

# Chapter 2

## Precocious Puberty

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### Abbreviations

BMI	Body mass index
CPP	Central precocious puberty
GDPP	Gonadotropin-dependent precocious puberty
GIPP	Gonadotropin-independent precocious puberty
GnRH	Gonadotropin-releasing hormone
MAS	McCune–Albright syndrome
PP	Precocious puberty
PPP	Peripheral precocious puberty
TBI	Traumatic brain injury

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## Introduction

Puberty is defined as the transition from sexual immaturity to sexual maturity. The two main physiological events that occur during puberty include the activation of the gonads by the pituitary hormones also known as “gonadarche” and the production of androgens by the adrenal cortex also known as “adrenarche.”

The normal onset, progression, tempo, and completion of female puberty require a complex series of genetic and hormonal interactions, working together in biological and psychological concert. This is a gradual process with hypothalamic GnRH neurons, called the “gonadostat,” triggering a hormonal cascade and eventually resulting in the physical changes associated with puberty. The initial clinical sign of female puberty is breast development, or thelarche, which normally occurs between the ages of 8 and 13 years. Early, or precocious, puberty (PP) in females is defined as the appearance of thelarche at an age 2.5–3 standard deviations (SD) below the mean age of onset of puberty [1]. In the United States, the traditional definition of PP—thelarche before the age of 8 years old—is still an ongoing debate. It has been recommended that girls who develop signs of puberty between 7 and 8 years of age, the evaluation will depend on the degree, tempo of maturation, and family history [2]. Girls are nearly 12 times more likely to develop precocious puberty when compared with their male counterparts [3].

The causes of precocious puberty are expansive, ranging from variants of normal development to certain genetic syndromes to pathologic conditions with and/or without significant risks of morbidity and mortality. Evaluation involves a complete and thorough history and physical examination, detailing the signs of development, including when these signs began, the timing and progression of these signs, and associated changes in growth. Girls with true precocious puberty, in addition to physical findings of thelarche and pubarche (pubic hair), have early growth acceleration, premature bone maturation, and initially become taller than their peers, but, untreated, ultimately achieve shorter than predicted final adult heights due to premature epiphyseal fusion.

Laboratory analysis of gonadotropins and estradiol will help confirm the presence of true precocious puberty, as well as localize the source of hormone production. Two classifications of precocious puberty include central precocious puberty (CPP), under the influence of pituitary control, or peripheral precocious puberty (PPP), which is secondary to estrogen production outside the influence of pituitary control. Subsequent targeted imaging and/or more specific testing will lead the clinician to a particular etiology. This chapter will provide a case-based review of several causes of precocious puberty in girls as well as discuss diagnostic and treatment modalities.

## **Brain Tumor**

### ***Case Presentation***

A 3.5-year-old girl is referred for evaluation of pubic hair and breast development. The pubic hair was first noted approximately 6 months ago. At a recent well-child physical approximately 1 month ago, she was noted to have developed breast tissue, and she was referred for an endocrinological evaluation. While waiting for this endocrine appointment, there were two times that the parents noted dried blood in her pull-up diaper. She has been otherwise healthy with no other medical problems. She is developmentally appropriate and in pre-kindergarten classes. There is no significant family history. Mother's height is 62 in. and father's height is 66 in. Family denies any environmental exposures of exogenous hormones.

On examination, her height is 105 cm (41 in.) at the 75th percentile and weight was 17 kg (38 lb) at the 72nd percentile; BMI was 15.9 kg/m<sup>2</sup> at the 68th percentile. Review of her prior growth curves shows that she was measured at the 25th percentile for height at age 3 years. Her blood pressure is normal. She has no acne, hirsutism, or cutaneous findings. Pubertal status is Tanner stage 3–4 for breasts with estrogenization of the areolae. Pubic hair is Tanner 3. There is scant axillary hair. The vaginal mucosa appears slightly pink with minimal discharge. There is no clitoral enlargement.

