

Original Paper

# Pregnancy Outcomes in Women Infected With COVID-19: A Retrospective Cohort Study



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**Citation** Nikpour M, Sepidarkish M, Darzipoor M, Sadeghi Haddad Zavareh M, Mehraeein R, Pahlavan Z, et al. Pregnancy Outcomes in Women Infected With COVID-19: A Retrospective Cohort Study. *J Holist Nurs Midwifery*. 2023; 33(3):167-175. <https://doi.org/10.32598/jhnm.33.3.2351>

**Running Title** Pregnancy Outcomes in Women Infected With COVID-19

**doi** <https://doi.org/10.32598/jhnm.33.3.2351>



**Article info:**

Received: 08/11/2021  
 Accepted: 29/01/2023  
 Available Online: 01/07/2023

## ABSTRACT

**Introduction:** Studies of the impact of the novel coronavirus 2019 (COVID-19) on pregnancy outcomes have yielded conflicting results.

**Objective:** This study examined pregnancy outcomes in COVID-19-infected and non-infected pregnant women.

**Materials and Methods:** In this retrospective cohort study, we included all pregnant women with (n=42) and without COVID-19 infection (n=185) admitted to a training and treatment center in Babol City, Iran, from March to November 2020. We abstracted the records of all pregnancies in women with COVID-19 (exposed cohort) and women without COVID-19 (non-exposed cohort). Patient information was taken from their medical records. The chi-square test and Student t-test were used for data analysis. Modified Poisson regression and mixed linear model were used to assess the adjusted risk ratio (aRR) and adjusted mean difference (aMD) between COVID-19 infection and pregnancy outcomes.

**Results:** A total of 227 pregnant women (42 in the exposure group, 185 in the non-exposed group) were included in the study. The mean age of mothers was 28.12±6.27 years, and also 48.5% of them had their first pregnancy. In comparison with non-infected women, women with COVID-19 faced the highest risk of cesarean section (aRR: 2.22, 95% CI, 1.35%-3.65%, P=0.002) and preterm birth (aRR: 1.22, 95% CI, 1.02%-1.48%, P=0.026). Also, pregnant women with COVID-19 had a significantly higher duration of hospital stay (aMD: 2.20, 95% CI, 1.32%-3.08%, P=0.001) compared to pregnant women without COVID-19. There was no significant difference between the two groups in terms of postpartum hemorrhage and premature rupture of membranes.

**Conclusion:** This study suggests that COVID-19 infection is associated with an increased risk of cesarean section, preterm birth, and increased duration of hospital stay but not with other outcomes. However, the current evidence does not support its causal effects, given the methodological limitations and small sample size.

**Keywords:**

COVID-19, SARS-CoV-2, Cohort study, Pregnancy outcome

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## Highlights

- COVID-19 infection during pregnancy is associated with an increased risk of cesarean section and preterm birth.
- Pregnant women with COVID-19 had prolonged lengths of stay compared to non-infected women.
- Postpartum bleeding and premature rupture of membranes did not increase in pregnant women with COVID-19 compared to non-infected ones.

## Plain Language Summary

The effect of COVID-19 infection on obstetric performance is less clear, and the findings are inconsistent. At the same time, some studies have found increased incidences of cesarean delivery, intrauterine distress, premature membrane rupture, abnormal amniotic fluid, umbilical cord, and abnormal placenta in these women. In contrast, others have reported no effect of COVID-19 on certain pregnancy complications. This study aims to evaluate the risk of pregnancy outcomes among women diagnosed with COVID-19 infection during pregnancy, compared to women not diagnosed with this infection. This study selected all pregnant women referred to a teaching hospital in Babol City, Iran, for vaginal delivery from March 2, 2020, to September 30, 2020. Of 227 pregnant women, 42 were infected with COVID-19 infection, and 185 were not. This study showed that COVID-19 infection during pregnancy is associated with an increased risk of cesarean section and preterm birth. However, there was no difference between the two groups of pregnant women regarding postpartum bleeding and premature rupture of membranes. Also, pregnant women with COVID-19 had prolonged stays compared to non-infected women.

