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REVIEW ARTICLE

Eating disorders are associated with adverse obstetric and perinatal outcomes: a systematic review

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Objective: To systematically review the literature focusing on obstetric and perinatal outcomes in women with previous or current eating disorders (EDs) and on the consequences of maternal EDs for the offspring.
Methods: The study was performed following the systematic review and meta-analysis (PRISMA) statement. PubMed, SciELO, and Cochrane databases were searched for non-interventional studies published in English or Portuguese from January 1980 to December 2020. Risk of bias was assessed using the Methods guide for effectiveness and comparative effectiveness reviews (American Agency for Healthcare Research and Quality).
Results: The search yielded 441 records, and 30 articles were included. The psychiatric outcome associated with EDs in women was mainly perinatal depression. The most prevalent obstetric outcomes observed in women with EDs were vomiting, hyperemesis, bleeding, and anemia. Most studies found maternal anorexia nervosa and bulimia nervosa to be associated with low birth weight and slow fetal growth. Women with binge EDs delivered children with increased birth weight. Of the 30 studies included, methodological quality was good in seven, fair in eight, and poor in 15 studies.
Conclusion: A considerable body of evidence was reviewed to assess obstetric and perinatal outcomes in EDs. Acute and lifetime EDs, especially if severe, correlated with poor perinatal, obstetric, and neonatal outcomes. Obstetricians and general practitioners should be vigilant and screen for EDs during pregnancy.

Keywords: Eating disorders; anorexia nervosa; bulimia nervosa; pregnancy; perinatal; outcomes; risk factors; malnutrition

Introduction

The perinatal period is characterized by physiological and hormonal adaptations that modify women's eating habits and body appearance. Proper eating habits, with well-balanced meals and maintenance of adequate weight gain, are essential to ensure the health of mothers and babies.[1,2] Nevertheless, eating disorders (ED) are common among women of childbearing age[1]; at least 5% of women have inappropriate eating behaviors during pregnancy, and 7.5% have an ED.[2]

Maternal EDs may be associated with high-risk pregnancies. The reasons for the association between lifetime EDs and perinatal complications are unclear; however, possible contributing factors include malnutrition or overnutrition, increased stress reactivity,[1] residual ED symptoms, comorbidities, relapse in women at varying stages of recovery, and other qualitative variables.[2,3]

Albeit common during pregnancy, ED symptoms, as well as information about comorbidities, relapse, and other clinical aspects, are often omitted by women.[4,5] This omission is likely to result in ED being misdiagnosed and

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untreated during pregnancy. Franko & Spurrell[6] have suggested that antenatal care should routinely include questions about body weight, eating behavior, and weight control behavior in early pregnancy. Moreover, women are often dissatisfied with their body during the perinatal period, as reported by Watson et al.[7] in a systematic review that assessed 10 qualitative studies evaluating body image experiences through the perinatal period.

The course of EDs during pregnancy appears to be variable, with younger women with more severe disorders facing a less favorable prognosis.[8] In turn, the Norwegian Mother and Child Cohort Study (MoBa) reported remission in 78% to 29% of women depending on the type of ED.[9] Ulman et al.[10] observed that women with binge eating disorder (BED) before pregnancy remitted during childbearing. In parallel, Zerwas et al.[11] reported that mothers with EDs had more significant weight gain during pregnancy and higher weight loss in the first 6 months after delivery. The authors suggest that the observed change in women's body mass index (BMI) may result from a higher incidence of depressive and anxiety symptoms in the postpartum period in mothers with EDs.[8] Easter et al.[12] have also concluded that women with lifetime ED who become pregnant have higher levels of psychopathology during the antenatal and postnatal periods.

Offspring born to mothers with an ED may also face poor outcomes. The sum of stress, malnutrition, and a higher risk for comorbid postnatal depressive disorders or other mental disorders is a melting pot for a troubled beginning of life. A meta-analysis assessing the effects of maternal anorexia nervosa (AN) on offspring[13] concluded that maternal AN is a strong predictor of low birth weight (LBW). The review authors suggest that this negative outcome is related to malnutrition and poor maternal self-care due to psychiatric comorbidities.[13] A further literature review[14] investigating obstetric and gynecologic problems associated with EDs showed that AN is associated with increased risk of preterm birth, LBW, small for gestational age (SGA), and microcephaly.[14]

Whether or not EDs jeopardize obstetric and perinatal outcomes in women with a current or a previous ED seems controversial. To the best of our knowledge, no recent study has systematically reviewed the literature regarding both obstetric and perinatal outcomes of EDs. Thus, the present study aimed to perform a systematic review focusing on obstetric and perinatal outcomes in women with previous or current ED and on the consequences of maternal EDs for the offspring. We hypothesized that women with lifetime EDs face more adverse obstetric and perinatal outcomes than women without lifetime EDs. The present review intends to answer the following questions: 1) Does a current or a previous history of ED influence obstetric or perinatal prognosis? 2) Does the obstetric or perinatal course differ according to the type of ED? 3) Which demographic, psychological, and comorbid characteristics influence obstetric or perinatal outcomes in women with a history of or a current ED? The present study is thus the first to review all ED subtypes using a systematic design that includes quality appraisal of the studies available on the theme.

Methods

The review was performed following the Preferred reporting items for systematic review and meta-analysis (PRISMA) statement.[15]

Search strategy

PubMed, SciELO, and Cochrane databases were searched for papers published in English or Portuguese from January 1980 to December 2020. The initial date limit was adopted to reflect the inclusion of EDs in the DSM (after 1979). Articles were included if access to the full text was possible through the databases or if a reprint was provided upon request to the article's authors.

The following search strategy was used for PubMed: (((((Anorexia nervosa) OR (bulimia nervosa)) OR (binge eating disorder)) AND ((pregnancy) OR (perinatal))) AND ((“1980/01/01”[Date - Publication] : “2020/12/31”[Date - Publication]))). The authors also reviewed the reference lists of studies to find papers that might have been missed in the systematic review. After removal of duplicate articles, three reviewers (i.e., MCN, AAT, and FMG) independently searched all the titles and abstracts and selected those to be included. Consensus among reviewers resolved the discrepancies.

