We are grateful for Professor Cuckle’s interest in our work and his comment regarding the veracity of the manuscript’s concluding remark that “PAPP-A is as clinically effective as PlGF in first-trimester combined preeclampsia (PE) screening when used in combination with maternal characteristics, blood pressure and uterine artery Doppler”. Professor Cuckle contends that this conclusion is not supported either by the literature or the data in the study.

Previous literature

We concur with Professor Cuckle’s assertion when he states that the cited literature suggests that for a fixed 10% false-positive rate, there was an observed 5-7% higher detection rate using PlGF compared with PAPP-A for first trimester combined screening for preterm pre-eclampsia.1 Although the literature is based on a larger population of pregnancies, many of the cited publications use the same cohorts and the actual totals are lower than that claimed by Prof Cuckle. He highlights the strength of these studies as being prospective, but unfortunately overlooked the impact of the authors not correcting for aspirin use in pregnancy. In all of the cited studies, PAPP-A was revealed to the clinicians and PlGF concealed – at a time when the prevailing clinical guidance in the UK was to prescribe aspirin prophylaxis to women with low PAPP-A levels. As such, one would expect a clear effect of intervention bias from aspirin use in women with low PAPP-A, but not low PlGF levels. The magnitude of the impact of aspirin use was not apparent at the time the studies were conducted, but is now estimated to be a 60% reduction in the rates of preterm pre-eclampsia.2 To test the hypothesis of treatment paradox introduced by aspirin prophylaxis, we examined, in the literature cited by Professor Cuckle, the comparisons between PAPP-A and PlGF in prediction of term pre-eclampsia where aspirin is known to have a negligible effect. Here, we found no difference in the screening sensitivity between first trimester combined screening using PAPP-A versus PlGF (detection rates 42.3% versus 44%, difference in detection 1.8 [0.0-3.6], p=0.068).1

Study too small

On the matter of the size of our study, we acknowledged this as a limitation, but offered mitigation by summarising the existing high-quality published evidence from prospective studies that either corrected the data for aspirin use or where women were not prescribed aspirin (see Table).3-5 These studies total 28,740 pregnancies with 289 cases of preterm pre-eclampsia and all three reported no statistical difference between PAPP-A and PlGF in first trimester combined screening for preterm pre-eclampsia. Of note, this includes the SPREE study where a prospective head-to-head comparison was made between routine antenatal care and the use of first trimester combined screening for pre-eclampsia (with various combinations of markers.4 The authors of the SPREE study had not compared the use of PAPP-A to PlGF in their original analysis, but very kindly conducted a post-hoc analysis of their data using the McNemar test (p=0.10) for comparison of the screening using maternal characteristics, blood pressure, UtA Doppler and either PlGF or PAPP-A for detection of preterm PE at a 10% screen-positive rate.

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| --- | --- | --- | --- |
|  | **Pregnancies** | **Preterm PE** | **PAPP-A vs PlGF sensitivity** |
| Noël *et al.* (2021)3 | 1,094 | n=30 | 80.7% vs 72.7%\* |
| Poon L *et al.* (2020)4 | 16,747 | n=142 | 76.1% vs 81.7%\* |
| Hu J *et al.* (2021)5 | 10,899 | n=117 | 65.0% vs 56.4%# |
| **Total** | **28,740** | **n=289** | **72.0% vs 70.6%** |

\*Corrected for aspirin use, #Very low aspirin use (n=85, 0.75%)

Avoiding a dogmatic approach to absence of evidence

Professor Cuckle opines that our study represents a classic example of an absence of evidence of a difference being assumed to be evidence of absence of an effect. This is an often-used statement to question the value of studies with negative findings, contributing to the acknowledged systematic bias of academic journals to publish studies with positive findings. Professor Cuckle’s slogan sounds cautionary and plausible, to avoid hasty inferences drawn from a paucity of evidence, but there are significant concerns when this is deployed as an indisputable methodological principle. The same slogan was used by the then US Defence Secretary Donald Rumsfeld in 2002 to declare war in Iraq for possessing weapons of mass destruction, despite the lack of evidence that this was the case. If the latter is a consequence of the dogmatic application of Professor Cuckle’s statement, why would anyone believe it to be a compelling argument? We argue that we are justified to infer an absence of an effect where we could reasonably expect to find evidence if our hypothesis were true, our methodology sound, and when we do not obtain positive results. However, this is not how the burden of proof works. If we did not find a difference between the use of PAPP-A and PlGF in first trimester combined screening for preterm pre-eclampsia, we do not have the burden of proving that we are right. The burden rests with those who conduct equally rigorous studies to produce data to justify their findings are probable enough to be used in clinical practice.

Laure Noël

Basky Thilaganathan

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