

# Chapter 10

## Endocrine Disorders in Patients with Fanconi Anemia

### Introduction

Fanconi anemia (FA) and treatments used for the disease can adversely affect the endocrine system. Studies have shown that approximately 8 of every 10 patients with FA have at least one endocrine abnormality [1-10], although the origin of these abnormalities is unclear. Patients with FA experience endocrine disorders in myriad ways, including short stature, challenges with weight, abnormal glucose and insulin metabolism, hormonal deficiencies, and low bone mineral density. Endocrine abnormalities influence growth, development, and other aspects associated with the disease and its treatment. It is imperative that the clinical care team include an endocrinologist or pediatric endocrinologist, dietician, and, for females, a gynecologist or a reproductive endocrinologist. The endocrine team should work in close collaboration with other FA specialists to provide comprehensive care.

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### Evaluation of Growth

Growth should be closely followed in children with Fanconi anemia (FA) and nutritional and/or medical causes for poor growth should be identified as early as possible. Height

should be measured with a stadiometer and tracked using a growth chart. Children with FA who consistently track low on the growth chart compared with the average in the general population, or whose height gradually falls to a lower percentage, indicating a decline in annual growth velocity, should be evaluated by a pediatric endocrinologist. Endocrine evaluation should include a full assessment of growth and thyroid hormones, as well as pubertal status (Table 1).

## Short Stature

Short stature is a common characteristic of patients with FA. More than half (60%) of patients with FA are shorter than all but 2.5% of their healthy peers. In scientific terms, this means the average person with FA is two standard deviation (SD) units, or  $-2$  SD, shorter than the average person in the general population [7]. The average height of adult female patients with FA is about 150 cm (4 feet, 11 inches), while the average adult male patient with FA is 161 cm (5 feet, 3.5 inches). In children considered “short” by FA standards (at least shorter than 2 SD below the average in the general population, or  $< -2$  SD), body heights ranged from 7.8 SD to 2 SD shorter than the average in their healthy peers (median, about  $-3.4$  SD) [4, 7, 10]. However, there are individuals with FA who have a height in the normal range, and about 1 of every 10 patients is taller than the average in the general population [7]. Height is an inherited trait; however, using parental height to predict adult height of children with FA may not be helpful because their stature is influenced by other factors [7].

### Endocrine Abnormalities and Short Stature

Patients with FA who have hormone deficiencies tend to be shorter than patients with FA who have normal hormone levels [7, 10]. Adult patients with FA may be even shorter if they were not treated for growth hormone (GH) deficiency or hypothyroidism as children. One study described a patient with FA who had a genetic defect in the growth hormone receptor-signaling pathway that led to low insulin-like growth factor 1 (IGF-1) and primary IGF-1 deficiency, suggesting primary IGF-1 deficiency should be ruled out if clinical features are suggestive [1]. However, it is important to note that endocrine defects are not the only possible reason for short stature. Even FA patients with healthy hormone levels tend to be shorter than average for the general population, with only about half being within the height range considered normal. Some patients with FA are very short despite having normal hormone levels. As a result, hormonal replacement therapy does not always result in normal growth.

### Fanconi Anemia Variants and Short Stature

Certain genetic mutations are strong predictors of short stature in patients with FA, independent of hormone levels. For example, a subset of patients with the IVS4 A to T variant of the *FANCC* gene have an average height of 4.3 SD less than average for the general population; these patients are significantly shorter than patients with FA who have

other variants [10]. In contrast, patients with variants in the *FANCA* gene are of similar height to patients with other FA variants [7].

### **Birth Size and Short Stature**

Average birth weight in infants with FA is at the lower end of the normal range, typically about 1.8 SD less than average for the general population. Approximately half of all children with FA are considered small for gestational age (SGA) at birth, with length or weight about 2 SD less than average [7]. In the general population, about 90% of children who are considered SGA at birth catch up to the normal range for height. In contrast, only about 25% of FA children who are considered SGA at birth catch up to the normal range [7]. In one series, the median height of children considered SGA at birth was -2.6 SD, while the median height of children considered appropriate for gestational age at birth was -2 SD [7].

### **Poor Nutrition and Short Stature**

Being underweight is linked with short stature in patients with FA [7]. Suboptimal nutrition may predispose children to stunted growth, or growth failure; therefore, dietary changes may be indicated for maintaining optimal growth (see Chapter 9).

### **Hematopoietic Cell Transplantation and Short Stature**

It remains unclear whether hematopoietic cell transplantation (HCT) directly affects growth. However, medications used to treat patients with FA, such as androgens and corticosteroids, may affect growth and bone maturation, and impair adult height. Some medications or radiation used during HCT may affect thyroid or gonadal function, which in turn may negatively impact growth and adult height. In addition, total body, abdominal, or thoracic radiation used in preparation for HCT may directly influence growth of the spinal cord.

### **Targeted Testing for Short Stature**

Determining the patient's bone age (BA) is part of a standard endocrine evaluation for short stature and involves a radiograph of the left hand and wrist. Bone age may need to be reassessed every 1-2 years in children with FA who have short stature. The results of BA assessments are sometimes used in height prediction algorithms, wherein if BA appears younger than the patient's actual age, then the height prediction algorithm may suggest that normal adult height will be attained over time. This prediction assumes that the child will continue to experience healthy growth, optimal nutrition, normal hormone secretion, and normal timing of puberty. However, these assumptions are not necessarily correct in FA patients. Androgen therapy may accelerate BA, while hypothyroidism, GH deficiency, hypogonadism, and corticosteroid therapy may delay BA. Therefore, estimates of adult height based on BA may lead to over-optimistic height predictions in patients with FA. Adult height predictions should be re-evaluated after a decrease in the growth velocity or following initiation of androgen therapy and after HCT [11].