Eligibility criteria

Animal studies, expert opinions, and reviews were excluded, as well as studies reporting only on reproductive or sexual health outcomes and interventional studies in pregnant women with EDs. Non-interventional, observational studies were included – case reports, cross-sectional studies, and prospective studies, as well as studies that assessed obstetric or perinatal outcomes of women with a history of or current ED, of all ages, races, with or without psychiatric or clinical comorbidities, currently treated or not for an ED.

Data extraction and analysis

After the initial selection based on titles and abstracts, the authors read the full text of articles to retrieve the following data: 1) bibliographic reference; 2) study design; 3) primary goals; 4) sample profile; 5) results (i.e., obstetric and perinatal outcomes); and 6) main limitations as reported by the study.

Quality (risk of bias) assessment

This review assessed quality (risk of bias) of included studies using the Methods guide for effectiveness and comparative effectiveness reviews of the American Agency for Healthcare Research and Quality.[15] The studies were rated poor in quality if they presented three or less of the assessed criteria; fair valid if they met four or five criteria; and good if they met six or more criteria. Quality assessments of studies included in this review are provided in Table S1, available as online-only supplementary material.

Results

The flow diagram (Figure 1) shows the quantitative results of the bibliographic search. The search yielded 441 papers, 396 from PubMed and 45 from the Cochrane database. After the exclusions detailed in Figure 1, 30 articles were analyzed in the review.

Tables 1 (case reports) and 2 (observational studies) summarize the data extracted from the included studies. Table S1, available as online-only supplementary material, summarizes the quality appraisal of the studies included in the analysis. In brief, of the 30 studies included in the review, only seven presented good quality. Fifteen were classified as poor quality, 12 of which were clinical reports. Eight studies were classified as fair valid, mostly because the sample size was too small to achieve statistical power, or because the analysis was not adjusted for the possible influence of psychiatric comorbidities.

As shown in Table 1, 12 case reports described significant obstetric or perinatal consequences of AN; eight case reports described maternal complications in the perinatal period, and two case reports described adverse outcomes in children born from women with AN.

The results of 18 observational studies (Table 2) were grouped according to type of ED, as presented next.

Anorexia nervosa

In a cross-sectional study, Wentz et al.[31] recruited 48 women with AN and 51 healthy women in a populational survey that assessed individuals from schools in Sweden. At the endpoint, they included six women with current ED, 27 with previous AN, and 31 healthy women. In this sample, five women with AN had postpartum depression, and children of women with AN presented lower birth weight but no other gestational or delivery complications. The authors found no apparent differences in AN women as compared to other groups regarding the number of premature births, instrumental deliveries, and weight

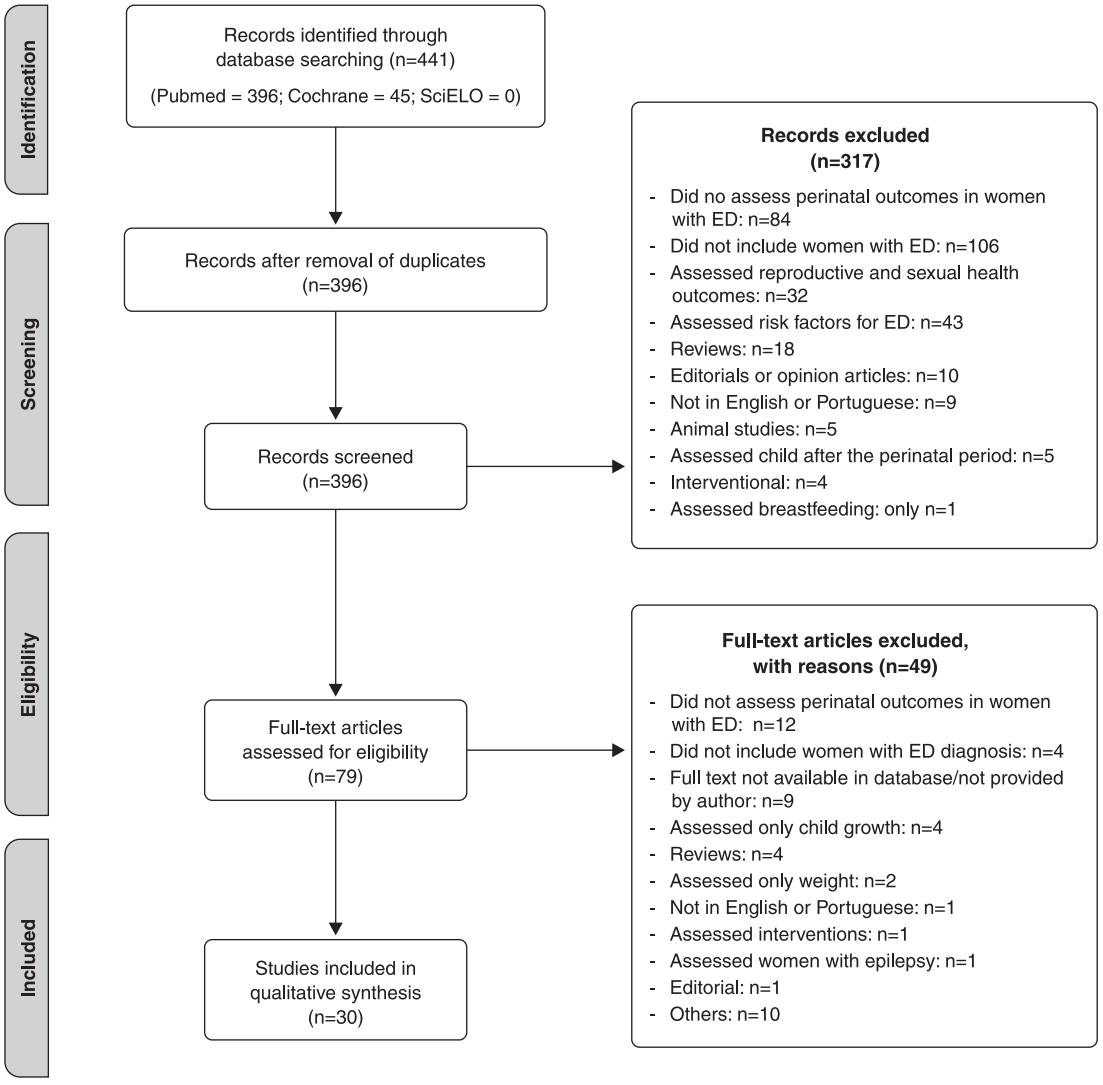

Figure 1 Preferred reporting items for systematic review and meta-analysis (PRISMA) flow diagram of selection process.

