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ORIGINAL RESEARCH

Impact of Recurrent Miscarriage on Maternal Outcomes in Subsequent Pregnancy: The Mutaba'ah Study

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Purpose: To estimate the prevalence of recurrent miscarriage (RM) and investigate the association between RM and adverse maternal outcomes in subsequent pregnancies.

Participants and Methods: This is an interim analysis of a prospective study of 1737 pregnant women with gravidity of two or more prior to the current pregnancy. These women joined the Mutaba'ah Study between May 2017 and April 2019 and were followed up until they delivered. Hospital medical records were used to extract data on past pregnancy history and the progress and outcomes of the current pregnancy, such as gestational diabetes, preeclampsia, mode of delivery, preterm delivery, and complications at birth.

Results: Amongst pregnant women with at least two previous pregnancies (n=1737), there were 234 (13.5%) women with a history of two or more consecutive miscarriages. Women with RM were slightly older, more parous, and more likely to have had previous infertility treatment (all p-values <0.05). Women with a history of RM had independently significant increased odds of cesarean section (adjusted odds ratio (aOR) 1.81, 95% CI 1.24–2.65) and preterm (<37 weeks, aOR: 2.52, 95% CI 1.56–4.08) or very preterm delivery (<32 weeks, aOR: 7.02 95% CI 2.41–20.46) in subsequent pregnancies than women who did not have a history of RM.

Conclusion: Women with a history of RM were twice as likely to undergo cesarean section and seven times more likely to deliver prior to 32 weeks of gestation than women without a history of RM. The study findings support the need for early pregnancy monitoring or assessment units to ensure better follow-up and customized care for at-risk pregnant women with a history of RM.

Keywords: cesarean section, cohort study, miscarriage, preterm delivery, recurrent miscarriage

Introduction

Recognized miscarriages in clinical settings occur in approximately 15–20% of all pregnancies.[1] Recurrent miscarriages (RM), defined as two consecutive miscarriages before the 20th week of gestation,[2–6] are less common and affect 1–5% of fertile women.[7] The current available literature on RM primarily focuses on the possibility of future loss[8] and the psychological distress caused by RM,[9] such as poorer mental health outcomes after the loss[10] and during subsequent pregnancies.[11] While most women who experience RM proceed to have healthy live births,[12] studies show that RM is associated with some unfavorable outcomes, such as placental dysfunctions, preterm births, and assisted deliveries, in future

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pregnancies.[13–16] It has also been shown that women with RM are more likely to develop gestational hypertension and gestational diabetes mellitus [GDM] during their subsequent pregnancies.[12,17] Furthermore, babies born to women with a history of RM were at an increased risk of low birth weight and being small or large for gestational age.[12] Nevertheless, there is a need for further studies that investigate the influence of RM on a wider range of outcomes in future pregnancies.[18] Currently, there is a lack of data on RM in the United Arab Emirates (UAE) and the surrounding region.[19,20] The limited available research is generally focused on the biochemical processes of RM. Therefore, population-based studies with longitudinal designs are required to assess the epidemiological burden of RM and its influence on maternal health outcomes. This study aims to estimate the prevalence of RM and investigate the association between RM and adverse maternal outcomes in subsequent pregnancies in pregnant women who have had a gravidity of two or more in the UAE.

Participants and Methods
Study Design, Setting, and Participants

Pregnant women who participated in the Mutaba'ah Mother and Child Health Study were included in this analysis. The Mutaba'ah (Arabic for "to follow up") Study is a prospective cohort study that aimed to systematically recruit 10,000 pregnant women from the Emirati population during their antenatal care visits at three major health institutions in Al Ain, UAE. All pregnant women, and their newborns, from the Emirati population who were aged 18 years and above, resident in Al Ain, and able to provide informed consent were eligible for the study. Recruitment involved completing a baseline survey. Participants were followed up during pregnancy via medical records and other questionnaires. Mothers and their offspring will be subsequently followed up using questionnaires, medical record extractions, and interviews until the child turns 16 years old. More information about the Mutaba'ah Study can be found elsewhere.[21,22]

Variables and Measurements

Data for the current analysis were extracted from the baseline survey administered during the first point of contact with participants who were recruited between May 2017 and April 2019 and from their medical records. The survey included 67 questions regarding demographics, psychosocial factors, previous pregnancies, and lifestyle behaviors during the current pregnancy. The dataset from the medical records included information about previous pregnancy history and current pregnancy (from the first hospital visit until delivery and postnatal discharge).

