“Psychosis” is an abnormal condition of the mind that involves a "loss of contact with reality". People experiencing psychosis may exhibit personality changes and thought disorder. Psychosis can lead to changes in mood and thinking and to abnormal ideas. In order to understand the experience of psychosis, it is associated with confused thinking, false beliefs (delusions), hallucinations and changed feelings with poor emotions. The characteristics of psychosis varied from person to person considering their mental status and surrounding environment. Sometimes, psychosis may be induced by extreme use or withdrawal of drugs (including drugs of abuse), head injury or a physical illness (organ psychosis which disrupts brain functioning), traumatic stress, unplanned pregnancy, sudden demise of beloved person etc. There are several forms of psychotic illness which are associated to major brain disorders like Schizophrenia, Bipolar disorder (sometimes refer to mood disorder), Schizoaffective disorder (symptoms of both mood disorder and schizophrenic state), Psychotic depression (major depression with psychotic symptoms). Furthermore, hormonal fluctuations, emotional stress and other factors such as personal and social changes in the women set them on stage of psychosis.

The prevalence of psychiatric disorders in pregnancy ranged from 14% to 30.5 %. It is well documented that untreated psychiatric disorders during pregnancy are associated with increased risks of adverse pregnancy outcomes, and sometimes may affect pregnant mother and developing foetuses, concomitantly. Hence, there is need to select a suitable antipsychotic drug (APD); and decide the treatment regime and exposure period.
Antipsychotic drugs were discovered in the 1950s and currently over 20 compounds are approved (Medicine and Healthcare, 2015). For therapeutic management of vivid forms of psychosis several antipsychotic agents belong to diverse classes like first generation (classical or typical), second generation (novel or atypical) and third generation (atypical) are available in the global market. The typical or conventional antipsychotics drugs (APDs) like haloperidol and chlorpromazine are the best known classical antipsychotics. They continue to be useful in the treatment of severe psychosis and behavioural problems. However, these medications perform a high risk of side effects, some of which are quite severe. In response to serious side effects of typical antipsychotics, many second generation antipsychotic drugs were developed as another category and referred to as atypical antipsychotics drugs (AAPDs). These new medications were approved for use in the 1990s like clozapine, amisulpride, risperidone, Sertindole, olanzapine, quetiapine, ziprasidone, paliperidone, iloperidone and brexpiprazole etc. Aripiprazole is a relatively new approved antipsychotic drug and classified as third generation or novel antipsychotic drug on the basis of their unique mechanism action.

Antipsychotics such as typical antipsychotic drugs (APDs) like haloperidol and chlorpromazine tend to block dopamine D2 receptors in the dopaminergic pathways of the brain. In addition to the antagonistic effects of dopamine, second generation or atypical antipsychotics drugs (AAPDs) like quetiapine, risperidone and iloperidone etc. also antagonize 5-HT2A (Serotonin) receptors. The distinction between second- and third-generation antipsychotics has been made based on mechanistic differences. Specifically, aripiprazole (ARI) is the first approved antipsychotic that is a partial dopamine agonist and has been designated as a third-generation antipsychotic. It’s mechanism of action is unique,
compared to other FDA approved atypical antipsychotic drugs. It is partial agonist at D₂ and 5HT₁A receptors, but displays an antagonist profile at the 5HT₂A receptors. ARI also antagonise the 5HT₇ receptors and act as partial agonist at the 5HT₂C receptor with high affinity. Most atypical antipsychotic bind preferentially to extrastriatal receptors, but ARI appears less preferential, as binding rates are high throughout the brain.

It is well documented that first-generation APDs (typical) are associated with stereotypic side effects like extrapyramidal syndrome (EPS) and movement disorders. The reproductive toxicity and teratogenicity of first-generation APDs has been well established in clinical and non-clinical studies. Therefore, clinicians vacillate to prescribe typical antipsychotics to the pregnant women with psychosis considering teratogenic potential of classical APDs. Some investigators have revealed the effect of typical antipsychotics like haloperidol (HAL) on developmental structural changes in fetal brain whose mothers had taken either single (monotherapy) or multiple APDs (polytherapy) during first, second and third trimesters of pregnancy or throughout gestation period. Similar studies were also reported in rodent models.