Table 1 Case reports describing obstetric and perinatal outcomes of women with EDs

Study	Case	Outcomes associated with EDs
Kasahara[16]	Pregnant woman with coxalgia and pre-existing AN	A 40-year-old woman with AN and a subchondral insufficiency fracture of the femoral head when reaching 29 weeks of gestation.
Urueña-Palacio[17]	Woman with AN who developed hematomas, gingival bleeding, and intense fatigue during the perinatal period when breastfeeding	The patient was diagnosed with scurvy and started nutritional support and oral vitamin C supplementation.
Kasahara[18]	Primiparous 38-year-old woman with pre-existing AN	Magnetic resonance imaging revealed femoral neck fractures as well as diffuse marrow edema involving both femoral heads.
Miettinen[19]	30-year-old pregnant woman with pre-existing AN	The patient presented labor-related sacral and pubic fractures.
Zauderer[20]	27-year-old pregnant woman with pre-existing AN	Perinatal depression.
Takei[21]	25-year-old pregnant woman with pre-existing AN	The patient presented severe anemia (i.e., 6.5 g/dL), thrombocytopenia (i.e., 84,000/L), and leukopenia (i.e., 3,700/mm^3).
Hayashida[22]	26-year-old pregnant woman with pre-existing AN	The patient developed diabetes insipidus at the 29th week of pregnancy.
Mazer-Poline & Fornari[23]	29-year-old woman diagnosed with AN during pregnancy	The woman had edema, proteinuria, and ketonuria. She was hospitalized in a psychiatric ward for treatment.
Dinas[24]	23-year-old pregnant woman with pre-existing AN	The woman had premature labor, maternal microcytic hypochromic anemia, and perinatal depression.
Manzato[25]	19-year-old pregnant woman with pre-existing AN	The newborn needed hospitalization in an intensive care unit due to respiratory distress.
Schimert[26]	Pregnant woman with pre-existing AN, with a boy born at 38 weeks.	The newborn had hypochloremia due to the severe metabolic alkalosis of his mother. The potassium level of the mother was 1.5 mmol/L just before delivery.
Ahmed[27]	33-year-old pregnant woman with pre-existing depression and AN diagnosis in pregnancy	The patient had severe anemia (i.e., hemoglobin 6.8 g/dL), hypokalemia (i.e., 2.6 mmol/L), hyponatremia (i.e., 126 mmol/L), and hypoalbuminemia (i.e., 11 g/L) with cardiorespiratory arrest followed by death. An autopsy revealed focal myocarditis.

AN = anorexia nervosa.

gain during pregnancy. The study is limited by the small sample and memory bias, as no medical records were consulted.[31]

Four retrospective studies reported outcomes of pregnant women with AN. Ante et al.[29] assessed medical records from women with AN that required hospitalization before or during pregnancy (0.1% of women) from a regional database with 2,134,945 pregnancies. In this study, women with previous AN hospitalization had a 1.99 time higher risk of stillbirth (95% confidence interval [95%CI] 1.20-3.30), 1.32 time higher risk of preterm birth (95%CI 1.13-1.55), 1.69 time higher risk of LBW (95%CI 1.44-1.99), and 1.52 time higher risk of SGA offspring (95%CI 1.35-1.72). LBW and SGA were more severe in women hospitalized for AN during pregnancy or within 2 years of delivery than in the general population.[29]

In a retrospective study, Kasahara et al.[28] compared the outcomes of 13 women with AN and 240 healthy controls. The authors found that AN history was associated with an increased risk of premature birth and symmetric growth restriction. These outcomes were associated with low pre-pregnancy BMI and small gestational weight gain. The study includes a small sample, and the authors report information bias due to the lack of standardization in ED diagnosis records.[28]

Eagles et al.[30] performed a retrospective study with records from a North East Scotland psychiatric clinic belonging to Women with AN who gave birth at the Aberdeen Maternity and Neonatal Databank (AMND). The authors compared these data with those of healthy women matched by age, year of delivery of the first baby, and parity. In this study, women with AN delivered lower weight babies, although this difference was not significant after adjusting for maternal BMI in early pregnancy. Mothers with AN had higher risk of delivering babies with intrauterine growth restriction (i.e., relative risk [RR] = 1.54; 95%CI 1.11-2.13) and of antepartum hemorrhage (RR = 1.70; 95%CI 1.09-2.65). The study limitations are the use of local data and information, limiting generalizability to other populations, and a possible measure bias as the information collected originated from medical files

Table 2 Observational studies reporting obstetric and perinatal outcomes in women with ED