In addition to tracking the patient's bone age, GH secretion can be indirectly evaluated by measuring IGF-1 and IGF-binding protein 3 (IGFBP-3) levels. Levels of these proteins may be used to screen patients with short stature or growth failure. A thorough evaluation for GH deficiency by stimulation testing and magnetic resonance imaging (MRI) of the pituitary gland may be performed, along with consultation with a pediatric endocrinologist.

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## Weight Abnormalities in Patients with Fanconi Anemia

Approximately half of children with Fanconi anemia (FA) are born small for gestational age (SGA) [7]. In one series, infants with FA who were considered SGA were not only shorter but also were thinner than infants considered to fall within normal parameters at birth. Specifically, the average body mass index (BMI) was -1.3 SD in infants considered SGA, compared with -0.5 SD in infants considered to fall in the average range [7].

The BMIs of children and adults with FA generally are similar to those of the non-FA population, with average BMIs of -0.2 SD in children and -0.95 SD in adults. One study suggested a lower average BMI of -1.3 +/-0.2 SD in children and in a few adults with FA [10]. Other studies reported that about 25-33% of all patients with FA are thin or underweight, while a few are overweight [4, 7]. The frequency of overweight in children with FA is similar to that in the general population, with a range of 11-27% depending on the group of patients studied [4, 7].

In some cases, being underweight may stem from the nutritional and gastroenterological problems common in patients with FA. Some children may have less than the expected appetite; others have trouble absorbing nutrients from food (see Chapter 9). In addition, illnesses that affect FA patients can raise caloric requirements. Glucose intolerance and insulin deficiency also may contribute to poor weight gain. Excess weight gain, on the other hand, may reflect lifestyle factors and a genetic predisposition to obesity.

### Evaluation of Body Weight

Body weight of FA patients should be assessed at least annually, and more frequently if there is concern about failure to thrive or excessive weight gain relative to standard norms. If there are concerns related to body weight, a registered dietitian should assess the patient's nutritional intake. In addition, the primary care provider should thoroughly evaluate the patient for underlying medical conditions, concurrent medications, specific hormone-related conditions, and related co-morbidities.

## Dietary Intervention for Weight Abnormalities

Healthy dietary intake should be encouraged, including sufficient calcium and vitamin D from foods or supplements. Input from a registered dietician may be needed. The underlying causes of under- or overweight should be addressed, including treatment of endocrine or gastrointestinal disorders (see Chapter 9). Related co-morbidities due to obesity should be prevented and treated, as discussed later in this chapter in the sections on abnormal glucose metabolism, lipid abnormalities, and metabolic syndrome.

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## Abnormal Glucose or Insulin Metabolism

Diabetes mellitus occurs more commonly in patients with FA than in the general population [12]; moreover, patients with FA have a relatively high incidence of high blood sugars without meeting criteria for diabetes, also known as impaired glucose tolerance. Studies have shown that diabetes was detected in 5-10% of patients with FA, while an additional 24-68% of these patients had impaired glucose tolerance [2, 4, 6, 7, 10]. As many as 34-72% of patients with FA had elevated insulin levels 1-2 hours after eating. Interestingly, in other studies, insulin levels in patients with FA were low 10-45 minutes after an oral glucose test, suggesting slow initial insulin secretion, but became elevated 60-120 minutes after the test [2, 6]. Although the elevated levels suggest that insulin resistance may contribute to diabetes in patients with FA and markers of insulin resistance have been demonstrated in some cohorts [4, 10], these findings also support the possibility that insulin-producing  $\beta$ -cells do not function properly in patients with FA, which could impair first-phase insulin secretion [2, 6]; therefore, the diabetes observed in FA is not typical for either Type 1 or Type 2 diabetes.

The cause of impaired first phase insulin secretion in patients with FA is unknown but could stem from possible damage inflicted by enhanced reactive oxygen species (ROS) on the  $\beta$ -cells that secrete insulin or, alternatively, from iron overload in heavily transfused patients. Insulin resistance also appears to be related to ferritin levels and oxidative stress from iron overload in FA patients [13].

Several medications used in the treatment of FA, particularly androgens and corticosteroids, are known to alter glucose metabolism. Androgen treatment can significantly elevate both blood sugar and insulin levels [10]. Chronic steroid therapy also predisposes patients to insulin resistance and hyperglycemia [14-16]. The guidelines regarding glucocorticoid use in FA patients should be the same as in any other subject: Use the lowest possible dose of medication.

## Screening for Abnormal Glucose and Insulin Metabolism

All patients should be screened for abnormalities related to glucose and insulin homeostasis upon diagnosis with FA and, if possible, every year thereafter (Table 1). Patients can be screened for glucose tolerance by measuring blood sugar and insulin concentrations after fasting for 8 hours, and by measuring post-prandial blood sugar and insulin concentrations two hours after a meal. The danger of measuring only serum glucose values, or relying solely on fasting values, is that some patients may be overlooked—particularly those with impaired glucose tolerance whose blood sugar and insulin levels are normal after fasting but elevated two hours after a meal. Glycosylated hemoglobin (HbA<sub>1c</sub>) and fructosamine levels may be deceptively normal, presumably due to impaired glycosylation or elevated levels of fetal hemoglobin in patients with bone marrow failure [7]. Therefore, HbA<sub>1c</sub> scores may provide more useful information after HCT compared to before HCT.

