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Perinatal Outcomes of Pregnancies Conceived by Assisted Reproductive Technologies

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SUMMARY

Introduction Recent epidemiological studies showed significantly higher incidence of perinatal complications in newborns and women after the use of assisted reproductive technologies (ART). Multiple pregnancies are more frequent after the use of ART. Singleton pregnancies following ART are more prone to preterm birth, low and very low birth weight (LBW and VLBW), small for gestational age (SGA) and perinatal mortality.

Objective The aim of this study was to summarize the results of relevant articles and to evaluate whether the mode of conception is the determining factor for different pregnancy outcomes after assisted and natural conceptions.

Methods Eleven studies were included in this review. The following outcomes were observed: preterm and very preterm birth, SGA, LBW, VLBW, perinatal mortality, admission to neonatal intensive care unit (NICU), and Apgar score (As) ≤7 at fifth minute. Qualitative analysis and quantitative assessment were performed.

Results For singletons, odds ratios were 1.794 (95% confidence interval 1.660–1.939) for preterm birth, 1.649 (1.301–2.089) for LBW, 1.265 (1.048–1.527) for SGA. Admission to NICU, As≤7 at fifth minute and perinatal mortality showed significantly different frequency after assisted conception. Summary of results for twin gestations showed no significant difference between ART and spontaneous conception for preterm birth (32–36 weeks), very preterm birth (<32 weeks), LBW and VLBW.

Conclusion Analyzed studies showed that infants from ART have significantly worse perinatal outcome compared with natural conception. More observational studies should be conducted in order to establish the exact mechanism leading to more frequent perinatal morbidity and mortality after the use of ART.

Keywords: assisted reproductive techniques; fertilization in vitro; pregnancy outcome; newborn

INTRODUCTION

Approximately 9% of couples worldwide in some period of life confront the infertility problem [1]. In the USA nearly 12% of women in the reproductive period need some fertility treatment [2]. Since 1978, when the first baby conceived by in vitro fertilization (IVF) was born, over 4.3 million newborns have come to the world due to assisted reproductive technology (ART) [3]. First published articles about the safety of IVF were from Cohen et al. [4] and the American Society for reproductive medicine and the Society for Assisted Reproductive Technology [5]. Both investigations concluded that the risk for poor perinatal outcome after IVF was not increased. As the use of ART has become very frequent, it is essential to estimate success of pregnancy outcome. Ultimately, the aim of infertility treatment is the birth of a healthy child.

Increased prevalence of multifetal pregnancies is well-established risk factor for unsuccessful perinatal outcome in pregnancies conceived by artificial techniques [6, 7]. Human Fertilization and Embryology Authority in Great Britain approved transfer of at most two embryos in women younger than 40 years [8].

Frequency of preterm birth progressively increases every year and it currently varies from 7% to 13% of all deliveries [9].

OBJECTIVE

The aim of this study was to analyze collected results from the relevant studies investigating and comparing perinatal outcome after ART and natural conception. The authors tried to evaluate if the way of conception was the major reason for the differences in pregnancy outcome between these two groups.

METHODS

The search, evaluation of relevant articles, and their critical appraisal were performed by two independent investigators, blind to each other (the authors of the study, T.S. and O.K.V.). Literature search was performed in MEDLINE, using PubMed and Science Citation Index Expanded, Web of Science, Scopus, and The Cochrane Library database. The following combinations of keywords were used: "assisted reproductive technology" ("ART"), "in vitro fertilization" ("IVF"), "perinatal outcome," "pregnancy outcome," "singleton pregnancy," "twin pregnancy," "preterm delivery," "very preterm delivery," "small for gestational age" ("SGA"), "low birth weight" ("LBW"), "very low birth weight" ("VLBW"), "perinatal mortality," "perinatal morbidity," "stillbirth."