Study	Design	Main goal	Sample	Main results	Limitations informed by study
Kasahara[28]	Cross-sectional	To compare pregnancy outcomes between women with and without a lifetime history of AN in medical records of a Japanese tertiary hospital	13 single pregnancies of 11 women with lifetime AN	Pregnant women with AN were at higher risk of premature birth and symmetric growth restriction.	Only severe cases of AN were included
Ante[29]	Retrospective cohort study	To assess if hospitalization for AN before or during pregnancy is associated with increased risk of adverse maternal and infant birth outcomes	2,134,945 pregnancies	Women with previous AN admission had increased risk of stillbirth (OR = 1.99; 95%CI 1.20-3.30), preterm birth (OR = 1.32; 95%CI 1.13-1.55), LBW (OR = 1.69; 95%CI 1.44-1.99), and SGA (OR = 1.52; 95%CI 1.35-1.72). LBW and SGA birth were more severe in women hospitalized for AN during pregnancy or within 2 years of delivery.	Data collection was restricted to administrative hospital data and only severe cases of AN were assessed
Eagles[30]	Retrospective study	To compare the pregnancy outcomes of women with and without a history of AN	134 women with a lifetime history of AN and 670 healthy women from a local Aberdeen maternal and neonatal database	Women with AN delivered lower weight babies although this difference was not significant after adjusting for maternal BMI in early pregnancy. Standardized birth weight scores suggested that AN mothers were more prone to deliver babies with intrauterine growth restriction (RR = 1.54; 95%CI 1.11-2.13). AN mothers were more prone to experience antepartum hemorrhage (RR = 1.70; 95%CI 1.09-2.65).	Study did not evaluate comorbid disorders or medication use
Wentz[31]	Cross-sectional study	To compare complications during pregnancy and delivery in a community-based sample of teenage-onset AN vs. a well-matched control group in adult years	51 adolescent-onset AN cases initially recruited after community screening and 51 age-matched comparison cases; 6 women with current ED, 27 with previous AN, and 31 in the comparison group had children, 3 women developed an ED during pregnancy	27 AN woman and 31 matched comparison cases.	Small sample size and only mild cases
Ekeus[32]	Prospective cohort study	To assess maternal or fetal complications in women with AN in a nationwide study in Sweden	1,000 AN women and 827,582 healthy women	The birth outcome measures in women with a history of AN were similar to those of the healthy population.	Used self-report to identify women with AN; the database used did not allow ascertainment of diagnosis quality and excluded women treated as outpatients or not diagnosed with AN

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Table 2 (*continued*)

Study	Design	Main goal	Sample	Main results	Limitations informed by study
Mantel[33]	Longitudinal study	To investigate the RR of adverse pregnancy and neonatal outcomes for women with EDs (cohort study included all singleton births in the Swedish Medical Birth Register from January 1, 2003 to December 31, 2014)	1,236,777 births were evaluated; 1,378 (0.1%) occurred in women with BN, 2,769 (0.2%) in women with AN, and 3,395 (0.3%) in women with EDNOS	AN, BN, and EDNOS: increased risk of hyperemesis gravidarum, preterm birth, and SGA.	The study used data from public register sources, with the risk of introducing selection and/or recall biases
Eik-Nes[34]	Retrospective study	To compare the prevalence of obstetric and postnatal complications in a population-based study (The HUNT Study) linked to the Medical Birth Registry in Norway	Database including 19,049 women with 43,651 births and 272 women with lifetime ED and 532 births	Lifetime AN increased the odds of SGA; lifetime BN increased the odds of caesarian delivery; EDNOS/sub-threshold ED had higher likelihood of low Apgar score at 5 minutes.	Study lacked detailed information on length of illness and was unable to examine obstetric outcomes among women in remission compared to women with active ED
O'Brien[35]	Cross-sectional study	To assess predictors of self-reported ED and associations with later health events in the Sister Study cohort with a computer-assisted telephone interview	The study included sisters of women who had breast cancer from a database of 50,884 Americans or Puerto Rican women aged 35-74 years; 2% (967) of women had a history of ED, and for the study researchers included 462 self-reports of ED (202 AN cases, 207 BN, and 41 AN + BN)	Women reporting an ED presented higher chance of bleeding (OR = 1.37; 95%CI 1.11-1.69) and nausea or vomiting (OR = 1.25, 95%CI 1.08-145) during pregnancy.	The initial study was not designed for the assessed ED endpoint. The study used self-reported ED diagnosis, with a sample including more well-educated and non-minority women
Watson[3]	Longitudinal study	To assess if maternal ED increases risk of perinatal negative outcomes after evaluating the contribution of familial transmission of perinatal events in the MoBa	Cohort including 114,500 children and 95,200 mothers; samples included 70,881 grandmother-mother-child triads in dataset 1 (ED status during pregnancy), and 52,348 grandmother-mother-child triads in dataset 2 (lifetime ED status)	ED was associated with higher incidence of perinatal complications, even after adjusting for grandmaternal perinatal events; AN immediately prior to pregnancy was associated with shorter birth length (RR = 1.62; 95%CI 1.20-2.14); BN was associated with induced labor (RR = 1.21; 95%CI 1.07-1.36); and BED was associated with several delivery complications, higher birth length (RR = 1.25; 95%CI 1.17-1.34), and large-for-gestational-age (RR = 1.04; 95%CI 1.01-1.06). Maternal pregravid BMI and gestational weight mediated most associations.	Recall bias due to self-report measures. Low response rate and possible selection bias.
dos Santos[2]	Cross-sectional	To evaluate the association of ED and anxiety and depressive disorders in high-risk pregnancies	913 pregnant women from an outpatient clinic	The prevalence of ED was 7.6%, of AN 0.1%, of BN 0.7%, of BED 1.1%, and of pica 5.7%. EDs were significantly associated with depression and anxiety during pregnancy.	The study did not evaluate the effect of lifetime ED on pregnancy

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Table 2 (*continued*)

