# Reproductive issues in anorexia nervosa

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## Abstract

Despite a high prevalence of menstrual irregularities, women with anorexia nervosa are becoming pregnant. The physical and psychological demands of pregnancy and motherhood can represent an immense challenge for women already struggling with the medical and psychological stress of an eating disorder. This article summarizes key issues related to reproduction in women with anorexia nervosa, highlighting the importance of preconception counseling, adequate gestational weight gain, and sufficient pre- and post-natal nutrition. Postpartum issues including eating disorder symptom relapse, weight loss, breastfeeding, and risk of perinatal depression and anxiety are also discussed.

## Keywords

anorexia nervosa; eating disorders; mothers; nutrition; pregnancy

Anorexia nervosa is a devastating psychiatric illness marked by extremely low bodyweight, cognitive distortions related to body shape and weight perception, and either severe food restriction or a pattern of binge eating or purging behavior (Box 1). The medical and psychological consequences of anorexia nervosa are extensive; correlates of the eating disorder such as depression, anxiety, social withdrawal, heightened self-consciousness and fatigue, in addition to medical complications such as cardiac abnormalities and osteoporosis, can persist throughout life. The mortality associated with anorexia nervosa is high; the standardized mortality ratio estimates for all causes of death in females with anorexia nervosa range from 1.7 to 12.8 [1–4].

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**Box 1**

Diagnostic and Statistical Manual-IV criteria for anorexia nervosa

- Failure to maintain bodyweight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of bodyweight less than 85% of that expected or failure to make expected weight gain during period of growth, leading to bodyweight less than 85% of that expected)

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- Intense fear of gaining weight or becoming fat, even though underweight

- Disturbance in the way in which one's bodyweight or shape is experienced, undue influence of bodyweight or shape on self-evaluation, or denial of the seriousness of the current low bodyweight

- Amenorrhea in postmenarcheal females

**Restricting type**

- During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics or enemas)

**Binge-eating/purging type**

- During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

DSM-IV: Diagnostic and Statistical Manual IV.

An estimated 0.9% of women in the USA have met the threshold Diagnostic and Statistical Manual IV criteria for anorexia nervosa in their lifetime [5]. The mean age of onset for the disorder is approximately 19 years of age [5], affecting many women during their childbearing years. It was first believed that pregnancy in women with anorexia nervosa was rare owing to the endo-crinological disturbances associated with starvation coupled with the psychological and psychosocial features of the disorder. However, recent studies have failed to find differences in fertility between women with histories of anorexia nervosa and controls, demonstrating that despite high levels of menstrual disturbances, women with anorexia nervosa are becoming pregnant [6,7]. The physical and psychological demands of pregnancy and motherhood can represent an immense challenge for women already struggling with the medical and psychological stress of an eating disorder [8,9]. This article summarizes key issues related to reproduction in women with anorexia nervosa, highlighting the importance of preconception counseling, adequate gestational weight gain, and sufficient pre- and post-natal nutrition. Postpartum issues including eating disorder symptom relapse, gestational weight loss, breastfeeding and risk of perinatal depression and anxiety will also be discussed. In addition, we include a 5-year view that summarizes the emerging psychiatric epigenetics literature and proposes that epigenetics may explain the processes by which maternal undernutrition and anxiety in anorexia nervosa lead to long-term effects on offspring. For each topic discussed, we conducted a search using MEDLINE, PsycINFO and the Cochrane Library database to identify original research articles; we also conducted a secondary search of references from relevant review articles found in each search.

# Prepregnancy issues in anorexia nervosa

## Amenorrhea

Amenorrhea is currently a diagnostic criterion for anorexia nervosa, although this will change with the next diagnostic scheme. Of women presenting with anorexia-like illness, between 68 and 89% report absence of menstruation for at least 3 months during the course of their illness [10–13]. An additional 6–8% of women may not experience prolonged amenorrhea, but report menstrual irregularity or oligomenorrhea [11,13].

These disruptions in the normal menstrual cycle in many women with anorexia nervosa are probably manifestations of decreased systemic estrogen levels resulting from prolonged restriction of caloric intake and/or excessive exercise. Studies using pelvic ultrasonography

in postpubertal women with current anorexia nervosa have demonstrated that, after significant weight loss, the uterus regresses back to its prepubertal length and the endometrial stripe seen on ultrasound can be either very thin or undetectable [14]. The ovaries also regress to their prepubertal, immature size and some may not be visualized at all [14].

### Fertility

The high prevalence of menstrual disturbances led many to hypothesize that women with anorexia nervosa would be unlikely to conceive. However, outcome studies have consistently reported that fertility rates in women with a lifetime history of anorexia nervosa do not differ from women in the general population [6,7,15,16]. Two small studies have reported a high prevalence of lifetime eating disorder diagnoses (not exclusively anorexia nervosa) among women attending infertility clinics [17,18], but other studies have found no differences in the rates of fertility treatment in women with anorexia nervosa compared with women in the general population [6,7]. Thus, it appears that despite the high prevalence of menstrual irregularities, women with anorexia nervosa are becoming pregnant.

