INPLASY

INPLASY2023110007

doi: 10.37766/inplasy2023.11.0007

Received: 02 November 2023

Published: 02 November 2023

Association of assisted reproductive technology with attention-deficit/hyperactivity disorder in offspring: A protocol for a systematic review and meta analysis

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ADMINISTRATIVE INFORMATION

Support - National Natural Science Foundation of China(82271518).

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2023110007

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 November 2023 and was last updated on 02 November 2023.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis was to assess the possible association between assisted reproductive technology (ART) and attention deficit hyperactivity disorder (ADHD) risk in offspring.

Condition being studied Attention-deficit hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder characterized by age-inappropriate and impairing levels of inattention, hyperactivity, or impulsivity, or a combination. The global prevalence of ADHD was reported as 7.6% in children aged 3 to 12 years and 5.6% in teenagers aged 12 to 18. The prevalence of persistent adult ADHD from childhood and that of symptomatic adult ADHD were 2.58% and 6.76% in 2020. ADHD impairs multiple aspects of life, increasing the risk of health problems, psychiatric co-morbidities, social disability, academic and occupational failure, thus imposing a substantial humanistic and economic burden on affected individuals and society.

The etiology of ADHD is multifactorial, involving genetic, environmental, and possibly epigenetic factors. Evidence has indicated that several antenatal (ante-), perinatal (peri-), and neonatal environmental factors including advanced parental age, maternal diabetes and hypertension, threatened abortion may be associated with increased risk of ADHD in offspring. Assisted reproductive technology (ART) has also been suggested as a risk factor for ADHD in offspring.

Assisted reproductive technologies (ART) refers to the technologies used to manipulate sperm, oocytes, and embryos to address infertility, mainly including artificial insemination (AI), intracytoplasmic sperm injection (ICSI), in vitro fertilization (IVF) and embryo transfer (IVF–ET).The use of ART has risen rapidly worldwide and is responsible for over than 8 million births in all. While ART continues to benefit many couples around the world, studies have reported that ART conception is associated with higher risk of adverse outcome, particularly concerning preterm

birth, low birth weight, and birth defects and genetic imprinting disorders, which may account for the development of ADHD.
In recent years, several studies focused on the potential effects of ART on the risk of ADHD in offspring, however, the results of these studies were inconclusive. Some studies found that ART was associated with an increased risk of ADHD in offspring,though a similar association was not confirmed in other studies. Therefore, the purpose of this study will be to explore whether there is an association between ART and ADHD risk in offspring and investigate the possible change of the above association after controlling for confounding factors.

METHODS

Participant or population Pregnant women with assistant reproductive techniques and their offspring will beincluded.

Intervention Any types of ART, such as Intrauterine insemination (IUI), in vitro fertilization (IVF), ovulation induction (OI), intracytoplasmic sperm injection [ICSI], or other forms of treatment (frozen/thawed embryo transfer or performing assisted hatching before embryo transfer).

Comparator Pregnant women without assistant reproductive techniques and their offspring will be used as the control group.

Study designs to be included Observational studies, including cohort, case–control, and cross-sectional studies, will be included in this study.

Eligibility criteria (1) Observational studies, including cohort, case–control, and cross-sectional studies, will be included in this study.(2) These studies should have reported the relative risk (RR) or odds ratio (OR) and their corresponding 95% confidence interval (CI) of association of ART with the ADHD risk in offspring, or have reported sufficient data to calculate the aforementioned risk estimates and 95% CI.(3) If more than one study is generated from the same cohort, the study that reported the largest number of ADHD cases will be included.

Information sources Relevant studies will be identified by searching PubMed, The Cochrane Library, Web of Science, Embase, China National Knowledge Infrastructure and China Biology Medicine disc databases. All of the databases will be searched from inception to November, 2023.

Main outcome(s) The outcome is the incidence of ADHD, which will be ascertained by the International Classification of Diseases or the Diagnostic and Statistical Manual of Mental Disorders, or their related diagnostic tools.

Quality assessment / Risk of bias analysis To assess the methodological quality of each study included in the meta-analysis, we used the quality assessment Newcastle–Ottawa 9-point-scale tool for case–control and cohort studies.This tool evaluates the selection of study groups (maximum of 4 stars), comparability of the study populations (maximum of 2 stars), and ascertainment of outcomes (for cohort studies) or exposure (for case-control studies) (maximum of 3 stars). A high score indicates a low risk of methodological quality. The scale of the Agency for Healthcare Research and Quality will be used to assess cross-sectional studies. The Begg test and Egger test will be used to detect potential publication bias.

Strategy of data synthesis STATA version 12.0 (Stata Corporation, College Station, TX) will be used to perform the meta-analysis. The association between ART and ADHD risk in offspring will be quantified using OR values and the corresponding 95% CIs.
Between-study heterogeneity will be evaluated by the I2 statistic. The heterogeneity will be considered statistically insignificant if $I2 > 50\%$, then the fixed-effect model will be used to calculate pooled OR among the studies, otherwise, the random-effect model will be adopted. Subgroup analysis will be conducted according to study design, country, ART type, study quality, and adjustment for confounding factors. Sensitivity analysis will be performed by omitting the risk estimate of each study in turn to examine the robustness and stability of the pooled results.

Subgroup analysis Subgroup analysis will be conducted according to study design, country, ART type, study quality, and adjustment for confoundingfactors.

Sensitivity analysis Sensitivity analysis will be performed by omitting the risk estimate of each study in turn to examine the robustness and stability of the pooled results.

Language restriction There will be no language restriction.

Country(ies) involved China.

Keywords Attention Deficit Hyperactivity Disorder, assisted reproductive technology, meta-analysis, protocol, systematic review.

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