Association Between Isolated Single Umbilical Artery and Perinatal Outcomes: A Meta-Analysis

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Background: To evaluate the association between the isolated single umbilical artery (iSUA) and perinatal outcomes, including pregnancy outcomes and perinatal complications.

Material/Methods: We performed a meta-analysis of 15 eligible studies regarding the relationship between the iSUA and perinatal outcomes, including gestational age at delivery, nuchal cord, placental weight, small for gestational age (SGA), oligohydramnios, polyhydramnios, pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), preeclampsia, and perinatal mortality. The overall odds ratios (OR) or standardized mean difference (SMD) were calculated.

Results: The occurrence of nuchal cord was not found to be different between an iSUA and a three-vessel cord (TVC) fetus. For perinatal complications, the SGA, oligohydramnios, polyhydramnios, GDM, and perinatal mortality showed dramatic difference between women with an iSUA and women with a TVC fetus, which implied that the presence of iSUA significantly increased the risk of perinatal complications. For other perinatal complications, such as PIH and preeclampsia, no significant association was detected.

Conclusions: Our meta-analysis suggests that the presence of iSUA would increase the risk of perinatal complications such as SGA, oligohydramnios, polyhydramnios, GDM, and perinatal mortality. Therefore, pregnant women with an iSUA fetus have poorer perinatal outcomes and more attention should be given to the management of their pregnancy compared to women with a TVC fetus.

MeSH Keywords: Meta-Analysis • Perinatal Care • Pregancy Outcome • Single Umbilical Artery

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Background

Single umbilical artery (SUA) is characterized by the presence of one umbilical vein and the absence of one of the umbilical arteries instead of the normal umbilical cord containing one vein and two arteries (three-vessel cord), and is considered a malformation [1,2]. Among all deliveries, SUA is the most common anomaly of the umbilical artery and its incidence is approximately 0.5% to 1% [3]. It has been previously reported that the incidence of SUA was lowest in neonates and highest among aneuploidy fetuses with the rate ranging from 9% to 11% [4]. The precise explanation for the cause of SUA is not yet fully known and the most widely accepted hypotheses includes primary agenesis or later atrophy of one umbilical artery [5,6].

An association between the SUA and an increased risk of fetal defects and chromosomal abnormalities has been reported [7–9]. SUA is defined as an isolated SUA (iSUA), if no additional chromosomal or structural abnormalities occurs [2]. More than 90% of cases with SUA exhibit an isolated anomaly, based a report from the Spanish Society of Gynecology and Obstetrics [10].
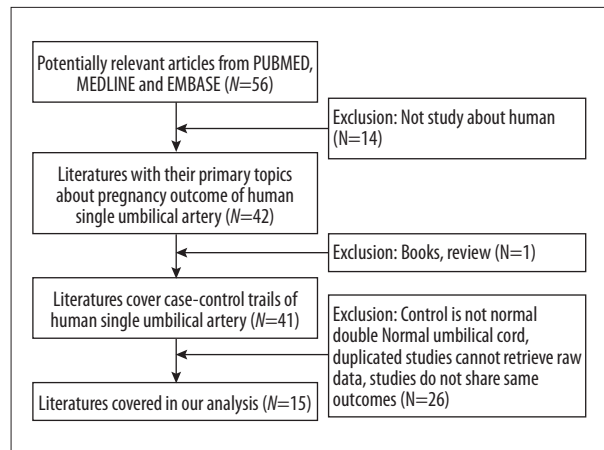
A meta-analysis performed in 2013, evaluated the relationship of iSUA to fetal growth, aneuploidy, and perinatal mortality, and reported no significant association was detected between iSUA and fetal growth and perinatal mortality; with respect to aneuploidy, there was insufficient data [6]. However, a controversy exists concerning whether iSUA is associated with adverse perinatal outcomes, with other studies presenting different views [1,11,12]. For example, when compared to fetuses with a TVC, fetuses with an iSUA are considered at increased risk of adverse perinatal outcomes, such as perinatal mortality [1], growth restriction [13], preterm labor [11], and pregnancy complication [2].

Our meta-analysis, which focused on investigating the association between iSUA and pregnancy outcomes and perinatal complications was performed to resolve the previously observed inconsistencies and to provide a more reliable estimation of the association between the iSUA and multiple perinatal outcomes.

