Treatment of precocious puberty

Author
Paul Saenger, MD, MACE

Section Editors
Peter J Snyder, MD
William F Crowley, Jr, MD
Mitchell Geffner, MD

Deputy Editors
Alison G Hoppin, MD
Kathryn A Martin, MD

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INTRODUCTION — Precocious puberty had been defined as the onset of secondary sexual development before the age of eight years in girls and nine years in boys. Because of trends towards earlier pubertal development, a substantial portion of healthy girls will have breast or pubic hair development before this age, and extensive evaluation and treatment usually are not required.

If the evaluation leads to a diagnosis of precocious puberty, treatment may be considered. The treatment options depend upon the cause of the precocious puberty, as discussed below. The definition, etiology, and evaluation of precocious puberty are presented separately. (See "Definition, etiology, and evaluation of precocious puberty".)

CLASSIFICATION — Precocious puberty can be classified based upon the underlying pathologic process.

- **Gonadotropin-dependent precocious puberty** — Gonadotropin-dependent precocious puberty (GDPP, also known as central precocious puberty or true precocious puberty) is caused by early maturation of the hypothalamic-pituitary-gonadal axis. GDPP is characterized by sequential maturation of breasts and pubic hair in girls, and by testicular enlargement and pubic hair development in boys. In these patients, the sexual characteristics are appropriate for the child's gender (isosexual). GDPP is idiopathic in more than 80 percent of cases, and almost all idiopathic cases occur in girls. In a small number of girls and boys, GDPP is caused by a central nervous system lesion (table 1A). (See "Definition, etiology, and evaluation of precocious puberty", section on 'Causes of gonadotropin dependent precocious puberty (GDPP)'.)

- **Gonadotropin-independent precocious puberty** — Gonadotropin-independent precocious puberty (GIPP, also known as peripheral precocious puberty or pseudoprecocious puberty) is caused by excess secretion of sex hormones (estrogens or androgens) derived either from the gonads or adrenal glands (table 1B). Puberty may be appropriate for the child's gender (isosexual) or inappropriate, with virilization of girls and feminization of boys (contrasexual). Similar findings can be induced by inadvertent exposure to exogenous sources of sex steroids or, in boys, by ectopic tumoral production of gonadotropin (ie, human chorionic gonadotropin [hCG]). (See "Definition, etiology, and evaluation of precocious puberty", section on 'Causes of gonadotropin independent precocious puberty (GIPP)'.)

- **Incomplete precocious puberty** — Incomplete precocious puberty is defined as isolated breast development in girls (premature thelarche) or isolated male hormone-mediated sexual characteristics, such as pubic and/or axillary hair, acne, and apocrine odor in boys or girls that results from increased adrenal androgen production (premature adrenarche) (table 1C). Both of these disorders can be a variant of normal puberty. However, these children should be monitored because some progress to precocious puberty. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Types of incomplete precocious puberty'.)

TREATMENT FOR GDPP — When gonadotropin-dependent precocious puberty (GDPP) is caused by an identifiable central nervous system lesion, therapy is directed toward the underlying pathology when possible. An important exception is a benign hypothalamic hamartoma, which is almost always left in situ and monitored neuroradiologically over time [1].

For most patients with GDPP, the primary treatment option is a gonadotropin-releasing hormone (GnRH) agonist. This treatment is often appropriate for patients with idiopathic GDPP, for GDPP caused by a benign hamartoma, or for secondary activation of GDPP, which may occur in patients who initially present with gonadotropin-independent precocious puberty (GIPP) [2]. For such patients, treatment with GnRH agonists is generally safe and effective. However, not all patients require treatment, as outlined in the following section.

Decision to treat — The primary goal of treatment for GDPP is to allow a child to grow to a normal adult height. Therefore, the decision to treat should include analysis of the predicted height benefit from treatment, as discussed in this section. Parents are often concerned about the prospect of early menses, which might be distressing in a very young girl. However, treatment primarily to address perceived psychosocial consequences of precocious puberty should be approached with caution because of scant data in this area [3].

The decision of whether to treat GDPP with a GnRH agonist depends upon the child's age, the rate of pubertal progression (sexual maturation), height velocity, and the estimated adult height as determined from the rate of bone age advancement. In the following discussion, pubertal progression would be considered slow if there is no change in stage of breast, pubic hair, or genital development during six or more months of observation (table 2) [4]. Height velocity is considered accelerated if it is more than 6 cm per year. The relationship between pubertal stages and height velocity in normally developing children is outlined in the figure (figure 1A-B) and discussed in detail elsewhere. (See "Normal puberty", section on 'Pubertal changes'.)

Clinical decision-making is guided by the following considerations:

- **Age** — Children with GDPP who present at a younger age and have a rapid progression of maturation will have early epiphyseal fusion and reduced adult height if they are not treated. These children will benefit the most from therapy [3]. In contrast, children who present close to the age of normal puberty or who have a very slowly progressive variant of precocious puberty may not require any therapy [5-8].
    - For girls, GnRH agonist treatment results in an average gain in adult height of 9 to 10 cm if therapy is begun before the age of six, and 4 to 7 cm if begun between six and eight years of age [3]. However, the height gain from GnRH therapy would be on the lower end of this range if the child's bone age is advanced.
    - For boys, fewer data are available. One study estimated that GnRH treatment beginning at an average of 7.6 years resulted in a mean height gain of 6.2 ± 8.7 cm [9]. An expert panel concluded that it is reasonable to consider GnRH agonist treatment for boys with progressive GDPP if they present before nine years of age [3]. As in girls, the height gain is likely to be attenuated if the child has advanced bone age at the initiation of GnRH agonist therapy.
    - Children who present later and have passed their peak height velocity may present with slow height velocity for their chronologic age. Although GnRH agonist therapy would be expected to further reduce the height velocity, it will also delay epiphyseal fusion. The net result is usually slow but progressively increases in predicted height, which may not be of sufficient clinical value to justify treatment in an individual patient [3,4,10].
- **Rate of maturation** — If precocious puberty is slowly progressive, it is unlikely to compromise adult height potential. In a study of 16 such girls who were followed for 12 years without treatment, all reached normal adult height [6]. Despite the early onset of breast development in this group, menarche occurred at a normal age (average age 11 years). Similarly, in a group of 35 boys with slowly progressive puberty (defined as progression from sexual maturity rating [Tanner] stage 2 to 3 over more than 18 months) who were not treated, adult height was within the range of their target height (table 3) [8]. Clinical experience has shown that many cases of precocious puberty, particularly in girls with onset after six years of age, will be slowly progressive.
- **Height prediction** — If the height prediction (based upon the height and height velocity, combined with bone

age) is above 150 cm in girls and above 160 cm in boys, therapy is probably not needed to achieve normal adult height, and a conservative approach is warranted [5]. (See "Diagnostic approach to children and adolescents with short stature", section on 'Prediction of adult height'.)

