International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Kumar M et al. Int J Reprod Contracept Obstet Gynecol. 2026 Mar;15(3):1149-1153
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20260588

Review Article

Aspirin history and its clinical applications in pregnancy

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Received: 01 December 2025
Revised: 31 January 2026
Accepted: 31 January 2026

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ABSTRACT

Aspirin (acetylsalicylic acid), derived from salicylate-containing plants and refined through major chemical advances in the 19th century, remains one of the most widely used NSAIDs. Its irreversible inhibition of COX-1 reduces thromboxane A_2 production, producing sustained antiplatelet effects central to its therapeutic use. Hypertensive disorders of pregnancy are major contributors to maternal and perinatal illness and death globally, with preeclampsia posing a significant clinical challenge. Low-dose aspirin (LDA) is extensively studied in pregnancy and is recommended for preventing preeclampsia, with strong evidence demonstrating reduced maternal and perinatal morbidity, particularly when initiated before 16 weeks. Additional benefits include lower rates of preterm birth, improved foetal growth in selected cases of IUGR, and enhanced pregnancy outcomes in women with APS and SLE when used alone or in combination with heparin. Major guidelines from ACOG, NICE, RCOG, WHO, and FIGO support LDA use in high-risk pregnancies.

Keywords: Aspirin, Preeclampsia, Gestational hypertension, IUGR, SLE

INTRODUCTION

Aspirin (acetylsalicylic acid) is among the oldest and most extensively studied drugs and remains fundamental to modern medicine. Classified as a non-steroidal anti-inflammatory drug (NSAID), it exhibits analgesic, antipyretic, anti-inflammatory, and antiplatelet effects that support its wide clinical use. The therapeutic use of salicylate-containing plants, particularly species of willow (*Salix*), can be traced to ancient civilizations. Greek, Assyrian, and Egyptian medical writings describe the use of willow bark preparations for the relief of pain, fever, and inflammation. Although these practices were rooted in empirical experience rather than scientific rationale, their clinical value was later validated through developments in pharmacology and chemistry. The first formal scientific assessment of willow bark was reported in 1763 by Reverend Edward Stone, who communicated its antipyretic properties to the royal society of London. The evolution of aspirin accelerated in the 19th century with major advances in organic chemistry. Salicin was isolated from willow bark in 1826, and salicylic acid was subsequently synthesized in 1838. While these agents were adopted for therapeutic use, their clinical utility was constrained by considerable gastrointestinal adverse effects. A landmark advance was achieved in 1897 when Felix Hoffmann at Bayer acetylated salicylic acid to create acetylsalicylic acid, a formulation that retained efficacy while offering improved gastrointestinal tolerability. Aspirin was commercially introduced by Bayer in 1899 and by 1900, became available in a stable, soluble tablet formulation.[1-5]

The widespread adoption of aspirin was unprecedented. By the early 20th century, it had gained global acceptance as a safe and effective analgesic and antipyretic. In 1915, aspirin became available without a prescription, further cementing its role as one of the most accessible and commonly used medications worldwide. Subsequent discoveries, particularly the elucidation of its mechanism of action through irreversible inhibition of cyclooxygenase (COX) enzymes and suppression of prostaglandin and thromboxane synthesis, expanded its clinical indications far beyond pain relief.[6]

PHARMACOKINETICS

After ingestion of non-enteric aspirin, absorption is rapid, but only about 70% reaches circulation unchanged due to first-pass liver hydrolysis. Most platelet inhibition occurs in the portal circulation.[7] Aspirin can be given orally, rectally, intravenously, or topically, depending on the required therapeutic effect.

After it is taken, the drug is quickly converted into salicylic acid, and both aspirin and its metabolites are rapidly absorbed, with salicylate showing a serum half-life of about 1-30 hours. Aspirin enters the bloodstream from the intestine by passive diffusion and rapidly deactivates platelets before reaching the liver for first-pass metabolism. Salicylic acid is eliminated in the liver. It diffuses into the mitochondrial matrix, where it is activated to an acyl-CoA by ACSM2B (Xenobiotic/medium chain fatty acid) and then conjugated with glycine by GLYAT (Glycine *N*-acyltransferase). This produces salicylic acid, which is excreted in urine, while CoA is regenerated.[8]

