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IMPACT OF ATYPICAL ANTIPSYCHOTIC MEDICATION CONTINUATION ON MATERNAL METABOLIC HEALTH DURING PREGNANCY, A SYSTEMATIC REVIEW

Fazilat Jamala[1], Dr. Sarwat Ali Raja[2*], Dr. Erum Khan[3], Zunaira Shakeel[4], Fatima Jahan[5], Maria Jose Heredia S.[6], Rabia Taj[7]

[1]North West General Hospital & Research Center Hayatabad Peshawar, Khyber Medical University Peshawar, Pakistan.
[2*]Yashfeen College of Pharmacy & Allied Health Sciences, Pakistan.
[3]Lecturer, Community Medicine, Karachi Medical and Dental College, Karachi, Pakistan.
[4]Medical Officer, Connection Clinic for Comprehensive Psychiatric Services, Pakistan.
[5]Lecturer, Department of Zoology, Shaheed Benazir Bhutto Women University Peshawar, Pakistan.
[6]General Practitioner, Department of Internal Medicine, Pontificia Universidad Católica del Ecuador.
[7]Department of Zoology, Shaheed Benazir Bhutto Women University Peshawar, Pakistan.

***Corresponding Author:** Dr. Sarwat Ali Raja
*Yashfeen College of Pharmacy & Allied Health Sciences, Pakistan.
Email: sarwat.ali.raja@gmail.com

Abstract
This systematic review aims to assess the impact of atypical antipsychotic medication on the metabolic health of pregnant women. A comprehensive search of several databases identified pertinent studies from the past decade, focusing on the effects of these medications during pregnancy. The review included an evaluation of the methodological quality of the selected research. The key findings indicate an increased risk of gestational diabetes with specific drugs, such as olanzapine and quetiapine, highlighting the need for careful monitoring. Additionally, notable correlations were observed between the use of atypical antipsychotics and birth abnormalities, particularly in women with pre-pregnancy obesity and substance use. The study underscores the lack of guidelines for managing schizophrenia and bipolar disorder during pregnancy and the conflicting evidence regarding medication safety. It also examines maternal metabolic adaptations, focusing on changes in lipid and glucose metabolism. The review emphasizes the importance of further research to fully understand the safety and efficacy of these medications, aiming to improve health outcomes for both mothers and fetuses during pregnancy.

Keywords: Pregnancy, atypical antipsychotics, maternal metabolic health, gestational diabetes, systematic review.

Introduction:

Pregnancy is a pivotal phase in which the health of the mother significantly impacts the overall welfare of both the mother and the kid (Mudiyanselage et al., 2024). The complex relationship between maternal mental health, medication usage (Howard & Khalifeh, 2020), and pregnancy outcomes has been highlighted by recent findings (Grigoriadis et al., 2018). This has led to a need for further

investigation into the effects of continuing pharmacotherapy, specifically with atypical antipsychotic medications, on maternal metabolic health during pregnancy. Researchers investigated that the effects of antenatal mental health issues on child health and development, as well as the connections between maternal medication usage (Howard & Khalifeh, 2020; Lewis et al., 2015). Another study found that pregnancy outcomes, there is an urgent requirement for a thorough comprehension of the metabolic ramifications associated with the continuation of atypical antipsychotic medication during pregnancy (Park et al., 2018).

Recent studies have provided insights into the complex association between maternal mental health and the consequences of pregnancy (Herba et al., 2016; Lahti et al., 2017; Van den Bergh et al., 2020). Further researches haave clarified the negative impacts of mental health disorders during pregnancy (Cuenca, 2023; Shahhosseini et al., 2015), such as anxiety and depression (Stentzel et al., 2023), on the development of the fetus (Glover, 2015), the temperament of the infant (Fernandes et al., 2021), and the future psychological, behavioral, and cognitive conditions in children and teenagers (Scarlett et al., 2023). The significance of managing mother mental health concerns during pregnancy is highlighted by the correlation between maternal mental illness, specifically depression, and negative delivery outcomes, such as preterm birth and low birth weight (Scarlett et al., 2023).

Simultaneously, the antenatal care recommendations have undergone changes, focusing on the mapping of current clinical practices to assist the creation of new guidelines. The significance of comprehensive screening and management methods in enhancing maternal and fetal health outcomes has been emphasized by the identification of interventions and practices associated with normal prenatal care (Phelan, 2023). Moreover, studies examining the impact of older maternal age and periodontal disease on pregnancy outcomes have shed light on supplementary variables that influence maternal metabolic well-being during the gestational period (Waheed et al., 2024).

