PJN
ISSN 1680-5194
ansinet.com/pjn

PAKISTAN JOURNAL OF NUTRITION

Science Alert
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OPEN ACCESS Pakistan Journal of Nutrition

ISSN 1680-5194
DOI: 10.3923/pjn.2020.460.467

Systematic Review
The Risk of Recurrent Pregnancy Loss in Patients with a High Body Mass Index: An Evidence-Based Case Report

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Abstract

Background and Objective: A high body mass index (BMI) has many negative health consequences. Recurrent pregnancy loss (RPL) has become an important issue in pregnancy outcomes. An increasing frequency of RPL not only in undernourished women but also in women with high BMIs suggested that there is an association between these variables. Lack of evidence urged the authors to determine the association between RPL and high BMI to understand the correlation between RPL in women with high BMI so that BMI can be considered in the prevention of RPL with nutritional approaches. **Materials and Methods:** This evidence-based case report used the population, intervention, control, outcome (PICO) method in the literature search. A literature search was performed by hand searches and database searches in Cochrane Library, Science Direct and PubMed. The included articles were appraised for their results and quality assessment using the Center for Evidence Based Medicine (CEBM) Oxford Appraisal Tools. **Results:** We found 308 articles; however, only one meta-analysis was included in the qualitative analysis. The article concluded that there was a significant correlation between a high BMI and RPL (OR = 1.34 [95% CI, 1.05-1.70]; p = 0.02), especially in obese patients (OR = 1.75 [95% CI, 1.24-2.46]; p = 0.001). These results were in line with those of several studies and reviews. While remaining unclear, various factors are considered to cause RPL in obesity, such as abnormalities in the hormonal axis, oocyte quality, embryo development, endometrial receptivity and inflammation markers. **Conclusion:** A high BMI in pregnant women is significantly correlated with a higher incidence of recurrent pregnancy loss. Thus, comprehensive management of prenatal care including a nutritional approach is required to prevent RPL.

Key words: Body mass index, recurrent pregnancy loss, obesity, reproductive diseases, prenatal care

Citation: Tofan Widya Utami, Lowilius Wiyono, Nathalia Isabella Muskitta, Nadine Herdwita Putri Soerojo, Karel Handito Syafi Sumarsudi and Ingrid Felicia, 2020. The risk of recurrent pregnancy loss in patients with a high body mass index: An evidence-based case report. Pak. J. Nutr., 19: 460-467.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The body mass index (BMI) is a tool to measure the weight-to-height ratio of a person to classify their nutritional status. A high BMI can be classified as overweight or obesity. Overweight and obesity are defined as conditions of excessive accumulation of fat that may impair health[1,2]. The WHO[1] European BMI classification defines overweight as a condition with a BMI of >25 kg m^{-2}, while obesity is defined as a condition with a BMI of >30 kg m^{-2}. However, the WHO has lowered the BMI cut-off in the Asian population to >23.5 kg m^{-2} for overweight and >27 kg m^{-2} for obesity.[2]

A high BMI, overweight and obesity are considered major problems in the modern age. While originally considered common in high-income countries, it has progressively affected low-to-middle-income countries, especially in urban areas. The change to a sedentary lifestyle and higher consumption has increased the prevalence of overweight and obesity. In 2016, there were 1.9 billion adults (>18 years old) and more than 640 million people with obesity. Obesity and overweight have rapidly increased since 1975 and continue to increase each year. The increasing prevalence of obesity and overweight has also been observed in Indonesia. Several studies have shown that the prevalence of overweight individuals has doubled from 17.1-33% between 1993 and 2014, while obesity affects 23.1% adults[3,4].

Overweight and obesity have been linked to various comorbidities, with obesity at the center. Overweight and obesity are linked to increased risks of other metabolic diseases and a redeemed to be key players in metabolic syndrome pathophysiology, which leads to an increase in the mortality rate comparable to an increasing BMI[5]. Obesity is a known risk factor of cancer, type 2 diabetes mellitus, hypertension, stroke, coronary artery disease, etc[5,6]. One of the major pathophysiological changes in obesity is the distribution of excess weight and fat (adipocytes). The accumulation of adipocytes is known to play a role in insulin resistance, which is part of the natural history of various diseases, particularly diabetes mellitus[5,6]. Adipocytes also contribute to the increase in reactive oxygen species (ROS) and pro-inflammatory cytokines. This phenomenon then leads to the dysfunction of blood vessels, which can lead to coronary artery disease and stroke[6]. Apart from its impact on physical health, obesity also impacts both mental and social health, such as low self-esteem and mood disorders[5].

