Research Article

# Trends, Prevalence, and Risk Factors of Anti-Depressant Use in Women of Reproductive Age Group

**Sabahat Asif[1], Sabeen Shafique[2], Safoora Saqib[3], Saira Qazi[4], Saira Shamim[5], M. Tayyab Khalid[6], M. Tayyab Mehdi[7], M. Umais[8], M. Umer Hassaan[9], M. Usama Khokhar[10], Faiza Aziz[11], Saira Tariq[12], Muhammad Tufail[13]**

*(13) University Hospitals of Leicester NHS Trust, United Kingdom.*
*(1-11) King Edward Medical University Lahore, Pakistan.*

**Abstract:**

**Background:** Major Depressive Disorder (MDD) is a psychiatric illness marked by a constant feeling of despair and alienation for two weeks that manifest as a hurdle in daily life activities. Depression is more prevalent in women owing to biological and psychosocial factors. Despite the severe outcomes of antidepressant use on mother and child, the prevalence rate in developed countries like USA and Netherlands is 8.7% and 2 % respectively. In this study, we are studying the trends, prevalence, and risk factors of antidepressant use among women of the reproductive age group.

**Methods:** The present systemic review is conducted using PRISMA guidelines and registered in PROSPERO. The search engines were PubMed, Google Scholar, and Science Direct. All those which didn't match the title, in other languages, and were duplicated were excluded from the study. The screening was done based on abstracts. Selected articles were studied and data was finalized.

**Results**: The risk factors in the reproductive age group are loneliness, marital conflicts, many Children, postpartum blues, postpartum depression, physical and sexual abuse, gender, cultural and racial differences, and socioeconomic status. The use of antidepressants gradually increased from 1995 to 2001 followed by a sharper increase till 2004 with a subsequent reduction in usage due to perinatal complications. The prevalence rate for antidepressant use is increasing steadily in developed countries with two third being SSRIs.it later on decreased or remained constant due to warnings.

**Conclusion:** The main risk factors are postpartum depression, gender differences, physical and sexual abuse, and poor socioeconomic status. The use of antidepressants increased followed by a decrease in later years. The prevalence rate varied geographically with most prevalence classes being SSRIs, SNRIs, and TCAs

**Corresponding Author:** Sabahat Asif

**Supervisor**: Dr. Saira Tariq | Department of Community Medicine, KEMU, Lahore

**Keywords:** Antidepressants, risk factors, prevalence, trends.

## INTRODUCTION:

Major Depressive Disorder (MDD) is a psychiatric illness marked by a constant feeling of despair and alienation for at least 2 weeks that manifests itself as a hurdle in daily life activities, cognitive impairment, asthenia, anorexia, insomnia, irresoluteness, and suicidal thoughts. Depression is a common mental health problem among the general population including the reproductive age group. A population-based epidemiological study has proved that the prevalence of depression is 21.3% in women and 12.7% in men. (1) Several studies have shown that anti-depressants are being used by women during all reproductive phases of their life – premenstrual stage, pregnancy, and the postpartum period.

Depression is more prevalent in women owing to biological and psychosocial factors such as hormonal changes, menopause, childhood abuse, tragic life experiences, parenthood, old maternal age, infertility, family issues, and the burden of responsibilities. Changing hormonal milieu in adolescence and other socioeconomic factors lead to a greater incidence of the first depressive episodes during young adulthood. (2) The gradual transition from menarche to menopause contributes to episodes of depression during different reproductive life stages.

The prevalence of prescribed antidepressants during pregnancy has been estimated to be approximately 2% in the Netherlands and 8.7% in the USA. (3) Antidepressant prescribing rates increased steadily from 1995-2001 followed by sharper increases from 2002-2004. (4) Another study has proved that the prevalence increased six folds from 1997-2011 but decreased sharply thereafter. (5) Despite the severe outcomes of antidepressants both on the mother and the fetus/child, they are still being prescribed by physicians due to the alarming increase in depression among women of childbearing age.

