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Maternal and neonatal outcome of vertical transmission in pregnant women during COVID-19 pandemic at Quetta, Balochistan.

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ABSTRACT… Objectives: To evaluate deleterious impact of novel coronavirus infection 2019 (COVID-19), on both maternal and fetal well being during pregnancy. **Study Design:** Hospital-Based Cross-sectional Survey. **Setting:** Department of Gynecology & Obstetrics, Combined Military Hospital, Chiltan Road, Quetta (Balochistan); Department of Gynecology & Obstetrics, Frontier Corps Hospital, Quetta Cantonment (Balochistan), and the Department of Otorhinolaryngology (ENT), Combined Military Hospital, Chiltan Road, Quetta (Balochistan). **Period:** March 2020 till July 2020. **Material & Methods:** Careful history, clinical and obstetrical examination radiology and real time polymerase chain reaction of nasopharyngeal swab were carried out in pregnant patients presenting for childbirth. Deliveries were conducted through spontaneous vaginal birth and caesarean section as per indication. Neonatal evaluation and nasopharyngeal swab for COVID-19 real time polymerase chain reaction in all delivered fetuses were performed. **Results:** 516 pregnant women underwent spontaneous vaginal delivery and caesarean sections at these hospitals during the study duration. 4.06% (n=21) were confirmed as COVID-19 infected. All of the fetuses born to these infected mothers were delivered healthy and COVID-19 negative, except for one preterm fetus born at 22nd week of gestation on account of maternal gestational hypertension. **Conclusion:** Trans-placental spread of COVID-19 infection to the fetus is unlikely. However, the infection places a pregnant mother at much higher risk to develop complications which may occasionally lead to adverse pregnancy outcome.

Key words: Coronavirus, Fetus, Pregnancy, Placenta, Pneumonia.

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INTRODUCTION

Viral pneumonias are known to cause morbidity and mortality globally in pregnant women.[1,2] Maternal pneumonias often carry eventful obstetrical outcomes, many a time ending up in preterm labor, miscarriage, fetal distress, still birth, intrauterine growth retardation and neonatal mortality.[2] Vertical transmission of microorganisms and pathogens from an infected pregnant mother to her fetus can have devastating outcome. COVID-19 infection results from single stranded positive-sense RNA genome severe acute respiratory syndrome coronavirus-2 (SARS CoV-2), which is a new enveloped RNA virus transmitted from human to human via airborne droplets, droplet nuclei and contact with infected fomites. At the time of writing this paper the pandemic has caused 11.8 million disease positive patients and a global death toll as high as 544000. National statistics confirm 235000 infected cases with 4839 fatalities due to COVID-19 infection. There are 10841 disease positive cases in Balochistan till to date.[3] The spectrum of manifestation range from fever, cough, headache, hyposmia, anosmia, fatigue, myalgia to life threatening pneumonia with acute respiratory distress syndrome in all ages affecting newborns to elderly. 49.6% women report of a non-specific respiratory tract infection at least once during pregnancy.[4] 14 to 45% of asymptomatic pregnant women test positive for COVID-19 on RT-PCR.[5-7] Respiratory complications and maternal mortality has been reported in women infected with coronavirus infection during

pregnancy.[8] In early May 2020, UNICEF warned about an expected 5 million still births attributed to COVID-19 pandemic in Pakistan, with an ever escalating number of expecting mothers infected with COVID-19 testing positive from various urban and suburban parts of Pakistan.[9] Concurrently, in another press release from Gujrat, Pakistan, 9.3% of pregnant women were tested positive on RT-PCR.[10] In another national research update, further to higher risk of pregnancy-related complications, increase in anxiety and psychological strain have been reported among pregnant women during the pandemic.[11]

Taking into account illiteracy, poverty, lack of communication/ transport infrastructure, inadequate access to screening, social, cultural and communal taboos, very little research has been performed in our part of the country and very sparse data is available on the subject from Balochistan. We aim in our study at evaluating risk of intrauterine vertical transmission of COVID-19 infection in pregnant mothers belonging to Quetta region of Balochistan who reported during early surge of pandemic for conduction of delivery.