In FA patients who have suspected endocrine abnormalities and possess risk factors such as overweight/obesity or hyperlipidemia, a more detailed evaluation is needed in consultation with an endocrinologist. This evaluation should include a two-hour oral glucose tolerance test (OGTT, 1.75 g glucose/kg body weight, maximum dose 75 g glucose). Some clinical centers obtain serum samples to measure blood sugar and insulin levels every 30 minutes during a two-hour OGTT. Patients with abnormal OGTTs must be followed at least annually with repeat testing. The prevalence of diabetes mellitus in patients with FA increases with age and disease progression, and the majority of FA patients may be at risk.

**Table 1. Endocrine screening recommendations for patients with Fanconi anemia.**

	<b>Annual screenings for all patients</b>	<b>Detailed testing for selected patients</b>
Growth	<ul style="list-style-type: none"> <li>Plot patient's height and weight on a growth chart</li> </ul>	<p>If patient exhibits signs of growth failure:</p> <ul style="list-style-type: none"> <li>Test levels of IGF-1, IGFBP-3</li> <li>Obtain a BA radiograph</li> <li>Test levels of FT4/TSH</li> </ul> <p>If patient has suspected GHD:</p> <ul style="list-style-type: none"> <li>Perform GH stimulation tests</li> <li>Obtain a pituitary MRI if evidence of pituitary hormone deficiency</li> </ul>
Thyroid Activity	<ul style="list-style-type: none"> <li>Plot patient's height and weight on a growth chart</li> <li>Perform early morning TSH and FT4 tests</li> </ul>	<p>If patient has suspected central hypothyroidism:</p> <ul style="list-style-type: none"> <li>Determine the ratio of early morning TSH to afternoon TSH [17]</li> <li>Evaluate for other pituitary hormone deficiency</li> </ul>
Cortisol Levels		<p>Perform low dose ACTH stimulation test if evidence of:</p> <ul style="list-style-type: none"> <li>Any other pituitary hormone deficiency</li> <li>A pituitary abnormality on MRI</li> </ul>
Glucose, Insulin, and Metabolism	<ul style="list-style-type: none"> <li>Consider fasting glucose and insulin testing; 2-hr post-prandial glucose and insulin tests</li> <li>Measure HbA1c (after HCT)</li> <li>Consider fasting lipid profile in patients older than 10 years</li> </ul>	<p>If patient is overweight/obese/has hyperlipidemia:</p> <ul style="list-style-type: none"> <li>Perform a 2-hour OGTT test</li> </ul> <p>If patient previously had an abnormal OGTT but does not have diabetes:</p> <ul style="list-style-type: none"> <li>Repeat OGTT yearly</li> </ul>
Puberty and Gonadal Function	<ul style="list-style-type: none"> <li>Perform pubertal staging of pubic hair and either breasts (girls) or testes (boys) during physical examination</li> <li>Assess menstrual history and clinical evidence of hypogonadism in post-pubertal patients</li> </ul>	<p>If patient has early/delayed puberty or suspected hypogonadism:</p> <ul style="list-style-type: none"> <li>Obtain a BA radiograph</li> <li>Test LH, FSH, estradiol, or testosterone levels</li> <li>Serum AMH may be useful as an early marker of ovarian insufficiency in female patients [18, 19]</li> </ul>
Bone Mineral Density	<ul style="list-style-type: none"> <li>Assess the patient's dietary calcium and vitamin D intake</li> <li>Measure 25OH-vitamin D level</li> </ul>	<p>Consider DXA scan to evaluate BMD:</p> <ul style="list-style-type: none"> <li>Every 5 years starting at age 14</li> <li>Before HCT and 1 year after HCT</li> <li>Repeat in 1 year if patient has low BMD</li> <li>Repeat every 2 years if patient has hypogonadism or premature ovarian failure, or post-HCT.</li> </ul>

Abbreviations: adrenocorticotropic hormone, ACTH; anti-Mullerian hormone, AMH; bone mineral density, BMD; dual X-ray absorptiometry, DXA; free thyroxine, FT4; follicle-stimulating hormone, FSH; glycosylated hemoglobin, HbA1c; growth hormone, GH; hematopoietic cell transplant, HCT; insulin-like growth factor, IGF-I; IGF binding protein 3, IGFBP-3; luteinizing hormone, LH; magnetic resonance imaging, MRI; oral glucose tolerance test, OGTT; standard deviation units (Z-score) from the mean, SD; Thyrotropin, TSH; 25-hydroxy-vitamin D level, 25OH-vitamin D.

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## Dyslipidemia and Obesity

In one study of 29 patients with FA, over half (55%) had unhealthy levels of cholesterol and triglycerides, a condition known as dyslipidemia. Of these patients, 21% had elevated levels of low-density lipoprotein (LDL), 31% had low levels of high-density lipoprotein (HDL), and 10% had elevated triglycerides [4]. Another study found 17% of pediatric and adult patients with FA had high cholesterol [7]. An abnormal lipid profile was observed in 40% of patients with hyperglycemia or insulin resistance. Of the patients with FA and diabetes, 75% were overweight or obese. Adults with FA and diabetes tended to be overweight or obese, compared with those without these metabolic abnormalities. About 1 in 5 (21%) adults with FA were diagnosed with metabolic syndrome, a condition in which patients are overweight/obese, have dyslipidemia, and develop resistance to the effects of insulin. Half of the 24 children tested had at least one metabolic abnormality, including 4 children with insulin resistance, 1 with diabetes, and 7 with dyslipidemia [4]. Patients with FA are at risk for metabolic syndrome, for which a healthy diet, a regular exercise regimen, and careful screening for blood pressure and lipid abnormalities are recommended.

