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Amnioreduction safety in singleton pregnancies; systematic review and meta-analysis

https://doi.org/10.1515/jpm-2024-0605
Received December 17, 2024; accepted March 26, 2025;
published online April 22, 2025

Abstract

Objectives: Prenatal ultrasound identifies polyhydramnios in approximately 0.7 % of pregnancies. Polyhydramnios (defined as amniotic fluid index >24 cm) is associated with maternal symptoms and preterm delivery. However, amnioreduction (AR) can effectively alleviate symptoms and reduce preterm delivery risks; its advantages remain controversial. This study aims to assess maternal safety following AR in singleton pregnancies systematically.
Methods: Databases searched included PubMed, Embase, Scopus, and Web of Science until April 2024. Pregnant patients with singleton pregnancy and polyhydramnios undergo AR included in our study. Statistical analyses were conducted using R software.
Results: From 574 initially identified articles, seven studies with 390 singleton pregnancies who underwent AR were included. The primary outcomes showed low odds of placental abruption 0.04 (95 % CI: 0.02–0.09, I^2=12 %) and chorioamnionitis 0.03 (95 % CI: 0.01–0.08, I^2=0 %). Secondary outcomes indicated a mean gestational age at birth of almost 36 weeks (95 % CI: 35.51–36.41, I^2=49 %) and low odds of cesarean delivery 0.45 (95 % CI: 0.30–0.61, I2=58 %), preterm delivery within 48 h after AR 0.10 (95 % CI: 0.07–0.15, I^2=9 %) and PPROM within 48 h after AR 0.03 (95 % CI: 0.02–0.04, I^2=0 %).
Conclusions: This study demonstrates that maternal complications are expected to be low following the AR procedure. However, given the lack of evidence for fetal benefit and pregnancy prolongation, future studies should directly compare the effects of AR with expectant management. Additionally, fetal survival is likely influenced more by the underlying fetal diagnosis or the etiology of polyhydramnios rather than AR itself. The current meta-analyses will serve as a guide for shared decision-making, and highlight the need for continued clinical trials powered to establish superiority or benefit with AR for singleton pregnancies.

Keywords: amnioreduction; safety; meta-analysis; systematic review

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Introduction

Polyhydramnios, characterized by an abnormal increase in amniotic fluid, can be attributed to maternal or fetal causes [1]. Different methods exist to identify normal and abnormal amniotic fluid volume levels [2]. The classifications of mild, moderate, and severe polyhydramnios are based on amniotic fluid index (AFI) measurements: mild is 24.0–29.9 cm, moderate is 30.0–34.9 cm, and severe is ≥35 cm. Alternatively, these classifications can also be determined by the deepest vertical pocket (DVP) dimensions: mild is 8–11 cm, moderate is 12–15 cm, and severe is ≥16 cm. [3–5]. Prenatal ultrasound identifies polyhydramnios in approximately 0.7 % of pregnancies, with severe classification accounting for 12 % of cases [4]. Pregnancies with polyhydramnios are associated with an increased risk of maternal complications, including maternal distress, cord prolapse, placental abruption, and postpartum hemorrhage [6, 7].

One method that can alleviate polyhydramnios is amnioreduction (AR). Initially described in 1933, AR was

frequently used to manage twin-twin transfusion syndrome (TTTS) in monochorionic (MC) twin pregnancies and for alleviating polyhydramnios in singleton pregnancies [8–10]. There are different protocols for fluid removal amounts, removal speed, or the use of tocolytics and antibiotics. Typically, the procedure involves ultrasound-guided insertion of an 18-gauge needle, suctioning fluid, and aiming to normalize the AFI without exceeding 2.5 L at a time or 1,000 mL over 20 min [10, 11]. Amnioreduction primarily aims to lessen maternal discomfort associated with severe polyhydramnios, and in certain cases, to manage fetal complications arising from underlying anomalies, such as hydrops or sacrococcygeal teratoma [12]. While the procedure may carry peri-procedural risks, such as preterm birth [13], these events are often linked to the underlying etiology of the condition rather than the intervention itself. Overall, there is ongoing uncertainty regarding the advantages of AR in terms of extending the duration of pregnancy, reducing the preterm premature rupture of membranes (PPROM) rate, increasing the likelihood of vaginal delivery, and decreasing the occurrence of uterine atony [11, 14, 15].

