Q1 Original article

# Anxiety and depression symptoms among sub-fertile women, women pregnant after infertility treatment, and naturally pregnant women

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ABSTRACT

Background: Infertility has been associated with psychological distress, but whether these symptoms persist after achieving pregnancy via assisted reproductive technology (ART) remains unclear. We compared the prevalence of anxiety and depressive symptoms between women seeking for infertility treatment and women who conceived after ART or naturally.
Methods: Four hundred and sixty-eight sub-fertile non-pregnant women, 2972 naturally pregnant women and 143 women pregnant after ART completed a questionnaire in this cross-sectional study. The Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A$\geq$8) and Edinburgh Postnatal Depression Scale (EPDS$\geq$12) were used for assessing anxiety and depressive symptoms, respectively. Multivariate Poisson regression models with robust variance were applied to explore associations with anxiety and depressive symptoms.
Results: The prevalence of anxiety and depressive symptoms among sub-fertile, non-pregnant women (57.6% and 15.7%, respectively) were significantly higher compared to women pregnant after ART (21.1% and 8.5%, respectively) and naturally pregnant women (18.8% and 10.3%, respectively). History of psychiatric diagnosis was identified as an independent risk factor for both anxiety and depressive symptoms. The presence of at least one unhealthy lifestyle behavior (daily tobacco smoking, weekly alcohol consumption, BMI$\geq$25, and regular physical exercise < 2 h/week) was also associated with anxiety (Prevalence Ratio, PR: 1.24; 95%CI: 1.09–1.40) and depressive symptoms (PR: 1.25; 95%CI: 1.04–1.49).
Conclusions: Women pregnant after ART showed no difference in anxiety and depressive symptoms compared to naturally pregnant women. However, early psychological counseling and management of unhealthy lifestyle behaviors for sub-fertile women may be advisable, particularly for women with a previous history of psychiatric diagnosis.

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## 1. Introduction

Infertility is a problem for individuals wishing to start a family and is costly for society. Approximately 10–15% of those who try to conceive suffer from infertility and often turn to medically assisted reproduction. The number of assisted reproduction technology (ART) treatment per year has increased steadily [1]. Lifestyle factors including obesity, stress, smoking, and – most importantly – postponing parenthood until advanced age, are believed to contribute to reduced fertility [2]. Additionally, factors such as development of newer and more successful techniques for infertility treatment and increasing awareness of available services have led to increases in ART cycles [3].

The causal link behind the association between psychological distress and infertility remains unclear. Different psychological factors have been shown to affect reproductive ability. Proposed mechanisms involve the pathophysiology of the depressed state, such as elevated prolactin levels, disruption of the

hypothalamic-pituitary-adrenal axis, and thyroid dysfunction [4]. Lynch et al. have reported an association between salivary stress biomarkers and time to pregnancy in sub-fertile patients [5]. Anxiety and depression have been shown to result in lower rates of both natural pregnancy and assisted reproduction cycles [6,7]. On the other hand, fertility problems can also lead to significant psychological stress, depression, anxiety, guilt, social isolation, and low self-esteem in women [8]. The stress from non-fulfilment of the wish for a child has been associated with anger, depression, anxiety, marital problems, and feelings of worthlessness [9–11]. A negative association has been found between levels of anxiety and depressive symptoms at baseline or during ART procedure and reproductive outcomes (based on biochemical or clinical pregnancy rate) [12–14]. Psychological distress can have an adverse effect on patients, treatment, and health-care providers; experiencing symptoms of anxiety, depression, or both are unpleasant for the patient, and working with anxious and/or depressed patients poses challenges to their caregivers [15].

The scientific discussion about the psychological aspects of pregnancies after in vitro fertilization (IVF) shows contradictory results [16]. The heightened emotional state and anxiety after a long, arduous, and uncertain journey is believed to remain with the couple, certainly during early pregnancy and, for some, into the later stages [17–19]. The absence of a national policy regarding antenatal visits following assisted conception has created gaps in women's care after successful infertility treatment [20]. Few studies have investigated how women having conceived after fertility treatment experience their pregnancy.

Therefore, our study aim was to investigate the prevalence of anxiety and depression symptoms among sub-fertile women seeking infertility treatment, and to compare them to women who conceived after infertility treatment and women who conceived naturally.

## 2. Materials and methods

### 2.1. Design

This was a cross-sectional analysis of baseline measurements from two larger, longitudinal cohort studies.