Early morning laboratory testing shows elevated gonadotropins (FSH 6.2 mIU/mL and LH 3.1 mIU/mL) and elevated estradiol of 27 pg/mL (normal range for prepubertal girls 5–20 pg/mL). 17-Hydroxyprogesterone is normal. Bone age X-ray is performed and read as advanced with a skeletal age of 6 years. MRI of the head/pituitary with and without contrast is performed, revealing a well-defined pedunculated hypothalamic mass, measuring  $3.4 \times 2.6$  cm.

## Discussion

This girl has developed glandular breast tissue (thelarche) prior to the age of 8 years in context of pubic hair growth (pubarche) and growth acceleration, consistent with PP. While most pediatric endocrinologists agree with 8 years as the lower limit of the normal onset of puberty in females, studies have shown that there may be racial differences as well as a general drift towards earlier onset puberty, with African American girls as young as 6 years and Hispanic and Caucasian girls as young as 7 years going into puberty without impacting growth potential [4, 5]. In addition, the increasing obesity epidemic in the pediatric population may play a role in this possible decreasing age of pubertal onset [6, 7]. Certain environmental exposures, including contact with exogenous hormones, have been implicated in cases of precocious puberty.

When examining children with concern for precocious puberty, it is important to consider normal variants of pubertal development as a possible alternate diagnosis. Premature thelarche, or isolated breast development without other signs of puberty, is a common and benign condition in girls younger than 3 years old and is often mistaken for precocious puberty. These children do not have pubarche nor growth acceleration or advanced bone ages [3, 7]. FSH levels tend to be elevated, though LH remains in the prepubertal range. Estradiol may intermittently rise into the early pubertal range, though this is not sustained. The breast tissue in these girls tends to regress or even completely resolve, and they will go on to have a normally timed onset of puberty and menarche. Estrogenization of the areolae, which appears as darkening and enlargement, may be present in these cases,

though typically not as marked as in true PP. Premature adrenarche, which may present as apocrine body odor, acne, or axillary and/or pubic hair development before age 8 years, is due to early activation of adrenal androgen production. Children with PA have been shown to exhibit higher early morning serum levels of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, testosterone, pregnenolone, and 17-OH-progesterone. The serum concentration of DHEA-S is the best marker for the presence of adrenarche (level greater than 40  $\mu\text{g/dL}$ ). The androgen levels in the above case are consistent with early Tanner II-III [8–10]. Levels of DHEAS  $>750 \mu\text{g/dL}$  or testosterone  $>150 \text{ ng/dL}$  should prompt evaluation for androgen-producing tumor. Patients with benign premature adrenarche do not have thelarche, growth acceleration, or advanced bone ages. It is important to rule out non-classic congenital adrenal hyperplasia in these patients by way of an early morning ( $\sim 8 \text{ AM}$ ) 17-OH-progesterone level. Girls with CAH will first show signs of early adrenarche, though this can stimulate CPP [3, 7]. Of note, girls who have premature adrenarche in youth may be at risk for developing insulin resistance and polycystic ovarian syndrome (PCOS) in adolescence or later, with some studies citing up to a 15–20 % risk [11–14].

In this case, the patient's labs show elevated gonadotropins and estradiol levels, consistent with central, or gonadotropin-dependent, precocious puberty (GDPP). The most common cause of GDPP in females, in approximately 75 % of cases, is idiopathic [3, 7]. Out of identifiable causes, CNS/hypothalamic tumors are the most common etiology, making up 5–10 % of GDPP cases in female patients [15].

