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Coronavirus Pandemic

Characteristics and Pregnancy Outcomes of Asymptomatic and Symptomatic Women with COVID-19: Lessons from Hospitals in Wuhan

Qingqing Luo[1,2], Dujuan Yao[1], Lin Xia[1], Yanxiang Cheng[3], Hui Chen[1]

[1] Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2] Department of Obstetrics, The Affiliated Hospital of Southwest Medical University, Luzhou, China
[3] Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan, China

Abstract

Introduction: The objective of the study was to compare the clinical characteristics and pregnancy outcomes of asymptomatic and symptomatic pregnant women with confirmed COVID-19 in the third trimester.

Methodology: Forty-one patients were enrolled in this study from two COVID-19 designated hospitals in Wuhan. Patients underwent chest CT scans for screening and were divided into two groups based on pneumonia-related syndromes. The clinical characteristics and pregnancy outcomes were reviewed and compared.

Results: Among the sample of pregnant women infected with SARS-CoV-2 in the third trimester, there was no mortality or severe complications in the mothers nor newborns. Nearly 40% of the patients in the study were asymptomatic. The most common pneumonia-related symptom in symptomatic pregnant patients was cough. Asymptomatic patients had a significantly shorter duration of hospitalisation and a lower rate of positive RT-PCR testing compared with symptomatic patients. There was no statistically significant difference in antibody test results between asymptomatic and symptomatic patients during hospitalisation, while the positive rate of IgM antibody testing was significantly lower in asymptomatic patients during follow-up.

Conclusions: Clinical manifestation of pregnant women infected with SARS-CoV-2 were atypical and concealed. Screening of possible COVID-19 patients should be strengthened, through serial or combined testing of laboratory testing or radiological testing, before pregnant women are admitted to hospital.

Key words: Pregnancy; asymptomatic; COVID-19; SARS-CoV-2.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in Wuhan, China, and has now spread to most regions and countries around the world. As of 15 September 2020, the World Health Organization reported 29,155,581 confirmed cases of COVID-19 worldwide, with 926,544 deaths. Pregnant women are considered to be more susceptible to coronavirus infections such as severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [1]. Moreover, respiratory infections during pregnancy are associated with unfavourable pregnancy outcomes [2]. Although several descriptive studies of the maternal and neonatal outcomes of pregnant women infected with SARS-CoV-2 have been published [3], the pregnancy outcomes in asymptomatic mothers with COVID-19 are rarely reported and there is a lack of comparison of symptomatic and asymptomatic patients. The aim of this study was to compare and evaluate the clinical characteristics and pregnancy outcomes of asymptomatic and symptomatic pregnant patients with COVID-19.

Methodology

Study design and participants

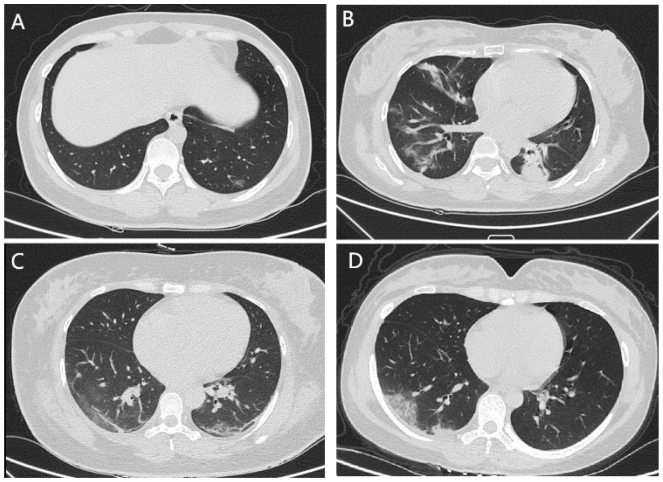
Forty-one pregnant patients were enrolled in the study. All patients were admitted to Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (HUST) or Renmin Hospital of Wuhan University between 30 January 2020 and 15 April 2020, due to confirmed or suspected COVID-19. These two hospitals are among the four designated hospitals assigned by the Chinese government to pregnant women with confirmed or suspected COVID-