Study	Design	Main goal	Sample	Main results	Limitations informed by study
Micali[36]	Longitudinal population-based cohort	To assess whether EDs are associated with smaller size at birth, symmetric growth restriction, and preterm birth, and whether pregnancy smoking explains the association between AN and fetal growth	Data from women of the DNBC (n=83,826)	Women with lifetime AN and lifetime AN + BN were more prone to restricted fetal growth and had higher odds of SGA (respectively, OR = 1.6; 95%CI 1.3-1.8 and OR = 1.5; 95%CI 1.2-1.9), compared with unexposed women. Active AN was associated with lower birth weight, length, head and abdominal circumference, ponderal index, higher odds of SGA (OR = 2.90; 95CI% 1.98-4.26) and preterm birth (OR = 1.77; 95%CI 1.00-3.12) compared with unexposed women. Pregnancy smoking only partially explained the association between NA and adverse fetal outcomes.	Ascertainment of exposure obtained by self-report
Linna[1]	Retrospective study	To evaluate pregnancy, obstetric, and perinatal health outcomes and complications in women with lifetime EDs	The study assessed women treated at the Eating Disorder Clinic of Helsinki University Central Hospital (2,257, 302 births of mothers with AN, 724 with BN and 52 with BED) compared to 9,028 unexposed women from the population	The prevalence of anemia was higher in women with AN vs. unexposed women (3.97 vs. 1.54%). BED women had higher risk of maternal hypertension than unexposed women (22.22 vs. 2.2%) Furthermore, slow fetal growth was observed more frequently in AN vs. unexposed women (4.64 vs. 1.93%). Women with AN and BN had increased odds of premature contractions vs. unexposed women (2.18 and 2.18 vs. 1%). Women with AN and BN gave birth to babies with lower birth weight vs. unexposed women (mean 3,302 g [SD 562], adjusted $p < 0.001$ in AN, mean 3,464 g [SD 563], adjusted $p = 0.037$ in BN, mean 3,520 g [SD 539] in unexposed women), whereas birth weight was higher among babies of women with BED (mean 3,812 g [SD 519]), adjusted $p < 0.001$). Babies of women with AN had a fourfold higher risk of perinatal death (adjusted OR = 4.06; 95%CI 1.15-14.35)	A sample representative of patients treated at a specialized clinic, representing more severe cases; used intake diagnosis to classify the cases, not considering evolution or diagnosis modification; used data from medical files

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Table 2 (*continued*)

Study	Design	Main goal	Sample	Main results	Limitations informed by study
Micali[37]	Longitudinal study	To assess adverse perinatal outcomes and gestational weight gain trajectories in women with lifetime EDs from a prospective general population cohort	Women with lifetime ED giving birth to a live singleton (5,256), including women with lifetime AN (129), lifetime BN (209), lifetime AN + BN (100), other lifetime psychiatric disorder (1,002), compared with unexposed women (3,816)	The prevalence of pregnancy complications was similar in women with ED and controls. Women with lifetime AN + BN had increased odds of being hospitalized during pregnancy (OR = 2.7; 95%CI 0.9-7.6). The study found no differences in mean birth weight, prevalence of a SGA, or premature birth.	Recall bias due to self-report measures. The lack of power to detect differences in rare outcomes between the various exposure groups.
Bulik[9]	Longitudinal study		All 35,929 pregnant women included in the MoBa cohort study: 35 women with AN, 304 with BN, 1,812 with BED, and 36 with EDNOS diagnosed 6 months before or during pregnancy	Pre-pregnancy BMI was significantly lower in mothers with AN and higher in mothers with BED vs. women without ED (i.e., referent). Mothers with AN, BN, and BED presented more significant weight gain during pregnancy and mothers with ED had a higher prevalence of smoking during pregnancy than the referent. Women with BED had higher birth weight babies, lower risk of SGA babies, and higher risk of large for gestational age babies and caesarean section than the referent.	Recall bias due to self-report measures; BED and purging criteria differed from DSM criteria; low response rate and possible selection bias
Torgersen[38]	Longitudinal study	To assess the prevalence of pregnancy-related nausea and vomiting and hyperemesis gravidarum in women with BN and EDNOS purging subtype in the MoBa	All 38,038 pregnant women included in the MoBa cohort study; 118 (0.8%) women with BN before pregnancy and 43 (0.1%) of women with EDNOS purging subtype	BN purging subtype was associated with higher odd of pregnancy-related nausea and vomiting. Women with EDNOS had higher odds of vomiting.	Memory bias due to the use of self-report measure; refusal rate of 42%
Kouba[39]	Longitudinal study	To compare the prevalence of pregnancy and neonatal outcomes in women with past or current EDs vs. a control group	49 nulliparous nonsmoking women previously diagnosed with EDs (24 AN, 20 BN, 5 EDNOS) and 68 controls recruited in early pregnancy	22% of women with a previously diagnosed ED relapsed during pregnancy; hyperemesis was more frequent in women with ED. Delivered infants of women with ED had LBW and smaller head circumference vs. controls. Infants of women with active ED had higher chance of microcephaly or SGA.	Small sample size

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Table 2 (*continued*)

Study	Design	Main goal	Sample	Main results	Limitations informed by study
Franko[40]	Longitudinal study	To report pregnancy complications and neonatal outcomes in 49 live births in a group of women with ED	246 women with AN and BN issued from a longitudinal study	The mean length of pregnancy was 38.7 weeks, mean birth weight was 7.6 lb, and mean Apgar scores at 1 and 5 minutes 8.2 and 9.0 respectively. Three babies (6.1%) had congenital disabilities, and 17 women (34.7%) experienced postpartum depression. The mean number of adverse obstetric outcomes in the ED group was 1.3; 13 women (26.5%) delivered by caesarean section. Women with active AN or BN during pregnancy had a higher frequency of birth by caesarean and postpartum depression than non-symptomatic women.	Small sample size, absence of comparison group, use of medical records as data source, lack of previous planning for longitudinal study
Conti[41]	Retrospective study	To investigate the factors associated with clinical ED and ‘‘normative’’ weight and shape concerns and disturbances in eating behavior that predict delivery of LBW infants as a result of growth retardation or prematurity	88 women delivering LBW infants (34 term infants SGA, 54 premature, and 86 women delivering infants above 2.5 kg [controls])	The prevalence of ED was higher in women delivering term, LBW infants. There was a decline in clinical ED during pregnancy.	Retrospective design precluding inference of causality; possible recall bias; small sample without statistically significant power; women evaluated only after delivery

