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Original Research Article

A cross sectional study on antipsychotic induced amenorrhoea in women attending a tertiary care centre in South India

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ABSTRACT

Background: Absence of menstrual period in a woman of reproductive age group could be physiological or pathological. Ascertaining the cause for this is a common clinical scenario faced by physicians. It is also a common clinical problem in women who are on treatment with antipsychotic medication. This cross-sectional study aimed to assess the occurrence of antipsychotic induced amenorrhoea among women aged 18-45 years, attending outpatient services of a tertiary care setting, the factors associated and to assess the effective strategies of treatment.
Methods: Retrospective chart review of clinical details of women in the reproductive age group who fulfilled the inclusion criteria was carried out. They were divided into two groups: Group A included 84 women with antipsychotic induced amenorrhea and Group B included 94 women on antipsychotics and had normal menstrual cycles. Various factors and strategies which worsened or alleviated the symptoms were noted.
Results: Women who were less than 35 years of age, on antipsychotic treatment for more than two years duration (52;83.9%) and those who were on treatment with Risperidone (69;73.4%) were identified as having the risk of developing antipsychotic induced amenorrhoea. The strategy of switch of medication to prolactin sparing antipsychotic was more effective in regularising the menstrual cycles (43;87.8%).
Conclusions: In women presenting with amenorrhoea, a possible medication induced aetiology need to be considered, especially use of antipsychotics. Further understanding of the complexities of this relationship may help to guide the assessment and proper treatment of women with antipsychotic related amenorrhoea.

Keywords: Amenorrhoea, Antipsychotic, Hyperprolactinemia, Risk factors

INTRODUCTION

The word "menstruation" in the minds of women is associated with femininity, youth, fertility, and health. In many cultures, menarche is celebrated as an event in the family and community. In African tradition, menstruation and menstrual blood is given a special place as they believe it carries life.[1] The transition of a girl to a woman following menarche is considered as a mark of womanhood.[2]

The absence of menstrual period in a woman of reproductive age is 'amenorrhoea', which could be physiological or pathological. Physiological or natural amenorrhoea is seen in childhood before the onset of puberty. Pregnancy, lactation and menopause are some of the natural causes of amenorrhoea and are given special importance in women's lives. Pathological amenorrhoea which can be classified as primary and secondary amenorrhoea can occur due to various causes. Primary amenorrhoea could be due to chromosomal or anatomical abnormalities resulting in failure to attain menarche. In

secondary amenorrhoea, menarche occurs normally, followed by the cessation of a regular menstrual cycle for three months or cessation of an irregular menstrual cycle for six months. More than half of the cases of secondary amenorrhoea are due an imbalance in the hypothalamo pituitary adrenal axis.[2] Some of the causes of secondary amenorrhoea are polycystic ovary syndrome (PCOS), hypothalamic amenorrhoea, hyperprolactinemia, or primary ovarian insufficiency. An understanding of the neuroendocrine causes of amenorrhoea is therefore critical when evaluating patients presenting with these complaints in order to implement the most appropriate treatment regimen.

Reproductive functioning in both sexes is influenced by the pituitary derived hormone, Prolactin (PRL). A raised prolactin level, biochemical hyperprolactinemia, is seen in 10% of the general population.[3] Hyperprolactinemia causes anovulation, amenorrhoea, galactorrhoea, and sexual dysfunction.

Prolactin secretion is under the dual control of thyrotropin releasing hormone (TRH), a stimulatory hormone which increases prolactin secretion and dopamine which inhibits prolactin secretion. The former is the cause for primary hypothyroidism causing menstrual irregularities and the latter is the mechanism most commonly seen in medication induced amenorrhoea. Increase in cortisol levels secondary to stress can also decrease the Gonadotropin-releasing hormone (GnRH) secretion. It also decreases the reproductive functioning at hypothalamus, pituitary and uterine levels. This results in Functional hypothalamic amenorrhoea (FHA) in women.[4]

Antipsychotic induced amenorrhoea is a common but neglected adverse effect in clinical practice.[5] It is the earliest sign of hyperprolactinemia with prevalence rates of approximately 45% for oligomenorrhoea/amenorrhoea and 19% for galactorrhoea.[6-8]

