

Lifestyle Risk Factors Associated with Threatened Miscarriage: A Case-Control Study

Tan TC^{1,4*}, Neo GH¹, Malhotra R^{2,3}, Allen JC², Lie D¹ and Østbye T^{2,3}

¹Duke-NUS Graduate Medical School, Singapore

²Programme in Health Services and Systems Research, Duke-NUS Graduate Medical School, Singapore

³Duke Global Health Institute, Duke University, Durham, Singapore

⁴Department of O & G, KK Women's and Children's Hospital, Singapore

Abstract

Background: Threatened miscarriage occurs in 20% of pregnancies. We conducted a case-control study to assess the association between maternal lifestyle factors and risk of threatened miscarriage.

Methods: Cases were 154 women presenting with threatened miscarriage in the 5th to 10th weeks of gestation; controls were 264 women without threatened miscarriage seen in antenatal clinic in the 5th to 10th week of pregnancy. Lifestyle variables were: current and past cigarette smoking, current second-hand cigarette smoke exposure, computer and mobile-phone use, perceived stress, past contraceptive use, past menstrual regularity and consumption of fish oils, caffeine and alcohol. Logistic regression was performed.

Results: In multivariate analysis, we found a positive association of threatened miscarriage with second-hand smoke exposure (OR 2.93, 95% CI 1.32–6.48), computer usage (>4 hours/day) (OR 6.03, 95% CI 2.82–12.88), mobile-phone usage (>1 hour/day) (OR 2.94 95% CI 1.32–6.53) and caffeine consumption (OR 2.95 95% CI 1.57–5.57). Any fish oil consumption was associated with reduced risk of threatened miscarriage (OR 0.20, 95% CI 0.09–0.42).

Conclusions: Prolonged mobile phone and computer use and fish oil supplementation are potential novel correlates of threatened miscarriage that deserve further study.

Keywords: Threatened miscarriage; Lifestyle risk factors

Introduction

Threatened miscarriage, defined as vaginal bleeding before the 20th week of gestation, occurs in about 20% of pregnancies [1]. One in three women with threatened miscarriage subsequently suffers a complete miscarriage [2]. The remaining women are at increased risk of complications during their pregnancies [3]. Threatened and actual miscarriage is associated with serious subsequent adverse effects on marriage and health. A systematic review suggests wide variation in miscarriage rates between the 5th and 14th weeks, with the highest rates seen during the 5th to 11th weeks of gestation [4]. Several studies have examined risk factors for threatened miscarriage, and while non-modifiable fetal chromosomal anomalies and maternal systemic disease are known to predispose to threatened and actual miscarriage, there is little consensus on the association between modifiable lifestyle risk factors (other than smoking and alcohol consumption [5,6] and the risk of threatened miscarriage [7]. Thus clinicians may not feel adequately prepared to respond to pregnant women's concerns about lifestyle factors. Electromagnetic field (EMF) exposure associated with appliances like microwave ovens, computer use and mobile phone devices, has been linked in epidemiological studies to both leukemia risk and early pregnancy loss [8]. Prolonged mobile-phone use, computer use and exposure to second-hand smoke are increasingly common and research is needed to establish whether these exposures are associated with risk of threatened miscarriage.

On the other hand, Decosahexaenoic Acid (DHA), a long-chained fatty acid in fish oil supplements, has been shown to play a role in fetal eye and brain development. It has been suggested that fish oil supplementation in pregnant women may protect against threatened miscarriage [9,10]. For example, Rossi *et al* demonstrated a reduction in the spontaneous miscarriage rate with DHA use in women with anti-phospholipid-syndrome with a history of recurrent miscarriages but the benefit of DHA in sporadic miscarriage is unknown [11].

This is a case-control study to examine the association of several potentially modifiable maternal lifestyle risk factors with threatened miscarriage. We hypothesized that current and past smoking, exposure to second hand smoke, self-reported stress, alcohol intake during the first trimester and any computer and mobile phone usage are associated with a higher risk of threatened miscarriage during 5th to 10th weeks of gestation. We also hypothesized consumption of DHA to be inversely associated with the outcome.

Materials and Methods

This was a single-center, case-control study conducted at KK Women's and Children's Hospital (KKH) in Singapore, which is the largest maternity hospital in the island nation of Singapore, with over 12,000 deliveries a year for a population of 5.5 million. This amounts to about one-third of all deliveries in Singapore. The study received ethical approval from the Singhealth Centralised Institutional Review Board (CIRB Ref: 2010/620/D) and was exempted from full review by the Duke University Health System Institutional Review Board. At the KKH, all pregnant women are offered routine first-trimester dating ultrasound scan at their first presenting visit.

