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Review article

Evaluation of umbilical cord entanglement as a predictive factor of adverse pregnancy outcomes: A meta-analysis

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ABSTRACT

The purpose of the present systematic review is to summarize current data concerning the impact of umbilical cord entanglement on adverse pregnancy outcomes. We used the Medline, Scopus, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases. We selected all observational (both prospective and retrospective) studies for inclusion. Meta-analysis of the risk ratios (RR) was performed with RevMan 5.3 software. Univariate meta-regression and leave-one-out meta-analysis was performed with Open Meta-Analyst statistical software. Trial sequential analysis was performed with the TSA software. Overall, twenty studies were included in the present study with 267,233 pregnant women (50.103 with cord entanglement and 217,130 controls). An increased risk of neonatal Apgar score <7 at the first minute of life was observed among cases with cord entanglement (RR = 1.75, 95% CI 1.46, 2.11). Fetal distress was significantly higher in the entanglement group (RR 1.50, 95% CI 1.33, 1.69). The incidence of fetal pH < 7.1 was also significantly higher in the entanglement group (RR 1.73, 95% CI 1.48, 2.03). Adequate power was observed in all investigated outcomes of our primary analysis after evaluating the results of the TSA analysis. Prediction intervals designated that future studies were likely to report increased risk of low Apgar score at the first minute of life, increased risk of fetal distress as well as of observing a fetal pH < 7.1. Concluding, the findings of this systematic review suggest that there is sufficient evidence to support the involvement of cord entanglement to adverse neonatal perinatal outcomes.

Contents

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Introduction

Umbilical cord entanglement (UCE) is the most commonly detected complication of the umbilical cord and is defined as wrapping of the cord around fetal structures. Nuchal entanglement (that surrounds the fetal neck) is the most prevalent form and its incidence is estimated to range between 14,7 % and 33,9 % of pregnancies [1]. The incidence of trunk entanglement is estimated around 4,7 %, whereas entanglement of limbs is 4,2 % and multiple parts of the fetal body is 6,4 % [2]. The majority of nuchal cords are single and loose, which means that the cord could be easily be uncoiled before delivery of the newborn [3].

Despite the fact that the presence of nuchal cord can be diagnosed antenatally with the use of ultrasound, to date, the clinical significance of UCE as an antenatal finding remains controversial. The last decade several studies have been published in this field and report that UCE is associated with higher rates of adverse perinatal outcomes. In their latest population based study, Linde et al observed that extreme umbilical cord length, cord knotting and cord entanglement at term is associated with increased risk of intrauterine death (Odds Ratio (OR) 1.94), low 5 min Apgar score (OR 1.40) and perinatal death (OR 1.72) [4]. The extreme number of included singleton pregnancies in this study leaves little space to argue regarding the scientific importance of their findings. In the present systematic review, we accumulated all remaining available data in the field to evaluate the external validity of the study of Linde et al and to describe the discrepancies in terms of outcome reporting in order to help reach in the future consensus concerning the optimal management of these women.

