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COVID-19 impact in early pregnancy losses: A retrospective study

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Abstract

Background: Severe acute lung disease, known as coronavirus disease 2019 [COVID-19] had multifaced impacts on human lives especially in pregnant women. However, no clear-cut consensus have been made on the effect of COVID 19 on pregnancy and fetal effects due to limited data.

Aim: To study pregnant women presenting to our department with missed miscarriages or early fetal demise in the COVID pandemic time for a period of 2 years (April 2020 to March 2022) and to assess the risk of early pregnancy loss due to COVID 19 infection if any.

Materials and Methods: A Retrospective comparative study was carried out among pregnant women attending the department of Obstetrics & Gynaecology for MTP at SVS Medical College, Mahabubnagar in view of miscarriages both embryonic and anembryonic and early fetal demise till 20weeks Gestational age in the period April2020 to March 2021 and a control group of pregnant ladies who presented for MTPs before 20 weeks for miscarriages and early IUFDS till 20 weeks gestational age in the period of April 2019 to march 2020 were taken.

Results: A total of 232 women were registered during pre-pandemic period and 180 women were registered during pandemic period for the study. The two groups were similar in demographic characteristics including the mean maternal age in both the groups which were 22+/-2 and 23+/-2yrs. Parity affected in both the study groups i.e, precovid which were 38.2% in primigravida and 61.7% in multigravida and the pregnancy loss during covid-there were 44.6% in primigravida and 55.3% in multigravida, showing no significant difference in pregnancy loss during and before covid. The percentages of missed miscarriages, early IUFDS less than 20 weeks Gestational age, MTPs done for various congenital anomalies also showed only marginal changes in both the groups.

Conclusion: In our study, we did not find any significant difference between the early fetal demise, missed miscarriages, MTPs done for congenital anomalies during the pre-covid and COVID periods. Though some studies support early pregnancy loss due to COVID infection, because of our small sample size, we could not find attribute the marginal changes in the study group i.e, during COVID pandemic due to small sample size and also many studies reporting no significant difference, large multicentric studies are needed to evaluate any association between the COVID-19 SARS virus infection and its effect on fetal demise, any miscarriages or congenital anomalies.

Keywords: SARS Virus, COVID19, Miscarriages, MTPs

Introduction

Severe acute lung disease is known as coronavirus disease 2019 [covid 19]. As of early 2021, covid 19 virus is estimated to have infected more than 181 million people and caused nearly 4 million deaths [WHO 2021]

Numerous studies have reported on the clinical characteristics and the results of covid 19; however, there is little information when considering infection in pregnant women and even less relating to the 1st trimester of pregnancy [Allotey *et al.* 2020] [1].

During any epidemic, pregnant women constitute an extremely sensitive group due to physiological and immunological changes making them more susceptible to infection and more in severity [Chen H *et al.* 2020] [2]. Viral infections during pregnancy have a broad spectrum of placental pathology. It can lead to fetal malformation, preterm birth, growth restriction, spontaneous abortion, and premature rupture of membranes [Prochaska *et al.*, 2020] [3]. Pregnancy outcomes may also be influenced by associated chronic stress [Keasley J 2017] [4].

Some studies analyzed that the effect of in-vitro exposure to maternal stress increases miscarriage [Valente c 2015] ^[5] and also reported a connection between preconception and pregnancy exposure to stress which increases the risk of spontaneous miscarriage [Weinstock T *et al.* 2013] ^[6]. The increased susceptibility during 1st-trimester pregnancy in viral infection may be due to a pro-inflammatory status which can interrupt the structural and functional conditions of the human placenta. [Liu *et al.* 2020] ^[7]. As the fetal organs develop during the first trimester of pregnancy, maternal infections may be more severe compared to later gestational age [silasi *et al.* 2015; Alvarado Schwartz, 2017] ^[8]. Data on the effects of SARS cov 2 infections in pregnancy are still emerging. Two systematic reviews and maternal analysis reported an increased risk of preterm birth, cesarean delivery, maternal morbidity [Khalil *et al.*, 2020] ^[9], and stillbirth [Allotey *et al.*, 2020] ^[11], thromboembolism. However, the relationship between SARS-COV-2 infection and the risk of miscarriage is unclear. SARS-COVID 2 transmission from mother to fetus is controversial. Studies stated that SARS-COVID 2 nucleocapsid protein, viral RNA, and particles consistent with coronavirus were found in the placenta and fetal tissues [Valdespino-vazquez *et al.* 2021] ^[10]. Few also inferred that Pregnant women with a self-reported diagnosis of covid 19 in 1st trimester had a higher risk of miscarriage [Neerujah Balachandren *et al.* 2022] ^[11]. Several cross-sectional studies have shown a high rate of asymptomatic miscarriages among pregnant women. Thus, there is a plausibility that women during the early stages of pregnancy may have had an asymptomatic infection. The purpose of this study was to discover whether there is an association between SARS-COV-2 infection and early fetal demise.

