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European Journal of Obstetrics and Gynecology 275 (2022) 12–16

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Recruitment of pregnant women to randomised trials of COVID 19 treatments, and pharmaceutical treatments received outside such trials: A research article

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ARTICLE INFO

Keywords:
COVID-19
Pregnancy
Randomized controlled trials
Case reports
Case series

ABSTRACT

Objectives: To document how many pregnant women with COVID-19 reported in the literature had participated in randomised trials, what treatments they received outside such trials and compare the latter with evidence-based treatment recommendations.
Study design: A systematic review of observational studies.
Methods: Two clinical trial registries were searched to identify COVID-19 trials open to pregnant women. Studies were then extracted from a regularly updated list of scientific case reports and case series of confirmed or suspected maternal COVID-19 in pregnancy to identify the number of women enrolled into a trial and the pharmaceutical treatments they received outside such trials.
Results: 156 studies (case reports, case series and registries) reporting 43,185 pregnant women with COVID-19, after de-duplication. Of these 2,671 (6.2%) were potentially eligible for a randomised trial but only seven women (0.26%) were reported to have enrolled.
For 2,839 women the papers included information on treatment received, 1515/2829 (54%) women had received $\geq$ 1 treatment and in total a COVID-19 pharmaceutical treatment was administered 1,296 times outside of a trial. In 566 (44%) cases the treatments administered to the pregnant women were not recommended by the National Institutes of Health (NIH) at the time of administration.
Of 179 case reports of women with COVID 19 in pregnancy, 109/179 women received $\geq$ 1 COVID-19 pharmaceutical treatment and in total COVID-19 experimental pharmaceutical treatments were administered 274 times.
Conclusion: During the early phase of the COVID-19 pandemic, pregnant women excluded from randomised trials did not avoid unproven or ineffective treatments.

Introduction

The historical exclusion of pregnant populations from clinical trials is not unwarranted. Legitimate ethical concerns surrounding harm to the developing fetus, the complex everchanging physiology of pregnant women, their willingness to participate and special protection bestowed upon them by the rest of society all complicate their recruitment. There may also be concerns surrounding budgeting for unexpected costs of complications and liability in the case of an unwanted outcome [1].

However, the result of not testing in pregnant populations is gradually gaining recognition amongst scientific communities as an equally legitimate ethical concern [2–3]. There has been a shift towards respecting autonomous decision making, encouraging pregnant women to make their own informed decisions about the potential risk of participating in a trial. The absolute number of pharmacokinetic studies has steadily increased over the past 40 years, however the proportion of studies involving pregnant women has been relatively constant since around 1990. This is despite the Institute of Medicine advising that pregnant women should be 'presumed eligible' for research participation since 2001. There are exceptions, for example antiretroviral drugs

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https://doi.org/10.1016/j.ejogrb.2022.05.009
Received 31 January 2022; Received in revised form 5 May 2022; Accepted 11 May 2022
Available online 14 May 2022

are tested in a larger proportion of pharmacokinetic trials including pregnant women [4].

Participation of pregnant women in randomised trials is associated with better health outcomes than for non-participants [5].

The well-documented exclusion of pregnant women from post-marketing evaluations of licensed drugs, and trials of "off-label" use is difficult to justify, if pregnant women are treated outside such trials. We measured the off-label use of experimental treatments for COVID-19 in pregnant woman as recorded in published case reports.

Methods

The aim of this study was to document the exposure of pregnant women with COVID-19 to treatments. Firstly, we aimed to identify how many pregnant women with COVID-19 participated in randomised trials. Then we aimed to determine what treatments pregnant women received outside such trials and compare this with treatment recommendations.

RCTs open to pregnant women and the eligibility of pregnant women from case reports, case series and registries.

ClinicalTrials.gov and the ISRCTN trial registry were searched to identify COVID-19 RCTs that were open to pregnant women in October 2020.