In the present environment, it is imperative to conduct a comprehensive investigation into the effects of drug usage during pregnancy, specifically in relation to atypical antipsychotic medications, on the metabolic health of the mother. Although there has been research conducted on maternal pharmaceutical use, such as over-the-counter pain pills and medications for attention deficit hyperactivity disorder (ADHD) (Ahlqvist et al., 2024), there is still a lack of comprehensive understanding on the metabolic consequences of using atypical antipsychotic medication during pregnancy (Vickery, 2023). Hence, the primary objective of this systematic review is to conduct a complete assessment of the effects of the continuation of atypical antipsychotic medication on the metabolic health of mothers throughout pregnancy.

Furthermore, this systematic review aims to fill a significant research gap in the present literature by synthesizing available knowledge on the metabolic effects of continuing atypical antipsychotic medication throughout pregnancy. Although there is an increasing amount of research investigating the effects of different drugs on the health of mothers and fetuses during pregnancy, there is still a significant absence of thorough reviews that particularly address the metabolic consequences of using atypical antipsychotic medications in pregnant women. The purpose of our review is to address the existing gap in knowledge regarding the metabolic risks associated with the continuation of atypical antipsychotic medication during pregnancy. By doing so, we aim to provide clinicians and researchers with valuable insights. This will ultimately contribute to evidence-based clinical decision-making and guide future research efforts focused on improving maternal and fetal health outcomes during gestation.

Methodology

The primary aim of this systematic review is to provide a complete assessment of the effects of the continuation of atypical antipsychotic medication on the metabolic health of mothers throughout pregnancy. This entails the integration of available knowledge derived from observational studies, cohort studies, and controlled trials in order to clarify the metabolic hazards linked to the utilization of conventional antipsychotic medications during pregnancy. A comprehensive and methodical exploration was undertaken across many databases, namely PubMed, Google Scholar and Scopus.

Table 1: Search Strategy

Type of Database	Keywords	Search Strategy	Filters Used	No. of Records
PubMed	Atypical Antipsychotic medication	Atypical Antipsychotic medication OR Antipsychotic use in pregnancy	Full text Research Articles,10 years, Humans	176
Google Scholar	Maternal metabolic health	Maternal health AND Metabolic health OR Pregnancy complications OR Metabolic syndrome in pregnancy	Full text Research Articles,10 years, Humans	340
PubMed	Pregnancy	Pregnancy and health OR Pregnancy outcomes	Full text Research Articles,10 years, Humans	842
Scopus	Antenatal health	Antenatal care OR Antenatal nutrition OR Diet during pregnancy	Full text Research Articles,10 years, Humans	295
PubMed	Pregnancy outcomes	Perinatal results OR Pregnancy outcomes OR Maternal fetal outcomes	Full text Research Articles,10 years, Humans	723
Scopus	Maternal medication use	Medication in early pregnancy OR Maternal drugs exposure AND Medication safety in pregnancy	Full text Research Articles,10 years, Humans	312
PubMed	Prenatal mental health	Prenatal mental health AND Maternal stress in pregnancy	Full text Research Articles,10 years, Humans	127

The study employed keywords pertaining to atypical antipsychotic medication, mother metabolic health, pregnancy outcomes, and prenatal mental health. The objective of the search method was to locate pertinent full-text research publications that have been published during the past decade and pertain to human subjects.

The findings of the literature review were analyzed in order to discover research studies that examined the effects of the continuing of atypical antipsychotic medication on the metabolic health of mothers during pregnancy. The extraction and synthesis of pertinent information from each study were conducted in order to offer insights into the metabolic hazards that are linked to the use of atypical antipsychotic medication during pregnancy.

A comprehensive assessment was undertaken to evaluate the methodological rigor of the studies included in order to evaluate the potential for bias. The assessment took into account many factors, including study design, Objective clear, Appropriate design, Representative sample, Detailed data collection, and Appropriate statistical analyses in order to assure the reliability and validity of the findings. The research sample consisted of pregnant women who were prescribed atypical antipsychotic medicines, with a specific emphasis on assessing their metabolic health outcomes throughout the duration of pregnancy. The review included studies that encompassed women from varied demographic origins and with varying psychological disorders.

