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Insufficient iodine nutrition status and the risk of pre-eclampsia: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Although subclinical hypothyroidism (SCH) in pregnancy is one of the established risk factors for pre-eclampsia, the link between iodine deficiency, the main cause of hypothyroidism and pre-eclampsia remains uncertain. About two billion people live in areas with iodine insufficiency. The increased renal blood flow during pregnancy leading to increased renal iodine clearance together with the increased placental transfer of iodine to the fetus leads to further iodine deficiency in pregnancy. Iodine is one of the most potent exogenous antioxidants whose deficiency is associated with oxidant imbalance and endothelial dysfunction, one of the mechanisms associated with increased risk of pre-eclampsia.

Methods and analysis A systematic search of published literature will be conducted for case–control studies that directly determined the iodine nutrition status of women with pre-eclampsia and appropriate normotensive controls. A similar search will be conducted for cohort studies in which the incidence of pre-eclampsia among pregnant women with adequate and inadequate iodine nutrition status was reported. Databases including MEDLINE, EMBASE, Google Scholar, SCOPUS and Africa Wide Information will be searched up to 31 December 2018. Screening of identified articles and data extraction will be conducted independently by two investigators. Risk of bias of the included studies will be assessed using a Newcastle-Ottawa Scale. Appropriate meta-analytic techniques will be used to pool prevalence and incidence rates, odds and relative risk of pre-eclampsia from studies with similar features, overall and by geographical regions. Heterogeneity of the estimates across studies will be assessed and quantified and publication bias investigated. This protocol is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) 2015 guidelines.

Ethics and dissemination Since the proposed study will use published data, there is no requirement for ethical approval. This review seeks to identify the risk of pre-eclampsia associated with insufficient iodine nutrition in pregnancy. This will help to ascertain whether insufficient iodine intake may be an independent risk factor for pre-eclampsia. This will advise policy makers on the possibility of maximising iodine nutrition in pregnancy and reproductive age as one of the remedies for prevention of pre-eclampsia among populations at risk of inadequate iodine intake. This review is part of the thesis that will be submitted for the award of a PhD in Medicine to the Faculty of Health Sciences of the University of Cape Town. In addition the results will be published in a peer-reviewed journal.

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Strengths and limitations

- To our knowledge, this is the first systematic review and meta-analysis that is aimed at ascertaining the relationship between insufficient iodine nutrition status and pre-eclampsia.
- This review may however be limited by the small number of eligible studies and small sample sizes that may make it liable to a considerable degree of heterogeneity.
- The eligible studies may have varied research designs that may potentially preclude the pooling of the test results.

INTRODUCTION

Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide.[1] Although the actual cause of pre-eclampsia remains unknown, the risk factors of pre-eclampsia are multifactorial.[2–4]Subclinical hypothyroidism (SCH) in pregnancy is one of the established risk factors for pre-eclampsia.[5–7] Given that iodine deficiency is the leading cause of hypothyroidism,[8 9] iodine deficiency could be an independent risk factor of pre-eclampsia especially in settings with endemic iodine deficiency. Although some studies have reported an association between iodine nutrition status and pre-eclampsia,[10 11] it is not yet certain whether this association is consistent across different settings around the world.

The WHO estimates that about two billion people live in areas with iodine insufficiency.[12] In addition, iodine deficiency is on the rise in areas originally thought to be iodine sufficient.[13] This is due to inadequate iodisation

in the background of increased amount of perchlorate and thiocyanate in water sources and the diet.[14–16] Both perchlorate and thiocyanate significantly diminish the uptake of iodine by the thyroid gland especially in states of increased thyroid stimulation by thyroid stimulating hormone (TSH) secondary to iodine deficiency.[15 16]

