Summer Internship Report

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A report on

Effect of In-Utero Exposure to SARS-CoV-2 infection on pregnancy outcomes, growth, and development of infants.

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Acknowledgement

Any successful project cannot be completed with great efforts from the team that planned it and implemented it. And so is the same for my project. I successfully completed research on the topic "**Effect of In-Utero Exposure to SARS-CoV-2 infection on pregnancy outcomes, growth, and development of infants.**" I hereby take this wonderful opportunity to thank and show my gratitude to my best support team and my spine. Best mentors can fine tune the best students and I am glad to work under the mentorship of many such fine minds and assistance of other people made lots and loads more easier.

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11	Mukesh Saini	IT Operator
12	IIHMR Delhi Batch 2021-2023	Classmates helping all the time in clearing doubts

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Annexure : Operation Definitions

1. Anaemia during pregnancy – Haemoglobin level of less than or equal to 10.9 grams/dL, assessed using acid hematin/ cyanmethemoglobin/ oxyhemoglobin/ alkaline hematin method.

2. Gestational Diabetes Mellitus – 2-hour plasma glucose level of more than or equal to 140 milligrams/dL after administration of 75 grams of oral glucose, assessed using plasma standardized glucometer.

3. Preterm labour – Labour that starts before 37 completed weeks of gestation, calculating from the first day of the last menstrual period.

4. Prolonged labour – Combined duration of the first and second stage of labour is more than duration of 18 hours.

5. Live birth – Complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy, which, after such expulsion or extraction, breathes, or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached.

6. Stillbirth – Birth of a newborn after 28 completed weeks (weighing 1000 grams or more) when the baby does not breathe or show any sign of life after delivery.

7. Preterm birth – Birth of a newborn before 37 completed weeks of gestation, calculating from the first day of the last menstrual period. • Extremely preterm (less than 28 weeks) 9 • Very preterm (28 to 32 weeks) • Moderate to late preterm (32 to 37 weeks)

8. Full term birth – Birth of a newborn between 37 completed weeks and 42 completed weeks of gestation, calculating from the first day of the last menstrual period.

9. Low birth weight – Newborn whose birth weight is less than 2500 grams irrespective of the gestational age. • Very low birth weight (birth weight less than 1500 grams) • Extremely low birth weight (birth weight less than 1000 grams)

10. Birth injury – Any trauma to the soft tissue or bone of a newborn that occurred during labour, delivery or immediately after delivery.

11. Weight-for-age – Body weight (in kg) of the infant plotted against age (in completed weeks) on gender specific WHO weight-for-age growth chart (percentile).

12. Length-for-age – Length (in cm) of the infant plotted against age (in completed weeks) on gender specific WHO length-for-age growth chart (percentile).

13. Head circumference-for-age – Circumference (in cm) of the infant's head around the widest possible circumference of the head plotted against age (in completed weeks) on gender specific WHO head circumference-for-age growth chart (percentile).

14. Chest circumference – Circumference (in cm) of the infant's chest measured at the level of the nipples

Effect of In-Utero Exposure to SARS-CoV-2 infection on pregnancy outcomes, growth, and development of infants.

Introduction

As the world witnessed an entire 180^0 transformation from the cheering competitive and fast paced environment to the saddened grave by the onset of new pandemic SARS Covid 19 infection. A couple of months changed the lives of millions. An invisible miscreant from sources unknown shattered the world and played stakes on the lives of many. And pregnant ladies are one in those many.

The coronavirus disease 19 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single stranded positive sense RNA virus belonging to the family of coronavirus.AS of today there are a registered cases of 61.2 Cr people effected, and more than 65.3 Lakhs people lost their lives in the battle with an invisible virus[1]. The flu-like symptoms COVID-19 presents with include fever, coughing, shortness of breath, exhaustion, and headache. COVID-19 mostly appears as a pulmonary disease. SARSCoV-2 infection severity spans from having no symptoms to being serious respiratory failure and pneumonia-causing conditions.[2] The primary source of transmission is respiratory droplets that could lead to slow and mutation and starts with epithelial cell damage in a layered manner.

Other effects would be the Type I and II pneumocytes may suffer damage e, there may be inflammation and bleeding in the lungs as a result of SARS-CoV-2 infection.[5,6] Post to this, the vascular leakage provided a mechanism for the SARS- Cov-2 to gain access to other organs by entering into the circulatory system.[7]

The incubation period for the virus in the people during the first variant in India at May 2020 was about 5 days post infection or exposure, the symptoms started showing up.[3,4] However the incubation period in the pregnant women might change accordingly with her condition and with respect to the heath indicators of the respective subject as there are severe confounders like pneumonia, gestational diabetes and other pre existing comorbidities with the subject and in the subject's genetic hierarchy.

Regardless of these, there are always extrapulmonary manifestations of the infection during the first wave. Even though SARS-CoV-2 RNA has been found in patient plasma, no infectious virus has yet been produced from blood.[8.9] There is no particular study that elucidates the pregnancy and growth outcomes subjecting to the Indian demography with the variants and the mutations with this genesis and there is especially limited studies available with questionable future outcomes when it comes to the pregnancy outcomes in the covid effected mothers. There is a high necessity of it and thus this research has been towering on.

