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Full length article

Using simple clinical and ultrasound variables to develop a model to predict first trimester pregnancy viability

Maya Al-Memar [a,1], Hanine Fourie [a,1], Thibaut Vaulet [b], Kim Lawson [c], Shabnam Bobdiwala [a], Srdjan Saso [a], Jessica Farren [a], Maria Pipi [a], Bart De Moor [b], Catriona Stalder [a], Phillip Bennett [a], Dirk Timmerman [c,d], Tom Bourne [a,c,d,e,*]

[a] Tommy's National Early Miscarriage Research Centre, Queen Charlotte's & Chelsea Hospital, Imperial College, Du Cane Road, London W12 0HS, UK
[b] ESAT-STADIUS, Stadius Centre for Dynamical Systems, Signal Processing and Data Analytics, Kasteelpark Arenberg 10 -box2446, 3001 Leuven, Belgium
[c] Queen Charlotte's and Chelsea Hospital, Imperial College, London, UK
[d] KU Leuven, Department of Development and Regeneration, Leuven, Belgium
[e] Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium

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ABSTRACT

Introduction: Early prediction of pregnancies destined to miscarry will allow couples to prepare for this common but often unexpected eventuality, and clinicians to allocate finite resources. We aimed to develop a prediction model combining clinical, demographic, and sonographic data as a clinical tool to aid counselling about first trimester pregnancy outcome.

Material and methods: This is a prospective, observational cohort study conducted at Queen Charlotte's and Chelsea Hospital, UK from March 2014 to May 2019. Women with confirmed intrauterine pregnancies between 5 weeks and their dating scan (11–14 weeks) were recruited. Participants attended serial ultrasound scans in the first trimester and at each visit recorded symptoms of vaginal bleeding, pelvic pain, nausea and vomiting using validated scoring tools. Pregnancies were followed up until the dating scan (11–14 weeks). Univariate and multivariate analyses were performed to predict first trimester viability. A model was developed with multivariable logistic regression, variables limited by feature selection, and bootstrapping with multiple imputation was used for internal validation.

Results: 1403 women were recruited and after exclusions, data were available for 1105. 160 women (14.5 %) experienced first trimester miscarriage and 945 women (85.5 %) had viable pregnancies at 11–14 weeks' gestation. The average gestational age at the initial visit (calculated from the menstrual dates) was 7 + 1 weeks (+/-12.2 days). A multivariable logistic regression model was developed to predict first trimester viability and included the variables: mean gestational sac diameter, presence of fetal heart pulsations, difference in gestational age from last menstrual period and from mean sac diameter on ultrasonography, current folic acid usage and maternal age. The model demonstrated good performance (optimism-corrected area under curve (AUC) 0.84, 95 % CI 0.81–0.87; optimism-corrected calibration slope 0.969).

Conclusion: We have developed and internally validated a model to predict first trimester viability with good accuracy prior to the 11–14 week dating scan, which now needs to be externally validated prior to clinical use.

Introduction

Pelvic pain and vaginal bleeding are common symptoms in early pregnancy and often reasons for clinical assessment [1]. With the development of sensitive home pregnancy testing kits, more women are attending for ultrasound scans at earlier stages of pregnancy [2] which

Abbreviations: PUV, pregnancy of uncertain viability; LMP, last menstrual period; GA, gestational age; CRL, crown rump length; MSD, mean sac diameter; FH, fetal heartbeat; OR, odds ratio; AUC, Area under the curve of the receiver operator characteristics curve; CI, confidence interval.

* Corresponding author at: Tommy's National Early Miscarriage Research Centre, Queen Charlotte's & Chelsea Hospital, Imperial College, Du Cane Road, London W12 0HS, UK.
E-mail address: t.bourne@imperial.ac.uk (T. Bourne).

[1] Joint first authors.

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are commonly inconclusive, with a high proportion of pregnancies classified as 'pregnancies of uncertain viability' (PUV) [2]. Even in those where a fetal heartbeat is detected, the risk of subsequent miscarriage is 12 % [3]. Following an initial visit, women are often left uncertain, which can cause great anxiety [4].

Prediction of first trimester viability has been attempted to allow couples to psychologically prepare for a poor outcome, aid clinical counselling, and enable resource allocation to pregnancies deemed at risk of miscarriage. Variables including demographics, clinical symptoms, ultrasound data and serum hormone levels, have been combined to develop multivariable prediction models [5–12].

Current models have not been applied clinically due to several limitations. A recent large study of 10,060 singleton pregnancies aimed to develop a multivariable prediction model for viability [13]. However, in this study, ultrasonography was performed at a specific gestational age in pregnancies conceived using in vitro fertilization (day 27–29 after embryo transfer) and so may not be generalizable [13]. Another logistic regression model to predict viability in PUV has been developed and externally validated [7,8]. One limitation of this study is that the initial model was built using older definitions of PUV [14], and validated combining both old and new definitions of PUV [8]. The change in the diagnostic criteria of miscarriage has affected a number of these studies [5,6]. Diagnostic criteria for miscarriage became more conservative in 2011 to reduce the risk of a false positive diagnosis of miscarriage- the size cut-off for crown-rump-length (CRL) without heartbeat increased from 6 to 7 mm, and for gestation sac with no fetal pole from 20 mm to 25 mm [15]. Studies also differ in their inclusion and exclusion criteria, with some attempting to predict viability in PUVs [5,7,8] and some after an initial viable pregnancy [12,13,16,17]. Models have also included different subtypes of PUV [5] and final outcomes have varied [6,18–20].

