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Are false-positive, second-trimester maternal serum screens for fetal aneuploidy associated with adverse outcomes amongst singleton pregnancies globally? A protocol for a systematic review and meta-analysis.

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ABSTRACT

Background: Multiple-marker, maternal serum screening (MSS) has been the cornerstone of prenatal diagnosis since the 1970s. While combinations of these markers are used to predict the risk of Down syndrome there is some literature to suggest that individual markers may also predict an increased risk of other adverse pregnancy outcomes.

OBJECTIVE: To investigate the association between false-positive, second-trimester MSS tests and the risk of adverse pregnancy outcomes amongst singleton pregnancies globally.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: Electronic searches of Pubmed, Medline, Embase, CINAHL, Web of Science, and Scopus databases, as well as hand-searches of scientific meeting abstracts (Fetal Medicine Foundation, Society of Maternal-Fetal Medicine, and the International Society for Prenatal Diagnosis) andother grey literature sources (ProQuest Dissertations and Google Scholar) to latest available date (estimated Dec 2018).

STUDY SELECTION: Observational studies comparing the risk of adverse pregnancy outcomes amongst singleton pregnancies with false-positive second-trimester maternal serum screening tests to those of screen-negative singleton controls. Outcomes of interest include preeclampsia, fetal growth restriction, preterm birth, and stillbirth.

DATA EXTRACTION (& Methods): Using a standardized data extraction form, the author will independently screen studies, extract data, and assess quality of eligible studies. Following a qualitative synthesis of relevant studies, a meta-analysis will be performed. Odds ratios and 95% confidence intervals will be pooled by individual outcome and type of maternal serum screen test type to generate summary effect estimates for the outcomes of interest.

CONCLUSIONS: There is conflicting evidence in the literature about the relationship, if any, between false-positive, second-trimester maternal serum screens and risk of placentally-mediated complications of pregnancy. Given that this research question can only be explored using observational studies, it lends itself ideally to pursuit of a systematic review and synthesis of results using meta-analysis.

ATTACHMENTS

FP MSS MetaAnalysis_PROTOCOL_2018.pdf

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KEYWORDS

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1 Are false-positive, second-trimester maternal serum screens for fetal aneuploidy associated with adverse outcomes amongst singleton pregnancies globally? A protocol for a systematic review and meta-analysis.

[Prepared for LSHTM EPM500 Coursework on 01 August 2018]

BACKGROUND

2 INTRODUCTION

Prenatal screening is evolving quickly.[1] Originally created for prenatal detection of spina bifida,[2] current prenatal screening programs offer surveillance for Down syndrome in addition to other genetic conditions.[1,3] Second-trimester, multiple-marker, maternal serum screening (MSS) has been available since the 1970s. As an optional test offered to pregnant women between 15 to 20 weeks of gestation, it involves a blood draw to measure the levels of four serum analytes: alpha-fetoprotein (AFP); human chorionic gonadotropin (hCG); unconjugated estriol (uE3); and direct inhibin-A (DIA).[1] These analytes are then used in combination to calculate the individual pregnancy risk of fetal Down syndrome.[1,3] Women with a pregnancy affected by fetal Down syndrome typically have increased levels of hCG, and DIA, and lower levels of AFP and uE3 when compared to pregnancies without fetal Down syndrome.[4] But with a false-positive rate of ~5%, many pregnancies that screen positive for Down Syndrome by MSS do not actually have the condition.[5]

There has been some suggestion in the literature that the individual serum analyte levels assessed by MSS to determine risk of fetal Down syndrome may actually reflect underlying placental implantation.[6] As such, in the setting of a structurally normal fetus with no evidence of Down syndrome, a positive MSS screen resulting from abnormalities in these analyte levels may instead signify a pregnancy at increased risk of adverse pregnancy complications associated with impaired placental functioning.[6]

However, there remains no clear guidance in the literature about the exact magnitude of risk or about how such pregnancies with false-positive MSS results should be managed.