It is widely recognised that maternal infections, particularly those of viral origin, during pregnancy can negatively affect the developing foetus and raise the chance of cerebral palsy and autism spectrum disorders in the offspring.[10-12] Some of the research that have happened are already showing that the viral infection manifestation in pregnant women can lead to unhealthy outcomes on the pregnancy and sometimes on the infant. Those research works are mostly based on the SARS infection and not pertaining to the Corona Virus. Preterm deliveries, low birth weight, and an increase in admissions to neonatal intensive care units have apparently been linked to corona virus infection during pregnancy.[13-16]

Though many researchers have studied the risk of adverse perinatal outcomes among women who contracted COVID-19 infection during pregnancy, not enough evidence is available regarding the effect of maternal infection on the growth and development of these children. Therefore the need arises to study COVID-19 infected pregnant mothers and observe the growth and development pattern in their children.

Several studies have stated that there are adverse effects of the Corona Virus on the the pregancy outcomes of the pregnant women but none stated the growth outcomes of the infants born to the covid mothers. Certain studies stated the possibility of vertical transmission is high and the infants are at a risk.

The physiology of the pregancy states that the umbilical cord of the pregnant woman is designed to not let any viruses into the system of foetus. Certain clinical reports and clinical studies have stated that there is a vertical transmission happening while a few do not. One of the major confounder of the study is that there is a vast diversity in the population. The virus has a different effects on the different people and their respective lifestyles also makes a great deal of difference among them and thus are the effects of it.

A study by David A Schwartz states that there is a low possibility of the vertical transmission unlike the other viruses like Ebola, Zika, and AIDS. These prior experiences with coronavirus infections during pregnancy suggest that these pathogens can result in harmful clinical outcomes, such as life-threatening maternal illness that, in certain cases, necessitates hospitalisation, intensive care, and ventilatory support. The particular risk factors for a deadly outcome during pregnancy have not been determined, yet in a small but considerable number of cases, both of these coronaviruses can cause maternal death. The effects of coronaviruses on the foetus and newborn can also include intrauterine growth restriction, preterm delivery, admission to the intensive care unit, spontaneous abortion, and perinatal death. SARS or MERS are not viral infections, such as the Ebola or Zika viruses, Since there have been no confirmed cases of vertical transmission of SARS or MERS, the chance of intrauterine maternal-fetal transmission of coronaviruses is low. During the current Wuhan 2019-nCoV epidemic, it is still unknown how this newly-emerging coronavirus affects pregnant women and their unborn children. It is also unknown which factors, such as the timing of maternal coronavirus exposure by gestational age, the effects of medications or other treatment regimens, variations in host immune responses, the occurrence of coexisting medical and obstetrical conditions, and other covariables, may modulate obstetrical disease and outcomes. However, during this present outbreak of 2019-nCoV, pregnant women should be thought of as being at a high risk for having a serious infection.[24,22,23]

There are other certain studies done with 38 participants cohort and 40 participants cohort but none of which are addressed on a large scale. A study in Nigeria led by Ashley L Graham stated that all the pregnant positively tested for corona virus women lost there pregnancy after developing pneumonia. Severe Endothelial cell damage developed pneumonia that resulted 25% of the women in hospitalization but however the termination of pregnancy was inevitable.

A research study by Bethany Kotlar, Emily Gerson, Sophia Petrillo, Ana Langer & Henning Tiemeier was done by yielding 396 publications out which 95 were included.

Pregnant women might be at risk for severe corona virus disease as that there is a 598 sample size. They studied the direct effects on the pregnancy and the report is morbid mortal weekly

report, population surveillance at 13 states. It was concluded that pregnant women might be at risk for severe corona virus.[26]

Another study by Marian Knight with a participant count of 427 subjects which is a peer reviewed population cohort study subjected to the direct effects on pregnancy and intrauterine transmission. The majority of SARS-CoV-2-infected pregnant patients admitted to hospitals were in their late second or third trimester. SARS-CoV-2 transmission to new-borns was rare, and most patients had successful outcomes. There needs to be immediate examination into and justification for the disproportionate percentage of black or minority ethnic women admitted with infection.[27]

A study on "Clinical manifestations, risk factors and maternal and perinatal of corona virus disease 2019 in pregnancy: Living systematic Review and Meta Analysis" which is a peer reviewed systematic review and meta-analysis with direct effects on pregnancy. This study was done on a global on direct effects of pregnancy with a study population of 11432, Women who are pregnant or recently gave birth have lower rates of myalgia and fever associated with COVID-19 than non-pregnant women of reproductive age, and they may also require more intensive care for the condition. High maternal age, pre-existing comorbidities, and a high BMI appear to be risk factors for severe COVID-19. Preterm birth rates are higher in covid-19-positive pregnant women than in covid-19-negative pregnant women.[28]

Blitz et al , a research team made a peer reviewed case studies on direct effects on pregnancy on Maternal Mortality among Women with Coronavirus Disease 2019 Admitted to the Intensive Care Unit with 462 participants stated that 15% of patients admitted to the ICUs for COVID-19 and 25% of those who required invasive mechanical ventilation had maternal mortality. All patients who required invasive mechanical breathing and half of the COVID-19 patients admitted to the ICUs experienced delivery. The majority of the study's participants were Hispanic women, which may indicate that minority groups have a disproportionate burden of disease.[30]

A research study on "Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies." by Zaigham and team peer review and systematic review paper on labor and delivery with 108 subjects from global level stated that 91% of the deliveries happen to the covid effected mothers was by one caesarean section.[30]

A review on labour and delivery in China with 118 subjects stated that 63 of the 68 subjects went through caesarean section deliveries.