As an example, a child presenting with GDPP before the age of six with breast and pubic hair development, advanced bone age, and accelerated height velocity is likely to benefit from GnRH agonist therapy. Conversely, in a child with early onset of puberty and historically slow progression of pubertal development and height velocity, it is appropriate to monitor without treatment for three to six months to establish the pace of the pubertal progression (table 2) before making treatment decisions [3].

GnRH agonist treatment — For GDPP, GnRH agonist therapy is a safe and effective treatment [8,10-17]. GnRH agonist administration results in an initial stimulation of pituitary gonadotropin secretion, followed by a complete but reversible suppression of the pituitary-gonadal axis, making this an ideal option for treatment of precocious puberty and other diseases mediated by gonadal steroids. GnRH agonist administration slows accelerated puberty and improves final height compared with pretreatment predicted height. Treatment should be given until it appears that it is safe and appropriate for puberty to proceed.

Effects on height — The efficacy of long-term treatment with a GnRH agonist was illustrated in a report of 98 children with GDPP [10]. Treatment with deslorelin or histrelin was begun at an average age of 5.3 years and continued for an average of 6.1 years. The final height in the 80 girls was 159 ± 7.6 cm, which was greater than the pretreatment predicted height of 149.3 ± 9.6 cm but less than the midparental height of 163.7 ± 5.6 cm. Final height in the 18 boys was 171.1 ± 8.7 cm, greater than the pretreatment predicted height of 156.1 ± 14.2 cm but less than midparental height of 178.3 ± 5.2 cm. As expected, earlier initiation of treatment led to the best outcomes: in 54 patients who had less than a two-year delay between the onset of puberty and initiation of treatment, adult heights were similar to the midparental height, suggesting that treatment was effective in preserving growth potential; 21 children exceeded the midparental height.

Formulations and dosing — Sustained-release formulations of several GnRH agonists have been developed for monthly or three-monthly dosing (table 4) [4]. The choice of GnRH agonist formulation depends on patient and clinician preference and local regulatory approvals [3]. These preparations have not been directly compared in randomized trials but appear to be comparably effective in suppressing the gonadotropic axis, as illustrated by the following examples:

- A randomized trial compared dosing schedules of leuprolide acetate 7.5 mg monthly, 11.25 mg every three months, and 22.5 mg every three months [18]. The incidence of subjects with inadequate pubertal suppression (stimulated luteinizing hormone [LH] levels >4 IU/L) during the first year of therapy was higher in the group treated with 11.25 mg every three months (7/21 subjects, 30 percent), as compared with the 7.5 mg monthly group (1/18 subjects) and 22.5 mg every three months group (1/13 subjects). However, most of these cases resolved on a subsequent visit, and inadequate suppression was rare during the second year of therapy. Thus, the 11.25 mg three-month preparation appears to be efficacious for most patients, and the 22.5 mg dosage is slightly more effective during the first year of therapy.

- Dosing of the three-month depot preparation of leuprolide acetate was further evaluated in a dose-ranging study, in which patients were treated with either a 11.25 mg or 30 mg dose for 36 months [19]. The mean peak-stimulated LH concentrations were lower in the 30-mg dose group compared with the 11.25-mg dose group. However, both doses maintained sex steroid concentrations at prepubertal levels, with no clinical progression of puberty, and were well tolerated.

- In an open-label trial, a depot preparation of triptorelin was administered at a dose of 11.25 mg every three months for 12 months. This treatment inhibited the gonadotropic axis, as demonstrated by peak LH values after GnRH stimulation of less than 3 mIU/mL in over 95 percent of children after 6 and 12 months of treatment [20]. However, the effects on estradiol and testosterone suppression were not as consistent as those achieved with monthly administration.

- A formulation of histrelin provides long-term gonadotropin suppression in children with GDPP for up to one year with a single implantation, and is approved in the United States for this use. In a multicenter trial of this formulation in boys and girls with GDPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant adverse effects were noted [21]. Positive two-year safety and efficacy data have been reported [22]. This formulation provides treatment for GDPP without the pain and inconvenience of monthly injections but does require a minor surgical procedure to insert the implant and to remove it. One study suggests that the suppressive action of an implant may last for two years [23]. An observational study reported that menarche occurred at a mean of 12.75 months after removal of the implant [24].

A typical approach to GnRH agonist dosing using formulations available in the United States is described below. (See 'Our approach' below.)

Monitoring — After GnRH agonist therapy is begun, follow-up monitoring should be performed to ensure that the goals of GnRH agonist therapy are being achieved (eg, suppression of the pituitary-gonadal axis, slowing accelerated puberty and bone age advancement, and ultimately improving final height). Monitoring should include evaluation of pubertal development and growth every three to six months. Bone age should be measured radiographically every 6 to 12 months [3,25]. If treatment is effective, further breast and testicular development should cease, and height velocity and rate of bone age advancement should decline. Pubic hair stage may advance due to adrenarche despite effective treatment with GnRH agonists because these have no effect on adrenal androgen production [26].

One method of monitoring these patients is to perform serial measurements of LH and sex steroid levels (estradiol in girls and testosterone in boys). In our practice, we monitor LH and sex steroid concentrations one to two months after initiating therapy or changing a dose. These are measured just **prior to administering a dose** of GnRH agonist. In general, suppression of LH and sex steroids to prepubertal levels suggests adequate dosing of the GnRH agonist. However, sex steroids may be less useful than LH for monitoring because both serum estradiol and testosterone typically become undetectable with therapy, even when using the most sensitive assays available [27].

If there is clinical evidence of **pubertal progression**, one of the following methods should be used to determine whether the dose of GnRH agonist is sufficient:

- GnRH (or GnRH agonist) stimulation test — Stimulation testing with either GnRH or GnRH agonist can be used to assess the degree of suppression of the pituitary-gonadal axis during GnRH agonist therapy. GnRH is available in many countries but is not available in the United States, so GnRH agonist is used for stimulation testing. When there is complete suppression, there is no significant LH response to either GnRH or GnRH agonist stimulation. On the other hand, if the axis is **not** completely suppressed (due to inadequate GnRH agonist dose or noncompliance), the serum LH concentration will rise briefly within two hours in response to the stimulation dose of GnRH or GnRH agonist because the pituitary gonadotrophs are not completely desensitized. By contrast, the goal of the pretreatment diagnostic GnRH agonist stimulation test is to determine if there has been maturation of the hypothalamic-pituitary-gonadal axis; if so, the LH concentration will rise in response to GnRH or GnRH agonist. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Serum LH concentrations after GnRH agonist stimulation'.)