Rationale

Iodine deficiency has been shown to be associated with defective trophoblast proliferation and migration, which are some of the mechanisms proposed in the aetiology of pre-eclampsia.[17 18] The placenta is a highly metabolic organ with potential for production of reactive oxygen species. It is also one of the organs with high physiological concentrations of iodine whose antioxidant effect reduces lipid peroxide formation and may ensure normal placentation and function.[19–21]

During pregnancy, there is increased renal perfusion with increased iodine filtration and urinary iodine excretion in addition to increased transfer of iodine to the fetus.[22] Hence women with inadequate iodine intake are at risk of developing iodine deficiency in pregnancy and possibly at increased risk of developing subclinical or overt hypothyroidism and pre-eclampsia.[21–23]

Furthermore, the elevation in serum TSH that occurs in overt or SCH, is associated with hyperstimulation of the thyroid gland excessive superoxide production among individuals with iodine deficiency, which when released into the circulation, causes endothelial dysfunction and atherosclerosis.[24 25] These are known pathological pathways of pre-eclampsia.[26]

Objectives

This systematic review and meta-analysis is intended to ascertain whether insufficient iodine nutrition status is associated with increased risk of pre-eclampsia.

Review questions

The purpose of this review is to address the following questions:

1. Do pregnant women with insufficient iodine nutrition status have an increased risk of pre-eclampsia compared with pregnant women with adequate iodine nutrition status?
2. Is there a difference in the urinary iodine concentration (UIC) of pregnant women with pre-eclampsia versus that of normotensive pregnant women?

METHODS

This protocol is developed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) 2015 Guidelines.[27]

Eligibility criteria

Inclusion criteria

The selection of studies for inclusion in the review will be guided by the Population, Intervention/exposure, Comparison and Outcome protocol as stipulated below:

1. Population: pregnant women.
2. Exposure: the exposure is insufficient iodine nutrition status during pregnancy for both case–control and cohort studies. In this systematic review this will be defined according to the WHO/International Council for Control of Iodine Deficiency Disorders (ICCIDD) classification of iodine intake of populations using median UIC.[28] For pregnant women, a urine iodine concentration (UIC) <150, 150–249, 250–499 and >500 µg/L is considered an estimate of, respectively, insufficient, adequate, more than adequate and excessive iodine nutritional status.
3. Comparator: for both case–control and cohort studies the comparator will be the participants with sufficient iodine nutrition status (UIC >150 µg/L) during pregnancy.
4. Outcome: the outcome is the prevalence (for case–control studies) and the incidence (for cohort studies) of pre-eclampsia among women with and without adequate iodine nutrition status in pregnancy from which the ORs will be determined.

   Pre-eclampsia has been defined as new onset hypertension after 20 weeks of amenorrhoea characterised by elevated systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg or more or both, measured twice with a gap of 4 hour or one measurement of systolic blood pressure of ≥160 mm Hg or diastolic blood pressure of ≥110 mm Hg or both accompanied by one of the following: proteinuria in 24 hour-urine ≥300 mg or protein/creatinine ratio ≥0.3 or urine protein measured by dipstick ≥1+; or thrombocytopenia (platelets less than 150 000/µL), kidney insufficiency (concentration of creatinine in serum above 97 µmol/L), decreased liver function (enzyme activity of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) twice higher than the upper limit of the referential interval), compromised pulmonary function or pulmonary oedema or visual or other symptoms and signs of deficient cerebral function.[29] There may be considerable heterogeneity if pre-eclampsia has been variably defined in different studies that are eligible for inclusion in the current systematic review.

Exclusion criteria

- Studies in which none of the following parameters was computed: means, medians, ORs, incidence and prevalence rates and with absence of data to compute them.
- Eligible studies that are missing some critical data where after repeated attempts to contact an author via email for relevant information, no response is gotten.
- Letters to editors, reviews, commentaries, editorials and any publication without primary data.
- Duplicate publications from the same study. For studies published in more than one journal/conference, the most recent and comprehensive publication will be used.

