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Early pubertal development in five children born after assisted reproduction techniques

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Summary

Children born after assisted reproduction techniques are exposed to high doses of hormones in the intrauterine period. The long-term health status of children exposed to high doses of hormones especially during early prenatal development is not known. However, it is discussed that these children may have a risk for low birth weight, prematurity, high blood pressure and high blood glucose and precocious puberty. Here, five subjects who were born with low birth weight using assisted reproduction techniques and who were diagnosed as premature puberty are presented to draw attention to the relation between prenatal exposure to hormones and precocious puberty. (*Turk Arch Ped* 2012; 47: 211-213)

Key words: Assisted reproduction, low birth weight, precocious puberty

Introduction

Puberty is a developmental process which starts in the late childhood and in which reproductive capacity is obtained (1). Precocious puberty is defined as development of secondary sex characteristics before the age of eight in girls and before the age of nine in boys. Currently, it is recommended that the age of onset of puberty be reduced from eight to seven in caucasian girls and to six in African-American girls (2).

Non-organic causes of early puberty include obesity, environmental endocrine disrupters (chemicals, toxins, plastics, hair and body cosmetics, assisted reproduction techniques (ART), psychosocial stress and early sexual stimuli (1). Recently, low birth weight (LBW) has also been shown to cause precocious puberty (3,4).

In this article, cases of precocious puberty in two twin mates who were born with assisted reproduction technique and who had a history of LBW and in one female twin mate were presented and the etiology was discussed.

Case 1,2

A girl aged six and a half years was referred with complaints of breast development and appearance of pubic hair. The male twin mate of this subject was referred with a

complaint of growth of testicle. In their history, it was learned that they were born at the 35th gestational age with a birth weight of 2000 and 1700 g, respectively and microinjection method had been performed because of infertility in the father. Physical examination of the first subject revealed a body mass index (BMI) in the 85-95th percentile, stage III thelarche in both breasts and stage II pubarche. The bone age evaluated with Greulich-Pyle atlas was 8.5 years which was two years advanced compared to the calendar age. The target height was 168 cm, the predicted height calculated with the help of the bone age was 157 cm and retardation was present in comparison to the target height. On physical examination of the second subject, the body mass index (BMI) was in the 50-75th percentile according to age, both testicles had a size of 6 ml, the bone age was 9 years, the target height was 181 cm and the predicted height was 173 cm. Stimulation test with gonaderelin acetate (LHRH) was performed in both subjects. The peak LH response during the test was found to be 11.7 and 13.5 mIU/ml, respectively which were at the pubertal level.

Case 3,4

A seven year-old female subject was referred with a complaint of breast development. Her male twin mate was referred for checking puberty because of his sister. In their

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history, it was learned that they were born at the 37th gestational age after twin pregnancy with birth weights of 2200 and 2100 g and microinjection method had been performed because the father had infertility. On physical examination, the body mass index was found to be in the 50-75th percentile in the female subject and in the 75th percentile in the male subject. The female subject had stage III thelarche in both breasts and stage III pubarche. Both testicles of the male subject were found to have a size of 4 ml. The peak LH response to gonaderelin acetate were found to be 7.2 and 8.3 mIU/mL, respectively which were at the pubertal level.

Case 5

A seven-year old female subject was referred with complaints of breast development and appearance of pubic hair. In her history, it was learned that she was born at the 37th gestational age with a birth weight of 2200 g and microinjection method had been performed because the father had infertility. On physical examination, the BMI was found to be in the 75-85th percentile, pubic hair growth was evaluated as stage II and breast development was evaluated as stage II. The peak LH response to LHRH was found to be 9,6 mIU/mL which was at the pubertal level.

Hormones and their doses which the subjects were exposed to in the intrauterine period due to use of assisted reproduction method could not be learned, but it was learned that a certain protocol was performed.

Clinical and laboratory findings of all subjects are shown in Table 1. No fetal (chromosomal anomaly, metabolic disease, congenital infections and malformation) or maternal (hypertension, diabetes mellitus, smoking, placental failure) factor which could have led to LBW could be found. There was no history of asphyxia or head trauma, consanguineous marriage or precocious puberty in the family.

All subjects caught up with their peers in terms of height and weight by two years of age. There was no history of premature birth or exaggerated adrenache.

Insulin resistance in the subjects was checked using the formula of (HOMA-IR= fasting insulin level (µIU/ml) x fasting

blood glucose (mg/dL) x 0.0555/22.5) and a HOMA-IR value of <3 was evaluated as absence of insulin resistance (5). Accordingly, none of the subjects had insulin resistance. In all subjects, T4, T3, TSH, DHEA-SO₄, ACTH, cortisol and prolactin levels were found to be normal.

Magnetic resonance imaging of the pituitary gland and the brain was normal in all subjects. Ovarian and uterine sizes were compatible with the pubertal period on pelvic ultrasonographic examination of the female subjects.

With these clinical and laboratory findings a diagnosis of idiopathic central precocious puberty was made in all subjects.

