Review

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Congenital Malformations in Infants of Mothers Undergoing Assisted Reproductive Technologies: A Systematic Review and Meta-analysis Study

Hayedeh Hoorsan[1], Parvin Mirmiran[2], Shahla Chaichian[3], Yousef Moradi[4], Roza Hoorsan[5], Fatemeh Jesmi[6]

[1]Department of Nursing and Midwifery, Islamic Azad University Sanandaj Branch, Sanandaj; [2]National Nutrition and Food Technology Research Institute, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran; [3]Minimally Invasive Techniques Research Center in Women, Islamic Azad University Tehran Medical Branch, Tehran; [4]Department of Epidemiology, School of Public Health, Shahid Beheshti University of Medical Sciences, Tehran; [5]Department of Nursing and Midwifery, Islamic Azad University Tehran Medical Branch, Tehran; [6]Pars Advanced and Minimally Invasive Medical Manners Research Center, Pars Hospital, Iran University of Medical Sciences, Tehran, Iran

Objectives: This meta-analysis aimed to evaluate congenital malformations in infants conceived by assisted reproductive techniques (ART), compared with infants conceived spontaneously.

Methods: In this study, available resources searched to find relevant articles included PubMed, ScienceDirect, Scopus, Google Scholar, Cochrane, ProQuest, Iranmedex, Magiran, and Scientific Information Database. After extracting the necessary information from evaluated articles, meta-analysis on the articles' data was performed using Stata version 11.2.

Results: In this study, from a total of 339 articles, extracted from the initial investigation, ultimately 30 articles were selected for meta-analysis that assessed the use of ART on the risk of congenital abnormalities and some birth complications on 5 470 181 infants (315 402 cases and 5 154 779 controls). The odds ratio (95% confidence interval [CI]) for low birth weight was 1.89 (95% CI, 1.36 to 2.62), preterm labor 1.79 (95% CI, 1.21 to 2.63), cardiac abnormalities 1.43 (95% CI, 1.27 to 1.62), central nervous system abnormalities 1.36 (95% CI, 1.10 to 1.70), urogenital system abnormalities 1.58 (95% CI, 1.28 to 1.94), musculoskeletal disorders 1.35 (95% CI, 1.12 to 1.64), and chromosomal abnormalities in infants conceived by ART was 1.14 (95% CI, 0.90 to 1.44), which were all statistically significant, except chromosomal abnormalities.

Conclusions: The risk of congenital abnormalities and some birth complications were significantly higher in ART than normal conception, while chromosomal abnormalities were not; therefore, the application of ART should be selected individually for patients by detailed assessment to reduce such risks in the population.

Key words: Assisted reproductive technologies, Intracytoplasmic sperm injection, *In vitro* fertilization, Meta-analysis

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Corresponding author: Shahla Chaichian, MD, PhD
Khaghani St., Shariati Ave., Tehran 193951495, Iran.
Tel: +98-218-895-2035, Fax: +98-218-898-9690
E-mail: shchaichian@gmail.com

INTRODUCTION

Assisted reproductive technologies (ART) include 1% of births in the US and 4.3% of births in European countries and Australia [1]. Scientific and medical advances have increased the pregnancy rates and births following ART can be expected to rise. Any method or medication to achieve pregnancy is accepted as a broad definition of the concept of ART, which in-

cludes ovulation induction, intrauterine insemination, *in vitro* fertilization (IVF), and intracytoplasmic sperm injection (ICSI) [2]. Application of these methods has solved the infertility problem of human and had multiple health benefits for millions of couples suffering from fertility problems [3]. During the past 36 years, ART has reformed from a miracle to a standard and common part of medical practice. More than 200 000 infants are annually born worldwide by this technology [2]. It is estimated that over 5 million children worldwide have been born after ART procedures [1]. There are worldwide 72.4 million infertile women and 21-22% of women in our country experience primary infertility in their marital life. Worldwide, about 40 million couples benefit from reproductive medicine [4,5]. All these figures indicate that since the birth of Louise Brown, the first baby born after artificial insemination in 1978 in the UK, ART have advanced quickly that have attracted more and more researcher's attention towards the risks and complications of this method [6]. Developed and advanced use of this method has increased the rate of infants born by this method and have pursued researchers to follow these children's health status [7].

After 30 years of using ART, there are evidence of increased adverse perinatal outcomes such as premature birth (PTB), low birth weight (LBW) and small for gestational age infants, compared with children conceived spontaneously [8]. Studies show that ART can increase the incidence of congenital malformations at 25-40% [9] and these children are at risk of a range of disabilities [10].

Various artificial methods, performed during ART treatment, imply the concern that infants conceived through these methods are at higher risk than infants conceived spontaneously. In such methods, firstly, many drugs are prescribed to stimulate ovulation, oocyte retrieval, and embryos cultured, frozen and melt *in vitro*, and high doses of progesterone for luteal phase support, which may all damage gametes or embryos. In addition, ICSI method, in which an egg is fertilized by injecting sperm directly into ooplasm, is considered more invasive than IVF. It also significantly increases the risk of multiple pregnancies by transferring more than one embryo, which leads to risk of complications such as PTBs and LBW [3].

The results of some studies indicate that infants conceived through ART are at higher risk of congenital abnormalities than normal pregnancies, but some other studies have not observed such difference or have even reported less risk, especially in multiple pregnancies [6].

Regarding the conflicting results and as far as some complications can cause malformations that increase in infants conceived through this method, such as preterm labor and LBW, thus, this meta-analysis study aimed to assess the complications and the risk of some congenital malformations including cardiovascular, central nervous system, musculoskeletal, urogenital and chromosomal abnormalities in newborns conceived following ART compared to infants conceived spontaneously.

METHODS

In this study, available resources searched to find relevant articles included PubMed, ScienceDirect, Scopus, Google Scholar, Cochrane, ProQuest, Iranmedex, Magiran, and Scientific Information Database (SID) databases, published from 2005 to 2015. We retrieved 201 citations in PubMed, 38 citations in Scopus, 55 citations in EMBASE, 10 citations in Google Scholar, 15 citations in Cochrane, 16 citations in ProQuest, 4 citations in Iranmedex, 0 citation in Magiran and 0 citation in SID.

