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Stormy clouds in seventh heaven

Meijer, Judith Linda

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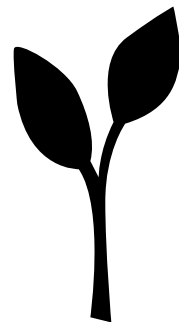
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***Predictive accuracy of the six-item State
and Trait Anxiety Inventory assessment
during pregnancy for the risk of developing
postpartum symptoms of anxiety: a
prospective cohort study.***

Judith L Meijer
Huibert Burger
Tjitte Verbeek
Chantal Beijers
Ronald P Stolk
Mariëlle G van Pampus
Claudi LH Bockting



chapter 5

Abstract

Background

To investigate whether the six-item State and Trait Anxiety Inventory (STAI) assessed antenatally is accurate in predicting postpartum symptoms of anxiety, and whether antenatal Edinburgh Postnatal Depression Scale (EPDS) can improve the prediction.

Methods

A prospective, population-based cohort study in the obstetric care in the Netherlands, $n=4,856$. Mean values, odds ratios, area under the receiver operating characteristics curve (AUC), sensitivity, specificity and predictive values of antenatal STAI for the risk of postpartum symptoms of anxiety (STAI score ≥ 42) were calculated. Analyses were repeated for each trimester and several cut-off values. Odds ratios were also calculated including antenatal symptoms of depression.

Results

The AUC was only reasonable in the second and third trimester (0.73). Using the prevailing cut-off (≥ 42) in the first trimester, the odds ratio was 3.49 [95%CI 2.61, 4.67]. Adding symptoms of depression did not improve the prediction. Sensitivity and positive predictive value were approximately 30%, specificity and negative predictive value were around 90%. Using a lower cut-off value (≥ 36) in the second trimester, sensitivity and specificity were both approximately 67%, but positive predictive value was low (22.9%, [95%CI 21.0, 24.9]). Negative predictive value increased to 93.2% [95%CI 92.3, 94.1].

Conclusions

The six-item STAI was not sufficiently accurate in predicting risk of postpartum symptoms of anxiety, irrespective of trimester and cut-off value. Women scoring below cut-off may be reassured that postpartum symptoms of anxiety are unlikely. Adding symptoms of depression did not improve the prediction.

Introduction

Due to a paucity of studies on specific symptoms of anxiety during pregnancy and in the postpartum period, it remains unclear how many women are affected by these symptoms^{1,2}, with estimates ranging from 7% to 33%³⁻¹³. Consequences that are associated with antenatal anxiety, however, have been studied relatively well. Multiple studies focus on unfavourable obstetric outcomes in terms of low birth weight and preterm birth^{14,15}. In addition, associations between maternal anxiety/stress and multiple adverse outcomes in the child, such as cognitive, behavioral and emotional problems, were found in numerous studies^{10,16-19}. Furthermore, antenatal anxiety often precedes postpartum symptoms of anxiety or depression^{3,7,20}, or both, as they are known to be highly comorbid^{3,6}.

A commonly used instrument in the identification of symptoms of anxiety is the State and Trait Anxiety Inventory (STAI)²¹, which was validated both in samples of pregnant and postpartum women²¹. Although it is known that having symptoms of anxiety is a risk factor for developing an anxiety disorder⁵, the STAI has not extensively been studied for its accuracy in predicting future symptoms of anxiety. As far as we know, only one study has been conducted on the predictive accuracy of the STAI in the postpartum period. This study showed that women with a high risk of anxiety symptoms in the first two months after delivery (n=522) can already be identified in the first days postpartum using the STAI²². Knowing that symptoms of anxiety that exist during pregnancy can have serious adverse outcomes for both mother and child, and that a psychological therapy such as cognitive behavioral therapy is a treatment with a high success rate for symptoms of anxiety, it is essential to identify these symptoms as early as possible.

In the current prospective study, we therefore examined to what extent the STAI applied during the first, second, and third trimester of pregnancy was accurate in predicting the absolute risk of postpartum symptoms of anxiety. In addition, we determined which cut-off value yielded the most accurate prediction. In view of the established co-morbidity of anxiety and depression, we also investigated whether assessing antenatal depressive symptoms would give a more accurate prediction of postpartum symptoms of anxiety.