Material and Methods

Search strategy

We searched multiple databases, including PUBMED, MEDLINE and EMBASE for relevant literatures by using terms: "single umbilical artery" or "two umbilical vessels" or "SUA" and ("fetal" or "prenatal") and ("three-vessel cord" or "normal umbilical cord" or "control" or "two umbilical arteries" or "three vessel disease"). All the studies published in English before July 31, 2015 were included. For the overlapped studies, the ones covering the most extensive information were selected.

Figure 1. Flow diagram of study selection and specific reasons for exclusion from the meta-analysis.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) studies reporting iSUA and pregnancy outcomes; 2) participants in case group studies were singletons of at least 24 weeks' gestation with iSUA identified by ultrasound scan [5]; 3) participants in control groups were single pregnancy with the normal three-vessel cord; 4) retrospective studies and prospective studies. The exclusion criteria were: 1) iSUA first diagnosed at birth; 2) studies were only on twin pregnancies; 3) the presence of any fetal malformation and/or marker of chromosomal abnormalities; and 4) absence of a SUA at delivery or by pathology report [14].

Data extraction

According to the inclusion and exclusion criteria, the candidate studies were evaluated independently by two authors. In addition, we manually examined the reference lists for potentially relevant studies. The following information was extracted from the eligible studies: first author, year of publication, design type of study, study population, numbers of participants in case and control groups, age, gravidity and parity of maternal, body mass index (BMI) of neonatal, fetal gender, and perinatal mortality.

Statistical analysis

In our study, perinatal outcomes were estimated by pregnancy outcomes including gestational age at delivery, nuchal cord, and placental weight [5,15–17] and perinatal complications including small for gestational age (SGA), oligohydramnios,

Table 1. Summary of characteristics of studies included in the meta-analysis.

Study	Study population	Type of study	Number*	Maternal age*	Gravidity*	Parity*	BMI* (kg/cm)	Fetal sex* (male%)	Perinatal mortality*%
Mladen Predanic (2005)	American	Retrospective case-control study	84/ 84	(31.2±5.2)/ (33.4±4.7)	[2(1,3)]/ [2 (1, 2)]	[0(0,1)]/[0 (0,1)]	NR	NR	NR
Annette E. Bombrys (2008)	American	Retrospective case-control study	255/ 289	(26.9±6.2)/ (24.9±5.9)	(2.7±1.7)/ (2.9±2.4)	(1.2±1.4)/ (1.3±1.4)	NR	NR	NR
Shu-Chi Mu (2008)	Taipei	Retrospective case-control study	14/ 28	(30.7±3.9)/ (29.5 ± 4.2)	(1.9±1.0)/ (2.0±1.1)	(1.3±0.5)/ (1.5±0.6)	NR	NR	NR
Amanda L. Horton (2010)	American	Retrospective cohort study	68/ 68	(27.3±4.6)/ (25.4±5.1)	NR	NR	(24.2±1.1)/ (6.1±1.3)	47/ 51.4	NR
Lynn Murphy Kaulbeck (2010)	Canada	Retrospective cohort study	725/ 196024	NR	NR	NR	NR	NR	3.35/ 0.39
Meiling Hua (2010)	American	Retrospective cohort study	392/ 63655	(29.8±6.4)/ (30.2±6.3)	(2.5±1.3)/ (2.7±1.6)	(1.0±1.1)/ (1.1±1.2)	NR	46.0/ 50.8	NR
Shilpa Chetty-John (2010)	American	Prospective study	263/ 41415	(25.02±5.6)/ (24.08±6.0)	–	–	NR	41.1/ 49.8	NR
Shimon Burshtein (2011)	Russia	Retrospective cohort study	243/ 194566	(28.5±5.6)/ (28.5±5.9)	–	–	NR	NR	6.6/0.9
Mohamed Ibrahim Khalil (2013)	Saudi Arabia	Retrospective cohort study	159/ 35026	(31.41±6.3)/ (31.57±6.5)	(4.5±2.6)/ (4.5±2.7)	(2.8±2.0)/ (2.8±2.0)	(24.1±4.56)/ (24.5±5.01)	NR	3.14/0.99
Eran Ashwal (2014)	Israel	Retrospective cohort study	91/ 182	(28.8±5.1)/ (28.8±4.5)	[2(2-3)]/ [2(1-3)]	[1(0-2)]/ [1(0-2)]	NR	38.5/ 47.8	NR
Joel Baron (2014)	Israel	Prospective case-control study	29/ 29	(29.7±5.3)/ (30.3±5.2)	NR	NR	NR	NR	NR
Lorena Mesquita Caldas(2014)	Brazil	Retrospective case-control study	134/ 759	(30.8±6.7)/ (30.3±6.6)	NR	NR	NR	NR	NR
S. Doğan (2014)	Turkey	Retrospective cohort study	77/ 95	(30.3±5.1)/ (29.6±5.9)	(1.9±1.0)/ (2.1±1.2)	(0.7±1.0)/ (0.76±0.8)	NR	NR	NR
Fırat Tülek (2015)	Turkey	Retrospective cohort study	93/ 100	(27.1±5.37)/ (27.4±5.28)	(3.9±2.0)/ (3.8±1.0)	(2.1±1.0)/ (2.3±1.2)	(28.3±4.28)/ (28.3±3.38)	NR	NR
Mariella Mailath-Pokorny (2015)	Austria	Retrospective cohort study	136/ 500	28.6±6.5	2.7±1.6#	1.1±1.1#	–	48.1#	NR