In order to avoid losing resources, congress performances, theses, books and other domestic and foreign valid websites were manually searched. List of references used in all articles and related reports found by the electronic search were evaluated manually to include other possible sources in the study.

The searched keywords included (birth defect or congenital malformation or congenital abnormalities) and (ART or IVF or ICSI). After preparation of the initial list, two colleagues examined titles and abstracts independently and identified relevant articles. Then, they registered closely-related or possibly-related studies and selected related studies by examining the full text of articles. At the end, among the articles selected based on critical evaluation, articles that met the inclusion criteria were finally selected (Table 1).

To include the study objectives, all articles with the following inclusion criteria were extracted: Access to full-text articles in English; Cohort or case-control studies; The study population including infants conceived through ART vs. control group over a period of time.

Data Extraction and Quality Evaluation

All identified papers were critically appraised independently by two reviewers (SC and YM). Any disagreement was assessed by both and if a consensus was not reached, a third author (HH) evaluated the study. Two independent matched reviewers (PM

and YM) extracted data according to a uniform Excel sheet. Disagreements between reviewers were resolved by consensus. Appraisal was guided by checklist assessing clarity of the aims and research questions. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist score was used as a standard checklist for reporting the results of the included studies. Then, the closely-related or possibly-related studies were listed and selected by examining the full text of eligible articles. At the end, among selected articles, based on critical evaluation, articles that met the inclusion criteria were ultimately selected (Table 1). Some of the information, including odds ratio (OR) in some studies and confidence interval (CI), *p*-value, number of samples extracted from the articles, the standard error, variance and the logarithm of the variance and weight of articles were calculated using available data in the literature.

Data Analysis

After extracting the necessary information from evaluated articles, meta-analysis on the articles' data was performed using Stata version 11.2 (StataCorp, College Station, TX, USA). Metan order was used to analyze the data, and Q-test and I^2 were used to measure heterogeneity of studies and Begg's funnel plot to assess publication bias.

RESULTS

In this study, from a total of 339 articles extracted from the initial investigation, ultimately 30 articles were selected for meta-analysis tests that assessed the use of ART on the risk of congenital abnormalities and some birth complications on 5 470 181 infants (315 402 cases and 5 154 779 controls). All studies were evaluated by two independent researchers and, in case of disagreement, a third arbitrator examined to rule out the study.

Supplemental Tables 1 and 2 show the results of the meta-analysis, the OR for congenital malformations and birth complications among infants conceived through ART. The estimated OR for congenital abnormalities in infants conceived by ART was 1.53 (95% CI, 1.37 to 1.70), which was statistically significant. This means that infants conceived through ART are at 53% increased risk of congenital abnormalities than other infants. The results partly reflect the heterogeneity of the studies ($\chi^2=214.43$; $p<0.001$; $I^2=89.7\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results. The estimated OR for LBW in infants conceived by ART was 1.89 (95% CI. 1.36 to 2.62), which was statistically significant. This means that infants conceived through ART are at 89% increased risk of LBW than other infants. The results partly reflect the heterogeneity of the studies ($\chi^2=2174.05$; $p<0.001$; $I^2=99.3\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results.

The estimated OR for preterm labor in infants conceived by ART was 1.79 (95% CI, 1.21 to 2.63), which was statistically significant. This means that infants conceived through ART are at 79% increased risk of preterm labor than other infants. The results partly reflect the heterogeneity of the studies ($\chi^2=3089.90$; $p<0.001$; $I^2=99.6\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Table 2).

The estimated OR for cardiac malformations in infants conceived by ART was 1.43 (95% CI, 1.27 to 1.27), which was statistically significant. This means that infants conceived through ART are at 43% increased risk of cardiac malformations than other infants. The results partly reflect the heterogeneity of the studies ($\chi^2=31.12$; $p=0.003$; $I^2=58.2\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Table 2).

The estimated OR for central nervous system malformations in infants conceived by ART was 1.36 (95% CI, 1.10 to 1.70), which was statistically significant. This means that infants conceived through ART are at 36% increased risk of central nervous system malformations than other infants. The results partly reflect the heterogeneity of the studies ($\chi^2=25.67$; $p=0.002$; $I^2=64.9\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Supplemental Table 2).

The estimated OR for urogenital malformations in infants conceived though ART was 1.58 (95% CI, 1.28 to 1.94), which was statistically significant. This means that infants conceived though ART are at 58% increased risk of urogenital malformations than other infants. The results partly reflect the heterogeneity of the studies ($\chi^2=65.26$; $p<0.001$; $I^2=81.6\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Supplemental Table 2).

The estimated OR for musculoskeletal malformations in infants conceived by ART was 1.35 (95% CI, 1.12 to 1.64), which was statistically significant. This means that infants conceived through ART are at 35% increased risk of musculoskeletal mal-

