

RESEARCH

Exploration and confirmation of factors associated with uncomplicated pregnancy in nulliparous women: prospective cohort study

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Abstract

Objective To identify factors at 15 and 20 weeks' gestation associated with a subsequent uncomplicated pregnancy.

Design Prospective international multicentre observational cohort study.

Setting Auckland, New Zealand and Adelaide, Australia (exploration and local replication dataset) and Manchester, Leeds, and London, United Kingdom, and Cork, Republic of Ireland (external confirmation dataset).

Participants 5628 healthy nulliparous women with a singleton pregnancy.

Main outcome measure Uncomplicated pregnancy, defined as a normotensive pregnancy delivered at >37 weeks' gestation, resulting in a liveborn baby not small for gestational age, and the absence of any other significant pregnancy complications. In a stepwise logistic regression the comparison group was women with a complicated pregnancy.

Results Of the 5628 women, 3452 (61.3%) had an uncomplicated pregnancy. Factors that reduced the likelihood of an uncomplicated pregnancy included increased body mass index (relative risk 0.74, 95% confidence intervals 0.65 to 0.84), misuse of drugs in the first trimester (0.90, 0.84 to 0.97), mean diastolic blood pressure (for each 5 mm Hg increase 0.92, 0.91 to 0.94), and mean systolic blood pressure (for each 5 mm Hg increase 0.95, 0.94 to 0.96). Beneficial factors were prepregnancy fruit intake at least three times daily (1.09, 1.01 to 1.18)

and being in paid employment (per eight hours' increase 1.02, 1.01 to 1.04). Detrimental factors not amenable to alteration were a history of hypertension while using oral contraception, socioeconomic index, family history of any hypertensive complications in pregnancy, vaginal bleeding during pregnancy, and increasing uterine artery resistance index. Smoking in pregnancy was noted to be a detrimental factor in the initial two datasets but did not remain in the final model.

Conclusions This study identified factors associated with normal pregnancy through adoption of a novel hypothesis generating approach, which has shifted the emphasis away from adverse outcomes towards uncomplicated pregnancies. Although confirmation in other cohorts is necessary, this study implies that individually targeted lifestyle interventions (normalising maternal weight, increasing prepregnancy fruit intake, reducing blood pressure, stopping misuse of drugs) may increase the likelihood of normal pregnancy outcomes.

Trial registration Australian New Zealand Clinical Trials Registry ACTRN12607000551493.

Introduction

Standard pathways of antenatal care have developed from the perceived need to identify risk of adverse pregnancy complications, enabling stratification of care and appropriate targeting of prophylactic interventions. Comparatively little effort has been made to recognise predictors of healthy

outcomes, although the concept of “health” is an increasingly attractive addition to risk assessment.¹ Indeed it is now suggested that this concept be promoted and formulated as “the ability to adapt and to self manage,”² with the promotion of health enabling empowerment of someone through lifestyle changes. In its guidelines for antenatal care, the UK National Institute of Health and Care Excellence states “The ethos of this guideline is that pregnancy is a normal physiological process.”³ Promotion of this concept of normality would be facilitated by identification of those factors that make it more likely for a woman to have an uncomplicated pregnancy. Women could then make informed modifications to their lifestyle before or early in pregnancy, and antenatal care could be tailored to deliver advice appropriately in any resource setting.

In the United Kingdom, recent reports highlight the need to improve stratification of risk, enabling women to be offered midwifery led care if at low risk, or joint care with a specialist when additional needs are identified. The Confidential Enquiry into Maternal and Child Health reiterates the importance for risk and needs assessment at the first antenatal visit to offer the most appropriate care pathway and avoid those maternal deaths associated with substandard practice arising from incorrect assignment of risk.⁴ To date, the majority of research has focused on screening for pregnancy complications, such as pre-eclampsia, gestational diabetes, and preterm birth. NICE has identified the need for a validated assessment tool to predict pregnancy outcomes.³

To inform development of a comprehensive assessment tool, an understanding of the factors associated with subsequent normal pregnancy provides a valuable aid to stratification. Variables identified as being predictive of adverse outcomes cannot automatically be adopted, through assumption of an inverse relation, for identification of normal pregnancy.

We aimed to identify, replicate, and confirm variables at 15 and 20 weeks’ gestation associated with a subsequent uncomplicated pregnancy, and to highlight those factors amenable to modification before pregnancy, to inform interventions that could increase the likelihood of a normal outcome.

Methods

Between November 2004 and August 2008 we recruited nulliparous women with singleton pregnancies to the Screening for Pregnancy Endpoints (SCOPE) study, a prospective observational multicentre cohort study in Auckland, New Zealand; Adelaide, Australia; London, Manchester, and Leeds, United Kingdom; and Cork, Republic of Ireland.⁵ All women provided written informed consent.

We invited women before 15 weeks’ gestation and accessing antenatal care through hospital antenatal clinics, obstetricians, general practitioners, or community midwives to participate. Exclusion criteria included a recognised high risk for pre-eclampsia, delivery of a small for gestational age infant, or spontaneous preterm birth due to underlying medical conditions (chronic hypertension requiring antihypertensive drugs, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease, HIV), previous cervical knife cone biopsy, three or more terminations of pregnancy or three or more miscarriages, current ruptured membranes, known major fetal anomaly or abnormal karyotype, or an intervention that might modify the pregnancy outcome (for example, aspirin, cervical suture).⁵ A research midwife interviewed and examined participants at 14-16 and 19-21 weeks of gestation and the women underwent ultrasonography at 19-21 weeks. At the time of interview, data were entered into an internet accessed, central

database with a complete audit trail (MedSciNet, Stockholm, Sweden).

