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Electrocardiogram Changes Following the Treatment with Gonadotropin-Releasing Hormone Agonists in Patients with Precocious Puberty

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Abstract

Background: GnRH agonists are the standard treatment for precocious puberty. Studies on the side effects of these drugs in adults have shown that these drugs may cause changes in ECG and some cardiovascular effects; however, few studies have evaluated these effects in children. This study aims to investigate the effect of these drugs on ECG intervals in children with precocious puberty.

Methods: In this study with a pre-post design 50 children with precocious puberty referred to the endocrinology clinic of Tabriz Children's Hospital in 2019 for receiving GnRH agonists were included. From all patients, ECGs were obtained before starting the treatment and then 6, 12, and 18 weeks later and PR, QRS, and QTc intervals were extracted from ECG records.

Results: The mean age of the participants was 91±9 months including 48 (96%) girls and 2 (4%) boys. Triptorelin (GnRH agonist) was administered for all patients with the standard protocol. Comparison of pre- and post-treatment ECG intervals showed that the drug did not cause a significant change in PR ($p = 0.535$) and QTc ($p = 0.250$) intervals, whilst there was a significant increase in QRS interval after the treatment ($p = 0.001$).

Conclusion: The use of GnRH agonists in children can lead to some changes in ECG records by increasing in QRS intervals; and ECG could be used as a tool to detect these changes. Further studies are also needed to identify ECG changes in larger sample sizes and longer intervals.

Key Words: ECG, GnRH agonists, PR, Precocious puberty, QRS, QTc.

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1- INTRODUCTION

Normal puberty occurs in the ages of 8 and 12 years in girls and 9 and 14 years in boys (1). Precocious puberty is defined as the appearance of secondary sexual traits before the age of 8 years in girls and before the age of 9 years in boys (2), which affects 1 to 5 in 10,000 children (3-5) and is 10 times more common in girls (6). Precocious puberty occurs mainly due to premature activation of the hypothalamic-pituitary-gonadal axis (3) and is categorized into two types of central and peripheral (7). Causes of central type include central neural system (CNS) lesions and idiopathic etiologies (8). About 90% of affected girls have idiopathic central precocious puberty (CPP) and over 75% of affected boys have CNS lesions. Precocious puberty is usually sporadic (2) and mutations in the kisspeptin system (9) and defects in the MKRN3 gene have been detected in some cases (10). In central precocious puberty, the same sequence of events occurs as normal puberty (9) and is designated with the onset of breast growth in girls and the onset of testicular enlargement in boys (2). Bone maturity increases (2) and it leads to early epiphyseal closure and short stature in adulthood (8). Mood swings are common in these patients but severe mental health problems are rare (2). According to some studies, stress and anxiety are increased in affected girls (8). Long-term studies indicate good menstrual and reproductive function, but the prevalence of polycystic ovary syndrome may be higher than the general population (11). Diagnosis based on clinical and laboratory findings confirms the activity of the hypothalamic-pituitary-gonadal axis (9). Immunoassay techniques to accurately measure serum gonadotropins and gonadal steroids distinguish the central type from the peripheral (12). The female patients with rapidly progressive puberty, low birth weight children (due to high risk of short stature in adulthood), primary amenorrhea, or those patients with psychosocial concerns and all male patients should receive early treatment (2). The goals of treatment are to prevent psychosocial problems and to normalize the height of adulthood (13). In the idiopathic type, suppression of gonadal pituitary function is the goal of treatment methods (14); in non-idiopathic types of treatment, it is initially based on the treatment of the underlying problem (8). GnRH agonists are the treatment of choice for CPP (10, 15). These drugs are derived from natural GnRH by substituting amino acids, which increase their resistance to degradation (14) and increase their half-life by 3 to 10 times (15). Available formulations include leuprorelin, triptorelin, and goserelin in the form of monthly and 3-month depot products and 12-month continuous release subcutaneous implantation (histrelin) and short-acting products in the form of nasal sprays administered 1 to 3 times daily (nafarelin and buserelin as intranasal sprays) (4, 16). Several studies have demonstrated that treatment of precocious puberty with GnRH agonist is safe and has scarce long-term side effects (9, 17).