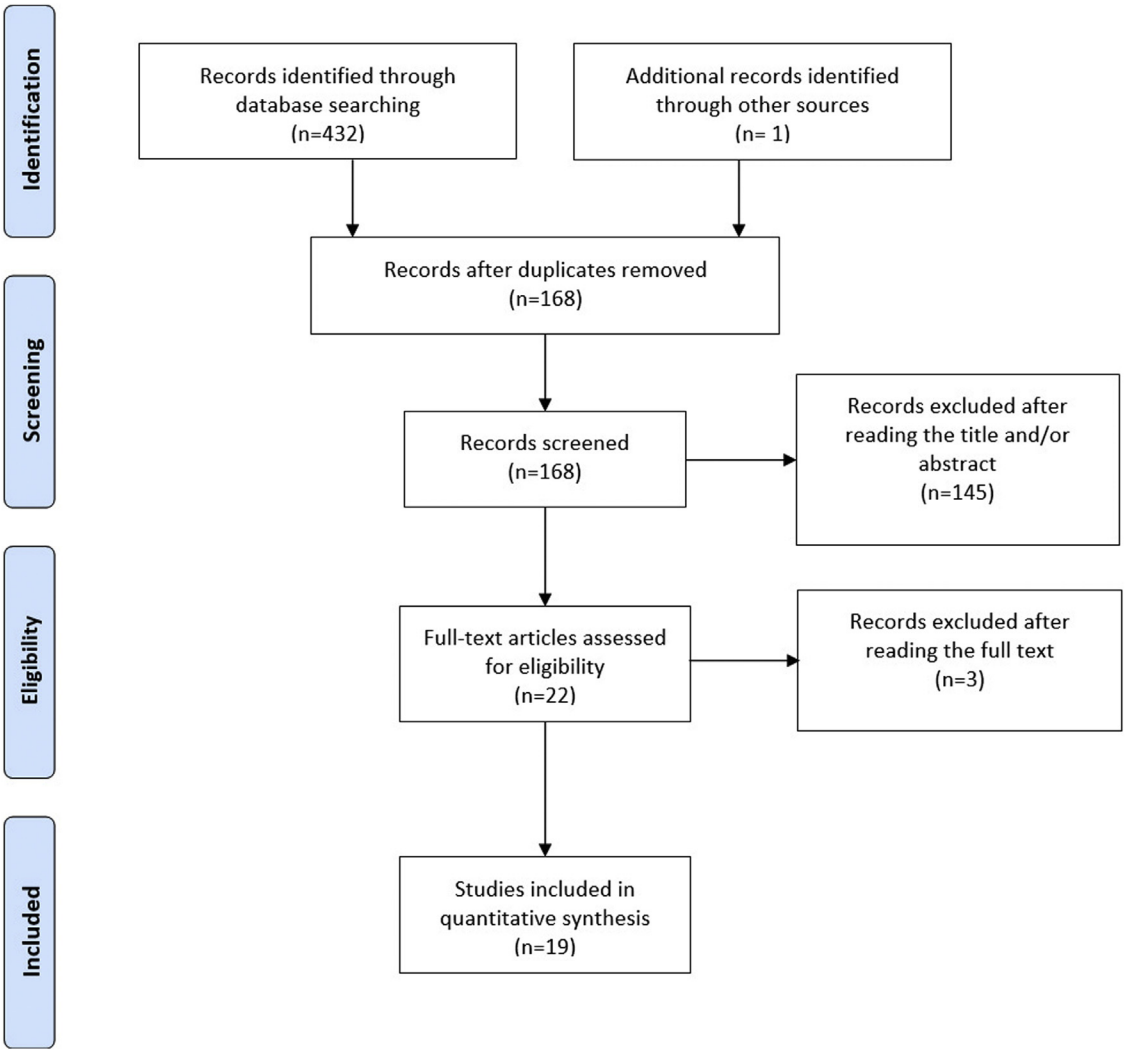

Fig. 1. Search plot diagram.

Table 1
Heterogeneity in outcome reporting.

Year; author	Study size (n)	Journal Impact Factor	PubMed	Multiple vs single loop	Malformation	Placental abnormalities	IUGR	Post-partum hemorrhage	Preeclampsia	PPROM	PTB	Abnormal fetal life	Fetal distress	Emergency C/S	C/S	Forceps	Intrauterine death	Perinatal death	NICU admission	5` Apar score <7	Fetal acidosis	Abnormal AFI
2018; Cursoy	100	0.545	+												+					+	+	
2018; Abdallah	455	1.493	+										+		+	+		+	+	+		+
2018; Vasa	2530	1.232	+				+				+		+		+				+	+		
2017; Akkaya	408	1.493	+										+	+	+					+		+
2017; BuyukkayaciDuman	120	1.493	+				+						+	+		+				+		
2016; Wang	1749	1.029	+	+	+				+	+			+	+	+	+				+		
2015; Kobayashi	6307	2.17	+												+	+				+	+	
2015; Kong	4404	1.493	+	+								+	+	+		+			+	+	+	
2008; Singh	367	NA	+			+							+		+					+		
2008; Onderoglu	320	0.339	+	+			+					+	+							+		
2006; Ogueh	57,853	2.426	+										+		+	+						
2005; Assimakopoulos	352	1.809	+										+		+	+						+
2005; Peregrine	289	5.654	+			+						+	+		+			+				+
2005; Sheiner	166.318	2.236	+												+			+				
2005; Mastrobattista	4426	1.623	+										+		+	+			+	+		
2005; Schaffer	11,748	4.932	+	+									+		+	+			+	+	+	
1995; Larson	8565	5.732	+	+		+							+		+	+				+	+	
1992; Miser	702	0.18	+			+							+		+	+				+		
1987; Hankins	220	5.175	+										+				+	+				
Total	**267233**		**19**	**5**	**1**	**4**	**4**	**0**	**1**	**1**	**1**	**3**	**16**	**4**	**15**	**12**	**1**	**5**	**5**	**16**	**6**	**4**

Blank spaces: Outcome was not available, +: outcomes was present.

