



Editorial

As some of our readers might already know AMPS also collaborates with many non-profit research and academic world organizations. The AMPS Board of Directors decided this policy several years ago with the aim to help and support research in the cardiac safety world. Several Universities and research centers worldwide have successfully benefitted of this initiative and we expect more will do in the future. At times, these collaborations are extremely rewarding and produce most interesting results, shedding light on aspects of ECG analysis that are normally underestimated if not altogether ignored. This is for example the case with the Clinical Investigation Center from the Pitié-Salpêtrière Hospital in Paris, led by Pr. Christian Funck-Brentano, a world-wide known scientist with more than 200 publications in major journals of pharmacology and cardiology.

Would you believe that there is a direct correlation between sex hormones and the QT interval? In this issue of AMPS-QT we are proud to host a contribution directly from Prof. Funck-Brentano and Dr. Joe-Elie Salem, a young and brilliant assistant professor from the same institute, who have published extensively on the topic. Based on recently published data, they tell us how menstrual cycle and sex hormones fluctuations in women, variables which are generally ignored in through QT studies, can cause fluctuations in the QTc interval duration by as much as 15 ms, i.e. well above the threshold of regulatory concern. We are sure you will enjoy the reading!!!

A Noteworthy Contribution:

Influence of sex hormones on the QT interval

By Joe-Elie Salem, MD and Christian Funck-Brentano, MD, Hôpital La Pitié-Salpêtrière, Paris, France

In this review, we summarize the results of published studies conducted at the Clinical Investigation Center Paris-Est (Department of Pharmacology, Pitié-Salpêtrière University Hospital, Paris, France), in collaboration with three endocrinology units of Paris metropolitan area where the influences of steroid hormones on ventricular repolarization were assessed. The research was part of an ancillary multicenter prospective observational case-control study and focused on reporting the combined influence of sex steroid hormones and gonadotropins on QT interval duration in healthy subjects and patients with congenital adrenal hyperplasia (CAH), a model of testosterone and progesterone overexpression [1].

Sex steroid hormones have inconsistently been suggested to explain the well known longer QT interval in women than in men [2]. Overall, progesterone and testosterone were expected to shorten QT, as opposed to estradiol and the influence of gonadotropins was unknown. Our specific goal was first to study if QTc is shorter in child-bearing age CAH women with progesterone overexpression than in healthy women volunteers and, secondly, to investigate the combined influence of gonadotropins and sex steroid hormones on duration of ventricular repolarization in both genders.

Methods. The dataset consisted of 84 CAH patients (58 women) and 84 healthy controls matched-paired for gender and age (± 5 years). All CAH subjects, referred in the multicenter study by the endocrinology units, and healthy subjects were investigated at our institution and underwent clinical examination including past medical history and a 12-lead digitized electrocardiogram 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), sex hormone-binding globulin (SHBG) 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 radioimmunoassay (KIP1409 Diasource).

QT and QTc (Fridericia formula) intervals were assessed with a semi-automated approach based on the representative beats generated from 30 consecutive seconds of good quality (low noise) signal extracted from the continuous electrocardiogram after at least 10 minutes of rest (CalECG, AMPS, LLC, New-York). The RR interval used for QT correction was the mean of all RR intervals from the 30 consecutive seconds. The global QT interval based on the 12-lead vector magnitude was first automatically computed and subsequently individually reviewed by a single blinded expert (Figure 1).

