

Transient Central Precocious Puberty: a new entity among the spectrum of Precocious Puberty?

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Research

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Abstract

Objective

The aim of this study is to evaluate clinical, hormonal and ultrasound features in girls with precocious puberty (PP).

Methods

96 girls referred to our center for PP between 1st January 2007 and 31th December 2017 fulfilled inclusion criteria and were recruited for the study. 3 groups of patients were considered. Group 1: 56 subjects with Central PP (CPP) requiring treatment with GnRH analogue; Group 2: 22 subjects characterized by some criteria of CPP without indication to treatment, "Transient CPP"(T-CPP); Group 3: 18 subjects with Isolated Thelarche (IT). A questionnaire about anamnestic and environmental data was provided to patients which were followed through normal clinical care.

Results

an increase in Groups 2 and 3 diagnosis was observed over the years. LH peak (UI/ml) at diagnosis was higher in Group 1 vs Group 2 (11.7 ± 7.8 vs 4.58 ± 1.60)($p < 0.001$) and 3 (11.7 ± 7.9 vs 2.18 ± 1.15)($p < 0.001$) and also in Group 2 vs Group 3 (4.58 ± 1.6 vs 2.18 ± 1.1)($p < 0.05$). At 6–12 months, LH peak of Group 2 was lower (2.35 ± 1.3) compared with diagnosis data (4.58 ± 1.60)($p < 0.05$). Uterine Longitudinal Diameter (ULD) (mm) was longer in Group 1 (42.53 ± 6.26) vs Group 2 (36.54 ± 4.86)($p < 0.001$) and 3 (30.70 ± 4.74)($p < 0.001$), and this difference is also found between Group 2 and 3 ($p < 0.005$). Potential exposure to herbicides and pesticides was reported in 17.5% in Group 2 vs 12.5% in Group 1 ($p < 0.001$).

Conclusions

This study seemed to indicate an increase in diagnosis of T-CPP and IT cases. To our knowledge, this is the first report of a form defined as T-CPP, characterized by a partial activation in the HPG axis normalizing over time. As for environmental factors, we indirectly evaluated the role of some endocrine disruptors (EDCs) affecting pubertal axis activation, without leading to a complete maturation.

Background

Precocious puberty (PP) in girls is defined as the onset of thelarche before 8 years of age[1].

The onset of puberty depends on many factors, such as family history, low birth weight, obesity in infancy and early childhood, international adoption (with a risk of 10-20 times higher), and exposure to

endocrine-disrupting chemicals (EDCs). However, these factors cannot completely explain the changes in the timing of pubertal onset [2,3].

Epidemiological studies reveal that 0.2% of girls showed some forms of PP, with a marked discrepancy based on geographical distribution, varying from 2.68/10.000 of incidence in France to 26.3/10,000 in South Korea[4-6]. The reason is not completely understood, but it seems that race, environmental factors and EDCs may play an important role.

Within idiopathic forms, Central Precocious Puberty (CPP) does not represent a single entity, but rather a spectrum of forms ranging from Isolated Thelarche (IT) to rapidly progressive CPP [7].

In particular, Stanhope et al. described for the first time a variant of PP with intermediate clinical, ultrasonographic and hormonal characteristics between IT and CPP. This form was called Thelarche Variant (TV), as it did not develop in CPP and had no response to GnRH analogue [8-10].

Our study aims to retrospectively evaluate the clinical, hormonal and ultrasound features of the different forms of PP in girls referred to our center between 2007 and 2017. We also evaluate the role of anamnestic, nutritional and environmental factors.

Patients And Methods

Patients and study design:

We evaluated retrospectively 96 girls referred to our Center for suspected PP between 1st January 2007 and 31th December 2017.

Inclusion criteria were: age at onset of pubertal signs between 3 and 8 years, availability of blood sampling for estradiol, basic and after stimulation gonadotropins, Bone Age (BA) and Pelvic Ultrasound at diagnosis and after 6-12 months, negative brain MRI in treated girls and at least a one-year-follow up after diagnosis.

The exclusion criteria were: isolated pubarche and other genetic or neurological syndromes including CPP.

