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REVIEW

Association of assisted reproductive technology with autism spectrum disorder in the offspring: an updated systematic review and meta-analysis

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Abstract

This study aims to provide an up-to-date meta-analysis of data from studies investigating the risk of bearing a child with autism spectrum disorder (ASD) after being conceived by assisted reproductive technology (ART). The study was conducted according to the PRISMA Statement. PubMed and Scopus databases were searched up to August 2, 2020. Observational studies using a type of conception of assisted reproductive technology and examined as outcome offspring with ASD were included. A random effect model was applied due to the heterogeneity of the studies. Statistical analysis was performed with Stata 13 software. The Newcastle–Ottawa scale was used to assess the methodological quality of the included studies. The search strategy identified 587 potentially relevant studies. A total of 15 studies provided adequate data for statistical comparisons and, therefore, were included in the meta-analysis. Analysis of the subset of studies that examined all offspring and controlled for confounder factors revealed that the use of ART is associated with a higher risk of ASD (RR = 1.11, 95% CI = 1.03–1.19, $p < 0.009$), while in the case of studies that focused on singletons, a statistically significant association between ART and ASD was not observed (RR = 0.96, 95% CI = 0.82–1.13, $p = 0.654$).

Conclusion: The present meta-analysis confirmed the existing positive correlation between ART and ASD in offspring, suggesting that ART is correlated with a higher risk for bearing a child with ASD. In contrast, this relationship is not confirmed in singletons. High quality prospective studies with a larger number of participants are still required.

What is Known:
- *Studies that investigated the association between ART and ASD in offspring have shown conflicting results.*
- *A previous meta-analysis showed that offspring conceived by ART are 1.35 times more likely to develop ASD than offspring spontaneously conceived.*

What is New:
- *This investigation separately considered studies with and without adjustment for confounders.*
- *The findings from the two analyses were similar.*

Keywords Assisted reproductive technology · Autism spectrum disorder · Infertility · Systematic review · Meta-analysis

Abbreviations

ART	Assisted reproductive technology
ASD	Autism spectrum disorder
ICSI	Intracytoplasmic sperm injection
LBW	Low birth weight
MAR	Medically assisted reproduction
NOS	Newcastle-Ottawa Scale

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Introduction

Autism spectrum disorder is a lifelong complex neurodevelopmental disorder characterized by persistent deficits in three vital domains, social interaction, communication, and repetitive stereotypical behaviors, activities, and interests. The first symptoms are present in early childhood,

usually after 36 months and before 3 years old, with different severity levels among individuals with ASD. The impact on the quality of their social life and autonomy and their families' lives is life-changing [1–3]. According to the last estimates from CDC's Autism and Developmental Disabilities Monitoring Network, 1 in 54 offspring is now born with ASD [4]. Despite many studies and extensive research, the exact etiology and the pathophysiologic mechanisms of ASD remain poorly understood.

Combinations of various heterogeneous causes that contribute to the pathogenesis of ASD have been described. These include prenatal, perinatal, postnatal and environmental factors [5–8]. Advanced parental age, preeclampsia, multiple pregnancies, pre-term delivery, and low birth weight (LBW) are some risk factors for ASD [9–12]. In addition, some studies have reported that parents of children with ASD are more likely to have infertility problems [13–15]. According to the World Health Organization, infertility affects 8–12% of couples of reproductive age worldwide.

Consequently, the percentage of couples who have offspring by ART has risen sharply over the last decade [16, 17]. ART includes all therapeutic procedures that intervene simultaneously in the gametes of both sexes. In contrast, it does not include therapies that intervene only in the sperm such as intrauterine or artificial insemination or drug treatments of ovarian stimulation which are not followed by ovulation, while medically assisted reproduction (MAR) includes ART procedures and/or the use of infertility medication [18].

Associations between ART and ASD might be anticipated because ART shares common risk factors with ASD such as multiple pregnancies, pre-term delivery, and LBW [19, 20]. Consequently, this field has attracted scientific interest and a large number of studies have attempted to investigate and determine the potential correlation between ART and ASD.

Sandin et al. [21] claimed that ART treatment using ICSI procedures has an increased risk of having offspring with intellectual disability and autistic spectrum disorder. To date, two systematic reviews and a meta-analysis have been published that attempted to combine the literature regarding the correlation between ART and the risk of ASD in offspring. Hvidtjørn et al. [22] conducted a systematic review of 41 studies, of which 31 studies examined all neurodevelopmental disorders and only eight focused on the autism spectrum. Their findings show that only the study of Klemetti et al. [23] resulted in a statistically significant correlation (OR 1.68, 95% CI 1.11–2.58) between ART and the risk of having offspring with a wide range of psychiatric disorders including ASD. In contrast, Maimburg et al. [24] detected a protective effect (OR 0.37, 95% CI 0.14–0.98) of ART concerning the risk of conceived offspring with ASD. Conti et al. [25] performed a systematic review of seven observational studies (five case–control and two cohorts), concluding that there is no significant association between ART and ASD in offspring. The meta-analysis of Liu et al. [26] found a statistically significant correlation (RR 1.35, 95% CI 1.09–1.68), showing that offspring conceived by ART are 1.35 times more likely to develop ASD than offspring spontaneously conceived.

This study aimed to present the results of a new systematic review and meta-analysis of the results of the studies that examined the association of the risk of conceiving offspring with ASD from ART and investigate the possible change of the above correlation after controlling for confounding factors. Also, an attempt was made to investigate separately the above correlation in the offspring of pre-term/full-term neonates, single/multiple births and according to sex.

Methods

The methods and the results of this study were carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [27]. The review protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews) with CRD (Centre of Reviews and Dissemination) report number CRD42020210749.

Search strategy

A systematic search was conducted to PubMed and Scopus until August 2, 2020, using the following specific keywords along with their combinations: "in vitro fertilization," "fertilization," "infertility," "assisted reproduction technologies," "intracytoplasmic sperm injection," "autism," "autistic," "Asperger syndrome," "Rett syndrome," and "developmental disorder." The keywords above were used to perform a thorough evaluation of the Medical Subject Headings (MeSH) with language and study population restrictions (only English and human studies). The complementary search was performed by scanning the references of the previous systematic reviews on the topic. The search strategy is shown in the Appendix.

Eligibility criteria

We considered all case–control and cohort studies that used as a type of conception the assisted reproductive technology and examined as outcome offsprings with autism according to the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM).

Studies without a control group, with a different outcome, and published in languages other than English were not considered inclusion criteria.

Study selection and data extraction

Two reviewers (M.T.A. and G.N.K.) independently screened the literature, reviewed the full text of all studies considered eligible according to the inclusion criteria and extracted the studies' data individually. Reviews, editorials, abstracts, letters to the editor, and studies with no adequate data were excluded. For all studies, the following data were recorded into Microsoft Excel spreadsheets: the name of the first author, year of publication, country of origin, the type of ART, the diagnostic criteria of ASD, the number of cases and controls and effect estimates and their corresponding 95% CI, and their adjusted factors in data analysis. In case that the effect estimates were not adjusted, we extracted a crude effect estimate. A third reviewer (P.T.) participated in resolving any queries derived from the process above.

