Hematologic adaptation to mask wearing and obstetrical outcome during the COVID-19 pandemic - a cohort study

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Abstract

Objectives: Mask-wearing can induce relative hypoxia, affecting hematologic parameters. We aimed to evaluate the effect of the COVID-19 mask-wearing on hematological laboratory components and obstetrical outcome among women delivering during this period. Design: Retrospective cohort study Setting: Tertiary medical center. Population: Pregnant women delivering a singleton gestation. Methods: Obstetrical outcome and laboratory results of women admitted for delivery throughout the mask-wearing period were compared to those delivering during the parallel period in 2019, and to a larger cohort derived from nine pre-pandemic years Main outcome measure: Hematological, delivery and neonatal outcomes characteristics. Results: Overall, 1,939 women delivered during the COVID-19 pandemic. Compared with the pre-pandemic period, the mean hemoglobin and fibrinogen levels were significantly higher during the mask-wearing period [12.15±1.1 vs. 11.96±1.2, p<0.001 and 472±103.6 vs. 448±85.1 (mg/dL), p<0.001, respectively]. Platelets levels were lower [200±56.0 vs. 206±57.5 (K/microL), p<0.001]. The rate of delivery<34 weeks of gestation was lower during the mask-wearing period [1.1% vs. 2%, OR-0.57 (95% CI, 0.37-0.88), p=0.01], while cesarean delivery and postpartum hemorrhage rates were higher [[26.7% vs. 24.4%, OR- 1.13 (95% CI, 1.02-1.25), p=0.022 and 4.1% vs. 2.8%, OR- 1.5 (95% CI 1.2-1.8), p=0.001, respectively], Conclusion: A hard-to-ventilate space created by wearing a mask may be the underlying cause of the observed higher hemoglobin level among pregnant women. This change might have a biological relation to changes in the rate of obstetrical outcome. Funding: no external funding. Keywords: COVID-19, preterm birth, cesarean delivery, composite neonatal outcomes, hemoglobin, fibrinogen, platelets, mask-wearing.

Introduction

Coronavirus disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, China, and resulted in an ongoing pandemic. On March 19, 2020, the Israeli government declared a national state of emergency and starting at April 12, Israelis were obligated to wear a face mask. Mask-wearing over the mouth and nose creates a hard-to-ventilate space which might accumulates CO^2 and induces a relative hypoxia[1]. Hypoxia stimulates erythropoietin secretion, leading to red blood cell production in the bone marrow and therefore elevated hemoglobin levels[2]. Although there is a debate regarding the impact of hypoxia on other hematologic parameters, when examining long term hypoxia exposure, prior research has found an elevated fibrinogen levels and lower platelets levels[3].

Currently, governments formulate regulations in order to suppress the spread of the COVID-19, and a better understanding of these regulations consequences is required. The hematological impact of wearing a mask

during the COVID-19 era is understudied. In this study, we aimed to underline the association of oxygen deprivation caused by mask-wearing and parturient hematologic and obstetrical outcomes.

Methods

This was a retrospective cohort study conducted at a single university affiliated, tertiary medical center. The center treats a heterogeneous population with over 10,000 deliveries per year. The study cohort included pregnant women admitted to the obstetrical emergency unit for delivery during the mask-wearing period during the COVID-19 pandemic (April 19 to June 27, 2020), starting seven days after initiation of the mask-wearing regulations in our country, to account for the delay between erythropoietin secretion and the rise in hemoglobin levels. We compared these women's characteristics and outcomes to two pre-pandemic time frames- the parallel period in 2019 (April 19 to June 27, 2019), and a longer period between March 21, 2011 and April 18, 2020.