In contrast to overweight and obesity, Lorem *et al.*[7] defined the underweight as a BMI < 18.5 kg m^{-2}. In 2016, 8.9% of people globally were underweight. Southeast Asia is the region with the highest prevalence of underweight individuals, estimated at 20.3%[8]. Not only a high BMI but also a low BMI have adverse health effects. A BMI <18.5 kg m^{-2} was reported to impair quality of life[7]. Studies have shown that being underweight increases the risk of cardiovascular diseases[9]. Psychologically, being underweight has been associated with depression[10].

Both low BMI and high BMI are linked to several reproductive diseases and issues. Prepregnancy underweight status was found to have a greater risk of preterm birth, low birth weight and intrauterine growth restriction[11]. Being underweight can affect the development of the placenta in pregnant women and affect the growth of the fetus due to a lack of nutrients[12]. Obesity is linked to erectile dysfunction and impairment in the hormonal axis in males. Similar effects have been observed in females, particularly for infertility[13,14]. Obesity and overweight are known to impair the hormonal axis, which leads to anovulation. Insulin resistance plays a role in polycystic ovarian syndrome (PCOS), which leads to a decrease in the ovulation rate[13]. Overweight status and obesity are also correlated with an increased risk of pregnancy complications, especially gestational diabetes and preeclampsia and an increased rate of cesarean delivery[14].

Both undernourishment and high BMI are correlated with infertility, including recurrent pregnancy loss (RPL). RPL is an important issue in reproductive health. It affects approximately 2-5% of couples. There are debates concerning the definition of RPL and how to diagnose it in patients. However, no consensus has been achieved. The American Society of Reproductive Medicine (ASRM) defines RPL as the loss of 2 or more pregnancies with a gestational age of less than 20 weeks[15,16].

RPL has several etiologies. Anatomic defects, either acquired abnormalities, such as myomas and endometrial polyps, or congenital abnormalities, such as a bicornuate uterus, were found in 19% of women with RPL. Approximately 6-42% of women with RPL were reported to have antiphospholipid syndrome (APS). Endocrine factors also play a role in recurrent pregnancy loss. Hyperprolactinemia and hypothyroidism were found to be associated with RPL. However, the etiology of RPL in some couples is unknown. Quick evaluation and management after a 2nd pregnancy loss are required to prevent RPL. The workup and management of RPL have been heavily targeted to treat genetic factors, uterine anatomy defects and autoimmune diseases. The treatment is focused on each known etiology. RPL with unknown etiologies is managed using an empirical treatment, such as progestin-only pills to strengthen the pregnancy[17].

RPL might not be considered a comorbidity in mothers but a significant psychological factor that might affect the

patient's functionality and mental health. Women with RPL have a good prognosis of being able to maintain their next pregnancy and have a healthy live birth. This outcome can be achieved by managing the etiology of the previous pregnancy losses and is supported by the mother having a healthy lifestyle. Body mass index is one of many environmental factors that need to be paid attention during pregnancy[15].

Obesity has been found to increase maternal and fetal morbidity during pregnancy[17]. Therefore, the authors wanted to determine the connection between high BMI and RPL so that BMI can be considered in the prevention of RPL. A nutritional approach is expected to help decrease the rate of RPL. Therefore, the authors conducted an Evidence-Based Case Report (EBCR) to objectively review several pieces of literature and determine the connection between high BMI and RPL.

CASE REPORT

A 26-year-old G3P0A2 female at 21 weeks of gestation was transferred to the delivery room due to active bleeding from the birth canal followed by strong and painful contractions. After the examination, she was unsuccessfully managed on tocolytic medications and tranexamic acid. A normal vaginal birth was conducted and a baby girl with a weight of 550 g was born. However, the baby died during her transfer to the NICU. The patient had two previous abortions at 16 and 18 weeks of pregnancy.

