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DOI:
10.1111/1471-0528.16510

Prediction of stillbirth: an umbrella review of evaluation of prognostic variables

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ABSTRACT

Background

Stillbirth accounts for more deaths worldwide than HIV and cancer, and yet prevention of stillbirth is a poorly understood public health problem. Improved antenatal tests and identification of high risk pregnancies are a key research priority. Multivariable prediction models are likely to be key to individualised recommendations to women for monitoring, therapeutic interventions and/or early delivery.

We undertook a systematic review to collate and critically evaluate the published systematic reviews of potential risk factors for stillbirth with the aim of identifying candidate variables that could be relevant to the development of a clinical prediction model for stillbirth.

Methods

Medline, Embase, DARE (Database of Abstracts of Reviews of Effectiveness) and Cochrane Library databases, from database inception to August 2018, and bibliographies of relevant articles were searched, without language restrictions, for systematic reviews and meta-analyses relating to risk factors for stillbirth. The quality of the included reviews was assessed using the AMSTAR tool and a modified QUIPS tool.

Results

The literature search identified 986 citations of which 196 were excluded. In all, 61 systematic reviews were included reporting on 62 variables associated with stillbirth. The majority of identified reviews focused on maternal characteristics associated with stillbirth. The most frequently reported were maternal age (particularly maternal age >35 years, n=5), body mass index (BMI) or other measures of maternal obesity (n=6) and maternal diabetes (n=5). Uterine artery Doppler (UtAD) measured in the second trimester appeared to have the best performance reported for any single test, with sensitivity for any abnormal UtAD of 65% (95%CI 38-85%) and specificity of 82% (95%CI 72-88%).

Biochemical markers included elevated alpha-fetoprotein (AFP) (two reviews) [AFP>2.0 MoM; sensitivity 11% (95% CI 9–13) specificity 96% (95% CI 96–96)] and low pregnancy associated placental protein-A (PAPP-A) (two reviews) [PAPP-A <0.4 MoM; sensitivity 15% (95% CI 8-26%) specificity 95% (95%CI 95-96)). Human chorionic gonadotrophin (hCG) was reported in two reviews and placental growth factor (PlGF) in one review. Several thrombophilia and autoimmune associated antibodies showed a strong association with stillbirth including lupus anticoagulant (two studies, OR 4.3-54.18) and anticardiolipin antibodies (two studies, OR 4.29-15.17). The Factor V Leiden mutation, protein S deficiency and activated protein C resistance were all also strongly associated with stillbirth with OR 6.11 (95% CI 2.8-13.2), 16.2 (95% CI 5.1-52.3) and 5.0 (95% CI 2.0-12.4), respectively.

Only two reviews reported on combinations of variables, including AFP and hCG with and without estriol and the combined (nuchal translucency, PAPP-A, maternal age and bHCG) screening test.

Conclusion

Our review of reviews has identified a large number of systematic reviews investigating more than 60 candidate variables relevant to the development of clinical prediction models for stillbirth. However, none of these markers, as a sole predictor, had useful screening performance, despite being consistently and strongly associated with stillbirth.

INTRODUCTION

Stillbirth accounts for more global deaths than HIV/AIDS or cancer; (1) yet stillbirth remains an often invisible public health problem.(2) Although recent years have seen an encouraging, if not yet adequate, fall in maternal and neonatal mortality the global incidence of stillbirth remains stubbornly high. Assessment of worldwide stillbirth rates is complicated by local and national variations in case definition, recognition and recording, but conservative estimates suggest that 2.62 million babies died before birth in 2015. (3) The majority of the stillbirth burden occurs in low and middle income settings, but stillbirth reduction is an urgent government priority in all settings. The UK incidence of stillbirth (defined as fetal death after 24 weeks) fell by a fifth between 1993 and 2015 to 4.5 per 1000 births,(4) but remains one of the highest in Europe.(5)

In the UK, national guidelines for stillbirth prevention recommend selecting women for monitoring or intervention by identifying those with risk factors including maternal characteristics (e.g. maternal age), ultrasound markers (e.g. second trimester uterine artery doppler) and biochemical markers (e.g. low PAPP-A [Pregnancy associated placental protein-A]), which are known to be associated with stillbirth.(6) The identified risk factors are effectively used as screening tests to triage women as 'high' risk of stillbirth, but in most cases, there has been no formal evaluation of the performance of these markers as predictive tests. Furthermore, no guideline considers the relationships between related risk factors or the possibility that certain factors may reduce the risk of stillbirth. In fact, only 19% of stillbirths occur in women with established risk factors at their booking appointment,(7) leaving significant room for improvement on current practice. Risk scores based on clinical characteristics alone have a high screen positive rate, limiting their clinical applicability.(8) Consultation with patients and expert stakeholders has demonstrated interest in developing new antenatal tests and using existing tests more efficiently to help reduce stillbirth.(9) With better prediction tools we could move beyond application of the same threshold for intervention to all women with a single risk factor and individualise the risk assessment and advice we give to pregnant woman accordingly.

The most important avoidable cause of stillbirth is placental dysfunction, although maternal and fetal co-morbidities and environmental and genetic factors also play a significant role.(10) It is accepted that given the heterogeneity of pathologies leading to intrauterine fetal demise, prediction of stillbirth by any single variable is unlikely to be clinically useful.(11) Instead, multivariable prediction models are most likely to yield clinically relevant results that could individualise recommendations to women for monitoring, therapeutic interventions and/or early delivery.(11) Selection of

variables for the development of prediction models is often limited by variables commonly available in large datasets, typically those obtained at the time of first trimester aneuploidy screening.(12,13) However, the ideal prediction model would not be limited by the data available. Optimal model development should take into account the all available evidence, including promising candidate variables.(14)

In order to prioritise variables for inclusion in any model built for the prediction of stillbirth one must map and critically appraise the relevant available evidence in this field. Where primary studies suggest the possibility of variable association with stillbirth, evidence is synthesised in systematic reviews of observational or prediction studies. We undertook a systematic review to collate and critically evaluate the published systematic reviews of potential risk factors for stillbirth with the aim of identifying candidate variables via a broad overview of the existing evidence that could be relevant to the development of a clinical prediction model for stillbirth.

METHODS

The systematic review was based on a prospective protocol according to current recommendations (15–17) and reported according to the PRISMA guidelines(18). The study was registered with the PROSPERO database (Registration number: CRD42017074061)

Literature search

We searched Medline, Embase and the Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), The Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessment Database (HTA) and NHS Economic Evaluation Database (NHS-EED) from inception to August 2018. We used combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “stillbirth”, “stillborn”, “metaanalysis” and “review” (Supplementary Material 1). No language restrictions were imposed. Reference lists of relevant articles and reviews were hand-searched to identify additional relevant papers.

