Suppression of Idiopathic Central Precocious Puberty in Girls with Goserline (Zolidex)

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Received 19 May 2013 **Accepted 28 July 2013**

Abstract

Background: The precise neuro-endocrine mechanisms underlying activation of hypothalamic-pituitary-gonad axis maturation are elusive. The wide age range of pubertal onset among normal individuals throughout the world may suggest that both genetic and environmental factors modulate the timing of puberty. Early activation of the hypothalamic-pituitary-gonad axis, termed central precocious puberty (CPP), causes psychosocial difficulties and may lead to compromised final height, especially if medical intervention is delayed

Objective: Depot Gonadotrophin releasing hormone analogues are widely used in the treatment of precocious puberty or suppression of relatively early puberty where growth or psychosocial well-being may be compromised. One example is Zolidex (goserelin 3.6 mg), which can be given every 4 weeks to stop hypothalamic –pituitary ovarian axis until suitable age to start normal activation.

Patients and Method: The study conducted in Babylon Maternity and Paediatrics Teaching Hospital during the period from September 2006 till September 2011. Ten girls with clinical evidence of central precocious puberty were started on Zolidex. Their ages at diagnosis ranged from eight months to 60months (mean 30.3 months).Treatment every four weeks with Zolidex and follow up the response regarding symptoms and signs, ultrasound findings and hormonal assay until the end of the study.

Results : At diagnosis their ages ranged between (8 – 60) months, their weight between (7.5-16) kg mean 12.1± 2.22, height (70 -105)cm mean 75.7±2.54, body mass index 14.51- 21.33 mean 12.15±2.01.clincal presentation breast development associated with pubic hair and vaginal bleeding in three cases. Ultrasound findings uterus large for age in all the cases except one and follicular activity in seven cases return to normal after treatment and remain as such for the rest of the study also Serum Follicular Stimulating Hormone (FSH) before treatment 12.8 IU/L, and 0.4 IU/L after treatment P value0.0001, serum Luteinizing Hormone (LH) before treatment was17 IU/L and after treatment 0.5 IU/L P value 0.0001 and remained normal for the rest of the follow up period..

Conclusion: Zolidex-LA induces a significant reduction in symptoms over 12weeks and great reduction in gonadotrophins within six months.

تثبيط علامات البلوغ المركزي المبكر للفتيات باستعمال الكوزرلين

الخلاصة

الاهداف: ليست هناك طريقة معينة لبدء تحفيز العملية العصبية والهرمونية لبدء النمو وهناك تباين في سن بدء النمو و البلوغ في العالم وهدا يؤيد ان هناك عوامل جينية وبيئية تؤثر على بداية البلوغ وادا بدء قبل السن المحدد يقال له بلوغ قبل الاوان المركزي وهو يؤثر على الحالة النفسية والاجتماعية والطول النهائي خصوصا ادا تاخر التشخيص والعلاج .ان استعمال الكوزرلين في علاج البلوغ قبل السن الطبيعي للبلوغ لتثبيط علامات النمو المبكر يكون كل اربعة اسابيع.

الطريقة: اجريت الدراسة في مستشفى بابل للولادة والاطفال التعليمي للفترة من ايلول ٢٠٠٦الى ايلول ٢٠١١ شملت الدراسة عشرة فتيات لديهن علامات نمو مبكر قبل السن الطبيعي للبلوغ وكانت اعمارهن تتراوح بين ٨ –٦٠ شهرا بعد اخد المعلومات والفحص السريري واجراء التحاليل اللازمة بدء العلاج الشهري الكوزرلين وتمت متابعة الحالات طيلة فترة الدراسة.

