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ORIGINAL ARTICLE

Risk factors for miscarriage among women attending an early pregnancy assessment unit (EPAU): a prospective cohort study

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Abstract

Background Miscarriage is the most common adverse outcome in early pregnancy; however, high proportion of miscarriages are classified as unexplained. In addition, pregnant women attending early pregnancy assessment units might be more vulnerable.

Aims The purpose of this study was to explore the risk factors that might be associated with miscarriage among women attending an early pregnancy assessment unit (EPAU).

Methods A prospective cohort study was undertaken. The study was conducted on women attending an EPAU at a large, tertiary hospital. A detailed lifestyle questionnaire was completed. In addition, data from validated psychometric scales were collected. Participants were followed up to determine pregnancy outcome. The relative risk was calculated to estimate the probability of having a miscarriage for all independent variables.

Results A total sample of 293 women were included in this study. Well-established risk factors for miscarriage were found in this group including advanced maternal age and high-risk pregnancy (i.e. threatened miscarriage and recurrent miscarriage). In addition, lack of emotional wellbeing did contribute to an increased risk of miscarriage. Conversely, presenting with nausea or low-medium energy levels early in pregnancy were associated with a decreased risk of miscarriage. Finally, our results did not find any association between stressful life events, general health and lifestyle factors in this group.

Conclusions Our findings indicated that maternal, psychological and obstetric factors may have an influence on miscarriage among women attending an EPAU. The insight of a relationship between emotional wellbeing and miscarriage opens a window for prevention in this area.

Keywords Early pregnancy assessment unit · Emotional wellbeing · Miscarriage · Perceived stress · Pregnancy history

Introduction

Miscarriage is considered the most common adverse outcome in early pregnancy. It is defined as the spontaneous demise of a pregnancy from the time of conception until 24 weeks gestation [1]. It can be clinically classified as first-trimester miscarriage (within 13 weeks gestation) or second-trimester miscarriage (after 12 and before 24 completed weeks gestation) [1, 2]. Miscarriage is a public health issue that affects women all around the world. When a pregnancy loss is based on decreasing serum or urinary human chorionic gonadotropin (hCG or β-hCG), it is defined as biochemical pregnancy loss. The number of biochemical miscarriages are estimated to be at least 30% [3] When a miscarriage is confirmed by ultrasound or histology, it is defined as clinical miscarriage [1]. It is estimated that one out of four women will experience a clinically

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recognised miscarriage during the first trimester in their reproductive life [4] and less than 1% will experience a second-trimester miscarriage [5]. Approximately, 1% of couples trying to conceive will experience three or more consecutive miscarriages, also defined as a recurrent miscarriage [6].

Half of all miscarriages are attributed to chromosomal abnormalities and a high proportion of miscarriages are classified as unexplained [7]. Without a putative cause and without an available treatment, most pregnancy losses are considered unpreventable [8]. Consequently, identifying risk factors and effective interventions to prevent miscarriage has become a priority for both clinicians and researchers [9]. Well-documented risk factors include advanced maternal age, previous miscarriage, previous infertility and heavy smoking [10). Nevertheless, controversy remains when investigating the effect of lifestyles and psychological wellbeing as modifiable and preventable factors [11] as these studies were limited by their design and how they measured confounding and multifactorial variables [12]. For example, extremes of maternal weight, which are defined as a body max index (BMI) less than 18.5 kg/m^2 or above 25 kg/m^2, have been associated with an increased risk of miscarriage [13]; whereas other studies have not shown any association [14]. Similarly, caffeine intake and alcohol consumption have generally, but not consistently, been associated with an increased risk of miscarriage [14]. Other risk factors which have been explored in the literature are exercise, lifting more than 20 kg daily, work schedule and occupational status during pregnancy [10].

The psychological morbidity among women who experience miscarriage and their partners have been extensively studied worldwide [15]. However, the impact that antenatal maternal psychological distress might has on adverse obstetrics and foetal outcomes is less clear [16]. Evidence in this topic is controversial depending on the psychological stressor which is investigated (i.e. depression, anxiety, life events factors, stress at work, perceived stress, physiological stress) and the design of the study. For example, few studies found an association between depression or anxiety and risk of miscarriage [17]. While there are a considerable number of studies that reported an association between life events, work stressors or perceived stress and miscarriage [10, 18], others did not [19, 20]. Similarly, though much less investigated, some studies reported an increased risk of miscarriage after measuring physiologic stress factors (i.e. urinary cortisol or salivary alpha-amylase) [21], whereas others did not find any association [22].