Materials and methods

Study design

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. Eligibility criteria were pre-determined by the authors. An institutional board approval was not obtained as this study was based in published aggregated data.

Literature search

Two authors performed an independent search of the international literature using the Medline (1966–2019), Scopus (2004–2019), EMBASE (1980–2019), Cochrane Central Register of Controlled Trials CENTRAL (1999–2019) and Google Scholar (2004–2019) databases as well as the reference lists (snow-balling) of electronically retrieved full-text papers. The date of our last search was set at April 30th 2019. The search strategy included the words "umbilical; cord; entanglement; wrapping; nuchal cord; and pregnancy" and is schematically presented in the PRISMA flow diagram (Fig. 1).

Study selection

We did not apply language, country or date restrictions in our search strategy to minimize the possibility of selection bias. The retrieval of articles was completed in three consecutive stages. Following deduplication of the sum of collected articles, their titles and abstracts were screened to evaluate their eligibility. Conference proceedings and abstracts were also considered to be eligible, provided that the outcome of interest was available within their context. Articles that met or were presumed to meet the criteria were retrieved in full text. In the final stage, all observational (both prospective and retrospective) studies that reported adverse antenatal and perinatal outcomes in pregnancies complicated by cord entanglement were considered as eligible for inclusion in the present systematic review and meta-analysis. The method of determination of cord entanglement (antenatal ultrasound or postnatal assessment) did not influence the decision for inclusion of articles. Animal studies, case reports, case series and review articles were excluded from inclusion. Congress abstracts were also considered for inclusion in the present systematic review, provided that they mentioned the actual prevalence of the various investigated outcomes within their context. In case of duplicate articles, or articles that included identical or overlapping population samples we chose to include those with the most complete outcome set. Any discrepancies in the methodology, retrieval of articles and statistical analysis were resolved by the consensus of all authors.

Selection of outcomes and data extraction

Data extraction was performed by two independent reviewers (V.P. and M.F.) After an initial evaluation of the outcomes that were investigated in the study of Linde et al. [4] and in a previous meta-analysis that evaluated the impact of umbilical cord coiling on pregnancy outcomes [6] we structured a pre-determined table of potential core outcomes that could be influenced by cord entanglement (Table 1). The impact factors of journals that published the included studies were also included as they may serve as an indirect potential index of the scientific importance, measured in terms of acceptability, of each study [7]. Data extraction was based on Table 1 and performed using a modified data form that was based in Cochrane`s data collection form for intervention reviews for RCTs and non-RCTs [8].

Definitions

Significant heterogeneity was noted in the definition of fetal distress among the various studies that were included and data relevant to this are summarized in Supplemental Table 1.

Assessment of risk of bias

The methodological quality of included studies was assessed by two reviewers independently (V.P. and M.F.) using the Newcastle-Ottawa Scale (NOS), which evaluates the selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest [9].

Primary statistical analysis

Meta-analysis of the risk ratio (RR) among cases with cord entanglement and controls was performed with RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals were set at 95 %. The DerSimonian–Laird random effect model was selected to calculate the reported RRs and MDs as well as the 95% confidence intervals (CI), due to the significant heterogeneity of the methodological characteristics of the included studies (Table 1). Publication bias was evaluated for the sum of studies included in our primary analysis using funnel plots constructed with the Review manager software. A pre-requisite to evaluate the funnel plots was the inclusion of at least 10 studies. Egger`s test and Begg & Mazumdar`s rank correlation tests were also calculated using the regtest function in R. The Trim & Fill method was selected as a method to correct funnel plot asymmetry and to estimate the effect of oligohydramnios on pregnancy and neonatal outcomes following adjustment for the publication bias if this would have been observed.

Secondary statistical analysis

Secondary statistical analysis was performed only for outcomes that were reported in at least 10 studies in the primary analysis. The impact of tight loops and multiple loops in the perinatal outcome was evaluated separately during this step.

Univariate meta-regression was performed with Open Meta-Analyst statistical package. We evaluated the impact of the year of publication, type of study (prospective/retrospective), method of diagnosis (ultrasound/postpartum), origin of researchers/participants (in continents) and sample size (arbitrary cut-off: 1000 patients) on outcomes of our primary analysis.

The influence of individual studies was explored by performing leave-one-out analyses; one study was sequentially omitted at a time in order to evaluate its effect in the outcome of the meta-analysis using the Open Meta-Analyst software.

