Title

A meta-analysis of global stillbirth rates during the COVID-19 pandemic.

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Running head

Global stillbirths during COVID-19 pandemic.

Tweetable abstract

A meta-analysis of stillbirth changes with the COVID-19 pandemic around the world along with a comparison of the pre-pandemic period.

Abstract

Background

The global effect of the COVID-19 pandemic has had an impact on pregnancy and outcomes. There has been recently some conflicting evidence on the stillbirths during the COVID-19 pandemic. This meta-analysis attempts to resolve this through a systematic approach.

Objectives

To analyse and determine the impact of COVID-19 on the stillbirth rate.

Search strategy

We searched PubMed, Embase, Cochrane library, ClinicalTrials.gov and Web of Science from inception to 05 March 2021 with no language restriction for this meta-analysis.

Selection criteria

Publications (a) with stillbirth data on pregnant women with COVID-19 (b) comparing stillbirth rates in pregnant women with and without COVID-19 and (c), comparing stillbirth rates before and during the pandemic.

Data collection and analysis

The included studies were all observational studies, and we used the Newcastle Ottawa score for risk of bias. We performed the meta-analysis using Comprehensive meta-analysis software, version 3.

Main results

A total of 29 studies were included in the meta-analysis; from 17 of these, the SB rate was 7 per 1000 in pregnant women with COVID-19. This rate was much higher (34/1000) in low- and middle-income countries. The odds ratio of stillbirth in pregnant women with COVID-19 compared to those without was 1.89. However, there was no significant difference in population SB rates before and during the pandemic.

Conclusions

There is some evidence that the stillbirth rate has increased during the COVID-19 pandemic, but this is mainly in low- and middle-income countries. Inadequate access to healthcare during the pandemic could be a contributing factor.

Funding

Non funded study

Keywords

COVID-19, pandemic, population, stillbirth, intra-uterine fetal death, fetal-demise, obstetrics, pregnancy, women, observational studies, meta-analysis, systematic review

Introduction

The global burden of stillbirth(SB) continues[1] with an estimated 2 million every year. COVID-19 has an adverse effect on pregnancies[2,3], but there have been conflicting reports on increasing SB rates during the pandemic.[4–7]

A population study from two Philadelphia Hospitals, USA[8] did not detect any stillbirth changes with COVID-19, but the study from Nepal[9] showed a higher rate of stillbirth during the COVID-19 lockdown and an associated increase in neonatal deaths[10]. Similarly, pregnancy outcomes from St Georges University Hospital, London, UK[6] also showed an increased SB rate, but reports from the Spanish population study[11], Hospital episode statistics in England[12] and a case-control study from Lady Hardinge Medical College, India[7] showed no change. The population study from Nepal[9] suggested that the increase may be due to decreased access to high-quality healthcare rather than a direct effect of the viral illness on pregnant women. While there are currently published protocols about ongoing studies to determine the adverse effects in pregnancy, such as the COVID-19 in

pregnancy in Scotland (COPS) study[13]; published studies, however, do not provide a clear overview of the impact on stillbirths during the pandemic.

We, therefore, undertook a meta-analysis of published studies on the impact of COVID-19 on Stillbirths with the hope of providing more robust data on overall population rates and comparison between pregnant women with and without COVID-19 as well as before and during the pandemic. Furthermore, we also examined the contribution of the income status[14] of countries on SB rates.

Method

Sources and searches

A systematic search and screening were conducted by two independent reviewers (MM&KA) with the support of AP on the databases - Embase, PubMed, Cochrane library, including clinicaltrials.gov and Web of Science. The search terms used were " COVID-19 Pregnancy, Stillbirth, Intrauterine fetal death/demise" (Appendix 1 Search Strategy). The initial screen was done using titles and abstracts (MM&KA) and then further screening using pre-agreed eligibility criteria. All studies from similar countries of origin were checked to avoid data duplication, and five studies were excluded[6,15–18], as shown in Figure 1.

