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Pregnancy Outcome and Sars-Cov-2: A Systematic Review and Meta-Analysis of Record from Published Research Articles: January'2020 to December'2020.

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Abstract
Background: *Prevention and control of infection among pregnant women and their foetus is one of the greatest important in public health services.*
Objective*: The objective of this meta-analysis is to explore the evidence based precise view related to the association of SARS-COV-2 viral infection with risk of pregnancy outcome in prospective epidemiological studies.*
Design: *Systematic review and meta-analysis of prospective study.* ***Data sources****: PubMed (n=20), Google Scholar (n=5), CINHAL (n=5), Scopus (n=5), others (n=8) and MEDLINE (n=7) database.*
Study selection: Prospective population based *Cohort studies, observational studies.*
Data extraction*: Both the two authors have independently screens the search results using titles and abstracts.*
Results: *Overall total 12 studies 4 studies were included in systematic review and meta-analysis. Total sample subjects were 839 pregnant mothers. Meta-analysis of all 4 individual studies shows (CMA) Odds ratio 0.03, 0.01, 0.06 and 0.18 in the individual studies respectively which indicates there is a lower association between SARS-COV-2 infection and neonatal outcome (LSCS Mode). In maternal outcomes Odds Ratio (CMA Software) 11.766 indicates greater odds of association with disease and outcome, i.e. there is an association between the SARS-COV-2/COVID-19 infected mothers and pregnancy outcome in study 1.*
Conclusion*: Pregnant women with SARS-COV-2 / COVID-19 are more likely to deliver still borne, preterm baby and pre-pregnancy termination also may arise. There is an increased risk of maternal death and of being admitted to the ICU.*
*****PROSPERO ID No CRD42021229992, International prospective register of systematic reviews.***
Key word: SARS-COV-2, Pregnancy outcome, neo-natal outcome*.*

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I. Introduction:

Pregnancy is a state where the risk and severity of specific infections are increased due to a combination of physiological and immunological changes [1].The physiological adaptive changes can render the pregnant women intolerance to hypoxia [2]. The origin of SARS-CoV-2 infection was first reported in people exposed to a seafood market in Wuhan City, China in December 2019.It also known as COVID-19[3]. Evidence suggests that SARS-COV-2 infection during pregnancy may affect maternal-foetal outcomes [4].
On 30 January 2020, the WHO declared COVID-19 as the sixth public health emergency of international concern [5].It was being rapidly spread worldwide, and declared a pandemic infection on March 11 by the World Health Organization (WHO) [6].

OBJECTIVES: The objective of this meta-analysis is to explore the evidence based precise view related to the association of SARS-COV-2 viral infection with risk of pregnancy outcome in prospective epidemiological studies.

BACKGROUND: COVID-19 is a global public health emergency during pregnancy [7]. Preventive measures, such as frequent hand washing, avoiding infected individuals, crowded places and public gatherings, should be strictly followed by pregnant women [8]. Prevention and control of infection among pregnant women and their foetus is one of the greatest important in public health services. More evidenced based research is an outmost goal in future perspective to save the life of two vulnerable groups in our society [9].

METHODOLOGY: The proposal for Systematic Review and Meta-analysis is based on the **PROSPERO, International prospective register of systematic review** checklist. **Search Strategy: The** actual date for starting was 01/01/2021. Stage of review includes **Preliminary** searches, Piloting of the study selection process, Formal screening of search results against eligibility criteria.

Review question: What is the effect of SARS-COV-2 on pregnancy outcome? After a review of literature on Published study a systematic search has been conducted in the PubMed (n=20), Google Scholar (n=5), CINHAL (n=5), Scopus (n=5), others (n=8) and MEDLINE (n=7) database. The literatures searched were in English language. The retrieval period is from **January'2020 to December'2020. PROSPERO ID No CRD42021229992, International prospective register of systematic reviews.**

Participants/population: Pregnant mother with SARS-2 or COVID-19 positive cases.

