Prenatal Depression, Prenatal Anxiety, and Spontaneous Preterm Birth: A Prospective Cohort Study Among Women With Early and Regular Care

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Objective: This article investigates the effects of antenatal depression and anxiety on spontaneous preterm birth resulting either from preterm labor or preterm premature rupture of membranes. **Methods:** We conducted a prospective cohort study of 681 women with singleton pregnancies consecutively recruited between 20 and 28 weeks of gestation in the Obstetrics Department of the French University Hospital of Caen. Most were of European ethnic origin and received early and regular antenatal care. The assessment of gestational age was based on ultrasound examination (occurring before 13 weeks of gestation for 94.9% of the women). Depression and anxiety were assessed using self-administered questionnaires: the Edinburgh Postnatal Depression Scale and the Spielberger State-Trait Anxiety Inventory. Logistic regression analysis, controlling for sociodemographic factors (e.g., maternal age, occupation) and obstetric factors (e.g., previous preterm birth, cervical or vaginal infection), provided adjusted odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** Spontaneous preterm birth occurred in 31 women (4.8%). The rate of spontaneous preterm birth was significantly higher among women with high depression scores (9.7%) as opposed to other women (4.0%) even after adjustment for potential confounding factors (adjusted OR = 3.3, 95% CI = 1.2–9.2, $p = .020$). Anxiety was not significantly associated with the outcome. There were no significant interaction effects between psychological and biomedical factors. **Conclusions:** These findings provide evidence that antenatal depression is significantly associated with spontaneous preterm birth in a population of European women receiving early and regular care. **Key words:** anxiety, depression, preterm birth, pregnancy, risk factors.

CRH = corticotropin-releasing hormone; **EPDS** = Edinburgh Postnatal Depression Scale; **STAI-Y** = State-Trait Anxiety Inventory; **BMI** = body mass index; **HPA** = hypothalamic–pituitary–adrenocortical; **ACTH** = adrenocorticotropin hormone.

INTRODUCTION

Preterm delivery, which occurs in approximately 5% to 10% of all births, is the leading cause of neonatal morbidity and mortality (1). Several sociodemographic and biomedical risk factors are now well identified but, in more than 50% of all preterm deliveries, the cause remains unknown or unclear (1,2).

The role of psychological factors in the etiology of preterm delivery, more specifically maternal stress and prenatal anxiety, has been studied for many years. Most of the recent prospective studies suggest an association with maternal stress (3,4) but not with prenatal trait or state anxiety (5–8).

During the last decade, more attention has been paid to the influence of antenatal depression, an easily detectable and common mental disorder, with a prevalence ranging from 5% to 17% during pregnancy (9–11). Recent research suggests a potential biological pathway to explain a possible role of depression in the occurrence of preterm birth. In particular, cortisol and certain other stress hormones—whose production tends to be increased in cases of major depression (12)—have been shown to heighten the release of placental corticotropin-releasing hormone (CRH) (13,14), which plays a key role in the triggering of parturition (15,16).

Considering the most recent and well-designed studies, a significant association between prenatal depression or distress and preterm birth was reported in three studies (17–19), whereas in four other studies (4,5,7,8), there was no evidence of a link.

We presented in a previous paper (20) the results of a cohort study investigation of the effects of antenatal depression and anxiety on the onset of preterm labor, an obstetric event preceding spontaneous preterm birth in approximately 50% of cases. We showed, using multiple logistic regression analysis with interaction effects, that depression was strongly associated with spontaneous preterm labor among underweight women, defined as women with prepregnancy body mass index below 19 kg/m^2. An association was also observed for trait anxiety in women with a history of preterm labor. The association was close to significance for state anxiety in women with vaginal bleeding.

The purpose of the present analysis, based on the same cohort of mostly European women receiving early and regular antenatal care, is to investigate if prenatal depression and anxiety are also associated with spontaneous preterm birth.

METHODS

Study Population

The study was conducted prospectively between October 1997 and September 1998 at the University Hospital of Caen, France. Women were consecutively recruited during a prenatal visit to the Department of Obstetrics. To be eligible for inclusion in the study, they had to be French-speaking, between 18 and 45 years of age, and between 20 and 28 weeks of gestation. Exclusion criteria were multiple gestation, placenta praevia, and cervical cerclage. Of those eligible, 721 women agreed to participate and 22 refused (3%). Postenrollment, cases of medically indicated preterm births (e.g., severe maternal hypertension, abruptio placentae, severe intrauterine growth retardation, nonreassuring fetal state) ($n = 12$) and delivery at another hospital ($n = 28$) were further excluded. A total of 681 women finally met the requirements of the protocol. The study protocol was approved by the Regional Ethics Committee.