Selection criteria

We included studies that published data on stillbirths in pregnant women with COVID-19 and studies that compared population (women with and without COVID-19) SB rates before and during the COVID-19 pandemic with no language restrictions. The included studies did not specifically define stillbirths, hence we assumed there would be variations on the gestational ages of stillbirths as represented from different countries. We included observational prospective and retrospective studies, case series and letters with observational data. We excluded case reports and studies on multinational registries that overlapped across countries to avoid duplication.

Data extraction

All articles obtained were in English, or those in other languages had published English versions. Two independent reviewers (MM&AO) extracted the data onto a pre-defined Microsoft Excel spreadsheet. This was done after the exclusion of possible duplicated data. We cross-checked that studies from the same counties were from different hospitals and population groups. As shown in the PRISMA flow chart, we removed studies with suspicion of duplication (Figure 1). Two of the included studies had data queries. Therefore, we contacted the authors for details of the information and received clarification and thus had that data in this analysis.[19,20]

Outcome measures

Three separate outcomes related to SB were assessed.

1. SB rate in pregnant women with COVID-19
2. SB rates in pregnant women with and without COVID-19 at the same time period
3. Population SB rates in pre-pandemic and pandemic periods.

Risk of Bias

Two independent reviewers (MM&AO) completed the quality assessment of each identified publication separately, and uncertainty or disagreements were resolved by consensus with further review by SWL & JCK. Studies were deemed appropriate by all authors for inclusion after the qualitative assessment.

We used the Newcastle - Ottawa quality assessment scale (NOS)[21] to define the eligibility of the observational epidemiology studies. This tool based on 8 items has 3 categories - the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies. As per the tool, a study could be given a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars within the comparability category. Studies with total scores of 0-3 stars (red

color), 4-6 stars (yellow color) and 7-9 stars (green color) are classified as studies with high, moderate or low risk of bias, respectively.

Meta-analysis

The Comprehensive Meta-Analysis version 3 (CMA version 3)[22] was used for analysis. We estimated the SB rate based on the number of stillbirths and deliveries from each included study. The studies were pooled using mixed-effect meta-analysis with a 95% confidence interval. In the mixed effect analysis, a random effects model is used to combine studies within each subgroup. A fixed effect model was used to combine subgroups to generate an overall effect. The study-to-study variance (Tau-squared) as expected was not assumed to be the same for all subgroups; this value was computed within subgroups and not pooled across subgroups. We present the pooled overall event rate along with subgroup event rates. When two groups were compared, we used the SB and total pregnancies from each study, both in the SB and comparison groups, and a pooled estimate (odds ratio) with a 95% confidence interval is provided.

Heterogeneity

We took into consideration the weighted pooled effect size and considered how much the effects varied from study to study. The relevant statistics are given with Q-value with the degrees of freedom and a P-value. For statistical heterogeneity and variance interpretation[22], we have also provided the I-squared and Tau-squared.

Sensitivity analysis

We did a sensitivity analysis as pre-planned from our protocol to determine the robustness of the first outcome by arbitrarily changing the commonalities and or by removing studies with a high risk of bias to ensure that changes are not significant with our obtained results.

Results

The 29 studies included in this meta-analysis were both from high-income(HIC) [United States of America, United Kingdom, Ireland, Sweden, Spain, Italy, Israel, Kuwait, French Guiana] and low- and-middle-income countries[14](LMIC) [Oman, Botswana, Peru, India, and Nepal]. Seventeen studies were of low risk of bias, and twelve were of moderate risk of bias. A funnel plot of the precision by rate was used to depict the publication bias in the included observation studies (Appendix 2).

For the first outcome, we included 17 studies[23,24,33–39,25–32] with 9476 pregnancies and 95 stillbirths in women with COVID-19 (Figure 2). The overall pooled SB rate was 0.7% (95% CI 0.4% – 0.9%).

