The Effects of Progestin-Only Hormone Treatment on QT Interval in the Adolescent Female

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Abstract:

We describe the effect of exogenous progestin on the corrected QT interval (QTc) in adolescent females. In post-menarcheal females, <18 years old, we compared QTc in milliseconds (ms) on ECG evaluations in those taking exogenous progestin vs those who are not. There were 40 controls and 21 treated participants. The age range was 10 – 17 years. There were no differences between the groups with regard to race, height, weight, BMI, or blood pressure. In the controls, the mean QTc was 403 +/-19 milliseconds (ms) vs. 397 +/-15 ms in those treated (p=0.22). Those on progestin therapy had a shorter QTc by the same magnitude difference (six ms) as the hormonal naïve group in the adult literature. We report no adverse effects of progestin associated with QTc prolongation and a trend suggesting a decreased QTc in a population of post menarcheal-adolescent females.

Key Words: Progestin, ECG, QTc, Adolescent
Introduction

The corrected QT interval (QTc), an electrocardiogram (ECG) measurement approximating the cardiac ventricular action potential duration, is a time-period important in maintaining the normal heart rhythm. It has been established that the QTc varies throughout development and differs by gender in pre-adolescent children, post-adolescent females, and post-adolescent men\(^1\). Moreover, the QTc varies temporally in premenopausal adult women throughout their menstrual cycle\(^2\). Specifically, during the follicular phase of dominant estradiol, the QTc interval lengthens and during the luteal phase of dominant progesterone, the QTc shortens. It has further been shown that at times of increased serum synthetic progestin, the QTc shortens\(^3\). More recently, metabolic pathway by which progesterone attenuates drug-induced prolongation has been described\(^4\).

The baseline QTc measurement is of particular importance for those taking medication that is known to prolong the QTc and those individuals with genetic variants that predispose to prolongation of the QTc, so-called Congenital Long QT syndrome (LQTS). Such individuals have an increased risk for ventricular arrhythmias and sudden cardiac arrest\(^5\). While there are many types of LQTS, types 1-3 account for 75%\(^6\). It has additionally been shown that at times of increased progesterone to estrogen ratio in patients with LQTS, such as pregnancy, there are fewer cardiac events when compared to baseline, before or after pregnancy\(^7\). Further, animal studies show that estradiol increases the likelihood of sudden cardiac death and progesterone is protective in Long QT type 2 rabbits\(^8\). In contrast, a retrospective study involving patients known to have a prolonged QT syndrome, showed no difference in cardiac events between those who used oral contraceptives and those who did not\(^9\). Interestingly, the effect of progestin-only treatment on QTc interval was not specifically addressed\(^10\).
The importance of these sex hormones relative to QTc is reflected in the growing body of literature in adult, non-menopausal women regarding the role of different types of exogenous hormone treatments to attenuate this measurement (in both drug induced QT prolongation and LQTS). The QTc between premenarcheal females and males are similar (4–6 ms difference) with a mild increase (5–10 ms difference) between post-menarcheal female and populations. To our knowledge, none of the prevailing literature on the topic addresses the QT changes in post-menarcheal adolescent females.

Agents with potential unintended cardiac protection have been somewhat repurposed as cardiac medicines (e.g. aspirin). In contrast, there is no shortage of medications with adverse cardiovascular effects. More specifically, many medications carry an increased risk for cardiac arrhythmia due to a prolongation of the QTc interval. To this point, assessing QTc prolongation is a defining test in the pharmaceutical industry for novel drug safety, essentially measuring how a new drug interacts (or does not interact) with hERG (human Ether-a-go-go-Related Gene, KCNH2) that codes for the alpha sub-unit of a potassium ion channel conferring prolongation of the QTc.

The QTc has been shown to decrease, in direct response to increased progesterone levels in adult premenopausal women. The authors suggest that exogenous progestin treatment may be superior to combined contraceptive treatment in women at increased risk for QTc prolongation. Moreover, there may be a possible role of exogenous progestin as a primary medication for women at increased risk for sudden cardiac arrest (such as those with congenital LQTS) with the possible benefit of menstrual suppression.