Using previously reported search and disambiguation methods [6] from 8 April to 8 November 2020, we identified non-duplicated case reports, case series and registries reporting pregnant or postnatal women with COVID-19. For the seven countries (Nigeria, Republic of Ireland, Denmark, Spain, United Kingdom, United States of America and Canada) where a randomised trial for which pregnant women were eligible to be included was open, we recorded how many women had been reported to have participated in those trials. For each individual study, we checked that there was a randomised controlled trial open to recruitment at the time that the woman received hospital care for COVID-19, in the country where the woman received hospital care. We did not check whether the individual hospital where the woman was receiving care was participating in the randomised controlled trial. For all countries we recorded any reported treatments received outside of any trials. We report totals and results by country.

The first data abstraction from both cases series and case reports was done by OG, assisted by EY JO, JS, and YK. No formal double data extraction was done but ambiguous papers were reviewed by KW and JT.

Case reports of COVID-19 in pregnancy

Using previously reported search and disambiguation methods [6] from 31 January 2020 to 31 January 2021, we identified non-duplicated case reports of pregnant women with COVID-19, and extracted demographic details, disease severity and what pharmacological treatment (s) was reportedly given.

We identified only case reports to extract more detailed information on pharmaceutical treatments administered to pregnant women as treatments were largely unreported in case series and registries.

This curated list of case reports, case series and registries is listed in Appendix A, and the list of all case reports with duplicates removed in Appendix B.

RCTs open to pregnant women and the eligibility of pregnant women from case reports, case series and registries.

We found ten completed or actively recruiting randomised controlled trials for participants with COVID-19 for which pregnant women were eligible (Appendix C). Five tested pharmacological treatments, and five non-pharmacological treatments.

It was difficult to be sure whether a significant number of cases were duplicated in case series and case reports. We therefore restricted our detailed analysis to case reports (Appendix B).

After removing duplicates, we found 43,185 pregnant women with COVID-19 reported in peer reviewed publications. For 2,241 women sufficient information was given to be clear that they were not eligible to participate in one of the ten trials. In 38,273 cases insufficient details were given to judge eligibility. This left 2,671 pregnant women with COVID where the timing and location suggested that they were potentially eligible due to country of residence and timing to participate in a randomised trial. Of these, seven women were reported to have participated in a randomised trial (Appendix D). No women were reported to have been offered and declined randomisation, or to have participated in any clinical trial outside the ten we identified from the registries. The seven women who participated in a randomised trial participated in two different unnamed trials, one involving remdesevir [7] and one trial of remdesevir versus hydroxychloroquine [8].

The treatments received by women in case series outside of clinical trials

These are detailed in Appendix E. Of 43,185 women COVID-19 pharmaceutical treatments were largely unreported. For 2,839 women in these papers there was information about treatment or not. Among these women, COVID-19 treatments were reported on 1,296 occasions. Of the 1,296/2839 instances reported in the literature, in which pharmaceutical treatments were administered to women outside of a trial, 444 (34%) were hydroxychloroquine, 108 (8.3%) were remdesivir, 76 (5.9%) were lopinavir-ritonavir and 75 (5.9%) were steroids. In 566 (44%) of all cases hydroxychloroquine, lopinavir-ritonavir, darunavir, ritonavir, zinc and tocilizumab were administered. These treatments are not recommended by the National Institutes of Health (NIH) so 44% of pharmaceutical treatments administered were not recommended for COVID-19 at the time of administration [9].

It proved impossible, to extract a clear list of treatments given to individual women from the various case series. We therefore focused on individual case reports. We were able to study these over studies over a longer time period.

Case reports of COVID-19 in pregnancy

We found 179 case reports of pregnant women with COVID-19.

Table 1 shows the clinical characteristics of these women.

Table 2 lists the pharmaceutical treatments received by more than five women. Treatments received by fewer than five women are shown in Appendix F.

Table 3 shows the number of women who received the four most popular treatments, chloroquine, remdesivir, corticosteroids and tocilizumab, by country. Since the evidence supports steroid treatment for

Table 1
. The clinical characteristics of pregnant women with COVID-19 reported in published case reports.

	Number (%) with data item reported Total = 179	Mean (sd) or number (%)
Age	166 (93)	31 (5.6) years
First pregnancy	114 (64)	30 (26%)
BMI	38 (21)	33 (9.1) Kg/M^2
Severity	72	Asymptomatic 8 (11%) Mild 23 (32%) Moderate 1 (1.4%) Severe 29 (40%) Critical 11 (15%)
Disease onset	183	1st trimester 10 (15%) 2nd 30 (16%) 3rd 127 (69%) Post-partum 16 (8.7%)

Table 2
All COVID-19 pharmacological treatments received from case reports of pregnant women with COVID-19.