Elevation of prolactin levels occurs within a few minutes to hours of treatment initiation and persists with long-term treatment. 54% of males with a diagnosis of schizophrenia who are taking antipsychotics experienced moderate to severe sexual dysfunction and 91% of females reported menstrual changes.[9] As early as 1956, Polishuk et al reported the prevalence of amenorrhoea on antipsychotics as 15-97% with the use of typical antipsychotics. Different antipsychotic medications vary in their potency as well as in their hyperprolactinemia inducing property. Prolactin levels begin to rise within few hours following risperidone use, reaching their maximum by 8 weeks and thereafter, the high levels are maintained.[9] Depot preparations have a longer duration of effects, as long as six months.[9] In an extensive study conducted in India, the prevalence of amenorrhoea in women on Risperidone was 60%.[7] Among atypical antipsychotics, the worst offenders were Risperidone and Amisulpride.[10,11] In a 1-day point prevalence assessment, the prevalence of amenorrhoea in patients taking Risperidone was 48%, even at a relatively low dose of 2 mg/day.[12]

It is important to make an effort to identify cause of amenorrhoea in a clinical setting as it indicates possible underlying mental health conditions. Also, persistently raised prolactin levels are associated with endometrial and breast cancer and osteoporosis.[9,13]

Abnormalities in menstrual cycles are associated with several psychological abnormalities that include apprehensions of infertility, lowered mood and quality of life. Other phenomenological problems that could arise from amenorrhoea include delusions of pregnancy or pseudocyesis or denial of pregnancy and delusions of pseudo transsexualism (hirsutism in hyperprolactinemia).[5,12]

If unaddressed, it can affect compliance with treatment in women suffering from schizophrenia or other psychotic disorders.

In clinical practice, the history of amenorrhoea alone suffices for intervention as it is indicative of twice the normal prolactin level (corresponds to 60-100ng/ml).[6] Clinical guidelines state that basic laboratory investigations should be done to exclude other aetiologies for menstrual dysfunction as well as follow a hierarchical therapeutic approach. Basic laboratory measurements include prolactin levels, thyroid stimulating hormone levels, urine pregnancy test and renal function parameters. Management includes considering change of antipsychotic to prolactin sparing agents like Olanzapine, Quetiapine and Aripiprazole as first line therapy, augmentation with Aripiprazole as second line and combination therapy with dopamine agonists as third line.[7] Traditional remedies such as jasmine flower extracts and Chinese herbs are known to lower prolactin levels.[14] Although several interventions are used by clinicians, there has been no consensus regarding interventional strategies for antipsychotic-induced amenorrhoea, nor a systematic review of the evidence of the effects of these strategies.[7]

This study was carried out to identify the rates of menstrual dysfunction in women on antipsychotics, to identify the most common antipsychotic causing menstrual irregularities and to chart the intervention (both basic work-up and medications) done in a tertiary care facility in the event of menstrual irregularities in women on antipsychotics.

METHODS

The data was collected from the outpatient notes of patients who were reviewed during their outpatient visits to a tertiary care centre from October 2017 to December 2017. Clinical details of women of reproductive age group from 18 to 45 years of age with a diagnosis of

Schizophrenia according to ICD10 classification and who were on regular treatment with antipsychotic medication were screened for inclusion in the study. It is a cross sectional study done by using retrospective chart review.

Amenorrhoea was defined as absence of menstrual period longer than three consecutive cycles in a previously regular menstrual cycle and oligomenorrhea as fewer cycles per year or cycles every 35 days.[7] Menstrual history, the regularity and abnormalities in menstrual cycle at any point of time after the use of antipsychotic were reviewed.

Women in the age group of 18-45 years with a diagnosis of schizophrenia who were on treatment with antipsychotic of doses equal to or above the chlorpromazine equivalent of 200mg per day for a period of at least a year, were considered for inclusion in the study. 178 women who fulfilled the inclusion criteria were recruited.

All women with history of physiological amenorrhoea, post-menopausal/post hysterectomy state and those on oral contraceptive medications were excluded. Also, women with a clinical diagnosis of affective syndrome, neurosis or women with intellectual disability where an underreporting of menstrual irregularities was anticipated and those with other structural abnormalities secondary to congenital syndromes were also excluded. Women who were on low doses of antipsychotic medication of chlorpromazine equivalent of less than 200mg per day, on treatment with antidepressants or mood stabilisers, also were excluded. A total of 425 women were excluded from the study.