***Corresponding author:** Tan Thiam Chye, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore, Tel: +65 62934044; Fax: +65 62986343; E-mail: drtctan@me.com

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Participants

Participants were women in their first trimester of pregnancy seen at the KKH between November 2010 and February 2011. We decided a priori to examine cases that presented during the 5th to 10th weeks of gestation because of the higher rates of threatened miscarriage during this gestation period. Cases consisted of women presenting to the KKH 24 hour emergency clinic with threatened miscarriage. For the purpose of our study, threatened miscarriage was defined as vaginal bleeding between the 5th and 10th completed weeks of gestation, presenting with a closed cervix in a woman with an ongoing, viable singleton pregnancy. A qualified specialist doctor examined all potential cases before enrolment. Women who had local causes of bleeding (e.g., cervical polyps) were excluded. Controls consisted of pregnant women recruited in the routine antenatal clinics between the 5th and 10th completed weeks gestation with no history of vaginal bleeding. Gestational age was determined for both cases and controls by last normal menstrual period and confirmed by ultrasound measurement. All participants provided written informed consent prior to study participation. 23.4% women had prior history of miscarriages compared to 20.4% of women in the control group.

Data Collection

Potentially modifiable lifestyle factors were assessed by face-to-face interview with cases and controls, conducted at the time of recruitment. The modifiable lifestyle factors examined were: current and past cigarette smoking, exposure to second-hand cigarette smoke at home, current and past alcohol consumption, current and past caffeine consumption, current mobile phone/computer usage, perceived stress levels, DHA consumption, and most recent contraceptive use. We also elicited potential confounding factors for threatened miscarriage (maternal age, paternal age, gestational age, ethnicity, height, weight, regularity of menstrual cycle, housing type, educational level, past medical/pregnancy/gynaecological/psychiatric history). Mobile phone and computer usage were quantified as self-reported number of hours of use per day based on the most recent one week.

Smoking history and alcohol consumption were recorded as non-use, previous use (use prior to pregnancy) or current use. Caffeine consumption, DHA consumption and past contraceptive use were documented as either yes or no without quantifying the amount of exposure.

Perceived stress levels were quantified using the Perceived Stress Scale (PSS) designed by Cohen et al., [12]. The PSS has been shown to be highly correlated to the affective and physical symptoms of stress in different populations [13], and its use has been validated in different populations, including Brazilian and Japanese populations [14,15]. Women were asked to answer the PSS questions based on symptoms experienced in the last four weeks before the interview date. The PSS comprises 10 questions, each scored from 0 to 4 (higher numbers indicate greater stress), which are added to derive total score.

Data Analysis

We sought to compare modifiable lifestyle risk factors between women with and without threatened miscarriage between the 5th and 10th completed weeks of gestation. Data was analysed using SAS statistical software (Figure 1).

Chi-square or Fisher-Exact tests were used to test for significant differences in the distribution of lifestyle factors and potential confounders between women with threatened miscarriage controls. Gestational age was compared between the two groups of women using