Methods

Sample

The current study was conducted within the prospective Pregnancy, Anxiety and Depression (PAD) cohort study in the Netherlands (n=7,275), which included women in their

first trimester between May 2010 and September 2014, and aims to investigate antenatal and postpartum symptoms of and risk factors for anxiety or depression²³. Midwives and gynaecologists of participating obstetric care centres (n=116) invited all visiting pregnant women to participate in the study. Due to logistic reasons, we are unable to determine how many women have actually been invited and, of these, how many agreed to participate. The number of participants was however considerably lower than we expected based on the number of participating centres. A survey among participating midwives showed that pressure of time meant that they could not hand out the forms to all visiting women and that they did not specifically invite women they suspected to have an increased risk of depressive symptoms. Therefore, we do not think that participants and non-participants differed in any considerable way with respect to characteristics relevant to the study due to selective inviting²². All participants gave written informed consent.

The study population of the current study was formed by 4,856 women who were five months postpartum (range four to seven months) at the time of database closure in December 2014. Of these women, 74.1% (n=3,600) responded by filling out the postpartum follow-up questionnaire on anxiety symptoms. Compared to these responders, non-responders were younger (difference less than a year, $p=0.001$), more often multiparous ($p=0.001$), had a lower educational attainment level ($p=0.003$) and higher scores on anxiety symptoms and depressive symptoms at all antenatal measurement waves ($p < 0.01$).

The medical ethical review board of the University Medical Center Groningen approved this study.

Measures

Symptoms of antenatal anxiety and depression were measured at 12, 23 and 35 weeks of gestation. Postpartum symptoms of anxiety were assessed at five months postpartum. Anxiety was measured using the Dutch six-item version of the STAI²⁴, which has acceptable concurrent validity when compared to the full 20-item form ($r=0.92$), and a good internal consistency (Cronbach's $\alpha=0.82$)²¹. The questionnaire measures state anxiety ('how do you feel at the moment'), and was validated on a sample of pregnant women²¹. Scores are on the original scale from 20 to 80, with scores of ≥ 42 indicating an increased risk on anxiety²¹, postpartum scores were dichotomized accordingly.

To measure antenatal depressive symptoms, we used the validated Dutch 10-item Edinburgh Postnatal Depression Scale (EPDS)²³, which has shown good internal consistency

(Cronbach's $\alpha=0.82$)²³. The scale ranges from 0 to 30. Total scores of 13 or higher indicate an increased risk of minor or major depression during pregnancy^{24,25}.

Multiple imputation of missing data

Complete information for all variables was present for 2,248 women, i.e. 46.3% of women who were at least four months postpartum. The percentage of missing data in the present study ranged from 7.8 (age at inclusion) to 26.1 (EPDS five months postpartum) for the variables of main interest. To avoid potential bias and decreased statistical power^{26,27}, we imputed all missing data on item level, using multiple imputation by chained equations under the assumption that missing values were missing at random (MAR) or missing completely at random (MCAR). For all variables of main interest, we assessed to what extent we could predict their values being missing, using logistic regression, in order to substantiate the assumption that the missing data mechanism was MAR. Independent variables were all variables that were considered potential predictors of missingness of a value^{27,28}, i.e. antenatal symptoms of anxiety and depression, age at baseline, parity and maternal educational attainment level. The explained variance (Nagelkerke R²) from these analyses ranged from 1.2% to 8.2%, which suggests that data are MAR to some extent, and imputation of missing values would likely improve the validity of our analyses. Therefore, all of these variables as well as the outcome variable, i.e. postpartum symptoms of anxiety, were included in the imputation model. All results were pooled using Rubin's method for multiple imputation inference²⁹. However, the possibility that data were missing not at random has to be borne in mind²⁸. We therefore performed a complete case analysis to compare the results with the results of the imputed dataset as a sensitivity analysis. Multiple data sets (n=5) were generated.

Statistical analysis

We first calculated the prevalence of symptoms of anxiety (STAI ≥ 42) and depression (EPDS ≥ 13) at all antenatal measurements, and the prevalence of postpartum symptoms of anxiety. Using a paired samples t-test, we tested whether antenatal levels of anxiety and depression significantly differed from postpartum levels. Subsequently, descriptive statistics were calculated for demographic variables and scores on the antenatal STAI and EPDS assessments. These calculations were done for the total sample and according to the presence of postpartum symptoms of anxiety. We tested whether mean values differed between women with and women without postpartum symptoms of anxiety, using an

independent samples t-test.