Many studies have thrown light on the fact that antidepressant prescriptions during gestation are less than the postpartum and other phases of reproductive life. The prevalence of antidepressant use in one year after birth was higher than antidepressant use during pregnancy but lower than antidepressant use in one year before pregnancy. (5) Considering the negative impact of antidepressants on the developing fetus, women tend to prefer non-pharmacological interve-ntions which have lessened the use of antidepressants among women over the years.

To our knowledge, there has been no review article on the prevalence and trends of antidepressant use among women of the reproductive age group. This study specifically summarizes the prevalence and trends of antidepressants.

## METHODS AND MEASURES:

### 2.1 Search Strategy:

The literature search was conducted for published articles in English from the inception of time till 12th June 2022. Three search engines are used for this systematic review; PubMed, Google Scholar, and Science Direct. The keywords used were “Antidepressants” OR “Trends” OR “Prevalence” OR “Risk Factors” OR “Pregnancy” OR “Women of Reproductive Age”.

### 2.2 Study Selection:

The inclusion criteria were applied to collect the

articles with study designs like cross-sectional, cohort, systematic review and meta-analysis that described trends, prevalence and risk factors of anti-depressants among females of reproductive age on the above-mentioned search engines were searched, studied, and isolated. The exclusion criteria were applied to all those articles, papers, and systematic reviews and meta-analyses that didn't match our title, and study designs and were published in languages other than English. Duplicate articles were also excluded.

### 2.3 Data Extraction:

The data extraction was done in four groups. Two groups used the search engine Google Scholar. One group searched PubMed and the remaining group studied Science direct. The related articles were selected and inclusion-exclusion criteria were applied to them. The data extracted from the included articles were based on the general study characteristics (the first author, year of publication, study design, and duration of study), the relevant aspects of the articles (trends, risk factors, and prevalence of the antidep-ressant use in women of reproductive age) and the main outcomes.

First, we selected articles relevant to our title of study, and then trends, prevalence, and risk factors for the use of antidepressants in reproductive-age females were studied. The reproductive age group selected was 15-49 years according to the WHO definition of reproductive age for females. The data regarding the title was screened based on the abstracts of the selected articles. The full articles were studied and the data was finalized.

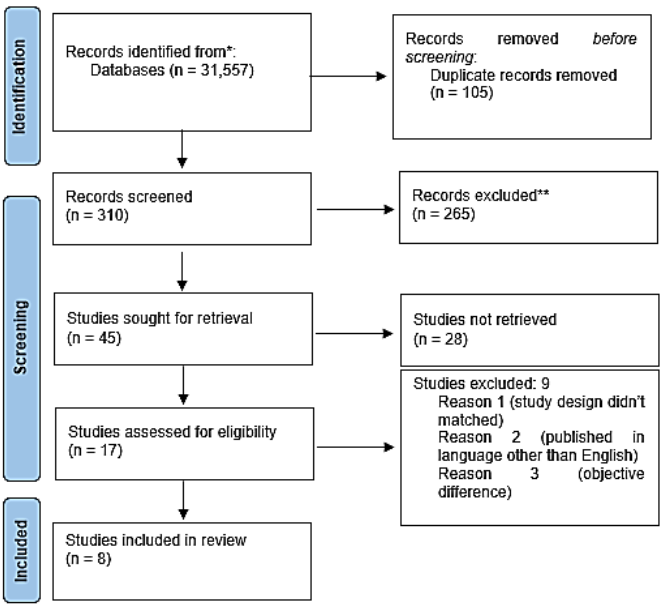


**Figure 1;** Flowchart for literature search and study selection

## RESULTS:

### 3.1 Trends of anti-depressants (AD) use:

Major depressive disorder is a serious concern in women whose rate in women is twice as seen in men (Lee S. Cohen MD). There is about five-fold increase in use of anti- depressants from age group 15-19(4.8%) to the age group 40-45(24.6%)(6). US Food and drug administration (FDA) in June 2004 and health Canada two months later issued health advisory warnings related to the risk of perinatal complications of anti-depressants. For many years selective serotonin reuptake inhibitors (SSRIs) were consid-ered safe for use in pregnancy but these warnings changed the trend of anti-depressants use as there was a gradual increase in anti-depressants use from 1995 to 2001 which followed a sharper increase between 2002 and late 2004. After that, there was a reversal of this trend as there was a decrease in anti-depressants usage. However, some studies also showed there was no subsequent decrease in anti- depressants prescriptions after 2004(4).