The effect of the infection on the pregnant ladies took a toll on the mental health of the pregnant women and their families aswell. A cross sectional study and peer reviewed report was done in China with 4124 pregnant women which is a multi-centric study and peer reviewed paper stated that When compared to pregnant women assessed prior to the proclamation of the coronavirus illness 2019 epidemic, pregnant women assessed after the epidemic declaration had considerably greater prevalence of depressive symptoms. These ladies had higher rates of suicidal thoughts as well. The depression rates were positively correlated with the number of coronavirus disease cases that were newly confirmed in 2019 as well as with suspected infections and daily mortality.[32]

Methodology

The research was aimed to study the effect of SARS-CoV-2 infection on pregnancy outcomes, growth and development of infants born to COVID-19 positive mothers. The study is designed to be an ambispective study at multicentric level covering almost all the geographic bases that compiles all the categories of demography and different lifestyles of all the people from different sites.

The primary objective of the study was to find the association between the in-utero exposure to SARS-CoV-2 infection and pregnancy outcomes. Post that are the secondary objectives which is to explore the effect of maternal COVID-19 infection during pregnancy on neonatal outcomes and to explore the effect of maternal COVID-19 infection during pregnancy and growth and development of infants.

The current report is concentrated on the retrospective aspect of the study as the number of covid cases have fallen and considering the non-approachability and ease of primary data collection being infinite with the declining number of cases, the prospective part has been terminated. The study design thus, has been fixed with this limitation.

As mentioned the study is multicentric and this report is subjected to the Gandhi Medical College and Hospital, Secunderabad from the southern state of Telangana and Andhra Pradesh.

The respective college sites and the hospitals are designated to be the follow up sites of the participants for their medical check up and the interview. The offsprings of the participants were also encouraged to be brought by the parents to the institute so as to get them checked for the medical examination and to file the proof of milestones. And in case of any abnormality in the infant like being unable to achieve the milestones with respective to the particular age, capillary filling time, general condition of the child, abnormalities like visible and internal, anterior fontanelle, colour of the pupils, secretion from eyes, condition of the nostrils, discharge from nose etc are being examined and are reported by the respective designated medical partner of the project from the department that overtook the study.

For the research, the study population is taken as exposure cohort and comparision cohort. Infants that are born to the pregnant women who are tested positive for SARS-CoV-19 infection at any time during pregnancy. Comparision cohort are the infants born to the pregnant women who are negative and never got tested positive for the SARS-Cov-19. In informal language , children born to the covid virgins.

Inclusion Criteria for the participants is that the pregnant women who have tested positive for SARS-CoV-2 using a molecular-based test (RT-PCR, CBNAAT, TruNAT, or Rapid Antigen Test) at any point during their pregnancy are considered members of the exposure cohort. Pregnant women having a negative SARS-CoV-2 Molecular report are used as the comparison group. Rapid Antigen Test or RT-PCR, CBNAAT, or TruNAT during pregnancy are the different testing procedures that are trusted. On a scale, the least priority is given to the Rapid antigen test as the normal viral fever is also being projected as a positive report while the highest trust is on to the cultures of the molecular test are given the most priority. A molecular test (RT-PCR/ CBNAAT/ Tru NAT)

Pregnant women who did not gave the consent of participation and the women who reported for covid 19 infection symptoms during the pregnancy but were not tested or the test results

are unable for verification are the women who are being rejected from the study. The definition of the exclusion criteria has been later modified during the study based on the details provided by the study subjects. The participants with the improper details and the details that do not match the logical sequence of nature's creation are being eliminated.

External variables are the Maternal COVID-19 infection cases based on SARSCoV-2 Molecular based test (RT-PCR/ CBNAAT/ TruNAT) or Rapid Antigen Test report, ascertained from case records as a categorical variable, COVID-19 positive/negative during pregnancy. Co-factors are Determined from the mother's positive history and from records as categorical variables (where possible)

Other cofactors are history of household contact and the high risk contact as per the ICMR Definition, with covid 19 confirmed and suspected cases anytime during pregancy. There are certain pregancy related factors such as anaemia during pregancy, gestational diabetes mellitus, hypertension in pregnancy ,preterm in labour, prolonged labour, history of infections/ fever during pregnancy, intake of any medications for any illness during pregnancy. Nutrition factors such as breast-feeding practices , infant and young child practices. There are other cofactors such as Socio-environmental factors as such hand washing practices, source of drinking water , food hygiene etc.

The outcome variables are pregancy outcomes, presence of any congenital anomalies, variables related to the growth, variables related to development.

Study duration is the duration of the recruitment till the required sample size is achieved by both cohorts. The follow up of the details shall be happening till the baby attains one year of age.