Study selection and data extraction

Two reviewers (RT and FS) reviewed all abstracts independently. Any discrepancies on the potential relevance of the papers were resolved by consensus. We obtained full text copies of reviews that met the inclusion criteria. We included reviews that assessed the predictive accuracy of clinical, biochemical or ultrasound-based predictors for stillbirth (Table 1). We excluded reviews considering the association of therapeutic drugs with stillbirth and other risk factors, as determined by consensus

within the steering group to be unlikely to contribute to a useful clinical prediction model, including rare co-morbidities and environmental exposures. Air pollution, for example, may be known for a geographical area without being able to quantify exposure for the individual. (Supplementary Table 1b) Reviews reporting exclusively on variables related to stillbirth in LMIC settings (e.g. malaria and dengue fever) were excluded, since the focus of this work is on prediction of stillbirth within a high resource context. The contributory factors(19) and available variables in LMIC are so different as to mandate a separate approach to prediction of stillbirth and assessment of obstetric risk.(8,20)

The clinical characteristics identified included maternal age, parity, body mass index (BMI), cigarette smoking, pre-existing medical conditions (epilepsy, vitamin D deficiency, hypertension, asthma, chronic kidney disease, sickle cell disease, bipolar disorder, Sjogren's syndrome, psychotic illness, diabetes). Any biochemical markers such as soluble fms-like tyrosine kinase-1 (sFlt-1), alpha fetoprotein (AFP), pregnancy-associated plasma protein A (PAPP-A), anticardiolipin antibodies (ACA), anti-B2 glycoprotein 1 antibodies (Anti-B2 GP1), human chorionic gonadotrophin (hCG) were grouped as biochemical tests, while uterine artery Doppler, fetal nuchal translucency, ductus venosus Doppler and echogenic bowel were categorised as ultrasound variables. We included reviews evaluating tests in the first and second trimester. We accepted and noted the authors' definition of stillbirth, which included accepting gestational limits applied by the review authors and noted any pregnancies excluded from the definition of stillbirth (e.g. multiple pregnancies, known fetal anomalies, 'explained' stillbirths).

We defined a review as systematic if they included an explicit method for searching the literature, searched two or more databases, and if they provided well defined inclusion and exclusion criteria for studies. Case reports, case series, individual observational or randomised studies, narrative reviews, rapid reviews, editorials and poster abstracts were excluded. Two reviewers (RT, FS) independently extracted relevant data. We obtained data on year of publication, study funding, human development index of the countries in which data was gathered, number of databases searched, number of studies included, number of pregnancies/women and the number of stillbirths included, definition of stillbirth used, inclusion and exclusion criteria, screening tests evaluated, timing of the screening test application and the performance of the tests.

Quality assessment of the included reviews

Two independent reviewers (RT, FS) assessed the methodological quality of the included systematic reviews using the AMSTAR tool (supplementary Figure 1). (21) The tool evaluates whether the reviewers incorporated the following: a prospectively

designed study with a clear research question, a comprehensive literature search, relied on the status of publication as an inclusion criterion, duplicated study selection and data extraction, gave details of both the included and excluded studies, assessed and documented the risk of bias of the included studies, included information on the funding of primary studies, used appropriate statistical methods to combine the findings of studies and considered the impact of the risk of bias and study heterogeneity in primary studies on the analysis and results, assessed the likelihood of publication bias and reported any conflict of interest.

Because the outcome of interest was the prognostic value of the variables considered, we additionally considered for each review whether the risk of bias in the included studies in each of the key domains identified by the Quality In Prognosis Studies tool (QUIPS) had been assessed (supplementary Figure 2). The six domains are study participation, study attrition, measurement of the predictive variable and the study outcome, adjustment for confounders and the quality of statistical analysis and reporting.

RESULTS

The literature search identified 986 citations. After screening abstracts, 257 full text papers were retrieved for review, of which 196 were excluded (Figure 1, Supplementary Table 1) as not relevant to the purpose of prediction model development, duplicates, wrong study design or reporting outcomes other than stillbirth. In all, 61 systematic reviews were included in this study.

Quality assessment using AMSTAR

The methodological quality of the included systematic reviews was assessed using the AMSTAR checklist (Figure 2). The mean score was 7.4/11 and 70.1% (43/61) of the included studies had an AMSTAR score greater than or equal to 7. Most reviews undertook a comprehensive literature search (54/61, 88.5%) but only 17/61 (27.9%) utilised a prospectively specified protocol and only 20/61 (32.8%) specifically sought to include 'grey literature'. Most reviews (56/61, 91.8%) used duplicate study selection and data extraction but only 12/61 (19.8%) provided a full list of both included and excluded studies. The majority of reviews (44/61; 72.3%) provided a table of the characteristics of included studies, assessed the scientific quality of included studies (47/61, 77.1%) and then used the quality of the included studies in drawing conclusions from the analysis (36/61, 59.0%). Nearly all investigators appropriately combined findings (59/61, 96.7%) but only 31/61 (50.8%) assessed the likelihood of publication bias. Fifty papers made a formal declaration of conflicts of interest. Seventeen studies did not specify funding sources and 11 reported no additional study funding. Of the studies that did declare their funding sources, 6

Commented [AH1]: Did you use AMSTAR or AMSTAR2? There is an updated version which was published before you completed your searches. Will a reviewer wonder why you've not used the most up to date version?

Commented [rt2]: We considered AMSTAR 2 – the main differences between the two are additional domains heavily weighted towards intervention studies and does not necessarily address the bias important in prognostic studies, which is why we included a consideration of the QUIPS domains as a supplementary quality assessment (this combination of tools was also used in our published review of reviews of predictive variables for pre-eclampsia)

received funds from academic institutions, 9 from non-profit organisations, 15 from regional or national governments, 2 from industry sponsors and 1 from the United Nations Population Fund (UNFPA).

Quality assessment relating to prognostic research using QUality In Prognosis Studies (QUIPS)

We assessed the risk of bias in the included studies relating specifically to domains that are important in the area of prognostic research as outlined in the QUIPS tool (Figure 2). Although most included studies suggested that the variables they reported might be relevant to the prediction of stillbirth, no paper reported fully on the risk of bias in all QUIPS domains in the included primary studies. Most studies (47/61, 77.0%) considered the definition and representativeness of the participants in the primary studies and the adequacy of definition and assessment of exposure (50/61, 81.9%) and outcome (46/61, 75.4%). There was significant variation in outcome reporting in the reviews and the included primary studies – most reviews simply accepted the primary study authors definitions of stillbirth. Reported definitions of stillbirth varied in the gestational cut offs which ranged from 10-28 weeks and in the pathology of stillbirth assessed - several studies excluded congenital anomalies or 'explained' stillbirths. Only 38/61 (62.3%) noted adjustment for potential confounders or the lack of it in the included studies and just 10/61 (16.4%) considered the impact of attrition and loss to follow up on the performance of the predictive variables.

Characteristics of the included studies

Table 2 and Figure 3 demonstrate the characteristics and key findings of the included studies. The identified reviews included between 3 and 426 primary studies including 854 to 184 million participants in the largest review (5) The included reviews considered 61 individual variables associated with stillbirth. The majority of included reviews reported on maternal characteristics such as commonly collected demographic variables like maternal age, parity, body mass index (BMI), smoking, caffeine and alcohol intake. Medical co-morbidities and past obstetric historical factors were additionally classified as maternal characteristics. Ultrasound markers reviewed included uterine artery Dopplers, nuchal translucency, echogenic bowel, fetal sex and suboptimal fetal growth. Biochemical parameters investigated included thrombophilia associated markers (including anticardiolipin antibodies, lupus anticoagulant and homocysteine), markers of fetoplacental unit function (human chorionic gonadotrophin (hCG), alpha feto protein (AFP), pregnancy associated plasma protein-A (PAPP-A)) and a variety of other markers including thyroid stimulating hormone (TSH), soluble fms-like tyrosine kinase-1, serum uric acid, vitamin D, proteinuria and cell free fetal DNA (cffDNA). The majority of biochemical

tests were done in the course of clinical care rather than in diagnostic accuracy studies where the results of the tests would have been blinded to the managing clinicians. Several reviews reported on multiple markers in one review but only two reviews reported on combinations of variables. Combinations assessed included alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) with and without estriol (E3),(22) and the combined (nuchal translucency, PAPP-A, maternal age and bHCG) screening test for Trisomy 21.(11)