SELECTION CRITERIA:

Inclusion criteria:

1. Prospective Population based cohort study/ and Observational studies with Covid-19.
2. Description of signs and symptoms of covid-19 and pregnancy outcome.

Exclusion Criteria:

1. Re-published studies.
2. Studies with incomplete data.

Comparator(s)/control for the present Systematic review and meta-analysis was none.

Types of study included: Prospective Population based cohort study and Observational study.

Context: Published research study conducted in hospital/ MCH clinic. **Main outcome(s):** Pregnancy outcome in terms of - Live birth/still born/ abortion. **Measures of effect:** Risk difference, and odds ratios.

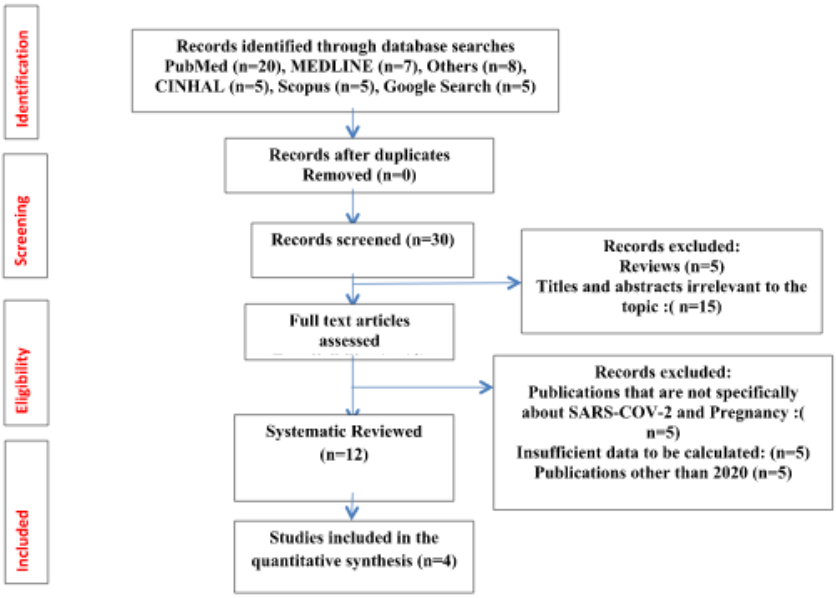

Figure: 1 Flow diagram of the search for eligible studies SARS-COV-2 and Pregnancy Outcome.

Data extraction (selection and coding):

On the basis of search strategy, inclusion and exclusion criteria, we the two reviewers conduct independent review of the literature for extraction of data. The following data are extracted from the selected articles: the surname of the first author, year of publication, study location (country), study design, pregnancy, diagnostic methods, pregnancy outcome, and neonatal outcome. These data are extracted in standardised forms designed exclusively for this review.

Risk of bias (quality) assessment: Risk of bias (quality) assessment was conducted by using the quality evaluation tool of Institute of Health Economics (IHE) case series methodological quality evaluation tool for

evaluation of 8 areas of the literature. The selected four studies had quality values more than 70%, i.e. 75% and was accepted quality. **Source: Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.**

Strategy for data synthesis: Statistical analysis:
The Statistical Analysis has been conducted using CMA (comprehensive meta-analysis software).
I^2 statistics is used to assess the heterogeneity among the studies. **According to the theory of Professor** Julian Higgins **a rough guide to interpretation of heterogeneity is as: 0% to 40%: might not be important, 30% to 60%: moderate heterogeneity, 50% to 90%: substantial heterogeneity, 75% to 100%: considerable heterogeneity.**

Changing the effect measures – we use the Risk Difference and have high heterogeneity, then try out Odds Ratio. Source: https://s4be.cochrane.org/blog/2018/11/29/what-is-heterogeneity/. Heterogeneity: what is it and why does it matter? 29th November 2018 by Maximilian Siebert.