At 14-16 weeks’ gestation we collected a comprehensive dataset: personal information including socioeconomic index; participant’s birth details; obstetric, gynaecological, and medical history; family history of obstetric complications and medical conditions; early pregnancy complications; dietary information before conception and during pregnancy (food frequency questionnaire); and use of therapeutic medication and drugs of misuse, cigarettes, and alcohol. The women completed a lifestyle questionnaire on work, exercise, and sedentary activities; snoring; domestic violence; and social supports. Psychological scales were completed measuring perceived stress,⁶ depression,⁷ anxiety,⁸ and behavioural responses to pregnancy (adapted from the behavioural responses to illness questionnaire⁹). Maternal measurements included blood pressure, height, weight and waist, hip, arm and head circumference, urinalysis, random blood glucose levels, and ultrasound examination of the fetus and uterine arteries at 19-21 weeks’ gestation. Full details of the dataset have been previously described.¹⁰

We followed the participants prospectively, with pregnancy outcome data and infant measurements collected by research midwives. To minimise information bias, data monitoring included an individual check of all data for each participant, including a check for transcription errors of the lifestyle questionnaire and ultrasound scan data; and detection of illogical or inconsistent data and outliers using customised software. Collection of outcome data aimed to be as comprehensive as possible; we made multiple attempts to trace women with missing data.

Primary outcome

The primary outcome was uncomplicated pregnancy, defined as a normotensive pregnancy, delivered at >37 weeks, resulting in a liveborn baby who was not small for gestational age, and did not have any other significant pregnancy complications. We defined these pregnancy complications before the analysis. If the pregnancy had been otherwise uneventful for those babies who were admitted to the neonatal unit for transient observation, we classified the pregnancy as uncomplicated.

Statistical analysis

Definition of datasets

We divided the dataset of 5628 women into three parts: an exploration dataset of two thirds of the women from Australia and New Zealand, chosen at random (n=2129); a local replication dataset of the remaining third of women from Australia and New Zealand (n=1067); and an external, geographically distinct confirmation dataset of 2432 European women from the United Kingdom and Republic of Ireland.

Selection of variables

The analysis strategy and variable selection was decided before any statistical analysis. We carried out a detailed inspection of the variables and rejected those that were not comparable across different settings (for example, public or private maternity care differed across the various settings; n=10), those that were not measured in all women (for example, work related variables, additional dietary questions; n=8), and those that were not completed by at least 95% of women (for example, participant’s birth weight; n=4). Where possible we used the variable based on the response to the directly asked question; for those where a large number of responses was possible (for example,

ethnicity), we used a derived variable based on clinically relevant and generalisable collapsed groupings (for example, white, non-white).

We selected a total of 86 variables, either based on directly asked questions or derived as described, for further analysis, in 10 groups. Group 1 related to personal and family circumstances, including ethnicity, personal characteristics, maternal birth history, and obstetric history of relatives (16 predictors); group 2 related to general risk factors, including deprivation (eight predictors); group 3 related to medical risk factors (19 predictors); group 4 related to obstetric history (six predictors); group 5 related to minor early pregnancy complications (eight predictors); group 6 related to diet (10 predictors, five relating to prepregnancy period, five to pregnancy); group 7 related to drug use (legal and illegal; six predictors); group 8 related to physical examination (four predictors); group 9 related to current workload and stress (six predictors); and group 10 related to the 20 week Doppler scan (10 predictors).

Variable reduction in the exploration dataset

The variable reduction process used the exploration dataset only. Firstly, we discarded any potential predictor not significantly ($P < 0.05$) related to uncomplicated pregnancy by simple t test or χ^2 test. Using logistic regression, we found that questions about diet from the pregnancy period were less useful than questions about the month before pregnancy and so they were also discarded. Secondly, we replaced categorical predictors with more than two levels by a series of binary indicator variables. For unordered variables, these were mutually exclusive, but for ordered categories (time to conceive, vaginal bleeding, diet, smoking, alcohol consumption, misuse of drugs, moderate and vigorous physical activity), we set up indicator variables so that with increasing exposure, more questions would be answered as “yes.” For example, a former smoker who gave up smoking during her pregnancy would be recorded as “ever–yes,” “during pregnancy–yes,” and “currently–no.” With this method, unlike the more usual dummy variables, combining the categories by reducing the number of indicator variables gave a simpler but coherent scale. The stepwise regression automatically selected the best cut points.

During development of the model, we performed each analysis on all available data without any imputation or recoding of missing values. Thirdly, to further reduce the number of predictors we fitted 10 backward stepwise logistic regression models ($P < 0.05$), one model for each of these 10 groups. The key predictors that remained significant in the exploration dataset were taken forward to the replication and confirmation datasets.

Model local replication and external confirmation

We fitted the key predictor variables using unadjusted log probability regression to the replication and confirmation cohorts. The final list of consistent predictors was those that remained significant in the external confirmation dataset. Final results were presented as unadjusted risk ratios¹¹ for a healthy pregnancy outcome. The model for adjusted risk ratios failed to converge (that is, no usable results were produced); with the outcome having a prevalence of over 50% and strong predictor variables, certain women might be given an impossible estimated probability of over 100% when using adjusted risk ratios. For presentation purposes in the final model, we split the socioeconomic index into five groups at the quintiles, calculated separately for each setting (Australasia versus United Kingdom and Republic of Ireland). To give the risk ratio for clinically

relevant increments we rescaled continuous predictors: 5 mm Hg systolic and diastolic blood pressure–5 mm Hg; uterine artery resistance index–0.1; paid employment/week–eight hours; we categorised body mass index using standard World Health Organization thresholds of 25 and 30. For categorical variables we chose the healthiest group to be the reference. For the variables in the final model, data were available on 100% of women apart from two variables; 19 (0.3%) values were missing for hours worked in paid employment and 243 (4.3%) values were missing for uterine artery Doppler resistance index.