The first SSRI fluoxetine was introduced in 1987 which was followed by serotonin and norepinephrine reuptake inhibitors (SNRIs). After 25 years these two especially SSRIs substituted TCAs in North America, most of Europe, and Asia as main anti-depressants(3). There are different trends of anti-depressants use across different countries like SSRIs in Europe, TCAs in Germany, Citalopram in Denmark, Sertraline in Iceland, and Escitalopram in Norway. In Denmark, overall trends of anti-depressants prescription from 1997 to 2011 increased steadily but then decreased sharply thereafter in 2016. However, the use of anti-depressants was lower during pregnancy as compared to their use in the year before and after pregnancy(5). Another study showed that women using antidepressants before pregnancy shifted to other classes of antidepressants during pregnancy. 6.1% of women switched to another type of anti-depressants during the first trimester. SSRIs were the most switched class (1.6%) followed by serotonin modulators (1.2%) and SNRIs (1%). Paroxetine (1%) and venlafaxine (1%) were the anti-depressants to which women shifted the most (7)

### 3.2 Prevalence:

In the national co-morbidity survey, the prevalence rate for major depression was 21.3% for women and 12.7% for a man. The female-to-male ratio ranges from 1.6 – 3.1 for major depressive disorder(8). The prevalence of major depressive disorder in Europe is estimated to be 3.0 to 11.2%. In North America, rates of prenatal and postpartum depression rates were 12%-18% (9). In Europe and North America, anti-depressants use had been increasing steadily. In 2009, the prevalence of anti-depressants prescription was estimated to be 16.3% out of which two-thirds were SSRIs. The prevalence of different anti-depressants classes was as; 12.6%, TCA 2.7%, MAOI 0.0%and other antidepressants 2.9%(6). There were different prevalence rates of anti-depressants reported in different countries. For example, in Italy in 1999-2004, it was between 5.9% and 11.6%. In Germany in 2000-2002, it was 10.2%. In a Pan-European study from 2001-2003, the prevalence rate was 5.8%. In Canada in 2002, it was 7.6%. In the USA from 2001-2003, it was 13.8% and in 2005 it was 13.4(6).

In another study, overall anti-depressants prescribing prevalence increased by the rate of 0.046 prescriptions per 1000 women per month until May 2004 which was the period just before USA FDA and Health Canada warning. After this warning, the prevalence decreased by 1.48 prescriptions per 1000 women per month. However, in a larger study of pregnant women in the US, 8.1% of anti-depressants were used during pregnancy from 2000-2007 suggesting that these warnings didn't bring significant changes in the prevalence(4). A study in the Netherlands indicated that anti- depressants prevalence (SSRIs and TCA) was 2%. A national birth defect prevention study estimated the increased anti-depressants usage in pregnancy was 300% from 1998-2005(3). In Denmark, the anti-depressants prescriptions in pregnancy rose gradually from 0.4% in 1997 to 4.6% in 2011. Then decreased to 3.1% in 2016(5). The most prevalent classes of anti-depressants used during pregnancy were SSRIs (64.4%), SNRIs (12.3%), and TCAs (12.1%). The

least used class was MAOIs (0.1%) (7).

### 3.3 Risk factors:

The studies showed that hormonal changes in females contribute to mood changes and depression. The prevalence rate of depression shows a dramatic shift in adolescence (2). Progesterone levels during the luteal phase of the menstrual cycle play a role in premenstrual syndrome and similar hormonal changes result in depression during the premenstrual period, during menopause, and as side effects of oral contraceptives. The pre-menstrual dysphoric disorder is another risk factor if depression, serotonin being a hormonal stimulus for depression in PMDD(1) Similarly, pregnancy is another important risk factor for depression. The prevalence of depression during pregnancy has a prevalence of 25-35% with 10% meeting the criteria of a major depressive disorder(1). Another study indicates a 9% prevalence rate of major depression in pregnant women(7) The risk factors for depression in pregnancy include a history of depression, younger age, loneliness, marital conflicts, a large number of children, closely spaced pregnancies, death of some significant person or previous children and comorbid illness(1)