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Exposure Variables

Women were asked to complete self-report instruments for psychological assessment before their consultation in a specially isolated and quiet place in the waiting room. They were invited to participate by a psychologist and a midwife, who could also provide help with the questionnaires. Depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS) (21,22), a 10-item screening tool providing an indication of the severity of symptoms. Items are rated on a 4-point Likert scale ranging from 0 to 3. They are nonintrusive and well accepted in a community sample and, unlike other scales, do not include somatic items such as weight change, loss of energy, and tiredness that may be misleading as indicators of depression in pregnancy. The EPDS is the only rating scale for depression validated during both the antenatal and the postnatal period. Its validation during pregnancy was established by comparing mean scores with Research Diagnostic Criteria for minor to major depression (21). The French version of the scale was validated in 1995 (23). Reliability of the scale in the current study was found to be good (Cronbach $\alpha = 0.86$). A score of 14+ was taken to indicate the presence of antenatal depression. This high cutoff value allows good detection of both major and minor depression in childbearing women (21). For major depression, a mental disorder that needs specific attention, the sensitivity is 100% and the specificity is 94%.

The widely used 40-item forms of State-Trait Anxiety Inventory (STAI-Y) (24), validated in French (25) and already administered in a variety of populations, including pregnant women, were chosen to measure state and trait anxiety symptoms. State anxiety is defined as an unpleasant emotional arousal in face of threatening demands or dangers. Trait anxiety reflects relatively stable individual differences in anxiety proneness (24). Each item is scored on a 4-point scale (from 1 to 4) with overall scores varying from 20 to 80. Reliability was high for both measures in our study (Cronbach $\alpha = 0.94$ and 0.88, respectively). Because the STAI-Y was not designed or validated to be used with a cutoff, the two scores were kept in their continuous form for the analysis.

Outcome Variable

Gestational age was based on early ultrasound examination to obtain an accurate assessment of the term of the pregnancy. It was performed before 13 weeks of gestation for 94.9% of the women and before 20 weeks for the remaining women. Spontaneous preterm birth resulting either from preterm labor or preterm prelabor rupture of membranes (1) was defined as delivery before 37 completed weeks of gestation.

Potential Confounding Factors

Potential confounding factors were defined from findings of previous studies and consultation with experts in the field of obstetrics. Data concerning the current pregnancy were directly extracted from the standardized, computerized medical records system routinely used by obstetricians and midwives in our hospital. The system is derived from a computerized file used in a French sentinel network of gynecologists, obstetricians, and pediatricians called "Audipog" (26). Records are systematically and prospectively updated at each consultation during pregnancy, at delivery, and during hospitalization before or after birth. All midwives and obstetricians are regularly trained to use the system and a member of the staff is specifically dedicated to verify data quality. Data about previous pregnancies were collected either from participants' reports at interview or by chart review.

Obstetric and biomedical characteristics included previous preterm birth, parity, prepregnancy body mass index (BMI; weight (kg)/height (m^2)), gestational age at first consultation and at enrollment, hospitalization, and complications of the current pregnancy: vaginal bleeding, urinary tract infection, cervical or vaginal infection, polyhydramnios, preeclampsia, or gestational hypertension (≥140 and/or 90 mm Hg).

Because psychological questionnaires were completed by the women just before a prenatal visit, depression and anxiety scores could be increased, at this particular time, by the stressful nature of the consultation. This could bias the results by artificially strengthening the association between preterm birth and psychological factors. To control for this potential bias, we categorized the enrollment consultation as either a "high stress" consultation (morphological ultrasound examination, amniocentesis for suspected malformation, admittance examination before hospitalization) or "low stress" consultation (routine visits or routine ultrasound examinations).

Sociodemographic characteristics included mother's age, ethnicity, education, occupation, marital status, and smoking habits during pregnancy. Data on partner violence were also collected through a questionnaire.