Trial sequential analysis (TSA) was performed to limit the possibility of type I error using the TSA v. 0.9.5.10 Beta software (http://www.ctu.dk/tsa/). The methodology was similar to that reported in our previous publication [6]. Briefly the risk for type I errors was set at 5 % and for type II errors at 80 %. The power of the sample size for each investigated outcome was evaluated using the required information size (RIS) function of TSA. The TSA analysis was performed.

Prediction intervals

Furthermore, prediction intervals were calculated as they provide an estimation of the effects to be expected by future studies in the field. More specifically, prediction intervals take into account the inter-study variation of the results and express the existing heterogeneity at the same scale as the examined outcome. As proposed by IntHout et al. [10], prediction intervals are calculated in the logarithmic scale as $logRR \pm t \times SD_{PI}$, where RR represents the meta-analytic risk ratio, t the two-sided critical t-value and SD_{PI} the standard deviation of the prediction interval. It should be noted that t is estimated at k-1 degrees of freedom, with k indicating the number of studies included in the meta-analysis. Calculation of SD_{PI} is performed according to the following formula: $SD_{PI} = \sqrt{\tau^2 + SE^2}$, where τ^2 represents the existing heterogeneity and SE the standard error of logRR. Exponentiation of the limits provides the prediction intervals at the RR scale. Moreover, the probability that the true effect would be on the other side of the null was estimated using the one-tail cumulative t-distribution with k-1 degrees of freedom.

Results

Included studies

Overall, 22 articles were considered to be eligible for inclusion and were retrieved in full text [1,2,8,11–29]. None of those referred was an abstract or a conference proceeding. Three studies did not include a control group and were excluded [27,12–29]. The methodological characteristics of included studies are summarized in Table 2. Overall, nineteen studies were finally included in the present study with 267,233 pregnant women (50.103 with cord entanglement and 217,130 controls). The diagnosis of entanglement was observed antenatally in three studies. Fifteen studies reported that the diagnosis was made postpartum. Four studies compared patients with tight nuchal cord with patients without cord entanglement. Six studies investigated the impact of multiple loops on adverse pregnancy outcomes.

Confounding factors that could potentially interfere with the results of our analysis are summarized in Supplemental Table 2. Significant differences were noted in gestational age at delivery and birth weight among cases with entanglement and controls in several studies; however, these were subtle and; hence, of limited clinical value. Operative vaginal delivery was also less frequent in control cases.

The significant heterogeneity in outcome reporting is noted in Supplemental Table 1. The majority of included studies investigated less than 50 % of outcomes that were predefined in our study as necessary to extract safe conclusions concerning the perinatal outcome of pregnancies complicated by cord entanglement.

Primary results

Ten studies investigated the impact of cord entanglement on Apgar score values at the 1st minute of life and a significant risk of having a value <7 was observed in the entanglement group (RR = 1.75, 95 % CI 1.46, 2.11, Fig. 2). Twelve studies evaluated the impact of cord entanglement in Apgar score values at the 5th minute of life. Differences concerning the number of cases with values <7 at this time point were not significant (RR 1.24, 95 % CI 0.81, 1.90, Fig. 2).

Fetal distress was significantly higher in the entanglement group (RR 1.50, 95 % CI 1.33, 1.69, Fig. 3). The incidence of fetal pH < 7.1 was investigated in 7 studies and was also significantly higher in the entanglement group (RR 1.73, 95 % CI 1.48, 2.03, Fig. 3).

Publication bias was not significant among investigated parameters hence, a trim and fill analysis was not performed (Supplemental Table 4).

The results of the leave-one-out meta-analysis revealed that the individual exclusion of studies did not alter the significance status that was observed in the primary analysis (Supplemental Table 3). Meta-regression analysis (Supplemental Table 3) revealed that Asian studies tended to overestimate the impact of cord entanglement on

Table 2
Methodological characteristics of included studies.

