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The association of assisted reproductive technology with fetal malpresentation: a systematic review and meta-analysis

Konstantinos Stavridis^a , Maria Pisimisi^b , Olga Triantafyllidou^a, Theodoros Kalampokas^a , Nikolaos Vlahos^a and Stavroula L. Kastora^c 

^a2nd Department of Obstetrics and Gynecology, "Areteieion" University Hospital, Athens, Greece; ^bSchool of Medicine, National and Kapodistrian University of Athens, Athens, Greece; ^cEGA Institute for Women's Health, University College London, London, UK

ABSTRACT

Background: Since its introduction, assisted reproductive technology (ART) has developed into a common clinical practice around the world; yet it still raises a lot of questions. Throughout time, many researchers have investigated its association with several obstetric incidences and its consequences on perinatal outcomes. The aim of the current meta-analysis was to estimate the correlation between ART procedures and malpresentation of the fetus in singleton pregnancies.

Methods: The study was conducted according to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines and prospectively registered under the PROSPERO database (CRD42023458084). Five databases (Embase, MEDLINE[®], APA PsycInfo, Global Health, Health Management Information Consortium (HMIC)) and two additional sources were searched from inception to 31 May 2023. Quality of the included studies was assessed using the ROBINS-1 scale, whilst quality of evidence by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Summative and subgroup data as well as heterogeneity were generated by the Cochrane platform RevMan Web.

Results: Overall, 11 studies were included in the study with a total of 3,360,134 deliveries. Results indicate a higher risk of malpresentation at delivery in fetuses conceived through ART than those conceived naturally (RR: 1.50, (95% confidence interval (CI):1.30, 1.73)). This risk decreased when adjustments for potential confounders were applied (RR = 1.12, 95% CI 1.02, 1.23).

Conclusions: Based on observational studies, this meta-analysis indicated that singleton pregnancies conceived through ART are associated with higher risk of malpresentation than those conceived naturally, albeit the difference was lower when potential confounders were examined. Thus, future large studies are required to better understand possible reversible and irreversible factors of this relationship.

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KEYWORDS

ART; IVF; malpresentation; meta-analysis; systematic review

Introduction

Fetal malpresentation, including breech, transverse/oblique, and compound position, refers to a fetus with a fetal part apart from the head engaging the maternal pelvis. Breech presentation, the most common malposition, constitutes a rather challenging obstetrical condition, accounting for 3–4% of term deliveries [1]. Its etiology is not yet clarified; however, several factors have been identified as predisposing; preterm labor, placental location, advanced maternal age, previous breech presentation, congenital uterine malformation, and nulliparity seem to increase the risk of

malpresentation [2–6]. Breech presentation is strongly implicated in adverse perinatal outcomes [7,8]. However, breech presentation may not be an independent risk factor for adverse neonatal outcomes [9,10]. The optimal way of treating a breech delivery remains a controversial topic of discussion among obstetricians. Cesarean section is typically considered a safe way of delivery in these cases; nonetheless, it is linked to an increase in maternal morbidity and mortality [11–13].

Increasing demand has led assisted reproductive technology (ART) to gain ground in modern societies. Since the first successful pregnancy after IVF treatment in 1978, over 10 million infants have been born using

CONTACT Konstantinos Stavridis  stavridis.kost@gmail.com  2nd Department of Obstetrics and Gynecology, "Areteieion" University Hospital, Leof. Vasilisis Sofias 76, Athens GR 11528, Greece

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ART procedures [14]. However, emerging evidence suggests that despite its popularity, ART may be associated with multiple adverse obstetric and perinatal outcomes, such as low birth weight, preterm birth, small for gestational age fetuses, stillbirth, and perinatal mortality, when compared to spontaneously conceived pregnancies [15,16].

Studies comparing the incidence of breech delivery in singleton pregnancies following ART and natural conception (NC) have led to inconsistent results [7, 16–18]. Since the presentation of the fetus is a crucial factor affecting the choice of delivery, and hence, predisposing several possible obstetric complications, it is essential that this subject is studied more thoroughly.

The aim of the present meta-analysis is to report the incidence of fetal malpresentation following ART procedures, compared to spontaneously conceived pregnancies.

Materials and methods

Search strategy

A systematic review was conducted according to the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) [19]. The study protocol was registered prospectively and accessed under the PROSPERO database (CRD42023458084). We performed an independent literature search for relevant studies from inception to 31 May 2023 across five databases: Embase (OVID), MEDLINE (OVID), APA PsycInfo (OVID), Global Health (OVID), and Health Management Information Consortium (HMIC) (OVID). Additional records were identified through registers, including Research Square and MedRxiv. The MedRxiv search was simplified according to database search functionality. The following search was applied in OVID: (malpresentation or malposition or impacted head or transverse or occiput posterior or oblique or breech).mp AND (*In vitro* fertilization or IVF or ART or assisted reproduction or IUI or ICSI).mp AND (Caesarian or CS or vaginal or SVD or spontaneous or delivery or birth).mp. Cross references were hand-searched.