* (Isolated SUA/normal umbilical artery); # total (all the fetal); BMI – body mass index; NR – no refer; '–' – cloud not collect from article.

polyhydramnios, pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), preeclampsia, and perinatal mortality [1,2,5,11–15,18,19]. Gestational age at delivery was defined based on the description in a previous study [14]; and SGA was defined as a birth weight less than the 10th percentile [12,15]. The statistical analysis was conducted using STATA

12 software (STATA Corp LP, College Station, Texas, USA) and *p* value <0.05 was considered statically significant.

In our meta-analysis, we applied the Mantel-Haenszel (M-H) fixed-effects model for the calculation of I² index, which was used to assess the heterogeneity among eligible studies.

Table 2. Meta-analysis for the outcome during pregnancy stage.

Analysis model	Analysis method	Number of studies	Total people (case/control)	Heterogeneity		OR or SMD	SMD		p-value	Publication bias	
				I² (%)	p-value		95% CI			Begg	Egger
Gestational age	D-L random	11	1361/238015	84.2	0.000	−0.145*	−0.315	0.024	0.094	0.876	0.513
Nuchal cord	M-H fixed	3	368/41625	0.00	0.565	0.880	0.522	1.483	0.234	1.000	0.926
Placental weight	D-L random	2	277/41443	72.8	0.055	−0.466*	−1.097	0.166	0.148	1.00	−
SGA	D-L random	11	1836/233155	69.5	0.000	2.514	1.806	3.505	0.000	0.640	0.886
Oligohydramnios	M-H fixed	3	427/194848	0.000	0.617	2.71	1.747	4.204	0.000	0.296	0.082
Polyhydramnios	M-H fixed	4	1218/425798	0.00	0.767	3.090	2.259	4.228	0.000	0.308	0.237
PIH	D-L random	7	1593/232880	85.7	0.000	1.097	0.921	1.308	0.229	0.548	0.678
GDM	M-H fixed	7	2135/490950	36.1	0.153	1.367	1.116	1.675	0.003	0.764	0.572
Preeclampsia	M-H fixed	3	783/64443	0.00	0.852	0.820	0.557	1.205	0.312	0.296	0.491
Perinatal mortality	D-L random	3	1127/425616	66.30	0.052	4.681	2.637	8.309	0.000	1.000	0.931

For dichotomous data, when I² index was less than 50%, the Mantel-Haenszel (M-H) fixed-effects model was adopted to calculate the OR and 95% CI. Otherwise, the DerSimonian and Laird (D-L) random-effects model was chosen. With respect to the continuous data, when I² index was less than 50%, the Inverse-Alteration (I-V) fixed-effects model was used to calculate the SMD and 95% CI. Otherwise, the DerSimonian and Laird (D-L) random-effects model was applied.