Some women with anorexia nervosa may become pregnant during one of several intermittent phases (few months) of 'regular' ovulation and accompanying menstruation that may occur throughout the course of their illness. In others, pregnancy may occur in the absence of menstruation and can be explained similarly to rare cases of pregnancy in premenstrual adolescents (on menarche), nursing mothers and perimenopausal older women [10]. When ovulation occurs for the first time after a period of amenorrhea and anovulation, it is possible for this first egg to become fertilized. The endometrial lining will then be maintained by the newly fertilized egg, and menstruation will not occur. Thus, a woman with anorexia nervosa may become pregnant without having experienced a resumption of menstruation.

## Prenatal issues in anorexia nervosa

### Unplanned pregnancy

Two large population-based studies have found that women with current anorexia nervosa have an earlier age of pregnancy compared with women in the general population without eating disorders [19,20]. Further investigation in the Norwegian Mother and Child Cohort Study (MoBa; including 62,060 births in Norway) found that the risk of having an unplanned pregnancy was significantly increased in women with current anorexia nervosa in the 6 months before pregnancy, with 50% reporting that their pregnancy was unplanned compared with only 18.9% in the referent group [21]. In addition, women with anorexia nervosa were significantly more likely to report a past induced abortion than the referent group (24.2 vs 14.6%).

While the explanation for this finding requires additional study, the authors hypothesize that the absence or irregularity of menstruation in these women may lead them to the belief that conception is unlikely and that there is less need for adherence to guidelines for proper contraceptive use. To our knowledge, there are currently no published studies evaluating fidelity of contraceptive use in women with anorexia nervosa.

This finding is particularly concerning, as unplanned pregnancies may decrease the opportunities these women have to establish critical nutritional and emotional support to help them manage the physical and psychological demands of pregnancy and motherhood.

### Prenatal eating behavior

**Remission of eating disorder symptoms during pregnancy**—Rigorous evaluation of the eating behaviors of women with anorexia nervosa during pregnancy is exceedingly difficult owing to the relatively low prevalence of the disorder in the general population (0.9%) [5] and the difficulty of assessing the weight criterion for anorexia nervosa during pregnancy. Nevertheless, early retrospective investigations of clinical samples found some women with eating disorders (not solely anorexia nervosa) report temporary improvement in eating disorder symptomatology during pregnancy, with a resurgence of symptoms postpartum [22].

Three large prospective studies addressing eating behavior during pregnancy in women with eating disorders have replicated the findings of these early retrospective reports. In the MoBa cohort, remission rates during pregnancy across the eating disorder subtype were between 29 and 78%, although this study did not evaluate remission of anorexia nervosa specifically, owing to difficulty assessing the weight criterion during pregnancy [23]. With respect to body-image concerns, cohort studies in both the UK and the USA found that concerns over shape and weight were seen to decrease during pregnancy in women with active eating disorders (not solely anorexia nervosa) [20,24,25].

Of note, approximately one-third of women struggling with eating disorders (including, but not limited to anorexia nervosa) believe that pregnancy could provide a means to recover from their disorder [22], even though they also report fear that their gestational weight gain will be out of their control. Many also report that they view gestational weight gain and a larger body size as more acceptable during pregnancy than under other circumstances [22,26].

**Relapse of eating disorder symptoms during pregnancy**—While some women may experience a remission from eating disorder symptoms during pregnancy, several studies report that women recovered from eating disorders experience relapses during pregnancy. A prospective study in Sweden that followed individuals with a past diagnosis of anorexia nervosa prior to pregnancy found that eight out of 24 women (33%) had a verified relapse of their eating disorder during pregnancy that led to contact with a psychologist or psychiatrist [27], and a UK study reported that women with past eating disorders (not solely anorexia nervosa) reported an increase in overall weight and shape concerns during pregnancy [20].

**Disordered eating behaviors during pregnancy**—Women with recent and past anorexia nervosa report very low use of laxatives and self-induced vomiting during pregnancy, but are more likely to engage in a high level of exercise (defined as greater than 1 h of moderate to vigorous activity daily) during pregnancy than nonobese women without eating disorders [20].

Women with anorexia nervosa before pregnancy are also more likely to smoke during pregnancy (37.1% compared with 9.2% in women without eating disorders) [19]. While concerns about weight and appetite control may be associated with this increase in smoking during pregnancy, a separate study found that individuals with eating disorders score higher on a scale of nicotine dependence than those without eating disorders [28], suggesting that giving up smoking during pregnancy may represent a greater challenge for these women.