All following analyses were repeated for all three antenatal measurement waves. We determined several performance parameters. First, we calculated the odds ratio for the association between increased antenatal and postpartum levels of anxiety or depression by conducting a logistic regression analysis. We added symptoms of antenatal depression to investigate whether this would give a more accurate prediction of postpartum symptoms of anxiety.

Subsequently, we constructed receiver operating characteristic (ROC) curves and calculated the area under the ROC-curve (AUC). Next, sensitivity, specificity and predictive values were calculated using several cut-off values for the antenatal STAI to define test positive. We started with the commonly used cut-off value of ≥ 42 . Based on the results and the ROC-curve, we gradually lowered the cut-off value, and repeated all analyses. Measures of predictive accuracy were supplied with 95% confidence intervals.

Additionally, test positive was defined as a score exceeding the cut-off of ≥ 42 on the STAI at all three antenatal measurements, to test whether repeating the assessment of anxiety symptoms would give a more accurate prediction, compared to having a score above cut-off at one of the antenatal measurements. We repeated this analysis using a lower cut-off, i.e. ≥ 36 for all antenatal measurement waves.

Based on a previous study conducted by Dennis et al.¹², in which the time interval between measurements was four to eight weeks, we conducted a sensitivity analysis in which we repeated our analyses and calculated the predictive accuracy with the first trimester as predictor variable and the third trimester as outcome variable. Lastly, we performed a complete case analysis as a sensitivity analysis.

Multiple imputation and statistical analyses were carried out using IBM SPSS Statistics 20.

Results

Sample description

At baseline, 619 women (12.7%) experienced symptoms of anxiety (≥ 42), and 177 women (3.6%) experienced symptoms of depression (≥ 13). Prevalence rates of levels of anxiety and depression were highest in the second trimester ($n=717$, 14.8% and $n=187$, 3.9% respectively). Postpartum symptoms were experienced by 621 women (12.8%), i.e. the prior risk. A total of 164 women (3.4%) scored above the cut-off of ≥ 42 on the STAI at all antenatal measurement

Table 1 Demographic characteristics of the study population (n=3,612) according to the presence of postpartum anxiety symptoms ^a

	Total (n=3,612)	No postpartum anxiety symptoms (n=3,185, 88.2%) ^a	Postpartum anxiety symptoms (n=427, 11.8%) ^a	Fraction of missing data
Age, mean (min-max)	30.1 (17-45)	30.1	30.1	44.6%
Primiparity ^b , n (%)	1489 (41%)	1337 (42%)	152 (36%)	34.3%
Educational level, n (%) ^c	-	-	-	32.5%
Elementary education	18 (<1%)	17 (<1%)	1 (<1%)	-
Lower tracts of secondary education	331 (9%)	282 (9%)	48 (11%)	-
Higher tracts of secondary education	1171 (32%)	1045 (33%)	126 (30%)	-
Higher vocational education	1422 (39%)	1251 (39%)	171 (40%)	-
University education	670 (19%)	590 (19%)	80 (19%)	-
Anxiety level first trimester^{bd}, mean (SD)	32.52 (8.19)	31.73 (7.50)	38.47(10.38)	19.9%
Anxiety level second trimester^{bd}, mean (SD)	33.08 (8.94)	31.98 (8.11)	41.22 (10.54)	12.8%
Anxiety level third trimester^{bd}, mean (SD)	33.17 (8.57)	32.12 (7.69)	41.04 (10.49)	14.5%
Anxiety level postpartum^{bd}, mean (SD)	32.11 (9.35)	29.55 (5.92)	51.19 (8.06)	19.0%
Depression level first trimester^{bd,e}, mean (SD)	4.37 (3.39)	4.054 (3.09)	6.86 (4.40)	20.5%
Depression level second trimester^{bd,e}, mean (SD)	5.02 (3.55)	4.60 (3.17)	8.17 (4.50)	12.9%
Depression level third trimester^{bd,e}, mean (SD)	4.92 (3.51)	4.52 (3.17)	7.92 (4.39)	14.9%
Depression level postpartum^{bd,e}, mean (SD)	4.66 (3.77)	3.78 (2.64)	11.18 (4.46)	19.5%

^a According to six-item State and Trait Anxiety Inventory (STAI), cut-off ≥ 42 , min-max=20-80