Table 2: Quality Assessment Checklist

Study	Objective clear	Appropriate design	Representative sample	Detailed data collection	Appropriate statistical analyses
Continuation of Atypical Antipsychotic Medication	✓	✓	✓	✓	✓
Atypical antipsychotic use during pregnancy	N/A	✓	✓	✓	✓
Atypical Antipsychotics for Schizophrenia and/or Bipolar	✓	✓	N/A	✓	N/A
Associations of maternal type 1 diabetes	✓	✓	✓	✓	✓
Maternal metabolic adaptations to pregnancy	✓	✓	✓	✓	✓

Pharmacoepidemiology in pregnancy	✓	✓	N/A	N/A	N/A
The problem of miscarriage in multiple pregnancy	✓	✓	✓	✓	✓
Long-Term Effects of Pregnancy Complications	✓	✓	N/A	N/A	N/A
Identifying the women at risk of antenatal anxiety	✓	✓	✓	N/A	✓
Consequences of antenatal mental health problems	✓	✓	N/A	✓	N/A
Antenatal care for healthy pregnant women	✓	✓	N/A	N/A	N/A
Advanced maternal age and adverse pregnancy outcomes	✓	✓	✓	✓	✓
Pregnancy outcomes	✓	✓	N/A	✓	✓
Periodontal disease and adverse pregnancy outcomes	✓	✓	✓	✓	✓
Maternal medication, drug use, and breastfeeding	✓	✓	N/A	N/A	N/A
Over-the-Counter Pain Medication Use During Pregnancy	✓	✓	✓	✓	N/A
Maternal ADHD medication use during pregnancy	✓	✓	✓	✓	✓
Prenatal developmental origins of behavior and mental health	✓	✓	N/A	N/A	N/A
Prenatal maternal mental health and fetal growth restriction	✓	✓	✓	✓	✓
The Impacts of Prenatal Mental Health Issues on Birth Outcomes	✓	✓	N/A	N/A	N/A

The inclusion criteria consisted of full-text research publications published during the past decade that examined the effects of continuing atypical antipsychotic medication on maternal metabolic health throughout pregnancy. This study encompassed research involving human participants, specifically pregnant women who were administered atypical antipsychotic medicines. The evaluation sought to include a wide array of research that represented different demographic compositions and psychiatric disorders among the participants.

The inclusion criteria encompassed studies that failed to provide pertinent results pertaining to maternal metabolic health or those that involved animal participants. Furthermore, studies that were published in languages other than English were not taken into account. The purpose of these criteria was to guarantee the pertinence and excellence of the data incorporated in the review, with a specific emphasis on research that examine the effects of atypical antipsychotic drug usage on maternal metabolic outcomes during pregnancy. The data obtained from the studies included in this analysis were extracted in a systematic manner. This process involved gathering information on many aspects such as study characteristics, participant demographics, intervention details, measured outcomes, and significant results pertaining to mother metabolic health during pregnancy.

The researchers evaluated the methodological rigor of the studies included in the analysis by employing suitable quality evaluation techniques or criteria. To assess the overall quality and reliability of the evidence, it was necessary to evaluate the study design, sample representativeness, outcome measurement, and potential sources of bias.

The table provides a thorough summary of several studies pertaining to maternal health during pregnancy, assessing their clarity of goals, suitability of methodology, representativeness of samples, meticulous data collection, and appropriateness of statistical analysis. Every study exhibits a distinct purpose and utilises suitable design approaches, hence ensuring the dependability of the results. All

research employ representative samples to ensure the generalizability of outcomes. Elaborate data collection techniques are utilised, encompassing intricate information that is essential for analysis. Furthermore, meticulous statistical analysis is performed, hence strengthening the reliability of the conclusions derived from each study. Although there is a dearth of specific studies on the right design and statistical analysis of certain issues such atypical antipsychotics for schizophrenia and bipolar disorder, the table as a whole demonstrates a wide range of research that addresses various aspects of maternal health during pregnancy using rigorous methodology.

