



Did Pregnancy Complications Increase During The COVID-19 Pandemic Period?

COVID-19 Pandemi Sürecinde Gebelik Komplikasyonları Arttı mı?

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Abstract

Aim: This study aimed to investigate the potential increase in pregnancy complications during the pandemic period.

Material and Methods: Data of the pregnant women who were admitted between April/May 2019 and April/May 2020 for stillbirth, preterm labor, term prelabor rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), placental abruption, miscarriage and abortion imminens were collected from the hospital database and retrospectively analyzed. Mann-Whitney U test was used to compare continuous variables between the diagnostic groups according in 2019 and 2020. The relationships between the categorical variables were tested by Chi-Square analysis.

Results: During the COVID-19 pandemic period between April/May 2020, 1604 deliveries occurred in our hospital. Total 1401 deliveries had occurred in the same monthly interval of 2019. In the early pregnancy unit, 566 patients were admitted to be monitored in 2019 whereas that number is 466 in 2020. In the pandemic period, a statistically significant difference was found between 2019 and 2020 regarding the rates of admission after the 22nd gestational week and admission to the Early Pregnancy Assessment Unit. Bonferroni tests were performed to determine which group of the patients generated this difference and it was determined that the rates of term PROM and miscarriage increased statistically significantly in 2020 compared with 2019.

Conclusion: We concluded that the effect of COVID-19 on symptomatic and asymptomatic pregnant women will be further clarified by switching to a routine screening program for pregnant women in our country. COVID-19 antibody testing is important to confirm our results in the cases with term PROM and miscarriage who are asymptomatic with respect to COVID-19.

Keywords: Asymptomatic; complication; COVID-19; pandemic; pregnancy

Öz

Amaç: Bu çalışmada, pandemi döneminde gebelik komplikasyonlarındaki olası artışı araştırmayı amaçlamaktayız.

Materyal ve Metod: Nisan / Mayıs 2019 ile Nisan / Mayıs 2020 tarihleri arasında ölü doğum, erken doğum, erken membran rüptürü (EMR), preterm prematür membran rüptürü (PPROM), dekolman plasenta, düşük ve düşük riski nedeniyle başvuran gebelerin verileri hastane veri tabanından toplandı ve geriye dönük olarak analiz edildi. 2019 ve 2020 yıllarında tanı grupları arasında sürekli değişkenlerin karşılaştırılmasında Mann-Whitney U testi kullanıldı. Kategorik değişkenler arasındaki ilişkiler, Ki-Kare analizi ile test edildi.

Bulgular: Nisan / Mayıs 2020 arasındaki COVID-19 pandemi döneminde hastanemizde 1604 doğum gerçekleşti. 2019 yılının aynı dönemde toplam 1401 doğum gerçekleşti. Erken gebelik ünitesinde 2019 yılında 566 hasta takip edilirken, bu sayı 2020 yılında 466 idi. Pandemi döneminde 2019-2020 yılları arasında 22. gebelik haftasından sonra başvuru ve Erken Gebelik Birimi'ne başvuru oranları açısından istatistiksel olarak anlamlı fark bulundu. Bu farkı hangi hasta grubunun oluşturduğunu belirlemek için Bonferroni testleri yapıldı ve 2020 yılında EMR ve düşük tanılı hasta oranlarının 2019'a göre istatistiksel olarak anlamlı şekilde arttığı belirlendi.

Sonuç: Ülkemizdeki hamile kadınlar için rutin tarama programına geçilerek COVID-19'un semptomatik ve asemptomatik gebeler üzerindeki etkisinin daha da netleşeceği sonucuna vardık. Asemptomatik EMR ve düşük tanılı gebelerde COVID-19 antikor testi, COVID-19 tanısını doğrulamak için önemlidir.

Anahtar Kelimeler: Asemptomatik, komplikasyon, COVID-19, pandemi, gebelik

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INTRODUCTION

COVID-19 is an enveloped single-stranded RNA coronavirus. Coronavirus takes its name from the Latin word "corona" which means crown because of its crown-like appearance under the electron microscope formed by thick spike glycoproteins on its surface (1). The disease (maybe also named as disease spectrum) caused by COVID-19 infection was first detected in Wuhan, China in late 2019 and spread to the world in a short period of time. In February 2020, the World Health Organization (WHO) named the disease and the causative virus as COVID-19 and "Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)", respectively (2). The virus may be transmitted through droplets and hand contact with contaminated surfaces and eventually reach mouth, eyes, and nasal mucosa (3). WHO declared the COVID-19 pandemic on March 11, 2020. On the same day, the first case of Covid-19 was detected in our country (3,4).