A miscarriage was defined as all pregnancy losses from the time of conception (fertilized ovum) to neonate in this study.[3] Only data from the medical records on previous pregnancy history were used to confirm the history of miscarriage and form exposure groups. As per inclusion criteria, in this analysis, only women with two or more previous consecutive miscarriages were included in the RM group, while women with a gravidity of two or more and no history of two consecutive losses were included in the comparison group. This definition of quantifying RM (using two or more losses) is as per the European Society of Human Reproduction and Embryology guidelines, the American Society of Reproductive Medicine as well as the American College of Obstetricians and Gynecologists and the Dutch Society of Obstetrics and Gynecology although they have varying definitions of what constitutes a miscarriage.[3–6] Other institutions define RM with a diagnostic definition of three or more consecutive losses.[7] This definition was used in a supplementary analysis.

Medical records were also used to obtain information about the current pregnancy and delivery. This included information on maternal anthropometry, pregnancy outcomes (eg, diagnoses of GDM and preeclampsia), mode of delivery, and gestational age at delivery. Options for mode of delivery included spontaneous vaginal delivery, assisted vaginal delivery (including the use of vacuum and forceps), and cesarean section. We also extracted data on blood loss during delivery. We were unable to elucidate if the current pregnancy was achieved via assisted conception (eg, via ovulation induction, intrauterine insemination, or any type of in vitro fertilization) as this information was confidential. Information on maternal age, gestational age at booking, body mass at first visit, and blood pressure at first visit were also collected from medical records.

Demographic and other pregnancy-related characteristics obtained from the questionnaire included maternal education, employment, number of people living in the house, number of previous pregnancies (gravidity), number of children (parity), ever been treated for infertility, pregnancy planning status, maternal and paternal smoking status, consanguinity, perceived social support, and childbirth anxiety.

Assuming an exposure level of 10% (a history RM) and an outcome of 30% (for instance, cesarean section) in the unexposed group, a cohort of 1700 pregnant women

will allow the detection of as low as 1.6-fold increase in odds of the outcome in the exposed group compared to the unexposed group with 80% power and a 5% Type I error probability.

Statistical Analyses

Descriptive statistics were performed to compare the distribution of characteristics of the study population by RM status. Continuous variables were presented as means and standard deviations, while categorical variables were presented as counts and percentages. Student's t-tests were used to determine differences between group means for continuous variables, while Pearson Chi-square tests were used for categorical variables. Univariate and multivariate regression models were used to quantify the association between exposure to history of RM (coded as yes/no) and current pregnancy maternal outcomes (cesarean section or preterm or very preterm delivery, preeclampsia and GDM) [all coded as yes/no], and blood loss during delivery (coded as a continuous variable). Factors associated with a history of RM in the crude model and other relevant factors were added to the multivariate model. All models were adjusted for age, gravidity, body weight and gestational age at delivery unless stated otherwise. Crude odds ratio (OR) and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. Stata 16 (Stata Corp, College Station, TX) was used to perform statistical analyses. Statistical significance was defined by a p-value less than or equal to 0.05.

Results

Between May 2017 and April 2019, 2769 women consented and participated in the Mutaba'ah Study and completed their pregnancies at the time of this analysis. Of these 2769 women, 542 (19.6%) were primiparous (did not have a history of pregnancies) and 490 (17.7%) had only one previous pregnancy (gravida = 1). The remaining 1737 women had a gravidity of two or more prior to the current pregnancy and were included in this analysis.

