Complex influence of gonadotropins and sex steroid hormones on QT interval duration

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Context: QT interval duration is longer in women than in men. Sex steroid hormones have inconsistently been suggested to explain this difference. Implication of gonadotropins has never been studied.

Objective: We here report the combined influence of sex steroid hormones and gonadotropins on QT interval duration in healthy subjects and patients with congenital adrenal hyperplasia (CAH) as a model of testosterone and progesterone overexpression.

Design: Patients. Eighty four CAH patients (58 women) and 84 healthy subjects matched-paired for sex and age were prospectively included. Circulating concentrations of 17-OH-progesterone, progesterone, testosterone, estradiol, FSH and LH, were measured concomitantly to recording of a digitized electrocardiogram.

Results: QTcFridericia(QTcF) was shorter in women with CAH than in control women (404$\pm$2 msec vs. 413$\pm$2.1 msec, p$\leq$0.001). 17-OH-progesterone, progesterone, progesterone/estradiol ratio and total testosterone were higher in women with CAH than in women controls (p$<$0.05) whereas FSH was lower (p$\leq$0.05). According to multivariable analysis in all women, progesterone/estradiol ratio (β=-0.33) and FSH levels (β=0.34) were related to QTcF (r=0.5, p$<$0.0001) with no influence of CAH or healthy status. QTcF was not different between CAH (404.7$\pm$3.7 msec) or healthy men (396$\pm$2.8 msec). For men, QTcF (r=0.48, p$<$0.01) was negatively related to free testosterone (β=-0.29) and positively to FSH levels (β=0.34).

Conclusion: Cardiac repolarization is influenced by complex interactions between sex steroid hormones and gonadotropins depending on gender. Our results indicate that progesterone/estradiol ratio, in women, testosterone, in men, and FSH, in both genders, are major determinants of ventricular repolarization with opposite effects on QTc interval.

Key Points:

1/ QTc duration, in contrast with what is generally considered, is not determined by only one sex steroid hormone level such as testosterone, progesterone or estradiol but is influenced by complex interactions between sex steroid hormones and gonadotropins, particularly FSH. The influence of

Abbreviations:

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FSH on ventricular repolarization is a new finding. Furthermore, there is a gender specificity in steroid hormones influence on ventricular repolarization.

2/ In women, FSH is positively correlated while progesterone/estradiol ratio is negatively correlated to QTc interval duration. This finding underscores the potential for progesterone to be used in women as an anti-arrhythmic or prophylactic treatment of drug-induced or spontaneous "torsades de pointes" particularly in patients with congenital long QT syndromes.

3/ In men, FSH is positively correlated while free testosterone is negatively correlated to QTc interval duration. As opposed to women, progesterone/estradiol is not associated to QTc duration in men. This finding highlights how peripheral hypogonadism favors QTc prolongation in men and underscores the importance of correcting this risk factor by testosterone administration in men with susceptibility to QTc prolongation and "torsades de pointes".

4/ Women affected by congenital adrenal hyperplasia have shorter QTcF intervals than healthy women and this appears to be related to higher progesterone and lower FSH levels. QTcF intervals tended to be higher in CAH men as compared to healthy men due to lower free testosterone levels.

Background:

In the healthy population, from puberty to menopause, women have longer QTc interval duration (QTc) than men (1, 2). This is associated with a higher risk of torsades de pointes or drug-induced arrhythmia (3–5). The role of sex steroid hormones on cardiac repolarization, mainly estradiol, progesterone and testosterone, has been suggested for many years but is still a matter of debate. In men, despite discordant findings (6–14), testosterone is currently considered to shorten QTc. Studies evaluating the prolonging effect of estradiol on QT duration in women were highly controversial and are still a matter of debate (12, 14–23). The negative correlation between testosterone level and QTc in women was not found in studies involving healthy or post menopausal women but was only confirmed in women with testosterone overexpression secondary to polycystic ovary syndrome (12, 14, 21, 22, 24). Data suggesting an influence of progesterone and progesterone/estradiol ratio on QTc shortening in women were issued from studies in healthy women evaluated at different times of their menstrual cycle (12, 21, 25, 26) or from studies in postmenopausal women under hormone replacement therapy (15, 17, 18). Except for Δ4-androstenedione (16), the potential influence of other sex steroid hormones on QT interval duration, or even of the gonadotropins regulating their production, has never been studied. To further investigate these issues, we studied for the first time the combined influence of several sex steroid hormones and gonadotropins on QTc interval duration in healthy subjects and in patients with congenital adrenal hyperplasia (CAH) due to 21α-hydroxylase deficiency. 21α-hydroxylase deficiency leads to decreased cortisol and aldosterone production (*Supplemental Figure 1)*. Cortisol deficiency results in the ACTH-induced accumulation of substrate precursors such as 17OHP and progesterone, and to increased secretion of adrenal androgens, especially androstenedione. Symptoms associated to this condition are related to salt loss in both gender and virilization in women.