- Measurement of serum LH concentrations after a therapeutic depot dose of GnRH agonist — Although this approach is less common, some providers assess for adequate dosing of GnRH agonist therapy by measuring serum LH 30 to 90 minutes after the injection of a therapeutic GnRH agonist dose [3,28]. Note that this test is not useful in the first few months after initiating GnRH agonist treatment because serum LH concentrations will not yet be suppressed; they will rise after each dose of GnRH agonist. In one study, an LH value of <2.5 mIU/mL measured 90 minutes after administration of GnRH agonist confirmed adequate pubertal suppression with sensitivity and specificity of 100 and 88 percent, respectively (as compared with the gold standard of an intravenous GnRH stimulation test) [29]. Therefore, patients with LH concentrations greater than this cutoff should have their dose of GnRH agonist increased.

Intravenous GnRH stimulation tests are now rarely performed as the drug is typically unavailable. In addition, the test is time-consuming, and clinical management can be based upon clinical findings and measuring serum LH immediately before or (less commonly) after a therapeutic dose of GnRH agonist.

Safety — Treatment with GnRH agonists appears to have no significant long-term effects on the pituitary-gonadal axis, as illustrated by the following studies:

- A systematic review of published studies confirmed that pituitary-gonadal axis suppression was reversible after cessation of GnRH agonist therapy [30]. These agents did not appear to induce polycystic ovary syndrome or have negative repercussions on bone mineral density or body composition.
- Normal puberty typically returns within one year after termination of GnRH agonist therapy when monthly depot preparations are used, but with wide variability. In one study, menarche occurred 17.5 ± 11.2 months after the last injection of GnRH, and was somewhat earlier in girls who had menstruated prior to GnRH treatment (remenarche) as compared with those who had not previously menstruated [17]. In boys, the interval between the last injection of GnRH and achievement of adult testosterone levels was 11 ± 10.9 months. If histrelin implants are used, preliminary reports suggest that the average length of time between removal of the implant and resumption of menses is approximately 12 months, with wide variability [23,24]. (See 'Formulations and dosing' above.)
- Treatment with GnRH agonists does not affect gonadal function during adulthood. This was shown in a randomized trial of triptorelin treatment in girls with slowly progressive GDPP with long-term follow-up [31]. Girls were treated with triptorelin for an average of 25 months, or observation alone. At follow-up in early adulthood (mean of 33 months after cessation of treatment), there were no significant differences between the groups in serum hormone levels or ovarian or uterine volume, and these measures were also similar to normal controls.
- Small studies in boys also show normal gonadal function after treatment with GnRH agonists [3].

Although earlier pubertal development is associated with obesity, long-term treatment with GnRH agonists does not appear to cause or exacerbate obesity [3,32].

Bone density may decrease during prolonged therapy, but bone mass is regained after treatment, and peak bone mass is normal, so monitoring of bone density is not required [3,33]. We suggest ensuring adequate intake of calcium and vitamin D during and after treatment.

Our approach — The choice of GnRH agonist formulation depends on patient and clinician preference and local regulatory approvals. A variety of dosing schemes appear to be effective, and starting doses used in Europe tend to be somewhat lower than those in the United States (table 4). The dose chosen for an individual patient should be adjusted based on the clinical response. Families should be counseled that some vaginal bleeding may occur after the initiation of GnRH agonist therapy, due to withdrawal of progesterone.

In our practice, we generally use leuprolide depot (Lupron Depot PED [one month]) given intramuscularly (IM) once monthly, with a starting dose of either 7.5 mg, 11.25 mg, or 15 mg, depending on the child's weight (approximately 0.3 mg/kg/dose). Younger children (girls <8 years and boys <9 years) may require higher per-kg doses of GnRH agonist than older children.

Alternatively, we offer a three-month preparation of leuprolide depot (Lupron Depot PED [three month]) to families who desire the less frequent administration, although administration of this dosing form is supported by somewhat less clinical evidence (see 'Formulations and dosing' above). In most patients, we start with the lower dose (11.25 mg) and titrate upwards if puberty is not adequately suppressed. However, for males and/or children with hypothalamic hamartomas (groups in which control of puberty is more difficult), we generally select the 30 mg dose for three-month administration. The side effect profile of these three monthly preparations appears to be independent of the dose.

We monitor the response to the GnRH agonist by assessing pubertal development and growth every three months, and adjust the dose of GnRH agonist upward if pubertal progression is not suppressed. We also measure LH or sex steroid levels just prior to administering a dose of GnRH agonist one to two months after initiation of therapy or change in dose, as described above. (See 'Monitoring' above.)

We generally continue treatment until about age 11 in girls and age 12 in boys. The decision of when to discontinue GnRH agonist therapy is individualized; contributing factors include the age of the child, bone age and height age, predicted height, and social desire to join their peers in puberty.

TREATMENT FOR GIPP — Gonadotropin-independent precocious puberty (GIPP, also referred to as peripheral precocious puberty) is caused by excess secretion of sex hormones (estrogens or androgens) derived from the gonads, adrenal glands, or exogenous sources (table 1B). The causes and evaluation of GIPP are discussed in a separate topic review. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Causes of gonadotropin independent precocious puberty (GIPP)'.)

General approach

GIPP does not respond to GnRH agonist therapy. Instead, treatment is directed at the underlying pathology:

- Children with tumors of the testis, adrenal gland, and ovary are treated by surgery. Those with human chorionic gonadotropin (hCG)-secreting tumors may require some combination of surgery, radiation therapy, and chemotherapy depending upon the site and histologic type.
- A large functioning follicular cyst of the ovary is the most common cause of GIPP in girls. Cysts develop and regress spontaneously, so conservative management without surgery is generally appropriate [34]. Patients should be followed to document regression of the cyst.
- Children whose sexual precocity is caused by exposure to exogenous sex steroids must have that exposure identified and removed; after removal of the exposure, the pubertal changes are likely to regress.
- Children with identifiable defects in adrenal steroidogenesis, such as classic congenital adrenal hyperplasia, should be treated with glucocorticoid therapy. (See "Genetics and clinical presentation of classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency".)