Postpartum blues is another risk factor for depression that occurs in a new mother 2 weeks after delivery. 50% to 80% of women experience postpartum blues and about 25% of women are affected with major depression (1) Postpartum depression is another risk factor for anti-depressants usage. The shift from normal menstrual cycles to the cessation of menses-premenstrual transition- is also a contributor to depressive episodes(2) The hormonal changes involved in menopause include a decrease in estrogens, FSH, inhibin, activing, follistatin, and insulin-like factors. The decrease in estradiol levels is the major contributor to depression due to menopause (1)

Gender differences are also a risk factor, as the studies show higher, approximately twice, incidence rates of depression in females as compared to females. By the age of 18, a consistent female: male ratio of 2: 1 is seen in America. Some studies show a genetic role in vulnerability to depression and further evidence suggests that this genetic vulnerability is more pronounced in females than males(2). Race discrimination is another chronic stressor for depression in women. Studies also show that women are more likely to suffer from major depression due to a stressful life event(2) Physical and sexual abuse is also a major cause of depression in women. The lifetime prevalence rate of depression is almost double (52%) in victims of childhood rape than it is for non-victimized women (27%)(2). Similarly, the prevalence rate of depression in battered women is 48%. Childhood physical abuse is also a strong predictor of depression in adult life. (2) Poverty and socioeconomic status are also a stressor that leads to depression.

The National Health and Nutrition Examination Survey III indicates that ethnic-racial differences also contribute to depression and it also affects types of depressive disorders. Dysthymic disorder affects Black Americans and Mexican Americans more ($P < 0.05$), whereas white Americans have a higher susceptibility for major depressive disorder ($P < 0.01$

and P = 0.05, respectively). On the other hand, although black Americans have less chance to get major depressive disorder than white Americans when they suffer from it, it tends to be more severe and chronic(2) The research data shows that 10.4% of African Americans, 17.9% of non-Hispanic white Americans and 12.9% of Caribbean black Americans had the major depressive disorder at some point in life irrespective of education and income differences(2) Cultural differences also contribute to depression. The lifetime rate of depression in females born in Mexico, or immigrant Mexicans, or that have not migrated is less (8%). However, the rate increases significantly in females who migrated from Mexico to the United States (2).

**TABLE 1 A summary of relevant studies**:

| Title | Author | Year of Publication | Study Design | Main Outcome |
|---|---|---|---|---|
| Prevalence and predictors of antidepressant use in a cohort of pregnant women | Ramos | 2007 | Retrospective Longitudinal cohort | Antidepressant utilization clines once pregnancy is diagnosed |
| The effect of regulatory advisories on maternal antidepressant prescribing, 1995-2007: An interrupted time series study of 228,876 pregnancies | Bobo W | 2014 | Cohort | Antidepressant prescribing to pregnant women in Tennessee Medicaid increased from 1995–late 2004. |
| Trend of antidepressants before, during, and after pregnancy across two decades—A population-based study | Sun Y | 2019 | Population-based Study | Prescription of ADs during pregnancy in Denmark increased steadily from 1997 to 2011 but decreased sharply thereafter. |
| Risk factors for hospitalizations associated with depression among women during the years around a birth: A retrospective cohort study | Fairthrone J | 2019 | Retrospective cohort | Barriers to treating depression with ADs in mothers from low-income areas during the years around a birth might contribute to their increased risk of a HAWD associated with non-pharmacologically treated depression. |

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|---|---|---|---|---|
| Gender-Specific Considerations in the Treatment of Mood Disorders in Women Across the Life Cycle | Cohen L | 2003 | | The successful diagnosis and treatment of depression disturbance in mood may be seencoincident with crit – ductive biology such as during the time prior to m – menopause. |
| Psychosocial and Cultural Contributions to Depression in Women: Considerations for Women Midlife and Beyond | Keita G | 2007 | | One of the explanations for the higher rate of depression in women is that women have a greater incidence of first depressive episodes, which often begin during adolescence or young adulthood. |
| The use of antidepressant medication in pregnancy | Ray S | 2014 | | Similarly, antidepressant use during the perinatal period should be considered carefully with all the evidence being equally and impartially weighed. |
| Prevalence and sociodemographic patterns of antidepressant use among women of reproductive age: A prescription database study | Wemakor*A* A | 2014 | Prescription database study | Antidepressant use is high among women of childbearing age in NI and increases with age and socioeconomic deprivation. |
| Depression in women | Nobel R | 2005 | | Depression in women may develop during different phases of the reproductive cycle (premenstrual dysphoric disorder, depression during pregnancy, postpartum depressive conditions, and menopausal depression). Other reproductive events such as infertility, miscarriage, oral contraceptives, and hormone replacement treatment have been reported to cause depression in women. |