For the sample size estimation, we used the probability that pregnant women who tested positive for COVID-19 would deliver preterm babies. The odds of premature birth among pregnant women who catch COVID-19 are 1.47, according to research by Allotey et al. Odds Ratio typically approximates Relative Risk in situations with unusual outcomes.[17,18]

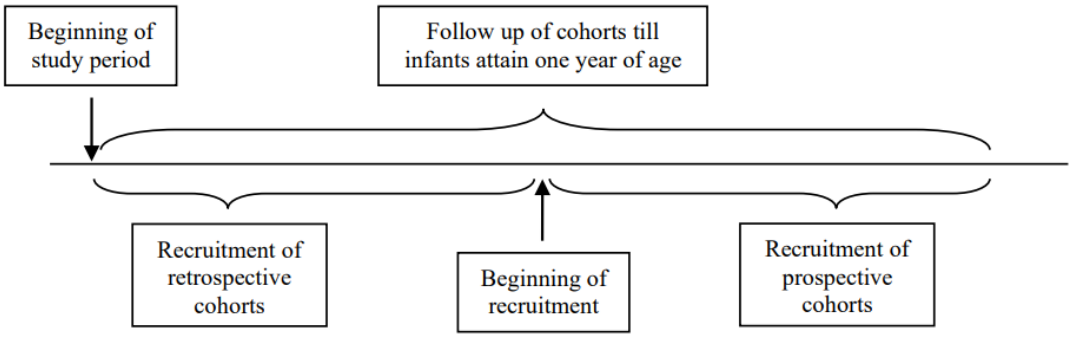
With a sample size of 984 for each exposure and control cohort, which we rounded off to 1000 to produce a total sample size of 2000, we can assume that the relative risk of preterm birth babies among COVID-19 positive mothers is 1.47, the rate of preterm birth among pregnant women in India is 13%, a confidence level of 95%, a power of 80% for a two-sided test, a loss to follow-up of 10%, and a non-response rate.[19,20]

Six research sites will be used to conduct the investigation. From each study location, a total of 400 pregnant women will be enrolled. 200 of these women will be recruited at each study site either prospectively (100 exposed and 100 compared) or retrospectively (100 exposed and 100 compared).

The source of retrospective cohorts are hospital records of the women who delivered at the facilities that are designated for the study. The sampling of the exposure cohort in the retrospective cohort is that all pregnant participants will be recruited at research sites where the number of COVID-19 positive women who delivered in the institution up until recruitment is less than or equal to the necessary sample size (after fulfilling selection criteria and giving consent). If there are more women at a research location than the required sample size, a frame

of all the women will be created for sampling, and the desired sample will be gathered using simple random sampling.

For the comparision cohort in the retrospective study, for each COVID-19 positive woman selected for the study, a sampling frame of all the COVID-19 negative pregnant women who delivered on the particular date will be made and one will be selected by simple random sampling method. In case more than one COVID-19 positive women who have delivered on a particular date has been included in the study, an equal number of COVID-19 negative women will be selected randomly from the sampling frame for that date.



Data will be collected with respect to the following tools, Hospital records for data on COVID-19 infection during pregnancy ascertained by positive SARS-CoV-2 Antigen test report. The medical data stored and shared by the hospital will also be used to collect the data on the exposure variables during pregnancy, delivery outcomes and anthropometric measurements of the child.

Other tools for the follow up are like the a semi-structured, previously tested questionnaire will be used to gather information on sociodemographic facts as well as exposure variables linked to pregnancy, nutrition, socioenvironmental factors, and medical history. developmental milestones up to one year of age: a checklist (pictorial). Digital infant weighing scale with an accuracy of 0.01 kg. Infant meter with an accuracy of 0.01 cm. non-stretchable measuring tape with an accuracy of 0.01 cm.

The women will receive a telephone explanation of the study's goal, and their verbal agreement will be sought. Hospital records will be consulted for information on pregnancy and birth results. On the phone, information about COVID-19 exposure during pregnancy will be gathered. The women will be urged to bring their infants to the hospital for measles/MR vaccination, and this visit will be used to examine the child (anthropometry and attainment of age-appropriate developmental milestones), gather information about immunizations, feeding habits, illnesses of the mother and child, and socio-environmental details, as well as to collect the history of immunizations. Additionally, the women's written informed permission will be obtained during this visit. The above-mentioned history and examination will be carried out at both follow-up appointments for any lady who is prepared to come in for an earlier follow-up at 6 months after delivery.

Data analysis has been started with a rigorous cleansing process of the data and coding according to the infant growth outcomes with respect to the RMNCH suggested methodology. Post that, the correlation between the factors subjecting to the primary objective and secondary objective are used for testing the strength of association between the factors. The data will be displayed as a percentage, median (IQR), and mean (SD). The Kolmogorov-Smirnov test will be used to determine whether the data are normal. Using the Chi square test, comparisons across groups will be evaluated for statistical differences.

To evaluate the impact of co-factors on the relationship between exposure and outcome variables, a stratified analysis will be carried out. It will be possible to compare infections that were acquired in the first wave to those acquired in the second wave using sub-group analysis based on the trimester in which the infection was acquired. Values for Attributable Risk and Relative Risk will be computed. Statistical significance will be determined by a p-value below 0.05.

The Institutional Ethical Review Boards of IIHMR Delhi and the participating institutions will provide their approval in matters of ethics (medical colleges and hospitals). All information gathered will be kept private and used only for research. Before any subject is allowed to participate in the study, their written informed consent will be sought; in some cases, video consent will be used in place of written consent. Participants' names and signatures that appear on the consent form won't be connected to any identifiers in the study instrument. Only subjects who voluntarily agree to participate in the study and meet the inclusion requirements will be included. Participants' phone numbers collected throughout the survey will be strictly kept private and used exclusively for the study and any required follow-up. Any new born disease brought on by maternal COVID-19 or its aftereffects that develops throughout the course of the trial will be referred for medical care.