Drug	Women who received treatment* n, (%) Total women = 179
hydroxychloroquine	39 (22)
Antivirals	62 (35)
Corticosteroids	52(29)
tocilizumab	8 (4.5)
convalescent plasma therapy	10 (5.6)
Antibiotics	71 (40)
Immunoglobulin	8 (4.5)
Interferon	8 (4.5)
other	16 (8.9)

*treatments were not mutually exclusive. All treatments that were given to less than 5 women are documented in a supplementary table, Appendix 6. The breakdown of the type of antibiotics, corticosteroids and antivirals used is in supplementary table, see Appendix 7.

severe disease but not for mild we show the number of women given this drug by disease severity in Table 4.

Discussion

Main findings

Of the 2,671 pregnant women with COVID-19 with sufficient details to judge that they were potentially eligible to join an RCT, only seven (0.26%) women were reportedly randomised into a trial.

For 2,839 women the papers included information on treatment received, 1515/2829 women had received ≥ 1 treatment and some sort of COVID-19 pharmaceutical treatment had been administered 1,296 times outside of a trial. In 566 (44%) cases the drugs administered to the pregnant women were not recommended by the national COVID-19 treatment guidelines.

Of 179 case reports of women with COVID 19 in pregnancy, 109/179 women received ≥ 1 COVID-19 pharmaceutical treatment and in total COVID-19 experimental pharmaceutical treatments were administered 274 times.

Table 4
The severity of COVID-19 disease with the administration of steroids in case reports of pregnant women with COVID-19.

		Number of COVID-19 patients administered steroids N (%)			
		Yes	No	Not reported	Total
Severity of COVID-19 disease	Severe	17 (45%)	15 (38%)	6 (16%)	38
	Not severe	6 (18%)	20 (61%)	7 (21%)	33
	Severity not reported	29 (27%)	58 (54%)	21 (19%)	108

Table 3
. The pharmacological treatments received by pregnant women with COVID-19, by country.

Country	Total mothers N	COVID-19 pharmacological treatment			
		Hydroxychloroquine	remdesivir	corticosteroids	tocilizumab
China	**23**	0	0	11	0
USA	**47**	14	10	14	4
Honduras	**1**	0	0	0	0
Sweden	**3**	0	0	1	0
Korea	**3**	0	0	0	0
Turkey	**7**	5	0	1	1
Italy	**15**	1	0	4	0
Portugal	**3**	0	0	0	0
Australia	**2**	0	0	0	0
Canada	**2**	0	0	0	0
France	**6**	2	0	2	0
Peru	**2**	1	0	0	0
Spain	**3**	2	0	2	1
India	**9**	0	0	0	0
Iran	**13**	7	0	4	0
Jordan	**2**	1	0	0	0
UK	**7**	0	0	2	0
Ireland	**1**	0	0	0	0
Belgium	**1**	0	0	0	0
Netherlands	**4**	0	1	2	0
Japan	**3**	0	0	1	1
Brazil	**5**	2	0	2	0
Morocco	**1**	1	0	1	0
Norway	**1**	0	0	0	0
Saudi Arabia	**1**	0	0	0	0
Mexico	**2**	0	0	1	0
Oman	**1**	0	0	1	0
Granada	**1**	0	0	0	0
Switzerland	**1**	0	0	0	0
Thailand	**1**	0	0	0	0
Greece	**1**	0	0	0	0
Pakistan	**2**	0	0	0	0
Venezuela	**1**	0	0	0	0
Iraq	**1**	1	0	0	0
Kyrgyzstan	**1**	0	0	0	0
Romania	**1**	1	0	1	0
Qatar	**1**	1	0	1	1
Total	**179**	**39**	**11**	**51**	**8**

Strengths and comparison with previous studies.

