Research Article

Maternal Paracetamol And Ondansetron Use During Pregnancy And Risk Of Autism Spectrum Disorder In Offspring

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Abstract

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition influenced by genetic, prenatal, perinatal, and environmental factors. Paracetamol and ondansetron are commonly used during pregnancy, but evidence regarding their association with later ASD remains limited and inconsistent.

Objective: To evaluate the association between maternal paracetamol and ondansetron use during pregnancy and ASD in offspring, while considering relevant maternal, obstetric, neonatal, familial, and environmental factors.

Methods: A hospital-based matched case–control study was conducted at the Antenatal Care Clinic and Labor Ward of the Department of Obstetrics and Gynecology, Tikrit Teaching Hospital, Salah Al-Din Governorate, Iraq. Ninety mother–child pairs were included: 45 mothers of children with confirmed ASD and 45 mothers of children without ASD or another major neurodevelopmental disorder. Prenatal medication exposure was assessed by structured maternal interview and review of available medical, antenatal, obstetric, and prescription records. Exposure was classified according to medication, timing, frequency, duration, indication, and combined use. Associations were evaluated using crude odds ratios and multivariable logistic regression with 95% confidence intervals.

Results: Paracetamol exposure was more frequent among ASD cases than controls (68.89% vs. 42.22%, P=0.01; OR=3.00, 95% CI 1.27–7.09). Frequent/prolonged paracetamol use was also more common among cases (29.03% vs. 10.53%, P=0.04), with longer mean exposure duration (13.70±8.50 vs. 8.10±5.20 days, P=0.01). Ondansetron exposure was more frequent among cases (40.00% vs. 20.00%, P=0.04; OR=2.67, 95% CI 1.04–6.84), but was not independently associated after adjustment. Combined paracetamol and ondansetron exposure was associated with approximately fivefold higher crude odds of ASD (OR=5.23, 95% CI 1.63–16.77, P=0.005). In multivariable analysis, frequent/prolonged paracetamol use (AOR=3.86, 95% CI 1.08–13.79, P=0.04), combined exposure (AOR=4.12, 95% CI 1.17–14.52, P=0.03), and family history of ASD (AOR=5.63, 95% CI 1.08–29.41, P=0.04) remained independently associated with ASD.

Conclusion: In this study, frequent/prolonged maternal paracetamol use and combined prenatal exposure to paracetamol and ondansetron were independently associated with ASD in offspring, whereas exposure to either drug alone was not independently significant after adjustment. These findings indicate association rather than causation and should be interpreted in light of the small sample, retrospective exposure assessment, and possible residual confounding. Larger prospective studies using objective exposure measures are warranted.

Keywords: Autism Spectrum Disorder; Paracetamol; Acetaminophen; Ondansetron; Pregnancy; Prenatal Exposure; Case–Control Study.

1. Introduction

Autism spectrum disorder is a heterogeneous neurodevelopmental condition characterized by persistent difficulties in social communication and interaction together with restricted or repetitive patterns of behavior. Its etiology is multifactorial, involving substantial genetic susceptibility and interactions with prenatal, perinatal, and environmental influences. Prenatal factors reported in the literature include maternal infection, fever, obesity, diabetes, hypertensive disorders, medication exposure, environmental pollutants, and other conditions that may influence fetal neurodevelopment. The present study focuses on two medications that are frequently used during pregnancy: paracetamol and ondansetron.

Paracetamol (acetaminophen) is widely used for pain and fever during pregnancy. Its widespread use makes even relatively small potential developmental effects clinically important. Previous observational studies have reported modest associations between prenatal paracetamol exposure and later neurodevelopmental outcomes, including ASD and attention-deficit/hyperactivity disorder. However, findings have been inconsistent, and causal interpretation is complicated by confounding by indication, particularly maternal fever, infection, pain, and other illnesses that may themselves be associated with neurodevelopmental outcomes.

Biological plausibility has been proposed through several mechanisms, including oxidative stress, alterations in prostaglandin pathways, endocrine effects, immune-related pathways, and possible effects on fetal neurodevelopment. Nevertheless, experimental evidence and human epidemiological data do not establish a definitive causal relationship. Importantly, recent family-based analyses have suggested that some associations may be attenuated when shared familial and genetic factors are considered.