Analysis of subgroups or subsets: Because of small number of selected studies we used fixed effects model and 95% confidence interval.

Ethics and dissemination: Ethical approval is not required because this review will draw on publicly available scientific literature. The findings of this systematic review will be published in a peer-reviewed journal and updates will be conducted if there is new evidence that may cause any changes in the conclusions of the review.

TABLE 1: SYSTEMATIC ANALYSIS OF THE SELECTED STUDY:

Sl. No.	Author	Name of the study	Date of Publication	Method of study	Place of study	Sample size
1.	Huijun Chen et. al.	Clinical Characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women	7.3.2020	Retrospective review of medical records	Wuhan, China	9
2	Gillian A Ryan, et. al.	Clinical Update on COVID-19 in pregnancy:	7.5.20220	A review Article	Wuhan, China	7
3	Chen,S; et. al.	Pregnancy with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases	8.5.2020	Retrospective study	Tongji Medical College	3
4	Nan Yu, et, al.	Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, china	May' 2020	Retrospective study	Wuhan,China	7
5	Knight, Marian; et, al.	Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-COV-2 infection in UK: national population based cohort study.	8.6.2020	Prospective Population based cohort study	Obstetric units in UK.	427
6	Yan-Ting Wu et. al.	Neonatal outcome in 29 pregnant women with Covid-19, Wuhan, China	28. 7.2020	Retrospective study	Wuhan, China	29
7	Jie Yan, et. al.	Coronavirus disease 2019 in pregnant women: a report based on 116 cases	July 2020	Retrospective study	China	116
8	Mahtab Sattari(MSc) et. al.	Evaluating Clinical Course and Risk Factors of infection and Demographic characteristics of Pregnant Women with COVID-19	17.8.2020	A retrospective cohort study	West of Iran	50
9	Antoun,Lina; et. al.	Maternal COVID-19infection, clinical characteristics, pregnancy, and neonatal outcome:	September 2020	Prospective cohort study		23
10	Sarah Jane Stock et. al.	COVID -19 IN Pregnancy in Scotland(COPS): An observational study using linked Scottish national data	26.10.2020	Prospective cohort study	Scotland,UK.	125
11	Emily H. et. al.	Pregnancy outcome among women with or without Severe Acute Respiratory Syndrome Coronavirus 2 infection	19.11.2020	Observational Cohort Study	Parkland (Dallas and Texas)	3374
12	Najeh Hcini, et al.	Maternal, fetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peri-partum period	30.112020	Prospective comparative study	West French	507

Table 2: Screening of Selected Studies for Meta-Analysis:

Sl. No.	Selected study	Author	Method of the study	Sample size with SARS-COV-2 infection	Mean age of the study sample	Gestational age on admission/at delivery	Mode of delivery	Pregnancy outcome
1	Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-COV-2 infection in UK: national population based cohort study [study 1].	Knight, Marian; et, al.	Prospective Population based cohort study	427	<20=4(1) 20-34 =248(58) >35=175(45)	29 to 36 weeks mean of 33.1 weeks gestation.	Caesarean section	266(41%) Pregnancy loss, 196(73%) term birth, 5(1%) women died.
2	Maternal COVID-19infection, clinical characteristics, pregnancy, and neonatal outcome[study 2]:	Antoun,Lina ; et. al.	Prospective cohort study	23	29.3±2.9	8.7±21.4 Third trimester	Caesarean section	7(36.8%) Preterm birth, 2(10.5%) preeclampsia, 1(4.3%) died.
3	Pregnancy outcome among women with or without Severe Acute Respiratory Syndrome Coronavirus 2 infection[study 3]	Emily H. et. al.	Observational Cohort Study	252	27.0 ±26.6	27 (11)	LSCS, sponteneous vaginal delivery	7(3%) abortion, 239(94.84%) delivered, LSCS 65(27%), spontaneous vaginal delivery 174(71%)
4	Maternal, foetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peripartum period [study 4]	Najeh Hcini, et al.	Prospective comparative study	137(27%)	Median(IQR)= 25(21.31)	-	LSCS, sponteneous vaginal delivery	127(92.7%) Alive neonates, 7(5.1%) Foetal death, 3(2.2%) Termination of pregnancy for foetal abnormalities.

