

# Perinatal Factors and the Risk of Developing Anorexia Nervosa and Bulimia Nervosa

Angela Favaro, MD, PhD, MSc; Elena Tenconi, PhD; Paolo Santonastaso, MD

**Context:** Few prospective studies to date have investigated the role of obstetric complications in anorexia nervosa, and no study to our knowledge exists for this in bulimia nervosa.

**Objective:** To explore the role of obstetric complications in the development of eating disorders.

**Design:** A blind analysis of the obstetric records of a sample of subjects with anorexia nervosa, with bulimia nervosa, and normal subjects was performed. All of the subjects included in the study belong to the same population birth cohort and were born in the 2 obstetric wards of Padua Hospital, Padua, Italy, between January 17, 1971, and December 30, 1979.

**Settings and Participants:** Part of the sample of subjects with eating disorders and all of the controls took part in a prevalence study carried out in 2 randomly selected areas of Padua. In addition, all of the subjects with anorexia nervosa and bulimia nervosa of the same birth cohort who were referred to an outpatient specialist unit were included. The final sample comprised 114 subjects with anorexia nervosa, 73 with bulimia nervosa, and 554 control subjects.

**Results:** Several complications, such as maternal anemia ( $P=.03$ ), diabetes mellitus ( $P=.04$ ), preeclampsia ( $P=.02$ ), placental infarction ( $P=.001$ ), neonatal cardiac problems ( $P=.007$ ), and hyporeactivity ( $P=.03$ ), were significant independent predictors of the development of anorexia nervosa. The risk of developing anorexia nervosa increased with the total number of obstetric complications. In addition, an increasing number of complications significantly anticipated the age at onset of anorexia nervosa ( $P=.03$ ). The obstetric complications significantly associated with bulimia nervosa were the following: placental infarction ( $P=.10$ ), neonatal hyporeactivity ( $P=.005$ ), early eating difficulties ( $P=.02$ ), and a low birth weight for gestational age ( $P=.009$ ). Being shorter for gestational age significantly differentiated subjects with bulimia nervosa from both those with anorexia nervosa ( $P=.04$ ) and control subjects ( $P=.05$ ).

**Conclusions:** A significantly higher risk of eating disorders was found for subjects with specific types of obstetric complications. An impairment in neurodevelopment could be implicated in the pathogenesis of eating disorders.

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EATING DISORDERS ARE CONSIDERED psychiatric disturbances of complex etiology. It is hypothesized that several genetic and environmental factors interact with each other to determine the development of eating disorders. Although much empirical data are available about the possible role of a variety of putative risk factors,<sup>1,2</sup> almost nothing is known about the possible pathways to the illness. Observation of neuropsychological deficits,<sup>3</sup> subtle neurological abnormalities,<sup>4</sup> and nonreversible morphological brain changes<sup>5,6</sup> might suggest that an impairment in neurodevelopment could be one of the possible pathways to anorexia nervosa.<sup>7</sup> Obstetric complications might have more than 1 role in the etiopathogenesis of eating disorders: first, they may cause

hypoxic-induced damage to the brain that impairs the neurodevelopment of the fetus,<sup>8-10</sup> and second, the adequacy of nutrition during pregnancy and in the immediate postnatal period seems to influence the nutritional status of the adult and appetite programming throughout life.<sup>11,12</sup>

Since obstetric complications have been implicated in the pathogenesis of several psychiatric and nonpsychiatric conditions,<sup>8-14</sup> it is possible that their pathogenetic role could become evident only with the presence of other more specific genetic or environmental risk factors.<sup>14</sup>

Several studies<sup>15-17</sup> have revealed a high incidence of obstetric complications in anorexia nervosa, but many of these studies are seriously limited by small sample size, the use of only aggregated measures of obstetric complications, and retrospective

**Author Affiliations:**  
Department of Neurosciences,  
University of Padua,  
Padua, Italy.

collection of obstetric data by parental recall. Only 2 studies,<sup>18,19</sup> which used the Swedish birth register, used a prospective design. They found that obstetric complications might have a role in increasing the risk of developing anorexia nervosa and, in particular, that there is a significant association with very preterm birth and cephal-hematoma. In these 2 studies, the cases were all subjects who were discharged from any hospital with a diagnosis of anorexia nervosa. This type of design limits the generalizability of the findings to the subgroup of subjects with anorexia nervosa who required admission. To our knowledge, only 1 study<sup>20</sup> has considered the role of perinatal factors in bulimia nervosa.