The patient had a BMI of 31 kg m^{-2}. She and her husband asked the physician whether her nutritional status according to her BMI, in addition to other risk factors, increased her risk of recurrent pregnancy loss.

CLINICAL QUESTION

In pregnant women with a history of pregnancy loss, does high body mass index increase the risk of recurrent pregnancy loss?

MATERIALS AND METHODS

Search strategy and screening process: We used the PICO model to describe our clinical question for the search query used in every database. The PICO was pregnant women with a history of pregnancy loss (population), high BMI/overweight/obesity (intervention), normal BMI (comparison) and recurrent pregnancy loss/recurrent miscarriage (outcome). The literature search was conducted in three databases: Cochrane Library, Science Direct and PubMed. In each of these databases, we used Boolean terms to incorporate our PICO model using the key terms "pregnant women", "obesity" and "recurrent pregnancy loss", which were then combined for the literature search including their synonyms and MeSH terms. The used terms and keywords for our search query are summarized in Table 1.

Eligibility criteria: Prior to the literature search, we determined the inclusion and exclusion criteria used in this review. The inclusion criteria are listed below:

- Article written in English or Indonesian
- A systematic review, meta-analysis, randomized control trial, cohort study, or case-control study
- Article available in full text
- BMIs of the subjects in the studies are more than 25 or more than 30
- Subjects in the study with a history of two or more pregnancy losses at an age of gestation less than 24 weeks
- Article published in the last 5 years

The studies excluded from this study are listed below:

- Literature reviews
- Ongoing studies
- Studies in which the PICO method was not focused on pregnancy loss and a high BMI

Our screening process was performed using these criteria by evaluating the titles, abstracts and full text of the articles to determine their PICO parameters and study designs.

Critical appraisal and quality assessment: The critical appraisal process was performed using the Center of Evidence Based Medicine (CEBM) Oxford Appraisal Tools of Systematic Review[18]. The appraisal process was separately performed by each author. Disputes among the authors were resolved by discussion. Quality assessment was subjectively performed by each author before finalizing the assessment.

Table 1: PICO model for the clinical question

PICO	Case
Population/problem	Pregnant women with history of pregnancy loss
Intervention	High BMI, Overweight, Obesity
Comparison	Normal BMI
Outcome	Recurrent pregnancy loss, Recurrent miscarriage

RESULTS AND DISCUSSION

A total of 307 articles were found in the selected databases and screened based on the eligibility criteria in this review. No articles were eligible for the appraisal process. The reasons for exclusion of the remaining articles were as follows: 271 articles were not related to a high BMI and RPL, 14 articles were not specific to RPL, 21 articles were not specific to a high BMI and 1 article did not match the study type. A hand search was conducted to complement our literature search and one article was included in this study. An appraisal of one systematic review was conducted for study analysis. The condition of very limited resources and research conducted on this topic, especially in the last 10 years, limited our evidence-based analysis of this topic. The details and flowchart for the article selection process are shown in Fig. 1. The details of the article appraised in this study are shown in Table 2.

We conducted a critical appraisal of a systematic review by Cavalcante *et al.*[19] using the CEBM Oxford appraisal tools and the results are shown in Table 3[18]. The article used a similar PICO to that of this study and was determined to have an appropriate search strategy. The study used a total of six articles, which consisted of one case-control and five observational/cohort studies. We concluded that Cavalcante *et al.*[19] included suitable study types for this particular topic. The classification of BMI used in the study was based on the WHO classification, which was also used by the individual studies included. It classifies women in a low-weight group (BMI, <18.5 kg m^{-2}), a normal weight group (BMI, 18.5-24.9 kg m^{-2}), an overweight group (BMI, 25.0-29.9 kg m^{-2}) and an obesity group (BMI, >30.0 kg m^{-2}). RPL was defined traditionally as the loss of two or more consecutive pregnancies with a gestational age of less than 24 weeks[19].