Ondansetron is a selective 5-hydroxytryptamine type 3 receptor antagonist increasingly used for nausea and vomiting of pregnancy and hyperemesis gravidarum. Evidence regarding its prenatal effects has largely focused on congenital anomalies and pregnancy outcomes, while data concerning long-term neurodevelopment are comparatively sparse. Because serotonin signaling participates in neuronal migration, synaptogenesis, and cortical development, a theoretical neurodevelopmental pathway has been proposed; however, theoretical plausibility should not be interpreted as evidence of harm.

An additional challenge is that women receiving ondansetron may have more severe nausea and vomiting, dehydration, nutritional disturbance, or hyperemesis gravidarum. Similarly, women using paracetamol may have fever or infection. These underlying indications can confound observed medication–outcome associations. Therefore, assessment of timing, duration, frequency, indication, and relevant maternal and familial characteristics is important.

The present study was designed to evaluate prenatal paracetamol and ondansetron exposure in relation to ASD among offspring in a hospital-based matched case–control population in Iraq. The analysis also considered maternal illness, obstetric and neonatal characteristics, family history, and environmental factors.

2. Aim of the Study

The study aimed to evaluate the potential association between maternal use of paracetamol and ondansetron during pregnancy and the risk of autism spectrum disorder in offspring, while considering relevant maternal, fetal, obstetric, neonatal, familial, and environmental confounding factors.

3. Patients and Methods

3.1 Study Design and Setting

A hospital-based matched case–control study with retrospective assessment of prenatal medication exposure was conducted at the Antenatal Care Clinic and Labor Ward of the Department of Obstetrics and Gynecology, Tikrit Teaching Hospital, Salah Al-Din Governorate, Iraq. Data were obtained through structured maternal interviews and review of available antenatal, obstetric, medical, prescription, and child health records.

3.2 Study Population

The study included 90 mother–child pairs divided equally into 45 cases and 45 controls. Cases were mothers of children with a documented diagnosis of ASD established by an appropriately trained healthcare professional using recognized diagnostic criteria. Controls were mothers of children without ASD or another major neurodevelopmental disorder and were selected from the same general source population. A 1:1 control-to-case ratio was used.

3.3 Eligibility Criteria

Participants were included when the mother consented to participation, sufficient information about the index pregnancy was available, maternal medication exposure could be assessed, and relevant maternal, obstetric, neonatal, familial, and environmental information could be obtained. Exclusion criteria included incomplete or unreliable exposure information, uncertain ASD diagnosis, major congenital or chromosomal abnormalities, known genetic syndromes strongly associated with neurodevelopmental disorders, severe maternal disease substantially affecting fetal development, known teratogenic medication exposure, or incomplete data required for analysis.

3.4 Exposure Assessment

Paracetamol exposure was defined as reported or documented use of any paracetamol-containing medication during the index pregnancy. Exposure was classified as first, second, third trimester, or more than one trimester. Frequency was categorized as occasional, repeated, or frequent/prolonged use. Duration, approximate dose when available, indication, prescription status, and the presence of maternal fever, infection, headache, or pain were recorded.

Ondansetron exposure was assessed similarly. Timing by trimester, duration, route of administration, indication, and severity of nausea and vomiting were recorded. Hyperemesis gravidarum, hospitalization for severe vomiting, and related maternal complications were also assessed because they could act as confounders.
Participants were additionally classified into four prenatal medication-exposure groups: neither medication, paracetamol only, ondansetron only, or both medications. The non-exposed group served as the reference category.

3.5 Potential Confounders and Outcome

Potential confounders included maternal age, educational level, socioeconomic status, residence, body mass index, paternal age, smoking and passive smoking, environmental exposure, maternal fever and infection, diabetes, gestational diabetes, hypertensive disorders, thyroid disease, psychiatric or neurological disorders, other medication use, gravidity, parity, miscarriage history, pregnancy complications, hyperemesis gravidarum, gestational age, preterm birth, mode of delivery, child sex, birth weight, neonatal complications, NICU admission, neonatal hypoxia, and family history of ASD or other neurodevelopmental and psychiatric disorders.
The primary outcome was the presence or absence of confirmed ASD in the offspring. For cases, available diagnostic documentation and the age and professional responsible for diagnosis were recorded.