Maternal characteristics

The majority of identified reviews focused on maternal characteristics associated with stillbirth. The most frequently reported were maternal age (particularly maternal age >35 years, n=5), BMI or other measures of maternal obesity (n=6) and maternal diabetes (n=5). Of the maternal medical conditions reported on, the strongest association (OR>2) was found with sickle cell disease (1 review, RR 3.99, 95% CI 2.63-6.04). A mother's obstetric history was strongly associated with stillbirth; a prior stillbirth (2 reviews, one reporting a pooled OR of 4.83, 95% CI 3.77-6.18),(23) a prior preterm birth (1 review, OR 2.98, 95% CI 2.05-4.34) and a prior delivery of a small-for-gestational-age (SGA) baby before 34 weeks (1 review, OR 6.00, 95% CI 3.43-10.49).(24) Several socioeconomic factors ranging from social deprivation and inequality to immigration status and education were found to be associated with stillbirth, but in all cases the studies identified reported odds ratios of less than 2. Only one review considered ethnicity as a risk factor in relation to aboriginal women, where aboriginal status was consistently associated with stillbirth in several countries. Maternal smoking or smoke exposure was consistently seen to be associated with an increased risk of stillbirth, with two studies demonstrating a plausible biological gradient of increasing risk with increasing exposure.(25,26) Caffeine and alcohol use were both investigated but not consistently associated with stillbirth.

Three of the included reviews were broad overviews of risk factors for stillbirth specifically in low and middle income (LMIC) countries. These reviews identified syphilis (OR 3.34; P = 0.028)(19) and malaria 1.9 (95% CI 1.2–9.3) (19) as important maternal conditions contributing to stillbirth and associations with malnutrition, lack of access to healthcare and socioeconomic disadvantage.(19,27,28)

Ultrasound markers

Uterine artery Doppler (UtAD) measured in the second trimester appeared to have the best performance reported for any single test or variable with sensitivity for any abnormal UtAD of 65% (95%CI 38-85%) and specificity 82% (95%CI 72-88%), although most reviews reported odds ratios rather than sensitivity and specificity,

Commented [ML3]: Wasn't this excluded as an exposure based on the appendix or have I misunderstood?

Commented [rt4]: Yes it was – these three reviews were included because they reported generalizable risk factors (age, parity, smoking etc .. most did not perform meta-analysis and the one that did was low quality. I picked up their findings about the LMIC specific risk factors here because that was the focus of their discussion, but it isn't the point of this paper so we could remove it.

Commented [U5]: I would suggest that we leave it. If the reviewers/Editor ask us to remove it, then it is ok.
Asma

limiting direct comparisons.(29) Another review reporting only UtAD RI>0.58 reported sensitivity of 16% (95% CI 10-27) and specificity 91% (95% CI 91-92%)(11). Similarly, suboptimal fetal growth by any definition was associated with stillbirth with sensitivity of 32% (95% CI 31-34) and specificity 75% (95%CI 75-75). Other markers considered and found to be associated with stillbirth included fetal nuchal translucency, echogenic bowel and male sex.(11)

Biochemical markers

Although a wide range of biochemical markers have been extensively investigated for prediction of pre-eclampsia (30) relatively few reviews have summarised studies of biochemical markers associated with stillbirth. Key biochemical tests measured in the first half of pregnancy include elevated AFP (two reviews) [AFP>2.0 MoM; Sens 11 (95% CI 9–13) Spec: 96 (95% CI 96–96))(11) and low PAPP-A (two reviews) [PAPP-A <0.4 MoM; Sens. 15% (95% CI 8-26%) Spec 95% (95%CI 95-96)).(11) Human chorionic gonadotrophin (hCG) was reported in two reviews. One found a pooled sensitivity of 4% (95% CI 1-14%) and sensitivity 94% (95% CI 93-94%) for hCG below the 5th centile MoM when analysed independently.(11) The other found that although associated with stillbirth, hCG seemed to add little value to AFP when used in combination.(31) Placental growth factor (PlGF) is known to be associated with placental function and is used in clinical practice for prediction and triage of pre-eclampsia, and would be a plausible predictor for stillbirth. Only one systematic review has evaluated PlGF; the two primary studies included were not suitable for meta-analysis although both suggested that low PlGF was associated with a heightened risk of stillbirth.(32).(32) Several thrombophilia and autoimmune associated antibodies showed a strong association with stillbirth including lupus anticoagulant (two studies, OR 4.3-54.18) (33,34) and anticardiolipin antibodies (two studies, OR 4.29-15.17).(34) The Factor V Leiden mutation, protein S deficiency and activated protein C resistance (APCR) were all also strongly associated with stillbirth with OR 6.11 (95% CI 2.8-13.2), 16.2 (95% CI 5.1-52.3) and 5.0 (95% CI 2.0-12.4), respectively.(34)

DISCUSSION

Summary of the key findings

This review has identified 61 systematic reviews examining over 60 variables potentially associated with stillbirth. No marker on its own had useful screening performance, but several were consistently and strongly associated with stillbirth. Only two reviews reported on combinations of variables, including AFP and hCG with and without estriol and the combined (nuchal translucency, PAPP-A, maternal age and bHCG) screening test.

Commented [AH6]: Just checking that there is no variance on this 95% CI.

Commented [rt7]: Yes double checked the paper this is correct

Commented [AH8]: I realise that this is outside the timeframe of your searches but we have just completed a Cochrane DTA review of biochemical factors. Cochrane Database Syst Rev. 2019 May 14;5:CD012245.

Commented [rt9]: Thanks I will add to the discussion

Commented [ML10]: OR and 95% CI?

Commented [AH11]: See above, PlGF was the strongest biochemical predictor our Cochrane DTA review.

Commented [AH12]: See above, PlGF was the strongest biochemical predictor our Cochrane DTA review.

Commented [ML13]: Ukah et al Hypertension 2017 also looked at stillbirth in the context of hypertensive pregnancy. I don't see that this was included. Can you comment why please?

Commented [rt14]: This paper wasn't captured in the literature search – probably because stillbirth and perinatal death aren't in the title or abstract. On review, the paper includes one primary study that reported on perinatal death so would have been excluded for that reason, but I will add to the discussion point on PLGF

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Strengths and limitations

Strengths of this review include the comprehensive literature search and critical evaluation in synthesising a massive quantity of existing literature. The study was limited by the quality of included reviews, notably in relation to factors important to prediction. Few studies considered the effect of subject attrition on the strength of observed associations. There was substantial missing information relating to measurement of exposures and outcomes and significant variation in outcome reporting was noted.

The problem of competing risks of stillbirth or delivery may negatively affect the observed predictive accuracy of tests, but was not considered in the included reviews. Where a high risk of stillbirth is identified but delivery occurs before stillbirth, the case will seem to be a false positive. This is particularly significant for 'late' stillbirths, since it is increasingly likely that birth will supervene and consistent with the observation that tests for predicting early stillbirth are more accurate than those predicting later stillbirth. (11)

Arguably, early delivery is most likely to occur in those at highest risk because clinicians act on risk factors for stillbirth. Where clinicians are blinded to the tests intervention bias is reduced, but many clinical characteristics are of necessity known. Only three reviews considered this risk of bias and of these, the risk was low in the reviews assessing biochemical markers(22) and Doppler (29) but increased in the review including clinical characteristics.(11)

Interpretation of findings and comparison with existing evidence

Previous reviews of individual predictors of stillbirth have concluded that multivariable models are likely to be required for meaningful clinical impact.(5,11) In this review we have considered the factors potentially associated with stillbirth in order to identify variables most relevant to the development of such models.

