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Assisted reproductive technology and risk of asthma and allergy in the offspring: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

The use of assisted reproductive technology (ART) procedures has increased globally over the last three decades. Recent studies suggest that children born through ART may be at increased risk of asthma and atopic disease compared to children born naturally, but findings are mixed. We aim to synthesise the evidence on the impact of ART on the risk of asthma and atopic disease in the offspring.

Methods and analysis

We will identify relevant studies by searching MEDLINE, EMBASE, Cochrane Library, ISI Web of Science, CINAHL, Scopus, Google Scholar, AMED, Global Health, PsychINFO, CAB International, and WHO Global Health Library between 1978 and 2016. We will locate additional studies through searching databases of the proceedings of international conferences, contacting international experts in the field, and searching the references cited in identified studies. We will include analytic observational studies (cohort, case-control, and cross-sectional studies) that have investigated the impact of any type of ART on offspring's asthma and atopic disease up to the age of 17 years. Screening of identified records, data extraction from eligible studies, and risk of bias assessment of eligible studies will be independently undertaken by two reviewers, with arbitration by a third reviewer. The Effective Public Health Practice Project will be employed for risk of bias assessment. Estimates from studies judged to be clinically, methodologically, and statistically homogeneous will be synthesized using random-effects meta-analysis.

Ethics and dissemination

As this study is based solely on the published literature, no ethics approval is required. We will publish our findings in a peer-reviewed scientific journal and present the results at national and international scientific conferences.

Protocol Registration

We will register a detailed protocol for the review with the International Prospective Register of Systematic Reviews (PROSPERO) prior to commencing the review.

Strengths and limitations of this study

- As the use of assisted reproductive technology becomes more common, clarifying its impact on the offspring, such as risk of asthma and allergy, is essential for decision-making
- This is the first systematic review of the impact of assisted reproductive technology on asthma and allergy in the offspring and it will provide a comprehensive synthesis of the underlying evidence base.
- The identification of studies from leading medical and public health databases with no geographical or language limitations will advance import of this evidence synthesis across settings.

INTRODUCTION

Since its inception in 1978, the use of assisted reproductive technology (ART) has dramatically increased globally.[1-6] It is now estimated that ART accounts for between 1 and 4% of all births, particularly in industrialised societies, but anecdotal data suggest that its use is rising in low and middle income countries as well.[1-6] Until recently, in vitro fertilization constituted the majority of ART methods, but the use of intracytoplasmic sperm injection has steadily increased in recent times, now believed to comprise up to 70% of all ART procedures; the use of other procedures, such as fresh and frozen embryo transfers and intra-uterine insemination is steadily increasing.[1,2]

Over the years, concerns have been raised about the short- and long-term risks for children born through ART compared to those naturally conceived.[1,2,7] Children conceived through ART are believed to phenotypically and biochemically differ from those born naturally, but it is unclear the mechanisms underlying these differences and the subsequent health implications.[2] Amidst conflicting findings, some studies have suggested that ART children are at increased risk of key perinatal outcomes, including congenital malformations, prematurity, low birth weight, hypertensive disease, diabetes, perinatal mortality, imprinting disorders, and certain cancers.[1-6] However, some investigators suggest that these observations may be a consequence of potential biases inherent in studies, underlying maternal factors such as subfertility, age, and parity, or a combination of these factors and ART, and not necessarily the ART procedure alone.[1,2,7]

More recently, some studies have investigated the relationship between ART and the risk of asthma and atopic disorders in children born through ART compared to children conceived naturally, but findings are conflicting.[8-15] Whist the possible biological mechanism for these associations, like other perinatal outcomes, are not clearly addressed, some argue that the observed associations may be attributed to maternal subfertility, residual confounding, or other immune-modifying maternal factors during pregnancy, such pre-existing conditions like asthma or allergy or other extrinsic factors like medications and smoking.[16] Furthermore, it has been suggested that, since women undergoing ART procedures are generally of higher social economic status, and have higher body mass with increased prevalence of metabolic disorders, their offspring may be at an increased risk of adverse outcomes.[16] The high prevalence of metabolic impairment in the infertile patient population may therefore have long-term trans-generational impact, either through genetic or epigenetic mechanisms as a result of embryo culture and the potency of the fertility drugs used for treating resultant ovarian hyperstimulation.[16,17]

Given the increasing number of studies relating ART to asthma and atopic disease in the offspring and mixed findings now being observed, a comprehensive synthesis of these studies is essential in order to clearly appreciate the underlying evidence relating ART to the aetiology and outcomes of asthma and atopic disease in the offspring. A synthesis of the evidence base will also help to identify relevant gaps in research in this area and suggest key steps in addressing these gaps. Therefore, in this study, we aim to identify, critically appraise, and synthesize the evidence on the use of ART and the risk of asthma and atopic disease in the offspring.