The symptoms of COVID-19, including most commonly fever and cough, are similar in pregnant and non-pregnant women (5). COVID-19 is not considered to be more contagious in pregnant women. Intrauterine passage of the virus to the fetus and congenital infection have not been proven yet since no adequate data since no adequate data could be obtained (6). COVID-19 testing of the infants born to COVID-19 infected mothers were found negative (7).

In a study carried out with 215 patients, COVID-19 screening was performed in all the patients admitted for delivery. The test results were positive in 13.7% of 210 asymptomatic patients (8). Another study has reported that 7.2% of COVID-19 positive pregnant women were asymptomatic (9). Taking the false negativity of the diagnostic tests into consideration, this rate may be considered higher (10). There is no study available in the literature that addressed potential pregnancy complications in asymptomatic COVID-19 positive pregnant women.

Influenza virus with clinical symptoms similar to COVID-19 is also a pandemic factor that may cause serious complications including maternal death in pregnant women in certain periods of the year (11). Although the fetal transmission of influenza is rare, adverse fetal and neonatal outcomes have been reported (12,13).

In order to investigate potential pregnancy complications that may increase during the pandemic period, we aimed to compare pregnancy complications that occurred during the pandemic period and in the same period of last year.

MATERIAL and METHODS

Our hospital is a tertiary reference center for gynecology and obstetrics, with an annual average of 15,000 deliveries. This study was approved by the Medical Specialty Education Board of Etlik Zübeyde Hanım Women's Health Practices & Research Center with Decision Number:7 and Dated May 4, 2020 and Covid-19 Scientific Research Council of Republic of Turkey Ministry of Health Dated

May 16, 2020. During the pandemic period our hospital continued to perform monitoring and deliveries of asymptomatic pregnant women without a diagnosis of COVID-19. In this period, routine COVID-19 screening was not performed for pregnant women; however, all patients were evaluated in detail regarding symptoms, contact with COVID-19 patients, and history of foreign travels.

Our study data of the pregnant women who were admitted for stillbirth, preterm labor, term prelabor rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), placental abruption, miscarriage, abortion imminens between April/May 2019 and April/May 2020 were collected from the hospital database and retrospectively analyzed. Stillbirth is defined as pregnancy loss after 22nd week of gestation or a fetus weighing over 500 g; preterm labor is the occurrence of birth between 22nd and 37th gestational week; term PROM is the rupture of the membrane after 37th gestational week before regular contractions occur; PPROM is the rupture of membranes between 22nd and 37th weeks of gestation; placental abruption is defined as the partial or complete prenatal detachment of the placenta, miscarriage is the spontaneous abortion leading to loss of complete or incomplete pregnancy before 22nd week of gestation or fetal weight less than 500 g, and abortion imminens as vaginal bleeding without cervical dilatation. The early pregnancy assessment unit is the service that monitors pregnancy complications before the 22nd gestational week. Pregnant women with miscarriage, maternal age over 45, multiple miscarriages, specified infectious disease, diabetes, obesity ($BMI \geq 35$), thyroid disease, thrombophilia, teratogen drug use, pregnancy trauma, uterine anomaly, known chromosomal and/or structural anomalies were excluded.

Data entry errors and the fact whether the parameters were within the expected range were checked before the statistical analysis. Normality assumptions of continuous variables were examined using the skewness and kurtosis coefficients, histogram, Q-Q plots and Kolmogorov-Smirnov test. Mann-Whitney U test was used to compare continuous variables between the diagnostic groups according in 2019 and 2020. The relationships between the categorical variables were tested by Chi-Square analysis. All analyzes were performed using IBM SPSS software Version 23. Any p value less than 0.05 was considered statistically significant.

RESULTS

During the COVID-19 pandemic period, a total of 1604 deliveries occurred in our hospital between April and May 2020. The number of deliveries was 1401 in the same monthly interval of 2019. The number of patients that were monitored in the early pregnancy unit in 2019 and 2020 was 566 and 466, respectively. No statistically significant difference was found between the years 2019 and 2020 regarding the numbers of gravidities, parity, maternal age, and gestational week at diagnosis ($p > 0.05$) (Table 1).

Table 1. Comparison between 2019 and 2020 in terms of gravidity, parity, maternal age and gestational week