There has been much debate in the literature as to the risk of hyperemesis gravidum (HG) during pregnancy in women with eating disorders [10,27,29,30]. When HG was defined as vomiting during pregnancy requiring hospitalization, women with purging-type eating disorders were not found to have statistically significant elevated odds of HG (1.9–3.8% of

women with purging-type eating disorders and 1.3% of controls) [29]. However, when HG was identified by symptoms reported in medical records, but not necessarily that requiring hospitalization, women with past or current eating disorders had significantly increased risk of HG (67% of women with eating disorders and 13% of controls) [27]. In general, women with purging-type eating disorders are significantly more likely to report both pregnancy-related nausea and pregnancy-related vomiting than women without an eating disorder [29]. Thus, while the increased risk of HG in women with eating disorders appears to depend on the stringency of the definition of HG used, women with purging-type eating disorders (including the binge–purge subtype of anorexia nervosa) are more likely to experience both nausea and vomiting during their pregnancy and should be closely monitored to ensure that the severity of these symptoms does not lead to inadequate weight gain and nutrition.

**Weight gain & nutrition during pregnancy—**In the Norwegian MoBa cohort, women with current anorexia nervosa before pregnancy gained significantly more weight [23] and gained weight more quickly [Zerwas SC, Von Holle A, Perrin EM *et al.* Patterns of pregnancy and post-partum weight change in mothers with eating disorders from the Norwegian Mother and Child Cohort Study (MoBa); Submitted Manuscript] during pregnancy than women with no eating disorder (17.8 kg compared with 14.9 kg). Institute of Medicine guidelines recommend a weight gain of 12.7–18 kg for women with a BMI of less than 18.5, and thus weight gain of 17.8 kg may signal appropriate concern with adequate gestational weight during this critical time. Greater weight gain in women with anorexia nervosa during pregnancy could ensure that the nutritional demands of the developing fetus are met [19,23,31,32]. However, there is an additional need to examine the nutritional quality of food women with anorexia nervosa are consuming during this time.

Little is known about the nutritional status of women with anorexia nervosa at conception, during pregnancy and the post-partum period. Macronutrient composition for women with anorexia nervosa during pregnancy may be qualitatively different and include less protein and fat than women with no eating disorder [31,33–35]. However, even less is known about their micronutrient status. Although much attention has been paid to adequate folate in order to protect against neural tube defects, inadequate stores of micronutrients such as iron, B vitamins, vitamin A and iodine have also been linked to pregnancy outcomes and fetal neural development [36]. Moreover, multiple micronutrient deficiencies during pregnancy and lactation may also have an additive effect [36]. In the Norwegian MoBa cohort, approximately 44–75% women with current anorexia nervosa before pregnancy did take nutritional supplements during pregnancy, which included these important micronutrients [37]. However, given their possibly nutritionally depleted status, it is unclear whether these supplements adequately met their and their child's nutritional needs.

## Perinatal issues in anorexia nervosa

### Delivery

Despite having less gestational weight gain and babies with lower birthweights than the general population [27,31,38], women with anorexia nervosa do not appear to have increased complications with most aspects of delivery. There are no differences in pre-term births, gestational hypertension/preeclampsia, induced labor, vacuum extraction, use of forceps, or breech presentation in women with past or recent anorexia nervosa compared with the general population [19,27,31,38,39]. However, women with anorexia nervosa may have a higher risk of cesarian section. Higher rates of cesarian delivery in women with recent anorexia nervosa were seen in a small USA cohort (compared with nonsymptomatic women with eating disorders) and in a larger controlled study in New Zealand (compared with non-eating disorder controls) [6,39], but risk of cesarian delivery was not increased for women with current anorexia nervosa before pregnancy in the Norwegian MoBa population-

based cohort or in a large controlled study in Sweden [19,27]. It is possible that this discrepancy could reflect cross-national trends in cesarean rates, or that eating disorder symptoms were more severe in women before pregnancy in both the USA and New Zealand cohorts compared with the Norwegian and Swedish cohorts, which included women with a wider range of disease severity. Women with more severe, active symptoms of anorexia nervosa during pregnancy may be viewed as high risk by their obstetricians, resulting in more frequent cesarian sections [10].

## Birth outcomes

Women with both recent and past anorexia nervosa have babies with lower birthweights in comparison to women with no history of eating disorders [6,7,27,31,38,40]. One study found that this lower birthweight was largely explained by the lower prepregnancy BMI of mothers with anorexia nervosa [31]. Several controlled studies have also shown that women with any history of an eating disorder (not specifically anorexia nervosa) are at increased risk for having small-for-gestational-age babies [27,40]; however, this increased risk was not found in a study specifically evaluating women with histories of anorexia nervosa [19].