Assessment of methodologic quality

To assess the methodological quality of each study included in the review, we used the quality assessment Newcastle–Ottawa 9-point-scale tool for case–control and cohort studies [28]. Two independent reviewers subsequently evaluated the included articles and scored them according to the criteria that existed in each domain. We assessed three main domains: selection, comparability, and outcome or exposure for cohort and case–control studies, respectively. Allocation of a study as a high, moderate or low quality is done using a star grading system. A study with a NOS score of more than seven stars was regarded as high methodological quality since a standard cut-off score for what is classified as a high-quality study has not been established.

Data analysis

A systematic review was performed for the studies that were regarded as eligible for the inclusion criteria. We also performed a meta-analysis using the studies that provided adequate data for statistical comparison. The relative ratios (ORs) calculated in the prospective and retrospective studies, and the relative risks (RRs), calculated in all studies above except the retrospective studies, show small numerical differences, unless a large extrapolation was observed. As the risk of autism was low, the relative risks and the corresponding 95% confidence interval (95% CI) were used as summary statistics to assess the association between assisted fertilization and the risk of autism in our systematic review and meta-analysis [29]. To assess the statistical significance of pooled RRs we performed a Z-test. The meta-analysis was performed using Stata 13 software [30]. The main analysis, and the subgroup analysis were performed using the random effect model due to the heterogeneity of the studies [31]. The I^2 test was used to assess statistical heterogeneity between the analyzed studies (significance level: $P \leq 0.1$) and the I^2 statistic, applying the following interpretation for I^2: $< 50\%$, low heterogeneity, 50–75%, moderate heterogeneity, and $> 75\%$, high heterogeneity [32]. Heterogeneity was investigated using subgroup analysis according to the geographical origin of the study and study type. We also performed sensitivity analysis by excluding each of the analyzed studies at a time in sequence to assess the stability of our results. Additionally, to further explore the source of study heterogeneity, we used the Galbraith plot [33, 34]. The publication bias was assessed using the Egger test and a p-value of < 0.05 stated statistically significant publication bias [35, 36].

Results

Search results

The initial search procedure yielded 587 studies. After removing duplicates, we screened 570 studies by title and abstract, and from them, 496 were excluded subsequently, and 74 studies were screened by full text for eligibility (Fig. 1). Finally, 16 studies [13, 15, 21–24, 37–46] were included in our systematic review, and 15 studies [15, 21–24, 37–46] provided adequate data that enabled for statistical comparisons and, therefore, were included in our meta-analysis. The detailed flow diagram of the study selection process and the various reasons for exclusion studies are shown in Fig. 1.

All included studies were published between 2006 and 2020. Among them, eight studies were cohort [13, 21–23, 37, 38, 43, 44] and eight case–control [15, 24, 39–42, 45, 46]. Six studies were performed in Europe [21–24, 40, 44], five in America [15, 37–39, 41], and five in Asia [13, 42, 43, 45, 46].

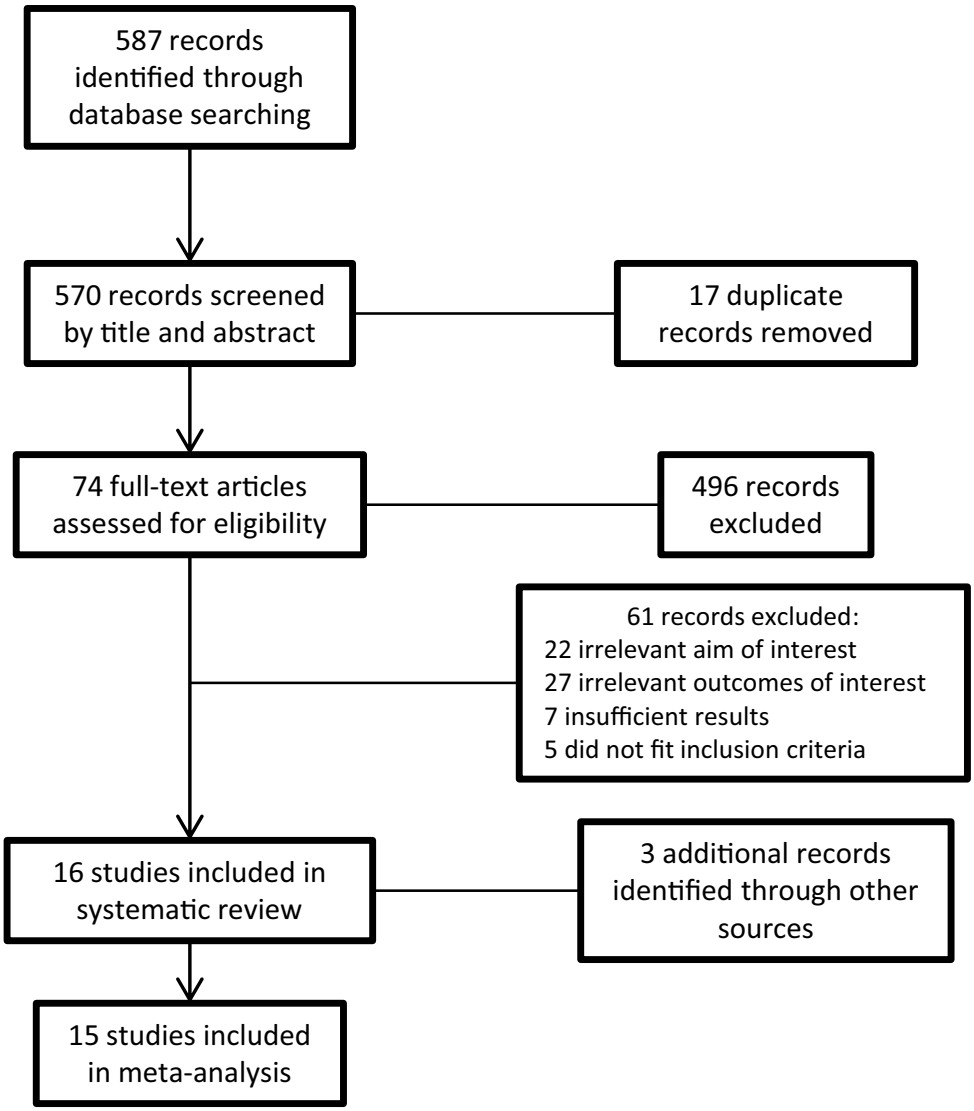

Fig. 1 Flow diagram. A total of 587 studies were obtained with the search strategy of which 16 were included in the systematic review and 15 in the meta-analysis

Regarding the type of ART, we found that nine studies examined all types of ART [15, 24, 37–39, 41, 42, 44, 46], four studies examined in vitro fertilization [13, 21, 23, 40], and three studies assessed in vitro fertilization in combination with ICSI or ovulation induction (Table 1) [22, 43, 45].