Table 1. Characteristics of the studies included in the analysis

Study	Author, publication year	Country	Characteristics of the studied population	Type of study	Data assessed	Results
Neonatal outcome after PGD	Eldar-Geva et al. 2014 [11]	Israel	242 PGD, and 242 ICSI infants (158 singletons and 42 twins) and 733 infants born by SC in the control group (493 singletons and 120 twins), matched for maternal age, parity and BMI between groups	Cohort	Gestational age, birth weight, prematurity (34-37 wk), LBW (<2500 g), VLBW (<1500 g), and IUGR	In singleton pregnancies, mean birth weight was more than ICSI compared with the control group, LBW and IUGR rates were 4.4 and 12.0%, respectively, in PGD group, 5.7 and 5.1% in ICSI group, and 9.5 and 5.5% the control group
Children born after assisted fertilization an increased rate of major congenital anomalies	Klemetti et al. 2005 [9]	Finland	4559 infants conceived by IVF, and 4467 infants through other ART methods, and 27 078 naturally conceived infants as the control group, with matched number and gender of infants	Cohort	Major congenital malformations, chromosomal defects, and hypothyroidism	The OR for major birth defects in the IVF group was estimated to be 1.30, showing an increased risk only in boys, and reduced risk was observed in woman infants of IVF multiple deliveries (OR=0.5); the results were also statistically significant The risk after other ART was only slightly increased
IVF is associated with an increase in major birth defects	Olson et al. 2005 [12]	USA	1462 IVF infants (645 singletons), 343 IUI-conceived infants (264 singletons) and 8432 control infants (4590 singletons)	Cohort	Gestational age, birth weight, prematurity (<32 wk), LBW, VLBW and major birth defects (eyes, ears, cardiovascular, urogenital, musculoskeletal, nervous system, respiratory, skin, oral abnormalities, syndromes, tumors, and chromosomal defects)	In IVF-conceived groups, the aOR of having a baby with a major birth defect was 1.30 (statistically significant), and in the IUI group, this ratio was 1.11 Cardiovascular, musculoskeletal disorders and congenital syndromes were more common in the IVF group Among IVF-conceived children, there was no difference in birth defect rates after (ICSI) or after transfer of cryopreserved embryos
IVF in Sweden: child morbidity including cancer risk	Källén et al. 2005 [13]	Sweden	A total of 16 280 newborns (11 283 IVF, 4949 ICSI, and 48 infants conceived by other ARTs and 1 473 577 infants as the control group were matched for year of birth, maternal age, parity and smoking habits	Cohort	Number of hospitalization days due to specific diagnosis and childhood cancer	Overuse of hospital care was observed in the ART group, largely related to maternal characteristics Diagnoses representing brain injury (mental retardation, cerebral palsy, epilepsy and behavioral problems) were higher in ART children, which were associated with PTB; 29 cases of cancer have been reported in this group (21 expected)
Risk of birth defects increased in pregnancies conceived by assisted human reproduction	El-Chaar et al. 2009 [14]	Canada	1399 ART infants (298 infants after ovulation induction, 173 infants born after IUI and 319 IVF infants); 60 170 infants as the control group	Cohort	Risk of major birth defects was evaluated (cardiovascular neural tube defects, gastro-intestinal, musculoskeletal and facial defects)	Prevalence of birth defects had a 1.55-fold increase in ART (that was statistically significant); specific anomalies, including gastro-intestinal malformations (OR=9.85), cardiovascular (OR=2.30), and musculoskeletal (OR=1.54) were observed more in recipients of ART The risk of birth defects in the ovulation induction method was 2.35, IUI 2.89 and IVF 3.45%
Infant outcome of 957 singletons born after frozen embryo replacement: the Danish National Cohort Study 1995-2006	Pinborg et al. 2010 [15]	Denmark	957 singleton cryo-ART (660 newborns conceived by cryo-IVF, 244 infants by cryo-ICSI, and 55 by cryo-IVF/ICSI); the first control group included infants conceived following fresh ART (6904 IVF and 3425 ICSI) The second control group included 4800 infants conceived without the use of ARTs Date and year of birth was matched between the groups	Cohort	LBW, PTB, birth defects congenital malformations, mortality, and morbidity were examined	No significant differences were observed in the prevalence of birth defects, neurologic consequences, malignancies and diseases associated with genetic transcription in the cryotherapy group compared with the control group, although major abnormalities and cerebral palsy in the fresh ART group were more common than in the second control group
Perinatal risk in singleton afte IVF	Fujii et al. 2010 [16]	Japan	53 939 singleton infants of spontaneous pregnancies and 1408 singleton infants after IVF were matched in terms of maternal age, gestational age, placenta previa and mothers' characteristics.	Cross-sectional (case-control)	Perinatal deaths, LBW, SGA, congenital malformations and gender ratio were investigated	Perinatal mortality, SGA, congenital anomalies and gender ratio at birth were not associated with IVF pregnancies, but LBW increased after IVF

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Table 1. Continued from the previous page