The entire research has been done after achieving concerned approvals and the consent from the participation. A rigorous and thorough interview has been conducted with each participant for the proper primary data collection and is cross verified with the medical documentation presented. There is a recall bias with many participants, but the bias has been eliminated by the second questionnaire that was designed. The questionnaire suggests the participant to look at the photos of the child at several instances when they are captured and that helped the parents to realise the proper dates of the outcomes.

All the details are being crosschecked and a conformation has been take by the medical reports of the participants to allocate the designated cohorts. The subjects are interviewed telephonically and are requested to come to the study site for physical examination. While for those participants who cannot make it to the organization, a telephonic interview and a video conferencing interview has been performed.

As the interview begins, the demographic details of the participant are taken and are cross checked. Most of the times, for the data sourced from the medical records department, the demographic details are already present and for the data that is sourced from the Obstetrics and gynaecology department, the nursing heads only provided with the name of the patient, patient ID and the mobile number. In those cases, the demographic details from the patients are being collected.

The interview questionnaire is about 200 questions, and each interview took around an hour to an hour and half. There are certain cases when the participants data is extremely low in quality and an MDRU Lab assistant support has been taken at times to avoid the interviewer bias, but the judgement calls are being made at times. When the milestones data are not in logical sequence and when there is a severe recall bias, the participant is suggested to go through the photos of the child in their mobiles. When there is a heavy recall bias, there has always been a high scope for the interviewer bias aswell, and the subject is eliminated at times.

The questionnaire consists of questions of demographic details, history of past illness, interview regarding the experiences of symptoms etc. Also, there is evidence of higher uneasy rashes for the covid effected people.[21] The interrogation consists of fever, cough, fatigue, myalgia, shortness of breath, loss of smell/taste, headache, joint pain, diarrhoea, discoloration of fingers and toes, rashes on the skin, anytime during the pregnancy.

Did the subject covid test anytime during pregnancy and the reason for the test like covid 19 symptoms, high risk contact, routine testing in ANC. Time period between the first symptom and last contact. The type of Covid 19 diagnostic done is a crucial factor to know.

The questionnaire consists of the interview regarding the details of the following aspects that are taken at the time of recruitment and they are the outcome variables of the study.

Pregnancy outcomes:

Live birth/ stillbirth, Pre term/ full term, Normal/ low birth weight, Birth injury present/ absent ascertained from records as categorical variables (definitions in annexure)

Presence of any congenital anomaly

Variables related to growth: Weight-for-age, length-for-age, head circumference-for-age and chest circumference of the infant ascertained from records or measured during follow up as continuous variables (definitions in annexure)

Variables related to development:

Age of attainment of the following developmental milestones recorded in weeks.

Motor development

1. Head holding

2. Pushing up when lying prone

3. Rolling over

4. Sitting with support

5. Sitting without support

6. Crawling

7. Standing with support

8. Standing without support

Language development

9. Turning head towards sounds

10. Responding to sounds by making sounds

11. Repeating monosyllable words

12. Trying to copy said words

Cognitive development

13. Watching objects as they move

14. Reaching for objects with one hand

15. Passing objects from one hand to the other

16. Searching for things they see someone hide

Social development

17. Social smiling

18. Recognizing familiar people

19. Responding to own name

20. Showing affection to caregivers

Spells of sickness

1. Respiratory infections and diarrhoeal

3. Any other significant illness lasting for >2 weeks

4. Any history of hospitalization

The interview consists of data retrieval from the medical reports aswell like GPLAD Score of the mother that indirectly influences the growth outcomes of the baby. The data collected also reported few outliers in the cases with respect to GPLAD score and the are also considered into the cohort as they are matching the criteria. Other aspects of medical report data retrieval are the APGAR Scores of the infants.The clinical examination of the infants consists of the following questionnaire details

1. Weight of the infant
2. Length of the infant
3. Head Circumference
4. Chest Circumference
5. Mid upper arm Circumference
6. Skin temperature
7. Axillary
8. Heart rate
9. Respiratory rate
10. Capillary filling time
11. General Condition
12. Appearance with normal and no visible abnormality

13. Colour of the infant
14. Anterior Fontella
15. Pupil colour and status
16. Secretion from eyes
17. Secretion from nose
18. Secretion from Umbilical cord
19. Nostril status – patent or blocked
20. Neck short , webbed, or palpable
21. Cardiac rhythm and sound
22. Cardiac murmurs
23. Grunting
24. Respiratory sounds
25. Shape of abdomen
26. Bowel sounds
27. any skin infection
28. Hips
29. Genetalia
30. Hearing
31. Vision
32. Presence of new born reflexes.

The above all are the clinical aspects that are studied when the infant is being brought to the study site. Along with these, the vaccination status of the infant is also studied. It is suggested to get all the vaccinations for the infant to be done on time , and the following are the vaccinations and the time of vaccine injection is also recorded. For most of the home delivery cases the vaccinations like BCG, Hep B, OPV 0, PCV are not done. But for the rest the following vaccinations are suggested to be completed and all the study subjects are not immune compromised as they are completely vaccinated at respective PHC's.

1. BCG
2. Hep B
3. Oral Polio 0,1,2,3
4. Penta 1,2,3
5. Rota 1,2,3
6. MR 1

Every study have its own limitations and so does this study too and they are listed below.