The introduction of early pregnancy assessment units (EPAU) has improved the quality of antenatal care for women with complications in early pregnancy [23]. The most common reasons for attending EPAU are seeking reassurance of viability of the ongoing pregnancy among women with a history of pregnancy loss, but also those women who present with vaginal bleeding or pelvic pain [23]. Although several epidemiological studies have explored the association of risk factors and miscarriage in the general population of pregnant women [10, 14], to our knowledge, no studies have assessed the risk factor for this targeted group of women who attend the EPAU. Therefore, we carried out a prospective cohort study to determine the relationships between risk factors that might be associated with miscarriage among women attending an EPAU.

Methods

Study design

This prospective cohort study was conducted at Cork University Maternity Hospital, a large, tertiary maternity hospital with approximately 8000 deliveries annually. Eligible participants included pregnant women attending the EPAU in their first weeks of pregnancy, generally between 10 and 14 weeks of gestation. The EPAU is a custom designed unit in the hospital that provides care to pregnant women who present with complications in early pregnancy.

Recruitment and follow-ups

The EPAU is an appointment-only clinic from 8 a.m. to 1 p.m., Monday to Friday. Pregnant women were approached by the research midwife on randomly selected days ($n = 45$) from the beginning of April to the end of July in 2012. Upon agreement to participate, the women's age, gestation at recruitment, parity and marital status were determined from her obstetric case-notes. Women were then asked to complete a detailed self-completed lifestyle questionnaire. Weight and height were self-reported questions (i.e. what was your weight before you become pregnant? what is your height without shoes?). After filling the questionnaire in, participants returned the survey on site or by post in a stamped, addressed envelope. Women were followed up, whereby hospital records were reviewed after 20 weeks by the research midwife through to delivery in order to ascertain pregnancy outcome. Follow-ups were completed by the end of November 2012.

Outcome measure

Our primary outcome of interest was miscarriage. This was defined as any pregnancy loss which occurred before 24 weeks gestation in a foetus weighing less than 500 g [2].

Risk factors

This study explored the following potential risk factors for miscarriage: socioeconomic characteristics, past reproductive history, diet and lifestyle factors, physical activity and

partners' characteristics. They survey was developed through a review of the literature. For example, demographic questions reflected those collected by other national collections or census by the Central Statistics Office (CSO). Questions about diet and lifestyle factors were selected using the Pregnancy Risk Assessment Monitoring System (PRAMS)—Ireland [24]. The remaining sections were not collected using validated questionnaires. Nevertheless, all the questions were reviewed by a multidisciplinary team of experts in pregnancy loss. In addition, all the questions were reviewed by the Clinical Research Ethics Committee of the Cork Teaching Hospital to assess appropriateness. This study also included information on a range of traumatic events, e.g. loss of job, separation or divorce, serious accident or illness, death of someone close, previous miscarriage, stillbirth and death of a child, based on a list developed by Maconochie et al. [10]. Women were asked to indicate if they experienced a traumatic event in the last 12 months, more than 12 months ago or not at all.

In the context of this study, women were categorised as either at high or low risk for miscarriage. High risk was defined as a woman who presented to the clinic with a threatened miscarriage or/and a history of recurrent miscarriage, i.e. three or more consecutive miscarriages. Women who did not meet these criteria were defined as low risk for miscarriage. Confirmation of risk status was determined through review of the women's obstetric chart.

Psychometric scales were also used to assess women's psychological state during early pregnancy. The item perceived stress scale (PSS) developed by Cohen, Kamarck and Mermelstein was designed to measure the degree to which situations in one's life are appraised as stressful [25]. The PSS is not a diagnostic instrument, but intended to make comparisons of subjects' perceived stress related to current, objective events. In this study, the PSS-4 was used as a simple psychological instrument to comprehend and score general queries about relatively current levels of perceived stress. Using a 5-point Likert scale ranging from never to very often, women were asked to indicate how often feelings, thoughts or life situations were perceived as uncontrollable, unpredictable and stressful in the past month [25]. A total score ranging between 0 and 16 was obtained by summing across all four items, after appropriate items were reversed. Higher summary scores indicate greater perceived stress. The internal consistency in our study (Cronbach's alpha) was 0.70.

The RAND 36-Item Health Survey is one of the most widely used instruments to assess health-related quality of life [26]. It is comprised of eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional wellbeing, energy/fatigue, pain and general health perceptions [26]. It includes the same items than the SF-36 but with different scoring algorithm. In this study, the RAND-36 scale was used to calculate aggregate scores to measure participant's energy/fatigue balance and emotional wellbeing. Women were asked to report how often they had felt happy, tired, worn out, nervous, downhearted or sad over the past four weeks. Responses for energy/fatigue balance were measured on a 6-point scale ranging from 'all of the time' (score of 100) to 'none of the time' (score of zero). For example, a score of 100 represented high energy with no fatigue; therefore, a lower score of 40% suggests the participant is experiencing a loss of energy and is experiencing some fatigue [27]. The internal consistency (Cronbach's alpha) was 0.84. Responses for emotional balance were measured on a 6-point scale ranging from 'all of the time' (score of zero) to 'none of the time' (score of 100). The internal consistency (Cronbach's alpha) was 0.76. Higher summary scores indicate a more favourable state of emotional wellbeing.