Prevalence of RM and Characteristics of the Study Population

Approximately 13.5% (N = 234) of these women had a history of two or more consecutive miscarriages. They formed the RM group. Table 1 shows the characteristics of women in the RM and non-RM groups. In brief, women with history of RM were slightly older, more gravid, and

more likely to have had prior infertility treatment (all p-values <0.05). The mean (±SD) age of women with a history of RM was 33.7 ± 5.6 years, while that of women without a history of RM was 32.6 ± 5.2 years. In general, women with a history of RM had on average two more pregnancies than those without a history of RM (mean ± SD gravidity of 6.2 ± 2.6 versus 4.0 ± 2.0, respectively). However, there was no difference in the number of children (parity) the two groups were having at this index pregnancy (3.3 ± 0.1 versus 3.4 ± 0.05). More than one-fifth (22.1%) of women with RM had self-reported that they had previously undergone infertility treatment during their reproductive career prior to this pregnancy, compared to 8.1% of those without a history of RM. There were no significant differences in the planning status of the current pregnancy, education, or consanguinity between the two groups.

History of RM and Adverse Outcomes in the Current Pregnancy

Figure 1 shows adverse outcomes in the current pregnancy by RM status. Women with a history of RM were significantly more likely to deliver via cesarean section (34.2% versus 21.1%, p <0.001) or preterm (<37 weeks' gestation, 16.2% versus 7.5%, p < 0.001) or very preterm (<32 weeks of gestation, 4.6% versus 0.6%, p < 0.001) and to experience preeclampsia (3.2% versus 1.2%, p = 0.021) than women with no history of RM (Figure 1). The two groups showed no significant difference for GDM in the current pregnancy (24.2% versus 26.1%, p = 0.557). The mean (± SD) blood loss during delivery was 446 ± 306 mL for women with a history of RM and 355 ± 276 mL in women with no history of RM (p <0.05).

Table 2 shows crude and adjusted associations between RM and maternal outcomes in the current pregnancy. In the crude model, a history of RM was associated with increased odds of cesarean section (OR 1.87, 95% CI 1.39–2.51), preterm (OR 2.39, 95% CI 1.55–3.67) and very preterm delivery (OR 7.92, 95% CI 3.02–20.77), increased blood loss during delivery (OR 1.36, 95% CI 1.13–1.63), and preeclampsia (OR 2.74, 95% CI 1.12–-6.67). Some of the associations remained statistically significant after controlling for potential confounding factors, including age, gravidity, body mass, gestational age at delivery. Women with a history of RM had independent associations with cesarean section (aOR 1.81, 95% CI 1.24–2.65), preterm delivery (aOR 2.52, 95% CI

Table 1 Characteristics of 1737 Pregnant Women with Gravidity of two or More Prior to the Current Pregnancy According to Their History of Recurrent Miscarriage (RM) Status (Has a History of Two or More Consecutive Miscarriages) in Al Ain, UAE: The Mutaba'ah Study

Characteristics	RM	No RM	p-value
N (%)	**234 (13.5)**	**1503 (86.5)**	
Age (years)[‡] Missing data	33.7 ± 5.6 11	32.6 ± 5.2 71	0.005
Number of pregnancies[‡]	6.2 ± 2.6	4.0 ± 2.0	<0.001
Number of children[‡] Missing data	3.3 ± 0.1 68	3.4 ± 0.05 304	0.278

Education
   High school and below
   Diploma and above
Missing data
	
	137 (61.7%)
	85 (38.3%)
	12
		
		891 (62.7%)
		530 (37.3%)
		82
			0.777

Employment
   Employed
   Unemployed/student
Missing data
	
	96 (43.1%)
	127 (56.1%)
	11
		
		525 (37.1%)
		889 (62.9%)
		89
			0.090

Number of people living in home[‡] Missing data	11.5 ± 7.7 21	12.2 ± 8.1 176	0.230
Age of menarche (years) Missing data	12.6 ± 1.9 20	12.9 ± 2.0 197	0.104

Previous infertility treatment
   Yes
   No
Missing data
	
	48 (22.1%)
	169 (77.9%)
	17
		
		112 (8.1%)
		1276 (91.9%)
		115
			<0.001

Consanguinity
   Yes
   No
Missing data
	
	84 (44.0%)
	107 (56.0%)
	43
		
		582 (47.2%)
		650 (52.8%)
		271
			0.401

Body weight (kg) at first visit Missing data	72.9 ± 14.3 31	72.1 ± 14.7 212	0.479

Planned pregnancy
   Yes
   No
Missing data
	
	114 (51.8%)
	106 (48.2%)
	14
		
		652 (46.5%)
		751 (53.5%)
		100
			0.140

Notes: Missing data were excluded from the calculation of proportions and means presented for each variable; [‡]Mean and standard deviation.