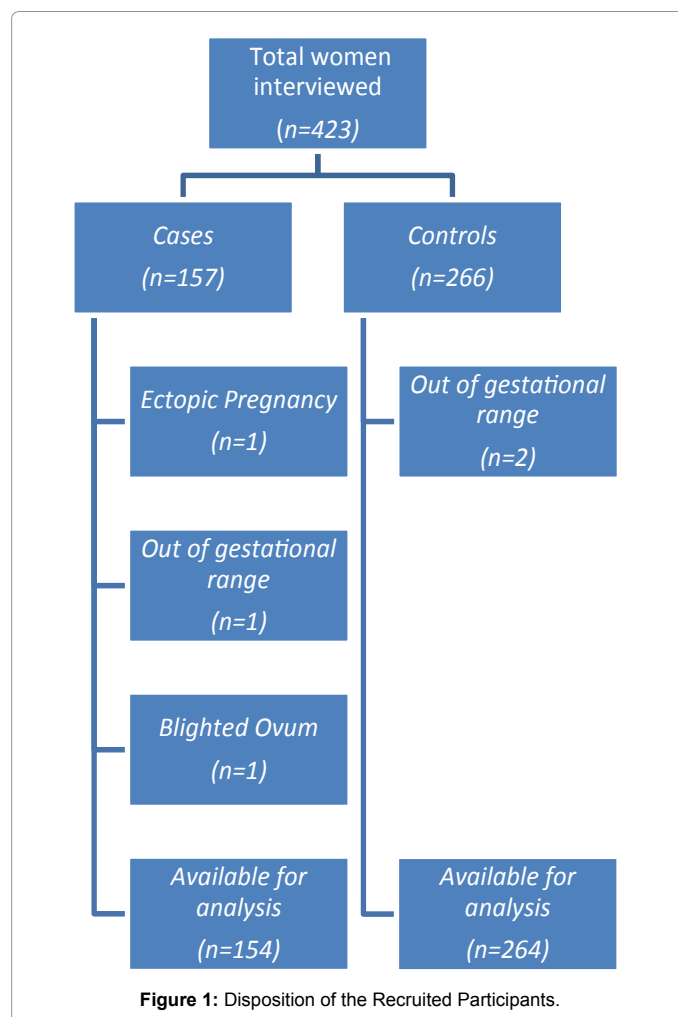


Figure 1: Disposition of the Recruited Participants.

two-sample t-test. Logistic regression was used to assess the associations (odds ratios and corresponding 95% confidence intervals) between threatened miscarriage and each variable of interest. The association between the lifestyle factors and risk of threatened miscarriage was further examined after adjusting for potential confounders using multivariate logistic regression. Gestational age at study enrolment was included as a potential confounder in all analyses. For the multivariate analysis, the Hosmer and Lemeshow Goodness-of-fit test was not rejected ($p=0.7095$), suggesting that the fitted model was adequate. For all analyses, a p -value ≤ 0.05 indicated statistical significance. Unadjusted p -values are reported for all tests. P -value adjustments for multiple tests are left to the discretion of the reader.

Results

Participant characteristics and pregnancy outcomes

The baseline characteristics of the participants in the final analysis sample of 418 women, with 154 cases and 264 controls (control-to-case ratio of 1.71) are summarized in Table 1. Of the 157 recruited women with threatened miscarriage, one was subsequently diagnosed with ectopic pregnancy, one had a blighted ovum and one confirmed a gestation of <5 weeks. These women were excluded leaving 154 cases for analysis. Two of the 266 controls were subsequently excluded as the ultrasound scans deemed gestation to be >10 weeks, leaving 264 controls for analysis.

Characteristic	Threatened Miscarriage % (n=154)	Controls % (n=264)	p-value
Potential lifestyle risk factors			
DHA* Intake			
Yes	9.1	31.1	<0.001
Smoking history			
Non-smoker	85.0	83.6	0.39
Ex-smoker	10.4	13.7	
Smoker	4.6	2.7	
Smoking family members			
Yes	32.5	13.6	<0.001
Alcohol use			
No	79.2	93.1	<0.001
Ex-alcohol use	15.6	6.1	
Current	5.2	0.8	
Perceived stress score			
Low (17)	48.7	59.9	0.03
High (≥ 17)	51.3	40.1	
Mean (SD)	16.1 (5.4)	14.6 (6.5)	0.02
Caffeine use			
Yes	67.5	47.4	<0.001
Mobile use per day			
0 to <1 hour	52.6	84.5	<0.001
≥ 1 to <2 hours	24.0	9.1	
≥ 2 hours	23.4	6.4	
Computer use per day			
0 to <1 hour	8.8	15.7	<0.001
≥ 1 to <4 hours	25.5	43.8	
≥ 4 hours	65.7	40.5	
History of Contraceptive use			
Yes	35.3	18.2	<0.001
Potential confounders			
Maternal Age			
<35 years old	76.0	70.5	0.26
≥ 35 years old	24.0	29.5	
Mean age (SD)	30.2(5.5)	30.7(5.2)	0.37
Gestational Age			
Mean (SD)	6.9 (1.5)	8.1 (1.6)	<0.001
Marital Status			
Married	93.5	96.6	0.14
Single/divorced	6.5	3.4	
Paternal age (years)			
20-30	37.0	26.5	0.08
31-40	50.7	59.5	
≥ 41	12.3	14.0	
Mean (SD)	33.6 (6.6)	34.3 (5.9)	0.30
Ethnicity			
Chinese	59.1	47.7	0.15
Malay	20.1	25.0	
Indian	11.0	15.9	