We aimed to develop a new model to predict first trimester viability (at the time of the 11–14 week dating ultrasound scan) using a multivariable strategy incorporating clinical, demographic, and ultrasound data. We have used updated definitions of PUV and miscarriage and have developed a model that can be applied to all patients with an intrauterine pregnancy on ultrasound scan.

Materials and methods

Study design

This was a prospective, observational cohort study based at Queen Charlotte's and Chelsea Hospital, London, between March 2014 and May 2019. All participants provided written informed consent. Any patient attending the early pregnancy unit with a confirmed single intrauterine pregnancy on ultrasonography aged 16–50 years who were able to provide informed consent were eligible for recruitment to the study. A detailed questionnaire was completed. Folic acid use during pregnancy (yes/no) was recorded. The last menstrual period (LMP) was recorded, and a participant's certainty of this date was recorded using a scale scored from 0 (uncertain) to 10 (very certain) [21]. Participants were also asked about their symptoms using validated symptom scores at each visit [21–23]. Discrepancy in gestational age (GA) was examined at the initial visit. Expected gestational age was based on the last menstrual period. For estimated gestational age from ultrasound we used a formula incorporating the embryo crown-rump length (CRL) measurement and/or mean sac diameter (MSD) measurements if no fetal pole was visible. The equation for GA from CRL was as per Robinson et al. [24]. GA was derived from MSD with the equation MSD (mm) + 30 [25].

On average, participants were seen between two and five times in the first trimester. This was more than standard clinical practice, where patients with PUV would on average have two visits to the early pregnancy unit. Serial ultrasound scans were performed until the routine first trimester dating scan at 11–14 weeks' gestation. Ultrasonography measurements including the MSD, mean yolk sac diameter and CRL were taken at each visit. Pregnancy outcomes (first trimester miscarriage or viable pregnancy) were collected. Diagnosis of miscarriage was based on strict criteria [14]. This study is reported according to the TRIPOD guidelines (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) (Appendix 5) [26].

Statistical analysis

The endpoint of the study was defined as first trimester viability at the time of the dating scan. In addition to miscarriage being an important clinical entity to predict, this endpoint facilitated the development of a valid model due to the high number of miscarriage cases. Most women with a viable pregnancy at 11–14 weeks had an eventual live-birth, but the sample size was not sufficient to predict later complication such as second trimester miscarriage or preterm birth. For each patient we selected the first scan demonstrating an intrauterine pregnancy (PUV or viable pregnancy). A restricted set of potential predictors was first defined by expert knowledge and previously published studies [5,19] to lower the risk of overfitting the data [27]. These are defined in Table 2. The variable MSD*FH is an interaction term combining the presence of a fetal heartbeat (FH) and MSD measurement [19]. It is derived by multiplying the MSD with the binary indicator FH (0 if FH absent, or 1 if FH present). Comparison of the cohort characteristics in the outcome groups was assessed with the Student's *t*-test for continuous variables and the chi-square test for binary or categorical variables.

Univariate analysis

Univariate logistic regression was used to assess the association between each potential variable and first trimester viability. Odd Ratios (OR) with 95 % confidence intervals (CI) and corresponding p-values are reported. Predictive performance of each individual variable was estimated with optimism-corrected area under the curve (AUC) of the receiver operating characteristics (ROC) curve with 95 % CI.

Multivariable models

Multivariable logistic regression was used to build two predictive models for first trimester viability. The first one included all the predefined variables, irrespective of their univariate performance, aiming to maximize performance. The minimal sample size was determined with the pmsampsize R package ([28] with a prevalence of miscarriage of 0.15, a targeted AUC of 0.8 and an initial number of variables of 17, resulting in a sample size of 930 patients, including 140 miscarriage cases.

To reduce the number of variables to facilitate ease of clinical use, a second model was developed using stability selection within bootstrap imputation (BI-SS) ([29]), a robust feature selection method. The discrimination ability of the models was estimated with the optimism-corrected AUC (and 95 % CI) and the calibration was estimated with the optimism-corrected calibration slope and calibration curves.

Performance of the model was assessed on the entire data set, and also on a subset of patients who had ultrasound assessment for reassurance without any symptoms (n = 298) and those with an uncertain LMP (n = 166).

Internal validation

The enhanced bootstrap procedure [27,30] was used as internal validation instead of the traditional training-test sets approach to take advantage of the whole dataset during the modelling process. Testing a model performance with the same data used to develop it naturally produces optimistic estimations, which are referred here as apparent metrics. To account for this effect, optimism corrected metrics, i.e., optimism-corrected AUC and optimism-corrected calibration slopes, were used. These adjusted metrics are more likely to reflect the

Table 1
Table describing the cohort characteristics of the study population.