In twin pregnancies, the prevalence of polyhydramnios is notably higher, primarily due to the complications of placentation [1]. To date, there is a paucity of published series on AR, with most of the available data coming from twin pregnancies complicated by TTTS, a condition with distinct pathophysiological characteristics [16–19]. Fewer published studies have discussed complications of AR with singleton pregnancies [11, 12, 15, 20, 21]. The objective of our study is to conduct a systematic review and quantitative analysis of studies on adverse events related to safety following AR in singleton pregnancies, parsed by maternal and fetal measures of efficacy and risk.

Materials and methods

The Preferred Reporting Items for Systematic Reviews (PRISMA) 2020 guidelines were used to conduct this study. A protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024548134).

Search strategy and study selection

A systematic search was conducted through databases (Pubmed, Embase, Scopus, and Web of Science) from inception until April 2024. Two authors performed the initial search and abstract screening process independently using Rayyan software (N.Z. and M.H.) and conflicts were resolved by a third author (A.S.). The full-text screening was also done by two authors independently (N.Z. and M.H.) and conflicts were resolved through discussion with a third author (A.S.). The search strategy included relevant keywords and Medical Subject Heading (MeSH) terms such as “Amnioreduction” and “Polyhydramnios”.

Inclusion and exclusion criteria

The PICO framework was used for the eligibility criteria composing the following.

(P) Population: singleton pregnancy with polyhydramnios,
(I) Intervention: Amnioreduction,
(C) Comparison: None,
(O) Outcome: Primary outcome included placenta abruption or chorioamnionitis occurrence after AR. We reported secondary outcomes including gestational age (GA) at delivery, cesarean delivery, preterm birth (<37 weeks of gestation), PPROM, PPROM within 48 h (H) of intervention, delivery within 48 h of intervention, birth weight, maternal sepsis, intrauterine uterine fetal death (IUFD), stillbirth, and neonatal death.

Included studies were observational studies (cohort, case-control, and case series with >5 cases) from inception until April 2024. Studies lacking a control group, but having a full report of the population of the AR group, were included. Excluded studies included systematic reviews, case reports, conference abstracts, non-French/English papers, and editorials. Studies that did not report mentioned outcomes or did not provide separate data for the amnioreduction group were also excluded.

Data extraction and outcomes

Two authors performed the data extraction independently (N.Z. and M.H.) using data extract sheets and a third author resolved conflicts (A.S.).

A standardized data extraction sheet was created which contained the following study characteristics:

(1) Study demographic: first author name, year of publication, country, institution, study period range, and sample size.
(2) Maternal demographic information: age, nulliparity, and BMI
(3) Data related to intervention: total number of AR, number of AR per patient, GA at first AR, and volume removed per AR (ml)
(4) Obstetric outcomes: mean GA at delivery, mode of delivery, preterm delivery (defined as delivery <37 weeks of gestation), delivery within 48 h after AR, PPROM, PPROM within 48 h after AR, placental abruption, maternal sepsis, and chorioamnionitis

(5) Fetal outcomes: birth weight, IUFD, stillbirth, and neonatal death

For studies with overlapping patient populations, such as those done at the same institutions and/or during the same period, the studies with a larger population reporting relevant outcomes were included.

Assessment of risk of bias

The Newcastle-Ottawa scale (NOS) for cohort studies was used to assess the risk of bias for the cohort studies.

Data synthesis and statistical methods

Programming language software R (version 4.0.5) was used to perform the meta-analysis [22] All statistical analyzes were done with "meta", "PerformanceAnalytics", "metafor", and "forestplot", R packages. Continuous variables that were reported in the form of median (range) or median (interquartile range) were converted to mean ± standard deviation by Wan's formula [23].

For dichotomous variables, the "metaprop" R function was used to compute pooled proportion. The logit transformation was applied for the proportions before the meta-analysis. Due to the considerable between-study heterogeneity in the effect sizes, the random-effects model was applied. The variance correction with the Hartung-Knapp method was applied for the accurate confidence interval estimation (5). Between-study heterogeneity was assessed by chi-square test of heterogeneity and reported by heterogeneity variance (τ2) and I2 indices.