Statistical Analyses

Forty women (5.9%) were excluded from the analysis because they left at least one of the questionnaires completely unanswered. For 28 women of the remaining sample, a single item was missing from the questionnaires; for eight women, two items were missing; and for one woman, four. To avoid the exclusion of these 37 women, missing values were in those cases replaced by the median value for the item (48 values were thus imputed, which represents only 0.15% of the overall questions presented to the women). The final sample consisted of 641 women.

We first assessed the relationships between psychological factors and each of the sociodemographic and biomedical variables to better visualize potential confounding effects. Pearson χ^2 tests or Fisher exact tests were used to test associations between depression and categorical variables, and Student t tests were used for continuous variables. Associations between continuous scores of anxiety and categorical variables were assessed with Student t tests for dichotomous variables and one-way analyses of variance for the other variables. Pearson correlation coefficient tests were used for the association between anxiety scores and continuous variables.

The association between spontaneous preterm birth and each of the independent variables was then assessed using univariate logistic regression models. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were computed. A forward multiple logistic regression analysis was then applied on an initial model composed of the exposure variables (psychological factors). Potential confounding factors related to the outcome at the $p < .25$ level in the univariate analysis were sequentially tested for inclusion in the model. They were included providing their effect was significant or if their inclusion changed the ORs associated with the psychological factors by more than 10%. Adjusted OR with 95% confidence limits were computed. Interactions among the variables of the final model were tested. Statistical significance was defined as $p < .05$. Data were analyzed with SPSS software, version 11.5 (27).

RESULTS

Sociodemographic and obstetric characteristics of the women are shown in Tables 1 and 2. Mean maternal age was 28.5 years (standard deviation [SD]: 5.5; range, 18–45 years). Women were mainly European in origin and were provided early and regular prenatal care: the median gestational age at first consultation was 8 weeks, 90.0% of the women consulted at or before 12 weeks, and the average number of prenatal visits was 10. Parity ranged from 0 to 7 with a mean of 1.1. Frequencies of obstetric risk factors were usually below 10% except for cervical and vaginal infections, which occurred in 21.8% of the cases.

Mean depression score was 7.2 (SD: 5.6; range, 0–28). A score of 14+ was obtained by 93 women (14.5%). Mean state anxiety score was 36.4 (SD: 12.2; range, 20–80). Mean trait anxiety score was 38.8 (SD: 9.1; range, 20–73).

Women categorized as depressed (Tables 1 and 2) had a lower level of education, were more likely to be a victim of partner violence, were more frequently hospitalized during the second trimester, and more frequently attended a high stress prenatal visit at enrollment in the study. Higher levels of state and trait anxiety were observed in the presence of gestational hypertension, hospitalization during the second trimester, and attending a high-stress consultation examination at enrollment

TABLE 1. Sociodemographic Characteristics of Nondepressed and Depressed Women (n = 641)

	Overall n (%)	Nondepressed EPDS <14 n (%)	Depressed EPDS ≥14 n (%)	p Value[a]
Maternal age				.447
<20	31 (4.8%)	27 (4.9%)	4 (4.3%)	
20–34	520 (81.1%)	448 (81.8%)	72 (77.4%)	
≥35	90 (14.0%)	73 (13.3%)	17 (18.3%)	
Marital status				.591
Living alone	71 (11.1%)	59 (10.8%)	12 (12.9%)	
Married or cohabiting	570 (88.9%)	489 (89.2%)	81 (87.1%)	
Ethnicity				.468
Europe	604 (94.2%)	518 (94.5%)	86 (92.5%)	
Other	37 (5.8%)	30 (5.5%)	7 (7.5%)	
School education				.018
Primary school	50 (7.8%)	41 (7.5%)	9 (9.7%)	
Secondary school	421 (65.7%)	351 (64.1%)	70 (75.3%)	
Higher education	170 (26.5%)	156 (28.5%)	14 (15.1%)	
Occupation				.129
Not employed	240 (37.4%)	199 (36.3%)	41 (44.1%)	
Lower level	265 (41.3%)	226 (41.2%)	39 (41.9%)	
Middle and higher level	136 (21.2%)	123 (22.4%)	13 (14.0%)	
Smoking habits				.130
Non smoking	421 (65.7%)	368 (67.2%)	53 (57.0%)	
0–9 cigarettes/day	140 (21.8%)	116 (21.2%)	24 (25.8%)	
≥10 cigarettes/day	80 (12.5%)	64 (11.7%)	16 (17.2%)	
Partner violence				.026
No	547 (85.3%)	475 (86.7%)	72 (77.4%)	
Yes	94 (14.7%)	73 (13.3%)	21 (22.6%)	

EPDS = Edinburgh Postnatal Depression Scale.
[a] p values obtained from Pearson χ^2 test or Fisher exact test.

