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Potential Depot Medroxyprogesterone Acetate-Triggered Torsades de Pointes in a Case of Congenital Type 2 Long QT Syndrome

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INTRODUCTION

Congenital or acquired long QT Syndrome (LQTS) stems from disordered myocardial repolarization and is characterized by a prolonged QT interval on electrocardiogram (ECG) and an increased risk of syncope and sudden death secondary to *torsade de pointes* (TdP). Female gender is an independent risk factor for the development of TdP in both forms of LQTS.^{1,2} Furthermore, while women with congenital LQTS have a reduced risk of TdP-triggered cardiac events during pregnancy, the 9-month postpartum period represents a temporal window of increased arrhythmogenicity.³ Interestingly, these postpartum-timed cardiac events are more commonly observed in women with type 2 LQTS (LQT2), which stems from mutations in the *KCNH2*-encoded human ether-a-go-go related gene (hERG/Kv11.1) cardiac potassium (K⁺) ion channel.⁴ Although several studies suggest that sex-specific hormonal and autonomic differences that impact cardiac repolarization underlie the longer heart rate-corrected QT intervals (QTc) and higher incidence of TdP observed in postpubertal LQTS females, the precise mechanisms underlying these differences remain poorly understood.⁵

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CONFLICTS OF INTEREST

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A systematic review of PubMed from 1966 to August 2011 using the search terms contraception or contraceptive and QT or LQTS or long QT syndrome or HERG yielded a single relevant reference, a case series linking subdermal levonorgestrel (Norplant II), a synthetic progestin, to QT prolongation and QTc dispersion in otherwise healthy Nigerian females.⁶ A repeat search using medroxyprogesterone and QT revealed three hits. Two of these studies involved hormone replacement therapy in postmenopausal women and the third was a case of TdP attributed to terfenadine overdose in a woman who was concurrently taking cefaclor, ketoconazole, and medroxyprogesterone acetate (MPA).⁷ This patient had completed a 10-day course of MPA 2.5 mg administered for control of menorrhagia (her last dose coincided with symptom onset). The authors commented that cefaclor and MPA were not known to be associated with TdP.

This present case report is the first report suggesting a possible association between the synthetic progestin MPA (Depo-Provera) used as a contraceptive and TdP in a woman with congenital type 2 LQTS (LQT2).

CASE REPORT

A 25-year-old white female, gravida 3, para 2, with clinically diagnosed LQTS was referred from the emergency department for further evaluation of appropriate ventricular fibrillation (VF)-terminating shocks from her implantable cardioverter defibrillator (ICD). The ICD had been placed at age 16 following an LQTS-triggered out-of-hospital cardiac arrest. She was later genetically diagnosed with a single nucleotide deletion, annotated as c.2958del in the LQT2-associated *KCNH2* gene resulting in a frameshift mutation annotated as p.R1005fs + 50X in Kv11.1 (Figure 1).

The patient's clinical history includes an uncomplicated spontaneous miscarriage at 8 weeks gestation at the age of 18. At age 19, she had a rotational forceps delivery at 39 weeks gestation complicated by a shoulder dystocia. Her male infant weighed 4290 grams with Apgars of 9¹ and 9⁵ and was LQT2 genotype positive. Intramuscular depot MPA 150 mg was administered prior to hospital discharge for contraception. Four weeks postpartum, she experienced an appropriate VF/TdP-terminating ICD shock (Figure 2A) and was converted to sinus tachycardia without further symptoms. She was evaluated in the emergency department three days later following a syncopal episode precipitated by TdP, which spontaneously converted to normal sinus rhythm prior to delivery of an ICD shock (Figure 2B).

The patient's β -blocker therapy was resumed and she elected to stop breastfeeding. She was advised to stop her intramuscular MPA, use alternative forms of birth control, and to avoid the use of hormonal contraceptives in the future. She subsequently discontinued β -blocker therapy secondary to symptoms of mood change, depression, and fatigue.

At age 23, she again had a relatively uncomplicated pregnancy except for significant interval and pregnancy weight gain. Labor was induced at 38 weeks gestation and was followed by vaginal delivery of a 3530-gram male infant with Apgars of 9¹ and 9⁵. This child was also genotype positive for LQT2. At the strong suggestion of her physicians, the patient began a titrated β -blocker regimen during the third trimester of pregnancy and continued this regimen for 6 months after the birth of her second child. She again elected to stop pharmacotherapy secondary to undesired side effects. Notably, during the roughly 5-year interval between her two pregnancies, the patient did not use depot MPA or experience any cardiac events or VF/VT-terminating ICD shocks.

Following the birth of her second son, the patient immediately resumed intramuscular MPA 150 mg for birth control and received a total of 5 injections at 3-month intervals. Nearly a

year after the birth of her second son, the patient experienced a brief episode of spontaneously terminating ventricular tachycardia. One month after this episode and in the days just before her presentation to the emergency department at age 25 the patient experienced two brief runs of polymorphic ventricular tachycardia with ICD charge diversion and an appropriate ICD shock delivered during a second VF-initiated syncopal episode.