## Introduction

**C** OVID-19 is the name of a newly diagnosed respiratory disease known as coronavirus or 2019-nCoV. Respiratory infections caused by coronavirus were first observed as an epidemic in Wuhan, China, in December 2019 and quickly became one of the most important health problems in the world [1-4]. The spread rate of coronavirus was such that the [World Health Organization \(WHO\)](#) identified it as a contagious pandemic disease [5, 6]. Coronaviruses can cause various illnesses, from cold to acute respiratory symptoms, and even death due to pneumonia and respiratory problems [7].

With the spread of coronavirus, the infection of pregnant women has also increased [8, 9]. Several viruses have produced maternal and fetal effects during pregnancy and may provide information on the potential impact and mechanism of COVID-19 in pregnancy [10]. Prevention and control of COVID-19 and similar diseases in pregnant women and the potential risk of vertical transmission are considered a concern [11].

In pregnant women, their tolerance to hypoxia decreases due to weakness of the immune system and physiological changes in the respiratory system (decreased diaphragm height, increased oxygen consumption, mu-

cosal edema of the respiratory tract) [12-14]. Respiratory problems are expected to increase in pregnant women with COVID-19 [14]. Decreased leukocytes and lymphocytes, increased C-reactive protein, and increased blood transfusions in pregnant women with COVID-19 have been reported in laboratory studies [9, 13, 15].

In normal pregnancy, the coagulation agents increase with raised thrombin production and intravascular inflammation [16]. Higher levels of circulating coagulation and fibrinolytic factors, such as plasmin, may be involved in the pathogenesis of SARS-CoV-2 infection [17]. Therefore, pregnant women with COVID-19 may have an increased risk of thrombosis, resulting in miscarriage and placental abruption. Community-level surveillance and further research are needed to ascertain the possible increase in abortions with COVID-19 [10].

The effect of COVID-19 on obstetric performance is less clear, and the findings are inconsistent [11]. While some studies have found increased incidences of caesarian section (CS), intrauterine distress, premature rupture of membranes (PROM), abnormal amniotic fluid, umbilical cord, and abnormal placenta in these women, others have reported no COVID-19 effect on certain pregnancy complications [9, 18-21]. A new review reports that as of January 2020, several case and cohort studies have described the presentation and clinical course of COV-

ID-19 in pregnancy. Most studies have been reassuring, and the risk of severe COVID-19 in pregnancy appears to be no higher than in the general population [10].

Although various vaccines against the coronavirus have decreased the deaths caused by it, there is still a possibility of contracting weaker and deformed strains of this virus [22].

Increased knowledge about COVID-19 infection and its new strains may enhance awareness in the health policymakers' sector, generate life-saving interventions, and improve the treatment guideline for pregnant women. This retrospective cohort study aims to evaluate the risk of pregnancy outcomes among women diagnosed with COVID-19 infection during pregnancy, compared to women not diagnosed with this infection.

## Materials and Methods

In this retrospective cohort study, all consecutive pregnant women hospitalized for vaginal delivery at a training and treatment center in Babol City, Iran, were enrolled from March to November 2020. Forty-two pregnant women had symptoms of COVID-19, and 185 had no symptoms (Figure 1). The eligibility criteria for the participants consisted of a singleton pregnancy, no history of CS, no contraindication for vaginal delivery, and no other infected disease. In this study, the data was collected from archive files.

The clinical data (signs and symptoms, underlying comorbidities, pharmacological and supportive treatments, and laboratory results) were extracted from hospital records and checked by two specialists: One specializes in Infectious Diseases and another in Health Sciences.

At admission, sputum and throat swab specimens were obtained from all pregnant women with suspected symptoms of COVID-19 and maintained in the viral-transport medium. The real-time polymerase chain reaction (RT-PCR) test for SARS-Cov-2 RNA was performed. This initial test was performed for all patients with suspected symptoms of COVID-19 who were referred to the hospital. Pregnant women were confirmed cases if the PCR test was positive for 2019-nCoV and were assigned to the exposed group. Then, women with COVID-19 infection (exposed group) underwent chest CT examinations according to infectious specialist advice for more assessment. The pregnant women were covered with a lead blanket before undergoing an abdominal and pelvic CT scan and were exposed to a low

radiation dose ( $4.1 \pm 0.9$  mGy). Pulmonary involvement was assessed by criteria such as consolidation, ground-glass opacity (GGO), and mixed GGO. Two experienced radiologists and an infectious diseases specialist evaluated all imaging features.

