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Morris, R. Katie; Bilagi, Ashwini; Devani, Pooja; Kilby, Mark

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Association of serum PAPP-A levels in first trimester with small-for-gestational-age and adverse pregnancy outcomes: systematic review and meta-analysis.

R.Katie Morris[1,2,3], Ashwini Bilagi [1,2,3], Pooja Devani[1], Mark D. Kilby[1,2,3].

[1] Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, B15 2TT, UK.

[2] Fetal Medicine Centre, Birmingham Women's Hospital NHS Foundation Trust, Birmingham, B152TG, UK.

[3] Centre for Women and New born Health, Birmingham Health Partners, Edgbaston, Birmingham, B15 2TT.

Corresponding author:

Dr R K Morris

Institute of Metabolism and Systems Research

University of Birmingham

Birmingham

B15 2TT

Tel: 00 44 121 623 6652

E-mail: r.k.morris@bham.ac.uk

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Disclosure of interests

Dr Morris is an author of the RCOG Greentop guideline on Investigation and Management of the Small for Gestational Age Fetus .

What's already known on this topic?

Low levels of PAPP-A are associated with small for gestational age and pre-eclampsia.

What does this study add?

Low maternal serum PAPP-A in the first trimester has an association with adverse pregnancy outcome particularly if levels are very low (<1st centile).

For an individual prediction is poor thus the majority of adverse outcomes will occur in the group without an abnormally low PAPP-A.

Future research is required to develop prediction models and effective interventions.

Abstract

Objectives

To determine association, and predictive ability, of first trimester maternal serum pregnancy associated plasma protein A (PAPP-A) with adverse pregnancy outcomes.

Method

Searches of Medline, Embase and CINAHL (inception-September 2015) for studies including pregnant women with first trimester PAPP-A and assessment of pregnancy outcomes.Study characteristics, quality and results extracted. Meta-analysis of odds ratios (OR), and likelihood ratios (LR) and 95% confidence intervals (CI).

Results

Thirty-two studies including 175,240 pregnancies. PAPP-A <5th centile had a moderate association with: Birthweight <10th centile OR 2.08 (95% CI 1.89 – 2.29), <5th centile OR 2.83 (95% CI 2.52 – 3.18); pre-eclampsia OR 1.94 (95% CI 1.63 – 2.30), preterm birth <37 weeks OR 2.09 (95% CI 1.87 – 2.33), and composite adverse outcome OR 3.31 (95% CI 1.80 – 5.11). The predictive ability was poor: Birthweight <10th centile LR+ve 1.96 (95% CI 1.58 -2.43), LR-ve 0.93 (95% CI 0.89 – 0.98); Birthweight <5th centile LR+ve 2.65 (95% CI 2.35 -2.99), LR-ve 0.85 (95% CI 0.74 – 0.98); PTB <37 weeks LR+ve 1.84 (95% CI 1.41 – 2.39), LR-ve 0.92 (95% CI 0.87 – 0.98).

Conclusions

First trimester low maternal serum PAPP-A is associated with adverse pregnancy outcome but predictive values are poor. Further work should address PAPP-A as a continuous variable in combination with other prognostic markers as a prediction model.

Keywords: PAPP-A, pregnancy associated plasma protein A, small for gestational age, pre-eclampsia, adverse pregnancy outcomes, systematic review, prognosis

Introduction

Adverse pregnancy outcomes [stillbirth, preterm birth (PTB), small for gestational age (SGA), and hypertensive disorders of pregnancy] have a major psychological impact for the family as well as an increased cost for the healthcare system. Accurate methods of predicting these outcomes would allow health professionals to provide increased surveillance and offer optimum management, which could possibly improve the outcome of the pregnancy.

Pregnancy associated plasma protein A (PAPP-A) is a placental glycoprotein produced by syncytial trophoblast, which cleaves insulin-like growth factor binding protein 4 (IGFBP4) and is a positive regulator of insulin-like growth factors (IGFs)[1]. Biochemical measurement of placental derived factors has been suggested as a means to improve fetal and maternal outcome of pregnancy. Previous studies have tested the hypothesis that low maternal serum levels of PAPP-A in the first trimester can predict adverse pregnancy outcomes associated with poor placental function [2,3,4,5,6]. The recently published Royal College of Obstetricians and Gynaecologists (RCOG) Green top Guidelines assessed all the available evidence prior to their publication in 2013 and recommended that in women with a serum PAPP-A <0.415 multiples of the median (MoM) (5th centile) in the first trimester receive increased ultrasound surveillance for growth disorders[7]. This recommendation was based on a previous systematic review by our group in 2008 assessing Down's syndrome markers to predict pre-eclampsia and SGA[8]. This review included only 16 studies,

did not assess all outcomes and did not distinguish between prognosis and prediction[8]. In 2010, first trimester combined screening was routinely introduced in the United Kingdom as the recommended screening for Down's syndrome[9]. This test involves assay of PAPP-A between 10 and 13+6 weeks. Thus since this time, there has been a substantial increase in the number of published articles related to this placental analyte and therefore a need to systematically review this evidence.

When assessing a biomarker it is important to assess whether there is any prognostic association between the "analyte" and outcomes of interest before considering the predictive ability of the biomarker to predict the outcome of interest in an individual[10]. It is also important to determine whether PAPP-A has a true prognostic ability for adverse pregnancy outcome to determine its use in pregnancy surveillance with newer methods of aneuploidy screening such as non-invasive prenatal testing with cell free fetal DNA. The aim of this systematic review and meta-analysis is to improve our understanding of the association between first trimester maternal serum PAPP-A levels and pregnancy outcomes and where appropriate to evaluate the predictive ability for adverse pregnancy outcomes.

Methods

A protocol driven systematic review was performed in accordance with published guidelines [11 12-15]. The reporting of the review meets the criteria specified in the PRISMA guidance [15]. This is a systematic review consisting of analysis of previously reported data and thus ethics approval is not required.

Sources

A literature search was performed in electronic databases from inception till September 2015. We searched Embase, MEDLINE, CINAHL (current nursing and allied health literature) and Web of Science (grey literature) using combinations of relevant medical subject heading (MeSH) terms, keywords and word variants (Appendix S1). The reference lists of all included primary and review articles were examined to identify articles not captured by electronic searches. A comprehensive database collating all citations was constructed using Endnote 7 (Thomson Reuters)[16].

Study selection and data extraction

Two independent reviewers scrutinised the data base (RKM and AB partly in duplicate). The first stage of study selection was identifying articles based on title or abstract with translation of articles with abstracts not in English and removal of duplicates. In the second stage, all the citations that were thought to meet the predefined selection criterion were obtained. Following examination of full text articles by the same reviewers the following inclusion and exclusion decisions were made according to adherence to the following criteria:

- *Population:* Pregnant women any health care setting, any level of risk.
- *Tests:* Serum pregnancy associated plasma protein A measured in the first trimester (<14 weeks)
- *Reference standard/outcome:* Birth weight, birth weight centile (population or customised), maternal (pre-eclampsia, pregnancy induced hypertension, gestational diabetes, abruption) and pregnancy outcomes (miscarriage, stillbirth, preterm delivery) and a composite adverse pregnancy outcome.

- *Study design:* Observational test accuracy studies (cohorts, case-control prospective) allowing generation of 2x2 tables of accuracy. Case series <10 cases and case-control studies defined by reference standard outcome were excluded, these study designs have been shown to be associated with bias [17].

No language restrictions were applied to the study. All manuscripts were carefully examined to identify overlapping populations. Where this was the case most recent and complete manuscripts were selected. Data were extracted on study characteristics, quality assessment criteria and results for 2x2 tables (true positive, false positive, false negative, true negative) comparing the same threshold of PAPP-A with an individual outcome were obtained and entered into an Excel spread sheet in duplicate by three reviewers (RKM, AB and PD). Discrepancies in data were resolved by a fourth reviewer (MDK).