1.56–4.08), and very preterm delivery (aOR 7.02, 95% CI 2.41–20.46) (Table 2).

Supplementary Analysis

In a supplementary analysis, calculations were repeated with RM defined as three or more consecutive losses (data not shown). Accordingly, 76 (5.8%) women were identified as having a history of RM amongst 1316 pregnant women with gravidity of three or more prior to the

current pregnancy. Overall, women with a history of three or more consecutive miscarriages had similar risks for cesarean section, preterm delivery, and very preterm delivery to women identified using the diagnostic definition of RM as two or more consecutive losses.

Discussion

This prospective cohort study provides the first population-based estimates on the prevalence of RM and the
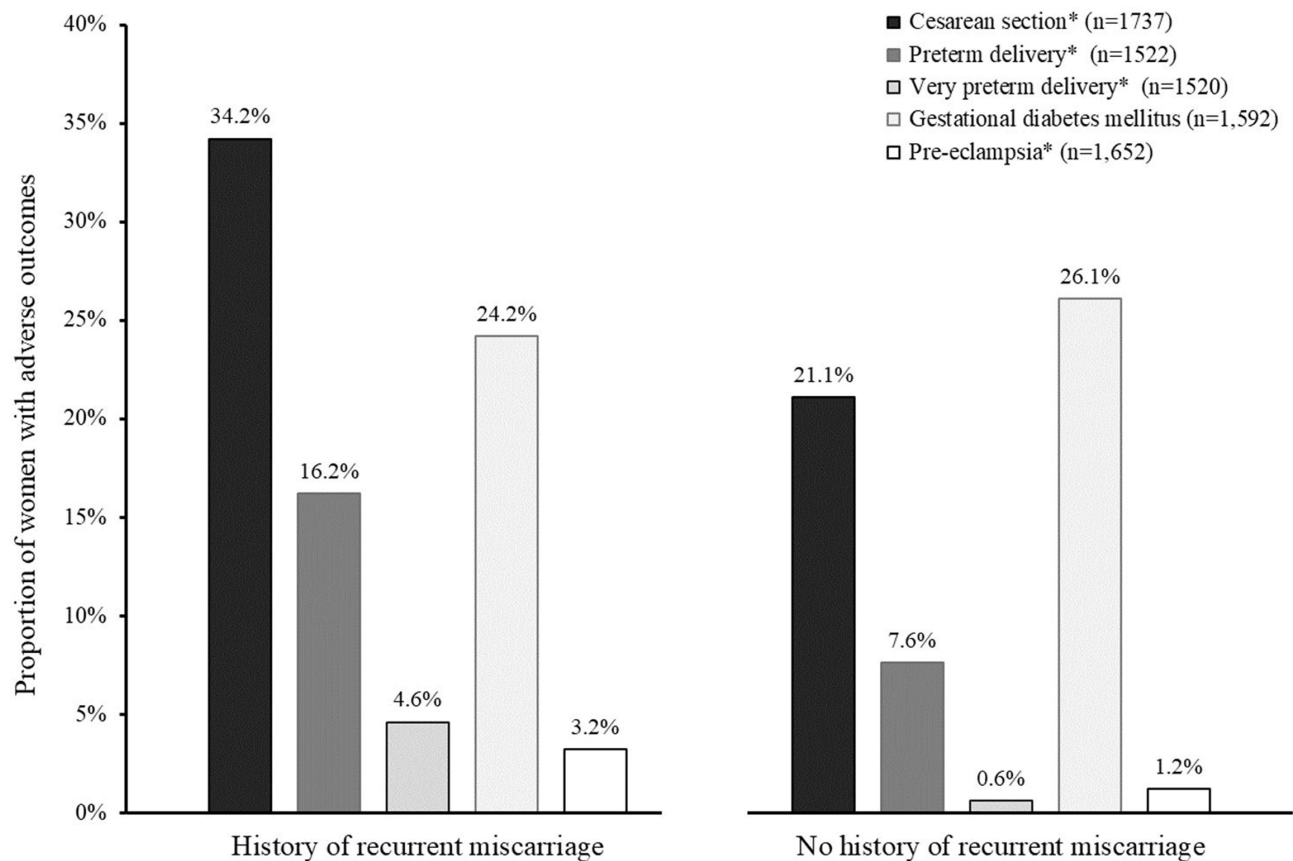
Figure 1 Adverse pregnancy outcomes in 1737 pregnant women with gravidity of two or more prior to the current pregnancy by history of recurrent miscarriage (RM) status (history of RM: n = 234, no history of RM: n = 1503) in Al Ain, UAE: The Mutaba'ah Study.
Notes: *Adverse outcomes were significantly different between RM and no-RM groups (p <0.05).