For the purpose of the study, girls were divided into three Groups:

- Group 1: 56 subjects with idiopathic progressive CPP who required treatment with GnRH analogue (Triptorelin Depot 3.75 mg every four weeks by intramuscular injection), according to Consensus Criteria [11,12]
- Group 2: 22 patients with a form of CPP characterized by an intermediate response of LH (3-5 IU/mL) at the GnRH test, progression of BA \leq 1 year, longitudinal uterine diameter > 36 mm and/or uterine volume > 3.5 ml. These parameters have moreover normalized until 6-12 months of follow-up. We defined this form as Transient CPP (T-CPP).

- Group 3: 18 patients with Isolated Thelarche (IT) without any other sign of central activation of the Hypothalamic-Pituitary-Gonadal (HPG) axis.

Methods:

For all patients we retrospectively investigated from medical records: familiar history, socio-economic condition, pregnancy and delivery, age at mother's menarche, urban or rural residence. Subjects were asked to reply to a questionnaire, sent by post, investigating the use of assisted reproduction techniques, use of drugs during pregnancy, breastfeeding, exposure to smoking, use of herbal supplements or homeopathic drugs, eating habits, use of soy-based products, distance between 50-1000 meters from an intensive farming or an industry capable of exposing to environmental pollutants or use of cosmetic products containing placenta extracts.

Overall 50/96 subjects (50%) completed the questionnaire, 34/56 (60.7%) in Group 1 and 16/22 (72.7%) in Group 2. In Group 3, only 2 patients have accepted to complete the questionnaire, so these data were not included into the study. Pubertal development was assessed according to Tanner and Whitehouse's criteria [13]. The height was measured using Harpenden stadiometer and expressed as Standard Deviation Score (SDS). BA was evaluated using the atlas of Greulich and Pyle [14]. The BMI was calculated according to the formula: weight (kg) / height (m²), and the BMI SDS was calculated according to age and sex. The socio-economic condition was calculated according to the Socio-Economic Status of Hollingshead, taking into account the level of education and the profession of both parents [15].

Blood samples were collected in fasting conditions between 07.00 and 09.00 in the morning. The levels of gonadotropins (LH and FSH) and 17- β estradiol were analyzed by an immunochemiluminometric method (ICMA, AxSYM Abbott) with a sensitivity threshold of 0.1 IU/mL for gonadotropins. The conventional GnRH stimulus test was performed by intravenous administration of 50-100 μ g of drug, with samples taken at 0', 30', 60' [11,16].

The levels of TSH and FT4 were evaluated by means of a chemiluminescent assay (Bayer, Fenwald, Germany) (normal range: TSH 0.5-4.5mU/L, FT4 9-17 pg/mL). Pelvic ultrasound was performed trans-abdominally by a group of experts in pediatric evaluations [17].

For statistical analysis the results were expressed as mean \pm SDS. The Kruskal Wallis test with independent samples was used to evaluate the normal distribution of the parameters. The Chi-Squared test was used to evaluate whether or not to reject the null hypothesis, using a 95% confidence interval. The Mann Whitney test was used to verify the differences between independent groups. A value of $p < 0.05$ was considered significant in all cases. Statistical analyzes have been performed using STAT program for Windows.

Our study was approved by the ethics committee of the hospital (197/2016/O/Oss) and written informed parental consent was obtained before the start of the study.

Results

Figure 1 shows the distribution of the different forms of PP in our Center from January 2007 to December 2017.

Fig. 1 - Distribution of the diagnosis (%) of the different forms of PP in our center between 2007 and 2017.

We observed a significative increase in Group 2 and Group 3 diagnosis over the study period ($P < 0.05$).

Auxological and anamnestic data

Table 1 shows some auxological and anamnestic features at the first evaluation in the groups of subjects.