During 1990s, several atypical antipsychotics (AAPDs) like clozapine, olanzapine (OLZ), ziprasidone, quetiapine (QUE), risperidone (RIS) and iloperidone (ILO) were launched in the world market to treat different forms of psychosis in young and adult population with different mechanism of action than typical APDs, but drug safety for pregnant population was not well established in clinical settings due to paucity of accumulating data. The general safety concerns of antipsychotics have been improved enormously from development of classical APDs to novel AAPDs, considering their efficacy, pharmacokinetics and pharmacodynamic; and drug interactions, but none of the
drug has been found to be safer for the treatment of pregnant population suffering from psychosis.

The second-generation antipsychotic drugs (AAPDs) like clozapine, olanzapine, ziprasidone, quetiapine (QUE), risperidone (RIS), and iloperidone (ILO) show low incidence of extrapyramidal side effects (EPS) than APDs due to their low affinity for $D_2$ receptors and antagonistic characteristics of $5HT_2$ receptors. Although reproductive and teratogenic safety of AAPDs has been improved to a great extent than classical antipsychotic drugs (APDs) like haloperidol, but literature indicates that second generation APDs are coupled with metabolic dysregulation, especially the weight gain.

In the past decade, use of atypical antipsychotic drugs (AAPDs) has been drastically increased in the pregnant women with psychiatric disorders including schizophrenia and bipolar disorder. Epidemiological studies documented that use of atypical antipsychotic drugs (AAPDs) has been increased from 16.6 to 51.2% during 1998 to 2007. Among the SGAPDs, olanzapine (OLZ) ranked first, followed by quetiapine (QUE) and risperidone (RIS) for their use during pregnancy. Thus, use of these drugs in pregnant women is increasing as add-on therapy or alternative drug of choice.

Earlier, some studies revealed that prenatal exposure to typical APDs may induce adverse effects on fetal brain development, neurostructural morphology and neurobehavioural changes in later life in animal models. Williams et al., 1992 reported that HAL was administered during gestation period displayed altered structural and cytoarchitectural changes as well as substantive deficit of neuronal density in fetal brain. Some investigators have also reported decreased neuronal cell packing density, increased
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in neuronal size (synaptic plasticity) in the striatum and striatal enlargement when APDs were administered during prenatal period in rats.

Additionally, limited information is available on effects of in utero administration to AAPDs on postnatal development and growth; and neurobehavioral consequences in young/adult rodent offspring. The clinical and non-clinical studies on these issues are very limited. Limited information is available on neurobehavioural consequences (cognitive impairment) in rodents to draw a definite conclusion. Recently, our laboratory has reported developmental neurotoxic and neurobehavioural potential of quetiapine, aripiprazole and risperidone in fetuses and young rat offspring, respectively.

Therefore, health care providers always have a dilemma for selection of safe and efficacious novel antipsychotic drug for therapeutic management of pregnant women suffering from different forms of psychiatric disorders, considering drug safety concerns for potential benefits to diseased mother and possible risks to developing foetus, respectively.

Despite better efficacy and improved pharmacokinetic and pharmacodynamic properties of RIS and ILO in respect to in utero exposure and its safety concerns, as well as paucity of literature on fetal brain development; and long-lasting impact on neurobehavioral consequences, therefore present study has been undertaken to elucidate the effects of prenatal exposure to RIS and ILO, at equivalent therapeutic doses, on maternal toxicity (food consumption and body weight gain), placental toxicity, reproductive toxicity and teratogenicity, fetal toxicity, developmental neurotoxicity (neocortex, hippocampus, striatum and choroid plexus in fetal brain), postnatal
development & growth, and neurobehavioural changes (anxiety, depressive and cognitive impairment) in young rat offspring, as translational approach.