Materials and Methods

We conducted a 2-year retrospective observational study at SVS medical college and hospital in mahabubnagar. A total of 232 miscarriages were registered, out of which 116 cases [control group] were reported before covid, during 1 year from April 2019 to march 2020, and 180 cases [study group] were reported during covid in 1 year from April 2020 to March 2021.

All pregnant women who came to OPD or emergency with early fetal demise [upto 20wks] including missed miscarriages {both anembryonic pregnancy, embryonic pregnancy loss}, congenital anomalies were included. Only pregnancies that were

spontaneously conceived, Ultrasound confirmed pregnancies, irrespective of their covid 19 status were studied in this period. The pregnancies were terminated by medical methods.

We have excluded the induced miscarriages by maternal demand or miscarriages due to any other reason like GDM, VDRL positive status, TSH abnormalities, TORCH positive, Uterine anomalies, APLA syndrome, previous H/O known Genetic abnormalities which lead to IUDs or miscarriages etc., Also we excluded ectopic and molar pregnancies.

A total of 412 miscarriages were registered, out of which 232 cases [control group] were reported before covid during 1 year period, and 180 cases [study group] were reported during covid in 1 year.

So, we wanted to conduct this study to assess the risk of early pregnancy loss if any due to covid 19 infection by comparing early pregnancy loss before and during covid pandemic.

Results

A total of 232 women with miscarriages were registered during the pre-pandemic period [control group], and 180 women were registered during the pandemic period [study group] for the study.

The two groups were similar in demographic characteristics.

The mean maternal age was 24+/-3 in the study group and 25+/-4 in the control group.

The baseline investigations including thyroid stimulating hormone levels were in normal ranges in both the groups, and other investigations related to pregnancy loss, like impaired or abnormal GCT, TORCH infections, APLA, VDRL, uterine anomalies, Genetic abnormalities which can recur leading to miscarriages or IUDs, were also ruled out before enrolling them in this study. Those who were not willing to do the investigations that cause pregnancy loss were not included.

The pregnancy loss before covid - there were 68 [29.3%] cases of anembryonic pregnancy, 140[60.3%] cases of embryonic missed miscarriages, 16[6.8%] cases of congenital anomalies, and 8 [3.4%] cases of early fetal demise were noted.

The pregnancy loss during covid -there were 40[22.2%] cases of anembryonic pregnancy, 120 [66.6%] cases of missed miscarriages, 12[6.6%] cases of congenital anomalies, and 8[4.4%] cases of early intrauterine fetal demises were noted.

There is no significant difference in pregnancy loss during and before covid. [Table-1]

Table 1: Pregnancy outcomes before and during COVID 19 pandemic

	An embryonic Miscarriages	Embryonic Miscarriages	Fetal Congenital Anomalies	Early Intrauterine Fetal demise
Before covid (April2019-March 2020)	68(29.3%)	140(60.3%)	16(6.8%)	8 (3.4%)
During Covid (April2020-March2021)	40 (22.2%)	120(66.6%)	12(6.6%)	8(4.4%)

In the control group, all the cases of anembryonic pregnancy and 2/3rd [39.6%] of embryonic miscarriage cases were noted in less than 12 weeks of gestational age, and after 12 weeks, about 1/3rd [20.6%] early intrauterine fetal death presenting as miscarriages were recorded

In the study group ie during covid, all the cases of anembryonic pregnancy and the majority [5/6th] of the embryonic miscarriage cases were noted in less than 12 weeks of gestational age, and after 12 weeks, about 1/6th of miscarriages presented as early intra uterine fetal deaths. These observations showed minimal differences in both the groups with marginal rise of embryonic losses in more than 12 weeks observed in study group.

Before covid group, there were 72 cases of primigravida women and 160 cases of multigravida women were noted, but in during

covid 19 study, 72 cases of primigravida women and 104 cases of multigravida women were noted.so there is no significant difference in parity of both groups [Table-2]

Table 2: Parity of pregnant women before and during covid.

Parity	Primigravida	Multi
Before covid	72(31%)	160(68.9)
During covid	76(42.2%)	104(57.7%)

Discussion

Despite the large and rapidly growing no of cases worldwide, there is limited data on covid 19 in pregnancy. Few studies focussed mainly studies related to the 2nd and 3rd trimesters of pregnancy, lacking studies on the 1st trimester of pregnancy.