For the calculation of OR or SMD and 95% CI, the data from the control group (participants with a TVC fetus) served as reference). Forest plots were generated to summarize the results. An OR >1 or SMD >0 for any of the perinatal outcomes signified that, compared to TVC fetuses, there was an increased risk of a perinatal outcome of fetuses with an iSUA. Begg's funnel plots and Egger's tests were conducted to examine publication bias. The noticeable asymmetry in funnel plots provided the evidence for the publication bias and the significance level was set at 0.05 for Egger's tests.

Results

Study characteristics

Overall, 56 papers were retrieved from the three databases after the first search, from which 14 studies that were irrelevant to human were excluded. Another 27 studies that did not meet the inclusion criteria were also excluded; leaving 15 studies [1,2,5,11–13,15,17,18,20–25] included in our meta-analysis. The selection process and reasons for exclusion are described in Figure 1. The eligible studies included two prospective studies and 13 retrospective studies. The main characteristics of all the 15 included studies are displayed in Table 1.

Evaluation of the association between iSUA and pregnancy outcomes

The association between iSUA and pregnancy outcomes, including gestational age, nuchal cord, and placental weight, were evaluated and the results are represented in Table 2. For gestational age, 11 eligible studies were included and the SMD was −0.145 (95% CI: −0.315–0.024, p=0.094, Figure 2A), suggesting that the gestational age in fetuses with iSUA was similar with that in TVC fetuses and no significant association was detected between iSUA and gestational age. For nuchal cord, three eligible studies were included and the OR was 0.880 (95% CI: 0.522–1.483, p=0.234, Figure 2B), indicating that there was no significant difference in the occurrence of nuchal cord between fetuses with iSUA and fetuses with TVC and no significant association was observed between iSUA and nuchal cord. For placental weight, two eligible studies were included and the SMD was −0.466 (95% CI: −1.097–0.166, p=0.148, Figure 2C), which signified that placental weight in fetuses with iSUA was similar to placental weight in TVC fetuses, and no significant association was found between iSUA and placental weight.

Evaluation of the association between iSUA and perinatal complications

The association between iSUA and perinatal complications, including SGA, oligohydramnios, polyhydramnios, PIH, GDM,
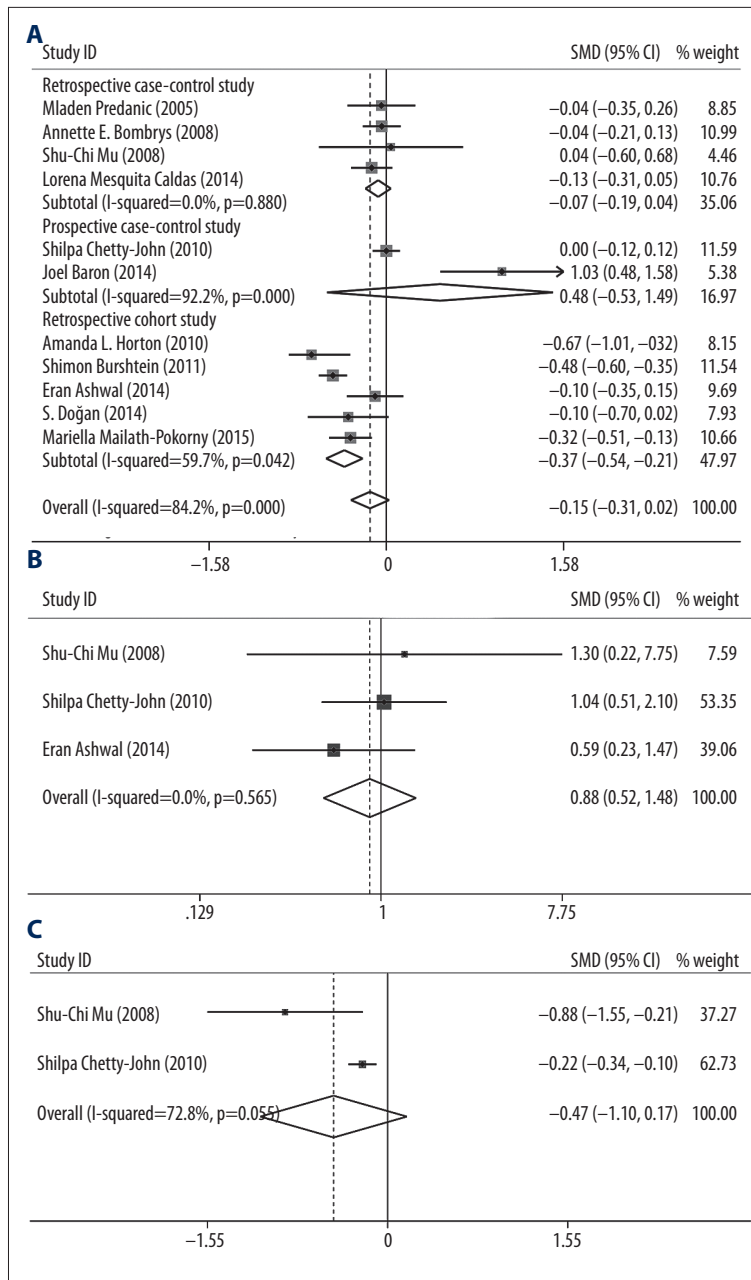
Figure 2. Forest plot of study evaluating the association between iSUA and gestational age at delivery (**A**); nuchal cord (**B**); and placental weight (**C**).