BACKGROUND

Basis of prenatal screening for fetal aneuploidy:

The normal human complement of chromosomes is 46 and consists of 22 pairs of autosomes plus one pair of sex chromosomes.[1,6-7] Aneuploidy refers to an abnormal number of chromosomes.[1] Down syndrome (also known as Trisomy 21) occurs when there are three copies of chromosome 21 instead of the usual two.[6-7] Down syndrome remains the most common autosomal trisomy amongst livebirths and is the main target of prenatal screening today.[7] Because of the relatively high prevalence of Down syndrome in the absence of screening, availability of confirmatory diagnostic tests, possibility of prenatal management and planning, and a potentially significant burden of disease amongst affected individuals and their families, maternal serum testing in pregnancy fulfills many of the criteria required of a screening test.[7]

Evolution of second-trimester MSS:

The association between advanced maternal age and an increased risk of fetal Down syndrome was established in the 1950s and '60s.[1,8-9] Because of this association, initial prenatal 'screening' relied solely on maternal age to predict risk of fetal Down syndrome and high-risk women were offered diagnostic testing directly.[5,7] Not only is maternal age alone a poor predictor of fetal Down syndrome (sensitivity 44% and false-positive rate 16%), but most babies with Down syndrome are born to younger mothers.[5,6] There is also the potential complication of miscarriage associated with invasive diagnostic testing.[5,10] Subsequently, several studies began reporting variations in the levels of individual serum analytes in pregnancies affected by fetal Down syndrome. From this, formal prenatal screening programs were developed to better refine individual pregnancy risk of fetal aneuploidy based on quantitative, laboratory measurement of these analytes.

AFP had been used since the 1960s to screen for spina bifida in the fetus.[4,6] AFP is produced by the fetal yolk sac in early pregnancy and by the fetal liver later pregnancy.[6] It is excreted by the fetus and can be detected in amniotic fluid and maternal blood.[6] In cases of fetal Down syndrome, AFP levels were lower than average.[ref] When combined with maternal age, AFP improves sensitivity and false-positive rates of Down syndrome. Use of serum analytes also reduces the risks associated with direct-to-amniocentesis testing based on maternal age alone.[5,6,10]

hCG is a hormone produced by the placenta after implantation and is the compound routinely tested for with 'pregnancy tests'.[1,6] hCG levels are higher in pregnancies affected by fetal Down syndrome. uE3 is a steroid hormone synthesized by the placenta during pregnancy[6]. In the setting of fetal Down syndrome, uE3 levels are extremely low[6.7]. Both double-marker MSS (AFP and hCG) and triple-marker MSS (AFP, hCG and uE3 improved performance of prenatal screening for Down syndrome when compared to single analyte testing.[6,11]The triple-marker MSS testing was associated with a sensitivity 66-71% and false-positive rate 7.2%.[3,7]

DIA is another hormone synthesized by the placenta and found to be elevated in the setting of fetal Down syndrome[6]. In the early 2000s, DIA was incorporated with the three aforementioned analytes into quadruple-marker MSS testing.[12] With a detection rate of fetal Down syndrome of ~77-80% and a false-positive rate ~5%, "quad screening" offered the best option for prenatal screening for Down syndrome at the time.[6,12]

Possible relationship between maternal serum analytes and adverse pregnancy outcomes:

There is some evidence that the individual serum analyte levels assessed by maternal serum screen to determine fetal genetic risks may also be used to prognosticate other pregnancy complications.[6]Independent of the prediction of genetic aneuploidies, these analytes may actually reflect placental implantation and functioning. For instance, pregnancies complicated by abnormal alpha-fetoprotein (AFP) levels show an increased risk of placental vascular lesions and chorionic villitis, which may allow AFP from the fetal compartment to leak into the maternal compartment. There is also evidence that smaller, growth restricted fetuses produce less AFP and this variation can also be detected in maternal blood.[6,13-15]High levels of hCG have been attributed to hypoxic placental cells which increase proliferation and subsequently hCG production.[6.15-20] Fetal loss, growth restriction, gestational hypertensiom disorders, preterm

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birth, oligohydramnios (decreased amniotic fluid production), and abruption (premature separation of the placenta) have all been described in the context of abnormal AFP, hCG, uE3, and DIA levels in pregnancy.[6,13-20]