While Cavalcante *et al.*[19] included 6 articles for their appraisal and analysis, there were only 2 articles that were then used in the meta-analysis. A total of 7,805 women with RPL were included in all studies to be evaluated for subsequent pregnancy loss. There were 4 studies[20-23] whose results demonstrated an increased risk of RPL in overweight and obese women. The case-control and prospective cohort studies of declared an odds ratio(OR) and relative risk(RR) >1; hence, the RPL incidence significantly correlated with a high BMI[15]. In contrast, a study by Bhandari *et al.*[24] declared that obese women had a better fertility rate and higher cumulative pregnancy rate than women of normal weight. Cavalcante *et al*[9]. then proceeded to conduct a quantitative analysis using the studies of Metwally *et al.*[21] and Lo *et al.*[22] as the only two studies with sufficient data for the meta-analysis. Cumulative statistical analysis of both the studies conducted by Metwaly *et al.*[21] and Lo *et al.*[22] revealed a correlation

Table 2: Appraised study detail

Authors	Population	Outcome	Study design	Level of evidence
Cavalcante *et al.*[19]	Women with a history of recurrent miscarriage	Recurrent miscarriage	Systematic Review	V

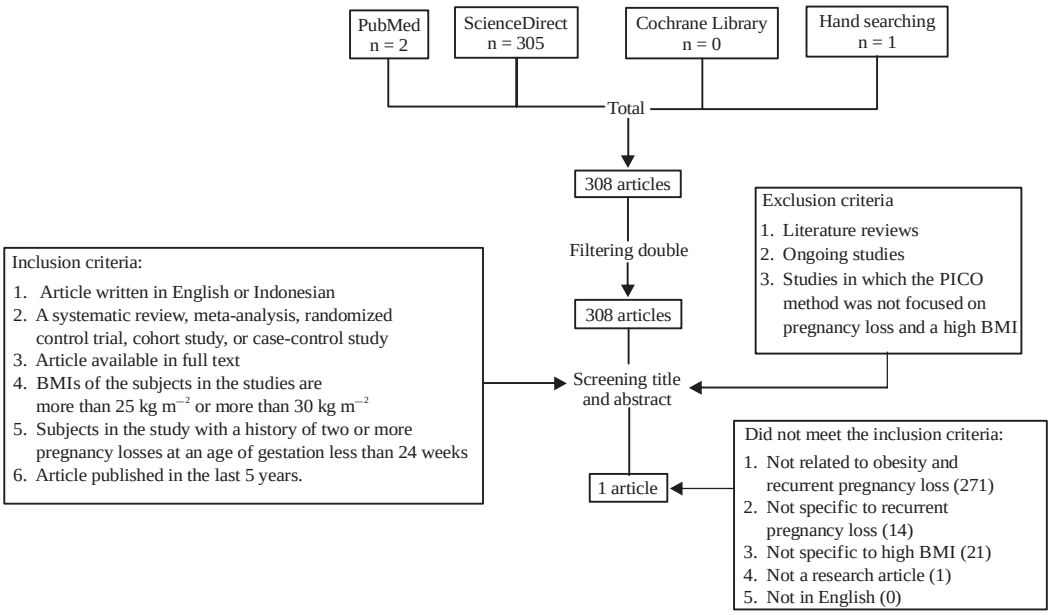

Fig. 1: Article selection flowchart

Table 3: Critical appraisal parameters

Parameters	Cavalcante *et al.*[19]
What question (PICO) did the systematic review address?	P: Women with a history of recurrent miscarriage I: Overweight and obesity C: Normal body mass index O: Recurrent miscarriage
Is it unlikely that important, relevant studies were missed?	Yes, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to perform this systematic review. The publications were discovered in the PubMed and MEDLINE databases. The keywords used were 'recurrent pregnancy loss', 'body mass index' 'overweight' and 'obesity'
Were the criteria used to select articles for inclusion appropriate?	Yes, the inclusion criteria limited the article selection based on the type of study, English language only, women with a history of recurrent miscarriage as the study population, overweight and obesity as the risk factors assessed and miscarriage as the outcome. The articles included were only those that studied humans
Were the included studies sufficiently valid for the type of question asked?	No, the quality assessment of the paper was only performed with an independent evaluation by the author based on the inclusion criteria written on the parameters above. There was no assessment on the quality of the studies using randomization, blindness, or completeness of follow-up
Were the results similar from study to study?	Unclear, this paper recognized that the population evaluated could have limited the conclusion regarding the relation of obesity and pregnancy losses in women who have PCOS or with unknown causes of abortion
What were the results?	Of the six studies obtained for qualitative evaluation, only two could be used for statistical analysis, namely, those by Metwally *et al.*[21] and Lo *et al.*[22] The OR of the statistical analysis for obesity and overweight with RPL were 1.34 (95% CI, 1.05-1.70; p = 0.02). However, an isolated analysis revealed that there was only a correlation between obesity and RPL with an OR of 1.75 (95% CI, 1.24-2.46 p = 0.001),while the results of the statistical analysis for the comparison of overweight with RPL was 1.15 (95% CI, 0.87-1.51; p = 0.33). The conclusion from the results of the statistical analysis was that there is a correlation between obesity and RPL but not between overweight and RPL