Table 1 Auxological and anamnestic data in the 3 groups of patients at the first evaluation

	Group 1 (n° 56)	Group 2 (n° 22)	Group3 (n°18)
CA at onset of pubertal signs	7.00 ± 1.00*	6.35 ± 1.20°	4.85 ± 1.90
CA diagnosis	7.58 ± 0.73§	6.75 ± 1.06	6.25 ± 0.35
BA diagnosis	9.55 ± 1.00§	7.20 ± 1.70	7.94 ± 1.04
Height at diagnosis (SDS)	1.19 ± 0.82§	0.50 ± 1.20	0.80 ± 0.76
BMI at diagnosis	0.56 ± 0.90	0.29 ± 0.90	0.98 ± 0.69**

* $p < 0.05$ vs Group 3; ° $p < 0.05$ vs Group 3; § $p < 0.05$ vs Group 2 and 3; ** $p < 0.05$ vs Group 2

CA (Chronological Age), BA (Bone Age)

Caucasian race was reported in 51/56 (91%) girls in Group 1, 20/22 (90%) in Group 2 and 16/18 (88.8%) in Group 3. Seven girls were adopted from foreign countries, 6/56 (10%) in Group 1 and 1/22 (4.8%) in Group 2. They were adopted at an average Chronological Age (CA) of 2.42 ± 3.10 (3.4 ± 1.2 years before the onset of pubertal signs). In Group 2 we also found 2/22 (9%) girls born from mothers emigrated from Russia and South America about 2 years before conception. We did not find comparable cases in Groups 1 and 3. There were no statistical differences regarding familiarity for PP. Group 3 shows a significantly lower neonatal weight than Group 2 (2870 ± 634 grams vs 3270 ± 546 grams) ($p < 0.05$), without differences from Group 1.

In Group 1, patients started Triptorelin therapy at an average CA of 7.58 ± 0.73 years. The therapy was suspended at mean CA of 10.1 ± 0.60 years (mean BA of 11.5 ± 0.7 years). The age at menarche was 11.4 ± 0.9 years (age of maternal menarche 11.08 ± 1.28).

Group 2 and 3 patients were followed for 24 ± 4.1 months and 24 ± 3.2 months respectively. The age at menarche was 12 ± 0.7 years in Group 2 (age of maternal menarche 12.45 ± 1.25) and 11.5 ± 0.7 years in Group 3 (age of maternal menarche 11.33 ± 0.87). The age at menarche for Groups 2 and 3 was extrapolated from the questionnaire responses and was available for 5/22 in Group 2 and 2/18 in Group 3.

Laboratory and Ultrasound data

Hormonal measurements revealed baseline and after stimulation gonadotropin values as predictable by the study design. LH peak at diagnosis was significantly higher in Group 1 compared to Group 2 (11.7 ± 7.8 UI/mL vs 4.6 ± 1.6 UI/mL) ($p < 0.001$) and Group 3 (11.7 ± 7.8 UI/mL vs 2.2 ± 1.15 UI/mL) ($p < 0.001$) and also in Group 2 compared to Group 3 (4.6 ± 1.6 UI/mL vs 2.2 ± 1.15 UI/mL) ($p < 0.05$). At 6-12 months, LH peak levels of Group 2 resulted significantly lower (2.35 ± 1.3 UI/mL) compared with LH peak at diagnosis (4.6 ± 1.6 UI/mL) ($p < 0.05$). Estradiol levels were undetectable in 20/56 (35%) in Group 1 and in all patients of other Groups. TSH values above 4.5 mU/L was reported at diagnosis in 4/22 patients of Group 2 (18%) and 2/18 patients of Group 3 (11%), and in no subject from Group 1. No subjects showed a TSH level > 10 mU/L. FT4 levels were always in the normal range, and thyroid antibodies were always negative.

At diagnosis, Uterine Longitudinal Diameter (ULD) was significantly longer in Group 1 (42.5 ± 6.3 mm) than in Group 2 (36.54 ± 4.9 mm) ($p < 0.001$) and 3 (30.7 ± 4.7 mm) ($p < 0.001$), and also between Group 2 and Group 3 ($p < 0.005$). After 12 months there was no longer any statistically significant difference between Groups 2 and 3. The uterine volume parameters at diagnosis and after 12 months of follow-up are shown in Figure 2.

Fig. 2 - Trend in Uterine Volume at Diagnosis and at 12 months of Follow-up in the 3 Groups

Environmental, pharmacological and socio-economic data

There were no differences between the groups for the following data: residency, use of techniques for assisted fertilization (hormonal therapies or in vitro fertilization), breastfeeding, use of supplements to promote breastfeeding, exposure to smoking, food containing soya, drugs during pregnancy and socio-economic condition.

The maternal use of cosmetic products containing placenta extracts, including creams and dyes, was reported in 2/16 patients in Group 2 (12.5%) and 2/34 patients in Group 1 (5.9%) ($p < 0.05$).