Inclusion and exclusion criteria

Retrospective, prospective, and case-control studies reporting fetal malpresentation in which the pregnancy was conceived with assisted reproduction techniques (*in vitro* fertilization or intracytoplasmic sperm injection) compared to NC were included in the present meta-analysis. Case series, case reports, conference

abstracts, and posters were excluded. Studies reporting twin pregnancies and multiple gestations were excluded. Randomized controlled trials were sought however due to the ethically sensitive nature of the subject, as expected none were identified. No geographical restrictions were applied.

Data extraction

After removing duplicates, citations were screened by title and abstract, and then full texts were appraised to determine their eligibility by two investigators (K.S., S.K.). The full manuscripts of studies that were deemed to meet our inclusion criteria were obtained. Where the reviewer disagreed on study eligibility, this was resolved by discussion with a third investigator. Data from each article were extracted by one investigator (K.S.) and re-validated by another (S.K.). The following data were obtained from each study: first author's name, publication year, study type, country, sample size (post withdrawals), numbers of patients in the two comparator groups (ART and NC), maternal age (mean \pm SD), birthweight (mean \pm SD), number of malpresentations, and inclusion and exclusion criteria (Tables 1 and 2).

Outcome

The primary outcome was the incidence of malpresentation per participating conception mode, including breech presentation, and transverse and oblique lie.

Quality assessment

The risk of bias was assessed by two independent reviewers (K.S., S.K.), using the ROBINS-1 tool for assessing the risk of bias in non-randomized studies [27]. Risk-of-bias assessment figures were created via the web-app robvis (Risk-Of-Bias VISualization) [28]. Overall, grading the quality of evidence was assessed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [29].

Data analysis and meta-analysis

After the data extraction, a statistical analysis was performed. Study context and design were compared, and the studies considered suitably homogeneous were used for pooling. A meta-analysis was conducted by computing the risk ratio (RR) and random effects (REs) from the original data using Haensel–Mantel method with Review Manager Web (RevMan Web) [30].

Table 1. Demographics of included studies.

Study	Study type	Country	Time period of study	Maternal age ART (mean \pm SD)	Maternal age NC (mean \pm SD)	Inclusion criteria	Exclusion criteria
Chen et al. [16]	Retrospective cohort	Australia	2012–2018	35.0 \pm 4.8	29.7 \pm 5.7	Singleton pregnancies, ART or OI or spontaneous conceived	Multiple pregnancy
Slavov [20]	Ambidirectional cohort	Bulgaria	2013–2017	NA	NA	Singleton pregnancy, gestational age > 22 weeks and birthweight > 600g	Multiple pregnancy
Noli et al. [21]	Retrospective cohort	Italy	2010–2015	NA	NA	Singleton pregnancy	Multiple pregnancy, transverse or oblique presentation, SGA
Stern et al. [22]	Retrospective cohort	United States	2004–2010	34.5 \pm 4.5	27.0 \pm 5.9	Singleton pregnancy or fetal death >20 weeks, primiparous women	NA
Zsirai et al. [23]	Retrospective cohort	Hungary	1996–2011	NA	NA	Singleton pregnancy	Multiple pregnancy, transverse or oblique presentation, <37 gestational weeks
Stojnic et al. [24]	Case-control	Serbia	2006–2010	36.450 \pm 4.218	35.391 \pm 4.174	Singleton pregnancy, >26 weeks gestational age	NA
Romundstad et al. [7]	Retrospective cohort	Norway	1984–2006	NA	NA	Singleton pregnancies with length of gestation of 22 weeks or more and offspring birthweight of at least 500g	Age < 20 years and parity \geq 5 in the spontaneously conceived group
Isaksson et al. [25]	Case-control	Finland	1993–1999	NA	NA	Pregnancies ending in birth	Triplet pregnancies and pregnancies resulting in abortion were excluded from analysis
Reubinoff et al. [26]	Case-control	Israel	1983–1993	32.7 \pm 4.1	33.5 \pm 4.2	Only pregnancies leading to live births (>25 weeks gestation or >500g birthweight), ART sample: IVF was the only way to conceive)	NA
Tan et al. [17]	Case-control	England	1978–1987	NA	NA	Patients who delivered live-born or stillborn babies at >28 weeks (cases), sequential deliveries to primiparous women in 1988, 1989 (controls)	NA
Frydman et al. [18]	Case-control	France	1981–1984	32.5 \pm 3.5	28.6 \pm 4.2	Pregnancies occurring between April 1981 and July 1984	NA

ART: assisted reproductive technology; NC: natural conception; NA: not applicable; OI: ovulation induction.

Table 2. Study characteristics and outcomes.