The meta-analysis of means was conducted with the "metamean" R function. The random-effects model with a restricted maximum-likelihood estimator (REML) was applied to estimate the between-study variance. The modified confidence interval for the summary effect was calculated by the Hartung-Knapp method.

Results

Study selection, study characteristics, risk of bias of included studies

The process of study selection is shown in Figure 1. Study characteristics are shown in Table 1. The results of the risk of bias assessment are reported in Supplementary Table 2.

Synthesis of results

Meta-analysis: amnioreduction characteristics, and outcomes

Between nine final included articles, two articles involved twin pregnancies in their populations and were subsequently excluded from the analysis [12, 27]. Finally, seven studies (8 populations) were included, reporting on 390 singleton pregnancies undergoing AR procedures across six countries, covering the years 2004–2023.

The pooled mean maternal age was 31.2 years (95 % CI: 30.34–32.00, I^2=23 %). The mean maternal BMI was 24 (95 % CI: 10.90–37.20, I^2=94 %). The proportion of nulliparous patients was 0.36 (95 % CI: 0.30–0.41, I^2=0 %). The mean AFI before amnioreduction was 38.3 cm (95 % CI: 37.34–39.18, I^2=0 %). The mean gestational age at the first AR was 31.8 weeks (95 % CI: 31.05–32.65, I^2=71 %). The mean number of AR procedures per patient was 1.82 (95 % CI: 1.10–2.54, I^2=86 %). The mean volume removed by each AR procedure was 1767.4 mL (95 % CI: 1,328.93–2205.83, I^2=94 %).

For our primary outcome, the pooled proportion of placenta abruption for 390 cases of AR was 0.04 (95 % CI: 0.02–0.09, prediction interval [0.01–0.18] I^2=12 %). The chorioamnionitis for 270 cases of AR was 0.03 (95 % CI: 0.01–0.08, prediction interval [0.00–0.19], I^2=0 %).

For other outcomes, the GA at birth for the 390 patients who underwent AR had a pooled mean of 35.96 weeks (95 % CI: 35.51–36.41, I^2=49 %). The proportion of cesarean delivery for 303 cases of AR was 0.45 (95 % CI: 0.30–0.61, I^2=58 %). The proportion of preterm delivery before 37 weeks of gestation occurring within 48 h after the AR procedure for 380 cases of AR was 0.10 (95 % CI: 0.07–0.15, I^2=9 %). The proportion of PPROM occurring within 48 h after the AR procedure for 380 cases of AR was 0.03 (95 % CI: 0.02–0.04, I^2=0 %). The proportion of preterm delivery before 37 weeks of gestation for 335 cases of AR was 0.42. The proportion of PPROM for 154 cases of AR was 0.14. The proportion of IUFD for 292 cases of AR was 0.09 (95 % CI: 0.01–0.51, I^2=80 %). The proportion of neonatal death for 148 cases of AR was 0.15 (95 % CI: 0.04–0.41, I^2=0 %). Our studies do not report any cases of maternal sepsis, maternal ICU, or maternal mortality admission.

More details on the secondary outcome results have been summarized in Table 2. Forest plots are in Supplementary Figure 1.

Discussion

Our meta-analysis and systematic review aimed to discuss the maternal safety of amnioreduction in singleton pregnancies diagnosed with polyhydramnios (Defined as