Placentally-mediated complications of pregnancy are those with pathophysiologic origin in the placental unit including gestational hypertension and preeclampsia, growth restriction, stillbirth, and neonatal complications related to preterm birth, amongst others.[21] Impaired placentation leads to production of cytokines and inflammatory mediators, all of which precipitate ongoing vascular constriction and further impairment of placental blood flow.[16,21] Impaired blood flow adversely affects fetal growth. Fetal growth restriction can be severe and is an independent risk factor for stillbirth.[6,13-15] Vascular constriction can lead to gestational hypertension including preeclampsia (new-onset hypertension and proteinuria)[17,21] for the mother. All of these complications individually and collectively increased the risk of preterm birth.[6,16-17]

Baseline prevalence of these complications vary worldwide. Prevalence of preeclampsia ranges from ~5 to 7% and it is emerging as the leading cause of maternal mortality in high income countries.[16,18] Fetal growth restriction (estimated fetal weight or birth weight less than the 10th percentile)complicates ~7 to 10% of pregnancies.[16] Preterm birth (prior to 37 weeks of pregnancy) occurs in ~5 to 15% of pregnancies[6], but is the leading cause of neonatal morbidity and mortality worldwide. Stillbirth rates are ~0.2 to 0.5% in high-income countries and upwards of 2-5% in some low-income countries.[6,17,21]

Importance of this review

There remains no clear guidance in the literature on how best to manage or counsel pregnancies following false-positive MSS results. There is also inconsistency in the literature regarding the exact risk, if any, of a false-positive MSS result and several small studies were underpowered to adequately assess risk for some of the rarer adverse outcomes.[13-21] If there is an association between false-positive MSS results and complications, then this information would better inform care providers about the need for increased antenatal surveillance or offer possible intervention strategies.[21] Conversely, if there is no association, patients can be reassured and spared the additional time and costs of increased surveillance.[6]

RESEARCH QUESTION & HYPOTHESIS

3 Overarching research question: Is there an association between a false-positive, second-trimester MSS for Down syndrome and an increased risk of adverse pregnancy complications?

Hypothesis: A false-positive, second-trimester MSS for Down syndrome is associated with a higher risk of pregnancy complications when compared to screen negative controls.

PURPOSE OF REVIEW

4 To synthesize and evaluate the data on the relationship between false-positive, second-trimester MSS and the risk of pregnancy complications. The four adverse pregnancy outcomes chosen as the focus of this review are the more common and clinically significant of the placentally-mediated complications.[6,21]

OBJECTIVE

5 To determine the association between a false-positive, second-trimester MSS for Down syndrome and an increased risk of preeclampsia, growth restriction, preterm birth, and/or stillbirth amongst singleton pregnancies globally.

METHODS

6 This review will be conducted using principles outlined in the Cochrane Handbook for Systematic Reviews (of Interventions)[22]. Both the Preferred reporting items for systematic reviews and meta-analyses (PRISMA)[22]and Meta-analysis of observational studies in epidemiology (MOOSE)[23]guidelines were consulted to best determine reporting standards for systematic reviews . Ultimately, the MOOSE guidelines were chosen for this project given the majority of observational studies on this topic, unlike PRISMA which is better suited to interventional studies.[23] Ethics approval for this review was sought from the Research Ethics Committee of the London School of Hygiene and Tropical Medicine at the University of London, however this study was deemed exempt.

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6.1 Eligibility Criteria of studies:

Types of Studies
All observational studies assessing the association between multiple-marker, second-trimester MSS and adverse pregnancy outcomes will be considered for this review. Only studies with both 'exposure' and 'control' groups will be eligible for inclusion.

Types of Participants
Pregnant women with singleton pregnancies undergoing multiple-marker, second-trimester MSS globally, and who were followed up until the date of confinement for possible adverse pregnancy outcomes are eligible for inclusion. Multiple gestations (twins and higher-order multiples) is an independent risk factor for pregnancy complications.[24] In order to best isolate the possible relationship between a false-positive MSS and adverse pregnancy outcomes, and reduce potential confounding by pregnancy type, this review was restricted to singleton pregnancies only.

Types of 'exposure'
A false-positive, second-trimester MSS is considered as the 'exposure'. The definition of "false-positive MSS" will be assigned in the setting of a screen-positive result (using the combined 'cut-off' pre-specified by the reporting institution – *not individual analyte levels*) that occurs with an otherwise structurally and chromosomally normal fetus. This 'exposed' group of singletons will then be compared to an 'unexposed' control group of singletons with screen-negative, second-trimester MSS.