The aim of the present study was to explore the role of perinatal factors in a more representative sample of subjects with anorexia nervosa and with bulimia nervosa. Since eating disorders are psychiatric disturbances with serious metabolic and neuroendocrinological impairments, we investigated both complications related to asphyxia and perinatal complications that are hypothesized to be implicated in the regulation and programming of body weight and appetite.

## METHODS

### STUDY POPULATION

All of the subjects included in the study were female, white, belonged to the same population birth cohort, and were born in the 2 obstetric wards of Padua Hospital, Padua, Italy, between January 17, 1971, and December 30, 1979. Part of the eating disordered sample and all of the controls took part in a prevalence study carried out in 2 randomly selected areas of Padua.<sup>21</sup> Of the 934 subjects aged 18 to 25 who were interviewed in the prevalence study, 832 had no eating disorders, 31 had anorexia nervosa, 34 had bulimia nervosa, and 37 reported an eating disorder not otherwise specified. Sixty-seven percent of the subjects without eating disorders ( $n=554$ ) and 57% (15 anorexia nervosa and 22 bulimia nervosa cases) of the 65 cases with full eating disorders were born in Padua Hospital. An additional sample of subjects with eating disorders (99 with anorexia nervosa and 51 with bulimia nervosa) were all cases referred to the outpatient Eating Disorders Unit of Padua and were born in the obstetric wards of Padua Hospital in the same period ( $\pm 18$  months). At that time, these wards were the only public obstetric facilities in the Padua area; the Eating Disorders Unit is located in the same hospital and is the only public Eating Disorders Unit in the city and surrounding area. The 2 samples were merged before analyzing obstetric records to allow for blindness of data collection.

The final eating disordered sample comprised 114 subjects with anorexia nervosa and 73 with bulimia nervosa. The distribution of eating disorders throughout the period of time was quite uniform: cases amounted to 25% to 26% of the total sample in each of the years considered in the study. Lifetime anorexia nervosa was defined according to the *DSM-IV* criteria, waiving the single criterion of amenorrhea for 3 consecutive months since, in some cases, hormone replacement therapy made it difficult to assess the presence of the criterion. Lifetime bulimia nervosa was defined according to *DSM-IV* criteria, excluding subjects who fulfilled a lifetime diagnosis of anorexia nervosa. The mean (SD) age at onset in subjects with anorexia nervosa was 17.5 (2.9) years, and it was 17.6 (3.0) years in those with bulimia nervosa. The mean (SD) lifetime lowest body mass index in anorexia nervosa cases was 15.5 (1.7) (range, 10.0-

17.5). Among anorexia nervosa cases, 61 subjects fulfilled the diagnostic criteria for restricting-type anorexia nervosa whereas 53 subjects developed bulimic symptoms either during or following the episode of anorexia nervosa.

### ASSESSMENT OF SUBJECTS

For the prevalence study, a detailed description of recruitment and assessment methods has been reported elsewhere.<sup>21</sup> All of the subjects were interviewed face-to-face. Subjects who were referred to the Eating Disorders Unit underwent a routine baseline assessment. In both samples, clinical interviews were performed using the eating disorders section of the Structured Clinical Interview for *DSM-IV*<sup>22</sup> and a semistructured interview to gather sociodemographic and clinical variables, including history of weight, the presence of alcohol and/or substance abuse, and history of suicide attempts. Social class was determined using an Italian adaptation of the Havighurst formula.<sup>21</sup> This formula calculates social class using paternal and maternal professional status and degree of education. The formula results in a score that ranges from 1 (very high social class) to 6 (very low social class). We considered subjects who scored 3 or less as high and medium-high social class. All of the subjects gave informed written consent for the use of data in an anonymous form. The assessment of subjects who were referred for treatment also included the collection of data about family psychiatric history in first-degree relatives. A positive psychiatric history was present in 46% of the eating disordered sample.