MATERIAL & METHODS

A formal approval for the study project from hospital research ethics committee was acquired. We obtained a comprehensive epidemiological, clinical and obstetrical history from all pregnant patients who had consented to undergo delivery at the departments of gynecology and obstetrics Combined Military Hospital Quetta Cantonment and Frontier Corps Hospital Quetta Cantonment from 1 March 2020 till 1 July 2020. Specific questions regarding pyrexia, myalgias, malaise, rigors, cough, dyspnea, sore throat, diarrhoea and chest pain were asked. Each patient was assessed clinically and pertinent obstetrical examination was conducted. Based on clinical suspicion, we requested for plain high resolution computed tomography scan of the chest in axial and coronal collimations (with abdominal shield) and nasopharyngeal swab for real time polymerase chain reaction for detection of COVID-19 RNA in every patient. Patients were recruited upon radiologic or pathologic confirmation of COVID-19 infection. Relevant radiological and pathological work up were completed and endorsed, namely baseline blood counts, hepatitis screening, liver functions, coagulation profile, c-reactive proteins, cardiac enzymes and ultrasonography of abdomen. An experienced consultant gynecologist carefully documented number of fetuses, lie, presentation, liquor volume, viability and placental localization. An experienced consultant anesthetist carried out pre-anesthesia assessment in all patients scheduled to undergo caesarean section. Nasopharyngeal swabs of babies delivered through either caesarean section or spontaneous vaginal birth were obtained for real time polymerase chain reaction analysis by a consultant neonatologist.

We recorded relevant maternal and neonatal parameters in Microsoft Excel-10 based electronic proforma. IBM®-SPSS® Statistics version-25 was used for data analysis. Descriptive statistics were applied for frequency variables. We applied binary logistic regression analysis to predict categorical variables of fetal outcome (e.g. low birth weight, prematurity, neonatal asphyxia, neonatal death and still birth) against maternal COVID-19 infection. Poisson regression analysis was applied to predict count variables of fetal outcome (e.g. APGAR scores) against maternal COVID-19 infection.

RESULTS

516 pregnant ladies reported and consented for conduct of delivery in both the hospitals since 1 March 2020 till 1 July 2020. 4.06% (n=21) patients were symptomatic and confirmed positive for COVID-19 infection. Mean age of patients was 29.57 years (SD±4.19) at presentation. Our youngest patient was 22 years of age and our eldest reporting patient was 38 years old (Figure-1).

Upon hospitalization, mean age of gestation was 36.67 weeks (SD±3.66). Minimum gestational age was 22 weeks and maximum being 41 weeks. Mean days of onset of delivery were 2.62 (SD±0.97), varying from a minimum of 1 to maximum 4 days. At the time of reporting we recorded gestation induced hypertension in 5% (n=1) patient; a 38 years old multiparous.