Study Quality assessment

All studies meeting the pre-defined selection criteria were assessed for methodological and reporting quality, defined as confidence that the study design, conduct, analysis and reporting minimised any bias in the estimation of the association. Quality assessment was based on published guidelines for reporting of diagnostic accuracy studies (STARD) and methodological quality (QUADAS-2) [18, 19 20, 21]. The methodological quality items were adopted for the review question and two authors independently judged each quality item. In case of discrepancies, consensus was reached by discussion.

Study quality was assessed in the domains of patient selection, index test, reference standard and flow and timing assessing risk of bias and applicability as per QUADAS-2[20]. For the population, consecutive or random recruitment of pregnant women was considered to be ideal. Prospective recruitment was considered to introduce less bias than retrospective recruitment. The description of the population was considered ideal if there was sufficient information about the pregnant women given to assign a level of obstetric risk, and ideally this risk level was stated by the authors in the study's methods.

The quality of performance and reporting of the index standard (PAPP-A) was assessed considering the processes reported for storage of the maternal serum sample if needed and the immunoassay analyser used in the lab to quantify the levels of serum PAPP A .For the reference standard, any outcome relating to maternal, pregnancy or neonatal outcome was considered and information collected on method of determination of reference standard, execution and blinding.

Ideal study design were trials or cohort studies, case-control studies were only included when cases were not determined by reference standard/outcome as it has been shown that this type of study design can affect accuracy [17].

The assessment of quality is represented by a bar chart. No attempt was made to apply a quality score as this has been shown to have little validity and quality was not an aspect for inclusion/exclusion of studies from meta-analysis instead an individual assessment was made and this was used to inform investigations into heterogeneity in results and sub-group analysis where appropriate [22].

Data synthesis and analysis

From the 2x2 tables the following were calculated with 95% confidence intervals (CI) for individual studies: odds ratio (OR), sensitivity, specificity and the likelihood ratios (LR). Results were pooled among groups of studies with similar characteristics, the same threshold for the index test and same reference standard definition and threshold. Studies also reported a composite adverse pregnancy outcome. These studies were included in a meta-analysis as long as it could be ensured that individuals were only counted once and that the individual outcomes of the composite were all of a similar magnitude and direction of effect across the studies [23]. The OR was selected as the summary statistic, as it represents the effect of the exposure on the odds in an unbiased fashion and enables the results of both case-control and cohort studies to be included and provides a measure of the test's prognostic ability [24].

Data were first displayed as forest plots of the OR and 95% CI to allow a visual inspection for heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic where I^2>50% is significant [25]. Random effects meta-analysis was used throughout in anticipation of significant clinical and statistical heterogeneity. Where there were zero cells within a table a value of 0.5 was added to allow the calculation of log ORs and their variances for meta-analysis [26].

To explore for the presence of funnel plot asymmetry (small study effects), and thus potential publication bias, the Peters test was performed in each meta-analysis [27].

Where there was a moderate statistically significant association between PAPP-A and an outcome measure (defined as OR>2 and 95% CI >1) then sensitivity, specificity and likelihood ratios were considered, using data from the 2x2 tables. Predictive summary measures were synthesised using the bivariate random effects prediction model where there were at least four studies in the meta-analysis and univariate meta-analysis where this was not possible [28]. These measures assess the predictive ability of the test i.e. whether the test can accurately discriminate between those who do and those who do not have the adverse outcome (sensitivity and specificity) and by how much a positive or negative test result modifies the odds of a poor outcome (likelihood ratios) [12]. Throughout $p<0.05$ was considered to be statistical significance.

All analyses were performed in STATA 10.0 (StataCorp, College Station, TX, USA) using the metan, metandi and metabias commands [29-31]. Univariate analyses were performed in Metadisc [32].

Results

Figure 1 demonstrates the study selection process with 32 studies being included reporting on 175,240 pregnancies [2, 5, 33-62]. All studies were performed on secondary or tertiary care settings in a low risk or unselected population. All were singleton pregnancies except 5 studies where it was not clear that multiples were excluded and all excluded fetuses with chromosomal or structural anomalies apart from 6 studies where again this was not clear. All studies were observational and non-interventional, 23 were a cohort design, 5 case-control and in 4 the design was unclear. Case series were not included as there were sufficient larger studies

(smallest n=198). Recruitment was prospective in 13 studies, retrospective in 16 and unclear in 3. PAPP-A was performed between 8-14 weeks and various thresholds were reported including centile cut-offs and multiples of the median (MoM). Outcomes included birth weight <10th centile in 17 studies, <5th centile in 15 studies or <3rd centile in 3 studies and >90th centile in 2 studies. Maternal outcomes assessed included: 11 studies assessing pre-eclampsia, pregnancy induced hypertension in 6 studies, preterm birth <37 weeks in 22 studies and <34 in 2 and <32 weeks in 3 studies respectively, gestational diabetes in 1 study, 4 studies assessed abruption and 4 studies pregnancy loss <24 weeks. Fetal outcomes assessed included 8 studies looking at stillbirth >24 weeks. Six studies reported results for a composite adverse pregnancy outcome. Table S1 describes the characteristics of the included studies.

Figure 2 displays the bar charts for methodological quality. The assessment of patient selection among the included studies showed that two publications were at high risk of bias because of being either a case control study (Pawlowski 2013) or because exclusions were not clearly described (Spencer 2005) [43, 59]. Sensitivity analyses with these studies excluded demonstrated no significant difference to results. In the other three domains (index test, reference standard and flow and timing) all studies were judged overall to have a low risk of bias. When assessing applicability one study was deemed to be at high risk as it included patients with early onset (second trimester) IUGR (Fox et al 2009)[40]. The overall high quality of the included studies meant that sub-group analysis based on quality was not required.

Prognostic association

Table 1 summarises the OR and 95% CI for all analyses. Forest plots for the main analyses are shown in Figure 3. Where data was available to look at odds of an adverse outcome with PAPPA < 1st centile this demonstrated increasing odds with decreasing PAPP-A (Table 1). Three of the analyses demonstrated significant heterogeneity (Birthweight <10th, PET and PTB). Inspection of the forest plots and table of characteristics could demonstrate no obvious cause for this.

Peter's test revealed no significant evidence of small study effect across all analyses (range p=0.39 – p=0.67) (Funnel plots shown for major meta-analyses in figure S1)

Predictive ability

Table 1 also summarises the sensitivity, specificity, likelihood ratios (LRs) and 95% CI for all analyses. Bivariate meta-analysis was possible for 6 test-outcome combinations: PAPP-A <10th centile and birth weight <10th; PAPP-A <5th centile and birth weight 10th and <5th centile, pre-eclampsia, preterm birth <37 weeks and stillbirth >24 weeks and the hierarchical summary receiver operating characteristic curves (HSROC) are shown in Figure S2. Considering those analyses where a moderate association had been demonstrated (OR > 2.0 and lower CI > 1.0) the following predictive abilities were demonstrated all with a threshold of PAPP-A < 5th centile: Birthweight <10th centile LR+ve 1.96 (95% CI 1.58 -2.43), LR-ve 0.93 (95% CI 0.89 – 0.98); Birthweight <5th centile LR+ve 2.65 (95% CI 2.35 -2.99), LR-ve 0.85 (95% CI 0.74 – 0.98); PTB <37 weeks LR+ve 1.84 (95% CI 1.41 – 2.39), LR-ve 0.92 (95% CI 0.87 – 0.98) and stillbirth >24 weeks LR+ve 1.58 (95% CI 0.67 – 3.71) and LR-ve 0.92 (95% CI 0.78 – 1.09).

