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## Reply to: Responsibility of scientific community in claiming to have found an association with recurrent pregnancy loss



Dear editor,

We read with interest the comments of Smits et al. 2019 (this issue) on the manuscript we recently published on the possible association between oral sex and the reduced incidence of recurrent miscarriage (Meuleman et al., 2019). We agree with the authors that one has to be careful before drawing any definitive conclusions as is also reflected by the discussion of our manuscript. However, we are very surprised by the statement that the biological rationale of our paper is not substantiated. Anybody, who is familiar with immunology, knows that a broadly accepted way to induce immunological tolerance is via the oral route. Actually, when one performs a search on “oral AND tolerance” in PubMed almost 34,000 papers show up. By the oral route, immunological tolerance can be induced to a variety of antigens including blood group antigens and the antigens of the major histocompatibility complex. Although many oral tolerance studies have been performed in mice, similar results are obtained in the human situation (Rezende and Weiner, 2017). A natural way to induce oral tolerance to blood group antigens and transplantation antigens is by breast feeding (Schonewille et al., 2019; Campbell, 1984). Based on all these studies we hypothesized that in case of oral sex the immune response to soluble paternal HLA antigens in the seminal plasma may affect the immune response of the pregnant mother towards the paternal HLA antigens inherited by the child. Actually, several studies suggest that regulatory T cells are crucial for a successful pregnancy, also in the man (Robertson, 2018). As the oral route of antigen presentation is known to facilitate the induction of these regulatory T cells, the biological rationale of our study is well established. We agree that the missing data in our study is a problem. A significant association between oral sex and a reduced incidence of recurrent miscarriage was only observed when cases and controls with complete data are compared. After imputation of the missing data the association is less strong. However, one has to realize that imputation was based on data derived from the general population, which will dilute the aberrant data in the study group. Therefore, confirmation of our results in a second independent cohort is crucial in order to draw a definitive conclusion. Nevertheless, the data are interesting and will stimulate studies on the immunological mechanisms involved in a proportion of so far unexplained recurrent miscarriages. Whether changes in sexual behaviour in the patient population will be beneficial remains to be established. It is up to the patients whether they consider this as a possible way to reduce the chance of recurrent pregnancy loss. Considering the fact that some patients are already open for treatments with corticosteroids (Kemp, 2016), this might be a less harmful and cheaper alternative.

### Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Tess Meuleman\*, N. Baden, G.W. Haasnoot, M.M. Wagner, C. Picavet,  
O.M. Dekkers, S. Le Cessie, J.M.M. van Lith, F.H.J. Claas,  
K.W.M. Bloemenkamp  
*Leiden University Medical Centre, Albinusdreef 2, 2300RC, Leiden, the  
Netherlands*  
E-mail address: [t.meuleman@lumc.nl](mailto:t.meuleman@lumc.nl) (T. Meuleman).

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\* Corresponding author.

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