Testosterone can cause shortening of QT interval (18). GnRH agonists by androgen suppression effects (19), lower testosterone, and thus can prolong QT interval. Androgen suppression therapy in prostate cancer due to prolongation of QT interval is associated with the increased risk of cardiovascular mortality and sudden cardiac death in adults (20). Therefore, there are some concerns that due to the same mechanisms, administration of GnRH agonists in children with CCP may cause some ECG alterations and consequently some cardiovascular complications. Therefore, this study aims to evaluate the effect of these drugs on ECG in children with precocious puberty.

2- MATERIALS AND METHODS

In this study with a pre-post design, 50 children (<12 years of age) with precocious puberty referred to the pediatric endocrinology clinic of the Tabriz Children Hospital of the Tabriz University of Medical Sciences were consecutively included during 2019. The inclusion criteria were age of <12 years, diagnosis of precocious puberty, and referral to the pediatric endocrinology clinic of the Tabriz Children Hospital. The exclusion criteria were existing congenital heart disease with hemodynamic effects, arrhythmia, taking other medications that could alter ECG parameters, and abnormal ECG at admission. The study was conducted according to the Helsinki declaration and written informed consents were obtained from the parents or guardians of the children after an appropriate explanation of the aim of the project. The protocol of the study was approved by the medical ethics committee of the Tabriz University of Medical Sciences.

Information about the age of the patients at the time of diagnosis (by month) and gender, as well as the type of administered GnRH agonist medication and its prescribed dose, history of other diseases or medications were recorded in a pre-prepared form.

Parents' referral dates (6, 12, and 18 weeks after the start of treatment) for ECG were calculated and announced to the parents.

Exactly before the initiation of the treatment with GnRH agonists, and after 6, 12, and 18 weeks of the treatment, 12-lead ECG was taken from all patients (a total of 4 ECGs). All ECGs were obtained using MAC 500 ECG machines (GE medical system, USA) with a paper speed of 25 mm/s and standard voltage. ECG analyses were conducted by an attending cardiologist who was blinded to the patients' clinical status, using digital calipers on a 12-lead ECG and magnified to 200% of normal size. The ECG analysis was repeated by another attending cardiologist and the discrepancies were resolved by consultation with the third cardiologist to mitigate intra-observer variability. Four parameters of PR, QRS, QT, and QTc intervals were extracted from each ECG.

To calculate the above intervals, lead II for PR interval or Lead V5 for QRS duration and mean precordial leads for QT interval were used which allow measurement of the considered intervals more accurately.

After calculating the QT interval, the corrected QT interval (QTc) was used as an alternative for more accuracy, which was calculated using the Bazett formula:

$$QTc = \frac{\text{QT interval in seconds}}{\sqrt{\text{cardiac cycle in seconds}}} = \frac{QT}{\sqrt{RR}}$$

Reference intervals related to PR, QRS, and QTc according to the age of each patient (**Table 1**) were extracted from the pediatric cardiology reference (Moss & Adams) (21), based on which these intervals were considered normal or increased or decreased for each ECG.

2-1. Data analysis

The collected data on dependent and independent variables were statistically analyzed by SPSS 22. To describe the data, descriptive statistics such as percentage, frequency, mean and standard deviation were used. Friedman test was used to compare PR, QRS, and QTc between pre-treatment and three post-treatment assessments. In those with significant differences ($P<0.05$), McNemar post hoc analysis was performed. A P-value less than 0.05 was considered statistically significant.

Table-1: The normal range of QTc, QRS duration and PR interval

		0–1 d	1–3d	3–7d	7–30d	1 –3 mo	3–6 mo	6–12 mo	1 – 3 y	3 -5 y	5 -8 y	8 -12 y	12 – 16 y
PR lead II (s)		59- 189	64- 197	76-191	7-160	30 - 115	7 - 105	6 - 98	7 -102	6 - 104	10 - 139	6 - 116	9 - 128
QRS duration Lead V5 (s)		0.02 – 0.07	0.02 – 0.07	0.02 – 0.07	0.02 – 0.08	0.02 – 0.08	0.02 – 0.08	0.03 – 0.08	0.03 – 0.08	0.03 – 0.07	0.03 – 0.08	0.04 – 0.09	0.04 – 0.09
QTc interval (s)	Boys	0.370 - 0.470											
	Girls	0.370 - 0.480											