Results of systematic review

Association of ART and ASD in offspring

A total of 15 studies evaluated the potential association between ART and the risk of ASD in offspring (Table 1) [15, 21–24, 37–46]. The 14 studies that did not check for confounding factors showed that offspring conceived by ART was 0.41–8.61 times more likely to present ASD compared to offspring spontaneously conceived (Table 1) [15, 21–24, 37–43, 45, 46]. In 11 studies the control for common confounders such as the mother's age and race, and gestational age was shown to reduce the risk of developing ASD to 0.37–4.98 (Table 1) [15, 21–24, 37, 38, 40, 41, 44].

Association of ART and ASD in pre-term offspring

One of 16 studies provided data regarding the potential association between ART and the risk of ASD in pre-term offspring and suggested that pre-term offspring conceived by ART are 1.57 times more likely to develop ASD compared to pre-term conceived spontaneously (Table 1) [37]. In two

Table 1 Characteristics of the studies included in the systematic review and meta-analysis

Author (year)	Country	Study design	ART type	Outcome	Diagnosis ASD	Case N (%)	Control N (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	Methodological assessment Total score (max 9★)
All offspring										
Sandin et al. 2013 [21]	Sweden	Cohort	IVF	Autistic disorder	ICD-9/ICD-10	30,959	251,0166	1.22 (1.01–1.49)	1.14 (0.94–1.39)[a]	8★
Fountain 2015 [38]	USA	Cohort	ART	Autism	DSM-IV	48,865	5,877,386	1.79 (1.63–1.95)	1.713 (1.551–1.892)[b]	7★
Lehti et al. 2013 [40]	Finland	Case–Control	IVF	ASD	ICD-9/ICD-10	4164	16,353	1.1 (0.8–1.5)	0.9 (0.7–1.3)[c],*	8★
Maimburg and Vaeth 2007 [24]	Denmark	Case–Control	ART	Infantile autism	ICD-9/ICD-10	473	473	0.41 (0.19–0.89)	0.37 (0.14–0.98)[d],*	8★
Diop et al. 2019 [37]	USA	Cohort	ART	ASD	ICD-9-CM	10,147	441,898	1.20 (1.00–1.45)	1.08 (0.89–1.31)[e],*	6★
Schieve et al. 2017 [15]	USA	Case–Control	ART	ASD	NM	26	30	1.3 (0.7–2.2)	1.3 (0.7–2.4)[f],*	6★
Svahn et al. 2015 [44]	Denmark	Cohort	ART	ASD	ICD-8/ICD-10	124,269	2,288,452	NM	1.06 (0.99–1.13)[g]	8★
Kamowski-Shakibai et al. 2015 [39]	USA	Case–Control	ART	ASD	NM	8	5	1.73 (0.33–9.08)*	NM	4★
Özbaran et al. 2011 [42]	Turkey	Case–Control	ART	ASD	DSM-IV/ADSI/ WISC-R	3	67	0.49 (0.04–5.61)	NM	3★
Lyall et al. 2012 [41]	USA	Case–Control	ART	Autism	NM	12	463	1.31 (0.69–2.48)	0.85 (0.40–1.78)[h],*	7★
Hvidtjørn et al. 2009 [22]	Denmark	Cohort	IVF or OI	ASD	F84.0, F84.1, F84.5, F84.8 and F84.9	33,139	555,828	1.25 (1.09–1.43)	1.13 (0.97–1.31)[i]	8★
Klemetti et al. 2006 [23]	Finland	Cohort	IVF	ASD	ICD-10	3737	188,298	1.18 (0.98–1.41)	1.18 (0.98–1.41)[j],*	7★
Shimada et al. 2012 [43]	Japan	Cohort	IVF/ICSI	More than ASD	DSM-IV-TR	467	100,118	1.84 (1.18–2.85)	NM	5★
Zachor and Ben Itzchak 2011 [45]	Israel	Case–Control	IVF and ICSI	ASD	DSM-IV-TR	285	53,080	2.78 (1.81–4.27)	NM	4★
Jenabi et al. 2020 [46]	Iran	Case–Control	ART	ASD	NM	100	200	8.61 (1.79–41.34)	4.98 (0.91–27.30)[k]	7★
Pre-term										
Sandin et al. 2013 [21]	Sweden	Cohort	IVF	Autistic disorder	ICD-9/ICD-10	5942	143,688	NM	1.10 (0.78–1.54)[a]	8★
Diop et al. 2019 [37]	USA	Cohort	ART	ASD	ICD-9-CM	NM	NM	1.57 (1.41–1.75)	1.31 (1.17–1.47)[e],*	6★
Term										
Sandin et al. 2013 [21]	Sweden	Cohort	IVF	Autistic disorder	ICD-9/ICD-10	25,017	2,366,478	NM	1.00 (0.79–1.28)[a]	8★
Schieve et al. 2017 2017[15]	USA	Case–Control	ART	ASD	NM	NM	NM	NM	1.5 (0.7–3.2)[f],*	8★
Singletons										
Sandin et al. 2013 [21]	Sweden	Cohort	IVF	Autistic disorder	ICD-9/ICD-10	22,228	2,455,493	0.96 (0.74–1.26)	0.89 (0.68–1.17)[a]	8★
Lehti et al. 2013 [40]	Finland	Case–Control	IVF	ASD	ICD-9/ICD-10	NM	NM	1.2 (0.9–1.7)	1.0 (0.7–1.5)[c],*	8★
Schieve et al. 2017 [15]	USA	Case–Control	ART	ASD	NM	NM	NM	NM	0.6 (0.2–1.8)[f],*	8★
Klemetti et al. 2006 [23]	Finland	Cohort	IVF	ASD	ICD-10	2930	186,216	1.03 (0.82–1.29)	1.03 (0.82–1.30)[j],*	7★
Pre-term singletons										
Sandin et al. 2013 [21]	Sweden	Cohort	IVF	Autistic disorder	ICD-9/ICD-10	1844	120,702	NM	0.71 (0.34–1.50)[a]	8★

Table 1 (continued)

Author (year)	Country	Study design	ART type	Outcome	Diagnosis ASD	Case N (%)	Control N (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	Methodological assessment Total score (max 9★)
All offspring										
Term singletons										
Sandin et al. 2013 [21]	Sweden	Cohort	IVF	Autistic disorder	ICD-9/ICD-10	20,384	2,334,791	NM	0.89 (0.67–1.19)[a]	8★
Multiple births										
Klemetti et al. 2006 [23]	Finland	Cohort	IVF	ASD	ICD-10	807	2084	0.91 (0.57–1.45)	0.95 (0.59–1.52)[j],*	7★
Male										
Davidovitch et al. 2018 [13]	Israel	Cohort	IVF	ASD	DSM-IV	975	107,573	1.00 (0.62–1.06)	0.704 (0.375–1.323)[f]	5★
Hvidtjørn et al. 2009 [22]	Denmark	Cohort	IVF or OI	ASD	F84.0, F84.1, F84.5, F84.8 and F84.9	NM	NM	1.18 (1.01–1.37)	1.07 (0.91–1.27)[i]	8★
Female										
Hvidtjørn et al. 2009 [22]	Denmark	Cohort	IVF or OI	ASD	F84.0, F84.1, F84.5, F84.8 and F84.9	NM	NM	1.55 (1.14–2.10)	1.32 (0.93–1.88)[i]	8★

ART assisted reproductive technology, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *ICD* International Classification of Diseases, *IVF* in vitro fertilization, *NM* not mentioned. Studies with Newcastle Ottawa Score ≥ 7 stars is considered of high methodological quality, and thus, of low risk of bias.