Study	Sample size (deliveries/ post-dropouts)	ART, <i>n</i>	NC, <i>n</i>	Breech after ART	Breech from NC	Transverse or oblique from ART	Transverse or oblique from NC
Chen et al. [16]	264,550	10,694	253,856	710/10,694	12,390/253,856	37/10,694	1012/253,856
Slavov [20]	925	402	523	44/402	23/523	4/402	2/523
Noli et al. [21]	432,822	8531	424,291	566/8531	15,959/424,291	NA	NA
Stern et al. [22]	173,130	5768	167,362	793/5768	19,202/167,362	NA	NA
Zsirai et al. [23]	1,270,061	7838	1,262,223	456/7838	41,242/1,262,223	NA	NA
Stojnic et al. [24]	1268	634	634	80/634	56/634	NA	NA
Romundstad et al. [7]	1,209,151	8229	1,200,922	419/8229	40,386/1,200,922	NA	NA
Isaksson et al. [25]	2315	1970	345	77/1970	11/345	NA	NA
Reubinoff et al. [26]	520	260	260	23/260	17/260	NA	NA
Tan et al. [17]	1472	494	978	20/494	59/978	NA	NA
Frydman et al. [18]	3920	79	3841	11/79	166/3841	NA	NA

ART: assisted reproductive technology; NC: natural conception; NA: not applicable.

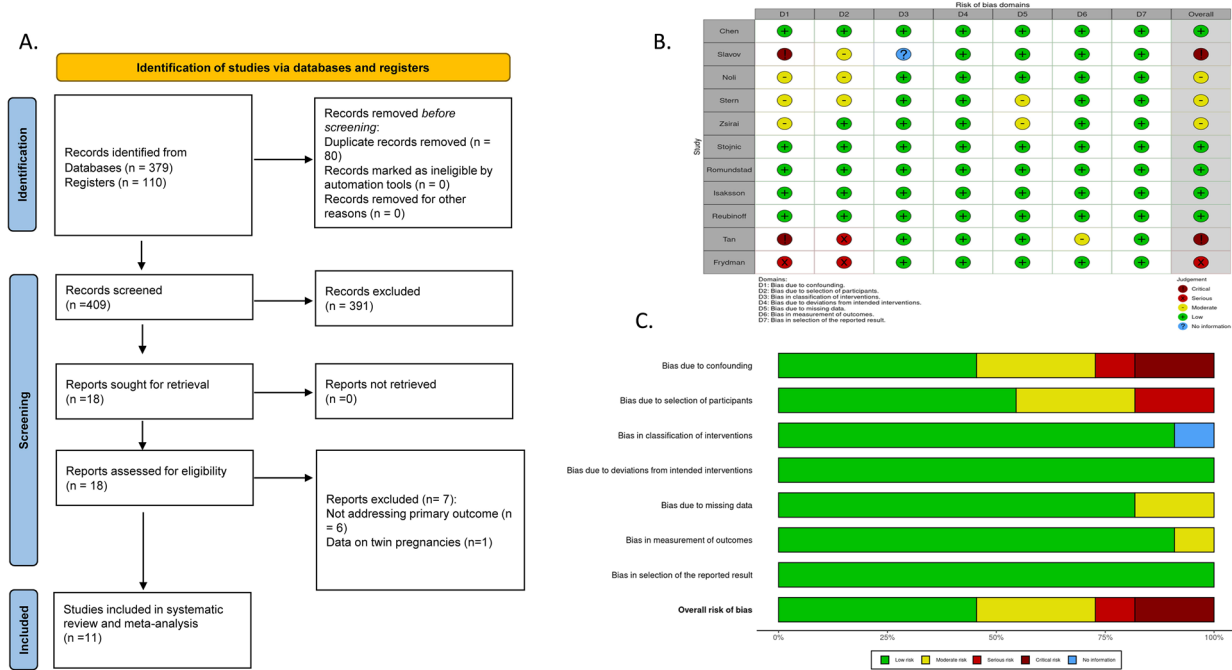


Figure 1. (A) Preferred reporting items for systematic reviews and meta-analyses flowchart, (B) ROBINS-1 per study, and (C) ROBINS-1 summary plot.

Statistical heterogeneity was quantified using I^2 statistics and Cochrane’s Q tests. Heterogeneity was further examined through clinically relevant subgroupings as follows: (a) subgroup according to study design, (b) subgroup according to study weight, and (c) subgroup according to risk of bias. Funnel plot was used to explore for publication bias.

Results

The initial search retrieved 489 results. After duplicates were removed, a total of 409 articles remained. We identified 18 studies eligible for full-text screening (Figure 1(A)). A total of 11 studies met eligibility

criteria, including five retrospective [7, 16, 21–23], one ambidirectional [20], and five case-controls [17,18, 24–26]. As no eligible RCT was identified, the ROBINS-1 tool for assessing the risk of bias was utilized. Five studies were considered of low risk of bias [7, 16, 24–26], three of moderate risk of bias [21–23], and three of serious or critical risk of bias [17,18, 20] (Figure 1(B,C)). Overall, the certainty of evidence based on the GRADE framework was deemed to be low (Figure 2).

Study characteristics


A total of 3,360,134 deliveries were included in the present meta-analysis. Of the included studies, one was

Author(s):

Question: [intervention] compared to [comparison] for [health problem and/or population]

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
Malpresentation												
11	observational studies	serious ^a	not serious	serious ^b	not serious	strong association all plausible residual confounding would reduce the demonstrated effect			RR 1.50 (1.30 to 1.73)	2 fewer per 1,000 (from 2 fewer to 1 fewer)	 Low	

CI: confidence interval; RR: risk ratio

Explanations

a. control for confounding factors not adequate from the majority of included studies

b. The research question of some included studies was not malpresentation, but this could be extracted indirectly

Figure 2. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.