Table 1 Search strategy for MEDLINE

Population: Pregnant women with Pre-eclampsia		
#1	MeSH terms	Pregnant Women [Mesh] OR Pregnancy [Mesh] OR Pregnancy Trimesters [Mesh]
#2	Free text	Pregnancy OR Pregnant women OR expectant mothers
#3	#1 OR #2	
#4	MeSH terms	Pre-Eclampsia [Mesh] OR Eclampsia [Mesh] OR Hypertension [Mesh]
#5	Free text	Preeclampsia OR Pre-eclampsia OR Eclampsia OR Hypertension OR Hypertensive OR High blood pressure
#6	#4 OR #5	
Exposure: Iodine deficiency		
#7	MeSH terms	Iodine [Mesh]
#8	Free text	Iodine
#9	#7 OR #8	
#10	#3 AND #6 AND #9	

- Studies not performed in human participants.
- No language restriction will be applied.

Patient and public involvement

The public or patients were not involved in the development of this protocol.

Search strategy for study identification

Electronic searches

We will search PubMed MEDLINE, Google Scholar, SCOPUS, ISI Web of Science (Science Citation Index) databases for all published studies on iodine deficiency and pre-eclampsia up to 31 December 2018. This search shall be conducted using a predefined comprehensive and sensitive search strategy combining relevant terms and synonyms which are variably used to denote abnormally high blood pressure in pregnancy and insufficient iodine intake or iodine deficiency. Table 1 depicts the main search strategy to be employed for MEDLINE database that will also be adapted for searches in other electronic databases.

We will search reference lists of relevant citations for articles of interest.

Grey literature

We will contact experts in the field, research organisations, conference websites and conference proceedings that dealt with micronutrient deficiency and pre-eclampsia, for any relevant data.

Study records

Data management

We will use an appropriate citation management software to remove duplicates from the references articles that will have been gathered. Prior to screening of studies, we will create a set of standardised questions according to the inclusion criteria which will then be pretested on a sample of eligible studies.

Screening

Two investigators will independently select studies that meet inclusion criteria. Citations and abstracts will be screened for possible inclusion, and duplicate citations will be excluded. Titles and abstracts will then be screened following inclusion criteria described above, following which the full texts of potentially eligible articles will be obtained. These full texts will be screened using a standardised and pretested form to include eligible studies. Disagreements will be resolved by consensus, with consultation of a third author (when resolution cannot be achieved). Corresponding authors of potentially eligible studies that did not report data that are relevant to our study analysis will be contacted. Reasons for exclusion of non-eligible studies will be documented. The whole review process will be summarised in a flowchart.

Data extraction

Two investigators will independently extract data from included studies, using a standardised and pretested data extraction form. Any inconsistencies or disagreement shall be resolved by consensus or consultation with the third investigator.

Data items

Data will include the geographic region and country where study was conducted, the year study was carried out and year of publication, the language of publication, demographic characteristics of participants, time of measurement of exposure (such as first, second or third trimester of pregnancy or preconception), study design, setting (rural or urban, health-facility or community-based), sample size and the criteria used for determination of the iodine intake. For cross-sectional and case–control studies, the median (25th–75th percentiles) and or mean (SD) UIC will be extracted. The overall mean UIC for cases and controls together with the mean UIC difference will be determined. The proportions of women with insufficient iodine nutrition among cases and controls will be extracted or determined based on the standard definition by WHO and the ICCIDD. Then the odds or data required to compute the odds of insufficient iodine nutrition among the cases will be extracted. Where applicable adjusted ORs will be extracted or computed so account for traditional risk factors for pre-eclampsia such as obesity, primigravida, advanced maternal age or diabetes. For cohort studies, the incidence rates and relative risk of pre-eclampsia according to baseline status for iodine nutrition will be extracted.