The purpose of this work was first to determine if QTc is shorter in premenopausal CAH women with progesterone overexpression than in healthy women volunteers. Secondly, our aim was to investigate the combined influence of gonadotropins and sex steroid hormones on duration of ventricular repolarization in both genders.

Materials and Methods

Study design

Our work is ancillary to CARDIOHCS [NCT01807364], a multicenter prospective observational case-control study comparing early cardiovascular damages in adult men and women with congenital adrenal hyperplasia (CAH) due to 21α-hydroxylase deficiency and healthy controls. All patients gave written informed consent to participate and the study was approved by each hospital ethics committee.

Study population

Eighty four subjects (58 women and 26 men) with CAH and 84 controls matched-paired for gender, age (±5 years) and smoking status (nonsmoking, past smoking, active smoking) were prospectively included in CARDIOHCS study between May 2011 and August 2015. CAH adult subjects included were diagnosed with CAH during childhood, proven by genetic testing confirming a 21α-hydroxylase deficiency. Exclusion criteria for CAH and healthy subjects were: known history of cardiovascular disease and pregnancy. Estradiol and/or progesterone contraception in the previous month was an exclusion criteria in healthy subjects and was encouraged in CAH patients. CAH subjects were treated with hydrocortisone or dexamethasone and some of them also received fludrocortisone. Nineteen subjects were excluded from our ancillary study because they were either taking hormonal drugs that could interfere with QT in-

terval duration (n = 14) or were postmenopausal (n = 5) (*Supplemental Figure 2*).

Study procedures and laboratory analysis

CAH subjects were referred in CARDIOHCS study by three endocrinology unit (Pitié-Salpêtrière hospital, Paris, France; Saint-Antoine Hospital, Paris, France; Bicêtre Hospital, Le Kremlin Bicêtre, France). CAH subjects and healthy subjects were explored at the Centre d'Investigation Clinique – Paris Est (CIC-1421, Pitié-Salpétrière hospital, Paris).

Participants had a clinical examination including past medical history and a 12-lead digitized electrocardiogram (ECG) was recorded for 3 to 5 minutes after at least 10 minutes of rest in the supine position. Blood samples for the determination of serum concentrations of 17-OH progesterone, progesterone, testosterone, estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH) were collected in a dry tube and further assayed at the immunology laboratory of Pitié-Salpêtrière. Estradiol, progesterone, FSH and LH plasma concentrations were assayed by chemiluminescence (Cobas E411 Roche), testosterone by chemiluminescence (Modular E 170 Roche), and 17-OH progesterone by radioimmunometry (KIP1409 Diasource).

Electrocardiography acquisition and analysis

Electrocardiograms (ECG) were acquired with CardioPlug (CARDIONICS S.A., Brussels, Belgium), a digital recording device designed as recommended by the AHA/ACCF/HRS 2007 (27). Subjects remained quietly in the supine position, eyes closed for a few minutes. QT interval was measured and corrected for heart rate by Fridericia's formula (QTcF = QT/RR 0.33) (28). Fridericia's methods was chosen, in accordance to ICH Guidelines issued from FDA (2005), because this latter correction is more accurate than Bazett's correction for patients with elevated or below 60 beat per minute heart rates (29–30). QTc normal values were defined as a function of age and gender (30). For each subject, QT interval duration was assessed with a semiautomatic approach based on the representative beats generated from 30 consecutive seconds of good quality and extracted from the continuous ECG after at least 10 minutes of rest (CalECG®, AMPS, LLC, New-York) (31). RR interval used for QT correction was the average RR computed from individual RR intervals from sinus rhythm beats in the 30-second long strip. A global QT interval based on the 12-lead vector magnitude was automatically computed and then individually reviewed by a single blinded expert in QT measurement (JES) on the overlapped (superimposed) display of the representative waveforms (*Supplemental Figure 3*). This version of CalECG® used was not suitable to directly measure QT dispersion but the method of square root of all squared leads used to compute global QT interval tended, by default, to annihilate any difference between the minimum vs the maximum (ie, the "dispersion") in QT duration.

Statistical analyses and power of the study

Data are described as mean ± standard deviations of the mean or median and interquartile range, as appropriate. Comparison of quantitative variables were analyzed by Student's *t* test, Mann-Whitney tests, ANOVA, Tukey's test or Kruskal-Wallis tests, as appropriate. Comparison of qualitative variables were analyzed by Chi-2 test. The correlation between linear variables was assessed by calculating Pearson's or Spearman's coefficient (r), as appropriate. A 95% confidence interval (CI) for the correlation coefficient was calculated by Fisher's method (Prism 6, GraphPad software®, San Diego, USA). Multivariable analysis was performed by ANCOVA (Xlstat software, Addinsoft®), Statistical significance was accepted for $P < .05$.