النتائج: عند التشخيص كانت اعمارهن تتراوح بين (٨ – ٦٠) شهرا و الوزن بين (٧,٥– ١٦) كيلوغرام والمعدل(٢,٢٢ ±١٢,١) والطول (٧٠ – ١٠٥)سنتمتر والمعدل٢,٥٤+ ٧٥,٧ ومعدل الكتلة للجسم ١٤,٥١ – ٢١,٣٣ والمعدل٢,٠١± ١٢,١٥ وكانت العلامات السريرية هي نمو الثدي وشعر العانة عند جميع الحالات وثلاث منهن هناك بدء الطمث مع العلامات السابقة وفحص الامواج فوق الصوتية بين ان الرحم اكبر من حجمه بالنسبة للعمر وهناك نشاط وبيوض في المبايض في سبعة حالات، توقف نشاطها بعد العلاج خلال ستة اشهر وبقيت حتى نهاية الدراسة حجم الرحم والمبايض طبيعي باالنسبة للعمر ونسبة الهرمون الانثوي قبل العلاج ١,٢٨ وبعد العلاج ٠,٤ وحدة اما الهرمون اللوتيني قبل العلاج كان ١,٧ وحدة وبعد العلاج ٠,٥ وحدة وبقي طبيعي خلال فترة الدراسة.

الاستنتاج: العلاج باستعمال زولدكس (كوزرلين) لعلامات البلوغ المبكر قبل سن البلوغ الطبيعي يقلل الاعراض خلال فترة ١٢ اسبوع والهرمونات خلال ستة اشهر.

Introduction

Precocious puberty may be defined as the appearance of secondary sexual maturation at an early age, before age of 8 years in girls and 9 years in boys. The Lawson Wilkins Paediatric Endocrine Society guidelines recommend that breast development or pubic hair in white girls before age of 7 and black girls before age of 6 should be evaluated for precocious puberty.[1] The aetiology of this is varied it can be due to ovarian tumour ,adrenal tumour ,Gonadotrophin-secreting tumours, exogenous estrogens, neurological (cerebral tumour), hydrocephalus, post meningitis or McCune-Albright Syndrome or idiopathic which constitutes 95% of all cases of precocious puberty. It's likely that is solely due to initiation of the normal process at a premature age.[2]Usually breast growth and the growth spurt occurs first, followed by the appearance of pubic then axillary hair and then menstruation. Stage I the pre-pubertal stage, no development has occurred, Stage II the breast bud begins to grow beneath the nipple Stage III the breast is more rounded, Stage I the nipple and areola project forward, Stage V full adult breast. While pubic hair stages include Stage I pre-pubertal stage no terminal hair is visible Stage II terminal hair on the vulva, Stage III the narrower triangular show darker colour, Stage IV a wider triangular area is covered and greater density, Stage V the adult stage. [3] Gonadotrophin -Dependant precocious puberty occurs ten times in girls than boys. [4]

Body Mass Index (BMI) for children is referred to as BMI-for-age because weight classifications are different at every age, a child's BMI, derived from height and weight measurements, can be plotted onto a gender-specific BMI-for-age growth chart and compared to standards for the child's age. Evaluation of BMI-for-age is based on 'percentile' The BMI-for-age chart helps differentiate between a normal weight gain during growth and excess weight gain BMI-for-age is not as simple as weight, but it is a more accurate measure of excess body weight. Children can be classified into four different categories based on their BMI. Children who are at a 'healthy weight' have a BMI in the healthy range for children of their age. The BMI of 'underweight' children is below the healthy weight range. Two classifications describe children whose BMI is above the healthy weight range – 'at risk of being overweight' and 'overweight'. 'At risk of being overweight' refers to children whose BMI-for-age is between the 85th and 95th percentiles. Children in this range are comparable to adults with a BMI of 25 to 29.9, a classification of being overweight. In children, 'overweight' corresponds to a BMI-for-age greater

than the 95th percentile[1]. This is comparable to adults with a BMI of 30 or more, a classification of obese. [5].
Treatment in cases of idiopathic precocious puberty is to ensure the normal onset of puberty so the treatment of choice is the use of gonadotropin releasing hormone (GnRH) analogues, which are extremely effective in obliterating follicle stimulating hormone (FSH) production by the pituitary by doing this the pre pubertal state is re-established and the child can remain on this when the therapy withdrawn and the onset of puberty will ensue. [2] The advantage of depot preparation which maintain fairly constant serum level of long acting GnRH analogues for weeks. The preparations approved Leuprolide acetate dose 0.25-0.3 mg/kg(maximum 7.5mg) I.M every four weeks, other long acting (D-Trip 6-GnRH Decapeptyl, goserlline acetate (Zolidex) are approved for treatment of precocious puberty [4].

