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Letter to the editor

No obviously adverse pregnancy complications and outcomes of the recovered pregnant women from COVID-19

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ABSTRACT

The effects of SARS-COV-2 infection on the pregnant women and their fetus growth have attracted worldwide concern. Our case study aimed to investigate the neonatal clinical outcomes of the recovered pregnant women from COVID-19 in China, expecting to provide the clinical references of urgent need for other countries. Our study recruited a total of 12 recovered pregnant women from COVID-19 prior to pregnancy termination. The maternal and neonatal clinical characteristics were recorded. Of them, the placental pathological characteristics of five participants were evaluated following the standard guidelines. Two of them chose induced labour due to being worry about the potential adverse effects of medical treatment for COVID-19 by themselves. For the others, 8 gave birth by cesarean section with certain indications and 2 by vaginal delivery. Their neonates were all live birth with $\geq$ 37 gestational weeks and high Apgar scores of 9 $\sim$ 10. For the neonate related biological samples, they all have negative results of RNA test, including nasopharyngeal swab, umbilical cord blood, amniotic fluid, vaginal fluid, placenta, or umbilical cord. Most of other pathological indicators of placental examination suggested no abnormal syndromes. Overall, we did not find any abnormal pregnancy complications and neonatal outcomes among them. We concluded that excess adverse effect on the fetus development due to COVID-19 in the recovered pregnant women should be less influential, especially, induce abortion due to the anxiety of COVID-19 treatment should be not advisable.

1. Main Text

The effects of SARS-COV-2 infection on the pregnant women and their fetus growth has attracted worldwide concern [1,2]. It was reported SARS-CoV-2 can localized predominantly at the maternal-fetal interface of the placenta, highlighting its potential reproductive toxicities [3]. Likewise, various medical treatments may cause harmful effects on the fetal development. As of now, previous published studies mainly focused on the clinical characteristics on infected women with Corona Virus Disease 2019 (COVID-19) and their neonates delivered during the infection period [1–6]. These could result in certain anxiety among the infected pregnant women. It was proposed that the psychological stress experienced by pregnant women during the COVID-19 outbreak could contribute to maternal mortality [7]. Thus, our case study aimed to investigate the neonatal clinical outcomes of the recovered pregnant women from COVID-19 in China, expecting to provide the clinical references of urgent need for other countries.

This study was mainly conducted in Renmin Hospital of Wuhan University and the near hospitals in Wuhan City, Hubei Province, China, which was approved by the institutional ethics board (No. WDRY2020-K015). All the pregnant women were diagnosed with COVID-19 referring to the "Diagnosis and Treatment Protocol for COVID-19 (Seventh Trial Edition) issued by the National Health Commission of P. R. China" [8]. The recovered pregnant women from COVID-19 prior to pregnancy termination were recruited, and 12 participants with the sufficient clinical information were finally included. Written informed consent from each participant was obtained. The COVID-19 infection was confirmed based on the laboratory detection of SARS-CoV-2 RNA in nasopharyngeal swab specimens using quantitative RT-PCR analysis following the instruction of the recommended Kit by Chinese Center for Disease Control and Prevention. Of them, the placental pathological characteristics of five participants were evaluated following the recommended guidelines [9], of which the selected indicators were summarized into four categories, i.e. (1) maternal vascular malperfusion, (2) fetal vascular malperfusion; (3) ascending intrauterine infection, and (4) fibrinoid. The continuous variables were described by mean value ± standard deviation.