McCune-Albright syndrome and familial male-limited precocious puberty require a different approach because they are caused by mutations resulting in overstimulation of the tissues that produce sex steroids. To preserve fertility, children with these disorders should be treated with drugs that inhibit gonadal steroidogenesis or gonadal steroid action, rather than surgery, as discussed in the following sections.

McCune-Albright syndrome — McCune-Albright Syndrome (MAS) is a rare disorder defined as the triad of peripheral precocious puberty, café-au-lait skin pigmentation, and fibrous dysplasia of bone. The clinical presentation and diagnosis of MAS is discussed separately. Affected girls tend to overproduce estrogens, whereas affected boys overproduce androgens. (See "Definition, etiology, and evaluation of precocious puberty", section on 'McCune-Albright syndrome'.)

Treatment for girls with MAS has included strategies to block estrogen biosynthesis with aromatase inhibitors or block estrogen action (figure 2). Testolactone, an early generation aromatase inhibitor, is partially effective for reducing the recurrence of ovarian cysts and slowing pubertal progression [35], but there is a loss of efficacy over time [36]. Use of the later-generation aromatase inhibitors fadrozole, anastrozole, or letrozole is largely ineffective for long-term treatment [37-40].

Treatment with tamoxifen, a selective estrogen receptor modulator (SERM), does not appear to be any more effective than aromatase inhibitors. Although one study demonstrated a reduction in vaginal bleeding, uterine volume increased and long-term data on outcomes such as skeletal growth are unavailable [41]. The most promising results thus far have been with fulvestrant, a pure estrogen receptor antagonist. In a one year open-label trial among 30 girls under age 10 years receiving monthly fulvestrant injections, most subjects who had vaginal

bleeding at baseline experienced either a substantial reduction or cessation of bleeding, and rates of bone age advancement decreased significantly [42]. Long-term safety or efficacy outcomes are not yet available.

A few patients with MAS will develop a component of GDPP. This is probably caused by prolonged exposure to elevated levels of sex steroids and is most often found in patients with advanced bone age. Such patients may respond to adjuvant treatment with a GnRH agonist, as do other children with GDPP [2]. (See 'GnRH agonist treatment' above.)

Very rarely, boys can be affected by MAS, in which case they tend to overproduce testosterone. A few reports describe successful treatment of these boys with an antiandrogen, in combination with an aromatase inhibitor, similar to the regimen used for familial male-limited precocious puberty described below [2] (see 'Familial male-limited precocious puberty' below). However, due to the rarity of this disorder in boys, information about treatment outcomes is very limited. The pathogenesis and presentation of MAS are outlined in a separate topic review. (See "Definition, etiology, and evaluation of precocious puberty", section on 'McCune-Albright syndrome'.)

Familial male-limited precocious puberty — Boys with familial male-limited precocious puberty, also called familial GIPP or familial testotoxicosis, have been treated with a combination of spironolactone (which inhibits androgen action) and testolactone (which blocks the conversion of androgen to estrogen) (figure 2) [43-45]. Testolactone may interfere with androgen assays and falsely elevate measured serum testosterone levels.

Ketoconazole, an inhibitor of androgen synthesis, is also effective [46-48]. It may be associated with hepatotoxicity, and may also lower cortisol levels, causing adrenal insufficiency [49].

Either treatment option (spironolactone/testolactone or ketoconazole) in combination with a GnRH agonist can normalize the growth rate over the long term, but benefits to adult height have not been established [45,48]. Secondary GDPP may develop in the course of this treatment and is treated with GnRH agonist therapy [2,50].

In a case report of two boys with familial male-limited precocious puberty, a regimen of bicalutamide (a highly selective nonsteroidal antiandrogen) and anastrozole (a third-generation aromatase inhibitor) was effective in reducing height velocity and decreasing secondary sexual characteristics without serious adverse effects [51]. In an open-label study in 14 boys, the same combination effectively reduced height velocity and bone maturation; gynecomastia and breast tenderness were the most common side effects [52].

INCOMPLETE PRECOCIOUS PUBERTY — Patients with idiopathic isolated premature thelarche or premature adrenarche need no therapy but should be reexamined regularly. In children with either variant, serial examinations serve to establish the diagnosis and to confirm that the initial physical development does not progress to more complete GDPP. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Types of incomplete precocious puberty'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient information: Early puberty (The Basics)")

SUMMARY AND RECOMMENDATIONS

- The etiology of precocious puberty is classified by the underlying pathogenesis into three categories:

gonadotropin-dependent precocious puberty (GDPP, also known as central precocious puberty), gonadotropin-independent precocious puberty (GIPP, also known as peripheral precocious puberty), and incomplete precocious puberty (table 1A-C). (See 'Classification' above.)

- The primary goal of treatment for GDPP is to allow a child to grow to a normal adult height. For patients with idiopathic GDPP, the decision about whether to treat depends on the rate of sexual maturation and the estimated adult height as determined by the rate of bone age advancement (table 2). Some forms of GDPP are slowly progressive and do not require treatment. (See 'Decision to treat' above.)

- If treatment for GDPP is indicated, we recommend treatment with a gonadotropin-releasing hormone (GnRH) agonist (**Grade 1B**). For children with progressive GDPP, younger age at initiation of therapy is associated with greater height benefits. (See 'Effects on height' above.)

    - Clinically significant increments in height potential are achieved with a variety of GnRH agonists, and outcomes data are insufficient to recommend one form over another; several preparations are listed in the table (table 4). The choice of GnRH agonist formulation depends on patient and clinician preference and local regulatory approvals; in our practice we use leuprolide depot given intramuscularly (IM) once monthly. (See 'Formulations and dosing' above and 'Our approach' above.)

    - During treatment with a GnRH agonist, patients should be monitored periodically for pubertal development and growth and bone age to determine whether the GnRH dose is adequate. In our practice, we also monitor GnRH efficacy by measuring concentrations of luteinizing hormone (LH) or sex steroids (just prior to administering a dose of GnRH agonist) one to two months after initiation of therapy or change in dose. (See 'Monitoring' above and 'Our approach' above.)

- GIPP is caused by peripheral secretion of sex hormones either from the gonads or adrenal glands, ectopic hCG production by a germ cell tumor, or by exogenous sources of sex steroids, and is independent from the hypothalamic-pituitary-gonadal axis. Causes of GIPP are listed in the table (table 1B).

