Worse Outcomes of Pregnancy in COVID-19 Infection during Parturition may be due to Referral Bias: Analysis in a Prospective Cohort of 963 pregnancies

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Sakir Ahmed has received honorarium as speaker from Pfizer(unrelated to the current study). The other authors have no potential conflicts of interest.

Worse Outcomes of Pregnancy in COVID-19 Infection during Parturition may be due to Referral Bias: Analysis in a Monocentric Prospective Cohort of 963 pregnancies

Initial studies of COVID-19 suggested that pregnant women have more severe COVID-19 with an increased risk of pre-term birth, pre-term rupture of membranes and even maternal deaths[1]. Later studies and systematic reviews showed different results[2]. When pregnant women were universally screened, severe disease rates mirrored those of the normal population[3]. Most studies on outcomes have not controlled for either pre-existing maternal risk factors or those acquired during pregnancy[2]. Also, there is still some grey area in understanding how COVID-19 infection around the time of delivery affects pregnant women. Thus, we analysed if the apparent high risk of severe COVID-19 in referral centres was confounded due to concomitant other risk factors.

In our cohort from a single tertiary referral hospital in India, all pregnant women coming for delivery or with labour pain were universally screened for SARS-CoV-2 infection using RT-PCR from oronasopharyngeal samples. Patients who left the hospital before delivery were excluded. Of 963 pregnant women, 127 were COVID-19 positive. They were compared using tests for proportions in terms of maternal complications (Caesarean sections, antepartum and postpartum haemorrhage, pre-term rupture of membrane and pre-labour rupture of membrane, puerperal sepsis and mortality) and neonatal outcomes (APGAR scores, low birth weight, intensive care requirement, neonatal COVID-19 infection, neonatal sepsis and death). Then GLM(generalized linear models) were built to assess the contribution of various maternal risk factors and COVID-19 positivity on these outcomes.

Age, gravida, parity, gestational diabetes and pregnancy induced hypertension rates were similar between COVID-19 positive and negative cohorts [Supplementary Table 1]. The COVID-19 cohort had overrepresentation of various other pregnancy risk factors [Table 1]. The COVID-19 cohort had higher caesarean deliveries [87(68%) versus 445(53.3%) in negative cohort; p=0.02], postpartum haemorrhage [6(4.7) versus 1(0.1%), p<0.001], and maternal mortality[2(1.6%) versus 1(0.1%), p=0.048] [Supplementary Table 2]. Amongst neonatal outcomes, APGAR score was lower at 1 minute [mean(SD): 7.20(1.63) in COVID-19 versus 7.54(1.69) in controls; p= 0.035] and at 5 minutes [mean(SD): 8.27(1.72) in COVID-19 versus 9.14(1.74) in controls; p<0.001] [Supplementary Table 3].

In the first GLM model on the mode of delivery, significant predictors were past caesarean sections, COVID-19 positivity, presence of PIH, and gestational diabetes [Supplementary Table 4]. In the second GLM model, bad maternal outcomes were only associated with the presence of PIH [Supplementary Table 5]. In the third GLM model, bad neonatal outcomes were associated with the presence of PIH or one of the seven other factors for high-risk pregnancy [Supplementary Table 6].

Thus, the associations found on univariate analysis reflects a possible referral bias where higher risk patients were being referred if they were COVID-19 positive than if negative.

This study reiterates that COVID-19 infection does not pose additional risk to pregnancy outcomes by itself. Earlier systematic reviews were hampered by the high heterogeneity of reported cohorts[4]. This was compounded by duplicate reporting of the same patients in different cohorts, variable inclusion criteria of systematic reviews, and scarce and missing data[5]. More recent systematic reviews have shown that maternal deaths and neonatal outcomes were similar in deliveries conducted in COVID-19 mothers as compared to non-COVID-19[6].

Limitations of our study include that we do not have the indications for caesarean deliveries in the cohort and that it was carried out in a tertiary centre that would receive more complicated cases.

It brings to light that COVID-19 positive mothers being treated at tertiary care centres have higher rates of caesarean section and higher morbidity and mortality possibly due to the extra underlying risk factors arising from a referral bias.

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112 **Table 1: Comorbidities and pregnancy risk factors**

Condition		**COVID-19 (n=127)**	**Controls (n=836)**	**P-value**
Pre-pregnancy comorbidity		26 (20.3%)	159(19.0%)	0.72
Hypertensive disease of pregnancy		9(7.0%)	64(7.7%)	>0.99
Gestational diabetes		6(4.7%)	32(3.8%)	0.62
Other pregnancy related risk	None	799(95.70%)	117(91.40%)	NA
	Twin pregnancy	7(0.80%)	1(0.80%)	<0.01*
	Breech presentation	10(1.20%)	8(6.30%)	<0.01*
	IUGR	3(0.40%)	1(0.80%)	<0.01*
	In-vitro fertilization	2(0.20%)	0	0.017*
	Rh negative pregnancy	8(1.00%)	1(0.80%)	<0.001**
	Thalassemia	2(0.20%)	0	0.017*
	Obstetric cholestasis	4(0.5%)	0	<0.001**