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## Bone Mineral Density

Bone mineral density (BMD) in FA has been reported in a few studies with differing conclusions. In 34 children and 3 adults with FA (including roughly equal numbers of patients with prior HCT and no HCT), lumbar spine BMD Z-scores adjusted for height age were in the normal range [8]. However, 3 of 9 children and adolescents <20 years with FA (33%) who were followed at the National Institutes of Health (NIH) had low height-adjusted BMD Z-scores (two of whom had undergone HCT) [20]. These children were older (13-18 years) and had normal height-adjusted BMD Z-score at the lumbar spine, but low values at the femoral neck; one child had vertebral compression fractures. It is recommended that the BMD of children with FA be adjusted for height and that Z-scores be calculated. An online calculator may be used to calculate the height-adjusted Z-score in children with FA [21].

Bone mineral density may decrease after HCT in many patients including those with FA, but the underlying reasons for this remain unclear [22, 23]. In a study of 49 children, including 12 with FA, BMD decreased during the first year after HCT, with the most significant bone loss occurring by six months [24]. The effects of HCT on BMD in children with FA were similar to those in children without FA. The average areal lumbar BMD Z-score declined 0.5 SD units during the first six months after HCT, and the number of patients with a Z-score below  $-1$  increased from 34% at baseline to 52% one year after HCT [1]. The reduction in lumbar BMD at six months correlated with the cumulative dose of glucocorticoids [23]. While BMD remained within normal limits, the average height-

adjusted lumbar BMD Z-score was lower in patients who had undergone prior HCT (-0.9) compared with those who had not had prior HCT (-0.3) [8]. Long-term prospective studies are needed to examine the mechanisms underlying decreased BMD following HCT in FA children.

In adults, HCT is associated with decreased bone formation and increased resorption, and similar mechanisms may apply in children [25]. Medications used during HCT, such as glucocorticoid therapy, also may contribute to low BMD. Long-term prospective studies should explore whether BMD declines further or recovers over time after HCT. Hypogonadism and growth hormone deficiency (GHD) may also predispose patients with FA to low BMD.

## Screening for Bone Health

Dual energy absorptiometry (DXA) should be used to evaluate BMD in FA patients before HCT and every two years after HCT [26]. The first DXA evaluation may be performed at about age 14 if the patient has not undergone HCT, and follow-up scans should be dictated by the patient's risk factors. Patients with FA who have hypogonadism and growth hormone deficiency should be evaluated for low BMD and treated as necessary. Levels of serum calcium, magnesium, and 25-OH vitamin D levels should be measured in HCT recipients and in patients with low BMD [27]. Patients exposed to prolonged or high doses of corticosteroids, or who have a history of fractures, immobility, hypogonadism, or hormone deficiencies should be referred to an endocrinologist.

## Therapies for Bone Health

Among other dietary recommendations, it is important to maintain adequate dietary intake of calcium and vitamin D to provide the opportunity for normal bone growth and mineralization. Supplementation should meet standard recommended dietary requirements. More aggressive intervention with calcium and vitamin D replacement may be indicated if the patient's BMD is low after adjusting for height. Vitamin D levels should be targeted to achieve sufficient concentrations (>30 ng/mL) [28]. Treatment of hormone deficiency—specifically treatment of pubertal delay, hypogonadism, and GHD—is beneficial for bone mineralization.

Bisphosphonates are effective in preventing bone loss after HCT in adults and may be effective in improving the BMD in HCT-recipient children as well, but more studies are needed before a routine recommendation can be made regarding their use for the treatment of low BMD [29]. Experienced endocrinologists or nephrologists may consider treatment with bisphosphonates in children with FA who, after vitamin D deficiencies have been addressed, sustain two or more low-impact fractures and have height-adjusted BMD Z-scores lower than -2 SD. Oral bisphosphonates should be used with caution as they may worsen esophageal reflux and have other potential health concerns. The risk/benefit ratio of this treatment must be evaluated by a specialist prior to treatment.

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# Hypothyroidism

Many children with FA (from 30-60%, depending on thyrotropin or thyroid stimulating hormone (TSH) cut off values) have mildly abnormal levels of serum thyroid hormones, including borderline low levels of thyroxine (T4) or Free T4 (FT4), or borderline high levels of TSH [3, 4, 7, 10]. This combination of test results is consistent with mild hypothyroidism. Mild hypothyroidism can occur either because the thyroid gland is abnormal and cannot make enough T4 hormone (known as primary hypothyroidism) or because the thyroid gland is normal, but the pituitary gland does not make enough TSH to stimulate the thyroid (known as central hypothyroidism). Central hypothyroidism was noted in 20-25% of patients with FA who were tested with overnight TSH or TSH surge due to low or low normal FT4 [4, 7, 17].