At admission, 5 mL of intravenous blood was taken from all pregnant women (exposed and non-exposed groups), and laboratory tests, including a complete blood count and serum biochemistry, were conducted. Routine tests were performed for both groups.

The consequences of delivery were compared in two groups of pregnant women with COVID-19 (exposed group) and non-infected pregnant women (non-exposed group). PROM is a rupture membrane before 37 weeks of pregnancy [15]. Preterm delivery (PB) is defined as babies born alive before 37 weeks of gestation [23]. Postpartum hemorrhage (PPH) is more bleeding than normal  $\leq 500$  mL in normal vaginal delivery or 1000 mL after the birth of a baby [9]. If the PPH medication prescription, such as misoprostol, methyl ergonovine, prostaglandin, and blood transmission, was recorded in the patient's hospital record, they were considered abnormal PPH [24]. Duration of hospital stay refers to the average number of days patients spend in hospital [25].

Continuous and categorical variables were described by Mean $\pm$ SD and percentage, respectively. Prenatal outcomes of the women with and without COVID-19 were compared using the chi-square test for categorical variables and the student t-test for continuous variables. Using the modified Poisson regression model, we estimated the adjusted risk ratio (aRR) and 95% CI for the history of laboratory-confirmed infection and categorical adverse pregnancy outcomes. Also, A linear mixed-effect model was used to analyze changes in continuous prenatal outcomes. The results showed by adjusted mean difference (aMD) with 95% CIs. The models were adjusted for the following variables: Gestational age (GA), parity, maternal age, adverse outcomes in previous pregnancies, previous pregnancy problems, pre-existing medical problems, and mode of delivery. Statistical analyses were performed on Stata software, version 16 (Stata Corp, College Station, TX, USA). All statistical tests were two-tailed at a significance level of  $P < 0.05$ .

## Results

During the study, 574 pregnant women were referred to the hospital for childbirth, of whom 247 had not entered the study due to a lack of inclusion criteria. Finally, 227 pregnant women (42 in the exposed group and 185

in the non-exposed group) were included in the study. Most mothers (70%) had diploma educations, 87.2% were homemakers, and 55.5% lived in rural areas. The mean age of mothers was  $28.12 \pm 6.27$  years, and also 48.5% of them had their first pregnancy.

The most common symptoms in pregnant women were fever (69.04%) and increased blood C-reactive protein (69%). Also, the most common lung lesion in chest computed tomography was GGO (83.33%).

There was no significant statistical difference between the two groups in demographic variables. Regarding midwifery variables, half of the women experienced the first pregnancy. 42.85% of pregnant women with COVID-19 had almost the same frequency of comorbidities (thyroid disorders, preeclampsia, hypertension, premature rupture of membrane) compared to pregnant women without COVID-19 (44.32%). Pregnant women with COVID-19 had a significantly lower GA (MD:  $-2.01$ , 95% CI,  $-3.23\%$  to  $-0.77\%$ ,  $P=0.002$ ) than pregnant women without COVID-19 (Table 1).

Bivariate analysis showed that the risk of CS (RR: 2.07, 95% CI, 1.40%-3.06%,  $P=0.001$ ) in women with COVID-19 was significantly higher than in non-exposed pregnant women. However, the risk of PB was identical between women with COVID-19 and controls (RR: 1.01, 95% CI, 0.77%-1.32%,  $P=0.948$ ). After adjusting for po-

tential confounders, the RR for CS remained significant (aRR: 2.11, 95% CI, 1.40%-3.18%,  $P=0.001$ ). Also, the RR for PPH became significant (aRR: 1.23, 95% CI, 1.02%-1.48%,  $P=0.026$ ). Pregnant women with COVID-19 had a significantly higher duration of hospital stay (MD: 3.58, 95% CI, 3.07%-4.10%;  $P=0.001$ ) compared to pregnant women without COVID-19. The estimated mean difference (MD) changed slightly but remained significant when adjusting for maternal age, parity, delivery type, ICU admission, GA, comorbidities, and PROM (aMD: 3.63, 95% CI, 3.10%-4.16%,  $P=0.001$ ). No significant association was found between COVID-19 infection and PROM. The estimate remained non-significant when adjusting for GA, parity, maternal age, previous pregnancy problems, and pre-existing medical problems. Also, there was no statistically significant difference between the two groups regarding postpartum hemorrhage. Adding the potential confounders to this model did not alter the estimated RR of experiencing a postpartum hemorrhage. The unadjusted and adjusted estimates for prenatal outcomes are presented in Table 2.