Author; Date	Study type	Sample size	Location	Diagnosis	Inclusion criteria	Exclusion criteria
Akkaya; 2016	Prospective cohort	408	Turkey	Ultrasound	Spontaneous, term, singleton pregnancies with vertex presentation	Multiple gestations, fetal or maternal infection, hypertensive disorders of pregnancy, gestational and pregestational diabetes mellitus, preterm labor, fetal congenital malformations, umbilical cord anomalies
Assimakopoulos; 2005	Prospective cohort	352	Greece	Ultrasound	Normal,singleton pregnancies, vertex presentation,37–39 weeks	Previous CS, uterine surgery, medical problems in current pregnancy(diabetes mellitus, hypertension, cardiac disease, renal disease, women under medications or drugs)
BuyukkayaciDuman; 2017	Retrospective case-control	120	Turkey	Postpartum	Term birth, cephalic presentation	Chronic systemic diseases, multiple pregnancies, preterm labor, premature rupture of membranes, abnormal fetal presentation, amniotic fluid anomalies
Kobayashi;2015	Retrospective cohort	6307	Japan	Postpartum	Singleton pregnancies, vaginal delivery, ≥37 weeks of gestation	Women with a serious complication(hypertension or diabetes), congenital anomalies, fetal malpresentation
Kong; 2015	Retrospective cohort	4404	China	Postpartum	Singleton, term pregnancies, spontaneous labor	Preterm infants, more prone to have poorer outcomes, higher incidence of low Apgar score, higher paediatric unit admission rate(complications of prematurity), multiple pregnancies, elective CS
Larson;1995	Retrospective case-control	8565	USA	Postpartum	Vertex presentation, singleton pregnancy undergoing labor at ≥37 weeks	Prior CS, active herpes virus infection, intrauterine fetal death, severe congenital anomalies, abnormal fetal lies
Mastrobattista; 2005	Retrospective case-control	4426	USA	Postpartum	Term pregnancies(37-42 weeks)	
Ogueh; 2006	Retrospective cohort	57,853	Canada	Postpartum	Singleton pregnancies, vertex presentation, birth weight ≥ 2500 g	Severe fetal malformations
Onderoglu; 2008	Retrospective cohort	320	Turkey	Postpartum	Term singleton pregnancies (37–42 weeks), spontaneous pregnancy, vertex presentation, no congenital malformation, no maternal medical problems, no evidence of infection, availability of all the study parameters	
Peregrine; 2005	Prospective cohort	289	UK	Ultrasound	Labor induction after 36 weeks of gestation	
Sheiner;2005	Retrospective cohort	166,318	Israel	Postpartum	Non-selective population based data	
Singh; 2008	Retrospective (unclear)	367	India	Postpartum		IUGR, oligohydramnion, antepartum hemorrhage, pregnancy induced hypertension, maternal medical complications
Wang; 2016	Retrospective cohort	1749	Japan	Postpartum	Singleton pregnancies, vaginal delivery	Multiple pregnancies, <22 weeks, or <37 weeks, CS owing to previous CS or breech presentation, increased need for care by neonatologist
Gursoy; 2018	Cross-sectional	100	Turkey	Postpartum	Uncomplicated single term gestations between 37-40 weeks, elective C-section due to a repeat C-section or foetal malpresentation	Chronic hypertension, preeclampsia, IUGR, pregestational or gestational diabetes mellitus, smokers, <18 and >35 years, placental insertion abnormalities, preterm deliveries (<37 weeks), maternal chronic diseases with or without any medication supplementation and emergency caesarean sections
Abdallah; 2018	Prospective cohort	455	Egypt	Ultrasound	Primigravida women, 18–35 years, singleton term pregnancy, ≥37 weeks	BMI > 30 kg/m^2, multiple pregnancy, malpresentation, fetal demise, chorioamnionitis, MSL, maternal medical disorder (hypertension, diabetes, autoimmune disease, etc), perinatal complication (e.g. placental abruption), abnormal fetal growth
Vasa; 2018	Retrospective cohort	2530	USA	Postpartum	Women delivered in 2012	
Miser; 1992	Retrospective case control	706	USA	Postpartum		Maternal or infant records could not be found
Schaffer; 2005	Retrospective case control	11,748	Switzerland	Postpartum	Singleton, vertex, term, postterm pregnancies with planned vaginal delivery	
Hankins; 1987	Retrospective case-control	220	USA	Postpartum	Term pregnancies, birth weight ≥ 2500 g	Hypertension, diabetes, maternal metabolic disorders, preeclampsia, Rh isoimmunization, chorioamnionitis, labor induced, augmentation with oxytocin

MSL: meconium stained liquor IUGR: intrauterine growth retardation, *Nuchal cord tight: cord was needed to be clamped and cut before delivery of the neonate, Nuchal cord loose: cord could be easily be uncoiled before delivery of the neonate, LBW: Low Birth Weight, CS: Cesarean Section, PIH: Pregnancy Induced Hypertension.

rates of 5' Apgar score <7 compared to studies of European and North American origin. This effect was also evident after comparing studies of Asian to those of North American origin. Adequate power was observed in all investigated outcomes of our primary analysis after evaluating the results of the TSA analysis.