Hypothalamic hamartomas are congenital, non-neoplastic, heterotopic masses of neurons, glia, and fiber bundles that arise from the floor of the third ventricle, tuber cinereum, or mammillary bodies. The prevalence of these CNS masses is thought to be 1–2 per 100,000 and can present with gelastic seizures or other epilepsy, cognitive impairment, psychiatric disorders, or other developmental problems [16, 17]. GDPP secondary to hypothalamic hamartoma is common in younger children, being described in as young as infancy and typically occurring before age 4 years. The method by which the hypothalamic hamartoma results in GDPP is thought to be due to

tumor-related production of pulsatile LH-releasing hormone, thereby overcoming the normal hypothalamic pubertal inhibition [18].

While overall more common in boys with GDPP than girls with GDPP, hypothalamic hamartomas are the classic CNS tumor associated with sexual precocity. Other CNS lesions that may result in CPP include astrocytoma [19], ependymoma, pineal tumors, and optic and hypothalamic gliomas. Patients with neurofibromatosis type 1 (von Recklinghausen disease) in particular may have precocious puberty in association with optic gliomas [20], though precocity may still appear in their absence [21].

The decision to order imaging studies is based on the clinical impression and results of the initial laboratory evaluation. Any physical or laboratory findings suggesting autonomously functioning ovarian cysts or ovarian tumors are indications to obtain a pelvic ultrasound. Pelvic ultrasonography is not indicated as part of the workup in cases of GDPP as there is no focal ovarian pathology. Pelvic ultrasound could be used to monitor pubertal progress in girls; with uterine volume changes above 2 mL suggest progressive puberty. Should a transabdominal pelvic ultrasound be performed in a patient with GDPP, one may simply see an increase in size of the uterus and ovaries similar to that of a pubertal female, possibly with multicystic ovaries; these ovarian changes may not regress following GnRH analogue treatment, though this does not appear to have any clinical implications [22].

Rarely, severe undiagnosed hypothyroidism may result in precocious puberty; the mechanism is not completely understood though thought to be due to increased TRH activation of gonadotropes. Treatment with levothyroxine will reverse the precocious puberty [23, 24].

## *Management*

The primary physical result of untreated precocious puberty is short final adult height due to premature fusion of the epiphyseal growth plates under the influence of excess estrogen production. In addition to the physical, there may be cases in which the final adult height is

not impacted, but psychological or psychosocial aspects of early puberty may be worrisome to the patient and/or the family. Precocity of secondary sexual characteristics has been linked to aggression, delinquency, negative self-image, and an increased risk of possible sexual exploitation/abuse [25–27]. Should children be seen by their parents or caregivers as too immature to handle physical changes associated with puberty, treatment may be indicated. In these cases of idiopathic GDPP, treatment to suppress pituitary gonadotropins using GnRH agonists, as detailed below, would be indicated.

FSH and LH rise in puberty due to the pulsatile release of GnRH from the hypothalamus [4, 5]. GnRH agonists, such as the monthly or quarterly leuprolide acetate depot IM injection or yearly histrelin subdermal implantation, will introduce a constant, non-pulsatile GnRH milieu, effectively desensitizing and decreasing gonadotropin release. The choice of formulation depends on family, the clinician, and the insurance preference. These formulations have not been directly compared to each other in randomized trials, but appear to have a similar effect in suppressing the axis. Response is judged on subsequent physical examination, during which signs of puberty should be noted to have stopped progressing and then to regress over the first 6 months of treatment. Growth velocity should return to a typical prepubertal rate. Gonadotropin and estradiol levels should decrease to prepubertal levels within a month following treatment. Labs should be routinely monitored during treatment, as should the bone age. Patients who do not have very advanced bone ages prior to treatment tend to have better results with respect to gaining back their height potential [3, 28]. Discontinuation of therapy should be based on the patient's age, growth velocity, bone age, height prediction, and psychosocial readiness. Treatment with GnRH agonists appears to have no significant long-term effects on the pituitary–gonadal axis. Bone density may decrease during prolonged therapy, but is regained after treatment, therefore monitoring of bone density is not required.