We abstracted labor and delivery charts from the electronic medical record database of the labor and delivery ward of our center. The following data were extracted: patient characteristics (age, body mass index, smoking, COVID-19 infection status and hemoglobin, platelets, fibrinogen and white blood cells levels); delivery and postpartum characteristics (gestational age at delivery, mode of delivery, postpartum hemorrhage, blood product transfusion); neonatal outcomes including birthweight, Apgar score, umbilical artery pH and base excess, neonatal intensive care unit (NICU) admission, stillbirth, neonatal death, mechanical ventilation, hypoxic-ischemic encephalopathy, convulsions, asphyxia and hypothermic treatment.

Maternal body mass index (BMI) was calculated according to height and weight at admission. Post-partum hemorrhage was defined by The American College of Obstetricians and Gynecologists as cumulative blood loss of greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours of the birth process. Composite bleeding was defined as the presence of post-partum hemorrhage of blood products transfusion. Composite neonatal outcome included the presence of any of the neonatal outcomes studied.

Institutional review board approval was obtained for this retrospective study on March 30,2020 (# 7068-20-SMC).

Statistical analysis

Patient characteristics are described as proportions for categorical variables and as means and standard deviations for continuous variables. Significance between study groups was assessed by the Chi square test and Fisher's exact test for categorical variables, t-test and the Mann-Whitney U test, were used as appropriate in relation to cohort distribution. We further divided the whole study cohort into two groups: hemoglobin <11g/dL and [?]11g/dL. A logistic regression analysis was performed to underline independent determinants associated with hemoglobin levels <11g/dL. The model included variables with a potential association with hemoglobin level, age, BMI, smoking status, parity, gestational age at delivery and the period evaluated with respect to the COVID-19 pandemic. A 2-sided P-value < 0.05 indicated statistical significance. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 24, IBM Corp, Armonk, NY).

Results

From April 19 to June 27, 2020, 1,838 women were referred to the delivery unit, compared to 88,973 women between March 21, 2011 and April 18, 2020. A comparison of clinical parameters, delivery data and neonatal outcomes between the mask-wearing period and pre-pandemic periods is presented in Table 1. Compared with the 2011 to 2020 pre-pandemic period, the mean hemoglobin levels and the proportion of women with hemoglobin>13 (g/dL) were significantly higher during the mask-wearing period [12.15±1.1 vs. 11.96±1.2, p<0.001; 21.5% vs. 16%, OR-1.43 (95% CI, 1.28-1.61), p<0.001 respectively], while the proportion of women with hemoglobin <11 g/dL was lower [13.5% vs. 16.5%, OR-0.79 (0.69-0.91), p=0.01]. Platelets levels were lower during the pandemic period compared to the pre-pandemic period [200±56.0 vs. 206±57.5 (K/microL),

p<0.001], while fibrinogen levels were higher [472±103.6 vs. 448±85.1 (mg/dL), p<0.001]. Cesarean delivery rates were higher during the mask-wearing period compared to the pre-pandemic period [26.7% vs. 24.4%, OR- 1.13 (95% CI, 1.02-1.25), p=0.022], while rates of delivery<34 weeks of gestation were lower [1.1% vs. 2%, OR-0.57 (95% CI, 0.37-0.88), p=0.010]. The rate of post-partum hemorrhage and the composite bleeding rate were higher during the mask-wearing period [4.1% vs. 2.8%, OR- 1.5 (1.2-1.8), p=0.01 and 5.1% vs. 3.8%, OR- 1.3 (1.07-1.60), p=0.07, respectively].

A comparison between the mask-wearing period and the parallel period in 2019 demonstrated the same hematologic findings, preterm delivery <34 weeks of gestation and post-partum hemorrhage rates.

Neonatal outcomes are presented in Table 2. Birthweights were higher during the mask-wearing period compared to the 2011-2020 pre-pandemic period (3,232 vs. 3,200 grams, p=0.009). Neonatal Apgar score <5 one minute after delivery was lower during the mask-wearing period as well as NICU admissions [0.2% vs. 0.6%, OR- 0.36 (0.13-0.97), p=0.03; 2.8% vs. 3.7%, OR- 0.75 (0.56-0.99), p=0.046, respectively]. Compared with the parallel period in 2019, the rate of composite neonatal outcome was lower during the mask-wearing period [3.8% vs. 5.8%, OR- 0.64 (0.47-0.87), p=0.004]. The same trend of higher birthweight and NICU admission during the mask-wearing period compared to the parallel period in 2019 was observed (p=0.015 and p<0.001 respectively).