The impact of tight loops on 1' Apgar score <7 rates was not significant (RR 2.39, 95 % CI 0.63, 9.04). The same was noted for

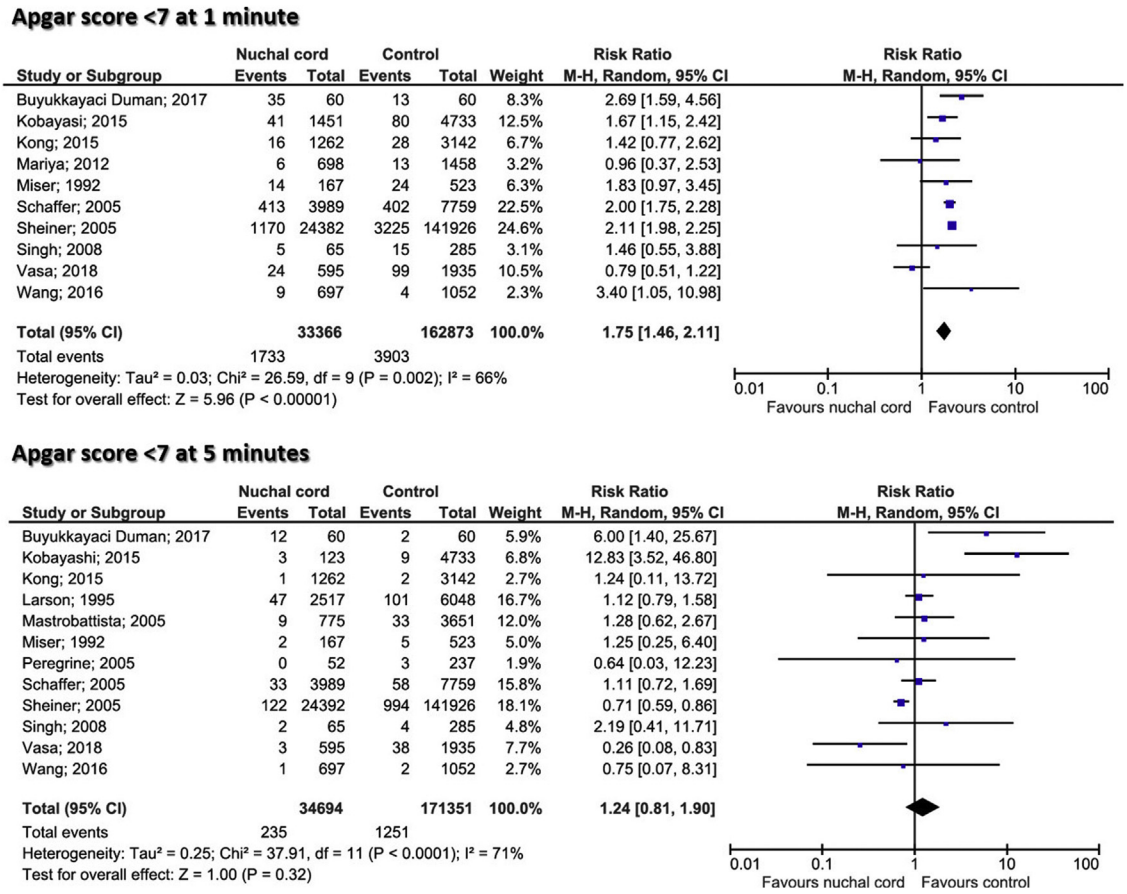

Fig. 2. Apgar score <7 at the first and fifth minute of life. Vertical line = "no difference" point between the two regimens. Squares = mean risk ratio; Diamonds = pooled risk ratio for all studies. Horizontal lines = 95 % CI.

5' Apgar score <7 rates (RR 1.60, 95 % CI 1.53, 1.68). Fetal distress was, however, more evident in tight loops (RR 1.60, 95 % CI 1.53, 1.68).

First minute Apgar score <7 rates were higher in pregnancies complicated by multiple loops (RR 3.09, 95 % CI 2.50, 3.83). However, differences were not significant in the 5th minute of life (RR 1.32, 95 % 0.75, 2.32). Fetal distress and fetal pH values <7.1 were however significantly increased in neonates with multiple loops (RR 1.83, 95 % CI 1.34, 2.49 and RR 3.82, 95 % CI 2.90, 5.03 respectively).