Clinical Interpretation

The predictive ability of PAPP-A can be converted to a probability of an adverse outcome for a low risk nulliparous woman (i.e. no known prior risk) in an unselected population with 8000 deliveries a year after a positive test (i.e. posterior test probability) using a nomogram (http://araw.mede.uic.edu/cgibin/testcalc.pl) (Table 2). Thus following a PAPP-A in the first trimester less than <5th centile a woman would have a 1 in 5.6 chance of an SGA baby (birth weight <10th centile) and a 1 in 3.7 of any adverse outcome. With lower levels of PAPP-A <1st centile the risks are considerably increased with a 1 in 3.6 chance of an SGA baby, 1 in 11 chance of pre-eclampsia, 1 in 3.7 chance of preterm birth (<37 weeks), 1 in 10 chance of late miscarriage and a 1 in 72 chance of stillbirth.

Conclusion

Main Findings

Low maternal serum PAPP-A in the first trimester has an association with adverse pregnancy outcome with a moderate association once levels are <5th centile for gestation and a stronger association <1st centile. The predictive values are poor, thus although women with a low PAPP-A are at increased risk of an adverse outcome, the vast majority of these women will have a normal pregnancy outcome and the majority of women with an adverse outcome will have a normal PAPP-A.

Strengths and Limitations

The strength of this review, and consequently the validity of the results for assessment of the prognostic and predictive value of PAPP-A, lie in its methodology. This included complying with recommended techniques for quality assessment [20] [13],

performing and interpreting meta-analyses and reporting of our findings [15, 28]. Our search strategies were comprehensive and robust, evidenced by Peter's test demonstrating no evidence of small study bias. We have considered all aspects of test performance and displayed both prognostic and predictive ability of the test as well as demonstrating how the test would perform in a sample population.

Limitations within the review relate in the first instance to limitations within the included studies. There was significant statistical heterogeneity in some analyses which could not be accounted for when examining clinical characteristics nor study design and was thus unexplained. Within some analyses there was a lack of data and thus for some bivariate meta-analysis could not be performed and for others test performance had to be assessed from a single study. We recognise that there are other variables that should be considered when assessing risk and that for the clinical interpretation we have assumed a background prevalence of the adverse outcome. It is not known how risk factors in obstetrics interact and how they modify risk in an individual. It is reasonable to assume however that in a woman with multiple risk factors e.g. previous SGA baby the risk will be higher than those discussed. One limitation in the methodology employed is the need to consider PAPP-A as a dichotomous variable i.e. categorisation using a threshold. This is a common technique in clinical research with dichotomization to simplify the analysis. This has limitations statistically as it can lead to a loss of power as much of the information is lost, classifying very similar factor values as different in opposite sides of the cut-off point and the concealment of a potential non-linear relationship between the outcome and the factor of interest [63-65]. One technique to overcome this is individual patient data meta-analysis (IPD), which uses original source data at the

participant level thus having many advantages such as being able to derive prognostic factor results directly, independent of study reporting and significance, and analyse continuous factors more appropriately [66, 67].

Interpretation

Prognostic factor research is important as it allows us to potentially improve outcome for patients by identifying modifiable factors by either intervention e.g. delivery or by different management pathways e.g. surveillance. If treatments are available that may modify disease then prognostic factors may have a role in predicting differential treatment response [68]. Even if a prognostic factor is insufficient as a stand-alone test, it may still add some independent prognostic value over other prognostic factors, and used in a multivariable prognostic model to help provide absolute risk predictions for women based on their individual characteristics [68]. It is therefore imperative to robustly and systematically assess prognostic factors as has been done in this review for PAPP-A.

Our results demonstrate evidence of associations between PAPP-A and adverse pregnancy outcomes. Future work should thus include IPD meta-analysis as previously discussed to allow assessment of PAPP-A as a continuous variable and its relationship with other prognostic markers available during the pregnancy; first trimester (e.g. crown rump length, nuchal translucency), second trimester (e.g. fetal biometry, uterine artery Doppler) and third trimester (e.g. placental biomarkers, placental morphology) [69, 70 71, 72 73]. Any prognostic model developed would then require validation in external data sets [74]. At present in UK practice PAPP-A is only used as part of combined screening for Down's syndrome and not as a biomarker for

adverse outcome. Before any test (either individual or as a model) is introduced in this capacity into practice there must be an assessment of the interventions that may be introduced e.g. increased surveillance or pharmacological, to ensure that screening in a population is justified and these interventions must be effective in the group identified as high risk via the test or model. At present although aspirin has been suggested as a possible intervention in certain groups (e.g. those at high risk of pre-eclampsia based on previous history) there is no evidence for the effectiveness in a group selected by either PAPP-A as a stand-alone test or a model including PAPP-A. This allows the clinical effectiveness in reducing the adverse outcome to be assessed. However, the results of this systematic review allow appropriate counselling of women who have had PAPP-A assessed as part of Down's syndrome screening.

Conclusion

Low maternal serum PAPP-A in the first trimester has an association with adverse pregnancy outcome particularly if levels are very low (<1st centile). It must be recognised that for the individual, predictive values are poor and the majority of adverse outcomes will occur in the group without an abnormally low PAPP-A. There are also no proven interventions in this group. Therefore, future research is required to develop robust and accurate prediction models and effective interventions that can allow modern day obstetrics to practice truly stratified medicine [75].

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Contribution to authorship

RKM, AB and MDK conceived the idea. AB, RKM and PD were responsible for data collection. All authors were involved in data analysis and drafting of the manuscript.

Disclosure of interests

Dr Morris is an author of the RCOG Greentop guideline on Investigation and Management of the Small for Gestational Age Fetus [76].

Ethics approval

This is a systematic review consisting of analysis of previously reported data and thus ethics approval is not required.

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Table 1: Meta-analysis summary of studies for systematic review of association and prediction of first trimester maternal serum pregnancy associated plasma protein A (PAPPA) and adverse pregnancy outcomes.

Pregnancy outcome/ PAPPA threshold	Number of included studies	Number included in analyses	Odds ratio	95% Confidence interval	Sensitivity	95% Confidence interval	Specificity	95% Confidence Interval	Positive Likelihood ratio	95% Confidence Interval	Negative Likelihood ratio	95% Confidence Interval
Birth weight <10th centile	17	65078										
<10th centile *	7	44316	1.88	1.72-2.05	0.16	0.14 -0.19	0.90	0.89 - 0.90	1.64	1.45 - 1.88	0.92	0.90 - 0.95
<5th centile *	12	59927	2.08	1.89-2.29	0.13	0.08 -0.2	0.94	0.90 - 0.96	1.96	1.58 -2.43	0.93	0.89 - 0.98
< 1st centile	2	39671	3.40	2.70 - 4.26	0.03	0.02 -0.04	0.99	0.99 - 0.99	3.49	2.51 - 4.89	0.98	0.98 - 0.99
<0.5MoM	3	4916	1.60	1.23 - 2.07	0.19	0.15 - 0.23	0.88	0.87 - 0.89	1.96	1.02 - 3.76	0.88	0.77 - 1.02
<0.3 MoM	2	3912	1.55	0.97 - 2.48	0.06	0.04 -0.09	0.96	0.96 - 0.97	1.93	0.72 - 5.20	0.97	0.90 - 1.04
Birth weight <5th centile	15	134825										
<10th centile	4	39714	2.29	2.01 - 2.60	0.20	0.18 - 0.22	0.90	0.90 - 0.90	2.17	1.64 - 2.87	0.90	0.85 - 0.94
<5th centile *	11	72245	2.83	2.52-3.18	0.22	0.10 - 0.41	0.92	0.84 - 0.96	2.65	2.35 - 2.99	0.85	0.74 - 0.98
<1st centile	2	45750	4.66	3.61 - 6.01	0.04	0.03 - 0.05	0.99	0.99 - 0.99	4.52	3.53 - 5.78	0.97	0.96 - 0.98
<0.5MoM	2	4550	2.12	1.53 - 2.95	0.25	0.19 - 0.32	0.86	0.85 - 0.87	1.99	1.23 - 3.22	0.84	0.68 -1.03
<0.3MoM	2	22464	3.13	2.30 - 4.26	0.12	0.09 -0.16	0.96	0.95 - 0.96	2.89	2.21 - 3.79	0.92	0.88 - 0.97
Birth weight <3rd centile	3	8935										
<5th centile	2	8108	2.76	1.78 - 4.28	0.12	0.08 -0.18	0.95	0.95 - 0.96	2.58	1.75 - 3.79	0.93	0.88 -0.98
<0.5 MoM	2	3692	1.89	1.19 - 3.01	0.23	0.15 - 0.32	0.87	0.85 - 0.88	1.69	1.18 - 2.42	0.89	0.80 -0.99
<0.3 MoM	2	3692	2.68	1.37 - 5.27	0.10	0.05 - 0.17	0.96	0.96 - 0.97	2.53	1.37 - 4.67	0.94	0.88 -1.00
Birth weight > 90th centile	2	35545										
<10th centile	2	35545	0.50	0.35 - 0.71	0.05	0.04 -0.08	0.90	0.90 -0.90	0.53	0.38 - 0.74	1.05	1.03 - 1.08
< 5th centile	2	35545	0.42	0.24 - 0.72	0.02	0.01 - 0.04	0.95	0.95 - 0.95	0.44	0.25 -0.75	1.03	1.02 - 1.04
Pre-eclampsia	11	71195										