Study	Author, publication year	Country	Characteristics of the studied population	Type of study	Data assessed	Results
IVF and preterm delivery, LBW, and admission to the NICU: a prospective follow-up study	Wisborg et al. 2010 [17]	Denmark	Among 20 080 primiparous women with a singleton pregnancy, 18 473 conceived spontaneously, 877 after non-IVF ART (351 hormonal stimulation and 526 IUI) and 730 after IVF/ICSI; the groups were matched in terms of maternal age, education, and marital status, consumption of alcohol, smoking and caffeine during pregnancy	Cohort	Preterm, LBW, NICU admission	Compared with fertile women, birth weight in the group using ART was significantly lower After matching the groups, preterm labor in the IVF/ICSI group was significantly more common than in spontaneous pregnancies There was no association between IVF/ICSI and the risk of LBW at term or admittance to the NICU
Congenital anomalies in offspring of subfertile couples: a registry-based study in the northern Netherlands	Seggers et al. 2015 [18]	Netherlands	4185 fertile women, 340 subfertile women (201 had conceived naturally after >12 mo and 139 cases of conception through IVF/ICSI)	Cohort	Different congenital malformations	In subfertile women, increased risk of abdominal wall defects (aOR=2.43), hypospadias (aOR=9.83), right ventricleular's outflow obstruction (aOR=1.77), and methylation defects (aOR=13.49) were observed, and IVF/ICSI was associated with an increased risk of polydactyly (OR=4.83) and more specifically polydactyly of the hands (OR=5.02)
Risk of major congenital anomalies after assisted hatching: analysis of 3 y data from the national assisted reproduction registry in Japan	Jwa et al. 2015 [19]	Japan	36 033 cases using ART (34 949 singleton and 1084 multiple pregnancies) were matched with 37 119 controls (36 157 singleton and 962 multiple pregnancies) in terms of maternal age, year of birth, gender of the fetus, embryo stage at transfer and status of cryopreservation	Cohort	Major congenital anomalies and stillbirth	The risk of congenital abnormalities was not significantly different between the 2 groups No significant differences were observed at the time of embryo transfer (early cleavage stages and blastocyst stage)
Congenital malformations associated with ART: a California statewide analysis	Kelley-Quon et al. 2013 [20]	USA	4795 infants after ART were matched with 46 025 children in the control group for mother's age, parity, plurality, and race	Cohort	Major congenital anomalies	Malformations were increased in ART infants (9.0 vs. 6.6%, $p=0.001$) ART infants exhibited increased odds of major malformations overall (OR=1.25), specifically defects of the eye (OR=1.81), head and neck (OR=1.37), heart (OR=1.4), and genitourinary system (OR=1.40) The risk of multiple defects increased in multiples (OR=1.35) The risk of anomalies was not statistically significant in the fertility-related services group
The prevalence of major congenital malformations during two periods of time, 1986-1994 and 1995-2002 in newborns conceived by ART	Merlob et al. 2005 [21]	Israel	Two periods of assessment were included: the first period included 31 007 infants, 278 of whom were conceived by IVF, and the second period included 53 208 infants, 1632 of whom were conceived by IVF	Cohort	Major congenital malformations, LBW, and genetic transcription disorders	In the first period, 26 IVF infants had major congenital abnormalities with an OR of 2.30 and in the second period, 147 infants in the IVF group had major deformities (OR=1.75)
A comprehensive assessment of outcomes in pregnancies conceived by IVF/ICSI	Wen et al. 2010 [22]	Canada	1044 infants conceived by assisted reproductive techniques (IVF and ICSI) and 1910 infants in the control group	Retrospective cohort	Preeclampsia, eclampsia, caesarean section, gestational diabetes or congenital anomalies, major birth defects, fetal death, PTB, fetal growth restriction, Apgar <7 at 5 min, intracranial hemorrhage seizures, sepsis, and mechanical ventilation	1.1% of infants conceived by IVF/ICSI, compared to 0.4% of infants in the control group had congenital heart defects ($p<0.01$) 5 cases of 138 infants of mothers using IVF method with a BMI over 30 kg/m^2 vs. none of 240 infants born to mothers in the control group with a BMI over 30 kg/m^2 had congenital heart defects ($p< 0.01$)
Men reproductive tract abnormalities: more common after assisted reproduction?	Funke et al. 2010 [23]	Hungary	890 infants conceived by IVF/ICSI, 14 316 infants in the control group	Cohort	Genital abnormalities in man infants (hypospadias and cryptorchidism, poor semen quality), prematurity, LBW, and multiple pregnancies	IVF and ICSI increased the risk of LBW, preterm labor, and multiple pregnancy, which increased the risk of genital tract anomalies The risk of hypospadias increased in this study in ICSI infants with normal weight and singleton pregnancies

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Table 1. Continued from the previous page

Study	Author, publication year	Country	Characteristics of the studied population	Type of study	Data assessed	Results
ART and major birth defects in Western Australia	Hansen et al. 2012 [24]	Australia	2911 infants born after ART, and 210 997 in the control group with and without birth defects diagnosed by age 6 and all terminations of pregnancy for fetal anomaly	Cohort	Major birth defects, as well as type of delivery, stillbirth, age at birth, and birth weight	The chance of major birth defects in singleton pregnancies in ART patients was 8.7%, compared to 5.4% in controls (OR=1.53), which was statistically significant and was estimated to be 7.1% in twin pregnancies following ART compared to 5.9% of controls (OR=1.08)
Surveillance of congenital malformations in infants conceived through ART or other fertility treatments	Heisey et al. 2015 [25]	USA	4064 infants born after ART treatment, 9589 after infertility treatments and 1 090 154 other in the control group	Cohort	Major birth defects	Congenital malformations in the ART group, compared with the control group, had an OR of 1.43 that was statistically significant; specific abnormalities included patent ductus arteriosus, hypospadias, obstructive defects in the kidney and urinary tract, while spina bifida, other specific anomalies of the spinal cord, atresia or stenosis of the pulmonary valve, hypospadias, and obstructive defects of the renal pelvis and ureter were associated with other fertility treatments
ART and major structural birth defects in the USA	Reefhuis et al. 2009 [26]	USA	51 newborns in the ART group and 4741 in the control group were matched for age, study center, parity, family income, prematurity (only septal heart defects)	Case-control	Major birth defects	In singleton pregnancies using ART, septal heart defects (aOR=2.1), cleft lip with or without cleft palate (aOR=2.4), esophageal atresia (aOR=4.5), and anorectal atresia (aOR=3.7), increased significantly In multiple pregnancies, no association was observed between ART and birth defects
Reproductive technologies and the risk of birth defects	Davies et al. 2012 [27]	Australia	6163 ART infants and 302 811 spontaneous pregnancies	Cohort	Birth defects	The OR of birth defects in the assisted conception group was 1.47 (1.26 for IVF, and 1.77 for ICSI) A history of infertility, either with or without assisted conception, was also significantly associated with birth defects
Increased risk of blastogenesis birth defects, arising in the first 4 wk of pregnancy, after ART	Halliday et al. 2010 [28]	Australia	6946 singleton pregnancies (3312 IVF and 3634 ICSI), and 20 838 infants in the control group were matched for maternal age, parity and infant's year of birth, and gender	Cohort	Major birth defects	Birth defects in infants born to mothers after the use of ART increased (statistically significant OR of 1.36) A history of infertility, either with or without assisted conception, was also significantly associated with birth defects Defects due to blasto genesis increased in fresh embryos in comparison to cryo-embryos, which was statistically significant
Twin pregnancies conceived by ART: maternal and perinatal outcomes	Ho et al. 2005 [29]	Taiwan	159 twin pregnancies, including 54 cases of spontaneous pregnancies, 31 case of ovulation stimulation and 74 cases of IVF	Cohort	Obstetric and perinatal complications (congenital malformations, neonatal hypoglycemia, use of mechanical ventilation, admission to the NICU and prenatal death)	In the ART group, the prevalence of congenital malformations, neonatal hypoglycemia, use of mechanical ventilation, admission to the NICU, and prenatal death significantly increased, compared to spontaneous pregnancies The rate of dichorionic pregnancies was significantly higher in the ART group