~The RRs were calculated from the raw data of studies

*Outcomes were measured as odds ratio (OR) between the two groups (intervention group and control/reference group). Also, the outcomes for each group were expressed as percentages (%). For each relationship measure, the corresponding 95% confidence interval (CI) was calculated

[a]Adjusted for sex, attained age, birth year, paternal age categorically, maternal age categorically, maternal psychiatric history at offspring birth, paternal psychiatric history at offspring birth

[b]Adjusted for year of birth, infant's gender, and mother's education and race

[c]Adjusted for maternal age, SES, gestational age, and parity

[d]Adjusted for mother's age, mother's country of origin, parity, multiplicity, birth weight, gestational age, and birth defect

[e]Adjusted for maternal demographics (maternal paternal age, race, education, marital status, nativity), insurance, smoking, prenatal care, parity, gender, method of delivery, chronic and pregnancy hypertension, gestational and chronic diabetes, breech

[f]Adjusted for maternal age at birth, maternal education at birth, maternal race-ethnicity, parity of index birth, and child sex

[g]Adjusted for year of birth, birth order, sex, maternal age at birth, paternal age at birth, and parental history of mental disorder

[h]Adjusted for maternal and paternal age, race, income, and birth order

[i]Adjusted for maternal age, educational level, parity, smoking, body weight, and multiplicity

[j]Adjusted for mother's socioeconomic position

[k]Adjusted for mother and neonate variables

studies, the adjustment for potential confounding factors did not significantly differentiate the observed association [21, 37].

Association of ART and ASD in term offspring

The possible association noted above was assessed in terms of offspring in two studies that check for confounding factors. The results showed that term offspring conceived by ART have a 1–1.5 times higher risk of developing ASD than term spontaneously conceived offspring (Table 1) [15, 21].

Association of ART and ASD in singletons and multiple births

According to three studies that provided data regarding the assessment of association only in singletons, the results indicated that offspring conceived by ART are 0.96–1.2 more likely to develop ASD than the spontaneously conceived pregnancies (Table 1) [21, 23, 40]. Adjustment for confounding factors revealed a reduction of correlation but not significantly (Table 1) [15, 21, 23, 40]. Regarding the assessment of association in multiple births, one study that focused on this category of pregnancies revealed that offspring by ART have a 0.91 times higher risk to develop ASD compared to offspring conceived spontaneously, without a statistically significant difference when the study checked for confounding factors (Table 1) [23].

Association of ART and ASD in pre-term and term singletons

One study that checked for confounding factors concluded that pre-term singletons conceived by ART have a 0.71 times higher risk to develop ASD than offspring conceived spontaneously. The same study found that the risk for the term singletons conceived by ART is 0.89 times higher compared to offspring conceived spontaneously (Table 1) [21].

Association of ART and ASD in males and females

Regarding sex, two studies with or without checking for confounding factors showed that males [13, 22] derived by ART have a lower risk compared to females [22] conceived by ART. The risk for males was calculated to be 1–1.18 compared to 1.55 for females and the adjustment for potential confounding factors did not significantly differentiate the observed association (Table 1).

Results of meta-analysis

From the above correlations, the two groups of studies that examined the association of ART and ASD in offspring and singletons provided sufficient data and were involved in our meta-analysis. Fourteen studies that did not check for potential confounders provided data regarding the risk of the autism spectrum in offspring conceived by ART. According

Table 2 Summary of meta-analysis results for the correlation of ART and ASD in offspring without control for confounding factors

Groups	Studies	Test of association				Heterogeneity			Publication bias	
		RR (95% CI)	*p*-value	Model	Z	X^2	*p*-value	I^2 (%)	Egger	Begg
Total studies	14	1.37 (1.15–1.64)	0.001	RE	3.45	66.89	< 0.001	80.6	0.484	0.352
Sub-group analyses										
Study design										
Cohort	5	1.32 (1.08–1.62)	0.007	RE	2.68	37.71	< 0.001	89.4	0.022	0.624
Case–control	9	1.44 (0.94–2.19)	0.090	RE	1.69	29.17	< 0.001	72.6	0.971	0.677
Region										
Europe	5	1.16 (1.00–1.34)	0.048	RE	1.98	8.13	0.087	50.8	0.020	0.050
America	5	1.44 (1.09–1.90)	0.011	RE	2.53	15.62	0.004	74.4	0.407	0.624
Asia	4	2.41 (1.41–4.13)	0.001	RE	3.22	5.94	0.114	49.5	0.949	1.000
After removing four studies	10	1.23 (1.14–1.33)	0.000	RE	5.14	4.79	0.852	0.00	0.660	0.788

RE random effects

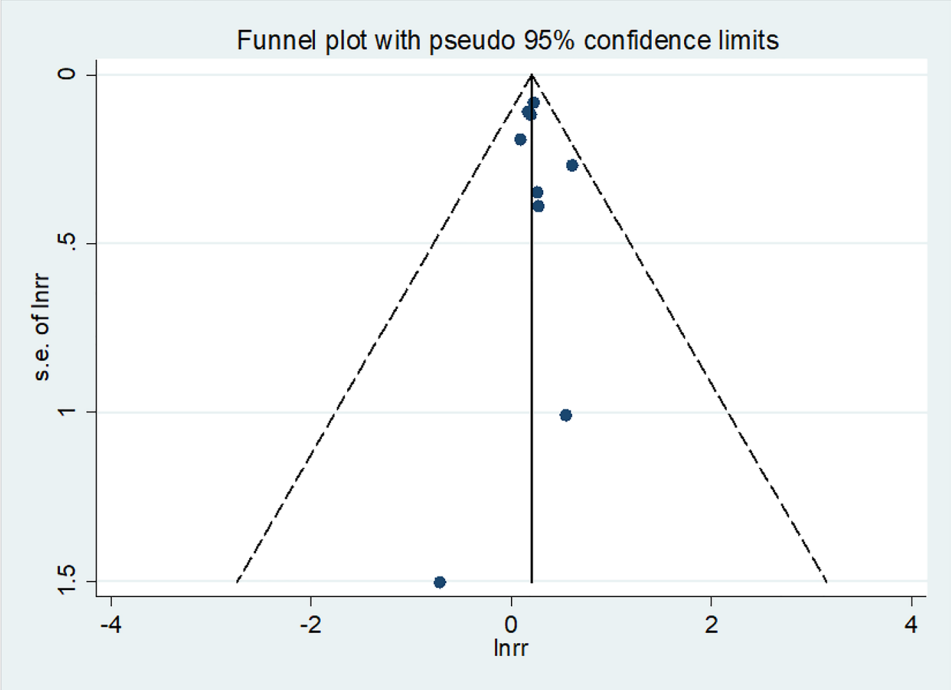

Fig. 2 Funnel plot of studies examining the association between ASD in offspring and ART without control for confounding factors