At present, the effect on the QTc of synthetic progestin on post-menarcheal adolescent females remains unclear. The specific aim of this study is to determine if there is an effect on the QT interval in the post-menarcheal adolescent female population taking progestin-only hormone treatment for any non-cardiac reason. More, importantly, is any such effect, clinically important such that future study for
therapeutic use can be investigated? We also will compare any such effect to those seen in adult females.

Methods

Study Design and Setting

We completed a prospective, observational analysis of ECG evaluations in progestin naïve, progestin treated, and those initiating treatment post-menarcheal females, <18 years old, using no medications with known ECG effects at urban adolescent medicine clinics. Treatment initiation was at the discretion of the provider and patient for reasons independent of this study. While a randomized control trial would most directly answer the question, given the important requirements needed to complete such trials in pediatric patients, we sought to generate initial data using a case-control methodology.

Initially three groups were designated: 1. Exogenous progestin naïve. 2. Currently taking exogenous progestin treatment. 3. Pre- and post- initiation of exogenous progestin treatment. Adolescent females with no recent exposure to exogenous progestins were eligible for the control group (Group 1). Those receiving the following continuous progestin treatments including depomedroxyprogesterone acetate (Depo-provera®) 150mg (intramuscular) or 104 mg (subcutaneous); norethindrone (Aygestin®), given in a minimal daily dose of 2.5 mg or greater; and subcutaneous progesterone implants, etonogestrel (Nexplanon®) would be considered eligible as a treatment group participant (Group 2). Those with plans to initiate exogenous progestin treatment would be enrolled as a self-control (Group 3). There was insufficient enrollment in Group 3 for meaningful analysis.

Study Population
Adolescent females were approached for enrollment after their scheduled clinical visit and after the research assistant verified that menarche had been achieved as well as their current medication list with their provider. For those adolescents who agreed to participate, informed consent was obtained from the guardian and assent from the adolescent. All participants received a five-dollar gift card as compensation for their time. The University’s Institutional Review Board had approved this study prior to its implementation. Data was gathered between November 1, 2017 and December 1, 2019.

Outcomes

Each participant recruited had an ECG administered and completed a short demographic questionnaire. Each ECG was interpreted by two board-certified pediatric cardiologists with expertise in electrophysiology on a 1-2-week basis. Any abnormal results present were communicated directly back to the consenting provider who, in-turn contacted the participant directly. Each ECG was then numerically coded for de-identification and stored electronically. ECG’s were read and data collected. Interpretations were performed twice with intra- and inter-interpreter variability assessed (each ECG assessed four times total).

Statistical Analysis

Demographic and ECG data were analyzed with descriptive statistics to assess for individual and cohort changes in comparison to the reference cohort as well as the treatment cohort including baseline and post treatment data. T-test and \( \chi^2 \) were conducted to detect significant difference in EKG intervals between the two groups. IBM SPSS Statistics version 26.0 (IBM Corporation Armonk, NY) was used for analysis.

Results
Demographic Data

The three cohorts are described in Table 1. There were 40 controls (no current use of hormonal contraception) and 21 participants currently using a progestin therapy with six individuals completing baseline and post-initiation (of progestin) ECGs (13 individuals were enrolled though seven failed to follow-up with a repeat ECG). The group 3 data is included for completeness though enrollment was insufficient to add meaningful data for analysis. The age range was 10–17 years with 83.7% of participants between 13–17 years. The mean age for Group One (no exposure) was 14.3 +/- 1.7 years vs. 15.5 +/- 1.8 years for the treated group, Group Two (p=0.01). There was no difference between the groups with regard to race, height, weight, BMI, or blood pressure.