< 10th centile	3	38956	1.42	1.18 - 1.72	0.14	0.12 - 0.16	0.90	0.89 - 0.90	1.55	1.06 - 2.27	0.94	0.88 - 1.01
< 5th centile*	8	132076	1.94	1.63-2.30	0.16	0.09 - 0.28	0.92	0.85 - 0.96	1.95	1.48 - 2.56	0.91	0.86 - 0.97
< 1st centile	2	45750	2.27	1.43 - 3.62	0.02	0.01 - 0.04	0.99	0.99 - 0.99	4.91	0.60 - 40.19	0.95	0.83 - 1.08
Pregnancy induced hypertension	6	8562										
< 10th centile	2	5561	2.83	1.71 - 4.68	0.24	0.15 - 0.34	0.90	0.19 - 0.91	2.47	1.68 - 3.63	0.91	0.73 - 1.13
< 0.5 MoM	2	2124	5.07	2.78 - 9.27	0.47	0.31 - 0.62	0.86	0.84 - 0.87	2.80	0.25 - 31.57	0.43	0.03 -7.48
< 0.4 MoM	2	877	2.68	1.40 - 5.10	0.18	0.1 - 0.28	0.92	0.90 - 0.94	2.31	1.37 - 3.90	0.91	0.83 - 1.00
Pre-term birth <37 weeks	22	107324										
< 10th centile	3	38956	1.52	1.35 - 1.71	0.15	0.13 - 0.16	0.90	0.89 - 0.90	1.45	1.31 - 1.60	0.95	0.93 - 0.97
< 5th centile*	7	66133	2.09	1.87-2.33	0.16	0.09 - 0.29	0.91	0.83 - 0.96	1.84	1.41 - 2.39	0.92	0.87 - 0.98
< 1st centile	2	45750	3.63	2.89 - 4.55	0.03	0.03 - 0.04	0.99	0.99 - 0.99	4.28	1.50-12.25	0.97	0.94 - 1.00
< 0.6 MoM	2	4938	1.69	1.36 - 2.11	0.32	0.27 - 0.37	0.78	0.77 - 0.80	1.48	1.21 - 1.80	0.87	0.81 - 0.94
< 0.5 MoM	3	2946	3.02	2.16 - 4.22	0.30	0.23 - 0.37	0.87	0.86 - 0.88	2.31	0.62 - 8.55	0.75	0.52 - 1.09
< 0.4 MoM	3	12231	1.94	1.50 - 2.49	0.10	0.08 - 0.12	0.95	0.95 - 0.95	1.85	1.48 - 2.32	0.95	0.90 - 1.00
< 0.3 MoM	3	13060	2.11	1.50 - 2.95	0.05	0.04 - 0.07	0.98	0.98 - 0.98	1.86	0.95 - 3.64	0.98	0.96 - 1.00
Pre-term birth <34 weeks	2	13012										
< 5th centile	2	13012	2.51	1.48 - 4.25	0.17	0.13 - 0.21	0.90	0.90 - 0.90	1.69	1.31 -2.16	0.93	0.88 - 0.97
< 1st centile	1	7769	2.37	0.57 - 9.81	0.02	0.02 - 0.07	0.99	0.99 - 0.99	2.34	0.58 - 9.41	0.99	0.96 - 1.02
Pre-term birth <32 weeks	3	42690										
<10th centile	2	35623	1.82	1.35 - 2.45	0.17	0.13 - 0.21	0.90	0.90 - 0.90	1.69	1.31 - 2.16	0.93	0.88 - 0.97
< 5th centile	3	42690	2.25	1.60 - 3.17	0.12	0.09 - 0.16	0.95	0.94 - 0.95	1.99	1.49 - 2.65	0.94	0.91 - 0.98
< 1st centile	1	33395	3.26	1.60 - 6.65	0.03	0.01 - 0.06	0.99	0.99 - 0.99	3.19	1.6 - 6.36	0.98	0.96 - 1.0
Stillbirth >24 weeks	8	47916										
< 10th centile	2	33593	1.84	1.08 - 3.12	0.17	0.10 - 0.26	0.90	0.90 - 0.90	4.74	0.43 - 52.33	0.85	0.43 - 1.70
< 5th centile*	5	44575	2.40	1.45-3.99	0.18	0.08 - 0.36	0.88	0.80 - 0.94	1.58	0.67 - 3.71	0.92	0.78 - 1.09
<1st centile	1	33395	3.04	0.96 - 9.63	0.03	0.01-0.09	0.99	0.99 - 0.99	2.97	0.97 - 9.09	0.98	0.94 - 1.01
< 0.5 MoM	2	2119	5.74	0.81 - 40.70	0.50	0.01 - 0.99	0.85	0.84 - 0.87	4.10	1.22 - 13.70	0.71	0.22 - 2.26

Pregnancy loss ≤24 weeks	4	49986										
< 10th centile	2	38692	2.12	1.62 - 2.77	0.19	0.15 - 0.24	0.90	0.90 -0.90	1.91	1.53 - 3.37	0.90	0.85 - 0.95
< 5th centile	2	38692	2.50	1.81 - 3.47	0.12	0.09 - 0.16	0.95	0.95 - 0.95	2.25	1.47 - 3.46	0.94	0.99 - 1.00
<1st centile	1	33395	5.48	3.28 - 9.17	0.05	0.03 - 0.09	0.99	0.99 - 0.99	5.24	3.21 - 8.53	0.96	0.93 - 0.98
Gestational diabetes	1	5243										
< 5th centile	1	5243	4.17	2.00 - 8.69	0.18	0.09- 0.32	0.95	0.94 - 0.96	3.59	1.97 - 6.55	0.86	0.75 - 0.98
Abruption	4	6368										
< 5th centile	2	2565	2.73	0.81 - 9.23	0.31	0.09 - 0.61	0.82	0.8 - 0.83	2.74	0.62 - 12.17	0.80	0.56 - 1.15
Composite adverse outcome	6	15930										
< 10th centile	2	1076	4.50	2.55 - 7.95	0.29	0.18 - 0.41	0.92	0.9 - 0.93	3.48	2.28 - 5.32	0.78	0.67 - 0.91
< 5th centile	3	13431	3.31	2.76 - 3.97	0.12	0.1 - 0.14	0.96	0.96 - 0.96	3.05	2.59 - 3.59	0.92	0.9 - 0.93
< 0.4 MoM	2	877	3.03	1.80 - 5.11	0.17	0.12 - 0.24	0.93	0.91 - 0.95	2.60	1.69 - 4.0	0.89	0.77 - 1.02

PAPPA - pregnancy associated plasma protein A

MoM multiples of median

* bivariate meta-analysis

Table 2: Clinical use of first trimester pregnancy associated plasma protein A.