A recent systematic review of prediction models in obstetrics found three models for stillbirth, only two including the full model, limiting independent external validation.(35) These models included UtAD and ethnicity with history of prior pregnancy loss in one and with BMI in the second.(36) They had good discrimination, but calibration, internal and external validation were not reported. Both were developed in the UK within a high resource antenatal care model at a time when national guidelines recommended induction of labour from 41+5 weeks gestation. Further models have subsequently been developed (20,37,38) but not yet externally validated. Although increasing interest in individualising care has led to increasing numbers of models, transfer to clinical practice has been hampered by a lack of subsequent external validation and clinical evaluation.(39)

Clinical and research implications

Informal screening to identify high risk pregnancies is embedded in practice and urgently needs to be improved. Development of robust models remains a challenge because of the rarity of stillbirth as an outcome and the multitude of potential causes of fetal death in utero. Where stillbirth is more common, access to care and poor quality record keeping compromise the data available for model development. The heterogenous causes of stillbirth may be best addressed by separate models; logically, the initial target should be placental dysfunction, representing the largest and most clearly defined factor contributing to global stillbirth rates. Separate models could also allow continuous risk assessment through pregnancy taking into account the most recently available patient data.

Model development requires a large volume of data with detailed information on a number of candidate predictors and should be optimised by maximising available data and minimising the candidate predictors in order to arrive at the best achievable effective sample size.(40)

In this review we have identified several key candidate variables which should be considered in model development; maternal age, BMI, history of previous stillbirth, cigarette smoking, uterine artery Doppler, PAPP-A and PlGF. We reported one review of PLGF, but a recently updated Cochrane review confirms the importance of this test in stillbirth prediction (41) and the related sFlt-1/PLGF ratio has good predictive performance for perinatal death.(42) Strongly associated variables included maternal thrombophilias, but these are too rare to contribute to a generalisable model.

Socioeconomic deprivation was consistently associated with stillbirth in both high and low income settings but is measured and defined heterogeneously, limiting the utility of this variable in prediction. Nonetheless, this finding reinforces the importance of addressing social inequality as a core strategy for the prevention of stillbirth in any setting. This review identified only one systematic review considering ethnicity, but it has recently been confirmed that Black women were at 1.5-2 fold higher risk than White women.(43) The association of ethnicity with adverse pregnancy outcomes is clear but problematic as a predictive variable. The association is potentially related to biological factors (length of pregnancy and cardiovascular parameters differ with ethnicity and are plausibly associated with stillbirth), but also with differing social norms like higher multiparity in selected social groups and with systemic inequality in access to healthcare.

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A large-scale, collaborative approach utilising individual participant data (IPD) meta-analysis offers an innovative approach to addressing the problems of stillbirth prediction. IPD meta-analysis allows the use of all original data and continuous variables with the flexibility to standardise variable and outcome definitions, their combinations and comparisons across datasets.(44) Existing models can be validated and tested against new models,(45) offering the opportunity to build consensus around development and validation of methodologically robust models. IPD may be derived, for example, from trial registries and routinely collected patient data.

In this era of increasingly personalised medicine, women want individualised recommendations for care and expect clinicians to make the most effective use of available tests. The global loss of millions of lives to stillbirth every year is too significant a tragedy to waste time generating excessive clinically irrelevant prediction models; the time has come to initiate a collaborative approach in order to definitively answer the question of how to predict, and ultimately prevent, stillbirth.

Conclusions

Our review of reviews has identified a list of candidate variables relevant to the development of clinical prediction models for stillbirth. Prospective, well-designed studies of predictive variables, combined through IPD meta-analysis, have the potential to develop and validate new prediction models, optimise the prediction of stillbirth and minimise further research waste in this field.

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636 **Table 1.** Prognostic variables for stillbirth investigated in systematic reviews

Parental characteristics and history • Extremes of maternal and paternal age • Parity • Body mass index • Pre-existing medical conditions (epilepsy, vitamin D deficiency, hypertension, asthma, chronic kidney disease, sickle cell disease, bipolar disorder, Sjogren's syndrome, psychotic illness, diabetes, sleep disordered breathing, endometriosis, acute kidney injury) • Obstetric history (previous Caesarean section, vaginal bleeding in pregnancy, antenatal care attendance, abruption, previous stillbirth, preterm birth, IVF) • Cigarette smoking, smokeless tobacco and second hand smoking exposure • Caffeine and alcohol intake • Immigration status • Perceived reduced fetal movements
Ultrasound markers • Uterine artery Doppler • Fetal nuchal translucency (NT) • Any suboptimal fetal growth • Fetal echogenic bowel • Male fetus
Biochemical markers *Prothrombotic markers* • Factor V Leiden gene mutation • Anticardiolipin Antibodies (ACA) • Lupus anticoagulant (LA) • AB2G1 • Protein S deficiency • Activated Protein C Resistance • G20210A mutation • MTHFR C677T mutation • Antithrombin III • Protein C • Homocystinaemia *Markers of fetoplacental unit endocrine dysfunction* • Human chorionic gonadotrophin (HCG) • Alpha-Fetoprotein (AFP) • Pregnancy-associated plasma protein A (PAPP-A) • Estriol • PLGF *Other markers* • Thyroid stimulating hormone (TSH) • Haemoglobin <10

• Soluble fms-like tyrosine kinase-1 (sFlt-1) • Serum uric acid • Vitamin D • Proteinuria • Free fetal DNA
Combination of markers
• Combined screening test for aneuploidy (bHCG, PAPP-A, nuchal translucency)
• Combinations of various biomarkers (AFP+hCG) (PAPP-A+hCG) (AFP+hCG+uE) (AFP+uE) (hCG+uE)
• Combination of maternal characteristics, NT, PAPP-A, and ductus venosus Doppler
• Combination of maternal characteristics and inhibin A

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641 **Table 2.** Characteristics and findings of the included systematic reviews
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Study	Variable investigated	Population	Definition of stillbirth used	No. of studies included	Findings of the review
Parental characteristics					
Berhan 2014 (2) (36)	Young maternal age (<20 years),	LMIC setting	Fetal death >28 weeks gestation	12	OR 1.19 (95% CI 1.07-1.33)
Gibbs 2012(37)	Young maternal age (<16 years or <2 years from menarche)	unselected	Accepted study authors definitions. (Range 20-23 weeks completed gestation.)	6	3 out of 6 found an association between young age and stillbirth but meta-analysis precluded by study heterogeneity.
Carolan 2011(38)	Maternal age 35-39	unselected	Accepted study authors definitions	8	7/8 studies found advanced maternal age (35-39) to be an independent risk factor for stillbirth"
Flenady 2011(4)	Maternal age >35	unselected	>22 weeks gestation and >500g birthweight	6	Age 35-39 ES 1.5 (95% CI 1.22-1.73) 40-44 ES 1.8 (95% CI 1.4-2.3) >45 ES 2.9 (95% CI 1.9-4.4)
Huang 2008(39)	Maternal age >35	unselected	Accepted study authors definitions	37	30/37 studies found a significant association
Lean 2017(40)	Maternal age >35	unselected	accepted study authors definition	44	OR 1.75 (95% CI 1.62-1.89)
Berhan 2014(36)	Nulliparity	LMIC setting	Fetal death >28 weeks gestation	11	OR 1.5 (95% CI 1.31-1.73)
Flenady 2011	Primiparity	unselected	>22 weeks gestation and >500g birthweight	3	ES 1.4 (95% CI 1.42-1.33)
Oldereid 2018(41)	Paternal age	unselected	accepted study authors definition	4	OR 1.19 (95% CI 1.1-1.3)