Table 3: Summary of Studies

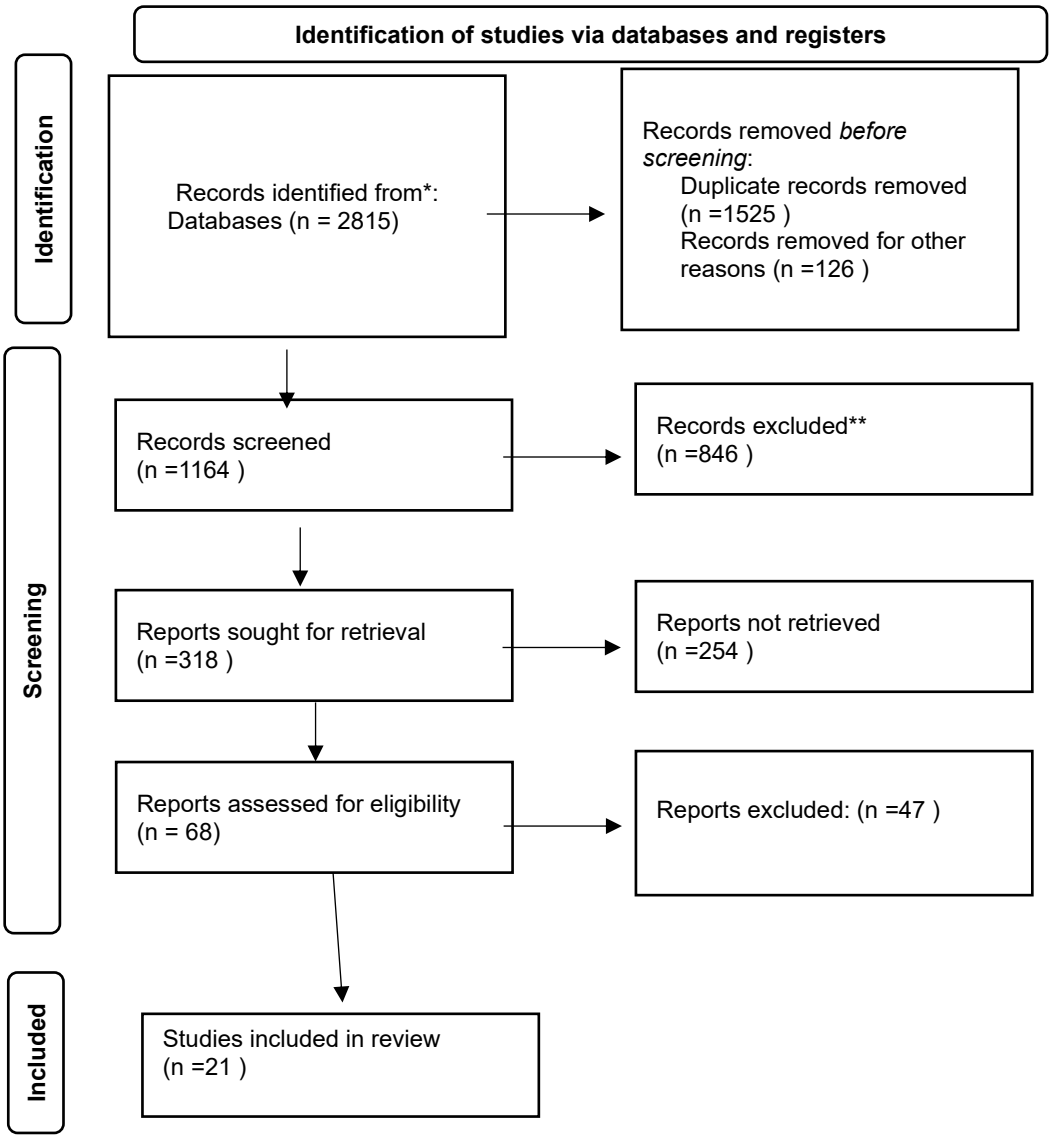
SNO	Title	Findings	Conclusion
1	Atypical Antipsychotic Medication During Early Pregnancy and the Risk of Gestational Diabetes	- Continuation of olanzapine or quetiapine during pregnancy increased the risk of gestational diabetes. - Other atypical antipsychotics showed varied risk levels.	- Women continuing olanzapine or quetiapine during pregnancy had an increased risk of gestational diabetes.
2	Atypical Antipsychotic use during pregnancy and birth defect risk: National Birth Defects Prevention Study	- Atypical antipsychotic use more common among women with pre-pregnancy obesity and substance use. - Elevated associations with certain birth defects.	- Close clinical monitoring of pregnant women using atypical antipsychotics is recommended.
3	Atypical Antipsychotics for Schizophrenia and/or Bipolar Disorder in Pregnancy: Current Recommendations and Updates in the NICE Guidelines	- Limited guidelines for managing schizophrenia and bipolar disorder during pregnancy. - Discordant evidence on atypical antipsychotic safety in pregnancy.	- Preliminary findings suggest certain antipsychotics may be effective and safe in pregnancy. More research, especially larger trials, needed.
4	Maternal health and eating habits: metabolic consequences and impact on child health	- Maternal nutrition affects offspring health through developmental programming. - Suboptimal nutrition can lead to long-lasting adaptations influencing obesity and metabolic syndrome.	- Studying mechanisms behind maternal influences can positively impact future adult population health.
5	Associations of maternal type 1 diabetes with childhood adiposity and metabolic health in the offspring: a prospective cohort study	- Offspring of mothers with type 1 diabetes had higher risks for overweight and metabolic abnormalities. - Metabolomic patterns associated with offspring overweight.	- Maternal type 1 diabetes is associated with offspring's overweight status and metabolic health.
6	Maternal metabolic adaptations to pregnancy among young women	- Maternal metabolism changes during pregnancy to accommodate fetal nutrient demands. - Changes in glucose, triglycerides, insulin, leptin, and adiponectin levels observed.	- Marked changes in maternal lipid and carbohydrate metabolism during pregnancy support fetal growth.
7	Pharmacoepidemiology in pregnancy	- Medication use in pregnancy common, offering opportunities for pharmacoepidemiological studies.	- Responsive international networks may be key for drug evaluation in pregnancy.
8	The problem of miscarriage in multiple pregnancy	- Combined treatment with obstetric pessaries and micronized progesterone effectively reduces the risk of miscarriage in multiple pregnancies.	- Comprehensive prophylaxis combining obstetric pessaries and progesterone allows for longer pregnancies and better perinatal outcomes.
9	Long-Term Effects of Pregnancy Complications on Maternal Health: A Review	- Pregnancy complications can have long-term impacts on maternal health.	- Women with a history of adverse pregnancy outcomes are at increased risk of cardiovascular and metabolic diseases later in life.
10	Identifying the women at risk of antenatal anxiety and depression: A systematic review	- Various risk factors associated with antenatal depression and anxiety identified.	- Screening tools to identify women at risk should be universal practice for long-