	MISCARRIAGE (N = 160)	VIABLE (N = 945)	TOTAL (N = 1105)	P VALUE
MATERNAL AGE				< 0.001
- MEAN (SD)	34.8 (5.3)	33.0 (5.2)	33.3 (5.2)	
- RANGE	22.0–46.0	17.0–53.0	17.0–53.0	
MATERNAL ETHNICITY				0.531
- CAUCASIAN	113 (70.6 %)	642 (68.0 %)	755 (68.4 %)	
- BLACK	15 (9.4 %)	90 (9.5 %)	105 (9.5 %)	
- ASIAN	15 (9.4 %)	130 (13.8 %)	145 (13.1 %)	
- MIXED	8 (5.0 %)	32 (3.4 %)	40 (3.6 %)	
- OTHER	9 (5.6 %)	50 (5.3 %)	59 (5.3 %)	
- MISSING	0	1	1	
BMI (KG/M^2)				0.014
- MEAN (SD)	25.8 (5.7)	24.6 (5.0)	24.8 (5.1)	
- RANGE	17.3–49.6	15.8–46.4	15.8–49.6	
- MISSING	32	15	47	
PREVIOUS MISCARRIAGES				0.274
− 0	74 (46.5 %)	482 (51.0 %)	556 (50.4 %)	
− 1	49 (30.8 %)	297 (31.4 %)	346 (31.3 %)	
− 2	21 (13.2 %)	118 (12.5 %)	139 (12.6 %)	
− 3 +	15 (9.4 %)	48 (5.1 %)	63 (5.7 %)	
-MISSING	1	0	1	
CERTAINTY OF LMP				0.694
- MEAN (SD)	9.8 (0.6)	9.8 (0.6)	9.8 (0.6)	
- RANGE	7.0–10.0	7.0–10.0	7.0–10.0	
SMOKING STATUS				0.251
- NO	139 (88.5 %)	858 (91.4 %)	997 (91.0 %)	
- YES	18 (11.5 %)	81 (8.6 %)	99 (9.0 %)	
- MISSING	3	6	9	
FOLIC ACID (YES/NO)				< 0.001
- NO	21 (13.4 %)	53 (5.6 %)	74 (6.7 %)	
- YES	136 (86.6 %)	890 (94.4 %)	1026 (93.3 %)	
-MISSING	3	2	5	
PARITY				0.566
− 0	77 (48.4 %)	486 (51.4 %)	563 (51.0 %)	
− 1	60 (37.7 %)	333 (35.2 %)	393 (35.6 %)	
− 2+	22 (13.8 %)	126 (13.3 %)	148 (13.4 %)	
- MISSING	1	0	1	
GRAVIDITY				0.183
− 1	31 (19.5 %)	225 (23.8 %)	256 (23.2 %)	
− 2+	128 (80.5 %)	720 (76.2 %)	848 (76.8 %)	
- MISSING	1	0	1	
CONCEPTION				0.213
- IVF	5 (3.2 %)	52 (5.5 %)	57 (5.2 %)	
-SPONTANEOUS	153 (96.8 %)	886 (94.5 %)	1039 (94.8 %)	
-MISSING	2	7	9	
PROGESTERONE USE				0.956
-YES	13 (8.2 %)	79 (8.4 %)	92 (8.3 %)	
–NO	145 (91.8 %)	866 (91.6 %)	1011 (91.7 %)	
-MISSING	2	0	2	
REASON FOR FIRST SCAN				0.098
-BLEEDING ONLY	27 (17.0 %)	167 (17.8 %)	194 (17.7 %)	
-PAIN ONLY	31 (19.5 %)	227 (24.3 %)	258 (23.6 %)	
-PAIN AND BLEEDING	44 (27.7 %)	242 (25.9 %)	286 (26.1 %)	
-REASSURANCE	54 (34.0 %)	244 (26.1 %)	298 (27.2 %)	
-HYPEREMESIS	3 (1.9 %)	41 (4.4 %)	44 (4.0 %)	
-OTHER	0 (0.0 %)	15 (1.6 %)	15 (1.4 %)	
MISSING	1	9	10	
WORST BLEEDING SCORE				0.648
− 0	88 (55.3 %)	525 (56.6 %)	613 (56.4 %)	
− 1	36 (22.6 %)	237 (25.6 %)	273 (25.1 %)	
− 2	27 (17.0 %)	122 (13.2 %)	149 (13.7 %)	
− 3	4 (2.5 %)	27 (2.9 %)	31 (2.9 %)	
− 4	4 (2.5 %)	16 (1.7 %)	20 (1.8 %)	
- MISSING	1	18	19	
PUQE SCORE				< 0.001
- MEAN (SD)	3.8 (1.7)	4.5 (2.3)	4.4 (2.2)	
- RANGE	3.0–10.0	3.0–15.0	3.0–15.0	
- MISSING	9	63	72	
FH PRESENCE (YES/NO)				< 0.001
- NO	108 (72.0 %)	274 (29.7 %)	382 (35.6 %)	
- YES	42 (28.0 %)	648 (70.3 %)	690 (64.4 %)	
- MISSING	10	23	33	
CRL (MM)				< 0.001
- MEAN (SD)	2.0 (3.7)	9.2 (11.3)	8.2 (10.8)	
- RANGE	0.0–18.7	0.0–70.4	0.0–70.4	
- MISSING	2	17	19	
MSD (MM)				< 0.001
- MEAN (SD)	11.5 (7.8)	19.3 (11.6)	18.1 (11.4)	
- RANGE	0.0–56.7	0.0–68.9	0.0–68.9	
- MISSING	3	51	54	
MYSD (MM)				0.099
- MEAN (SD)	2.3 (3.2)	2.6 (1.4)	2.6 (1.8)	
- RANGE	0.0–34.0	0.0–9.7	0.0–34.0	
- MISSING	26	119	145	
GA BY LMP (DAYS)				0.043
- MEAN (SD)	48.2 (11.7)	50.3 (12.2)	50.0 (12.2)	
- RANGE	20.0–89.0	18.0–96.0	18.0–96.0	
GA DIFFERENCE (LMP-MSD) (DAYS)				< 0.001
- MEAN (SD)	6.7 (9.8)	0.3 (7.9)	1.3 (8.5)	
- RANGE	−51.7–44.5	−35.0–49.3	−51.7–49.3	
- MISSING	5	52	57	