Maternal co-morbidities					
Allotey 2017(42)	Maternal epilepsy	Women with epilepsy	Fetal death	60	Prevalence: 0.8% (95% CI 0.5-1.1)
Amegah 2017(43)	Vitamin D deficiency	unselected	Fetal death >20 weeks gestation	4	RR 1.02 (95% CI 0.96-1.09)
Flenady 2011	Pre-existing hypertension	unselected	>22 weeks gestation and >500g birthweight	5	ES 2·58 (95% CI 2·13–3·13)
Murphy 2013(44)	Maternal asthma	A) unselected B) women with asthma	Accepted study authors definitions	8	RR 1.06 (95% CI 0.9-1.25)
Nevis 2011(45)	Chronic kidney disease	unselected	Not defined	13	Findings variable across studies
Oteng-Ntim 2015(46)	Sickle cell disease	unselected	Not defined	21	HbSS RR 3.94 (95% CI 2.6-5.96) HbSC RR 1.78 (95% CI 1.05-3.02) all SCD RR 3.99 (95% CI 2.63-6.04)
Rusner 2016(47)	Bipolar disorder	unselected	Not defined	9	No difference observed
Upala 2016(48)	Sjogren's syndrome	unselected	Not defined	3	OR 1.05 (95% CI 0.37-2.97)
Webb 2005(49)	Psychotic illness	unselected	Not defined	6	OR 1.89 (95% CI 1.36-2.62)
Wang 2013(50)	Gestational diabetes	LMIC setting	Not defined	17	Higher incidence of stillbirth associated with GDM
Wu 2018(51)	Lupus nephritis	Women with SLE	>20 weeks and >24 weeks	16	OR 1.68 (95% CI 0.95-2.98)
Glavind 2018(52)	Endometriosis	unselected	not defined	4	unclear association
Brown 2018(53)	Sleep disordered breathing	unselected	stillbirth or perinatal death	33	OR 2.02 (95% CI 1.25-3.28)

Warland 2018(54)	Obstructive sleep apnoea	unselected	not defined	3	The studies showed no significant association with OSA.
Zhao 2016(55)	ART: IVF/ICSI compared to FET	Women pregnant after ART	Not defined	6	OR 1.01 (95% CI 0.76-1.35)
Cavoretto 2018(56)	IVF/ICSI	unselected	not defined	2	OR 1.87 (95% CI 0.74-4.73)
Balsells 2009(57)	Type 1 versus Type 2 diabetes mellitus	Women with pre-existing diabetes	Accepted study authors definitions	19	RR 1.23 (95% CI 0.82-1.85)
Gizzo 2013(58)	Type 1 versus Type 2 diabetes mellitus	Women with pre-existing diabetes	Not defined	4	Mean prevalence across studies 2.8 v 1.9% (no CI given)
Flenady 2011	Pre-existing diabetes	unselected	>22 weeks gestation and >500g birthweight	5	ES 2·90 (95% CI 2·05–4·09)
Yu 2017(59)	Pre-existing diabetes	unselected	Fetal death >20 weeks gestation	12	Any diabetes OR 3.52 (95% CI 3.19-3.88) T1 OR 3.97 (95% CI 3.44-4.58), T2 OR 3.65 (95% CI 1.59-8.42)
Obstetric history					
Conditions occurring in the index pregnancy					
Ananth 1994(60)	Vaginal bleeding in pregnancy	unselected	Fetal death >28 weeks gestation	22	OR 4.1 (95% CI 3.6-4.7)
Berhan 2014(36)	Antenatal care non-attendance (ANC)	LMIC setting	Fetal death >28 weeks gestation	10	OR 3.17 (95% CI 1.03-9.71)
Flenady 2011	Abruption	unselected	>22 weeks gestation and >500g birthweight	2	strong association in both studies
Downes 2017(61)	Abruption	unselected	not defined	25	central location, detachment >45% and concealed bleeding more frequently associated with stillbirth

Bradford 2018(62)	Reduced fetal movements	women with high BMI	accepted study authors definition	19	OR 1.8 (95% CI 1.0-3.2)
Liu 2017(63)	Acute kidney injury	unselected	stillbirth or perinatal death	11	OR 3.39 (95% CI 2.76-4.18)
In previous pregnancies					
Lamont 2015(16)	Previous stillbirth	unselected	Fetal death >20 weeks gestation or >400g weight	16	OR 4.83 (95% CI 3.77-6.18)
Malacova 2018(17)	previous PTB, SGA or IUD	unselected	>20 weeks	17	PTB or SGA: OR 1.7 (95% CI 1.24-2.16) Preterm SGA: OR 4.47 (95% CI 2.58-7.76) PTB<34 weeks: OR 2.98 (95% CI 2.05-4.34) preterm SGA <34 weeks: OR 6.00 (95% CI 3.43-10.49)
Moraitis 2016(64)	Previous caesarean section	multiparous women with singleton pregnancies	Antepartum stillbirths between 24-42 weeks excluding fetal anomaly and multiple pregnancy	3	HR 1.40 (95% CI 1.1-1.77)
O'Neill 2013(65)	Previous caesarean section	multiparous women	Accepted study authors definitions (range 20-28 weeks, some excluding multiples and fetal anomaly)	11	OR all stillbirths 1.23 (95% CI 1.08-1.4) unexplained stillbirths OR 1.47 (95% CI 1.2-1.8) antepartum stillbirths OR 1.27 (95% CI 0.95-1.7) primips OR 1.29 (95% CI 1.12-1.49)
					multips OR 1.13 (95% CI 0.75-1.72)
Keag 2018(66)	Previous caesarean section	multiparous women	perinatal death (22 weeks gestation to 7 days of life)	80	OR 1.27 (95% CI 1.15-1.40)
Physical characteristics					
Aune 2014(6	Body Mass Index (BMI)	unselected	Fetal death beyond 20-	38	Stillbirth RR per 5 BMI units 1.24 (95%

7)			28 weeks completed gestation		CI 1.18-1.30). Fetal death RR per 5 BMI units 2.21 (95% CI 1.09-1.35). Perinatal death: RR per 5 BMI units 1.16 (95% CI 1.00-1.35)
Flenady 2011	BMI 25-30	unselected	>22 weeks gestation and >500g birthweight	5	BMI 25-30 ES 1.2 (95% CI 1.09-1.38)
Chu 2007(68)	BMI >30	unselected	Accepted study authors definitions	7	OR 1.47 (95% CI 1.08-1.94)
Flenady 2011	BMI >30	unselected	>22 weeks gestation and >500g birthweight	5	BMI >30 ES 1.6 (95% CI 1.35-1.95)
Liu 2016(69)	BMI >30	unselected	Not defined	60	OR 1.27 (95% CI 1.18-1.36),
Liu 2016	BMI >35	unselected	Not defined	60	OR 1.81 (95% CI 1.69-1.93)
Chu 2007	BMI >35	unselected	Accepted study authors definitions	8	OR 2.07 (95% CI 1.59-2.74)
Marchi 2015(70)	BMI	unselected	Not defined	22	Risk of stillbirth increases with increasing BMI
Slack 2018(71)	BMI	South Asian women	not defined	2	greater association between BMI and stillbirth in South Asian women than white women
<u>Socioeconomic factors</u>					
Shah 2011(72)	Aboriginal women	unselected	Not defined	7	OR 1.68 (95% CI 1.49–1.89)
Vos 2014(73)	Social deprivation	unselected	Fetal death >20 weeks gestation	3	OR 1.38 (95% CI 1.23-1.54) adjusted OR 1.33 (95% CI 1.21-1.45)
Weightman 2012(74)	Social inequality	unselected	Fetal loss >24 weeks gestation	2	OR 1.54 (95% CI 1.39-1.72)
Flenad	Smoking	unselect	>22 weeks	4	ES 1.4 (95% CI 1.27-