- Shifting of study design.
- Lack of vaccination details and vaccination influence being a cofactor.
- Lack of questions regarding the covid status of the infant.
- Severe cases in comparision group.
- Recall bias of fathers.
- Health details are asked upto 6 months, but the growth outcome objectives are upto 1.5 years.
- Questionnaire lack details for other cofactors.
- Not all the aspects are covered in the growth outcomes. Example Dental details.
- Gender of the new born is not asked.

Results and Discussion

The analysis part comprises of weightage scoring for the growth outcomes interviewed from the participants. From the RMNCHA site, the growth outcomes milestones are being sourced and the weightage is calculated accordingly. The growth outcomes are classified with respect to the following categories.

Motor outcomes and milestones are the ability to use the rise of hands and legs, head holding, rolling over, sitting with and without support, crawling, standing with and without support. Post that the cognitive outcomes are turning head towards sound, social smiling, recognizing familiar people, recognizing parents, responding to own name, searching for things someone hide etc. The communication outcomes are making sounds and responding to sounds, replying and acknowledging . Linguistic outcomes are the things like repeating monosyllable words and responding to sounds by making sounds.

These are categorized and are scored with respect to the milestone developmental aspects. For a clear elucidation consider the following example. If a child irrespective of cohort of the mother is born and his/her milestones data is collected. Now a comparision of the milestone achievement age of attainment is compared to the RMNCH standardized milestone attainment age, if they are equal then it is scored as 1. If the subjects age of attainment is less than the standardized, it is considered as a positive sign and the wise versa is negative. The positive sign is again scored as 1 and the negative sign is scored as 0. Now all the developmental details of the subjects of all categories are calculated and are summed up. Consider that there are 6 milestones in motor developmental category. Then the comparative standard score is 6 and its compared to the total sum of the motor category score of the subject. Incase if it is equal to 6, then there is no positive association and incase of it is less than six, there is an association indicating that there is a developmental delay.

The strength of association is proved by the significance test and the Chi Square Test.

The Chi Square test is done between the following aspects with and without including the still birth cases. The comparative analysis that happened with the growth outcomes excluded the still birth cases while the the comparative analysis that is done with the other data like exposure and term gestation and association between birthweight and the type of delivery included the still birth cases.

- Tests done excluding the still birth cases.
    - Association between Exposure and low Birth Weight.
    - Association between Exposure and Developmental Details
    - Association between Exposure and Motor outcomes.
    - Association between Exposure and Language outcomes.
    - Association between Exposure and Cognitive outcomes.
    - Association between Exposure and Social outcomes.
    - Association between Exposure and type of delivery.
    - Association between Exposure and Child NICU admission.

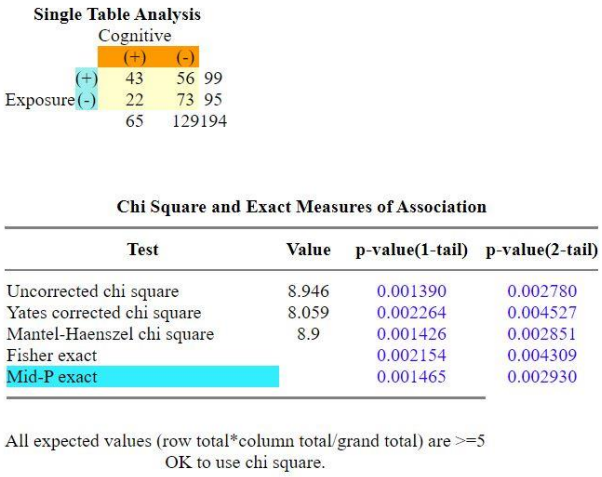
- Association between Exposure and APGAR at 1 and 5 min.
- Association between Exposure and term gestation.

- Tests done including the stillbirth cases
  - Association between Exposure and Term Gestation.
  - Association between Birth Weight and Type of delivery.

The results of the analysis are projected below in the table

S.No	Hypothesis	Calculated Chi Square Test (P)	Relative Risk	Significance
1	Motor	0.03346	1.5993	High
2	Communication	0.1471	1.022	High
3	Social	0.00322	9.59	High
4	Cognitive	0.00139	1.87	High
5	Aggregate Development	<0.00001	2.159	High
6	Birth Weight	0.3847	0.9362	High
7	Type of Delivery	0.001870	0.4478	High
8	Infant admission to NICU/SNCU/PICU	<0.000001	2.06	High
9	APGAR Score 1	0.2913	1.2594	High
10	APGAR Score 5	0.01626	1.850	High
11	Term Gestation	0.1380	0.78125	High
12	NVD APGAR @1 min	0.4450	1.2	High
13	NVD APGAR @5 min	0.1785	1.5384	High
14	Csec APGAR @1 min	0.7790	1.764	High
15	Csec APGAR @5 min	0.077900	3.01	High

The following are the associations between the above mentioned with their proof of calculation.



Single Table Analysis

		Cognitive (+)	Cognitive (-)	
Exposure	(+)	43	56	99
	(-)	22	73	95
		65	129	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	8.946	0.001390	0.002780
Yates corrected chi square	8.059	0.002264	0.004527
Mantel-Haenszel chi square	8.9	0.001426	0.002851
Fisher exact		0.002154	0.004309
Mid-P exact		0.001465	0.002930

All expected values (row total*column total/grand total) are >=5
OK to use chi square.