Data analysis was conducted in Stata version 11.2. We estimated risk ratios using binomial regression with a log link; using either maximum qualified likelihood (Fisher scoring) or maximum likelihood, depending on convergence.

The study has been reported in line with STROBE¹¹ recommendations.

Results

Of the 5628 women, 3452 (61.3%) had an uncomplicated pregnancy. Table 1 shows the personal data and pregnancy outcome characteristics for those women who had an uncomplicated pregnancy and those with complications. A lower proportion of women in the external confirmation dataset (United Kingdom and Ireland) had an uncomplicated pregnancy compared with women in Australasia (58.6% v 63.5%). Table 2 gives the reasons for defining a pregnancy as complicated; a woman could have several reasons. Table 3 shows the maternal and perinatal outcomes for the whole cohort.

Tables 4 and 5 show the clinical variables associated with subsequent uncomplicated pregnancy in univariable analysis. All variables significantly associated with uncomplicated pregnancy in the development dataset are shown; some variables lost significance in the local replication and external confirmation datasets. Table 6 shows the variables that remained after fitting the log probability regression model, presented as unadjusted risk ratios (relating to risk of uncomplicated pregnancy). Factors amenable to improvement that decreased the likelihood of an uncomplicated pregnancy (that is, were detrimental) were increasing body mass index and blood pressure and misuse of drugs (including binge alcohol use) in the first trimester. Factors amenable to improvement that increased the likelihood of an uncomplicated pregnancy (that is, were beneficial) were high fruit intake in the month before the pregnancy and being in paid employment at 15 weeks' gestation. Smoking in pregnancy was noted to be detrimental and leafy vegetable intake was beneficial for subsequent uncomplicated pregnancy in the initial two datasets, but neither variable remained in the final model. Factors not amenable to alteration that reduced the likelihood of an uncomplicated pregnancy were being in a lower fifth of socioeconomic index, the presence of hypertension before pregnancy while using oral contraceptive pills, family history of any hypertensive disorder in pregnancy, and vaginal bleeding during pregnancy.

Addition of ultrasound indices from the 20 week examination to the model resulted in one additional non-modifiable variable reducing the likelihood of an uncomplicated pregnancy: raised mean uterine artery resistance index.

Discussion

In our large prospective international cohort of healthy nulliparous women we identified factors related to maternal weight, diet, blood pressure (within the normal range), and misuse of drugs that are potentially amenable to modification

before pregnancy and could result in uncomplicated pregnancy outcomes. We recognise that identification of risk factors does not equate to utility for prediction (for example, through a risk algorithm), nor does it assume that modification would inevitably lead to improved outcomes. However, if confirmed in a further external dataset, knowledge of these factors could inform women, their healthcare providers, and policy makers on variables that could be targeted for change on an evidence based foundation, and inform future intervention trials.

To our knowledge this is the first study to comprehensively investigate and identify factors present early in pregnancy that are associated with an uncomplicated outcome. Although several variables have been shown to be associated with adverse pregnancy events,^{10 12} few studies have focused on normality as the outcome. The WHO recently reiterated the importance of Millennium Development goal 5 by promotion of universal access to reproductive health, in tandem with reducing maternal mortality.¹³

Strengths and weaknesses of this study

A major strength of this study is that we collected all data prospectively, from multiple centres in an international setting. The interviews were conducted by research midwives using a real-time internet database, automated data queries, and detailed standard operating procedures, which ensured high quality data with a high rate of follow-up and complete datasets. The research midwives collected all outcome data and these were reviewed by a principal investigator, avoiding the assignment errors associated with using routine hospital coding. The number of variables collected in our study enabled a comprehensive assessment of factors to be considered; while confounding can never be avoided completely, this was reduced by inclusion of terms for all major explanatory variables. Exploration of variables in the development dataset was followed by replication and confirmation in two other datasets, one local and one external, increasing the robustness of the associations and the generalisability of the results. The variables in the final model are consistent with biological plausibility, but the predictive nature of these variables requires validation in future studies. The study invited nulliparous women with no major medical conditions to participate, in order to assist in identification of risk factors without the additional complexities of pre-existing medical conditions. This enables the findings to be generalised to other similar populations of pregnant women but not automatically to other groups (nulliparous women with medical disorders or multiparous women). It is also possible that the method of variable selection could have omitted some predictive factors in favour of others that are even more useful, and therefore the list of variables identified is not all inclusive. However, the resulting list is intended to be both generally applicable and of a manageable size.

Comparisons with other studies

Many studies have investigated factors, often in relative isolation from confounders, and usually in association with adverse pregnancy outcome. We are not aware of any studies using a similar approach to that employed in the present study. Previous evidence of an association between a factor and adverse outcome cannot be extrapolated to indicate that the same variable reduces the likelihood of an uncomplicated pregnancy, but it may support biological plausibility. For example, (lower) maternal age was not included in the final list of variables associated with uncomplicated pregnancy in our study, despite many studies linking advanced maternal age to adverse pregnancy outcomes.^{14 15} Although it might seem intuitive that improvable

factors related to diet, blood pressure, heart rate, weight, and smoking would predict uncomplicated pregnancy, the evidence from well conducted prospective cohort studies has been lacking to date.