Their demographical and clinical characteristics were provided in Table 1. Overall, their age (years) and body mass index (kg/m^2) were 29.6 ± 3.2 and 23.4 ± 4.6, respectively. They all had singleton pregnancy and no adverse pregnancy history. Among them, the COVID-19 clinical syndromes were mostly ordinary (75%, 9/12), followed by asymptomatic types (17%, 2/12) and mild type (8%, 1/1). They were infected in three trimesters, i.e. 2 (first trimester), 5 (second trimester), and 5 (third trimester). Their mean duration from infection confirmation to being discharged from hospital were 22 ± 10 days. Prior to pregnancy termination, they were recovered from COVID-19 for 51 ± 34 days ranging from14 days (#12) to 111 days (#5). For the clinical therapeutics, 9 were treated with antibiotics, 12 with antiviral drugs, 6 with Chinese medicine, 4 with corticosteroid, and 4 with oxygen support. The detailed therapies using antibiotic and antiviral drugs, as well as the Chinese medicine, were provided in Table S1 in the Supplementary Materials. The usage of the antibiotic drugs varied with the individuals, of which Azithromycin was the most frequently used (4/10). For antiviral drugs, most of them used Abidor or Oseltamivir (10/12). Lotus Qingwen Capsules were used among all the five pregnant women who

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chose the Chinese medicine. Two of them chose induced labour due to being worry about the potential adverse effects of medical treatment for COVID-19 by themselves. For the others, 8 gave birth by cesarean section with certain indications and 2 by vaginal delivery, e.g. cervical scar, fetal macrosomia, gestational diabetes mellitus, preeclampsia, or pregnancy-induced hypertension.

Their neonates were all live birth with $\geq$ 37 gestational weeks and high Apgar scores of 9–10. For the neonate related biological samples, they all have negative results of RNA test, including nasopharyngeal swab, umbilical cord blood, amniotic fluid, vaginal fluid, placenta, or umbilical cord. For the serum antibody test, all the neonates had IgM negative. Whereas, 6 neonates had IgG positive. Of them, five participants had placental pathological examinations (see Table 2). Overall, some had certain placental infarct, increased syncytial knots, and increased focal perivillous fibrin depositions. Whereas, these symptoms were commonly observed histopathological changes compared to those of normal pregnant women empirically diagnosed by senior pathologists. Most of other pathological indicators suggested no abnormal syndromes. Overall, we did not find any abnormal pregnancy complications and neonatal outcomes among them. Unfortunately, two participants chose induced abortion because of worrying about the potential effects of medical intervention for COVID-19 treatment using various drugs, though they both did not have any adverse pregnancy complications or corticosteroid therapy.

As of the middle November 2020, more than 1.24 million of people died due to the pneumonia induced by SARS-CoV-2 infection. This sudden pandemic had caused increased strong stress and anxiety levels of pregnant women, which may prevent them from following the appropriate medical advice. From March to May, 16 pregnant women identified as being at high risk have died in Indonesia [7]. This could result in certain social panic among the pregnant women. To treat COVID-19, various drugs were inevitable to be used, including antibiotic therapy, antiviral therapy, and corticosteroid [2]. Their long-term potential effects on the fetal and neonatal developments are still under discussion. Overall, the clinical course and perinatal outcomes of our recruited 12 participants were better than the pregnant women suffering from severe acute respiratory syndrome (SARS) in the first and second trimester pregnancy [10], which is consistent with the weaker lethality of COVID-19 than the SARS for the pregnant women [11]. In our case study, the neonates were all live birth with full term of $\geq$ 37 gestational weeks. Also, their Apgar scores were in a high range of 9–10, which is comparable to the heathy ones. Thus, our preliminary study suggested

Table 1
Demographical and clinical characteristics of the recovered COVID-19 infected pregnant women.