(Table 3). State anxiety was also slightly higher in the presence of a cervical or vaginal infection. Women with the highest education or occupation levels were less prone to trait anxiety.

Gestational age at delivery ranged from 29 to 42 completed weeks with a mean of 39.2 weeks (SD: 1.5). Spontaneous preterm birth occurred for 31 women (4.8%) with 21 cases resulting from preterm labor and 10 cases resulting from preterm prelabor rupture of membranes.

Variables significantly associated with spontaneous preterm delivery in the univariate analyses (Table 4) were cervical and vaginal infections, polyhydramnios, hospitalization during the second semester, type of consultation at enrollment, and gestational age at enrollment. Maternal age and vaginal bleeding during the third trimester were close to significance. Depression during pregnancy was associated significantly with spontaneous preterm birth. The rate of spontaneous preterm birth was 9.7% for women with high depression scores as opposed to 4.0% for nondepressed women (p = .023). The association between spontaneous preterm birth and either state anxiety or trait anxiety was not significant.

In the multivariate analysis (Table 5), depression was the only psychological factor whose association with spontaneous preterm birth was statistically significant (adjusted OR = 3.3, 95% CI = 1.2–9.3, p = .020). No interaction effect was significant.

We verified that the fit of the model was not affected by possible colinearities among the depression and anxiety variables by comparing the final multivariate model with models containing only the depression score or only the anxiety scores. In case of colinearity, large variations of the estimated standard errors should be observed, which was not the case here.

DISCUSSION

Principal Findings

Women with high depression scores were at greater risk for spontaneous preterm birth. The association persisted even after adjustment for relevant confounding factors. No association was evidenced for state and trait anxiety.

Comparison With Other Studies

Our conclusion concerning prenatal depression is consistent with three previous studies in which higher risk of preterm birth was observed among depressed or distressed women (17–19). In four other studies, no association was found (4,5,7,8). We tried to analyze the dissimilarities in study design and methodology to better understand the discrepancies in the results. Differences are, however, so numerous (population characteristics, outcome variable, choice of psychological instruments, potential confounding factors) that it seems difficult to isolate enlightening elements that could explain the results. For instance, associations between depression and preterm birth have been evidenced in predominantly

TABLE 2. Obstetric and Clinical Characteristics of Nondepressed and Depressed Women (n = 641)

	Overall *n* (%)	Nondepressed EPDS <14 *n* (%)	Depressed EPDS ≥14 *n* (%)	*p* Value[a]
Parity				.148
0	236 (36.8%)	204 (37.2%)	32 (34.4%)	
1–2	339 (52.9%)	293 (53.5%)	46 (49.5%)	
≥3	66 (10.3%)	51 (9.3%)	15 (16.1%)	
Prepregnancy body mass index[b]				.413
<19	93 (14.5%)	76 (13.9%)	17 (18.3%)	
19–25	400 (62.4%)	342 (62.4%)	58 (62.4%)	
≥25	148 (23.1%)	130 (23.7%)	18 (19.4%)	
Prior preterm birth				1.0
No	606 (94.5%)	518 (94.5%)	88 (94.6%)	
Yes	35 (5.5%)	30 (5.5%)	5 (5.4%)	
Vaginal bleeding in first trimester				.219
No	588 (91.7%)	506 (92.3%)	82 (88.2%)	
Yes	53 (8.3%)	42 (7.7%)	11 (11.8%)	
Vaginal bleeding in second trimester				.558
No	618 (96.4%)	527 (96.2%)	91 (97.8%)	
Yes	23 (3.6%)	21 (3.8%)	2 (2.2%)	
Vaginal bleeding in third trimester				.349
No	619 (96.6%)	531 (96.9%)	88 (94.6%)	
Yes	22 (3.4%)	17 (3.1%)	5 (5.4%)	
Urinary tract infection				.200
No	575 (89.7%)	495 (90.3%)	80 (86.0%)	
Yes	66 (10.3%)	53 (9.7%)	13 (14.0%)	
Cervical and/or vaginal infection				.342
No	501 (78.2%)	432 (78.8%)	69 (74.2%)	
Yes	140 (21.8%)	116 (21.2%)	24 (25.8%)	
Gestational hypertension				.809
No	604 (94.2%)	517 (94.3%)	87 (93.5%)	
Yes	37 (5.8%)	31 (5.7%)	6 (6.5%)	
Polyhydramnios				.709
No	626 (97.7%)	534 (97.4%)	92 (98.9%)	
Yes	15 (2.3%)	14 (2.6%)	1 (1.1%)	
Hospitalization during first trimester				1.0
No	622 (97.0%)	531 (96.9%)	91 (97.8%)	
Yes	19 (3.0%)	17 (3.1%)	2 (2.2%)	
Hospitalization during second trimester				<.001
No	592 (92.4%)	516 (94.2%)	76 (81.7%)	
Yes	49 (7.6%)	32 (5.8%)	17 (18.3%)	
Gestational age at first consultation				.851
≤12 weeks	577 (90.0%)	494 (90.1%)	83 (89.2%)	
>12 weeks	64 (10.0%)	54 (9.9%)	10 (10.8%)	
Type of consultation at enrollment				<.001
Low-stress examination	561 (87.5%)	493 (90.0%)	68 (73.1%)	
High-stress examination	80 (12.5%)	55 (10.0%)	25 (26.9%)	

