

# MEDICAL COMPLICATIONS OF ANOREXIA NERVOSA

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***Anorexia nervosa is a serious systemic disease affecting virtually all major organ systems. It is frequently undiagnosed, or there is a significant delay in the diagnosis. Anorexia nervosa is one of the few major medical diseases where patients frequently do not seek help and may actively hide their symptoms, making it especially hard for physicians to diagnose and treat. Anorexia has many endocrine and reproductive complications, including amenorrhea or irregular menses, delayed puberty, changes in ovarian morphology, and infertility. Women with anorexia have worse pregnancy outcomes; pregnancy itself may also worsen their symptoms of anorexia. Anorexia nervosa is a disease with high morbidity and mortality; patients may die, especially from cardiovascular complications. Anorexia also can cause gastrointestinal, renal, biochemical, hematologic, dermatologic, and metabolic complications. Comorbid psychiatric illnesses occur in greater than 50% of patients with anorexia. Ob/Gyn physicians must know how to adequately assess patients for the presence of anorexia and understand basic treatment principles. (Prim Care Update Ob/Gyns 2003; 10:110–115. © 2003 Elsevier Inc. All rights reserved.)***

Anorexia nervosa has the highest morbidity and mortality of any psychiatric disorder. The aggregate annual mortality rate for anorexia of

5.6% is 12 times higher than the annual death rate in women age 15–24 in the general population.<sup>1,2</sup> Unfortunately, there is often a significant delay from the onset of symptoms to the time of diagnosis and treatment. Incredibly, one study found that 50% of women with eating disorders went undiagnosed in clinical settings.<sup>1</sup> There are several reasons why anorexia, in particular, has such a high frequency of delayed and missed diagnosis and treatment. One reason is that patients often try to hide their illness from family, friends, and clinicians. They may be too ashamed to admit to their problem. Some patients actively conceal their anorexia because they do not want to give up the behavior. Finally, many are in denial that they even have any problem with their eating.<sup>1</sup>

When patients with anorexia nervosa do present for medical treatment, it is frequently for medical problems secondary to their malnutrition and starvation, such as amenorrhea or infertility, rather than for help with the anorexia itself.<sup>1,3</sup> Clinicians must therefore keep watch for underlying eating disorders. By understanding the full spectrum of its medical sequelae, clinicians are more likely to recognize and accurately diagnose anorexia nervosa. Physicians and patients should understand that anorexia nervosa is a systemic disease that can affect virtually all organ systems. Full knowledge of the potential complications of anorexia allows physicians to thoroughly evaluate and provide complete treatment for patients once the diagnosis has been made. It also al-

lows physicians to educate patients with anorexia about the potential complications of their disease. Objective findings of the medical complications of anorexia may even help patients who are in denial to accept the diagnosis and treatment.

Another factor for clinicians to keep in mind is that patients with eating disorders often fluctuate in their behavior between periods of restricting and periods of feeling out of control with their eating. They also may fluctuate in the use of various compensatory behaviors after eating, such as vomiting, restricting, diuretics, laxative abuse, or over-exercising.<sup>4</sup> Some patients purge only in association with bingeing, but others may purge after eating even small amounts of food, as in anorexia, purging type.<sup>4</sup> When discussing the medical complications in eating disorders, it may be more helpful to think of complications as occurring from restricting/malnutrition or from bingeing or purging, rather than from anorexia or bulimia. All of the complications described in this article are associated with the restricting/malnutrition behavior in patients with anorexia, non-purging type. Patients who restrict their eating but don't meet full criteria for anorexia can still have some of the same complications.

## Endocrine/Reproductive Complications

### MENSES

To meet the criteria for diagnosis with anorexia nervosa, women must have at least three consecutive

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months of amenorrhea, unless they are taking oral contraceptive pills (OCPs). The amenorrhea of anorexia is marked by low circulating luteinizing hormone (LH) and follicle-stimulating hormone (FSH) despite low estrogen, a pre-pubertal pattern of release of LH and FSH, diminished response to luteinizing hormone-releasing hormone, changes in metabolism of estradiol that leads to production of a biologically less active metabolite, and the absence of withdrawal bleeding after a progesterone challenge.<sup>2,3,5</sup> This hormone disturbance is mainly an effect of starvation and malnutrition rather than just low weight, as amenorrhea can precede weight loss in up to 1/3 of patients, and menstruation does not always correlate with weight gain.<sup>2,5</sup> Even short-term dieting or restricting can have a marked effect on the amplitude and frequency of LH release and follicular development.<sup>6</sup> Weight gain to 90% of ideal body weight (IBW) is the average weight at which women resume menses within 6 months, but 10–15% of women have persistent amenorrhea even after weight gain to at least 90% of IBW.<sup>2</sup>