The patient discontinued MPA contraceptive after this episode. Because of profound β -blocker intolerance, she eventually underwent a left cardiac sympathetic denervation 3 months after the birth of her third child at the age of 29. Over the past 6 years, she has had no further exposure to MPA, 2 additional postpartum periods at age 29 and 31, and no LQT2-triggered cardiac events.

DISCUSSION

This case presents several findings regarding the possible physiologic effects of **progestin-only** contraception in premenopausal women with congenital LQTS that may be important. Before puberty, cardiac repolarization, as assessed by QTc, is similar between otherwise healthy boys and girls.² However, between the ages of 15 and 50 years, women display significantly longer QT intervals than men with about a 10 – 20 ms right-shift in their average QTc². Further, adult women with potassium channel-mediated LQTS (i.e. LQT1 and LQT2) who did not experience a cardiac event during childhood carry a significantly higher risk of cardiac events than men.⁸ Among women with LQTS, particularly LQT2, their risk of an LQT-triggered cardiac event was significantly higher during the 40 weeks following delivery compared to either the 40 week pregnancy period or the 40 weeks prior to conception in a large retrospective study.⁹

While a decrease in autonomic tone, marked changes in estrogen and progesterone levels, sleep deprivation, new auditory triggers, cessation of β -blocker therapy secondary to compliance issues, fatigue, breast feeding concerns, and increased psychological stress have all been hypothesized to contribute to the increased risk of cardiovascular events during the postpartum period, the exact mechanisms underlying this phenomenon remain unclear. The timing of this young woman's significant ventricular arrhythmias in relation to the hormonal changes of pregnancy, particularly with respect to the concurrent administration of synthetic hormonal contraception and cessation of β -blocker therapy after pregnancy, warrants further consideration.

Following menarche, women of reproductive age have several different estrogen/progesterone states. In normally menstruating women, characteristic cyclic changes are seen in the relative amounts and ratios of estrogen and progesterone. Menses is notable for low levels of both progesterone and estrogen. Ovulation is associated with a sharp peak in estradiol level relative to circulating progesterone; this ratio is reversed and maintained during the luteal phase of the menstrual cycle. These serum hormonal levels of cycling women are low relative to the estrogen and progesterone levels seen during pregnancy. Between the 7th and 10th week of gestation, the placenta becomes the major source of progesterone and levels rise during pregnancy increasing to 100–200 ng/ml at term. Estrogen levels increase similarly during pregnancy. After delivery of the term placenta (which produces ~250 mg of progesterone daily), the levels of progesterone and estrogen decline rapidly over the ensuing 3–4 days returning to levels seen during menses.

At present, only a limited number of studies have attempted to evaluate whether cyclic hormonal fluctuations can account for the QT interval variability observed in healthy premenopausal women. While several studies suggest that the QT interval and susceptibility

to drug induced QT prolongation by ibutilide in healthy young premenopausal females are the highest during the follicular phase (menses through ovulation) of the menstrual cycle^{10, 11}, other studies have failed to link hormonal fluctuations to significant changes in the QT interval.¹² Interestingly, the early follicular phase (menses) is associated initially with low levels of both estrogen and progesterone followed by a dramatic increase in the estrogen-to-progesterone ratio during the late follicular phase (proliferative) leading up to ovulation. While endogenous estrogens appear to increase QT intervals and exacerbate arrhythmia susceptibility, emerging evidence suggests that **endogenous** progesterone shortens the QT interval and protects against rhythm disturbances via the non-genomic activation of endothelial nitric oxide synthetase (eNOS).¹³ One would expect that the significantly higher levels of estrogen observed during pregnancy would be associated with an increased risk of cardiac events. However, it appears that the substantial amounts of progesterone present during pregnancy may counter/oppose the potentially pro-arrhythmic effects of estrogen on cardiac repolarization. Furthermore, given the similarity of the hormonal milieu present during the early follicular phase (menses) and the postpartum period, it is not entirely surprising that both these time points have been associated with QT prolongation and an increased risk of cardiac events.

The use of hormonal contraception, particularly during the sensitive postpartum period, adds an additional layer to the already complex interplay between hormones and cardiac repolarization. Hormonal contraception is common during the postpartum period with the synthetic-progestin only “mini-pill” or intramuscular MPA being favored in women electing to breast-feed. Following a single dose of intramuscular MPA, plasma concentrations of MPA increase to peak levels of 1 to 7 ng/ml (similar to endogenous progesterone levels at ovulation) approximately 3 weeks after injection. However, absorbed MPA is never converted to progesterone and neither MPA or any of its metabolites are naturally present in the human body.¹⁴ While the endometrial response to synthetic progestins, like MPA, is similar to endogenous progesterone, MPA appears to oppose many of progesterone’s known cardiovascular effects (Table 1).¹⁴ Importantly, MPA does not activate eNOS like progesterone. Although no link between MPA and QT prolongation currently exists, one cannot simply assume that the cardioprotective effects of endogenous progesterone are shared by synthetic progestins such as MPA and that MPA or one of its metabolites does not have a divergent effect on cardiac repolarization.