As for homeopathic drugs, in Group 2 was reported a significantly higher use of a homeopathic cough syrup (17.5%, 4/22), and a natural solution for the gas colic (5%, 1/22), than in Group 1 (12.5% and 0% respectively) ($p < 0.05$). These medicines contain different types of herbal extracts, in particular *Foeniculum Vulgare* in the second one, whose effects on pubertal axis are not still clarified, but a certain estrogen-stimulating activity has been reported [18].

In Group 2 was reported a significantly higher potential exposure to herbicides and pesticides than in Group 1, expressed as a distance <1000 meters from an intensive farming or industry (17.5% vs 12.5%)(p <0.001).

Discussion And Conclusions

Nowadays, it is well known that idiopathic CPP does not represent a single entity, but rather a spectrum of forms ranging from Isolated Thelarche (IT) to rapidly progressive CPP [7]. There are few data in literature on the nosography characteristics of non-progressive forms and, in particular, on the degree of activation of the HPG axis.

The results of our study showed changes of frequency of the different forms of CPP over years. On one hand, the diagnosis of rapidly progressive forms decreased over time, probably due to a better clinical selection of patients, on the other, a significant increase in non-progressive forms was observed. This appears in partial disagreement with a recent Danish study deriving from a population registry, which indicates an increase not only in benign pubertal variants (pubarche and IT) but also in CPP. Moreover, the two studies are difficult to compare due to characteristics and study design [19].

To the best of our knowledge, we reported for the first time a form of non-progressive PP that we have defined as “transient”CPP (T-CPP). Although the similar to TV, previously described in literature [10], T-CPP is characterized by the presence of a partial activation in the HPG axis, as demonstrated by hormonal and ultrasound features, able to normalize over time without any pharmacological treatment.

The pathogenesis of this nosographic variant appears unclear and may not be univocal. The role of EDCs on the development of PP is still under discussion, because pubertal timing, and subsequently the onset of puberty, can be strongly affected by [20-23]. The results of the questionnaire suggest a partial influence of some environmental factors. In fact, subjects reported an increased use of homeopathic drugs and exposure to environmental pollutants in Group 2. We could speculate that T-CPP consisted of a transient phase of estrogenization, due to a mild raise in plasma estrogen concentration, undetected in blood samples, able to activate the HPG axis. The method of questionnaire administration does not allow us to establish the time of EDC exposure and the effect of estrogenic reduction on the activation of HPG axis. However, we cannot exclude the possibility of a direct activation on HPG axis by these substances.

We found a significantly lower neonatal weight in Group 3 compared to Group 2. This result could be of non-univocal interpretation. In literature, it is described how intrauterine growth retardation may be a potential risk factor for PP or premature pubarche [24], but this is not clearly described for premature thelarche.

Surprisingly, we found a higher frequency of hyper-thyrotropinemia than in general population (2%)[25]. Several reports about forms of early pseudopuberty in subjects with primitive hypothyroidism have been already published [25]; this phenomenon was partially explained by the structural homology between TSH and gonadotropins, in particular FSH, with consequent activation of ovarian estrogen receptors. However,

in literature is reported that the physiologic baseline event in premature thelarche is the increase in FSH level. Inhibin B secreted from granulosa cells is thought to be responsible for this increase [26].

In agreement with the data of Soriano et al., our study confirmed the association between adoption and a precocious central activation of the HPG axis, probably due to psychological, nutritional and/or chemical influences on hypothalamic centers [27]. As for the incidence of girls born in Italy from mothers migrated from other countries, the association with an early pubertal development is currently being evaluated in literature, as a consequence of stressful social factor, but also improvement in quality of life and precedent exposure to environmental interferents [28].

The strength of our study is that subjects were followed by a single center without different diagnostic approaches. Weaknesses are represented by the poor compliance to the questionnaire, the absence of a control group and the impossibility to dosage EDCs in laboratory assay, allowing just an indirect evaluation of a possible role.

These results will be useful for the comprehension of recent changes in pubertal milestones. Anyway, further studies are needed to evaluate the role of environment and the interaction between the other possible causes. In the future, multicenter studies, supported also by laboratory data, will be necessary to evaluate the evolution of this form and the possible environmental influence on pubertal evolution in our female population.