The study had a 95% power to detect a QTcF difference of at least 10 milliseconds between healthy women and the other subjects (by ANOVA, alpha risk 0.05; standard deviation of QTc in each subgroup = 5 milliseconds; expected QTcF mean = 410 milliseconds in healthy women and 400 milliseconds in men and CAH women; considering n = 25 in each subgroup).

In women (n: 99), the study had a power of 80% to detect a significant correlation (with $r > 0.28$, alpha risk 0.05, Student approximation) between each hormone and QTcF duration.

In men (n: 50), the study had a power of 80% to detect a significant correlation (with $r > 0.38$, alpha risk 0.05, student approximation) between each hormones and QTcF duration.

Results

Clinical and electrocardiographic (ECG) evaluations

The clinical and ECG characteristics of the patients included in this study are shown in Table 1. In total, one hundred forty nine adult subjects of whom 99 were premenopausal women (44 CAH and 55 healthy) and 50 men (24 CAH and 26 Healthy) were available for final analysis (*Supplemental Figure 2*). PR interval did not differ among groups (Table 1), QRS were longer ($P < .001$) in healthy men (106.5 ± 1.4 milliseconds) compared to CAH females (99.3 ± 1.1 millisecond) or healthy female (100.3 ± 1.1 millisecond). QTcF was well corrected for heart rate (r = 0.04 for RR and QTcF, $P = .6$). CAH women had shorter QTcF compared to women controls (404 ± 2 milliseconds vs. 413 ± 2.1 millisecond, $P \leq .001$) but QTcF in CAH women was not statistically different from that in men with CAH (404.7 ± 3.7 milliseconds) or healthy men (396 ± 2.8 milliseconds) (Figure 1). QTcF was not significantly different between healthy and CAH men.

Biological evaluations

The results of biological evaluations in women are shown in Table 2. Compared to healthy women, women with CAH had higher levels of 17-OH progesterone (median and interquartile range: 15.7 ng/mL [4.7–54.2] vs. 1.2 ng/mL [0.7–2.1], $P < .0001$), progesterone (2.5 ng/mL [0.8–7.5] vs. 0.9 ng/mL [0.6–4.6], $P = .01$), progesterone/estradiol ratio (39 [8.6–84.3] vs. 19.4 [5.5–37], $P = .02$) and total testosterone (0.55 ng/mL [0.18–0.94] vs. 0.32 ng/mL [0.24–0.41], $P = .04$). In contrast, FSH was lower in women with CAH than in women controls (5.1 UI/L [3.2–6.5] vs. 5.8 UI/L [4–8.1], $P = .05$).

The results of biological evaluations in men are shown in Table 2. Compared to healthy men, men with CAH had higher levels of 17-OH progesterone (16 ng/mL [5.5–42] vs. 2 ng/mL [1.6–2.4], $P < .0001$) and progesterone levels

Table 1. Clinical and electrographic characteristics of the patients included in the study

	CAH males	Healthy males	CAH females	Healthy females	p
Number of subjects	24	26	44	55	
Age (years)	29.1 ± 1.7	28.6 ± 1.7	30.2 ± 1.3	29.8 ± 1	ns
Height (cm)	170.1 ± 1.3†‡	180.3 ± 1.3*†§	157.9 ± 1.1*‡§	166.7 ± 0.9†‡	<0.0001
Weight (kg)	74.9 ± 2.8*†	76.3 ± 2.2*†§	63.5 ± 1.8‡	66.1 ± 1.3‡§	<0.0001
Sedentary (%)	9 (37%)	7 (27%)	16 (37%)	13 (24%)	ns
Cardiovascular disease in family (%)	0 (0%)	1 (4%)	1 (2%)	5 (9%)	ns
SBP (mmHg)	117.3 ± 2†	118.9 ± 1.7*†	107.5 ± 1.8‡§	108.1 ± 1.4‡	<0.0001
DBP (mmHg)	69.1 ± 2	69.6 ± 1.43	67.6 ± 1.8	68.3 ± 1.1	ns
PR (msec)	155.3 ± 5.3	158.5 ± 5.1	149.1 ± 2.7	154.3 ± 3.7	ns
QRS (msec)	106.4 ± 2.5	106.5 ± 1.4*†	99.3 ± 1.1‡	100.3 ± 1.1‡	<0.001
QT (msec)	397.6 ± 5	393.5 ± 4.3	385.2 ± 4*	402 ± 3.7†	<0.05
RR (msec)	955.3 ± 30.7	983.6 ± 21.5†	872.4 ± 20.9‡	917.2 ± 20.7	<0.01
HR (bpm)	64.3 ± 2.1	61.7 ± 1.3†	70.4 ± 1.6‡	67.1 ± 1.4	<0.01
QTcF (msec)	406 ± 4.8	396.5 ± 2.8*	403.4 ± 2.1*	412.8 ± 2.1†‡	<0.001