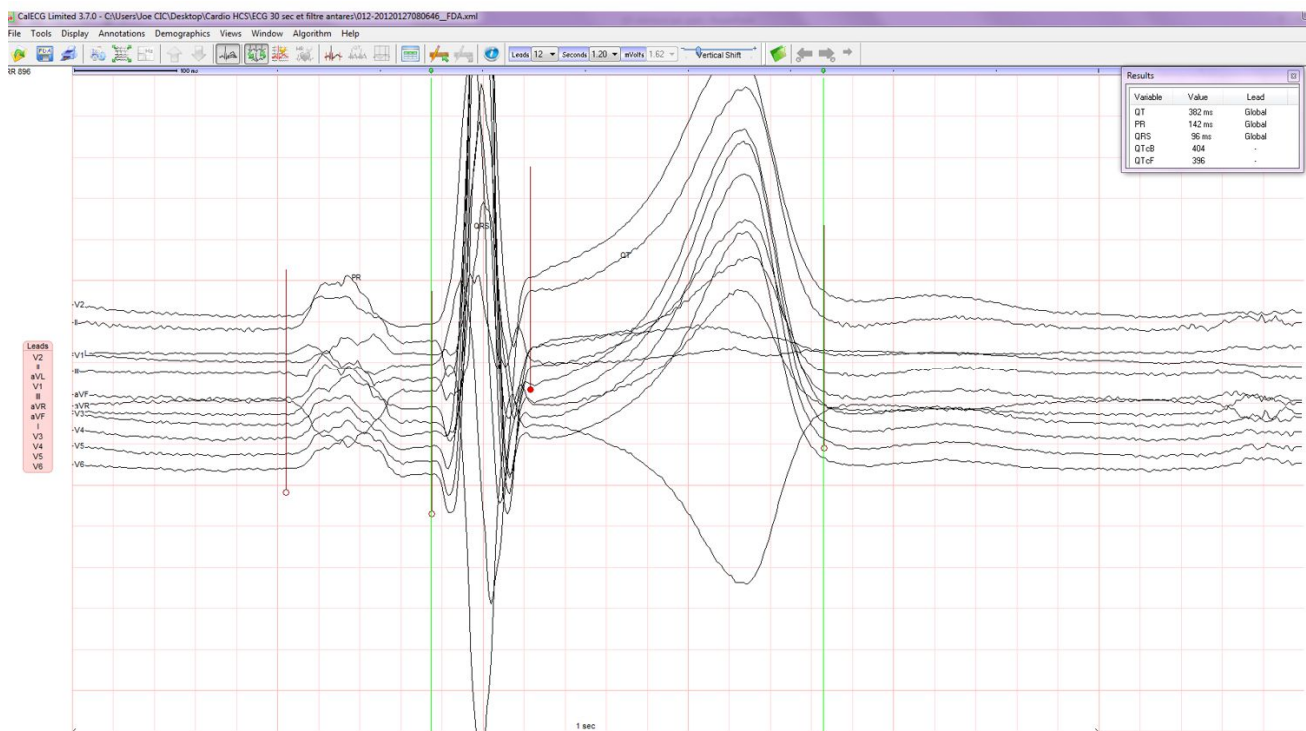


Figure 1: Example of the semi-automatic measurement of the QT interval on an overlapped representative beat generated using a 30 second digitized electrocardiographic recording (CalECG, AMPS-LLC).

Results and Discussion. Primary outcome of the study was that QTc interval is shorter in women with CAH than in control women (404 ± 2 ms vs. 413 ± 2.1 ms, $p < .001$). 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 ($p < 0.05$).

According to multivariable analysis in all women, progesterone/estradiol ratio ($\beta = -0.33$) and FSH levels ($\beta = 0.34$) were related to QTcF ($r = 0.5$, $p < 0.0001$) with no residual influence of CAH or healthy status. In men, QTcF was not significantly different between CAH and controls and was negatively correlated to free testosterone ($\beta = -0.29$) and positively to FSH

levels ($\beta=0.34$). For a more detailed and in-depth review of the results we refer to the main publication tabular and graphical results [1]. The key point outcome of the study can be summarized as follows:

1. QTc interval 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.
2. In women, FSH is positively correlated while progesterone/estradiol ratio is negatively correlated with QTc. 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 des Pointes, particularly in patients with long QT syndrome.
3. In men, FSH is positively correlated while free testosterone is negatively correlated to QTc, a finding that 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 or Torsades des Pointes.