Treatment of hypothalamic hamartoma is directed towards its removal, especially in those who have frequent seizures as a result of the mass. Over the past 2 decades, newer advances in surgical approach, including microsurgery, gamma knife surgery and stereotactic radiosurgery, and radiofrequency ablation, have allowed neurosurgeons to treat patients with minimal complications [29].

## ***Outcome***

The patient underwent placement of a histrelin implant, which halted further progression of puberty. Repeat labs ~3 months after implant showed prepubertal levels of FSH and estradiol; LH remained in the early pubertal range. She was referred to neurosurgery for her hypothalamic hamartoma, and the family elected to observe the mass with repeat MRI in 6 months. During the interval, though, the patient developed a seizure and the mass ultimately required resection. No further seizure activity occurred and her examination 1 year after treatment was significantly improved with near regression of all pubertal signs.

## ***Clinical Pearls/Pitfalls***

1. Central or gonadotropin-dependent precocious puberty is the most common cause of precocious puberty in females.
2. The first sign of puberty in females is thelarche in context of growth acceleration, advanced bone age, and possibly pubarche.
3. Laboratory testing will reveal elevated gonadotropins and estradiol; MRI of the brain is the diagnostic imaging of choice.
4. Following appropriate evaluation, most patients are found to have idiopathic GDPP.
5. CNS tumors, specifically hypothalamic hamartomas, are the leading identifiable cause of female CPP in young patients.
6. Treatment of CPP may involve GnRH agonist to suppress further gonadotropin release.

## **Ovarian Cyst**

### ***Case Presentation***

A 4.5-year-old girl is referred for evaluation of breast development and vaginal discharge. Her family states that she has been noted to have progressive breast enlargement over the preceding



6 months. This was first noted when the patient's mother was holding her and felt "a lump" on her chest. This concern was brought to the attention of the pediatrician, who reassured the family. Over the past 2 weeks, she has been noted to have some whitish appearing vaginal discharge. There has not been any pubic or axillary hair growth nor any acne or adult body odors. Her family states that there was one time, approximately 3 weeks ago, that they noted some dried blood in her underwear. Her general health has been otherwise good, and she has no other medical issues. Family denies any environmental exposure. Review of her growth curves shows increased height percentile since last year, from the 25th percentile to the now ~50th.

On examination, her height is 105 cm (41 in.) at the 56th percentile and weight is 16.5 kg (36.5 lb) at the 43rd percentile; BMI is 14.9 kg/m<sup>2</sup> at the 41st percentile. Her blood pressure is normal. She has no acne, hirsutism, or cutaneous findings. Pubertal status is Tanner stage 2 for breasts with estrogenization of areolae. Pubic hair is Tanner 1. The vaginal mucosa appears slightly pink with mild discharge. There is no clitoral enlargement.

Laboratory testing included gonadotropins and estradiol. Follicle-stimulating hormone (FSH) is 0.085 mIU/mL and luteinizing hormone (LH) is 0.01 mIU/mL, both low and in the prepubertal range. Estradiol is elevated at 270 pg/mL. Bone age X-ray is performed and read as consistent with the patient's chronologic age. Transabdominal pelvic ultrasound identifies a left ovarian simple cyst, measuring 3.8 cm. Endometrial thickness is 2 mm and within normal limits for age.

## ***Discussion***

Similar to the first case, this patient also has precocious puberty, evidenced by the presence of thelarche prior to the age of 8 years in association with growth acceleration. In this situation, though, while the estradiol is extremely elevated, the gonadotropins are suppressed. This is consistent with peripheral, or gonadotropin-independent, precocious puberty. GIPP in females is secondary to

autonomous secretion of ovarian estrogens (via cyst, tumor, or non-gonadotropin stimulation), adrenal neoplasm, or exogenous exposures to estrogens [5].

The most common cause of GIPP is autonomously functioning ovarian follicular cysts [30]. GIPP should be strongly considered in the differential diagnosis where thelarche is the predominant or initial sign of pubertal development (as opposed to pubarche). As detailed earlier, it is important to distinguish benign premature thelarche, the presence of breast tissue without other signs of puberty, from PP; girls with benign premature thelarche do not have growth acceleration or an advanced bone age.