SD = standard deviation, BMI = body mass index, LMP = last menstrual period, PUQE = pregnancy unique quantification of emesis score, FH = fetal heart, CRL = crown rump length, MSD = mean sac diameter, MYSD = mean yolk sac diameter, GA = gestational age. p-values correspond to independent Student t-tests for continuous variables (with equal variance, except for CRL: unequal variance) and chi-square tests for categorical and binary variables.

performance that would be observed on novel data [31]. To combine the enhanced bootstrap with the multiple imputation framework, we opted for single imputation nested in the bootstrap procedure [32]. Practically, we sampled with replacement 2000 datasets from the original data and then performed a single imputation on each bootstrap dataset. All analyses have been performed with R 3.6.0 (R Core Team 2017) [33].

Table 2
Univariate analysis on all potential variables predicting first trimester viability.

	OR (95 % CI)	p-values	AUC bootstrap corrected
CHARACTERISTICS			
Maternal Age	0.93 (0.90–0.97)	<0.0001	0.602 (0.552-0.652)
Maternal ethnicity			0.509
Intercept	6.00	<0.001	(0.468–0.549)
Asian	(3.47–10.36)	0.35	
Caucasian	1.44	0.86	
Mixed	(0.67–3.10)	0.40	
Others	0.95 (0.53–1.70)	0.87	
	0.67 (0.26–1.72)		
	0.93 (0.38–2.27)		
BMI	0.97 (0.94–1.00)	0.09	0.572 (0.528—0.616)
Number of previous miscarriages	0.87 (0.76–1.00)	0.05	0.529 (0.479–0.579)
Folic acid usage (yes or no)	2.63 (1.54–4.49)	<0.001	0.554 (0.517–0.591)
Smoking status (yes or no)	0.71 (0.41–1.22)	0.21	0.516 (0.487–0.545)
SONOGRAPHIC			
CRL (mm)	1.19 (1.13–1.25)	<0.0001	0.737 (0.703–0.771)
MSD (mm)	1.10 (1.07–1.12)	<0.0001	0.726 (0.687–0.765)
FH (presence or absence)	6.12 (4.18–8.98)	<0.0001	0.715 (0.677–0.752)
MSD*FH *interaction effect between MSD and FH*	1.23 (1.15–1.31)	<0.0001	0.783 (0.764–0.802)
Worst bleeding score at initial scan	0.93 (0.78–1.11)	0.42	0.502 (0.453—0.551)
PUQE score	1.23 (1.10–1-37)	<0.0001	0.630 (0.592–0.668)
GA difference (days) (LMP vs MSD)	0.91 (0.89–0.93)	<0.0001	0.735 (0.698–0.772)
GA by LMP (days)	1.02 (1.00–1.03)	0.04	0.549 (0.499–0.598)

CI = Confidence interval, AUC = Area under curve, BMI = Body mass index, CRL = crown rump length, MSD = mean sac diameter, FH = fetal heart, PUQE = pregnancy unique quantification of emesis, GA = gestational age, LMP = last menstrual period.

Ethics statement

The study was approved by NHS National Research Ethics Service (NRES) Riverside Committee London (REC 14/LO/0199) and NHS North East – Newcastle and North Tyneside Research Ethics Committee (17/NE/0121).

Results

1757 eligible women were invited to participate, and 1403 participants were recruited (Fig. 1). Those who underwent termination of pregnancy ($n = 28$), withdrew from the study ($n = 7$), and were lost to follow up ($n = 40$) were excluded from the analysis. Women whose LMP was unknown ($n = 57$) or not accurate (certainty score less than 7/10) were also excluded ($n = 166$). The final analysis ($n = 1105$) compared first trimester miscarriages (n = 160) with viable control pregnancies (n = 945) (Fig. 1).