Prediction intervals designated that future studies were likely to report increased risk of low Apgar score at the first minute of life, increased risk of fetal distress as well as of observing a fetal pH < 7.1 (Table 3).

Discussion

Main findings

The findings of our meta-analysis show that umbilical cord entanglement is associated significantly with adverse perinatal outcomes as it seems to increase the rates of fetal distress as well as rates of neonatal pH < 7.1.The secondary analysis included leave-one-out analysis, meta-regression analysis and trial sequential analysis and supported the finding of our primary analysis as their impact on the results of primary outcomes was not significant. Nevertheless, Asian studies tended to overestimate the impact of umbilical cord entanglement on low Apgar score rates.

Comparison with existing literature

The impact of cord abnormalities on adverse neonatal outcomes has been already designated in previous studies. Specifically, in our previous meta-analysis we have shown that abnormal umbilical cord coiling (either hyper- or hypo-coiling) is associated with a significant increase in neonatal pathology [6]. Similar to cord entanglement, conflicting data were also observed in this latter study among studies investigating cord hyper- or hypocoiling and its impact on neonatal outcomes. However, the quantitative meta-synthesis of their findings also supported its significant impact on perinatal outcome.

The long-term effects of cord entanglement on neonatal outcomes remain, however, to date unclear, as there is no specific evidence concerning the need for admission in a neonatal intensive care unit or long-term outcomes concerning potential neurodevelopmental disabilities among these children. Neonatal mortality rates were not reported among studies included in the present meta-analysis, as their majority was particularly underpowered to estimate this index; hence, a direct comparison with the findings of Linde et al is not possible [4].

Strengths and weaknesses of our study

To our knowledge, the present meta-analysis investigated for the first time in the literature the correlation of umbilical cord entanglement to adverse neonatal outcomes. It relies in a meticulous review of the literature and collected outcomes from a large number of studies. Nevertheless, its findings are partially limited by the inadequate power of several studies that were

