Impact Of NSAIDS During Pregnancy: Risks, Recommendations And Clinical Considerations

B.Dinesh kumar[1], P.kavya[1],R.Naseefa[1],T.Hariharan[1], T.Muthu[1] , Dr. C.Jagan mohan [1], Mufida Begum Ifthikhar[1]*

[1]Faculty of pharmacy,Karpagam Academy of Higher Education, Coimbatore.

Corresponding author Mufida Begum Ifthikhar*
orcid id:0009-0003-1057-5879
[1]email :mufinisar2010@gmail.com

Abstract

NSAIDs, or nonsteroidal anti-inflammatory medicines, are frequently used for fever, inflammation, and pain during pregnancy.However, their safety profile during gestation remains controversial. This review synthesizes current evidence on the risks of NSAID use in each trimester, safer alternatives, and recommendations for cautious prescribing. First and second trimester use at low doses is likely safe, but risks increase later in pregnancy, especially after 30 weeks. Reduced amniotic fluid, constriction or closure of the fetal ductus arteriosus, and possible effects on the kidneys, heart, and lungs of the fetus are among the significant side effects.Acetaminophen and non-pharmacological options are safer alternatives. If at all feasible, NSAIDs should be avoided during the third trimester. The lowest effective dose for the shortest amount of time under medical supervision—while taking into account the fetal state and newborn outcomes—should be used when use is clinically indicated.More research is warranted on long-term impacts of prenatal NSAID exposure

Key words : Pregnancy,NSAID,Neonatal, Premature,Miscarriage,Fertility, trimester, Newborn, risks, drug therapy.

1. Introduction

Drug classes in the world.NSAIDs have analgesic (pain-relieving), antipyretic, and anti-inflammatory properties, as their name implies.They work by inhibiting cyclooxygenase enzymes and reducing prostaglandin synthesis in the body. Since many NSAIDs don’t require a prescription to be purchased over-the-counter, self-medication is made simple. Ibuprofen (Advil, Motrin) and naproxen (Aleve) are among the most popular NSAID choices for treating various types of mild to moderate pain, including headaches, muscle aches, joint pain, menstrual cramps, toothaches and injuries. NSAIDs are also used to manage inflammatory conditions like arthritis. However, the wide availability and frequent use of these medications make their safety profile during pregnancy a major public health concern.

While NSAIDs are widely used by pregnant women, their safety during pregnancy has been controversial and debated for decades. Among the most widely prescribed pharmaceuticals in the world for the treatment of pain, fever, and inflammation are nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and naproxen. Pregnant women often take NSAIDs for conditions like headaches, back pain, and joint issues. However, the use of NSAIDs during pregnancy has long been a topic of concern and debate in the medical community. These drugs are able to cross the placenta and enter fetal circulation, raising fears about potential risks like miscarriage, birth defects, or complications[1]. There is evidence that NSAID usage during the third trimester might cause premature closure of the ductus arteriosus, pulmonary hypertension, and in extreme circumstances, stillbirths or newborn mortality, even though certain concerns may be exaggerated [2,3]. Earlier use in the first and second trimesters appears to be safer but may still impact fertility and increase risks slightly[4]. Given the widespread use of these drugs and the controversial nature of their safety profile during pregnancy, it is critical for expecting mothers and medical providers to carefully weigh the potential risks and benefits.