While birthweight may be significantly lower, no differences have been found in Apgar scores at 5 min for babies of women with anorexia nervosa compared with babies of women with no history of an eating disorder [19,27]. Earlier retrospective studies found that recent symptoms of restriction in anorexia nervosa were associated with lower Apgar scores at 5 min than babies of women who did not have active symptomatology at conception [41,42]. However, a recent prospective study reported no differences in Apgar scores for babies of women with current versus past symptoms of eating disorders [39]. Thus, it appears that the presence of eating disorder symptoms during pregnancy is not necessarily associated with lower Apgar scores 5 min after birth.

The presence of eating disorders during pregnancy may influence sex ratio at birth. In the Norwegian MoBa cohort study, women with active anorexia nervosa or bulimia nervosa before pregnancy were less likely to give birth to males than a non-eating disorder referent group [43]. It is known that lower caloric intake is associated with fewer male births [44], and that the nutritional content of foods ingested during pregnancy can influence sex ratio at birth. Interestingly, in animal studies, male fetuses appear to be more sensitive to fatty acid deficiencies than females [45]. Therefore, it is possible that the typical low-calorie, low-fat diets of many women with anorexia nervosa may be selectively harmful to male fetuses during gestation.

It is likely that sufficient gestational weight gain plays a crucial role in determining birth outcomes for women with anorexia nervosa. Earlier case studies describing women with severe restricting-type anorexia nervosa throughout pregnancy reported significantly worse outcomes on all measures (intrauterine growth restriction, preterm delivery, small for gestational age, high occurrence of breech presentation, increased vaginal bleeding and low Apgar scores) than more recent prospective controlled and population-based studies [7,41,42,46,47]. While these recent studies include larger sample sizes and greater statistical power to detect differences on many of these outcomes, the severity of illness in the women with eating disorders during pregnancy is probably much more varied than in the earlier case studies.

Indeed, in the population-based Norwegian cohort study, mothers with anorexia nervosa reported greater weight gain than mothers without eating disorders, suggesting that, in light of their lower prepregnancy BMI, they were gaining appropriate amounts of weight during their pregnancy. Potentially owing to this adequate weight gain, studies of this cohort found few differences in birth outcomes for women with anorexia nervosa than the referent group.

One early study of anorexia nervosa during pregnancy even reported that for those women with anorexia nervosa who achieved adequate weight gain during their pregnancy, the occurrence of delivery complications and rate of birth defects was no different than that of the general population [47]. Thus, in clinical practice, monitoring of gestational weight gain in women with suspected past or present anorexia nervosa throughout pregnancy appears to be critical and may mitigate against adverse outcomes.

## The postpartum period

The transition to motherhood is accompanied by dramatic physical and environmental changes. The following section will discuss issues related to anorexia nervosa during the postpartum period, including postpartum dieting and body image, perinatal mental health and breastfeeding.

### Postpartum dieting & body image

Caring for a newborn baby can be stressful and lead to disruptions in sleep and eating patterns [48]. Mothers of newborns are also often home alone for long periods of time, which gives them ample opportunity to return to familiar eating disorder behaviors in secret in order to cope with the stress of this life transition [49]. Increased concern over shape and weight in the first 6 months postpartum is generally normative. A significant proportion of new mothers (40%) report dissatisfaction with their weight during this time [50]. Furthermore, increased body fat and abdominal muscle loss from pregnancy may aggravate long-standing dissatisfaction with body shape and composition.

Women with anorexia nervosa lose weight more quickly during this period [30], which suggests that they may be resorting to restriction, compensatory measures or other extreme weight-control behaviors. In women who had experienced recovery during pregnancy but relapsed during the postpartum period, 80% attributed the relapse to a desire to lose weight and feeling fat [22]. Without the motivation to eat 'for the baby', women with anorexia nervosa may find it difficult to continue to eat for their own health [48]. In one study, women who had struggled with anorexia nervosa immediately before conception experienced symptom re-emergence during the postpartum period and returned to prepregnancy levels of psychiatric severity by 9 months postpartum [51,52]. For women who had been in recovery from anorexia nervosa prior to conception, adjustment to a postpartum body may also trigger dormant weight and shape concerns.

### Postpartum depression & relapse

Overall, anorexia nervosa is highly comorbid with depressive and anxiety disorders [53–57] and is particularly comorbid during the perinatal period [19,23,58–63]. In a population-based sample, 36.1% of those with a lifetime history of anorexia nervosa reported experiencing depression during their pregnancy and 45.5% reported postpartum depression [60]. In comparison, 36.8% of women with a lifetime major depression diagnosis and no eating disorder endorsed experiencing depression during pregnancy and 41.2% endorsed postpartum depression [60]. Furthermore, women with a history of anorexia nervosa were over-represented in a clinical sample of women seeking treatment for postpartum depression. Approximately 10% of women seeking treatment for postpartum depression in a tertiary care clinic had a previous history of anorexia nervosa [64]. Women with anorexia nervosa may have an equal or greater risk of developing perinatal and postpartum depression compared with women with a history of major depressive disorder and no eating disorder [60,65].