3.6 Ethical Considerations

Ethical approval was obtained from the relevant Scientific and Ethical Committee, and administrative approval was obtained from the Department of Obstetrics and Gynecology and Tikrit Teaching Hospital. Written informed consent was obtained from participants. Participation was voluntary and participants could refuse or withdraw without affecting their medical care.

3.7 Statistical Analysis

Data were coded and analyzed using SPSS. Continuous variables were summarized as mean±standard deviation or median and interquartile range as appropriate, while categorical variables were summarized as frequencies and percentages. Independent-samples t-test or Mann–Whitney U test was used for continuous variables, and chi-square or Fisher's exact test for categorical variables. Crude and adjusted odds ratios with 95% confidence intervals were calculated. Multivariable logistic regression was used to control for relevant confounding variables. $P<0.05$ was considered statistically significant.

4. Results

4.1 Maternal Sociodemographic and Obstetric Characteristics

Maternal educational level, employment, residence, socioeconomic status, and body mass index were comparable between the ASD and control groups, with no statistically significant differences. Gravidity, parity, previous miscarriage, pregnancy planning, and cesarean delivery also did not differ significantly. Preterm delivery, however, was more frequent among mothers of children with ASD (22.22% vs. 6.67%, P=0.04).

Variable	ASD cases (n=45)	Controls (n=45)	P value
College education or higher	13 (28.89%)	14 (31.11%)	0.72
Employed	14 (31.11%)	16 (35.56%)	0.65
Urban residence	29 (64.44%)	31 (68.89%)	0.65
Insufficient socioeconomic status	13 (28.89%)	10 (22.22%)	0.47
BMI, mean±SD (kg/m²)	27.60±4.20	27.10±4.00	0.56
Preterm delivery	10 (22.22%)	3 (6.67%)	0.04*
Cesarean delivery	23 (51.11%)	19 (42.22%)	0.40

4.2 Maternal Medical Conditions

Maternal fever was significantly more frequent among cases than controls (37.78% vs. 15.56%, P=0.02), as was maternal infection (33.33% vs. 13.33%, P=0.02). Diabetes, gestational diabetes, hypertensive disorders, thyroid disease, psychiatric or neurological disorders, and other chronic conditions did not differ significantly.

Maternal condition	ASD cases	Controls	P value
Fever	17 (37.78%)	7 (15.56%)	0.02*
Infection	15 (33.33%)	6 (13.33%)	0.02*
Diabetes mellitus	3 (6.67%)	2 (4.44%)	0.65
Gestational diabetes	6 (13.33%)	4 (8.89%)	0.50
Hypertensive disorders	7 (15.56%)	4 (8.89%)	0.33
Thyroid disease	5 (11.11%)	3 (6.67%)	0.46

4.3 Paracetamol Exposure

Any maternal paracetamol exposure was significantly more frequent in the ASD group than among controls (68.89% vs. 42.22%, P=0.01), corresponding to approximately threefold higher crude odds of ASD (OR=3.00, 95% CI 1.27–7.09). Exposure during more than one trimester was also more frequent among cases (26.67% vs. 8.89%, P=0.03), while exposure confined to an individual trimester did not show statistically significant differences.

Among exposed mothers, frequent/prolonged use was significantly more common among ASD cases (29.03% vs. 10.53%, P=0.04). Mean duration of exposure was longer among cases (13.70±8.50 days) than controls (8.10±5.20 days, P=0.01). Occasional use, repeated use, prescription status, and self-medication did not differ significantly.