19 in Wuhan. According to the policies of the Wuhan government, from the end of January to the end of June, all patients were required to undergo a chest CT scan and SARS-CoV-2 nucleic acid testing before hospitalization. Antibody tests for COVID-19 were added from the beginning of March. Patients with any abnormal results indicating SARS-CoV-2 infection were to be treated in designated hospitals. Thus, patients in the study were included because of typical CT images of viral pneumonia. The presence of SARS-CoV-2 was determined in throat swab or nasopharynx swab specimens from the upper respiratory tract by real-time (RT)-PCR, according to the guidelines for COVID-19 issued by the Chinese Center for Disease Control and Prevention (CDC). Laboratory-confirmed patients were those with positive results on SARS-CoV-2 nucleic acid testing. Clinically-confirmed patients were those with typical CT images of viral pneumonia but negative RT-PCR results. Patients who tested positive for influenza A or B, parainfluenza, or Chlamydia pneumonia were excluded from this study. This study was performed according to the Declaration of Helsinki and was approved by the Medical Ethical Committee of Union Hospital, Tongji Medical College, HUST (approval number 20200047). The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2000031140). Written informed consent was obtained from all enrolled patients. Before discharge from hospital, patients had to be recovered from COVID-19 with repeated negative results for the presence of SARS-CoV-2 and complete resolution of symptoms. The clinical characteristics and pregnancy outcomes of the enrolled patients were reviewed. All data were checked by two individuals.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means and standard deviations. Categorical variables were compared using chi-square or Fisher's exact test, as appropriate. A p value less than 0.05 was considered statistically significant. Analyses were conducted in SPSS (version 21.0).

Figure 1. CT scans of the patients.

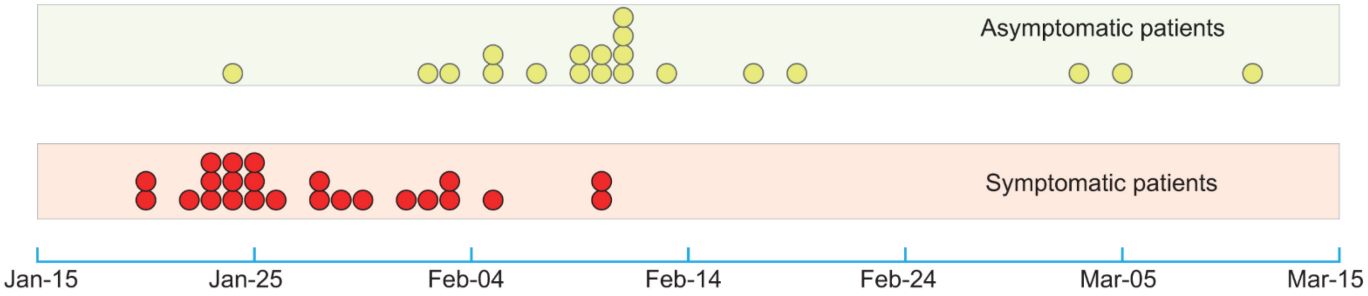


A. CT image of asymptomatic patient with negative RT-PCR result; B. CT image of asymptomatic patient with positive RT-PCR result; C. CT image of symptomatic patient with negative RT-PCR result; D. CT image of symptomatic patient with positive RT-PCR result.

Results

There was one twin pregnancy and 40 singletons among the included pregnant women. All patients were diagnosed during the third trimester. Patients were classified into two groups based on the presence or absence of pneumonia-related symptoms. The typical CT images of each group were presented in Figure1. There were 16 patients in the asymptomatic group and 25 in the symptomatic group. The diagnosis time of each patient is presented in Figure 2. Characteristics of the patients in the two groups are presented in Table 1. The average maternal age was 29.1 ± 3.7 y and 29.5 ± 3.9 y in the asymptomatic and symptomatic groups,

Figure 2. Date of illness onset in symptomatic patients and diagnosis in asymptomatic patients.



Every single dot represented a patient. Most of the asymptomatic patients were diagnosed before middle of February. The onset of symptomatic patients was all before middle of February.

Table 1. Characteristics of enrolled patients.