The association between obesity and adverse perinatal outcome has been well documented; obesity is strongly associated with an increased risk of maternal and fetal morbidity and mortality, including pre-eclampsia, gestational diabetes, thromboembolic disease, maternal mortality, congenital malformations, macrosomia, perinatal mortality, and subsequent adult cardiovascular disease for the infant.¹⁶ In our study, with confounding variables included in the model, overweight and obese women were less likely to have an uncomplicated pregnancy outcome when compared to those with a normal body mass index. We also found an inverse relation between blood pressure and uncomplicated pregnancy outcome. The majority of relevant studies relating blood pressure to pregnancy outcome have focused on the relation between high blood pressure and adverse outcomes. In a systematic review, significantly increased odds ratios for subsequent pre-eclampsia were found for systolic blood pressure >130 mm Hg and diastolic blood pressure >80 mm Hg, compared with women with blood pressures below those thresholds.¹⁷ Even in women with subsequent normal term pregnancy, established pre-eclampsia risk factors (for example, obesity, nulliparity) are associated with higher blood pressure in early pregnancy, suggesting that risk relates to a continuum rather than to a threshold.¹⁸

Our study also shows that a high fruit intake before pregnancy increases the likelihood of a normal pregnancy outcome. Previous reports have shown high fruit and vegetable intake in pregnancy to be associated with a decreased risk of pre-eclampsia¹⁹ and preterm birth²⁰ and increased infant birth weight (by 10.7 g, 95% confidence interval 7.3 to 14.2g per quintile).²¹ Women in Scotland from the most deprived 10th of the population with a diet lower in fruit and vegetable intake (and higher in processed food and other less healthy foods) had poorer perinatal outcomes than those in less deprived 10ths; the authors speculated that improving the nutrient intake of such women may improve pregnancy outcomes.²² In a study from England, only 53% of women of reproductive age said that they followed the recommendation to consume five or more portions of fruit and vegetables daily,²³ but our study suggests that preparation for pregnancy should include advice to increase fruit intake.

Illicit drug use²⁴ and binge alcohol drinking²⁵ have an association with adverse pregnancy outcomes and thus it is not surprising that in our study their use decreased the likelihood of an uncomplicated pregnancy. Rates of drug misuse in the first trimester (which included binge alcohol) were high, particularly in the United Kingdom and Republic of Ireland cohort but not inconsistent with estimates of binge drinking and illicit drug use in women of reproductive age.²⁶ The finding that paid employment is associated with an improved likelihood of uncomplicated pregnancy has been described previously,^{27 28} but there may well be confounding factors (even after adjustment) that account for some of this effect.

Identification of non-modifiable factors is useful for future research into prediction and generating hypotheses for understanding possible causation. Here we have identified that a history of hypertension with previous use of oral contraceptives was associated with a reduced likelihood of normal pregnancy outcome. Women who become hypertensive while using the oral contraceptive pill may have underlying cardiovascular risk factors that increase their predisposition to

hypertension both while using the contraceptive pill and while pregnant.

The socioeconomic index is influenced by many factors, and its pivotal role in determining health has been recognised by the recent strategic review of health inequalities led by Marmot²⁹; of the six policy objectives presented, the highest recommendation was to “Give every child the best start in life,” through “Giving priority to prenatal interventions that reduce adverse outcomes of pregnancy and infancy” and other postnatal strategies. For outcomes such as neonatal mortality, much of the gap between the most deprived 10th of the population and the least deprived could be explained by premature birth and congenital anomalies, suggesting a focus for future specific intervention³⁰: a similar deprivation gap exists for stillbirths,³¹ but there is little evidence on strategies that promote healthy pregnancy outcomes.

We have also observed that vaginal bleeding in early pregnancy significantly reduced the odds of an uncomplicated pregnancy. Several large systematic reviews all concur that vaginal bleeding increases the risk of subsequent pregnancy complications.^{32 33}

The finding of an increased uterine artery resistance index (with higher levels more abnormal) being associated with a reduced likelihood of uncomplicated pregnancy is in keeping with the conclusions from the largest systematic review and meta-analysis of uterine artery Doppler ultrasonography. In low risk women an abnormal uterine artery Doppler waveform was predictive of pre-eclampsia (positive likelihood ratio 7.5, 95% confidence interval 5.4 to 10.2; negative likelihood ratio 0.59, 95% confidence interval 0.47 to 0.71) and fetal growth restriction (positive likelihood ratio 9.1, 95% confidence interval 5.0 to 16.7; negative likelihood ratio 0.89, 95% confidence interval 0.85 to 0.93).³⁴

Clinical relevance

This study has identified factors that are potentially amenable to alteration, especially if implemented before pregnancy, and which, if improved, may improve the likelihood of an uncomplicated pregnancy. An understanding of both these and the non-modifiable factors associated with uncomplicated pregnancy provide potential to assist public health strategies and inform family doctors and maternal care providers when advising women planning a future pregnancy. The findings should be generalisable to other nulliparous women in high income settings; the full description of their personal characteristics and outcomes should enable comparison with other populations. Smoking in pregnancy was noted to be detrimental in the first two datasets and the association between smoking and subsequent adverse outcome is well recognised³⁵; recommendations for smoking cessation before and in pregnancy continue to be important in preventing infant morbidity and mortality.

Evidence based recommendations for lifestyle management already exist for non-hypertensive people to optimise their blood pressure through physical exercise, weight reduction, limiting sodium intake and alcohol consumption, and consuming a healthy diet.³⁶ Our study suggests that adoption of these choices seems to be beneficial in determining subsequent uncomplicated pregnancy. To illustrate the possible benefits a 5 mm Hg reduction of maternal systolic blood pressure (relative risk 0.95, table 5) would increase the proportion of uncomplicated pregnancies by 3.1% from 58.6% to 61.7%. Among 800 000 live births (the approximate annual number in the United Kingdom), this would equate to 24 674 more women having an uncomplicated pregnancy. A systolic blood pressure reduction

of this magnitude is comparable to that reported for interventions such as improved diet and exercise in a recent systematic review.³⁷ If it were achieved through lifestyle interventions to produce fitter, healthier women of reproductive age with lower blood pressure, there would be likely additional benefits (for example, on body mass index and glucose metabolism) that are difficult to quantify. The magnitude of benefit achievable by these interventions would none the less require demonstration in a well designed epidemiological cohort study or a randomised controlled trial. Health promotion interventions are of relevance to policy makers in the public health arena and all health professionals involved in the promotion of prepregnancy lifestyle.