METHODS

We have followed the recommendations of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist in reporting this protocol.[18]

Eligibility criteria

Types of studies

We will include all analytic observational epidemiologic studies (cohort studies; case control studies; and cross-sectional studies) that have been conducted on the topic. We will exclude reviews, case studies and case series, and animal studies.

Participants

Eligible participants will include women during pregnancy and their offspring ≤17 years.

Years considered

Given that the first ART procedure was undertaken in 1978,[1,2] we will consider all evidence emanating from this date up to 2016.

Language

There will be no language restrictions, and where possible we will translate literature published in languages other than English.

Information sources

Database searches and other sources to identify studies

We will search MEDLINE, EMBASE, Cochrane Library, ISI Web of Science, CINAHL, Scopus, Google Scholar, AMED, Global Health, PsychINFO, CAB International, and WHO Global Health Library. The databases will be searched for studies indexed from 1978 until 2016. We will locate additional references through searching the references cited in identified studies; through searching databases of the proceedings of international conferences, such as ISI Conference Proceedings Citation Index via Web of Knowledge, ZETOC (British Library); and by contacting international experts and authors who have published in the field. We will search trial registries, such as Current Controlled Trials (http://www.controlled-trials.com), ClinicalTrials.gov (http://www.clinicaltrials.gov), Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au) to identify ongoing studies.

Search strategy

Using the Ovid interface for MEDLINE, we have developed a highly sensitive and comprehensive search strategy (Appendix 1) to identify and retrieve relevant and eligible studies. This search strategy will be adapted in searching the other databases.

Study records

Data management

The retrieved records from all databases will be exported to Endnote Library, which will be used throughout the review for study screening, de-duplication, and overall management of the retrieved records.

Selection process
Titles and abstracts of retrieved articles will be screened and full text copies of potentially eligible studies will be assessed by two independent reviewers; a third reviewer will arbitrate any discrepancies. Studies that do not fulfil the inclusion criteria will be excluded.

Data extraction
Two reviewers will independently extract relevant study data from eligible studies onto a customized data extraction form; a third reviewer will arbitrate any discrepancies. Before using the form for all studies, we will pilot the data extraction form with a selected sample of studies in order to evaluate the ability of the form to capture the relevant study data of interest.

Data items
Descriptive summary tables will be produced to summarize the literature and we will tabulate all relevant study data. In addition to other relevant study data as may be available from each study, we aim to capture as a minimum the following data items from each study: study author; country of study; year of publication; type of study design; study size; source of study population; type of ART and method of assessment; singleton vs multiple pregnancy; length of follow-up (for follow-up studies); key potential confounders (maternal age, parity, subfertility, history of asthma/allergy, maternal smoking during pregnancy, and sex of child); study outcomes and methods of assessment; analysis methods; and key results. The PRISMA checklist will guide the reporting of the systematic review.[19]

Types of exposures
We will include all studies that have investigated the role of any type of ART (in-vitro fertilization, intrauterine insemination, intracytoplasmic sperm injection, zygote intrafallopian transfer, gamete intrafallopian transfer, medicinal and surgical infertility treatments) in comparison with natural births.

Outcomes and prioritization
Our primary outcomes will include: objectively-measured or self-reported asthma, atopic dermatitis/eczema, allergic rhinitis, anaphylaxis, urticaria, angioedema, and food allergy. The secondary outcomes will include: atopic sensitization as defined either by skin prick test or raised antigen specific immunoglobulin E; objective and subjective measures of disease severity and impact on quality of life, including asthma exacerbations, use of asthma medications, hospitalisation for asthma, wheeze as defined by self-report or objective diagnosis; indicators of airway function including (peak expiratory flow, forced expiratory volume in 1 second, forced vital capacity, forced expiratory flow rate or alternative age appropriate pulmonary function tests [oscillometry or exhaled nitric oxide analysis]); and measures of health-related quality of life.