Social support was evaluated using the Maternity Social Support Scale (MSS). This six-item scale measures support from the woman's spouse, family and their wider social network on a 5-point scale ranging from 'never' (score of one) to always (score of five). The total possible score was obtained by summing the response categories selected by the participants. Possible scores range from 6 to 30 points, with higher summary scores indicating higher levels of social support [28]. The internal consistency (Cronbach's alpha) was 0.63.

Finally, the Revised Life Orientation Test (LOT-R) is a measure of dispositional optimism. Studies indicate that having a positive outlook is beneficial for physical and psychological wellbeing and therefore has important health implications [29]. The scale assesses individual differences in generalised optimism versus pessimism. The LOT-R is a 10 item scale whereby women chose from a 5-point scale ranging from strongly disagree (score of zero) to strongly agree (score of 4). Higher summary scores are indicative of an optimistic rather than a pessimistic outlook. The internal consistency (Cronbach's alpha) was 0.77.

Statistical analysis

Cronbach's alpha was used to assess the internal consistency of the psychometric scales in the study [4]. The PSS-4 and the psychometric scales are not diagnostic instruments and no predetermined cutoff scores points have been differentiated. Instead, psychological scales were divided into equally weighted tertiles (low, medium and high scores). BMI was calculated using the self-reported height and weight variables using the formula BMI = weight (kg)/height^2 (metre).

Binary logistic regression was performed to determine if there was a relationship between levels of stress and miscarriage. The relationship between psychometric scales, general health and lifestyles factors and miscarriage was also explored using logistic regression. The odds ratio was calculated to estimate the probability of having a miscarriage for all

independent variables with their corresponding 95% confidence intervals. The first model included univariate analysis of all variables included in the study. The second model adjusted all variables by well-known confounder factors such as maternal age (continuous), body mass index (continuous), previous pregnancy loss (dichotomous), nausea and vomiting (dichotomous) and high or low risk presentation for miscarriage (dichotomous) upon recruitment at the EPAU. All the analyses were performed using SPSS 21.0 (IBM).

Sample size calculations

Sample size calculations were made using Power and Sample Size software (PASS 13). The main association under investigation was between levels of stress and miscarriage. We categorised stress scores into three equal groups (i.e. low, medium and high levels of stress). A sample size of 85 participants in each group allowed us to detect an odds ratio of 2.5 between two groups (i.e. high versus low stress) in relation to the outcome of miscarriage, with 80% power and 5% significance.

Ethical approval

This study received ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospital on ECM 4 (iii) 10/01/2012.

Results

A total sample of 293 women were included in this analysis. The average age of the women was 31.9 years (SD 5.8). The majority of women presented to the EPAU with either a threatened miscarriage (46.1%, $n = 135$) or to seek a reassurance scan (47.4%, $n = 139$) with just 6.5% ($n = 19$) of women attending with a history of recurrent miscarriage. Approximately 46% of women ($n = 134$) had a confirmed miscarriage. Only 29% ($n = 40$) of women who attended for a reassurance scan miscarried; however, two thirds of women who presented with threatened miscarriage and half of women with a history of recurrent miscarriage had a miscarriage (62%; $n = 82$ and 53%; $n = 10$, respectively). Women who attended the EPAU for threatened miscarriage and/or because of previous recurrent miscarriage had four times the risk of miscarrying than those who attending for a reassurance scan (OR 4.1; 95% CI 2.0–8.3; Table 1).

Women who miscarried were older than those who continued with pregnancy (mean 33.5 years old ± 6.1 versus 30.5 ± 5.2, respectively). Women who were 38 years or older had almost four times the risk of having a miscarriage compared to women younger than 38 years (OR 3.9; 95% CI 2.0–7.8) (Table 1). Women who had a previous pregnancy loss were more likely to have a miscarriage (OR 1.7; 95% CI 1.0–2.8); however, this association was not significant after adjusting for confounders (Table 2). Similarly, women who had three or more miscarriages had almost three times the risk of having a miscarriage without adjusting for confounder factors (OR 2.6; 95% CI 1.1–6.7). Those women who were in their first pregnancy (primigravida) and who reported to have taken 3 months or more to conceive had a higher risk of miscarriage compared to those who got pregnant in less than 3 months in the univariate analysis (OR 4.0; 95% CI 1.2–13.5) (Table 2). In addition, presenting with nausea and vomiting in the early stages of pregnancy was protective (OR 0.5; 95% CI 0.3–0.8), but not after adjusting for confounders (Table 2).