Abbreviations: bpm: beats per minute; CAH: Congenital adrenal hyperplasia; cm: centimeter; kg: kilograms; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; msec: millisecond

*Statistics: ANOVA test for quantitative variables and Chi2 for qualitative variables. Not significant (ns) if P > 0.05. Quantitative variables are represented by the mean +/- the standard deviation of the means. * Significant compared to healthy females; † Significant compared to CAH females; ‡ Significant compared to healthy males; § Significant compared to CAH males.*

which were not significantly different (respectively 1.3 [0.4–4.6] vs 0.8 [0.6–1] ng/mL). In contrast, bioavailable (2.1 ng/mL [1.2–2.9] vs. 2.9 ng/mL [2.5–3.4], $P < .01$) and free testosterone (93.5 pg/mL [51–124] vs. 122 pg/mL [109–143], $P < .01$) were lower in men with CAH than in healthy men. Of note, the only patient in whom QTcF was > 450msec with T-waves notching (QTcF 454msec, Figure 1) was a man with CAH. He had normal serum electrolytes (K+=4.3 mmol/l, Mg2+=0.77 mmol/l) but had peripheral hypogonadism with the lowest free serum testosterone (0.7 ng/ml, [1.3–4.1]) and highest FSH level (11.3 ui/l, [1.5–12.4]) among all men included in this study.

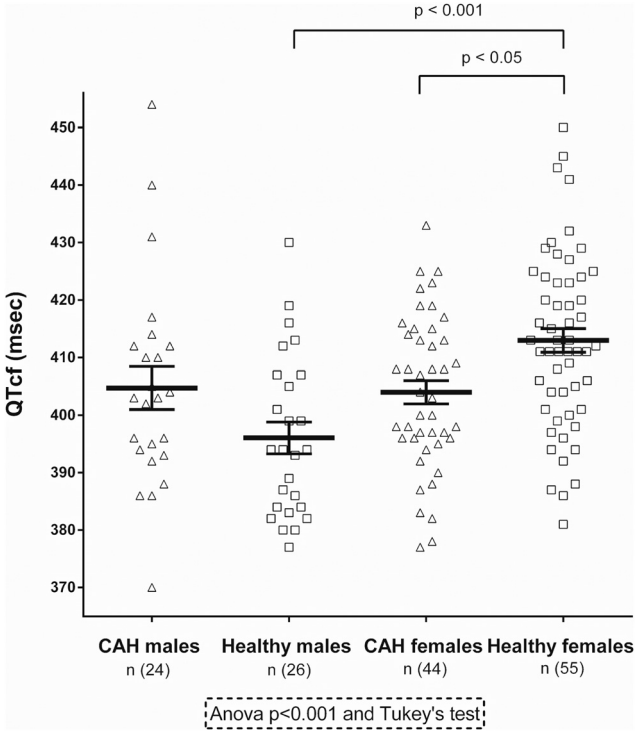

Figure 1. QTcF interval duration in healthy men, healthy women, and subjects with congenital adrenal hyperplasia (CAH) *Statistics: p values are given by one-way ANOVA with post hoc Tukey's test. The black line represent the mean and the error bars in black represent the standard error of the mean.*

Serum potassium and magnesium levels ranged within normal values respectively from 3.4–4.9 mmol/l and 0.74–0.87 mmol/l in almost all CAH patients. Kalemia and serum magnesium were unrelated to QTcF duration (*Supplemental Figure 4*). Serum potassium and magnesium levels were not measured in healthy volunteers.

Correlation between QTcF duration and sex hormones in women

According to univariable analysis in all women (Table 3, Figure 2, n = 99), QTcF duration was negatively correlated with 17-OH progesterone (r=-0.28, $P < .01$), progesterone (r=-0.29, $P < .01$), progesterone/estradiol ratio (r= –0.38, $P < .001$), total testosterone (r=-0.2, $P < .01$) and positively correlated with FSH (r = 0.38, $P < .001$) and LH (r = 0.3, $P < .01$). There was no significant correlation between QTcF and estradiol in women.