The mechanism causing hypothyroidism in FA patients remains unclear, but there is no indication that the primary hypothyroidism stems from an autoimmune process, in which the body mounts an immune attack against itself. Therefore, the thyroid appears to fail for other, yet-to-be-determined reasons in patients with FA. Hypothetically, some thyroid cells may die because of unrepaired DNA damage stemming from oxidative injury. One study described reduced thyroid hormone binding in persons with FA [10]. Although reduced thyroid hormone binding often is not clinically significant, it can make total T4 levels appear low and falsely suggest hypothyroidism without causing TSH elevation. Thyroid hormone binding globulin (TBG)-bound T4 (but not other bound forms) was lowest in patients with FA receiving androgen therapy [10], suggesting the need to use FT4 and TSH.

## Thyroid Evaluation

Thyroid function should be evaluated by obtaining an early morning (e.g., 8:00 am) blood sample and measuring FT4 and TSH levels. All FA patients should undergo screening for hypothyroidism once a year; or more often if clinically indicated. One example would be if the patient shows signs of growth failure (Table 1). Central hypothyroidism is suggested by low levels of FT4 and by a TSH ratio of less than 1.3 at 8:00 am compared to afternoon TSH [17]. Patients who are diagnosed with central hypothyroidism should undergo evaluation for other pituitary hormone deficiencies; specifically, the physician should rule out central adrenal insufficiency and consider ordering a pituitary MRI.

## Treatment of Hypothyroidism

Hypothyroidism should be treated promptly, particularly in children younger than 3 years of age. Thyroid hormone replacement treatment should be initiated just as in non-FA patients based on low thyroid hormone levels; specifically, a FT4 level below the laboratory reference range and/or a TSH level above the reference range. Thyroid

hormone therapy should strive to reduce TSH levels to the range of 0.5-2 mU/L in patients with primary hypothyroidism. In central hypothyroidism, therapy should aim to raise FT4 levels to just above the middle of the normal range.

There is ongoing controversy about the use of TSH levels greater than 3 mU/L as a threshold for the treatment of mild hypothyroidism [17]. Some endocrinologists may use a TSH level of 3 mU/L, or even 4.5-5 mU/L, as the upper limit of a normal TSH level in healthy individuals. However, treatment, especially in adults, is often not considered necessary unless TSH levels are persistently 10 mU/L or higher, or unless FT4 levels are low [30-32]. Among pediatric endocrinologists, some use the above approach, while others prefer to treat mildly elevated TSH levels in the hopes of improving their patients' growth [17].

In one study, eight children with FA were treated for seven months with thyroid hormone and for seven months with placebo; the treatment and placebo phases occurred in random order. Children grew significantly better on thyroid hormone than on placebo, and parents reported that their children had better energy levels during the thyroid hormone phase [3]. This study suggests that children with FA who have short stature and borderline results on thyroid function tests may benefit from using thyroid hormone therapy; however, it should be noted that only a small number of patients were studied.

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## Growth Hormone Deficiency

Growth hormone deficiency (GHD) has been described in case reports of a few patients with Fanconi anemia (FA) [33-37]. In one study, more than half (54%) of patients younger than 20 years failed to produce growth hormone (GH) in response to clonidine, a medication known to stimulate GH. Similarly, most patients (72%) failed to raise GH levels in response to another GH stimulator, arginine. Using a more stringent criterion for diagnosing GHD (specifically, peak GH levels  $\leq 5$  mcg/L), but without priming the patients in advance, 12% of 32 children tested had GHD and nearly half of them had a small pituitary gland on MRI [7]. In studies from other centers, nearly half of the patients evaluated for GHD had low GH levels [10]. One in five patients with suspected GHD had a midline defect on the brain MRI [4]. Growth hormone deficiency was more common in patients who had undergone HCT (25%) than in patients who did not have HCT (8%) [7]. The processes that underlie secretion of GH may be abnormal in children with FA during spontaneous overnight GH secretion studies [10], although these results are sometimes difficult to interpret because of the significant overlap with values observed in children without GHD [7]. Taken together, these test results suggest that while few children with FA have GHD, others may have an underactive hypothalamus, leading to "partial" GH deficiency or, alternatively, to neurosecretory GH deficiency. In these individuals, GH and

insulin-like growth factor 1 (IGF-1) values may not be as severely affected as the patient's height.

## Evaluation for Growth Hormone Deficiency

Screening for GHD in a child with poor growth can be performed by drawing a blood sample and measuring IGF-1 and IGFBP-3 levels (Table 2). If IGF-1 and IGFBP-3 values are below -2 SD for the patient's age, evaluation should include standard GH stimulation testing. One caveat is that IGF-1 is known to be a poor marker of GHD in thin individuals or in those who have received total body or cranial radiation. Sex steroid priming should be considered prior to GH stimulation testing in pre-pubertal girls age 10 years and older, and in pre-pubertal boys age 11 years and older or who are in stage two of puberty [38, 39]. Evaluation of GH secretion in a slowly growing child should be done through the use of two standard GH stimulation tests, including clonidine (150 mcg/m<sup>2</sup>, maximum dose 300 mcg), arginine (0.5 g/kg, maximum dose 20 g), or glucagon (0.3 mg/kg, maximum dose 1 mg) [39-41]. Peak GH levels are considered normal if they rise to 10 ng/mL or greater [42]. Patients diagnosed with GHD should be evaluated for central hypothyroidism, central adrenal insufficiency, and also should undergo an MRI scan of the pituitary gland.