between recurrent pregnancy loss and a high BMI. An analysis of overweight and obesity vs normal weight revealed a significant comparison between the two of them (OR = 1.34 [95% CI, 1.05-1.70]; p = 0.02). However, an isolated analysis revealed that only obesity significantly correlated with a higher risk of RPL. Cavalcante *et al.*[19] concluded that there is a higher risk of RPL in women with a high BMI based on a literature review and meta-analysis.

These results are in line with those of a case-control study conducted by Zhang *et al.*[25] that evaluated the correlation between BMI and the incidence of recurrent spontaneous pregnancy loss. Zhang *et al.*[25] found a significant correlation between BMI >24 kg m^{-2} and RSM (OR = 1.54 [95% CI, 1.12-2.14]). An isolated analysis also reported a significant correlation between a BMI of >24 kg m^{-2} and 3 pregnancy losses[25]. Similar results have also been reported by Metwally *et al.*[21], who observed 16,000 patients. There was a significant increase in the pregnancy loss rates in women with a BMI >25 kg m^{-2} (OR = 1.67; [95% CI, 1.25-2.25)[26]. A review by Talmor and Dunphy[27] observed ovulation induction in overweight and obese patients. There was a significant increase in pregnancies after receiving an oocyte donation (OR = 1.52 [95% CI, 1.10-2.09]) and ovulation induction (OR = 5.11 [95% CI: 1.76-14.83]), especially in obese patients (OR = 4.68; [95% CI: 1.21-18.13]).[27] These phenomena imply a decrease in the fertility rate in patients with a high BMI. The findings of a systematic review by Boots and Stephenson[28], who observed 20,946 women, including 3,800 obese women and 17,146 normal weight women, agreed with these findings. A pooled analysis revealed a significant correlation between a high BMI and RPL (OR = 1.31 [95% CI: 1.18-1.46])[28]. While the results remain unclear, factors affecting the increasing rate of RPL in patients with a high BMI could be inferred from several studies that reported a similar trend. In 2007, Metwally *et al.*[21] reported the impact of BMI on endometrial morphology and the peri-implantation period and concluded that there was a significant effect on endometrial steroids and leukocytes (r = −0.4, p = 0.02)[29]. Arendas *et al.*[30] also reported an increasing risk of preconception and post conception consequences, including pregnancy loss, in women with a high BMI[30].

Nutrition is an important aspect in pregnancy to determine long-term health of the mother and the fetus. It is imperative that a pregnant mother has more nutritional intake; thus, women who are pregnant are encouraged to eat more and women that are planning pregnancies "stock up" on nutrition for the fetus. Malnutrition during pregnancy in low- and middle-income countries is the most prominent

factor of maternal death and disabilities. The health of not only the mother but also the fetus is affected by malnutrition. The increasing nutritional needs for mothers during pregnancy can make maternal undernutrition very harmful for both the mother and the infant.

Maternal undernutrition can lead to low birth weight, serious damage to fetal development, preterm birth, or other unsuccessful birth outcomes. Micronutrient deficiencies, such as folate, vitamin B6, vitamin B12, vitamin C, zinc and iron, have serious impacts, one of which is spontaneous abortion[31,32]. Thoughts about the dangers of underweight mothers in pregnancy are quite obvious but the risk of overweight and obesity in pregnancy is not to be underestimated. Overweight and obesity are commonly associated with complications, such as preeclampsia, preterm birth, or gestational diabetes. They also might correlate with RPL[33].