Table 3. Clinical signs and symptoms of SARS-COV-2 infected pregnant women:

Sl. No.	Selected study	Asymptomatic	Mild	Moderate	Severe and critical	Death	Mean	Sample SD/population SD	IQR	95% CI
1	**Study 1, n=427**	**0(0%)**	**0(0%)**	0(0%)	342(81%)	5(1.5%)	69.4	152.40 136.31	173-0=173.5	54.95 and 83.85, Z=1.96
2	**Study 2, n=23**	**0(0%)**	13/23 (57 %)	2/23 (8.7 %)	8/23 (21.7 %)	1(4.3%)	4.8	5.54 4.95	10.5-0.5=10	2.54 and 7.06 Z=1.96
3	**Study 3, n=252**	163(65%)	133(53 %)	8(3%)	13(6%)	0(0%)	63.4	78.09 69.84	148-4=144	53.78 and73.02 Z=1.96
4	**Study 4, n=137**	n=87(63.5%)	**0(%)**	45(32.8%)	5(3.6%)	0(0%)	27.4	38.29 34.25	66-0=66	20.98 and 33.81 Z=1.96
Total	**839**	250	**146**	55	368	6	165	274.32	393.5	Z=1.96

Table 4: Meta-analysis of SARS-COV-2/ COV-19 infected mothers and pregnancy outcome.

Sl.No.	Selected Study	Sample size (n)	Developed Severe/critical symptoms	LB (LIVE BIRTH)	PTB (Pre-term)	Odds Ratio	Log Odds Ratio	Std Err	Variance
1	Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-COV-2 infection in UK: national population based cohort study.	**427**	**342**	**259**	**66**	**11.766**	**2.465**	**0.187**	**0.035**
2	Maternal COVID-19infection, clinical characteristics, pregnancy, and neonatal outcome:	**23**	**8**	**20**	7	**0.990**	**-0.010**	**0.641**	**0.411**
3	Pregnancy outcome among women with or without Severe Acute Respiratory Syndrome Coronavirus 2 infection	**252**	**13**	**245**	**52**	**0.202**	**-1.600**	**0.325**	**0.106**
4	Maternal, foetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peri-partum period	**137**	**5**	**127**	**12**	**0.363**	**-1.013**	**0.547**	**0.300**
5	**Total**	**839**	**368**	**651**	**137**				

	Study name	Subgroup within study	Group-A	Group-A	Group-B	Group-B	Odds ratio	Log odds ratio	Std Err	Variance
1	Knight,		342	427	66	259	11.766	2.465	0.187	0.035
2	Antoun,Lina;		8	23	7	20	0.990	-0.010	0.641	0.411
3	Emily H.et.al.		13	252	52	245	0.202	-1.600	0.325	0.106
4	Najeh Hcini,		5	137	12	127	0.363	-1.013	0.547	0.300

Fig: 1. Meta-analysis of SARS-COV-2/ COV-19 infected mothers and pregnancy outcome (in Table 4).

Table 5. Pregnancy outcome, Obstetric outcomes and maternal complication.

