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## **The embarrassed brain : towards a neurobiology of generalized social anxiety disorder**

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# **The effects of female reproductive hormones in generalized social anxiety disorder**

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## Abstract

**Objective:** Although generalized social anxiety disorder (gSAD) is more prevalent in women, the role of female reproductive hormones in gSAD has never been investigated. Therefore our aim was to make a first inventory of the influence of female reproductive hormones on gSAD symptoms. **Method:** Female patients with gSAD who had previously participated in our research projects in the University Medical Center Utrecht and the Leiden University Medical Center were recruited. A self-report survey with questions on the influence of menarche, the periods of the menstrual cycle, oral contraceptive use, pregnancy, lactation, postpartum period and menopause on gSAD symptoms was returned by 46% of 140 women suffering from gSAD. Non-parametric statistical tests were used to analyze the data. **Results:** A subgroup of patients reported an influence of female hormonal cycle on gSAD symptoms. In this subgroup, statistical differences were found for the menstrual cycle and pregnancy. In the premenstrual period, patients reported more severe gSAD symptoms. During pregnancy symptoms decreased, but postpartum symptom severity returned to the same levels as before pregnancy. **Conclusions:** A subgroup of women with gSAD seemed vulnerable for the influences of gonadal hormones. Prospective research in women with gSAD, in which the gonadal hormones are assessed, is warranted.

## Introduction

Social Anxiety Disorder (SAD) is one of the most common psychiatric disorders. In a review of European community studies, a lifetime prevalence of 3.9 to 13.7 % for SAD according to DSM-IV criteria was found. Moreover, the prevalence estimates were generally higher in women than in men (Fehm et al., 2005). Two subtypes can be distinguished: specific SAD and generalized SAD (gSAD) (DSM-IV-TR). The onset of gSAD is often in puberty and the symptoms of gSAD might be more severe in women (Keller, 2003; Wittchen and Fehm, 2003). Taken together, these findings might suggest that the gonadal hormones influence the onset and course of gSAD. This hypothesis is supported by literature on gonadal hormones and anxiety. The gonadal hormones estrogen and progesterone regulate the female hormonal cycle: menarche, menstrual cycle, pregnancy, postpartum period, lactation, and menopause. They also affect neurotransmitter systems that are associated with anxiety, such as the dopaminergic, serotonergic, and GABAergic system (for a review: Weinstock, 1999). Furthermore, the female hormonal cycle affects the course and severity of several symptoms of anxiety. Healthy women experienced an increase in anxiety symptoms during the third trimester of pregnancy (Rofe et al., 1993). Premenstrual increase of anxiety symptoms was reported in women with anxiety disorders, such as generalized anxiety disorder (GAD) and panic disorder (PD) (Hsiao et al., 2004; Brambilla et al., 2003). Finally, premenstrual dysphoric disorder and anxiety disorders are highly comorbid conditions (Hsiao et al., 2004).

In gSAD, the influences of female gonadal hormones on anxiety symptoms have never been investigated. The aim of the research described in this article was to explore whether there is an influence of the gonadal hormones on social anxiety and avoidance in women with gSAD. Therefore, we made a retrospective inventory of the course of gSAD symptoms during the female hormonal cycle. Based on the literature in other anxiety disorders, we hypothesized that premenstrually and in the last trimester of the pregnancy the levels of anxiety are higher.

## Materials and methods

### *Participants and procedures*

Participants were women over 18 years of age, with gSAD according to DSM-IV criteria, as confirmed with the MINI Plus 5.0.0 (Van Vliet and De Beurs, 2007). Comorbidity, contraception, and hormonal replacement therapy were allowed. Exclusion criterion was an endocrinological disorder of any kind. Patients who did not have a menstruation period for the past year or more were considered postmenopausal.

Female patients with gSAD who had previously participated in our research projects in the University Medical Center Utrecht (UMCU) and the Leiden University Medical Center (LUMC) were recruited.

