Use of Non-steroid anti-inflammatory drugs (NSAID) by mothers before birth and the risk of neurodevelopmental disorder in offspring: A discussion on community health, scientific evidence and the responsibilities of policy governors

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Non-steroidal anti-inflammatory drugs (NSAID) are one of the most commonly used classes of drugs worldwide due to their positive effects on pain, fever, and inflammation, and are included in the list of essential medicines regularly updated by the World Health Organization (WHO) (1,2). Most of these drugs, including acetaminophen (paracetamol), which is included in NSAIDs, can be sold without a prescription, and it is estimated that NSAIDs are used by approximately 30 million individuals worldwide every day (3). NSAIDs exert their effects by inhibiting prostaglandin synthesis and are estimated to be used in approximately 70.0% of all pregnancies. However, prostaglandins are also known to play a critical role in fetal development (1,4). The United States Food and Drug Administration (FDA) reported in 2020 that NSAID use after the 20th week of pregnancy may increase the risks of oligohydramnios, renal dysfunction in the fetus, and premature closure of the ductus arteriosus. It recommended that drug use be planned on an individual basis, weighing the benefits and risks, and based on a joint decision between the patient and clinician (5). In recent years, conflicting data obtained from studies focusing on the possible relationship between NSAID use during pregnancy and neurodevelopmental disorders, and the interpretation of this data by public officials and society outside of its context, have necessitated urgent and balanced consideration of the issue (6-8).

In studies, the odds ratios (OR) for attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and cognitive developmental delay in children of mothers who used NSAIDs during pregnancy were found to be 1.1-1.3, 1.1-1.2, and 1.1, respectively (9,10). A recent meta-analysis evaluating the results of 16 studies involving over two million children, conducted by Bérard and colleagues, found that NSAID use during pregnancy may only increase the risk for ADHD (OR= 1.2, 95% Confidence Interval= 1.1-1.3), this risk may also be dependent on confounding variables, and that the risk for other neurodevelopmental disorders is not increased (11). A review by Sheikh and colleagues also supports that NSAID use by mothers during pregnancy does not increase the risk of neurodevelopmental disorders in their children when other confounding variables, including the development of other siblings, are controlled (12). It should be noted that even in studies reporting an increase in risk, the increase is modest (13). OR is influenced by factors such as study design, effect size, and the prevalence of the disorder in the population, but in general, values of 2.0-3.0 and above are considered significant in epi-

DOI: 10.5505/kpd.2025.93271

Cite this article as: Tufan AE. Use of Non-steroid anti-inflammatory drugs (NSAID) by mothers before birth and the risk of neurodevelopmental disorder in offspring: A discussion on community health, scientific evidence and the responsibilities of policy governors. Turkish J Clin Psych 2025; 28: 298-300

The arrival date of article: 02.12.2025, **Acceptance date publication:** 15.12.2025

Turkish J Clinical Psychiatry 2025;28: 298-300

demiological studies (13). On the other hand, the relationships identified in observational studies do not indicate causality (14). It has been frequently observed that public administrators and the general public express the view that relationships observed at the group level are also valid at the individual level. These views are referred to as the “ecological fallacy” in epidemiology, and it is accepted that aggregate statistics cannot be directly applied to individual risks (15). Therefore, a meta-analysis reporting that NSAID use during pregnancy increases the risk of ADHD or ASD in children cannot be interpreted at the individual level as “every mother who uses NSAIDs increases the risk of ADHD or ASD in her child.” Relationships at the group level may not hold at the individual level due to different factors (genetic, environmental factors, etc.) (15). On the other hand, relationships observed at the individual level cannot be generalized to the group level, and such generalizations are called the “atomistic fallacy” (16). For example, the fact that some individuals have a relationship between their mothers' use of NSAIDs and their own ADHD or ASD diagnoses cannot be interpreted at the community level as “mothers' use of NSAIDs during pregnancy increases the risk of ADHD or ASD in their children.” The effect of NSAID doses and duration of use during pregnancy on children has also not been sufficiently evaluated (9-12). Therefore, it can be said that additional studies are needed in this area, controlling for confounding variables such as family history, birth weight, sibling development, and genetic predisposition (17). Current evidence, as emphasized by the Turkish Society of Gynecology and Obstetrics, suggests that the use of NSAIDs during pregnancy is safe and that these drugs can be used at the lowest effective dose, for the shortest duration, and under a doctor's recommendation. Ongoing debates do not provide scientific evidence sufficient to change existing clinical practices (7).

The ongoing debate regarding the use of NSAIDs during pregnancy can be evaluated in terms of limited scientific data, stakeholders' emotional investment in this issue, and public policies (8,18). The ongoing debate highlights the importance of developing scientific literacy among the general public and public administrators, planning public policies based on scientific data, and the need for independent, unbiased scientific rigor (8,17,18). From this perspective, inquiry-based, learner-centered learning, scientific methods, causal reasoning, probability, uncertainty, cognitive errors and biases, and critical thinking should be included among the fundamental steps of basic social education (19). Public administrators should align their policies with scientific principles and avoid the trap of populism (20). Scientists, on the other hand, can add their research protocols and analysis plans to pre-registration platforms, increase data sharing with their peers, and support the dissemination of their scientific findings through various platforms by summarizing them in a way that the public can understand (8, 18). The ability of scientists to conduct scientific research independently of political direction and pressure will increase the reliability of the data obtained (8). It should also be noted that the listed recommendations can be replicated and their effects can only be evaluated in the medium to long term.

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