Univariate analysis of demographic, clinical and ultrasound data variables

Table 1 represents the descriptive statistics for patient characteristics, first trimester symptoms and ultrasound variables for the 1105 patients. Patient characteristics that were different in the miscarriage and viable groups were maternal age (OR 0.93; 95 % CI 0.90–0.97) and current folic acid use (yes/ no) (OR 2.63; 95 % CI 1.54–4.49) (Table 2). A greater number of previous miscarriages was associated with an increased risk of subsequent miscarriage (OR 0.87; 95 % CI 0.76–1.00, $P = 0.05$). Higher PUQE scores were predictive of viability (OR 1.23; 95 % CI 1.1–1.37, P < 0001) but bleeding score was not (OR 0.93; 95 % CI 0.78—1.11). CRL (OR 1.19; 95 % CI 1.13–1.25), MSD (OR 1.10; 95 % CI 1.07–1.12), FH (OR 6.12; 95 % CI 4.18–8.98) and MSD*FH (OR 1.23; 95 % CI 1.15–1.31) were significant ultrasound-based predictors for viability ($P < 0.0001$).

Multivariable models

The first model (Model 1) including the whole set of predefined variables demonstrated an apparent AUC of 0.855 (95 % CI 0.826–0.883), and AUC of 0.837 (95 % CI 0.807–0.868) when corrected for optimism. The optimism-corrected calibration slope of this model was 0.943 (Table 3). Additional information is presented in Appendix 2.

After feature selection, a parsimonious model was built using maternal age, current folic acid use, the GA difference (LMP-MSD/CRL) and MSD*FH. This second model (Model 2) demonstrated similar discrimination performance (AUC 0.841; 95 % CI 0.811–0.871: optimism-corrected AUC 0.836; 95 % CI 0.806–0.866). The optimism-corrected calibration slope was 0.969 (Table 3). The corresponding calibration curves are reported in Supplementary Fig. 1 (Appendix 3). Performance of both models was overall reduced when applied to a small subset of the cohort with uncertain LMP (<7/10 certainty), which included 21 miscarriages and 145 viable pregnancies (Model 1: AUC 0.753; 95 % CI 0.647–0.858, Model 2: AUC 0.749; 95 % CI 0.639–0.859). The performance was also reduced when applied to a subset of patients with no symptoms, which included 54 miscarriages and 244 viable pregnancies (Model 1: AUC 0.81 (95 % CI 0.75–0.87), Model 2: AUC 0.81 (95 % CI 0.75–0.87). OR and p-values based on the regression coefficients of this parsimonious model are reported in Table 4.

Discussion

We have developed a simple tool using five variables (maternal age, folic acid use, gestational age by LMP, the difference in GA between LMP and MSD, and MSD in combination with FH presence (MSD*FH)) that has demonstrated good performance in predicting first trimester viability.

The objective of this study was development of a prediction model, but interesting observations about biological associations with miscarriage have also been highlighted. In the univariate analysis, modifiable risk factors for miscarriage were BMI and folic acid use. Large cohort studies have previously identified obesity as a risk factor for miscarriage [34,35] and we echo this finding. These associations underpin the recommendation that all couples experiencing a miscarriage should have access to a specialist graded package of care to address modifiable risk factors [36]. The World Health Organization recommends folic acid supplementation prior to conception until 12 weeks' gestation to reduce the incidence of neural tube defects (NTD) [37,38]. The impact on first trimester miscarriage remains controversial. Low plasma folate levels increase the incidence of miscarriage [39]. However a large population based study did not show a difference in miscarriage between women who were taking folic acid supplementation and those who did not [40]. Other studies have shown an association between lower folic acid intake and miscarriage [41–43]. Another possible explanation for this association is that folic acid use is a surrogate for general health.

Overall, this model has clinical utility as it can accurately predict first trimester viability from an initial ultrasound assessment in the early first trimester. The reduced model has excellent discrimination between outcomes that are subjectively difficult to predict. Previously published