A total of 140 patients were approached. We sent a letter to 96 UMCU female patients

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to ask their permission to call them for participation in the study. We used a directory of old addresses, because these patients did not receive treatment in the UMCU at the time of this study. Reminders were sent out to non-respondents. Patients who returned the permission form were called. We explained the procedures and asked if they wanted to participate. Then the survey was sent. In the LUMC, 44 women who participated in research or were treated for gSAD, were asked to participate during one of their visits. The survey was either given or sent to the patients.

The study was approved by the Medical Ethical Committees of the UMCU and LUMC. All subjects gave written informed consent prior to inclusion in the study.

### *Survey*

Patients received a self-report survey with questions regarding demographic data and the effects of the female hormonal cycle on social anxiety and avoidance. The phases that were studied were menarche, the periods of the menstrual cycle, oral contraceptive (OC) use, pregnancy, lactation, postpartum period, and menopause. For each phase the first question was on the influence of this particular phase on symptoms of social anxiety and of social avoidance. This question could be answered by “yes” or “no”. If the answer was “yes” on this question, they were asked to score the levels of social anxiety and avoidance retrospectively from 0 to 10 for that particular phase. Patients were asked to fill in the questions on the menstrual cycle if they had a regular cycle of 24 to 32 days and only for the time periods in which they had a natural menstrual cycle, without the use of oral contraceptives. Week 1 was considered the menstruation period, week 2 the late follicular phase, week 3 the early luteal phase, and week 4 the premenstrual phase. Questions on pregnancy and postpartum period were directed to the time before pregnancy, the first trimester, the second trimester, the third trimester, and the postpartum period.

### *Statistics*

Descriptive statistics were used for patient characteristics and for some outcome parameters.

Statistical analyses were performed only on data of patients who reported an influence of the female hormonal cycle on symptoms of social anxiety and avoidance, and on current social anxiety and avoidance scores. These were categorical data. We used non-parametric statistics to analyse the data to avoid the normality assumption. Spearman's Rank Order Correlation ( $\rho$ ) was performed to explore the relationship between the age of menarche and age of onset of gSAD. A Friedman Test was conducted to compare scores on social anxiety and avoidance across different time periods per phase. The Wilcoxon Signed Ranks Test was done for the comparison of social anxiety and avoidance as posthoc analysis for the significant outcome variables of the Friedman Test. This test analyses the direction and the relative magnitude of the differences within pairs.

## Results

### *Response*

We sent a letter to 96 female patients with gSAD from the UMCU with information and to ask for permission to call them. Twenty-nine patients (30%) returned the form. They were called and received a survey. Twenty-seven patients (93%) completed the survey. At the LUMC, 44 female patients were asked to participate during a treatment or research visit. All patients volunteered and 37 (84%) returned the survey. Overall, 64 completed surveys (46%) were received.

### *Patient characteristics*

The mean age of the patients was 42.0 years ( $\pm 11.7$ ; range 21-63 years). The mean age of onset for gSAD was 15.1 years ( $\pm 8.4$ ). The delay from the age of onset until the diagnosis gSAD was 22.6 years ( $\pm 14.0$ ). Eighty-six percent of the patients received treatment for gSAD during their life, and 45% are currently being treated. A positive family history for gSAD was reported in 50% of the patients. Many patients (75%) were part-time or full-time employed. The remaining 25% were unemployed (14%), incapable of working (3%), retired (3%), or student (5%). Level of education was divided in 3 groups: 24% had a low educational level (10 years or less), 43% had a medium educational level (10-14 years), and 33% had a high educational level (more than 14 years).

The mean current gSAD symptoms on a scale of 0-10 of the entire sample in each area of work, social life, and family life were compared. It appeared that there was a statistically significant difference in social anxiety ( $p < 0.001$ ,  $\chi^2 = 73.2$ ,  $df = 2$ ,  $n = 61$ ) as well as avoidance ( $p < 0.001$ ,  $\chi^2 = 62.3$ ,  $df = 2$ ,  $n = 61$ ) in these three areas. Social anxiety and avoidance are highest in social life and lowest in family life. There was no significant difference in social anxiety and avoidance between work situations and social life ( $p = 0.8$ ;  $p = 0.7$ ), but both were significantly higher than the symptoms in family life ( $p < 0.001$  in all cases).