y 2011		ed	gestation and >500g birthweight		1.46)
Leonardi-Bee 2011(75)	Second hand smoke	unselected	Fetal death >20 weeks gestation	5	ES 1.23 (95% CI 1.09-1.38)
Marufu 2015(18)	Smoking	unselected	Fetal death >20 weeks gestation	25	Any smoking OR 1.47 (95% CI 1.37-1.57). 1-9 cigarettes a day OR 1.09 (95% CI 0.97-1.24), >10 a day OR 1.52
Pineles 2016(19)	Smoking	unselected	Accepted study authors definitions (range 20-28 weeks, 400-1000g birthweight)	142	sRR any smoking 1.46 (95% CI 1.38-1.54), 1-10 cigarettes a day RR 1.1 (95% CI 0.98-1.24), 11-20 RR 1.3 (95% CI 1.22-1.38), >20 a day RR 1.24 (95% CI 1.03-1.5), ex smoker RR 1.12 (95% CI 0.91-1.37), second hand smoke RR 1.4 (95% CI 1.06-1.85)
Greenwood 2014(76)	Caffeine intake	unselected	Fetal loss >24 weeks gestation	5	RR 1.19 (95% CI 1.05-1.35)
Wikoff 2017(77)	Caffeine consumption >300 mg/day	unselected	not defined	4	2/4 studies reported increased risk with caffeine >300 mg/day
Henderson 2007(78)	Low-moderate alcohol exposure	unselected	Not defined	5	1/5 studies reported a significant association
Inamdar 2015(79)	Smokeless tobacco use	unselected	Fetal loss >24 weeks gestation	4	All 4 found a significant association
<u>LMIC setting specific factors</u>					
Di Mario 2007(20)	Multiple risk factors	LMIC setting	Accepted study authors definitions (range 20-28 weeks, 350-1000g	33	Five risk factors (maternal syphilis, chorioamnionitis, maternal malnutrition, lack of antenatal care, and maternal socioeconomic

			birthweight, some excluded multiples or malformations)		disadvantage) were found to be significantly associated with stillbirth (population attributable fraction (PAF) greater than 50%) in more than 1 study.
Berhan 2014 (2)	Multiple risk factors	LMIC setting	Fetal loss >28 weeks gestation	14	Urban residence OR 0.93 (95% CI 0.83-1.05) Maternal education OR 1.14 (95% CI 1.00-1.29) Maternal wealth index OR 1.02 (95% CI 0.95-1.10)
Aminu 2014(21)	Multiple risk factors	LMIC setting	Accepted study authors definitions	142	Factors associated with stillbirth included poverty, lack of education, maternal age (>35 or <20 years), parity (1, ≥5), lack of antenatal care, prematurity, low birthweight, and previous stillbirth.
			<u>Ultrasound</u>		
Allen 2016(23)	Uterine artery doppler (2nd trimester, any abnormal result)	unselected	Stillbirth after 23+6 weeks completed pregnancy	13	Sensitivity: 65% 95% CI 38–85%) Specificity: 82% (95% CI 72–88%) LR+ 3.5 (95% CI 2.3-5.5) LR- 0.43 (95% CI 0.22-0.85) OR 8.3 (95% CI 3.0-22.4)
Conde-Agudelo 2015 (7)	Uterine artery Doppler RI >0.58	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	2	Sens: 16 (95% CI 10–27) Spec: 91 (95% CI 91–92) LR+1.8 (95% CI 1.1–3.1) LR-0.9 (95% CI 0.8–1.0)
Conde-Agudel	Fetal nuchal translucency	unselected	Accepted study	4	Sens: 10 (95% CI 7–14) Spec: 95 (95% CI

o 2015*	(NT) - any increase		authors definitions (range 20-28 weeks completed gestation)		95–95) LR+ 2.0 (95% CI 1.4–2.8) LR- 0.9 (95% CI 0.9–1.0)
Conde-Agudelo 2015*	NT ≥2–3 mm	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	3	Sens: 13 (95% CI 6–23) Spec: 95 (95% CI 95–96) LR+ 2.6 (95% CI 1.3–5.0) LR-0.9 (95% CI 0.8–1.0)
Conde-Agudelo 2015*	Fetal isolated echogenic bowel presence	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	2	Sens: 4 (95% CI 3–7) Spec: 99 (95% CI 99–100) LR+ 8.3 (95% CI 5.2–13.3) LR-1.0 (95% CI 0.9–1.0)
Conde-Agudelo 2015*	Suboptimal fetal growth - any	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	4	Sens: 32 (95% CI 31–34) Spec:75 (95% CI 75–75) LR+1.3 (95% CI 1.2–1.4) LR-0.9 (95% CI 0.9–0.9)
Mondal 2014(80)	Male fetus	unselected	Accepted study authors definitions (range 20-28 weeks, >500g or unexplained at any gestation)	21	RR 1.10 (95% CI 1.7-10.6)
			Biochemical		
Abou-Nassar 2011(81)	Lupus anticoagulant	unselected	Intrauterine death of a morphologically normal fetus at >10 weeks gestation	10	Loss >10 weeks OR 4.73 (95% CI 1.08-20.81
Abou-	Lupus	unselect	Intrauterine	10	Loss >20 weeks OR

Nassar 2011	anticoagulant	ed	death of a morphologically normal fetus at >10 weeks gestation		54.18 (95% CI 2.45-1198.19)
Alfirevic 2002(27)	Lupus anticoagulant	unselected	Pregnancy loss >20 weeks gestation	2	OR 4.3 (95% CI 1.7-10.6)
Abou-Nassar 2011	Anti-cardiolipin antibodies	unselected	Intrauterine death of a morphologically normal fetus at >10 weeks gestation	19	IgG/IgM OR 4.29 (95% CI 1.34-13.68) IgG 15.17 (95% CI 4.29-53.59)
Alfirevic 2002	Anti-cardiolipin antibodies (IgG)	unselected	Pregnancy loss >20 weeks gestation	2	IgG OR 5.6 (95% CI 2.6-11.7)
Abou-Nassar 2011	Anti-B2 GP1 antibodies	unselected	Intrauterine death of a morphologically normal fetus at >10 weeks gestation	2	OR 23.46 (95% CI 1.21-455.01)
Alfirevic 2002	Factor V Leiden (heterozygous)	unselected	Pregnancy loss >20 weeks gestation	4	OR 6.11 (95% CI 2.8-13.2)
Alfirevic 2002	Protein S deficiency	unselected	Pregnancy loss >20 weeks gestation	3	OR 16.2 (95% CI 5.0-52.3)
Alfirevic 2002	APCR	unselected	Pregnancy loss >20 weeks gestation	2	OR 5.0 (95% CI 2.0-12.4)
Alfirevic 2002	Prothrombin gene mutation	unselected	Pregnancy loss >20 weeks gestation	2	OR 0.6 (95% CI 0.2-2.4)
Alfirevic 2002	MTHFR C677T (homozygoous)	unselected	Pregnancy loss >20 weeks gestation	2	OR 1.4 (95% CI 0.9-2.1)
Alfirevi	Protein C	unselect	Pregnancy	3	OR 1 (95% CI 0.1-