Further dividing the whole study cohort into two groups; a group with hemoglobin <11g/dL and the other [?]11g/dL, we performed a multivariate regression analysis, which has identified that pre-pandemic period is independently associated with hemoglobin level <11.0 g/dL (Table 3).

Discussion

Main findings

In this comparative study of the current COVID-19 pandemic versus the pre-pandemic period, we report an increase in hemoglobin and fibrinogen levels and a decrease in platelets and white blood cells levels. The periods analyzed were independently associated with hemoglobin level after adjusting for confounders in a regression analysis. Additionally, we report an increase in post-partum hemorrhage and a decrease in preterm delivery at <34 weeks gestation and in the occurrence of composite neonatal outcome during the mask-wearing period.

Interpretation

Wearing a mask can create a hard-to-ventilate space providing low oxygen environment that can have physiologic consequences. As an example, hypoxia may stimulate erythropoietin secretion, which in turn increases reticulocytes production[4]. The reticulocytes will eventually mature to red blood cells, manifested as elevated hemoglobin levels. A study conducted by Vij et al., investigated the effect of chronic hypoxia on hematologic parameters. The study followed 40 healthy men's hemoglobin, fibrinogen, platelets and white blood cells concentration at sea level and at the following 3- and 13-months sojourn at high altitude. The study's results suggest that prolonged stay at high altitude leads to elevated hemoglobin and fibrinogen levels and a lower platelet and white blood cells levels[3]. Due to the function of hemoglobin as an oxygen carrier throughout the cardiovascular system, higher levels of hemoglobin lead to greater Vo_2-max capacity, enabling better physical performance. A common practice in the elite athletes' field is training in high altitude, in an intent of utilizing this phenomenon[5]. Due to geographical limitations, not all athletes are able to train in high altitude, possibly preventing them from gaining high-altitude training advantages. For this reason, elevation-masks were developed in a purpose of imitating the oxygen deprivation conditions present in high-altitude. Theses masks use a valve system to reduce the amount of airflow to the lungs. In this study we report the same results as did Vij et al. Hemoglobin and fibrinogen levels increase while platelets and white blood cells levels decrease. A possible explanation is that wearing a mask throughout the day during the COVID-19 pandemic has the same hematologic effect as does the elevation-masks.

We have found higher post-partum hemorrhage rates during the mask-wearing period, and a lower platelet count. The American College of Obstetricians and Gynecologists classifies platelet count less than 70

k/microliter as a risk factor for post-partum hemorrhage. Nevertheless, Shravya et al. reported a twofold greater likelihood of post-partum hemorrhage among women with mild thrombocytopenia (platelet count 100–149 k/microliter)[6]. Our results may reflect the same consequences of mild thrombocytopenia on post-partum hemorrhage rates.

The elevated hemoglobin levels may be a plausible explanation to our reported lower rates of preterm birth and composite neonatal outcome. Hemoglobin concentrations greater than 14.6 g/dL at prenatal visits were previously associated with increased risk of preterm birth, stillbirth and growth restriction[7,8]. Conversely, relative elevations of hemoglobin levels can protect against anemia during pregnancy, previously associated with adverse obstetrical outcomes including preterm birth, low birth weight, stillbirth and neonatal mortality[9,10]. These results can potentially reflect an effect of anemia correction due to hemoglobin elevation. Additionally,

A proposed underlying mechanism for the pregnancy outcomes is the induction of heme oxygenase-1 (HO-1) during hypoxia[11]. HO-1 induction has been shown to improve pregnancy outcome, reduce the rate of placental mediated complications[12] and of spontaneous preterm birth[13].