### *Menarche and age of onset*

We found no correlation between age of menarche and age of onset gSAD ( $r = -0.01$ ,  $n = 63$ ,  $p = 0.9$ ).

### *Influence of female hormonal phase on social anxiety and avoidance*

Most patients did not report any influence of menarche, menstrual cycle, OC use, pregnancy, and lactation. However, most patients did notice any influence of the postpartum period and menopause on anxiety symptoms. For exact percentages see Table 1.

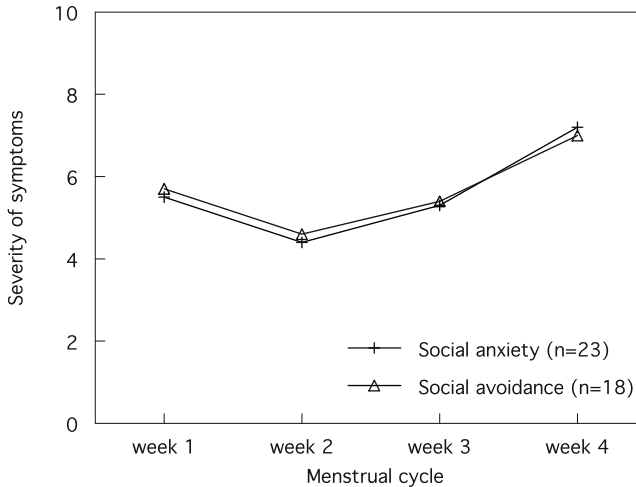
**Table 1** Influences of female hormonal cycle on gSAD symptoms

| Influence on Symptoms | Menarche (n=64) |           | Menstrual cycle (n= 51) |          | OC use (n=50) |          | Pregnancy (n=41) |           |
|-----------------------|-----------------|-----------|-------------------------|----------|---------------|----------|------------------|-----------|
|                       | soc.anx.        | soc.avoi. | soc.anx.                | soc.avoi | soc.anx.      | soc.avoi | soc.anx.         | soc.avoi. |
| Yes                   | 13%             | 8%        | 45%                     | 35%      | 12%           | 14%      | 41%              | 41%       |
| No                    | 78%             | 81%       | 55%                     | 65%      | 88%           | 86%      | 59%              | 59%       |
| Unknown               | 9%              | 11%       |                         |          |               |          |                  |           |

| Influence on Symptoms | Postpartum period (n= 38) |          | Lactation (n=30) |          | Menopause (n=13) |          |
|-----------------------|---------------------------|----------|------------------|----------|------------------|----------|
|                       | soc.anx.                  | soc.avoi | soc.anx.         | soc.avoi | soc.anx.         | soc.avoi |
| Yes                   | 56%                       | 53%      | 3%               | 7%       | 69%              | 62%      |
| No                    | 44%                       | 47%      | 97%              | 93%      | 31%              | 38%      |

Note: Percentages of patients who did or did not report an influence on the symptoms of social anxiety (soc.anx.) and avoidance (soc.avoi.).



**Figure 1** The mean social anxiety and avoidance scores (0-10) during the menstrual cycle, as obtained from the patients who reported an influence of the menstrual cycle on social anxiety and avoidance.