ECG Data and QTc Measurements

In the controls, the mean QTc was 403 +/- 19 ms vs. 397 +/- 15 ms in those treated (p=0.22). Only six participants completed enrollment for Group Three, where the mean QTc was unchanged pre- and post-initiation of hormonal progestin (410 +/- 13 ms vs. 411 +/- 13 ms, respectively; p = 0.76).

There was no significant inter-reader variability. The mean QTc for Group One/Reader One was 405 ms and Group One/Reader Two was 402 ms for a population difference of three ms (p=0.51). The mean QTc for Group Two/Reader One was 399 ms vs. Group Two/Reader Two of 396 ms; again, for a population difference of three ms (p=0.55). There were two abnormal ECG with criteria for left ventricular hypertrophy. Follow-up evaluation with echocardiography showed normal cardiac anatomy and LV systolic function in both.

Discussion

The primary finding of this study is that our data shows no adverse effects to the QTc with the use of progestin in post menarcheal adolescent females.
Progestin only contraception has gained increased use in long acting forms\textsuperscript{14}. Aside from its effect on the QTc, there is evidence showing no significant increase in cardio-metabolic parameters\textsuperscript{15}. Among post-menarcheal adolescents, some forms of progestin-only contraception have also shown to be effective and are widely used\textsuperscript{16}. For this patient population at risk for sudden cardiac arrest secondary to prolonged QTc, our data suggest no adverse effects in using progestin-only medication and further data is still needed to demonstrate its use as an adjunctive treatment to the standard beta-adrenergic blocker therapy.

Our study sought to determine the effects of progestin on the adolescent population as well as to see if they were similar to those found in adult premenopausal women, with the threshold of clinical significance being a decrease of at least 10 ms (though in reality >20ms would likely be required for true therapeutic benefit). Our results show that there may be a modest decrease in QTc in the setting of progestin treatment and that decrease is similarly small as noted in the adult population. The importance of the six ms difference, however, must not be overstated in the setting of questionable clinical significance as well as limited statistical significance.

A prior study evaluating ECG data in children and adolescents demonstrated that the median QTc in post-pubertal children as 413 ms with a standard deviation of 20.7 ms, or 5\%\textsuperscript{17}. In designing the study, we used a calculated sample size of 65 which would yield a p-value of 0.05 with 80\% power given a mean difference of 2.5\% (10ms). If the QTc difference was 20 ms, the sample need only be 18 patients. We hypothesized that a difference of at least 10ms must be present as any smaller difference would encroach on the age-based differences of 4 – 10 ms, the limits of measurement, and cease to be clinically relevant. Whether a measurable difference of six ms is enough to decrease the likelihood of a sudden cardiac arrest remains suspect. While the null hypothesis is only disproved for a shortened QTc to a p-value of 0.22, at a p-value of 0.05, it is accepted with no evidence of prolongation. Although
there may not be a clinically meaningful decrease in QTc, neither is there an increase, such that progestins may be consumed by the adolescent population without a noted risk of QTc prolongation.

Our findings are buoyed by their similarity to those found in the adult studies, which had the benefit of paired design analysis that was not available given our limited enrollment in the third cohort. Ultimately, the question remains as to whether there is a clinical benefit associated with a decrease in QTc of the magnitude six ms. Natural history data may speculate that a larger difference is needed\textsuperscript{18}. Given the presence of estrogen in hormonal contraception used by this population, an additional provocative comparison exists between combined estrogen/progestin treatment vs progestin only treatment. A reasonable hypothesis remains suggesting a larger and therefore more clinically important difference between these groups.

