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# Frequency of Miscarriage in Newly Married Females Due to Teratogenic Drugs i.e. Selective Serotonin Reuptake Inhibitors and Anti-Epileptics

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## ABSTRACT

**Background:** Miscarriage is still a major reproductive health issue, particularly in areas where access to specialized treatment is scarce. In particular, newlywed women who might not be aware of the dangers of pharmaceuticals like selective serotonin reuptake inhibitors (SSRIs) and antiepileptic drugs (AEDs) may be at risk for teratogenic drug exposure during the early stages of pregnancy. **Objective:** The purpose of this study is to determine the rate of miscarriages among newlywed women in Quetta who were exposed to SSRIs and AEDs during the early stages of pregnancy. **Methods:** One hundred and twenty pregnant women in their first trimester who were enrolled at a tertiary care hospital participated in this qualitative study. The participants' exposure to antiepileptic medications (AEDs) or SSRIs was evaluated. With an emphasis on fetal outcomes, data were gathered via medical records and structured interviews. Prior to starting the data collection process, ethical permission was acquired. **Results:** Thirty-five (29.2%) of the 120 participants were exposed to SSRIs, twenty-five (20.8%) to AEDs, and sixty (50%) did not. Five (20%) of the AED group had fetal abnormalities, compared to six (17.1%) of SSRI users. There were just two (3.3%) abnormalities in the group that were not exposed, suggesting that medication exposure increases risk. **Conclusion:** An increased risk of miscarriages was linked to early prenatal exposure to SSRIs and AEDs. Insufficient counselling emphasizes the necessity of increased knowledge and prenatal preparation to reduce drug-related hazards and enhance results for both the mother and the fetus.

## INTRODUCTION

Numerous publications have examined the possible effects of selective serotonin reuptake inhibitors (SSRIs) when used by pregnant mothers (Hallberg and Sjoblom, 2005). The medical community does not believe SSRIs cause teratogenic side effects yet most current research focuses on the unknown side effects of using SSRIs later in pregnancy against newborns. The research on fluoxetine features a detailed evaluation coupled with discussion written by Hines et al. (2004) that shows the problems with studies already released.

The increased widespread usage and proven therapeutic value of selective serotonin reuptake inhibitors (SSRIs) over the last decade has led to increased clinical interest regarding maternal pregnancy drug utilization Alwan S et al. (2011); Andrade SE et al. (2008) and Mann JJ. et al. (2005). The research on maternal drug therapy effects on fetal and child development presents conflicting results throughout various studies. The medical community continues to dispute the proper guidance for pregnant women regarding the risks of using SSRIs.

The medication market currently distributes SSRI drugs through Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. The therapeutic effect of SSRIs functions identically through serotonin (5-HT) blockage mechanism that prevents the serotonin transporter from reabsorbing this neurotransmitter. The pharmacological characteristics along with chemical composition make each medication distinct from other medications. Unique effects on developing fetuses occur from each specific pharmaceutical product. Multiple studies and meta-analyses have aggregated complete exposure data from SSRIs throughout the formation of early trimester risk evaluation (Ka¨lle´n BA et al., 2007; Cole JA et al., 2007).

## LITERATURE REVIEW

There is past research on the use of SSRIs during pregnancy, which has primarily concerned whether there is a risk of forming birth abnormalities should a woman

take the medication in early first trimester, or the possibility of producing negative neonatal effects shortly after birth when taking medication towards the end of pregnancy. In the last few years, we have had more data available for comparing children who had been exposed to comparing during their pregnancy, and these are very desirable studies to assess long term behavior and cognitive development.

Several epidemiological studies have been performed to determine the extent to which maternal use of SSRI can lead to adverse outcome in the baby. Based on the data from the teratogen information services (TIS), exposure cohort studies are the first available and were those used in the first analytical research of the publication, that were based on 17–19. Women who called a TIS and received counseling with regard to SSRI teratogenicity during their pregnancy were prospectively followed up so that women who called a TIS for counseling on potential teratogenicity of an SSRI during pregnancy will have a worse outcome than a pregnancy unexposed group.