## Discussion

Study results showed that after adjusting for potential confounders, the risk of CS and PB in women with COVID-19 was significantly higher than in non-exposed pregnant women. But there was no significant difference between the two groups in terms of PPH and PROM.

**Table 1.** Clinical characteristics of COVID-19 infected and non-infected mothers in the study groups

Variables	Mean $\pm$ SD/No. (%)		P
	Non-infected Pregnant Women (n=185)	Infected Pregnant Women (n=42)	
Age (y)	28.74 $\pm$ 6.46	27.51 $\pm$ 6.08	0.255*
Gestational age (wk)	37.84 $\pm$ 2.90	35.83 $\pm$ 5.94	0.001*
Gravidity	1.81 $\pm$ 1.01	1.97 $\pm$ 1.13	0.321*
Parity	0.56 $\pm$ 0.82	0.64 $\pm$ 0.85	0.570*
Miscarriage	0.26 $\pm$ 0.56	0.33 $\pm$ 0.61	0.570*
Level of education	Diploma	129(69.3)	0.60**
	University	56(30.3)	
Residence place	Urban	104(56.2)	0.65**
	Rural	81(43.8)	
Occupation	Housewife	162(87.6)	0.26**
	Worker	23(12.4)	

\*The independent t-test, \*\*The chi-square test.

**Table 2.** Association between maternal infection and prenatal outcomes

Pregnancy Outcome	Crude				Adjusted					
	RR*	SE	95% CI		P	RR	SE	95% CI		
			Lower	Upper				Lower	Upper	
Cesarean section	2.07	0.20	1.40	3.06	0.001	2.11	0.21	1.40	3.18	0.001
Premature rupture of membrane	0.92	0.76	0.21	4.05	0.912	0.83	1.03	0.11	6.20	0.863
Postpartum hemorrhage	2.77	0.71	0.69	11.17	0.151	3.57	0.82	0.72	17.74	0.120
Preterm birth	1.01	0.14	0.77	1.32	0.948	1.23	0.09	1.02	1.48	0.026

Pregnancy Outcome	Crude			Adjusted				
	MD**	95% CI		p	MD	95% CI		
		Lower	Upper			Lower	Upper	
Duration of hospital stay	3.58	3.07	4.10	0.001	3.63	3.10	4.16	0.001

Abbreviations: CI: Confidence interval; Upper B; Upper bound; Lower B: lower bound; RR: Risk ratio; MD: Mean difference; SE: Standard error.

\*Risk ratio estimated directly from Modified Poisson regression. The final multivariable models were adjusted for the following risk factors: gestational age, parity, maternal age, previous pregnancy problems, and pre-existing medical problems.