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Table 1. Characteristics of included studies examined perinatal outcome after ART and spontaneously conceived pregnancies

Name of study's author, year [reference number]	Period	Country	Number of cases	Number of controls	Type of ART	Type of study
Romundstad et al. 2008 [11]	1984–2006	Norway	7,474	1,127,739	1, 2	Cohort study
D'Angelo et al. 2011 [12]	2000–2003	USA	920	14,673	1, 2, 3, 4	Case-control study
Klemetti et al. 2002 [13] #1	1991–1993	Finland	1,015	190,697	1, 2, 3, 4	Case-control study
Klemetti et al. 2002 [13] #2	1998–1999	Finland	2,408	112,912	1, 2, 3, 4	Case-control study
Wisborg et al. 2010 [14]	1989–2006	Denmark	730	18,473	1, 2	Follow-up study
Koivurova et al. 2002 [15]	1990–1995	Finland	304	569	1, 2	Cohort study
Schieve et al. 2007 [16]	1997–1998	USA	3,316	157,066	1, 2, 3, 4	Case-control study
Fujii et al. 2010 [17]	2006	Japan	1,408	53,939	1, 2, 3, 4	Cross-sectional study
Kallen et al. 2005 [18]	1982–2001	Sweden	16,280	-	1, 2	Case-control study
Kallen et al. 2010 [19]	1982–2007	Sweden	1545	8,675	1, 2	Case-control study
Hansen et al. 2009 [20]	1993–2000	(West) Australia	700	4,097	1, 2, 3, 4	Cohort study
Boulet et al. 2008 [21]	1997–2000	USA	1,446	2,729	1, 2, 3, 4	Case-control study

ART – assisted reproductive technology; 1 – in vitro fertilization (IVF); 2 – intra-cytoplasmic sperm injection (ICSI); 3 – gamete intrafallopian transfer (GIFT); 4 – zygote intrafallopian transfer (ZIFT)

Table 2. Preterm birth in singleton pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Romundstad et al. [11]	1.690	1.547–1.846	39.72
D'Angelo et al. [12]	1.910	1.306–2.792	3.95
Klemetti et al. [13] #1	2.240	1.772–2.832	9.60
Klemetti et al. [13] #2	1.790	1.519–2.109	17.52
Wisborg et al. [14]	1.530	1.149–2.038	6.69
Koivurova et al. [15]	1.500	0.702–3.207	1.02
Schieve el al. [16]	1.903	1.648–2.196	21.49
Total	1.794	1.660–1.938	100.00

Heterogeneity: Tau^2=0.002; Q=7.235; df=6; p=0.3; I^2=17.068%. Overall effect: Z=14.811; p<0.00001

OR – odds ratio; CI – confidence interval

According to the type of analysis, we included the following observational studies: cohort, case-control and cross-sectional studies. They compared perinatal outcome after ART and spontaneous pregnancy adjusted for maternal age at least. We included articles in English and those found *in extenso*. Limitation referring to date of publication was not considered by the investigators. Only information available directly from the studies was used, without any further communication with authors. Studies taken into consideration were those with measured odds ratio (OR) and 95% confidence interval (CI), demonstrating the difference between control and study group, or those with enough information for calculating these parameters.

Exclusion criteria were as follows: reviews, editorials, case reports, letters to the editor, duplicate publications, animal studies and researches published only as abstracts. Studies which involved spontaneous pregnancies in previously infertile women, intrauterine insemination, pregnancies underwent multifetal and selective embryo reduction and donor embryos were also excluded from further investigation. After careful selection, we found 11 studies which fulfilled all the aforementioned criteria.

Investigated outcomes were as follows: preterm birth (<37 weeks of gestation), early preterm birth (<32 weeks of gestation), SGA, LBW (<2,500 g), VLBW (<1,500 g), perinatal mortality, admission to neonatal intensive care unit (NICU), Apgar score (AS) ≤7 at fifth minute.

Collected data were qualitatively analyzed using measures of descriptive statistics. Quantitative statistical analysis was performed by calculating total OR with 95% CI for each perinatal outcome. ORs were calculated by taking a weighted average of individual study results using a general variance-based, random effects model, weighting individual study results by the inverse of their variance. The significant levels of independent findings were combined and used for estimating the Z-score for the overall series of findings. Statistical heterogeneity was assessed with the degree of heterogeneity, I-squared (I^2) value. An I^2 value represents the percentage of total variation across studies due to heterogeneity rather than chance. It was tested using the general variance-based method in which a p-value <0.10 was used to classify the study results as heterogeneous [10]. Statistical analyses were performed using Comprehensive Meta-Analysis Version 2.0 Program (Biostat Inc, Englewood, NJ).

RESULTS

Studies evaluated by this analysis with their characteristics are shown in Table 1. Seven studies investigated perinatal outcomes in singleton pregnancies and four studies examined outcomes in twin pregnancies after ART and spontaneous conception.