Characteristics	Participants											
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
Age (year)	35	27	30	24	27	31	32	28	30	26	31	33
BMI (kg/m^2)	22.2	22.0	19.4	28.7	21.1	19.3	32.0	31.2	26.6	20.0	19.6	22.6
Gravidity	2	1	1	2	2	3	2	1	1	1	1	2
Parity	1	0	1	1	2	2	1	1	1	1	1	2
History of adverse pregnancy	N	N	N	N	N	N	N	N	N	N	N	N
History of immune disorders	N	N	N	N	N	N	N	N	N	N	N	N
COVID-19 clinical classification	O	A	O	O	O	A	O	O	O	M	O	O
Trimester of infection confirmation	1st	1st	2ed	2ed	2ed	2ed	2ed	3rd	3rd	3rd	3rd	3rd
Gestational age (weeks)												
Infection confirmation	9^{+1}	11^{+2}	17^{+1}	17^{+3}	20^{+4}	26^{+4}	28^{+0}	30^{+1}	31^{+6}	32^{+1}	35^{+5}	35^{+5}
Recovery	12^{+6}	14^{+2}	22^{+3}	19^{+2}	25^{+0}	29^{+3}	30^{+3}	33^{+0}	33^{+4}	37^{+0}	37^{+0}	36^{+6}
Duration (Infection → Recovery)	3^{+5}	3^{+0}	5^{+2}	1^{+6}	4^{+3}	2^{+6}	2^{+3}	2^{+6}	1^{+5}	4^{+6}	1^{+2}	1^{+1}
Pregnancy termination	21^{+0}	17^{+1}	37^{+0}	38^{+6}	40^{+6}	39^{+5}	38^{+2}	39^{+0}	38^{+2}	39^{+1}	41^{+0}	38^{+5}
Duration (Recovery → Pregnancy termination)	8^{+1}	2^{+6}	14^{+4}	19^{+4}	15^{+6}	10^{+2}	7^{+6}	6^{+0}	4^{+5}	2^{+1}	4^{+0}	2^{+0}
Complication	N	N	HHR	N	FM	/	PIH	GDM FM	PID MP	/	N	GDM
Delivery route	II	II	CS	CS	CS	VD	CS	CS	CS	VD	CS	CS
Indications of delivery	SR	SR	HHR	C-S	FM	/	PIH	GDM FM	PID MP	/	BF	SU
Medical treatment												
Antibiotics	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y
Antiviral drugs	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Chinese medicine	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N
Corticosteroid	N	N	N	Y	N	N	Y	N	N	Y	Y	N
Non-invasive oxygen support	N	Y	Y	N	N	Y	N	N	N	Y	N	N
Invasive oxygen support	N	N	N	N	N	N	N	N	N	N	N	N
Neonatal sex	/	/	F	F	M	F	M	F	M	M	M	M
Apgar score (1 min, 5 min)	/	/	9,10	9,10	9,10	9,10	9,10	9,9	9,9	9,10	9,10	9,10
Neonatal weight (kg)	/	/	3	3.5	4.2	3.5	3.6	4.5	3.2	2.7	3.5	3
Neonatal asphyxia	/	/	N	N	N	N	N	N	N	Y	N	N
Neonatal death	/	/	N	N	N	N	N	N	N	N	N	N
RNA test?	/	/	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
If Yes, Pos (+) or Neg (-)?	/	/	–	–	–	–	–	–	–	–	–	–
Nasopharyngeal swab		/	–	–	–	–	–	–	–	–	–	–
Umbilical cord blood	/	/	–	–	–	–	–	/	/	/	/	/
Amniotic fluid	/	/	–	–	–	–	–	/	/	/	/	/
Vaginal fluid	/	/	–	–	–	–	–	/	/	/	/	/
Placenta	/	/	–	–	–	–	–	/	/	/	/	/
Umbilical cord	/	/	–	–	–	–	–	/	/	/	/	/
Serum antibody test?	/	/	Y	Y	Y	Y	Y	N	Y	Y	Y	N
If Yes, Pos (+) or Neg (-)?	/	/	–	+	+	+	+	/	–	+	+	/
IgG	/	/	–	+	+	+	+	/	–	+	+	/
IgM	/	/	–	–	–	–	–	/	–	–	–	/

"/", not applicable or data missing; BF: Breech fetus; COVID-19 clinical classification: asymptomatic (A), mild syndrome (M), and ordinary type (O); CS: Caesarean section; C-S: Cervical scar; FM: Fetal macrosomia; GDM: Gestational diabetes mellitus; HHR: High fetal heart rate baseline; II: Induced labour; MP: Mild preeclampsia; PID: Pregnancy in diabetes; PIH: Pregnancy-induced hypertension; SR: Self-request; SU: Scarred uterus; VD: Vaginal delivery.

