavi et al. (10)	Eslamian et al. (11)	Maderia et al. (13)	Direkvand-Moghaddam et al. (7)	Kavitha et al. (9)	Edwards et al. (8)	Total	RR or MD (95% CI)	<i>I</i> ²
Cesarean (any indication)	10/101 (9.9%) vs. 16/94 (17.0%)	4/82 (4.9%) vs. 15/112 (13.4%)	24/147 (16.3%) vs. 35/153 (22.9%)	6/32 (18.8%) vs. 6/30 (20.0%)	2/30 (6.7%) vs. 4/30 (13.3%)	10/96 (10.4%) vs. 10/98 (10.2%)	18/105 (17.1%) vs. 23/105 (21.9%)	74/593 (12.5%) vs. 109/622 (18.1%)	0.70 (0.53–0.92)	0%
Cesarean for labor dystocia	10/101 (9.9%) vs. 15/94 (16.0%)	1/82 (1.2%) vs. 3/112 (2.7%)	1/147 (0.7%) vs. 10/153 (6.5%)	NR	NR	4/96 (4.2%) vs. 6/98 (6.1%)	10/105 (9.5%) vs. 9/105 (8.6%)	26/531 (4.9%) vs. 43/562 (7.7%)	0.60 (0.38–0.97)	18%
Cesarean for fetal well-being	0/101 vs. 1/94	3/82 vs. 10/112	23/147 vs. 25/153	NR	NR	6/96 vs. 3/98	6/105 vs. 10/105	38/531 (7.2%) vs. 49/562 (8.7101%)	0.83 (0.56–1.24)	0%
Cesarean for other indications	0/101 (0%) vs. 0/94 (0%)	0/82 (0%) vs. 2/112 (1.8%)	0/147 (0%) vs. 0/153 (0%)	NR	NR	0/96 (0%) vs. 1/98 (1.0%)	1/105 (0.9%) vs. 4/105 (3.8%)	1/531 (0.2%) vs. 7/562 (1.2%)	0.27 (0.06–1.28)	0%
Spontaneous vaginal delivery	69/101 vs. 63/94	NR	123/147 vs. 117/153	NR	NR	66/96 vs. 56/98	76/105 vs. 65/105	334/449 (74.4%) vs. 301/450 (66.9%)	1.11 (1.02–1.21)	0%
Operative vaginal delivery	22/101 (21.8%) vs. 15/94 (16.0%)	NR	0/147 (0%) vs. 1/153 (0.7%)	NR	NR	20/96 (20.8%) vs. 32/98 (32.7%)	11/105 (10.5%) vs. 17/105 (16.2%)	53/449 (11.8%) vs. 65/450 (14.4%)	0.81 (0.58–1.11)	34%
Augmentation of labor	51/101 (50.5%) vs. 61/94 (64.9%)	4/82 (4.9%) vs. 7/112 (6.3%)	12/147 (8.2%) vs. 33/153 (21.6%)	NR	6/30 (20.0%) vs. 7/30 (23.3%)	32/96 (33.3%) vs. 31/98 (31.6%)	62/105 (59.0%) vs. 60/105 (57.1%)	167/561 (29.8%) vs. 199/592 (33.6%)	0.83 (0.63–1.08)	55%
Duration of labor (min)*	484 ± 210 vs. 552 ± 267	312 ± 297 vs. 451 ± 213	253 ± 97 vs. 386 ± 110	626 ± 187 vs. 560 ± 387	NR	318 ± 143 vs. 349 ± 165	672 ± 288 vs. 672 ± 336	–	–64.38 min (–121.88 to –6.88)	83%
Length of second stage of labor (minutes)	71 ± 82 vs. 69 ± 80	33 ± 9 vs. 38 ± 16	16 ± 7 vs. 18 ± 10	NR	NR	NR	72 ± 90 vs. 78 ± 60	–	–2.80 (–4.49 to –1.10)	22%
Pulmonary edema	0/101 vs. 1/94 (1.1%)	NR	0/147 vs. 0/153	NR	NR	0/96 vs. 0/98	0/105 vs. 0/105 (0%)	0/449 vs. 1/450 (0.2%)	0.31 (0.01–7.53)	Not applicable
Chorioamnionitis	15/101 (14.9%) vs. 18/94 (19.1%)	NR	NR	NR	NR	0/96 vs. 0/98	16/105 (15.2%) vs. 12/105 (11.4%)	31/302 (9.9%) vs. 30/297 (10.1%)	0.99 (0.63–1.58)	22%
Postpartum hemorrhage	5/94 (5.3%) vs. 10/101 (9.9%)	NR	0/147 vs. 0/153	NR	1/30 (3.3%) vs. 2/30 (6.7%)	1/96 (1.0%) vs. 1/98 (1.0%)	7/105 (6.7%) vs. 5/105 (4.8%)	6/227 (2.6%) vs. 8/222 (3.6%)	0.72 (0.25–2.03)	0%
NICU Admission	8/94 (8.5%) vs. 1/101 (0.9%)	0/82 vs. 0/11	0/147 vs. 4/153 (2.6%)	NR	NR	NR	1/105 (0.9%) vs. 0/105	2/465 (0.4%) vs. 4/393 (1.0%)	1.31 (0.67–2.58)	0%
5-minute APGAR <7	0/94	NR	NR	NR	0/30 vs. 0/30	NR	1/105 (0.9%) vs. 0/105	2/465 (0.4%) vs. 4/393 (1.0%)	0.64 (0.16–2.46)	34%

