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Editorial comment

Pregnancy in women with genetic variants of dilated cardiomyopathy

Embarazo en mujeres con variantes genéticas de miocardiopatía dilatada

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Genetics has become an essential diagnostic tool in certain clinical settings and is a powerful driver of cardiovascular research. The incorporation of genetics into clinical practice, however, has brought new and complex challenges in patient management. In a recent article published in *Revista Española de Cardiología*, Restrepo-Córdoba et al.[1] described a cohort of 48 women of reproductive age (27 ± 5 years) with a history of pregnancy (83 full-term pregnancies) and genetic variants associated with dilated cardiomyopathy (DCM). Thirty of the 48 women had a phenotype consistent with DCM at their first evaluation, and 3 of the 18 asymptomatic carriers developed the phenotype during follow-up.

Considering how difficult it can be to obtain extensive records in this setting, the work of Restrepo-Córdoba et al.[1] is significant as it highlights the possible role of genetic testing in preventing cardiovascular disease during pregnancy and also provides insights into the natural history of hereditary DCM.[1] The study invites reflection on 3 key points: how genetic testing information can be used to our advantage, how familial DCM or genetic predisposition to DCM might affect the risk of adverse maternal and fetal outcomes, and how these risks can be prevented or at least mitigated.

THE VALUE OF GENOTYPING

The need for genetic and reproductive counseling in DCM has increased with the growing use of cascade genetic testing in this setting. Nonetheless, in the real-world cohort described by Restrepo-Córdoba et al.,[1] just 30 of the 48 women underwent a cardiac evaluation before their first pregnancy. Genetic testing can help determine the risk of DCM, enabling more precise and personalized follow-up. *TTN* was the most common causative gene identified (18/48 women), followed by *BAG3* and *LMNA* (6 women each). Considering the lack of real-world registries and guideline recommendations, the best way to achieve adequate follow-up and prevention strategies remains to be seen. These strategies may also vary according to the characteristics of the variants involved (penetrance, expressivity, and severity of the heart condition). Ultimately, the goal should be to prevent adverse outcomes and identify signs and symptoms of DCM that may be masked by pregnancy-associated changes.

Preimplantation genetic diagnosis is a fundamental part of reproductive counseling. Part of the information that should be given to couples in which one or both members are carriers of an inherited heart condition is that their children might not inherit the same predisposition. The work by Restrepo-Córdoba et al.[1] also highlights the lack of data on the number of patients in this setting using assisted reproduction technologies that include embryo selection. How ovarian stimulation and other hormonal treatments for in vitro fertilization affect this subgroup of patients is unknown.

STRATIFYING THE RISK OF ADVERSE MATERNAL AND FETAL OUTCOMES

The women in the retrospective cohort described by Restrepo-Córdoba et al.[1] experienced a high rate of adverse cardiovascular events (31%) and obstetric or fetal complications (14%) during and after pregnancy. In addition, 3 of the 18 asymptomatic carriers developed signs and symptoms of DCM while pregnant or during the first 6 months postpartum.

All the women who experienced a cardiac event had manifestations of DCM. They had a moderately reduced left ventricular ejection fraction (LVEF) (42% ± %) at the first evaluation and a New York Heart Association functional class of I or II. The estimated rate of maternal cardiovascular events in women with a moderately reduced LVEF (risk class III according to the World Health Organization) lies between 10% and 27%. Although pregnancy is not absolutely contraindicated in this setting, decisions must be taken on a case-by-case basis and always in consultation with an expert.[2] Work such as that of Restrepo-Córdoba et al.[1] is important for informing appropriate reproductive counseling in hereditary DCM. The rates reported might be underestimated considering that maternal and fetal risks increase significantly with age and that the mean age of the cohort is lower than the mean gestational age reported for developed countries (31.5 years for first-time mothers in Spain according to National Statistics Institute data for 2022). In other words, adverse events might be more common than thought. In the cohort described, for example, older women (30 ± 6 years) had a higher rate of adverse

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cardiac events than younger women (28 ± 5 years), although the difference was not statistically significant.

PREVENTING AND MITIGATING THE RISK OF ADVERSE MATERNAL AND FETAL OUTCOMES

As of the publication of this editorial, there is insufficient evidence that pharmacological treatment can prevent the clinical manifestations of DCM or the onset of left ventricular dysfunction and dilation in patients with genetically determined DCM. Management in such cases is typically limited to structured follow-up. In the cohort described by Restrepo-Córdoba et al.,[1] beta-blocker therapy was continued in 3 of the 7 women on this treatment before pregnancy, whereas renin-angiotensin-aldosterone system inhibitor therapy was discontinued in all cases (n = 7). An additional 2 women were started on beta-blocker therapy. These findings once again reflect the lack of evidence surrounding the use of pharmacological treatments in DCM and pregnancy and the difficulties associated with prescribing treatments with potential teratogenic effects. The treatment of cardiovascular events in pregnant women is currently limited to close monitoring of high-risk patients and symptomatic treatment (diuretics for heart failure and beta-blockers for arrhythmias).

Considering the treatment constraints in the setting of DCM and pregnancy, follow-up with a multidisciplinary team of obstetricians, anesthesiologists, cardiologists, and neonatologists is crucial, as is close monitoring throughout the postpartum period, given that events can occur up to 6 months after childbirth. Vaginal delivery is preferred wherever possible, except in women with obstetric complications or refractory heart failure.[3] Of the 56 deliveries described by Restrepo-Córdoba et al.,[1] 18 were cesarean sections (10 for cardiac indications) and the other 38 were uncomplicated vaginal deliveries.

Pregnancy is a natural physiological process that contributes to the onset and progression of genetically mediated DCM through poorly understood mechanisms and changes. Although the additive effect of pregnancy on genetic predisposition (Knudson's 2-hit hypothesis) has been attributed to adaptive changes in the cardiovascular system, scientific evidence and clear therapeutic targets are lacking. For the time being, the focus should be on early diagnosis, effective identification of candidates for screening, and appropriate reproductive counseling. Studies such as that of Restrepo-Córdoba et al.[1] are important for starting to build evidence.

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CONFLICTS OF INTEREST

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