## Treatment of Growth Hormone Deficiency

Patients with FA who have GHD can be treated with recombinant human GH therapy. A short child with FA is a candidate for treatment with GH if GHD has been convincingly documented by the child's short stature, slower than normal growth rate, and low GH peak on a stimulation test. Physicians should counsel FA patients and families about the risks and benefits of therapy. To date, there is no clear consensus on the safety of GH therapy in FA patients. Though having FA is not an absolute contraindication to GH treatment, there is some controversy surrounding the use of GH in patients without GHD. It should be recognized that in some instances, treatment with GH may be instituted in the absence of GHD if deemed appropriate by the patient care team, either before or after HCT. In the absence of safety data, GH therapy in FA patients should be titrated to achieve IGF-1 concentrations in the mid-to-normal range for the patient's age (i.e., between 0 and 1 SD). Therapy should be discontinued immediately if routine hematological examination reveals clonal hematopoietic stem cell proliferation. Growth hormone therapy should be temporarily discontinued immediately prior to HCT and for at least six months after HCT, as well as during critical illness [43].

One study found positive effects of GH treatment in 75% of children with FA treated with HCT, with at least a 0.5 SDS increase in height [44]. In studies of patients without FA, the response to GH treatment after HCT has varied [45-48]. Ongoing use of glucocorticoids after HCT may limit the patient's growth response. In a study that included HCT recipients, GH treatment was associated with significantly improved adult height (on average, patients treated with GH grew about 4-5 cm taller than untreated children) [49] and did

not increase the risks of recurrent leukemia, secondary malignancies, or diabetes in post-HCT patients treated with GH compared with those who were not treated. A beneficial effect of GH treatment on growth rate after HCT also has been reported by others [50, 51].

Patients with FA are inherently at an increased risk of cancer, particularly for acute leukemia prior to HCT, as well as malignancies of the head and neck, and gynecological cancers [52-54]. At this time, there is no evidence that this risk is enhanced in FA patients treated with GH. Patient registries have provided useful safety and efficacy data on the use of GH in the general population and in cancer survivors, but have included few patients with FA [55-61]. A large study of 13,539 cancer survivors, including 361 patients treated with GH, did not find an increased risk of cancer recurrence in GH-treated survivors [62]. However, the risk of a second neoplasm, mostly solid tumors, was slightly increased in survivors treated with GH.

Despite these possible risks, it should be noted that severe short stature may have a negative impact on the patient's quality of life and daily functioning. Patients and families should be counseled regarding the predicted adult heights, the effects of available treatment modalities on growth rate, and the potential risks and benefits of GH treatment—with the caveat that there is no clinical information about the long-term safety of GH therapy in patients with FA.

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## Cortisol Sufficiency

Most FA patients have normal circadian cortisol levels and experience normal responses to treatment with adrenocorticotrophic hormone (ACTH). ACTH stimulation testing has been normal even in patients with reported pituitary stalk interruption syndrome (PSIS) and multiple pituitary hormone deficiencies [4]. However, cortisol sufficiency should be evaluated in young children with FA who have poor growth and who require major surgery because of possible central hypothalamic dysfunction, even in the absence of a detectible midline central nervous system defect [9, 33]. Finally, ACTH stimulation testing is recommended to rule out central adrenal insufficiency if the patient has other pituitary hormone deficiencies.

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## Multiple Pituitary Hormone Deficiencies

In previous studies, MRI scans of the brain and pituitary gland have suggested that the pituitary gland is smaller and has a thinner stalk in patients with FA compared with age-matched children without FA [9, 63]. Studies also have shown midline and other central nervous system abnormalities on brain MRI [64]. Three patients with FA at the National

Institutes of Health (NIH) had pituitary stalk interruption syndrome (PSIS) with or without septo-optic dysplasia. This syndrome has previously been reported in eight other patients with FA [34, 65-67], and was associated with permanent GHD and severe growth failure. Specifically, the average height SD of all the children with PSIS at diagnosis was -4.6, with a range of -3.7 to -5.7. These patients also were at risk for multiple pituitary hormone deficiencies: 5 of 10 patients with FA and PSIS had hypothyroidism, 1 of 10 patients had hypogonadotropic hypogonadism, and the remaining 4 patients were too young to evaluate. Furthermore, 5 of 6 male patients had cryptorchidism, in which one or both testicles fail to descend, and 4 of 6 male patients had microphallus. Together, these findings suggest that in addition to GHD, the male patients had hypogonadotropic hypogonadism, a condition in which the testes produce lower than normal amounts of sex hormones due to an underlying problem with the pituitary gland or hypothalamus.

Based on the available evidence, a brain MRI with emphasis on the pituitary/hypothalamic area should be obtained in any FA patient who has one or more pituitary hormone deficiencies, including GHD, central hypothyroidism, or ACTH deficiency. Serum IGF-1 testing has been proposed as a screening test, as all patients with PSIS and GHD had low IGF-1 levels [67]. Serial endocrine testing is essential in patients with PSIS because pituitary hormone deficiencies may evolve over time.

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## Genital Tract Abnormalities

Developmental anomalies of the genital tract are more frequent in patients with FA than in the general population. Male patients with FA may be born with undescended testicles and hypospadias, a condition where the urethra opens on the underside of the penis. Many boys with FA have small testes for their age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis. Female patients with FA may be at higher risk for certain reproductive malformations, including a smaller than normal uterus, half-uterus, or uterus that does not open into the vagina [68].