to the findings of these studies, offspring conceived by ART have a statistically significant increased risk to develop autism spectrum compared to offspring spontaneously conceived (RR = 1.37, 95% CI 1.15–1.64, $p = 0.001$) with no significant publication bias in our study (Egger test = 0.484) (Table 2). The heterogeneity in this group of studies was also significant ($I^2 = 80.6$, $p < 0.001$). To explore the heterogeneity between studies, we performed sub-group analyses based on the study type and geographical origin of the study. The results revealed a non-statistically significant association between ART and the risk of ASD in studies designed case–control (RR = 1.44, 95% CI 0.94–2.19, $p = 0.090$) with no publication bias (Table 2).

Since no significant reduction of between studies heterogeneity was observed, we performed a Galbraith plot to evaluate the source of heterogeneity graphically. According to the Galbraith plot four studies were outside the bounds and were identified as the primary source of heterogeneity. After removing these studies, the heterogeneity was eliminated ($I^2 = 0.0\%$, $p = 0.852$), even though a slight asymmetry in the funnel plot (Fig. 2) was found, there was no publication bias (Egger test = 0.660) and the association between ART and ASD remained statistically significant (RR = 1.23, 95% CI 1.14–1.33, $p < 0.001$) (Fig. 3) (Table 2).

The assessment of the impact of the individual study on the effect size of our result, by performing a sensitivity analysis suggested that no obvious changes were found after removing each study at the time (data not shown). The group of eleven studies that examined the association of ART and ASD in offspring and controlled for main common confounding factors indicated that there was no statistically significant association between ART and ASD (RR = 1.14, 95% CI 0.95–1.36, $p = 0.158$) (Table 3). No statistically significant publication bias was observed (Egger test = 0.138). The heterogeneity in this group of studies was also significant ($I^2 = 83.3$, $p < 0.001$). We proceeded to investigate heterogeneity by performing subgroup analysis, which did not significantly change the above correlation.

Subsequently, because no significant reduction in heterogeneity was observed, we explored the source of study heterogeneity, using the Galbraith plot. After removing the two studies identified from the Galbraith plot, the heterogeneity was eliminated ($I^2 = 0.0\%$, $p = 0.603$). Even though a slight asymmetry in the funnel plot (Fig. 4) was found, no publication bias was noticed (Egger test = 0.556), and the association between ART and ASD in offspring changed to statistically significant (RR = 1.11, 95% CI 1.03–1.19 $p = 0.009$) (Fig. 5) (Table 3).

To assess the impact of each study on the effect size of our result, we performed a sensitivity analysis that suggested no obvious changes were found after removing each study at the time (data not shown). The meta-analysis of the

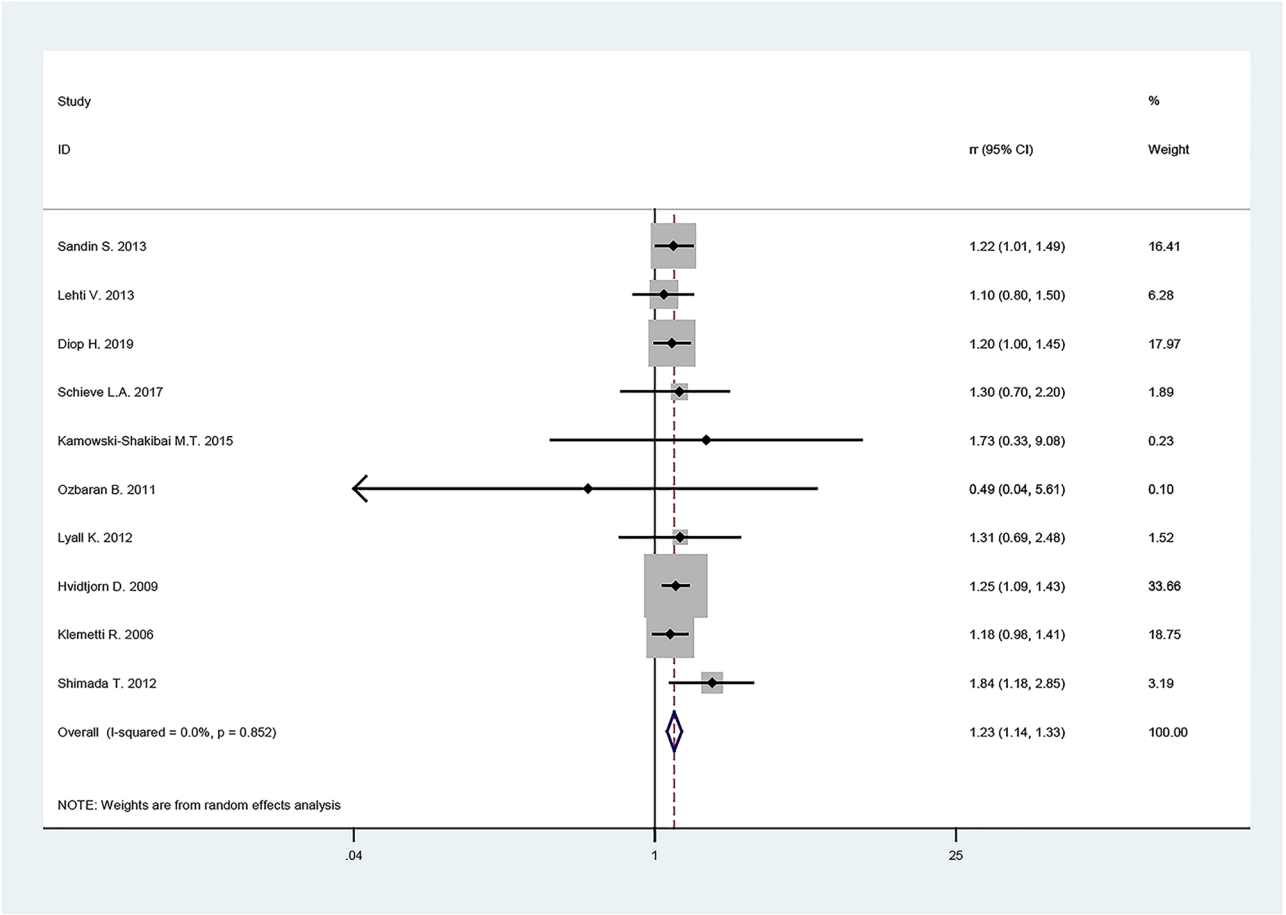

Fig. 3 Forest plot of ASD risk in offspring associated with ART, without control for confounding factors

studies that focused on singletons demonstrated a no statistically significant association between ART and ASD without (Fig. 6) or with control for confounding factors (Fig. 7) (Table 4).