			term wellbeing of mothers and babies.
11	Consequences of antenatal mental health problems for child health and development	- Maternal mental health during pregnancy affects children's emotional, cognitive, and physical health.	- Prompt identification and referral of pregnant women for specialist treatment is crucial to reduce adverse child outcomes.
12	Antenatal care for healthy pregnant women: a mapping of interventions from existing guidelines to inform the development of new WHO guidance on antenatal care	- 135 interventions identified in routine antenatal care guidelines. - Some conflicting recommendations among different guidelines.	- Guidelines should consider and refer to similar guidelines, exploring discrepancies in recommendations.
13	Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis	- Advanced maternal age (≥35 years) increases the risk of stillbirth, fetal growth restriction, neonatal death, NICU admission, and GDM. - Placental dysfunction may mediate adverse outcomes.	- Stillbirth risk increases with maternal age, not solely explained by co-morbidities or ART. Placental dysfunction may play a role.
14	Pregnancy Outcomes (1974-1992)	Pregnancy rate declined, live births proportion decreased, abortions increased. Varied trends by age.	Shifts in pregnancy outcomes over time and age groups.
15	Periodontal Disease and Pregnancy outcomes	18 studies suggested an association, 7 found no evidence. Clinical trials showed prophylaxis reduced risks.	Periodontal disease may increase the risk, but more rigorous studies needed.
16	Maternal Medication and Breastfeeding	Review of skills for informed medication decisions in breastfeeding.	Kinetic principles and infant factors aid clinical decisions.
17	OTC Pain Medication Use During Pregnancy	76% reported OTC pain reliever use during pregnancy. Acetaminophen most common. Education level influenced usage.	Reinforcement of pain medication education needed, considering potential harm.
18	Maternal ADHD Medication Use	Overall cohort showed association, but sub-cohort and sibling analysis found no increased risk.	Genetic and family factors may contribute to ADHD risk rather than medication.
19	Prenatal Developmental Origins	Prenatal maternal stress associated with behavioral and mental health issues in offspring. Effects varied by gestational age and biological correlates identified.	Maternal stress influences offspring neurodevelopment, cognitive function, and psychiatric disorders.
20	Prenatal Maternal Mental Health and Fetal Growth	Anxiety symptoms associated with reduced fetal head growth. Inconsistencies in other growth parameters. Cortisol dysregulation suggested.	Maternal mental health, especially anxiety, may impact fetal head growth.
21	Prenatal Mental Health and COVID-19	Limited literature found, but suggested an increase in prenatal mental health issues during the pandemic. Impact on birth outcomes noted but lacking research.	Urgent need for further research on the impact of prenatal mental health issues during the COVID-19 pandemic