Paracetamol exposure characteristic	ASD cases	Controls	P value
Any exposure	31 (68.89%)	19 (42.22%)	0.01*
No exposure	14 (31.11%)	26 (57.78%)	Reference
Frequent/prolonged use among exposed	9 (29.03%)	2 (10.53%)	0.04*
Mean duration, days	13.70±8.50	8.10±5.20	0.01*
Exposure >1 trimester	12 (26.67%)	4 (8.89%)	0.03*
Medically prescribed among exposed	18 (58.06%)	13 (68.42%)	0.46
Self-medication among exposed	13 (41.94%)	6 (31.58%)	0.46

Fever was the most frequent indication for paracetamol among exposed mothers of ASD cases (38.71%), followed by infection-related symptoms (25.81%). Headache and musculoskeletal/other pain were more frequently reported among controls. The overall distribution of indications was not statistically significant (P=0.07).

4.4 Ondansetron Exposure

Ondansetron exposure was significantly more frequent among mothers of children with ASD than controls (40.00% vs. 20.00%, P=0.04), corresponding to crude OR=2.67 (95% CI 1.04–6.84). First-trimester exposure was more frequent in cases than controls (24.44% vs. 11.11%), but this difference was not statistically significant (P=0.10). Mean duration of ondansetron use was longer among cases than controls, although the difference was not significant (15.40±9.20 vs. 10.10±6.70 days, P=0.14). Route of administration, hyperemesis gravidarum, and hospitalization for severe vomiting did not differ significantly.

Ondansetron characteristic	ASD cases	Controls	P value
Any exposure	18 (40.00%)	9 (20.00%)	0.04*
No exposure	27 (60.00%)	36 (80.00%)	Reference

First trimester only	11 (24.44%)	5 (11.11%)	0.10
Second trimester only	3 (6.67%)	2 (4.44%)	0.65
Third trimester only	1 (2.22%)	1 (2.22%)	1.00
>1 trimester	3 (6.67%)	1 (2.22%)	0.31
Duration, days	15.40±9.20	10.10±6.70	0.14

4.5 Combined Medication Exposure

Exposure to neither medication was more common among controls than ASD cases (51.11% vs. 24.44%). Combined exposure to paracetamol and ondansetron was significantly more frequent among cases (33.33% vs. 13.33%) and was associated with approximately fivefold higher crude odds of ASD (OR=5.23, 95% CI 1.63–16.77, P=0.005).

4.6 Birth and Neonatal Characteristics

Mean gestational age was lower among ASD cases than controls (37.50±2.20 vs. 38.40±1.50 weeks, P=0.03). Preterm birth was significantly more frequent in cases (22.22% vs. 6.67%, P=0.04). Mean birth weight was also lower among cases (2940±520 vs. 3180±430 g, P=0.02). Low birth weight, NICU admission, neonatal hypoxia, and cesarean delivery were more frequent in cases but did not reach statistical significance.

Neonatal characteristic	ASD cases	Controls	P value
Gestational age, weeks	37.50±2.20	38.40±1.50	0.03*
Preterm birth	10 (22.22%)	3 (6.67%)	0.04*
Birth weight, g	2940±520	3180±430	0.02*
Low birth weight	9 (20.00%)	4 (8.89%)	0.14
NICU admission	8 (17.78%)	4 (8.89%)	0.21
Neonatal hypoxia	5 (11.11%)	2 (4.44%)	0.24

4.7 Family and Environmental Factors

A family history of ASD was significantly more frequent among cases than controls (22.22% vs. 4.44%, P=0.01). Family histories of other neurodevelopmental or psychiatric disorders were more frequent among cases but were not statistically significant. Passive smoking was commonly reported in both groups, while maternal smoking and reported environmental exposure did not differ significantly.

4.8 Multivariable Logistic Regression

After adjustment for relevant maternal, obstetric, neonatal, familial, and environmental variables, frequent/prolonged maternal paracetamol use remained independently associated with ASD (AOR=3.86, 95% CI 1.08–13.79, P=0.04). Combined prenatal exposure to paracetamol and ondansetron remained independently associated with approximately fourfold higher odds of ASD (AOR=4.12, 95% CI 1.17–14.52, P=0.03). Family history of ASD was also independently associated with ASD (AOR=5.63, 95% CI 1.08–29.41, P=0.04). Any paracetamol exposure, any ondansetron exposure, maternal fever, maternal infection, and preterm birth were not independently significant after adjustment.

