

restriction.³ Another potential link between pre-eclampsia and COVID-19 is the presence of anti-phospholipid antibodies (aPLA). aPLA is a well-known major risk factor for pre-eclampsia and one study found that 52% of COVID-19 patients had elevated aPLA levels.⁴ Alpha-1-antitrypsin (AAT) has been shown to prevent apoptosis as well as reduce oxidative stress and inflammation in endothelial cells. AAT has been shown to be a protective factor in pre-eclampsia through activating Smad2 and inhibiting DNA binding 4 in both an animal model and human placenta tissue.⁵ AAT also inhibits TMPRSS-2,⁶ the host serine protease that is required for processing of the spike protein of SARS-CoV-2 before the virus binds to its receptor to gain entry into the cells. The shared pathophysiology between COVID-19 and pre-eclampsia should be further studied and may lead to novel therapeutics which may include AAT. ■

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Authors' reply

Sir,

We thank Dr Sholapurkar for showing interest in our register-based study on the risk of postpartum haemorrhage (PPH) in relation to depression and use of selective serotonin reuptake inhibitors (SSRIs) and for opening an important debate.¹

In his letter, Dr Sholapurkar raises possible limitations with register-based data. Specifically, that with large sample sizes, small effect sizes can be identified as statistically significant. What is a clinically relevant effect size is still a topic for debate. We would argue that an odds ratio of about 1.3 for having a postpartum bleeding of more than 1000 ml (a strictly pre-defined outcome in our study)² is not minimal. When dealing with prevalent exposures such as depression with/without use of SSRIs (at 20%), the public health impact of relatively small effect sizes is considerable.

Also, women who have suffered from depression are at higher risk for postpartum depression (PPD). PPH, and especially postpartum anaemia and a negative delivery experience (often following a PPH), are further risk factors for PPD³. PPD has a devastating effect on women and the whole family and costs about US\$ 32,000 per mother.⁴ In this context, we believe that further evaluation of extra vigilance and consideration of practical preventive measures, with low costs and associated risks, should be further assessed. Preventing even some PPH cases among these high-risk groups not only

would alleviate suffering but also seems like a highly cost-effective measure.

It was argued in the letter that in clinical situations, one would not need to take any extra precautions for a patient with 9% risk for PPH instead of 7% and that other risk factors such as twin pregnancies are far more important. We of course agree that twin pregnancy confers much higher risk, and that is why we have specifically excluded these from our study, to focus on a low-risk population. A possible interaction effect of SSRI use and twin pregnancy should be further tested. Blood loss as a continuous variable was also analysed, confirming the association of SSRIs with increased postpartum bleeding, but it was not included in the article because of word constraints. We believe that the chosen primary outcome is much more clinically relevant.

In research in general, and with large datasets specifically, there is a risk of selective reporting of specific analyses, as indirectly implied by the exposure-wide study by Patel et al.⁵ cited by Dr Sholapurkar. This was nevertheless not the case for this study, which was founded on a hypothesis based on solid pathophysiological grounds; SSRIs increase bleeding tendency in non-pregnant populations. In the case of a potential association between SSRIs and PPH, as Dr Sholapurkar writes, there have been conflicting results. Indeed, real-world observational data do not allow for full control of confounders, and every dataset may have its own biases. As the question would hardly be ethical to investigate in a randomised controlled trial, we strove to advance knowledge by reproducing previous results in a real-world Swedish setting. However, we acknowledge that further studies, preferably with a complete preregistered study protocol, are needed. ■

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Re: SSRI use during pregnancy and risk for postpartum haemorrhage: a national register-based cohort study in Sweden

This registry-based large study of postpartum haemorrhage with SSRI usage, despite crucial limitations, shows any increased risk to be reassuringly low and clinically non-significant

Sir,

The Swedish national register-based study by Skalkidou et al,¹ despite critical drawbacks, adds worthwhile information on the increased postpartum haemorrhage (PPH) with selective serotonin reuptake inhibitors (SSRIs). Previous studies have shown increased as well as decreased risk of PPH,¹ as is common when the effect is small or nil. The painstaking analysis in this study creates the opportunity for valuable debate and conclusions.

The foremost strength is professed to be the very large sample size of 305 321

women, comprising 90% of the pregnant population of Sweden over several years. Although a major asset for prospective studies (with due caution), it is a common hazard to be managed during retrospective analysis of mega-databases (even starting with a specific hypothesis). As the sample sizes become enormous, increasingly insignificant/minuscule clinical effects assume 'statistical significance'. The results can be mostly false due to pure chance and persistent unseen/un-characterised confounders, despite good analysis.² To demonstrate this, Prof. Ioannidis' team analysed the data for all medical prescriptions and incidence of all cancers over many years for an entire country (Swedish register).² Out of all 500+ medication classes examined, incredibly 75% 'significantly' increased or decreased the risk of cancers – 'giving wrong signals right and left' (with enormously significant *P* values).² They had enough material for 100 registry-based publications² (popular with leading journals). Another elaborate analysis of the Swedish registry concluded that a family history of PPH significantly increased the risk of PPH due to genetic factors (inherited bleeding disorders excluded).³ A woman's risk of PPH was 'significantly' increased even when her sister-in-law had had PPH, presumably through the feto-placental genes.³ Following a robust challenge,⁴ it is hoped that vast research funds are not being spent on studying the 'polygenic inheritance theory' of common PPH as envisaged. A good remedy against over-reading into Big-data would be to define the clinically relevant magnitude of the key effect first (in this case, an increase in actual blood loss by say 500 ml) and then to test any statistical significance for that and other sizes of effects.

A further unnoticed crucial limitation of the current study¹ is the incomplete data, i.e. the actual blood loss (average and SD) has not been mentioned/analysed; despite the midwives recording it as a continuous variable and binary data (≤ 1000 ml, >1000 ml) in the register. The number of cases crossing any threshold (all arbitrary, none watershed) is a very inferior statistic. It is unknown if a small excess of average blood loss (e.g.

<100 or 200 ml) could be responsible for increasing the risk of PPH (>1000 ml) from a background of 7.0% to 9.1% with SSRI use in this study. Nevertheless, what is the clinical implication of this 30% increased risk of PPH? What extra or different measures should one take antenatally or intrapartum for a 9.1% risk of PPH, that one would not for a 7.0% risk of PPH? Justifiably nothing different! This contrasts with the many-fold increased risk of substantial PPH associated with obstetric risk factors. Hence, the results of this study do not warrant warning the patients (unnecessary anxiety) or incorporating the risk of PPH in the treatment decisions regarding SSRI usage.

Thus, the reported rhetorical conclusion of this study¹ that 'its results prompt design and implementation of studies testing effectiveness of risk evaluation of using SSRIs and the psychiatric illness itself with regard to reducing PPH' seems incongruous with its findings. Birth attendants do not become distracted by any formal 'PPH-risk-stratifying-matrix'. The correct conclusion seems that the observed increased risk of PPH with SSRIs is reassuringly very low and does not justify any additional steps. ■

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