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Table 1. Continued from the previous page

Study	Author, publication year	Country	Characteristics of the studied population	Type of study	Data assessed	Results
Congenital malformations in infants born after IVF in Sweden	Källén et al. 2010 [30]	Sweden	15 570 infants born after IVF, 689 157 newborns in the control group (all infants born in Sweden from 2001 to 2007), matched by year of birth, maternal age, parity, smoking, and BMI	Cohort	Congenital malformations	There was an increased risk of heart and limb defects in both periods of the study; a risk of neural tube defects, septal heart defects and gastrointestinal tract atresia occurred in the second period but less than in the first period; during the first stage of the study, an increased risk of small bowel abnormalities, gastrointestinal tract atresia, anal atresia, and hypospadias was observed, but faded in the second phase; increased risk of some syndromes was associated with genetic transcription error
Similarly increased congenital anomaly rates after IUI and IVF technologies: a retrospective cohort study	Sagot et al. 2012 [31]	France	1348 singleton pregnancies using ART (903 IVF, and 445 IUI) were matched with 4044 singleton infants in the control group and 552 ART twin cases (362 IVF, and 190 IUI) were matched with 1656 twins in the control group	Cohort	Major birth defects (central nervous system, eyes, ears and neck, respiratory system, cardiovascular system, cleft lip and palate, gastrointestinal tract, urinary tract, reproductive system, skeletomuscular, and genetic abnormalities)	Compared with naturally conceived singletons, singletons born after IUI and IVF had a higher prevalence of major congenital malformations All twins and unlike-gender twins born after IVF (but not IUI) had an increased prevalence of major birth defects compared with naturally conceived twins When comparing IUI with IVF, no differences were observed for singletons, all twins and unlike-gender twins
ART and pregnancy outcome	Shevell et al. 2005 [32]	USA	34 286 infants in the control group, 1222 infants after ovulation induction and 554 after using IVF, matched for age, race, marital status, education, history of preterm labors, malformations in previous infants, BMI, and history of smoking and bleeding in the current pregnancy	Cohort	Chromosomal defects, congenital abnormalities and adverse pregnancy outcomes	There was no association between ART and fetal growth restriction, aneuploidy, or fetal anomalies after adjustment Ovulation induction was associated with a statistically significant increase in placental abruption, fetal loss after 24 wk, and gestational diabetes after adjustment Use of IVF was associated with a statistically significant increase in preeclampsia, gestational hypertension, placental abruption, placenta previa, and risk of cesarean delivery
Obstetric and perinatal outcomes of dichorionic twin pregnancies according to methods of conception: spontaneous vs. IVF	Yang et al. 2011 [33]	Korea	286 spontaneously-conceived twins were matched with 134 IVF twins after adjustment for maternal age and parity	Cohort	Obstetric and perinatal outcomes	There were no risk differences between the 2 groups regarding obstetric complications No differences were shown in the 2 groups for the risk estimates of perinatal outcomes However, twins conceived after IVF were less likely to be admitted to the NICU than those conceived spontaneously (aOR, 0.49; 95% CI=0.26 to 0.91) In dichorionic twins, IVF may not be associated with adverse perinatal and obstetric outcomes compared with SC
Perinatal outcomes in 375 children born after oocyte donation: a Danish national cohort study	Malchau et al. 2013 [34]	Denmark	Group of infants conceived by oocyte donation included 375 infants (251 singletons and 124 twins), the first control group consisted of infants conceived following IVF (11 060 singletons and 6532 twins), and ICSI (5866 singletons and 3101 twins) and the second control group consisted of 33 852 singleton infants of SC were matched by date and year of birth	Cohort	Birth weight, gestational age, LBW, congenital anomalies, cesarean delivery, preeclampsia and admission to the NICU, malformations, cesarean delivery, preeclampsia, and admittance to NICU	The aOR of PTB in OD singletons was 1.8, 2.5, and 3.4 compared with IVF, ICSI, and SC, respectively The risk of LBW was also increased The aOR of LBW was 1.4, 1.8, and 2.6 compared with IVF, ICSI, and SC The risk of preeclampsia was increased in OD pregnancies with an aOR of 2.9, 2.8, and 3.1 compared with IVF, ICSI, and SC After additional adjustment for preeclampsia, perinatal outcomes improved Among the twins, the difference between the groups was less pronounced

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Table 1. Continued from the previous page