Abbreviations

PP: Precocious Puberty

CPP: Central Precocious Puberty

T-CPP: Transient-Central Precocious Puberty

IT: Isolated Thelarche

TV: Thelarche Variant

EDC: Endocrine Disrupter Chemicals

CA: Chronological Age

BA: Bone Age

ULD: Uterine Longitudinal Diameter

HPG axis: Hypothalamic-Pituitary-Gonadal axis

Declarations

Statement of ethics: Written informed consent was obtained from the patient's parents or from the patients, if adult, for being included in the study. Study protocol was approved by the institute's committee on human research. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Author contributions: Each author have made substantial contribution to the production of this work and approve the submitted version.

Disclosure statements: the authors declare that they have no conflict of interest.

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Figures

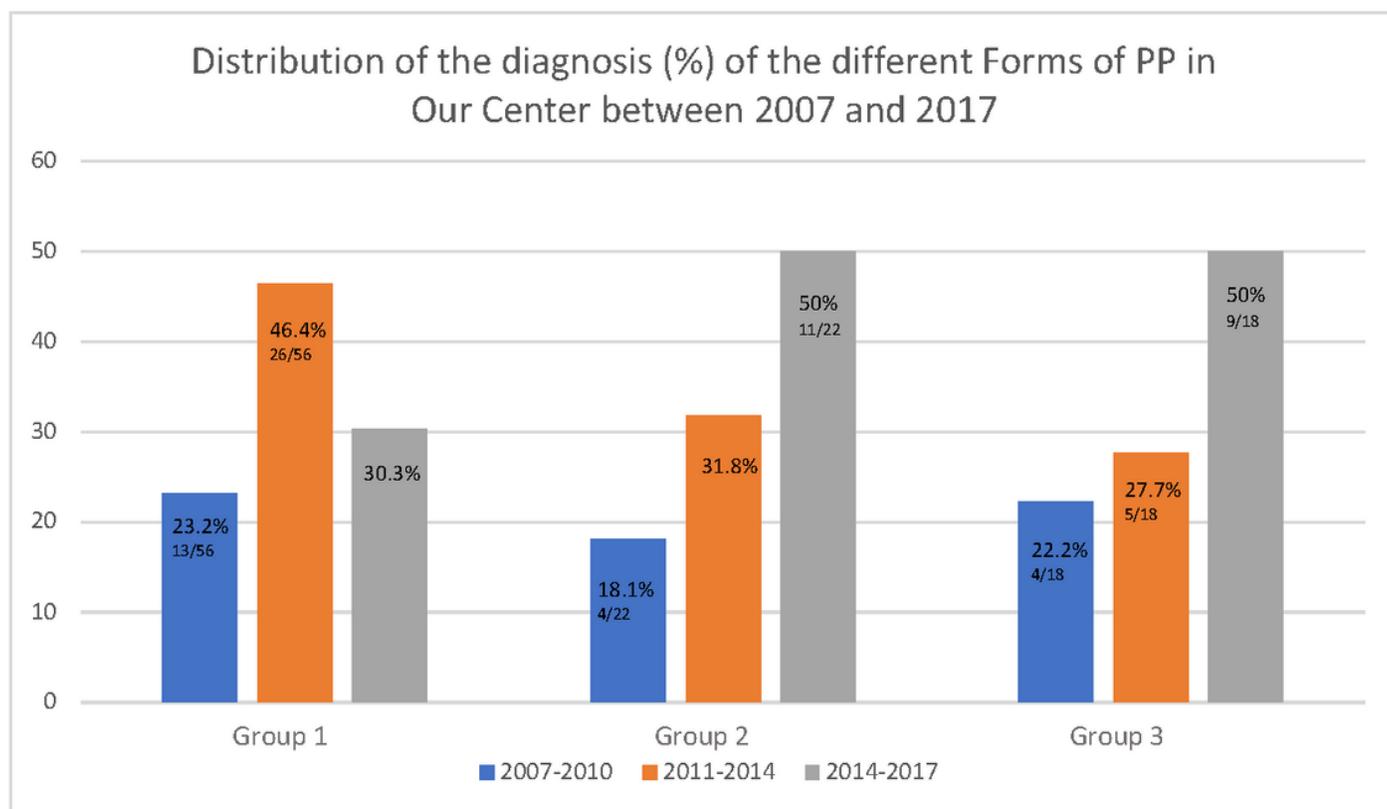


Figure 1

Distribution of the diagnosis (%) of the different forms of PP in our center between 2007 and 2017.