Reported preterm birth rates during the COVID-19 pandemic are scarce, and mainly include women infected with COVID-19[14]. A previous report regarding preterm births during the pandemia among women who were mostly not infected with COVID-19 did not find a difference in preterm birth rates[15]. A possible explanation for the difference between the two studies are different populations studied and different sample sizes.

Mask wearing may also have significant impact on high risk populations such as elderlies, patients suffering from cardiac and hematologic diseases, as well as patients with lung diseases such as chronic obstructive pulmonary disease and asthma. First and foremost, these populations may bare increased sensitivity to altered blood composition, as described, and consequent cardiac activity. Additionally, though not evaluated in our study, the presence of a mask may also increase air-flow resistance, thereby deteriorating spirometric measurements.

Strengths and Limitations

The retrospective design of this study raises the possibility of biases inherent to such investigations. Therefore, we cannot exclude the possibility that additional unknown factors could explain the differences observed between the groups. Moreover, while some women were a surgical mask, others prefer to wear N-95 mask or cloth. Our study did not account for this variation. Moreover, our results may have been masked by patients who spent shorter time periods wearing a mask during the day, or the short period of time evaluated after wearing a mask was obligatory. Finally, the conduct of the study in a single tertiary care center may limit the generalizability of the results. On the other hand, the main strengths of our study include its relatively large cohort of patients and the meticulous data collection on a large set of variables.

Conclusion

In this study, we demonstrate significant hematologic changes among pregnant women admitted to the obstetrical emergency unit during the COVID-19 pandemic, after initiation of mask-wearing regulations. Our clinical results present a decrease in composite neonatal outcomes and lower preterm birth rates, possibly secondary to elevated hemoglobin levels measured during the COVID-19 pandemic. These hematologic changes may carry substantial impact on high risk non-pregnant populations as well. Further research is required to better understand the consequences of long-term mask-wearing among high-risk populations including pregnant women.

Disclosure of interests: The authors declare that they have no conflicts of interest including financial, personal, political, intellectual or religious interests.

Contribution to authorship:

LF, NM, GL, YY and RM contributed to the conception and design of the work. LF, GL, YB, AT and RM contributed to the acquisition and interpretation of the data. LF, GL and RM wrote the paper. All authors

revised and approved the final manuscript.

Details of ethical approval:

Institutional review board approval of the Sheba Medical Center was obtained for this study (7068-20-SMC, 03/30/2020).

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Table 1. Comparison of clinical parameters, delivery data and neonatal outcomes between the mask-wearing period and pre-pandemic periods