### Trauma & abuse history

Women with anorexia nervosa binge–purge subtype are also more likely to report a history of childhood sexual abuse and physical abuse than women with nonbulimic eating disorders [66–73]. Both are considered nonspecific risk factors for the development of eating psychopathology [74–76]. Trauma and abuse histories also independently increase the risk of perinatal and postpartum depression and other psychiatric comorbidity [77–81]. Women with comorbid perinatal depression and lifetime anorexia nervosa are significantly more likely to report a history of sexual trauma abuse in comparison to women with perinatal depression and no eating disorder history (62.5 vs 29.3%; p < 0.05) [64]. Traumatic life events are independently associated with pregnancy complications including miscarriages, high-risk pregnancy, hyperemesis, preterm contractions [82] and delivery complications [83–88]. Thus, special care should be taken to educate women about the increased risk for postpartum depression and pregnancy complications in women with comorbid anorexia nervosa and trauma history. Proactive mental healthcare before symptoms appear could be the optimal way to prevent both perinatal mental health issues and obstetric complications.

### Breastfeeding

Research evidence on the frequency and duration of breastfeeding in women with anorexia nervosa is inconsistent. While one study reported that women with a history of anorexia nervosa are more likely to initiate breastfeeding and breastfeed for just as long, or longer, than women in the general population [33], several others have reported that women with anorexia nervosa stop breastfeeding earlier than women with no eating disorder [51,89,90]. The following section will discuss possible reasons why women with anorexia nervosa may continue breastfeeding longer or stop breastfeeding earlier than women without eating disorders.

**Breastfeeding anxiety—**Some studies report that breastfeeding is anxiety-provoking to women with eating disorders. Mothers report worrying that their breast milk will be insufficient for their infants' needs or that their infant may be allergic to their breast milk [91]. Furthermore, breast milk quantity and quality is difficult to measure and intake cannot be visually estimated. Women with anorexia nervosa may worry that they are giving their children 'enough' to eat and may turn to formula feeding in order to have reassuring visual cues about their infant's intake. Women with eating disorders who do breastfeed have been reported to be more likely to adhere rigidly to a prescribed feeding schedule as recommended by their children's physician and to experience anxiety when their infant signals hunger cues outside of the prescribed feeding window [91]. In addition, women with anorexia nervosa in general experience heightened self-consciousness and social anxiety [53,54], and some have reported embarrassment about the opportunity for self-exposure that accompanies breastfeeding in public [63].

**Postpartum distress & breastfeeding—**Difficulties with breastfeeding may also be due to the increased risk for postpartum depression and anxiety in women with anorexia nervosa [60,64]. Epidemiologic studies have identified an association between breastfeeding difficulty and perinatal depression, with depressive symptoms often preceding difficulty with lactation. In women with eating disorders, maternal distress from perinatal depression and anxiety partially mediates the relationship between eating disorder status and early infant feeding difficulties [92]. Thus, the relationship between maternal eating disorders and trouble with infant feeding is partially due to maternal perinatal depression and anxiety [92].

**Weight concerns & child outcomes—**For women with anorexia nervosa, the postpartum period and accompanying gestational weight retention could potentially trigger a relapse of eating disorder cognitions and a desire to lose weight rapidly. While some have

found that women with eating disorders may choose to breastfeed in order to lose pregnancy weight more quickly [93], others have found that when women with eating disorders are focused on weight loss in the immediate postpartum, they are less likely to intend to breastfeed [94].

These conflicting findings are mirrored in the contradictory literature on postpartum weight retention and breastfeeding. While some research has demonstrated that women who exclusively breastfeed for 6 months and continue supplemental feedings across the first 12 months postpartum do sustain greater long-term weight loss [95], others report that breastfeeding women lose whole-body, arm and leg fat at a slower rate in the first 6 months than women who chose not to breastfeed [96]. There are no studies that measure the association between breastfeeding, weight loss and body composition in women with anorexia nervosa.

Some women with anorexia nervosa may be unwilling to consume the additional 500–600 kcal per day to sustain breast-feeding [97], and may be uncomfortable with the fat retention associated with breastfeeding in the first 6 months postpartum. They may stop breastfeeding in order to engage in more extreme weight-loss measures, or engaging in extreme weight-loss measures could jeopardize their lactation. Other women with anorexia nervosa may find that breastfeeding does result in a reduction in weight and fat, and thus breastfeed for longer than women without eating disorders.

Considerably more work needs to be done to understand breast-feeding patterns in women with anorexia nervosa. Food restriction during this time could result in suboptimal breast milk quality, and more specifically, could reduce breast milk fat content. Poor maternal nutrition predicts less volume and lower fat content in breast milk [98].