Multivariable analysis (ANCOVA) was performed in all women to overcome significant autocorrelations between sex hormones and gonadotropins (Supplemental Table 1). This multivariable analysis showed that progesterone/estradiol ratio (β=-0.33, $P < .001$) and FSH levels (β=0.35, $P < .001$) were independently related to QTcF

Table 2. Biological evaluations in females and males

	FEMALES		
	CAH females n: 44	**Healthy females n: 55**	**p**
17-OH progesterone (ng/mL)	15.7 [4.7–54.2]	1.2 [0.7–2.1]	**< 0.0001**
Progesterone (ng/mL)	2.5 [0.8–7.5]	0.9 [0.6–4.6]	**0.01**
Bioavailable testosterone (ng/mL)	0.13 [0.04–0.3]	0.08 [0.04–0.14]	0.09
Free testosterone (pg/mL)	5.9 [1.7–14]	3.7 [1.9–6.3]	ns
Total testosterone (ng/mL)	0.55 [0.18–0.94]	0.32 [0.24–0.41]	**0.04**
Estradiol (pg/mL)	71 [44 – 171.5]	93 [46–171]	ns
FSH (UI/liter)	5 [3.2–6.5]	5.8 [4–8.1]	**0.05**
LH (UI/liter)	5.6 [3.2–8.8]	6.3 [5.1–10.6]	0.07
Progesterone/Estradiol	39 [8.6–84.3]	19.4 [5.5–37]	**0.02**
MALES			
	CAH males n: 24	**Healthy males n: 26**	**p**
17-OH progesterone (ng/mL)	16 [5.5–42]	2 [1.6–2.4]	**< 0.0001**
Progesterone (ng/mL)	1.3 [0.4–4.6]	0.8 [0.6–1]	ns
Bioavailable testosterone (ng/mL)	2.1 [1.2–2.9]	2.9 [2.5–3.4]	**<0.01**
Free testosterone (pg/mL)	93.5 [51–124]	122 [109–143]	**<0.01**
Total testosterone (ng/mL)	4.6 [3.1–6.6]	5.9 [4.9–6.6]	ns
Estradiol (pg/mL)	27.9 [19.3–32.4]	28.3 [24.7–37.3]	ns
FSH (UI/liter)	3.5 [2.3–6.5]	3.4 [2.6–5.2]	ns
LH (UI/liter)	4.5 [1.9–5.6]	4.5 [3.5–5.3]	ns
Progesterone/Estradiol	5.1 [1.5–12.4]	2.6 [1.5–3.1]	**0.03**

Abbreviations: FSH: follicle stimulating hormone; LH: luteinizing hormone; SHBG: Sex hormone-binding globulin; ACTH: Adrenocorticotropic hormone

Statistics: Mann-Whitney test for quantitative variables. Quantitative variables are represented by the median and the interquartile interval Not significant (ns) if P > 0.05. Significant results are in bold.

(r = 0.5, $P < .0001$) without influence of CAH or healthy status.

Correlation between QTcF duration and sex hormones in men

According to univariable analysis in all men (Table 3, Figure 3, n = 50), QTcF duration was negatively correlated with free testosterone (r=-0.34, $P = .01$), and positively correlated to FSH (r = 0.39, $P < .01$). There was no significant correlation between QTcF and progesterone or estradiol in men.

According to multivariable analysis (ANCOVA) in all men free testosterone (β=-0.27, $P < .05$) and FSH levels (β=0.4, $P < .01$) were independently related to QTcF (r = 0.49, p 0.001) with no influence of CAH or healthy status.

Discussion

The objective of this work was to investigate the influence of complex interactions between gonadotropins and several sex steroid hormones on the duration of ventricular repolarization in humans, depending on gender. We found that: 1/ CAH women with high progesterone and low FSH levels, have shorter QTcF intervals than healthy women; 2/ in women, FSH is positively correlated while progesterone/estradiol ratio is negatively correlated to QTcF interval duration; 3/ in men, FSH is positively while free testosterone is negatively correlated to QTcF interval duration. These findings support the hypothesis of a regulation of QT interval duration not by a single sex hormone as previously suggested, but by an integrated complex hormonal system depending on gender, gonadotropins and peripheral sex steroid hormones. Our results indicate that progesterone/estradiol ratio, in women, testosterone, in men, and FSH, in both genders, are major determinants of ventricular repolarization with opposite effects on QTc interval.