preeclampsia, and perinatal mortality, were also estimated and the results are shown in Table 2. For SGA, 11 eligible studies were included and the OR was 2.514 (95% CI: 1.806–3.505, *p*=0.000, Figure 3), indicating that the incidence of SGA in iSUA fetuses was significantly higher than that in TVC fetuses and iSUA was associated with the occurrence of SGA. For the oligohydramnios and polyhydramnios, three and four eligible studies were included respectively; the ORs were 2.71 and 3.090, respectively (for oligohydramnios: 95% CI: 1.747–4.204, *p*=0.000; for polyhydramnios: 95% CI: 2.259–4.228, *p*=0.000, Figure 4). These results suggest that the incidence of oligohydramnios or polyhydramnios in iSUA fetuses was significantly

higher than in TVC fetuses, and iSUA increased the risk of oligohydramnios or polyhydramnios.

For GDM, seven eligible studies were included and the OR was 1.367 (95% CI: 1.116–1.675, *p*=0.003, Figure 5A), suggesting that the incidence of GDM in iSUA fetuses was significantly higher than in TVC fetuses, and iSUA increased the risk of GDM. For perinatal mortality, three eligible studies were included and the OR was 4.681 (95% CI: 2.637–8.309, *p*=0.000, Figure 5B), implying that the incidence of perinatal mortality in iSUA fetuses was significantly higher than in TVC fetuses, and iSUA increased the risk of perinatal mortality. For PIH and
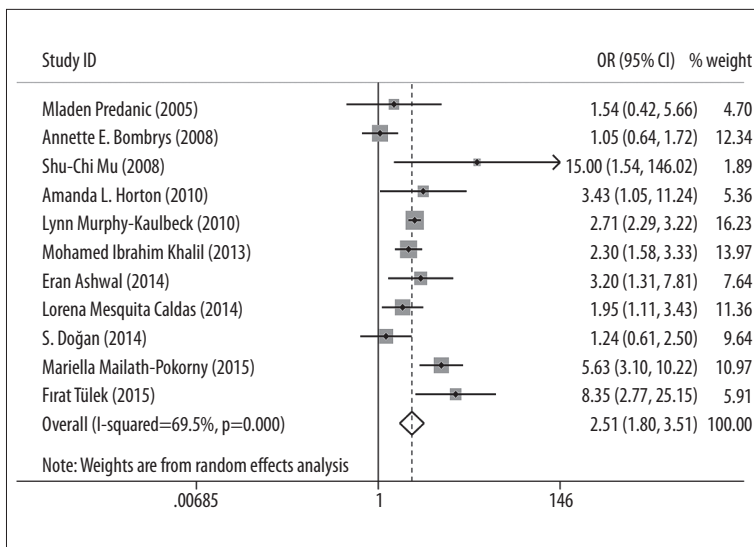
Figure 3. Forest plot of study estimating the association between iSUA and SGA.
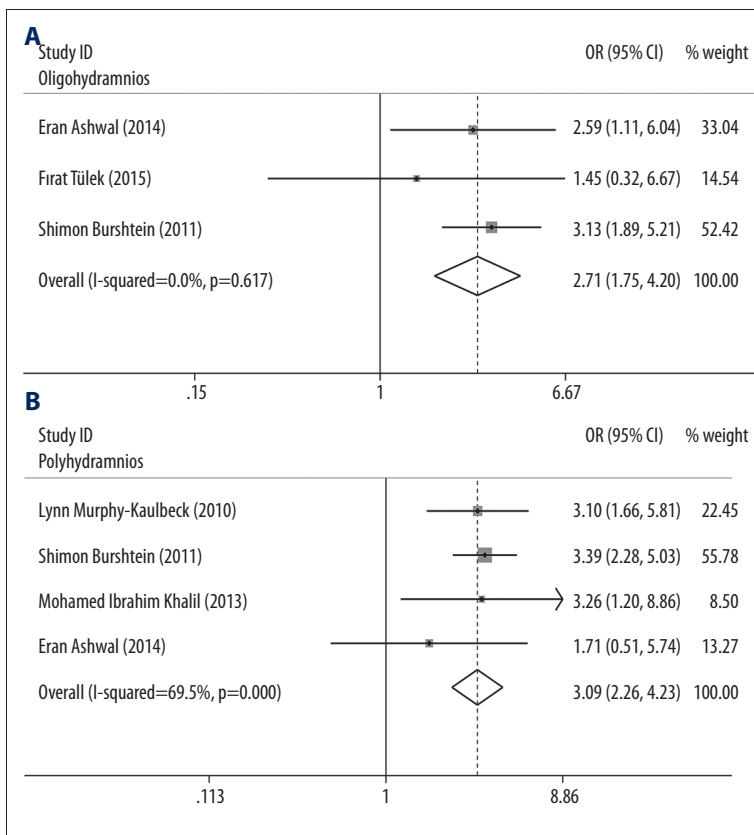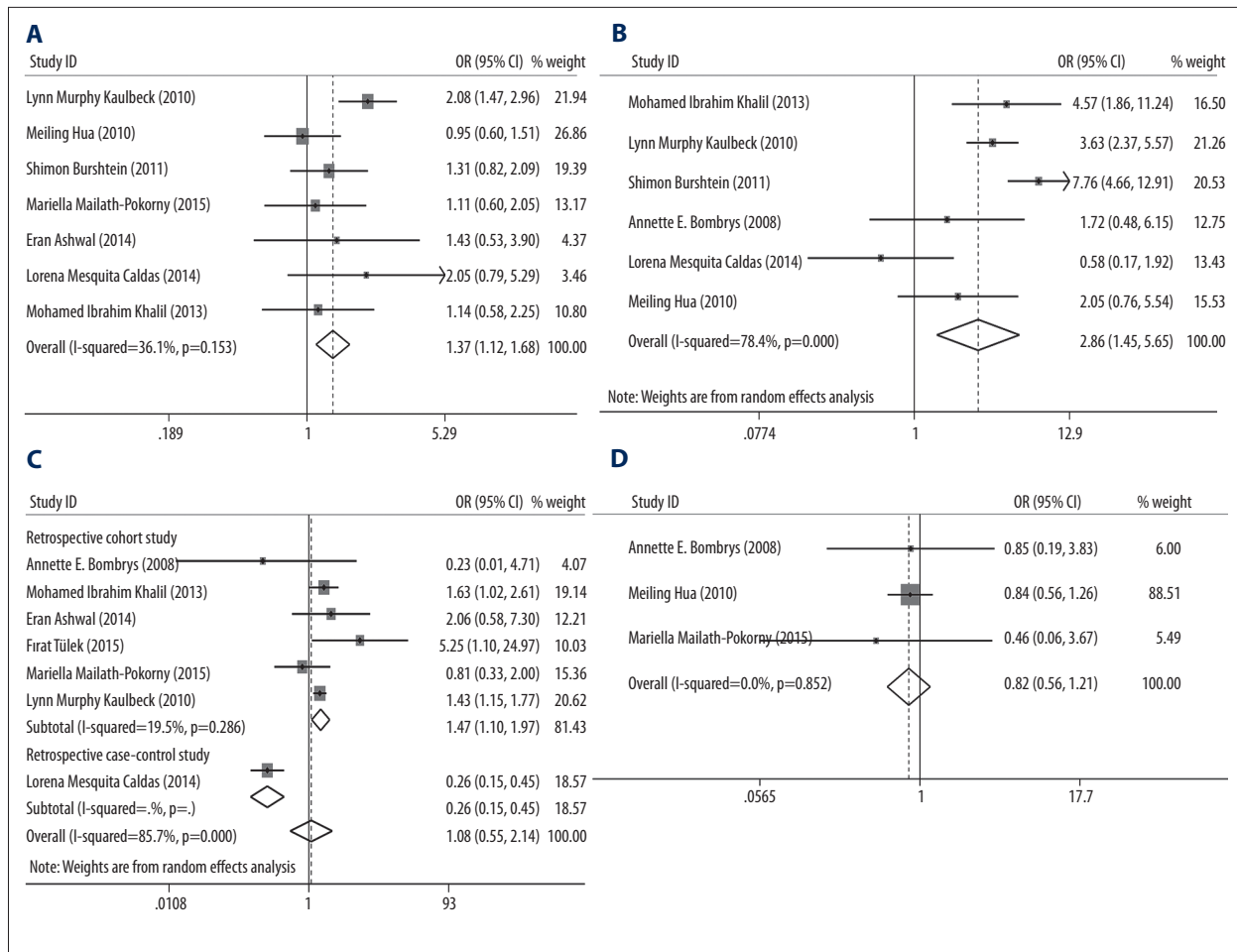