Others	9.8	11.4	
Education			
Secondary school and below	31.2	28.8	0.03
Vocational institute to polytechnic	5.8	6.8	
University and above	63.0	64.4	
Housing			
Public Housing 1-3 rooms	56.5	59.9	0.40
Public Housing 4-5 rooms	33.1	27.3	
Private housing	10.4	12.8	
BMI* kg/m²			
<23	58.4	62.5	0.41
≥ 23	41.6	37.5	
Mean (SD)	23.2 (4.4)	22.5 (4.0)	0.11
Are periods regular			
Yes	72.1	88.3	<0.001
Nausea during pregnancy			
Yes	53.3	72.4	<0.001
Past history of miscarriage			
Yes	23.4	20.8	0.54
Is current pregnancy planned			
Yes	54.5	63.3	0.08
Past history of abortion			
Yes	21.4	14.4	0.06
Any depression/schizophrenia			
Yes	7.1	1.9	0.007

Table 1: Baseline Characteristics of analysis sample.

The mean age of cases and controls were 30.2 and 30.7 respectively (Table 1). The mean gestation age was 6.9 weeks for cases and 8.1 weeks for controls. Seventy six percent of the women who experienced threatened miscarriage were below the age of 35. Most women had no history of prior miscarriages or abortions. Ninety six percent had no history of thyroid diseases, diabetes mellitus or hypertension or psychiatric illness. Eight five percent were non-smokers and 79% did not consume alcohol. Comparison between the two groups showed that women with threatened miscarriage were significantly more likely to have a higher perceived stress score, exposure to second-hand smoke at home, consume caffeine or alcohol, report prolonged usage of mobile phone/computer, have irregular menses, report previous use of contraceptive or have a history of psychiatric illness; and were less likely to have nausea or to consume DHA supplements

Bivariate Analyses of lifestyle factors

Table 1 shows the bivariate relationships between the various risk factors and threatened miscarriage, adjusted for gestational age, and Table 2 shows the unadjusted and adjusted Odd Ratios (ORs) for threatened miscarriage. In bivariate analysis (Table 1), the risk of threatened miscarriage was lower with DHA consumption before or during pregnancy. A higher risk of threatened miscarriage was seen with exposure to second-hand smoke, previous/current alcohol use, prolonged mobile phone (≥ 2 hours/day) or computer usage (≥ 4 hours/day), any caffeine consumption and any history of contraceptive use. (Table 2)

Multivariate Analyses of lifestyle factors

The association of any DHA consumption with reduced risk of

Characteristic	Unadjusted odds Ratio* (95% Confidence Interval)	Adjusted odds ratio† (95% Confidence Interval)
Potential lifestyle risk factors		
DHA[‡] Intake		
Yes	0.23 (0.12–0.43)	0.20 (0.09–0.45)
No	1	1
Smoking history		
Non-smoker	1	1
Ex-smoker	0.88 (0.45–2.71)	0.18 (0.06–0.51)
Smoker	2.07 (0.63–6.84)	0.35 (0.04–3.10)
Smoking family members		
Yes	3.69 (2.15–6.35)	2.93 (1.32–6.48)
No	1	1
Alcohol use		
No	1	1
Ex-alcohol use	3.09 (1.50 - 6.37)	4.63 (1.63–13.17)
Current	5.41 (1.04 - 28.13)	21.70 (0.73–649.42)
Perceived stress score		
Low (<17)	1	1
High (≥ 17)	1.53 (0.99 - 2.35)	1.09 (0.59 - 2.01)
Caffeine use		
Yes	2.68 (1.71 - 4.22)	2.95 (1.57–5.57)
No	1	1
Contraceptive use		
Yes	2.19 (1.34–3.57)	1.75 (0.90–3.43)
No	1	1
Handphone use		
0 to <1 hour	1	1
≥ 1 to <2 hours	2.35 (1.25–6.32)	2.94 (1.32–6.53)
≥ 2hours	5.84 (2.32–11.49)	6.32 (2.71–14.75)
Computer use		
0 to <1 hour	1	1
≥1 to <4 hours	1.65 (0.90–3.02)	2.66 (1.16–6.09)
≥4 hours	4.43 (2.58–7.60)	6.03 (2.82–12.88)
Potential confounders		
Age		
<35	1	1
≥ 35	0.62 (0.38–1.02)	0.51 (0.24–1.10)
Marital status		
Married	1	1
Single/divorced	1.86 (0.68–5.12)	1.12 (0.25–5.25)
Paternal age		
≥ 20–30	1	1
31–40	0.57 (0.35–0.92)	0.73 (0.35–1.53)
≥ 41	0.60 (0.29–1.21)	1.57 (0.52–4.70)
Ethnicity		
Chinese	1	1
Malay	0.72 (0.42–1.23)	0.66 (0.30–1.45)
Indian	0.70 (0.36–1.37)	0.76 (0.30–1.89)
Others	0.86 (0.42–1.78)	1.09 (0.40–3.02)
Education		
Secondary school and below	1.29 (0.80–2.07)	1.58 (0.75–3.33)
Vocational institute to polytechnic	0.79 (0.32–1.93)	0.72 (0.22–2.40)