Study	Author, publication year	Country	Characteristics of the studied population	Type of study	Data assessed	Results
A multi-centre cohort study of the physical health of 5-y-old children conceived after ICSI, IVF and natural conception	Bonduelle et al. 2005 [35]	European countries (Belgium, Sweden, Denmark, Greece, and UK)	540 5-y-old children conceived after ICSI, 437 IVF and 538 infants in the control group were matched for demographic factors	Cohort	The mother's health in pregnancy was recorded, including chronic maternal illnesses, maternal smoking/drinking and pregnancy complications. Neonatal history included birth weight, gestational age, neonatal unit admission and treatments, and infant feeding details, as well as type of delivery and congenital anomalies (heart, eyes, ears, face, urogenital, gastrointestinal, musculoskeletal and skin anomalies)	Congenital malformations in the ICSI group had an OR of 2.77 (statistically significant) and 1.80 in the IVF group, compared to the control group Most abnormalities observed in newborn after ICSI were related to the boys' urogenital system In addition, infants conceived by ART, compared to the control group, experienced more complicated childhood diseases, required more medical and surgical treatment and experienced more admissions to the hospital
Obstetric outcome of twin pregnancies conceived by IVF and ovulation induction compared with those conceived spontaneously	Adler-Levy et al. 2007 [36]	Israel	558 twins conceived following IVF and 478 twins following ovulation stimulation were compared to 3694 SC that were matched for the mother's age and parity	Case-control	Obstetric characteristics (perinatal mortality, preterm delivery, caesarean section, maternal diabetes and SGA)	Mothers treated with ART were significantly more likely to develop gestational diabetes than the control group (OR=2.41 for IVF and 1.71 for ovulation induction) The results showed a higher rate of caesarean sections and preterm infants after IVF and ovulation induction compared to the control group (OR=2.17, 1.76) Lower gestational age at birth was observed in the IVF group (OR=0.91)
Comparison of perinatal outcomes of twin births conceived using ART vs. spontaneous	Barat et al. 2009 [37]	Iran	40 cases of twin pregnancies resulting from ART, were matched by age with 80 cases of spontaneous twin pregnancies	Cohort	Complications during pregnancy, such as preeclampsia, gestational diabetes, preterm labor and fetal complications such as IUGR, LBW, and NICU admission	Gestational diabetes and NICU admission were significantly more common in the ART group than the control group (13 vs. 8 cases, $p=0.004$, and 3 vs. 0 cases, $p=0.03$, respectively), as well as transfer to NICU 30 cases vs. 26 ($p<0.001$) The birth weight of twins were significantly lower in the ART group than the control group Premature rupture of membrane, preeclampsia, placental events, intrauterine fetal death and gestational age did not show a significant difference between the 2 groups
ART and risk of exstrophy-epispadias complex: a German case-control study	Zwink et al. 2013 [38]	German	129 982 cases of pregnancies resulting from ART compared with a control group of live births (9 940 004)	Cohort	Exstrophy-epispadias complex	Conception by ART was associated with a more than 8-fold increased risk of exstrophy-epispadias complex compared to SC (OR=8.3). Separate analyses showed a significantly increased risk of exstrophy-epispadias complex in children conceived by IVF (OR=14.0) or ICSI (OR=5.3)
Comparison of congenital abnormalities of infants conceived by ART vs. infants with natural conception in Tehran	Farhangniya et al. 2013 [39]	Iran	362 infants as cases (ART) and 652 infants as controls (SC) were matched between groups by mothers' age and the infant's gender	Cohort	Mother's age, infant's gender, ART, type of delivery, still birth, abortion, major congenital malformations (visual system, ears/nose/throat, cardiovascular, urogenital, musculoskeletal, nervous system, endocrine system, and genetic disorders)	The OR of birth of an infant with congenital defects in ART group was estimated to be 1.94, which was statistically significant The OR of congenital disorders in IVF group, compared to ICSI, was 2.73 that was statistically significant ($p=0.02$)

aOR, adjusted odds ratio; ART, assisted reproductive technology; BMI, body mass index; ICSI, intracytoplasmic sperm injection; IUGR, intrauterine growth restriction; IUI, intrauterine insemination; IVF, *in vitro* fertilization; LBW, low birth weight; NICU, neonatal intensive care unit; OR, odds ratio; PGD, preimplantation genetic diagnosis; SGA, small for gestational age; VLBW, very low birth weight; PTB, preterm birth; OD, oocyte-donation; SC, spontaneous conception; CI, confidence interval.

Table 2. Results of the meta-analysis of the odds of preterm labor and cardiovascular abnormalities in ART infants

Studies	Adjusted OR (95% CI)	Logarithm of OR	Articles' weight (%)
Preterm labor			
Eldar-Geva et al. 2014 [11]	-	0.25	7.39
Pinborg et al. 2010 [15]	-	0.25	7.87
Wisborg et al. 2010 [17]	1.53 (1.15, 2.04)	0.28	7.35
Jwa et al. 2015 [19]	-	0.14	7.93
Kelley-Quon et al. 2013 [20]	-	0.66	7.92
Merlob et al. 2005 [21]	-	-0.66	7.75
Wen et al. 2010 [22]	0.82 (0.60, 1.11)	-0.30	7.64
Funke et al. 2010 [23]	-	1.25	7.85
Hansen et al. 2012 [24]	-	1.60	7.91
Reefhuis. et al. 2009 [26]	-	1.83	6.75
Davies et al. 2012 [27]	-	1.52	7.92
Olson et al. 2005 [12]	-	0.77	7.78
Malchau et al. 2013 [34]	1.70 (1.28, 2.26)	0.04	7.93
Total OR and 95% CI (pooled)		1.79 (1.21, 2.63)	
		Heterogeneity (τ^2): 0.49 χ^2: 3089.90 (df=12); $p<0.01$; $I^2=99.6\%$ Testing the total effect of Z: 2.93 ($p=0.003$) Begg's test: Z= 0.24 ($p=0.81$) Egger's test: $t=0.69$; $p=0.51$; 95% CI=-10.85, 20.73	
Cardiovascular abnormalities			
Klemetti et al. 2005 [9]	1.33 (0.99, 1.80)	0.37	11.67
El-Chaar et al. 2009 [14]	2.30 (1.11, 4.77)	0.99	2.50
Pinborg et al. 2010 [15]	-	0.35	7.95
Seggers et al. 2015 [18]	-	0.18	6.44
Jwa et al. 2015 [19]	0.94 (0.75, 1.18)	-0.03	10.96
Kelley-Quon et al. 2013 [20]	1.41 (1.22, 1.64)	0.50	13.09
Wen et al. 2010 [22]	4.58 (1.48, 14.18)	1.06	1.51
Hansen et al. 2012 [24]	1.65 (1.06, 2.57)	0.54	7.35
Davies et al. 2012 [27]	1.33 (1.08, 1.63)	0.39	11.44
Halliday et al. 2010 [28]	-	0.18	7.52
Källén et al. 2010 [30]	1.30 (1.13, 1.49)	0.30	13.30
Sagot et al. 2012 [31]	2.10 (0.70, 5.60)	0.94	3.60
Yang et al. 2011 [33]	-	0.22	1.60
Farhangniya et al. 2013 [39]	-	0.32	1.06
Total OR and 95% CI (pooled)		1.43 (1.27, 1.62)	
		Heterogeneity (τ^2): 0.03 χ^2: 31.12 (df=13); $p=0.003$; $I^2=58.2\%$ Testing the total effect of Z: 5.72 ($p<0.01$) Begg's test: Z=0.60 ($p=0.55$) Egger's test: $t=0.89$; $p=0.39$; 95%, CI=-1.02, 2.44	

ART, assisted reproductive technology; OR, odds ratio; CI, confidence interval.

formations at 35%. The results partly reflect the heterogeneity of the studies ($\chi^2=34.93$; $p<0.001$; $I^2=74.06\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Table 3).