### OBSTETRIC COMPLICATIONS

Data records about obstetric complications were available from hospital archives. Recorded information about the mothers included age in completed years at birth of the infant, mother's marital status at birth, parity (number of births, including the present birth), weight gain during pregnancy, outcome of previous pregnancies (stillbirth, premature birth, severe obstetric complications; calculated as the percentage of the total number of previous pregnancies), and pregnancy-related diseases, such as bleeding, preeclampsia, diabetes mellitus, threatened miscarriages, and anemia. Information available about the infants was gestational age (in completed gestational weeks from the mother's last menstruation), birth weight (in grams), birth length, head circumference, any delivery complication (multiple birth, inertia uteri, preterm rupture of the membranes, breech delivery, placental infarction or abruption, placenta previa, meconium staining of the amniotic fluid, cesarean delivery owing to acute fetal distress, forceps, or vacuum extraction, umbilical cord knotted or wrapped tightly around the neck, and cephalopelvic disproportion), and any neonatal complications (cyanosis, respiratory and cardiac problems, cephalhematoma, jaundice, neuromuscular disturbances such as hyporeactivity, hypotonia, and tremors, hypothermia, need for resuscitation, need for oxygen, need for intubation, early feeding difficulties, and hospital admissions in the first year of life). Head circumference data were available only for the 250 most recent records. Weight, length, and head circumference were considered low or high when they were respectively below or above the 10th percentile for sex and gestational week. Ponderal index was expressed as  $1000 \times (\text{birth weight in grams})/(\text{length in centimeters})^3$ .

The McNeil-Sjöström Scale<sup>23</sup> was used for the definition of obstetric complications. Only those complications scored at level 3 (potentially harmful) or more (clearly harmful) by the McNeil-Sjöström Scale were considered in the present study. The scoring was made by 2 of us (A.F. and E.T.) with the supervision of a gynecologist (Silvia Narne, MD).

**Table 1. Characteristics of Pregnancy in Subjects With Anorexia Nervosa, Subjects With Bulimia Nervosa, and Controls**

Characteristic	Controls (n = 554), No. (%)	Anorexia Nervosa (n = 114)		Bulimia Nervosa (n = 73)	
		No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
High or medium-high social class	168 (30)	45 (41)	1.6 (1.0-2.4)*	41 (56)	2.9 (1.8-4.8)†
Mother's age, y					
≤18	16 (3)	3 (3)	0.9 (0.3-3.2)	3 (4)	1.4 (0.4-4.9)
19-39‡	509 (94)	105 (94)	1.0	68 (93)	1.0
≥40	16 (3)	4 (4)	1.2 (0.4-3.7)	2 (3)	0.9 (0.2-4.2)
Mother not married	1 (0.2)	2 (2)	9.9 (0.9-109.8)	1 (1)	7.7 (0.5-124.1)
Parity, No.					
1‡	280 (51)	51 (45)	1.0	43 (59)	1.0
2-3	221 (40)	54 (47)	1.3 (0.9-2.0)	26 (36)	0.8 (0.5-1.3)
≥4	51 (9)	9 (8)	1.0 (0.4-2.1)	4 (5)	0.5 (0.2-1.5)
Previous miscarriage or neonatal death§	106 (18)	28 (23)	1.3 (0.8-2.1)	12 (21)	1.2 (0.6-2.3)
Previous premature birth§	35 (6)	9 (7)	1.2 (0.6-2.6)	3 (5)	0.8 (0.3-2.8)
Perinatal complications in previous pregnancies§	36 (6)	7 (6)	0.9 (0.4-2.1)	6 (10)	1.7 (0.7-4.3)
Pregnancy maternal weight gain, kg					
<7	13 (2)	1 (1)	0.4 (0.1-2.8)	2 (3)	1.2 (0.3-5.3)
7-15‡	491 (89)	104 (92)	1.0	65 (89)	1.0
>15	48 (9)	8 (7)	0.8 (0.4-1.7)	6 (8)	0.9 (0.4-2.3)
Birth weight, g					
<2500	38 (7)	9 (8)	1.2 (0.6-2.5)	3 (4)	0.6 (0.2-1.9)
2500-4000‡	493 (89)	99 (87)	1.0	68 (93)	1.0
>4000	23 (4)	6 (5)	1.3 (0.5-3.3)	2 (3)	0.6 (0.2-2.7)
Gestational age, wk					
≤32	6 (1)	1 (1)	0.8 (0.1-6.9)	0 (0)	NA
33-36	27 (5)	6 (5)	1.1 (0.4-2.7)	3 (4)	0.9 (0.3-2.9)
37-42‡	514 (93)	104 (91)	1.0	68 (93)	1.0
≥43	7 (1)	3 (3)	2.1 (0.5-8.3)	2 (3)	2.2 (0.4-10.8)
Obstetric complications, No.					
0‡	152 (27)	18 (16)	1.0	14 (19)	1.0
1-5	348 (63)	75 (66)	1.8 (1.1-3.2)*	50 (69)	1.6 (0.8-2.9)
>5	54 (10)	21 (18)	3.3 (1.6-6.6)	9 (12)	1.8 (0.7-4.4)