Data are presented as number in the 250 mL/h group vs. number in the 125 mL/h group, as number (percentage) or as mean ± standard deviation. Boldface data, statistically significant.

CI, confidence interval; MD, mean difference; NICU, neonatal intensive care unit; NR, not reported; RR, relative risk.

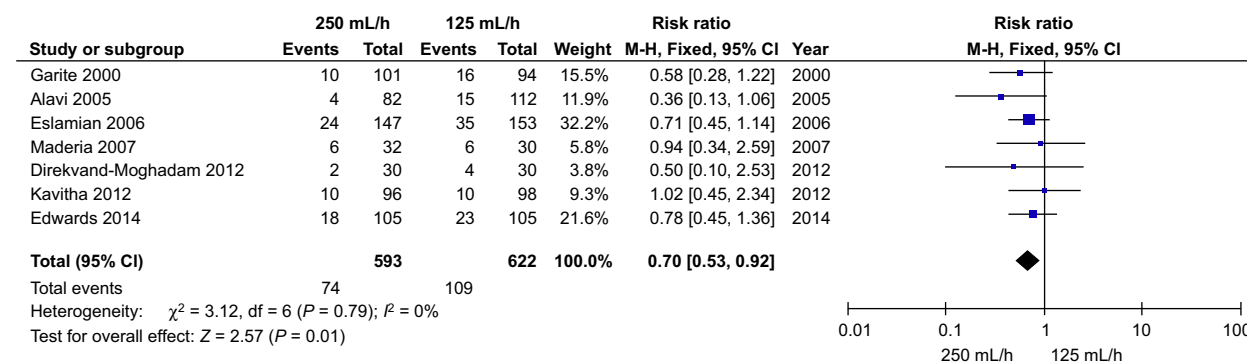


Figure 4. Forest plot for primary outcome, i.e. incidence of cesarean delivery. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel. [Color figure can be viewed at wileyonlinelibrary.com]

was reduced with 250 mL/h (13.3 vs. 19.2%; RR 0.67, 95% CI 0.50–0.90; five studies, 961 participants; $I^2 = 0\%$) compared with the 125 mL/h policy. In the two studies (7,9) with unrestricted oral intake, the incidence of cesarean delivery for any indication was not significantly different (9.5 vs. 10.9%; RR 0.87, 95% CI 0.42–1.81; two studies, 254 participants; $I^2 = 0\%$).