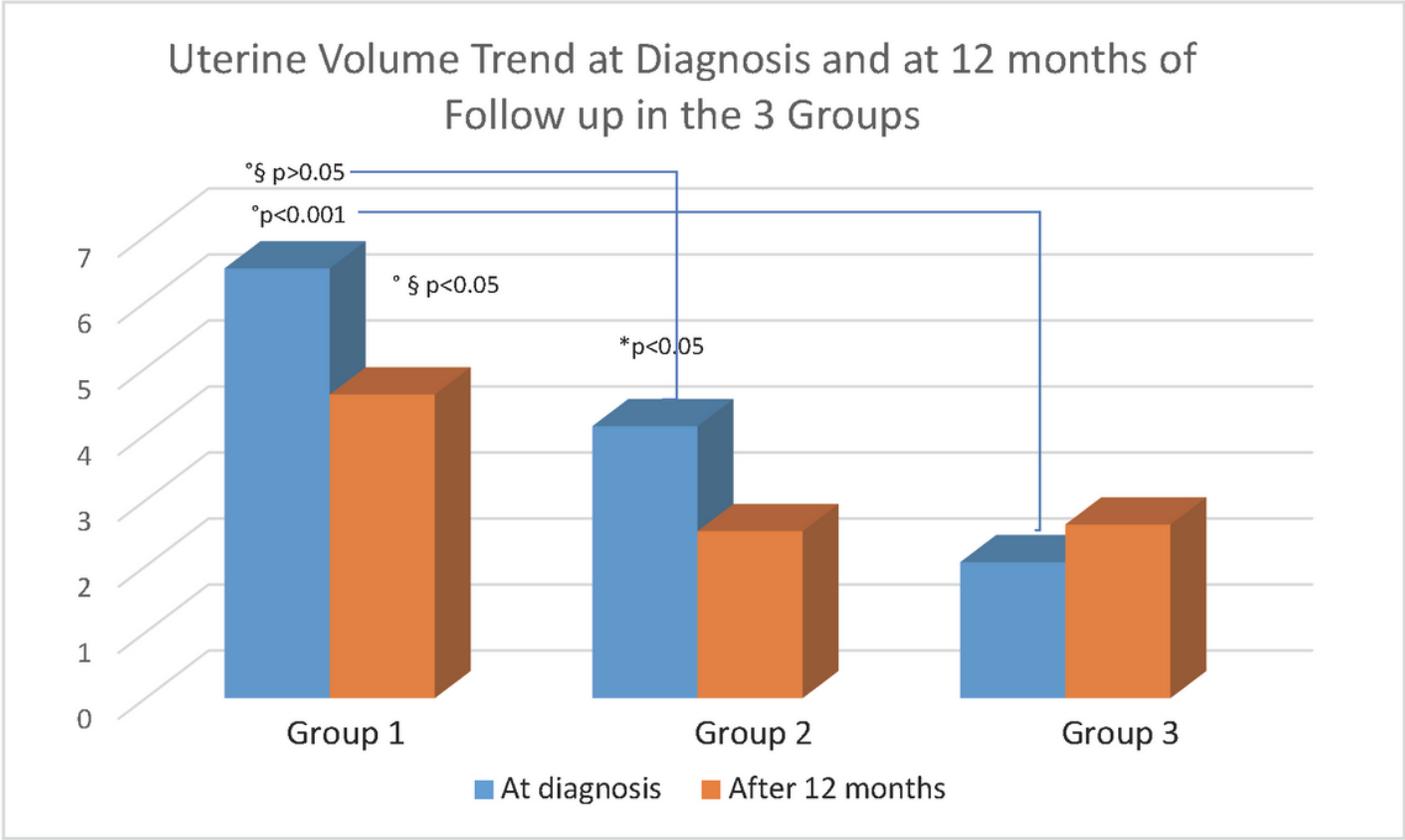


Figure 2

Trend in Uterine Volume at Diagnosis and at 12 months of Follow-up in the 3 Groups