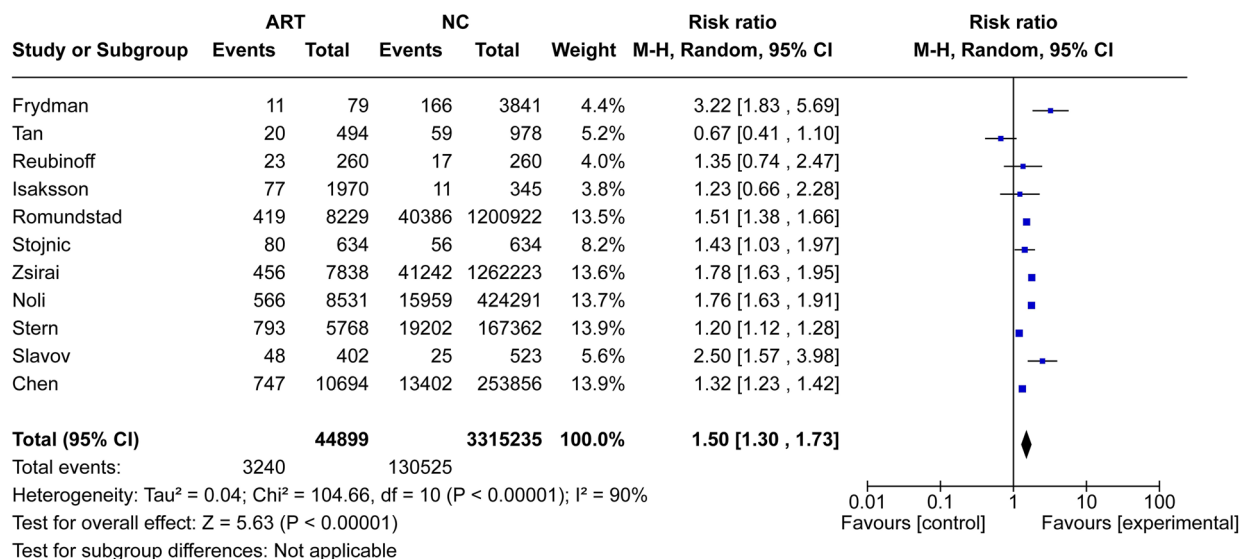


Figure 3. Maternal age (mean \pm SD) (A) birthweight (mean \pm SD) (B). Images generated with GraphPad Prism V. 9 (GraphPad Software, La Jolla, CA).

conducted in Australia [16], one in Bulgaria [20], one in Italy [21], one in the USA [22], one in Hungary [23], one in Serbia [24], one in Norway [7], one in Finland [25], one in Israel [26], one in England [17], and one in France [18]. Most of the studies under-reported the ethnicity of the participants. Of the total patient sample, 3,315,235 (98.7%) pregnancies were conceived naturally, whereas 44,899 (1.3%) were conceived through ART. There was no statistical difference between the mean maternal age and the mean birthweight of the two groups, $p = .1$ and $p = .35$, respectively (Figure 3).

Meta-analysis

Collectively, regarding total malpresentation events, RR was 1.50 (95% confidence interval (CI) 1.30, 1.73),

$I^2 = 90\%$ (Figure 4), suggesting that ART pregnancies are associated with 50% higher malpresentation risk than of those conceived naturally. To explore the notable heterogeneity, subgroup analyses, either by study design (cohort studies; RR = 1.38, 95% CI = 0.86, 2.20)/case-control studies; RR = 1.55, 95% CI = 1.33, 1.82) or by study weight (large studies; RR = 1.50, 95% CI = 1.27, 1.76/small studies; RR = 1.53, 95% CI = 0.99, 2.35) did not explain the high heterogeneity (Figures 5 and 6). However, when accounting only the low risk of bias studies in the meta-analysis, summative heterogeneity was successfully reduced to 15%, suggesting that subgrouping by risk of bias explained the differences between studies. As such, when introducing only the low risk of bias in the meta-analysis, RR was 1.43 (95% CI 1.32, 1.54), $I^2 = 15\%$ (Figure 7). To