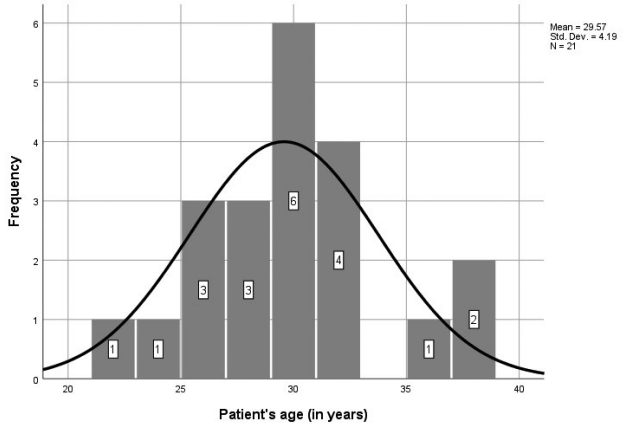

Figure-1. Age histogram

Only 4.8% (n=1) patient had moderate remitting pyrexia on admission. 4.8% (n=1) patient developed post-partum fever. Myalgias were reported in 100% (n=21) patients, and malaise was narrated by 95.2% (n=20) patients. None of our patients had rigor. 4.8% (n=1) patient arrived with cough, dyspnea and intermittent chest discomfort as her associated symptoms. None had a sore throat or diarrhea on arrival. Mean total leukocyte count was 12.32 x 10^9/L (SD±4.199), minimum and maximum recordings being 7.7 x 10^9/L and 22 x 10^9/L. Leukopenia was observed in 23.8% (n=5) patients, with lymphopenia in 9.5% (n=2) patients. Mean lymphocyte count was 20.09 x 10^9/L (SD±6.27), ranging between 9 x 10^9/L though 30 x 10^9/L. 4.8% (n=1) patient, a 25 years old full term primigravida, was clinically diagnosed as suffering from viral pneumonia, and was managed accordingly with empirical systemic antibiotics. We documented mean level of serum c-reactive proteins to be 41.15 mg/L (SD±36.34), highest being 167 mg/L. All of our patients had elevated c-reactive proteins in serum. No recordable derangement in hepatic enzymes was found, mean serum ALT and AST were 23.00 U/L (SD±7.70), and 26.66 U/L (SD±2.00), respectively.

Real time polymerase chain reaction RT-PCR of nasopharyngeal swab confirmed COVID-19 infection in 95.2% (n=20) of these patients. We found typical signs of viral infection on high resolution computed tomography scan of the chest in 52.4% (n=11) patients carried out pre-operatively. In 76.2% (n=16) patients, delivery was conducted through standard lower segment caesarean section under spinal epidural anesthetic agent. Indications for caesarean sections are given in Figure-2.

All our patients who would undergo caesarean sections were documented as ASA-2E during pre-anesthesia assessment, and as a standard protocol, systemic Dexamethasone 8 milligrams was administered invariably to all these patients in post operative recovery room. None of our patients required Oxygen inhalation through nasal cannula, nor was anyone prescribed antiviral therapy post-operatively.

However a standard regime of Azithromycin 500 milligrams and Metronidazol 400 miligrams orally once in a day for seven days was prescribed to all patients undergoing spontaneous vaginal delivery. Intravenous Ceftriaxone 1 gram was administered during labor to all patients planned for caesarean section. 4.8% (n=1) patient with pre-operative respiratory symptoms was maintained on intravenous Dexamethasone 8 milligrams BID for 5 days.

All of the fetuses born to these infected mothers were delivered healthy except for one preterm fetus born at 22nd week of gestation on account of maternal gestational hypertension. Nasopharyngeal swabs from all these neonates tested negative for coronavirus infection.

Binary logistic regression model was performed to ascertain the effects of quantitative COVID-19 RT-PCR on the likelihood of neonatal low birth weight, premature delivery, neonatal asphyxia, neonatal death and still birth. The logistic regression model was statistically insignificant at 95% confidence interval (p value 1.000 in each case) (Table-I). A Poisson regression was run to predict neonatal gestational age (in weeks) at delivery, neonatal birth weight (in Kg), neonatal APGAR score at 1 and 5 min; based on RT-PCR. The results were again statistically insignificant at 95% confidence interval (p value 0.790, 0.905, 0.751 and 0.318 in each case, respectively) Table-II.