Suboptimal maternal and child nutrition during this early period could be especially critical as it may inform children's future weight trajectories. There are no studies to our knowledge that have examined milk volume and breast milk composition in women with anorexia nervosa.

## In practice: reproductive counseling for women with anorexia nervosa

### Preconception

As previously discussed, women with anorexia nervosa do become pregnant and are more likely to have unplanned pregnancies. It may be that menstruation absence or irregularity leads women with anorexia nervosa to believe that they are infertile when at a low weight, and that conception is unlikely or impossible. However, amenorrhea does not indicate conclusively an absence of ovulation. Therefore, special attention should be paid at routine obstetrician–gynecologist visits to inform patients about the possibility of pregnancy in order to ensure that patients are making informed decisions about their reproductive health and understand their need for family planning even when at a low weight.

Although oral contraceptives are often prescribed in order to restore menses and prevent bone loss in women with anorexia nervosa, data do not support this clinical practice [99]. However, in addition to preventing sexually transmitted diseases, barrier contraceptive use is also necessary to prevent unplanned pregnancy in sexually active women with anorexia nervosa [100]. Furthermore, given the fact that women with anorexia nervosa who experience unplanned pregnancies are likely nutritionally depleted at conception, routine visits should also include counseling about the need for daily vitamins and adequate fat and protein intake to ensure optimal absorption.

Reproductive counseling is also needed in cases of infertility. One study found that, of patients who present for treatment to an infertility clinic with oligomenorrhea or amenorrhea, 58% met clinical indicators for eating disorders, but none had disclosed these problems to their providers [18]. In another clinic sample, 60% of infertile women with ovulatory dysfunction had anorexia nervosa, bulimia nervosa or eating disorders not otherwise specified. Therefore, appropriate infertility treatment includes adequate treatment of the eating disorder. Treating anorexia nervosa first, through proper nutrition, weight restoration and psychotherapy could probably also treat infertility without the significant costs, stress and complications associated with assisted reproductive technology [10]. In addition, when patients with active eating disorders pursue infertility treatment, assisted reproductive technologies may also be less effective [101].

## Screening

Adequately assessing eating disorder history early in pregnancy is necessary in order to forestall the possible physical and mental health consequences for women suffering with anorexia nervosa during the perinatal period, and the long-term physical and mental consequences for her children. Routine perinatal care offers providers a unique window of opportunity for mental health screening [102,103], which could facilitate improved detection of anorexia nervosa during this critically important time.

Standardized instruments such as the Eating Disorders Examination Questionnaire (EDE-Q) [104] and use of the SCOFF questionnaire [105,106] could assist obstetrician–gynecologists in assessing eating disorders. The EDE-Q is a 36-item self-report instrument that requires approximately 15 min to complete. Questions assess the presence and severity of symptoms including eating restraint, and eating, weight and shape concerns over the past 28 days. It is a reliable measure that could be used by clinicians who want to screen for an undiagnosed or unreported eating disorder and requires little mental health training [107]. The SCOFF questionnaire includes just five short yes/no questions about possible eating disorder symptoms [106]:

- Make yourself SICK when you feel uncomfortably full?

- Worry you have lost CONTROL over how much you eat?

- Recently lost more than 14 pounds within 3 months? (ONE stone's worth of weight)

- Believe you are FAT when others say you are too thin?

- Would you say that FOOD dominates your life?

A positive screen on either instrument would indicate that referral to an eating disorder specialist is necessary. In addition, clinical assessment could also include a thorough menstrual history, including age at onset, the number of cycles in the past 12 months, cycle regularity and length of flow [100].

Unfortunately, individuals with anorexia nervosa are often hesitant to bring their eating disorder status to their providers' attention and their providers are often hesitant to ask about eating disorder status. In a survey of obstetrician–gynecologists, just over half (54%) believed that eating disorder assessment fell within their scope of practice and a large majority (88.5%) rated their training in assessing eating disorders as barely adequate [108]. However, almost all generalists (90.8%) agreed or strongly agreed that eating disorders can negatively impact pregnancy outcome [108]. Furthermore, most mothers (64%) do not reveal their eating disorder status to their obstetrician–gynecologists and had negative reactions towards the routine weighing common in obstetric care [22]. Of those who did discuss their eating disorder with their provider, only half perceived it to be beneficial [22].

Furthermore, the typical frequent measurement of pregnancy-related weight gain in the clinic can exacerbate symptoms or trigger long dormant weight concerns and eating disorder behaviors in women with anorexia nervosa. Lectures about weight gain, and even well-meaning appearance-based comments by clinical staff can also be triggers [100]. Armed with the knowledge about a patient's eating disorder history, clinicians could make appropriate accommodations including reducing appearance-based comments by clinicians and staff, and modifying weight assessments to include blind weigh-ins.