Risk of bias in individual studies
Risk of bias in eligible studies will be assessed by two reviewers; a third reviewer will arbitrate any discrepancies. We will assess the risk of bias by using the Effective Public Health Practice Project (EPHPP) tool (www.ephpp.ca). We will grade the following components of each study: suitability of the study design for the research question; risk of

selection bias; exposure measurement; outcome assessment; and generalizability of findings. From these component-specific assessments, we will derive an overall grading for each study.

Data synthesis

To summarize the overall evidence, we will undertake a narrative synthesis of the data. Additionally, for clinically, methodologically, and statistically homogeneous studies, we will perform meta-analyses using random-effects models to quantify a pooled estimate of the effect of specific types of ART on the risk of asthma and atopic disease in the offspring. Meta-analyses will be undertaken separately for each specific study design. In comparison to fixed-effect meta-analysis, using random-effects models to compute the pooled estimates presents a more conservative option, as the underlying assumption of random-effects meta-analysis of non-common effect across studies is more realistic when involving studies obtained solely from the published literature.[20] The random-effects model also takes into account potential heterogeneity between studies when computing the pooled estimates.[20] We will quantify the heterogeneity between studies using the I^2 statistic. We will undertake the following subgroup analyses: by type of ART; singleton vs multiple pregnancy; single vs double embryo transfers; parity; and length of subfertility. We will undertake a sensitivity analysis by the grading of study quality in order to evaluate the robustness of our findings. The meta-analyses will be performed using Stata 14 statistical package.

Publication bias

We will evaluate the potential for publication bias by using funnel plots and Begg and Egger tests.[21,22]

Protocol registration

A detailed protocol for the review will be registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/prospero/ prior to commencing the review.

Confidence in the cumulative estimate

We will evaluate the strength of the overall evidence through assessment of the clinical and methodological heterogeneity across studies and on the basis of the risk of bias assessment in included studies. We will consider these lines of impact on the overall evidence in reaching a conclusion on the import of findings and in recommending for future direction for the field.

CONCLUSION

The increasing use of ART and its potential implication for increased risk of asthma and atopic disease in offspring now requires a comprehensive evidence synthesis, which will provide us with the opportunity to appreciate the underlying evidence base and assess its policy, practice, and public health implications. In addition, this evidence synthesis provides the opportunity to identify the research gaps in studies linking ART to the development of asthma and atopic disease in the offspring. We aim to report the findings from this review by autumn 2016.

COMPETING INTERESTS

The authors declare no competing interest related to this work.

AUTHORS' CONTRIBUTIONS

BN conceived the idea for this work and is the guarantor. AS contributed subject expertise to the development of the protocol. The protocol was drafted by BN and was then revised after several rounds of critical comments from AS and additional feedback from ME, MK, SV and NM. All authors will be involved in the systematic review process.

FUNDING

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APPENDIX 1:

MEDLINE Search Strategy

1. assisted reproductive technology.mp. or exp Reproductive Techniques, Assisted/
2. in-vitro fertilization.mp. or exp Fertilization in Vitro/
3. exp Insemination, Artificial/ or Insemination, Artificial, Homologous/ or intrauterine insemination.mp.
4. intracytoplasmic sperm injection.mp. or exp Sperm Injections, Intracytoplasmic/
5. exp Embryo Transfer/ or exp Zygote Intrafallopian Transfer/ or zygote intrafallopian transfer.mp.
6. gamete intrafallopian transfer.mp. or exp Gamete Intrafallopian Transfer/
7. infertility treatment.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Asthma/ or asthma.mp.
10. wheeze.mp.
11. exp Dermatitis, Atopic/ or atopic eczema.mp.
12. exp Hypersensitivity, Immediate/ or exp Hypersensitivity/ or atopy.mp. or allergy.mp. or atopic sensitisation.mp. or allergic sensitisation.mp.
13. exp Rhinitis, Allergic, Seasonal/ or exp Rhinitis, Allergic, Perennial/ or exp Allergens/ or allergic rhinitis.mp.
14. exp Conjunctivitis, Allergic/ or Rhinoconjunctivitis.mp.
15. exp Conjunctivitis, Allergic/ or Rhinoconjunctivitis.mp.
16. exp Urticaria/ or urticarial.mp.
17. exp Angioedema/ or angioedema.mp.
18. exp Food Hypersensitivity/ or food allergy.mp.
19. exp Anaphylaxis/ or anaphylaxis.mp.
20. lung function.mp.
21. airway function.mp. or exp Bronchial Hyperreactivity/
22. exp Forced Expiratory Volume/ or forced expiratory volume in 1 second.mp.
23. exp Peak Expiratory Flow Rate/ or peak expiratory flow.mp.
24. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 8 and 24
26. limit 25 to yr="1978-2015"

