

## Two-dose vs single-dose methotrexate for treatment of ectopic pregnancy



TO THE EDITORS: Dr Alur-Gupta et al<sup>1</sup> published a systematic review and metaanalysis concerning 2-dose vs single-dose methotrexate for treatment of ectopic pregnancy. However, their statistical analyses are confounded by several potential biases.

First, their systematic review should have been registered with an International Prospective Register of Systematic Reviews (PROSPERO, <https://www.crd.york.ac.uk/>) or other international databases of prospective registration to avoid duplication and reduce the opportunity for reporting bias by enabling comparison of the completed systematic review with what was planned in the protocol.

Second, the primary outcomes, treatment success, were 87.2% and 78.9% for 2-dose and 1-dose groups, respectively; however, their metaanalysis used of the odds ratio to estimate pooled treatment effects. It seems that they have not followed the Cochrane Handbook,<sup>2</sup> which stated that odds ratios are more difficult to interpret than risk ratio and can overestimate and magnify risk when events are not rare.<sup>3</sup>

Third, publication bias was assessed via funnel plots in their study. That is incorrect. The use of funnel plots to analyze publication bias went to the 1980s and 1990s. However, over time, researchers realized that there could be numerous causes for asymmetry of funnel plots. Asymmetry

in a funnel plot does not tell whether there is publication bias. Therefore, the term *publication bias* has been replaced largely with the term *small study effects* in the analysis of funnel plots.<sup>2</sup> ■

Yijie Zhou, MD  
Hui Huang, MD  
Department of Gynecology  
Guiyang Maternal and Child Health Care Hospital  
Guizhou, China  
[twh666@outlook.com](mailto:twh666@outlook.com)

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## Artificial placenta: Miles to go before I sleep...



TO THE EDITORS: First of all, we would like to congratulate the authors for this adventurous novel piece of research.<sup>1</sup> With advancement in technology and better medical care the survival of premature infants has improved drastically over the last few decades. However, the survival of micro preemies in the periviable period (22–25 weeks) and the associated long-term morbidities have not changed meaningfully. Hence, prevention of spontaneous prematurity is a real challenge and requires scientific breakthrough in the form of artificial placenta. The development of artificial placenta has been a subject of investigation over the last 50 years with limited success. Definitely, this technology has potential to do miracles in intact survival of neonates born at periviable period (22–25 weeks); if found successful, its use is likely to be expanded to cover much wider gestation.

As compared with a recent invention in this field, the authors rightly have improvised the technique towards a more real-life human fetus scenario.<sup>2</sup> Salient points are the use of more immature ewe fetuses (95 days; weight 600–700 g, which is equivalent to a human fetus at 20–24 weeks

gestation), the sole use of umbilical catheterization for vascular access instead of carotid artery and jugular vein cannulation, prostaglandin E1 infusion for patency of umbilical vessel, and, last but not the least, a lower concentration of heparin (12.5 units/kg/hr) in the circuit to prevent intracranial hemorrhage in these premature fetuses.

The study has a few concerns that need to be clarified by authors for the easy comprehension of readers and for future applicability:

1. The duration of use of the artificial womb in the current study was nearly 5 days, which is much shorter compared with the usual period of ventilation and nutrition support in human fetuses who are born in the periviable period.
2. To prevent infection, the authors have used prevention measures like empiric antibiotics (meropenem) and antifungal (fluconazole). However, because of the potential risk of adverse effects (such as thrombocytopenia) with these antibiotics, it may not be advisable to use them as empiric therapy in human fetuses. Despite this, the authors have demonstrated infection in 1 of the fetus in experimental arm.

3. The authors have used prophylactic hydrocortisone in all ewe fetuses to avoid fluctuations in blood pressure and to prevent hypotension, which is very common in this age group. But it should be used more cautiously in human fetuses, given the fact that there is proven long-term neurologic adverse effects on the developing brain with exposure to corticosteroids; further studies are warranted on this matter.
4. The procedure of transition from intrauterine period to extra uterine environment (artificial womb) required nearly 15 minutes. The readers would be interested to know how stabilization was done in the transition period and what extra support was needed. Because a 15-minute period may be long enough for the initiation of first breath, thereby resulting in infliction of lung injury.
5. Differences in the maturation process of fetal lung and brain in ewes and humans may have resulted in a favorable outcome for fetal ewes; the same result might not be replicated in human fetuses.
6. Because the fetus will be grown in artificial environment, it will be exposed to all types of noxious stimulus, to the risk of infection, and to the risk of brain injury, compared to natural pregnancy of the same gestation.
7. Last, there are some long-standing unsolved ethical issues that need to be answered before this technology gets adapted to humans.
  - What should be the ideal gestation age for use of this technology? Although the authors have mentioned it to be of 20–24 weeks gestation, with passage of time and increase in awareness, this technology will be used/misused in a wider gestation.
  - Similarly, it might push the limit of viability and force the age of abortion lower.
  - It might replace the role of a woman in natural pregnancy, which might be considered risky and stigmatized. People will adapt to partial ectogenesis, even without any valid underlying reason. This might result in questioning facilities like “maternity leave” in employment for women.
  - Who should use? Use of artificial womb technology may give a false sense of security and promote its use in lower middle income countries where there is a lack of adequate infrastructure and supportive care. It might promote unjustified use of limited resources especially in lower middle income countries.
  - Legal rights? Because the hypothetical human fetus (so called *gestateling*) would be growing in the artificial womb, who will bear the legal responsibility? Is it the neonatologist? The obstetricians? Or the fetal surgeons. Would it have all legal rights like that of a born neonate?

Finally, we would conclude that this is definitely cutting edge technology. Until the challenges that are related to technical limitation, the provision of adequate nutrition, the prevention of infection, and the ethical issues are addressed systematically, there is a long way to go before it replace the natural womb. ■

Tanushree Sahoo, MD, DNB, DM  
ICMR Consultant  
All India Institute of Medical Sciences  
New Delhi, India  
[tanushree\\_sony206@yahoo.co.in](mailto:tanushree_sony206@yahoo.co.in)

Krishna Mohan Gulla, MD, FNB, DM  
ECMO trainee  
NTU Hospital  
Taipei, Taiwan

The authors report no conflict of interest.

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## REPLY



We thank Drs Sahoo and Gulla for their commentary on our recent publication<sup>1</sup> that described the preclinical development of an artificial placenta for extremely preterm infants. As discussed in our submission, an abbreviated study period was selected because of a lack of performance data for extremely preterm fetuses that are supported via an artificial placenta-based platform; moreover, there are good data to show that a significant percentage of morbidity and death occurs acutely after extreme preterm birth,<sup>2</sup> hence the duration of the studies undertaken. Drs Sahoo and Gulla are also quite correct to suggest, as we have done previously, that there are, of course, significant differences between ovine-based model systems and human beings.

The correspondents raise several interesting points in relation to the use of therapeutic steroids and antimicrobial agents during this experiment, highlighting the potential risk of their application. Although we do not disagree with the need to proceed cautiously, it is important to assess the use of these agents against the current expected outcomes for extremely preterm infants using existing technology, which are more often than not extremely poor.<sup>3</sup>

From an ethical standpoint, we agree that a robust conversation should take place well in advance of artificial placenta technology being adopted for use in the clinic. However, we do not share the same concerns as the correspondents regarding the potential for misuse of this platform. Given the profound improvements in preterm outcomes once 26–28 weeks gestation is achieved, it seems quite unlikely that an artificial placenta would be used across a wide range of