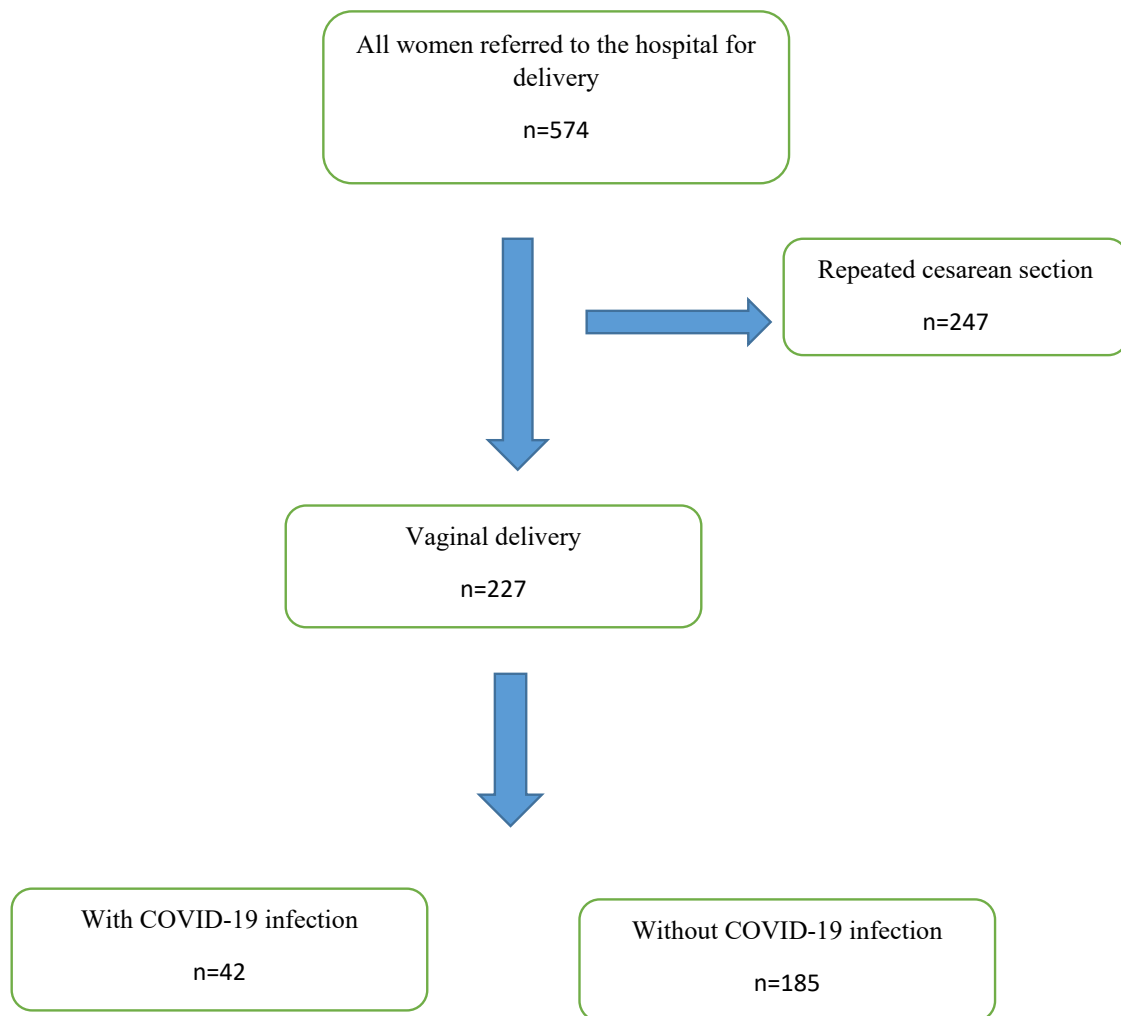
\*\*Mean difference is estimated directly from a linear mixed-effects model. The final multivariable models were adjusted for the following risk factors: Gestational age, parity, maternal age, previous pregnancy, and pre-existing medical problems.

Zhang et al. reported no significant statistical difference between pregnant women with COVID-19 and non-infected women in terms of CS [26], and our finding was inconsistent with that study. The decision to have a CS or vaginal delivery in pregnant mothers with COVID-19 depends on the severity of the symptoms in the mother and its effect on the mother and fetus [27]. In Zhang et al. study [26], only one of the 16 patients had severe symptoms, and 15 had ordinary type. In the present study, fever and dyspnea were present at 100% and 60%, respectively, in the pregnant women; therefore, the treatment teams preferred CS and terminated the pregnancy as soon as possible. These findings were against other studies [4, 28, 29]. In our study, 18% of deliveries in the exposed group were performed by CS. In the studies of Chen et al. [4] and Yu et al. [9], 100% and 19% of deliveries in pregnant women with COVID-19 were performed, respectively, by CS prematurely. A possible explanation for CS in pregnant women with COVID-19 was the lack of possible vertical transfer of the mother to the fetus and the need to save the mother's life to start antiviral treatment. Timely termination of pregnancy in COVID-19-infected pregnant women will not increase the risk of PB and infant asphyxia [2]. Also, the stress and hypoxia-induced by pneumonia lead to placenta abruption and CS [28]. Lack of information

about the possible complications of the natural delivery process and fear of legal claims were other reasons for the increase in the rate of CS during the first peak of the COVID-19.

Pregnancy may be associated with a higher respiratory problem [30]. Pregnant women experience physiological changes in their immunological and respiratory systems [31, 32]. These changes lead to respiratory complications during viral infections and increase fetal-maternal mortality. In addition, pregnant women are at higher risk in the third trimester than in the first and second trimesters because the delayed diagnosis of COVID-19 is associated with acute respiratory distress syndrome due to cytokine storm [32]. The right decision for the type of delivery and the time of termination of pregnancy for pregnant mothers with COVID-19 requires further study.