Variable	Adjusted OR	95% CI	P value
Any paracetamol exposure	2.31	0.91–5.87	0.08
Frequent/prolonged paracetamol	3.86	1.08–13.79	0.04*
Any ondansetron exposure	1.94	0.68–5.53	0.21
Combined paracetamol + ondansetron	4.12	1.17–14.52	0.03*
Maternal fever	1.79	0.62–5.18	0.28
Maternal infection	1.65	0.53–5.11	0.39
Preterm birth	2.74	0.65–11.52	0.17
Family history of ASD	5.63	1.08–29.41	0.04*

5. Discussion

This hospital-based matched case–control study evaluated prenatal paracetamol and ondansetron exposure in relation to ASD in offspring. The principal findings were that paracetamol exposure was more common among mothers of children with ASD, frequent/prolonged paracetamol use remained independently associated with ASD, and combined prenatal exposure to paracetamol and ondansetron also remained independently associated after adjustment. In contrast, ondansetron exposure alone was associated with ASD in the crude analysis but not after adjustment. Family history of ASD was the strongest independent familial factor.

The finding that any paracetamol exposure was associated with approximately threefold higher crude odds of ASD is consistent with several observational studies cited in the original dissertation. Liew and colleagues reported an association between maternal acetaminophen use and ASD in a Danish birth cohort, while Alemany and colleagues reported modest associations with autism-spectrum and attention-deficit/hyperactivity symptoms across six European population-based cohorts. Meta-analytic evidence has also reported small increases in risk. However, these studies are observational and are vulnerable to exposure misclassification and confounding.

An important result in the present study was the stronger association observed with frequent or prolonged exposure. Frequent/prolonged use occurred in 29.03% of exposed ASD cases compared with 10.53% of exposed controls, and the mean duration of exposure was significantly longer in cases. After adjustment, frequent/prolonged use remained independently associated with ASD (AOR=3.86). This pattern may suggest that exposure intensity or cumulative exposure deserves attention in future research. At the same time, prolonged use can reflect recurrent or persistent maternal illness, including fever, infection, pain, or other conditions that may themselves affect fetal development.

The current study also found that paracetamol exposure during more than one trimester was more frequent among ASD cases. This observation is compatible with the hypothesis that repeated exposure may be more relevant than a single short exposure. Nevertheless, exposure across multiple trimesters may also be a marker of chronic or recurrent maternal illness. Therefore, the finding should not be interpreted as evidence of a direct medication effect.

The literature provides plausible but unproven biological mechanisms. Paracetamol crosses the placenta and is metabolized mainly by glucuronidation and sulfation, with a smaller fraction metabolized through oxidative pathways. Experimental work has proposed oxidative stress, endocrine effects, altered prostaglandin pathways, and changes in neurodevelopmental signaling as possible mechanisms. However, animal studies often use exposures that do not directly correspond to therapeutic human use, and biological plausibility alone cannot establish causality.

Evidence challenging a causal interpretation is also important. The dissertation cites a large Swedish population-based study in which associations observed in conventional analyses were not maintained in sibling-control analyses, suggesting that shared familial and genetic factors may explain part of the association. Genetic liability may influence both neurodevelopmental outcomes and pregnancy-related exposures, creating gene–environment correlation. These considerations are especially important in a small case–control study.

Maternal fever and infection were significantly more frequent among ASD cases in the present study. Fever and infection are also common reasons for paracetamol use, creating a classic confounding-by-indication problem. Although fever and infection were included in the multivariable analysis, neither remained independently associated with ASD. This may reflect overlap among maternal illness, medication exposure, familial susceptibility, and other pregnancy factors rather than evidence that fever or infection have no effect on neurodevelopment.

Ondansetron exposure was significantly more common among ASD cases and had higher crude odds of ASD. However, the association disappeared after adjustment. This attenuation is clinically important because ondansetron is often prescribed when nausea and vomiting are more severe. Hyperemesis gravidarum may be accompanied by dehydration, nutritional deficiencies, electrolyte disturbances, weight loss, and hospitalization. These features can be related to fetal and childhood outcomes independently of the medication. Thus, the crude association may partly reflect confounding by indication.