Fig 2 : Association between Cognitive and Exposure

Single Table Analysis

		Communication (+)	Communication (-)	
Exposure	(+)	98	1	99
	(-)	92	3	95
		190	4	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	1.107	0.1471	0.2942
Yates corrected chi square	0.2992	0.2922	0.5844
Mantel-Haenszel chi square	1.102	0.1477	0.2954
Fisher exact		0.2952	0.5903
Mid-P exact		0.1754	0.3508

Fig 3 : Association between Communication and Exposure

Single Table Analysis

		Csec APGAR 1 (+)	Csec APGAR 1 (-)	
Exposure	(+)	18	68	86
	(-)	7	52	59
		25	120	145

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	2.016	0.07790	0.1558
Yates corrected chi square	1.43	0.1161	0.2323
Mantel-Haenszel chi square	2.002	0.07862	0.1572
Fisher exact		0.1148	0.2297
Mid-P exact		0.08129	0.1626

Fig 4 Association between APGAR Score at first minute of birth and Exposure

Single Table Analysis

		Csec APGAR 5 (+)	Csec APGAR 5 (-)	
Exposure	(+)	22	64	86
	(-)	5	54	59
		27	118	145

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	6.758	0.004667	0.009333
Yates corrected chi square	5.676	0.008599	0.01720
Mantel-Haenszel chi square	6.711	0.004790	0.009580
Fisher exact		0.007046	0.01409
Mid-P exact		0.004350	0.008701

Fig 5 : Association between APGAR Score at five minutes of birth and exposure

		Motor (+)	Motor (-)	
Exposure	(+)	30	69	99
	(-)	18	77	95
		48	146	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	3.357	0.03346	0.06691
Yates corrected chi square	2.775	0.04788	0.09576
Mantel-Haenszel chi square	3.34	0.03381	0.06762
Fisher exact		0.04747	0.09493
Mid-P exact		0.03493	0.06986

Fig 15 : Association between Exposure and Motor milestones

Single Table Analysis

		NVD APGAR 5 (+)	NVD APGAR 5 (-)	
Exposure	(+)	5	8	13
	(-)	9	2736	
		14	3549	

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	0.8481	0.1785	0.3571
Yates corrected chi square	0.3167	0.2868	0.5736
Mantel-Haenszel chi square	0.8308	0.1810	0.3621
Fisher exact		0.2817	0.5634
Mid-P exact		0.1920	0.3839

Fig 6 : Association between Normal Vaginal Delivery APGAR Score at one minute of birth and Exposure

Single Table Analysis

		NVD APGAR 1 (+)	NVD APGAR 1 (-)
Exposure	(+)	3	1013
	(-)	9	2736
		12	3749

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	0.0191	0.4450	0.8901
Yates corrected chi square	0.05665	0.4059	0.8119
Mantel-Haenszel chi square	0.01871	0.4456	0.8912
Fisher exact		0.6049(P)	>0.9999999
Mid-P exact		0.4590(P)	0.9180

Fig 7 : Association between Normal Vaginal Delivery APGAR Score at 5 minutes and Exposure

Single Table Analysis

		Social (+)	Social (-)	
Exposure	(+)	10	89	99
	(-)	1	94	95
		11	183	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	7.421	0.003223	0.006447
Yates corrected chi square	5.826	0.007897	0.01579
Mantel-Haenszel chi square	7.383	0.003293	0.006586
Fisher exact		0.005841	0.01168
Mid-P exact		0.003150	0.006300

Fig 8 : Association between Social and Exposure

Single Table Analysis

Term Gestation

		(+)	(-)	
Exposure	(+)	25	77	102
	(-)	32	70	102
		57	147	204

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	1.193	0.1380	0.2759
Yates corrected chi square	0.8765	0.1746	0.3492
Mantel-Haenszel chi square	1.187	0.1386	0.2771
Fisher exact		0.1746(P)	0.3492
Mid-P exact		0.1402(P)	0.2805

Fig 9: Association between Term Gestation and Exposure

Single Table Analysis

type of delivery

		(+)	(-)	
Exposure	(+)	14	85	99
	(-)	30	65	95
		44	150	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	8.406	0.001870	0.003740
Yates corrected chi square	7.441	0.003188	0.006375
Mantel-Haenszel chi square	8.363	0.001915	0.003830
Fisher exact		0.003029(P)	0.006058
Mid-P exact		0.002004(P)	0.004007

Fig 10 : Association between Type of Delivery and Exposure

Single Table Analysis

Admission into PICU/NICU/SNCU

		(+)	(-)	
Exposure	(+)	97	2	99
	(-)	45	50	95
		142	52	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	63.29	<0.0000001	<0.0000001
Yates corrected chi square	60.74	<0.0000001	<0.0000001
Mantel-Haenszel chi square	62.97	<0.0000001	<0.0000001
Fisher exact		<0.0000001	<0.0000001
Mid-P exact		<0.0000001	<0.0000001

Fig 11 : Association between Admission of infant into NICU with exposure

Single Table Analysis

Aggregate

		(+)	(-)	
Exposure	(+)	72	27	99
	(-)	32	63	95
		104	90	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	29.71	<0.0000001	<0.0000001
Yates corrected chi square	28.17	<0.0000001	0.000000111
Mantel-Haenszel chi square	29.56	<0.0000001	<0.0000001
Fisher exact		<0.0000001	<0.0000001
Mid-P exact		<0.0000001	<0.0000001

All expected values (row total*column total/grand total) are >=5
OK to use chi square.