Pregnancy outcome/ PAPPA threshold	Positive Likelihood ratio	95% Confidence Interval	Negative Likelihood ratio	95% Confidence Interval	Prevalence[$] (%)	Posterior probability after positive test % (number with positive test who have outcome)	Posterior probability after negative test % (number with negative test without outcome)
PAPPA <5th centile							
Birth weight<10th centile [*]	1.96	1.58 -2.43	0.93	0.89 - 0.98	10	18% (1 in 5.6)	9% (1 in 1.1)
Birth weight <5th centile[*]	2.65	2.35 - 2.99	0.85	0.74 - 0.98	5	12% (1 in 8.2)	4% (1 in 1.0)
Pre-eclampsia	1.95	1.48 - 2.56	0.91	0.86 - 0.97	2	4% (1 in 26)	2% (1 in 1.0)
Preterm birth <37 weeks	1.84	1.41 - 2.39	0.92	0.87 - 0.98	8	12% (1 in 8.1)	7% (1 in 1.1)
Preterm birth <34 weeks	1.69	1.31 -2.16	0.93	0.88 - 0.97	2.4	4% (1 in 25)	2% (1 in 1.0)
Preterm birth <32 weeks	1.99	1.49 - 2.65	0.94	0.91 - 0.98	1.4	3% (1 in 36)	1% (1 in 1.0)
Pregnancy loss < 24 weeks	2.25	1.47 - 3.46	0.94	0.99 - 1.00	2	4% (1 in 23)	2% (1 in 1.0)
Stillbirth>24 weeks[*]	1.58	0.67 - 3.71	0.92	0.78 - 1.09	0.47	1% (1 in 135)	0% (1 in 1.0)
Composite adverse outcome	3.05	2.59 - 3.59	0.92	0.9 - 0.93	11	27% (1 in 3.7)	10% (1 in 1.1)
PAPPA <1st centile							
Birth weight <10th centile	3.49	2.51 - 4.89	0.98	0.98 - 0.99	10	28% (1 in 3.6)	10% (1 in 1.1)
Birth weight <5th centile	4.52	3.53 - 5.78	0.97	0.96 - 0.98	5	19% (1 in 5.2)	5% (1 in 1.1)
Pre-eclampsia	4.91	0.60 - 40.19	0.95	0.83 - 1.08	2	9% (1 in 11)	2% (1 in 1.0)
Preterm birth <37 weeks	4.28	1.50-12.25	0.97	0.94 - 1.00	8	27% (1 in 3.7)	8% (1 in 1.1)
Preterm birth <34 weeks	2.34	0.58 - 9.41	0.99	0.96 - 1.02	2.4	5% (1 in 18)	2% (1 in 1.0)
Preterm birth <32 weeks	3.19	1.6 - 6.36	0.98	0.96 - 1.0	1.4	4% (1 in 23)	1% (1 in 1.0)
Pregnancy loss < 24 weeks	5.24	3.21 - 8.53	0.96	0.93 - 0.98	2	10% (1 in 10)	2% (1 in 1.0)
Stillbirth > 24 weeks	2.97	0.97 - 9.09	0.98	0.94 - 1.01	0.47	1% (1 in 72)	0% (1 in 1.0)

PAPPA - pregnancy associated plasma protein A

MoM multiples of median

* bivariate meta-analysis

$ Prevalence data obtained from ONS 2014 (http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2015-07-15)

Pre-eclampsia prevalence from NICE guidelines "Hypertension in Pregnancy: the management of hypertensive disorders during pregnancy" . National Collaborating Centre for Women's and Children's Health. 2010

Late miscarriage prevalence from Wyatt PR,OwolabiT, Meier C, Huang T.Age-specific risk of fetal loss observed in a second trimester serum screening population.Am J Obstet Gynecol 2005;192:240–6

Composite adverse outcome prevalence calculated from included studies

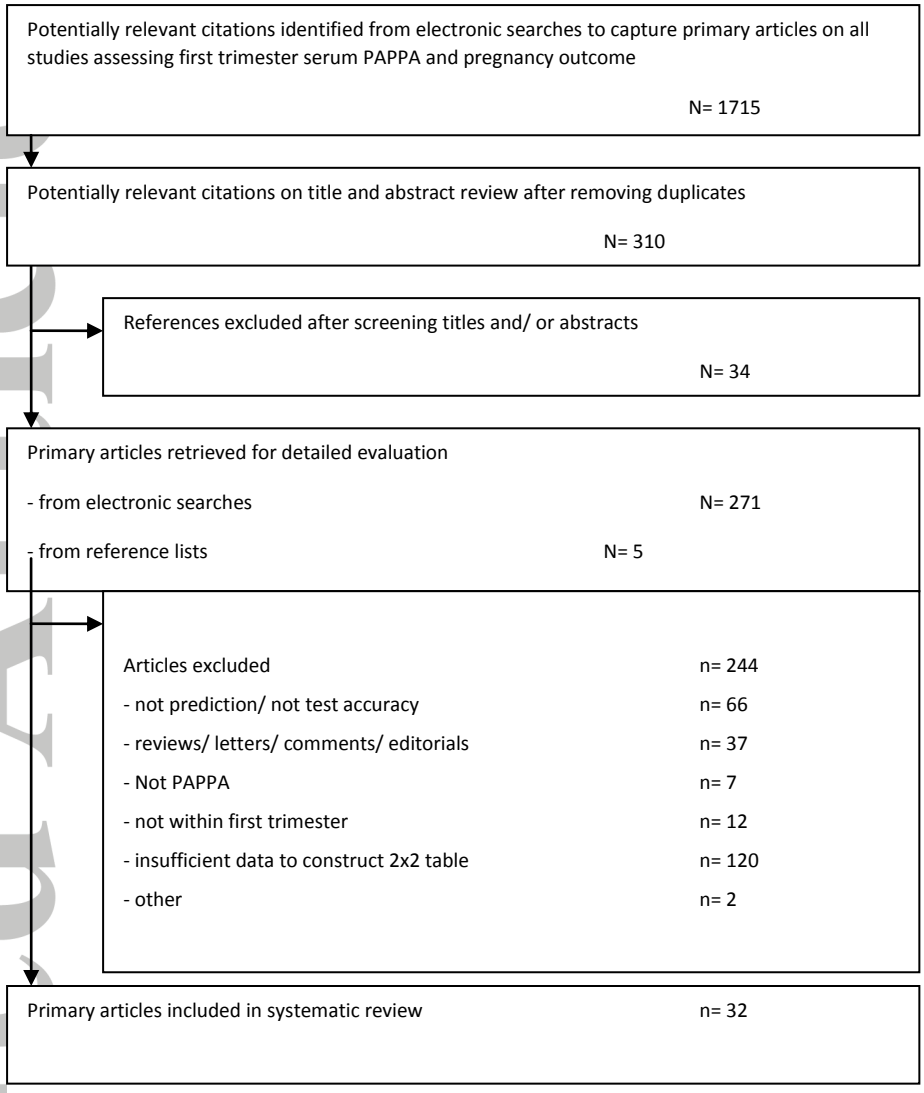

Figure 1 Process from initial search to final inclusion for association and prediction of first trimester serum pregnancy associated plasma protein A (PAPPA) with adverse pregnancy outcomes (inception to September 2015).