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

\* $P < .05$ .

† $P < .001$ .

‡Reference group.

§Percentages are calculated as the number of previous pregnancies.

|| $P < .01$ .

## STATISTICAL ANALYSIS

Crude odds ratios (ORs) with 95% confidence intervals (CIs) and the Mantel-Haenszel statistics were used as measures of the relative risk of developing anorexia nervosa and bulimia nervosa. To study the relationships between perinatal factors and clinical characteristics of the eating disordered sample, we compared subjects without obstetric complications, those with 1 to 5 complications, and those with more than 5 complications using the Kruskal-Wallis test. In addition, linear multiple regression analysis was used to test the effects of the total number of obstetric complications on the age at onset, controlling for possible confounder variables such as maternal age, socioeconomic status, diagnostic eating disorder subtype, and presence of psychiatric disturbances in the family. Subjects with eating disorders who were recruited from the general population sample were compared with those recruited in the clinical setting by means of the generalized Mantel-Haenszel test ( $\chi^2$ ) and Mann-Whitney U test ( $z$ ). Finally, a logistic regression analysis was used to derive a multivariate model of the risk of developing anorexia nervosa and bulimia nervosa while taking into account potential confounder variables such as socioeconomic status, marital status, parity, and maternal age, and to control for possible correlations among complications. These

procedures were implemented with Statistical Product and Service Solutions software (SPSS, Inc, Chicago, Ill).

## RESULTS

### ANOREXIA NERVOSA

**Table 1** shows the frequencies and ORs for maternal factors, gestational age, birth weight, and total number of obstetric complications. Similar rates of anorexia nervosa and control cases were found for having a low birth weight for gestational age (18% vs 17%, respectively) or for being short for gestational age (6% vs 9%, respectively). A ponderal index below 25 was reported for 12% of the subjects with anorexia nervosa and 18% of the control subjects (OR, 0.6; 95% CI, 0.3-1.2). In regard to pregnancy complications for the subjects with anorexia nervosa and the control subjects, maternal anemia (11% vs 5%, respectively; OR, 2.1; 95% CI, 1.0-4.1;  $P < .05$ ), diabetes mellitus (4% vs 1%, respectively; OR, 4.0; 95% CI, 1.1-15.1;  $P < .05$ ), and pre-eclampsia (8% vs 2%, respectively; OR, 3.3; 95% CI, 1.4-