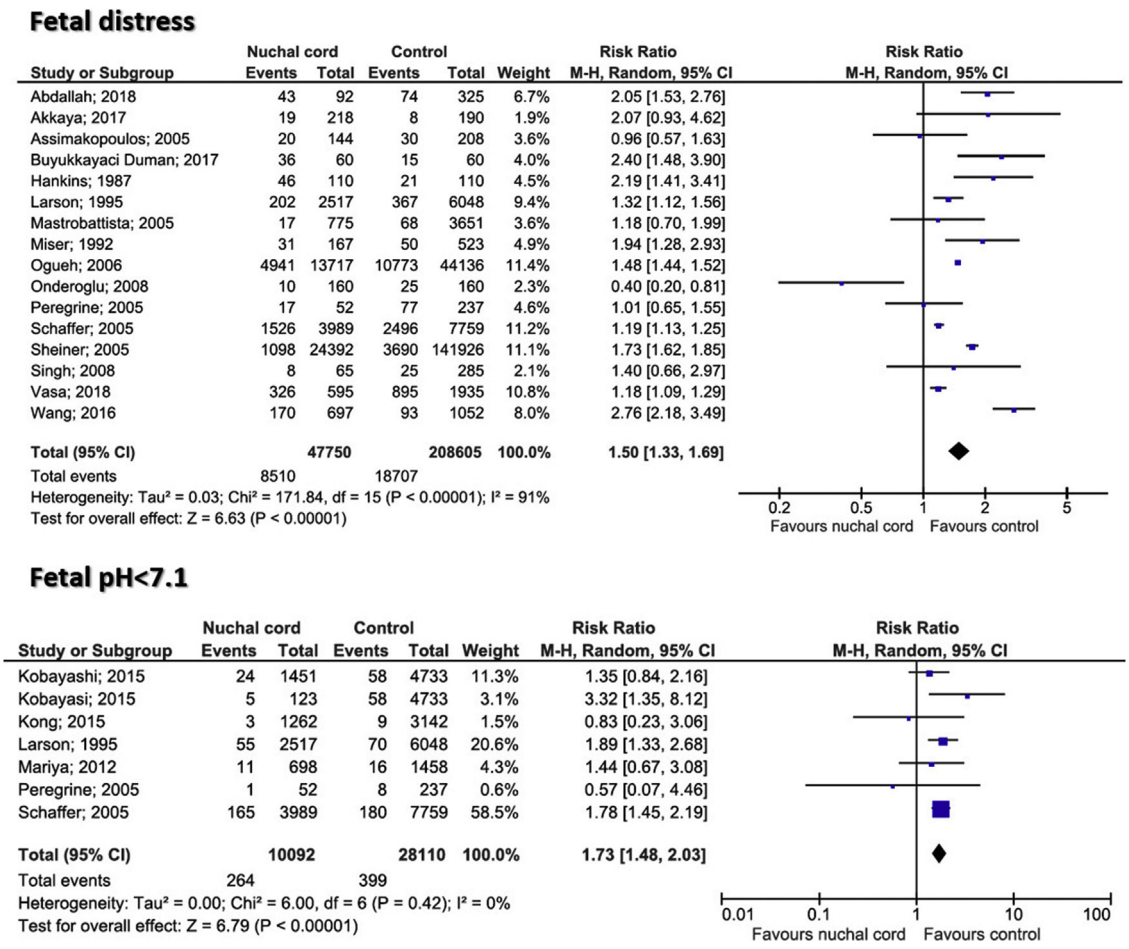

Fig. 3. Risk of encountering intrapartum fetal distress and fetal pH < 7.1. Vertical line = "no difference" point between the two regimens. Squares = mean risk ratio; Diamonds = pooled risk ratio for all studies. Horizontal lines = 95 % CI.

Table 3
Estimation of prediction intervals. k: number of studies; I^2: inconsistency index; SD_{PI}: standard deviation of the prediction interval.

Outcome	Apgar score <7 at 1 min *(k = 10)*	Apgar score <7 at 5 min *(k = 12)*	Fetal distress *(k = 16)*	Fetal pH < 7.1 *(k = 7)*
Risk ratio	1.75	1.24	1.50	1.73
95 % Confidence Interval	[1.46, 2.11]	[0.81, 1.90]	[1.33, 1.69]	[1.48, 2.03]
I^2	66 %	71 %	91 %	0 %
τ^2	0.03	0.25	0.03	0
SD_{PI}	0.197	0.545	0.184	0.081
95 % Prediction Interval	**[1.12, 2.73]**	**[0.37, 4.11]**	**[1.02, 2.22]**	**[1.42, 2.11]**

included as well due to differences in terms of selected population (single vs multiple loops, tight vs loos entanglements, nuchal entanglements vs other involved parts). The heterogeneity concerning the definition of intrapartum fetal distress, also limits the clinical importance of this finding, although the various definitions that were used to define it may serve as a precursor for the conduct of future research in this field. Finally, given the fact that inclusion/exclusion criteria were rather vague in certain studies (Table 2) we can only speculate that the majority of data referred to singleton term vertex uncomplicated pregnancies. Therefore, it is unknown whether potential confounders could contribute to the results of the analysis which was based on crude estimates. Given the fact that the analysis was based on aggregated data further investigation was not possible. This is why it would be of use to evaluate in the future the impact of nuchal cords in uncomplicated and complicated pregnancies as well as in preterm births.

Conclusions and implications for future research

The findings of this systematic review suggest that there is sufficient evidence to support the involvement of cord entanglement to adverse neonatal perinatal outcomes and are in agreement to those of the study conducted by Linde et al. However, standardization of outcome reporting and outcome reporting measures is required to draw definitive conclusions concerning the need for routine screening during the antenatal period (and particularly during the third trimester of pregnancy). Nevertheless, it is our belief that physicians should screen antenatally women during the third trimester of pregnancy and keep in mind the presence of UCE intrapartum during the assessment of fetal neonatal status.

The additive negative prognostic value of cord entanglement in specific populations, such as pregnancies complicated by fetal growth restriction, gestational diabetes mellitus etc should be also evaluated as well as the characteristics of cord entanglement (one

vs multiple loops, nuchal cords vs multiple parts and particularly tight loops). To accomplish this, we included in the present review a minimum set of proposed outcomes which, pathophysiologically, seem relevant to cord entanglement. The rationale behind the use of commonly reported outcomes relies in the future usage of findings of forthcoming articles in this field in synthetic studies which will help provide robust evidence to guide clinical practice.

Contribution to authorship

VP and MF performed the literature search, tabulated data and wrote the manuscript, IB conducted the statistical analysis and the quality assessment. DL and GD conceived the idea and wrote the manuscript. DL and AT tabulated the data and wrote the manuscript. GD contributed to the quality assessment and critically revised the manuscript.

Ethics approval

Not needed.

Funding

None received.

Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.10.038.

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