Table 3 Summary of meta-analysis results for the correlation of ART and ASD in offspring with control for confounding factors

Groups	Studies	Test of association				Heterogeneity			Publication bias	
		RR (95% CI)	*p*-value	Model	Z	X^2	*p*-value	I^2 (%)	Egger	Begg
Total studies	11	1.14 (0.95–1.36)	0.158	RE	1.41	59.79	< 0.001	83.3	0.138	0.938
Subgroup analyses										
Study design										
Cohort	6	1.21 (1.00–1.46)	0.055	RE	1.92	44.18	< 0.001	88.7	0.007	0.851
Case–control	5	0.95 (0.60–1.50)	0.824	RE	0.22	8.42	0.077	52.5	0.723	0.624
Region										
Europe	6	1.09 (0.98–1.21)	0.130	RE	1.51	7.43	0.191	32.7	0.011	0.091
America	4	1.27 (0.89–1.81)	0.185	RE	1.33	19.95	< 0.001	85.0	0.355	0.497
After removing two studies	9	1.11 (1.03–1.19)	0.009	RE	2.61	6.40	0.603	0.00	0.556	0.677

RE random effects

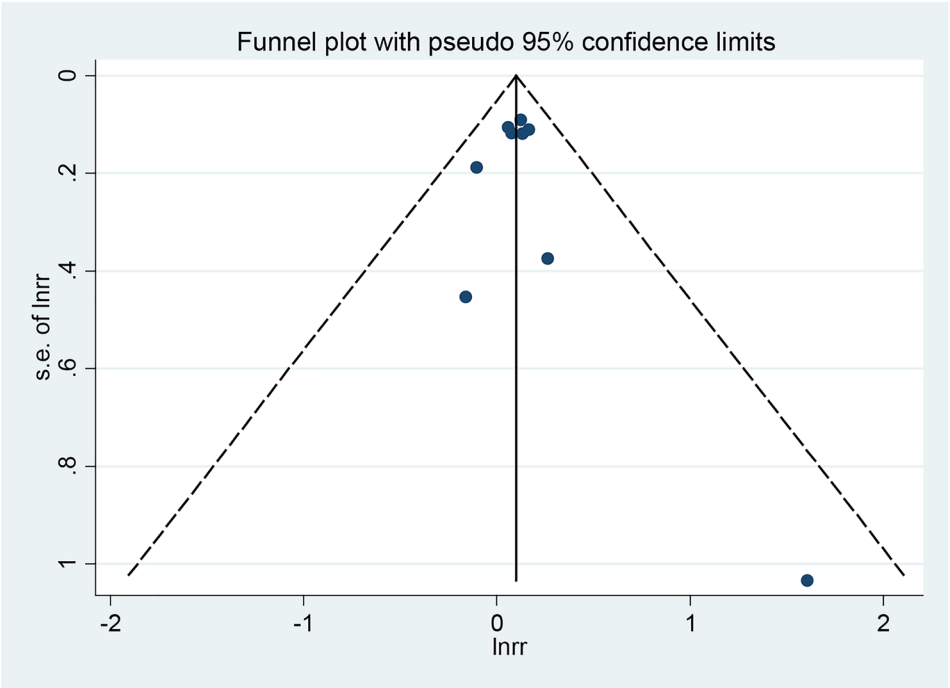

Fig. 4 Funnel plot of studies examining the association between ASD in offspring and ART, controlling for confounding factors

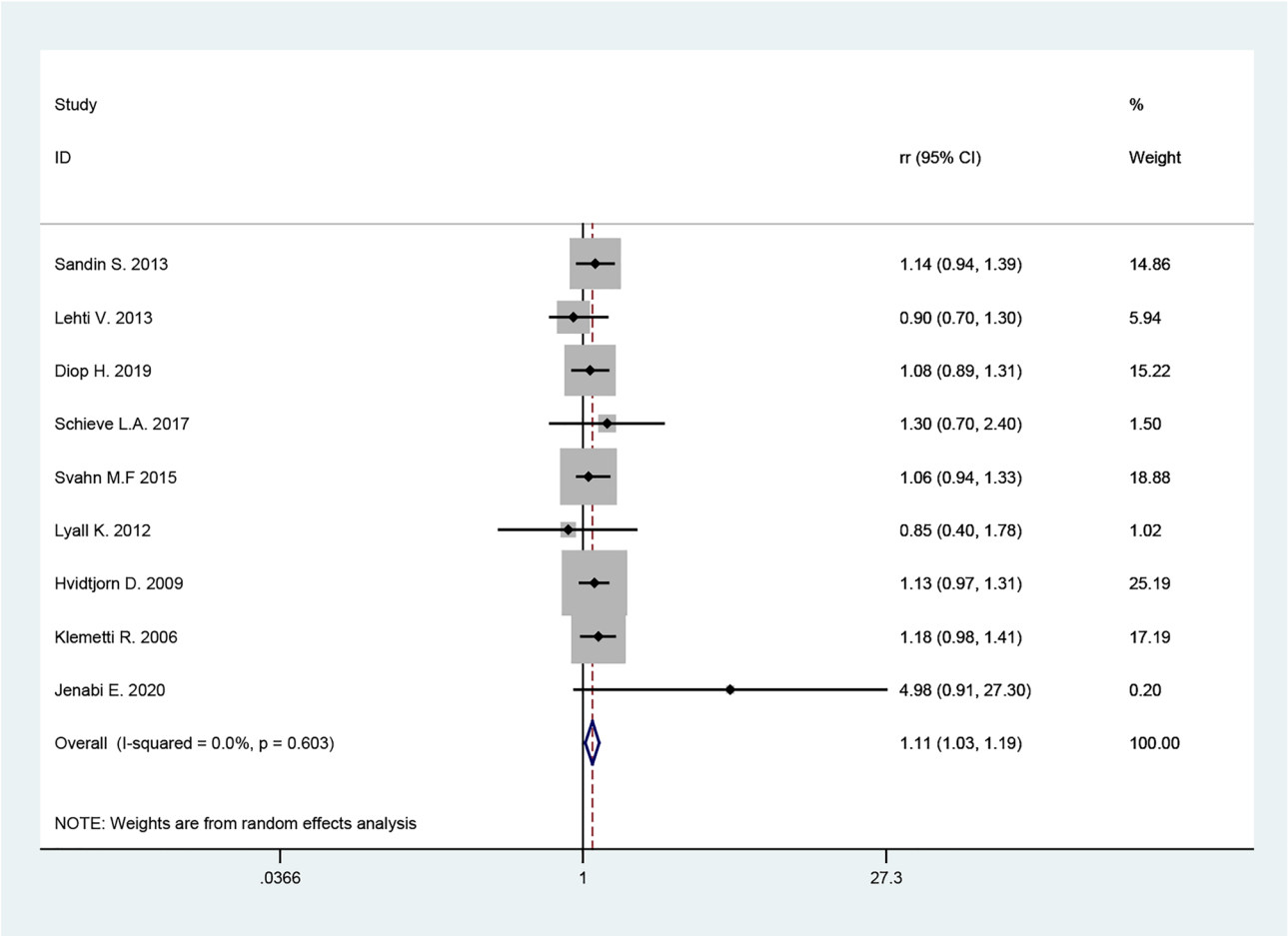

Fig. 5 Forest plot of ASD risk in offspring associated with ART, controlling for confounding factors