If a diagnosis of precocious puberty is made in context of an autonomously functioning ovarian cyst, the patient should be evaluated for possible McCune–Albright syndrome (MAS). MAS is a genetic condition in which a somatic mutation in the *GNAS1* gene results in constitutively activating the  $G_s\alpha$  protein present in many tissues. In addition to GIPP, the classic findings of the syndrome include large café-au-lait macules with irregular borders (referred to as “coast of Maine” in appearance) and polyosteoitic fibrous dysplasia, a slowly progressive bone disorder [5]. Hyperfunctioning autonomous endocrinopathies in MAS are typically associated with the ovary, though due to the presence of the  $G_s\alpha$  protein in the receptor for other pituitary hormones, patients with MAS may also develop hyperthyroidism, Cushing syndrome, gigantism/acromegaly, or hyperparathyroidism. Diagnostic workup for these patients involves skeletal X-rays to look for the bony findings of MAS, as well as endocrine investigation for these other associated conditions.

Ovarian tumors are rare in the prepubertal period and usually present with abdominal pain or distention, though they may present with signs of virilization or early puberty. While adult ovarian tumors tend to arise from the ovarian epithelium, pediatric tumors usually originate from germ cells or sex cord-stromal cells [31]. The most common of these rare tumors is the granulosa cell tumor, followed by the theca cell tumor and sex cord-stromal cell tumors. Estrogen may be produced by the tumor and result in signs of precocious puberty. Tumor markers, anti-Müllerian hormone (AMH)

and inhibin, can be used for screening or during recovery [32]. Sex cord-stromal cell tumors may result in elevated testosterone levels and should be examined in context of possible Peutz–Jeghers syndrome, a condition characterized by mucocutaneous hyperpigmentation, gastrointestinal hamartomatous polyposis, and an increased risk of malignancy due to a mutation in serine/threonine kinase 11 (STK11), a tumor-suppressing gene [33]. Surgical resection is the treatment of choice for ovarian tumors and in young girls prognosis tends to be favorable.

Transabdominal pelvic ultrasound in a patient with GIPP may identify a large tumor or one or more cysts of the ovary. Small, unilocular ovarian cysts of less than 1 cm in diameter in prepubertal girls are clinically insignificant, while ovarian cysts associated with GIPP are generally larger than 2 cm in diameter [34].

## ***Management***

Most autonomously functioning ovarian cysts will spontaneously involute, thereby removing the estrogen production and causing the precocious puberty to regress. Surgical excision of the cyst is reserved for refractory cases, complex ovarian masses, or large cysts where there is a risk for ovarian torsion [35]. Those patients who do not meet criteria for surgery can be clinically monitored with examination and repeat labs and ultrasound every 6 weeks.

In contrast, patients with MAS have a somatic (postzygotic) mutation of the alpha subunit of the G3 protein that leads to continued stimulation of endocrine function. Thus, for those patients who have progressive GIPP, simple observation may not be appropriate as functional ovarian cysts may not spontaneously involute, and new cysts will invariably develop. Medical therapy with aromatase inhibitors such as Letrozole, which block the production of estrogens, and estrogen-receptor modulators such as Tamoxifen have been attempted with success as adjuvant therapy with surgical resection of large cysts, though with limited patient data and no long-term outcome studies [36, 37].

## ***Outcome***

The patient was initially observed clinically over the next month, during which time her breast development began to regress. Repeat ultrasound showed a similarly sized cyst, though with newly noted possible septations. Due to change in appearance, she was referred to pediatric surgery for consultation, who recommended continued observation. Three months later, the cyst had nearly completely involuted and her labs showed a prepubertal estrogen level. Repeat bone age showed no further advancement. She continued to follow every 6 months for monitoring of her growth.