**Table 2** Statistical differences during the 4 weeks of the menstrual cycle

|        | Social anxiety (n=23) |          |          |        | Social avoidance (n=18) |          |          |        |
|--------|-----------------------|----------|----------|--------|-------------------------|----------|----------|--------|
|        | Week 1                | Week 2   | Week 3   | Week 4 | Week 1                  | Week 2   | Week 3   | Week 4 |
| Week 1 | -                     | -        | -        | -      | -                       | -        | -        | -      |
| Week 2 | p=0.02*               | -        | -        | -      | p=0.010*                | -        | -        | -      |
| Week 3 | p=0.772               | p=0.005* | -        | -      | p=0.532                 | p=0.016* | -        | -      |
| Week 4 | p=0.002*              | p=0.000* | p=0.000* | -      | p=0.015*                | p=0.001* | p=0.002* | -      |

Note: *P*-values of the post hoc analysis with the Wilcoxon Signed Rank Test on the retrospective social anxiety and avoidance scores in the different weeks of the menstrual cycle. Week 1 represents the menstruation, week 2 the late follicular phase, week 3 the early luteal phase, and week 4 the premenstrual phase.

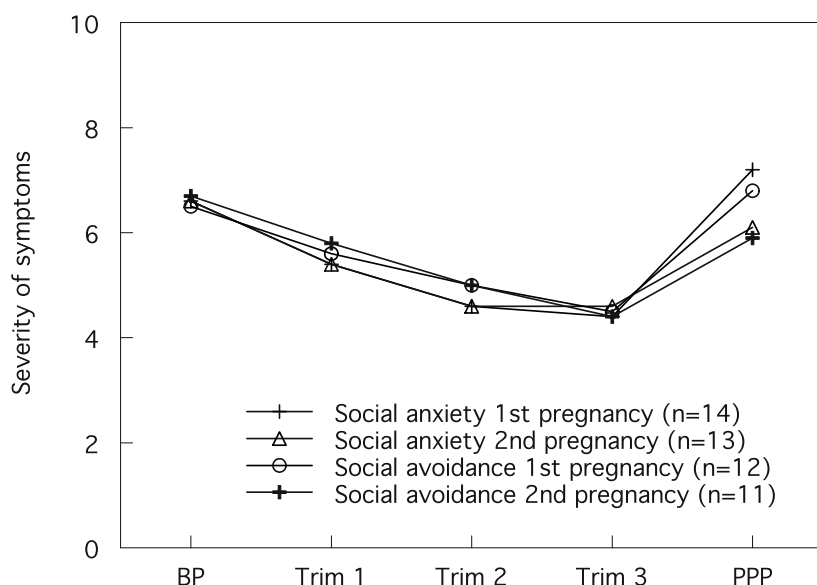
**Table 3** Statistical differences before, during, and after the 1<sup>st</sup> and 2<sup>nd</sup> pregnancy

| <b>Social anxiety 1<sup>st</sup> pregnancy (n=12)</b>   |           |               |               |               |            |
|---|-----------|---------------|---------------|---------------|------------|
|   | <b>BP</b> | <b>Trim 1</b> | <b>Trim 2</b> | <b>Trim 3</b> | <b>PPP</b> |
| <b>BP</b>   | -         | -             | -             | -             | -          |
| <b>Trim 1</b>   | p=0.022*  | -             | -             | -             | -          |
| <b>Trim 2</b>   | p=0.005*  | p=0.040*      | -             | -             | -          |
| <b>Trim 3</b>   | p=0.003*  | p=0.054       | p=0.339       | -             | -          |
| <b>PPP</b>  | p=0.301   | p=0.016*      | p=0.005*      | p=0.005*      | -          |
| <b>Social avoidance 1<sup>st</sup> pregnancy (n=10)</b> |           |               |               |               |            |
|   | <b>BP</b> | <b>Trim 1</b> | <b>Trim 2</b> | <b>Trim 3</b> | <b>PPP</b> |
| <b>BP</b>   | -         | -             | -             | -             | -          |
| <b>Trim 1</b>   | p=0.036*  | -             | -             | -             | -          |
| <b>Trim 2</b>   | p=0.011*  | p=0.071       | -             | -             | -          |
| <b>Trim 3</b>   | p=0.007*  | p=0.099       | p=0.713       | -             | -          |
| <b>PPP</b>  | p=0.889   | p=0.167       | p=0.090       | p=0.056       | -          |
| <b>Social anxiety 2<sup>nd</sup> pregnancy (n=11)</b>   |           |               |               |               |            |
|   | <b>BP</b> | <b>Trim 1</b> | <b>Trim 2</b> | <b>Trim 3</b> | <b>PPP</b> |
| <b>BP</b>   | -         | -             | -             | -             | -          |
| <b>Trim 1</b>   | p=0.070   | -             | -             | -             | -          |
| <b>Trim 2</b>   | p=0.016*  | p=0.014*      | -             | -             | -          |
| <b>Trim 3</b>   | p=0.010*  | p=0.010*      | p=0.102       | -             | -          |
| <b>PPP</b>  |           | p=0.414       | p=0.072       | p=0.011*      | p=0.007*   |
| <b>Social avoidance 2<sup>nd</sup> pregnancy (n=9)</b>  |           |               |               |               |            |
|   | <b>BP</b> | <b>Trim 1</b> | <b>Trim 2</b> | <b>Trim 3</b> | <b>PPP</b> |
| <b>BP</b>   | -         | -             | -             | -             | -          |
| <b>Trim 1</b>   | p=0.205   | -             | -             | -             | -          |
| <b>Trim 2</b>   | p=0.026*  | p=0.034*      | -             | -             | -          |
| <b>Trim 3</b>   | p=0.017*  | p=0.016*      | p=0.059       | -             | -          |
| <b>PPP</b>  | p=0.279   | p=0.776       | p=0.221       | p=0.042*      | -          |