All values are 2nd percentile to 98th percentile (upper and lower range). Derived from normal ECG Standards for children by age table, Moss and Adams Heart Disease in Infant, Children and Adolescents textbook of pediatric cardiology; d = days, mo = months, y = years

3- RESULTS

3.1 Baseline characteristics

Fifty patients met the inclusion criteria. None of the patients had a previous disease and had no previous disorder in ECG. None of the patients had a history of previous use of any drug. Of the studied patients, 2 (4%) were male and 48 (96%) were female. The mean age of the patients was 91±9 months (**Table 2**).

3.2. Drug administration

The GnRH agonist used to treat children with precocious puberty was triptorelin. Three pharmaceutical brands of this GnRH agonist (triptorelin) included variopeptyl, diphereline, and microrelin. Among the included patients, 35 (70%) received the variopeptyl, 11 (22%) received diphereline and 4 (8%) received microrelin. Forty patients (80%) received a dose of 3.75 mg every 28 days and another 10 (20%) received a dose of 11.25 mg every three months. Four patients (88%) received the drug subcutaneously and 6 patients (12%) received it intramuscularly (**Table 2**).

Table-2: Baseline and treatment characteristics of the patients

		Value
Age (months) Mean ± SD		91±9
Gender n (%)	Male	2 (4%)
	Female	48 (96%)
GnRH agonist brands (triptorelin) n (%)	Variopeptyl	35 (70 %)
	Diphereline	11 (22 %)
	Microrelin	4 (8%)
Dosage n (%)	3.75 every 28 days	40 (80%)
	11.25 every 3 months	10 (20%)
Route of administration n (%)	Subcutaneous	44 (88%)
	Intramuscular	6 (12%)

3.3. Effects of the drug on ECG intervals

Evaluation and comparison of the pre-treatment PR interval with the sixth, twelfth and eighteenth weeks of the treatment showed that the drug did not

significantly change PR interval (P = 0.535) **(Table 3, Fig. 1).** Nevertheless, there was a significant difference in this interval and this interval increased after the treatment (p = 0.001). Post hoc test showed a significant difference comparing the pre-treatment results with the results of the sixth (p = 0.001), twelfth (p = 0.001), and eighteenth (p = 0.001) weeks, and confirmed the increase in this interval **(Table 3, Fig. 2).**

Moreover, the treatment showed that the drug did not cause a significant change in QTc interval (p = 0.250) **(Table 3, Fig. 3).**

Table-3: QTc, QRS duration and PR interval before the treatment and the 6th, 12th and 18th weeks of the treatment

		First ECG (before treatment)		Second ECG (6th week)		Third ECG (12th week)		Fourth ECG (18th week)		P-value
		n	%	n	%	n	%	n	%	
QTc	Reduced	0	0	0	0	0	0	0	0	0.250
	Normal	50	100	47	94	50	100	50	100	
	Increased	0	0	3	6	0	0	0	0	
QRS duration	Reduced	0	0	0	0	0	0	0	0	0.001
	Normal	50	100	35	70	37	74	35	70	
	Increased	0	0	15	30	13	26	15	30	
PR interval	Reduced	0	0	2	4	1	2	1	2	0.535
	Normal	50	100	43	86	48	96	48	96	
	Increased	0	0	5	10	1	2	1	2	