Our study is limited in the following manners. First, though the initial study design intended to follow patient longitudinally, pre- and post- progestin exposure, limited anticipated recruitment prevented this, leaving use with a cross-sectional study design. Also, the lack of randomization leaves the possibility of other differences between groups. Second, serum progestin levels were not obtained as a verification of treatment receipt (though not an issue for intramuscular or subcutaneous formulations) or to assess potential differences in metabolism, and therapeutic levels of progestin, which could question an association. Additionally, we did not aim to evaluate differences between progestins and were therefore not powered to do so. Third, despite focusing on the cross-sectional study design, there were a number of obstacles limiting enrollment from our urban clinics including the appropriate exclusion of participants taking medications known to impact the QTc (including SSRI and many psychiatric medications) and patients presenting to the office independent of a legal guardian to sign consent. This ultimately led to a lack of power due to the difficulty in recruitment. Fourth, the study was designed to determine difference in QTc and not the more important outcome of the potential clinical benefit of decreasing morbidity, i.e. the risk of ventricular tachycardia or fibrillation.
In conclusion, we report no adverse effects of progestin associated with QTc prolongation and a trend suggesting a decreased QTc in a population of post menarcheal-adolescent females. Further study may identify progestin as a safe medication for adolescent females with QTc prolongation.

Author contributions

Adam C. Kean, MD, MPH – Concept, data interpretation, drafting article, critical revision, and approval.

Anne Farrell, MD - Data interpretation, literature review, critical revision, and approval.

Mark Ayers, MD - Data interpretation, critical revision, and approval.

Kelly Kean, PhD, FNP-BC – Data analysis/interpretation, critical revision, and approval.

Patricia Brooks - Data interpretation, critical revision, and approval.

Marcia Shew, MD, MPH – Concept, data interpretation, drafting article, critical revision, and approval.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References:


Table 1. Patient Cohort Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (no BC) N=40</th>
<th>Cohort 2 (progestin) N=21</th>
<th>Cohort 3 (starting progestin) N=6</th>
<th>P-value (Cohort 1 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr): mean, range (SD)</td>
<td>14.3, 11 - 17 (1.7)</td>
<td>15.5, 10 - 17 (1.8)</td>
<td>15.3, 11 - 17 (2.3)</td>
<td>0.01</td>
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<td>Age at menarche (yr)</td>
<td>11.6, 7 - 15 (1.6)</td>
<td>12.2, 9 - 14 (1.5)</td>
<td>11.8, 10 - 13 (1.2)</td>
<td>0.3</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>Hispanic/Latina</td>
<td>4 (9.1%)</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Not Hispanic/Latina</td>
<td>40 (90.9%)</td>
<td>22 (95.7%)</td>
<td>6 (100%)</td>
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</tr>
<tr>
<td>*Race</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White</td>
<td>33 (75%)</td>
<td>17 (73.9%)</td>
<td>2 (33.3%)</td>
<td>0.6</td>
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<td>Black</td>
<td>11 (25%)</td>
<td>7 (30.4%)</td>
<td>4 (66.7%)</td>
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<td>Asian</td>
<td>2 (4.5%)</td>
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<td>1 (16.7%)</td>
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<tr>
<td>NA/AN</td>
<td>1 (2.3%)</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>NH/PI</td>
<td>1 (2.3%)</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Declined</td>
<td>0</td>
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<td>0</td>
<td>N/a</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4.5%)</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
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<tr>
<td>Height (cm):</td>
<td>162.6 (7.5)</td>
<td>164.7 (8.0)</td>
<td>160 (5.7)</td>
<td>0.3</td>
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<tr>
<td>Weight (Kg):</td>
<td>73.1 (22.7)</td>
<td>70.5 (14.1)</td>
<td>57.5 (17.6)</td>
<td>0.7</td>
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<tr>
<td>BMI (Kg/m^2):</td>
<td>27.5 (7.6)</td>
<td>25.9 (4.6)</td>
<td>22.3 (6.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>Systolic (mmHg):</td>
<td>117.2 (11.9)</td>
<td>116.7 (13.1)</td>
<td>111.2 (9.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Diastolic (mmHg):</td>
<td>68.1 (9.7)</td>
<td>71.2 (9.6)</td>
<td>70 (11.7)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Abbreviations used:
NA=Native American
AN= Alaskan Native
NH= Native Hawaiian
PI= Pacific Islander
SD= Standard Deviation
*Participants were able to select more than one race explaining totals greater than 100%