Rationale for a complex hormonal system regulating QTcF

Previous studies evaluating the role of sexual hormones on QTcF duration only evaluated the isolated role of testosterone, progesterone and estradiol and did not assess the multivariable influence of complex interactions between several sex hormones and gonadotropins. Sex steroid hormones secretions are constantly regulated by the hypothalamic-pituitary axis and, as occurs in other organs such as ovaries, testes or bone (32), the influence of sex steroid hormones on QT interval duration may be counterbalanced by the direct effects of gonadotropins. The rationale for a complex hormonal system regulating QTcF is supported by the fact that RNA of gonadotropins re-

Table 3. Correlation between QTcFridericia and sex hormone or gonadotropins in men and women

	Female (n: 99)	Male (n: 50)
17-OH progesterone (ng/mL)	**r: −0.28 [-0.08;-0.45]**	r: 0.07
	$P < 0.01$	ns
Progesterone	**r: −0.29 [-0.1; −0.46]**	r: −0.02
(ng/mL)	$P < 0.01$	ns
Estradiol	r: −0.02	r: 0.01
(pg/mL)	ns	ns
Progesterone/Estradiol	**r:-0.38 [-0.2; −0.54]**	r: −0.02
(Ratio)	$P < 0.001$	ns
Bioavailable testosterone (pg/mL)	**r:-0.25 [-0.05; −0.43]**	**r: −0.32 [-0.04; −0.55]**
	p 0.01	p 0.03
Free testosterone (ng/mL)	r: −0.2	**r: −0.34 [-0.07; −0.57]**
	ns	p 0.01
Total testosterone (ng/mL)	**r: −0.26[-0.07; −0.44]**	r: - 0.16
	$P < 0.01$	ns
FSH	**r: 0.38 [0.2; 0.54]**	**r: 0.39 [0.12; 0.6]**
(UI/liter)	$P < 0.001$	$P < 0.01$
LH	**r: 0.3 [0.1; 0.47]**	r: 0.02
(UI/liter)	$P < 0.01$	ns

Abbreviations: FSH: follicle stimulating hormone; LH: luteinizing hormone; NA: Not applicable; SHBG: Sex hormone-binding globulin

Statistics: Correlations were assessed within female and male subgroups by Spearman's or Pearson's coefficient (r) with its 95% confidence interval [;] when significant. A 95% confidence interval for the correlation coefficient was calculated by Fisher's method. Not significant (ns) if P > 0.05. Significant results are in bold.

ceptors are expressed in the myocardium (33). Our study including postpuberty healthy subjects, and CAH patients overexpressing progesterone and testosterone in women is unique, in that subjects were exposed to a wide range of sex steroid hormones and gonadotropins levels.

Influence of sex steroid hormones on QTcF in men and women

The mechanisms underlying the difference between QTc interval duration in men and women are poorly understood. Differences in gonadic steroid hormones expression cannot fully explain this difference and nongonadal, gender-specific, mechanisms involving ventricular ion channel expression or modulation have been demonstrated in nonclinical models (14, 34–35). Our results support the hypothesis that testosterone is the main steroid hormone modulating QTc in men while QTc is influenced by serum progesterone or progesterone/estradiol ratio in women. Interestingly, other studies have emphasized the influence of testosterone on QTc in men (11–14) and of progesterone (more than estradiol) in women (21). Furthermore, in nonclinical models, testosterone and progesterone have been shown to shorten ventricular action potential duration while estradiol was associated with action potential prolongation (34–39). As a consequence, CAH women expressing higher progesterone levels than healthy subjects had a shorter QTcF than control women, therefore reaching QTcF duration observed in CAH men. Of note, Annekin et al have recently reported a QTc shortening in women after clominophen administration despite an important estradiol release (40). Clomiphene, as a fertility inducer exert an antiestradiol effect on pituitary axis and might have also antiestradiol properties on heart repolarization. Thus, the negative correlation found between estradiol and QTc postclomiphene administration had to be interpreted with great caution.

Role of FSH on QTcF interval duration

To our knowledge, this is the first study assessing the potential influence of gonadotropins on QTcF duration. Our findings add new insight to the understanding of the observed differential regulation of QTc interval in healthy women compared to healthy men. They indicate that it results, at least in part, from the combined higher gonadotrophin levels in women and higher testosterone levels in men. Despite significant autocorrelations between FSH and LH, our multivariable analysis supports a major role of FSH in regulating QTc interval duration. Interestingly, Turner syndrome, a congenital condition associated with ovarian steroid hormones deficit counterbalanced by high FSH concentrations, is associated with QTcF prolongation (41). In premenopausal women, bilateral oophorectomy followed by FSH increment was associated with prolongation of T wave duration. Estradiol administration in these women decreased FSH level and corrected T wave duration (20). In hypogonadotropic hypogonadic men (low FSH level), there was no difference in QTc compared to healthy control (7). Men with peripheral hypogonadism, presenting low testosterone concentrations and high FSH concentrations, had longer QTc compared to healthy men (11). Finally, patients with polycystic ovary syndrome in whom there is QTcF shortening (22) have an increase in testosterone levels but also an increase in LH/FSH ratio with relatively low FSH levels compared to LH (11, 42).