Assessment of methodological quality and risk of bias

Two reviewers will independently score the quality of included studies. The risk of bias in individual studies will be assessed using the Newcastle-Ottawa scale[30] and the

Cochrane guidelines available in Review Manager V.5.3 (http://tech.cochrane.org/revman). Discrepancies will be resolved by consensus or by consulting the third investigator. Inter-rater agreement on screening, data abstraction and methodological quality (selection, comparability of groups and ascertainment of exposure/outcome) will be assessed using Cohen's κ coefficient.[31]

Data synthesis, analysis and assessment of heterogeneity

For data unsuitable for meta-analysis, we will provide a narrative description of major study characteristics and findings. For outcomes of interest consistently reported across studies, random effects model meta-analyses will be used to pool estimates across those studies.[32] In process, the Freeman-Tukey double Arcsine and square-root transformation will be applied, respectively, to stabilise the variances of prevalence and incidence rates prior to meta-analysis, and estimates back-transformed for reporting. The degree of heterogeneity across studies will be assessed using the Cochrane Q statistic and inconsistency index (I^2) statistic and will be classified respectively as low: I^2 <25%; moderate: 25%–50%; high: I^2 >50%).[33] For studies with high heterogeneity subgroup and metaregression analyses will be performed to investigate the sources of heterogeneity. The following grouping variables will be used where appropriate: time of measurement of exposure (first, second or third trimester), study setting (rural vs urban, health-facility vs community based), geographical region (continental and or endemicity of iodine deficiency), high income versus low or middle-income status, and study quality. The Begg test and Egger funnel plot will be used to check for the publication bias.[34 35]

Sensitivity analysis

Sensitivity analysis will be carried out to check the effect of every study on pooled estimates by removing one study at a time and assessing the effect on pooled estimates and heterogeneity statistics. The Duval and Tweedie trim-and-fill will be used to adjust estimates for the effects of potential publication bias. Data analyses will use the 'meta' package of the statistical software R (V.3.3.3 [2017-03-06], The R Foundation for statistical computing, Vienna, Austria), and the 'meta' package.

Confidence in cumulative evidence

We will assess the strength of evidence provided by studies included in the review, using the Grading of Recommendations Assessment, Development and Evaluation approach. This assessment of the quality of evidence would include risk of bias, consistency and publication bias. Studies in which further research is unlikely to change effect estimates, or likely to have a considerable impact on effect estimates, or capable of changing the effect estimates, or those in which there is uncertainty in effect estimates, will be respectively described as 'high', 'moderate', 'low' or 'very low' qualities.

Reporting of this review

The proposed systematic review will be reported following the PRISMA guidelines.[36] We intend to publish a PRISMA checklist alongside the final report.

Potential amendments

We do not intend to make any amendments to the protocol, to avoid the possibility of outcome reporting bias. However, any amendments that do prove necessary will be documented and reported transparently.

CONCLUSION

Iodine deficiency whose degree is exacerbated by pregnancy has recently been associated with oxidative imbalance and endothelial dysfunction which are some of the pathophysiological mechanisms that precede the clinical manifestation of pre-eclampsia. Although iodine deficiency is the the most common cause of hypothyroidism, one of the established risk factors of pre-eclampsia, the association between iodine deficiency in pregnancy and pre-eclampsia is still uncertain. This review aims to decipher if iodine deficiency in pregnancy, which can be corrected through supplementation, increases the risk of pre-eclampsia in various settings worldwide.

Possible limitations of this study would include very few studies with small sample sizes and uncertain quality that may generate significant heterogeneity precluding further analysis.

Ethics and dissemination

The current study is based on published data, and hence does not require ethical approval. This review is part of the thesis that will be submitted for the award of a PhD in Medicine to the Faculty of Health Sciences of the University of Cape Town. The final report of this review in the form of a scientific paper will be published in a peer-reviewed journal. Findings will also be presented at conferences and submitted to relevant health and policy authorities. We also plan to update the review in the future to monitor any progressive changes on the subject.

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