Sl. No.	Selected Study	Outcome of pregnancy	Obstetrical outcome	Maternal Complication
1	Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-COV-2 infection in UK: national population based cohort study.	Ongoing pregnancy=161(38%) Pregnancy completed=266(62%) Pregnancy loss=4(1%) Still birth=3(1%) Live birth(including Twin)=259(97%) Neonatal death=2(1%)	LSCS=156 NVD=106	Required respiratory support=41 Death=5
2	Maternal COVID-19infection, clinical characteristics, pregnancy, and neonatal outcome:	Preterm delivery (7), fetal distress (1) missed miscarriage (1)	C-section in 16(84%) patients, normal vaginal delivery in 3 patients	Severe adult respiratory distress syndrome complications requiring ICU support=4(17.4%) Maternal death=1(4.3%)
3	Pregnancy outcome among women with or without Severe Acute Respiratory Syndrome Coronavirus 2 infection	Primary outcome, composite=52(21%) Secondary outcomes: Gestational age <37 wk at delivery =27(11), <34wk=9(4%), >40 wk=62(25%) Preeclampsia with severe features=26(11%)	Caesarean delivery=65(27%) For abnormal fetal heart rate=7(3%) Spontaneous vaginal delivery=174(71%) Excessive blood loss= 17(7%)	Bacterial infections=3(23%) Developed severe COVID-19 pneumonia=6(3%) Hospitalised for COVID-19=14(6%)
4	Maternal, fetal and neonatal outcomes of large series of SARS-CoV-2 positive pregnancies in peripartum period	Alive neonate=127(92.7%) Intrauterine fetal death=7(5.1%) Termination of pregnancy for fetal abnormalities=3(2.2%)	Spontaneous preterm delivery<37+0weeks=11(8.7%) Spontaneous preterm delivery<34+0weeks=1(0.8%) Normal vaginal delivery=101(79.5%) Operative vaginal delivery=7(5.5%) Cesarean delivery before labour=6(4.7%) Cesarean delivery during labour=13(10.2%) Postpartum haemorrhage>500 cc=18(14.2%) Transfusion after haemorrhage=7(5.5%) Readmission=4(3.1%)	Intensive care unit admission=5(3.6%) Intensive care unit admission directly related to COVID-19 =3(2.2%) Oxygen support related to COVID-19=3(2.2) Re hospitalization related to COVID-19 =4(2.9%)

TABLE 6: Analysis of SARS-COV-2 infected mothers and pregnancy outcome, obstetrical outcome and maternal outcome

SL. NO.	SELECTED STUDY SAMPLE SIZE (N)	PREGNANCY OUTCOME				OBSTETRICAL OUTCOME			MATERNAL OUTCOME		
		LB (LIVE BIRTH)	PTB (Pre-term)	IUD/ SB (Still Born)	PT(Pregnancy Termination)	NVD (Normal Vaginal Delivery	LSCS	PPH	ICU	ICU due to Covid-19	Oxygen support
1	423	259(97%)	66	3	4	106	156	0	41	104	41
2	23	20	7	0	1	3	16	0	4(17.4%)	3	4
3	252	245	52(21%)	0	0	174(71%)	72()	17(7%)	0	14(6%)	6(3%)
4	137	127(92.7%)	12	7	3(2.2%)	101(79.5 %)	19	18(14.2%)	5(3.6%)	3(2.2%)	3(2.2)
Total	839	651 (77.6%)	137 (16.3%)	10(1. 2%)	8 (0.95%)	384 (45.8%)	263(31.3 %)	35(4.2%)	50(5.6%)	124(14.8%)	54(6.4%)

TABLE 7: Meta - analysis of SARS-COV-2 infected neonates and neonatal outcome

Sl.No.	Selected Study	Sample size of Live borne neonates (n)	Tested positive SARS-COV-2infection (RT-PCR Testing) (n)	Sample size of Live borne neonates (n)	LSCS	Odds ratio	Log odds ratio	Std Err	Variance
1	Knight, Marian; et, al.	259	12	259	156	0.03	-3.44	0.32	0.10
2	Antoun,Lina; et. al.	20	0	20	16	0.01	-5.01	1.53	2.33
3	Emily H. et. al.	251	6	251	72	0.06	-2.83	0.44	0.19
4	Najeh Hcini, et al.	127	4	127	19	0.18	-1.69	0.57	0.32
Total		658	22(3.3%)	658	263(31.3%)	0.28			