Perspectives

The lengthening effect of FSH on QTc is a new finding that should be confirmed. Polycystic ovary syndrome patients may require recombinant FSH administration to improve their fertility (42). It would be worth evaluating if the short QTc found in this disease (22) is corrected by

FSH administration. One could also test if subjects with FSHR polymorphisms (43) leading to either hyperactivated or inactive FSH receptor have longer or shorter QTc intervals, respectively, than carriers of the wild FSHR gene.

The results of our study suggest a protective effect of

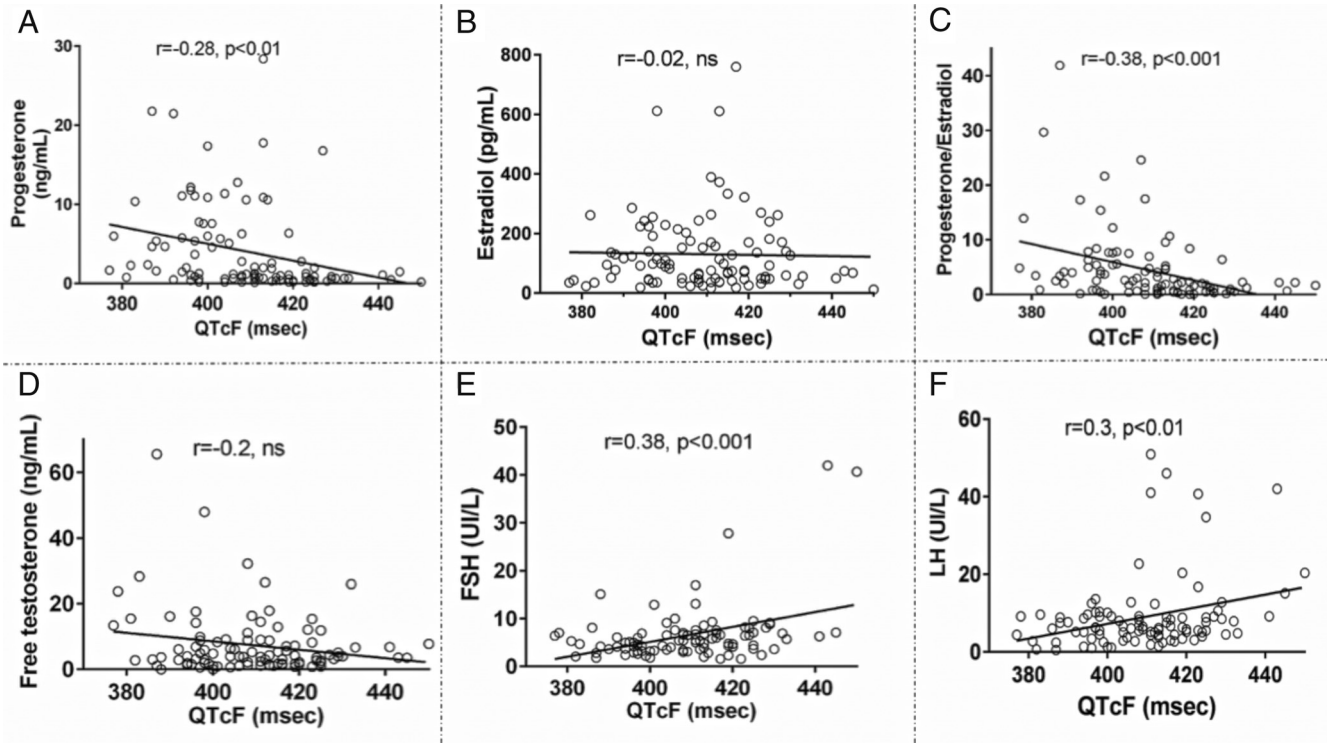

Figure 2. Correlations between levels of progesterone (A), estradiol (B), progesterone/estradiol ratio (C), free testosterone (D), FSH (E), LH (F) and QTcF in all women (n = 99).