EPDS = Edinburgh Postnatal Depression Scale.

[a] p values obtained from Pearson χ^2 test or Fisher exact test.

[b] Weight (kg)/height (m^2).

black women (17,19) as well as in European populations (18). The nature of the outcome variable (spontaneous preterm birth (4,7,8,19) versus all forms of preterm birth (5,17,18)) is not a discriminating factor either. The diversity of instruments used to assess depression (General Health Questionnaire (5,18), Beck Depression Inventory (17), Center for Epidemiologic Studies Depression Scale (4,19), PRIME-MD classification system (8), and EPDS) also make it difficult to compare the results. In two studies with comparable populations and similar screening instruments, conclusions nevertheless differed (4,19). It could, however, be explained by the different ways depression scores were coded in the statistical models; an association was found when the score was dichotomized (19), which could express a possible "threshold" effect of depression; no association was evidenced with a trichotomized (4) score (more suggestive of a dose–response effect).

TABLE 3. State and Trait Anxiety: Potential Confounding Factors (n = 641)

	n	State Anxiety		Trait Anxiety	
		mean ± SD	p Value[a]	mean ± SD	p Value[a]
School education					.006
Primary school	50	—		39.3 ± 9.2	
Secondary school	421	—		39.5 ± 8.9	
Higher education	170	—		36.9 ± 9.5	
Occupation					.001
Not employed	240	—		39.7 ± 9.0	
Lower level	265	—		39.3 ± 9.2	
Middle and higher level	136	—		36.2 ± 8.9	
Cervical and/or vaginal infection			.031		
No	501	35.8 ± 12.0		—	
Yes	140	38.3 ± 12.9		—	
Gestational hypertension			.014		.008
No	604	36.1 ± 12.1		38.6 ± 9.0	
Yes	37	41.2 ± 14.4		42.7 ± 10.1	
Hospitalization during second trimester			<.001		.002
No	592	35.8 ± 12.1		38.5 ± 9.1	
Yes	49	43.0 ± 12.5		42.7 ± 8.1	
Type of consultation at enrollment			<.001		<.001
Low-stress examination	561	35.4 ± 11.6		38.3 ± 9.0	
High-stress examination	80	43.4 ± 14.0		42.2 ± 9.1	

SD = standard deviation.
[a] p values obtained from Student t test or one-way analysis of variance.

The use of a validated depression scale is an important issue in interpreting the results. Among the scales used in the different studies, only the EPDS was validated during pregnancy. An instrument validated in primary care settings (PRIME-MD) and conforming to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition was used in one study (8). No association was observed with preterm birth. However, the PRIME-MD classification system includes several items for depression that are susceptible to be observed in the normal course of the pregnancy. Another interesting point is that the instrument was administrated between 16 and 18 weeks of gestation. A general tendency seems to emerge from the comparison of all the studies, which indicates that no association could be evidenced when depression was assessed early in pregnancy (before 20 weeks). In the only case in which an explicit comparison of different timing of assessment was planned in the study (at 16 and 30 weeks), an association was only evidenced late in pregnancy (18). Those findings should warrant further study.