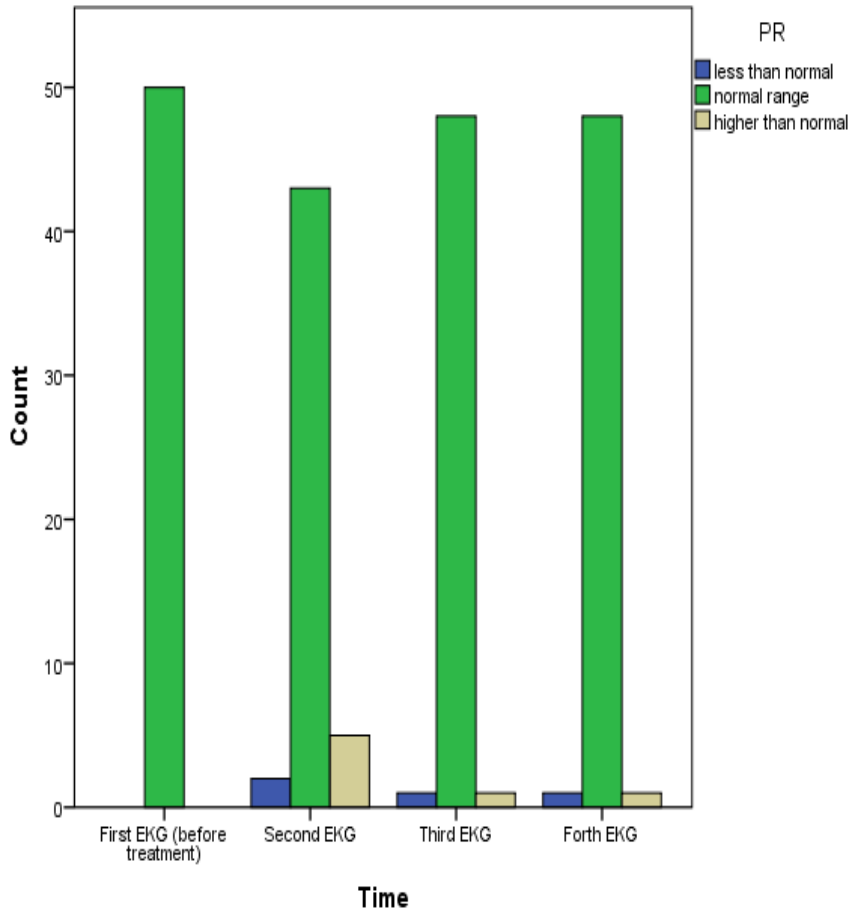

Fig. 1: pre- and post-treatment PR interval

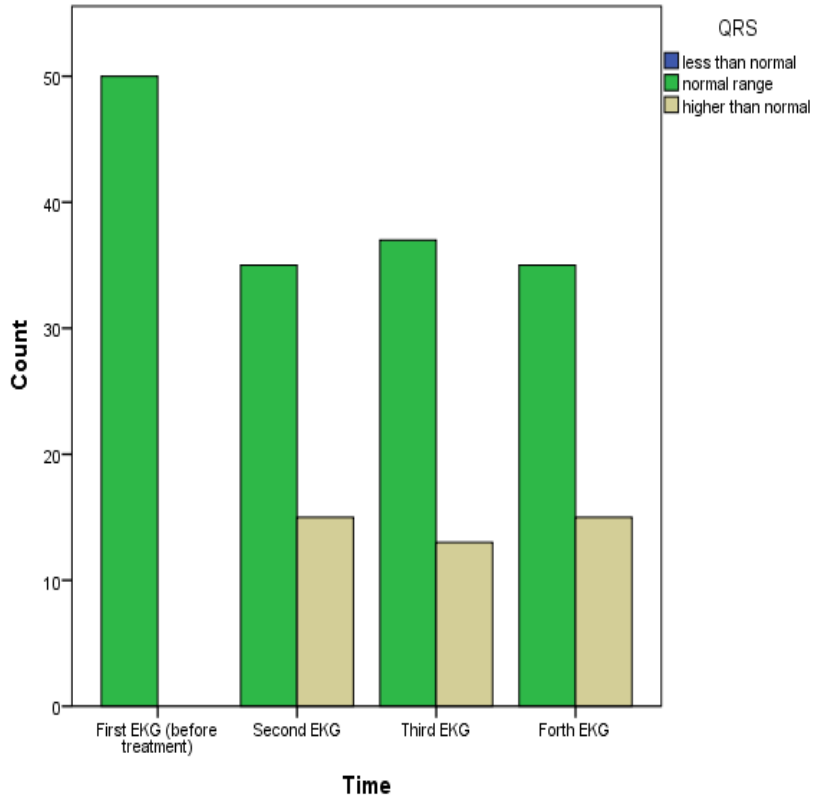

Fig. 2: pre- and post-treatment QRS interval

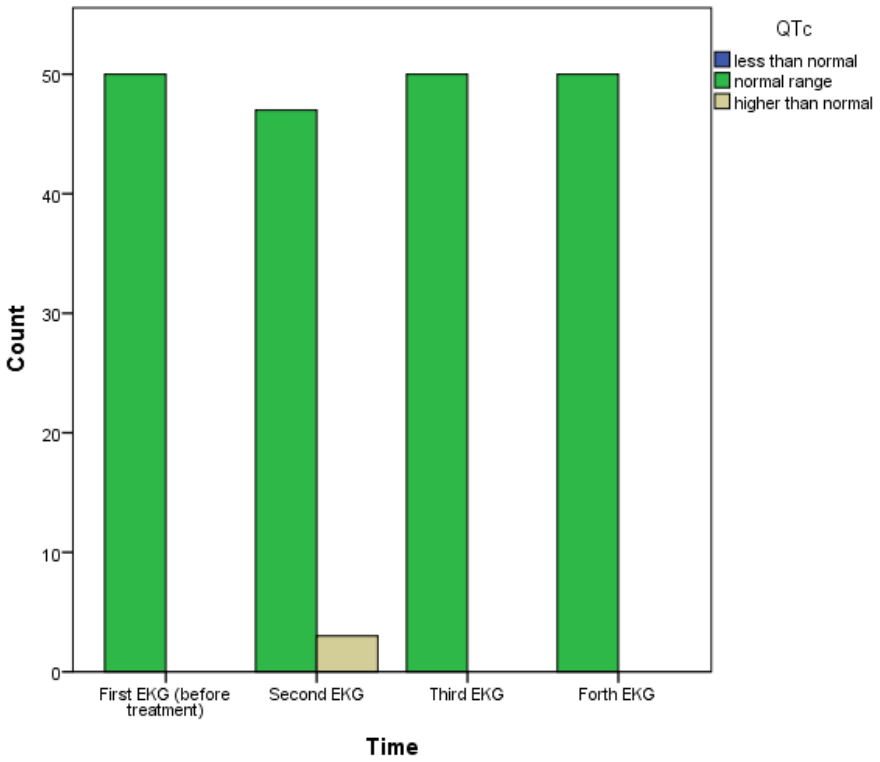

Fig. 3: pre- and post-treatment QTc interval

4- DISCUSSION

Precocious puberty increases bone maturity (2) leading to early epiphyseal closure and short stature in adulthood (8) and therefore has significant health and social consequences (6). GnRH agonists are the treatment of choice for CPP (15). This study evaluated the effect of GnRH agonist drugs on ECG of children with precocious puberty who are being treated with these drugs. Administration of GnRH agonists (triptorelin) had no significant effect on PR and QTc intervals but significantly increased QRS wave duration. The increase in QRS duration has been demonstrated to be associated with the risk of sudden cardiac death, congestive heart failure, and some arrhythmias such as complete heart block, intraventricular block, Wolff-Parkinson-White syndrome, ventricular arrhythmias such as premature ventricular contraction, and ventricular tachycardia, as well as ventricular fibrillation and hypertrophy in patients with cardiovascular diseases (22-25). Furthermore, a study on 46,933 consecutive participants from the general medical population at the Palo Alto Veterans Affairs Medical Center revealed that QRS duration is a significant and independent predictor of cardiovascular mortality (26). There was an 18% increase in the risk of cardiovascular mortality per each 10 ms increase in QRS duration (26). QRS duration is the most widely accepted criterion to diagnose ventricular dyssynchrony which is defined as uncoordinated or heterogeneous activation and contraction of the ventricles (21). An increase in QRS duration after administration of GnRH agonists brings about the concern that these medications may lead to ventricular dyssynchrony in some patients. Therefore, ECG monitoring

of patients under treatment with GnRH agonists should be considered on a regular basis after the treatment initiation.