Figure 4. Forest plots of studies assessing the association between iSUA and oligohydramnios and polyhydramnios.

preeclampsia, seven and three eligible studies were included respectively, and the ORs were 1.082 and 0.820, respectively (for PIH: 95% CI: 0.547-2.141, p=0.229; for preeclampsia: 95% CI: 0.557–1.205, p=0.312, Figure 5C, 5D), revealing that there was no association between iSUA and PIH and preeclampsia.

Sensitivity analysis

We performed the sensitivity analysis to explore the effect of a single study on the overall meta-analysis by omitting individual trials sequentially. As shown in Supplementary Figure 1, no significant difference occurred after the omission of any study, which signified that our results were statistically reliable.

Figure 5. Forest plots of studies evaluating the association between iSUA and GDM (**A**); perinatal mortality (**B**); PIH (**C**); and preeclampsia (**D**).
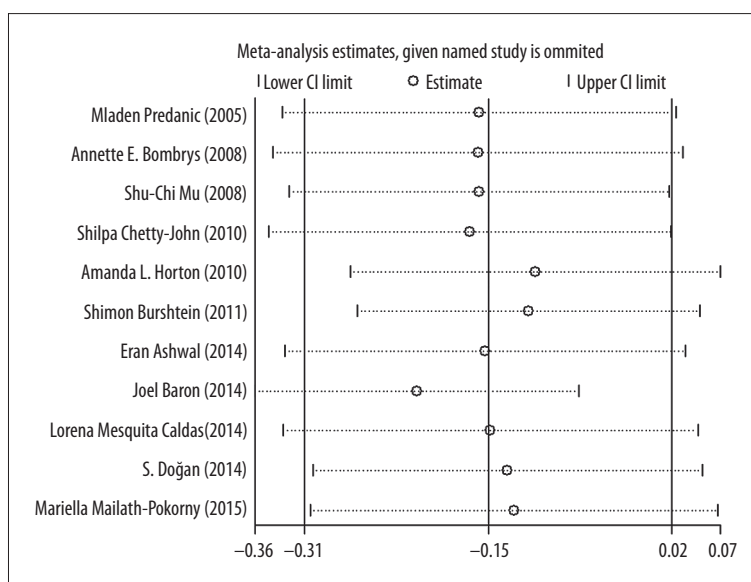
Supplementary Figure 1. Result of sensitivity analysis.

Publication bias

Begg's plot and Egger's test were applied for the evaluation of publication bias and the results are exhibited in Table 2. The *p* values of all analyses were higher than 0.05, indicating that no significant publication bias was observed in any individual investigation that was part of our meta-analysis.