Perspectives. Better understanding of pathophysiological hormonal processes leading to increased susceptibility of women and hypogonadic men to drug-induced arrhythmia may foster preventive or curative treatments. We therefore recently summarized [2] updates on the influence of steroid hormones and gonadotropins on heart repolarization.

The key points are as follows:

1. Progesterone has been successfully used to reduce the incidence of spontaneous ventricular

arrhythmias in a rabbit model of congenital type 2 long QT syndrome [3]. Tisdale et al. have just showed in a prospective, double-blind, placebo-controlled, crossover study involving 15 healthy women, that use of 400 mg oral progesterone once daily for 7 days during the follicular phase decreased ibutilide-induced QTc prolongation [4]. This finding confirms the potential of progesterone as a preventive and maybe curative treatment for drug-induced Torsades de Pointes in women.

2. Endogenous but also exogenous sex steroid derived hormones have variable influences on the duration of ventricular repolarization, depending on genders (Table 1). Exogenous hormonal intake might offer new therapeutic opportunities or, alternatively, increase the risk of Torsades de Pointes. We highlighted that some exogenous sex steroids may have paradoxical effects on ventricular repolarization. As an example, administration of some androgenic anabolic steroids increased QT duration, rather than shortening it in men [5]. The selective estrogen receptor modulator tamoxifen, used for oncology purpose, may increase QT duration rather than shorten it in women [6].
3. Lastly, variations of QT duration in women are linked to sex hormone fluctuations during the menstrual cycle and this is generally ignored in regulatory thorough QT studies. These variations of susceptibility to drug-induced QT prolongation in women can contribute to as much as 15 ms changes in QTc interval duration, i.e. well above the threshold of regulatory concern. Investigators and regulatory agencies promoting inclusion of women in thorough QT studies should be aware of this source of variability especially when studying drugs over several days of administration (Figure 2).

Table 1: Summary of steroid hormones and gonadotropins influence on QTc (adapted from [2])

Hormone	Men	Women
Progesterone	- No influence within physiological ranges	- QTc shortening
Estradiol	- No influence within physiological ranges	- QTc lengthening (when low level of progesterone)
Testosterone	- QTc shortening	- QTc shortening
Gonadotropins	- QTc lengthening	- QTc lengthening
Exogenous steroids	- QTc lengthening (some androgenic anabolic steroids) - QTc lengthening (peripheral anti-androgens, e.g. bicalutamide)	- QTc lengthening (after clomiphene, tamoxifen) - QTc shortening (some progestins, not all)