- Treatment for GIPP is directed at the underlying pathology or removal of any exogenous exposure, as described in the table; these patients do not respond to GnRH agonist therapy. (See "Definition, etiology, and evaluation of precocious puberty", section on 'Causes of gonadotropin independent precocious puberty (GIPP)' and 'Treatment for GIPP' above.)

- Incomplete precocious puberty consists of isolated breast development (premature thelarche) or isolated characteristics such as pubic hair development mediated by androgens produced in the adrenal glands (premature adrenarche). Either of these patterns usually is a variant of normal puberty and requires no intervention. However, a percentage of these patients will develop precocious puberty, so they should be followed closely. (See 'Incomplete precocious puberty' above.)

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Topic 16318 Version 17.0

GRAPHICS

Evaluation of gonadotropin-dependent ("central") precocious puberty

Etiology	Gonadotropin levels	LH response after GnRH stimulation	Sex steroid hormone levels	Clinical features	Additional evaluation
Idiopathic *(80 percent of girls with GDPP)* or CNS tumor	Pubertal levels, with prominent LH pulses during sleep: LH >0.6 IU/L	Pubertal response: LH level post GnRH >7 IU/L	Pubertal values of estradiol (>9 pg/mL), testosterone (20-1200 ng/dL), and DHEAS	Pubertal development accelerated, but proceeds in normal timing and sequence Enlargement of ovary/uterus (by ultrasound) or testes (by exam) Bone age >height age >chronological age Responsive to GnRH agonist therapy	Contrast-enhanced MRI of brain to rule out CNS abnormality In boys, measure hCG to exclude an hCG-secreting tumor Skin examination and skeletal survey to rule out McCune-Albright syndrome

LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone; CNS: central nervous system; DHEAS: dehydroepiandrosterone sulfate; MRI: magnetic resonance imaging; hCG: human chorionic gonadotropin.

Graphic 52565 Version 9.0

Evaluation of gonadotropin-independent ("peripheral") precocious puberty

Etiology	Gonadotropin levels	LH response after GnRH stimulation	Sex steroid hormone levels	Clinical features	Additi evalua
Congenital adrenal hyperplasia (untreated)	Prepubertal	Absent LH response	Sex hormone levels vary depending on the adrenal enzyme block	Boys have prepubertal testes with enlarged phallus and pubic hair development. Girls with "nonclassic" CAH may present with early pubic and/or axillary hair, and other signs of androgen excess.	After ther with glucocort GDPP ma develop a require G agonist th
Leydig cell tumor (boys)	Suppressed	Absent LH response	Very high levels of testosterone	Irregular and asymmetrical enlargement of testes	Tumor ma be palpab testicular ultrasoun in diagno
Ovarian cyst	Suppressed	Absent LH response	Normal or elevated estradiol; occasionally elevated androgens	Pubertal development accelerated; occasionally presents with ovarian torsion and abdominal pain	Abdomina ultrasoun and/or MI
hCG-secreting germ cell tumors (boys)	High hCG or positive pregnancy test	Absent LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for the degree of pubertal development Precocious puberty is seen	These tur may occu gonads, l liver, retroperit or medias When in a mediastir karyotype be perfor because

				only in boys as hCG only activates LH receptors (estrogen biosynthesis in the ovaries requires both FSH and LH receptor activation)	strong associatio this findir Klinefelte syndrome
Familial male-limited (gonadotropin-independent) precocious puberty (boys)	Suppressed	Absent LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for degree of pubertal development; spermatogenesis may occur Familial: Male-limited autosomal dominant trait Precocious puberty is seen only in boys as there is only activation of the LH receptors, and ovarian estrogen biosynthesis requires both FSH and LH receptor activation	
McCune-Albright syndrome (girls>>boys)	Suppressed	Absent LH response	Pubertal values of estradiol in girls and testosterone in boys	Ovaries: Enlarged for age and usually containing multiple large cysts Testes: Symmetric and >2.5 cm	Ultrasour Ovaries enlarged, follicular c May have hyperacti endocrine disorders thyrotoxi

				diameter (>4 mL volume), but smaller than expected for pubertal development Skin: Multiple irregular-edged café-au-lait spots Bone: Polyostotic fibrous dysplasia	and/or gi
Virilizing adrenal tumor	Suppressed	Absent LH response	High DHEA or DHEAS*; high androstenedione and testosterone	Testes prepubertal	CT, MRI, c ultrasoun adrenal g to locate if still undetecta selective sampling androger
Adrenal cancer	Suppressed	Absent LH response	High DHEA or DHEAS*; high 17-ketosteroids in urine	May present with signs of glucocorticoid excess, and may be associated with hereditary cancer syndromes	CT, MRI, c ultrasoun adrenal g to locate if still undetecta selective sampling androger
Exogenous sex steroids (eg, testosterone creams and estradiol spray or creams)	Suppressed	Absent LH response	Elevated testosterone in boys and estradiol in girls	Estrogen preparations cause feminization, while topical androgens cause virilization in both sexes	Clinical hi explores exogenou steroids b caretaker folk reme Monitor s steroid h levels an clinical st after rem inciting a

GDPP: gonadotropin-dependent precocious puberty; LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone; CAH: congenital adrenal hyperplasia; hCG: human chorionic gonadotropin; FSH: follicle-stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; CT: computed tomography; MRI: magnetic resonance imaging; 17-OHP: 17-hydroxyprogesterone.
* If adrenal tumor tissue loses sulfokinase activity, DHEAS may not be elevated.

Graphic 59268 Version 8.0

Clinical findings and evaluation strategy in apparent idiopathic forms of incomplete precocious puberty

Etiology	Clinical features	Bone age*	Sex steroid hormone levels (if performed)	Stimulation testing (if performed) ¶Δ◇	Additional evaluation
Premature adrenarche (boys or girls)	Isolated pubarche, with normal growth rate. Gonads prepubertal in size and no breast development in girls. Onset usually after 6 years of age. Associated more frequently with obesity, having been born SGA, or brain injury.	Bone age may be normal or slightly advanced (about 10 to 20 percent more than chronological age)*	DHEAS values elevated for age (ie, at Tanner 2 levels).§ Prepubertal levels of 17-OHP and testosterone.§	ACTH stimulation test¶ (if performed): 17-OHP response is consistent with early puberty (versus marked elevations, which suggest CAH).	Monitor for possible further progression to full puberty.
Premature thelarche (girls)	Isolated breast development, with no other signs of pubertal development and normal growth rate. Typical onset at 1 to 3 years of age.	Bone age is normal or slightly advanced (about 10 to 20 percent more than chronological age)*	Prepubertal levels of estradiol¥	GnRH stimulation test◇ (if performed): No or minimal LH and estradiol response.	Monitor for possible further progression to full puberty.