Parameter	Dependent variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI	
								Lower	Upper
Quant RT-PCR	Neonatal low birth weight	18.25	40192.9	.000	1	1.000	85024992.8	.000	
	Premature delivery	19.006	40192.9	.000	1	1.000	179497207.1	.000	
	Neonatal asphyxia	18.258	40192.9	.000	1	1.000	85024992.8	.000	
	Neonatal death	19.006	40192.9	.000	1	1.000	179497207.1	.000	
	Still birth	19.006	40192.9	.000	1	1.000	179497207.1	.000	

Table-I. Binary logistic regression model variables in the equation

Parameter	Dependent variable	B	Std. Error	95% Wald CI		Wald Chi Square	df	Sig.
				Lower	Upper			
Quant RT-PCR	Neonatal gestational age	-.044	.1664	-.371	.282	.071	1	.790
	Neonatal birth weight	-.028	.2355	-.490	.433	.014	1	.905
	APGAR score @ 1 min	-.029	.0915	-.208	.150	.100	1	.751
	APGAR score @ 5 min	-.118	.1179	-.349	.113	.998	1	.318

Table-II. Poisson regression analysis parameter estimates

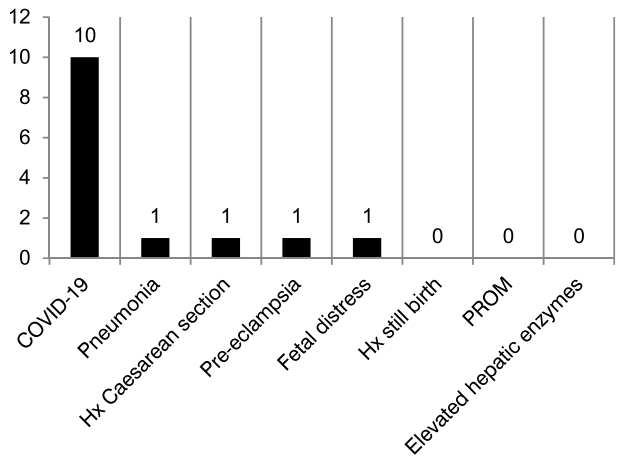

Figure-2

DISCUSSION

Advancing human pregnancy can exhibit tri-modal mechanism of fetal insult following exposure to infections; embryopathy can result in first trimester, fetal infection in second trimester, and immune-response-related damage in second and last trimester. Respiratory viruses undermine pregnant mothers in diverse ways. In 2017, Mor et al and Aghaeepour et al described unique metamorphosis of human immunologic dynamics during the course of healthy gestation favoring reception, establishment and growth of implanting blastocyst thereby developing and maintaining tolerance against growing fetus and simultaneously protecting against infections.[12,13] This process of transformation is governed by a biologic clock continuously modifying the chronology of these adaptations. Starting from implantation through placentation, fetal growth and parturition, each phase requires a unique immunologic environment to confront challenges exclusive to individual phase. They described a more pro-inflammatory T_H-1 type response during implantation and placentation; with a T_H-2 type anti-inflammatory switch during fetal growth, and lastly a second T_H-1 type pro-inflammatory shift during third trimester. Pregnancy induced a surge in endogenous STAT5 antibodies enhancing interaction between cytokines ($CD4^+$ and $CD8^+$ T cells), $FoxP3^+$ Treg cells, and $_{\Upsilon}\delta$ T cells, defending more efficiently against invading foreign pathogen. Accelerated response of NK cells has also been found to neutralize viruses. Some down-regulation of T and B lymphocytes has also been observed. Simultaneously, gestation-related rise in estrogen and progesterone lead to congestion in upper airway, and restricted lung expansion due to expanding uterus place a pregnant woman more at risk to contract respiratory infections rather easily.