Women who had high levels of perceived stress or who self-reported having high energy with no fatigue were more likely to have a miscarriage, but only before adjusting for confounder factors (OR 1.9; 95% CI 1.13.5 and OR 1.9; 95% CI 1.1–3.3, respectively) (Table 3). Conversely, those who had an emotional balance were less likely to have a miscarriage in the multivariate model (OR 0.4; 95% CI 0.2–1.0) (Table 3). No differences were found in relation to maternal social support or for life orientation (Table 3).

Women who had a higher BMI had a slightly higher risk of miscarriage (OR 1.1; 95% CI 1.02–1.14). Women who self-reported that their workplace was stressful had almost four times the risk of having a miscarriage than those who report that they had never had a stressful workplace (OR 3.4; 95% CI 1.0–11.1) (Supplemental Table 1). Women who worked with a computer screen were more likely to have a miscarriage (OR 1.6; 95% CI 1.0–2.8), but this association was not significant after adjusting for confounders. No differences were found among any other general health factor or lifestyle behaviours (Supplemental Table 1). However, women whose partner was unemployed or worked part time had twice the risk of having a miscarriage than those who worked full time (OR 2.3; 95% CI 1.0–5.2) (Supplemental Table 2). In the univariate analysis, women whose partner was 35 years or older had a higher risk of miscarriage than those whom had a partner younger than 35 years (OR 1.8; 95% 1.1–2.9); however, this analysis were not significant in the multivariate analysis. Finally, no differences were found among any traumatic and stressful life events (Supplemental Table 3).

Discussion

Main findings

In this prospective cohort study, almost half of the women went on to have a miscarriage (46%). The main objective was to examine the relationship between risk factors and miscarriage among women who attended an EPAU. Advanced maternal age and high-risk pregnancy were associated with an increased risk of miscarriage in this targeted group. For

Table 1 Odds ratios for miscarriage (< 24 weeks): socioeconomic characteristics

	Pregnancy *n* (%)	Miscarriage *n* (%)	Model I OR (95% CI)	*P* value	Model II OR (95% CI)	*P* value
Total (*n*)	159	134				
Age (*n*)	107	97				
Age, mean (SD)	30.5 (5.2)	33.5 (6.1)	1.1 (1.0, 1.2)	0.011	1.1 (1.1, 1.2)	0.001
Under 38 years	94 (56.6)	72 (43.4)	1.0		1.0	
38 years or more	13 (34.2)	25 (65.8)	2.5 (1.2, 5.2)	0.014	3.9 (2.0, 7.8)	0.000
Ethnicity (*n*)	158	134				
White Irish	132 (55.2)	107 (44.8)	1.0		1.0	
Other ethnic background	26 (49.1)	27 (50.9)	1.3 (0.7, 2.3)	0.415	0.9 (0.4, 2.3)	0.874
Country of birth (*n*)	159	134				
Republic of Ireland	125 (56.1)	98 (43.9)	1.0		1.0	
Outside Ireland	34 (48.6)	36 (51.4)	1.4 (0.8, 2.3)	0.274	1.2 (0.5, 2.9	0.686
Marital status (*n*)	158	134				
Married	95 (52.8)	85 (47.2)	1.0		1.0	
Non married	63 (56.3)	49 (43.8)	0.9 (0.6, 1.4)	0.563	1.1 (0.5, 2.5)	0.742
Education (*n*)	157	133				
Undergraduate or postgraduate degree	57 (59.4)	39 (40.6)				
Some primary/certificate and/or higher diploma	100 (51.5)	94 (48.5)	1.4 (0.8, 2.3)	0.209	2.0 (0.9, 4.3)	0.079
Household income (*n*)	152	126				
40,000 or more	68 (59.1)	47 (40.9)	1.0		1.0	
Below 20,000 till 39,999	84 (51.5)	79 (48.5)	1.4 (0.8, 2.2)	0.211	0.6 (0.3, 1.3)	0.191
Current employment status (*n*)	159	134				
Full-time paid work	77 (52.7)	69 (47.3)	1.0		1.0	
Part-time/unemployed/student	82 (55.8)	65 (44.2)	0.9 (0.6, 1.4)	0.601	1.0 (0.5, 2.1)	0.988
BMI	149	123				
Mean (SD)	26.9 (5.01)	30.1 (22.80)	1.0 (0.99, 1.08)	0.093	1.1 (1.02–1.14)	0.013
Previous miscarriage (*n*)	150	121				
No	68 (63.0)	40 (37.0)	1.0		1.0	
Yes	82 (50.3)	81 (49.7)	1.7 (1.0–2.8)	0.041	1.6 (0.8–3.2)	0.190
Nauseas and vomiting (*n*)	152	123				
No	40 (44.0)	51 (56.0)	1.0		1.0	
Yes	112 (60.9)	72 (39.1)	0.5 (0.3–0.8)	0.008	0.6 (0.3–1.2)	0.131
Presentation (*n*)	159	134				
Low-risk presentation	99 (71.2)	40 (28.8)	1.0		1.0	
High-risk presentation	60 (39.0)	94 (61.0)	3.9 (2.4, 6.3)	0.000	4.1 (2.0, 8.3)	0.000