## ***Clinical Pearls/Pitfalls***

1. Estrogen-producing ovarian cyst should be considered in girls with isolated thelarche.
2. Simple ovarian cysts that autonomously produce estrogen tend to involute on their own without treatment; in most cases patients can be observed over time for resolution/regression of their GIPP.
3. Surgical referral is indicated for complex or large ovarian cysts.
4. GnRH agonists are not indicated in the treatment of GIPP.

## **Head Trauma**

### ***Case Presentation***

A 5-year-old female is referred for breast development, pubic hair, and vaginal secretions. She was born full term to a healthy mother and had normal growth and development until age 4 years when the patient was a restrained passenger in a severe automobile accident. Sustaining multiple fractures and a closed head injury with depressed skull fractures, she was hospitalized for a prolonged

period, including inpatient rehabilitation. She currently resides at home, though she has severe developmental delay and learning disabilities. Her home nurse noted breast and pubic hair development around 3–4 months ago and more recently saw whitish vaginal discharge in her diaper last month and once again last week. There is no pertinent family history and maternal menarche was at age 11 years.

On examination, her height is 109 cm (43 in.) at the 59th percentile and weight is 22 kg (48.5 lb) at the 89th percentile; BMI is 18.5 kg/m<sup>2</sup> at the 96th percentile. Her blood pressure is normal. She has no acne, hirsutism, or cutaneous findings. Pubertal status is Tanner stage 3 for breasts with estrogenization of areolae. Pubic hair is Tanner 2. The vaginal mucosa appears slightly estrogenized. There is no clitoral enlargement.

Laboratory testing shows an FSH of 9.1 mIU/mL, LH of 4.5 mIU/mL, and estradiol of 25 pg/mL (range for prepubertal girls 5–20 pg/mL). Thyroid function is normal for age. Prolactin is 9 ng/mL (normal 3–24 ng/mL). Bone age X-ray is performed and read as consistent with the patient's chronologic age. Her most recent MRI, performed 1 month ago, shows generalized cortical atrophy, though a normal appearing pituitary.

## ***Discussion***

This patient has survived a traumatic brain injury (TBI) and now has signs of precocious puberty. Laboratory analysis shows a GDPP picture, similar to Case #1. GDPP resulting from TBI has been well described in the literature [38–42], though not completely well understood. The presumed mechanism of TBI-related PP is through the loss of hypothalamic inhibition of pituitary gonadotropins. Infundibular-hypophyseal structures are at particularly high risk of mechanical and vascular damage due to their anatomic placement and blood supply [28].

In a study of 31 children post-TBI, 29 % of patients had endocrine dysfunction at 12 months after injury, half of which showed precocious puberty [43]. In contrast, another study of 198 survivors

of TBI, only 2 patients had precocious puberty, a rate consistent with the general population [44].

Beyond GDPP, patients with a history of TBI are at risk for other pituitary endocrine abnormalities, including growth hormone deficiency, central hypothyroidism, secondary adrenal insufficiency, and diabetes insipidus.

## ***Management***

The treatment of TBI-related GDPP is the same as idiopathic GDPP—with use of GnRH agonists to suppress the usual pulsatile action and subsequent gonadotropin release.

## ***Outcome***

This patient underwent placement of a histrelin implant. Repeat labs 3 months following the implantation showed improvement of gonadotropins and estradiol. Six months following the implantation, the breast development had completely regressed.

## ***Clinical Pearls/Pitfalls***

1. TBI brain injury may result in precocious puberty, as well as other endocrine abnormalities.
2. TBI-related precocious puberty is gonadotropin dependant.
3. The mechanism of this finding is not completely understood, but thought to be due to disinhibition of the pituitary gonadotropes at the level of the hypothalamus.
4. Treatment typically involves depot leuprolide acetate injections or long-acting yearly histrelin implantation.