## DISCUSSION:

In this systematic review, we screened journal articles and selected which reported sufficiently similar outcomes and results related to the worldwide use of antidepressants amongst women of reproductive age. The existing literature either separately studied the adverse effects of antidepressants or provided prevalence statistics across individual countries. Almost none of the available studies explicitly addressed the collective causes, determinants, and risk factors combined with prevalence studies. Consequently, a literature gap existed which warranted the need for this systematic review. Our review identified twice the rate of major depressive disorder and subsequent prescription of antidep- ressants in women as compared to men. When stratified results were looked upon, a nearly fivefold increase in usage was observed in the age group of 40-45 as compared to 15-19.

Existing reviews on clinical depression in women have focused on particular risk factors and thus have been able to comment on the leading causes irrespective of age group. These include both biological and psychosocial factors. Childhood abuse, traumatic life experiences, the burden of responsibilities, pregnancy, hormonal changes, ethnic racial differences, socioeconomic factors, and genetic vulnerability of the gender were identified as repeated major findings across such studies. Our review focusing solely on reproductive ages interpreted these results to deduce that postpartum hormonal changes, pregnancy, and the gradual transition from menarche to menopause were the leading risk factors in the population under study. However, more contextual and longitudinal qualitative research focusing on the different phases of reproductive life would be needed to fully address and identify age-specific risk factors.

Several individual reviews provided promising results regarding the frequency of prescription of antide-pressant drugs throughout the reproductive life cycle of women. The most notable trends depicted an increase in prescription rates of up to six fold from 1997 to 2011. The highest prevalence rate for any given country during this period was 13.8% in the USA during 2001-2003 while a study spanning European and North American countries showed a prevalence of 16.3%. A notable decrease in both prescription and usage was then observed during the last decade from 2011 onwards till 2017. Upon analysis, our review attributes this decrease in prevalence to increased warnings by health authorities regarding the adverse health effects of antidepressants and the subsequent perception by pregnant women. A prominent finding was that prevalence during pregnancy was lesser than that of the year before and after gestation. This finding may be attributed to the preference of pregnant women for non-pharma-cological interventions due to the unfavorable effects of antidepressants on fetal health. However, this interpretation should be approached with caution as this review did not include studies on the perception of drug effects.

It must also be acknowledged that the studies included in this article, with a few exceptions, were all from Anglo-Saxon, Northern European, and North American countries and thus the prevalence may not be representative of a universal trend. This review is also subject to intrinsic limitations of publication bias as only literature in the English language was included. Another limitation was the unavailability of data on the actual usage of antidepressants and thus there may be discrepancies between the prescription frequency and actual usage.

## CONCLUSION:

This qualitative review has analyzed the literature on the risk factors and prevalence of anti-depressant usage by reproductive age group females. Many gaps in the existing literature were addressed and this review identified key themes in both risk factors and prevalence. This review will help in the improvement of public health policies regarding the well-being of women. This study will help to understand the importance of prompt diagnosis and treatment plans for depression in women and devise actions that can make life easier for mothers around the world. More

comprehensive studies will help to fully understand and contextualize the varying trends and draw firm conclusions. Age-specific studies over wider geographical areas would be a welcome addition to the limited existing literature.

## ACKNOWLEDGMENTS:

We would like to express our sincere gratitude and appreciation to Dr. Muhammad Tufail, Dr. Saira Tariq and Ms. Faiza Aziz for their unwavering support and assistance in this research work. Their valuable guidance and input have been instrumental in ensuring the success of our publication. We are truly grateful for their contributions.

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