Case notes of all women who fulfilled the inclusion criteria were reviewed and details like age, marital status, medical comorbidities, menstrual history prior to starting antipsychotic and after starting antipsychotics were collected. The dose and duration of treatment with antipsychotic medication, interventions carried out for those who had developed amenorrhoea and the outcome with that intervention were recorded.

SPSS version 16 was used for analysis of the data. Categorical variables were reported as frequencies and continuous variables with means and standard deviation. Association between variables was measured using Odds Ratios with 95% Confidence Interval (CI) and chi-square test. A p value of <0.05 was taken as statistical significance. Logistic regression was used to adjust for confounders.

RESULTS

A total of 2721 patients (both male and female) had registered during this period of which 530 patients were new and 2191 were patients for review (1074 males and 1117 females). The total number of patients registered for repeat visits were 603. One seventy-eight women fulfilled the inclusion criteria and were recruited. The selection of patients is given in Figure 1. Among the 178 women identified using inclusion and exclusion criteria, nearly fifty percent (84;47.2%) had amenorrhoea (henceforth referred to as Group A) and more than fifty percent (94;52.8%) had no amenorrhoea (henceforth referred to as Group B). Percentage of women with amenorrhoea among those exposed to antipsychotic was 47%.

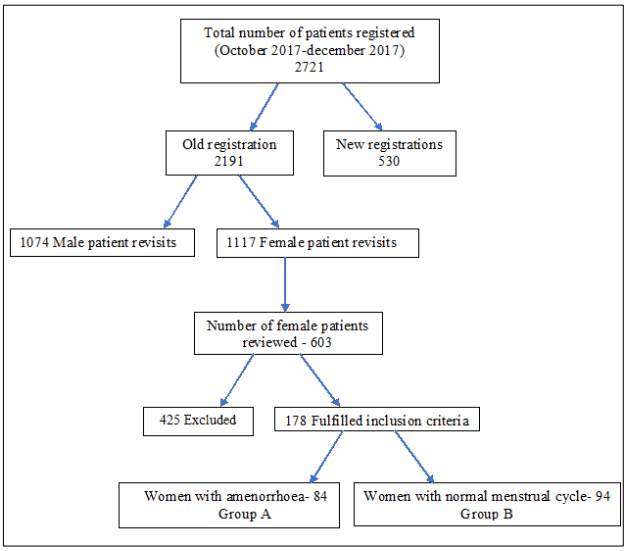

Figure 1: Sample selection.

Descriptive on the whole group of women studied is given in Table 1. The study population included a heterogenous group of women (N=178) and with age group ranging between 18 years to 45 years with an age of 35.6 (±SD 6.4). Among this population of 178 women, 81 (45.5%) were single, 83 (46.6%) were married and 14 (7.9%) were separated or widowed.

Table 1: Sociodemographic and associated medical comorbidity of the group of women exposed to antipsychotics.

Variables		N=178
Age	≤35	72 (40.4%)
	>35	106 (59.6%)
Menstrual cycles after starting antipsychotics	Amenorrhoea	84 (47.2%)
	Regular cycles	94 (57.8%)
Medical comorbidity	Hypothyroidism	7 (3.9%)
	PCOS	3 (1.7%)
	None	168 (94.4%)
Marital status	Single	81 (45.5%)
	Married	83 (56.6%)
	Others	14 (7.9%)

Among 84 women in group A, one had a medical comorbidity of hypothyroidism and was on thyroxine replacement and was clinically and biochemically euthyroid. In this patient amenorrhoea had set in after

initiating antipsychotic. 9 women among those included in group B had medical comorbidity (6 with hypothyroidism and 3 with PCOD) but had regular menstrual cycles.

Overall out of 94 women who had a positive history of use of risperidone, nearly two third (69;73.4%) had developed amenorrhea and nearly a quarter (25;26.6%) had regular cycles. women who were not exposed to risperidone but on other antipsychotics also were recorded to have amenorrhea (15;7.9%). Other antipsychotics used were olanzapine (3;3.5%), clozapine (1;1.1%), amisulpride (1;1.1%), chlorpromazine (3;3.5%), depot preparation of fluphenazine decanoate (7;8.3%).

Risk factors for amenorrhoea among women exposed to antipsychotics are listed in Table 2. In this study, use of antipsychotics for more than two years (52;83.9%) was found to be a risk factor for developing amenorrhoea. Also, a higher proportion of people on risperidone (69;73.4%) had developed amenorrhoea in comparison to other antipsychotics (15;17.9%).