A subgroup analysis showed the SB rate in the HIC group to be 0.6% (95% CI 0.4% – 0.8%), compared to that of 3.4% (95% CI 2% – 4.4%) in the LMIC group. (Figure 2)

We did a sensitivity analysis to explore the robustness of our results from the 17 included studies. We did this firstly by removing 5 of the included studies from USA[23,27,29,31,34], as the USA was the largest representing country, and this showed a similar pooled SB rate of 0.8% (95%CI 0.5% – 1.2%). A further sensitivity analysis was done by including only studies with a low-risk of bias[23,24,26–28,30], and the pooled rate was 0.6% (95%CI 0.2% – 1.1%). This sensitivity analysis confirmed the robustness of the results from the 17 studies.

For the second outcome of SB rates in concurrent pregnancies in those with and without COVID-19, we included 7 studies.[23,24,26–28,33,40] All were from HIC, and therefore we used a random effect model for comparison. There were 7587 pregnancies with 49 stillbirths and 407139 pregnancies with 1330 stillbirths in women with and without COVID-19, respectively (Figure 3). The odds ratio of SB in pregnant women with COVID-19 was 1.897 (95% CI 1.262 – 2.851) compared to those without.

For our third outcome, SB rates in pre-pandemic and pandemic periods, we included 12 studies[7,8,45,46,9,12,19,20,41–44] - 184288 pregnancies and 1038 stillbirths and 292159 pregnancies and 1517 stillbirths in the pre-pandemic and pandemic periods, respectively. We used a mixed-effect

model similar to outcome one for this analysis, and the results are shown in Figure 4. The odds ratio of SB during the pandemic period was 1.184 (95%CI 0.970 – 1.445) compared to the non-pandemic period.

The subgroup analysis showed that HIC had an OR of 1.113 (95% CI 0.834 – 1.485) versus 1.252 (95% CI 0.951 – 1.648) for LMIC (Figure 4).

Discussions

Pregnant patients with COVID-19 had increased stillbirth rates but this was mainly in the LMIC group. The risk of SB was much higher in pregnant women with COVID-19 compared to those without, but the overall population SB rate was not different between the period before (pre-pandemic) and during the pandemic.

There are significant variations in SB rates (1.4 – 32.2 per 1000 total births) across the world[47], with a much lower rate in HIC.[48] In LMIC countries, the overall stillbirth rate was high at 28.9/1000 (range 13.9 to 56.5/1000) in 2010 and 2013[49] . Since then, there has been a reduction to 2.4 – 5.8/1000 in HIC and 5.6 – 17.9/1000 in LMIC respectively from the countries included in this study during 2019.[47] This may partly be because of global initiatives such as Every Newborn Action Plan and Millennium Developmental Goals (United Nations).[50]

Our meta-analysis showed higher stillbirth rates but mostly in LMIC, which are above the Every Newborn Action Plan (ENAP)[51,52] target of 12/1000 or fewer by 2030. However, the contribution from LMIC regions such as Nepal[9] with increased SB rates suggests that regional variations are a result of access to high-quality care. This could be a feature in poor resource areas where the pandemic has affected or disrupted pregnant women's care.

The PAN COVID study[53], suggested no difference in SB rates in COVID-19 affected pregnancies. Similarly, an analysis from Spain showed no difference in stillbirths during and before the pandemic period.[11] However, the SB rate from other HIC groups such as the UK[6] showed an increase in

stillbirths during the pandemic compared to the 2019 stillbirth data from the Global Health Observatory data repository.[47] This finding is similar to Hospital Episode Statistics (HES) data and the Office for National Statistics (ONS) data from England.[54] Reported SB rates from LMIC[3] in 2019 was 13.9/1000 (India) [5–37] & 7.1/1000 (Peru). [47] Our meta-analysis shows that these rates have increased considerably to 58 and 32-40/1000 in both India and Peru, respectively, which is represented in our subgroup analysis.