Unanswered questions and future research

Although this study has elucidated associations between certain variables and uncomplicated pregnancy outcome, further investigations are required to determine whether these have causal importance. These factors could be incorporated into a predictive algorithm for evaluation in a larger cohort to identify women who are likely to have an uncomplicated pregnancy; antenatal care could be tailored to such risk stratification. The few studies that have examined health promotion interventions specifically to modify risk factors before pregnancy were varied, and follow-up of pregnancy outcome was of mixed quality leading the authors of a systematic review to recommend that more research was needed.³⁸ Considerable effort would be required to determine, through a theoretically based approach, the most effective means of delivery of the interventions to women of reproductive age and in pregnancy to assess whether the targeted behaviours change as anticipated and to determine whether these relate to improved pregnancy outcome.

Conclusions

There is growing interest in promotion of health and normality, rather than an exclusive focus on adverse outcomes. Based on a large prospective cohort study of healthy nulliparous women, we identified, replicated, and externally confirmed improvable factors associated with uncomplicated pregnancy; these related to optimising weight, diet, cardiovascular fitness, and cessation of illicit drug use. Providing confirmation is forthcoming from other cohorts, this study should inform development of interventions to increase normal pregnancy outcomes.

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Contributors: LCC and RAN designed this component of the SCOPE study, analysed and interpreted the data, drafted the article and revised it critically for important intellectual content, and gave final approval of the version to be published. JM, LCK, GAD, JJW, LMEMcC, and LP conceived and designed the study, interpreted the data, and critically revised the paper for important intellectual content. RST was designed the study, coordinated the clinical study, and revised the article critically for important intellectual content. PTS carried out the statistical analyses, interpreted the data, and revised the article critically for important statistical content. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. RAN is guarantor. RAN and LP are joint senior authors.

What is already known on this topic

Previous literature has focused on the association between risk factors and subsequent adverse pregnancy outcomes
Little is known of factors associated with subsequent healthy pregnancies

What this study adds

Factors associated with subsequent uncomplicated pregnancy amenable to alteration include normalising maternal weight, increasing prepregnancy fruit intake, reducing blood pressure, stopping misuse of drugs (including binge alcohol use), and being in paid employment
Identification of these factors could inform development of interventions to increase normal pregnancy outcomes

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that RAN, LMEMcC, JM, GAD, LP, RST, and LCK declare their institutions received money to fund the SCOPE study including some salary component (except for GAD).

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Data sharing: Additional data are available from RAN on request (robyn.north@kcl.ac.uk).

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Tables

Table 1 | Maternal characteristics at first visit (15 weeks' gestation). Values are numbers (percentages) unless stated otherwise

Characteristics	Development dataset (n=2129)		Local replication dataset (n=1067)		External confirmation dataset (n=2432)	
	Uncomplicated	Complicated	Uncomplicated	Complicated	Uncomplicated	Complicated
Total	1351 (64)	778 (36)	677 (63)	390 (37)	1424 (59)	1008 (41)
Mean (SD) maternal age (years)	28.2 (5.7)	27.7 (6.0)	28.2 (5.8)	27.6 (6.1)	29.7 (4.8)	29.3 (5.0)
White ethnicity	1183 (88)	667 (86)	587 (87)	337 (86)	1337 (94)	950 (94)
<12 years schooling	634 (47)	404 (52)	324 (48)	206 (53)	294 (21)	262 (26)
Unemployed	97 (7.0)	96 (12)	57 (8.4)	44 (11)	74 (5.2)	59 (5.9)
Single	98 (7.3)	68 (8.7)	51 (7.5)	32 (8.2)	153 (11)	138 (14)
In relationship (unmarried)	459 (34)	310 (40)	267 (39)	150 (39)	337 (24)	267 (26)
Married	794 (59)	400 (51)	359 (53)	208 (53)	934 (65)	603 (60)
Primigravid	1027 (76)	558 (72)	497 (73)	288 (74)	1165 (82)	796 (79)
Previous miscarriage	167 (12)	119 (15)	97 (14)	57 (15)	185 (13)	150 (15)
Previous abortion	182 (14)	112 (14)	100 (15)	52 (13)	83 (5.8)	68 (6.7)
No smoking in pregnancy	1078 (80)	596 (77)	538 (80)	281 (72)	1053 (74)	717 (71)
Quit smoking in pregnancy	154 (11)	73 (9.4)	69 (10)	50 (13)	237 (17)	175 (17)
Smoking at first visit	119 (8.8)	109 (14)	70 (10)	59 (15)	134 (9)	116 (12)
No alcohol in pregnancy	679 (51)	426 (54)	349 (52)	205 (52)	314 (22)	218 (22)
Quit alcohol in pregnancy	612 (45)	307 (40)	293 (43)	171 (44)	861 (61)	621 (61)
Continuing to drink alcohol at 15 weeks	60 (4.4)	45 (5.8)	35 (5.2)	14 (3.6)	249 (17)	169 (17)
Misuse of drugs in first trimester*	165 (12)	127 (16)	96 (14)	65 (17)	574 (40)	466 (46)
Body mass index:						
<18.5	21 (1.6)	15 (1.9)	13 (1.9)	7 (1.9)	18 (1.2)	10 (1.0)
18.5-24.9	771 (57)	342 (44)	411 (61)	174 (44)	897 (63)	528 (52)
25-29.9	385 (28)	237 (30)	166 (24)	109 (28)	370 (26)	309 (30)
≥30	174 (13)	184 (24)	87 (13)	100 (25)	139 (9)	161 (16)
Mean (SD) blood pressure (mm Hg):						
Systolic	107 (9)	110 (11)	106 (10)	110 (10)	104 (10)	107 (11)
Diastolic	64 (7)	67 (9)	64 (8)	66 (8)	65 (7)	67 (8)

See table 2 for reasons pregnancy was considered complicated.

