

Prenatal olanzapine exposure and congenital talipes equinovarus (clubfoot): a case report and review of emerging evidence

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Abstract

Recently, concerns have emerged about the potential teratogenic effects of olanzapine, particularly its association with congenital malformations such as congenital talipes equinovarus (clubfoot). Evidence from a large Finnish study, which reported a 2.5-fold increase in musculoskeletal anomalies, as well as various case reports, suggests a significant link between in-utero exposure to

olanzapine and these anomalies. This case report aims to add to the growing body of evidence by detailing a new instance of clubfoot following prenatal olanzapine exposure. A 25-year-old woman suffering from bipolar I disorder with psychotic features was treated with olanzapine during pregnancy, resulting in the birth of a male infant with clubfoot but no other malformations. This case underscores the importance of careful risk assessment and monitoring for pregnant women undergoing psychiatric treatment with olanzapine. Potential mechanisms, such as disrupted fetal musculoskeletal development due to olanzapine's pharmacological effects, warrant further investigation. Comparative analysis with other cases highlights consistent patterns, emphasizing the need for further research to elucidate the mechanisms and risk factors involved.

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Introduction

Olanzapine, a medication commonly prescribed for bipolar disorder, has raised significant concerns regarding its safety profile during pregnancy due to its high rate of placental passage compared to other antipsychotics such as haloperidol, risperidone, and quetiapine.^{1,2} Despite these concerns, sufficient human studies have not been conducted, and the potential benefits of olanzapine might warrant its usage in pregnant women despite the associated risks.³ Consequently, the Food and Drug Administration advises that olanzapine should only be used during pregnancy if the benefits outweigh the risks.⁴

Recently, there has been growing apprehension about its potential to cause congenital malformations, including congenital talipes equinovarus (clubfoot), which is a condition characterized by the inward and downward twisting of a baby's foot, affecting bones, muscles, tendons, and blood vessels.⁵⁻⁹ Emerging evidence suggests that in-utero exposure to olanzapine may be linked to various birth defects such as hip dysplasia, meningocele, and ankyloblepharon.^{5,6} For instance, a large Finnish study involving 1,273,987 pregnant women found a statistically significant association between olanzapine use during pregnancy and musculoskeletal malformations, including clubfoot.⁵ Additionally, case reports from Nepal, India, and Israel have documented instances of babies born with clubfoot following the maternal use of olanzapine during pregnancy.⁷⁻⁹

Despite these findings, there remains a lack of comprehensive understanding regarding the mechanisms through which olanzapine may cause such defects. The present case report aims to contribute to this growing body of evidence by detailing a new instance of clubfoot associated with prenatal olanzapine exposure. By examining this case in detail, we hope to shed light on potential mechanisms and risk factors, thereby informing clinical decisions and guiding future research directions.

Case Report

A 25-year-old married woman from Iran visited the psychiatry outpatient service, presenting with heightened euphoria, irritability, reduced sleep requirements, rapid flow of ideas, and excessive chattiness. These symptoms emerged abruptly after a severe argument involving verbal and physical elements with her sister-in-law, persisting for two weeks before she sought help. Previously, she had been hospitalized for a similar condition and was effectively managed with six sessions of electroconvulsive therapy and a daily intake of 10 mg of olanzapine. She had no significant medical or familial history of mental disorders or genetic abnormalities. During her mental status evaluation, she exhibited delusions of grandeur and persecution. Based on the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, Text Revision) criteria, she was diagnosed with bipolar I disorder with psychotic features and prescribed olanzapine. Her physical and systemic examinations did not reveal any notable findings. The symptoms gradually subsided after resuming olanzapine at 10 mg daily. Two months into treatment, she became pregnant without prior pre-conception counseling. After discussing the importance of continuing treatment during pregnancy and understanding the associated risks, she chose to proceed with olanzapine. Throughout her pregnancy, she was closely monitored by both a psychiatrist and an obstetrician, showing no signs of oligohydramnios, maternal obesity, or gestational diabetes. She received supplements including folic acid, iron, calcium, and tetanus toxoid, and experienced a smooth antenatal period. There was no indication of medication or substance use during pregnancy, nor was there any paternal smoking prior to conception. Early sonographic tests showed no anomalies; however, a routine 21-week ultrasound scan detected clubfoot in the fetus. She delivered a healthy male infant weighing 3.3 kg *via* cesarean section at 39 weeks who had an immediate post-birth Apgar score of 7/10. No additional malformations were noted upon examination by a neonatologist, and further assessments of genetics, the spine, and the brain showed no irregularities. The baby's clubfoot was classified as grade III (severe) congenital talipes equinovarus according to the Dimeglio classification.¹⁰ Breastfeeding continued, and at eight months old, the infant displayed mild sedation linked to the mother's ongoing olanzapine treatment. The mother maintained mental stability post-delivery. An orthopedic surgeon initiated manual manipulation on the infant's feet using the Ponseti technique, a globally recognized conservative treatment for clubfoot, starting at one week old. Subsequently, a clubfoot brace was applied, with continued follow-up by the orthopedic team.