Model I univariate unadjusted model; *Model II* multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous) and body mass index (continuous)

instances, being 38 years old or older was associated with fourfold higher risk of having a miscarriage. Interestingly, this study did not find an association between advanced paternal age and miscarriage. Some work conditions were found to have an influence in the risk of miscarriage. For example, women who reported to have a stressful workplace had a higher risk of miscarriage. Contrary to other studies, working with a computer screen was not found to be associated with miscarriage in this study. In addition, women whose partners had a part-time job or were unemployed did also have a higher risk of miscarriage in this sample. When looking at women's emotional and psychological wellbeing, this study found that women who self-reported having balanced emotional wellbeing were at a lower risk of miscarriage. However, this study did not find any association between stressful life events, high levels of stress and high energy levels with no fatigue and miscarriage. Similarly, we did not find an association between an increased risk of miscarriage and women's general health, lifestyle factors or past reproductive history. Finally, the only protective factor which was found in this study was nausea and vomiting, which were associated with a decreased risk of miscarriage.

Table 2 Odds ratios for miscarriage (< 24 weeks): past reproductive history

	Pregnancy *n* (%)	Miscarriage *n* (%)	Model I OR (95% CI)	*P* value	Model II OR (95% CI)	*P* value
Age at first period (*n*)	141	115				
More than 13 years old	46 (57.5)	34 (42.5)	1.0		1.0	
13 years old or younger	95 (54.0)	81 (46.0)	1.2 (0.7–2.0)	0.600	1.6 (0.7–3.6)	0.222
Age at first period, mean (SD)	13.0 (1.4)	12.6 (1.9)	0.9 (0.7–1.0)	0.056	0.8 (0.6–1.0)	0.082
Age at first delivery (*n*)	100	84				
30 years old or younger	66 (60)	44 (40)	1.0		1.0	
More than 30 years old	34 (45.9)	40 (54.1)	1.8 (1.0–3.2)	0.062		
Age at first delivery, mean (SD)	26.3 (6.7)	28.0 (6.2)	1.0 (1.0–1.1)	0.072	1.0 (0.9–1.1)	0.889
Live births (*n*)	153	125				
No	54 (57.4)	40 (42.6)	1.0		1.0	
Yes	99 (53.8)	85 (46.2)	1.2 (0.7–1.9)	0.564	0.7 (0.3–1.5)	0.347
Stillbirth (*n*)	100	84				
No	137 (55.0)	112 (45.0)	1.0		1.0	
Yes	7 (58.3)	5 (41.7)	0.9 (0.3–2.8)	0.822	0.6 (0.1–2.6)	0.465
Weeks of gestation at delivery: first child (*n*)	100	84				
Term	89 (53.0)	79 (47.0)	1.0		1.0	
Preterm	11 (68.8)	5 (31.3)	0.5 (0.2–1.5)	0.233	0.6 (0.1–2.3)	0.426
Weeks of gestation at delivery: second child (*n*)	35	38				
Term	32 (48.5)	34 (51.5)	1.0		1.0	
Preterm	3 (42.9)	4 (57.1)	1.3 (0.3–6.0)	0.777	4.2 (0.3–77.9)	0.332
Type of delivery: first child (*n*)	100	84				
Assisted/Caesarean delivery	52 (52.5)	47 (47.5)	1.0		1.0	
Normal delivery	48 (56.5)	37 (43.5)	1.2 (0.7–2.1)	0.592	0.8 (0.3–1.8)	0.553
Type of delivery: second child (*n*)	35	37				
Normal delivery	24 (44.4)	30 (55.6)	1.0		1.0	
Assisted/Caesarean delivery	11 (61.1)	7 (38.9)	0.5 (0.2–1.5)	0.224	0.2 (0.02–1.1)	0.058
Delivery early in previous pregnancies (*n*)	82	64				
No	62 (59.6)	42 (40.4)	1.0		1.0	
Yes	20 (47.6)	22 (52.4)	1.6 (0.8–3.3)	0.188	1.7 (0.6–4.7)	0.314
Previous miscarriage (*n*)	150	121				