*Use of marijuana, cocaine/crack, amphetamines, 3,4 methylenedioxymethamphetamine, opiates, hallucinogens, and binge alcohol ≥6 units/session.

Table 2| Reasons for complicated pregnancy (non-exclusive) in 5628 women

Reasons	No (%) of total		
	Development dataset (n=2129)	Local replication dataset (n=1067)	External confirmation dataset (n=2432)
Maternal complications:			
Gestational hypertension	158 (7.4)	75 (7.0)	238 (9.8)
Pre-eclampsia	113 (5.3)	67 (6.3)	100 (4.1)
Gestational proteinuria	18 (0.8)	13 (1.2)	6 (0.3)
Gestational diabetes	65 (3.1)	26 (2.4)	54 (2.2)
Antepartum haemorrhage, placenta praevia, or placenta accreta	124 (5.9)	63 (5.9)	245 (10)
Placental abruption	17 (0.8)	7 (0.7)	16 (0.7)
Chronic hypertension (mild, diagnosed in pregnancy)	10 (0.5)	1 (0.1)	6 (0.3)
Renal tract complications*	16 (0.8)	9 (0.8)	17 (0.7)
Gastrointestinal tract or hepatic complications	8 (0.4)	4 (0.4)	12 (0.5)
Respiratory complications†	8 (0.4)	6 (0.6)	7 (0.3)
Other obstetric complications‡	45 (2.1)	22 (2.1)	80 (3.3)
Other medical complications§	17 (0.8)	11 (1.0)	41 (1.7)
Maternal death during pregnancy	1 (0.1)	0	0
Fetal complications:			
Small for gestational age infant (<10th customised birthweight centile)	227 (11)	115 (11)	291 (12)
Spontaneous preterm birth	104 (4.9)	50 (4.7)	79 (3.3)
Other fetal problems (including severe neonatal morbidity¶)	58 (2.7)	24 (2.2)	65 (2.7)
Fetal anomalies	54 (2.5)	27 (2.5)	51 (2.1)
Fetal death in utero ≥20/40 or neonatal death	22 (1.0)	8 (0.7)	15 (0.6)
Fetal death in utero <20/40	11 (1.4)	3 (0.3)	10 (0.4)
Miscarriage or abortion <20/40	9 (0.4)	5 (0.5)	4 (0.3)

*For example, pyelonephritis.

†For example, pneumonia.

‡Obstetric cholestasis, sustained gestational thrombocytopenia, cervical cerclage, oligohydramnios, polyhydramnios, chorioamnionitis, surgery in pregnancy, admitted to hospital for threatened preterm labour but delivered at term, genital tract problems, major postpartum complications.

§Venous thromboembolism; neurological, haematological and cardiac conditions; other medical conditions leading to hospital admission.

¶Grade II or III hypoxic ischaemic encephalopathy; ventilation >24 hours; neonatal unit admission >4 days; Apgar score <4 at five minutes; cord arterial pH <7.0 or base excess ≥15, or both; or neonatal seizures.

Table 3| Maternal and perinatal outcomes. Values are numbers (percentages) unless stated otherwise

Outcomes	Development dataset		Local replication dataset		External confirmation dataset	
	Uncomplicated (n=1351)	Complicated (n=778)	Uncomplicated (n=677)	Complicated (n=390)	Uncomplicated (n=1424)	Complicated (n=1008)
Maternal outcomes						
Mean (SD) blood pressure (mm Hg):						
Systolic	120 (11)	130 (25)	120 (11)	130 (25)	121 (27)	132 (25)
Diastolic	73 (8)	80 (18)	73 (8)	80 (18)	76 (20)	84 (18)
Mean (SD) gestation at delivery (weeks)	40.1 (1.2)	38.2 (4.1)	40.0 (1.2)	38.3 (4.0)	40.3 (1.1)	39.1 (3.0)
Unassisted vaginal delivery	684 (51)	344 (44)	363 (54)	158 (41)	562 (40)	423 (42)
Operative vaginal delivery	293 (22)	139 (18)	147 (22)	74 (19)	517 (36)	312 (31)
Prelabour caesarean section	76 (5.6)	79 (10)	44 (6.5)	52 (13)	126 (8.8)	121 (12)
Caesarean section in labour	298 (22)	206 (27)	123 (18)	101 (26)	218 (15)	147 (15)
Perinatal outcomes						
Mean (SD) infant birth weight (g)	3586 (416)	3030 (823)	3548 (401)	3015 (797)	3582 (408)	3169 (708)
Median (interquartile range) customised centile	54 (33 to 75)	32 (9 to 69)	51 (30 to 74)	29 (7 to 60)	52 (31 to 76)	32 (8 to 64)
Admission to neonatal unit	61 (4.5)	203 (26)	19 (2.8)	96 (25)	67 (4.7)	201 (20)

Table 4| Unadjusted comparisons on all variables in development and local replication datasets. Unless stated otherwise all parameters relate to first visit at 15 weeks' gestation, and results are numbers (percentages)