	Asymptomatic group N = 16	Symptomatic group N = 25	P value
Maternal average age (yr) (mean±SD)	29.1 ± 3.7	29.5 ± 3.9	0.709
BMI (mean±SD)	28.5 ± 3.6	27.4 ± 3.2	0.367
Primiparae n (%)	10 (62.5%)	16 (64%)	0.923
Chronic disease n (%)	1 (6.3)	4 (16.0)	0.632
Cardiovascular system	0 (0)	2 (8.0)	0.512
Endocrine system	0 (0)	1 (4.0)	0.610
Blood system	0 (0)	1 (4.0)	0.610
Digestive system	1 (6.3)	0 (0)	0.390
Obstetric complications n (%)	5 (31.3)	10 (40.0)	0.742
PROM	3 (18.8)	3 (12.0)	0.662
GDM	1 (6.3)	3 (12.0)	0.488
Gestational hypertension	2 (12.5)	1 (4.0)	0.550
Oligohydramnios	0 (0)	2 (8.0)	0.512
Twin	1 (6.3)	0 (0)	0.390
Polyhydramnios	0 (0)	1 (4.0)	0.610
Malpresentation	0 (0)	1 (4.0)	0.610
Placenta previa	0 (0)	1 (4.0)	0.610
ICP	0 (0)	1 (4.0)	0.610

PROM: premature rupture of membranes; GDM: gestational diabetes mellitus; ICP: intrahepatic cholestasis of pregnancy.

respectively. The average body mass index (BMI) of the two groups was 28.5 ± 3.6 and 27.4 ± 3.2, respectively. Five patients had chronic diseases involving the cardiovascular, endocrine, blood, and/or digestive system. In total, 15 patients experienced obstetric complications. There were no significant differences between the groups in terms of the above characteristics ($p > 0.05$).

COVID-19-related epidemiological features and laboratory findings are displayed in Table 2. The number of laboratory-confirmed patients in the asymptomatic group was smaller than the symptomatic group (4 vs 18, 25.0% vs 72.0%, $p < 0.05$). None of the patients had a history of exposure to the Huanan Seafood Wholesale Market. One patient (6.3%) in the asymptomatic group and seven (28.0%) in the symptomatic group reported having had contact with

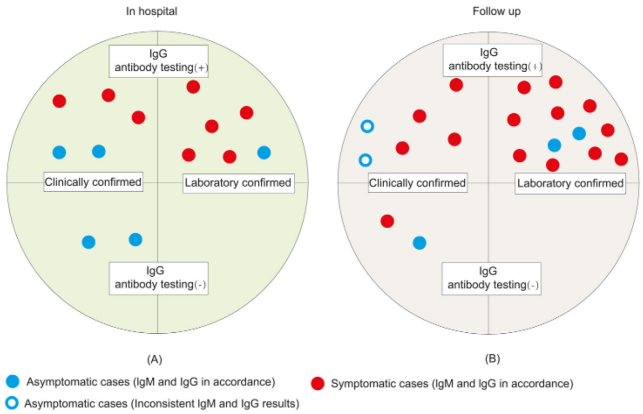
Table 2. COVID-19 related epidemiological features and laboratory findings.

	Asymptomatic group N = 16	Symptomatic group N = 25	P value
Diagnosis n (%)			
Laboratory confirmed	4 (25.0)	18 (72.0)	0.003*
Clinically confirmed	12 (75.0)	7 (28.0)	0.003*
Contact history n (%)			
Exposure to Huanan Seafood Market	0(0)	0 (0)	-
Contact with confirmed patients	1 (6.3)	7 (28.0)	0.12
Hospital-related contact	0(0)	3 (12.0)	0.268
Symptoms n (%)			
Cough	0(0)	19 (76.0)	-
Fever	0(0)	17 (68.0)	-
Dyspnea	0(0)	6 (24.0)	-
Myalgia	0(0)	3 (12.0)	-
Diarrhea	0(0)	3 (12.0)	-
Labor or threatened labor on administration n (%)	10 (62.5)	6 (24.0)	0.014*
Laboratory findings n (%)			
Elevated leucocyte (>9.5 × 10^9 cell/L)	7 (43.8)	2 (8.0)	0.017*
Lymphopenia (<10^9 cell/L)	2 (12.5)	9 (36.0)	0.098
Antibody test	N = 5	N = 8	
Positive IgM antibody	3 (60.0)	8 (100)	0.128
Positive IgG antibody	3 (60.0)	8 (100)	0.128

