Response to Letters Regarding Article, “Systemic and Pulmonary Vascular Dysfunction in Children Conceived by Assisted Reproductive Technologies”

We thank Philips and O’Leary for their interesting comments on our study. They suggest that considering pubertal maturation as a potential confounding factor would have been important for the interpretation of the results, because it has been reported that in prepubertal boys, pulse-wave velocity is lower than in prepubertal girls, a difference that disappears after puberty.1 In our study, the very large majority of the participants was prepubertal, the mean age of the group conceived by assisted reproductive technologies (ART) tended to be lower, and there were proportionally more boys than girls in this group. Taken together, the combination of these factors would have been expected to result in lower pulse-wave velocity in the ART group than in the control group. This is exactly the opposite of what we found, which suggests that we may even have underestimated the detrimental effects of ART on this variable. They also suggest that the influence of estrogens should be considered. As noted above, there were only a few peripubescent girls included in our study. Moreover, to the best of our knowledge, there is no published evidence indicating that flow-mediated dilation increases between prepubertal and postpubertal girls. In line with this concept, age was not related to flow-mediated dilation in the girls included in our study. We would like to take the opportunity to indicate that in the few postpubertal girls included in our study, vascular function was tested during the early follicular phase (day 1–7 of the menstrual cycle), because vascular responsiveness varies during the menstrual cycle.2 Thus, we are confident that endogenous feminizing hormones were not a confounding factor in our study. Finally, they suggest that overweight should have been considered. We are very well aware of the effects of obesity on cardiovascular and metabolic regulation3,4; however, there were no overweight participants in our study. In summary, we are very confident that the large differences in vascular function and vascular morphology between these young ART and control children are valid and related to the ART procedure. Future studies that plan to examine older and/or obese participants should take into account the suggestions by Philips and O’Leary when interpreting the data.

Dr Andreassi suggests to be cautious about extrapolating findings showing epigenetic alterations in ART mice to humans and refers to studies that did not find alterations of DNA methylation in peripheral blood samples obtained from ART children. While we agree that one has to be cautious when extrapolating from one species to another, it is nevertheless intriguing that ART induces vascular dysfunction in offspring of sterile humans and normal fertile mice.5 Moreover, preliminary data in mice suggest that ART-induced epigenetic alterations may be tissue specific and therefore undetectable when searching for alterations of DNA methylation in whole blood samples or amnion/chorion tissue.5 We are confident that our study will greatly stimulate research on the potential role of epigenetic and other mechanisms such as alterations of telomere length proposed by Dr Andreassi to find ways to prevent ART-induced vascular dysfunction in the future.

Dr Irion wonders whether the fact of being informed about the study hypothesis may have altered the findings. As requested by the ethics committee, participants were informed about the hypothesis that ART may alter vascular responsiveness (no mention about future risk of myocardial infarction was made, since this issue was not tested in our study). To the best of our knowledge, there is no published evidence that emotional stress of short duration alters carotid intima media thickness or hypoxia-induced pulmonary hypertension. Mental stress increases flow-mediated dilation in healthy young subjects.6 If, as suggested by Dr Irion, ART children were more stressed than control children, we may even have underestimated the effects of ART on flow-mediated dilation.

Disclosures

None.

Urs Scherrer, MD
Stefano F. Rimoldi, MD
Emrush Rexhaj, MD
Thomas Stuber, MD
Swiss Cardiovascular Center
Bern University Hospital
Bern, Switzerland

Hervé Duplain, MD
Sophie Garcin, MD
Botnar Center for Extreme Medicine and Department of Internal Medicine
Lausanne, Switzerland

Stefano F. de Marchi, MD
Swiss Cardiovascular Center
Bern University Hospital
Bern, Switzerland

Pascal Nicod, MD
Hirslanden Group
Lausanne, Switzerland

Marc Germond, MD
Centre de Procréation Médicalement Assistée
Lausanne, Switzerland

Yves Alleman, MD
Claudio Sartori, MD
Swiss Cardiovascular Center
Bern University Hospital
Bern, Switzerland

References


Response to Letters Regarding Article, "Systemic and Pulmonary Vascular Dysfunction in Children Conceived by Assisted Reproductive Technologies"

Urs Scherrer, Stefano F. Rimoldi, Emrush Rexhaj, Thomas Stuber, Hervé Duplain, Sophie Garcin, Stefano F. de Marchi, Pascal Nicod, Marc Germond, Yves Allemann and Claudio Sartori

_Circulation_. 2013;127:e478
doi: 10.1161/CIRCULATIONAHA.112.134833
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/9/e478

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/