In this case, the timing of the peak in MPA levels coincided with the ICD firing during the postpartum period following her first pregnancy. After her first exposure to MPA, the patient was instructed not to use hormonal contraception. During the roughly five-year period where the patient refrained from hormonal contraception use, she did not experience a cardiac event despite electing to stop β -blocker therapy for the bulk of this time. However, following her second pregnancy, she again elected to use MPA for contraception. She had a total of five injections of intramuscular MPA prior to her next symptomatic event.

One possible explanation for the lack of cardiac events following first four doses could include inadvertent subcutaneous administration rather than the manufacturer recommended intramuscular injection. Notably, the patient had gained more than 100 pounds since the time of her last use of intramuscular MPA. A prospective study using computed tomography (CT) evaluation of intramuscular injections, using a standard 23-gauge needle, found that only 32% of the cohort actually received the intended intramuscular injection.¹⁵ The majority of the patients who received a subcutaneous injection were female with an average fat thickness of >2cm (range 2.5–8.7cm) and a gluteal muscle thickness of <3cm (range 0–5.2cm) providing compelling evidence that obesity significantly complicates the administration of intramuscular agents such as MPA.¹⁵ Compared to intramuscular

injections, subcutaneous administration of MPA reaches a lower maximum serum progesterin concentration at a mean of 8.8 days, likely altering any potential adverse actions of MPA.

Following this second set of possible MPA-triggered events after her second pregnancy, she discontinued MPA and has now been LQT2 event free for over 6 years which has included 2 additional postpartum periods. Importantly, 2 out of the 3 TdP-triggered events experienced by this patient over the course of 30 years, the majority of which were spent without β -blocker protection, occurred within a 16 month window where the patient was actively receiving MPA injections. At the very least, this suggests that the complex interplay between fluctuating endogenous hormones and environmental stressors during the legally defined postpartum period, presence of synthetic MPA, and the patient's decision to forego β -blocker pharmacotherapy may have contributed ultimately to her increased risk of events during the 16 month interval when she was receiving MPA injections.

Data on the direct effects of endogenous and synthetic hormones on cardiac repolarization in healthy premenopausal women and postmenopausal women with underlying cardiac channelopathies such as LQTS remain sparse. Importantly, synthetic progestins such as MPA cannot be equated with endogenous progesterone, while the two compounds share a comparable anti-proliferative effect on the endometrium, their known effects on the cardiovascular system, including endothelial nitric oxide synthesis, appear to be diametrically opposed (Table 1).¹⁴ Further investigation of the potential genomic and non-genomic effects of MPA on cardiac repolarization and the possibility that the use of intramuscular MPA may contribute to an increased risk of cardiac events during the postpartum period by enhancing an existing hormonal imbalance, specifically in women who elect to forego β -blockers for primary prevention, is necessary. The potential link between hormonal variations and particularly the effects of synthetic progestin-based hormonal contraception in premenopausal women warrants increased scrutiny to ascertain the precise effect(s) on cardiac repolarization, particularly in women with underlying cardiac channelopathies such as LQT2.

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Abbreviations

CT	computed tomography
ECG	electrocardiogram
eNOS	endothelial nitric oxide synthetase
ICD	implantable cardioverter defibrillator
LQTS	long QT syndrome
MPA	medroxyprogesterone acetate
QTc	heart rate-corrected QT interval
TdP	torsades de pointes
VF	ventricular fibrillation

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Figure 1. The molecular genotype of a LQT2-positive case with potential MPA-triggered TdP
(A) The location of the patient's 1 base pair deletion on an intron/exon schematic of *KCNH2*. **(B)** The location of patient's R1005fs+50X frame-shift mutation in the protein topology of the hERG/Kv11.1 potassium channel.

Figure 2. Electrophysiological phenotype of the R1005fs+50X-KCNH2-positive case with potential MPA-triggered TdP

(A) ICD recording of the patient's first postpartum cardiac event displaying the patient in TdP before the delivery of an appropriate ICD shock that reportedly occurred when the patient awoke from a nightmare. (B) ICD recording of the patient's second postpartum cardiac event displaying the patient's TdP and the ICD charging before the patient spontaneously converted to sinus rhythm documented during a syncopal episode.

Table 1

Differential effects of MPA and endogenous progesterone

<u>Effects/Actions</u>	<u>MPA</u>	<u>Progesterone</u>
Overall Actions		
Endometrial anti-proliferative effect	Yes	Yes
Coronary artery reactivity	Increased	Decreased
Vasoconstriction duration and magnitude	Increased	Decreased
Cardiac Repolarization (QTc)	Unknown	Decreased
Effect on Steroid Receptors		
Progesterone receptor	Agonist	Agonist
Androgen receptor	Agonist	Antagonist
Mineralcorticoid receptor	Agonist	Antagonist
Glucocorticoid receptor	Agonist	Antagonist
Intracellular Effects		
Synthesis of endothelial nitric oxide	No effect	Increased
Calcium signaling in vascular muscle cells	Increased	Decreased
Thromboxane receptor expression	Increased	Decreased

Adapted from Hermesmeyer *et al.*, *Nat Clin Pract Cardiovasc Med* Jul 2008;5:387–395.