Raschetti R *et al.*, 2020^[12] suggested that there is a possibility of fetus during the 1st trimester in women infected with covid 19, and it is to be considered a new factor in the epidemiology of the disease during pregnancy. In our study, we assessed the influence of the pandemic environment rather than the disease itself on early pregnancy. We found no statistical difference in the no of early pregnancy losses between covid and pre covid period. We also wanted to assess whether the stress associated with the pandemic and undetected asymptomatic infections would have any role in early pregnancy loss. This stress-related pregnancy loss may be due to a rise in cortisol and possible negative effect on the immune system [Geisler M *et al.* 2020, Seing J S *et al.* 2001]^[13, 14].

Some studies suggested the mechanism of infection by the covid 19 by the activation of angiotensin-converting enzyme receptor type 2[ACE-2] and the transmembrane protease, serine 2 enzyme [TMPRSS2] to cause the internalization of the virus. Both these are required for the cell to get infected. However, the TMPRSS2 enzyme may only be expressed after 24 weeks of pregnancy and only in the extravillous trophoblast, thus limiting the timing of infection of the pregnancy tissue [D'Ardes D *et al.*, 2020; Li M, Chen L, *et al.*, 2020]^[15, 21].

There are some studies suggested that there is an increased risk of embryo implantation failure and miscarriage during the periconceptional period in women with covid 19. This reproductive failure was due to systemic inflammation and interference with trophoblast-endometrium molecular signaling rather than a direct action of SARS-COV 2 at the implantation site.

Some studies reported that most of the miscarriages due to covid 19 in 1st trimester were due to placental insufficiency (Ryan GA *et al.* 2020, Rana MS *et al.* 2021)^[16, 17].

The immunopathology of covid 19, cytokine storm of covid 19 induces a hypercoagulable state that is detrimental to normal in-utero blastocyst or fetal development as well as an unfavorable uterine immune response to embryo implantation (Sills and Wood 2020)^[18]. However, the 1st study on the pregnant women with covid 19 found no increased risk of miscarriage among these patients (Yan *et al.*, 2020)^[19].

A meta-analysis /systematic review was conducted by M.B. Cavalcante *et al.* in 2021 and, based on the data in his literature, reported that the miscarriage rate in less than 22weeks gestation in women with SARS-COV-2 infection is in the range of the normal population^[20].

Some other studies also support that there is no significant increased risk of pregnancy loss in the 1st trimester with covid 19 infection (IA Cour *et al.* 2021)^[21].

Another study also supports that the risk of 1st-trimester spontaneous miscarriages was not affected by SARS-COV 2 infection after being adjusted for age (S. Cosma *et al.*, 2021)^[22].

In our study, we did not find any significant difference in the rate of early fetal demise during both covid and pre-covid period in gestational ages less than 20 weeks, because of the small sample size which could be the cause of statistical insignificance.

The no of cases of anembryonic pregnancy and missed miscarriages during the covid period have decreased when compared to pre covid period it can be because of reduced hospital visits by the patients due to the fear of getting infected unnecessarily as ours was a covid nodal hospital though this decrease is not statistically significant. There is no difference in congenital anomalies and early intrauterine fetal demises in both control and study groups.

In our study, we have noted that the no of missed miscarriages

was more before 12 weeks of gestation during the covid period when compared to before the covid period. This could be because of the stress related to the pandemic. As for the infection. We did have few confirmed cases after routine RTPCR test, Women coming to our hospital with fetal demise, most of them denied the symptoms of the disease, but we can assume that viremia, minor infections signs like pyrexia few days earlier could be identified through their history, although the number being small, COVID positive could still be not ruled out.

There is no significant difference in congenital anomalies and early intrauterine fetal demises in both groups. Also, there is no significant difference in parity of both groups.

Conclusion

During COVID-19 pandemic, there has been a reduction in the non-emergency services and supplies related to reproductive health, especially due to fear of getting infected with covid 19 on their visits to the hospital. Many pregnant women with fetal demise could not seek medical advice early when these patients had some threatening symptoms.

We should also consider the stress associated with covid as a causative factor for early fetal demise. Several strains of SARS-COV-2 have emerged since our study period, and infection with these variants may not pose the same risk as the original virus. Large study population is the need to rule out the impact of COVID19 in early fetal demise especially in 1st trimester which happens to be the period of fetal organogenesis.

In our study, we did not find any significant difference between the early fetal demise during the pre-covid and covid periods. Our sample size being small could be the main reason for minimal differences in both the study groups. Hence further studies are needed to evaluate any association between the infection and its effect on fetal demise.

Conflict of Interest

Not available

Financial Support

Not available

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