*: The difference was statistically significant.

other COVID-19 patients. Three patients (12.0%) in the symptomatic group were considered to be infected because of possible hospital-related transmission. There was a significantly higher proportion of women with a manifestation of labour in the asymptomatic group (10 vs 6, 62.5% vs 24.0%, $p<0.05$). There was no significant difference in contact history between the asymptomatic group and symptomatic group. Although a higher proportion of patients in the asymptomatic group showed had an increased white blood cell count (43.8% vs 8.0%, $p<0.05$), there was no significant difference in the rate of lymphopenia between the two groups (12.5% vs 36.0%, $p>0.05$). Because antibody testing was applied in the clinic from March, only 13 patients received antibody tests for SARS-CoV-2 before delivery (five in the asymptomatic group and eight in the symptomatic group). The IgM and IgG antibody test results of each patient were consistent. The rate of positive antibody results in the symptomatic group was higher than that of the asymptomatic group (100% vs 60.0%), although this difference was not statistically significant ($p>0.05$). The relationship between the antibody test results and nucleic acid test results during hospitalization are displayed in Figure 3 (A). The clinical outcomes of the mothers and infants

Figure 3. SARS-CoV-2 antibody testing results.



A. Testing during hospitalization. All the symptomatic patients received antibody tests had both positive IgG and IgM. Two patients from asymptomatic group with negative RT-PCR results had negative IgG and IgM results. B. Testing during follow-up. Most of the symptomatic patients received follow-up had both positive IgG and IgM. Results of asymptomatic patients were complicated: two had both positive IgG and IgM, one had both negative IgG and IgM and the other two had positive IgG but negative IgM.

Table 3. Maternal and neonatal outcomes.

	Asymptomatic group	Symptomatic group	P value
Maternal outcomes	N = 16	N = 25	
Cesarean section n (%)	15 (93.7)	21 (84.0)	0.632
Vaginal delivery n (%)	1 (6.3)	4 (16.0)	0.632
Postpartum fever n (%)	1 (6.3)	4 (16.0)	0.632
Duration of hospitalization (d) (mean±SD)	10.9 ± 6.1	17.5 ± 8.7	0.007*
Neonatal outcomes	N = 17	N = 25	
Premature delivery n (%)	4 (23.5)	5 (20.0)	0.537
Gender n (%)			
Male	8 (47.1)	16 (64.0)	0.276
Female	9 (52.9)	9 (36.0)	0.276
Average birth weight (g) (mean ± SD)	3105.0 ± 123.5	3044.8 ± 491.3	0.705
Respiratory symptom at birth	0 (0)	0 (0)	-
Neonatal death	0 (0)	0 (0)	-
Positive nucleic acid testing of SARS-CoV-2[#]	0 (0)	1 (4.0)	0.676
Admission to neonatology department[#]	12 (75.0)	22 (88.0)	0.401
Follow-up	N = 5	N = 17	
Mothers			
Cough	0 (0)	3 (17.6)	0.442
No symptom	5 (100)	14 (82.4)	0.442
Positive nucleic acid testing of SARS-CoV-2	0(0)	0 (0)	
Antibody test of SARS-CoV-2	N = 5	N = 15	
Positive IgM antibody	2 (40.0)	14 (93.3)	0.032*
Positive IgG antibody	4 (80.0)	14 (93.3)	0.447
Infants			
Respiratory symptom	0 (0)	0 (0)	-
Positive nucleic acid test of SARS-CoV-2	0 (0)	0 (0)	-
Positive IgM antibody test of SARS-CoV-2	0 (0)	0 (0)	-
Positive IgG antibody test of SARS-CoV-2	0 (0)	1 (4.0)	0.676

*: The difference was statistically significant; #: Five neonates did not receive PCR test at birth.