University and above	1	1
Housing		
Public Housing 1-3 rooms	1.15 (0.58–2.30)	1.13 (0.42–3.06)
Public Housing 4-5 rooms	1.24 (0.59–2.61)	1.73 (0.61–4.89)
Private housing	1	1
BMI[§] Kg/m²		
<23	1	1
≥ 23	1.08 (0.70–1.68)	1.22 (0.66–2.26)
Are periods regular		
Yes	0.33 (0.19–0.58)	0.41 (0.19–0.88)
No	1	1
Nausea during pregnancy		
Yes	0.50 (0.32–0.78)	0.70 (0.38–1.28)
No	1	1
Past history of miscarriage		
Yes	1.17 (0.70–1.96)	0.16 (0.57–2.36)
No	1	1
Is current pregnancy planned		
Yes	1	1
No	1.44 (0.93–2.22)	1.37 (0.72–2.58)
Past history of abortion		
Yes	1.55 (0.89–2.68)	1.31 (0.58–2.96)
No	1	1
Any depression/ schizophrenia		
Yes	4.22 (1.32–13.45)	3.23 (0.73–14.40)
No	1	1

*Univariate analysis unadjusted for confounders but adjusted for gestational age.
 †Multivariate analysis adjusting for all confounders and for gestational age.
 ‡Decosahexaenoic Acid
 §Body Mass Index

Table 2: Association between potential lifestyle risk factors and threatened miscarriage: Results of unadjusted and adjusted logistic regression analysis.

threatened miscarriage was maintained in the multivariate analysis (OR=0.20, 95% CI=0.09–0.45). The increased risk associated with exposure to second-hand smoke also persisted in multivariate analysis (OR=2.93, 95% CI 1.32–6.48). A previous history of smoking was associated with reduced risk (OR=0.18, 95% CI 0.06–0.51) while previous consumption of alcohol was associated with an increased risk of threatened miscarriage (OR=4.63 95% CI 1.63–13.17). Greater duration of mobile phone use or computer use was associated with higher risk and a dose-response relationship was suggested by the data. Compared to <1 hour/day of mobile phone use, use for 1-2 hours/day had an OR of 2.94 (95% CI 1.32–6.53) and use for >2 hours/day had an OR of 6.32 (95% CI 2.71–14.75). Similarly, compared to women who spent <1 hour/day in front of the computer, women who spent >1 hour/day had an OR of 2.66 (95% CI 1.16–6.09), while those spending >4 hours/day had an OR of 6.03 (95% CI 2.82–12.88). Self-reported caffeine consumption was associated with a higher risk of threatened miscarriage compared to no caffeine consumption (OR=2.95 95% CI 1.57–5.57).

A history of regular menses was associated with a lower risk compared with irregular menses in the multivariate analysis (OR=0.41, 95% CI=0.19–0.88).

Discussion

We conducted a case control study on women presenting to a large obstetric hospital in the 5th to the 10th weeks of gestation, to examine factors associated with risk of threatened miscarriage. In our study, exposure to second-hand smoke, current caffeine consumption and high computer and mobile phone usage were associated with greater risk of threatened miscarriage. We also confirmed our secondary hypothesis that use of DHA and a history of regular menses were associated with a lower risk of threatened miscarriage. Our findings are consistent with past reports [6-30]. But the finding that current smoking, current alcohol use and higher stress scores were not associated with higher risk was unexpected and differed from the reported literature [30]. This could be due to the small sample size of ex-smokers and current smokers in our study.