Discussion

This document presents a case study of a woman suffering from bipolar I disorder with psychotic features who was on olanzapine medication during her pregnancy. She gave birth to a baby boy with bilateral clubfoot, a condition potentially associated with olanzapine exposure. The potential biological mechanisms by which olanzapine might contribute to such anomalies are multifaceted and involve several pathways. Firstly, olanzapine's pharmacological profile includes antagonism of multiple neurotransmitter receptors, including dopamine, serotonin, histamine, and adrenergic receptors. This broad receptor activity can disrupt normal embryonic development, particularly during critical periods of limb formation. Dopamine and serotonin play crucial roles in cellular proliferation, differentiation, and migration during embryogenesis. Disruption of these pathways could interfere with the normal signaling required for limb bud

development, potentially leading to malformations like clubfoot. Another plausible mechanism involves olanzapine-induced oxidative stress. Studies have shown that olanzapine can increase the production of reactive oxygen species (ROS) while simultaneously decreasing antioxidant defenses.¹¹⁻¹³ In one study, Stanisavljevic *et al.* demonstrated that olanzapine-treated mice exhibited a significant increase in ROS levels compared to controls.¹³ Excessive ROS can damage cellular components, including DNA, proteins, and lipids, disrupting normal cellular functions and leading to developmental abnormalities. In the context of fetal development, increased oxidative stress could impair the signaling pathways and cellular processes necessary for proper limb formation.¹³ Lastly, olanzapine's influence on placental function could also play a role in the development of congenital anomalies. The placenta is crucial for nutrient and gas exchange between the mother and fetus. Olanzapine has been shown to affect placental blood flow and function, potentially leading to a suboptimal intrauterine environment. Impaired placental function can result in fetal growth restriction and hypoxia, both of which are risk factors for congenital malformations, including clubfoot.^{11,12}

Notably, other common risk factors for clubfoot, such as smoking by either parent, maternal obesity, genetic factors, amniocentesis, certain medications (*e.g.*, selective serotonin reuptake inhibitors), and specific maternal conditions (*e.g.*, maternal single status and gestational diabetes), were absent in this case.¹⁴ However, this was the mother's first pregnancy, which itself is a risk factor that may increase the possibility of clubfoot in the baby.¹⁴ Similar cases have been reported in Nepal,⁷ India,⁸ and Israel,⁹ where infants developed clubfoot after their mothers took olanzapine during early pregnancy, with the male sex of the newborns being the only additional risk factor. Animal studies have also shown that olanzapine can cause significant developmental issues, including lower bone density and weight in adult male mice.^{15,16}

This case report has several limitations. Firstly, it is based on a single case, which limits the generalizability of the findings. Additionally, while other risk factors were excluded, the potential for unidentified confounding variables cannot be entirely ruled out. Further large-scale studies are needed to establish a definitive causal link between prenatal olanzapine exposure and clubfoot.

Practical implications for healthcare providers involve a careful assessment of the risks and benefits of prescribing olanzapine to pregnant women or those planning to conceive. It is essential to consider alternative treatments that may pose fewer risks to fetal development. For patients who require olanzapine to manage severe psychiatric symptoms, close monitoring and collaboration with obstetricians and pediatricians are crucial to ensuring both maternal and fetal well-being. Future research should also focus on large-scale, prospective studies that can provide more definitive evidence regarding the safety profile of olanzapine during pregnancy. These studies should aim to control for confounding factors such as maternal health conditions, concomitant medication use, and genetic predispositions.¹⁴ Additionally, research into the mechanisms by which olanzapine might contribute to congenital anomalies could offer valuable insights into safer therapeutic options.^{11,12}

Conclusions

In conclusion, while olanzapine remains an important medication for managing psychiatric disorders, its use during pregnancy warrants careful consideration due to potential risks such as clubfoot. Ongoing research and vigilant clinical practice are essential to optimizing outcomes for mothers and their children.

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