are shown in Table 3. Among the asymptomatic group, 15 patients (93.7%) had a caesarean delivery and one patient (6.3%) had a vaginal delivery. The numbers of caesarean deliveries and vaginal deliveries in the symptomatic group were 21 (84.0%) and 4 (16.0%), respectively. There was no significant difference in the ratio of delivery modes between the two groups (p>0.05). One patient (6.3%) in the asymptomatic group and four (16.0%) in the symptomatic group had postpartum fever (p > 0.05). Asymptomatic patients had a significantly shorter hospitalization duration than symptomatic patients (10.9 ± 6.1 days vs 17.11 ± 8.7 days, p<0.05). Four babies (23.5%) delivered to asymptomatic mothers were premature while five (20.0%) born to symptomatic mothers were premature (p > 0.05). The average birth weight was 3105.0 ± 123.5 g and 3044.8 ± 491.3 g in the asymptomatic and symptomatic group, respectively (p > 0.05). None of the newborns showed respiratory syndromes at birth. Twelve neonates (75.0%) in the asymptomatic group and 22 (88.0%) in the symptomatic group were sent to the neonatology department for medical observation. Thirty-seven neonates (12 in the asymptomatic group and 25 in the symptomatic group) received nucleic acid testing for SARS-CoV-2 at birth or after admission to the neonatology department. Only one neonate returned a positive result; the baby was delivered to a symptomatic mother with confirmed COVID-19. The neonate was sampled in the neonatology department on day two of life. There were no significant differences in pregnancy outcomes between the groups, except for the duration of maternal hospitalization. Twenty-two families agreed to be followed up one month after delivery, among which 5 were from the asymptomatic group and 17 were from the symptomatic group. None of the asymptomatic patients reported any discomfort after leaving hospital while three from the symptomatic group (16.7%) reported occasional cough. Throat swab samples testing for the presence of SARS-CoV-2 were negative in all of the follow-up mothers. Twenty women underwent antibody testing, 5 from the asymptomatic group and 15 from the symptomatic group. Among the asymptomatic patients, two returned positive results for IgM (60.0%) and four returned positive IgG testing (80%). IgM and IgG antibody tests for each patient were consistent in the symptomatic patients, with a positive rate of 93.3%. There was a statistically significant difference in the IgM positive rate between the groups (p < 0.05) while there was no difference in the IgG positive rate (p>0.05). The relationship between antibody test results and nucleic acid test results of mothers at follow-up is displayed in Figure 3 (B). SARS-CoV-2 nucleic acid testing was performed via throat swab in 18 infants (4 in the asymptomatic group and 14 in the symptomatic group). The results were all negative. None of the infants had pneumonia-related symptoms by the time of follow-up. Specific antibody tests were performed in 15 infants (4 in the asymptomatic group and 11 in the symptomatic group). All results were negative, except for one infant who returned a positive IgG test; this baby was born to an asymptomatic mother with confirmed with COVID-19.

Discussion

COVID-19 represents a major public health threat with high infectivity and rapid transmission. In this study, we reported and analysed maternal and neonatal outcomes in a series of pregnant women with confirmed COVID-19 in the third trimester, with and without pneumonia-related syndromes. The pregnancy outcomes of SARS-CoV-2 infection during the third trimester were good, with no mortality or severe complications observed in the mothers and newborns. Although severe cases were reported in a previous study [4], in our cohort, none of the patients developed severe symptoms of COVID-19. Our study revealed that clinical manifestation in pregnant women infected with SARS-CoV-2 were concealed and atypical. Nearly 40% of the patients in the study were asymptomatic. Among the sample, over 60% attended hospital because of signs of labour rather than for pneumonia symptoms. Similarly, Breslin et al. studied 43 pregnant women who tested positive to COVID-19 in New York city and found that nearly a third of the patients were asymptomatic [5]. It is reported that most asymptomatic patients gradually develop symptoms [6]. However, we failed to observe such development in our cohort. We speculate that this is because some women had experienced very mild syndromes that they were not aware of and had already recovered when they came into the hospital. Unlike a previous study conducted at the beginning of the crisis, the most common symptom in our symptomatic pregnant patients was cough rather than fever [7]. Further, 3 out of the 41 patients were believed to have caught COVID-19 through hospital-related transmission, including one member of the medical staff; all of these patients exhibited pneumonia-related syndromes. At present, there are no effective therapies or vaccines available for COVID-19. The best approach to decrease the risk of COVID-19 is to reduce person-to-person contact. In this study, there was an obvious cluster of patients with onset of illness in the middle of February. After this time, there were only