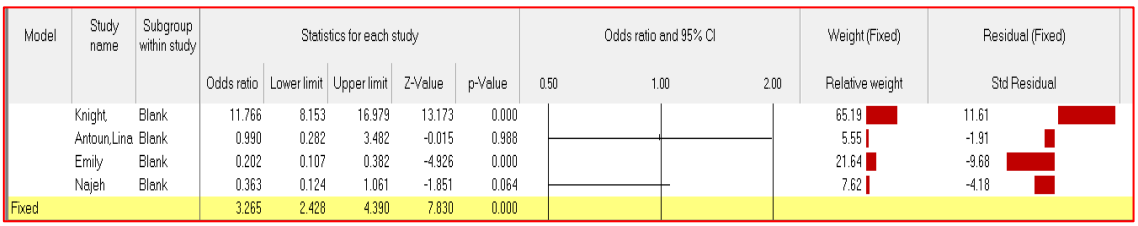

Fig: 2. CMA Computation of Odds ratio and 95%CI at Fixed effect Model.

Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	4	3.265	2.428	4.390	7.830	0.000	139.904	3	0.000	97.856	6.019	6.137	37.661	2.453
Random	4	0.976	0.085	11.257	-0.020	0.984								

Fig: 3. CMA computation of heterogeneity.

Model	Study name	Subgroup within study	Statistics for each study							Risk difference and 95% CI					Weight (Fixed)	Residual (Fixed)
			Risk difference	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	-1.00	-0.50	0.00	0.50	1.00	Relative weight	Std Residual
	Knight,	Blank	-0.56	0.03	0.00	-0.62	-0.49	-16.80	0.00						31.57	-7.96
	Antoun,Lina	Blank	-0.80	0.10	0.01	-0.99	-0.61	-8.38	0.00						3.79	-4.93
	Emily	Blank	-0.27	0.03	0.00	-0.33	-0.21	-8.81	0.00						36.79	2.79
	Najeh Hcini,	Blank	-0.12	0.04	0.00	-0.19	-0.05	-3.35	0.00						27.85	7.35
Fixed			-0.34	0.02	0.00	-0.37	-0.30	-18.18	0.00							

Fig: 4. Fixed model analysis (CMA) of Risk difference for each study.

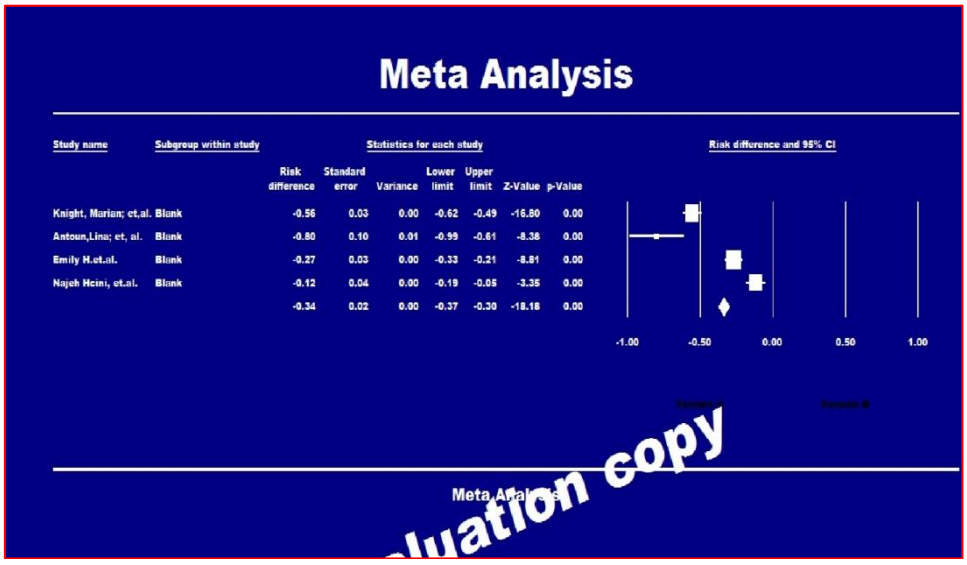

Fig: 5. Evaluation copy of meta-analysis shows the Forest plot of selected study.