Zhang et al. conducted a study that showed that 50 ms increase in QT interval was associated with the relative risk of 1.20 for overall mortality, 1.29 for cardiovascular mortality, 1.49 for coronary heart disease mortality, and 1.24 for sudden coronary heart disease and the length of QT interval determines mortality in the general population (27). Degarelix (GnRH antagonist) has been reported to treat advanced hormone-dependent prostate cancer. Because androgen deprivation therapy is associated with QT prolongation, a study was conducted by Olsson et al. to investigate the inherent effect of Degarelix at super-therapeutic concentrations on cardiac repolarization and QT interval. ECGs taken up to 24 hours after the administration were analyzed by assessing QT interval simultaneously with Degarelix plasma concentration. In this study, the corrected QT interval did not increase more than 10 ms with a maximum dose of Degarelix. In addition, analyses showed no effect of Degarelix on QT prolongation, and no significant effect was found on any other cardiac parameters. The results showed that Degarelix itself had no effect on QT interval and cardiac repolarization at super-therapeutic concentrations (28). Of note, the results of our study on the QTc interval showed that GnRH agonist (triptorelin) did not cause a significant change in QTc interval at 6, 12, and 18 weeks after the treatment compared to the pre-treatment QTc ($p = 0.250$).

The mean age of patients in our study was 91±9 months. Previous studies in this field provided similar results as the present study. For example, Cisternino et al. investigated the causes and age of precocious puberty in girls; most girls with CPP (59.6%) were 7 to 7.9 years old, 22.4% were 6 years old, and only 18% were under 6 years old (29). In a study by Prété et al., who assessed the frequency of breast growth-related symptoms and effective factors on manifestations of girls with CPP, CPP age was less than 3 years in 2%, 3-7 years in 38% and 7-8 years in 60% (31). In the present study, 2 (4%) out of 50 patients were boys and 48 (96%) were girls, which, consistent with the results of previous studies, shows a high prevalence of precocious puberty in females. For example, in a study by de Vries et al., 147 out of 156 children with idiopathic central precocious puberty were girls and 9 were boys (30). In a study by Kaplowitz, most of the children (87%) examined for signs of precocious puberty were female (31).

Carel et al. evaluated pituitary and gonadal suppression in 40 girls and 9 boys treated with depot leuprorelin (3.75 mg for 20 kg body weight, 1.87 mg for <20 kg body weight) every 28 days for CPP. According to the results of this study, gonadal suppression was achieved in most children with this dose; 3 months after starting treatment, 85% of children had maximum plasma LH response (less than $3^{IU/L}$) to gonadotropin-releasing hormone and the gonadal axis remained suppressed throughout the studied period (up to 24 months) (32). In a study by Oostdijk et al. on children with CPP diagnosis treated with 3.75 mg intramuscular triptorelin every four weeks, bone maturation decreased during the treatment and the predicted adult height increased from 158.2 cm to 163.9 cm at the end of the treatment ($p<0.001$) (33).

Our study had some limitations that should be noted. It was conducted as a single centric study and did not include a control group.

5- CONCLUSION

The results of this study showed that the administration of GnRH agonists to treat precocious puberty in children could

alter cardiac electrical activity. A significant increase in QRS duration of these patients' ECG was observed as compared with their pretreatment ECG. Other studied intervals including PR and QTc did not significantly change following the administration of GnRH agonists. Therefore, ECGs should be taken at various intervals after starting the treatment to identify possible changes in ECG and to prevent potentially dangerous complications following the treatment with GnRH agonists.

6- ETHICAL CONSIDERATIONS

The present study was conducted after it was approved by the Ethics Committee of Tabriz University of Medical Sciences based on the Helsinki Declaration (Research ethics approval ID: IR.TBZMED.REC.1397.1072, IRCT code: IRCT20190314043051N1). Patients were enrolled after explaining the objective of the study and procedures to parents and obtaining their informed consent. Except for ECG, no additional intervention was performed. No costs were incurred for patients and the project was funded by the author. Moreover, part of the costs of the project and ECGs were paid with the support of the Deputy of Research, Tabriz University of Medical Sciences.

7- CONFLICT OF INTEREST: None.

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