Our finding of the increased risk associated with second-hand smoke exposure confirms previous studies that examined early pregnancy losses [16,17]. The mechanisms by which passive smoking increases the risk of miscarriage are believed to be similar to those of active smoking, mainly vasoconstriction [18], reduced placental blood flow due to nicotine [19], and maternal and fetal hypoxia due to carboxyhemoglobin formation [20-22]. The association of caffeine consumption with an increased risk of threatened miscarriage is not surprising and confirms previous findings from other studies [23,24].

Our finding that women who reported any DHA supplementation before or during pregnancy were five times less likely to experience threatened miscarriage than those who did not take DHA supplementation is novel. No previous study has examined this potential benefit of DHA on sporadic threatened miscarriage. This finding has only been noted among women with a history of recurrent miscarriage [11]. We speculate that fish oil may modify and stabilize the membrane lipids of endothelial cells in the placenta or decidua [25], reducing their sensitivity to damaging agents; and/or reduce lipooxygenase and cyclooxygenase levels, counteracting inflammatory processes which would otherwise increase the risk of miscarriage [25,26]. There is also a possible protective role of DHA in the estrogen/progesterone hormonal pathway to explain this protective effect [27].

The association between a past history of regular menses and lower risk of threatened miscarriage that we found may simply reflect the association of irregular menstrual cycles with underlying infertility or other conditions such as Polycystic Ovarian Syndrome, which confers an increased risk of miscarriage [28,29].

We had hypothesized current and past smoking to be risk factors for threatened miscarriage. However, in this study, we found that past smoking was associated with a lower risk of threatened miscarriage; further, the point estimate of current smoking also suggested an inverse, though not significant association. We believe these unexpected inverse associations to be spurious, related to under-reporting of current and past smoking. Under-reporting will lead to increased numbers of actual current or past smokers being classified as non-smokers, which will increase the reference risk levels of the non-smokers, possibly leading to the observed inverse association of past and current smoking. The small number of women reporting any alcohol use may also account for the lack of an association with risk of threatened miscarriage. In our study, previous consumption of alcohol was associated with an increased risk for threatened miscarriage, as has been documented in the literature [30].

Our most significant finding is that both prolonged computer use (≥ 4 hours/day) and mobile phone use (≥ 2 hours/day) were associated

with a 6-fold increase in the risk of threatened miscarriage. This finding is in contrast to other studies suggesting computer usage to be safe during pregnancy [31,32] and warrants further verification in future studies.

There is currently no consistent evidence of a causal relationship between exposure to radiofrequency fields from mobile phone usage and any adverse pregnancy effect. However, a recent study conducted in Spain found that children born to women who had excessive mobile phone usage during pregnancy were 40% more likely to develop behavioral problems [33]. Ingole et al., [34] demonstrated that radiation from mobile phones increased the risk for embryo death in chicken embryos. Thus the question of whether EMF exposure is a risk factor still remains to be answered in future studies [35].

The strengths of the present study include a relatively large sample size and the women with threatened miscarriage and the controls were drawn from the same population with similar demographic characteristics. Potential study limitations include the small number of women who reported some lifestyle factors (smoking and alcohol consumption); as a result the study was underpowered to detect the association of these factors with risk of threatened miscarriage. The lifestyle factors were self-reported and not verified by objective measures—however, this reflects real life clinical practice where clinicians have to rely on patient self-report when counseling about risk factors. Also we did not elicit exposure by dosage for smoking, alcohol consumption and DHA supplementation and were thus unable to assess for a dose-response relationship.

Inferences about causal relationships between the assessed risk factors and threatened miscarriage must be drawn with caution because of the study limitations. However we identified new potential factors worthy of further examination in future, prospective and larger cohorts. This study may add to the evidence of the Danish nationwide study which identifies risk factors such as older age; being underweight or overweight before pregnancy; and alcohol consumption, lifting heavy weights, and night work during pregnancy [36] and by reducing these risk factors in the Danish study, over a quarter of miscarriages might be prevented [36].

Conclusion

This study identified some modifiable lifestyle factors as correlates for threatened miscarriage. Some findings from the study supported previous studies and some provided new evidence for future examination. Novel factors include DHA supplementation and computer and mobile phone usage. Establishing and distinguishing among actual and spurious risk factors is an important goal of future research to provide clinicians with tools with which to both reassure and counsel women on optimal health lifestyles to minimize the risk of threatened miscarriage.

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