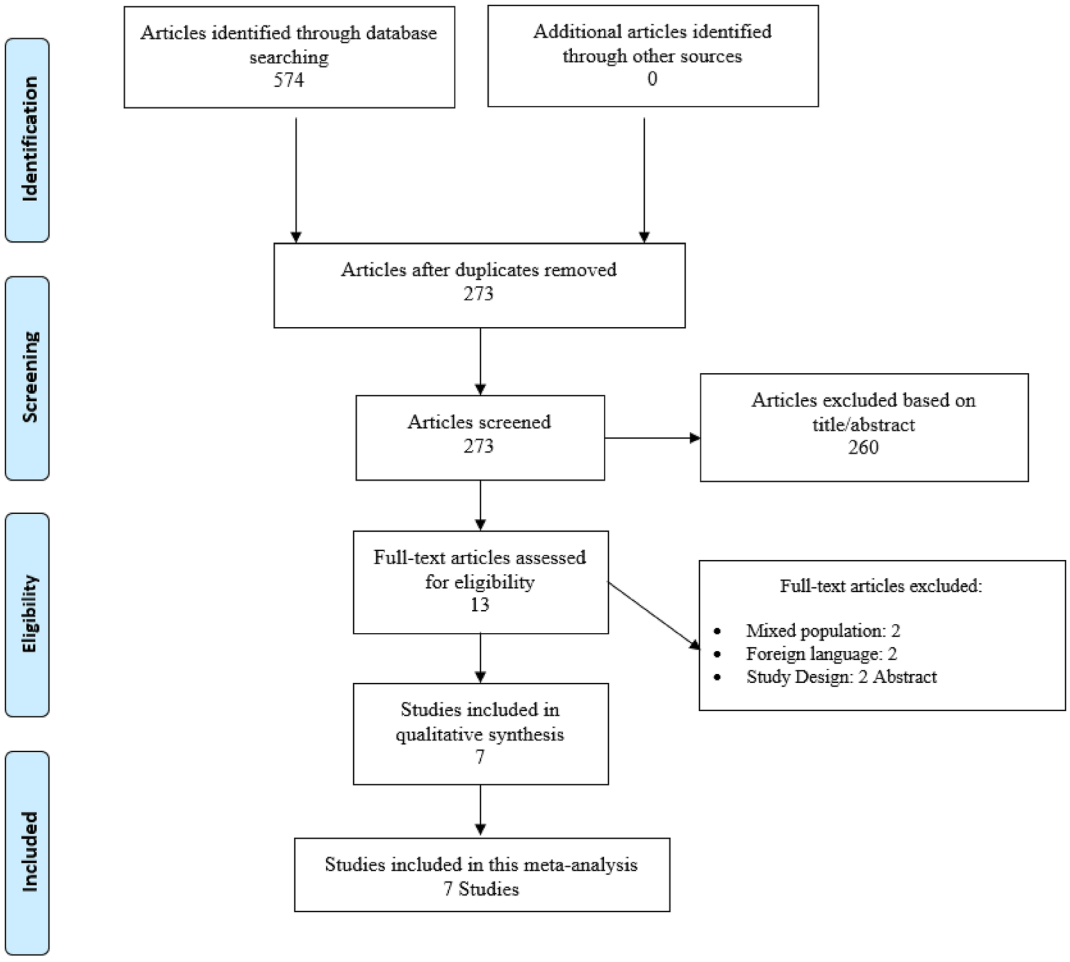

Figure 1: Flow diagram of the study selection process.

Table 1: Study characteristics.

Studies	Year	Country	Study period	Twin/singleton	Population, n
Piantelli et al. [24]	2004	Italy	2000–2003	Singleton	10
Dickinson et al. [11]	2014	Australia	2000–2012	Singleton	138
Kleine et al. [25]	2016	Brazil	2001–2014	Singleton	44
Ali et al. [26]	2018	India	2000–2012	Singleton	28
Erfani et al. [15]	2019	USA	2011–2018	Singleton	33
Katsura et al. [20]	2019	Japan	2017–2018	Singleton + symptomatic	18
Katsura et al. [20]	2019	Japan	2017–2018	Singleton + asymptomatic	9
Soni et al. [21]	2023	USA	2013–2021	Singleton	110
Leung et al.[a] [27]	2004	UK	1995–2002	Singleton/twin	37
Laoreti et al.[a] [12]	2024	Italy	2010–2023	65 singleton/21 twin	86

[a]Excluded studies due to pooled population of singleton and twin pregnancies.

AFI ≥24 cm or DVP ≥8 cm). Although fetal mortality and mode and timing of delivery are influenced by and reflect the underlying fetal anomalies causing the polyhydramnios, our results showed that maternal complications – including placental abruption, chorioamnionitis, PPROM, and delivery within 48 h – appear to be low, highlighting the relative safety of this procedure.

In addition to safety, procedures performed during pregnancy should have demonstrable benefit such that any residual risk can be justified. In considering the risk to

Table 2: Secondary outcomes.