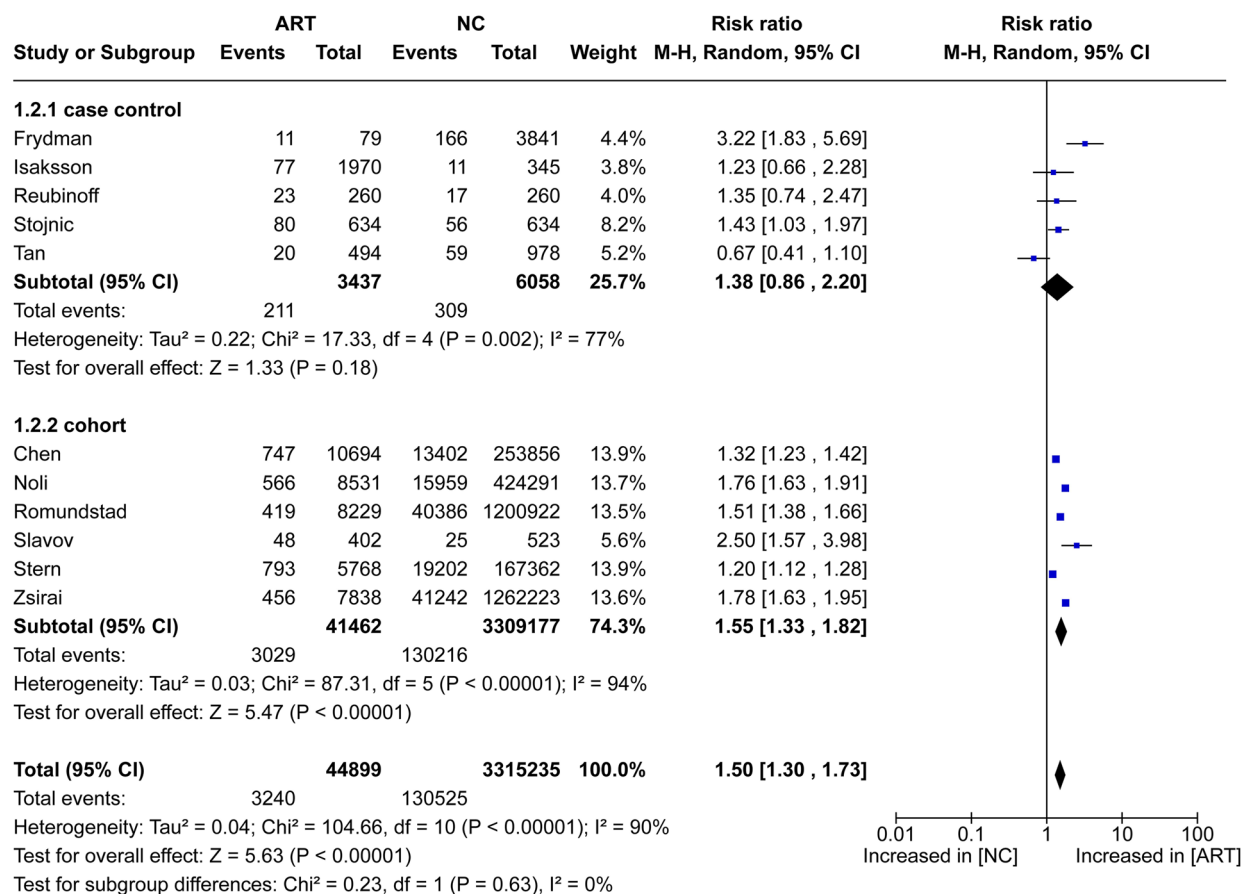


Figure 4. Forest plot regarding total malpresentation events.

account for confounders after adjusted RRs, a further analysis ($n = 4$ studies) highlighted that ART pregnancies are associated with 12% higher malpresentation risk than those achieved naturally ($RR = 1.12$, 95% CI 1.02, 1.23) (Figure 8). The confounders that the studies adjusted for, namely maternal age, parity, birthweight, gestational age, maternal education, smoking, etc., are partially dissimilar. Therefore, the results of the adjusted RR forest plot should be examined with caution.

Lastly, publication bias was considered to be low, based on the symmetric appearance of the funnel plot (Figure 9).

Discussion

In the present systematic review and meta-analysis, we aimed to explore the association of ART with fetal malpresentation compared to fetal malpresentation in spontaneously conceived pregnancies. The pooled estimated indicated that ART pregnancies may have 50% higher incidence of malpresentation than naturally conceived pregnancies, albeit the notably high heterogeneity.

A previous meta-analysis of observational studies regarding the same topic, concluded similar results with the present study ($RR = 1.58$; 95% CI: 1.17, 1.98) [31]. However, no analysis of available adjusted RRs was reported. As strong confounders can interfere in the association of the research question, we believe that an inclusion of adjusted RRs analysis is crucial.

The high heterogeneity between studies could be explained by the different characteristics of the included studies, the various confounding factors that have been taken into consideration in the analyses, and possibly the differentiation in ART techniques throughout time.