Another element that could account for some of the discrepancies is the varying complexities of the psychological constructs assessed in the different studies. In the three cases in which an association between depression and preterm birth was observed (17–19), depression was the only psychological factor analyzed. In the other cases, anxiety and depression were assessed concomitantly in the multivariate analysis in two studies (5,8). The lack of association concerning depression could, however, not be explained by a confounding effect of anxiety because, in both cases, the effect of depression was not even significant in univariate analyses. We did not find any clue of confounding between the two constructs in our own study. In the last two studies (4,7), more complex constructs of psychological factors were modeled combining anxiety, depression, and different measures of stress. However, in both cases, again, depression was not significantly associated with preterm birth in univariate analyses.

No clear explanation can yet be given concerning those inconsistencies. Maybe depression is a marker of a still-undetected variable that would be present in only certain populations, which could help account for the varied results. Further research is still needed on that point.

Concerning state or trait anxiety, nonsignificant results have been found in recent prospective studies (5–8) and confirmed by our own study. A significant association was observed in only one study focusing on another form of anxiety that the authors named pregnancy-related anxiety (4). It was, however, evaluated through the use of an ad hoc six-item questionnaire whose validity had not been demonstrated before. Furthermore, internal consistency (e.g., Cronbach α) was not assessed, which makes it difficult to get an idea of the reliability of the scale.

In our previous paper on spontaneous preterm labor (20), we observed significant interaction effects between anxiety and specific biomedical factors. We showed that state and trait anxiety, whose mean effects on the overall population were not statistically significant, had a significant or close to significant influence in specific subgroups: state anxiety in women with vaginal bleeding (adjusted OR = 3.6, 95% CI = 0.9–14.7) and trait anxiety in women with a history of preterm labor (adjusted OR = 4.8, 95% CI = 1.1–20.4). We could not reproduce those results with spontaneous preterm birth. Although the two outcomes are generally statistically associated,

TABLE 4. Crude Odds Ratios of Spontaneous Preterm Birth for Selected Variables[a] and Psychological Factors ($n = 641$)

	n	Percent Spontaneous Preterm Birth	Crude Odds Ratio	95% Confidence Interval	*p* Value
Maternal age (years)					.059
<20	31	0.0%	1.0[b]	Referent	
20–34	520	4.4%			
≥35	90	8.9%	2.2	0.97–5.2	
Smoking habits during pregnancy					.21
Nonsmoking	421	4.0%	1.0	Referent	
0–9 cigarettes daily	140	5.0%	1.3	0.51–3.1	
10 cigarettes or more daily	80	8.8%	2.3	0.91–5.7	
Vaginal bleeding in third trimester					.064
No	619	4.5%	1.0	Referent	
Yes	22	13.6%	3.3	0.93–11.9	
Cervical and/or vaginal infection					.007
No	501	3.6%	1.0	Referent	
Yes	140	9.3%	2.7	1.3–5.8	
Polyhydramnios					.013
No	626	4.5%	1.0	Referent	
Yes	15	20.0%	5.3	1.4–20.0	
Hospitalization during second trimester					.017
No	592	4.2%	1.0	Referent	
Yes	49	12.2%	3.2	1.2–8.1	
Type of consultation at enrollment					.001
Low-stress examination	547	3.7%	1.0	Referent	
High-stress examination	94	12.5%	3.7	1.7–8.1	
Gestational age at enrollment					.018
1-week increase	641	—	1.20	1.03–1.39	
Partner violence					.21
No	547	4.4%	1.0	Referent	
Yes	94	7.4%	1.8	0.73–4.2	
Depression score					.023
<14	548	4.0%	1.0	Referent	
≥14	93	9.7%	2.6	1.1–5.8	
State anxiety score					.97
5-point increase[c]	641	—	1.0	0.86–1.2	
Trait anxiety score					.96
5-point increase[c]	641	—	0.99	0.82–1.2	