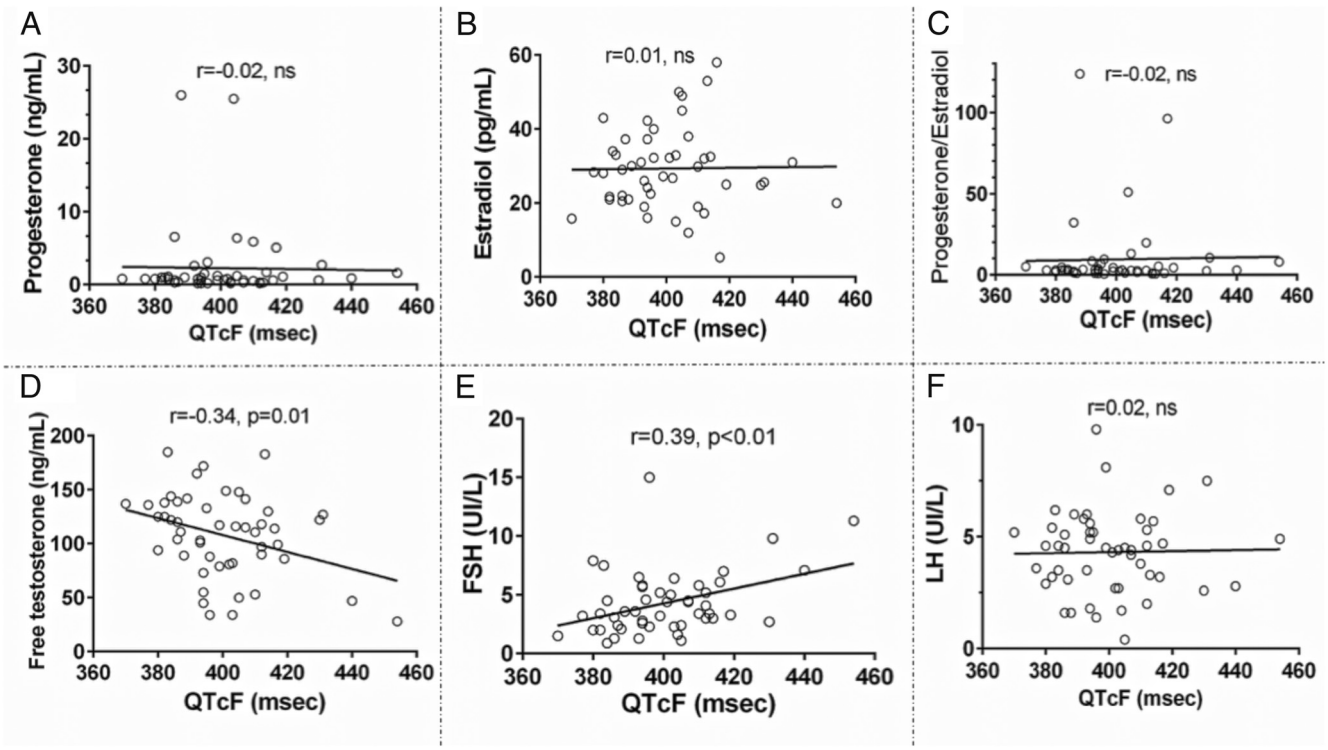

Figure 3. Correlations between levels of progesterone (A), estradiol (B), progesterone/estradiol ratio (C), free testosterone (D), FSH (E), LH (F) and QTcF in all men (n = 50).

progesterone administration on QT lengthening in women. Progesterone has already been successfully used to prevent induction of ventricular arrhythmia in a rabbit model of congenital long QT syndrome (44). Further investigations are needed to confirm if progesterone can prevent or even cure drug-induced torsades de pointes by shortening QTc duration specifically in women. New nonclinical models using human cardiomyocytes derived from induced pluri-potent stem cells of normal or long QT syndrome patients could be used for this purpose (45, 46). We believe our results may lead to new developments in the field of antiarrhythmic drugs, particularly concerning use of exogenous hormonal administration. A blinded randomized trial evaluating drug-induced QTc interval changes (21) in women taking different progestin-derived pill with different androgenic power or a placebo could be performed to evaluate if those different strategies lead to differential QTc lengthening.

Limitations

In our study, we found only moderate correlations between individual sex hormones and QTc. This issue raises the question of whether the effect of sex hormones on ion channels and cardiac repolarization is direct or indirect. Several nonclinical studies indicate that sex steroid hormones may lead to a transcriptional, post-transcriptional or post-translational effect on ion channels expression and regulation more than a direct channel on/off effect (37–40).

The analysis of QTcF interval duration in the present study relies on gender and sex hormones plasma levels. This analysis could be improved by adding other parameters known to influence QTc interval duration such as kalemia and plasma aldosterone (47) or information about genetic polymorphisms or mutations associated with QTc prolongation (48). Thus, kalemia imbalance alters QTc duration in very abnormal situation such as severe hypokalemia when fusion between T and U wave might contribute artificially to QTc prolongation (49). No subjects included in this study presented U wave and kalemia was lacking only in healthy volunteers for whom kalemia is expected to be within normal range.

Conclusion

Cardiac repolarization is influenced by complex interactions between sex steroid hormones and gonadotropins depending on gender. Our results indicate that progesterone/estradiol ratio, in women, testosterone, in men, and FSH, in both genders, are major determinants of ventricular repolarization with opposite effects on QTc interval.

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