This article will provide an extensive examination of the latest research into how common NSAIDs may impact pregnant women and their developing fetuses at different stages of gestation. Evidence-based recommendations will be provided to help inform clinical practice and guide educated decisions about the cautious use of NSAIDs during pregnancy. Aspirin, ibuprofen, naproxen, diclofenac, and other nonsteroidal anti-inflammatory medicines (NSAIDS) are among the most widely used prescription NSAIDs can pass through the placenta and enter the fetal bloodstream, unlike many other medications. This has raised concerns among researchers and physicians about potential risks to the developing fetus[1]. NSAID use has been related in certain studies to major hazards such as premature closure of the ductus arteriosus, kidney dysfunction, miscarriage, or a variety of birth abnormalities, particularly during the third trimester[2,3]. However, the data is not conclusive, with some studies showing minimal risks[4]. Due to the widespread use of over-the-counter NSAIDs by pregnant women and the uncertain but potentially severe risks, medical experts caution against casual NSAID use in pregnancy.It is advised to use the least amount of medication for the shortest amount of time. Until more definitive research is available, pregnant women and their physicians must carefully weigh the benefits against potential harms when considering NSAIDs, especially later in pregnancy. Caution and limitation of use are warranted.

2.Risks of NSAIDs in Pregnancy

Recent data reviews reveal that prolonged use of NSAID medications like ibuprofen or naproxen for more than a few days during the second half of pregnancy (after 20 weeks gestation) may pose serious risks to the fetus. Specifically, extended NSAID use from week 20 onwards has been associated with impaired fetal kidney function leading to low amniotic fluid (oligohydramnios), as well as constriction of the ductus arteriosus blood vessel in the fetal heart. These conditions can restrict fetal development and create cardiac dysfunction, underscoring the need for cautious use of NSAIDs in the later stages of pregnancy. Healthcare providers are advised to avoid prescribing systemic NSAIDs after 20 weeks unless there is a

strong clinical necessity. In such cases, the lowest effective dose should be used for the shortest possible duration. If a pregnant patient has taken NSAIDs for several days after week 20, doctors may want to monitor for oligohydramnios, discontinue use if detected, and confirm ongoing need. As always, providers should document all current and recent medication use at antenatal visits, including over-the-counter drugs[5,6].Crucially, NSAIDs are still not recommended in the third trimester (after 28 weeks) because of the higher risks of ductal constriction, renal damage, maternal hemorrhage, and the prevention of labor contractions as the birth date draws near.Judicious use based on fetal safety should guide NSAID prescribing for pregnant patients in mid to late gestation[7].

3. Ductus Arteriosus Constriction/Closure

Using NSAIDs in the later stages of pregnancy might cause the ductus arteriosus to constrict or close early, which is one of the most concerning adverse effects. The ductus arteriosus, which routes blood away from the lungs, is a vital blood vessel in the fetal circulation. Towards the end of gestation, this vessel typically closes naturally as the baby's lungs prepare to function after birth. However, NSAID exposure in the third trimester can trigger early constriction or closure of the ductus arteriosus[8].

Several studies have shown that NSAIDs inhibit the production of prostaglandins that normally maintain the patency and dilation of the ductus arteriosus. When exposed to NSAIDs like indomethacin or ibuprofen late in pregnancy, up to 50% of fetuses show signs of constricted ductal flow. More severe cases progress to complete ductal closure, depriving the baby's circulation of a critical outlet.Elevated pulmonary vascular resistance, pulmonary hypertension, and higher pressure on the right side of the heart result from this .In utero, the fetus may develop right-sided heart failure, hydrops fetalis , or even die. After birth, persistent pulmonary hypertension and impaired cardiac function can be life-threatening[7].

All major classes of NSAIDs have been implicated in constricting or closing the fetal ductus arteriosus during the third trimester. This adverse effect appears most pronounced with NSAIDs that selectively inhibit COX-2 enzymes. For this reason, indomethacin and celecoxib are contraindicated near term. However, frequently used NSAIDs like ibuprofen and naproxen also carry risks. Unless there is a strong medical necessity, NSAIDs should be avoided after 30 weeks gestation[8].

4.Miscarriage

NSAID use during early pregnancy or around the time of conception may raise the risk of miscarriage, according to some study. Proposed mechanisms include impaired implantation, placental abnormalities, and reduced production of pregnancy-sustaining hormones like progesterone[10].