Note: *P*-values of the post hoc analysis with the Wilcoxon Signed Rank Test on the retrospective social anxiety and avoidance scores before (BP), and during pregnancy (1<sup>st</sup> trimester = Trim 1, 2<sup>nd</sup> trimester = Trim 2, 3<sup>rd</sup> trimester = Trim 3), and in the postpartum period (PPP) as measured in the first and second pregnancy of the patients who reported an influence of pregnancy and postpartum period on social anxiety and avoidance.

Statistical analyses were performed only on data of patients who reported any influence of the female hormonal cycle on symptoms of social anxiety and avoidance. We report the analyses of the hormonal phases in which more than 10 subjects reported these influences. This was only the case for the menstrual cycle and pregnancy with postpartum period. Seventy-one percent of the patients who reported influences of the menstrual cycle also reported influences of pregnancy when applicable.





**Figure 2.** Means of social anxiety and avoidance scores (0-10) before (BP) and during pregnancy (1<sup>st</sup> trimester = Trim 1, 2<sup>nd</sup> trimester = Trim 2, 3<sup>rd</sup> trimester = Trim 3), and in the postpartum period (PPP) as measured in the first and second pregnancy of patients who reported an influence of pregnancy and postpartum period on social anxiety and avoidance.

### Menstrual cycle

A difference was found in social anxiety ( $p < 0.001$ ,  $\chi^2 = 39.2$ ,  $df = 3$ ,  $n = 23$ ) and avoidance ( $p < 0.001$ ,  $\chi^2 = 26.6$ ,  $df = 3$ ,  $n = 18$ ) between the 4 weeks of the menstrual cycle. The symptoms of social anxiety and avoidance were highest in week 4 of the menstrual cycle, and significantly different from week 1, 2 and 3. For more details, see Figure 1 and Table 2.

### Pregnancy and postpartum period

The group of patients that reported an influence of pregnancy on social anxiety and avoidance was not entirely the same as the group of patients that reported an influence of the postpartum period. We only included data of patients who reported an influence of both the pregnancy and postpartum period in the statistical analysis. This made it possible to compare the social anxiety and avoidance scores of the period before pregnancy, the three trimesters of pregnancy, and the postpartum period.

We found a difference in social anxiety and social avoidance between the period before pregnancy, all trimesters of pregnancy, and the postpartum period for the first pregnancy ( $p < 0.001$ ,  $\chi^2 = 27.4$ ,  $df = 4$ ,  $n = 12$ ;  $p < 0.001$ ,  $\chi^2 = 24.2$ ,  $df = 4$ ,  $n = 10$ ). The same results were seen for the second pregnancy ( $p = 0.003$ ,  $\chi^2 = 15.8$ ,  $df = 4$ ,  $n = 11$ ;  $p = 0.002$ ,  $\chi^2 = 16.8$ ,  $df = 4$ ,  $n = 9$ ). Social anxiety and avoidance were highest before pregnancy and in the postpartum period. During pregnancy, patients reported less severe symptoms. For details see Figure 2 and Table 3.