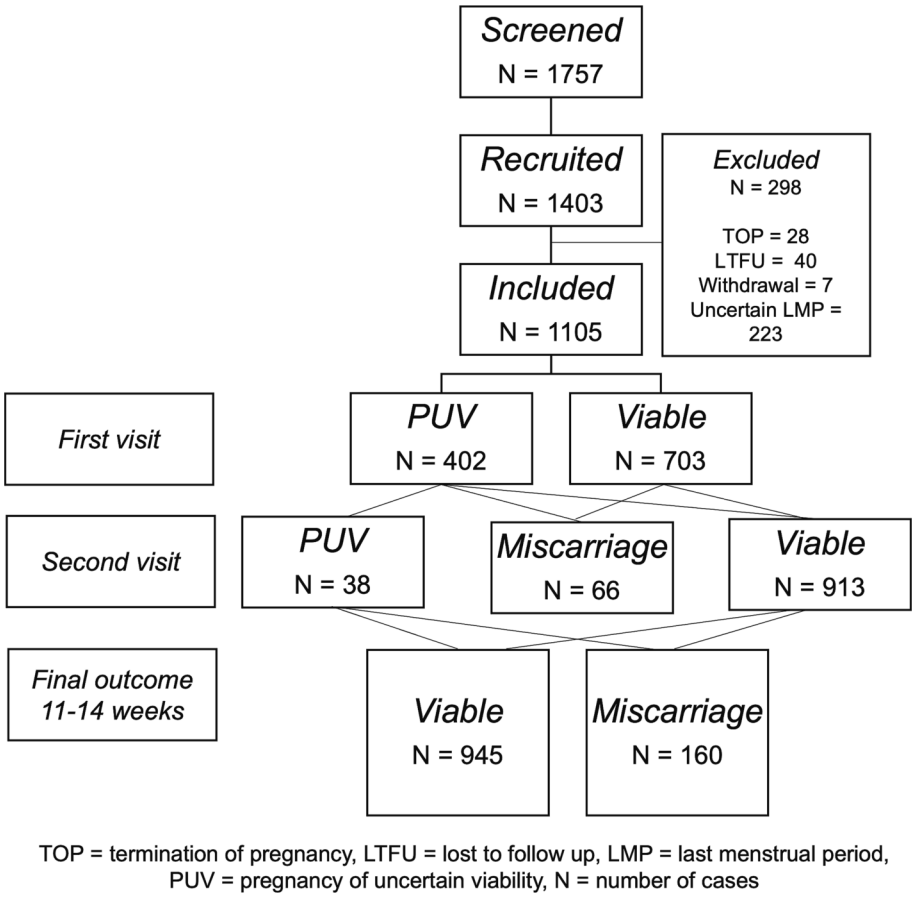

Fig. 1. Flowchart of study population The numbers of participants included in the study with pregnancy outcomes reported at the first visit, second visit and 11–14 weeks of pregnancy.

first trimester outcome prediction models report similar AUC metrics of 0.771 – 0.901 [6,8,19], but as these models are for different populations with old definitions of PUV, and different validation strategies, direct comparison is not possible.

The strengths of our study are the prospective design, well-characterized patient cohort and use of validated symptom scores. The simple nature of the model means it can be easily used to adjust the risk of miscarriage in all women with an ultrasound confirmed intrauterine pregnancy. The model use is not limited by a gestational age cut-off and can be applied to both PUV and viable intrauterine pregnancies in the first trimester. It has utility in allocating finite early pregnancy resources and in improving the patient's experience. Although it may not reduce psychological morbidity associated with uncertainty, it may benefit the patient with the provision of individualized counselling [44].

One limitation of our study is the need for women to recall with certainty their menstrual dates for the model to be applied. In our dataset, 233 cases were excluded as 15 % had an unknown LMP. The model demonstrated weaker performance in this cohort. However most women can recall their LMP with accuracy, e.g. in one study 81 % of women recalled their LMP within two days [45]. Another perceived limitation is the absence of a blood biomarker, such as beta hCG or progesterone, and fetal heart rate in the model. The addition of blood markers may have improved the ability of the model to discriminate between a viable pregnancy and miscarriage, but the aim of this study was to produce a simple clinical tool accessible to all early pregnancy care providers. Although a recent *meta*-analysis concluded that fetal heart rate is the best sonographic predictor of miscarriage [46], the addition of this variable would make the model unsuitable for women with a PUV which accounts for up to 20 % of early pregnancy assessments [7]. A large proportion of the population had no symptoms, but were motivated to participate in the study due to anxiety, previous poor pregnancy outcome or the altruism to aid better understanding of miscarriage. In this subgroup the model accuracy was reduced, but still good with an AUC of 0.81, suggesting applicability to a general early pregnancy population. The study acknowledges the limitation of testing a model on the same data used to develop it, and therefore presents metrics that have been corrected for this possible 'optimism'.

Further external validation is now required, and then individual units and clinicians will then have to determine how the model will be useful to their service. Appropriate risk thresholds depend on the clinical scenario and setting, and can only be employed clinically once a health economic analysis has also been performed [47]. However one strategy would be to discharge patients from early pregnancy care to antenatal care if they have a threshold for viability of more than 70 %, which equates to a 91.9 % chance of viability at 11–14 weeks (Appendix 4). A low threshold of viability may then lead to a recommendation for more intensive follow up and supportive care. This prediction of viability will be available via an accessible on-line calculator.

Conclusion

We have developed a model that enables accurate prognostication of first trimester outcome which is applicable to all confirmed intrauterine pregnancies, prior to the dating scan at 11–14 weeks. Our model uses the updated criteria for miscarriage diagnosis, which supersedes many pre-existing models. Use in the clinical setting may allow for better psychological preparedness when miscarriage is anticipated. Our model has identified strong modifiable predictors of miscarriage which supports recent petitions that all women experiencing miscarriage should qualify for specialist, supportive care [48].

Table 3
Multivariable models.

	Apparent	Corrected for optimism (bootstrap n = 2000)
Full Model 1		
AUC	0.855 (0.826–0.883)	0.837 (0.807–0.868)
Calibration Slope	1.013	0.943
Final Reduced Model 2		
AUC	0.841 (0.811–0.871)	0.836 (0.806–0.866)
Calibration Slope	1.007	0.969
Predictive performance of models on subset of cohort with uncertain LMP (21 miscarriages, 145 viable pregnancies)		
Full Model 1 AUC	0.771 (0.664–0.879)	0.753 (0.647–0.858)
Final reduced Model 2 AUC	0.770 (0.666–0.873)	0.749 (0.639–0.859)
Predictive performance of models on subset of cohort with no symptoms (54 miscarriages, 244 viable pregnancies)		
Full Model 1 AUC	0.83 (0.78–0.90)	0.81 (0.75–0.87)
Final reduced Model 2 AUC	0.83 (0.78–0.89)	0.81 (0.75–0.87)

Full model:
Formula:
FirstTrimesterOutcome ~ MaternalAge + MaternalEthnicity + BMI + X1sTMiscarriage + FolicAcid + SmokingStatus + MSD_trun * FH + CRL + PUQEscore + GAdiff_MSD_trun + WorstBleedingScore + GAbyLMP.
Reduced model:
Formula:
FirstTrimesterOutcome ~ MaternalAge + GAbyLMP + GAdiff_MSD_trun + FolicAcid + MSD_trun*FH.
AUC = area under curve.