Patients and Methods

This prospective clinical study conducted in Babylon Maternity and Paediatrics Teaching Hospital involved ten patients complained of idiopathic precocious puberty during five years period of treatment and follow up from September 2006 till September 2011, their ages ranged between eight months old and five years. All patients underwent detailed history regarding age, age of onset of symptoms, the presenting symptoms; all were having negative family history and drug history. Detailed physical examination then all sent for ultrasound, hormonal assay including luteinising hormone (LH), follicle stimulating hormone (FSH), estradiol, 17–hydroxy progesterone, thyroid stimulating hormone (TSH), wrist radiograph, magnetic resonance imaging (MRI). To examine the effects of using long acting GnRH analogue (Zolidex) 3.6 mg, subcutaneous injection monthly, follow up the patients monthly by symptoms and signs, ultrasound findings and hormonal assay after six months from starting treatment. Then continue treatment by monthly injection and follow up for the next twelve months, and repeating hormonal assay then follow up for the rest 3.5 years by symptoms and signs and ultrasound findings.
The results were statistically analysed by the help of SPSS version 15 software statistical package using P value at level of significance equal or less than 0.05.

Results

Our study included ten patients with idiopathic precocious puberty their ages at time of presenting symptoms ranged between eight months old and five years old, their height ranged between(70 cm- 105 cm),and their weight (7.5 kg- 16 kg) , body mass index 14.51- 21.33 mean 12.15±2.01 .as in Table -1.
Regarding their symptoms at time of presentation, all the patients had bilateral enlarged breasts stage II, and pubic hair stage I, two patients presented with vaginal bleeding (menstruation) Patient No.1 who was eight months old and Patient No.10 who was five years old while Patient No.4 presented with spotting the rest of the patients had no bleeding as in Table -2.
About pelvic ultrasound findings all of them having large uterus for their age mean 4.9 mm before treatment and six of them with follicular activity and only one had small ovarian cyst as in Table No. 3, cranial MRI was negative for all the patients. After treatment mean uterine length been 2.6 mm and no follicular activities and remained not changed for the rest of the study.

Regarding hormonal assay as in Table No.5, serum LH before treatment range between (1- 2.2) IU/L with a mean of 1.7200 ± 0.35528 and after treatment serum LH mean 0.5400 ± 0.14298 with P value 0.0001, serum FSH level before treatment range between (0.9 - 1.8) IU/L with a mean of 1.2800 IU/L ± 0.33528 and after treatment mean 0.4100 ± 0.14491 with P value of 0.0001, serum estradiol level ranged between (5 -1 5) ng/dl with a mean before treatment 8.200 ±2.85968 and after treatment serum Estradiol mean 2.8000 ± 0.78881 and P value 0.0010 while serum TSH within normal range (1.2 – 2.1) with a mean before treatment 2.2400 ± 0.42216 and after treatment the mean 1.6700 ±0.36833 and P value 0.002.

After six months of treatment symptoms and signs had been controlled, ultrasound findings return to normal as well hormonal assay and remained as such for the rest of the study.

Table 1 Characteristics of patients with Precocious Puberty

Variables	Minimum	Maximum	Mean	SD	95% CI
Age (months)	8.0	60	30.3	13.25854	20.82 – 39.78
Height (cm)	70.00	105.00	75.70	25.48224	57.47 – 93.93
Weight (kg)	7.50	16.00	12.15	2.22424	10.48 – 13.74
Body Mass Index (BMI)	14.51	21.33	17.925	2.01600	16.48 – 19.37

Table 2 Patient's Symptoms at time of presentation

Patient's No.	Presenting Symptoms		
	Bilateral breast development	- Pubic hair	Menstruation
Patient No. 1	+ ve	+ ve	+ ve
Patient No. 2	+ ve	+ ve	- ve
Patient No.3	+ ve	+ ve	-ve
Patient No. 4	+ ve	+ve	+ ve
Patient No. 5	+ ve	+ ve	- ve
Patient No. 6	+ ve	+ ve	- ve
Patient No. 7	+ ve	+ve	- ve
Patient No. 8	+ ve	+ ve	- ve
Patient No. 9	+ ve	+ ve	-ve
Patient N0. 10	+ ve	+ve	+ ve