Discussion

In this study we performed a meta-analysis that included 15 studies that considered the relationship between iSUA and perinatal outcomes, including gestational age at delivery, nuchal cord, placental weight, SGA, oligohydramnios, polyhydramnios, PIH, GDM, preeclampsia, and perinatal mortality. For the pregnancy outcomes, our results suggested that no significant difference was observed between women with an iSUA fetus and women with a TVC fetus, and there was no association between iSUA and pregnancy outcomes such as gestational age, nuchal cord, and placental weight. For perinatal complications, we compared the risk of SGA, oligohydramnios, polyhydramnios, GDM, and perinatal mortality between women with iSUA and TVC fetus, all the ORs were higher than 1 and *p* values were lower than 0.05, implying that the incidence of these complications was correlated with iSUA, and that iSUA may increase the risk of these complications. The comprehensive analysis in our study illustrated that compared with pregnant women with a TVC fetus, women with an iSUA fetus had poorer perinatal outcomes and were more likely to suffer from SGA, oligohydramnios, polyhydramnios, GDM, and perinatal mortality.

In terms of gestational age at delivery, a study by Shilpa et al. showed no significant difference between iSUA fetuses and TVC fetuses [5], results which were consistent with our study. As for the occurrence of nuchal cord, a retrospective cohort study published in 2014 suggested that there was no significant difference between iSUA fetuses and TVC fetuses [22], an observation also suggested by our study. However, for placental weight, the results of two previous studies [5,15] were opposite to that of our meta-analysis; the false positive in these two previous studies might be partially responsible for the inconsistency, and our meta-analysis might have eliminate the false positive by enlarging the sample size. With respect to perinatal complications, our results were in accordance with those of previous studies [1,11–13,18,24,25].

A previous meta-analysis [6] showed that fetuses with iSUA were more likely to suffer from SGA and perinatal mortality when compared with TVC fetuses, even if no statistical difference was detected for the two outcomes. Yet, the results of our meta-analysis suggest that the presence of iSUA significantly increased the risk of SGA and perinatal mortality, a finding inconsistent with the previous meta-analysis. As stated in the previous study, the limited sample size might be responsible for the non-significant result. The previous study included only seven eligible papers covering 928 pregnancies with iSUA, while our meta-analysis included 15 eligible papers covering 2763 pregnancy with iSUA. Additionally, in our meta-analysis, except for SGA and perinatal mortality, we also estimated the relationship between iSUA fetuses and other perinatal complication-related symptoms to increase the reliability of our conclusions.

Since large or extreme heterogeneity may lead to a misleading conclusion, the degree of heterogeneity is one of the main concerns in meta-analysis. In our study, large heterogeneity existed in the analysis of gestational age (I^2=84.2%, *p*=0.000) and PIH (I^2=85.7%, *p*=0.000). Heterogeneity may be caused by confounding factors among different studies. We performed subsequent subgroup analysis stratified by study type for gestational age and PIH. Our results (Figures 2A, 5C) showed that the two prospective case-control study [5,23] might be the source of heterogeneity for gestational age; and heterogeneity for PIH might have resulted from one retrospective case-control study [24]. Thus, we suggest that when pooling eligible studies for meta-analysis, the heterogeneity of different study types should be considered, and subgroup analysis based on study type should be performed if sufficient data is available.

There were limitations to our meta-analysis. First, for the analysis of placental weight, only two eligible studies were retrieved; an analysis of a large sample size should be conducted to get a more reliable estimation. Second, as we discussed earlier, for the analysis of gestational age and PIH, large heterogeneity occurred, hence these results should be interpreted with caution.

Conclusions

To the best of our knowledge, our study is the most comprehensive meta-analysis evaluating the association of iSUA and perinatal outcomes. Our results suggest there is no significant association between iSUA and pregnancy outcomes, including gestational age at delivery, nuchal cord, and placental weight. In terms of perinatal complications, the incidence of PIH and preeclampsia has no correlation with the presence of iSUA, while the presence of iSUA could increase the risk of SGA, oligohydramnios, polyhydramnios, GDM, and perinatal mortality. Our results suggest that compared to pregnant women with a TVC fetus, women with an iSUA fetus have a poorer perinatal outcomes, and more attention should be paid to the management of pregnant women with an iSUA fetus.

Declaration of conflicting interest

There is no special conflict of interest in our study.

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