Several studies have suggested that the perinatal outcomes of ART pregnancies may be worse than those of naturally conceived pregnancies, primarily due to the increased maternal age and the resulting consequences in perinatal morbidity and mortality [32,33]. However, even in naturally conceived pregnancies with a fetal malposition, there is a higher incidence of low birth weight and prematurity [15, 34]. The reason why ART technology is associated with adverse perinatal outcomes is multifactorial and could be attributed to the IVF or ICSI technology, the

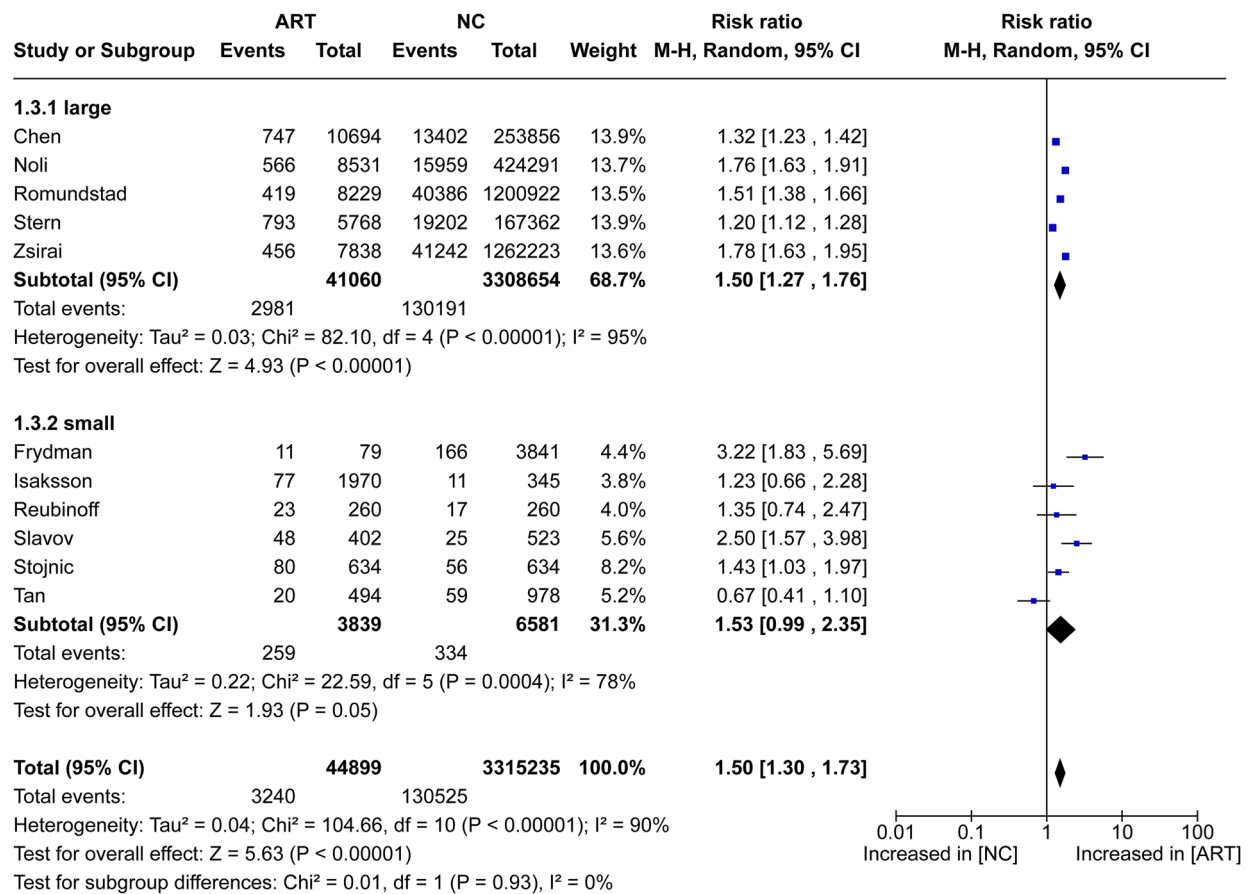


Figure 5. Forest plot subgroup by study type.