Discussion

It is known that the environment which the fetus is exposed to in the intrauterine period has outcomes which may affect the future life. Less frequent breast cancer in girls whose mothers have placental dysfunction and increased risk of prostate cancer in boys with a heavier birth weight are only a few among these outcomes (3). The fact that all of our subjects were twin mates and had LBW suggests that they might have been exposed to the same intrauterine pathology. All of our subjects in whom we could not find any maternal or fetal cause explaining low birth weight were born with microinjection method. In sources, the probability of congenital defects (atrial septal defect, ventricular septal defect, anal atresia and esophageal anomalies) have been reported to be increased by 40% in children in whom assisted reproduction techniques have been used compared to children whose parents have not received infertility treatment and the most common complication in these children has been reported to be LBW (6,7,8). Therefore, we think that LBW in our subjects might be related to use of ART.

In recent years, the course of puberty has been shown to have changed in children with a history of LBW (3). In sources, menarche has been reported to be moved to an earlier time in girls with LBW even though they enter the puberty at a normal age and therefore their final height are affected (9,10).

Studies have shown that central body fat deposition is increased to a great extent in girls with LBW, they have higher IGF-I levels and have early menarche and in contrast, children

Table 1. Physical examination and laboratory findings of the subjects at presentation

Subjects	Birth weight (kg)	Age (years)	Bone age (years)	Target height (cm)	Predicted height (cm)	BMI percentile	Puberty stage	Peak LH response (mIU/mL)	HOMA
1 (F)	2	6.5	8.5	168	157	85-95	T3-P2	11.7	1.7
2 (M)	1.7	8	9	181	173	50-75	Testis 6-6 ml	13.5	1.9
3 (F)	2.2	7	8.5	170	161	50-75	T3-P3	7.2	2
4 (M)	2.1	8	9	183	172	75	Testis 4-4 ml	8.3	2.1
5 (F)	2.2	7	9	172	160	75-85	T2-P2	9.6	2.1

*BW: Birth weight, BA: Bone age, BMI: Body mass index

with a heavier birth weight have lower IGF-I levels and later menarche (11). Although these children do not become obese during the catch-up period, they have relatively higher fat fraction. Therefore, they have a relative insulin resistance, hyperinsulinemia and high IGF-I levels in the early childhood. It is known that hyperinsulinemia moves the onset of puberty to an earlier time and advances the course of the puberty (10). This risk is higher especially in children who catch up with their peers before the age of two (12). All of our subjects who had a low birth weight caught up with their peers before the age of two. Therefore, we believe that LBW might have caused precocious puberty in our female subjects. On the other hand, a number of studies have reported that the pubertal age of boys with LBW is not different from the boys with a normal birth weight in contrast to girls (3,4).

Although we blamed LBW as the cause of precocious puberty in girls, a common cause which could explain precocious puberty was investigated in our twin subjects who shared the same intrauterine environment, since none of our female subjects were obese and had insulin resistance and LBW does not lead to precocious puberty in boys.

It is known that the development of the endocrine system and maturation of endocrine-control systems are affected by intrauterine hormonal changes or intensities (13). Anderson et al.(14) reported that exposure of the fetus to estrogene during the intrauterine period might lead to complications in the future years. Animal experiments (sheep) have shown that increase in pubertal LH occurs earlier as the level of testosterone exposed to during the prenatal period increases (15). Children whose parents use assisted reproduction techniques are also exposed to high levels of hormones in the intrauterine period. Therefore, studies investigating if the onset of puberty changes in children whose parents use ART have been conducted in recent years. In a study performed in Denmark which is the country where assisted reproduction techniques are used with the highest frequency, no difference was found between children whose parents used and did not use ART in terms of onset of puberty (16).

In a study performed in Holland, the bone age was found to be more advanced and LH and DHEA-SO₄ levels were found to be higher in pubertal girls whose parents used in vitro fertilization (IVT) compared to girls who were born as a result of spontaneous pregnancy. However, hormonal levels were not found to be different between boys whose parents used and did not use IVF (17).

Rojas-Marcos et al. (13) found precocious puberty in six subjects and pubic hair growth in one subject among individuals whose parents used ART and whose ages ranged between 5 and 21 years. They reported that pubertal findings did not progress in the follow-up. In this article, it was reported that β hCG levels in the mother and in the amniotic fluid were much higher in subjects with a history of use of ART compared to subject with a history of spontaneous pregnancy. It was reported that β hCG increased androstenedione and DHEA-SO₄ levels and thus the fetus was exposed to high androgene and estrogene, but comprehensive studies were required (13).

Conclusively, exposure of the hypothalamic-pituitary-gonadal axis to high doses of hormones in the intrauterine period may affect the age of onset of puberty. Since there are few publications in sources on this subject, we do not know if ART caused precocious puberty in our subjects. Although assisted reproduction techniques are used widely in our country, there are no studies performed about the age of onset of puberty in these subjects. Therefore, we think that ART should be interrogated in each patient who is referred with precocious puberty. In addition, we believe that subjects with a history of ART should be followed up from birth to the end of the puberty in terms of both potential hormonal changes and the age of onset of puberty.

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