SGA: small for gestational age; DHEAS: dehydroepiandrosterone sulfate; 17-OHP: 17-hydroxyprogesterone; ACTH: adrenocorticotropic hormone; CAH: congenital adrenal hyperplasia; GnRH: gonadotropin-releasing hormone.

* If bone age is normal and clinical features are consistent with idiopathic premature adrenarche or idiopathic premature thelarche, follow-up rather than further evaluation usually is appropriate. If

the bone age is advanced, or if age of onset is atypical, then further evaluation for precocious puberty should be performed, as described below.

¶ For boys or girls with premature pubarche, an ACTH stimulation test is performed if DHEAS, testosterone and/or 17-OHP results are **not** consistent with idiopathic isolated premature adrenarche, to further evaluate for CAH.

Δ For children with premature pubarche, a GnRH stimulation test is performed only if there is rapid growth velocity and bone age maturation, **and** concomitant testicular enlargement in boys, or breast development and ovarian enlargement in girls.

◇ For girls with premature thelarche, a GnRH stimulation test (including measurements of basal and stimulated LH and estradiol) is performed only if the bone age is advanced and/or if there are clinical features that raise concern for premature puberty (eg, rapid pubertal progression, growth velocity, bone age maturation, or ovarian enlargement on ultrasound).

§ Boys or girls with isolated pubarche and moderately advanced bone age (>20 percent of chronological age) should be further evaluated by measuring DHEAS, 17-OHP, and testosterone in the early morning (8 to 9 AM). These tests assess for pathologic causes of excess androgen, such as CAH. Idiopathic premature adrenarche is characterized by DHEAS concentrations between 40 and 115 micrograms/dL (1.1 to 3.1 micromol/L), with testosterone ≤20 ng/dL (0.7 nmol/L), and 17-OHP <200 ng/dL (6 nmol/L).

¥ For girls with idiopathic premature thelarche, early morning (8 to 9 AM) estradiol levels should be in the prepubertal range <45 pmol/L (12 pg/mL).

Graphic 72054 Version 7.0

Clinical characteristics of nonprogressive versus progressive precocious puberty

	Nonprogressive precocious puberty	Gonadotropin-dependent (central) precocious puberty	Gonadotropin-independent (peripheral) precocious puberty
Physical examination: Advancement through pubertal stages (Tanner stage)	No progression in Tanner staging during 3 to 6 months of observation	Progression to next pubertal stage in 3 to 6 months	Progression
Growth velocity	Normal for bone age and relationship to peak height velocity	Accelerated (>6 cm per year)*	Accelerated*
Bone age	Normal	Advanced for height age	Advanced for height age
Serum estradiol concentration (girls)•	Undetectable	Measurable, variable, and increasing	Measureable, variable, and increasing
Serum testosterone concentration (boys, or girls with virilization)•	Prepubertal	Pubertal and increasing	Pubertal and increasing
Basal (unstimulated) serum LH concentration•	Normal (prepubertal)Δ	Normal or elevated (as compared to prepubertal levels)Δ	Suppressed or normal (prepubertal)Δ
GnRH (or GnRHa) stimulation test•	LH peak in the prepubertal range◇	LH peak elevated (in the pubertal range)◇	No change from baseline, or LH peak in the prepubertal range

* UNLESS the patient has already passed his or her peak height velocity at the time of evaluation, in which case growth velocity may be normal or decreased for chronological age.

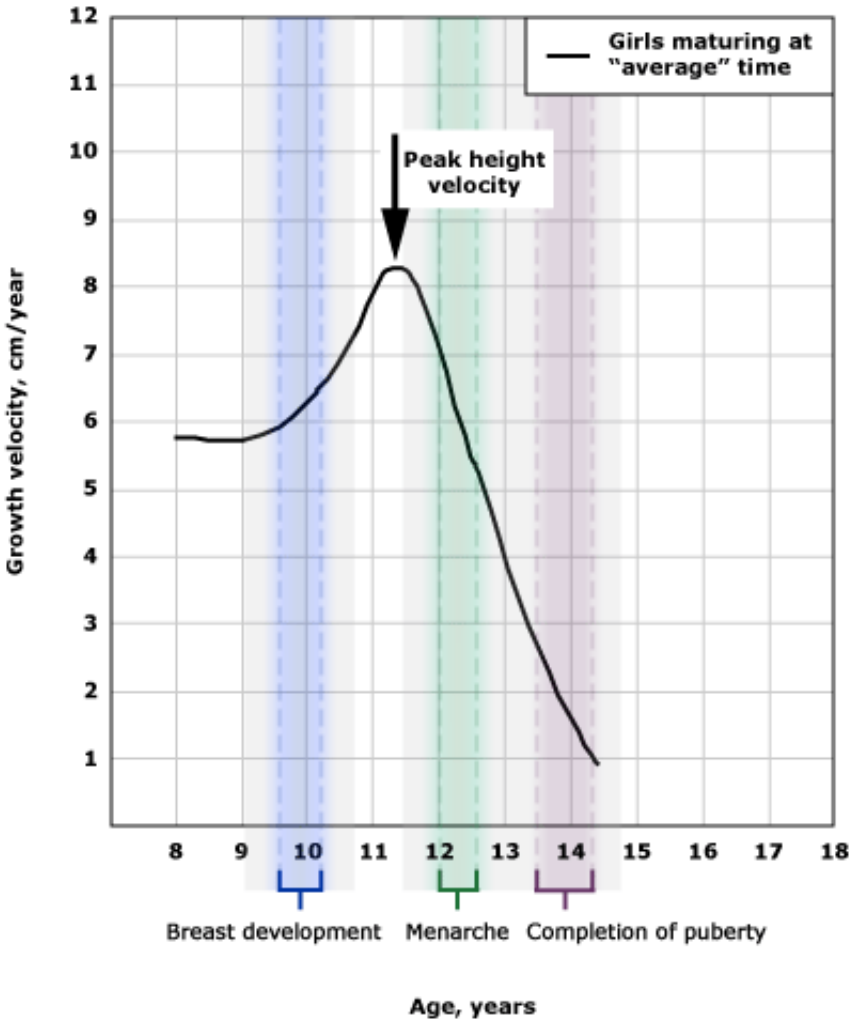
• Serum concentrations of gonadal steroids and LH should be measured using ultrasensitive assays with detection limits adapted to the pediatric age group (ie, LH detection limits near 0.1 mIU/mL).