^b Scores were statistically significantly higher in the group with postpartum anxiety symptoms than in the group without postpartum symptoms of anxiety, with $p < 0.001$

^c Numbers may not add to the total due to rounding of imputed values

^d Based on STAI at approximately 14 weeks pregnancy, min-max=20-80

^e Based on EPDS at approximately 14 weeks pregnancy, min-max=0-30

Table 2 Test characteristics for predicting postpartum anxiety symptoms from antenatal anxiety symptoms ≥ 42

	STAI score cut-off $\geq 42^a$			
	First trimester (n=619, 12.7%) ^b	Second trimester (n=717, 17.8%) ^b	Third trimester (n=650, 13.4%) ^b	All antenatal scores above cut-off (n=164, 3.4%)
Odds Ratio [95% CI]	3.49 [2.61, 4.67]	4.72 [3.78, 5.88]	5.15 [4.21, 6.28]	7.40 [5.24, 10.5]
Odds Ratio [95% CI] ^c	2.67 [2.00, 3.55]	3.73 [2.90, 4.79]	3.96 [3.13, 5.01]	5.64 [3.76, 8.47]
Sensitivity, % [95% CI]	28.7 [25.1, 32.4]	37.7 [33.9, 41.6]	36.4 [32.6, 40.3]	13.0 [10.5, 15.9]
Specificity, % [95% CI]	89.6 [88.6, 90.5]	88.6 [87.6, 89.6]	90.0 [89.0, 90.9]	98.0 [97.6, 98.4]
Positive Predictive Value, % [95% CI]	28.8 [25.2, 32.5]	32.6 [29.2, 36.2]	34.8 [31.1, 38.6]	49.5 [41.5, 57.3]
Negative Predictive Value, % [95% CI]	89.5 [88.6, 90.5]	90.7 [89.7, 91.5]	89.5 [88.5, 90.4]	88.5 [87.5, 89.4]

^a Based on six-item State and Trait Anxiety Inventory (STAI), min-max=20-80

^b Number and percentage of women scoring above the cut-off

^c Including symptoms of depression as assessed by Edinburgh Postnatal Depression Scale (EPDS), min-max=0-30

Table 3 Test characteristics for predicting postpartum anxiety symptoms from antenatal anxiety symptoms ≥ 36

	STAI score cut-off $\geq 36^a$			
	First trimester (n=1,726, 35.5%) ^b	Second trimester (n=1,801, 37.1%) ^b	Third trimester (n=1,901, 39.1%) ^b	All antenatal scores above cut-off (n=702, 14.5%)
Odds Ratio [95% CI]	2.80 [2.19, 3.57]	4.10 [3.37, 4.99]	3.65 [2.99, 4.47]	4.54 [3.61, 5.72]
Odds Ratio [95% CI]^c	2.01 [1.57, 2.58]	2.88 [2.30, 3.62]	2.62 [2.06, 3.34]	2.79 [2.21, 3.52]
Sensitivity, % [95% CI]	57.2 [53.2, 61.1]	66.5 [62.6, 70.2]	66.3 [62.5, 70.1]	36.4 [32.6, 40.3]
Specificity, % [95% CI]	67.6 [66.2, 69.0]	67.3 [65.8, 68.7]	64.9 [63.4, 66.3]	88.8 [87.8, 89.7]
Positive Predictive Value, % [95% CI]	20.6 [18.7, 22.6]	22.9 [21.0, 24.9]	21.7 [19.9, 23.6]	32.2 [28.7, 35.8]
Negative Predictive Value, % [95% CI]	91.5 [90.5, 92.5]	93.2 [92.3, 94.1]	93.0 [92.0, 93.9]	90.5 [89.5, 91.4]

^a Based on six-item State and Trait Anxiety Inventory (STAI), min-max=20-80

^b Number and percentage of women scoring above the cut-off

^c Including symptoms of depression as assessed by Edinburgh Postnatal Depression Scale (EPDS), min-max=0-30

instances. Seventy-six of these women did not experience postpartum symptoms of anxiety (47.8%). Of all women experiencing symptoms of either anxiety or depression at baseline (n=662, 13.6%), the vast majority experienced specific symptoms of anxiety (n=484, 73.1%), compared to a combination of both anxiety and depression (n=135, 20.4%) or specific symptoms of depression (n=43, 6.5%).