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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- This is the first systematic review of the impact of assisted reproductive technology on asthma and allergy in the offspring and it will provide a comprehensive synthesis of the underlying evidence base.
- The identification of studies from leading medical and public health databases with no geographical or language limitations will advance import of this evidence synthesis across settings.

INTRODUCTION

Since its inception in 1978, the use of assisted reproductive technology (ART) has dramatically increased globally.[1-6] It is now estimated that ART accounts for between 1 and 4% of all births, particularly in industrialised societies, but anecdotal data suggest that its use is rising in low and middle income countries as well.[1-6] Until recently, in vitro fertilization constituted the majority of ART methods, but the use of intracytoplasmic sperm injection has steadily increased in recent times, now believed to comprise up to 70% of all ART procedures; the use of other procedures, such as fresh and frozen embryo transfers and intra-uterine insemination is steadily increasing.[1,2]

Over the years, there have been concerns have about the short- and long-term risks for children conceived through ART compared to those naturally conceived.[1,2,7] Children conceived through ART are believed to phenotypically and biochemically differ from those conceived naturally, but it is unclear the mechanisms underlying these differences and the subsequent health implications.[2] Amidst conflicting findings, some studies have suggested that ART children are at increased risk of key perinatal outcomes, including congenital malformations, prematurity, low birth weight, hypertensive disease, diabetes, perinatal mortality, imprinting disorders, and certain cancers.[1-6] However, some investigators suggest that these observations may be a consequence of potential biases inherent in observational epidemiological studies, underlying maternal factors such as subfertility, age, and parity, or a combination of these factors and ART, and not necessarily the ART procedure alone.[1,2,7]

More recently, some studies have investigated the relationship between ART and the risk of asthma and atopic disorders in children conceived through ART compared to children conceived naturally, but findings are conflicting.[8-15] Whist the possible biological mechanism for these associations, like other perinatal outcomes, are not clearly addressed, some argue that the observed associations may be attributed to maternal subfertility, residual confounding, or other immune-modifying maternal factors during pregnancy, such pre-existing conditions like asthma or allergy or other extrinsic factors like medications and smoking.[16] Furthermore, it has been suggested that, since women undergoing ART procedures are generally of higher social economic status, and have higher body mass with increased prevalence of metabolic disorders, their offspring may be at an increased risk of adverse outcomes.[16] The high prevalence of metabolic impairment in the infertile patient population may therefore have long-term trans-generational impact, either through genetic or epigenetic mechanisms as a result of embryo culture and the potency of the fertility drugs used for treating resultant ovarian hyperstimulation.[16,17]

Given the increasing number of studies relating ART to asthma and atopic disease in the offspring and mixed findings now being observed, a comprehensive synthesis of these studies is essential in order to clearly appreciate the underlying evidence relating ART to the aetiology and outcomes of asthma and atopic disease in the offspring. A synthesis of the evidence base will also help to identify relevant gaps in research in this area and suggest key steps in addressing these gaps. Therefore, in this study, we aim to identify, critically appraise, and synthesize the evidence on the use of ART and the risk of asthma and atopic disease in the offspring.

METHODS

We have followed the recommendations of the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist in reporting this protocol.[18]

Eligibility criteria

Types of studies

We will include all analytic observational epidemiologic studies (cohort studies; case control studies; and cross-sectional studies) that have been conducted on the topic. We will exclude reviews, case studies and case series, and animal studies.

Participants

Eligible participants will include women with evidence of conception history and their offspring of any age.

Years considered

Given that the first ART procedure was undertaken in 1978,[1,2] we will consider all evidence emanating from this date up to 2016.

Language

There will be no language restrictions, and where possible we will translate literature published in languages other than English.