p-value	OR (95% CI)[a]	Pre-pandemic period (4-6/2019), (n=1,890)	p-value	OR (95% CI)	Pre-pandemic period (3/2011-4/2020), n=88,973	Mask wearing period (4-6/2020), n=1,838	Characteristi
Background and laboratory characteristics	**Background and laboratory characteristics**	**Background and laboratory characteristics**	**Background and laboratory characteristics**	**Background and laboratory characteristics**	**Background and laboratory characteristics**	**Background and laboratory characteristics**	**Background and laboratory characteristics**
0.944		32 ± 5.3	0.165		32 ± 5.21	32 ±5.3	Age, years
0.458		28.4 ±4.6	0.057		28.1 ±4.4	28.3 ±4.5	Body mass index, mean, kg/m^2
0.245		72 (3.8%)	0.919		4,111 (4.6%)	84 (4.6%)	Smoking
		4[b]			4[b]	6	COVID-19 positive
0.286		1±1.63	0.139		1±1.4	1±1.4	Parity
<0.001		12.00 ±1.1	<0.001		11.96 ±1.2	12.15 ±1.1	Hb, g/dL
0.005	1.26 (1.07-1.49)	338 (17.9%)	<0.001	1.43 (1.28-1.61)	14,244 (16.0%)	395 (21.5%)	Hb>13.0
0.662		58 (3.1%)	0.022	1.35 (1.04-1.75)	2,202 (2.5%)	61 (3.3%)	Hb>14.0
0.033	0.82)0.68-0.98)	303 (16.0%)	0.001	0.79 (0.69-0.91)	14,638 (16.5%)	249 (13.5%)	Hb<11
<0.001		210 ±58.8	<0.001		206 ±57.5	200 ±56.0	PLT, K/microL
<0.001	1.63 (1.35-2.0)	203 (10.7%)	<0.001	1.27 (1.12-1.43)	11,928 (13.4%)	302 (16.4%)	PLT<150 K/microL
0.341		10.99 ±3.2	<0.001		11.40 ±3.2	10.87 ±2.9	WBC, K/microL
0.590		468 ±95.0	<0.001		448 ±85.1	472 ±103.6	Fibrinogen, mg/dL
0.121		172 (9.1%)	<0.001	2.24 (1.93-2.61)	4,465 (5.0%)	195 (10.6%)	Fibrinogen>50 mg/dL,
0.019	1.63 (1.08-2.43)	40 (2.1%)	<0.001	2.39 (1.85-3.11)	1,276 (1.4%)	62 (3.4%)	Fibrinogen>60 mg/dL
Delivery characteristics	**Delivery characteristics**	**Delivery characteristics**	**Delivery characteristics**	**Delivery characteristics**	**Delivery characteristics**	**Delivery characteristics**	**Delivery characteristics**
0.058		$39^{0/7}$ $\pm 2^{2/7}$	0.693		$39^{1/7}$ $\pm 2^{0/7}$	$39^{1/7}$ $\pm 1^{5/7}$	Gestational age at delivery, weeks
0.195		154 (8.1%)	0.846		6,398 (7.2%)	130 (7.1%)	$<37^{0/7}$ weeks

p-value	OR (95% CI)[a]	Pre-pandemic period (4-6/2019), (n=1,890)	p-value	OR (95% CI)	Pre-pandemic period (3/2011-4/2020), n=88,973	Mask wearing period (4-6/2020), n=1,838	Characteristi
<0.001	0.37 (0.23-0.62)	56 (3.0%)	0.010	0.57 (0.37-0.88)	1,765 (2.0%)	21 (1.1%)	$<34^{0/7}$ weeks
0.002	0.37 (0.19-0.72)	35 (1.9%)	0.027	0.54 (0.31-0.94)	1,150 (1.3%)	13 (0.7%)	$<32^{0/7}$ weeks
0.606		1,239 (65.6%)	0.005	0.86 (0.78-0.95)	61,786 (69.4%)	1,220 (66.4%)	Spontaneous delivery
0.690		137 (7.2%)	0.191		5,487 (6.2%)	127 (6.9%)	OVD
0.720		514 (27.2%)	0.022	1.13 (1.02-1.25)	21,700 (24.4%)	491 (26.7%)	Cesarean delivery
0.695		143 (27.8%)	0.480		5,488 (25.3%)	131 (26.7%)	Intrapartum CD
0.026	1.49 (1.04-2.13)	53 (2.8%)	0.001	1.5 (1.20-1.80)	2,470 (2.8%)	76 (4.1%)	Post-partum hemorrhage
0.898		35 (1.9%)	0.780		1,489 (1.7%)	33 (1.8%)	Blood products transfusion
0.173		78 (4.1%)	0.007	1.3 (1.07-1.60)	3,347 (3.8%)	93 (5.1%)	Composite bleeding

Data are mean ± standard deviation or number (%)[a]Compared to the mask-wearing period

[b] COVID-19 infection was evaluated only during the COVID-19 pandemia.

OR- odds ratio, CI- confidence interval, COVID-19- Coronavirus Disease 19, Hb- hemoglobin, PLT- platelets, WBC- white blood cells, OVD- operative vaginal delivery, CD- cesarean delivery

OR was calculated only for significantly different categorical variables.