No	68 (63.0)	40 (37.0)	1.0		1.0	
Yes	82 (50.3)	81 (49.7)	1.7 (1.0–2.8)	0.041	1.6 (0.8–3.2)	0.190
Number of miscarriages (*n*)	24	25				
Never	68 (63.0)	40 (37.0)	1.0		1.0	
Once	53 (50.5)	52 (49.5)	1.7 (1.0–2.9)	0.067	0.7 (0.2–2.8)	0.561
Twice	20 (57.1)	15 (42.9)	1.3 (0.6–2.8)	0.539	1.2 (0.3–5.2)	0.823
Three or more times	9 (39.1)	14 (60.9)	2.6 (1.1–6.7)	0.039	0.7 (0.1–3.9)	0.716
Type of treatment first miscarriage (*n*)	78	78				
Conservative treatment	40 (51.3)	38 (48.7)	1.0		1.0	
Medical or surgical treatment	38 (48.7)	40 (51.3)	1.1 (0.6–2.1)	0.749	0.6 (0.2–1.6)	0.305
Bleeding during sexual intercourse (*n*)	110	86				
Never	83 (58.0)	60 (42.0)	1.0		1.0	
Sometimes/rarely	27 (50.9)	26 (49.1)	1.3 (0.7–2.5)	0.374	0.8 (0.3–2.1)	0.586
Time to conceive (primigravida, *n*)*	30	20				
Less than 3 months	19 (76.0)	6 (24.0)	1.0		1.0	
Three months or more	11 (44.0)	14 (56.0)	4.0 (1.2–13.5)	0.024	–	–
Interpregnancy interval (multiparas, *n*)	117	99				
Less than 3 months	20 (62.5)	12 (37.5)	1.0		1.0	
Three months or more	97 (52.7)	87 (47.3)	1.5 (0.7–3.2)	0.307	1.3 (0.4–3.8)	0.639
Nauseas and vomiting (*n*)	152	123				
No	40 (44.0)	51 (56.0)	1.0		1.0	
Yes	112 (60.9)	72 (39.1)	0.5 (0.3–0.8)	0.008	0.6 (0.3–1.2)	0.131
Pre-eclampsia previous pregnancy (*n*)	107	88				
No	103 (55.7)	82 (44.3)	1.0		1.0	
Yes	4 (40)	6 (60)	1.9 (0.5–6.9)	0.339	2.2 (0.3–15.8)	0.446
Family history of pre-eclampsia (*n*)	130	113				
No	127 (54.7)	105 (45.3)	1.0		1.0	
Yes	13 (61.9)	8 (38.1)	0.8 (0.5–1.5)	0.528	1.7 (0.4–7.1)	0.442
Folic acid (*n*)	155 (54.8)	128 (45.2)				
No	36 (52.9)	32 (47.1)	1.0		1.0	

Table 2 (continued)

	Pregnancy *n* (%)	Miscarriage *n* (%)	Model I OR (95% CI)	*P* value	Model II OR (95% CI)	*P* value
Yes	119 (55.3)	96 (44.7)	0.9 (0.5–1.6)	0.728	1.4 (0.7–3.2)	0.360
Fertility treatment recent pregnancy (*n*)	150	121				
No	142 (55.3)	115 (44.7)	1.0		1.0	
Yes	8 (57.1)	6 (42.9)	0.9 (0.3–2.8)	0.890	1.5 (0.3–8.6)	0.643

Model I univariate unadjusted model; *Model II* multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous) and body mass index (continuous)

*Excluded from multivariate model as a highly imprecise odds ratio was reported

Interpretation

One explanation of our higher incidence rate of miscarriage may be that the majority of women who are referred to the EPAUs have a history of poor obstetric outcomes, which are associated with higher risk of miscarriage [30]. For instance, similar to our results, a study evaluating the value of introducing EPAUs in Canada found that 47.7% (691/1448) of women who attended the EPAU had a miscarriage [30]. Our results reaffirm previous findings of well-established obstetric risk factors for miscarriage, such as advanced maternal age [10, 11, 31] and high-risk pregnancy, including threatened and recurrent miscarriage [32]. The delaying of the time of conception and its relationship with an increase of adverse pregnancy outcomes is a well-known public health issue; however, little is known about the underlying causes of this relationship [33]. Some authors claim that advanced maternal age can be considered a 'preventable' factor, although cultural and social conditions, which influence this tendency, might limit its modification [11].