Information sources

Database searches and other sources to identify studies

We will search MEDLINE, EMBASE, Cochrane Library, ISI Web of Science, CINAHL, Scopus, Google Scholar, AMED, Global Health, PsychINFO, CAB International, and WHO Global Health Library. The databases will be searched for studies indexed from 1978 until 2016. We will locate additional references through searching the references cited in identified studies; through searching databases of the proceedings of international conferences, such as ISI Conference Proceedings Citation Index via Web of Knowledge, ZETOC (British Library); and by contacting a panel of international experts and authors who have published in the field. We will search trial registries, such as Current Controlled Trials (http://www.controlled-trials.com), ClinicalTrials.gov (http://www.clinicaltrials.gov), Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au) to identify ongoing studies.

Search strategy

Using the Ovid interface for MEDLINE, we have developed a highly sensitive and comprehensive search strategy (Appendix 1) to identify and retrieve relevant and eligible studies. This search strategy will be adapted in searching the other databases.

Study records

Data management

The retrieved records from all databases will be exported to Endnote Library, which will be used throughout the review for study screening, de-duplication, and overall management of the retrieved records.

Selection process
Titles and abstracts of retrieved articles will be screened and full text copies of potentially eligible studies will be assessed by two independent reviewers; a third reviewer will arbitrate any discrepancies. Studies that do not fulfil the inclusion criteria will be excluded.

Data extraction
Two reviewers will independently extract relevant study data from eligible studies onto a customized data extraction form; a third reviewer will arbitrate any discrepancies. Before using the form for all studies, we will pilot the data extraction form with a selected sample of studies in order to evaluate the ability of the form to capture the relevant study data of interest.

Data items
Descriptive summary tables will be produced to summarize the literature and we will tabulate all relevant study data. In addition to other relevant study data as may be available from each study, we aim to capture as a minimum the following data items from each study: study author; country of study; year of publication; type of study design; study size; source of study population; type of ART (and comparison group) and method of assessment; singleton vs multiple pregnancy; length of follow-up (for follow-up studies); key potential confounders (maternal age, parity, subfertility, history of asthma/allergy, maternal smoking during pregnancy, and sex of child); study outcomes and methods of assessment; analysis methods; and key results. The PRISMA checklist will guide the reporting of the systematic review.[19]

Types of exposures
We will include all studies that have investigated the role of any type of ART (in-vitro fertilization, intrauterine insemination, intracytoplasmic sperm injection, zygote intrafallopian transfer, gamete intrafallopian transfer, medicinal and surgical infertility treatments) in comparison with natural conception or any other comparison group as reported in the studies.

Outcomes and prioritization
Our primary outcomes will include: objectively-measured or self-reported asthma, atopic dermatitis/eczema, allergic rhinitis, anaphylaxis, urticaria, angioedema, and food allergy. The secondary outcomes will include: atopic sensitization as defined either by skin prick test or raised antigen specific immunoglobulin E; objective and subjective measures of disease severity and impact on quality of life, including asthma exacerbations, use of asthma medications, hospitalisation for asthma, wheeze as defined by self-report or objective diagnosis; indicators of airway function including (peak expiratory flow, forced expiratory volume in 1 second, forced vital capacity, forced expiratory flow rate or alternative age appropriate pulmonary function tests [oscillometry or exhaled nitric oxide analysis]); and measures of patient-reported health-related quality of life related to asthma or allergy.

Risk of bias in individual studies

Risk of bias in eligible studies will be assessed by two reviewers; a third reviewer will arbitrate any discrepancies. We will assess the risk of bias by using the Effective Public Health Practice Project (EPHPP) tool (www.ephpp.ca). We will grade the following components of each study: suitability of the study design for the research question; risk of selection bias; exposure measurement; outcome assessment; and generalizability of findings. From these component-specific assessments, we will derive an overall grading for each study.