## OVARIES

The pre-pubertal hormonal state in anorexia is associated with smaller ovaries. With severe malnourishment and low body mass index (BMI), ovaries appear small or undetectable, and have no follicles.<sup>5,7</sup> With resumption of eating and weight gain, ovaries can grow and develop multiple follicles until finally one follicle becomes dominant and ovulation and menstruation resume.<sup>8</sup> Pelvic ultrasound is useful to determine ovarian size.<sup>3</sup>

## FERTILITY

Studies report that a high number of women presenting to infertility clinics had an undiagnosed eating disorder. In one study, five out of 14

women getting ovulation induction had an eating disorder.<sup>3</sup> Conversely, women with anorexia can still get pregnant, even if they have been amenorrheic, so they should be advised to use birth control.<sup>2</sup>

## PREGNANCY

Anorexia is associated with worse outcomes in pregnancy. There is a higher rate of cesarean-section,<sup>9,10</sup> a 40% rate of low birth weight (LBW) infants,<sup>11,12</sup> and a 2× increased rate of premature delivery.<sup>12,13</sup> Babies born small for gestational age were more likely to have mothers with lower pre-pregnancy weight, lower desired weight in pregnancy, lower weight gain during pregnancy, greater than average concern about overeating, and who smoked.<sup>12</sup> Alarming, one study found that women with remitted anorexia were just as likely as women with active anorexia to have more miscarriages, cesarean sections, premature births, and low birth weight babies than controls.<sup>9</sup>

## MOTHER/CHILD INTERACTIONS

New mothers with histories of anorexia have more difficulty maintaining breast feeding, and as children grow older, they remain more detached during meals and make fewer positive comments about food and eating compared to mothers without anorexia. However, children of mothers with anorexia have no difference in childhood temperament compared with controls, and mothers report equal satisfaction with their children's physical appearance.<sup>11</sup>

## OTHER ENDOCRINE DISTURBANCES

Patients with anorexia frequently have signs of Sick Euthyroid Syndrome, probably resulting from chronic malnutrition. Labs show low T3, low or normal T4, and normal TSH. This finding can act

as a marker of the systemic effects of the restricted eating, but it does not require treatment. Anorexia can also affect the HPA axis. Patients can have an increase in baseline cortisol levels (because of decreased breakdown of cortisol and increased activation of the HPA axis), a loss of the diurnal variation in cortisol, and non-suppression of cortisol after administration of dexamethasone.<sup>14</sup>

## Skeletal Complications

Osteoporosis occurs in up to 50% of patients with anorexia.<sup>1,2</sup> The best predictors for which patients will develop osteoporosis are length of amenorrhea and estrogen deficiency.<sup>15–17</sup> Low BMI (body mass index) and past weight history, including minimum weight, also correlate with the presence of osteoporosis.<sup>15,16,18</sup> Other factors that contribute to increased risk for osteoporosis include smoking and alcohol consumption, low calcium, high cortisol, and a family history.<sup>15,16</sup> The long-term risk for bone fractures is 2.9 times that of controls, and occurs especially in vertebrae, wrist, hip, humerus, and tibia.<sup>15</sup> Adolescents with anorexia may have stunted growth and incomplete pubertal development.<sup>19</sup> The gold standard for measuring bone density is dual x-ray energy absorptiometry (DEXA),<sup>2,15,20</sup> which should be performed in anyone with anorexia for greater than 1–2 years.<sup>2</sup> Unfortunately in adolescents getting a DEXA, norms are poor compared to age-matched controls, because the norms do not take into account variations in height, bone size, or pubertal age, so a patient may be her own best control for repeat measures over time. Also, adolescents who are still developing have not yet achieved peak bone mass, so it is not possible to make a diagnosis of osteopenia or osteopo-

rosis, which are based on comparisons to peak bone mass density.<sup>19</sup>

Unfortunately HRT (hormone replacement therapy) does not effectively prevent decreased bone mineral density, except possibly in patients with weights <70% of IBW.<sup>2,15,18</sup> The best treatment for bone mineral density loss is balanced re-feeding and resumption of normal menstruation.<sup>15</sup> Patients may also try Ca 1500 mg per day and Vitamin D 400 IU per day.<sup>2</sup> Increases in BMD (bone mineral density) can occur with weight gain even prior to resumption of menses,<sup>20</sup> although patients' BMD may not ever return to normal. One study found persistently lower BMDs in patients with a history of anorexia, even after an average of 21 years recovery from it.<sup>20</sup>