7.8;  $P < .01$ ) significantly raised the risk of developing anorexia nervosa. In 1 case of anorexia nervosa, an infection with rubella during the fourth month of pregnancy was reported. At delivery, subjects with anorexia nervosa were significantly more likely than control subjects to have the umbilical cord wrapped around the neck (11% vs 6%, respectively; OR, 2.0; 95% CI, 1.0-4.0;  $P < .05$ ) and to have had placental infarctions (7% vs 1%, respectively; OR, 5.2; 95% CI, 1.9-14.0;  $P < .001$ ). Considering early neonatal complications and symptoms, subjects with anorexia nervosa were significantly more likely than control subjects to show hypothermia (31% vs 18%, respectively; OR, 2.1; 95% CI, 1.3-3.3;  $P < .001$ ), tremors (12% vs 6%, respectively; OR, 2.1; 95% CI, 1.1-4.0;  $P < .05$ ), hyporeactivity (9% vs 2%, respectively; OR, 4.0; 95% CI, 1.7-9.4;  $P < .001$ ), and hypotonia (8% vs 4%, respectively; OR, 2.3; 95% CI, 1.0-5.2;  $P < .05$ ) immediately after their birth. Subjects with anorexia nervosa also had early cardiac problems more often than controls (usually a congenital cardiomyopathy: 7% vs 2%, respectively; OR, 3.1; 95% CI, 1.3-7.8;  $P < .01$ ). In addition, subjects with anorexia nervosa were significantly more likely than control subjects to have needed oxygen administration (15% vs 8%, respectively; OR, 2.0; 95% CI, 1.1-3.6;  $P < .05$ ). No other significant association with any of the complications considered was found for anorexia nervosa. Subjects with the restricting subtype and those with comorbid bulimia did not differ regarding any of the perinatal factors considered.

#### BULIMIA NERVOSA

We did not find significant associations between the risk of developing bulimia nervosa and maternal factors, gestational age, and complications during pregnancy (Table 1). Subjects with bulimia nervosa had a birth weight below the 10th percentile significantly more often than controls (30% vs 17%, respectively; OR, 2.1; 95% CI, 1.2-3.7;  $P < .01$ ) as well as a birth length below the 10th percentile significantly more often than controls (17% vs 9%, respectively; OR, 2.0; 95% CI, 1.0-3.9;  $P < .05$ ) and subjects with anorexia nervosa (17% vs 6%, respectively; Mantel-Haenszel  $\chi^2 = 4.64$ ;  $P < .04$ ). A ponderal index below 25 was reported for 13% of the subjects with bulimia nervosa and 18% of the control subjects (OR, 0.7; 95% CI, 0.3-1.4). In the whole sample, no difference was found between subjects with normal weight or length and those with low weight or who were short for gestational age regarding their body mass index as adults. Subjects with bulimia nervosa had a head circumference below the 10th percentile significantly more often than controls (24% vs 8%, respectively; OR, 3.6; 95% CI, 1.3-9.9;  $P < .05$ ). In the available sample, subjects with a head circumference below the 10th percentile had a significantly higher lifetime body mass index than controls (mean [SD], 23.6 [3.0] vs 21.9 [2.9], respectively;  $P < .003$ ). At birth, subjects with bulimia were significantly more likely than controls to have placental infarctions (6% vs 1%, respectively; OR, 4.0; 95% CI, 1.2-13.5;  $P < .05$ ), hyporeactivity (8% vs 2%, respectively; OR, 3.8; 95% CI, 1.4-10.3;  $P < .01$ ), and early feeding problems (8% vs 2%, respectively; OR, 5.0; 95% CI, 1.7-14.0;  $P < .01$ ). No other significant association emerged from univariate analyses.

With the exception of being short for gestational age, no other perinatal complication significantly distinguished anorexia nervosa and bulimia nervosa cases.

#### PERINATAL FACTORS AND CLINICAL CHARACTERISTICS OF THE EATING DISORDERED SAMPLE

Subjects without obstetric complications, those with 1 to 5 complications, and those with more than 5 complications have been compared regarding the age at onset and some indicators of illness severity, such as lifetime lowest body mass index, presence of purging behavior, presence of substance and/or alcohol abuse, and history of attempted suicide. In the anorexia nervosa sample but not in the bulimia nervosa sample, the 3 groups differed regarding age at onset (Kruskal-Wallis  $\chi^2 = 7.73$ ;  $P < .03$ ). The mean (SD) age at onset was 16.3 (1.9) years in the group with more than 5 complications, 17.5 (3.0) years in the group with fewer complications, and 18.8 (2.8) years in the group without complications. In a multiple linear regression model, the number of perinatal complications remained a significant predictor of the age at onset in anorexia nervosa cases ( $\beta = -0.24$ ;  $t = -2.28$ ;  $P < .03$ ), even after adjusting for maternal age, socioeconomic status, diagnostic eating disorder subtype, and presence of psychiatric disturbances in the family. No difference was found between the 3 groups regarding the other clinical variables.