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1 **Supplementary Table 1: Demographics of the cohort**

	COVID-19 positive (n=127)		**COVID-19 negative (n=836)**		
	Mean	Std. Deviation	Mean	Std. Deviation	P-value
Age	28.18	4.64	27.71	4.23	0.29
Gravida	1.69	0.98	1.72	0.87	0.74
Parity	0.42	0.58	0.51	0.59	0.11
Period of gestation at delivery	36.94	3.14	37.42	2.90	0.10
Body Mass Index	28.00	1.33	28.12	1.35	0.34

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Supplementary Table 2: Maternal outcomes (univariate analysis)

	COVID-19 (n=127)	Controls (n=836)	P-value
Caesarean delivery	87(68%)	445(53.3%)	0.002*
Maternal ICU requirement	3(2.3%)	6(0.7%)	0.10
Antepartum haemorrhage	0	15(1.8%)	0.11
Pre-term pre-mature rupture of membranes	1 (0.8%)	35(4.2%)	0.036*
Pre-term rupture of membranes	2(1.6%)	38(4.6%)	0.08
Postpartum haemorrhage	6(4.7%)	1(0.1%)	<0.001**
Puerperal sepsis	0	0	NA
Maternal mortality	2(1.6%)	1(0.1%)	0.048*

Supplementary Table 3: Neonatal outcomes (univariate analysis)

	COVID-19 (n=127)	Controls (n=836)	P-value
APGAR score at 1min Mean (SD)	7.20(1.63)	7.54(1.69)	0.035*
APGAR score at 5min Mean (SD)	8.27(1.72)	9.14(1.74)	<0.001**
Low birth weight <2kg	16(17.4%)	127(24.1%)	0.19
Neonatal ICU requirement	28(21.9%)	206(24.7%)	0.58
Neonatal COVID-19 positivity	5(3.9%)	0	<0.001**
Neonatal sepsis	0	2(0.2%)	0.75
Neonatal death	2(1.6%)	14(1.7%)	0.64

Supplementary Table 4: GLM model for mode of delivery

Parameter	B	Std. Error	Wald Chi-Square	P-value
(Intercept)	-2.625	2.0160	1.696	.193
Past LSCS	-2.590	.2819	84.436	<.001*
[COVID status=negative] vs [COVID status=positive]	.655	.2196	8.909	.003*
[hypertensive disease of pregnancy=no] vs [hypertensive disease of pregnancy=yes]	1.330	.3307	16.173	<.001*
[Gestational diabetes = no] vs [Gestational diabetes = yes]	1.184	.4248	7.771	.005*
[Other risk factor = no] vs [Other risk factor = yes]	.607	.3412	3.167	.075
BMI	-.002	.0535	.002	.965
Haemoglobin	.050	.0812	.377	.539
Gravida	-.068	.1277	.284	.594
Parity	.120	.2087	.332	.564
Period of Gestation at delivery	-.032	.0232	1.883	.170

Supplementary Table 5: GLM model for maternal complications

Parameter	B	Std. Error	Wald Chi-Square	P-value
(Intercept)	.237	2.8844	.007	.935
Past LSCS	.472	.3010	2.456	.117
[COVID status=negative] vs [COVID status=positive]	-.204	.3296	.381	.537
[hypertensive disease of pregnancy=no] vs [hypertensive disease of pregnancy=yes]	.971	.3157	9.464	.002*
[Gestational diabetes = no] vs [Gestational diabetes = yes]	.502	.4711	1.135	.287
[Other risk factor = no] vs [Other risk factor = yes]	.586	.3929	2.228	.136
BMI	-.011	.0797	.020	.888
Haemoglobin	.171	.1133	2.275	.131
Gravida	-.055	.1804	.093	.760
Parity	-.229	.2953	.602	.438
Period of Gestation at delivery	-.033	.0355	.864	.353

Supplementary Table 6: GLM model for poor neonatal outcomes

Parameter	B	Std. Error	Wald Chi-Square	Sig.
(Intercept)	-2.836	2.0216	1.967	.161
Past LSCS	.335	.1940	2.984	.084
[COVID status=negative] vs [COVID status=positive]	-.298	.2286	1.695	.193
[hypertensive disease of pregnancy=no] vs [hypertensive disease of pregnancy=yes]	1.129	.2533	19.850	<.001*
[Gestational diabetes = no] vs [Gestational diabetes = yes]	.290	.3614	.642	.423
[Other risk factor = no] vs [Other risk factor = yes]	.730	.3219	5.145	.023*
BMI	.115	.0548	4.383	.036
Haemoglobin	-.054	.0836	.416	.519
Gravida	-.124	.1221	1.034	.309
Parity	.070	.2070	.114	.735
Period of Gestation at delivery	-.013	.0239	.308	.579