Preterm birth was investigated in six studies included in this trial. Prevalence was 7.8–16.1% and 4.5–8.0% in ART and natu-rally-conceived groups, respectively, with total OR (95%CI) 1.794 (1.660–1.939) (Table 2). This result showed statistically significant increase of preterm birth after assisted conception. In twin pregnancies delivery between 32 and 36 weeks of gestation occurred in 42.7–55.4% of ART and 33.3–51.6% of spontaneous pregnancies (1.206, 0.928–1.567) (Table 3). Early preterm birth in our groups had a frequency of 10.6–16.3% and 5.9–12.4% (1.238, 0.737–2.077) (Table 4). Synthesis of four studies included in previous results referring to twin pregnancies did not show any statistical significance between investigated groups.

Table 3. Preterm birth in twin pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Kallen et al. [19]	1.140	0.974–1.335	30.84
Hansen et al. [20]	1.700	1.307–2.212	25.72
Boulet et al. [21]	0.930	0.797–1.086	30.98
Koivurova et al. [15]	1.300	0.717–2.356	12.45
Total	1.206	0.928–1.567	100.00

Heterogeneity: Tau^2=0.051; Q=15.493; df=3; p=0.001; I^2=80.636%.
Overall effect: Z=1.4; p=0.162

Table 4. Early preterm birth in twin pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Kallen et al. [19]	1.520	1.176–1.964	34.08
Hansen et al. [20]	1.700	1.202–2.404	31.87
Boulet et al. [21]	0.750	0.580–0.970	34.06
Total	1.238	0.738–2.077	100.00

Heterogeneity: Tau^2=0.187; Q=19.946; df=2; p=0.000; I^2=89.973%.
Overall effect: Z=0.811; p=0.418

Table 5. Low birth weight in singleton pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Wisborg et al. [14]	1.440	0.780–2.659	8.58
Klemetti et al. [13] #1	2.410	1.855–3.131	16.25
Klemetti et al. [13] #2	1.700	1.386–2.085	17.63
Fujii et al. [17]	1.080	0.907–1.286	18.27
D'Angelo et al. [12]	2.019	1.555–2.621	16.27
Schieve el al. [16]	1.488	1.247–1.776	18.22
Koivurova et al. [15]	1.931	0.750–4.970	4.78
Total	1.649	1.301–2.089	100.00

Heterogeneity: Tau^2=0.072; Q=32.574; df=6; p=0.000; I^2=81.581%.
Overall effect: Z=4.143; p<0.00001

Table 6. Low birth weight in twin pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Kallen et al. [19]	1.160	0.956–1.408	28.05
Hansen et al. [20]	1.354	1.153–2.591	29.91
Boulet el al. [21]	0.890	0.766–1.034	30.49
Koivurova et al. [15]	1.172	0.675–2.037	11.56
Total	1.122	0.892–1.411	100.00

Heterogeneity: Tau^2=0.039; Q=14.361; df=3; p=0.002; I^2=79.111%.
Overall effect: Z=0.983; p=0.325

Table 7. Very low birth weight in twin pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Kallen et al. [19]	1.150	0.919–1.439	35.70
Hansen et al. [20]	1.400	0.990–1.980	29.67
Boulet el al. [21]	0.750	0.586–0.960	34.63
Total	1.051	0.741–1.492	100.00

Heterogeneity: Tau^2=0.076; Q=10.276; df=2; p=0.006; I^2=80.536%.
Overall effect: Z=0.28; p=0.779

Table 8. Small for gestational age in singleton pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Romundstad et al. [11]	1.260	1.101–1.442	46.22
Fujii et al. [17]	1.120	0.954–1.315	42.01
D'Angelo et al. [12]	1.980	1.210–3.240	11.77
Total	1.265	1.048–1.527	100.00

Heterogeneity: Tau^2=0.015; Q=5.015; df=2; p=0.081; I^2=60.118%.
Overall effect: Z=2.445; p=0.014

Table 9. Admission to neonatal intensive care unit in singleton pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Schieve et al. [16]	1.260	1.101–1.442	46.22
D'Angelo et al. [12]	1.150	0.501–2.637	19.11
Wisborg et al. [14]	1.100	0.840–1.440	38.27
Total	1.417	0.872–2.302	100.00