Comparing the SB in concurrent pregnant women with and without COVID-19 showed an increased SB rate. However, these studies did not provide an accurate representation of the non-COVID-19 group as only the women with COVID-19 had been tested positive for severe acute respiratory corona virus -2 (SARS-CoV-2) infection (COVID-19), and therefore the non-COVID-19 category may have included non-tested, asymptomatic, or mild COVID-19 pregnancies that may have fetal implication. We, therefore, explored the subsequent outcome below to understand the stillbirth difference in a completely different dimension with a population study comparing the pandemic with the pre-pandemic group.

In our pre and post-pandemic period comparative meta-analysis, there was no statistically significant increase in the SB rate during the pandemic period compared to the non-pandemic period. When we looked at the economic income subgroups, there was no statistically significant difference in SB in either the HIC or the LMIC groups.

It is possible that during the COVID-19 pandemic, the diversion of resources (doctors and premises) towards the prevention and treatment of COVID resulted in the neglect of maternity services. This neglect might have produced a deficiency in care in both HIC and LMIC that has resulted in an increase in SB in some of the reported individual studies. Furthermore, pregnant women might be reluctant to access hospitals for fear of becoming infected and ignoring or forgetting to report adverse pregnancy symptoms such as a small antepartum hemorrhage or reduced fetal movements.

In the individual studies[27,31,40,55,56] that presented data on the causes of stillbirths, there was no clear evidence to suggest that COVID-19 increased the risk of SB unless there was significant maternal hypoxic or a terminal event that might lead to fetal compromise and intra-uterine fetal demise[29] a fact supported by the findings in the UKOSS data[40] highlighting the need for further information to evaluate the likely impact of significant hypoxia on possible SB rates.[40]

Global health focus on stillbirth is ongoing, and there is a need to continue to investigate and identify the causes,[57], especially in LMIC.[58] The causes in countries where SB rates continue to be high could be multifactorial with varied factors such as cut off points for reporting stillbirths, poverty, education and maternal diseases such as syphilis, HIV etc.[58]

Our meta-analysis was not able to identify possible factors accounting for the increase in stillbirths; however, there are ongoing studies that may provide further information on the relationship between COVID-19 and stillbirths.[59–62]

Strengths and limitations

This meta-analysis included 29 studies making it the largest on this topic. We included not only the SB rates in those with COVID-19 but also a comparison between those with and without COVID-19 as well as comparisons in SB rates before and during the pandemic. The main limitations were that only observational data were analysed and furthermore in some of the comparison groups, the number of studies was small.

Conclusion

This meta-analysis shows an overall increase in stillbirths in pregnant women with COVID-19 and predominantly in LMIC. However, when population SB rates were compared between the pre-pandemic and pandemic periods, there was no increase. These findings suggest that while current attention to ensuring that SB rates are unaffected by the pandemic worldwide continues, greater focus must remain on LMIC (bearing in mind that SB rates are in general higher in these countries

compared to that in HIC) to ensure the provision of adequate healthcare access during the pandemic while at the same time continuing to investigate all causes of stillbirth and understanding the contribution of the pandemic to regional variations in stillbirths.

Disclosure of interest

All authors have no conflicts of interest to disclose.

Contribution to authorship

JCK conceived the idea, MM&KA completed the initial search and repeated search with the support of AP. All three reviewers (MM, KA and AP) worked for the study selection process. MM& AO completed data collection and quality assessment for the included studies. Conflicts resolved with SWL and JCK involvement. MM conducted the meta-analysis, and all authors contributed equally to the manuscript preparation.