This study's findings demonstrated a significant difference between the two groups regarding preterm delivery after adjusting for the confounders. Yee et al. in a meta-analysis study of 9032 pregnant women with COVID-19 infection, showed that about 30% experienced preterm delivery [33]. Also, this result is consistent with other studies [9, 32, 34]. Other studies reported that



**Figure 1.** Flow diagram of sampling

pneumonia can increase the risk of preterm labor [28, 35-38]. For example, Tang et al. [35] reported that complicated pregnancies with pneumonia were associated with high maternal morbidity and mortality, such as preterm birth. Plasmin levels increase 50% during pregnancy compared to non-pregnancy time [39]. Plasmin and other proteases activate the surface protein of the SARS-CoV2 [32]. This protein activates the production of prostaglandins by binding and stimulating the cyclooxygenase enzyme. Therefore, high prostaglandins and other inflammatory mediators in COVID-19 with excessive immunological expression may be a potential cause of premature uterine contractions and preterm labor during COVID-19 pneumonia [40].

Study findings also showed that the hospital stay duration rate among the exposed group was significantly longer than the non-exposed group. A meta-analysis revealed that influenza infection in pregnant individuals resulted in a higher risk of hospital admission than in non-pregnant individuals [41]. The increased duration of

hospital stay in the exposed group was also due to the need for antibiotics, antiviral treatments, and oxygen support (nasal cannula) for patients. Pregnant women in the non-exposed group only receive postpartum care and discharge.

Study findings also showed no significant difference between the two groups in terms of postpartum hemorrhage after adjusting for the confounders. This finding is similar to Liu et al.'s study (15). The present study showed a 20% difference between the two study groups regarding postpartum hemorrhage in the exposed and 6% in the non-exposed groups. This difference may be significantly enhanced by increasing the sample size (in the exposed group). In the Zhang et al. study, using an analog of oxytocin (carbetocin) to treat uterine contraction fatigue in mothers with COVID-19 was significantly higher than in non-infected mothers. Zhang et al. recommend to reduce the incidence of postpartum hemorrhage during cesarean in a mother with COVID-19, it is best to use an analog of oxytocin prophylactic [26].



Our study found no significant difference between the two groups regarding PROM after adjusting for the confounders. A probable explanation for this outcome may be pregnant women with COVID-19 and GA<32 weeks were diagnosed and treated immediately. So, they were discharged in good condition after treatment. The pregnant women over 32 weeks had no difference from the control group regarding PROM. Morken et al. [42] reported that the link between maternal infection and preterm delivery may vary in different populations and healthcare settings.

The first limitation of this study was using a retrospective cohort design. Future studies are recommended to use cohort designs to provide more reliable data about the effect of COVID-19 on pregnancy outcomes. The sample size was limited. The low number of pregnant mothers in our study was related to the limited number of pregnant mothers with COVID-19 in the area (Babol in north of Iran).

This study suggests that COVID-19 infection is associated with an increased risk of CS, PB, and increased duration of hospital stay but not with other outcomes such as PROM and postpartum hemorrhage. However, given the methodological limitations and small sample size, the current evidence does not support its causal effects.

## Ethical Considerations

### Compliance with ethical guidelines

This study was approved by the Institutional Review Board of [Babol University of Medical Sciences](#) (Code: IR.MUBabol.HRI.REC.1399.074).

### Funding

This study was funded by the Health Research Institute at [Babol University of Medical Sciences](#) (Grant No.: 724132942). The funder had a role in data collection and analysis but had no role in deciding to publish or prepare the manuscript.

### Authors' contributions

Data collection: Mahboobeh Darzipoor; Draft the manuscript: Maryam Nikpour and Fereshteh Behmanesh; Review and editing: Mahdi SepidarKish, Mahmoud Sadeghi Haddad Zavareh, Rahele Mehraeein and Mahdi SepidarKish; Conceptualisation and final approval: All authors.

### Conflict of interest

The authors declared no conflict of interest.

## Acknowledgments

We want to thank Shabnam Mehdinia, Fatemeh Shafizadeh, Zinatossadat Sadat Bouzari, and Mahsa Adnani, the gynecologists of Rohani Hospital, Babol, Iran. We are also thankful to Health Center, Babol.

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