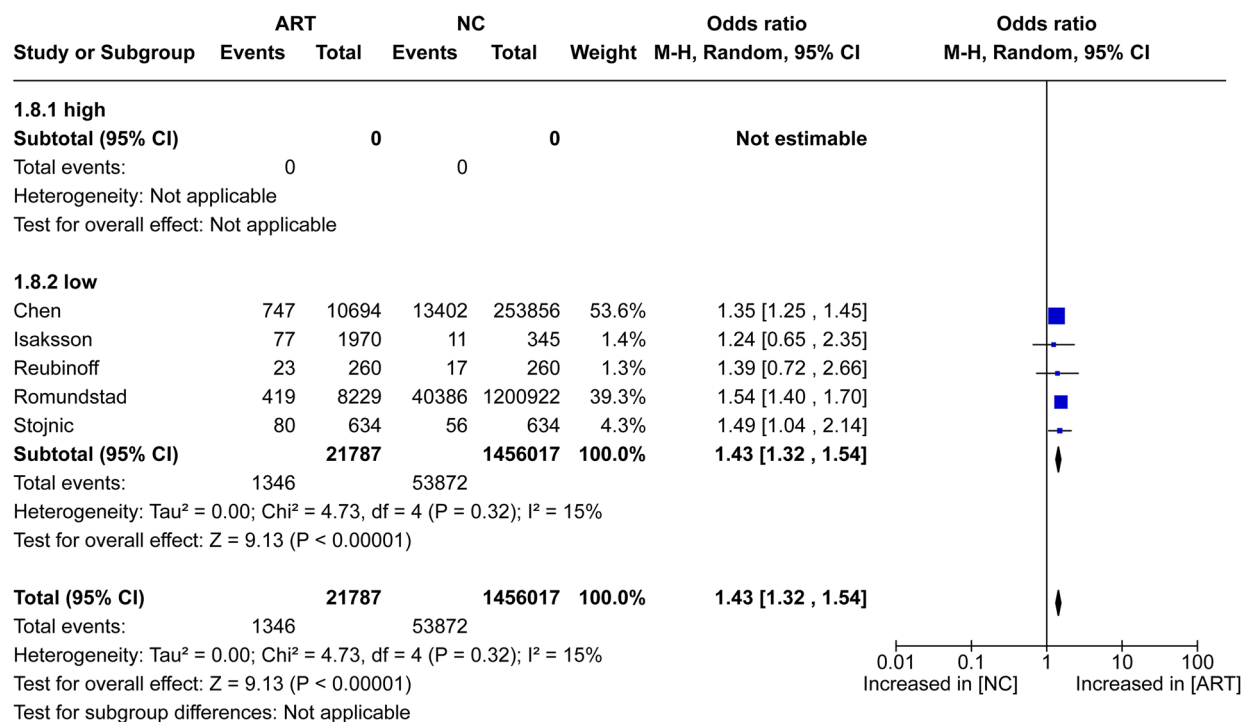


Figure 6. Forest plot subgroup by study weight.

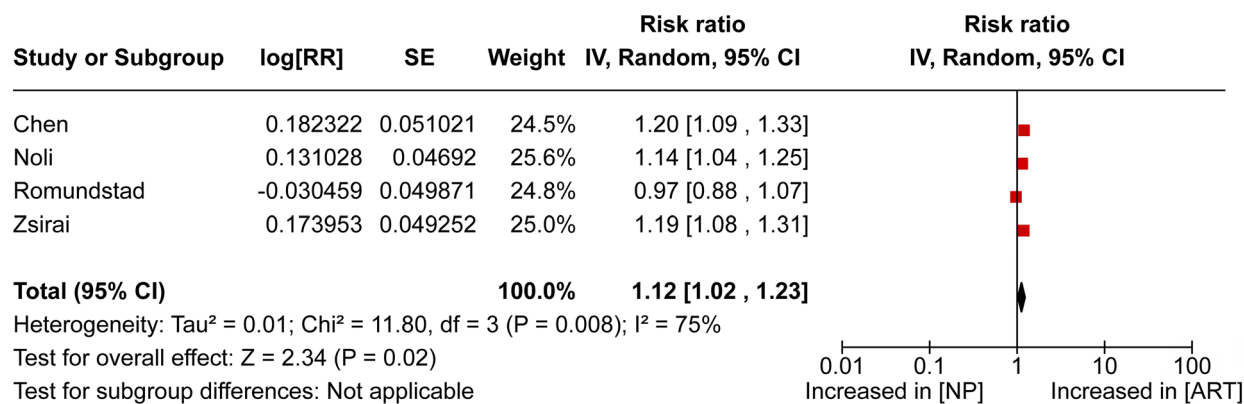


Figure 7. Forest plot subgroup by risk of bias.

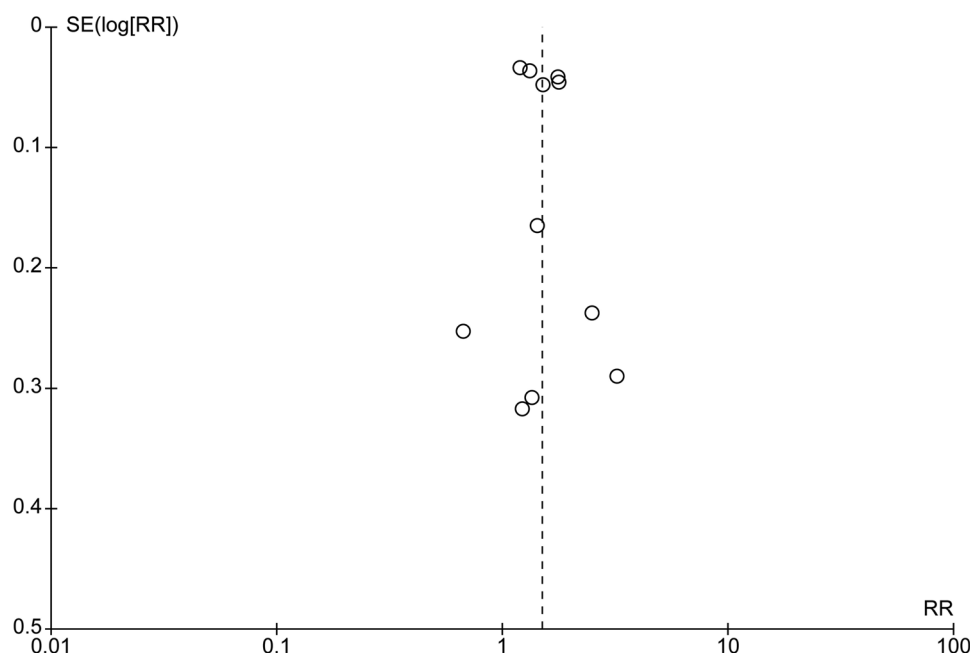


Figure 8. Forest plot of studies with adjusted RR.

