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Letter

Use of Metformin for COVID-19 Treatment in Pregnant Individuals

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ABSTRACT

Pregnant individuals have been excluded from participation in the randomized trials currently in the guidelines for outpatient COVID-19 treatment during pregnancy. However, there has been a randomized trial of outpatient COVID-19 treatment that found metformin to be effective in preventing hospitalizations and death in pregnant individuals. COVID-OUT was a phase 3, quadruple-blinded, placebo-controlled randomized clinical trial assessing the outpatient treatment of COVID-19 with three medications. Because the trial published the results of all three medications in the same paper, this striking result in pregnant individuals was only visible in the supplementary appendix and has therefore understandably been missed by committees writing guidelines for outpatient COVID-19 treatment. According to guideline recommendation rating schemes, metformin meets AI criteria for being added to outpatient treatment guidelines for COVID-19. Metformin is safe for use during pregnancy and lactation, inexpensive, widely available, and should be added to outpatient COVID-19 treatment guidelines during pregnancy.

Keywords: Metformin; COVID-19; COVID-19 treatment; Pregnant individuals; Pregnancy

LETTER

Pregnancy is a risk factor for severe COVID-19 and yet most randomized trials of outpatient treatment for COVID-19 have excluded pregnant individuals [1]. This is of critical importance because maternal mortality rates increased by 40% from 2020 to 2021, compared to a 15% increase from 2018 to 2019 before the COVID-19 pandemic [2]. Maternal mortality rates increased for all racial and ethnic groups and remain highest for Hispanic and Black individuals, perpetuating health disparities across generations [2,3].

Pregnant individuals have been excluded from participation in the randomized trials of the therapies currently in the guidelines for outpatient COVID-19 treatment during pregnancy. Nirmatrelvir-ritonavir has been studied in two case series of pregnant individuals with mild to moderate COVID-19 and short follow-up. In Garneau et al., after receiving nirmatrelvir-ritonavir, 3/47 (6.4%) developed gestational hypertension; 2/47 (4.3%) were hospitalized; 2/47(4.3%) discontinued due to side effects; 2/47(4.3%) developed fetal growth issues; 2/47 (4.3%) had fetal anomalies; and 1/47 (2.1%) had fetal loss at 12 weeks. Of the 25/47 (53.2%) who delivered after nirmatrelvir-ritonavir, 12/25 (48%) underwent cesarean delivery [4].

In the case series by Loza et al., seven participants had six days of follow-up: 1/7 (14.3%) developed dysgeusia and stopped treatment after two days [5]. The remaining participants completed treatment with symptom resolution and no adverse effects during the six days of follow-up [5]. In addition to these case series being very short and small and with a relatively high degree of adverse outcomes, data from case series is of lower quality evidence than data from subgroups of randomized trials [6].

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There has been a randomized trial of outpatient COVID-19 treatment with metformin that did include pregnant individuals, and all three outcomes for severe COVID-19 were in the placebo group, with none in the metformin group [7]. COVID-OUT was a phase 3, quadruple-blinded, placebo-controlled randomized clinical trial assessing the outpatient treatment of SARS-CoV-2 infection with three generic medications: Metformin, Ivermectin, and Fluvoxamine. The trial used a 2 × 3 factorial design which allowed for the efficient, simultaneous comparison of three distinct treatments by sharing controls. The COVID-OUT trial enrolled adults aged (30-85+) within three days of a documented positive SARS-CoV-2 test and pregnant individuals down to age 18 years. Individuals who were pregnant or lactating were randomized to metformin or placebo and were not randomized to the fluvoxamine or ivermectin groups because those medications have less safety data during pregnancy [7,8].

In the COVID-OUT trial, 47 participants (7%) were pregnant at the time of enrollment: 23 were randomized to the metformin group and 24 to the placebo group. One participant in each group (4%) was lost to follow-up for the primary outcome, which was severe COVID-19 by day 14. Of those randomized to the placebo group, 3/23 (13%) went to the ER or were hospitalized compared to 0/22 (0%) of those randomized to the metformin group [7]. Because the primary outcome paper for the COVID-OUT trial published all three medications in the same paper, this striking result in pregnant individuals was only visible in the supplementary appendix and has therefore understandably been missed by committees writing guidelines for outpatient COVID-19 treatment.

There is a large body of literature to support the safety of metformin use during pregnancy and lactation [9-12]. Ongoing surveillance studies and meta-analyses have found metformin use during pregnancy is not associated with increased risk of birth defects or adverse maternal outcomes. Metformin has been studied during pregnancy for decades, including in randomized trials with almost ten years of follow-up data [9-11]. Metformin has proven to be a safe and effective option for pregnant individuals with diabetes, polycystic ovarian syndrome, obesity, and hypertensive disorders of pregnancy [12].

According to guideline recommendation rating schemes, metformin meets AI criteria for being added to outpatient treatment guidelines for COVID-19 and infectious disease leaders are pushing for it to be added to guidelines [6,13,14]. In summary, metformin is the only drug that has been tested in pregnant women in a randomized, quadruple-blinded, placebo-controlled clinical trial and found to prevent ER visits/hospitalizations/death due to COVID-19 [7]. Given that metformin is safe during pregnancy and lactation, inexpensive, widely available, and has few contraindications or medication interactions, metformin should be added to outpatient COVID-19 treatment guidelines during pregnancy.

The recommendation rating scheme is as follows:

Strength of recommendation A

Strong recommendation for the statement.

1. **Evidence I:** High-quality evidence, which includes one or more randomized trials without major limitations, well-powered subgroup analyses of such trials, or meta-analyses without major limitations.

Strength of recommendation B

Moderate recommendation for the statement.

1. **Evidence IIa:** Moderate quality of evidence from randomized trials and subgroup analyses of randomized trials that do not meet the criteria for a rating of I.
2. **Evidence IIb:** Moderate quality of evidence from observational studies without major limitations.

Strength of recommendation C

Weak recommendation for the statement.

1. **Evidence III:** Based on expert opinion.

DECLARATIONS

Conflict of interest

The authors report no conflicts of interest.

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