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EDITORIAL COMMENT

Does Fertility Therapy Hamper Cardiovascular Outcome?*

Jolien W. Roos-Hesselink, MD, PhD,†
Mark R. Johnson, MD, PhD‡
Rotterdam, the Netherlands; and
London, United Kingdom

Infertility affects 1 in 8 couples, but over the 17 years of the study Udell et al. (1) reported in this edition of the *Journal*, the proportion of pregnancies conceived after fertility treatment rose from 1 in 400 to 1 in 80. These data support the idea that although the prevalence of infertility is stable over time, the number of couples with infertility would have been substantially higher if in vitro fertilization and other types of assisted conception had not been introduced. Thanks to these techniques, many couples are successfully treated and happily raise a family.

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We know pregnancy is a "stress test" for later cardiovascular and metabolic disease. Indeed, complications arising during pregnancy may actually be the first presentation of a subclinical disease. For instance, in the case of gestational diabetes mellitus, women diagnosed with gestational diabetes mellitus have a 50% to 60% chance of diabetes developing in the next 10 to 15 years. Further, the occurrence of pre-eclampsia is a strong predictor for hypertension and subsequent cardiovascular events, perhaps by unmasking subclinical endothelial dysfunction.

The study reported by Udell et al. (1), in this issue of the *Journal*, examines whether fertility treatment, either by inducing extremely high levels of sex steroids or by another mechanism, results in an increase in later cardiovascular and metabolic disease. Does the therapy influence the occurrence of thromboembolic events? Personally, I have seen a woman treated for infertility who subsequently had major pulmonary emboli and pulmonary hypertension. She was severely disabled after this event. In addition, when we consider the population who seek fertility treatment, we know there is an excess of women with polycystic ovarian disease and other cardiovascular risk factors, as also shown by the current study. These women are at greater risk of gestational diabetes mellitus and pre-eclampsia, both associated with later metabolic and cardiovascular disease, as also found in the current study. It has been proven that lifestyle changes, including diet, exercise, and behavioral modification, appear to improve the metabolic and reproductive abnormalities of overweight and obese patients with polycystic ovary syndrome (2). However, the important question posed by this study is, does fertility treatment increase the risk of cardiovascular events? If it were to do so, then the next question is, is this an effect of the treatment or is the treatment and subsequent pregnancy revealing an already-existing tendency to a disease. Either mechanism would result in an increase in disease diagnosis within a defined period, the former by a direct adverse effect and the latter by hastening the time of diagnosis of a subclinical condition.

It is important to study the effects of fertility treatment on cardiovascular outcomes in women. However, although the question is of great clinical relevance, it is not easy to design a study to elucidate this question. A randomized controlled trial is not an option as infertility itself is a confounding factor, and also a case-control study is not possible. A large population-based study seems the best way of approaching this problem. It is, however, difficult to retrieve reliable data in a large cohort of patients. Therefore, Udell et al. (1) should be congratulated on completing a well-designed and well-performed study. They have investigated a population-based cohort of 1,186,753 women who delivered between 1993 and 2010, of whom 6,979 gave birth after fertility therapy.

Interestingly, after 10 years of follow-up, the researchers found that the rate of the primary outcome, namely, a composite of death or hospitalization for a major adverse cardiovascular event including nonfatal coronary ischemia, stroke, transient ischemic attack, thromboembolism, or heart failure, was lower among women who had received fertility treatment. In terms of the individual components, mortality (adjusted hazard ratio: 0.50, 95% confidence interval: 0.31 to 0.80, $p = 0.004$) and thromboembolic events (adjusted hazard ratio: 0.45, 95% confidence interval: 0.21 to 0.94, $p = 0.03$) were significantly reduced, but crude rates of coronary ischemic events, heart failure, and cerebrovascular events were higher, yet each association was not significant after multivariable adjustment. Similarly, after excluding women who had evidence of cardiovascular disease, hypertension, diabetes (including gestational diabetes), or hyperlipidemia at baseline, the development of risk factors occurred more frequently among women after fertility therapy than among controls. However, again after adjustment with the multivariate analysis, these changes were reversed. These data show that not only was fertility treatment associated with a reduction in death and thromboembolic disease, but it also seemed to protect against the development of risk factors for cardiovascular disease.

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From the †Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; and the ‡Department of Obstetrics and Gynaecology, Imperial College London, Chelsea and Westminster Hospital, London, United Kingdom. Both authors have reported they have no relationships relevant to the contents of this paper to disclose.

The investigators suggest 3 possible explanations for the beneficial effect of successful fertility treatment. First, women who have had successful fertility treatment opt for a healthier lifestyle than women who conceived without fertility treatment; second, that the treatment has some beneficial effect; and third, that women who have unhealthy lifestyles do not choose to have fertility treatment. Given that the population receiving fertility treatment at baseline had more cardiovascular risk factors, then it would seem unlikely that they were a particularly healthy group. Fertility treatment is unlikely to have some intrinsic health-promoting effect, suggesting that the last option, the adoption of a healthy lifestyle, is the most likely. However, this would be very difficult to prove.

Of course, longer duration of follow-up is warranted and the discussion is not yet closed, but the findings in this study are reassuring for women who need fertility treatment. However, some methodological issues of the study need attention. Especially, the large differences found at baseline, such as a difference in age, make reliable comparison difficult. Udell et al. (1) have tried to correct this, but that could not be done for all parameters. In addition, in this study, no information is obtained about unsuccessful fertility treatment, especially that these patients may have received higher cumulative doses of hormones with consequently more effect on cardiovascular outcome.

The current data are reassuring as they suggest that fertility treatment does not itself increase the risk of cardiovascular events or risk factors and may actually have a direct or indirect beneficial effect, but overall, we should remember that the population needing fertility treatment is actually at increased risk of cardiovascular and metabolic disease. Further, these data can only be applied to women who conceived and had a live birth. The outcome for women whose treatment is unsuccessful may be very different and should be investigated.

Reprint requests and correspondence: Dr. Jolien W. Roos-Hesselink, Department of Cardiology, Erasmus Medical Center, Gravendijkwal 230, Rotterdam 3015 CE, the Netherlands. E-mail: j.roos@erasmusmc.nl.

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