The estimated OR for chromosomal disorders in infants conceived by ART was 1.14 (95% CI, 0.90 to 1.44), which was not statistically significant. This means that infants conceived through ART are at 14% increased risk of chromosomal disorders than other infants that was not statistically significant. The results partly reflect the heterogeneity of the studies

Table 3. Results of the meta-analysis of the odds of musculoskeletal abnormalities and chromosomal abnormalities in ART infants

Studies	Adjusted OR (95% CI)	Logarithm of OR	Articles' weight (%)
Musculoskeletal abnormalities			
Klemetti et al. 2005 [9]	1.55 (1.05, 2.27)	0.38	12.13
El-Chaar et al. 2009 [14]	1.54 (0.48, 4.94)	-0.41	1.69
Pinborg et al. 2010 [15]	-	0.19	12.98
Seggers et al. 2015 [18]	-	-0.21	8.54
Jwa et al. 2015 [19]	0.82 (0.58, 1.14)	-0.20	10.99
Wen et al. 2010 [22]	0.59 (0.24, 1.54)	-0.07	4.17
Hansen et al. 2012 [24]	1.75 (1.30, 2.35)	0.61	12.45
Heisey et al. 2015 [25]	-	0.33	6.87
Davies et al. 2012 [27]	1.26 (1.06, 1.50)	0.45	13.84
Halliday et al. 2010 [28]	-	0.71	8.48
Sagot et al. 2012 [31]	1.90 (1.00, 3.80)	0.79	7.84
Total OR and 95% CI (pooled)		1.35 (1.12, 1.64)	
		Heterogeneity (τ^2): 0.06 χ^2: 34.93 (df=10); $p<0.01$; $I^2=74.06\%$ Testing the total effect of Z: 3.08 ($p<0.01$) Begg's test: Z=0.54 ($p=0.59$) Egger's test: $t=0.79$; $p=0.45$; 95% CI=-3.74, 1.80	
Chromosomal abnormalities			
Klemetti et al. 2005 [9]	-	0.16	9.13
Pinborg et al. 2010 [15]	-	0.13	6.72
Jwa et al. 2015 [19]	0.92 (0.71, 1.20)	-0.10	14.27
Kelley-Quon et al. 2013 [20]	0.31 (0.15, 0.63)	-0.91	7.44
Wen et al. 2010 [22]	0.82 (0.19, 3.52)	-0.36	2.57
Hansen et al. 2012 [24]	1.89 (1.00, 3.60)	0.71	11.47
Heisey et al. 2015 [25]	-	0.29	7.16
Davies et al. 2012 [27]	0.82 (0.55, 1.21)	0.26	11.75
Halliday et al. 2010 [28]	-	0.02	13.57
Källén et al. 2010 [30]	0.98 (0.70, 1.37)	0.20	12.56
Sagot et al. 2012 [31]	3.10 (0.60, 13.10)	1.1	3.35
Total OR and 95% CI (pooled)		1.14 (0.90. 1.44)	
		Heterogeneity (τ^2): 0.08 χ^2: 27.93 (df=10); $p=0.002$; $I^2=64.2\%$ Testing the total effect of Z: 1.1 ($p=0.27$) Begg's test: Z= 0.3 ($p=0.82$) Egger's test: $t=0.36$; $p=0.73$; 95% CI=-2.27, 3.14	

ART, assisted reproductive technology; OR, odds ratio; CI, confidence interval.

($\chi^2=27.93$; $p=0.002$; $I^2=64.2\%$), but since the CI of test (Egger's test) included zero, no significant bias occurred in the publication of the results (Table 3).

DISCUSSION

Systematic review and meta-analysis of results of studies indicated that the risk of congenital malformations in infants conceived by ART increases, compared with infants of spontaneous conception (SC; OR, 1.53; 95 CI, 1.37 to 1.70) that was statistically significant; meaning that infants conceived by ART are at 53% greater risk for congenital malformations. The results of the study by Shevell and colleagues [32] showed that abnormalities were more in IVF group than SC. Simpson [1] suggested that the use of ART are associated with a relative increase in birth defects (OR, 1.30). The meta- analysis by Hansen and Bower [40] on systematic reviews and meta-analysis studies on ART and birth defects showed that the results of six studies indicated an increase of 30-70% (OR, 1.31 to 1.70) in birth defects in the ART group. In the meta-analysis study by

Pandey and colleagues [41], the OR of congenital malformations in ART infants was estimated 1.67 (95% CI, 1.33 to 2.09). The results of the study by Jie et al. [42] indicated no significant differences between the two groups of ART and SCs regarding the prevalence of birth defects ($p=0.07$). In the meta-analysis by Hansen et al. [43] on 45 studies, the OR of congenital malformations in infants conceived through ART was 1.32 (95% CI, 1.24 to 1.42) and in ART twin infants was 1.11 (95% CI, 0.98 to 1.26), which was not statistically significant.

In the present study, the results significantly showed that infants conceived by ART are 89% more born with low weight (OR, 1.89; 95% CI, 1.36 to 2.62). The results by Jamshidi et al. [44] suggested that 1% of singleton SCs were LBW, compared with 19% in singleton IVF group, with a statistically significant OR of 2.5; while, the research by Hajishafiha and colleagues [45] showed that the growth parameters and fetal development including birth weight was not statistically different between two groups of users of ART methods and SC. In the research by Yasaei and Ataei [46] birth weight and gestational age in three groups of spontaneous twin pregnancies, after IVF, and ovulation induction had no significant differences. The OR estimated in the meta-analysis of results by Helmerhorst et al. [47], Jackson et al. [48], McDonald et al. [49], and Pandey et al. [41] have reported LBW in ART group, compared to spontaneous pregnancies, OR, 1.7; 95% CI, 1.5 to 1.9; OR, 1.8; 95% CI, 1.4 to 2.2; OR, 1.6; 95% CI, 1.3 to 2.0; and OR, 1.67 95% CI, 1.6 to 1.8, respectively.