Table 2
Pathological examination of the placental samples of the selected five pregnant women.

No.	Pathological indicator	#3	#4	#5	#6	#7
Category 1: Maternal vascular malperfusion		0 = No; 1 = Yes				
1.1	Placental infarct (s)	1	1	1	1	0
1.2	Distal villous hypoplasia	0	0	0	0	0
1.3	Accelerated villous maturation pattern	0	0	0	0	0
1.4	Increased syncytial knots	0	1	0	1	1
1.5	Villous agglutination	0	0	0	1	0
Category 2: Fetal vascular malperfusion						
2.1	Avascular fibrotic villi	0	0	0	0	0
2.2	Thrombosis	0	0	0	0	0
2.3	Intramural fibrin deposition	0	0	0	0	0
2.4	Villous stromal-vascular karyorrhexis	0	0	0	0	0
2.5	Stem villous vascular obliteration	0	0	0	0	0
2.6	High-grade fetal vascular malperfusion	0	0	0	0	0
Category 3: Ascending intrauterine infection						
3.1	Maternal inflammatory response (exclude subchorionitis)	0	0	0	0	0
3.2	Fetal inflammatory response	0	0	0	0	0
Category 4: Fibrinoid						
4.1	Increased focal perivillous fibrin depositions	1	1	1	1	1
4.2	Massive perivillous fibrin deposition pattern	0	0	0	0	0
4.3	Maternal floor infarct pattern	0	0	0	0	0
Category 5: Chronic inflammation						
5.1	Chronic intervillositis	0	0	0	0	0
5.2	Chronic plasma cell deciduitis	0	0	0	0	0
5.3	Chronic chorioamnionitis	0	0	0	0	0
Category 6: Evidence of maternal decidual arteriopathy						
6.1	Insufficient vessel remodeling	0	0	0	0	0
6.2	Fibrinoid necrosis	0	0	1	0	0

that there were no significant adverse neonatal outcomes of the recovered pregnant women, if they were treated using appropriate medical care. In China, the guideline to treat the infected pregnant women was regulated in time since February 10th, 2020 by China State Council and updated accordingly [12]. Therefore, the related clinical diagnosis and treatment can be standardized with appropriate therapeutic means. As of now, there were very scarce reports about the death of pregnant women in China.

During the COVID-19 infection period, high ratio of pregnant women chose caesarean section [1,2,6], which is reasonable due to the potential adverse effect of their high body temperature or various drug intake. Similar results were also found in other countries [13]. But, for the recovered ones without severe or critical illness, the excess anxiety about the harmful effect on their fetuses induced by COVID-19 infection should be lowered. This viewpoint was also supported by their placental pathological examination results, which were overall consistent with those from the pregnant women who gave birth during the infection period [4]. In addition, we found that RNA test results for all the neonate-related biological samples were negative. Some of their serum antibody test results were positive, but they did not have IgM positive, which were the critical evidence confirm their infection status. It has been known that IgG has relatively smaller molecular weight than IgM, and may be originated from mothers' body, which has no injuries to the fetus. Our study revealed that placenta seems to protect the fetus from the infection of SARS-CoV-2 with high efficiency after their mothers were cured. Heretofore, the previous reports with large population size did not suggest a significantly increased risk of severe disease among pregnant women [2,6,14]. Our study further indicated that excess adverse effect on the fetus development due to COVID-19 in the recovered pregnant women should be less influential, especially, induced abortion due to the anxiety of COVID-19 treatment should be not advisable. However, it is noted that our clinical case study has very small size of pregnant women and more population should be included in future. Our study results can provide important information of the previous recovered pregnant women from COVID-19 for reference. This is a unique perspective to initiate more researchers to provide more scientific study design to confirm.

Data description

The data will be available by contacting the corresponding author of this study.

Declaration of Competing Interest

All authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reprotox.2020.11.008.

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