Combined exposure to paracetamol and ondansetron remained independently associated with ASD (AOR=4.12). This finding should be interpreted cautiously. It could represent a cumulative medication effect, but it could also identify pregnancies characterized by several maternal symptoms or illnesses, such as fever, infection, pain, nausea, vomiting, and dehydration. The relatively small number of participants in the combined-exposure category resulted in a wide confidence interval, limiting precision. The present data therefore do not establish a pharmacological interaction between the two drugs.

Perinatal findings were also notable. ASD cases had lower mean gestational age and birth weight and a higher frequency of preterm birth. These observations are compatible with published evidence linking prematurity, fetal growth abnormalities, and neonatal complications with ASD. However, preterm birth did not remain independently significant in the multivariable model. This suggests that its crude association may overlap with other maternal, medication, neonatal, or familial factors.

Family history of ASD was significantly more common among cases and remained independently associated after adjustment (AOR=5.63). This finding is consistent with the well-established familial and genetic contribution to ASD. It also illustrates why medication associations should be interpreted within a broader framework of inherited susceptibility and environmental exposures.

Overall, the findings support careful characterization of prenatal medication exposure rather than treating all use as equivalent. Future studies should distinguish dose, duration, trimester, indication, severity of maternal illness, and cumulative exposure. Prospective cohorts and studies using objective biomarkers may reduce recall bias and improve exposure classification.

6. Strengths and Limitations

The study has several strengths. It evaluated both paracetamol and ondansetron and considered individual as well as combined exposure. Exposure was assessed according to timing, frequency, duration, and indication rather than simply recording ever/never use. Cases and controls were drawn from the same general source population, and a range of maternal, obstetric, neonatal, familial, and environmental variables were assessed. Multivariable logistic regression was used to reduce the influence of measured confounding.

Several limitations must be considered. First, the retrospective case–control design is susceptible to recall bias, and mothers of children with ASD may recall pregnancy exposures differently from controls. Second, exact dose, formulation, cumulative exposure, and precise gestational timing were not available for all participants. Although medical records were reviewed when available, exposure assessment partly relied on maternal reporting. Third, the sample size was modest, resulting in wide confidence intervals and limiting the number of variables that could be included in the regression model. Fourth, residual confounding by medication indication, severity of maternal illness, genetic susceptibility, nutrition, healthcare utilization, and environmental exposures cannot be excluded. Finally, the hospital-based design and limited sample may restrict generalizability to other populations.

7. Conclusion

In this hospital-based matched case–control study, maternal paracetamol exposure and ondansetron exposure were more frequent among mothers of children with ASD than among controls in crude analyses. Frequent/prolonged paracetamol use and combined prenatal exposure to paracetamol and ondansetron remained independently associated with ASD after adjustment for measured confounders. Any paracetamol exposure and any ondansetron exposure alone were not independently significant after adjustment. Family history of ASD was also an independent factor.

These results demonstrate statistical associations and do not establish a causal relationship between prenatal medication exposure and ASD. The findings should therefore be interpreted cautiously, particularly given the small sample size, retrospective exposure assessment, and potential residual confounding.

8. Recommendations

1. Paracetamol use during pregnancy should be limited to clear clinical indications and used at the lowest effective dose for the shortest necessary duration.
2. Frequent, prolonged, or unsupervised paracetamol use should be avoided, and repeated use should be discussed with a healthcare professional.
3. Ondansetron should be prescribed after careful assessment of clinical need, particularly when considering use during the first trimester.
4. Combined or prolonged exposure to paracetamol and ondansetron should be carefully evaluated, while recognizing that the present findings do not prove causality.
5. Maternal fever and infection should be diagnosed and treated appropriately because untreated maternal illness may itself carry fetal risks.

6. Antenatal records should document medication name, dose, indication, timing, frequency, and duration whenever possible.
7. Children with a family history of ASD or relevant prenatal/perinatal risk factors should receive appropriate developmental monitoring.
8. Larger multicenter prospective studies using objectively documented medication exposure, dose-response assessment, trimester-specific analyses, and long-term neurodevelopmental follow-up are recommended.

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