Variables	Development dataset (n=2129)			Local replication dataset (n=1067)		
	Uncomplicated (n=1351)	Complicated (n=778)	Risk ratio or mean difference	Uncomplicated (n=677)	Complicated (n=390)	Risk ratio or mean difference
Potentially improvable factors						
Decreased risk of uncomplicated pregnancy:						
Mean (SD) body mass index	25.0 (4.5)	26.7 (5.9)	-1.7 (-2.2 to -1.3)	24.9 (4.9)	26.9 (6.5)	-2.0 (-2.7 to -1.2)
Mean blood pressure (mm Hg):						
Systolic	107 (10)	111 (11)	-4 (-5 to -3)	106 (10)	110 (10)	-4 (-5 to -3)
Diastolic	64 (7)	67 (9)	-3 (-4 to -2)	64 (8)	66 (8)	-3 (-4 to -2)
Mean (SD) maternal pulse	76 (11)	79 (11)	-3 (-4 to -2)	76 (11)	80 (11)	-4 (-5 to -2)
Current smoking	119 (9)	109 (14)	0.81 (0.71 to 0.92)	70 (10)	59 (15)	0.84 (0.71 to 0.99)
Any alcohol use in pregnancy	672 (50)	352 (45)	1.07 (1.00 to 1.14)	328 (48)	185 (47)	1.01 (0.93 to 1.11)
Misuse of drugs in first trimester*	161 (12)	127 (16)	0.86 (0.78 to 0.96)	96 (14)	65 (17)	0.93 (0.81 to 1.07)
Unemployed or sickness beneficiary	103 (8)	102 (13)	0.77 (0.67 to 0.89)	60 (9)	44 (11)	0.90 (0.76 to 1.07)
Increased risk of uncomplicated pregnancy:						
Prepregnancy intake:						
Fruit ≥1-2/week	1241 (92)	635 (85)	1.35 (1.17 to 1.55)	618 (91)	346 (89)	1.12 (0.94 to 1.33)
Fruit ≥3-4/day	337 (25)	124 (17)	1.19 (1.11 to 1.27)	184 (27)	62 (16)	1.25 (1.14 to 1.36)
Leafy vegetables ≥1-2/day	718 (53)	321 (43)	1.17 (1.09 to 1.24)	362 (54)	159 (41)	1.20 (1.10 to 1.32)
Mean (SD) hours worked in paid employment/week	32.3 (15.8)	29.7 (17.3)	2.5 (1.0 to 4.0)	32.2 (16.4)	30.5 (17.0)	1.7 (-0.4 to 3.8)
Non-modifiable factors						
Decreased risk of uncomplicated pregnancy:						
Participant was born preterm	59 (4)	56 (7)	0.79 (0.66 to 0.95)	30 (5)	28 (7)	0.80 (0.62 to 1.04)
Mean (SD) lower socioeconomic index	42 (17)	39 (17)	3 (2 to 5)	41 (16)	39 (16)	2 (0 to 4)
Hypertension during oral contraceptive pill use before pregnancy	14 (1)	23 (3)	0.59 (0.39 to 0.90)	7 (1)	12 (3)	0.58 (0.32 to 1.04)
Duration of sex without contraception before pregnancy ≥3 months	458 (34)	312 (40)	0.90 (0.84 to 0.97)	247 (37)	166 (43)	0.91 (0.83 to 1.00)
Family history of any hypertensive complications in pregnancy	243 (18)	184 (23.9)	0.87 (0.80 to 0.96)	120 (18)	97 (25)	0.84 (0.74 to 0.96)
Family history of any diabetes	168 (12)	134 (17)	0.86 (0.77 to 0.96)	66 (10)	57 (15)	0.83 (0.70 to 0.98)
Gastroenteritis during pregnancy	57 (4)	57 (7)	0.78 (0.65 to 0.94)	39 (6)	30 (8)	0.88 (0.72 to 1.09)
Vaginal bleeding (more than spotting <15 weeks)	251 (19)	187 (24)	0.88 (0.81 to 0.96)	135 (20)	101 (26)	0.88 (0.78 to 0.99)
Currently using β ₂ agonist inhaler	130 (10)	114 (15)	0.82 (0.73 to 0.93)	62 (9)	46 (12)	0.90 (0.76 to 1.06)
Fetal abnormality present (20 weeks)	20 (2)	30 (4)	0.62 (0.44 to 0.87)	11 (2)	16 (4)	0.63 (0.40 to 1.00)
Mean (SD) uterine artery resistance index (20 weeks)	0.55 (0.09)	0.58 (0.10)	-0.03 (-0.04 to -0.02)	0.56 (0.09)	0.58 (0.10)	-0.03 (-0.04 to -0.01)
Increased risk of uncomplicated pregnancy:						
Primigravid	1027 (76)	558 (72)	1.09 (1.01 to 1.18)	497 (73)	288 (74)	0.99 (0.90 to 1.10)
Immigrant partner	342 (26)	152 (20)	1.13 (1.05 to 1.21)	169 (25)	80 (21)	1.10 (0.99 to 1.21)

*Use of marijuana, cocaine/crack, amphetamines, 3,4 methylenedioxymethamphetamine, opiates, hallucinogens, and binge alcohol ≥6 units/session.

Table 5| Unadjusted comparisons on all variables in external confirmation dataset. Unless stated otherwise all parameters relate to first visit at 15 weeks' gestation, and results are numbers (percentages)