The results of an appraised systematic review by Cavalcante *et al.*[19] agree with those of a previous study by Sugiura-Ogasawara[34] who concluded that BMI >30 kg m^{-2} is an independent risk factor of RPL. Obesity increases the susceptibility of patients with RPL to further pregnancy loss. A similar result was found in the ESHRE guideline[35] on RPL. This guideline mentioned the strong association between maternal obesity and negative impact on the chances of live birth and that lifestyle modification, especially having a normal BMI, is relevant for reducing the risk of RPL[34,35].

Obesity is a risk condition of health that contributes to the etiology of many reproductive issues, including RPL. Obese patients commonly have poorer fertility prognoses compared to normal BMI controls. The mechanism behind the higher risk of RPL in patients with obesity remains unclear. Cavalcante *et al.*[19] mentioned that RPL in obese patients is associated with abnormalities in the hypothalamic-pituitary-gonadal hormonal axis and obesity directly affects oocyte quality, embryo development and endometrial receptivity. A study by Pearson and Mahmood[36] also showed that obesity affects oocyte quality and endometrial development and Bahadur and Chaturvedi[37] explained that endocrine changes in obese patients results in embryo viability.

Cavalcante *et al.*[19] explained the effects on oocyte quality and analyzed the assisted reproduction outcome based on BMI. This study showed that obese patients have significantly fewer mature oocytes than non-obese patients[19]. Obesity also affects endometrial receptivity even though the precise mechanism is still not fully understood. In addition, obese patients experience changes in the secretion of ghrelin, leptin, resist in and adiponectin. Alterations in the secretion of these hormones affects early embryo development and implantation. The quality of oocytes and the receptivity of the endometrium during embryo development and the implantation window are important components of good fertilization, resulting in a higher risk of RPL in patients with obesity[36].

Although, it is more often used in explaining the association of RPL in patients with polycystic ovarian syndrome (PCOS), one of the mechanisms for the relationship between obesity and RPL is insulin resistance. In hyperinsulinemia, plasminogen activator inhibitor-1 (PAI-1) increases. Another mechanism in obese patients that could cause RPL is chronic inflammation. Not only the increase in PAI-1 but also increases in C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha have been shown. These inflammatory markers have harmful effects on the reproductive cycle and are associated with RPL[27,36].

Looking at the association between obesity and RPL from a nutritional perspective, a dietary plan is one of the ways to reduce the risk of RPL. Weight reduction targeting a normal BMI is a rational recommendation to improve the pregnancy outcomes in obese patients with RPL. Based on a nutritional approach, a protein-rich and very low-calorie diet are useful to reduce PAI-1 activity and improve insulin sensitivity. Dietary components that increase the levels of inflammatory markers, such as large amounts of high-fat dairy, red meat, or simple carbohydrates, should be avoided in obese patients with RPL. Obese patients with RPL should find diets that lower inflammatory markers that increase in RPL patients, such as the Mediterranean diet. This dietary plan consists of fish, fruits, leafy greens and grains, which are associated with low amounts of inflammatory markers. Even though the evidence of this dietary plan is not strong enough to be a dietary plan in patients with RPL, it is still healthy, is aligned with weight loss and has low inflammatory markers. A study by Vahid *et al.*[38] also concluded that consuming a more pro-inflammatory diet has a higher risk of pregnancy loss than consuming an anti-inflammatory diet. Nevertheless, comprehensive approaches, such as exercise and pharmacology (insulin-sensitizing agents, immunological agents, or supplementation with progesterone therapy), need to be considered[19,27,36].

CONCLUSION

High BMI is correlated with the incidence of recurrent pregnancy loss, whereas pregnant women with BMIs of 25.0-29.9 kg m^{-2} are not. The mechanism of recurrent pregnancy loss in women with obesity is unclear; possible mechanisms are disturbances in the hypothalamic-pituitary-

gonadal hormonal axis, oocyte quality, endometrial receptivity and inflammatory markers. In clinical settings, we recommend a comprehensive approach in the antenatal care of pregnant women with obesity to undergo nutritional assessment and management, hoping to reduce the probability of recurrent pregnancy loss.

ACKNOWLEDGMENT

This research was not funded by any means and was fully supported by the Department of Obstetrics and Gynecology of Faculty of Medicine Universitas Indonesia.

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