Our findings support previous reports of gross underrepresentation of pregnant women in clinical trials, including COVID-19 trials [10–12]. For example, Taylor *et al.* identified 124 (80%) trials specifically excluding pregnant women, out of all COVID-19 treatment studies of non-biological drugs [13]. Their study reviewed 10 registries, including the ISRCTN and ClinicalTrials.gov registries assessed in this study. Our findings confirm these reports and extend the findings by determining if pregnant women were eligible to COVID-19 trials and identifying cases where pregnant women were not randomised despite being eligible.

However, we have gone further and shown both that exclusion from trials did not protect women from harmful treatments nor ensure that they got effective ones. For example, chloroquine is now known to be 'associated with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death' [14], but was the drug treatment most often given. No fewer than 444 women out of 2,839 (16%) received it in our larger series. This is likely an underestimate since details of drug treatments were scanty in the larger case series. Among case reports, chloroquine was given to 39/197 (22%) of women. Even this figure is likely to be underestimate.

On the other hand we have also shown that trial exclusion did not mean that pregnant women always got effective treatment. For example more than half of women with severe disease were not documented to have been given corticosteroids. Although this might again be an overestimate due to poor reporting.

Limitations

Much of the primary data for this project consisted of case series and reports to extract more detailed information such as the treatments received. However, case series and reports are subject to bias. There is a lack of uniform reporting as many studies did not report all the variables collected in this study and the reporting was inherently biased by reporting and publication bias. Asymptomatic and mild cases may have been underreported. On top of this, there is the potential for major duplication between registries and case reports and series, for instance the UKOSS reported 100% return from UK obstetric units. It was difficult to be sure whether a significant number of cases were duplicated in case series and case reports. We therefore restricted our detailed analysis to case reports (appendix B).

Implications.

The vast majority of COVID-19 trials identified in this study specifically excluded pregnant women. This exclusion stops the provision of evidence-based care that is representative of all groups of the population. Even trials testing medications endorsed for use in pregnancy exclude pregnant women. A recent search of the 21 online International Committee of Medical Journal Editors (ICMJE) registries and WHO-approved clinical trial registries showed that trials including medications with known safety in pregnancy still routinely excluded pregnant women [13].

Crucially, this study identified the administration of investigational drugs to pregnant women outside the context of a clinical trial. This included ineffective and potentially harmful drugs. When choosing to exclude pregnant women from clinical trials, it should be considered that they may receive the same treatment outside an RCT. They may also receive medications with less evidence to support them, or even evidence against their use. This was demonstrated by the 566 cases of pregnant women who received medications, outside of a trial, that are not recommended by the NIH COVID-19 Treatment Guidelines [9]. So, whilst in many cases the reasons behind their exclusion include potential harm to the fetus or neonate and risk to the mother, counterintuitively, the exclusion of pregnant women does not protect them from harm. The Council for International Organizations of Medical Sciences (CIOMS) published international ethical guidelines in 2016 that specified how to include pregnant women in trials safely and ethically [15]. Trials should aim to follow these principles and justify the exclusion of pregnant women, where applicable.

The Institute of Medicine recommended that pregnant women are 'presumed eligible' for participation in research unless evidence proves otherwise, justifications for non-enrolment should be published [16].

Conclusions

The outcomes of this study have highlighted the systematic exclusion of pregnant women from randomised clinical trials, despite large numbers being eligible. Whilst we recognise legitimate concerns regarding potential harm to the fetus, consideration must also be given to the inevitable damage caused by excluding a population from research. Not only does it limit the evidence-base for the safe use of medicines in pregnant women, but it may also lead to the use of ineffective or harmful medications. This study has highlighted the use of COVID-19 pharmacological treatments, administered to pregnant women that are not recommended. We urge those conducting clinical trials to follow the Institute of Medicine recommendations. This will ensure the results can be applied to a larger proportion of the population and inform the safe and effective treatment that pregnant women deserve.

Ethics Approval.

Ethical approval was not required.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Thank you to Dr Kate Walker and Dr Keelin O'Donoghue for their work on the systematic review that preceded this study and their contributions to the manuscript. Thank you also to Professor Jim Thornton for his work in curating the list of scientific reports of COVID-19 in pregnancy and his contributions to the manuscript. Thank you to Eloise Young, Jemma Oberman, Joel Stewart and Yasmin King for their contribution to data collection.

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