Table 2: Risk factors for amenorrhoea among women on antipsychotics.

Variables		Group A N= 84	Group B N= 94	Odds Ratio OR (95% CI)	Adjusted OR (95% CI)	P value for chi-square
Age in years	≤35	42 (50.0%)	30 (41.7%)	2.13 (1.16-3.92)	1.02 (0.43-2.38)	0.973
	>35	42 (50.0%)	64 (60.4%)			
History of risperidone use	Yes	69 (73.4%)	25 (26.6%)	12.696 (6.17-26.13)	14.65 (5.93-36.20)	<0.001
	No	15 (17.9%)	69 (82.1%)			
Duration of antipsychotic use in years	>2	52 (83.9%)	10 (16.1%)	0.07 (0.03-0.16)	18.28 (6.46-51.72)	<0.001
	≤2	32 (27.6%)	84 (72.4%)			

Table 3: Interventions implemented and their effects on women with amenorrhoea while on treatment with antipsychotic medication.

Strategies taken	Resumed regular cycles (N=60)	Amenorrhoea persisted (N=24)
Lowering the dose	17 (70.8%)	7 (29.2%)
Change of antipsychotic	43 (87.8%)	6 (12.2%)
No changes made	0 (0%)	11 (100%)

The strategy of change of antipsychotics had been effective in regularizing the menstrual cycle in a good proportion of women (43;87.8%). The second strategy of lowering the dose of initial antipsychotic was also helpful in resuming the menstrual cycle (17;70.8%). Some patients were unwilling to change the medications after discussion about possible risks (13.09%). The above interventions were effective in regularizing the cycles in comparison to continuing the same antipsychotics. The strategies followed and their effects are reported in Table 3.

DISCUSSION

In this study, the proportion of women who had amenorrhoea while on treatment with antipsychotics was 47 per cent which was similar to earlier studies.[9] Risperidone is the commonest drug prescribed for a psychotic disorder in view of its efficacy and cost effectiveness. Our study had found that women who were prescribed Risperidone were found to have an increased risk of amenorrhoea (69;73.4%) as opposed to people treated with other antipsychotics. This observation is in agreement with reports from an extensive study done in India, which showed an increased risk of amenorrhoea in women on treatment with Risperidone with a prevalence of 60 per cent.[13]

Use of antipsychotics for more than 2 years was also found to be significantly associated with amenorrhoea in this study. Kinon et al, has reported multiple clinical symptoms like menstrual irregularities in women, galactorrhea and sexual dysfunction as a result of hyperprolactinemia caused by continuous exposure to antipsychotic.[15] In the present study, longer duration of use of antipsychotic for more than two years had remained a significant risk factor (OR-16.28, P<0.001, 95% CI) for developing amenorrhoea after adjusting for other significant factors in logistic regression. Likewise, the effect of risperidone in causing amenorrhoea persisted (OR-12.696, P<0.001, 95% CI) even after adjusting for age and duration of antipsychotic use, thus making it a statistically significant risk factor for causing amenorrhoea in women exposed.

A switch over to other antipsychotics (43;87.8%) showed regularization of menstrual cycles thus serving as an effective alternative to improve compliance to treatment.

This is in consensus with other studies which had showed women resuming regular menstrual cycles following a prescription of a prolactin sparing antipsychotic.[9] Lowering the dose of the antipsychotic also had been effective in regularizing the cycles (17;70.8%) as evidenced by 17 of 24 women reporting regular cycles when the dose was lowered without relapse of psychotic symptoms. This is in congruence with the finding of the earlier cross sectional study on the effect of antipsychotic dose reduction regularizing menstrual irregularities in women with antipsychotic induced amenorrhoea.[16] In this population, any of the two interventions, lowering the dose or changing the drug seemed to be more effective in regularizing the cycles (chi-square- 33.904, p value <0.001) as opposed to not making any changes in the medication. The reasons for not changing the antipsychotic included increase risk of relapse following medication change, patient preference and affordability.

This study was a retrospective review of charts. Limitations included small sample size. Abstractors were not blinded which increases reviewer bias.

CONCLUSION

Nearly fifty per cent of women who were on treatment with antipsychotics had developed the side effect of amenorrhoea. Specific strategies used to alleviate the side effect in clinical practice were effective. Prospective follow up of women who are started on antipsychotics may improve understanding of the complexities of this problem.

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