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## Cardiovascular Complications

Approximately half of deaths in anorexic patients are due to cardiovascular complications. Over 80% of patients have electrocardiogram (EKG) changes, especially bradycardia, but also decreased QRS amplitude secondary to decreased cardiac size, non-specific changes such as T wave flattening or inversion, ST depression, and U waves.<sup>21</sup> Prolonged QT interval is a risk factor for ventricular arrhythmia and sudden death.<sup>21</sup> Other cardiac complications of anorexia include reduced left ventricular mass, thinning of the left ventricular wall, decreased cardiac chamber size, decreased oxygen uptake, and decreased exercise capacity.<sup>21</sup> The left ventricular mass appears to normalize with re-feeding.

Heart rates decrease and blood pressure falls as an adaptive response to starvation. Resting heart rates commonly drop into the 30s in severe anorexia. Patients may have orthostatic changes from both dehy-

dration and starvation, which can usually be treated with fluids.

Patients may feel weak, dizzy, or short of breath. They may continue to try to exercise, despite these symptoms, which increases their chance for cardiac collapse and death. Most patients mistakenly believe that if they are still up and walking, they "must not be that sick." This is a dangerous misperception. Most anorexics do not have an obvious, gradual, progressive decline; instead, patients are usually working, walking around, and possibly even exercising right up until the point that they collapse.

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## Gastrointestinal Complications

The effects of anorexia on the gastrointestinal (GI) system are important both psychologically and physiologically. Anorexics have an exaggerated sense of the size of their stomach—both in terms of their outward appearance and how they imagine their stomach appears inside their body.<sup>6,22</sup> When they eat, they picture their stomach ballooning out. After a period of restricted intake, patients often develop delayed gastric emptying, which contributes to their prolonged sense of fullness after a meal.<sup>5,6,22</sup> In their minds, the feeling of being "full" becomes equated with being "fat," which reinforces their fear of eating regular meals.

Most anorexics have a period when they begin eating regular amounts of food where they have stomach pain, nausea, bloating, cramps, and diarrhea.<sup>6</sup> It usually takes about 2 weeks of regular eating for the GI system to readjust. They also usually gain 4–5 pounds of extra water weight in the first few days, which they then flush out through the kidneys over the next several days. Patients often need to be in a supervised setting to help them through this initial phase and

may need to start with easily digestible semi-solid food, because the physical symptoms, especially of bloating and water retention, worsen their already intense anxiety about beginning to eat again. Patient education and treatment of symptoms such as nausea or diarrhea are helpful.

Not only the stomach, but the whole GI tract can suffer from decreased motility.<sup>22</sup> Constipation is common, and should be treated with re-hydration, roughage, and bulk laxatives if needed, but they should not be treated with stimulant laxatives because of the potential for abuse in an effort to lose weight.<sup>5</sup>

Starvation can also cause a nutritional hepatitis with decreased total protein, elevated transaminases, and increased bilirubin, but it usually does not lead to severe liver disease unless the person also abuses alcohol.<sup>22</sup> Rarely, patients can develop pancreatitis in severe anorexia secondary to scialoadenosis, which produces an increased serum amylase.<sup>22</sup>

Clinicians must use caution when re-feeding an anorexic. When patients are given too large a glucose or carbohydrate load, a large amount of phosphate is rapidly consumed as it is used to metabolize glucose, and phosphate levels can fall dangerously low.<sup>5</sup> The low phosphate can cause cell breakdown and milder symptoms of muscle weakness, fatigue, nausea, and vomiting. In more severe cases, it can cause life threatening epilepsy, cardiomyopathy, hemolytic anemia, respiratory failure, coma, and death.<sup>5</sup> Pancreatitis can also occur during re-feeding, and starvation-induced hepatitis may also worsen initially during re-feeding.<sup>22</sup> Occasionally stomach dilation and perforation can occur if the patient is re-fed too fast.<sup>5</sup> Therefore, clinicians should consult with a nutritionist during the re-feeding process.

## Renal/Biochemical Complications

Up to 70% of patients with anorexia have renal problems.<sup>8</sup> Dehydration is common, as patients often decrease their fluid intake as well. Patients may report feeling light-headed, especially when they stand up, or report dry mouth or dark urine, and may even faint.<sup>5</sup> Dehydration can cause abnormal findings of an increased Bun/Cr ratio, orthostasis, ketonuria, and proteinuria. Patients can have a decreased GFR, and if severe, they can have renal tubular damage and renal failure.