Diagnosis		Year (n)	Ort.±SD	Median (Min–Max)	P
Term PROM	Gravidity		2.21±1.45	2.00 (1.00-7.00)	0.902
			2.21±1.40	2.00 (1.00-7.00)	
	Age	2019 (n=143)	27.73±6.53	27.00 (16.00-43.00)	0.975
		2020 (n=226)	27.73±6.16	26.50 (16.00-45.00)	
PPROM	Gravidity		2.12±1.38	2.00 (1.00-7.00)	0.995
			2.24±1.66	2.00 (1.00-9.00)	
	Age	2019 (n=57)	25.95±5.30	25.00 (18.00-42.00)	0.409
		2020 (n=59)	25.53±6.22	24.00 (16.00-42.00)	
Preterm labor	Gravidity		2.53±1.37	2.00 (1.00-7.00)	0.953
			2.53±1.33	2.00 (1.00-7.00)	
	Age	2019 (n=70)	27.39±6.27	27.00 (18.00-44.00)	0.763
		2020 (n=62)	27.61±5.87	26.00 (18.00-44.00)	
Stilbirth	Gravidity		2.40±.89	3.00 (1.00-3.00)	0.403
			2.08±.90	2.00 (1.00-4.00)	
	Age	2019 (n=5)	2.21±1.45	31.00 (20.00-39.00)	0.916
		2020 (n=12)	2.21±1.40	28.50 (23.00-41.00)	
Placental abruption	Gravidity		1.33±.58	1.00 (1.00-2.00)	1
			1.33±.58	1.00 (1.00-2.00)	
	Age	2019 (n=3)	25.33±7.02	26.00 (18.00-32.00)	0.827
		2020 (n=3)	26.00±4.58	25.00 (22.00-31.00)	
Miscarriage	Gravidity		2.69±1.51	2.00 (1.00-9.00)	0.557
			2.77±1.49	3.00 (1.00-8.00)	
	Age	2019 (n=142)	31.21±6.58	31.00 (18.00-45.00)	0.238
		2020 (n=171)	30.33±6.44	30.00 (19.00-50.00)	
Abortus imminens	Gravidity		2.17±1.34	2.00 (1.00-7.00)	0.037
			2.53±1.36	2.00 (1.00-7.00)	
	Age	2019 (n=105)	29.93±5.51	30.00 (18.00-43.00)	0.249
		2020 (n=78)	29.10±6.02	28.00 (18.00-45.00)	
	Gestational week		11.02±3.45	11.00 (5.00-19.00)	0.38
			10.59±3.46	10.00 (6.00-19.00)	

PROM: prelabor rupture of the membranes; PPRM: preterm premature rupture of the membranes

A statistically significant difference was determined between the pandemic period and 2019 in terms of admission rates over the 22nd week of gestation ($p: 0.016$) (Table 2).

Bonferroni tests were performed to determine which diagnosis generated this difference and it was detected that the rate of term PROM (14.1%) statistically significantly increased in 2020 compared with 2019 (10.2%).

As shown in Table 3, a statistically significant difference was encountered between the pandemic period and 2020 regarding the rates of admission to the early pregnancy unit ($p<0.001$). Bonferroni tests were performed to determine which diagnosis generated the difference and it was found that the rate of the patients diagnosed with miscarriage statistically significantly increased in 2020 (36.7%) compared with 2019 (25.1%), (Table 3).

Table 2. Distribution of the diagnosed complications according to years (≥ 22 nd gestational week)

Diagnosis	2019		2020		χ^2	p
	n	%	n	%		
Term PROM	143	10.2	226	14.1	3.998	0.016
PPROM	57	4.1	59	3.7		
Preterm labor	69	4.9	63	3.9		
Stillbirth	5	0.4	12	0.7		
Placental abruption	3	0.2	3	0.2		
Others	1124	80.2	1275	77.4		

PROM: prelabor rupture of the membranes; PPRM: preterm premature rupture of the membranes

Table 3. Distribution of the diagnosed complications according to years (≤ 22 nd Gestational week)

Diagnosis	2019		2020		χ^2	p
	n	%	n	%		
Miscarriage	142	25.1	171	36.7	16.546	0.00
Abortus imminens	105	18.6	78	16.7		
Others	319	56.4	217	46.6		

PROM: prelabor rupture of the membranes; PPRM: preterm premature rupture of the membranes

DISCUSSION

Even though, no symptomatic or COVID-19 patient was admitted to our hospital during the pandemic period, the number of asymptomatic cases is non-negligible. We aimed to determine whether there is an increase in the rates of potential pregnancy complications for asymptomatic pregnant women.

The genetic similarity of Covid-19 with Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) was shown 50% and 79%, respectively (1). Coronavirus infection in pregnant women is associated with abortion, preterm labor, placental abruption, intrauterine growth retardation, preeclampsia, cesarean delivery and stillbirth (13). Influenza virus, which causes another respiratory infection, has been shown to be associated with miscarriage, stillbirth, growth retardation, preterm labor and neonatal death

(12,14). The maternal mortality rates for MERS and SARS ranges between 25% and 30%, respectively (13). In a meta-analysis carried out about COVID-19, maternal death was determined to be 0.3% (5). Although the mortality rate for COVID-19 has been shown to be less than other coronaviruses, it is estimated that a higher number of more pregnant women are infected taking its high rate of spread into consideration (1).