Huang et al described COVID-19 infection to be linked with a very high plasma concentration of cytokines (interleukin-2, 7 and 10), granulocyte - colony stimulating factor, interferon Υ-inducible protein 10, macrophage inflammatory protein1α,

tumor necrosis factor α and monocyte chemoattractant protein 1.[14] In view of assumption made by Mor et al, this 'cytokine storm' initiated by COVID-19 infection can perpetuate more sinister outcome during the pro-inflammatory durations of pregnancy. As a consequence central neurologic and behavioral dysfunctions may result in the developing fetus.[15]

Chen et al pointed out a high risk of maternal mortality due to COVID-19 infection during perinatal period of gestation.[16] The research incorporated placental tissue testing for COVID-19 nucleic acid detection, and computed tomography of the lungs in three confirmed COVID-19 infected pregnant mothers who had to undergo emergency caesarean section in third trimester. Two babies were delivered healthy, the third one being premature. Their throat swabs were negative for COVID-19. Albeit recovery of mothers and their neonates remained uneventful, however, one placenta revealed findings corresponding to chorionic hemangioma, and the other had massive infarcts, none of the placentae revealed villitis or chorioamnionitis. The three placentae did not reveal any evidence of COVID-19 nucleic acid.

In early outbreak, the Iranian Ministry of Health and Medical Education documented three neonates who were born to mothers infected with COVID-19 during gestation. Two of these three mothers met a fatal outcome consequent to acute respiratory distress (ARDS) at the time of delivery. All three neonates were however tested to be negative for COVID-19.[17]

In a research letter Baud et al described a case of placental infection and eventual miscarriage; whereupon a 28 years old primigravida lady turned symptomatic with COVID-19 infection at 19th week of her gestation. A COVID-19 negative still born fetus was delivered after 10 hours of preterm uterine contractions. Her amniotic fluid and vaginal swab during labor remained negative for COVID-19. Fetal autopsy did not reveal COVID-19, and there was no evidence of gross dysmorphism. The maternal nasopharyngeal swab yielded a positive test for COVID-19 at 48 hours after parturition. The umbilical cord was inflammed and placenta gave a strong evidence of polymorphonuclear infiltrate, enhanced fibrin deposition in subchorial space and villi and an increased syncytial nodularity.[18] Likewise, placental infection on maternal aspect with resultant miscarriage has also been reported in Middle Eastern Respiratory Syndrome (MERS) coronavirus.[19]

Although evidence does not support detection of COVID-19 infection in fetus, however, the potential indirect risk of harm to the fetus secondary to excessive circulatory cytokines must always be borne in mind. In 2016, Choi et al described a link of autism-like phenotype and anomalous brain development with increased maternal IL-17α in murine model.[20] Fried et al documented adverse pregnancy outcome associated with higher concentrations of maternal cytokines in response to malaria, in 2017.[21] Yockey and Iwasaki studied in mice that inappropriate expression of maternal circulatory cytokines and interferons can have a myriad of teratogenic results spanning from birth defects to pregnancy complications.[22] Another alarming symptom associated with COVID-19 infection is fever. In 2016, Werenberg Dreier et al found maternal exposure to fever and usual infections during gestation could interfere with fetal neuro-development, and might result in cerebral palsy, autism spectrum disorders, and psychotic disorders in early life.[23]

Our results conform to the US statistics as the prevalence coronavirus infection in pregnant mothers presenting for childbirth was 4.06%, where Campbell et al reported less than 3% of such cases.[24] In a case reported by Tarar et al, fetal outcome in a COVID-19 infected mother was normal.[25] Good feto-maternal oucome with no vertical transmission has also been documented by Munir et al.[26]

CONCLUSION

As opposed to severe fetal respiratory disease reported during outbreak of SARS-CoV-2003 and MERS CoV-2012, we conclude that COVID-19 infection does not show evidence of trans-placental vertical transmission, however fetal

and maternal well being is at high stakes due to indirect detrimental impact of viral illness on maternal health. Since no definitive treatment is known till the date of submission of this paper, it is prudent to anticipate modes of disease spread and its possible outcome. Practicing austere prevention is paramount to avert any eventuality. Potential risk of infected pregnant mother and fetus must always be borne in mind. Albeit vertical transmission is infrequent, screening is mandatory to preempt and limit unforeseen obscurity and concurrently to avoid exposure to the OR and labor-room staff.

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