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Review article

Depression during the perimenopause: A meta-analysis

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ABSTRACT

Background: Women are believed to be more vulnerable to develop a depression or depressive symptoms during the perimenopause. Estimates from individual studies are heterogeneous and hence true risk estimate is unknown.
Objective: This study investigated the risk on clinical depression and depressive symptoms during the perimenopause when compared to other female hormonal stages.
Methods: We performed a meta-analysis of 11 studies identified in Pubmed, Web of Science and the Cochrane library (up to July 2015). Studies were included when the perimenopause was defined according the criteria of Stages of Reproductive Aging Workshop (STRAW). The outcome measures were Odds Ratio's (OR) on depression diagnosis and depressive symptoms and standardized mean difference (Hedges's g) in depression scores during each menopausal stage.
Results: The odds to develop a *depression* were not significantly higher during the perimenopause than in the premenopause (OR=1.78 95% CI=0.99–3.2; p=0.054). A higher risk was found *on depressive symptoms* during the perimenopause as compared to the premenopause (OR=2.0, 95% CI=1.48–2.71; $p<0.001$) but not compared to the postmenopause (OR=1.07, 95% CI=0.737–1.571; $p=0.70$). There was a higher *symptom severity* of depression in the perimenopause when compared to the premenopause (Hedges's $g=0.44$, 95% CI=0.11–0.73, p=0.007). The odds on vasomotor symptoms and depression were 2.25 (95% CI=1.14–3.35; $p<0.001$) during the perimenopause.
Limitations: Time interval in measuring the depressive symptoms was different in studies. Menopausal symptoms possibly may have confounded our results by increasing the scores on depression questionnaires. Publication bias needs to be considered.
Conclusion: The perimenopause is a phase in which women are particular vulnerable to develop depressive symptoms and have higher symptom severity compared to the premenopause. There are indications that vasomotor symptoms are positively related to depressive symptoms during menopausal transition.

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1. Introduction

The perimenopause is the transitional phase to non reproductive life. During the perimenopause ovarian follicular function declines, leading to fluctuating and in the end decreased levels of estrogen and progesterone and high levels of Follicle Stimulating Hormone (FSH). The presence of the hormonal fluctuations during perimenopause results in menstrual cycle irregularity (Burger et al., 2008; Gibbs et al., 2013), vasomotor instability (WHO, 1996) and cognitive (Weber et al., 2013), metabolic (Liczano and Guzmán., 2014), and somatic changes (Ripa et al., 2015).

Definitions for the different menopausal stages have been changed over the years. Before 2001, the perimenopause was described as a phase with changed lengths of the menstrual cycle length compared to the established premenopausal pattern (McKinlay et al., 1992; WHO, 1996). In 2001 consensus was reached with the Stages of Reproductive Aging Workshop (STRAW) criteria for defining menopausal stages (Soules et al., 2001). The STRAW criteria provide a uniform definition to determine the menopausal stages. The premenopausal phase is based on a bleeding pattern with regular menstrual cycles in the 22–35 d range. The perimenopause is characterized by changes in cycle length of 7 days or longer in either direction from the participant's own baseline for at least 2 cycles to 11 months of amenorrhea. Women in the postmenopausal phase have amenorrhea for at least 12 months. These strict definitions for menopausal stages pave the path to comparability of studies on this topic.

Although the majority of women do not experience negative mood consequences during menopausal transition, the risk to develop a (major) depression or depressive symptoms during perimenopause is higher than in the premenopausal stage (Bromberger et al., 2011; Soares and Zitek, 2008). However, estimates from individual studies are heterogeneous and hence the true risk estimate is unknown.

The aim of this study is to determine the risk of depression and depressive symptoms during the perimenopause compared to the pre- and postmenopause by meta-analysis. A secondary objective is to determine if vasomotor symptoms and depression are related during the perimenopause. In our analyses the strict STRAW menopausal criteria (Soules et al., 2001) will be followed in order to obtain as much uniformity as possible.

2. Methods

We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement as a guideline for this study (Moher et al., 2009).

The database of Pubmed, Web of Science and Cochrane library have been systematically searched for published papers, or papers that were published advance online before up to July 2015.

Combinations of search terms 'depression' and 'depressive disorder' with 'climacteric, 'perimenopause', 'menopause', 'female hormones' and 'gonadal steroids' have been used. Exclusion terms as 'bipolar disorder', 'drug abuse', 'premature ovarian failure' and 'breast neoplasm' were applied with the restriction 'human' and 'female'. The search was performed by two independent researchers. In case of uncertainty or incongruences the researchers discussed the concerning paper and agreed at all times.

A total of 2495 articles have been found (see Fig. 1 for the flow chart). In order to be included, studies had to: (1) apply the STRAW criteria (Soules et al., 2001) to define menopausal status, (2) use a (semi-) structured interview for a depression diagnosis (captured by a DSM diagnosis (APA, 2000)), standardized questionnaires for depressive symptoms or symptom severity and (3) to report sufficient data to perform a meta-analysis. In case of (partly) overlapping study populations among papers, we chose to stay with the largest *N* or the longest follow-up. In case of lack of usable data, the corresponding authors were asked by email to provide the necessary information.

Comprehensive Meta-Analysis (CMA) software (Borenstein et al., 2006) was utilized to perform the meta-analysis. Random Effect models were used to estimate the overall summarized (log) odds ratios and 95% Confidence Interval (CI) on a diagnosis of depression or an above cut-off depressive symptom score as a function of menopausal status. Hedges' g was used as effect-size estimate for potential differences in continuous depressive symptom severity scores among the different menopausal phases. Possible heterogeneity was assessed by the I^2 and assessed for statistical significance using the Q statistic (Higgins et al., 2003). The potential moderators age, depression questionnaire and duration of study were related to outcome. Results were considered statistical significance at $P < 0.05$. There were no patients or direct patient data involved in this study. Yet, the objective to study this topic is driven by questions from patients in the target population on their odds on perimenopausal depression.

Eleven studies met the inclusion criteria and were evaluated in this analysis. In 2 publications (Bromberger et al., 2010; Woods et al., 2008) perimenopausal data were split according to early and late perimenopausal phase. Outcomes were pooled to obtain data about the perimenopausal stage as a whole for the second mentioned publication (Thierney et al., 2007). For the study of Bromberger et al. (2010), this was not possible due to lack of data on the number of subjects that were either in the early or the late perimenopausal phase. The results of this particular study on presence of depressive symptoms were entered in CMA twice as perimenopausal versus early and late premenopausal.

3. Results

Table 1 shows a summary of the studies that have been included. The number of women included in the studies ranged from 138 to 3296 subjects, with comparable mean ages at baseline. There were 5 studies with a longitudinal design, 6 studies were cross sectional. The time interval for measurements in longitudinal studies differed between studies: from every 6 months (Cohen et al., 2006) to annually (Bromberger et al., 2010). Only one study published the data on women without a history of depression (Cohen et al., 2006).

3.1. Clinical depression

Two longitudinal studies described the odds to develop a depression during the perimenopause compared to the premenopause (total N=874) (Cohen et al., 2006; Freeman et al.,