Table 3 Ultrasound findings for the patients before treatment

Patient's No.	Ultrasound findings		
	Uterine length (large for age)	Follicular activity	Ovarian size (large for age)
Patient No. 1	5 mm	Present	enlarged
Patient No. 2	6 mm	Present	enlarged
Patient No.3	4 mm	Not present	enlarged
Patient No. 4	6 mm	Present	enlarged
Patient No. 5	5 mm	Present	enlarged
Patient No. 6	6 mm	Present	enlarged
Patient No. 7	5 mm	Not present	enlarged
Patient No. 8	3 mm	Not present	Normal ovaries
Patient No. 9	5 mm	Not present	enlarged
Patient N0. 10	4 mm	Present	enlarged

Table 4 Ultrasound findings for the patients after treatment

Patient's No.	Ultrasound Findings after treatment		
	Uterus size	Follicular activity	Ovarian size
Patient No. 1	3 mm	no	Decreased
Patient No. 2	3 mm	no	Decreased
Patient No.3	2 mm	no	Decreased
Patient No. 4	3 mm	no	Decreased
Patient No. 5	2.5 mm	no	Decreased
Patient No. 6	3.5 mm	no	Decreased
Patient No. 7	2 mm	no	Decreased
Patient No. 8	2.5 mm	no	Decreased
Patient No. 9	2.5 mm	no	Decreased
Patient N0. 10	2 mm	no	Decreased

Table 5 Hormonal assays before and after treatment with GnRH analogue

Hormonal Assay	Mean(IU/L)	STD. Deviation	P value
S. FSH before treatment	1.2800	0.35528	
S. FSH after treatment	0.4100	0.14491	0.0001
S. LH before treatment	1.7200	0.35528	
S.LH after treatment	0.5400	0.14298	0.0001
S.Estradiol before treatment	8.2000	2.85968	
S. Estradiol after treatment	2.8000	0.78881	0.001
S. TSH before treatment	2.2400	0.42216	
S TSH after treatment	1.6700	0.36833	0.002

Discussion

We have assessed the symptoms and signs associated with idiopathic central precocious puberty (CPP) in ten girls for five years with their treatment and follow up. The breast development was associated with other signs in all of cases at presentation, leading to the immediate exclusion of premature thelarche,

The distribution of ages at onset of puberty was (8 -60 months) with a mean of 30 months ± 13.25 SD this is differ from that reported in a multicenter study by Cisternino M, et al [6]. In this study, as in Couto-Silva et al [7], the age at onset of CPP was 7–8 years in 60% of cases. : Taher et al [8] the mean age for girls was 4.1year ± 2.5 SD. Midyett et al [9] reported that signs of puberty at 6–8 years should not be considered normal or benign.

The association of CPP with a rapid increase in weight is a difficult confounding factor; it may contribute to the earlier onset of puberty. Researchers around the world develop their conclusions on children and weight using the same Body Mass Index (BMI) formula that is used for adults. In adults, the same BMI chart applies to everyone. Because children grow rapidly, and boys and girls grow at different rates, children's BMI charts are based on age and gender. In our study all BMI for girls within the normal range for age. BMI-for-age is not as simple as weight, but it is a more accurate measure of excess body weight. It corresponds well to levels of body fat and can be used to follow body size from childhood through adolescence and into adulthood. Palmert et al [10] found that those girls with slowly progressing idiopathic CPP had lower BMIs than girls with classical CPP ($P < 0.02$)