Composite bleeding was defined as the presence of post-partum hemorrhage of blood products transfusion.

Table 2. Comparison of neonatal outcomes between the mask-wearing period and pre-pandemic periods

p-value	OR (95% CI)[a]	Pre-pandemic period (4-6/2019), (n=1,890)	p-value	OR (95% CI)	Pre-pandemic period (3/2011-4/2020), n=88,973	Mask wearing period (4-6/2020), n=1,838	Characteristi
0.015		3,190±552	0.009		3,200±533	3,232±513	Birthweight
0.708		9±1.0	0.038		9±1.1	9±0.9	Apgar 1 min.
0.711		10±1.0	0.132		10±1.1	10±0.9	Apgar 5 min.

p-value	OR (95% CI)[a]	Pre-pandemic period (4-6/2019), (n=1,890)	p-value	OR (95% CI)	Pre-pandemic period (3/2011-4/2020), n=88,973	Mask wearing period (4-6/2020), n=1,838	Characteristi
0.388		8 (0.4%)	0.030	0.36 (0.13-0.97)	532 (0.6%)	4 (0.2%)	Apgar 1 min. <5
0.727		5 (0.3%)	0.899		306 (0.3%)	6 (0.3%)	Apgar 5 min. <7
0.021	0.11 (0.01-0.90)	9 (0.5%)	0.181		170 (0.2%)	1 (0.1%)	Umbilical artery pH <7.0
0.854		9 (0.5%)	0.852		362 (0.4%)	8 (0.4%)	Umbilical artery base excess > 12
<0.001	0.54 (0.38-0.76)	95 (5.0%)	0.046	0.75 (0.56-0.99)	3,253 (3.7%)	51 (2.8%)	NICU admission
0.913		15 (0.8%)	0.268		911 (1.0%)	14 (1.5%)	Stillbirth
1.0		1 (0.1%)	0.593		43 (0.01%)	1 (0.1%)	Death in 24 hours
1.0		3 (0.2%)	0.231		79 (0.1%)	3 (0.2%)	Death in 30 days
0.926		17 (0.9%)	0.851		812 (0.9%)	16 (0.9%)	Mechanical ventilation
1.0		2 (0.1%)	1.0		86 (0.1%)	1 (0.1%)	Hypoxic ischemic encephalopath
0.375		4 (0.2%)	0.727		101 (0.1%)	1 (0.1%)	Convulsions
1.0		1 (0.1%)	0.409		73 (0.1%)	0 (0%)	Asphyxia
1.0		2 (0.1%)	1.0		68 (0.1%)	1 (0.1%)	Cooling protocol
0.004	0.64 (0.47-0.87)	110 (5.8%)	0.073		4,184 (4.7%)	70 (3.8%)	Composite neonatal outcome [b]

Data are mean ± standard deviation or number (%)

[a] Compared to the mask-wearing period

[b] Composite neonatal outcome consisted of any of the following: stillbirth, neonatal death during first 24 hours, mechanical ventilation during first 24 hours, asphyxia, hypoxic ischemic encephalopathy and neonatal intensive care unit admission.

OR- odds ratio, CI- confidence interval, NICU- neonatal intensive care unit

OR was calculated only for significantly different categorical variables.

Table 3. Multivariate analysis of factors associated with hemoglobin <11 g/dL

Variable	aOR (95% CI)	P value
Pre-pandemic period	1.39 (1.22-1.58)	<0.001
Age, years	1.02 (1.22-1.58)	<0.001
Body mass index	1.001 (0.998-1.005)	0.475
Smoking	0.70 (1.12-1.48)	<0.001
Parity	0.78 (0.77-0.79)	<0.001
Gestational age	1.09 (1.08-1.10)	<0.001

aOR- adjusted odds ratio, CI confidence interval