Discussion

This meta-analysis of seven RCTs, evaluating the effectiveness of IV fluids 250 mL/h compared with standard care of 125 mL/h, demonstrated a reduction in the rate of cesarean delivery (12.5 vs. 18.1%) and approximately a one-hour reduction in the length of labor. The number needed to treat to prevent one cesarean delivery is 18. Pooled data also showed a significantly shorter mean of duration of labor of about one hour and of length of second stage of labor.

Our meta-analysis included appropriately well-designed RCTs. Test of heterogeneity and statistical analyses all point to the efficacy of increased hydration. The findings persisted regardless of the type of intravenous fluid used. No significant reduction in the incidence of cesarean delivery was demonstrated in women with unrestricted oral intake; however, this was limited to only two studies evaluating 254 women.

Our data support earlier findings of a Cochrane review broadly evaluating intravenous hydration in labor (14). However, they did not include all RCTs published so far and the number of included women was lower. Additionally, we analyzed all trials comparing these two rates of infusion and then performed pre-planned sensitivity analysis. Our findings are consistent with those in that review, providing further support for increased hydration among nulliparous women in labor when oral intake is restricted.

Our study has several strengths. It is the largest meta-analysis to date, to our knowledge, comparing intravenous

fluid rates in labor. The trials were all well-designed, with a low risk of bias, and they were clinically similar in design with low statistical heterogeneity. A sensitivity analysis was performed for fluid type and restriction of oral intake, as these were the most clinically relevant differences among the studies. Statistical tests showed no significant potential publication biases. Intention-to-treat analysis was used, and both random and mixed effects models were used when appropriate. These are key elements that are needed to evaluate the reliability of a meta-analysis (15).

Limitations of our study are inherent to the limitations of the included studies and the overall small sample size. Only one of the studies made an attempt to blind the providers to the treatment. All of the studies included only healthy nulliparous women in spontaneous labor. Thus, the effectiveness and safety of this intervention in multiparous women, in those undergoing induction of labor or in those with medical comorbidities is unclear. No increase in adverse outcomes was noted, but electrolyte levels, indicators of renal function or objective assessment of intravascular volume status was not performed in any of the studies. The small sample size of women with unrestricted oral intake precludes a meaningful comparison of intravenous fluid rates in this subset of women. Whereas in the USA general practice is to administer IV fluids to all laboring women, in many other countries, IV fluids are not routinely administered and women are freer to drink and eat. In fact, only two trials (7,9) (both from Asia) in our meta-analysis allowed unrestricted oral intake (Table 1). It could be that allowing larger oral input of fluids for pregnant laboring women would lessen or even eliminate the benefits found with 250 mL/h of IV fluid in this meta-analysis. Moreover, a recent systematic review and meta-analysis of 10 RCTs including 3982 laboring women, found that low-risk singleton pregnancies who were allowed to eat more freely during labor had a shorter duration of labor, and

higher satisfaction, and that a policy of less-restrictive food intake does not influence other obstetric or neonatal outcomes or increase the incidence of vomiting (17). Finally, fluid management is only one aspect of labor management and therefore there may be several other factors driving the findings of these trials.

In conclusion, our findings support increased hydration for low-risk nulliparous women in spontaneous labor. Administering 250 mL/h as opposed to 125 mL/h appears to be a safe method of reducing the risk of cesarean delivery and length of labor in nulliparous women in spontaneous labor at term. If this approach is broadly applied, there is a potential for significant public health benefits. For the year 2013 in the USA, there were 341 532 cesarean deliveries of low-risk nulliparous women at term (1). A 30% reduction in the incidence of cesarean delivery would prevent 102 459 cesarean deliveries. Further study is needed regarding risks and benefits of increased hydration among women with unrestricted oral intake, those undergoing induction of labor, and those with medical comorbidities. Based on our results and the small sample size, no recommendation can be made regarding the optimal rate of fluid infusion for women with unrestricted oral intake.

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