Δ In most laboratories, basal prepubertal concentrations of LH are below 0.1 mIU/mL.

◇ In most laboratories, the upper limit of normal for LH after GnRH stimulation is 3.3 to 5.0 mIU/mL.

Graphic 72017 Version 2.0

Sequence of puberty in girls

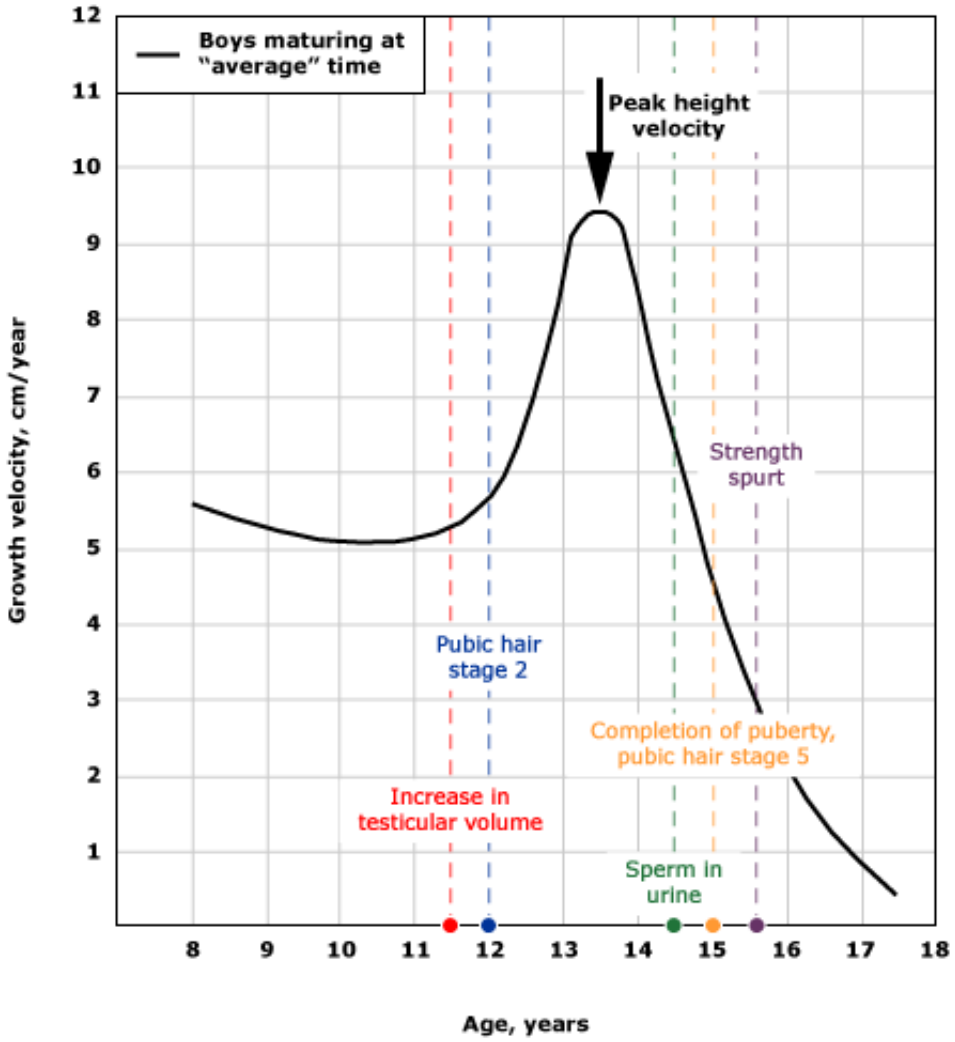


Sequence of events in girls with average timing of pubertal development in the United States. Black girls tend to reach a milestone at a younger age (left-hand side of the bracket) than white girls (right-hand side of the bracket). The median length of time between the onset of puberty (breast tanner stage 2) and menarche is 2.6 years, and the 95th percentile is 4.5 years.

Data from: Biro FM, Huang B, Lucky AW, et al. Pubertal correlates in black and white US girls. J Pediatr 2006; 148:234, and from: Tanner JM, Davies PS. J Pediatr 1985; 107:317.

Graphic 52047 Version 4.0

Sequence of puberty in boys



Sequence of pubertal events in boys with average timing of pubertal development in the United States.

Data from: Biro FM et al, Pubertal staging in boys. J Pediatr 1995;127:100; Karpati AM et al, Stature and pubertal stage assessment in American boys: the 1988-1994 Third National Health and Nutrition Examination Survey. J Adolesc Health 2002;30:205-12; Dore E et al. Gender differences in peak muscle performance during growth. Int J Sports Med 2005; 26:274; Neu CM et al. Influence of puberty on muscle development at the forearm. Amer J Physiol Endocrin Metab 2002;283:E103; and Tanner et al. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 1985; 107:317.

Graphic 72046 Version 1.0

Sexual maturity rating (Tanner stages) of secondary sexual characteristics

Boys - Development of external genitalia
Stage 1: Prepubertal
Stage 2: Enlargement of scrotum and testes; scrotal skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker
Stage 5: Adult genitalia
Girls - Breast development
Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3: Further enlargement of breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above level of breast
Stage 5: Mature stage: projection of papilla only, related to recession of areola
Boys and girls - Pubic hair
Stage 1: Prepubertal (the pubic area may have vellus hair, similar to that of forearms)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult female in type and quantity, with horizontal upper border

Graphic 55329 Version 7.0

Long-acting gonadotropin-releasing hormone (GnRH) agonists for treatment of gonadotropin-dependent (central) precocious puberty