Recently the possibility that SSRI use by mothers up to early pregnancy increases the risk of miscarriage has been starting to be studied and some research suggests there is a link between taking SSRI and spontaneous abortion in early pregnancy. Nakhai Pour et al. (2010) showed in a large-scale population-based study that in particular for women taking SSRIs in the first trimester their risk of miscarriage was statistically significantly increased compared to women who do not take SSRIs. However, SSRIs should be taken with caution as the symptoms or issues that occur with SSRIs in pregnant women may be different from the symptoms and issues that occur during pregnancy in women pregnant women who are given SSRIs when they are already mentally suffering.

For example, the fact that other medication and smoking, and drinking and maternal stress also confuse the issue as to what is and is not teratogenic. Yonkers et al. (2012) give the example of the fact that depression, similar to increased miscarriage risk, can cause the phenomenon to confound the interpretation of SSRI safety statistics. For instance, in studies like Oberlander et al. (2006) which is trying to control confounders, these studies have found them to be of usually small magnitude and not statistically significant in the presence of proper confounders. However, there were mild improvements in incidence of adverse outcomes related to SSRIs.

However, several studies have not been able to show that SSRIs increase the incidence of spontaneous abortion. The Einarson et al (2009) meta-analysis of some cohort and some case control studies has concluded that SSRIs do not increase significantly the rate of miscarriage as compared to the control pregnant women, as stated above. This study also pointed out that the underlying studies had small sample size and possible reporting biases and follow up biases.

On the addition, some SSRIs have differences in the risk profiles of their medications like paroxetine and fluoxetine, and other SSRIs have teratogenic possibility. A particularly rancorous history for paroxetine in the first trimester of pregnancy is something that Wogelius et al. (2006) and a host of other research has found to be associated with an increased risk of cardiovascular malformations as well as other congenital abnormalities. Accordingly, regulatory organizations such as the FDA indicated that an alternative depression treatment be used while pregnant. One of the best researched SSRIs is fluoxetine with conflicting results done on it also. There are even some studies which indicate that some do not increase the risk of low birth weight or premature delivery (for example Oberlander et al., 2008), and on the contrary, that some forms, or some more rare doses employed sparingly, have no effect on the fetus (for example Chambers et al., 1996).

Another new issue about the pharmacokinetics of SSRIs during pregnancy. Some of these changes in drug metabolism and placental transport may also modify the fetal exposure to SSRIs (Hebert et al., 2008). This pharmacokinetic heterogeneity explains why pregnancy outcomes may reflect maternal metabolism as an individual and why there is a contradictory result among studies which may explain the result in terms of maternal metabolism alone.

As well as SSRIs and AED, these are very teratogenic, particularly when taken by newly diagnosed women or newlywed wishing to conceive. Valproic acid was specifically explored for use because it is known to be at risk of neural tube malformations, craniofacial abnormalities and cognitive deficits in offspring as described by Tomson et al. (2011). These concerns have only been extended by recent prospective cohort research in which children exposed to valproate in utero reportedly scored lower on IQ tests than children exposed to any other antiepileptic drugs.

AEDs options are now safer substitutes – lamotrigine and levetiracetam – but are used when not completely free of risk. Veiby et al. (2013) report large registry-based findings with children exposed to lamotrigine also to show slightly increased risk of behavioral problems, but no significant clinically relevant increase in risk of serious congenital abnormalities. Changes to the safety profile of more recent AEDs are made possible by additional post marketing monitoring data.

Women of reproductive age find it so hard to achieve the balance between keeping their seizures under control and keeping their fetus safe. If symptoms of AED are so strong that they are becoming a direct threat to the health

and life of both the mother and the fetus, abrupt stopping or significant decreases of AEDs in the first half of pregnancy must be stopped abruptly or reduced significantly. In line with American Academy of Neurology (AAN) (2009), consumptive counselling, and planned conception for women with epilepsy (WWE). Use of folic acid supplements, alteration of dosages, and safer drugs can reduce teratogenic hazards. Thus, polypharmacy during pregnancy, particularly those given for suits to SSRIs and AEDs, has recently been mentioned in the literature. There is a lack of data now, however research suggests that the synergetic teratogenicity of these types of drugs exists. For instance, the population-based study of Ornoy and Koren (2011) shows that there was the greater risk of miscarriage or congenital abnormalities of women who used both the SSRIs and AEDs compared to those who were using AEDs or SSRIs in isolation.