95%CI = 95% confidence interval; AN = anorexia nervosa; BED = binge eating disorder; BMI = body mass index; BN = bulimia nervosa; DNBC = Danish National Birth Cohort; ED = eating disorder; EDNOS = ED not otherwise specified; LBW = low birth weight; MoBa = Norwegian Mother and Child Cohort Study; OR = odds ratio; RR = relative risk; SD = standard deviation; SGA = small-for-gestational-age.

without any specific validated questionnaire to phenotype the subjects.[30]

Finally, Ekeus et al.[32] selected a sample of 1,000 women hospitalized at least once for treatment of AN from a national database of 828,582 primiparous women. Women with a previous hospitalization for AN presented an increased odds ratio (OR) for delivering babies with 44-g lower mean birth weight. No differences were observed regarding Apgar score at 5 minutes, cephalohematoma, stillbirths, preterm rupture of membranes, pre-eclampsia, multiple pregnancies, need for instrumental deliveries (i.e., cesarean section, forceps delivery, and vacuum extraction), or anesthetic procedures. This study's limitations comprise the analysis of the most severe AN cases, with hospitalization being an inclusion criterion, and exclusion of women with AN treated as outpatients or of women with some diagnostic criteria for AN. Moreover, the study yields data from a national database issued from medical files and may present incorrect classification or coding of diagnosis.[32]

Bulimia nervosa (BN)

One retrospective study was identified comparing obstetric and perinatal outcomes in 122 women treated in a specialist ED service for BN symptoms during pregnancy vs. 82 women with quiescent bulimia (i.e., women with a history of BN but without ED during the pregnancy, including ED not otherwise specified [EDNOS]). In this study, women with current BN had an increased OR for postnatal depression (OR = 2.8; 95%CI 1.2-6.2), miscarriage (OR = 2.6; 95%CI 1.2-5.6), and preterm delivery (OR = 3.3; 95%CI 1.3-8.8) when compared with women with quiescent BN. Differences in adiposity, demographics, alcohol/substance/laxative misuse, smoking, or year of birth did not explain the risk estimates. The study's retrospective design and a possible recruitment bias limited the generalization of the results to other samples. The study included a clinical sample, which may not represent BN in the general population. Moreover, statistical power was achieved at the expense of a retrospective study design.[42]

Binge eating disorder (BED)

One study assessed factors associated with the incidence and course of broadly defined binge ED (BED) in pregnancy in the MoBa. The study found that BED in pregnancy associates with lifetime major depression, anxiety and depression symptoms, smoking, and alcohol use.[43]

Any eating disorder (ED)

Two cross-sectional studies[2,35] assessed obstetrical and perinatal outcomes in women with EDs. Dos Santos et al.[2] evaluated the association of EDs with perinatal psychiatric outcomes (i.e., anxiety and depressive disorders) in a sample of 913 women from an outpatient clinic. The reported prevalence rates were 7.6% for ED, 0.1% for AN, 0.7% for BN, 1.1% for BED, and 5.7% for pica. EDs were significantly associated with depression and anxiety during pregnancy.[2] O'Brien et al.[35] assessed a subsample of the Sister Study cohort, a large study designed to evaluate risk factors in sisters of women with breast cancer. The subsample comprised 462 women who re-affirmed having an ED (202 AN, 207 BN, and 41 AN + BN). The study found that women reporting an ED showed higher chance of bleeding (OR = 1.37; 95%CI 1.11-1.69) nausea, or vomiting (OR = 1.25, 95%CI 1.08-145) during pregnancy.[35]

The search also yielded three retrospective studies.[1,34,41] Conti et al.[41] investigated the factors associated with clinical EDs and "normative" weight and shape concerns and disturbances in eating behavior that predict delivery of LBW infants as a result of term growth retardation or prematurity. The study included 34 women with LBW infants born at term, 54 women with premature LBW infants, and 86 women with infants above 2.5 kg. The study found that the prevalence of EDs was higher in women delivering term LBW infants. There was a decline in clinical EDs during pregnancy.[41] Another study assessing medical records from a specialized clinic found that women with AN had higher prevalence of anemia than unexposed women (3.97 vs. 1.54%). Women with BED were at higher risk of maternal hypertension than unexposed women (22.22 vs. 2.2%).[1]

Furthermore, slow fetal growth was observed more frequently in fetuses of mothers with AN than unexposed women (4.64 vs. 1.93%). Women with AN and BN presented increased odds of premature contractions than unexposed women (2.18 and 2.18 vs. 1%). They more frequently gave birth to babies with lower birth weight than unexposed women (3,302 $\pm$ 562 g, adjusted $p < 0.001$ in AN, mean 3,464 $\pm$ 563 g, adjusted $p = 0.037$ in BN, mean 3,520 $\pm$ 539 g in unexposed women). In contrast, birth weight was higher in babies of women with BED (3,812 $\pm$ 519 g), adjusted $p < 0.001$).[1] In a retrospective study linking data from a hospital register and a population-based study, Eik-Nes et al.[34] found that, after adjusting for parity, maternal age, marital status, and year of delivery, lifetime history of AN was associated with higher odds of SGA (OR = 2.7, 95%CI 1.4-5.2). Women with a lifetime history of BN had an OR = 1.7 (95%CI 1.1-2.5) of having a caesarian section, and women with EDNOS/sub-threshold EDs presented an OR = 3.1 (95%CI 1.1-8.8) of low Apgar score at 5 minutes.[34]

Eight longitudinal studies[3,9,33,36-40] assessed obstetric outcomes in patients with EDs. Two assessed clinical samples. One study reported pregnancy complications and neonatal outcomes in 49 live births in a cohort of 246 women with EDs. The study reported prevalence rates of 6.1% for congenital disabilities, 49% for instrumental delivery in symptomatic women during pregnancy, and 26% in asymptomatic women. Postpartum depression occurred in nearly one-half of the symptomatic women. The study found no differences in Apgar scores, infant birth weight, or length of pregnancy. The study limitations are the small sample size, the absence of a comparison group, having used medical records as data source, and lack of a planned longitudinal design.[40] Kouba et al.[39] compared the prevalence of pregnancy and neonatal outcomes in 49 nulliparous non-smoking women

previously diagnosed with EDs vs. 68 healthy women recruited in early pregnancy. The study found that 22% of women with a once diagnosed ED relapsed during pregnancy and presented hyperemesis more frequently than women without ED (67.3 vs. 13.4% respectively). Delivered infants of women with EDs showed LBW and smaller head circumference when compared to controls. Infants of women with active EDs had a higher chance of presenting microcephaly or being small for gestational age. The results of the study should be interpreted with care given the small sample size.[39]