Heterogeneity: Tau^2=0.141; Q=16.558; df=2; p=0.000; I^2=87.921%.
Overall effect: Z=1.409; p=0.159

LBW in singleton pregnancies showed statistically significant increase in the ART group (1.9–20.6%) in comparison to natural conception (1.1–17.1%) with total OR 1.649 (1.301–2.089) (Table 5). Frequency of birth weight between 1,500 and 2,500 g and VLBW in newborns from twin pregnancies were not significantly different between the ART and the control group (LBW 12.8–61.4% and 10.4–57.7%) (1.122, 0.892–1.411) (Table 6) (VLBW 8.7–11.3% and 6.3–10.0%) (1.051, 0.741–1.492) (Table 7).

Three of the studies included in this trial investigated SGA prevalence in singleton pregnancies. Statistics showed significant difference between ART (3.0–13.0%) and spontaneous conception (2.0–11.8%) with OR 1.265 (1.048–1.527) (Table 8), which represents a greater risk for SGA presence in newborns after using some type of ART.

Admission to NICU was researched by three available clinical studies. The results demonstrated significantly increased admission to NICU after artificial conception in comparison to the control group (9.8–53.4% and 7.9–37.0%) (1.417, 0.872–2.302) (Table 9).

After generating results from the three relevant studies, we found significantly lower frequency of As≤7 at fifth minute in the ART group compared with spontaneous pregnancies (1.2–3.4% and 1.3–7.5%) with OR 0.783 (0.632–0.970) (Table 10).

Analysis of four studies which investigated frequency of perinatal death in singleton pregnancies revealed significantly increased risk for this parameter in ART pregnancies (0.8–1.7%) compared with control (0.6–1.1%). Total OR is 1.351 (1.143–1.597) (Table 11).

DISCUSSION

Our analysis showed significantly increased frequency of poor perinatal outcomes in singleton ART pregnancies, including preterm birth, LBW, SGA and perinatal mortality, compared with spontaneous conception. Previous meta-analysis referring to singleton pregnancies showed similar results [5, 22]. Existence of such data imposes the need to

Table 10. Apgar score ≤7 at fifth minute in singleton pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Koivurova et al. [15]	0.428	0.158–1.158	4.57
Schieve et al. [16]	0.947	0.601–1.492	21.02
Kallen et al. [18]	0.770	0.616–0.963	74.41
Total	0.783	0.632–0.970	100.00

Heterogeneity: Tau^2=0.003; Q=2.109; df=2; p=0.348; I^2=5.164%.
Overall effect: Z=-2.239; p=0.025

Table 11. Perinatal mortality in singleton pregnancies after ART compared with spontaneous conception

Name of study's author [reference number]	OR	95% CI	Study weight
Romundstad et al. [11]	1.310	1.045–1.642	48.87
Klemetti et al. [13] #1	2.410	1.380–4.209	17.77
Klemetti et al. [13] #2	1.270	0.594–2.717	10.74
Fujii et al. [17]	1.200	0.748–1.925	22.62
Total	1.426	1.090–1.867	100.00

Heterogeneity: Tau^2=0.025; Q=4.425; df=3; p=0.219; I^2=32.204%.
Overall effect: Z=2.584; p=0.010

clarify whether the techniques of ART alone or the underlying characteristics of mother or father are responsible for such outcome. Numerous researches showed a connection between male subfertility and pregnancy outcome without the use of any artificial technique [23]. Some investigations showed a higher probability for good perinatal outcome in a group of women with long-term infertility who succeeded to get pregnant spontaneously [24]. After comparing healthy women with subfertile women who get pregnant spontaneously, Wisborg et al. [14] found that newborns in the subfertile group did not have an increased risk for preterm birth. Authors suggested possible effect of IVF treatment on time of delivery.

Despite the fact that ART pregnancies are more carefully controlled, they are also more often followed by delivery induction and/or elective caesarean section [6, 15, 25]. These interventions could hardly be an explanation for the appearance of SGA, increased rate of perinatal mortality, early preterm birth and VLBW. It is still unclear what factors influence fetal growth potential during ART pregnancies and critical time frame for action. Recent investigation associated total fetal growth restriction in singleton pregnancies with the use of ART [25]. Nevertheless, it could be stated that routine antenatal supervision and identification of intrauterine growth restriction is insufficient in these pregnancies [26].