Types of outcomes
Given the association between serum analytes and placental function, 4 placentally-mediated complications of pregnancy have been chosen as the main outcomes of interest: 1) preeclampsia (blood pressure >140/90 with proteinuria); 2) fetal growth restriction (weight less than the 10thpercentile at birth); 3) preterm birth (delivery prior to 37 weeks of gestation); and 4) stillbirth (fetal death in utero after 20 weeks of gestation). Diagnostic definitions of these outcomes were consistent with ICD-9 and/or 10 diagnostic codes[25] and consistency with professional guidelines[6,16,21].

Inclusion criteria
i) Singleton pregnancy
ii) Second-trimester, multiple-marker MSS (double-, triple-, and/or quadruple-marker screens) with reported screen-positive cut-offs for Down syndrome (or 'Trisomy 21')
iii) Observational design with suitable control group (ie: cohort or case-control studies)
iv) Report on ≥1 outcome(s) of interest
v) Report at least one measure of association (either risk ratio or odds ratio) for the relationship between MSS test status and the development of adverse pregnancy outcomes, or report the raw number of events between groups so that a measure of association could be calculated by the reviewer

Exclusion criteria
i) Multiple gestations
ii) No screen-positive cut-off for Down syndrome reported (ie: individual analyte levels utilized instead of a combined/integrated result)
iii) No control group
iv) None of the outcomes of interest were assessed
v) Non-English language publication

6.2 Search Methods:

Electronic searches
We plan to search the following bibliographic databases electronically (anticipated access starting January 2018 until the latest available year): PubMed, Medline, Embase via Ovid, Web of Science, Cumulative Index to Nursing and Allied Health (CINAHL), and Scopus. PubMed and Embase have both been chosen to ensure comprehensiveness of the biomedical citations given the geographic variations of studies indexed within each. Medline will be used additionally due to its ability for adjacency searching. Web of Science, CINAHL and Scopus will be used to insure that smaller studies were located.

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Hand-searches of available abstracts from major conference proceedings will also be screened for eligibility including the Fetal Medicine Foundation (UK), the Society for Maternal-Fetal Medicine (USA), and the International Society for Prenatal Diagnosis. Grey literature will be identified using Google Scholar and Proquest Dissertations. Studies published from inception until latest available year are eligible for inclusion.

Search strategies
The search strategy will comprise of three general concepts: i) “maternal serum screening”; 2) “false-positive results”; and 3) “adverse pregnancy outcomes”. Medical subject headings (or equivalent) and text word terms were used for all search concepts along with their related words and synonyms, and search strategies will then be individualized to the specific databases mentioned previously. A preliminary sample search strategies of the PubMed database and others appear in the enclosed attachment (Pages 8-11 and Appendices A to E).

6.3 Data Collection and Analysis:

Study Selection
All citations will be managed using RefWorks reference manager software (ProQuest LLC, Ann Arbor, MI, USA). The author of this manuscript will perform the selection of studies independently. First, all titles will be reviewed for possible relevance. Abstracts of relevant citations will then be screened for inclusion criteria. Based on this review of abstracts, all potential studies will be classified as: include, exclude, unclear or duplicate. The full text of all reports classified as either ‘include’ or ‘unclear’ will then be retrieved and reviewed for possible inclusion in this manuscript.

Data abstraction and management
Once the final roster of ‘included’ papers is assembled, the authors will independently assess the full text of all these remaining studies using a standardized form (Appendix F). Data will be entered into a Microsoft Excel database (Excel v.14, Microscoft Corp., Redmond, WA, USA). Once this review of the literature was completed, a PRISMA flow diagram will be constructed to illustrate the number of records and full-text reports reviewed and their status in the review (ie: included or excluded).

Assessment of risk of bias
Internal validity of included trials will be assessed using the nine-item Newcastle Ottawa Screening tool (NOS)[26], with each item rated as low, high, or unclear risk of bias. If one or more areas is adjudicated as having a high risk of bias, the study will be classified as being a high risk of bias and excluded from the meta-analysis. If all components of a trial were classified as having a low risk of bias, the trial was included in the meta-analysis. In cases of mixed assessments of low and/or unclear risk of bias, overall classification will be of moderate or unclear bias. In cases where missing background information about the study design/methodology was responsible for the ‘unclear’ adjudication, attempt will be made to contact the primary authors via email on two separate occasions for additional clarification. Information on risk of bias for each study will be used to explore possible sources of heterogeneity and in order to guide sensitivity analyses when relevant.