Outcome	Number of cases	Pooled mean or odds ratio	95 % CI	Prediction interval	I^2
GA at birth, weeks	390	35.96	35.51–36.41	35.62–36.29	49 %
Cesarean delivery	303	0.45	0.30–0.61	0.19–0.75	58 %
Preterm delivery (<37 weeks)	335	0.42	0.22–0.65	0.07–0.88	83 %
PPROM	154	0.14	0.02–0.53	–	0 %
Preterm delivery (<37 weeks) within 48 h after amnioreduction	380	0.10	0.07–0.15	0.04–0.22	9 %
PPROM within 48 h after amnioreduction	380	0.03	0.02–0.04	0.01–0.06	0 %
IUFD	292	0.09	0.01–0.51	–	80 %
Neonatal death	148	0.15	0.04–0.41	–	0 %

benefit ratio, one must consider that pregnancies with polyhydramnios have a higher prevalence of structural and congenital fetal anomalies, associated with an inherently high incidence of perinatal death [4, 5, 28]. Consequently, patients with severe polyhydramnios are often referred to specialized centers for delivery due to the risk of undetected anomalies [1]. Our included studies report a list of prenatal malformations, as summarized in Supplementary Table 1.

It is important to note that based on recommendations from multiple scientific societies [1], AR is primarily indicated for the relief of severe maternal symptoms, and appears to be the preferred option in moderate to severe cases [29, 30]. Also, considering the high rate of cesarean deliveries in pregnancies complicated by polyhydramnios, it is noticeable that AR may offer potential for vaginal birth when a Cesarean might otherwise be performed [31, 32]. The high cesarean delivery rate in cases requiring amnioreduction reflects contributions from both the amnioreduction procedure and the presence of underlying fetal anomalies, making it challenging to isolate the specific impact of each factor.

The sole previous meta-analysis examining the complications of AR in singleton pregnancies incorporated merely four small case series. However, in contrast to our study, the authors failed to reliably quantify risk due to a low confidence in the complication rate, reflecting a limited number of cases and wide heterogeneity [33]. A 5-year retrospective study from Israel reported that the isolated polyhydramnios at birth correlated with prolonged labor, placental abruption, and fetal heart rate abnormalities [34]. Several studies have indicated a heightened incidence of postpartum hemorrhage (PPH) in patients with polyhydramnios [34, 35]. On the other hand, our study demonstrated a low occurrence of placental abruption and chorioamnionitis in the AR group. This data holds significance for patient counseling and should be integrated into the informed consent process. Additionally, for healthcare providers, this study contributes insights for evidence-based practices in the side effects due to the management of pregnancies complicated by polyhydramnios.

While bolstered by inclusion of a larger number of cases and thus improved over prior analyses, our study similarly suffers from a small overall population and lack of robust assessment for causes of polyhydramnios. As the fetal safety of AR is associated with the underlying fetal anomalies causing polyhydramnios, the evaluation of fetal safety of AR *per se* is not theoretically possible. For whatever reason, amnioreduction in singleton gestations has become remarkably rare at our institutions, necessitating future multicenter collaboration to generate robust data and inform best practices. It is the first systematic review in over a decade to thoroughly examine the AR procedure in singleton pregnancies. Despite this limitation, our confidence in demonstrating low parsed maternal risk in largest number is significant.

In conclusion, our study demonstrated that complications – such as placental abruption, chorioamnionitis, PPROM, and delivery within 48 h – are unlikely following the AR procedure. This study serves as an initial step in compiling the safety data on AR and highlighting it as a safe option for maternal symptom relief. The prolongation of pregnancy and fetal survival should be compared with expectant management, in future studies, including appropriately and adequately powered randomized trials.

Acknowledgments: We gratefully acknowledge the support and resources provided by Boston Children's Hospital in conducting this study.

Research ethics: Not applicable.

Informed consent: Consent was not required for this study as it used collected data from previously published studies. All data used were anonymized and submitted with relevant ethical regulations.

Author contributions: N.Z: Drafting the manuscript, Interpretation of data; M.H: Acquisition of data; M.A: Data analysis; A.J, E.K, S.S: Revise the manuscript; K.A: conception and design; A.S: conception and design, supervising. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Use of Large Language Models, AI and Machine Learning Tools: None declared.

Conflict of interest: The authors state no conflict of interest.

Research funding: None declared.

Data availability: The supporting data of this study are available from the corresponding author upon reasonable request.

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Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/jpm-2024-0605).