Data synthesis

To summarize the overall evidence, we will undertake a narrative synthesis of the data. Additionally, for clinically, methodologically, and statistically homogeneous studies, we will perform meta-analyses using random-effects models to quantify a pooled estimate of the effect of specific types of ART on the risk of asthma and atopic disease in the offspring. Meta-analyses will be undertaken separately for each specific study design. In comparison to fixed-effect meta-analysis, using random-effects models to compute the pooled estimates presents a more conservative option, as the underlying assumption of random-effects meta-analysis of non-common effect across studies is more realistic when involving studies obtained solely from the published literature.[20] The random-effects model also takes into account potential heterogeneity between studies when computing the pooled estimates.[20] We will quantify the heterogeneity between studies using the I^2 statistic. We will undertake the following subgroup analyses: by age of offspring at onset/diagnosis of outcomes (where possible using the following age groups: <5 years, 5-12 years, >12 years); singleton vs multiple pregnancy; single vs double embryo transfers; parity; and length of subfertility. We will undertake a sensitivity analysis by the grading of study quality in order to evaluate the robustness of our findings. The meta-analyses will be performed using Stata 14 statistical package.

Publication bias

We will evaluate the potential for publication bias by using funnel plots and Begg and Egger tests.[21,22]

Protocol registration

A detailed protocol for the review will be registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/prospero/ prior to commencing the review.

Confidence in the cumulative estimate

We will evaluate the strength of the overall evidence through assessment of the clinical and methodological heterogeneity across studies and on the basis of the risk of bias assessment in included studies. We will consider these lines of impact on the overall evidence in reaching a conclusion on the import of findings and in recommending for future direction for the field. Furthermore, we will grade the strength and quality of the overall evidence by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[23]

CONCLUSION

The increasing use of ART and its potential implication for increased risk of asthma and atopic disease in offspring now requires a comprehensive evidence synthesis, which will

provide us with the opportunity to appreciate the underlying evidence base and assess its policy, practice, and public health implications. In addition, this evidence synthesis provides the opportunity to identify the research gaps in studies linking ART to the development of asthma and atopic disease in the offspring. We aim to report the findings from this review by autumn 2016.

COMPETING INTERESTS

The authors declare no competing interest related to this work.

AUTHORS' CONTRIBUTIONS

BN conceived the idea for this work and is the guarantor. AS contributed subject expertise to the development of the protocol. The protocol was drafted by BN and was then revised after several rounds of critical comments from AS and additional feedback from ME, MK, SV and NM. All authors will be involved in the systematic review process.

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Assisted reproductive technology and risk of asthma and allergy in the offspring: protocol for a systematic review and meta-analysis

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Supplementary File

APPENDIX 1:

MEDLINE Search Strategy

1. assisted reproductive technology.mp. or exp Reproductive Techniques, Assisted/
2. in-vitro fertilization.mp. or exp Fertilization in Vitro/
3. exp Insemination, Artificial/ or Insemination, Artificial, Homologous/ or intrauterine insemination.mp.
4. intracytoplasmic sperm injection.mp. or exp Sperm Injections, Intracytoplasmic/
5. exp Embryo Transfer/ or exp Zygote Intrafallopian Transfer/ or zygote intrafallopian transfer.mp.
6. gamete intrafallopian transfer.mp. or exp Gamete Intrafallopian Transfer/
7. infertility treatment.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Asthma/ or asthma.mp.
10. wheeze.mp.
11. exp Dermatitis, Atopic/ or atopic eczema.mp.
12. exp Hypersensitivity, Immediate/ or exp Hypersensitivity/ or atopy.mp. or allergy.mp. or atopic sensitisation.mp. or allergic sensitisation.mp.
13. exp Rhinitis, Allergic, Seasonal/ or exp Rhinitis, Allergic, Perennial/ or exp Allergens/ or allergic rhinitis.mp.
14. exp Conjunctivitis, Allergic/ or Rhinoconjunctivitis.mp.
15. exp Conjunctivitis, Allergic/ or Rhinoconjunctivitis.mp.
16. exp Urticaria/ or urticarial.mp.
17. exp Angioedema/ or angioedema.mp.
18. exp Food Hypersensitivity/ or food allergy.mp.
19. exp Anaphylaxis/ or anaphylaxis.mp.
20. lung function.mp.

21. airway function.mp. or exp Bronchial Hyperreactivity/
22. exp Forced Expiratory Volume/ or forced expiratory volume in 1 second.mp.
23. exp Peak Expiratory Flow Rate/ or peak expiratory flow.mp.
24. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 8 and 24
26. limit 25 to yr="1978-2016"

Assisted reproductive technology and risk of asthma and allergy in the offspring: protocol for a systematic review and meta-analysis

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	6
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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