One study found women who took NSAIDs in the week prior to conception had an 80% higher risk of miscarriage. The rates were elevated regardless of which NSAID was used. Another study saw increased risks when NSAIDs were taken around conception or during the first trimester. The more frequent the usage, the higher the observed risks[5,8].

However, other studies found no linkage between sporadic first trimester NSAID use and miscarriage. The data is mixed, with some research showing a weak association but other studies showing no clear evidence. The relationship may depend on dosage, duration, and exact

timing of use[6]. Nonetheless, experts recommend caution with NSAID use when trying to conceive or early in pregnancy. For those requiring pain relief, acetaminophen may be a safer alternative during this critical developmental window[8].

5. Potential Birth Defects

Particularly after first trimester use, certain epidemiological studies have indicated a link between prenatal NSAID exposure and specific fetal malformations. Proposed mechanisms involve disturbing prostaglandin balance, interrupting normal cell growth, or impacting the fetal cardiovascular system[9,10].

Gastroschisis, where the baby's intestines protrude outside the abdomen through an opening, shows the strongest link with early NSAID use. One meta-analysis found NSAID use in the first trimester doubles the risk of gastroschisis[11].Neural tube anomalies, congenital heart disease, and orofacial clefts are further defects that may be linked. [9,12].

However, the data is conflicting. Some studies demonstrate correlations while others find no increase in birth defect rates with NSAID use. Dosage and timing may play a role. Given the conflicting evidence, most experts conclude occasional use of NSAIDs does not pose a major teratogenic risk in healthy pregnancies. However, until more conclusive evidence is available, cautious use is advised, especially for high-risk pregnancies[10].

6. Reduced Fertility and Ovulatory Disorders

Some research indicates that chronic NSAID use may inhibit ovulation, reduce fertility, and increase time to conception. Proposed mechanisms again involve disruption of normal prostaglandin balance. Prostaglandins play an important role in the ovulatory process[12,13].

Studies associate NSAID use with higher rates of anovulatory cycles, luteinized unruptured follicle syndrome, and impaired corpus luteum function. These effects appear most pronounced with frequent or long-term use[11]. One study found women taking NSAIDs during the periovulatory period were 2-3 times more likely to have an anovulatory cycle[9]. Another study saw increased incidence of luteinized unruptured follicles among regular NSAID users[10].

Therefore, experts recommend women trying to conceive avoid routine NSAID use and limit usage to the lowest effective dose for the shortest duration possible[13]. Those struggling with infertility or ovulatory disorders may want to minimize NSAID use under medical guidance. However, occasional use for limited periods may not substantially impact fertility. More research is still needed into the nuances of how NSAIDs effect aspects of menstrual cycling[12].

7. Safe Options in Pregnancy

7a .Acetaminophen

Acetaminophen (Tylenol) is considered the first-line pain reliever for pregnant women because substantial evidence indicates it has a good safety profile throughout pregnancy[9-11]. Multiple studies have found no increased risk of major birth defects, miscarriage, preterm birth, or other adverse outcomes when acetaminophen is used at recommended doses[12,13].

Unlike NSAIDs, acetaminophen is not associated with premature constriction or closure of the fetal ductus arteriosus even with third trimester use. It also does not appear to impact ovulation

or fertility[11]. The only demonstrated risks are liver toxicity when high doses are exceeded or use is prolonged[13]. As long as dosing guidelines are followed, acetaminophen is deemed safe by obstetricians and pediatricians.

The American College of Obstetricians and Gynecologists recommends acetaminophen as the pain/fever reliever of choice for pregnant women throughout all trimesters[9]. The fetus is exposed to lower levels compared to the mother since acetaminophen undergoes metabolic inactivation via glucuronidation in the placenta before crossing over[12]. Experts conclude acetaminophen has no detectable adverse effects when used intermittently at therapeutic doses during pregnancy[11,13].