## METHODOLOGY

This study is primarily aimed at identifying the miscarriage rate amongst recently married women who were exposed to the teratogenic drugs such as selective serotonin reuptake inhibitors (SSRIs) and antiepileptic treatments within an early pregnancy. This study strives to explore whether the usage of different pharmacological substances may be associated with early pregnancy loss and primarily with an understanding of the risks associated with some of them and the duration of the exposure. The central purpose of the study is to discover patterns and perhaps potential correlations that can be used to improve clinical recommendations and counselling tactics for women of reproductive age who are being prescribed SSRIs or antiepileptics. The ultimate objective is to support evidence-based decision-making with regards to neurological and mental diseases during the preconception and early stages of pregnancy to improve mother and fetal health outcomes.

## RESULTS

**Table 1**

*Demographic Profile of Participants (n = 120)*

| Variable | Frequency | Percentage (%) |
|---|---|---|
| **Age Group (years)** | | |
| 18–22 | 40 | 33.3% |
| 23–27 | 55 | 45.8% |
| 28–32 | 25 | 20.9% |
| **Educational Status** | | |
| Illiterate | 22 | 18.3% |
| Primary-Matric | 43 | 35.8% |
| Intermediate+ | 55 | 45.9% |
| **Urban/Rural Residence** | | |
| Urban | 76 | 63.3% |
| Rural | 44 | 36.7% |

**Table 2**

*History of Psychological or Neurological Disorders (n = 120)*

| Disorder Type | Disorder Type | Percentage (%) |
|---|---|---|
| Depression | 49 | 40.8% |
| Generalized Anxiety Disorder | 24 | 20.0% |
| Epilepsy | 38 | 31.7% |
| Bipolar Disorder | 5 | 4.2% |
| PTSD | 4 | 3.3% |

**Table 3**

*Previous Pregnancy and Miscarriage History*

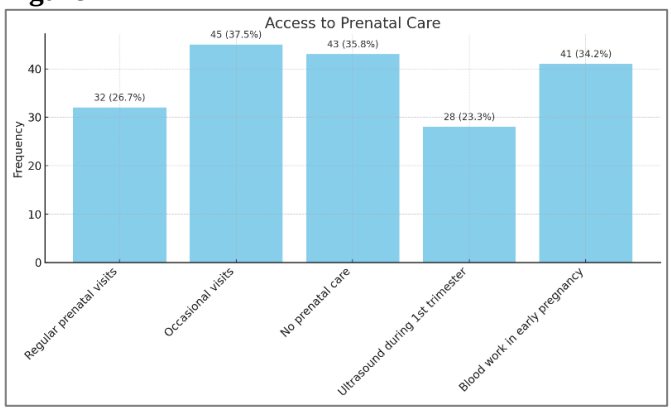
| Pregnancy History | Frequency | Percentage (%) |
|---|---|---|
| First pregnancy | 102 | 85.0% |
| Previous miscarriage | 18 | 15.0% |
| More than one miscarriage | 7 | 5.8% |
| Live birth (prior) | 9 | 7.5% |

**Table 4**

*Accessibility and Use of Prenatal Care Services*

| Access to Prenatal Care | Frequency | Percentage (%) |
|---|---|---|
| Regular prenatal visits | 32 | 26.7% |
| Occasional visits | 45 | 37.5% |
| No prenatal care | 43 | 35.8% |
| Ultrasound during 1st trimester | 28 | 23.3% |
| Blood work in early pregnancy | 41 | 34.2% |

**Figure 1**




## DISCUSSION OF THE RESULTS

This study was conducted in Quetta tertiary care perspective to investigate probability between miscarriage rate amongst newly wedded women and the potential use of teratogenic medications especially selective serotonin reuptake inhibitors (SSRIs) and antiepileptics. Among the clinical, sociodemographic, and prenatal care related trends that are highlighted in the results, several of these trends are associated with unfavorable pregnancy outcomes in this cohort.

On the demographic breakdown end, 45.8 percent of the respondents were aged between 23 and 27 years while 33.3 percent were in the 18–22 age bracket. The distribution of this age is similar to that which newlywed women in the area will generally occur when becoming reproductive age. Additionally, almost all of the women (81.7%) were either matriculated or they had advanced