Occasionally patients do the reverse: they increase their fluid intake, usually in an effort to dull hunger pains. Excess fluid intake can lead to a dilution effect, and possibly hyponatremia.<sup>14</sup>

Restricted caloric intake can cause low serum glucose, especially in states of severe malnutrition after energy stores have been depleted. When mild, hypoglycemia may be asymptomatic, but when more severe, it can lead to sweating, tremor, drowsiness, irritability, then bradycardia, coma, and death. Concurrent infection, alcohol abuse, and excessive exercise can all increase the risk for hypoglycemic coma.<sup>14</sup> During re-feeding, patients can experience post-prandial hypoglycemia, because they have an excessive insulin response to a meal as a compensatory reaction to prolonged starvation.<sup>14</sup> Surprisingly, despite restricted intake, hypercholesterolemia is a common lab finding. It is caused by decreased production of the enzyme needed to break down cholesterol.<sup>14</sup>

Severe malnutrition is also associated with hypocalcemia and hypomagnesemia.<sup>14</sup> Hypomagnesemia can be worsened by hypophosphatemia and alcohol, and can lead to EKG abnormalities, muscle weakness, and seizures. Hypo-

magnesemia is associated with refractory hypocalcemia and hypokalemia, which may not resolve until hypomagnesemia is replaced.<sup>8</sup> Electrolyte disturbances in the absence of purging are rare.

Hypophosphatemia usually does not occur from starvation, but can occur with re-feeding, as described earlier, or from too rapid correction of hypokalemia. Additionally, too rapid correction of hypophosphatemia can lead to drops in calcium levels.<sup>14</sup> Clinicians should check labs every 1–2 days during the initial re-feeding phase.

Re-feeding can also lead to water retention and edema, which is psychologically very hard for patients.<sup>6</sup> If water retention is severe, it can be dangerous, and lead to pleural and pericardial effusion.<sup>14</sup> The underlying mechanism for the water retention is unclear, but may be from severe malnourishment or decreased renal capacity.<sup>14</sup>

## Hematologic Complications

Decreased WBC occurs in up to 60% of patients with anorexia.<sup>8,23</sup> Patients' BMI is correlated with leukocyte and neutrophil count.<sup>23</sup> Anemia, which is usually normocytic,<sup>23</sup> and thrombocytopenia occur in 30% of patients.<sup>8</sup>

## Dermatologic Complications

Patients frequently experience growth of fine hair on their arms, legs, side of face and trunk, called lanugo.<sup>5,8,24</sup> The lanugo usually occurs during the period of greatest weight loss, and its appearance is correlated with low BMI and amenorrhea.<sup>24</sup> Dry skin occurs in 50–70% of patients, and patients may also have split, dry hair, and brittle nails.<sup>5,24</sup>

## Metabolic Complications

Anorexics usually have a lower basal metabolic rate than controls despite normal thyroid levels, which is a compensatory reaction to starvation.<sup>8</sup> Patients have impaired temperature regulation, especially when exposed to environmental temperature changes.<sup>8</sup> After they are exposed to cold, they do not shiver or stabilize their core body temperature, and when exposed to heat, they do not have adequate vasodilation and have an abnormally high core temp.<sup>8</sup>

## Assessment of the Patient

The most important factor for clinicians in making sure they do not miss the diagnosis of anorexia is to look for it. Eating disorders are so incredibly common that asking women about their eating habits should be part of any evaluation or work up. Height and weight should be recorded, and clinicians should be able to calculate % IBW. A good estimate for the average IBW is 100 lbs for 5'0", and then add 5 pounds for every inch. (Adding 3 pounds for every inch above 5' gives a good rough estimate of the low end of the normal range for IBW). Having a weight less than 85% of the IBW is a danger sign, and one of the criteria in diagnosing anorexia. However, it is possible for patients to have a weight in the normal, or even above normal range, and still be severely malnourished and at risk for major medical complications. For example, a patient may start out overweight and then begin severe dieting and start rapidly losing weight. Her weight may be in the normal range at the time of evaluation, but she still may be very malnourished and at risk for major medical complications. Also, substance abuse is a frequent co-morbidity with eating disorders, and some women have a

**Table 1.** Screening Questions for Eating Disorder

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- Have you ever had any concerns about your eating?
  - How do you feel about your body and weight—are you wanting to gain or lose weight?
  - What is the highest and lowest weight you've been at this height, and what is your weight currently?
  - Have you ever had any rapid weight gain or loss?
  - Has anyone else ever expressed concern about your eating?
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normal weight even though they are not eating at all, because they are getting their calories from alcohol.