In the total sample, mean levels of anxiety and depression were rather stable (table 1), and did not significantly differ ($p=0.168$). In women experiencing symptoms of anxiety in the postpartum period, levels did increase significantly between the baseline and postpartum measurements ($p<0.001$). Parity and all scores of antenatal anxiety or depression differed significantly between women with and without postpartum symptoms of anxiety ($p<0.0001$, table 1).

Predictive accuracy of STAI

The performance parameters were calculated in all trimesters for several different cut-offs. Table 2 and 3 only show the results for the respective cut-offs ≥ 42 and ≥ 36 , as the first is the prevailing cut-off, and the latter yielded the most accurate prediction in terms of predictive parameters. The odds ratios ranged from 2.86 [95% CI 2.23, 3.67] at the baseline measurement with cut-off ≥ 33 to 5.15 [95% CI 4.21, 6.28] at the third trimester measurement with cut-off ≥ 42 . This same trend was observed after adding symptoms of depression to the model, with odds ratios ranging from 1.99 [95% CI 1.56, 2.56] at the baseline measurement with cut-off ≥ 33 to 3.96 [95% CI 3.13, 5.03] at the third trimester measurement with cut-off ≥ 42 .

For STAI only, the AUC's were only reasonable in the second and third trimester (0.74 and 0.73 respectively)³⁰. After adding symptoms of depression to the models, the AUC was below 0.64 in all trimesters.

Furthermore, for the STAI with a cut-off value of ≥ 42 in the first trimester, the sensitivity was low with 28.7% [95% CI 25.1, 32.4], as was the positive predictive value (28.8% [95% CI 25.2, 32.5]). Specificity and negative predictive values however, were high (89.6% [95% CI 88.6, 90.5] and 89.5% [95% CI 88.6, 90.5] respectively). When we lowered the cut-off to ≥ 36 in the first trimester, the sensitivity increased to 57.2% [95% CI 53.2, 61.1] and the negative predictive value to 91.5% [95% CI 90.5, 92.5], especially at the expense of specificity (67.6% [95% CI 66.2, 69.0]).

Including only women who scored above ≥ 42 at all three antenatal anxiety measurements yielded a sensitivity of 13.0% [95% CI 10.5, 15.9] and a positive predictive value of 49.5% [95% CI 41.5, 57.3]. Lowering the cut-off value to ≥ 36 increased the sensitivity to 36.4% [95% CI 32.6, 40.3], but decreased the positive predictive value to 32.2% [95% CI 28.7, 35.8].

Sensitivity analyses

In general, the results of the complete case analysis were comparable. Sensitivity and positive predictive values appeared to be higher in the complete case analyses, whereas specificity and negative predictive values were slightly lower in the complete case analyses. When using the levels of anxiety in the first trimester as predictor variable and the levels of anxiety in the second trimester as outcome variable, we found a sensitivity of 38.4, specificity of 91.7 and 44.4 and 89.6 for the positive and negative predictive values respectively.

Discussion

Main Findings

In this large prospective cohort study, we found that antenatal symptoms of anxiety are a strong predictor of symptoms of anxiety in the postpartum period. However, although we found reasonable overall discriminatory power in the second and third trimester (AUC 0.74 and 0.73 respectively), we found a low sensitivity for the prevailing cut-off (i.e. ≥ 42). Lowering the cut-off to ≥ 36 somewhat improved the predictive performance. For both cut-off values, we found exceedingly high negative predictive values; $\geq 89\%$ for the cut-off value of ≥ 42 and $\geq 91\%$ for the cut-off value of ≥ 36 . This suggests that the prior risk for developing symptoms of anxiety in the postpartum period, i.e. 12.8%, could be nearly halved to 6.8% when using the cut-off of ≥ 36 in the second trimester. Although the odds ratios were reasonable after adding antenatal symptoms of depression as assessed by the Edinburgh Postnatal Depression Scale (EPDS), they were higher without symptoms of depression.