Measures of effect
The data from included studies will be analyzed using Review Manager v5.3.5 (RevMan V.5.3.5, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and the formal meta-analysis is planned using Comparative Meta-Analysis (CMA) v2.0 software. The CMA software was chosen instead of other potential statistical software platforms given its ability to allow for input of multiple different data types.

Given the dichotomous nature of the outcomes of interest, a decision has been made a priori to present pooled odds ratios as the measure of effect. Pooled odds ratios will be calculated for each outcome by subgroup of MSS testing (ie: double-marker or triple-marker) and as a pooled combined estimate overall. A random-effects model has been chosen to calculate the pooled odds ratios given that the background literature suggested there could be variability of the effect size amongst studies.[27] Whenever outcomes were reported by individual studies as number of events per group or as proportions, those values will be transformed into odds ratios with 95% confidence intervals using the CMA statistical software when appropriate. When an external correlation (EC) was required but not

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reported, then a range of plausible ECs will be used in order to conduct formal sensitivity analyses to test the robustness of the calculated analyses.

Dealing with missing data
In the event of missing data or questions regarding methodology and statistical analysis, primary authors will be contacted via email on several occasions. As previously mentioned, analysis using raw event numbers would be performed whenever outcomes were reported as proportions, or in the event of missing data (ie: standard deviations and/or specific p-values).

Subgroup and sensitivity analyses
While all four outcomes are known to be mediated by placental functioning, the pathophysiology of each remains different and complex.[6,16] Preterm birth and stillbirth are particularly thought to be multifactorial in origin, and thus it is anticipated that there would be differential risks between false-positive MSS and each adverse outcome.[16-21]For these reasons, subgroup analyses are planned for each of the four main outcomes separately.
Subgroup analyses are also planned based upon different patient characteristics known to be risk factors of adverse pregnancy outcomes and potential confounders (maternal age, smoking, and ethnicity), and by type of MSS testing (double-, triple-, and quadruple-marker tests), pending availability of the relevant demographic information.

Assessment of heterogeneity
Statistical heterogeneity of the data will be determined using the Q statistic, Tau^2 and the I^2 statistics. For the I^2test, uncertainty intervals were not planned a priori.[27] The suspicion of significant heterogeneity (I^2 >50%)[28] will be followed-up with further analysis when required to determine potential sources of the heterogeneity.

Assessment of publication bias
Publication bias will be assessed by the trim and fill, fail safe N, and funnel plot methods (with imputed studies when less than 10 were found).[27, 28]

Grading the evidence
Strength of evidence will be assessed using evidence of individual domains (risk of bias, inconsistency, indirectness, imprecision, publication bias and other factors including upgrading) and ultimately classified as high, moderate, low or very low.[27]

ANTICIPATED RESULTS/GRAPHS

7 Sample Titles of the Planned Figures & Tables:

Figure 1: Sources from searches of electronic databases.

Figure 2: Sources from searches of grey literature.

Figure 3: PRISMA flow diagram of studies.

Table 1. Baseline characteristics of included studies.

Table 2. Design characteristics and methods of individual studies.

Figure 4: Risk of bias summary of review author's judgments for each risk of bias item for included studies.

Figure 5: Risk of bias graph of review author's judgments for each risk of bias item (%) across studies.

Figure 6: Forrest plot of pooled odds of preeclampsia, by MSS test type.

Figure 7: Forrest plot of pooled odds of stillbirth, by MSS test type.

Figure 8: Forrest plot of pooled odds of preterm birth, by MSS test type.

Figure 9: Forrest plot of pooled odds of fetal growth restriction, by MSS test type.

Figure 10: Funnel plot assessment of publication bias for citations about preeclampsia, including Fail Safe N.

Figure 11: Funnel plot assessment of publication bias for citations about stillbirth, including Fail Safe N.

Figure 12: Funnel plot assessment of publication bias for citations about preterm birth, including Fail Safe N.

Figure 13: Funnel plot assessment of publication bias for citations about fetal growth restriction, including Fail Safe N.

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Figure 14: Summary table of evidence by GRADE.

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