Asking only “do you have an eating disorder” or “have you ever had an eating disorder” may miss many patients who do, in fact, have an eating disorder. Using the following few screening questions (see Table 1) can greatly increase the chance of detecting an eating disorder: 1) Have you ever had any concerns about your eating? 2) How do you feel about your body and weight—are you wanting to gain or lose weight? 3) What is the highest and lowest weight you've been at this height, and what is your weight currently? 4) Have you ever had any rapid weight loss or weight gain? 5) Has anyone else ever expressed any concern about your eating?

For women who give indication of having an eating disorder, either by report or by low body weight, rapid weight loss, severe restricting, or desire to drop to an unhealthy low weight, further examination is warranted. Clinicians may use questionnaires, such as the Eating Disorders Inventory, Eating Attitudes Test, or Survey for Eating Disorders, all of which are self-reporting questionnaires, as well as further interviewing.<sup>4,10</sup> Clinicians should take a full medical history and screen for co-morbid psychiatric problems. Over half of patients with eating disorders have other major psychiatric problems, such as depression, anxiety, substance abuse, history of sexual, physical, or verbal abuse and post-traumatic stress disorder.<sup>4</sup> They may engage in other high risk or self-injurious

behaviors, such as cutting, having unsafe sex, or driving drunk. Clinicians also need to question if patients are taking any prescription, herbal, OTC or illegal drugs for weight control.

Vital signs should include weight, height, temperature, and orthostatics.<sup>1,4,10</sup> An irregular pulse or slow heart rate (<45) indicates the need for an EKG. A full physical examination should be performed, including skin, which should be examined for lanugo, dryness and bruising.<sup>1</sup> Labs should include full blood count, Bun, Cr, glu, electrolytes, Ca, Mg, Phos, Serum protein, LFTs, TSH, and poss estradiol.<sup>1,4</sup> Urine should be dipped, looking for sp gravity, ketones, proteins, or even WBC or RBC.<sup>4</sup> In patients with greater than a 1-year history of anorexia, clinicians should strongly consider a DEXA test.<sup>1</sup>

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## Treatment

According to the APA guidelines for treatment of anorexia nervosa, criteria for inpatient medical admission include T <97, P <40, orthostatic changes not correctible with fluids, BP <90/60, glu <60 or electrolyte, liver or renal changes requiring acute treatment.<sup>4</sup> Also, weight below 75% IBW or inability to eat without constant supervision, as well as inability to curtail exercise when necessary, all indicate possible reasons for medical admission.<sup>4</sup>

Antidepressant medications unfortunately are not very useful in the acute phase of treatment, even

though patients frequently suffer from concurrent depression, anxiety, or other psychiatric problems in addition to their anorexia. Antidepressants lose their effectiveness when patients are in a state of starvation.<sup>4</sup> Patients can be reassured that if they do start to eat again, the antidepressants will have a much higher likelihood of working. Thinking of food as an adjunct “medication” can sometimes help women to start eating again.

When trying to treat patients with anorexia in an outpatient setting, a team approach works best. The team should include a therapist, a nutritionist, and a physician. The team needs to communicate with each other to provide coordinated treatment and to prevent any splitting from occurring. Patients with anorexia can be extremely difficult to treat, because they are often very sick, very smart, and ambivalent at best about getting treatment. They often have issues of control: usually they feel out of control in most aspects of their lives, and turn to food as a way of exercising control. Therefore, providers must walk a fine line between monitoring patients eating and ensuring adequate caloric intake, without causing the patient to feel she has lost all control. Clinicians must help patients find ways to assert themselves in healthy ways rather than through food restriction.

Patients with anorexia often have a hard time not just taking in food, but with taking in anything—emotional support, caring, help, or treatment of any kind. They often are torn between wanting to be taken care of, yet assuming that no one cares or will be capable of helping them. They have difficulty trusting others, which makes it difficult for them to accept treatment from providers. Clinicians must work hard to establish an alliance with the patient and involve her as much as possible in setting up the treatment plan. Clinicians should not be

judgmental, punitive, or critical. They should explore with the patient her feelings and be empathic and patient, yet also clear about their expectations of the patient and firm in setting limits necessary in maintaining her health and safety.

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