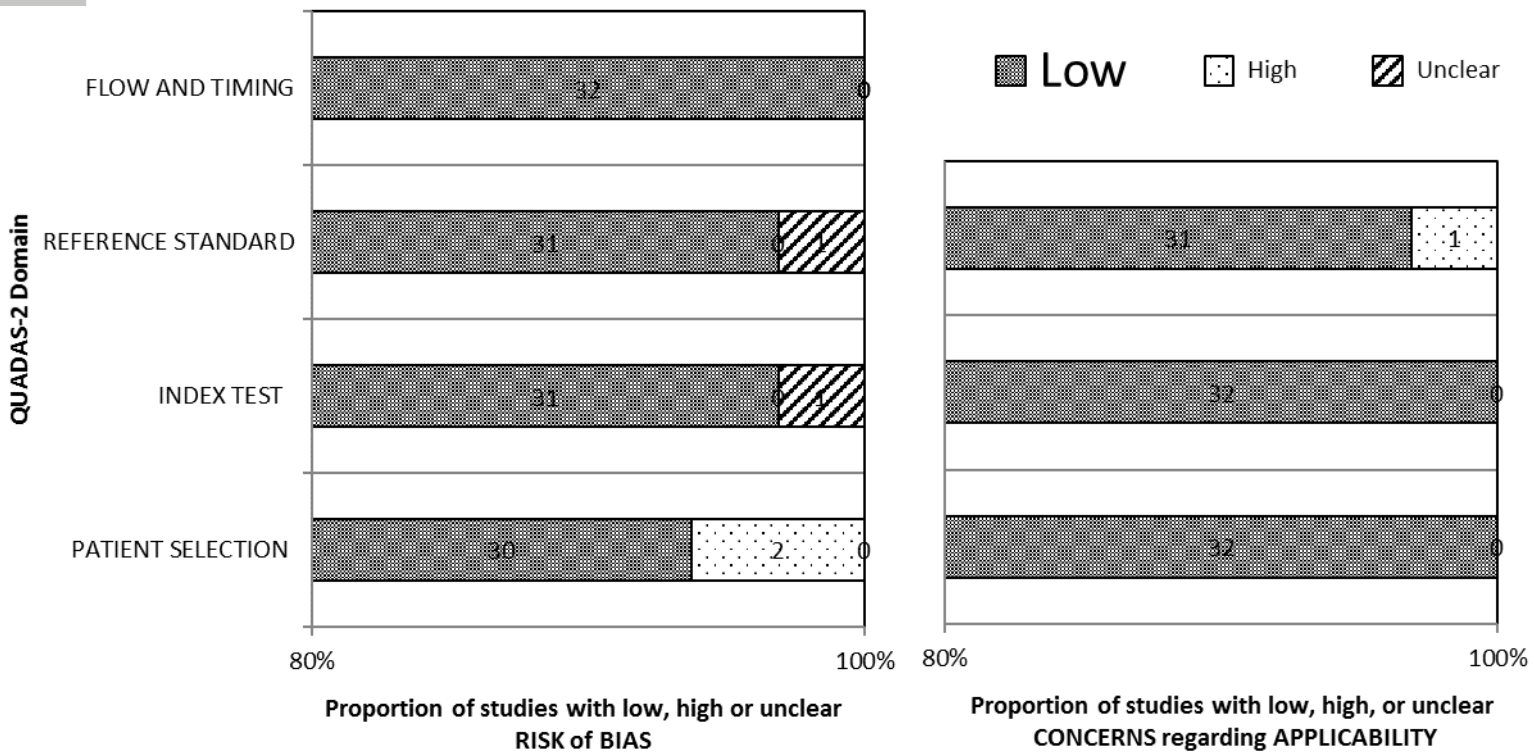

Figure 2: Bar chart to demonstrate methodological quality of included studies in systematic review of association of pregnancy associated plasma protein A with adverse pregnancy outcomes assessed by QUADAS-2[19]

Figure 3: Forest plots of odds ratios in systematic review of pregnancy associated plasma protein A with adverse pregnancy outcomes.

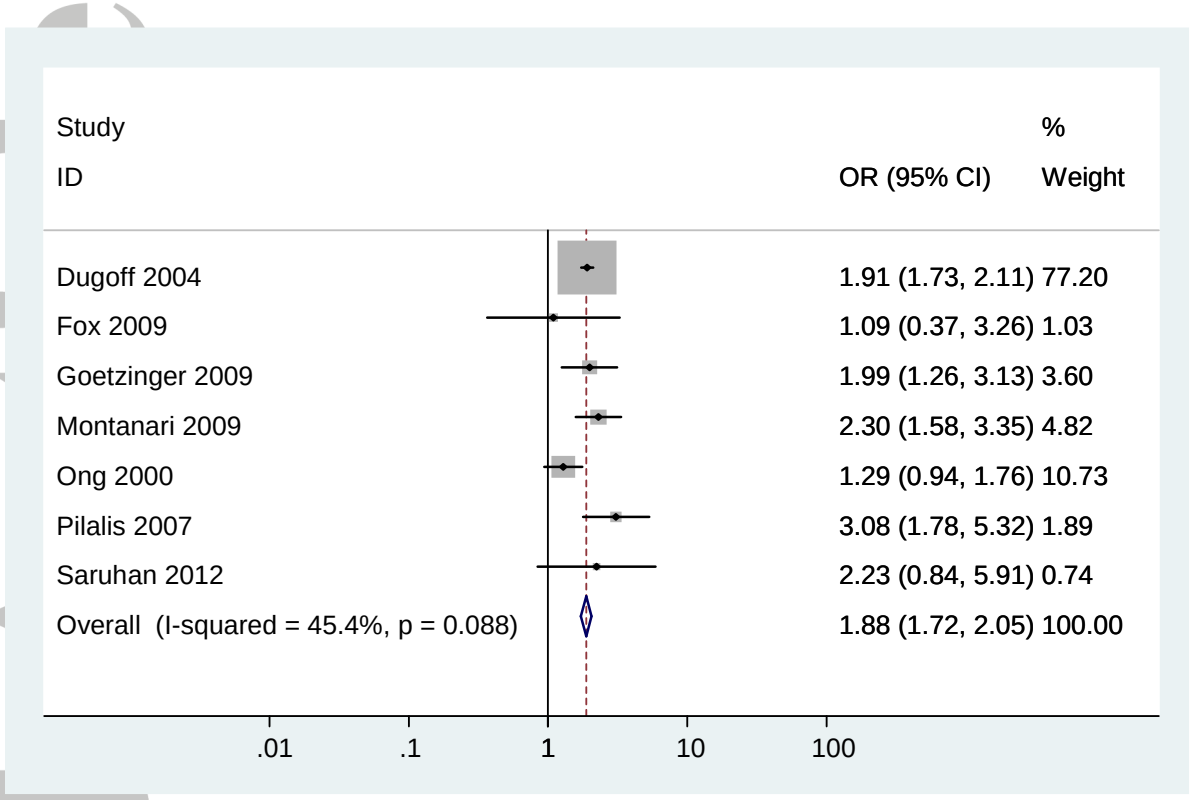

Figure 3A: Forest plot for association (odds ratio) of pregnancy associated plasma protein A (PAPPA) <10th centile with birth weight <10th centile