## Exogenous Hormones

### *Case Presentation*

Two sisters, ages 4 and 7, are referred for breast development. Both girls are otherwise healthy, with the exception of eczema, treated with topical over-the-counter moisturizers. Their mother had noticed some breast development in her older daughter approximately 9 months ago and then in her younger daughter 4 months ago. She has not seen any axillary or pubic hair. There has been no vaginal bleeding, but mother is unsure about vaginal discharge. There is no family history of precocious puberty. Maternal menarche was at 14 years of age. The girls were both products of in vitro fertilization as the mother was 41 at the time of the first pregnancy and had difficulty conceiving; she is now menopausal.

On examination of the 7 year old, her height is 120 cm (47 in.) at the 37th percentile and weight is 31 kg (68 lb) at the 94th percentile; BMI is 21.5 kg/m<sup>2</sup> at the 98th percentile. Her blood pressure is normal. She has no acne, hirsutism, or cutaneous findings. Pubertal status is Tanner stage 3 for breasts with estrogenization of the areolae. Pubic hair is Tanner 1. There is no axillary hair. The vaginal mucosa appears slightly pink. There is no clitoral enlargement.

On examination of the 4 year old, her height is 107 cm (42 in.) at the 91st percentile and weight is 17 kg (37 lb) at the 69th percentile; BMI is 14.8 kg/m<sup>2</sup> at the 35th percentile. Her blood pressure is normal. She has no acne, hirsutism, or cutaneous findings. Pubertal status is Tanner stage 2 for breasts with estrogenization of the areolae. Pubic hair is Tanner 1. There is no axillary hair. The vaginal mucosa appears slightly pink. There is no clitoral enlargement.

Early morning laboratory testing on both girls shows low prepubertal gonadotropins and elevated estradiol (26 pg/mL for the 7 year old, 37 for the 4 year old). Adrenal androgens are prepubertal. 17-Hydroxyprogesterone is normal. Thyroid function was normal. Bone age X-rays are performed and read as slightly advanced for both girls. Pelvic ultrasound on both girls revealed normal ovaries without any masses or cysts.

## ***Discussion***

Examination and laboratory testing for these sisters shows a picture consistent with GIPP (low gonadotropins, elevated estradiol), though the ovaries appear normal on ultrasound. Prepubertal girls have an average ovarian size of  $2.0 \pm 1.5 \text{ cm}^3$  and by Tanner II, the average right ovarian size increases to  $3.2 \pm 3.0 \text{ cm}^3$  and  $2.7 \pm 1.8 \text{ cm}^3$  for the left ovary [45].

The fact that siblings developed the same condition at the same time should raise suspicions of an environmental factor. Exogenous estrogens can be found in multiple different places, from medications such as estrogen creams and oral contraceptive pills to contaminated foods, milk, from excessive drinking of soy formulas to many over the counter herbal remedies or multivitamins [46–49]. When taking a history with respect to precocious puberty, an astute clinician should inquire about exposures to other people's medications, herbal supplements or remedies, or other possible sources of exogenous estrogens.

## ***Management***

Upon removal or avoidance of the offending external source of estrogen, the symptoms should resolve and abate. Unfortunately, the source may not always be readily apparent and may require a detailed social, medical, and family history.

## ***Outcome***

Upon further questioning, it was discovered that the girls' mother has been using an estrogen cream, prescribed by her gynecologist. The girls, thinking that they were using a moisturizer for their eczema, were applying the estrogen cream to their skin when their parents were not watching them. Upon cessation of the cream, the girls' breast development regressed over the course of <6 months.



### ***Clinical Pearls/Pitfalls***

1. Exposure to exogenous estrogens can cause GIPP.
2. A careful history help along with traditional laboratory testing and imaging are useful tools to make this diagnosis.
3. Removal of the exposure will cause the signs and symptoms of precocious puberty to resolve.