In line with our findings, previous evidence has shown that women who present with bleeding and/or pain in emergency departments have a higher risk of miscarriage [32]. However, contradictory results are also found in the literature [34]. Stressful life events and work stress have also been associated with miscarriage by several studies [10]. However, in this study, only perceiving work as stressful was found to be associated with an increased risk of miscarriage. The only partner' characteristic which was found to be associated with an increased risk of miscarriage was to have a part time job or being unemployed. Previous studies have found an association between higher risk of pregnancy loss and economic disparities [35]. For instance, Bruckner found that at least 15% of pregnancy losses were statistically attributable to woman's unexpected high unemployment rate in the previous month [35]. In addition, our results did not find any association between general health and lifestyle factors and miscarriage. Smoking and alcohol during pregnancy are considered well-recognised risk factors for miscarriage [36]. However, contradictory evidence has also been published [37]. One explanation may be that women who had already had previous miscarriages or other types of pregnancy complications might be keener to improve their lifestyle behaviour to increase the chances of successful pregnancies [11].

In contrast with previous studies, our results did not find an increased risk of miscarriage after previous pregnancy loss when adjusting for confounding factors [10, 11]. Similarly, the presence of nausea and vomiting [10] have been previously associated with a decreased risk of miscarriage, but this study did not find an association after adjusting for confounders. This might suggest that the variables which were used as a confounding factor including maternal age, body mass index and high or low risk presentation might have a stronger predictor factor than previous pregnancy loss or nausea in our sample population.

There is a growing trend in the literature focusing on the effect of psychological wellbeing on subsequent pregnancy loss. Our results suggest that having balanced emotional wellbeing was the only psychological factor which was associated with a decreased risk of miscarriage after adjusting for confounding factors. In contrast to our results, the presence of pregnancy symptoms such as low/medium energy [38] have been previously associated with a decreased risk of miscarriage. Several studies have evaluated and reviewed the impact of stress on pregnancy loss [18]. In addition, psychological stress has been associated with an increased risk of preterm labour, low birth weight and unsuccessful outcomes for in vitro fertilisation (IVF) [39]. Immunological imbalances have been linked to miscarriage in women who reported high perceived stress [18] and women who reported feeling stressed, anxious, depressed, out of control or overwhelmed in their first trimester had higher odds of miscarriage [10]. Very recently, a systematic review and meta-analysis concluded that maternal psychological stress and traumatic life events are risk factors for miscarriage [40]. Nevertheless, the effect of maternal stress on miscarriage has not been publicly accepted yet by well-known and reputable medical and health institutions [41]; maybe because of the contradictory evidence in the field.

Reasons why obtaining conclusive evidence about risk of stress for miscarriage is challenging might be related to the wide range of scales for measuring different type of stress

Table 3 Odds ratios for miscarriage (< 24 weeks): perceived stress and psychometric scales

	Pregnancy *n* (%)	Miscarriage *n* (%)	Model I OR (95% CI)	*P* value	Model II OR (95% CI)	*P* value
Total						
Perceived stress (*n*)	152	127				
Low (0–4)	57 (58.8)	40 (41.2)	1.0		1.0	
Medium (5–7)	60 (60.0)	40 (40.0)	0.9 (0.5–1.7)	0.860	0.9 (0.4–2.1)	0.735
High (≥ 8)	35 (42.7)	47 (57.3)	1.9 (1.1–3.5)	0.033	2.4 (1.0–5.8)	0.063
Maternal social support (*n*)	146	121				
Low support (7–23)	42 (59.2)	29 (40.8)	1.0		1.0	
Medium support (24, 25)	45 (54.2)	38 (45.8)	1.2 (0.6–2.3)	0.538	1.2 (0.4–3.1)	0.773
High support (26–30)	63 (52.5)	57 (47.5)	1.3 (0.7–2.4)	0.372	1.6 (0.6–3.9)	0.0.325
Life orientation (*n*)	147	127				
Pessimistic (0–12)	38 (54.3)	32 (45.7)	1.0		1.0	
Neutral (13–15)	44 (54.3)	37 (45.7)	0.99 (0.5–2.0)	0.997	0.8 (0.3–2.1)	0.675
Optimistic (16–24)	65 (52.8)	58 (47.2)	1.1 (0.6–1.9)	0.847	0.7 (0.3–1.7)	0.715
Energy fatigue balance (*n*)	158	130				
Low energy with lot of fatigue (0–35)	60 (65.2)	32 (34.8)	1.0		1.0	
Medium energy with some fatigue (36–45)	26 (50.9)	26 (49.1)	1.8 (0.9–3.6)	0.093	1.1 (0.4–3.2)	0.881
High energy with no fatigue (46–100)	71 (49.7)	72 (50.3)	1.9 (1.1–3.3)	0.020	1.8 (0.8–4.2)	0.160
Emotional wellbeing (*n*)	158	129				
Little emotional balance (0–60)	32 (41.6)	45 (58.4)	1.0		1.0	
Some emotional balance (61–76)	58 (62.4)	35 (37.6)	0.4 (0.2–0.8)	0.007	0.4 (0.1–0.9)	0.034
Emotional balance (77–100)	68 (58.1)	49 (41.9)	0.5 (0.3–0.9)	0.025	0.4 (0.2–1.0)	0.042