7b.Low-Dose Aspirin

Low-dose aspirin (60-80mg) may be used under medical supervision in high-risk pregnancies. Small aspirin doses are sometimes prescribed to help prevent preeclampsia in women at elevated risk for the condition[9,11] .Preeclampsia is characterized by high blood pressure and signs of damage to other organ systems, potentially with severe complication.[10]. The exact mechanisms are unclear, but aspirin may improve placental blood flow and limit damage from oxidative stress and inflammation[12,13]. This needs to be balanced with the anti-platelet effects of aspirin which could increase bleeding risks[10]. Therefore, low-dose aspirin therapy is only initiated when the benefits are deemed to outweigh the risks.

Use of low-dose aspirin in pregnancy should always be monitored by a physician through regular follow-up[9]. Women on aspirin therapy need close monitoring for bleeding complications and appropriate dosing adjustments if complications develop. The goal is to use the minimum effective dose for the shortest amount of time[13]. When managed carefully under medical supervision, low-dose aspirin can be considered safe for high risk pregnancies[12].

7c.Alternative Pain Relief Options

Pregnant women concerned about medications often seek out alternative options for relief like hot/cold therapy, massage, acupuncture, chiropractic, yoga, physical therapy or cognitive behavioral approaches[9-11]. Complementary health approaches without pharmacological components may alleviate some types of acute or chronic pain[12,13].

Heat packs can soothe sore muscles and joint pain[10]. Ice packs help reduce swelling and inflammation[9]. Therapeutic massage targets tense muscles as well as back, hip, and pelvic pain triggered by pregnancy biomechanics[11]. Trained prenatal massage therapists know modifications that ensure comfort and safety[12]. Acupuncture and chiropractic care may ease certain types of musculoskeletal pain[13]. A physiotherapist can provide exercises and modalities for pelvic girdle or low back pain[9]. Mind-body techniques help patients cope with pain perception[11].

Non-pharmacological remedies may be beneficial as an adjunct or alternative to pain medications when feasible[10]. However, they should not replace necessary pharmacological pain relief.[12] It is important to consult doctors to help determine the most suitable options during pregnancy for each woman’s unique circumstances and health status[13].

8. Recommendations for NSAIDs Use

8a.Avoid in Third Trimester, Especially Near Delivery

NSAIDs should be avoided entirely during the third trimester if possible, particularly after 30 weeks gestation. The risks of premature ductal constriction increase as pregnancy progresses.Within 1-2 weeks of delivery, NSAID use can lead to serious adverse effects like pulmonary hypertension, impaired circulation, or even fetal demise [14,15]. If NSAIDs are used close to delivery, the newborn will require careful monitoring and potential treatment for ductal closure [16]. Elective use is never recommended this late in pregnancy [17].

8b.Use Lowest Effective Dose for Shortest Time Possible

If NSAIDs are deemed medically necessary in the first or second trimester, use the lowest effective dose for the shortest duration possible [2,5]. Long-term daily use should be avoided [14]. Intermittent or short-term use of over-the-counter doses minimizes risk [18]. For chronic conditions, the benefits and harms of continued NSAID use in early pregnancy should be weighed carefully [17].

8c.Discuss Risks and Benefits with Doctor Before Using

Women should have an informed discussion with their provider when considering NSAIDs in pregnancy [18]. The latest evidence on potential risks at different gestational ages should be explained [15]. The medical necessity, alternative options, and planned monitoring should be reviewed [14]. An individual risk-benefit assessment is needed to guide clinical decisions [17].

8d.Monitor Newborn After Third Trimester Exposure

If NSAIDs are used in late pregnancy, newborns require close monitoring after delivery [18]. Signs of pulmonary hypertension, right-heart dysfunction, or impaired transition should be evaluated with potential treatment [14]. Oxygen levels, blood pressure, echocardiography, and clinical status need monitoring in the first days of life [17].