c 2002	deficiency	ed	loss >20 weeks gestation		11.1)
Conde-Agudelo 2015*	Alphafetoprotein (AFP) ≥1.7–1.8 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	2	Sens: 13 (95% CI 10–17) Spec: 95 (95% CI 95–95) LR+2.6 (95% CI 2.1–3.3) LR- 0.9 (95% CI 0.9–0.9)
Conde-Agudelo 2015*	Alphafetoprotein (AFP) ≥2.0 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	10	Sens: 11 (95% CI 9–13) Spec: 96 (95% CI 96–96) LR+3.1 (95% CI 2.6–3.7) LR-0.9 (95% CI 0.9–0.9)
Conde-Agudelo 2015*	Alphafetoprotein (AFP) ≥2.5 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	8	Sens: 9 (95% CI 8–11) Spec: 98 (95% CI 98–98) LR+ 4.0 (95% CI 3.4–4.7) LR- 0.9 (95% CI 0.9–0.9)
Conde-Agudelo 2015*	Alphafetoprotein (AFP) <0.4–0.5 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	4	Sens: 6 (95% CI 4–7) Spec: 94 (95% CI 94–95) LR+ 1.0 (95% CI 0.8–1.3) LR- 1.0 (95% CI 1.0–1.0)
Conde-Agudelo 2015*	Human chorionic gonadotrophin (hCG) ≥2.0–2.5 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	11	Sens: 12 (95% CI 10–14) Spec: 93 (95% CI 93–93) LR+1.6 (95% CI 1.4–1.9) LR- 1.0 (95% CI 0.9–1.0)
Conde-Agudelo 2015*	Human chorionic gonadotrophin (hCG) <0.5 MoM	unselected	Accepted study authors definitions (range 20-28 weeks	2	Sens: 4 (95% CI 1–14) Spec: 94 (95% CI 93–94) LR+ 0.7 (95% CI 0.2–2.7) LR- 1.0 (95% CI 1.0–1.1)

			completed gestation)		
Conde-Agudelo 2015*	Free b-hcg ≤5th centile MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	2	Sens: 12 (95% CI 8–16) Spec: 93 (95% CI 93–94) LR+1.8 (95% CI 1.3–2.5) LR-0.9 (95% CI 0.9–1.0)
Conde-Agudelo 2015*	Unconjugated estriol ≤0.5–0.7 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	3	Sens: 15 (95% CI 11–20) Spec: 96 (95% CI 96–96) LR+4.0 (95% CI 3.0–5.3) LR-0.9 (95% CI 0.8–0.9)
Conde-Agudelo 2015*	Pregnancy-associated plasma protein A (PAPP-A) <0.4–0.5 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	7	Sens: 14 (95% CI 11–17) Spec 95 (95% CI 95–95) LR+2.7 (95% CI 2.1–3.4) LR- 0.9 (95% CI 0.9–0.9)
Conde-Agudelo 2015*	Pregnancy-associated plasma protein A (PAPP-A) <0.25–0.30 MoM	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	2	Sens: 15 (95% CI 8–26) Spec: 95 (95% CI 95–96) LR+3.3 (95% CI 1.8–6.0) LR-0.9 (95% CI 0.8–1.0)
Conde-Agudelo 2015*	TSH >95th centile	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	4	Sens: 2 (95% CI 1–7) Spec: 97 (95% CI 97–97) LR+ 0.8 (95% CI 0.3–2.4) LR- 1.0 (95% CI 1.0–1.0)
Conde-Agudelo 2015*	Haemoglobin <10–11 g/dl at <13 weeks	unselected	Accepted study authors definitions (range 20-28 weeks completed	2	Sens: 9 (95% CI 7–10) Spec: 89 (95% CI 89–89) LR+ 0.8 (95% CI 0.7–0.9) LR-1.0 (95% CI 1.0–1.0)

			gestation)		
Conde-Agudelo 2015*	25-hydroxyvitamin D <25 nmol/l or ≤20 ng/ml	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	2	Sens: 15 (95% CI 7–28) Spec:90 (95% CI 89–91) LR+1.5 (95% CI 0.8–3.0) LR- 0.9 (95% CI 0.8–1.1)
Thangaratinam 2006(82)	Serum uric acid	women with pre-eclampsia	Not defined	16	LR- 0.53 (95% CI 0.27-1) LR+ 2.0 (95% CI 1.5-2.7)
Sherrell 2018(83)	PLGF	unselected	accepted study authors definitions	2	associated in both included studies
			Urine tests		
Thangaratinam 2009(84)	Proteinuria	women with pre-eclampsia	Not defined	18	Narrative synthesis found no association.
Combinations					
Conde-Agudelo 2015*	Second-trimester Down screening risk ≥1:190–270	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	5	Sens: 67 (95% CI 53–80) Spec: 61 (95% CI 60–63) LR+1.8 (95% CI 1.4–2.2) LR-0.5 (95% CI 0.3–0.8)
Conde-Agudelo 2015*	First-trimester Down screening risk ≥1:270–300	unselected	Accepted study authors definitions (range 20-28 weeks completed gestation)	3	Sens: 10 (95% CI 5–19) Spec: 96 (95% CI 96–97) LR+2.8 (95% CI 1.5–5.5) LR-0.9 (95% CI 0.9–1.0)
Hui 2012(25)	Combinations of biomarkers: (AFP+hCG) (PAPP-A+hCG) (AFP+hCG+uE) (AFP+uE)	unselected	Fetal loss >24 weeks gestation	7	Most commonly reported combination was AFP+hCG. Reported LR+ ranges from 4.28 (95% CI 1.15-15.53) to 8.86 (95% CI 0.85-39.96)

	(hCG+uE)				and LR- from 0.92 (95% CI 0.83-1.0) to 0.77 (95% CI 0.22 to 1.01)

*Conde-Agudelo 2015: from this paper only the pooled sensitivities of tests reported in more than one primary study are included in the table

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Supplementary Table 1a. Studies excluded at full text review as they did not meet the inclusion criteria and the reason for exclusion

Study author and year	Reason for exclusion
Aune 2014	Duplicate
Coleman 2012	Duplicate
Darmstadt 0001	Duplicate
Flenady 2011	Duplicate
Goffinet 1997	Duplicate
Kyrgiou 2016	Duplicate
Lamont 2015	Duplicate
Malacova 2018	Duplicate
Moraitis 2015	Duplicate
Polyzos 2011	Duplicate
Viale 2015	Duplicate
Yazdani Brojeni 2012	Duplicate
Li 2015	Full text not available
Makarechian 1998	Full text not available
Attini 2018	Only 1 included study reporting stillbirth
Jacobs 2011	Only 1 included study reporting stillbirth
Ramakrishnan 2012	Only 1 included study reporting stillbirth
Delabaere 2014	Only 1 included study reporting stillbirth
Boga 2016	Review article /commentary
Carp 2008	Review article /commentary
Gaccioli 2018	Review article /commentary
Herrera 2017	Review article /commentary
Krassas 2000	Review article /commentary
Gilbert 2009	Review article /commentary
Bell 2014	Review article /commentary
De Montalembert 2015	Review article /commentary
Fretts 2005	Review article /commentary
Liu 2014	Review article /commentary
Li 2018	Study protocol
Allen 2007	Stillbirth not reported as an outcome
Duong 2015	Stillbirth not reported as an outcome
Henderson 2007	Stillbirth not reported as an outcome
Nazarpour 2015	Stillbirth not reported as an outcome
Piccoli 2013	Stillbirth not reported as an outcome
Rodger 2010	Stillbirth not reported as an outcome
Roozbeh 2017	Stillbirth not reported as an outcome
Smyth 2010	Stillbirth not reported as an outcome
Berhan 2014	Stillbirth not the outcome - comparison of perinatal mortality rates between centres

Cohen 2005	Conference speech
Coleman 2015	Intervention
Gagnon 2008	Guideline
Gamble 2006	Intervention
Gamble 2007	Intervention
Goffinet 1997	Intervention
Grand'Maison 2014	Intervention
Gurung 2013	Intervention
Heazell 2008	Intervention
Heazell 2015	Intervention
Hodnett 2000	Intervention
Imdad 2012	Intervention
Johnson 2012	Guideline
Syed 2011	Intervention
Van Ravenswaaij 2011	Primary study
Webster 2017	Intervention
American Society for Reproductive Medicine 2002	Registry data
Tieu 2008	Intervention
Goffinet 1997	Intervention

Supplementary Table 1b. Studies investigating variables associated with stillbirth excluded as not clinically relevant to the development of a prediction model for stillbirth.