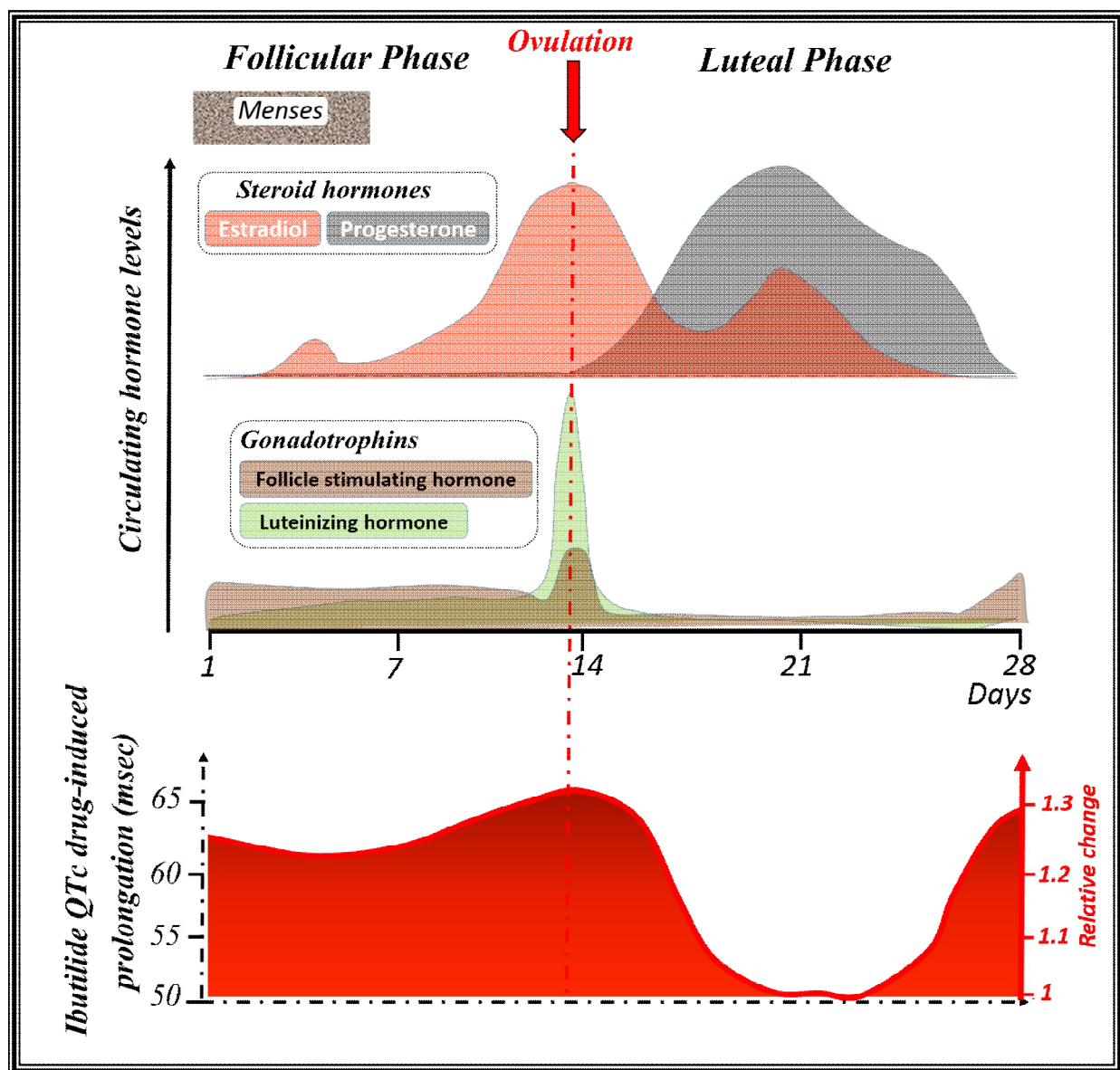


Figure 2: Low-dose ibutilide induced QTc interval prolongation depending of the time of menstrual cycle (adapted from [2,7]).

Conclusion. In conclusion, our results confirm the complexity of interactions between QT interval, steroid hormones and gonadotropins depending on gender. Progesterone might offer new anti-arrhythmic therapeutic opportunities and, in contrast, some exogenous steroid intake might increase the risk of Torsades de Pointes. Sex hormones fluctuations during menstrual cycle may increase inter- and intra-subject variability of thorough QT studies.

References

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Products News

Latest Releases

In Q3 2016 we have released a new version of CER-S, including the revised “aECG Generator” (aka Pollux) platform, for fully FDA Warehouse compliant Continuous aECG FDA XML file generation.

Looking forward

In Q4 2016 AMPS is planning to release:

- A new version of Fat-QT and TrialPerfect with the latest version of BRAVO algorithm, released in Q1.
- A new version of CER-S, including the following revised platforms:
 - Continuous ECG beat detection and classification
 - ECG beat editor
 - Arrhythmia detection and Arrhythmia editor

AMPS Notebook

Fabio attended the 43rd **Computing in Cardiology** Conference, held in Vancouver, Canada in September.

He will be attending the **American Heart Association**, Scientific Session, that will be held from November 12th to 16th in New Orleans, LA.

He will also be attending **CSRC Annual Meeting** that will be held in Washington DC on December 6th and 7th.