8e.Research and Development

While our understanding of the risks of NSAIDs during pregnancy has improved significantly, important questions remain unanswered [14-18]. Long-term follow-up studies tracking the development and health of children exposed to NSAIDs in utero could provide valuable insight into potential lasting impacts [15]. Research into whether fetal programming and gene expression is affected by early NSAID exposure may reveal subtle effects [18]. Comparing newer COX-2 selective NSAIDs to traditional NSAIDs in pregnancy outcomes can refine safety profiles within this medication class [14].

Additionally, it will be important to study if certain high-risk pregnant populations are more susceptible to NSAID-related complications like obese, hypertensive, or diabetic women [17]. Optimal monitoring and risk mitigation approaches for clinically necessary NSAID use need to be established [18]. Developing evidence-based decision tools to weigh risks and benefits at different gestational ages can enhance clinical practice [15]. Reducing inappropriate NSAID prescribing through provider education and guidelines is also critical [18].

Finally, further exploration of effective non-pharmacologic pain management options can potentially minimize need for NSAIDs among pregnant women [14]. Continuously updated meta-analyses and safety monitoring systems are warranted as new evidence emerges [17]. While current data is reassuring for cautious use in early pregnancy, there are still knowledge gaps about NSAID risks later in gestation and lasting impacts that require further research [18].

9. Conclusion

NSAIDs may have a role in early pregnancy but risks increase later on based on current evidence, NSAIDs appear relatively safe during the first half of pregnancy if used sporadically in low doses. Short-term use does not substantially increase risks of miscarriage or birth defects. The data supports cautious use in very early pregnancy and the first two trimesters when medically warranted.

However, risks appear to increase significantly as pregnancy advances, especially after 30 weeks gestation. There is good evidence that NSAID exposure in the third trimester can lead to ductus arteriosus constriction or closure, elevated pulmonary pressures, and impaired fetal circulation. This can progress to right heart failure, fetal hydrops or demise if NSAID use continues. Premature ductal constriction may also impact transitional circulation after delivery. Therefore, while the risks of occasional NSAID use in early pregnancy seem modest, medical experts strongly caution against use in the later stages of gestation. Women with painful conditions or fever should opt for acetaminophen later in pregnancy under medical guidance. Elective NSAID use in the third trimester should be avoided entirely due to adverse effects on fetal cardiovascular physiology.

Patients and Doctors Should Weigh Pros and Cons of Use Because the risks are dose-dependent and vary by gestational timing, it is important for patients and doctors to carefully weigh the potential benefits against the risks when considering NSAID use at different points in pregnancy.

Occasional use of ibuprofen or naproxen in the first 20 weeks may be deemed acceptable if needed to improve a mother's quality of life and ability to function. However, as pregnancy progresses, risk-benefit calculations may start to discourage further use. By the third trimester, risks often clearly outweigh benefits for most patients. Elective use should be avoided, and even short-term use warrants close monitoring.

Doctors can help educate patients on the gestational week-specific risks of NSAIDs based on the latest evidence and provide tailored recommendations. The medical necessity and appropriateness of NSAIDs needs to be evaluated on an individual basis through shared decision-making.

More Research Needed on Long-Term Impacts of Fetal Exposure, While the short-term risks of NSAID use at different pregnancy stages have been studied, less is known about potential long-term impacts of fetal exposure. Questions remain about effects on child development, immunity, neurological function, or disease risks later in life.

Some researchers hypothesize that anti-prostaglandin effects of NSAIDs may impact kidney development or raise blood pressure long-term. However, current studies are limited and conflicting. Continued research is warranted on whether in utero NSAID exposure has subtle effects on childhood growth and susceptibility to chronic diseases. Tracking development of children exposed to NSAIDs at different gestational ages can provide valuable safety data.

In summary, judicious use of NSAIDs under medical guidance may be appropriate earlier in pregnancy. However, women and doctors are advised to exercise an abundance of caution with NSAID use as pregnancy advances towards term. Continued research can further refine risk-benefit assessments to optimize maternal-fetal outcomes.

10. Abbreviations:

a. NSAIDS- Non steroidal anti-inflammatory drugs.
b.COX- Cyclooxygenase.

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