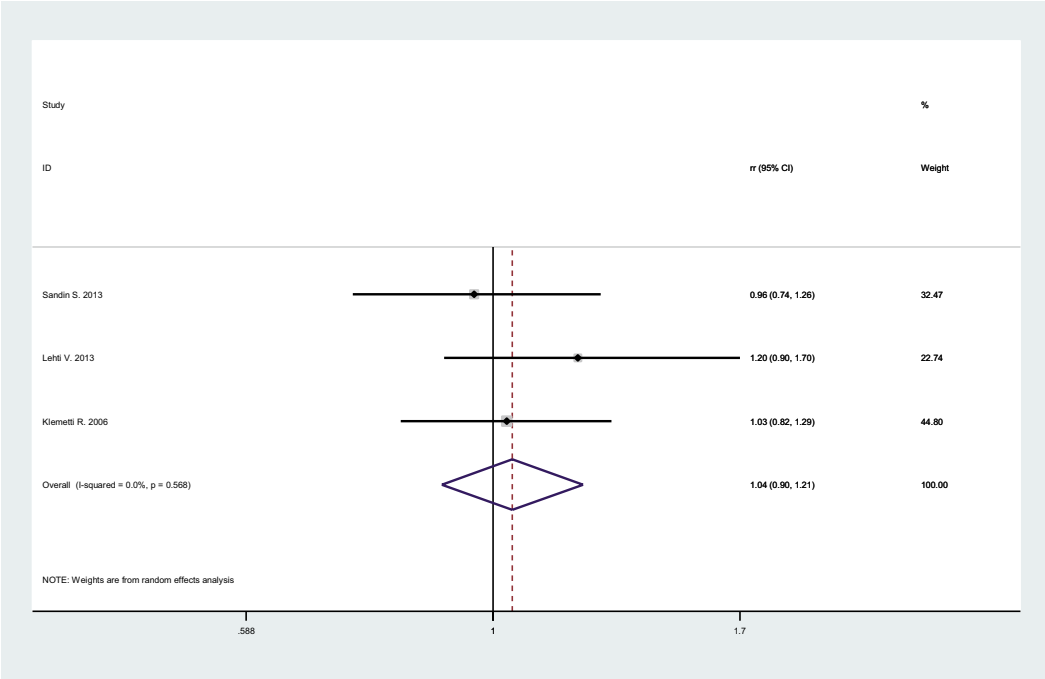

Fig. 6 Forest plot of ASD risk in singletons associated with ART, without control for confounding factors

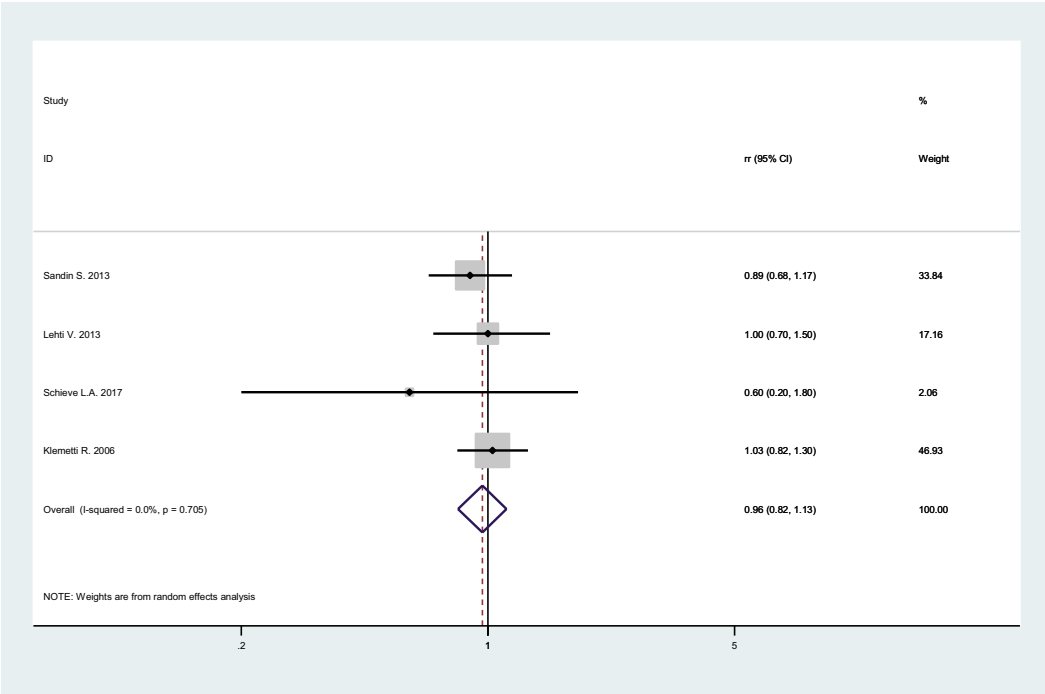

Fig. 7 Forest plot of ASD risk in singletons associated with ART, controlling for confounding factors

Table 4 Summary of meta-analysis results for the correlation of ART and ASD in singletons without and with control for confounding factors

Groups	Studies	Test of association				Heterogeneity			Publication bias	
		RR (95% CI)	*p*-value	Model	Z	X^2	*p*-value	I^2 (%)	Egger	Begg
Total studies (crude RRs)	3	1.04 (0.90–1.21)	0.592	RE	0.54	1.13	0.568	0.00	0.561	0.602
Total studies (adjusted RRs)	4	0.96 (0.82–1.13)	0.654	RE	0.45	1.40	0.705	0.00	0.295	0.174

RE random effects

Discussion

This study aimed to provide an up-to-date meta-analysis of available data from studies that assessed the risk of bearing a child with autism spectrum disorder (ASD) after being conceived by assisted reproductive technology (ART). The results of this meta-analysis indicated that ART is associated with a higher risk of ASD in offspring (RR = 1.11, 95% CI = 1.03–1.19, $p < 0.009$), except in the cases of singletons (RR = 0.96, 95% CI = 0.82–1.13, $p = 0.654$).

A previous meta-analysis by Liu et al. [26] which included 11 studies, similarly found that offspring conceived by ART are more likely to develop ASD than offspring spontaneously conceived (RR 1.35, 95% CI 1.09–1.68) [26]. Our results are in line with those of Liu et al. [26]; however, our study has several important strengths.

First, the present meta-analysis included new recently published studies and only studies that distinctly examined the assisted reproductive technology, as a way of treating infertility, while Liu et al. [26] included two studies with an unknown way of infertility treatment and one study that generally used MAR.