Schieve et al. [16] and Kallen et al. [18] compared spontaneous conception and artificial techniques divided into groups based on the following characteristics: fresh and frozen embryo, donor or own oocytes, classical IVF or intra-cytoplasmic sperm injection, embryos in the third or fifth day. Results showed a greater risk for preterm birth, preterm LBW and VLBW in every ART group. Authors proposed some segments of ART treatment mutual for all technique as the underlying cause. Ovarian hyperstimulation and human chorionic gonadotropin administration could lead to non-physiological estrogen, progesterone and relaxin levels, further causing adverse influence on endometrial and cervical tissue, placentation and even poor embryo–endometrial synchronization [27-32]. In vitro surrounding of an embryo could also have the effect on embryo characteristics and consequently change development of an embryo and fetus in vivo [33]. Some investigators explained increased relaxin level, maintained throughout pregnancy, as causative for the decrease in collagen synthesis. Such condition might threaten the structure and function of the cervix. Consequently, it shortens and becomes vulnerable and weak, increasing the chances for preterm birth [34].

Newborns from singleton pregnancies have more appropriate gestational age birth weights after transfer of one compared to two embryos [35, 36]. Two-embryo transfers could be followed by the phenomenon well known as "vanishing twin." One study showed that 10.4% of singleton ART pregnancies are the result of one embryo loss in cases where early ultrasound confirmed two implanted embryos [37]. Consequent singleton pregnancies have a higher risk for LBW and later neurological consequences in survived twin [38]. Although Schieve et al. [16] included only pregnancies with one heart beat registered in the first trimester ultrasound, result of the study once again showed a greater risk for poor perinatal outcome after the use of ART. Besides the comparison with the general population, Romundstad et al. [11] also compared newborns after natural and assisted conception from the same mother. Results did not show significant difference, suggesting that ART should not jeopardize perinatal outcome. Suggested explanations could be possible genetic basis for poor perinatal outcome.

Our research showed significantly increased admission to NICU after the use of ART, most frequently for prematurity and LBW. According to the literature, these two entities are associated with 75% of newborns admitted to NICU and are also recognized as the primary cause of perinatal morbidity and mortality [26, 39, 40].

Koivurova et al. [15] and Schieve et al. [16] showed no difference in frequency of AS≤7 in the fifth minute between artificial and spontaneous conception. On the other hand, Kallen et al. [18] after adjustment only for the date of birth got OR showing more frequent appearance of AS≤7 in the ART newborns group. After adjustment for age, parity, years of unsuccessful natural conception and smoking, Kallen et al. [18] showed a significantly decreased prevalence in favor of assisted conception. The results of the analysis of synthesis of these three studies also showed significantly low rate of AS≤7 at fifth minute in ART group. It should be mentioned that Kallen's study had the greatest influence (study weight was 74.41%). Accordingly, the potential effect of assisted conception on poor postnatal adaptation of newborn could be, at least partially, attributed to maternal characteristics, like advanced age and long-term problem of unsuccessful spontaneous conception.

Well-recognized complication of ART conception is a high percentage of multifetal pregnancies. Twin pregnancies are associated with increased risk for preterm birth, LBW, neonatal mortality, congenital malformations. Preterm birth occurs in 44% of all twins while singleton preg-

nancies have prevalence of 9% [41]. Compared to monofetal pregnancies, twins have six-fold higher mortality risk and 1:13 risk for perinatal morbidity [42].

Studies included in this analysis showed conflicting results regarding twins' perinatal outcomes. Hansen et al. [20] and Kallen et al. [18] showed significantly higher percentage of poor perinatal outcome, while Boulet et al. [22] suggested possible protective effect of artificial reproduction on pregnancy outcome. Data synthesis from these three studies found no difference between twins in the ART and natural conception group, when they compared for LBW, VLBW, birth between 32 and 36 weeks of gestation and early preterm birth (<32 weeks of gestation). These results are similar to results of other studies, which indicate greater influence of multifetal pregnancy on perinatal outcome than any ART effect alone [43]. Better pregnancy monitoring, prenatal and perinatal care in the ART group could be the reason for previously mentioned results. Also, ART twins are mainly dizygotic as the result of the two-embryo transfer, compared to spontaneous twins that are monozygotic in large percentage [44]. Monozygotic twins, associated with higher risk for unfavorable perinatal outcome, have prevalence of 30% in spontaneous versus 5–7% in assisted conception [41]. Some researchers specifically have studied only dizygotic twins in assisted and natural conception. Again, results were controversial. Hansen et al. [20] showed elevated risk in the ART group, while Pinborg et al. [45] and Boulet et al. [21] did not find any adverse effect of mode of conception on perinatal outcome. Ombelet et al. [46] after comparison of all twins did not find the difference, but when comparing only dizygotic ones they found a higher risk for preterm birth, LBW, perinatal mortality and stillbirth. McDonald et al. [47] in their meta-analysis showed significantly greater prevalence of preterm birth, LBW and lower mean birth weight in the ART group after adjustment for maternal age. Date of conception is presumably more precise in ART compared to natural pregnancies and could influence definitive percentage of preterm delivery in both groups.