## Discussion

Most respondents did not report any influence of the female hormonal cycle on gSAD symptoms. However, the subgroup who did, reported more severe social anxiety and avoidance in the premenstrual period and, as opposed to our hypothesis less severe symptoms during pregnancy. In this subgroup, the vulnerability for the effects of the gonadal hormones on neurotransmitter systems associated with anxiety may be increased. If corroborated in further studies, it would be interesting to investigate whether this enhanced vulnerability is associated with fewer effects of treatments aimed at these neurotransmitter systems.

The literature on the influence of gonadal hormones on the course of anxiety disorders shows that these influences exist only in a subgroup of women. The premenstrual worsening of symptoms in a subgroup of women as shown in this study was also found in GAD, and obsessive compulsive disorder (OCD) (Hsiao et al., 2004; McLeod et al., 1993; Vulink et al., 2006; Labad et al., 2005; Williams and Koran, 1997). In one study on panic disorder (PD) an exacerbation of symptoms was also seen in the premenstrual period in some patients, whereas other studies in PD found no differences (Hsiao et al., 2004; Pigott, 1999; Breier et al., 1986; Kaspi et al., 1994; Stein et al., 1989; Cook et al., 1990; Cameron et al., 1988). The decrease of symptoms during pregnancy, as we found in gSAD, had previously been described in some, but not all, studies in PD (Hertzberg and Wahlbeck, 1999; Cohen et al., 1994; Klein et al., 1994; Altshuler et al., 1998). In OCD, the effects of pregnancy are not clear yet, as unchanged symptoms as well as worsening and improvement of symptoms were described (Vulink et al., 2006; Labad et al., 2005; Williams and Koran, 1997). In line with the present study, the same studies showed a postpartum increase of symptoms in a subgroup of OCD patients (Vulink et al., 2006; Labad et al., 2005; Williams and Koran, 1997).

There are also some limitations of the present study to discuss. As a result of the self-report survey and the retrospective nature of this study, the results are likely to be affected by a significant recall bias. However, in the absence of prospective studies, these retrospective data provide a first impression of the nature and extent of the influences of gonadal hormones in gSAD. Furthermore, no data were collected on the comorbidity between gSAD and premenstrual syndrome and premenstrual dysphoric disorder. Unfortunately, only 46% of the gSAD patients returned the surveys. This is mainly caused by the UMCU patients of whom we did not have recent addresses. In the LUMC group, of which we had recent addresses, the response rate was good (84%). However, we cannot rule out the possibility of responder bias, meaning that the women who believe in the influence of hormones on their gSAD symptoms or who experienced such an effect were more likely to respond. Our sample was not representative for the general population of female gSAD patients, as our respondents were prior participants in research studies in two university clinics. They were relatively highly educated and most of them had a job. Furthermore, we are not able to draw conclusions on differences in gSAD symptoms in OC use, lactation, and menopause, because of the small groups that were analyzed. Also the sub-analyses were carried out with very small sample sizes and therefore should be carefully interpreted. Other limitations are that there are many factors that could have influenced the gSAD symptoms besides the gonadal

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hormones. For example, during pregnancy and in the post partum period life changes dramatically, which we did not take into account in the present study.

The clinician should take into account that there probably is at least a subgroup of female gSAD patients whose symptoms are influenced by fluctuations in female gonadal hormones: they have more severe symptoms premenstrually and less severe symptoms during pregnancy. Prospective studies will have to elucidate how large this proportion is and how much influence the gonadal hormones have on symptoms and treatment effects. Ultimately, this may lead to more tailor made treatments for gSAD patients.

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