Mechanism of action

COX, or prostaglandin endoperoxides synthase, is a membrane-bound glycoprotein with three forms (COX-1, COX-2, and COX-3). COX converts arachidonic acid into prostaglandin H_2 (PGH_2), the precursor for various other prostaglandins.[9] COX-1 is present in many cells, including endothelial cells and platelets. Aspirin irreversibly inhibits COX-1 by acetylating the serine 530 residue in its active site, preventing arachidonic acid from binding and blocking the formation of prostaglandin G2/H2. The reaction with COX-2 occurs at a rate that is 10 to 100 times slower than that with COX-1.[10] It is the only COX inhibitor that causes irreversible enzyme inactivation.[11] Because platelets cannot synthesize new COX-1, this inhibition persists for their entire lifespan (7-10 days). By suppressing COX-1 activity and prostaglandin production, aspirin reduces the formation of thromboxane A2, a key promoter of platelet activation, thereby helping prevent cardiovascular events through reduced platelet aggregation.[7]

Indications

Hypertensive disorders in pregnancy are a major contributor to maternal and perinatal illness and death globally, with preeclampsia posing a particularly significant challenge in obstetric care. Over the last twenty years, low-dose aspirin (LDA) has gained recognition as an effective preventive measure for lowering the risk of preeclampsia and its related complications. Preeclampsia is a multisystem condition marked by sustained high blood pressure during pregnancy or after delivery, often accompanied by findings such as proteinuria, low platelet count, liver dysfunction, declining kidney function, pulmonary edema, or neurological symptoms.[12] The disorder is widely thought to originate in the placenta, where inadequate trophoblast invasion and poor spiral artery remodelling reduce blood flow and create cycles of placental hypoxia and reperfusion. These disturbances lead to excess production of reactive oxygen species and the release of cytokines, lipid peroxides, and syncytiotrophoblast fragments into the maternal bloodstream. As a result, heightened inflammation, oxidative stress, and endothelial dysfunction are central to the disease process.[13]

The CLASP Trial (1994), one of the earliest large-scale studies on LDA in pregnancy, reported a modest 12% relative reduction in preeclampsia risk, although this decrease did not reach statistical significance across all subgroups.[14] The American College of Obstetricians and Gynaecologists advises aspirin use for women who have had preeclampsia in more than one pregnancy or who previously developed preeclampsia requiring delivery before 34 weeks of gestation.[15] Professional organizations endorse using LDA (60–80 mg daily) as a preventive measure for women at high risk of developing preeclampsia. In the United Kingdom, the National Institute for Health and Clinical Excellence recommends defining this high-risk group using a set of ten factors based on maternal characteristics and both medical and obstetric history.[16] The ASPRE trial showed that in women with singleton pregnancies classified as high risk for preterm preeclampsia through first-trimester combined screening, taking 150 mg of aspirin daily from 11-14 weeks until 36 weeks of gestation reduced the incidence of preterm preeclampsia by more than 60%.[17]Although current findings are encouraging, evidence on the early use of LDA to prevent preterm birth remains limited. One preconception trial and several meta-analyses focusing on women who began LDA at or before 16 weeks have shown a consistent benefit. For instance, in a meta-analysis of 22 trials involving 11,302 participants, Roberge et al reported a 19% reduction in overall preterm birth. When the analysis was limited to women who started aspirin before 16 weeks, the reduction increased to 65%.[18] The EAGeR (Effects of Aspirin in Gestation and Reproduction) trial in the USA examined whether starting aspirin before conception influences live-birth rates. Women trying to conceive were randomized to folic acid plus either 81 mg aspirin daily (n=535) or placebo (n= 543) and continued treatment for up to six cycles or through 36 weeks if pregnancy occurred. Aspirin increased ultrasound-confirmed pregnancies (70% vs 64%; RR: 1.10, 95% CI:1.01-1.19), but overall live-birth rates did not differ

significantly (58% vs 53%). In per-protocol analysis, aspirin use corresponded to 15 more live births per 100 women. No serious safety concerns were identified.[19] A randomized controlled trial done by Mohammed K et al, at Woman's Health Hospital, Assiut, Egypt (June 2016 to January 2017) included 60 pregnant women (28–30 weeks) with idiopathic asymmetrical IUGR and abnormal umbilical artery Doppler indices. Participants were randomized to receive either daily aspirin 75 mg for 4 weeks or no intervention. The primary outcome was fetal weight, and secondary outcomes included umbilical artery doppler changes, delivery, and neonatal outcomes. Aspirin significantly increased fetal weight and improved umbilical artery blood flow (p=0.00) compared to no intervention. Neonatal outcomes were also better in the aspirin group (p<0.05), indicating that aspirin benefits fetal growth and circulatory function in this population.[20] antiphospholipid syndrome (APS) is an autoimmune disorder defined by the presence of antiphospholipid antibodies (APL).

Table 1: Comparison of different clinical trials on aspirin in pregnancy.