CONCLUSION

Evaluation of ART singleton pregnancies alone has revealed higher risk for preterm birth, LBW, SGA, perinatal mortality and admission to NICU compared with natural conception. Despite the measures employed to limit the possibility of multifetal pregnancies, twin pregnancies are still presented in substantial proportions in many countries. As they impose higher risk of adverse perinatal outcome, as well as higher financial costs, single embryo transfer should be considered whenever possible. Additionally, the exact mechanism leading to increased perinatal morbidity and mortality after the use of ART is still unclear.

This research is one of few articles that are referring to perinatal outcome after the use of ART. It gives information about potential risks in regard to procedure looking through synthesis of 11 observational studies' results. On the other hand, each of these studies had its own specific methodology and criteria. They may have influenced their final results and, in turn, had potential negative effect on our investigation and consequently conclusions about its side effects. Although our findings indicate potential risk of poor perinatal outcome, overall effect of ART reflects as increased percentage of birthrate worldwide. In order to get more precise answers about ART safety, more observational studies including subfertile women succeeded in natural conception as a control group are needed.

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Перинатални исходи трудноћа зачетих поступком вантелесног оплођења

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КРАТАК САДРЖАЈ

Увод Савремене епидемиолошке студије су показале значајно већу учесталост перинаталних компликација код новорођенчади и породиља након примене асистираних репродуктивних технологија (АРТ). Учесталост вишеплодних трудноћа је већа након АРТ у односу на спонтано зачеће. Показано је да је код једноплодних трудноћа насталих вантелесним оплођењем повећан ризик од појаве претерминског порођаја, мале и веома мале телесне масе детета на рођењу (*LBW* и *VLBW*), мале телесне масе за гестацију (*SGA*) и перинаталне смртности.

Циљ рада Циљ истраживања је био да се сумирају резултати релевантних студија и утврди да ли је начин концепције фактор који одређује разлике у исходу трудноћа након асистираног и спонтаног зачећа.

Методе рада У преглед је укључено 11 студија. Анализирани су следећи исходи: превремени и рани превремени порођај, *SGA*, *LBW*, *VLBW*, перинатална смртност, пријем у јединицу неонаталне интензивне неге (ЈНИН) и Апгар скор у петом минуту по рођењу ≤7. Урађене су квалитативна анализа и синтеза података, као и њихова квантитативна обрада.

Резултати Код једноплодних трудноћа однос шанси је био 1,794 (95-процентни интервал поверења: 1,660–1,939) за претерминski порођај, 1,649 (1,301–2,089) за *LBW*, а 1,265 (1,048–1,527) за *SGA*. Учесталост пријема у ЈНИН, Апгар скора у 5. минуту ≤7 и перинаталне смртности била је статистички значајна након примене АРТ. Код близаначких трудноћа појава претерминског порођаја (између 32. и 36. недеље гестације), раног претерминског порођаја (пре 32. недеље), *LBW* и *VLBW* у групи где је примењена АРТ није се статистички значајно разликовала у односу на спонтано зачеће.

Закључак Анализиране студије су показале да је код новорођенчади зачетој поступком АРТ повишен ризик од лошијег перинаталног исхода у односу на децу која су спонтано зачета. Потребно је обавити још опсервационих студија којима би се утврдио тачан механизам којим АРТ доводи до веће учесталости перинаталног морбидитета и морталитета.

Кључне речи: асистиране репродуктивне технологије; фертилизација *in vitro*; исход трудноће; новорођенче

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