

## PERIPARTUM CARDIOVASCULAR DISEASE MINI-FOCUS ISSUE

### VIEWPOINT: VOICES IN CARDIOLOGY

# Clinical Challenges for Women of Modern Societies and Potential Cardiovascular Consequences



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During the last decade, modern societies have witnessed an increase in the availability of options to assist human reproduction for infertile couples. Assisted reproductive technology (ART) includes all fertility treatments that involve procedures in which both eggs and embryos are handled, such as in vitro fertilization (IVF) and intrauterine insemination (IUI). They do not include treatments in which only sperm are handled (i.e., intrauterine or artificial insemination) or procedures in which a woman takes medication only to stimulate egg production without the intention of having eggs retrieved. More than 99% of ART procedures consist of IVF following several cycles of high doses of hormone stimulation to then retrieve the human eggs (1). According to the last reports from the Centers for Disease Control and Prevention (CDC), between 2006 and 2015, there was a 32% increase in performed ART cycles that was parallel to the increase in the proportion of women who could then consider an option of childbearing at a more advanced age (1). Because of the presence of hormone receptors through the cardiovascular (CV) system, the use of supraphysiological levels of hormones has the potential to affect the CV system. Studies on the role of exogenous hormone therapy have mainly focused on the perimenopausal period, and only a few studies have looked at CV health among women undergoing ART. Despite the limited evidence, some studies have suggested the possibility of an increase in CV events, including heart failure, cerebrovascular events, and venous

thromboembolism, especially after prolonged and unsuccessful ART.

Current evidence on the use of fertility therapies and CV health in younger groups of women has been inconclusive largely because of differences in study designs. A recent study by Udell et al. (2) found that failure to deliver a baby within a year of monthly cycles of ART was associated with increased CV events, such as heart failure, cerebrovascular events, and venous thromboembolism, compared with women who had the same exposure but were successfully delivered of an infant. However, the cause and effect of this phenomenon could not be established because infertility itself could mediate the risk for CV disease. An earlier study by the same group found that ART in women with successful pregnancy was associated with a decreased risk of CV-related morbidity and mortality, a finding suggesting a potential protective effect on women who become pregnant (2). However, the generalizability of the study is uncertain, given that it excluded pregnancies that were terminated early and women who did not conceive. Additionally, the protective effect of pregnancy noted could be related to the lack of known CV or pregnancy-related risk factors in those patients that could stem from superior CV health that would permit achievement of pregnancy and also be associated with lower future CV events. Furthermore, the study did not adjust for fertility treatment types, smoking status, body mass index, or adverse pregnancy outcomes such as preeclampsia, intrauterine growth restriction, and preterm birth, all which are associated with future CV disease risk. A similar study conducted by Westerlund et al. (3) that did adjust for body mass index and smoking status found an increased risk of hypertension in women undergoing ART, but not higher risk of stroke, coronary heart

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disease, or diabetes. However, limitations in this study did exist as well. Their study group consisted of women who were successfully delivered after IVF compared with natural birth with a mean follow-up <10 years, which would not allow an estimation of the incidence of CV disease in this group. In addition, similar to the studies mentioned earlier by Udell et al. (2), women with early pregnancy termination or those who did not successfully conceive were not included.

Currently, the CV effect of supraphysiological levels of estrogens in women undergoing ART have not been fully elucidated. Moreover, women are undergoing ART at a later age, which also means that potential age-related CV risk factors, together with high doses of hormone therapy, could further influence CV risk. A national survey estimated that only 25% of women who attempted ART successfully conceived, thus indicating that most women have not been accounted for in previous studies (1). To date, there is a need for increased funding and attention to the design of studies to clarify the CV effects of ART in women. The CDC has been collecting data on successful pregnancy outcomes from all ART cycles performed in the United States through the National ART

Surveillance System (NASS) and has expanded a surveillance system for fetal and maternal outcomes with the integration of NASS to vital records, hospital discharge, birth defect registries, cancer, and other monitoring systems to a States Monitoring ART (SMART) Collaborative in Massachusetts, Connecticut, Michigan, and Florida (1). These resources provide an opportunity to further study and improve previous study designs to attempt to include comparisons of all exposed women with control subjects adjusted by confounding variables such as traditional CV risk factors and adverse pregnancy outcomes. In summary, there is a need to investigate the impact of ART on CV health further. This topic is timely in an era where more women are undergoing ART at a later age and recommendations for CV health and future consequences are not well known.

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