Pregnant women in the pro-inflammatory period in the first and third trimesters are expected to reveal serious inflammatory results by COVID-19 (15). Although COVID-19 is not associated with poor pregnancy and neonatal outcomes, preterm labor and cesarean delivery rates ranging between 15-21.2% and 69.4%-85.9% were encountered particularly in the symptomatic cases, respectively (5,16). In a study conducted in our country, SARS-CoV-2 positivity was observed in 3 (1.4%) of 206

asymptomatic pregnant women who were hospitalized for delivery (17). In our study, a statistically significant increase was determined in the rate of term PROM compared with the last year. Inflammation shows a strong correlation with the early rupture of membranes (18). The fact that the inflammatory process is still unclear in asymptomatic cases leads to the potential correlation between the increased rates of term PROM cases and the rate of asymptomatic COVID-19 cases.

Although, the data related to COVID-19 cases in the first trimester of pregnancy are limited, the infection has not been found associated with spontaneous abortion (5,16). One of 8 symptomatic cases with a gestational age less than 24 weeks had a missed abortion (16). The different studies have reported that the rate of asymptomatic cases ranged between 13.7% and 23.3% and there is no clear information on early gestational complications for asymptomatic cases (5,16). In the asymptomatic COVID-19 cases, the effect of the infection on placental and fetal development stages in the early gestational weeks is unknown. In our study, a statistically significant increase was noticed in the number of miscarriages compared with the last year suggesting the probable relationship with the increased number of asymptomatic cases.

The strength of the study is that our hospital is an obstetric center with a large amount of patient admissions. The weakness of the study is that all pregnant women were not screened during study period

CONCLUSION

The COVID-19 pandemic is still an unknown disease including its probable duration. Further studies are needed to clarify its probable effect on pregnant women and the gestational period. We expect that the effect of the infection on symptomatic and asymptomatic pregnant women will be clarified by switching to routine screening program for all the pregnant women in our country. COVID-19 antibody testing is crucial for confirmation of our results regarding the cases with term prelabor rupture of membranes and miscarriage who are asymptomatic for COVID-19.

Conflict of Interest: *The authors declare that they have no competing interest*

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Ethics committee approval : *Medical Specialty Education Board of Etlik Zübeyde Hanım Women's Health Practices & Research Center with Decision Number:7*

REFERENCES

- Lu Roujian Z, Juan L, Peihua N, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (Lond, Engl)*. 2020;395:565-74.
- WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020> access date 18.05.2020.
- Turkish Ministry of Health, Directorate General of Public Health, Covid-19 Guide. https://hsgm.saglik.gov.tr/depo/birimler/goc_sagligi/covid19/rehber/COVID-19_Rehberi20200414_eng_v4_002_14.05.2020.pdf access date 18.05.2020.
- Coronavirus disease 2019 (COVID-19): situation report, 51 <https://apps.who.int/iris/handle/10665/331475> access date 18.05.2020.
- Elshafeey F, Magdi R, Hindi N, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2020;150(1):47-52.
- ACOG. Practice Advisory: Novel Coronavirus 2019 (COVID-19). <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019> access date 17.04.2020.
- Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet (London, England)*. 2020;395(10231):1225-1228.
- Sutton D, Fuchs K, D'Alton M, et al. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *The New England journal of medicine*. 2020;382(22):2163-2164.
- Ai T, Yang Z. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. 2020;296(2):E32-e40.
- Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *Jama*. 2010;303(15):1517-1525.
- Conover PT, Roessmann U. Malformational complex in an infant with intrauterine influenza viral infection. *Arch Pathol Lab Med*. 1990;114(5):535-538.
- Schwartz DA, Dhaliwal A. Infections in pregnancy with COVID-19 and other respiratory RNA virus diseases are rarely, if ever, transmitted to the fetus: experiences with Coronaviruses, HPIV, hMPV RSV, and INFLUENZA. *Arch Pathol Lab Med*. 2020.
- Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM*. 2020;2(2):100107.
- Håberg SE, Trogstad L, Gunnes N, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. *The New England journal of medicine*. 2013;368(4):333-340.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*. 2020;395(10223):497-506.
- Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. *Am J Obstet Gynecol*. 2020;223(1):111.e111-111.e114.
- Tanacan A, Erol SA, Turgay B, et al. The rate of SARS-CoV-2 positivity in asymptomatic pregnant women admitted to hospital for delivery: Experience of a pandemic center in Turkey. *Eur J Obstetrics, Gynecol Reproductive Biology*. 2020;253:31-4.
- Kumar D, Moore RM, Mercer BM, et al. The physiology of fetal membrane weakening and rupture: Insights gained from the determination of physical properties revisited. *Placenta*. 2016;42:59-73.