## **Endocrine Disruptors**

### ***Case Presentation***

A 6-year-old girl is referred for evaluation of pubic hair and breast development. She is recent immigrant to the United States, having moved here with her family from Colombia only 2 months prior. The family were farmers back in their home country, and the patient indicated that she misses being able to play in the fields all day with her father while he worked. She is otherwise healthy and has no other medical problems. She is developmentally appropriate and there is no significant family history.

On examination, her height is 125 cm (49 in.) at the 97th percentile and weight is 25 kg (55 lb) at the 89th percentile; BMI is 16 kg/m<sup>2</sup> at the 69th percentile. There are no prior growth records to review, but her midparental height is 64". Her blood pressure is normal. She has no acne, hirsutism, or cutaneous findings. Breast development was Tanner stage 3 and pubic hair was Tanner stage 2. The vaginal mucosa was pink and physiologic discharge was present.

Early morning laboratory testing shows elevated gonadotropins (FSH 7 mIU/mL and LH 4.3 mIU/mL) and elevated estradiol of 40 pg/mL. Adrenal androgens are consistent with mid-puberty. 17-Hydroxyprogesterone is normal. Bone age X-ray is performed as read as advanced with a skeletal age of 10 years. MRI of the head/pituitary with and without contrast is performed and is normal. Further discussion reveals that the patient was likely chronically exposed to her father's pesticides while in the fields.

## ***Discussion***

Endocrine disruptors are environmental chemicals, either natural or manmade, that can interact with the normal hypothalamic–pituitary–gonadal axis [50–52]. In the case of female precocious puberty, this can be via directly binding to and activating estrogen receptors, by increasing aromatase activity, or through GnRH stimulation [53]. Therefore, PP due to endocrine disruptors may cause either GDPP or GIPP.

Phytoestrogens, such as daidzein, genistein, glycitein, and biochanin-A, are relatively weak estrogen mimetics and can be found naturally in certain foods. One would need to consume very large amounts of these foods—garlic, apple, legumes, and coffee—to see an observable estrogenic effect [54].

Synthetic endocrine disruptors are becoming increasingly cited as the cause for the ever-drifting lower age of the normal onset of puberty. These chemicals—diethylstilbestrol (DES), DDT, dioxin, and many other pesticides, industrial products, and compounds—have been implicated in affecting pubertal development in animal and human studies [35, 55]. DDT in particular, an organochlorine pesticide, can be biologically broken down into p,p'-DDE, a central disruptor of puberty. Though not commercially available in the United States and Europe since the 1970s, DDT is still used in developing countries worldwide [56]. Phthalates in plastics, including food containers, medical equipment, and children's toys, have been implicated in similar processes [57, 58].

## ***Management***

As with direct exogenous estrogen exposures, removal of the offending agent should improve the symptoms. Prior long-term chronic exposure to the agent, though, may result in the precocity taking a long time to resolve. Avoidance of PVC products and phthalate-containing plastics for play or food-storage should be maintained. If by removing the offending agent, the pubertal

manifestations regress or stop progressing, no treatment is necessary. Although the mechanism underlying these cases of nonprogressive precocious puberty is unclear, it is known that the gonadotropic axis is not activated. In contrast, for cases in which precocious puberty progresses due to activation of the gonadotropic axis, removal of the offending agent does not result in regression of symptoms or arrest of progressive bone age advancement. In these cases, medical treatment with GnRH agonists may be indicated. In other cases, anti-estrogen or anti-androgen agents may be considered [50].

## *Outcome*

After being exposure-free from DDT products, the patient's puberty did stop progressing, but due to such significant prior advancement in puberty, she was treated with histrelin (GnRH agonist) implant to prevent further progression of pubertal development.

## *Clinical Pearls/Pitfalls*

1. Environmental compounds, either natural or manufactured, can cause disruption in the normal hypothalamic–pituitary–gonadal axis, resulting in precocious puberty.
2. A detailed history is necessary to decipher these difficult and varied disruptors.

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