Fig 11 : Association between exposure and Aggregate outcomes

Single Table Analysis

APGAR @1 minute

		(+)	(-)	
Exposure	(+)	21	78	99
	(-)	16	79	95
		37	157	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	0.5998	0.2193	0.4386
Yates corrected chi square	0.3501	0.2770	0.5541
Mantel-Haenszel chi square	0.5967	0.2199	0.4398
Fisher exact		0.2774	0.5548
Mid-P exact		0.2233	0.4467

All expected values (row total*column total/grand total) are >=5
OK to use chi square.

Fig 12 : Association between APGAR Score 1 and Exposure

2 x 2 Table Statistics

Single Table Analysis

APGAR @5 minute

		(+)	(-)	
Exposure	(+)	27	72	99
	(-)	14	81	95
		41	153	194

Chi Square and Exact Measures of Association

Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	4.571	0.01626	0.03252
Yates corrected chi square	3.85	0.02488	0.04976
Mantel-Haenszel chi square	4.547	0.01649	0.03297
Fisher exact		0.02434	0.04867
Mid-P exact		0.01711	0.03423

All expected values (row total*column total/grand total) are >=5
OK to use chi square.

Fig 13 : Association between APGAR Score 5 and Exposure

Single Table Analysis

		Birth Weight (+)	Birth Weight (-)	
Exposure	(+)	40	59	99
	(-)	41	54	95
		81	113	194

Chi Square and Exact Measures of Association

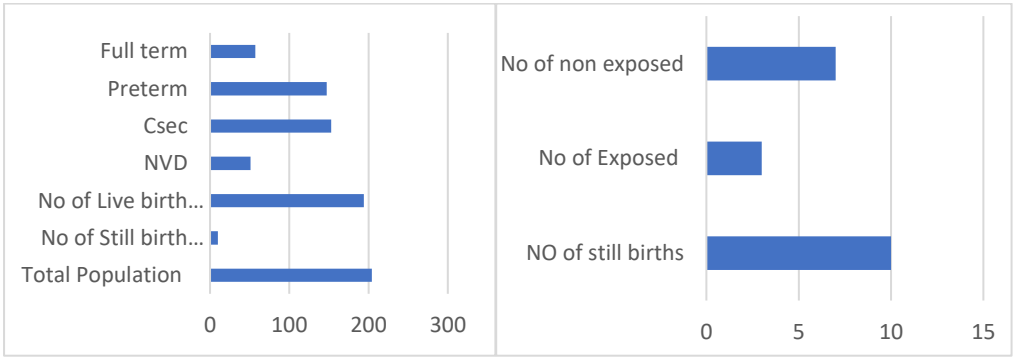
Test	Value	p-value(1-tail)	p-value(2-tail)
Uncorrected chi square	0.1512	0.3487	0.6974
Yates corrected chi square	0.05914	0.4039	0.8079
Mantel-Haenszel chi square	0.1504	0.3491	0.6982
Fisher exact		0.4039(P)	0.8078
Mid-P exact		0.3502(P)	0.7005

Fig 14 : Association between Birth Weight and Exposure

Conclusion

The research on Effect of In Utero Exposure to SARS COV 19 infection have had a significant outcome on the infants and on the pregancy. With the entire data collected and the analysis , it was observed that if the pregnant mother is infected with SARS Cov 19 Alpha, Beta and Delta Variants there is a high significant adverse outcome on the pregnancy. If the pregnant women got tested positive at first trimester of pregnancy, then the women is losing the pregnancy, if the same happens in second trimester of pregnancy, then there is a significant effect on the foetus with Intra Uterine Growth Restriction. If the same infection happens to the mother (pregnant women) at third trimester then there are chances where the mother might go to pneumonia effect and severe eclampsia. The initial cases where the pregnant women with covid got delivery were fallen into tachycardiac condition and have gone to vegetative state. That led to the decision that all the covid positive pregnant deliveries are to be gone through Caesarean Sections. There is a significant association stating that the exposure of a mother to SARS Covid infection is causing delayed outcomes, mainly targeting the communication outcomes and motor outcomes.

The following are the charts and graph presentation of the types of births in total population and classification of total still births.



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FEEDBACK FORM
(IIHMR MENTOR)

Name of the Student: Prudhvi Raj Gopisetty (PG/21/036)

Summer Internship Institution: Gandhi Medical College and hospital, Secundrabad.

Area of Summer Internship: COVID-19 (Viral Infection), MDRU and MRD.

Attendance: Regular

Objectives met: Yes

1. **Primary Objective:** Assistance in the study "Effect of in-utero exposure to SARS-CoV-2 infection on pregnancy outcomes, growth and development of infants"
2. **Secondary Objective:** Assistance in the MDRU operations in research works.

Deliverables:

1. Case sheet collection and updating them for the study" Effect of in-utero exposure to SARS-CoV-2 infection on pregnancy outcomes, growth and development of infants"
2. Organizational observation and assessment.
3. Little exposure to the hospital operations.

Strengths:

1. Hardworking
2. Sincere
3. Meticulous at work
4. Ready to help

Suggestions for Improvement:

Dr. Madhavi Latha. M
Signature of the Officer-in-Charge
(Internship)

Research Scientist -
Multi-Disciplinary Research Unit
GANDHI MEDICAL COLLEGE
SECUNDERABAD

Date: 17th June 2022.
Place: Secunderabad