maternal obstetric outcomes associated with RM among pregnant women in the UAE and the surrounding region. Approximately 13.5% of the pregnant women with gravidity of two or more prior to the current pregnancy in this study population had a history of RM. Moreover, women with a history of RM were twice as likely to undergo cesarean section and deliver prematurely and seven times more likely to deliver

before 32 weeks of gestation than women without a history of RM.

Using the definition of quantifying RM as two or more consecutive pregnancy losses, our study showed that one in eight women with a gravidity of two or more who were pregnant again during the study period had a history of RM. The relatively high prevalence of RM in this population is 2–13 times more common than in

Table 2 Crude and Adjusted Associations Between History of Recurrent Miscarriage and Maternal Outcomes in Current Pregnancy Among 1737 Pregnant Women with Gravidity of two or More Prior to the Current Pregnancy in Al Ain, UAE: The Mutaba'ah Study

Variables	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio* (95% Confidence Interval)
Cesarean section	1.87 (1.39–2.51)	1.81 (1.24–2.65)
Preterm delivery (<37 weeks of gestation)	2.39 (1.55–3.67)	2.52 (1.56–4.08)
Very preterm delivery (<32 weeks of gestation)	7.92 (3.02–20.77)	7.02 (2.41–20.46)
Blood loss during delivery (per SD)	1.36 (1.13–1.63)	1.03 (0.99–1.01)
Preeclampsia	2.74 (1.12–6.67)	2.81 (0.95–8.27)
Gestational diabetes mellitus	0.90 (0.65–1.27)	0.69 (0.47–1.02)

Notes: *All models were adjusted for age, gravidity, body mass, gestational age at delivery. Preterm delivery did not have gestational age as adjustment due to collinearity.
Abbreviation: SD, standard deviation.

other parts of the world (~1–5%)[8] and reflects that RM is an important public health and clinical issue in the UAE. However, caution must be made when comparing prevalence estimates of RM between studies due to the use of different definitions, i.e., two versus three miscarriages as the cutoff for RM. Moreover, whether a consecutive or non-consecutive loss pertains to RM also differs between studies.[23] The denominator used to calculate RM also varies in many studies and includes either women at risk of having a history of RM (by having had two or more pregnancies), all women in their reproductive years, or women intending to conceive.[24] Accurate estimates of these denominators are also difficult to obtain in many countries. While our population comprised pregnant women with gravidity of two or more prior to the current pregnancy, other similar studies tend to exclusively include women with a history of RM or women at the end of their reproductive career.[17,24] Nevertheless, it was envisioned that defining RM as two or more miscarriages would facilitate research and shared decision-making and enhance the psychological support available to couples.[10] Finally, testing for antiphospholipid syndrome (APS), a treatable autoimmune disorder and a common cause of RM, can be performed after two losses.[3] Hence, our study used two or more consecutive losses as the primary definition of RM for this population of pregnant women.

The study findings showed that a history of RM in currently pregnant women was associated with a greater likelihood of cesarean section, preterm delivery, and very preterm delivery. Similar associations were found using different RM definitions.[17,25–27] Caregiver bias, where cesarean section is chosen as a simple mode of delivery in high-risk pregnancies, has been postulated to explain the increased likelihood of cesarean section in women with a history of RM.[25,28] On the other hand, it has been suggested that both pregnancy loss and preterm delivery may be due to genital infections.[29] Other factors such as uterine malformations or endocrine issues such as polycystic ovarian syndrome (PCOS) can also be related to RM as well as poor pregnancy outcomes. Uterine abnormalities have been linked to RM as well as preterm labor and birth and abnormal fetal presentations.[30–32] Similarly, endocrine disorders such as PCOS, diabetes and hypothyroidism can be associated with miscarriage as well as poor pregnancy outcomes such as cesarean sections and inductions.[33] Unfortunately, due to the lack of availability of data on these factors, we were not able to investigate their effect on the association between RM and the adverse maternal outcomes.