Ethics approval

Not applicable

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Table 1

Characteristics of included studies

Sl No	Study (First Author)	Place of Study	Type of Study	Characteristic of pregnancy studied
1	Adhikari EH	USA	Observational Cohort	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison
2	Ahlberg M	Sweden	Retrospective Cohort	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison
3	Anand P	India	Observational Cohort	Stillbirth rates among confirmed Covid19
4	Ayed A	Kuwait	Retrospective Cohort	Stillbirth rates among confirmed Covid19
5	Hcini N	French Guina	Prospective Cohort	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison
6	Janssen O	USA	Retrospective Cohort	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison

7	Jering KS	USA	Research Letter	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison
8	Khoury R	USA	Prospective Cohort	Stillbirth rates among confirmed Covid19
9	Lokken EM	USA	Retrospective Cohort	Stillbirth rates among confirmed Covid19
10	Remaeus K	Sweden	Retrospective case-series	Stillbirth rates among confirmed Covid19
11	Martinez-Perez O	Spain	Research Letter	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison
12	Panagiotakopoulos L	USA	Observational Cohort	Stillbirth rates among confirmed Covid19
13	Knight M	UK	Observational Cohort	Stillbirth rates among confirmed Covid19 and real-time non-covid19 comparison
14	Maraschini A	Italy	Observational Cohort	Stillbirth rates among confirmed Covid19
15	Loyola E	Peru	Cross-sectional	Stillbirth rates among confirmed Covid19
16	Taya RM	Peru	Retrospective Cohort	Stillbirth rates among confirmed Covid19
17	Santhosh J	Oman	Retrospective Cohort	Stillbirth rates among confirmed Covid19
18	Handley SC	USA	Observational Cohort	Pandemic and Control group stillbirths
19	Stowe J	UK	Letter	Pandemic and Control group stillbirth
20	Mor M	Israel	Observational Cohort	Pandemic and Control group stillbirth
21	Ashish KC	Nepal	Prospective Observational	Pandemic and Control group stillbirth
22	Caniglia EC	Botswana	Retrospective Observational	Pandemic and Control group stillbirth
23	De Curtis M	Italy	Letter	Pandemic and Control group stillbirth
24	Kumar M	India	Case-Control	Pandemic and Control group stillbirth
25	Pasternak B	Sweden	Observational Cohort	Pandemic and Control group stillbirth
26	Meyer R	Israel	Observational Cohort	Pandemic and Control group stillbirth
27	McDonnell S	Ireland	Retrospective Cohort	Pandemic and Control group stillbirth
28	Justman N	Israel	Cross-sectional	Pandemic and Control group stillbirth
29	Stowe J	UK	Letter	Pandemic and Control group stillbirth

Table 2

Risk of bias using Newcastle – Ottawa score (NOS)

Studies with total scores of 0-3 stars (red color), 4-6 stars (yellow color) and 7-9 stars (green color) are classified as studies with high, moderate or low risk of bias, respectively.

Sl No	Study	NOS Selection	NOS Comparability	NOS Outcome	NOS Total Score
1	Adhikari EH	***	**	**	7
2	Ahlberg M	***	**	**	7
3	Anand P	***		***	6
4	Ayed A	***		***	6
5	Hcini N	***	**	***	8
6	Janssen O	**	**	***	7
7	Jering KS	***	**	**	7
8	Khoury R	***		**	5
9	Lokken EM	***		***	6
10	Remaeus K	***		**	5
11	Martinez-Perez O	**	**	**	6
12	Panagiotakopoulos L	***		*	4
13	Knight M	***	**	***	8
14	Maraschini A	***		**	5
15	Loyola E	**		**	4
16	Taya RM	**		**	4
17	Santhosh J	***		**	5
18	Handley SC	****	**	***	9
19	Stowe J	***	**	**	7
20	Mor M	***	**	**	7
21	Ashish KC	****	**	***	9
22	Caniglia EC	****	**	***	9
23	De Curtis M	**	**	**	6
24	Kumar M	****	**	***	9
25	Pasternak B	***	**	**	7
26	Meyer R	***	**	**	7
27	McDonnell S	***	**	***	8
28	Justman N	****	**	***	9
29	Stowe J	***	**	**	7