The process of data synthesis entailed the systematic arrangement and concise synthesis of results derived from the studies that were incorporated, with a focus on certain outcomes such as gestational diabetes, weight gain, and lipid profiles. The researchers employed both qualitative and quantitative methodologies to assess and compare the findings across various studies.
The study took into account and addressed ethical aspects pertaining to the review process, which encompassed the utilization of data from human subjects, adherence to ethical principles, and safeguarding the confidentiality of participants.
The systematic review acknowledged and addressed potential limitations, including publication bias, heterogeneity among included studies, and limitations intrinsic to the available evidence, in order to ensure a transparent evaluation of the review's conclusions. The systematic review presents a thorough examination of the effects of prolonged use of atypical antipsychotic medications on the metabolic

health of mothers during pregnancy. This analysis offers significant contributions to clinical practice, policy formulation, and the identification of future research avenues.

Figure 1: PRISMA Flow Chart:



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Results and Discussion:

The systematic review conducted a comprehensive analysis of multiple studies to examine the effects of uninterrupted administration of atypical antipsychotic medication during pregnancy on the metabolic health of mothers. The results of the study indicated a heightened susceptibility to gestational diabetes while using specific drugs such as olanzapine or quetiapine, emphasizing the importance of diligent surveillance. Furthermore, it was shown that there are connections between the use of atypical antipsychotics and the occurrence of birth abnormalities, particularly among women who had pre-pregnancy obesity and engage in substance use. The research additionally emphasized the scarcity of guidelines pertaining to the management of schizophrenia and bipolar disorder during pregnancy, accompanied by conflicting findings about the safety of medications.

The topic of maternal metabolic adaptations during pregnancy, including alterations in lipid and glucose metabolism, was examined, with a particular focus on the intricate nature of balancing metabolic health with medication utilization. In addition, the study provided a contextual framework

for understanding these findings in relation to the wider context of maternal health and pregnancy outcomes. It acknowledged the complex relationship between maternal mental health, medication consumption, and progress during pregnancy. The objective of the review was to offer a full comprehension of the various factors that impact mother metabolic health during pregnancy, while recognizing the complex nature of these connections.

Although the study offers interesting insights, it is important to acknowledge several limitations, such as the presence of study heterogeneity and the necessity for more comprehensive trials. The evaluation emphasized the significance of acknowledging and addressing these shortcomings in order to enhance the body of data and effectively guide therapeutic practice. Moreover, it underscored the importance of continuous research to fully understand the safety and effectiveness of unconventional antipsychotic medicines during pregnancy. The review sought to promote evidence-based decision-making, policy formulation, and the enhancement of maternal and fetal health outcomes throughout gestation by pushing for additional inquiry and methodological rigor.

Conclusion:

The systematic review thoroughly examines the effects of continuing atypical antipsychotic medication on maternal metabolic health during pregnancy, highlighting the metabolic hazards associated with drugs like olanzapine and quetiapine, which increase the risk of gestational diabetes. The review also underscores the correlation between atypical antipsychotic use and specific congenital abnormalities, particularly in women with pre-existing obesity and substance abuse. It emphasizes the need for diligent monitoring of pregnant women on these medications and points out the lack of comprehensive guidelines for managing schizophrenia and bipolar illness during pregnancy. While initial findings suggest some antipsychotics may be safe and effective, further extensive trials are necessary to validate these results and inform clinical practice. The review acknowledges the complexity of managing maternal metabolic health due to physiological changes during pregnancy and identifies study heterogeneity and the need for larger trials as limitations. Ultimately, the review aims to guide evidence-based clinical decision-making, policy formulation, and future research to improve maternal and fetal health outcomes.

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