### 2.2. Cohorts, participants and recruitment

#### 2.2.1. Sub-fertile cohort

Eligible women ($n = 882$) were invited to participate at their first visit to one of 10 fertility clinics in the central region of Sweden. Data collection took place from May 2013 through September 2015. Those who agreed to participate received a questionnaire to complete either at the clinic or at home (returning it by mail in a prepaid envelope). Of 882 eligible women, 784 (94.5%) agreed to participate and 485 (61.9%) completed the study. The final sample for analyses was 468 sub-fertile women who had a male partner. Further details on this cohort can be found in previous work [21]; it should be noted though that, in the current study, the number of participants is higher as a result of ongoing recruitment of participants in the meantime. The mean duration of infertility in the sub-fertile group was 1.8 years. In this cohort, 13.2% of the women used tobacco daily, 13.6% drank more than three cups of coffee per day, 11.6% consumed more than two glasses of alcohol weekly, 23.9% were overweight (body mass index, BMI 25–29.9 kg/m$^2$), and 12.5% were obese (BMI $\geq$ 30 kg/m$^2$).

#### 2.2.2. Pregnant cohort

Pregnant women ($n = 5493$) were recruited in the context of a cohort study. Particularly, they comprised pregnant women who consecutively visited any of the 153 antenatal clinics in the central and northern Sweden between the period September 2012 and July 2013. These women received written and oral information and were invited by a midwife to participate at registration at the antenatal clinic. Swedish-speaking women were offered a questionnaire to complete at the clinic or at home (returned after completion by mail in a prepaid envelope). Non-Swedish-speaking women provided written consent and were offered a questionnaire in English or Arabic. Details of this cohort can be found in previous article [22]. Among the 5796 women who were registered at the clinics, 5493 were invited to participate; among these, 90% ($n = 4968$) agreed to participate.

A total of 68% of women completed the study ($n = 3389$), 98% of whom used the Swedish questionnaire. Women aged 19–42 years with a male partner ($n = 3115$) were included in the current analysis so as to match the sub-fertile group.

For the purposes of these analyses, the pregnant women were divided into two subgroups based on self-report: those who had conceived after ART ($n = 143$) and those who had conceived naturally ($n = 2972$). A flowchart describing participant recruitment is presented in Fig. 1; a detailed description of this study's material has also been previously reported [21,22].

### 2.3. Instruments

A draft of group-specific (i.e., for pregnant and sub-fertile non-pregnant women) questionnaires was developed by the research team of experienced researchers and clinicians. A questionnaire was initially designed for pregnant women registered at antenatal clinics; questions were thereafter adapted for sub-fertile women at their first visit to a fertility clinic in the same region. Most items were designed as multiple-choice questions. For the questionnaire for the pregnant group, a pilot study was conducted among 270 women [23] and revisions were made based on these results and feedback. The final questionnaire consisted of 148 items for the pregnant women group and 71 items for the sub-fertile women group.

Domains covered included: age; partner's age; height and self-reported weight; country of birth; level of education; occupation and monthly household income; duration of infertility; and medical and reproductive history. Questions regarding lifestyle behaviors during the period when the woman tried to conceive covered: intake of folic acid and/or multivitamin supplements; daily tobacco use; weekly alcohol consumption (consumption of at least one unit of alcohol per week); daily coffee consumption; type of diet; and weekly physical activity (graded in number of hours).

The questionnaire also included instruments for assessment of psychological distress that have been specifically validated for use with both pregnant women and the general population. The anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) and the Edinburgh Postnatal Depression Scale (EPDS) were used for the assessment of anxiety and depression symptoms, respectively. Participants were classified according to their HADS-A score as normal (0–7), possible case (8–10) and case ($> 10$) [24]. For the EPDS, a score of $\geq 12$ points was considered indicative of depressive symptoms, as recommended for pregnant women by the Swedish Council on Health Technology Assessment (SBU) [25]. Although EPDS is originally validated for the peripartum period, we also used it for assessment of depressive symptoms among sub-fertile non-pregnant women for reasons of comparability between the groups. We preferred EPDS over a depression screening test for the general population due to the unique features of depression during pregnancy (2 of the 3 groups comprised of pregnant women) that are not addressed by general population instruments. Further, EPDS has been validated and shown to perform well on screening for major depressive episodes in community general population samples, although a lower cut-off