EDITORIAL COMMENTARY

Oral contraceptives and their effect on arrhythmogenesis in long QT syndrome: Does it matter?

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Decades ago, Hashiba[1] was the first to describe corrected QT (QTc) shortening after the age of 13–14 years (eg, the pubertal period) in 3 male Romano-Ward syndrome patients, effectively resulting in a shorter QTc interval in man than in women after the age of 20 years. Years later, when the diagnosis of long QT syndrome (LQTS) became more refined because of the developments in genetic testing, these findings were supported by additional research.[2] It also became clear not only that LQTS-related cardiac events depend on the degree of QTc prolongation but also that there is a complex interaction between age, sex, and genotype.[3] Hence, boys with LQTS type 1 (LQTS1) have a higher risk and earlier onset of cardiac events than do girls with LQTS1, while no sex-related differences in LQTS type 2 (LQTS2) are seen.[4–6] After puberty, changes in the risk of cardiac events occur with an increased risk in LQTS2 female patients compared with LQTS2 male patients while no sex-related differences in cardiac events are seen in LQTS1.[4–7] As puberty plays an important role in sex-related differences in cardiac events in LQTS1 and LQTS2, cardiac potassium channels seem to be important in the effect of sex hormones on LQTS-associated arrhythmogenesis. There also seems to be a different sensitivity to changes in these sex hormone concentrations between LQTS1 (impaired function of slowly activating delayed retifier potassium channels) and LQTS2 (impaired function of rapidly activating delayed retifier potassium channels). This is not only seen during puberty but also during other periods of sudden changes in sex hormone concentration, such as the postnatal period,[8,9] postpartum period,[10–12] and during the perimenopause period,[13] all episodes where LQTS2 female patients have an increased risk of cardiac events than LQTS1 female patients.

In this issue of *Heart Rhythm Journal*, Goldenberg et al[14] provide us with another clinical "model" of the influence of sex hormones on arrhythmogenesis in LQTS. They showed that from 3 types of oral contraceptives, that is, progestin-only, estrogen-only, and the combination of progestin and estrogen, progestin-only therapy is associated with an increased risk of cardiac events in LQTS. In addition, they found that LQTS2 female patients had an increased risk of cardiac events when on oral contraceptives as compared with other LQTS genotypes.

The mechanisms underlying the influence of sex hormones on repolarization and arrhythmogenesis in LQTS are complex and incompletely resolved. In general, the concentrations of sex hormones are influenced in children by the activity of the hypothalamic-pituitary-gonadal axis. The hypothalamic-pituitary-gonadal axis is active during the mid-gestation period in the fetus, first months of life, and the pubertal period.[15] During these periods, higher levels of testosterone are seen in boys and of estrogen and progesterone in girls. From observational studies, we have learned that testosterone decreases the L-type calcium current and increases the potassium channel currents and may shorten the QTc interval in boys through these mechanisms.[16] During adulthood, however, the changes in sex hormone concentrations especially in women are more complex because of the influence of the menstrual cycle, pregnancy, and menopause. Only a limited number of studies have focused on the influence of female sex hormones on the LQTS phenotype. One study including 3 LQTS2 female patients looked at the effect of the menstrual cycle on the QTc interval and showed that a high estrogen level was associated with a shortened QTc interval whereas no difference in QTc interval was apparent in relation to progesterone or the estrogen/progesterone ratio.[17] In addition, in a study including 2 LQTS female patients and malignant syncopal attacks in the premenstrual stage (phase with higher progesterone levels), estrogen therapy was given in an attempt to maintain the balance with progesterone, which turned out to be effective in preventing attacks during hospitalization.[18] Although the potentially protective effect of estrogen in LQTS was not directly demonstrated in the

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study of Goldenberg et al,[14] the finding that the *absence* of estrogen (expressed as progestin-only oral contraceptive therapy) is associated with an increased risk of cardiac events supports this hypothesis. To date, the modulating effects of estrogen on the specific cardiac potassium channels remains unclear; however, it seems plausible that there is a more pronounced influence on the I_{Kr} channels.

It is however noteworthy that in the study of Goldenberg et al,[14] women on oral contraceptives seem more severely affected than women not on oral contraceptives (ie, more patients on β-blocker therapy and more implantation cardioverter-defibrillator implantations). As also agreed on by the authors, this could have resulted in an overestimation of the effect of oral contraceptives for the total group. Underlying reasons for this difference may be that patients who are more severely affected are more likely to complete a questionnaire, recall arrhythmic events, or avoid the risks associated with pregnancy and stay on oral contraceptives for that reason. Not shown, however, is whether more severely affected patients were included in the progestin-only group and whether this partly relates to the result that more events occur in this group. What is shown is that although the percentage of β-blocker therapy was similar by oral contraceptive type, β-blocker therapy gives a more marked reduction in the number of cardiac events in the progestin-only group, suggesting more symptomatic women in this group. In addition, the same holds to a certain extent for patients with LQTS2 where it is unknown whether they were more affected than LQTS female patients with a different genotype. The results of the study from Goldenberg et al[14] must therefore still be interpreted carefully as cardiac events in the progestin-only group and LQTS2 femlale patients may also be a manifestation of a more severe phenotype of LQTS female patients included in these groups.

Taken together, physicians managing patients with LQTS should probably be vigilant about the use of oral contraceptives and preferably avoid progestin-only therapy, especially in (severely) affected LQTS female patients and LQTS female patients not on β-blocker therapy. Specifically in LQTS2 female patients, oral contraceptives should be used with caution.

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