Study author and year	Variable
Parental history and characteristics	
Kwong 2018	Bariatric surgery
Langagergaard 2011	Breast cancer
Garcia 2016	Chemotherapy for trophoblastic neoplasia
Saccone 2016	Coeliac disease
Tersigni 2014	Coeliac disease
Schinkel 2014	Hypertrophic cardiomyopathy
O'Toole 2015	Inflammatory bowel disease
Wendt 2012	Interpregnancy interval
Kangatharan 2017	Interpregnancy interval after miscarriage
Alfirevic 2000	Invasive prenatal testing
Deshpande 2012	Liver transplant
Owusu 2013	Maternal sleep practices
Blake 2014	Ovarian sex-cord stromal tumour
Garritsen 2017	Paternal exposure to immunosuppressant drugs
George 2011	Periodontal treatment during pregnancy
Polyzos 2010	Periodontal treatment during pregnancy
Polyzos 2009	Periodontal treatment during pregnancy
Howard 2005	Psychotic disorders
Dreier 2014	Pyrexia in pregnancy
Delamou 2016	Prior repair of obstetric fistula
Gao 2015	Radiotherapy for childhood cancer
Mogos 2013	Reproductive cancers
Ionescu 2015	SLE
Bundhun 2018	SLE/APS
Suliankatchi 2016	Tobacco chewing
Kyrgiou 2016	Treatment for cervical pre-invasive disease
Jin 2014	Treatment for cervical pre-invasive disease
Kyrgiou 2017	Treatment for cervical pre-invasive disease
Boelig 2016	Treatment for hyperemesis gravidarum
Infectious disease	
Ganer Herman 2015	Candida glabrata
Paixao 2016	Dengue fever
Xiong 2017	Dengue fever
Nan 2015	GBS

Seale 2017	GBS
Hall 2017	GBS
Keramat 2017	Hepatitis B
Rein 2012	Hepatitis E
Wedi 2016	HIV infection
Brocklehurst 1998	HIV infection
De Cock 1994	HIV infection
Shi 2018	HSV and CMV
He 2017	Influenza A in pregnancy
Moore 2017	Malaria
Thompson 2016	Rubella
Arnesen 2015	Syphilis
Qin 2014	Syphilis
Gomez 2013	Syphilis
McGready 2014	Typhus
Chibueze 2017	Zika virus
Drug safety reviews	
Rahimi 2008	5-ASA drugs
Terrana 2015	Anti-psychotic exposure
Coughlin 2015	Anti-psychotic exposure
Chan 2000	Anticoagulation (for mechanical heart valves)
Etwel 2017	Antihistamine exposure
Alemu 2015	Antiretroviral therapy
Quansah 2015	Arsenic
Manyando 2012	Artemether-lumefantrine exposure
Kovacs 2016	Artemisinin derivatives exposure
Tosato 2017	Atypical antipsychotics
Laughlin 2004	Corticosteroids
McLaughlin 2003	Corticosteroids
Ford 2014	Cotrimoxazole
Ford 2010	Efavirenz
Dellicour 2017	First trimester artemisinin derivatives and quinine
Kaplan 2015	First trimester exposure to topical retinoids
Kaplan 2016	Hydroxychloroquine
Bratton 2015	Influenza immunisation in pregnancy
McMillan 2012	Influenza immunisation in pregnancy
Yazdani Brojeni 0001	Interferon alpha
Pariente 2017	Lamotrigine
Gonzalez Blanco 2011	Lispro compared to regular insulin
Pasley 2013	Lopinavir/ritonavir

Radeva-Petrova 2014	Malaria prophylaxis
Galbally 2010	Mood stabilisers in pregnancy
Graner 2017	Neuraminidase inhibitors
Martinez Lopez 2008	NSAIDS
Oyebode 2012	Psychotropics in pregnancy
Bar-Oz 2009	Quinolones
Sawka 2008	Radioactive iodine for thyroid cancer
Dunn 2017	Sildenafil
Badell 2015	Smallpox vaccination in pregnancy
Einarson 1990	Spermicide exposure
Geert 2011	Tamoxifen
Mofenson 2017	Tenofovir exposure
Uthman 2017	Timing of ART intiation
Nielsen 2013	TNF-alpha inhibitor exposure
Marchioni 2013	TNF-alpha inhibitor exposure
Chi 2010	Topical corticosteriods
Chi 2009	Topical corticosteriods
Environmental factors	
Zhang 2016	Atmospheric particulate matter
Lai 2013	Air pollution
Bruce 2013	Air pollution
Glinianaia 2004	Air pollution
Siddika 2016	Air pollution
Jahn 1995	Dioxin exposure
Pan 2015	Dioxin-related toxicants exposure
Nieuwenhuijsen 2013	Environmental risk factors
Grant 2013	Exposure to e-waste
Balise 2016	Exposure to oil and natural gas extraction processes
Ashworth 2014	Exposure to waste incineration
Zhu 2015	Fine particulate matter exposure
Duong 2011	Formaldehyde exposure
Amadi 2017	Heavy metal exposure during pregnancy
Pan 2007	Mercury exposure
Yan 2012	Pesticide exposure
Shirangi 2011	Pesticide exposure
Amegah 2014	Solid fuel use
Sehgal 2014	Solid fuel use
Pope 2010	Solid fuel use
Zhang 2017	Temperature exposure during pregnancy
Thakur 2010	Toxic waste water exposure

Hwang 2012	Water disinfection by-products
Fetal factors	
Morris 1999	Down's syndrome
Morris 2010	Ductus venosus doppler
Ayed 2015	Fetal sacrococcygeal teratoma
South 2013	Gastroschisis
Rabie 2017	Oligohydramnios
Tuuli 2011	Subchorionic haematoma
Kennelly 2009	Ventriculomegaly
Carta 2018	Ventriculomegaly
Derricott 2013	Villitis of unknown etiology
Socioeconomic factors	
Keasley 2017	Armed conflict
Srinivasjois 2012	Biracial parents
Darmstadt 2009	Non-facility birth
Almeida 2013	Immigration status
Gissler 2009	Immigration status
Small 2008	Immigration status
Knight 2005	Imprisonment
Porter 2012	Indigenous ethnicities
Han 2014	Intimate partner violence
Conner 2016	Marijuana use
Wolf 2017	Multivitamin use
Dranitsaris 2005	Occupational exposure - chemotherapy
Peters 2010	Occupational exposure - hairdressers
Warembourg 2017	Occupational exposure - health care workers
Shah 2014	Occupational exposure - non-ionising radiation
Hall 2017	Pregnancy intention
Berhan 2014	Skilled birth attendance

FIGURE LEGENDS

Figure 1. PRISMA flow chart

Figure 2. Quality assessment charts

Figure 3. Characteristics of the included studies

Figure 4. Association of single variables and stillbirth

Supplementary Figure 1. AMSTAR checklist

Supplementary Figure 2. QUIPS checklist