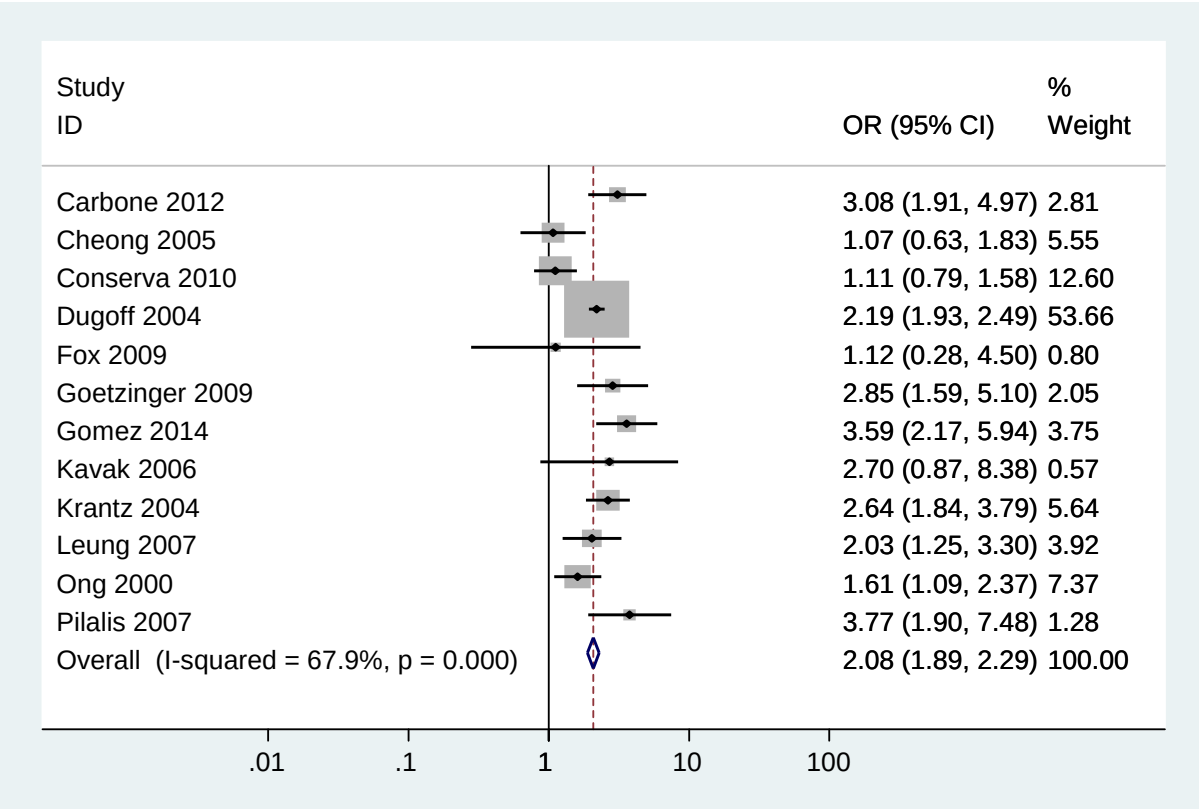

Figure 3B: Forest plot for association (odds ratio) of pregnancy associated plasma protein A (PAPPA) <5th centile with birth weight <10th centile

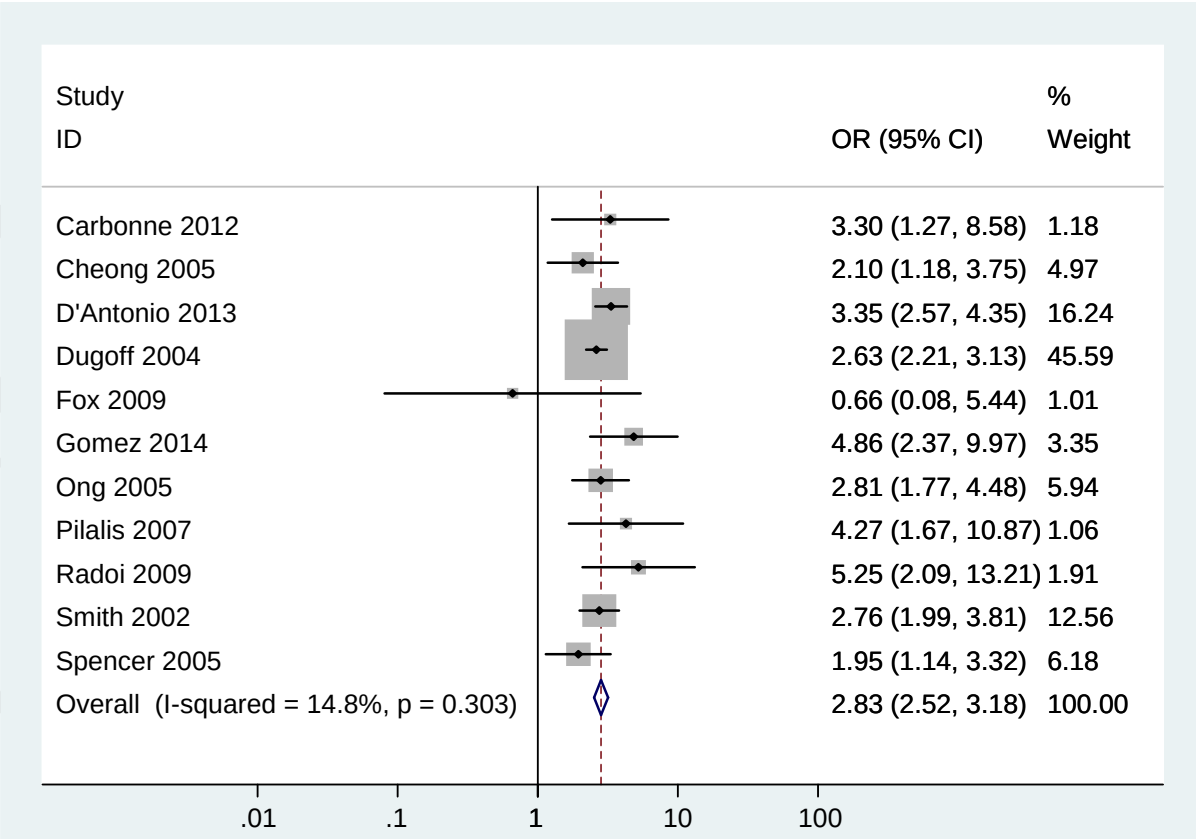

Figure 3C: Forest plot for association (odds ratio) of pregnancy associated plasma protein A (PAPPA) <5th centile with birth weight <5th centile

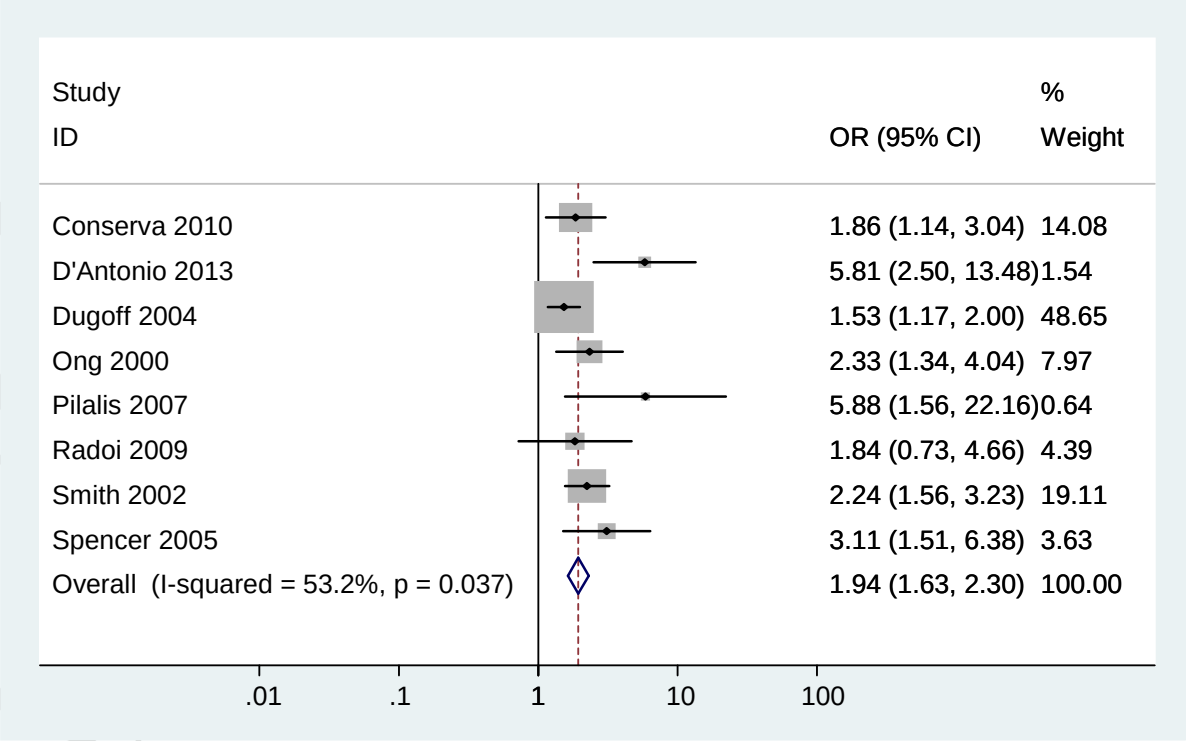

Figure 3D: Forest plot for association (odds ratio) of pregnancy associated plasma protein A (PAPPA) <5th centile with pre-eclampsia