[a] Variables associated with preterm birth at the $p < .25$ level in univariate analysis.
[b] The first two groups were combined because no preterm birth occurred in the "<20-yr" group.
[c] Odds ratio concerning anxiety scores are presented for 5-point increases, which is clinically more meaningful that a one-point change.

they are nonetheless different obstetric events. Spontaneous preterm labor is defined as frequent uterine contractions (at least one contraction every 10 minutes for at least an hour) and at least one cervical change as assessed by Bishop's score. Women diagnosed and treated for preterm labor will often deliver at term. It could be hypothesized that the final process leading from preterm labor to preterm delivery is less sensible to the action of mediators of anxiety. Another difference between our two studies relates to the number of events, which is smaller in the present study. It is thus more difficult to evidence significant interaction effects. However, in the rare studies of anxiety in which interactions with biomedical factors were tested, interaction effects were also nonsignificant (4,7), and it is less likely that it could be explained by a lack of power considering the large number of subjects included in those studies (approximately 2000 women each).

Strengths and Weaknesses

Taking into account the etiological heterogeneity of spontaneous and medically indicated preterm births (1), we restricted our study solely to spontaneous preterm births. The risk of miscalculating the length of gestation was small because ultrasound examinations were conducted early in pregnancy, contrary to some studies taking place in socioeconomically disadvantaged populations with irregular care.

In the analysis, we controlled for a potential confounding effect resulting from the stressful nature of the enrollment consultation, an effect that was rarely investigated in other studies. It is worth noting that not adjusting on that particular variable would have resulted in an overestimation of the strength of the association between depression and spontaneous preterm birth; the OR associated with depression increases by more than 20% (from 3.3 to 4.0) when the variable is excluded from the final model.

TABLE 5. Adjusted Odds Ratios of Spontaneous Preterm Birth for Variables in the Final Model[a] (n = 641)

	Adjusted Odds Ratio	95% Confidence Interval	p Value
Cervical and/or vaginal infection			.026
No	1.0	Referent	
Yes	2.4	1.1–5.2	
Polyhydramnios			.026
No	1.0	Referent	
Yes	4.8	1.2–19.3	
Type of consultation at enrollment			.010
Low-stress examination	1.0	Referent	
High-stress examination	3.1	1.3–7.5	
Depression score			.020
<14	1.0	Referent	
≥14	3.3	1.2–9.2	
State anxiety score			
5-point increase[b]	0.87	0.70–1.08	.20
Trait anxiety score			
5-point increase[b]	0.97	0.73–1.30	.84

[a] Model resulting from a forward multiple logistic regression analysis on the following variables: maternal age, smoking habits during pregnancy, vaginal bleeding in the third trimester, cervical and/or vaginal infection, polyhydramnios, hospitalization during the second trimester, partner violence, type of consultation at enrollment, gestational age at enrollment, depression, state anxiety, trait anxiety.
[b] Odds ratio concerning anxiety scores are presented for 5-point increases, which is clinically more meaningful that a one-point change.

Compared with other studies, a very small proportion of women (5.9%) had to be excluded from analyses owing to missing questionnaire data. These nonrespondents did not differ from women included in the study except that there were more unemployed women among nonrespondents. It is thus unlikely that our results could be explained by nonresponse bias.

We used a classic forward multiple logistic regression analysis to build the final model. That kind of strategy may, however, result in an overfitted model, particularly when the sample is small (28). To test for that potential bias, we conducted an additional analysis consisting of a one-step multiple logistic regression applied to a model comprising the exposure variables (depression and anxiety scores) and a fixed set of predefined covariates known, from the literature, to be well-established risk factors for preterm birth. To limit the number of variables in the model, we combined sociodemographic risk factors (maternal age, marital status, socioeconomic status, smoking habits) on the one hand and medical risk factors (prior preterm birth, vaginal bleeding in the second trimester, urinary tract infection, cervical and/or vaginal infection, gestational hypertension, polyhydramnios) on the other hand into two composite scores. The variable "type of consultation" was also added to the model. Results were entirely consistent with the original analysis with a significant association with depression (adjusted OR = 3.1, 95% CI = 1.1–8.7, p = .031) and no association with anxiety.