In this study, all pregnant rats (n = 54) were randomly segregated in three groups, i.e. group 1 (Control/Vehicle treated, n = 18), group 2 (RIS treated, n = 18), and group 3 (ILO treated, n = 18). The experimental doses of the drug were calculated as 0.8 mg/kg, 1.0 mg/kg, and 2.0 mg/kg RIS and 2.4 mg/m², 10.0 mg/m², and 15.0 mg/m² ILO on the basis of Maximum Human Recommended Doses (MHRD) and suitability to animals. These doses were administered to sperm positive dams daily from GD 6-20 orally through cannula. Twenty-four hour food intake and individual dam’s body weight were recorded daily in all the groups. Half of the drug treated and control dams of each group were sacrificed after anesthetization by pentobarbital on GD 21. Remaining (50%) dams of each group were survived and allowed to deliver normally, for further observation and records. Fetuses were collected by uterectomy and weighed individually without placenta. Litter size, gestational age, external anomalies, body length/weight, placental weight and fetal brain length/weight were measured. Histological slides of fetal brain were processed for Cresyl Voilet and Hematoxylin and Eosin staining with routine staining procedure. Selected fetal brain areas were identified and imaged under Eclipse CCD camera of Nikon 83I for light microscopy. The cortical thickness was measured in the medial frontal cortex and CA1 region of the hippocampus of developing fetal brain sections with the help of Image J software. For measurement of apoptotic neurodegeneration, confocal and electron microscopy was performed. Postnatal growth and development measures were assessed through weekly body weight gain by the neonates/pups up to 10th weeks of age.
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The neurobehavioral measurements of young-adult offspring were also studied on validated mazes designed to study the anxiety, depression and cognition like behavioral responses under controlled conditions. These behaviors were recorded by an automated video tracking device with ANYMAZE software (storling), USA.

The present study revealed that gestational administration to RIS or ILO from GD 6-21 at selected equivalent therapeutic doses couldn’t induce substantial decrease of food intake and body weight gain. Overall, this study elucidates that there was reduction in food intake by RIS (13–16 %) exposed dams; and these dams also expressed decrease (2–35 %) in weight gain. While ILO exposed dams shows decrease in food intake (9-30 %) and body weight gain (28-30 %) in comparison to control dams.

It is elucidated from this study that RIS did not produce hyperphagic and hyperactivity conditions during treatment. Therefore, food intake and body weight gain were found moderately altered/ reduced. It is hypothesized that moderately increase or decrease in food intake by RIS treated rats during short exposure period was not able to induce substantial weight gain, and it might be due to reduced activity.

The present study revealed that no external anomalies on fetusus were recorded in both drugs. Also, these drugs didn’t induce substantial reproductive toxicity as gestation age and aborted embryos, whereas litter size was found significantly decreased in prenatally exposed RIS and ILO rats.

The current study revealed that maternal exposure to equivalent therapeutic doses of RIS and ILO during organogenesis induced placental dystrophy (size and weight), disturbed cytoarchitectural organization (thickness of different placental layers), histopathological
lesions (necrosis in trophoblast with disruption of trophoblastic septa and rupturing of maternal fetal interface) and intrauterine growth restriction of fetuses (size and weight).

The present study revealed that maternal administration to RIS and ILO during critical period of brain development substantially induced developmental neurotoxicity and neurobehavioral impairments in young-adult rat offspring. The fetal neurotoxicity was depicted as significant stunting of fetal brain size and weight, altered neurocytoarchitecture with reduced cortical thickness of neuronal layers (total and differential), apoptotic neural cells, nuclear fragmentation and condensation of neuronal cells of neocortical region (a characteristic of apoptotic neurodegeneration).

The present study also revealed that maternal exposure to clinically relevant doses of RIS and ILO during the critical period of CNS development not only distorted the typical architecture of the fetal hippocampus along with dentate gyrus, structural changes in striatum and choroid plexus, but also induced long-lasting impact on cognitive impairment in young rat offspring.

Furthermore, confocal and electron microscopic examination of neocortex of RIS and ILO treated fetuses was associated with altered cytoarchitecture of neocortical neurons characterized by chromatin clumping, nuclear fragmentation and condensation, as well as irregular outlines of nuclei.

This study further demonstrated that postnatal growth of new born pups at PND 1 and up to first week of age (PND 7) was found non-significantly reduced (body weight), and later on, it was substantially decreased up to ten weeks of age (PND 70). The more severe deficit was expressed in post weanling period (after PND 21) as compared to pre-
weanling period. Overall, in utero exposure to RIS and ILO had substantial effect on the body growth in the offspring until PND 70.