Three studies[7,9,38] used the Norwegian database MoBa.[44] Torgersen et al.[38] assessed 38,038 pregnant women from the MoBa and found a prevalence of BN of 0.8% and 0.2% of EDNOS purging type. The study reported higher odds for the development of nausea and vomiting during pregnancy in women with BN and increased odds for vomiting in women with EDNOS. The study is limited by possible recall bias, considering that it used self-report measures. The low response rate, albeit common for this kind of research, may produce a selection bias.[38] In another analysis of the longitudinal MoBa study, Watson et al.[7] found that EDs are associated with a higher incidence of perinatal complications, even after adjusting for grandmaternal perinatal events. AN immediately before pregnancy was associated with shorter birth length (RR = 1.62; 95%CI 1.20-2.14), whereas BN was associated with induced labor (RR = 1.21; 95%CI 1.07-1.36), and binge- ED with several delivery complications, more substantially birth length (RR = 1.25; 95%CI 1.17-1.34), and large-for-gestational-age (RR = 1.04; 95%CI 1.01-1.06). Maternal pregravid BMI and gestational weight mediated most associations.[7] In a longitudinal study using the MoBa study sample, Bulik et al.[9] reported that mothers with AN and mothers with BED presented a lower and higher pre-pregnancy BMI respectively than healthy mothers. Mothers with AN, BN, and BED showed more significant weight gain during pregnancy, and mothers with any ED had a higher prevalence of smoking during pregnancy than the referent. Women with BED had babies with higher birth weight, lower risk of SGA, and higher risk of large for gestational age babies and caesarean section than the referent.[9] The study limitations include memory bias and non-disclosure, as the information provided was self-reported rather than obtained by a questionnaire or standardized tool.[38]

Micali et al.[37] assessed the Danish National Birth Cohort (DNBC) (n=83,826) to evaluate whether EDs are associated with LBW and if smoking explains this association. The authors reported that women with lifetime AN and lifetime AN + BN were more prone to restricted fetal growth and had higher odds of SGA (respectively, OR = 1.6; 95%CI 1.3-1.8, and OR = 1.5; 95%CI 1.2-1.9), compared with unexposed women. Active AN was associated with lower birth weight, length, head and abdominal circumference, ponderal index, and higher odds of SGA (OR = 2.90; 95%CI 1.98-4.26) and preterm birth (OR = 1.77; 95%CI 1.00-3.12) compared with unexposed women. Pregnancy smoking only partly explained the association between AN and adverse fetal outcomes.[37]

Micali et al.[36] assessed adverse perinatal outcomes and gestational weight gain trajectories in women with lifetime EDs in a general population cohort. The authors reported that the prevalence of pregnancy complications was similar in women with EDs and controls. Women with lifetime AN + BN presented increased odds of being hospitalized during pregnancy (OR = 2.7; 95%CI 0.9-7.6). No differences were found in mean birth weight, prevalence of SGA, or premature birth.[36]

Mantel et al.[33] assessed the RR of adverse pregnancy and neonatal outcomes for women with EDs in the Swedish Medical Birth Register. The study compared data from 7,542 women with EDs and 1,225,321 women without EDs. The study found a two-fold increased risk of hyperemesis during pregnancy for AN (RR = 2.1; 95%CI 1.8-2.5), for BN (RR = 2.1; 95%CI 1.6-2.7), and EDNOS (RR = 2.6; 95%CI 2.3-3.0). AN and EDNOS increased two-fold the risk of anemia (RR = 2.1; 95%CI 1.3-3.2 and RR = 2.1; 95%CI 1.5-2.8, respectively). Maternal AN was associated with increased risk of antepartum hemorrhage (RR = 1.6; 95%CI 1.2-2.1), which was more pronounced in active vs. previous disease. Women with EDs were at increased risk of preterm birth and of delivering neonates with microcephaly.[33]

Koubaa et al.[45] compared serum biomarkers related to nutrition and stress in pregnant women with previous EDs and healthy controls. The authors reported that women with AN presented a lower level of ferritin than controls. Ferritin levels correlated to impaired memory function in their children. Maternal levels of free thyroxine were associated with lower head circumference in children delivered by mothers with BN and AN. No significant differences were found in cortisol, thyroid-stimulating hormone (TSH), insulin, insulin-like growth factor (IGF), or IGF binding protein-1 (IGFBP-1). It is important to remark that the study collected blood samples only once, without considering the daily variation in biomarkers.[45]

Discussion

The present study reviewed the literature assessing obstetric and perinatal outcomes in women with an acute or lifetime ED diagnosis. It evaluated 33 articles providing evidence that a current or lifetime ED is related to poor perinatal, obstetric, and neonatal outcomes. Three *a priori* questions were satisfactorily answered, as discussed next.

Does a current or a previous history of EDs influence obstetric or perinatal prognosis?

The data analysis strongly suggests that EDs influence newborn weight and size, especially in women with an active ED during pregnancy. The findings suggest that unfavorable perinatal outcomes are associated with a higher prevalence of maternal comorbidities (i.e., malnutrition, psychiatric disorders, and tobacco abuse disorder).

In a previous systematic review and meta-analysis, Solmi et al.[13] evaluated perinatal outcomes in EDs. The review analyzed 14 studies and meta-analyzed nine. The meta-analysis found that maternal AN predicts a

decrease of 0.19 kg (95%CI 0.25-0.15) in offspring birth weight. The small number of studies may have influenced the small effect size found in the metanalysis.