GnRH agonist	Trade names and availability	Dose, frequency and method of administration
Histrelin acetate subcutaneous implant	Supprelin LA (US)	Subcutaneous implant. Children ≥2 years: 50 mg implant surgically inserted every 12 months. Releases approximately 65 mcg per day over 12 months.
Leuprolide (leuprorelin acetate)	Lupron Depot-Ped (one month) (US) Lupron Depot CPP (CAN) Eilgard, Lucrin (EU, AU, SA, elsewhere)	Intramuscular depot injection, given every 28 days. Initial dose by body weight: ▪ Patients weighing ≤25 kg: 7.5 mg ▪ Patients weighing 25-37.5 kg: 11.25 mg ▪ Patients weighing >37.5 kg: 15 mg Titrate dose upward by 3.75 mg every 4 weeks (increase of approximately 10 mcg/kg/day) as needed to achieve clinical response. Starting doses in Europe are typically lower (eg, 3.75 mg/dose).
	Lupron Depot-Ped (3 month)	Intramuscular depot injection, given every 12 weeks: ▪ 11.25 or 30 mg Criteria for selection of the 11.25 mg versus 30 mg dosage have not been established.
Goserelin	Zoladex (US, CAN, UK, EU, SA, elsewhere)	Subcutaneous implant injected in to the anterior abdominal wall: ▪ The 3.6 mg preparation is given once every 28 days ▪ The 10.8 mg preparation is given once every 12 weeks More frequent injections may be needed in some individuals.
Triptorelin	Gonapeptyl (UK, EU, SA, elsewhere)	Intramuscular depot injection. Initial dose by body weight: ▪ Patients weighing <20 kg: 1.875 mg ▪ Patients weighing 20-30 kg: 2.5 mg ▪ Patients weighing >30 kg: 3.75 mg Initial three doses given at 14-day intervals with further doses every four weeks. More frequent injections may be needed in some individuals. An 11.25 mg intramuscular depot injection given every 12 weeks is available in some countries.

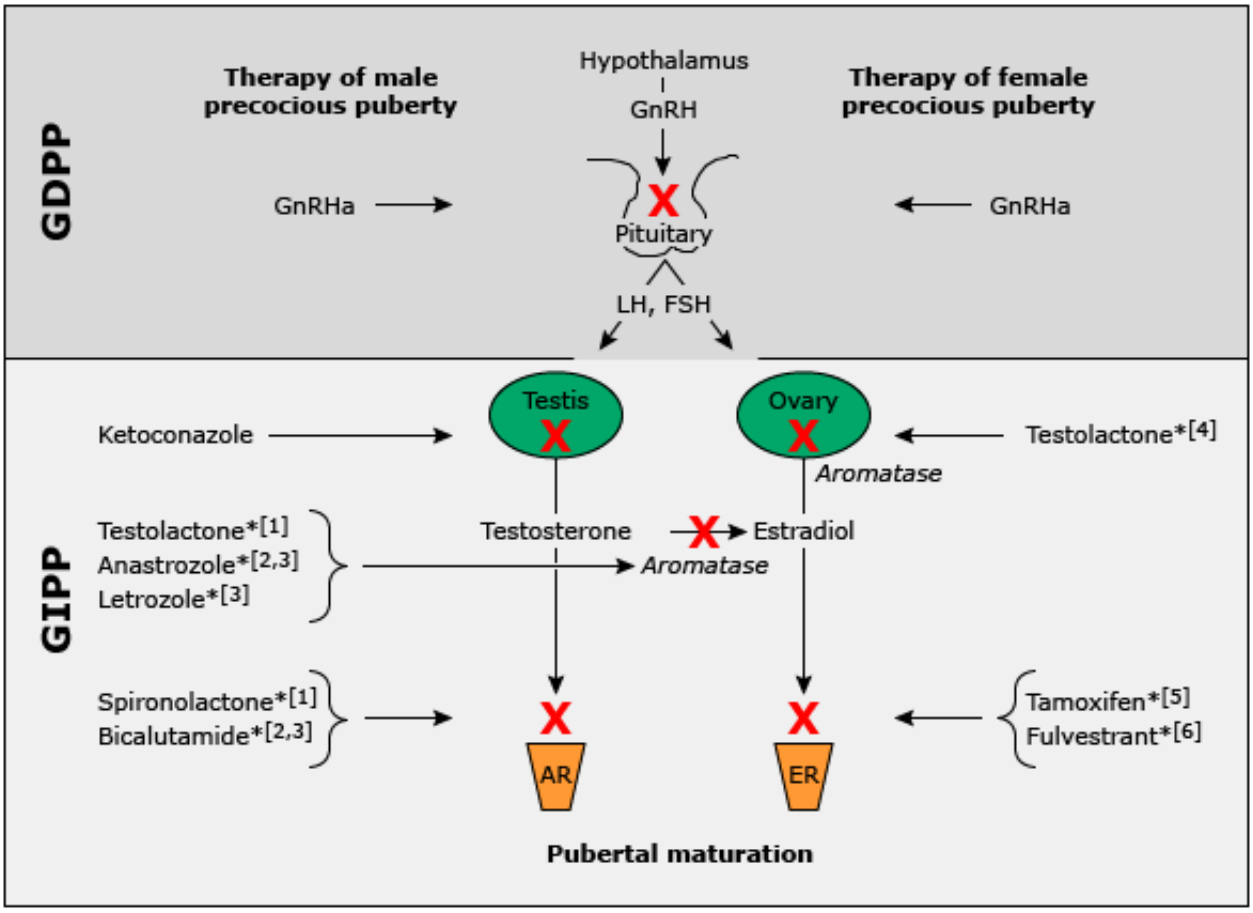
Approval of these GnRH agonists for use in gonadotropin-dependent precocious puberty (GDPP), dosing, and schedules of administration vary between products in different countries. Consult local product information. Short-acting GnRH preparations requiring daily subcutaneous injections or nasal spray are not recommended due to compliance difficulty; use

of these products usually is limited to patients with sterile abscesses from depot injections. Note that the doses used to treat GDPP in children are substantially higher than those used in adults for other indications, such as prostate cancer and endometriosis.

US: United States; CAN: Canada; EU: European Union; AU: Australia; SA: South America; UK: United Kingdom.

Graphic 72979 Version 6.0

Treatment of children with precocious puberty



Schematic depiction of the pathways leading to precious puberty and the mechanisms of action for several drugs used for treatment. For gonadotropin-independent precocious puberty (GIPP, also known as peripheral precocious puberty), the pathway for boys is shown on the left, and girls on the right.

GDPP: gonadotropin-dependent precocious puberty (central precocious puberty); GIPP: gonadotropin-independent precocious puberty (peripheral precocious puberty); GnRH: gonadotropin-releasing hormone; GnRHa: gonadotropin-releasing hormone analogue (eg, leuprolide, histrelin); LH: luteinizing hormone; FSH: follicle-stimulating hormone; AR: androgen receptor; ER: estrogen receptor.
* Preliminary data have been reported; treatment is still experimental.

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1. *Leschek EW, Jones J, Barnes KM, et al. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. J Clin Endocrinol Metab 1999; 84:175.*
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Fuqua JS. Treatment and outcomes of precocious puberty: An update. J Clin Endocrinol Metab 2013; 98:2198.

Graphic 62460 Version 4.0

Disclosures

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