This study further demonstrated that acquisition of spatial information in young offspring was disrupted by prenatal exposure to RIS and ILO as analyzed in various validated tests of cognitive performances like Morris water maze, active and passive avoidance tests. In these paradigms, prenatally drug exposed young subjects expressed impaired learning and memory in different tasks based on forced swimming (spatial learning and memory), active and passive avoidance (emotional/fear learning and memory), but no sex difference was noticed.

In neurobehavioral paradigms, RIS treated young offspring expressed substantially anxiety like responses, both explorative and emotional under selected drug regimes. These increased/decreased ambulatory and rearing activities were associated to exploratory or spontaneous responses, where as central/peripheral activities as well as self-grooming, urination and faecal pallets represent emotionality with fear fullness, in open-field arena. Similarly, time spent and entries made on open/enclosed arms by in utero RIS and ILO exposed subjects on elevated plus maze exhibited exploratory and fear fullness behavior. These indices were found variable at selected doses clearly represent that prenatally drug treated offspring did not cope-up or adapted well in the new environment, which is the basic characteristic of abnormal brain (neonates) development related to neuro-functional disorders, possibly associated to early disturbance of neurotransmitters (NTs) development.

In MWM task, multiple neural systems are involved in animal navigation. In this task, the hippocampus is involved to navigate the hidden goals (place response), whereas
dorsolateral striatum is involved in the learning of stimulus-response associations when navigating towards visible goals. In the present study, RIS and ILO exposed animals displayed dissociative behavior based on visual cues response controlled by striatum and hippocampus-mediated place response which was well integrated as spatial memory during the training session. Thus, drug-treated rats couldn't cope well with new test situation resulting into impaired spatial learning and memory performances as compared to control subjects.

In the active avoidance test (Shuttle box), three measures were analyzed for each phase of the test; avoidance, escape, and failure. All these measures reflect the learning. All learning indices show impairment in learning in all RIS and ILO exposed group compared to control group.

The current study also revealed that in passive avoidance test (step down latency test) displayed that there was significant decrease in learning performances between days, groups and days × group interaction.

The important findings of the present study are:

The present study concludes that prenatal exposure to clinically relevant doses of an atypical antipsychotic drug; RIS and ILO during the sensitive phase of brain development may induce neuroarchitectural and/or neurohistopathological changes in the neocortex, hippocampus, striatum and choroid plexus of fetal brain; and their long-lasting impact on cognitive (learning and memory) impairment in young rat offspring. Further, both clinical and non-clinical investigations are required to ascertain the neurotoxic potential of most prescribed AAPDs of the second generation and newly introduced AAPDs like paliperidone and iloperidone; and third generation antipsychotic drugs like aripiprazole during pregnancy and lactation.
Conclusion

1. The present study concludes that RIS and ILO couldn’t induce severe maternal toxicity in terms of metabolic disturbances related to food intake and body weight gain in pregnant rats, therefore these two drugs could be a better and safe option for pregnant women in clinical treatment regimes in future after extrapolation of these animal data to human beings.

2. The present study concludes that RIS and ILO couldn’t induce reproductive toxicity and teratogenicity, hence could be safer for pregnant population.

3. The present study concludes that RIS and ILO displayed feto-toxicity in the present regimen; hence their fetal safety concern should be scrutinized thoroughly before prescribing to pregnant population.

4. This study further concludes that RIS induced placental toxicity in this drug regime; hence precautions should be undertaken by the clinicians considering placental toxicity in rodent model. Therefore, more studies are required to assess the placental toxicity in other animal models and clinical settings.

5. This study further elucidated that RIS and ILO induced developmental neurotoxicity in fetal brain characterized by stunting of fetal brain, microhistopathology and apoptotic neurodegeneration (neuronal apoptosis) in different neuronal layers, therefore their (RIS and ILO) fetal neurodevelopmental safety may be in question. Therefore, cautions are urgently required by the health care providers considering possible and potential neurotoxicity during pregnancy in animal model, rat.
6. In neurobehavioral paradigms, RIS and ILO induced substantial increase of anxiety like responses (explorative and emotional), and cognition (spatial learning and memory) in drug treated young offspring.

7. Therefore, cautions must be taken by the health care providers before widely prescribing of atypical antipsychotics in general and RIS and ILO in particular to the pregnant psychotic population.