Table 4
Odds ratios (with 95 % CI) from the reduced multivariable regression model.

	OR	*P*-values
Intercept	**85.71 (20.61–356.99)**	<0.0001
Maternal Age	0.90 (0.87—0.94)	<0.0001
GA difference (LMP vs MSD)	0.91 (0.89–0.94)	<0.0001
MSD	0.95 (0.912–0.99)	0.008
FH	0.24 (0.08–0.70)	0.009
Folic Acid	2.34 (1.25–4.38)	0.007
MSD:FH	1.21 (1.13–1.30)	<0.0001

OR = Odds ratio, GA = gestational age, LMP = last menstrual period, MSD = mean sac diameter, FH = fetal heart, CI = confidence interval.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] Bigrigg MA, Read MD. Management of women referred to early pregnancy assessment unit: care and cost effectiveness. BMJ 1991;302(6776):577–9.
[2] Bottomley C, Van Belle V, Mukri F, Kirk E, Van Huffel S, Timmerman D, et al. The optimal timing of an ultrasound scan to assess the location and viability of an early pregnancy. Hum Reprod 2009;24(8):1811–7.
[3] Hill LM, Guzick D, Fries J, Hixson J. Fetal loss rate after ultrasonically documented cardiac activity between 6 and 14 weeks, menstrual age. J Clin Ultrasound : JCU 1991;19(4):221–3.
[4] Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet 2021;397(10285):1658–67.
[5] Elson J, Salim R, Tailor A, Banerjee S, Zosmer N, Jurkovic D. Prediction of early pregnancy viability in the absence of an ultrasonically detectable embryo. Ultrasound Obstet Gynecol 2003;21(1):57–61.
[6] Lautmann K, Cordina M, Elson J, Johns J, Schramm-Gajraj K, Ross JA. Clinical use of a model to predict the viability of early intrauterine pregnancies when no embryo is visible on ultrasound. Hum Reprod 2011;26(11):2957–63.
[7] Bottomley C, Van Belle V, Pexsters A, Papageorghiou AT, Mukri F, Kirk E, et al. A model and scoring system to predict outcome of intrauterine pregnancies of uncertain viability. Ultrasound Obstet Gynecol 2011;37(5):588–95.
[8] Guha S, Van Belle V, Bottomley C, Preisler J, Vathanan V, Sayasneh A, et al. External validation of models and simple scoring systems to predict miscarriage in intrauterine pregnancies of uncertain viability. Hum Reprod 2013;28(11):2905–11.
[9] Bignardi T, Condous G, Kirk E, Van Calster B, Van Huffel S, Timmerman D, et al. Viability of intrauterine pregnancy in women with pregnancy of unknown location: prediction using human chorionic gonadotropin ratio vs. progesterone. Ultrasound Obstet Gynecol 2010;35(6):656–61.
[10] Choong S, Rombauts L, Ugoni A, Meagher S. Ultrasound prediction of risk of spontaneous miscarriage in live embryos from assisted conceptions. Ultrasound Obstet Gynecol 2003;22(6):571–7.
[11] Achiron R, Tadmor O, Mashiach S. Heart rate as a predictor of first-trimester spontaneous abortion after ultrasound-proven viability. Obstet Gynecol 1991;78(3 Pt 1):330–4.
[12] Oates J, Casikar I, Campain A, Muller S, Yang J, Reid S, et al. A prediction model for viability at the end of the first trimester after a single early pregnancy evaluation. Aust N Z J Obstet Gynaecol 2013;53(1):51–7.
[13] Li Q, Zhu J, Hua K. Effects of subchorionic hematoma on pregnancy outcome: a meta analysis. Zhonghua Yi Xue Za Zhi 2016;96(17):1383–5.
[14] Abdallah Y, Daemen A, Kirk E, Pexsters A, Naji O, Stalder C, et al. Limitations of current definitions of miscarriage using mean gestational sac diameter and crown-rump length measurements: a multicenter observational study. Ultrasound Obstet Gynecol 2011;38(5):497–502.
[15] Preisler J, Kopeika J, Ismail L, Vathanan V, Farren J, Abdallah Y, et al. Defining safe criteria to diagnose miscarriage: prospective observational multicentre study. BMJ 2015;351:h4579.
[16] Stamatopoulos N, Lu C, Casikar I, Reid S, Mongelli M, Hardy N, et al. Prediction of subsequent miscarriage risk in women who present with a viable pregnancy at the first early pregnancy scan. Aust N Z J Obstet Gynaecol 2015;55(5):464–72.
[17] Papaioannou GI, Syngelaki A, Maiz N, Ross JA, Nicolaides KH. Ultrasonographic prediction of early miscarriage. Hum Reprod 2011;26(7):1685–92.