## Mental health treatment

Mental health professionals have noted that pregnancy and the transition to motherhood may be an opportune window for recovery in women with eating disorders. Engaging women with anorexia nervosa in treatment at this time and encouraging appropriate gestational weight gain could lead to permanent change in eating behavior [109]. In results from the MoBa study, on average women with anorexia nervosa shifted from the underweight BMI range to the normal weight range at 36 months postpartum and maintained a 9% increase in BMI [Zerwas SC *et al.*; Submitted Manuscript]. Treatment may be especially necessary in the immediate months following birth, as the 'justification' for gestational weight gain and weight maintenance are no longer operative. Increased attention and social support in the postpartum period would be critical to prevent the re-emergence of symptoms [34,110].

Following a comprehensive medical evaluation to rule out another cause, the first goal of anorexia nervosa treatment is weight restoration to bodyweight within the normal range for BMI (18.5–24.9). Proper nutrition and refeeding is critical. Individuals who fall to 75% of their ideal bodyweight or have complicating medical or psychiatric comorbidities may require inpatient care in order to achieve weight restoration. Treating anorexia nervosa can be complicated and requires multidisciplinary evidence-based programs with medical coverage by providers, including dieticians, internal medicine dieticians, nurses, social workers, psychologists and psychiatrists who are specialists in the management of eating disorders. Furthermore, for adolescents and adults, recruiting the additional support of the patient's partner, spouse, parents or other family members in the therapeutic process can be vital [111,112].

Given the increased risk of perinatal depression and anxiety in women with anorexia nervosa histories, additional screening for symptoms of depression and anxiety is also important.

Treatment of depression and anxiety is critically important for the well being of both mother and the newborn-to-be.

The American Psychiatric Association and the American College of Obstetricians and Gynecologists practice guidelines recommend outpatient psychotherapy such as cognitive behavioral therapy or interpersonal psychotherapy alone in cases of mild-to-moderate depression and anxiety.

However, women with more severe depression and anxiety symptoms may require pharmacological treatment including anti-depressants and anxiolytic medications. They recommend that psychiatrists carefully assess maternal–fetal risk and discuss these risks with their patient before initiating psychotropic medication use during pregnancy and the postpartum [113]. These practice guidelines were developed for women with perinatal depression without consideration of eating disorder status. No data exist to guide the treatment of depression and anxiety in pregnant women with anorexia nervosa.

In summary, effective care in the obstetrician–gynecologist setting during the preconception and perinatal period should include:

- Screening, assessment and documentation of eating disorder history and other comorbid psychiatric history;

- Education about the possibility for pregnancy in the presence of amenorrhea, the need for vitamin supplementation and the increased risk of perinatal depression and anxiety in women with anorexia nervosa;

- A collaborative discussion of patient emotions and weight assessment options at clinic visits;

- Referral to a multidisciplinary team of mental-health providers and dieticians for treatment as appropriate.

However, it is also critical that a system of referral algorithms and connection to mental-health treatment be developed in order to encourage mental-health screening by the community of obstetrician–gynecologists.

## Expert commentary

In summary, increased attention paid to reproductive outcomes in women with anorexia nervosa in recent years has vast implications for clinical practice and future research: from increased attention to contraceptive use and the prevention of adverse birth outcomes in these women to fostering a greater understanding of maternal–fetal relationships that may increase transgenerational transmission of eating disorders. More attentive and intensive preconception counseling for women with anorexia nervosa is essential. Not only should women with anorexia nervosa be aware of the risk of becoming pregnant despite menstrual irregularities, but they should also be well-informed of the nutritional demands of pregnancy and the potentially adverse consequences of inadequate gestational weight gain and continuation of eating disorder behaviors during pregnancy. Pregnancy in women with anorexia nervosa can create a unique therapeutic window where eating disorder symptoms remit and weight gain is viewed as acceptable. Future studies may provide more insight into potential methods to help maintain the improved eating habits developed during pregnancy and prevent the intense relapse in eating disorder symptoms that occurs postpartum in many women with current and past anorexia nervosa.

While reports of adverse birth outcomes in women with anorexia nervosa appear to be related to inadequate gestational weight gain, we know very little about the nutritional status of women with anorexia nervosa at conception, during pregnancy and in the postpartum period. Future study of potential mechanisms through which maternal nutrition status in women with anorexia nervosa could impact fetal development will be a critical step in understanding the cross-generational transmission of eating disorders and weight regulation.

## Five-year view

Prenatal nutrition status in women with anorexia nervosa is important in light of research on 'fetal programming', or the 'developmental origins of health and disease'. From a fetal programming perspective, environmental influences on fetal development during sensitive periods could significantly affect the organization of physiology and lead to long-term, and perhaps permanent, effects on the structure and functioning of organs [114–116]. Fetal environmental influences, depending on their timing and severity affect the long-term physical and mental health of offspring.