Model I univariate unadjusted model; *Model II* multivariate model adjusted for maternal age (continuous), presentation (dichotomous), previous miscarriage (dichotomous), nausea and vomiting (dichotomous) and body mass index (continuous)

responses (perceived levels of stress, life events and work stress). Also, the difficulty in distinguishing between the effect of other mental disorders, such as anxiety and depression, or between other lifestyle behaviours, such as smoking or alcohol consumption, which are also associated with an increased risk of poor pregnancy outcomes [40]. It is of note that only two of the eight studies identified in a systematic review [40] used a specific scale for measuring perceived levels of stress; and that they obtained contradictory results [20, 42].

Strengths and limitations

Most of the studies published in the research area are retrospective cohort studies or case-control studies. The study design of this prospective study is one of its main strengths and all risk factors were collected before the event (miscarriage) occurred. Although this study was undertaken in 2012 in a single EPAU at a maternity hospital which limits the generalisability of the findings for the general population, our sample size of almost 300 women is larger than most previous studies in this area and it gave the study power to detect relatively uncommon risk factors. A limitation of this study is that it was not possible to collect information on psychosocial factors for women who did not return the lifestyle questionnaire or who did not want to participate. This study did not keep a log of women who declined to participate before agreeing to take part in the study, neither it keep a log of women who did not send back the questionnaire. Therefore, we were unable to compare responders with non-responders in this regard. In addition this study did not include stable psychological variables or biological predictors of stress (i.e. cortisol) and our results are limited by self-reported data. Bias from self-reported data is well documented as some health behaviours are either sensitive or difficult to recall. However, studies have indicated that maternal recall regarding health behaviours during pregnancy is reliable. Another strength of this study is that we used validated questionnaires for assessing perceived stress; but our study also incorporated a wide range of psychological stressors such as life events, stress at work and emotional wellbeing.

Implications and conclusions

Women who attend EPAUs might need specific care because of a complex obstetric history. Identification of risk

factors in this targeted group might help clinicians to recognise and monitor with extra care those women who are at higher risk of subsequent miscarriage [18]. Although this study identifies some well-established risk factors (advanced age, threatened miscarriage, recurrent miscarriage), the alternatives to encourage their prevention are limited. Nearly half of the participants attended the EPAU for a reassurance scan (48%). Therefore, it could be argued that women who had a positive scan showing a healthy ongoing pregnancy may have a reduction in stress and anxiety compared to women who were attending the EPAU with a history of recurrent miscarriage or who were experiencing a threatened miscarriage. However, to our knowledge, no studies have investigated the effect of a positive reassurance scan and the potential benefits for pregnant women's psychological wellbeing who have a history of pregnancy loss.

Nevertheless, the insight of a relationship between emotional wellbeing and miscarriage opens a window for prevention in this area. To date, few studies have examined interventions aimed at reducing stress or promoting emotional wellbeing in pregnant populations with a history of miscarriage [43]. For instance, a recent systematic review did not find any randomised controlled study which examined non-pharmacological interventions aimed at reducing stress, anxiety or depression in pregnant women with a history of miscarriage [44]. The findings of our study suggest that such studies are warranted. Further work to develop and evaluate targeted interventions which could improve coping skills before getting pregnant or during pregnancy might be effective in lowering the risk of miscarriage among women who have a history of pregnancy loss.

Conclusion

Despite the prevalence of miscarriage, chromosomal abnormalities are only accounted for 50% of the cases. Therefore, identifying preventable and modifiable risk factors for miscarriage is becoming an area of interest worldwide. The results of this study reinforced that well-established risk factors such as advanced maternal age and high-risk pregnancies are associated with an increased risk of miscarriage in our targeted population. In addition, this study has provided evidence that contributes to the growing body of research by assessing the association of a large number of early maternal, psychological and obstetric factors and the potential risk of miscarriage. These conclusions underscore the need for supportive care in early pregnancy, particularly with women who may be more vulnerable.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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