Findings and Discussion: Overall total 4 studies were included in systematic review and meta-analysis [Table 1]. The result shows that, total sample subjects were 839 pregnant mothers. Combined result of 4 studies revealed that, 250(29.8%) were Asymptomatic, 146(17.4%) developed mild symptoms, 55(6.6%) developed moderate symptoms, 368(43.9%) and 6(0.72%) were death due to COVID-19 [Table 2]. Combined Maternal Outcome revealed 50 (5.6%) admitted in ICU, 124(14.8%) admitted in ICU due COVID-19, 54(6.4%) required Oxygen support [Table 3]. Regarding pregnancy outcome 651(77.6%) were Low Birth Weight Baby, 137(16.3%) Pre-Term Baby, IUD occur in 10(1.2%) and 8(0.95%) Pregnancy were Terminated. Obstetrical outcome shows 384(45.8%) NVD, 263(31.3%) LSCS and in 35(4.2%) cases developed PPH [Table 4]. Out of total 658 neonates 22(3.3%) developed and Tested SARS-COV-2positive [Table 5]. Meta-analysis of all individual studies shows when run in CMA Software, Odds ratio 0.03, 0.01, 0.06and 0.18 in the individual studies respectively which indicates there is a lower association between SARS-COV-2 infection and neonatal outcome (LSCS Mode) **[Table 5]**. In maternal outcomes Odds Ratio (CMA Software) 11.766 indicates greater odds of association with disease and outcome, i.e. there is an association between the SARS-COV-2/COVID-19

infected mothers and pregnancy outcome in study 1[Table 3]. **Fig: 3.** Shows the odds ratio and 95% CI, Weight (relative weight and residual weight) at fixed effect model. The combined value of each four studies shows the odds ratio=3.265, Lower limit= 2.428, Upper limit= 4.390, Z-Value= 7.830 and p- Value= 0.000 indicates highly significant at 95% CI. Risk difference in the present meta-analysis shows a negative result which indicate that the exposure of interest has a protective effect against the outcome. So, in this meta-analysis COVID-19 Vaccinations can be a protective measure. It determines how much risk can be prevented by an effective measure [Fig. 5]. Because the 95% confidence interval does not contain the null value, this study is likely to have a p value <0.05 and hence the differences observed in the study can be regarded as statistically significant [Fig.5].

The findings are consistent enough with the findings of **John Allotey, lecturer in epidemiology and women's health, Elena Stallings, researcher34, Mercedes Bonet, medical officer5, et.al.** [9]. **Siang Ing Lee, researcher** found that the rate for postpartum haemorrhage and High heterogeneity remains in the estimates for rates of clinical manifestations and outcomes [10]. An Iranian case series reported maternal deaths in seven of nine pregnant women with critical COVID-19[11]. The odds of admission to the neonatal intensive care unit (4.89, 1.87 to 12.81, I^2=96.2%) were higher in babies born to mothers with covid-19 versus those without covid-19[12]. John Allotey, lecturer in epidemiology and women's health, Elena Stallings, researcher34, Mercedes Bonet, medical officer5, **et.al. they found in their meta – analysis** (odds ratio 2.13, 1.53 to 2.95; I^2=71.2%) [13].**Strength and Limitations**: Small sample size may lower the credibility of meta-analysis. Further the study is limited for prospective data.

Conclusions: Pregnant women with covid-19 are more likely to deliver still born, preterm baby and pre pregnancy termination. There is an increased risk of maternal death and of being admitted to the ICU. Risk difference in the present meta-analysis shows a negative result which indicate that the exposure of interest has a protective effect against the outcome. Effective measures during ante-natal period as well as Vaccinations against COVID-19 can be protective measures. It determines prevention of risk by an effective measure.

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