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## Puberty

Children and adolescents with FA may enter puberty earlier than their healthy peers. If puberty starts too early or progresses too quickly, it may limit the number of years a child can grow and, thus, compromise adult height. A child with FA who experiences an early onset of puberty and has short stature may benefit from gonadotropin-releasing hormone agonist therapy. One study suggests this therapy can delay puberty to increase the patient's adult height by an average of 4-5 cm after four years of therapy [69]. More

commonly, children with FA enter puberty later than their healthy peers. Studies have shown that 12-14% of girls with FA had delays in starting their menstrual cycles [4, 7]. While delayed puberty is fairly common, its underlying cause is not well understood. There may be blunted and/or prolonged gonadotropin (primarily luteinizing hormone (LH)) responses to stimulation, suggesting abnormal regulation of the hypothalamic and pituitary glands (see Chapter 7). Chronic illness also is associated with delayed pubertal maturation. Total body radiation and some chemotherapy agents used during HCT also may affect gonadal function.

## Evaluation for Pubertal Disorders

In patients with FA, the onset, pubertal stage, and tempo of progression of puberty should be monitored during annual physical examinations. Physical exams should include Tanner staging of pubic hair, and assessments of breast development in girls and testicular size in boys (Table 1). Assessment of bone maturation can be useful in adolescent children who experience delayed or abnormal progression of puberty, while measuring the concentrations of certain hormones (particularly LH, FSH, estradiol, or testosterone) can be useful in adolescents and in adults who develop symptoms of hypogonadism.

## Treatment of Delayed Puberty

A boy with FA who shows no signs of puberty by age 14 years should be evaluated for possible causes of delayed puberty. After evaluation, low-dose testosterone therapy can be initiated according to the child's height and growth potential. Young boys with confirmed hypogonadism can be treated using topical gel preparations or by injections of testosterone started at an appropriately low dose and gradually increased over several years to adult replacement levels. It is important to avoid rapid increases in testosterone levels in adolescents to ensure continued height gain and avoid premature fusion of the growth plates. Bone age should be monitored during therapy.

Similarly, a girl with FA who shows no signs of puberty by age 13 years should receive a full hormonal work up. After evaluation, low-dose estrogen therapy may be started and slowly titrated under the care of the pediatric endocrinologist or adolescent gynecologist, taking into account the child's height and potential for growth. It is important to avoid rapid increase in estradiol levels in adolescents to ensure continuing height gain and to avoid premature fusion of the growth plates (see Chapter 7). Bone age should be monitored during therapy. Estrogen therapy will increase bone mineralization, optimize the child's growth rate, and achieve breast development. Progesterone (i.e., medroxyprogesterone, 10 mg by mouth daily for 10 days) should be added when breakthrough bleeding occurs or after two years of estrogen replacement therapy. Estrogen therapy is not needed if a female patient with FA has normal pubertal development or is having normal menstrual cycles, even if there is evidence of ovarian hormone deficiency.

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## Hypogonadism

Hypogonadism is very common in adults with FA. In addition, hypogonadism with small testes and penis size affects 64% of men with FA, while premature ovarian failure affects 77% of women with FA [4]. In another study, 40% of adults with FA had evidence of hypogonadism [7]. Both hypergonadotropic (either testicular or ovarian) hypogonadism [66] and hypogonadotropic (specific to the hypothalamic-pituitary glands) hypogonadism have been reported in FA patients. Gonadal function may be affected by several factors, including FA itself, SGA status at birth, gonadotropin deficiency, cryptorchidism, and/or the conditioning regimen used for HCT, including radiation and chemotherapy [67].

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## Fertility

Patients with FA often experience fertility problems, with males often being infertile and females often having premature menopause in their 20s or 30s, although pregnancies have been documented (see Chapter 7) [68, 70]. Contraception should always be used when pregnancy is not desired. Infertility may stem from a number of different factors, including a reduced sperm count in men, treatments for HCT, and the type of genetic mutation underlying FA. Gonadotropin-releasing hormone has been shown to acutely upregulate the expression of *FANCA* mRNA and protein, suggesting that *FANCA* plays a regulatory role in gonadal function [71]. Disruption of *FANCA* in mice is associated with hypogonadism and a reduction in fertility [72]. Animal studies also have shown that the *FANCC* protein is required for the proliferation of primordial germ cells [73]. Primary ovarian insufficiency also was observed in a mouse model with *FANCE* mutation [74]. In addition, radiation or chemotherapy with HCT may contribute to decreased fertility after HCT. Cryopreservation of embryos or sperm is being investigated as a reproductive option. Future studies are needed to more fully address the fertility issues in FA patients.

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## Endocrine Abnormalities Specific to Adults with Fanconi Anemia

Endocrinopathies clearly persist into adulthood, though the treatment of FA with hematopoietic cell transplant (HCT) can alter the course of disease. Early endocrine diagnosis and therapy may improve the patient's quality of life. Treatment of endocrine issues in adults with FA should be monitored by endocrinologists who care for adults, with attention to the patient's thyroid status, glucose tolerance, lipid abnormalities, maintenance of normal BMI, gonadal function, and bone mineral density. Thus far, results

from endocrine studies have been reported only for a small number of adults with FA [4, 7, 8, 10].

Lipid abnormalities were frequently seen in nearly 40 patients with FA who were followed at the NIH (unpublished data). More than half of the adults had one or more of the following lipid abnormalities: total cholesterol >200 mg/dL, HDL cholesterol <40 mg/dL, LDL cholesterol >129 mg/dL, or triglycerides >150 mg/dL. Insulin resistance, as determined by the homeostatic model assessment (HOMA), and metabolic syndrome also were common in adults.