In our study breast development was clinically found in all the cases associated with other signs. The differentiation is easy in a girl aged less than two years who presents with isolated breast development. However, breast development associated with light pubic hair development. This is probably due to the neonatal period gonadotropins

peak. In this situation, pubic hair development is associated with increases in the plasma concentrations of delta 4 androstenedione, but not that of DHAS, suggesting that it is of ovarian rather than adrenal origin [11]. Pescovitz and al [12] speculated that premature thelarche and CPP may be different positions along a continuum of hypothalamic GnRH neuron activation. The baseline evaluation of girls with premature thelarche who progressed during follow-up to early puberty established no characteristics that separated them from those who did not progress [13]. A comparison of the frequencies of premature thelarche and of precocious or early puberty showed different results. Kaplowitz et al [14] studied children over a 3 year period for signs of early puberty, and found that the two most common diagnoses were premature adrenarche (46%) and thelarche (18%), while only 9% had CPP. This differs from the data published by de Vries et al [15], who reported that more than half of the children they studied had either idiopathic CPP or early puberty. These authors suggested that the difference between the two studies could be due to the fact that all of their patients were followed for a minimum of 2 years, and that the diagnoses were deferred for at least 6 months when the clinical picture was not clear [16].

The development of pubic or axillary hair is the most frequent clinical sign associated with breast development in all of the cases in our study, Couto ,et al [7] pubic hair occurring in 67% of cases. The uterus length was ≥ 35 mm in 54.6% of the cases evaluated. De Vries et al [17] compared girls with CPP to girls with premature thelarche and showed that, uterine transverse diameter, and uterine volume were the most significant variables predicting CPP. In our study uterine volume large for age and follicular activity found in most of the cases 90%,60% respectively return back to normal for age after treatment. Menstruation found in three cases (30%), in our study been controlled after 12 weeks from starting treatment.

Our study showed means FSH before treatment was 1.28 IU/l. By 6 months of gonadotropins treatment were suppressed to 0.41 IU/l (P 0.0001), and mean LH was 1.72 IU/l and after 6 months of treatment mean LH were 0.54IUlL (P 0.0001). A study by Julie A. et al [18] median peak LH was 13.6 IU/l and median peak FSH was 12.0 IU/l. By 12 weeks gonadotropins were suppressed to 0.9 and 0.8 IU/l, respectively. Palmert et al [10] defined a pre-pubertal response as an FSH peak greater than the LH peak and an LH peak of less than 25 IU/L. The recently reported girl with CPP due to a GPR54-activating mutation had an LH peak of 8.5 IU/L and a plasma estradiol concentration of13 pg/mL during her initial evaluation [19]. The gonadotropin concentration also varies according to the assay used.

In our study Zolidex induces a significant reduction in symptoms and signs within 8-12 weeks and in gonadotropins level within six months. : Julie A., et al [18] found, median peak LH was 13.6 IU/l and median peak FSH was 12.0 IU/l. By 12 weeks gonadotropins were suppressed to 0.9 and 0.8 IU/l, respectively. In the previously treated group, median peak LH at diagnosis was 12.8 IU/l and median peak FSH was 15.0 IU/l with suppression to 0.8 and 1.1 IU/l, respectively, at 12 weeks. In the latter group peak FSH was higher than peak LH at both 8 and 12 weeks ($P < 0.05$) and there was a significant rise in peak LH ($P < 0.05$) and FSH ($P = 0.01$) between 8 and 12 weeks. There was no correlation between age at diagnosis and peak LH or FSH at 8 or 12 weeks. Nevertheless, individual patients in

both groups showed evidence of incomplete gonadotropin suppression at 12 weeks. Most centres are using the analogue leuprolide (aqueous form) at a dose of 20 mcg/kg, up to a maximum of 500 mcg. Some studies suggest that an increase in LH levels to more than 8 IU/L is diagnostic of central precocious puberty, but this depends on the specific LH assay used. A study by Carel et al stated that the peak LH level measured by ICMA that defined CPP was 4.1 IU/L in boys and 3.3 IU/L in girls.[20] Another study suggests that when the baseline LH level is prepubertal, an increase in LH level to 5 IU/L or more after leuprolide correlates well with progression of pubertal signs during a 6-month period of observation[21]

In Our study no family history of precocious puberty, Couto ,et al [7] found only 4% of the mothers of patients were aged less than 10 years at menarche, while de Vries et al [15] found familial factors in 36% girls with idiopathic CPP. This is probably due to the fact that they made a wide familial analysis, not limited to the maternal age at menarche. We did not collect data on the pubertal maturation of the fathers.

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