The two main processes proposed to underlie fetal programming (fetal undernutrition and overexposure to stress hormones) [117] overlap considerably with the core features of anorexia nervosa (poor nutrition and anxiety) [32]. Maternal malnutrition during pregnancy is associated with increased risk for obesity, coronary heart disease, metabolic disease and stroke in adult offspring [115,116,118]. Furthermore, infants born with surrogate markers of maternal undernutrition, including low birthweight and being small for gestational age, are also at increased risk for diminished cognitive function, behavioral problems, stress reactivity and psychopathology throughout their lifespan [114].

High levels of maternal anxiety and neuroendocrine (cortisol) indices of stress response during the prenatal period predict greater anxiety and cortisol stress response in infants, preadolescent children and young adults [22,119–121]. Poor nutrition and protein restriction during pregnancy interact with the maternal hypothalamic–pituitary–adrenal axis, which results in increased fetal exposure to maternal cortisol [122]. Thus, the synergistic effects of maternal malnutrition and anxiety due to anorexia nervosa could extend beyond the intrauterine environment and result in long-term effects on their children's wellbeing [32]. Furthermore, women with anorexia nervosa report experiencing anxiety during pregnancy related to their fear that their child may be damaged physically by their poor nutrition [22].

Epigenetics may explain the processes by which maternal nutrition and anxiety lead to long-term effects. Epigenetics refers to any factor that affects gene expression caused by mechanisms other than the genome. Identified epigenetic mechanisms include DNA methylation, histone modification and small-interfering RNA [123]. Epigenetic modifications are thought to be dynamic and the prenatal and early postpartum period is considered a critical window [124]. Animal studies demonstrate that prenatal nutrition, specifically micronutrient deficiencies, can alter gene expression through methylation mechanisms. Micronutrients such as vitamins B2, B6, and B12, folate, methionine and choline are required for methylation of DNA [125]. If micronutrients are deficient during pregnancy, offspring are more likely to display impaired CNS development and an increased risk of obesity. These effects of malnutrition on DNA methylation extend to the human epigenome as well. Individuals whose mothers experienced the Dutch Famine early in gestation had less DNA methylation of the imprinted *IGF-2* gene [126], although their birthweight was within a normal range. Moreover, these epigenetic marks may be heritable, and risk for disease can be passed on to subsequent generations [127]. The effects are not limited just to immediate offspring but can be passed on to grandchildren [128–131].

In the Norwegian cohort, 50% of women with anorexia nervosa reported an unplanned pregnancy [132], and prenatal vitamin consumption prior to conception or in very early pregnancy was unlikely. Only 29% of women with anorexia nervosa took a supplement containing folic acid in the 2 months prior to conception [37]. Depending on their nutritional status before conception, women with anorexia nervosa may be at increased risk for micronutrient deficiencies that have been linked to long-term and transgenerational fetal effects. Thus, only focusing rapid weight gain in women with anorexia nervosa, with little attention to macronutrient and micronutrient quality, prior to conception and during pregnancy may be insufficient to protect against possible long-lasting fetal programming effects of a poor-quality diet.

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Key issues

- Despite a high prevalence of menstrual irregularities, women with anorexia nervosa are becoming pregnant, and the risk of unplanned pregnancy is higher in these women than in women without eating disorders.

- Eating disorder symptoms may remit during pregnancy in women with anorexia nervosa, but there is often a resurgence of symptoms postpartum and rapid postpartum weight loss.

- Women with anorexia nervosa are more likely to experience pregnancy-related nausea and vomiting requiring close monitoring to ensure adequate nutrition and weight gain.

- Birth outcomes in women with anorexia nervosa are largely dependent on adequate gestational weight gain; women with more severe symptoms of anorexia nervosa prior to pregnancy may have lower gestational weight gain, an increased risk of cesarian section and babies with lower birthweights than women without eating disorders.

- Postpartum depression is common in women with anorexia nervosa.

- Literature on breastfeeding in women with anorexia nervosa suggests that there are two different patterns:

  – Women with anorexia nervosa may stop breastfeeding earlier based on an inability to sustain breastfeeding owing to severe restriction or other extreme weight-loss measures, or owing to anxiety about breastfeeding and/or postpartum distress;

  – Women with anorexia nervosa may breastfeed for longer in an effort to lose pregnancy weight more quickly.

- Clinicians should pay particular attention to gestational weight gain and postpartum mental health of individuals with current and past anorexia nervosa.

- Future research should focus on nutritional status and markers of stress in women with anorexia nervosa before and during pregnancy in an effort to better understand intrauterine and epigenetic effects on the physical and mental health of their offspring.