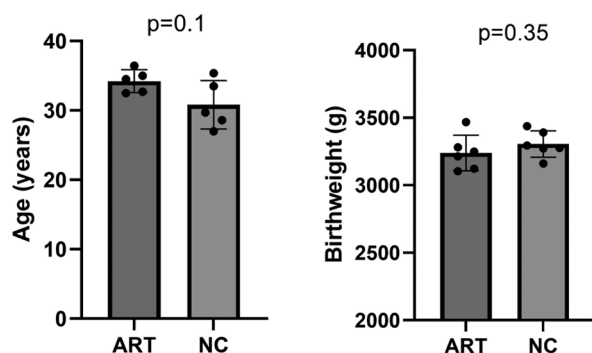


Figure 9. Funnel plot.

medications used, and the inherent patient characteristics [35]. Additionally, the choice of artificially thawed or fresh embryos for transfer may have different

implications regarding perinatal outcomes, as studies have shown that frozen embryo transfers may be associated with a higher risk of preterm birth compared to fresh embryo transfers [36,37]. Furthermore, the timing of embryo transfer and the quality of the embryos used can also impact perinatal outcomes in ART pregnancies [35].

Overall, breech presentation is linked to worse birth outcomes than cephalic presentation, regardless of how the pregnancy was conceived (naturally or with ART) [7,8]. The question of the present meta-analysis was whether ART technology could lead to worse perinatal outcomes by increasing the odds of breech presentation. Various studies have indicated a higher risk of breech presentation in ART pregnancies than naturally conceived pregnancies [18, 25,26, 38–40]. However, inter-ART approach comparison, IVF

vs. ICSI, in terms of perinatal outcomes, did not highlight a statistically significant difference between the two techniques [35]. Several confounding factors that may affect the propensity for increased breech presentation in ART conceived pregnancies have been recognized. The most significant ones are reported to be maternal age, birthweight, gestational age and parity [7, 16]. While the crude odds ratios (ORs) have been notably higher in many studies, the adjusted ORs failed to highlight a significant difference between naturally- and ART-conceived pregnancies. This has been further indicated in the adjusted RR pool estimate analysis, which indicated a 12% increase in malpresentation risk with ART pregnancies. However, it should be noted that confounding factors adjusted in the four studies [7, 16, 21, 23] are not identical, suggesting that interpretation of the results should be with caution. None of the included studies controlled for uterine malformations [7, 41] or familiar predispositions [42] to breech presentation, which could also interfere in the questioned association.

Our study has several limitations. First, our analysis included only observational studies, which are susceptible to confounding factors. Expectedly, due to the ethical implications, randomized trials were not recorded, increasing in turn selection and attrition bias. Additionally, a notably high heterogeneity between the studies was identified, which was largely attributable to inherent risk of bias. Confounding factors upon the risk of breech delivery and/or other malpresentations such as previous cesarean section, polyhydramnios, congenital fetal and uterine abnormalities and placentation disorders, as well as ART specific parameters (ovarian stimulation protocol employed, quality and characteristics of embryos transferred) have been significantly under-reported across studies, in turn potentially skewing analysis integrity.

Wider implications for clinical practice

Among the priority objectives of current obstetricians is the reductions of CS, since CSs are associated with worse maternal outcomes [11–13]. Regarding the management of breech deliveries, the findings from the Term Breech Trial (TBT) resulted in the adoption of CS for term breech pregnancies [43]. Following studies confirmed these results [44]. Consequently, to reduce the rate of CSs, the research community has focused on identifying risk factors related to breech presentation. This meta-analysis indicated that ART procedures are associated with an increased risk of malpresentation in general, albeit this association may be related to modifiable factors and underlying mechanisms that future studies should reveal.

Conclusions

Singleton pregnancies conceived through ART may be associated with a higher risk of fetal malpresentation at delivery than those pregnancies conceived naturally. Adjusted for potential confounding factors, analysis highlighted that the risk is considerably lower than what was reported from the crude numbers. Future larger studies, controlled for the aforementioned confounders, should identify reversible and irreversible factors of fetal malpresentation and to highlight a structured clinical approach toward a reduction of the resulting perinatal mortality and morbidity.

Author contributions

KS: conception of the idea, study design, screening, data extraction, data analysis, quality assessment, and writing. MP: study design, screening, data extraction, and quality assessment. OT: study design and writing. TK: study design and writing. NV: study design and writing. SLK: study design, data analysis and writing.

Disclosure statement

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ORCID

Konstantinos Stavridis  <http://orcid.org/0000-0001-6921-0573>
 Maria Pisimisi  <http://orcid.org/0000-0002-0913-5556>
 Theodoros Kalampokas  <http://orcid.org/0000-0003-1379-894X>
 Stavroula L. Kastora  <http://orcid.org/0000-0003-4470-5267>

Data availability statement

The data that support the findings of this study are openly available in figshare at <https://doi.org/10.6084/m9.figshare.24316978>.

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