Interpretation

Our findings appear to be contradictory to the findings of Dennis et al.¹². They used the STAI with a cut-off of >40 , which is comparable to ≥ 42 due to the scale of the six-item version of the STAI, and concluded that it can very well be used to identify one-week postpartum women who are at risk for symptoms of anxiety seven weeks later (sensitivity 67.5%,

specificity 87.1%, positive predictive value 53.0%, negative predictive value 92.5%). This difference might be due to the time between measurements; Dennis et al. tested intervals of three and seven weeks, whereas the time between the second antenatal and the postpartum measurement in our study was approximately 40 weeks. We therefore performed a sensitivity analysis between antenatal measurements in the first and second trimester, which equalled a time interval of 11 weeks. We then found a more comparable predictive performance (sensitivity 38.4%, specificity 91.7%, positive predictive value 44.4%, negative predictive value 89.6%), although the sensitivity in our analysis was lower, and the specificity was slightly higher. In addition, Dennis et al. stated to accurately classify 84% of all women who either did or did not develop symptoms of anxiety. We found the same percentage in our sensitivity analyses (83.8%) and a similar percentage between the antenatal and postpartum measurements (81.8%). This suggests that the time interval might very well explain the contradiction in findings.

Literature on psychometric properties of the STAI and on postpartum symptoms of anxiety as distinct from depression is growing. The consensus is that having antenatal symptoms of anxiety or depression is a risk factor for developing postpartum symptoms of anxiety or depression. We found high odds ratios in the current study, which substantiate these findings. However, the STAI appeared to have limited predictive accuracy for absolute risk stratification. Although having antenatal symptoms of anxiety may be a risk factor for postpartum symptoms of anxiety as reflected by the high odds ratios, based on antenatal STAI measurements, we are not able to accurately identify individual women with a high risk of postpartum symptoms of anxiety.

In line with a previous study, adding symptoms of depression based on the EPDS did not increase the prediction of postpartum symptoms of anxiety⁷. The authors explain their finding by the low prevalence rate of depressive disorders (9%) compared to anxiety (33%). In the current study, we found that the prevalence of symptoms of depression (range 8.0%-10.4%) was considerably lower compared to rates of anxiety symptoms (range 11.8%-13.4%), which might indicate that depression is not as comorbid in women with anxiety as anxiety is in women with depression^{7,31}.

In a previous study²³, we found comparable predictive parameters for postpartum symptoms of depression as assessed with the EPDS. Based on our findings and the extensive literature on risk factors of postpartum symptoms depression, we were then able to suggest a strategy on screening options. Unfortunately, this is impossible for postpartum symptoms

of anxiety, as studies on risk factors for such symptoms are scarce. Knowing the potential negative consequences for mother and child, the risk of anxiety in either pregnancy or the postpartum period, as distinct from depression, should be subject to future research.

Strengths and limitations

A few limitations have to be considered in the current study. First, both the STAI and EPDS are self-report questionnaires, and even though both tools are commonly used in the identification of current symptoms of anxiety or depression, it is not possible to diagnose a disorder based on these questionnaires. Second, selection bias may be introduced, as women who are familiar with symptoms of anxiety or depression may be more inclined to participate. This would, however, have led to an underestimation of the found effect. In addition, prevalence rates for mental health problems are higher in a population with lower educational attainment levels²⁰. In our sample, there is a significant difference between respondents and non-respondents on this specific characteristic. However, the percentage of women who have completed elementary school or lower tracts of secondary school does not considerably differ between respondents and non-respondents. Also, we found significant differences between respondents and non-respondents on age and antenatal symptoms of anxiety and depression. However, the difference in age was less than a year in absolute numbers and the mean scores on antenatal STAI and EPDS were below cut-off at all measurement waves for both groups. Therefore, we do not think that these differences affected our prevalence rates.

Several strengths have to be taken into account as well. The current study is a large prospective cohort (n=4,856) with a high percentage of women filling out the outcome measurement (74.1%). Moreover, by our knowledge, this study is the first to test the accuracy of the STAI over a considerably long period of time around childbirth, and to include the added value of depressive symptoms based on the STAI in predicting postpartum symptoms of anxiety.

Conclusion

Regardless of the cut-off value used or the trimester of administration, the overall predictive accuracy of the STAI appears to be limited, although we found a reasonable discriminatory power and an exceedingly high negative predictive value. In addition, although lowering the cut-off yielded a reasonable sensitivity and specificity, the positive predictive value was very low (24.3%). We think the STAI is therefore not suitable for absolute

risk stratification in individual women. However, pregnant women scoring below cut-off can be reassured that it is very unlikely that they will develop symptoms of anxiety in the postpartum period. While the potential adverse outcomes in physical and psychological health of both mother and child are relatively well known, future research should focus on the improvement of identifying the risk of antenatal and postpartum symptoms of anxiety as distinct from depression.

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