Does the obstetric or perinatal course differ according to the type of ED?

AN and BN were associated with LBW and slow fetal growth, and AN with SGA also. Conversely, birth weight was higher in babies born from women with BED, and maternal pregravid BMI may mediate some associations.[3]

Few studies have compared perinatal outcomes in samples with individual EDs. The evidence suggests that women with AN only are at higher risk of premature birth, stillbirth, symmetric growth restriction, and LBW. It seems that intensive specialized treatment for EDs during pregnancy may decrease those consequences in patients with AN.[32] Pregnant women with BN have been shown to have higher odds of developing postnatal depression, miscarriage, or preterm delivery.[22]

The present review concurs with that of Charbonneau & Seabrook.[46] Those authors also reported that AN increased the odds of LBW offspring, particularly when women enter pregnancy with a low BMI. BED was positively associated with large-for-gestational-age offspring. BN was associated with miscarriage when the woman was symptomatic during pregnancy.

Which demographic, psychological, and comorbid characteristics influence obstetric or perinatal outcomes in women with a history of or a current ED?

The psychiatric comorbidity associated with EDs was mainly depression (perinatal and postnatal), which occurred in 50-75% of pregnant women with an ED.[46] Depression tends to be severe in ED subjects, increasing the risk of suicide and reducing the likelihood of recovery.[46]

Mothers with EDs presented a higher prevalence of smoking during pregnancy.[9] Only two studies assessed the influence of smoking during pregnancy on the weight of babies. However, pregnancy smoking only partly explained the association between AN and adverse fetal outcomes.

At least two factors may explain why EDs may influence obstetric and perinatal outcomes: malnutrition and stress produced by psychiatric comorbidities. Maternal nutrition during pregnancy plays a pivotal role in the regulation of placental-fetal development.[47] Suboptimal maternal nutrition may produce LBW and a substantial effect on the newborn's short-term morbidity. Restrictive or monotonous eating behavior observed in subjects with EDs may yield suboptimal maternal nutrition, explaining the increased prevalence of symmetric growth restriction and LBW observed in the fetus of women with EDs. The findings that both adverse outcomes are more frequently reported in women with AN presenting with symptoms during pregnancy and in those with previous hospitalizations (i.e., more severe cases) reinforces this argument. Purgative behavior and again the monotonous eating habits observed in BN may also explain the malnutrition in mothers with BN.

Stress increases the body's physiological demands, and stressed subjects tend to demand ''comfort foods'' which lack the necessary nutrients, contributing to nutrient depletion and anxiety in women with EDs. These women perceive ''comfort foods'' as ''forbidden,'' increasing their ambivalence in terms of eating or not eating. Malnutrition is *per se* a stressing condition.[48] Moreover, women with EDs are more prone to present psychiatric comorbidities, which are also stressful conditions. Antenatal and postpartum depression produces additional stress, as it decreases self-care and jeopardizes the eating behaviors in women with EDs.[49] Psychiatric comorbidities may operate through stress production to increase the prevalence of obstetric and perinatal outcomes observed in women with EDs. Micali & Treasure,[5] who performed a non-systematic literature review, hypothesized that poor nutrition in pregnancy and comorbid anxiety and depression might influence the adverse obstetric results in AN. The most prevalent obstetric outcomes observed in women with EDs during pregnancy were vomiting and hyperemesis, bleeding, and anemia.

The appraisal of quality and risk of bias in the present study resulted in most studies being rated as poor or fair. Several studies are case reports or case series. The observational studies usually included small samples or used *ad hoc* analysis of samples primarily used to assess other issues. Some studies possibly have a phenotyping bias as they used unstandardized criteria or self-report measures to classify EDs or psychiatric comorbidities. Most studies assessed samples in developed countries, and the results may not be applicable to developing countries or countries with different health care models. No studies assessed unspecified feeding or ED (UFED) or other specified feeding or EDs (OSFED). Both these ED subtypes account for up to 60% of the ED cases in specialty clinics[50] and are highly prevalent in populations not receiving proper treatment, such as children, males, minorities, and now-western groups.[51]

Future research on the association of EDs with perinatal outcomes should comprise multicenter international samples that include developing countries. UFED and OSFED should also be covered in the samples assessed in future studies. Moreover, prospective studies should comprise the assessment of neurobiological, endocrine, genetic, and metabolomic parameters to improve the understanding of underlying mechanisms mediating the impact of EDs on perinatal outcomes.

The present review has strengths, such as the inclusion of all the main subtypes of EDs and the quality appraisal of included studies. Unfortunately, the present review did not perform a meta-analysis as previously performed by Solmi et al.[13] for AN for the other EDs subtypes, and assessed only three databases for bibliographic research.

The present review has some possible clinical recommendations. Health care teams should be especially aware of the need for ED screening in pregnant patients. The routine use of compact ED screening tools, like the SCOFF questionnaire,[52,53] should be part of the initial pregnancy assessment. The presence of dysmorphophobia, incompatible weight gain during the pregnancy, psychiatric comorbidities, and hyperemesis that persist after 12 weeks

should trigger an in-depth assessment of the eating behaviors and ED symptoms in pregnant women. Decreasing the time until the diagnosis and providing intensive specialized care to pregnant women with EDs may improve obstetric and perinatal outcomes.

In conclusion, a considerable body of evidence was examined to evaluate obstetric and perinatal outcomes associated with EDs. Acute and lifetime ED diagnosis is related to poor perinatal, obstetric, and neonatal outcomes. The outcomes appear to differ according to ED subtype. The prognosis for women and their offspring tends to be more severe in women with an active ED during pregnancy. Despite the evidence, longitudinal studies designed to measure the magnitude of the risk of maternal and child outcomes are still necessary to standardize the knowledge on this subject. Obstetricians and general practitioners should be vigilant and screen for ED during pregnancy, especially in women with low BMI, history of ED diagnoses, signs of hyperemesis that do not improve after 12 weeks, intense distress associated with weight gain, and depressive symptoms.

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