[18] RPL TEGGo, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss. Human Reproduction Open. 2018; 2018(2).
[19] Bottomley C, Van Belle V, Kirk E, Van Huffel S, Timmerman D, Bourne T. Accurate prediction of pregnancy viability by means of a simple scoring system. Hum Reprod 2013;28(1):68–76.
[20] Falco P, Milano V, Pilu G, David C, Grisolia G, Rizzo N, et al. Sonography of pregnancies with first-trimester bleeding and a viable embryo: a study of prognostic indicators by logistic regression analysis. Ultrasound Obstet Gynecol 1996;7(3):165–9.
[21] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res 2011;63(Suppl 11):S240–52.
[22] Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990;97(8):734–9.
[23] Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. American journal of obstetrics and gynecology. 2002; 186(5 Suppl Understanding):S228-31.
[24] Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975;82(9):702–10.
[25] Butt K, Lim KI. Guideline No. 388-Determination of Gestational Age by Ultrasound. J. Obstet Gynaecol Canada 2019;41(10):1497–507.
[26] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. BMC Med 2015;13:1.
[27] Harrell FE. Regression Modeling. Strategies Springer; 2014.
[28] Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ 2020;368: m441.
[29] Long Q, Johnson BA. Variable selection in the presence of missing data: resampling and imputation. Biostatistics 2015;16(3):596–610.
[30] Efron BTRJ. An Introduction to the. Bootstrap: CRC Press; 1994.
[31] Wynants L, Collins G, Van Calster B. Key steps and common pitfalls in developing and validating risk models. BJOG 2017;124(3):423–32.
[32] Brand J, van Buuren S, le Cessie S, van den Hout W. Combining multiple imputation and bootstrap in the analysis of cost-effectiveness trial data. Stat Med 2019;38(2):210–20.
[33] Team RC. R: A Language and Environment for Statistical Computing Vienna R Foundation for Statistical Computing 2017.
[34] Feodor Nilsson S, Andersen PK, Strandberg-Larsen K, Nybo Andersen AM. Risk factors for miscarriage from a prevention perspective: a nationwide follow-up study. BJOG 2014;121(11):1375–85.
[35] Zhou Y, Li H, Zhang Y, Zhang L, Liu J, Liu J. Association of Maternal Obesity in Early Pregnancy with Adverse Pregnancy Outcomes: A Chinese Prospective Cohort Analysis. Obesity (Silver Spring, Md) 2019;27(6):1030–6.
[36] Coomarasamy A, Gallos ID, Papadopoulou A, Dhillon-Smith RK, Al-Memar M, Brewin J, et al. Sporadic miscarriage: evidence to provide effective care. Lancet 2021;397(10285):1668–74.
[37] Pei L, Wu J, Li J, Mi X, Zhang X, Li Z, et al. Effect of periconceptional folic acid supplementation on the risk of neural tube defects associated with a previous spontaneous abortion or maternal first-trimester fever. Hum Reprod 2019;34(8): 1587–94.
[38] Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet (London, England). 1991;338 (8760):131-7.
[39] George L, Mills JL, Johansson AL, Nordmark A, Olander B, Granath F, et al. Plasma folate levels and risk of spontaneous abortion. J Am Med Assoc 2002;288(15): 1867–73.
[40] Gindler J, Li Z, Berry RJ, Zheng J, Correa A, Sun X, et al. Folic acid supplements during pregnancy and risk of miscarriage. Lancet (London, England) 2001;358 (9284):796–800.
[41] Ahmadi R, Ziaei S, Parsay S. Association between Nutritional Status with Spontaneous Abortion. Int J Fertility Sterility 2017;10(4):337–42.
[42] Gaskins AJ, Rich-Edwards JW, Hauser R, Williams PL, Gillman MW, Ginsburg ES, et al. Maternal prepregnancy folate intake and risk of spontaneous abortion and stillbirth. Obstet Gynecol 2014;124(1):23–31.
[43] Hu CY, Yang XJ, Hua XG, Jiang W, Huang K, Chen HB, et al. Risk factors for spontaneous abortion from a prevention perspective in rural China: a population-based follow-up study. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2019:1-9.
[44] Lawson K, Bourne T, Bottomley C. Psychological impact of simple scoring system for predicting early pregnancy outcome in pregnancy of uncertain viability: randomized controlled trial. Ultrasound Obstet Gynecol 2023;61(5):624–31.
[45] Wegienka G, Baird DD. A comparison of recalled date of last menstrual period with prospectively recorded dates. Journal of women's health (2002). 2005;14(3):248-52.
[46] Pillai RN, Konje JC, Richardson M, Tincello DG, Potdar N. Prediction of miscarriage in women with viable intrauterine pregnancy-A systematic review and diagnostic accuracy meta-analysis. Eur J Obstet Gynecol Reprod Biol 2018;220: 122–31.
[47] Wynants L, van Smeden M, McLernon DJ, Timmerman D, Steyerberg EW, Van Calster B, et al. Three myths about risk thresholds for prediction models. BMC Med 2019;17(1):192.
[48] Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, et al. Recurrent miscarriage: evidence to accelerate action. Lancet 2021;397(10285):1675–82.