Variables	External confirmation dataset (n=2432)		
	Uncomplicated (n=1424)	Complicated (n=1008)	Risk ratio or mean difference
Potentially improvable factors			
Decreased risk of uncomplicated pregnancy:			
Mean (SD) body mass index	24.4 (3.9)	25.6 (4.8)	-1.14 (-1.50 to -0.78)
Mean blood pressure (mm Hg):			
Systolic	104 (10)	107 (11)	-3 (-4 to -2)
Diastolic	65 (7)	67 (8)	-2 (-3 to -2)
Mean (SD) maternal pulse	77 (10)	78 (10)	-1 (-1 to 0)
Current smoking	134 (9)	116 (12)	0.91 (0.80 to 1.02)
Any alcohol use in pregnancy	1110 (78)	790 (78)	0.99 (0.91 to 1.07)
Misuse of drugs in first trimester*	574 (40)	466 (46)	0.90 (0.84 to 0.97)
Unemployed or sickness beneficiary	80 (6)	71 (7)	0.90 (0.77 to 1.05)
Increased risk of uncomplicated pregnancy:			
Prepregnancy intake:			
Fruit ≥1-2/week	1334 (94)	928 (92)	1.11 (0.96 to 1.29)
Fruit ≥3-4/day	343 (24)	205 (20)	1.09 (1.01 to 1.18)
Leafy vegetables ≥1-2/day	294 (21)	184 (18)	1.06 (0.98 to 1.15)
Mean (SD) hours worked in paid employment/week	33.8 (13.8)	32.4 (14.5)	1.3 (0.1 to 2.4)
Non-modifiable factors			
Decreased risk of uncomplicated pregnancy:			
Participant was born preterm	52 (4)	35 (4)	1.02 (0.85 to 1.21)
Mean (SD) lower socioeconomic index	45 (17)	42 (16)	3 (1 to 4)
Hypertension during oral contraceptive pill use before pregnancy	8 (1)	21 (2)	0.47 (0.26 to 0.85)
Duration of sex without contraception before pregnancy ≥3 months	559 (39)	393 (39)	1.00 (0.94 to 1.07)
Family history of any hypertensive complications in pregnancy	215 (15)	196 (19)	0.87 (0.79 to 0.97)
Family history of any diabetes	193 (14)	144 (14)	0.97 (0.88 to 1.08)
Gastroenteritis during pregnancy	36 (3)	35 (4)	0.86 (0.68 to 1.09)
Vaginal bleeding (more than spotting <15 weeks)	282 (20)	251 (25)	0.88 (0.81 to 0.96)
Currently using β ₂ agonist inhaler	75 (5)	66 (7)	0.90 (0.77 to 1.06)
Fetal abnormality present (20 weeks)	12 (1)	9 (1)	0.97 (0.67 to 1.41)
Mean (SD) uterine artery resistance index (20 weeks)	0.57 (0.10)	0.58 (0.11)	-0.02 (-0.02 to -0.01)
Increased risk of uncomplicated pregnancy:			
Primigravid	1165 (82)	796 (79)	1.08 (0.99 to 1.18)
Immigrant partner	277 (20)	197 (20)	1.00 (0.92 to 1.08)

*Use of marijuana, cocaine/crack, amphetamines, 3,4 methylenedioxymethamphetamine, opiates, hallucinogens, and binge alcohol ≥6 units/session.

Table 6 | Unadjusted risk ratios for variables associated with subsequent uncomplicated pregnancy remaining significant in log probability regression model

Variables	Risk ratio (95% CI)		
	Development dataset (n=2129)	Local replication dataset (n=1063)	External confirmation dataset (n=2432)
Potentially improvable			
Decreased risk of uncomplicated pregnancy/detrimental:			
Body mass index at 15 weeks' gestation:			
≥30 (v <25)	0.71 (0.63 to 0.79)	0.66 (0.56 to 0.78)	0.74 (0.65 to 0.84)
25-29.9 (v <25)	0.90 (0.83 to 0.97)	0.86 (0.77 to 0.96)	0.87 (0.80 to 0.94)
Mean blood pressure (per 5 mmHg increase) at 15 weeks' gestation:			
Diastolic	0.93 (0.91 to 0.94)	0.93 (0.91 to 0.96)	0.92 (0.91 to 0.94)
Systolic	0.94 (0.93 to 0.96)	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)
Misuse of drugs in first trimester*	0.86 (0.78 to 0.96)	0.93 (0.81 to 1.07)	0.90 (0.84 to 0.97)
Increased risk of uncomplicated pregnancy/ beneficial:			
Prepregnancy fruit intake at least 3 times/day	1.19 (1.11 to 1.27)	1.25 (1.14 to 1.36)	1.09 (1.01 to 1.18)
Hours worked in paid employment (per 8 hours increase) at 15 weeks' gestation	1.03 (1.01 to 1.04)	1.02 (1.00 to 1.04)	1.02 (1.01 to 1.04)
Non-modifiable			
Decreased risk of uncomplicated pregnancy/detrimental:			
Maternal socioeconomic index at 15 weeks' gestation:			
1st (bottom) fifth (v 5th (top) fifth):	0.84 (0.75 to 0.93)	0.95 (0.81 to 1.11)	0.83 (0.74 to 0.92)
2nd fifth (v top fifth)	0.86 (0.77 to 0.96)	0.91 (0.77 to 1.07)	0.88 (0.80 to 0.98)
3rd fifth (v top fifth)	0.97 (0.88 to 1.06)	1.07 (0.92 to 1.23)	0.88 (0.79 to 0.97)
4th fifth (v top fifth)	1.02 (0.93 to 1.12)	1.06 (0.92 to 1.23)	0.93 (0.85 to 1.03)
Hypertension with oral contraceptive pill use before pregnancy	0.59 (0.39 to 0.90)	0.58 (0.32 to 1.04)	0.47 (0.26 to 0.85)
Family history of any hypertensive disorder in pregnancy	0.87 (0.80 to 0.96)	0.84 (0.74 to 0.96)	0.87 (0.79 to 0.97)
Vaginal bleeding (more than spotting) in pregnancy before 15 weeks' gestation	0.88 (0.81 to 0.96)	0.88 (0.78 to 0.99)	0.88 (0.81 to 0.96)
Mean uterine artery resistance index (per 0.1 increase) at 20 weeks' gestation	0.91 (0.88 to 0.94)	0.91 (0.87 to 0.95)	0.95 (0.92 to 0.98)

*Use of marijuana, cocaine/crack, amphetamines, 3,4 methylenedioxymethamphetamine, opiates, hallucinogens, and binge alcohol ≥6 units/session.