Thyroid abnormalities remain prevalent in FA patients older than 18 years, with 37% to 57% of patients having hypothyroidism. These patients typically present with either elevated TSH levels or low Free T4 levels [4, 7]. In one study, a low stimulated GH peak was observed in a small number (6 of 16) of adults with FA [4, 7]. Hypogonadism with small testes was present in at least half (50%) of men with FA, and hypogonadism was present in one-third (30%) of women with FA. In addition, many women with FA experience premature menopause (see Chapter 7).

One study reported decreased BMD (osteopenia or osteoporosis) in 12 of 13 adults with FA [4]. Of the eight females with decreased BMD, seven experienced premature ovarian failure and early menopause [4]. In 15 adult female patients with FA from the same center, five (33%) had osteoporosis and all had hypogonadism, which appears to be the predominant cause of low BMD in adult female patients with FA [20]. However, the BMD was not adjusted for height in this study, and the measured BMD may have underestimated the volumetric BMD in several individuals with short stature whose bones were likely smaller than those of other participants [75]. It is not clear whether BMD in adults with FA should be routinely adjusted for height. The correlation of fracture risk with height-adjusted BMD in adults with FA also is unknown. Additionally, many FA adults have hypogonadism, other endocrine deficiencies, and have undergone HCT—all of which may adversely affect bone health and trigger the early development of osteoporosis.

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## Medications and Treatments That Affect Endocrine Function

### Androgen Therapy

Androgen therapy is used to improve the blood counts of patients with FA and can cause endocrine-related side effects that need to be monitored (see Chapter 3). Androgens can improve growth rates, but often hasten the maturation of growth plates, which reduces the time available for childhood growth. Children treated with androgens may appear to be growing well, but their potential adult height may decline due to rapid skeletal maturation

and premature fusion of cartilage plates at the end of long bones, known as epiphyseal fusion. Androgen use, in particular with oxymethalone, also may result in virilization in both males and females. The impact of androgen therapy on height and bone maturation should be discussed with the patient's family. Prior to beginning androgen therapy, a bone age X-ray should be performed. During androgen therapy, the patient's bone age should be reassessed periodically, and may be checked every 6-12 months.

## **Hematopoietic Cell Transplantation**

Transplantation is inherently associated with a state of illness. Illness is not an optimal time to assess any hormone concentrations, as illness often alters thyroid levels, growth, gonadal function, nutrition, and glucose regulation. The treatments and radiation used during HCT may exacerbate the patient's underlying intrinsic risk for endocrine disorders and lead to growth failure as a consequence of GHD, primary hypothyroidism, gonadal failure, and decreased BMD. Therefore, FA patients who undergo HCT should be closely monitored for hormonal abnormalities [26]. The late effects screening guidelines [26] recommend that a full endocrine evaluation including height/weight measurements, Tanner staging, bone age and growth factors should be assessed after HCT in children. In addition, screening is recommended for diabetes, dyslipidemia, vitamin D deficiency and osteoporosis (DXA scan before HCT and every two years after HCT). Some of these guidelines have been outlined by the Children's Oncology Group [76]. Many agents used in HCT have side effects on the endocrine system. Busulfan can adversely affect thyroid function [77] and sometimes growth [78, 79]. It is highly toxic to gonads and can lead to gonadal failure, particularly in females [80, 81]. Cyclophosphamide has a known dose-related effect on gonadal function in both males and females, particularly when used in combination with busulfan [25, 82-84]. Glucocorticoids can lead to increased appetite, weight gain, insulin resistance, and hyperglycemia, sometimes creating the need for insulin therapy. Prolonged use of glucocorticoids may cause linear growth failure and delayed puberty. Glucocorticoids adversely affect bone mineralization [5]. Methotrexate increases the risk for bone loss [85, 86]. Total body irradiation (TBI) increases the risk of primary hypothyroidism [87, 88], growth impairment [79, 89], hypogonadism [82, 90], and poor bone mineralization [91, 92].



## Summary

Endocrine problems are common in FA patients, who often—though not always—are shorter than the general population. Patients with FA may have reduced GH secretion, hypothyroidism, and abnormal glucose homeostasis with deficient pancreatic beta cell secretion of insulin and/or insulin resistance. Puberty, gonadal function, and fertility may be affected in these patients. Older children and adults with FA tend to have low BMD. Height adjusted BMD Z-scores should be used in children, but it is unclear if BMD should be adjusted for height in adults with FA and short stature, and if these measures correlate with the risk of bone fractures. However, the high incidence of endocrine dysfunction—especially hypogonadism, corticosteroid use, and HCT—may predispose adults with FA to osteoporosis.

The origin of endocrine disorders in FA patients remains unclear. Hypothyroidism generally is accompanied by elevated TSH levels and, thus, seems to arise from problems with the thyroid gland, although hypothalamic-pituitary dysregulation leads to abnormal central TSH release in some patients. Hyperglycemia/hyperinsulinemia generally is thought to arise from pancreatic beta cell dysfunction, but insulin resistance and metabolic syndrome also are common in patients with FA. In contrast, GH insufficiency probably arises from problems with the hypothalamus or pituitary gland. Currently, a single unifying cause for all of these endocrinopathies is not known. It is possible that endocrine secretory cells are damaged by excessive reactive oxygen species, with inadequate repair mechanisms in patients with FA. In addition, treatments used in FA such as androgens, glucocorticoids, chemotherapy, or radiation with HCT may contribute to endocrine dysfunction.

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