Subjects with eating disorders who were recruited from the general population sample did not differ from those recruited in the clinical setting regarding social class, degree of urbanization (57% vs 61%, respectively, were from urban areas), age at onset, indicators of illness severity, the mean number of obstetric complications (mean [SD], 2.5 [2.4] vs 2.8 [2.9], respectively; Mann-Whitney U test,  $z = 0.37$ ;  $P = .70$ ), or any of the perinatal factors considered in the study.

#### MULTIVARIATE ANALYSES

A conditional logistic regression model has been used to identify which complications were independently associated with an increased risk of developing anorexia nervosa and bulimia nervosa. Odds ratios were adjusted for socioeconomic status, maternal age, maternal marital status, parity, and multiple birth. The model that best fit the data for anorexia nervosa included anemia, diabetes mellitus, preeclampsia, placental infarctions, cardiac problems, and hyporeactivity (Table 2). For bulimia nervosa, the model that best fit the data included placental infarctions, having a low birth weight for gestational age, hyporeactivity, and early feeding problems (Table 3).

#### COMMENT

In the present study, we found a significant relationship between the occurrence of specific types of obstetric complications and the development of an eating disorder. Different types of obstetric complications have different implications for the risk of developing a psychiatric illness.<sup>9</sup>

**Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for the Association Between Obstetric Complications and Anorexia Nervosa\***

Complication	OR (95% CI)†	Wald $\chi^2$	P Value
Anemia	2.4 (1.1-5.1)	4.91	.03
Preeclampsia	3.1 (1.2-7.7)	5.44	.02
Diabetes mellitus	4.8 (1.1-21.6)	4.26	.04
Placental infarctions	6.4 (2.2-18.1)	12.00	.001
Ponderal index <25	0.5 (0.2-1.0)	4.07	.04
Cardiac problems	3.9 (1.4-10.3)	7.25	.007
Neonatal hyporeactivity	3.5 (1.1-10.9)	3.49	.03
1 of the previous complications‡	3.1 (1.9-5.2)	18.88	<.001
≥2 of the previous complications	15.7 (4.9-49.9)	21.64	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Likelihood ratio statistic for model = 51.52; *df* = 13; *P* < .001.

†Odds ratios were adjusted for socioeconomic status, maternal age, maternal marital status, parity, and multiple birth.

‡Excluding ponderal index greater than 25.

**Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for the Association Between Obstetric Complications and Bulimia Nervosa\***

Complication	OR (95% CI)†	Wald $\chi^2$	P Value
Placental infarctions	3.0 (0.8-11.4)	2.66	.10
Hyporeactivity	6.0 (1.7-20.9)	7.83	.005
Low birth weight for gestational age	2.3 (1.2-4.3)	6.87	.009
Early feeding problems	4.0 (1.2-13.2)	5.10	.02
1 of the previous complications	2.7 (1.3-5.9)	6.65	.01
≥2 of the previous complications	7.7 (2.7-21.6)	14.85	<.001

\*Likelihood ratio statistic for model = 49.88; *df* = 10; *P* < .001.

†Odds ratios were adjusted for socioeconomic status, maternal age, maternal marital status, parity, and multiple birth.

Anemia, diabetes mellitus, and preeclampsia that the mothers of subjects with anorexia nervosa have during their pregnancies can increase the risk of an impairment of central nervous system development owing to chronic insufficient supply of oxygen and other essential nutrients. Other complications such as placental infarctions, early respiratory and cardiac problems, and having the umbilical cord wrapped around the neck can cause a more acute form of hypoxia-ischemia that can result in brain damage, especially in the regions of the hippocampus and cortex, which are particularly vulnerable.<sup>9</sup> Both pregnancy and delivery complications can lead to the presence of signs of dysmaturity, such as hypotonia, hyporeactivity, hypothermia, and tremors. In the present study, we found that a combination of pregnancy and delivery or neonatal complications were independent predictors of the development of anorexia nervosa. Furthermore, we observed a dose-response effect for all of the obstetric complications in increasing the risk of anorexia nervosa, indicating a positive interaction between different types of complications. These findings seem to show some resemblance to what has been found in schizophrenia<sup>8-10</sup> and, with less evidence, in other severe psychiatric disorders.<sup>13,14</sup> However, this observation should lead to a search for other more specific risk factors that interact with perinatal factors and are able

to predict the development of 1 particular psychiatric disorder rather than another. Candidate factors could be sex, genetic liability, and other environmental risk factors.