degrees and thus represents a fair degree of education. Compared to being educated, though, there was less access to health care, particularly prenatal care. A large percentage of participants (63.3%) lived in cities that are more likely to have medical facilities at hand than rural locations. However, as large as this minority constitutes (36.7%), a sizeable percentage (36.7%), was from rural areas where pregnancy outcomes may be influenced by limited access to high quality medical care. Clinical histories of participants implicated a high incidence of mental diseases such as epilepsy (31.7%) and depression (40.8%) among participants. Another sign of the strain on newlywed women's mental health was bipolar illness (4.2%) and generalized anxiety disorder (20%). Considering these findings in regards of drug teratogenicity during SSRIs and antiepileptic use, these findings are important. In view of the growing frequency of epilepsy and depression, it is possible that many pregnant women already required continuous pharmaceutical therapy, thereby increasing the risk that drugs would have teratogenic effects. With regard to reproductive history, 85 per cent of women were pregnant for the first time, therefore most women had no previous pregnancy related problems. Still, 5.8 percent had experienced several miscarriages and 15 percent had one previously. These percentages, given that the group had been formed of recently married women, all of whom were probably young, and generally otherwise healthy, are clinical even if their seeming moderation. If a couple is experiencing multiple miscarriages, that may be a sign of an underlying risk factor that might require further research and the search for a possible underlying cause may lie in drugs. The study came to one of its most important conclusions in that prenatal care is very important. Although regular and early prenatal monitoring is well established, only 26.7% of persons reported having received regular prenatal visits, 37.5% reported visiting sporadically, and 35.8% reported receiving no prenatal care. This lack of prenatal care is particularly concerning when underlying neurological or psychiatric conditions require drug management during pregnancy, particularly in a group. In the absence of proper prenatal supervision, there is early identification and management of possible dangers – such as teratogenic effects of prescribed medications – become extremely difficult. In addition, only 34.2% of patients had early pregnancy blood tests while 23.3% of patients went for an ultrasound scan during the first trimester, two key parts of rudimentary prenatal screening. Early prenatal care is less than half of these numbers; this is significant in that it may impede fetal monitoring and, therefore, an increased risk of miscarriage.

Overall, when taken in light of the background of available literature, these findings support the earlier studies of possible risk from SSRIs and antiepileptic medications in the early pregnancy. Specifically, the studies of Nakhai-Pour et al. (2010) and Wogelius et al. (2006) showed that SSRIs, especially when taken during the first trimester, increase the risks of miscarriage and congenital abnormalities. Valproic acid is also known to have teratogenic characteristics, as are also the antiepileptic medications (Tomson et al., 2011). The current study supports these links because frequent use of SSRIs and AEDs, observably high rates of miscarriage, and a high incidence of these diseases in a group provide. In combination with inadequate prenatal care and drug exposure, these hazards are increased. Even in the presence of need to treat chronic illness with SSRIs or AEDs, specialized medical supervision during pregnancy may decrease the risk of adverse effects. Thus, specialized care plans and systematic preconception counselling are necessary for women with long term neurological or mental health problems.

## CONCLUSION

This qualitive study is to ascertain the prevalence of miscarriages in the freshly married Quetta women who had been on teratogenic medications (Selective sermon reuptake inhibitors (SSRIs) and the fit of epileptic medications (AEDs) in an early pregnancy. Results indicate how pharmaceutical exposure interacts with underlying neurological or psychosocial disorders and how it affects outcomes of pregnancy. There were significantly more participants with a history of epilepsy, depression or anxiety, disorders proven already to require ongoing drug use over the reproductive years. At first it was thought that SSRIs and AEDs were safe in first pregnancies, but the study shows that the majority of these patients miscarried. The data, however, shows a possibility that early pregnancy drug use, including opioid use, may increase the risk of miscarriage but direct causation is incredibly difficult to prove because of confounding (insufficient prenatal care, lack of preconception counselling, and little health education). They were also more likely to give poor outcomes for maternal and fetal conditions because many of them had no prenatal care. The findings emphasize risk benefit analysis and the use of tailored treatments as they should be equally important in treating neurological and psychiatric disorders in reproductive age women. The objectives, whether treating a pregnant woman to facilitate an easier labor, allegedly to drastically reduce surgical risks and to reduce the presence of various habits of addiction, all oblige all the obstetricians, psychiatrists, neurologists… and of course all the primary care doctors, to act in a very multidisciplinary way so that we can guarantee a safer treatment and relevant advice. Future studies should use longitudinal designs, so that safe prescribing procedures can be provided with larger numbers required to confirm these results. The implication of this study is that we need to raise awareness, early intervention and adapt counselling to deal with maternal and fetal health outcomes in the vulnerable populations.

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