Thirty-two women in our sample were using antidepressants or anxiolytics during their pregnancy. To test if the presence of such medication could modify the results, we reassessed the associations on the subsample of women using no psychotropic medication (n = 609). The variables included in the final multivariate model were identical to those included in the primary analysis. The associations with state and trait anxiety remained not significant with adjusted ORs very close to the original ones. For depression scores, the association was stronger when psychotropic users were excluded with an adjusted OR of 4.9 (95% CI = 1.6–14.9, p = .006), suggesting that the association between depression and preterm birth is weaker in women on psychotropic medication.

The main limitation of this research is the small sample size (n = 641) compared with most recent studies generally enrolling more than 1000 participants. It could explain why only nonsignificant increases were observed for some of the commonly accepted risk factors of preterm birth: previous preterm birth, prepregnancy BMI, and levels of education and employment. The relatively low proportion of disadvantaged families in our region, compared with deprived urban populations, could also minimize the impact of socioeconomic factors. Moreover, providing early and intensive antenatal care could have significantly improved pregnancy outcome in socially deprived women (29,30). Power was nevertheless sufficient to detect a significant association with depression. Concerning anxiety, we conducted a post hoc power analysis (31) to gain a better understanding of the nonsignificant result. With a type I error of 0.05, a preterm birth rate equal to 5% at the mean value of the anxiety score (either state or trait), and a sample of 641, power is equal to 60% to detect an OR of 1.5 (for an increase of one standard deviation, approximately 10 points, from the mean score), 90% for an OR of 1.8 and 95% for an OR of 2. Those results suggest that even if an association between anxiety and preterm birth exists, it is probably not very strong.

Possible Biological Pathways

The dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, mostly hyperactivity whose association with depression has been frequently observed, may be hypothesized to explain the potential role of depression in preterm birth. More precisely, a large body of evidence (32–34) shows

that a hyperactive CRH system, which plays a key role in the regulation of the HPA axis, is commonly associated with depression. Hypothalamic CRH is a 41 amino-acid peptide, which promotes the synthesis of pro-opiomelanocortin-derived peptides and the release of adrenocorticotropin hormone (ACTH) and beta endorphin. ACTH in turn stimulates the production and release of cortisol from the adrenal cortex. Markers of hypercortisolemia have been reliably demonstrated in depressed patients (12). Approximately 80% of patients with major depression show abnormal responses to stimulation tests of the HPA axis (35). CRH has been located not only in the hypothalamus, but also in a variety of regions in the human brain and also in the human placenta. Several in vitro and in vivo studies (14,15,36,37) suggest that the synthesis and the release of placental CRH are stimulated by stress hormones (as cortisol and ACTH). Placental CRH controls a cascade of events, which lead to parturition (15,16), and accelerating rates or excessive levels of placental CRH are significant risk factors for preterm birth (38–41). Modifications of the activity of the HPA axis may also be found in anxiety disorders, but they often differ from those observed in depression, particularly with hypocortisolism in place of hypercortisolism (42,43). Experimental studies have also shown that central CRF pathways may modulate anxiogenic-like effects of aversive events independently of the HPA axis (44). These findings may account for the differences between anxiety and depression in the association with preterm birth.

Another potential biological pathway to explain the possible role of depression in preterm birth is the activation of the inflammatory response system with increased concentrations of proinflammatory cytokines, prostaglandin E2, and negative immunoregulatory cytokines in peripheral blood (45,46). Prostaglandin E2, whose secretion is activated by cytokines (47) and cortisol (48), also plays a major role in uterine contractions. Increased inflammatory cytokine response has been associated with the occurrence of premature rupture of fetal membranes (49). By altering the inflammatory response, maternal depression may also favor vaginal infection and, by the way, reduce the length of gestation (50).

Future Research

We found evidence that depression was significantly associated with spontaneous preterm birth in a population of European women with early and regular antenatal care. However, no clear explanation seems to be given to account for the mixed results observed in the literature. We think that longitudinal studies based on psychological instruments validated during pregnancy and with multiple assessments of depression may represent valuable contributions. Depression is a mental disorder accessible to treatment. If its role could be clearly demonstrated, intervention studies assessing the effect of the treatment of antenatal depression on the incidence of preterm birth, particularly in high-risk populations, may lead to new psychosocial approaches to preventing preterm births.

Concerning anxiety, the present study and recent prospective studies accumulate arguments in support of a lack of association between state or trait anxiety and spontaneous preterm birth. The role of more specific forms of anxiety such as pregnancy-related anxiety may, however, warrant further study.

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