QTc prolongation in transgender female adolescents receiving gonadotropin-releasing hormone agonist: Preliminary data

Liat Perl, MD[1,3], Galit Israeli, MD[1], Livia Kapusta, MD[2,3] Anat Segev Becker, MD[1,3], Gil Beer, MD[2,3] , Asaf Oren, MD[1,3]

[1]Pediatric Endocrinology and Diabetes Unit and [2]Pediatric Cardiology Unit , Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, affiliated with
[3] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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BACKGROUND

- The QT interval of the electrocardiogram (ECG), corrected for heart rate (QTc), is a measure of the duration of ventricular repolarization and is a widely used marker of ventricular arrhythmia risk
- Testosterone has a shortening effect on QTc length, and the QTc interval in cisgender males is shorter than in cisgender females after the onset of puberty
- Transgender female adolescents are treated with GnRH agonists (GnRHa) that suppress gonadotrophins and endogenous testosterone secretion, and thus, might prolong the QT interval and increase the risk for malignant ventricular arrhythmia
- Little is known regarding the effect of hormonal therapy on QTc interval in transgender female adolescents

AIMS

- To analyze QTc interval in transgender female adolescents before and after receiving GnRHa and after adding estrogen treatment

STUDY DESIGN, PATIENTS & METHODS

Design: Prospective single center study between May 2017 to June 2020

Patients: 20 transgender female adolescents who started treatment at Tanner stage 4/5 of puberty

Data: QTc intervals of 12-leaded ECG were measured manually, using the Hodges formula (rather than the Bazette formula) to correct for heart rate.

QTc was measured , before and after GnRHa treatment initiation and after adding estrogen treatment

Outcome measures: Prolonged QTc was considered as greater than >450 milliseconds (ms).

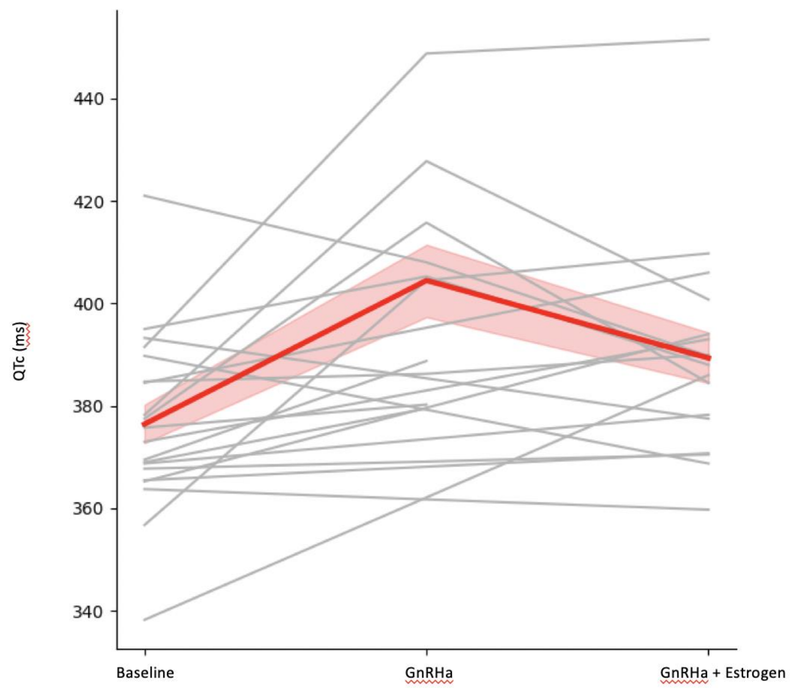
RESULTS

- 20 patients were included: Ten participants initiated GnRHa alone, while 10 participants initiated GnRHa and estrogen simultaneously
- Of those 10 participants initiated GnRHa alone, treatment was started at a mean age of 15.7±1.4 years and QTc was measured after 3.7±1.3 months
- **QTc was significantly prolonged compared to baseline (381.9 ±17.7 vs. 404.48 ± 22.2 ms, respectively, p =0.015), but did not increase>450 ms**
- Of these 10 participants, 7 continued to estrogen affirming treatment at a mean age of 16.7 ± 1.7 years. Using RM-ANOVA, QTc was observed to increase after GnRHa treatment and decrease back after adding estrogen treatment for 6.1± 2.4 months (386.4±19.8 vs 413.7±19.9 vs 402.0±23.5 ms, respectively, p=0.05)
- QTc did not increase significantly in 17 participants treated with both GnRHa and estrogen compared to baseline
- Nine patients were on one or more psychiatric medications known to increase QT interval. One participant, who was on 2 medications, was noticed to have a prolonged QTc (451.5 ms) after estrogen treatment.

	Started treatment with GnRHa alone (n=7)			
Parameter	Baseline	GnRHa treatment	GnRHa+Estrogen treatment	*P* value
QTc (ms) (n=10)	**381.9 ±17.7**	**440.48 ± 22.2**		**0.015**
QTc (ms)	386.4 ±19.7	413.7 ± 19.9	402 ±23.5	0.05
LH (mIU/mL)	3.2 ± 1.8	0.39 ± 0.5	0.26 ± 0.38	0.027
FSH (mIU/mL)	3.1 ± 0.9	1.0 ± 0.8	0.2 ± 0.3	0.05
Estradiol (pmol/L)	91.3 ± 75.2	35.6 ± 46	196.3 ± 161	0.02
Testosterone (nmol/L)	19.7 ± 7.2	0.5 ± 0.4	0.7 ± 0.4	<0.01
Data are presented as mean and SD, statistical analysis by ANOVA and paired T test				

	Started treatment with GnRHa and Estrogen (n=10)		
Parameter	Baseline	GnRHa+Estrogen treatment	*P* value
QTc (ms)	371 ±15.8	380.5 ±14.1	NS
LH (mIU/mL)	3.9 ± 1.2	0.4 ± 0.4	<0.01
FSH (mIU/mL)	4.2 ± 3.1	0.2 ± 0.3	0.06
Estradiol (pmol/L)	102 ± 43	120 ± 107	NS
Testosterone (nmol/L)	20 ± 3.7	1.1 ± 0.8	<0.01
Data are presented as mean and SD			

QTc interval before and after receiving GnRHa and after adding estrogen



DISCUSSION

- Our preliminary data suggest that QTc interval may prolong after GnRHa treatment in Tanner 4-5 transgender female adolescents, while estrogen and GnRHa combined treatment may not affect QTc length
- This may be of further concern, as incidence of mental health conditions requiring psychopharmacotherapy is high in transgender youth, with many psychiatric medications known to prolong the QT interval
- Larger prospective studies are required to further understand the effects of GnRHa and estrogen treatment on QTc interval