The crude association between history of RM and increased blood loss during delivery was an interesting finding in this study. However, this association seemingly attenuated and did not reach statistical significance in the multivariate model following the addition of cesarean section. Previous research has reported that placental management is usually manual during cesarean section and that spontaneous expulsion of the placenta is known to result in less blood loss compared to manual removal.[34] Increased blood loss can be related to cesarean section, but it may also be related to placental and cervical insufficiency and management, as well as trauma and uterine atony,[35] which can occur as a result of multiple miscarriages.[36] Fortunately, in the case of cervical insufficiency, which might be the primary cause of RM,[37] cervical cerclage can be performed to limit the occurrence of RM. Cervical cerclage can also assist in reducing other future negative outcomes, such as placental abruption and preterm labor,[38] which was independently associated with a history of RM in this population.

This study highlights the increased risk of adverse maternal outcomes that may occur in women who have had two or more consecutive miscarriages in the form of missed miscarriages, ectopic, molar, or therapeutic abortions. Pre-pregnancy planning in women with a history of RM should include optimizing preconception health. Also, at-risk women with a history of RM should meet with care providers early during pregnancy or even prior to conception to discuss potential risks (eg, fetal growth reduction, placental dysfunction, and spontaneous preterm labor) and the need for increased maternal and fetal monitoring. Managing early pregnancy problems led to the development of early pregnancy monitoring units around the world.[39] The implementation of such units has reduced admission times and costs associated with loss.[40] The early pregnancy monitoring units can also alert physicians and other healthcare professionals to a history of RM; this can ensure better follow-up and customized care. Health policy makers and hospital management may want to consider introducing and monitoring such services.

As medical records were the basis of this analysis, it is assumed that the pregnancies, their dating, and outcomes were accurate. The relatively large sample size and detailed dataset permitted robust analyses of less common but important outcomes, such as preterm and very preterm delivery. Furthermore, since the sites of recruitment of the

study population were the three major health institutions in Al Ain, the Mutaba'ah Study was an apt population to study the impact of RM. This provided a representative pregnant population and hence reduced the chances of selection bias. We were unable to categorize the RM of each participant according to the etiology of the losses as this data was unavailable. Future studies should consider exploring whether the outcomes differed according to the etiology of RM. A common outcome of having a history of RM is the advent of future pregnancy loss in the form of miscarriages and stillbirth.[15,41] However, a complete register of miscarriages cannot be captured by the data from this interim analysis. Hence, it was deemed inappropriate to investigate the association of loss after a history of RM. Furthermore, there may have been residual confounding for factors we could not control for such as the use of artificial reproductive technology in the current pregnancy. Future studies can endeavor to understand the impact of such factors.

Conclusion

To the best of our knowledge, this study is the first and largest population-based cohort study to report the prevalence of RM and future maternal outcomes associated with a history of RM in pregnant women in the region. One in eight mothers in our population of pregnant women with gravidity of two or more prior to the current pregnancy had a history of RM. This was independently associated with several serious subsequent maternal complications, such as cesarean section, preterm delivery, and very preterm delivery. The study findings support the need for early pregnancy monitoring or assessment units to ensure better follow-up and customized care for at-risk pregnant women with a history of RM.

Abbreviations

aOR, adjusted odds ratio; APS, anti-phospholipid syndrome; CI, confidence interval; CS, cesarean section; ESHRE, European Society of Human Reproduction and Embryology; GDM, gestational diabetes mellitus; OR, odds ratio; PCOS, polycystic ovarian syndrome; RM, recurrent miscarriage; SD, standard deviation; UAE, United Arab Emirates.

Data Sharing Statement

Data can be made available on reasonable request from the Mutaba'ah Study.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committees of the United Arab Emirates University (ERH-2017-5512), Al Ain Hospital (AAHEC-03-17-058), and Tawam Hospital (IRR–494), and was in complete agreement with the Declaration of Helsinki. All participants provided written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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