sever asymptomatic patients, indicating that the presence of SARS-CoV-2 in the community had subsided. It is reasonable to speculate that this phenomenon was due to the strict policies that had been implemented to reduce personal contact in Wuhan city [8]. As a highly contagious virus, SARS-CoV-2 is able to be transmitted via direct contact with an infected person or via indirect contact with objects used on or by an infected person. Transmission of COVID-19 is more likely to occur in wards since the environment is relatively closed [9]. Pregnant women are unable to avoid attending hospitals because of the need for pregnancy care and delivery. A report from a non-designated hospital in Wuhan indicated that 2.1% of pregnant women who were planned for admission presented with abnormal CT images indicating viral pneumonia [10]. This highlights the importance of screening pregnant patients before admission with the use of accurate and rapid testing. A positive RT-PCR test result in a sample from the respiratory tract confirms a diagnosis of COVID-19 without the need for further testing. However, caution should be taken with suspected patients who return a negative RT-PCR result since the performance of RT-PCR diagnostic testing can be influenced by many factors. The accuracy of RT-PCR relies on the infection course, viral shedding, and the sample collection technique. The sensitivity of RT-PCR to SARS-CoV-2 infection is around 66-80% according to a recent review [11]. In our study, the rate of positive RT-PCR results in symptomatic patients was 72%, which is in accordance with previous studies, while only 25% of the asymptomatic patients returned a positive RT-PCR test result. As an immune response to infection, serum antibodies recognize certain pathogens and provide protection from future infection by the same pathogen. Serological antibody examination serves as a supplementary measure to improve the accuracy of diagnosis. This is further highlighted by our study results, where the rate of positive RT-PCR testing was significantly lower in the asymptomatic group while the rate of positive antibody testing was statistically similar between the two groups. The median duration of IgM antibody detection is 5 days, while IgG is detected after 14 days [12]. Currently, the duration of detection of positive antibodies is largely unknown [13]. The results of antibody testing in our follow-up cohort further indicated that most of the patients still had antibodies detected one month after leaving hospital. This indicates that antibody testing may be more useful in distinguishing past infected patients. Patients in our study were all screened via chest CT scans. This strategy was employed for several reasons. First, there was limited ability to conduct RT-PCR testing and a shortage of antibody testing at the beginning of the epidemic in Wuhan. Second, the sensitivity of chest CT scans for early detection of COVID-19 has been confirmed [14]. Third, the safety of medically-indicated CT scans in pregnant women has been established [15]. Our study results also indicate that no single test is satisfactory for distinguishing COVID-19 patients; thus, serial testing or combined testing may need to be carried out according to the specific local conditions. The cesarean section rate in our study was relatively high. This was because little was known about the impacts of SARS-CoV-2 on pregnancy at the beginning of the epidemic. At this time, management was largely based on the experiences from other coronavirus infection, whereby cesarean section was deemed to be safer than vaginal delivery for infected mothers and their offspring. Another limitation of our study is the relatively small sample size. However, no new cases of COVID-19 among pregnant women were confirmed in Wuhan after the middle of March.

Conclusions

This study is the first to describe the clinical features and outcomes of COVID-19 positive pregnant women during the third trimester and after delivery. Our study showed that pregnancy outcomes of patients with confirmed or suspected COVID-19 in the third trimester are good. Clinical menifistation in pregnant women infected with SARS-CoV-2 were atypical and concealed. Screening for possible COVID-19 infection among pregnant women should be strengthened before hospitalisation through the use of serial testing or combined testing including laboratory and/or radiological testing.

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Authors' Contributions

QQL, DJY and LX contributed to data collection and manuscript preparation. QQL contributed to the original manuscript and revision of the manuscript. YXC and HC led the study. All authors read and approved the final manuscript.

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Corresponding authors

Professor Hui Chen, MD. PhD.
Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.
Tel: 86-27-84309761
Fax: 86-27-85726114
Email: chinachen67@hust.edu.cn

Professor Yanxiang Cheng, MD. PhD.
Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, Wuhan 430060, China.
Tel: 86-27-88041911
Fax: 86-27-88041911
Email: doctornancy@qq.com

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