Second, to assess the crucial role of confounder factors and the possibility to be a direct risk for ASD, we extracted and collected the crude and adjusted data separately from the studies and performed two independent meta-analyses. In contrast, Liu et al. [26] analyzed crude and adjusted data together, extracting a mixed effect size. On account of numerous and varied combinations of confounding factors controlled in each study we could not conduct a subgroup analysis according to each combination and for each type of ART due to the limitation of data. Most studies controlled for many potential environmental factors associated with ASD, like maternal age, maternal race, gestational age, maternal infertility, and parental infertility. The control for, maternal age and race, and gestational age was common in many studies.

It should be noted that our findings from the two meta-analyses confirmed the positive association between ART and ASD in different degrees, which is a field for further investigation, showing that ART may be an independent risk factor for ASD. Specifically, in the present meta-analysis, we found that ART may be associated with a higher risk of having offspring with ASD (RR = 1.23, 95% CI 1.14–1.33, $p < 0.001$), while when we proceeded to the meta-analysis only those studies that had controlled for confounding factors, the degree of correlation between the ART and ASD decreased (RR = 1.11, 95% CI 1.03–1.19, $p = 0.009$). To summarize, the results raise important questions about the impact rate of the involvement of the above factors in the risk of ASD in offspring and whether these factors are primary or play a secondary role in the development of autism.

Regarding singletons, we did not detect a positive association (RR = 0.96, 95% CI = 0.82–1.13, $p = 0.654$), suggesting that multiple pregnancies may be an independent direct risk for ASD. Consequently, more large studies are needed to better identify factors leading to ASD and whether the increased risk is due to the underlying cause of infertility, advanced parental age, or if it is due entirely to ART interventions [47–49].

Epigenetic changes might be a conceivable molecular mechanism linking ART with ASD. Many neurodevelopmental and neuropsychiatric disorders, characterized by autistic like features (e.g., ASD, Beckwith–Wiedemann syndrome, and Angelman syndrome) have been observed to be related to epigenetic mechanisms, such as a defect in genetic imprinting [50–52]. ART consists of a various in vitro manipulations and interventions at the cellular level, including repeated hormone exposure, retrieval and isolation of gametes, handling and culture of gametes and early embryos, cryopreservation, and embryo transfer procedures that appear to be prone to epigenetic changes [53, 54]. Also several parents with infertility problems were found to carry pre-existing imprinting errors, with the SNRP, UBE3A, H19, and LIT1 genes being some of those involved [55, 56]. Thus, it is crucial to develop a better understanding and determine whether any modified genes responsible for ASD are associated with infertility or the treatments used. As the epigenome is most vulnerable in the early developmental period, the potential imprinting disorders perhaps contribute to these major epigenetic in this early and crucial development time. Therefore, supplementary epigenetic studies will be required to understand the pathogenesis and the association of ART with ASD. Nevertheless, we must consider that the study of epigenetics is complicated because it is not clear

at what point these imprinting errors arise and epigenetics of any tissue can occur at any time.

Study limitations

This systematic review and meta-analysis, although performed using strict search strategy and methods, has limitations. First, we did not include data from unpublished studies. However, we assessed the potential presence of publication bias in all respective statistical analyses of the review/meta-analysis. Both prospective and retrospective studies were included. These studies are characterized by different methodological designs with retrospective studies including recall bias. This error was considered, and its consequence on the change of the effect size of assisted reproduction on the risk of having offspring with autism spectrum disorder was tested. We performed subgroup analyses based on the type of studies that participated.

Moreover, as the risk of autism was low, the relative risks and the corresponding 95% confidence interval (95% CI) were used as summary statistics to assess the association between assisted fertilization and the risk of autism in our systematic review and meta-analysis, although the relative ratios (ORs) were calculated in the prospective and retrospective studies, and the relative risks (RRs) were calculated in all studies above, except the retrospective studies. The language restrictions of this review should also be taken into consideration.

Also, we should note that we accepted all the diagnostic criteria for ASD as reported in the original papers. Finally, assisted reproductive technology is quite new in medicine and characterized by numerous and complex therapeutic procedures, making it particularly difficult to identify individual risk factors. Unmeasured and uncontrolled risk factors have the potential to produce biases. In the present study, we could not rule out the effects of infertility causes and their possible effect on ASD outcome. We could not interpret the potential biological mechanism of the association between ART and ASD. Therefore, more studies, mainly cohort, should be included in future reviews to confirm or refute and interpret the correlation of different assisted reproduction techniques with the risk of having offspring with autism spectrum.

Conclusion

This systematic review and meta-analysis evaluated the association between ART and the risk of ASD in offspring. According to our results, ART was associated with a higher risk of ASD except, in the cases of singletons. These results must be interpreted with caution since people requesting ART are usually at an advanced age with different infertility forms, all of which are risk factors for fetal and neonatal abnormalities. Further high-quality prospective studies with a larger number of participants are required to determine the association between ART and ASD.

Appendix

The search string that we used to Pubmed was: (((((in vitro fertilization[MeSH Terms]) OR (fertilization[MeSH Terms])) OR (infertility[MeSH Terms])) OR (assisted reproduction technologies[MeSH Terms])) OR (intracytoplasmic sperm injection[MeSH Terms]) AND ((humans[Filter]) AND (English [Filter]))) AND (((((autism[MeSH Terms]) OR (autistic[MeSH Terms])) OR (asperger syndrome[MeSH Terms])) OR (rett syndrome[MeSH Terms])) OR (developmental disorder[MeSH Terms]) AND ((humans[Filter]) AND (English [Filter])))). The search string that was applied to Scopus database was: ((TITLE-ABS-KEY (in AND vitro AND fertilization) OR TITLE-ABS-KEY (fertilization) OR TITLE-ABS-KEY (infertility) OR TITLE-ABS-KEY (assisted AND reproduction AND technologies) OR TITLE-ABS-KEY (intracytoplasmic AND sperm AND injection))) AND ((TITLE-ABS-KEY (autism) OR TITLE-ABS-KEY (autistic) OR TITLE-ABS-KEY (asperger AND syndrome) OR TITLE-ABS-KEY (rett AND syndrome) OR TITLE-ABS-KEY (developmental AND disorder))) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English")) AND (EXCLUDE (EXACTKEYWORD, "Nonhuman")).

Authors' contributions MTA: conceived the study, participated in its design, collection, and interpretation of the data; she also performed the data collection and extraction, as well as the statistical analyses, and helped draft the manuscript. GNK: contributed to the data collection and extraction, in the analysis of the results, and in drafting the manuscript. PT: contributed to the data collection and extraction, as well as in the analysis of the results. CD: participated in the manuscript's design and coordination. EZ: participated in the manuscript's design and coordination. IS: participated in the manuscript's design and coordination. All authors have read and approved the final version of the manuscript.

Declarations

Ethical approval All analyses were based on previous published studies; thus, no ethical approval was required.

Conflict of interest The authors declare no competing interests.

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