Similarly to what has been observed in schizophrenia,<sup>8,24,25</sup> the presence of a greater number of obstetric complications seems to anticipate the onset of the illness. Although an anticipation of the age at onset can be considered evidence in favor of a developmental hypothesis of anorexia nervosa, the clinical significance of this finding is not clear. Unlike in schizophrenia, several outcome studies have found that an early age at onset is a favorable prognostic factor in adult anorexia nervosa samples.<sup>1,26</sup> However, the onset of anorexia nervosa before puberty is described to be a condition of very poor outcome,<sup>26,27</sup> and to date, only in early-onset cases have neuroimaging studies provided evidence of limbic system dysfunction.<sup>6</sup>

It is difficult to compare our findings with those of the few prospective investigations on this topic. Our results neither confirm nor refute the findings of the 2 Swedish studies<sup>18,19</sup> because the prevalences of very preterm birth and cephalhematoma are very low, and sample size was perhaps insufficient to detect such a small effect. However, the selection of anorexia nervosa cases used by both of the Swedish studies limits the generalizability of their findings to the most severe cases and/or to those patients who needed admission because of their vulnerability to medical complications or psychiatric comorbidity. From this point of view, our sample can be considered more representative of the whole eating disordered population because it includes subjects who were never treated and those who required outpatient and/or inpatient treatment.

Our study is the first to explore, with a prospective design, the role of obstetric complications in the development of bulimia nervosa. Both subjects with bulimia nervosa and those with anorexia nervosa shared some significant perinatal risk factors that appear to have an independent effect on the risk of developing the illness. However, the main characteristic at birth of subjects with bulimia nervosa is retarded fetal growth as indicated by their birth weight, length, and head circumference, adjusted for gestational age. Although often associated with each other, the 3 problems are not equivalent. It has been hypothesized that fetal undernutrition in early pregnancy will affect both length and weight, resulting in a symmetrically growth-retarded infant. By contrast, third-trimester undernutrition is associated with asymmetric growth retardation (short babies with normal head circumference). Insufficient fetal growth has been associated with a greater risk of developing mood disorders,<sup>28</sup> suicidality,<sup>29</sup> cardiovascular diseases, diabetes mellitus, and obesity in adult life.<sup>11,12</sup> The development of the brain is obviously more at risk in the case of symmetric growth retardation.<sup>30</sup> Retarded fetal growth can be considered not only a sign of a possible alteration of neurodevelopment, as hypothesized for other psychiatric disorders,<sup>28-30</sup> but also an indicator of a metabolic impairment owing to some form of malnutrition during a critical period of development. This impairment might cause an alteration in the programming of some important physiological and endocrinological functions and might in-

crease the risk of developing both obesity<sup>12</sup> as well as depressive symptoms<sup>28</sup> in vulnerable subjects. In our study, the hypothesis that birth weight could influence appetite programming and/or the regulation of body weight appeared to be confirmed by our findings of a significantly higher body mass index in subjects who had a small head circumference and by the fact that retarded fetal growth is the only perinatal factor that significantly differentiates anorexia nervosa from bulimia nervosa. In anorexia nervosa, being very lean at birth as measured by the ponderal index appeared to be a protective factor as extrapolated by the multivariate model.

The present study has several methodological advantages as well as important limitations that should be taken into consideration. First, all of the subjects belong to the same population birth cohort. The 2 geographical areas where we carried out the prevalence study were randomly selected and were considered representative of the entire female population cohort of the city.<sup>21</sup> Furthermore, all of the subjects underwent a similar clinical assessment, allowing for the exploration of the impact of obstetric complications on the age at onset and other clinical aspects. The clinical assessment of all of the subjects also allowed us to exclude from the control group all of the subjects who had any type of eating disorder during their adolescence (about 10% of the population), limiting the occurrence of  $\beta$ -type errors, ie, the reporting of too-conservative results. Other important methodological strengths were the use of prospectively recorded data, avoiding the risk of recall bias, and the use of a multivariate statistical procedure to adjust our findings for a series of potential confounders and for correlations among perinatal factors.