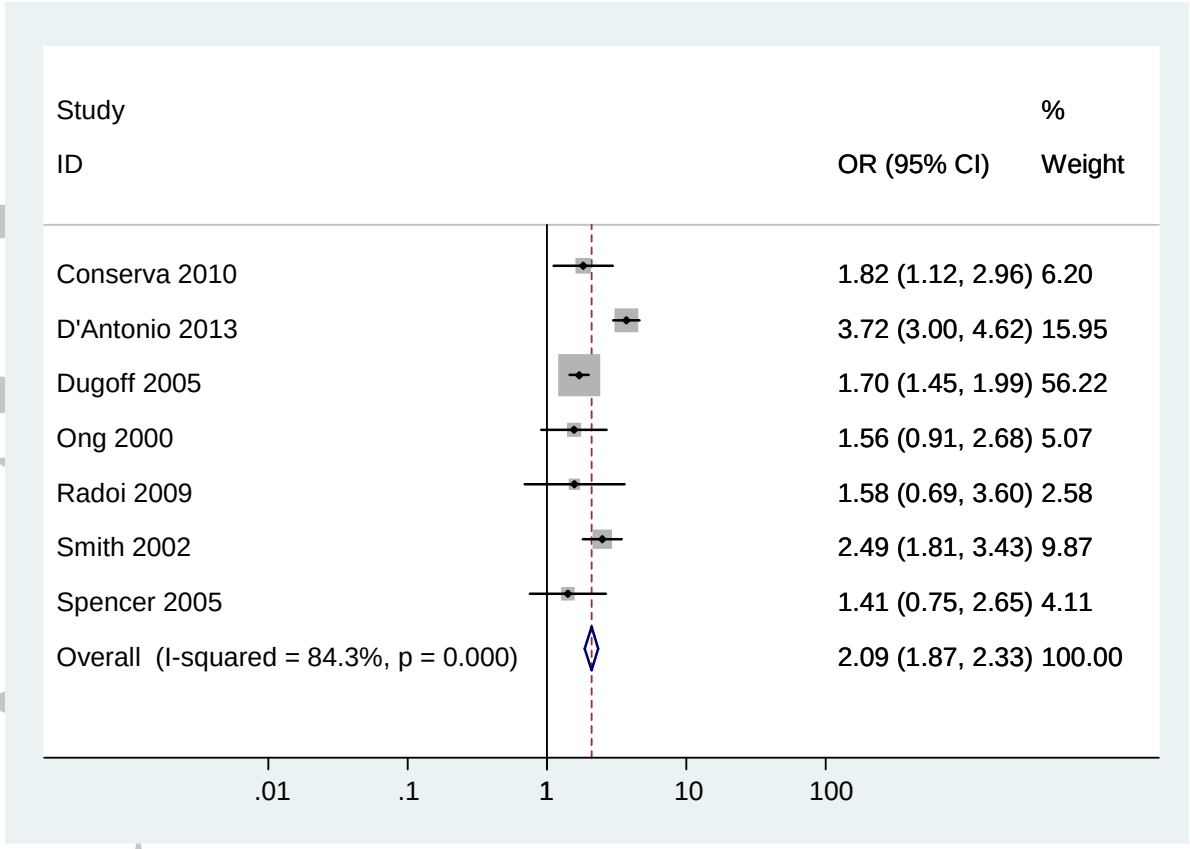

Figure 3E: Forest plot for association (odds ratio) of pregnancy associated plasma protein A (PAPPA) <5th centile with pre-term birth <37 weeks

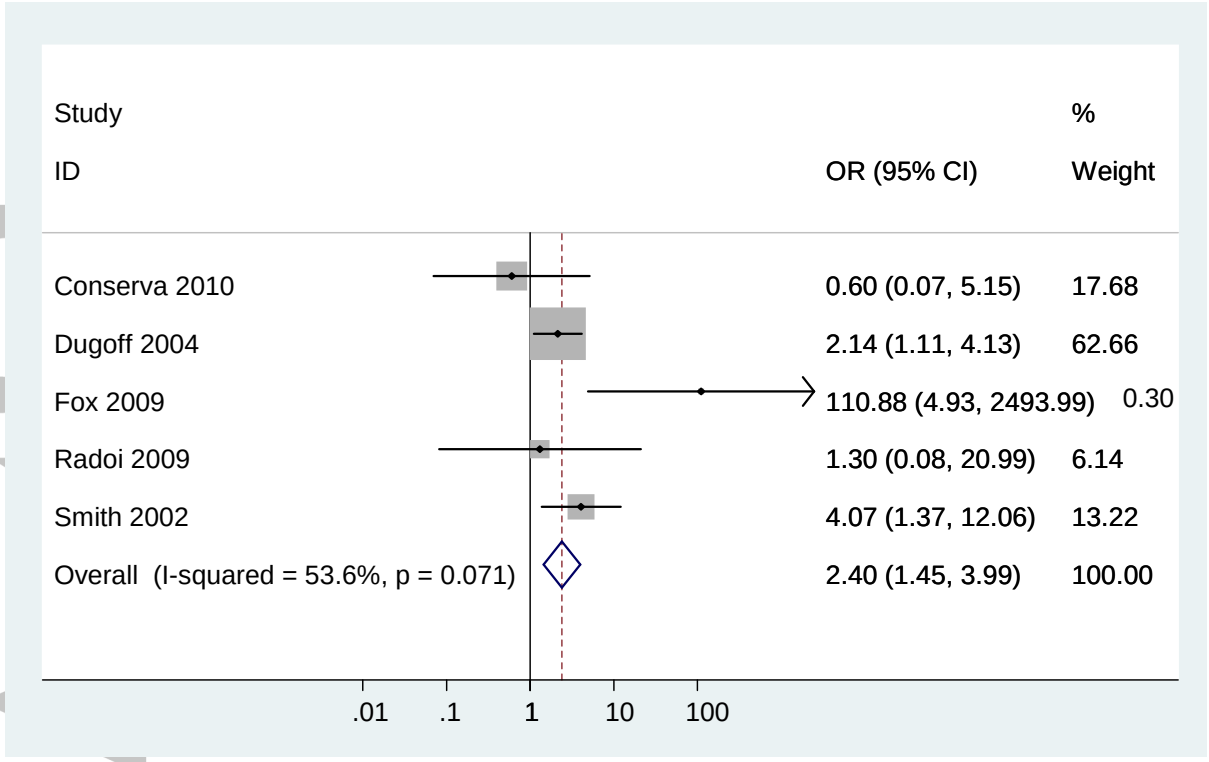

Figure 3F: Forest plot for association (odds ratio) of pregnancy associated plasma protein A (PAPPA) <5th centile with stillbirth >24 weeks