The results of the current meta-analysis on conception following ART indicated that these infants (OR, 1.79; 95% CI, 1.21 to 2.63), compared with normal pregnancies, have 79% more preterm labor that was statistically significant. Barat et al. [37] concluded in their study that the mean age in the group receiving ART were lower, compared with SC, but was not statistically significant.

Regarding the results of the meta-analysis on the likelihood of preterm labor in ART, compared with spontaneous pregnancies, Helmerhorst et al. [47] estimated the 2.0 (95% CI, 1.8 to 2.3); Jackson et al. [48] 2.0 (95% CI, 1.7 to 2.2); McGovern et al. [50] 2.0 (95% CI, 1.8 to 2.2); McDonald et al. [49] 1.8 (95% CI, 1.5 to 2.2); and Pandey et al. [41] 1.5 (95% CI, 1.5 to 1.6); these results were all significant and were almost similar to the results of the current meta-analysis.

Regarding the risk of major malformations (cardiovascular, central nervous system, musculoskeletal, urogenital and chromosomal abnormalities) in infants after ART, compared with SCs, the meta-analysis of the results indicated that infants conceived by ART were 43% more susceptible to cardiovascular abnormalities 1.43 (95% CI, 1.30 to 1.60) that was statistically significant. Among 14 studies, the OR was not only higher than one, but also statistically significant. In the meta-analysis by Wen et al. [51], the OR of births resulting from ART, compared with SC, was 1.64 (95% CI, 1.30 to 2.17) that was statistically significant.

The results of the meta-analysis of the results of the central nervous system disorders suggested that infants conceived by ART develop this complication 36% more than infants conceived spontaneously OR=1.36 (95% CI, 1.10 to 1.70). Among 10 studies included in the current meta-analysis, only one case estimated the OR of birth of an infant with central nervous system less than one and was in four studies not only higher than one, but also statistically significant. In the meta-analysis by Wen et al. [51] the likelihood of birth of an infant with central nervous system abnormalities in ART users, compared with SC, was estimated at 2.0 (95% CI, 1.3 to 3.2) that was statistically significant.

Regarding urogenital abnormalities, the results indicated that the probability of ART infants born with these abnormalities, compared with SCs, was 58% (OR, 1.58; 95% CI, 1.28 to 1.94), more statistically significant. From 13 studies included in the meta-analysis, only one cases [19] declared an OR of less than one regarding the probability of urogenital abnormalities in ART infants and 4 studies reported higher OR that were statistically significant. A meta-analysis conducted by Wen and colleagues [51] also reported the chance of having a baby with urogenital malformations in ART group OR=1.6 (95% CI, 1.3 to 2.1) that was statistically significant and is close to the OR estimated in the present study.

In the present meta-analysis, the risk of musculoskeletal disorders in infants receiving assisted reproductive therapy was 35% (OR, 1.35; 95% CI, 1.12 to 1.64) higher than infants of SC. From eleven articles included in the meta-analysis, 7 articles reported a statistically significant OR of higher than one regarding the risk of musculoskeletal disorders in ART infants. A meta-analysis by Wen et al. [51] also reported OR of 1.48 (95% CI, 1.09 to 2.03) in this regard.

The results of the risk of chromosomal abnormalities in infants conceived by ART showed that these infants are born with 14% increased risk of chromosomal abnormalities than infants with SC (OR,1.14; 95% CI, 0.90 to 1.44), which was not statistically significant. Among eleven studies that were evalu-

ated in the current meta-analysis, 4 studies reported an OR of less than one and only one that was statistically significant (The study by Hansen et al. [24] that estimated the possibility of having a baby with chromosomal abnormalities in infants using ART a little more than 2, compared to SCs).

The results of the current meta-analysis also indicated a remarkable discrepancy among studies that can be due to the method of assessing infants in case and control groups, as well as matching some confounding variables including mother's age, the reason and duration of infertility, previous treatments, exposure to some environmental factors, high-risk behaviors (smoking and alcohol), and variety of ART procedures. Some researchers have concluded that the increased risk associated with the use of ART should be sought more in couple's problems and the reason of infertility than infertility treatment.

European Society for Human Reproduction and Embryology reported on the status of patients after treatment that newborns after the use of ART methods such as IVF or ICSI are born with 40-50% more birth defects [52]. Similarly, an increased risk is reported in infertile couples conceiving spontaneously or with intervention after a long period of infertility. The main reason of this increased risk can be the genetic characteristics and special conditions occurring in couples, rather than the received treatment; it is thus suggested that future studies select the control group from infertile couples who have conceived spontaneously.

One of the most important individual effects on children's health following increased ART treatments is the chance of multiple pregnancies occurring following transferring more than one embryo. Total risk of multiple pregnancies demonstrably increases in women using ART. Notably, most of these pregnancies are dizygotic and as far as the adverse outcomes of monozygotic pregnancies are higher, this indicates the decreased possibility of congenital malformations in multiple pregnancies following ART, compared to SCs.

CONCLUSION

It is suggested that the future meta-analysis be conducted on more detailed factors, such as comparing ART with the possibility of birth of an abnormal infant or comparing the abnormalities in singleton pregnancies with multiple pregnancies or assess the infants' gender, in order to be able to select the safest treatment options for minimizing the risk of birth defects.

CONFLICT OF INTEREST

The authors have no conflicts of interest associated with the material presented in this paper.

ORCID

Hayedeh Hoorsan *https://orcid.org/0000-0003-2960-8821*
Parvin Mirmiran *https://orcid.org/0000-0003-2391-4924*
Shahla Chaichian *https://orcid.org/0000-0001-5772-8711*
Yousef Moradi *https://orcid.org/0000-0002-2936-5930*
Roza Hoorsan *https://orcid.org/0000-0003-0537-5875*
Fatemeh Jesmi *https://orcid.org/0000-0003-0120-1835*

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