The main limitation of the study is represented by the merging of 2 samples of subjects with eating disorders: 1 sample was recruited from the general population, and 1 sample from an outpatient setting. Subjects referred for outpatient treatment cannot be considered completely representative of all of the cases existing in the general population since usually only a percentage of subjects with eating disorders asks for some type of treatment.<sup>21</sup> The power of the analyses to identify significant differences between the general population and the outpatient eating disordered sample is not high. However, we have no reason to believe that the outpatient cases were drawn from a different population than that assessed in the prevalence study, as they are matched for sex, ethnicity, place of residence, period of birth, and hospital of birth. In addition, they were also found to be similar in social class and degree of urbanization. On the contrary, in comparison with previous studies<sup>18,19</sup> conducted with hospitalized subjects, our eating disordered sample can be considered more representative of the whole eating disordered population. Some caution is required when interpreting the findings about bulimia nervosa since the sample size was relatively small and the dose-response effect was not evident. The lack of information about the psychiatric morbidity of the first-degree relatives of the whole sample prevented us from investigating both the relative role of the presence of a genetic liability in the development of eating disorders and the role of maternal psychopathological abnormalities in increasing the risk of

obstetric complications.<sup>31</sup> Although it is unlikely that the presence of psychiatric disturbances in mothers could completely explain the association between obstetric complications and the development of eating disorders, maternal psychiatric morbidity could be a confounding factor. However, other types of maternal factors, including the outcome of previous pregnancies, did not seem to be associated with an increased risk of developing eating disorders. Finally, we cannot rule out that some controls might have developed an eating disorder after our assessment. An age at onset later than the mean age of our control sample is uncommon in anorexia nervosa, but it is not so rare in bulimia nervosa. For this reason, some caution should be applied before generalizing our findings to eating disorders with an age at onset after adolescence.

In conclusion, the findings of the present study highlight the importance of perinatal factors in the pathogenesis of eating disorders. Although few significant differences emerged between anorexia nervosa and bulimia nervosa, the study appears to indicate that perinatal factors might have a different pathogenetic role in the 2 disorders. In anorexia nervosa, both pregnancy and neonatal complications appear to have an independent role in the development of the disorder. In addition, obstetric complications seem to show a dose-response relationship with the risk of developing the illness and influencing the age at onset. This type of relationship is considered evidence of a causal link<sup>25</sup> and would indicate that an impairment in neurodevelopment could be implicated in the pathogenesis of anorexia nervosa. According to a neurodevelopmental hypothesis, it would be important to understand which specific functions of the brain are impaired by obstetric complications and how these alterations can lead to an increased risk of developing eating disorders. Some possible candidates as early precursors of eating disorders could be the presence of eating difficulties or anxiety disorders in childhood,<sup>32,33</sup> which have both been linked to obstetric complications and are considered risk factors for eating disorders.<sup>34,35</sup> Future studies should address the issue of the relationship between neuroimaging and neuropsychological impairments and the presence of obstetric complications in early- and late-onset anorexia nervosa. Moreover, they should try to assess the prognostic impact of the presence of obstetric complications and whether this factor might help in the choice of appropriate and effective treatment. Although more similarities than differences emerged from a comparison of subjects with bulimia nervosa and with anorexia nervosa, only some specific perinatal factors appear to be implicated in the pathogenesis of bulimia nervosa. In particular, the subjects with bulimia nervosa had a higher frequency of retarded fetal growth, which has been implicated in the regulation of appetite and in an increased risk of developing an overweight condition as well as depressive symptoms. All of these factors are considered important core features or risk factors for bulimia nervosa.<sup>1,21</sup>

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**Correspondence:** Paolo Santonastaso, MD, Dipartimento di Neuroscienze, Clinica Psichiatrica, via Giustiniani 3, 35128 Padova, Italy (paolo.santonastaso@unipd.it).

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