Study / trial	Study design	Population	Aspirin dose and timing	Key outcomes
CLASP trial (1994)	Multicentre RCT	9,364 pregnant women at risk of preeclampsia	60 mg daily, started after 12 weeks	12% relative reduction in preeclampsia (not statistically significant overall).[34]
EAGeR trial (2014)	RCT	Women attempting conception	81 mg daily preconception to 36 weeks	Increased pregnancy rates; no significant difference in live-birth rate.[19]
ASPRE trial (2017)	Double-blind RCT	High-risk singleton pregnancies identified by first-trimester screening	150 mg daily from 11-14 weeks to 36 weeks	>60% reduction in preterm preeclampsia.[35]
Ali et al (2018)[20]	RCT	Idiopathic asymmetric IUGR with abnormal doppler	75 mg daily for 4 weeks	Improved fetal weight and umbilical artery doppler indices.[36]
Roberge et al Meta-analysis[35]	Meta-analysis (22 trials)	11,302 women	≤100 mg daily, started ≤16 weeks	19% reduction in preterm birth overall; 65% reduction when started ≤16 weeks.[37]

In obstetric APS (OAPS), pregnancy complications can include recurrent unexplained early miscarriages, fetal death, or preterm birth resulting from severe preeclampsia, eclampsia, intrauterine growth restriction, or other outcomes related to placental insufficiency.[21] The current standard preventive treatment for APS involves anticoagulation and antiplatelet therapy. Combining heparin—either unfractionated (UF) or low molecular weight (LMWH)—with LDA has been associated with a live birth rate of 70-80%. For women who have experienced early miscarriages (pregnancy loss at or before 10 weeks) and have no history of thrombosis, LDA alone can be considered the initial treatment, particularly in younger patients with many reproductive years ahead. For those with a history of later fetal losses (beyond 10 weeks of gestation) and no prior thrombosis, a combination of LDA and prophylactic low-molecular-weight heparin (LMWH) may be the preferred approach. Whenever LDA is recommended, aspirin therapy should be initiated before conception.[22] Pregnancy in women with Systemic Lupus Erythematosus (SLE) remains high-risk because disease activity often increases and raises the likelihood of complications such as preeclampsia, miscarriage, preterm birth, and cardiac or renal problems. Since SLE patients, especially those with lupus nephritis or positive antiphospholipid antibodies, have a significantly greater risk of preeclampsia, LDA is recommended before conception and continued throughout pregnancy. LDA is also routinely advised for pregnant women with chronic kidney disease and may additionally help reduce cardiovascular events in SLE. Overall, aspirin use is appropriate and beneficial for most pregnant women with SLE.[23]

GUIDELINES AND RECOMMENDATIONS

Several major international organizations now support the use of LDA for preeclampsia prevention in women at elevated risk. ACOG recommends 81 mg daily for those with at least one high-risk or two moderate-risk factors, beginning between 12 and 28 weeks—preferably before 16 weeks—and continuing until delivery.[24] NICE and the RCOG both advise 150 mg daily starting from 12 weeks in high-risk women.[25] while the WHO recommends 75 mg daily initiated before 20 weeks.[26] FIGO further promotes universal first-trimester screening to identify high-risk patients who would benefit from aspirin prophylaxis.

ADVERSE EFFECTS

Generally, the daily use of LDA seems to be a safe intervention for reducing the risk of preeclampsia and preterm birth.[27] NSAIDs damage the gastrointestinal tract through both direct topical irritation of the mucosa and systemic suppression of COX-1–derived prostaglandins, with the systemic effect playing the major role.[28] Common gastrointestinal side effects of NSAIDs include dyspepsia, nausea, vomiting, abdominal pain, and heartburn. These symptoms are the most frequently reported GI complaints and may occur in up to 40% of users.[29] Some studies show that LDA recommendation in pregnancy was associated with increased risk for placental abruption and for postpartum hemorrhage.[30] A large Scandinavian Cohort study of 185,617 mother–child pairs investigated whether prenatal exposure to common analgesics—paracetamol, aspirin, and ibuprofen—was linked to cerebral palsy (CP) in children. Prenatal aspirin exposure, although much less common, was linked to a higher risk of bilateral spastic cerebral palsy. While the analysis adjusted for many potential confounders, the authors noted that underlying maternal conditions prompting analgesic use may still partly explain these observed associations.[31] Another retrospective study done by Sun et al, of 2,763 pregnant patients, found that LDA use (average 67.6 mg/day) did not increase the risk of fetal congenital anomalies, with similar rates between the aspirin and control groups. Overall, the findings indicate that LDA is safe to use during pregnancy with respect to congenital anomaly risk.[32]

CONTRAINDICATIONS

High-dose aspirin (>300 mg/day) is particularly unsafe in late pregnancy because it can cause premature constriction of the ductus arteriosus, oligohydramnios, and fetal platelet dysfunction. Aspirin should be avoided in individuals with known aspirin allergy, active peptic ulcer disease, bleeding disorders, or severe thrombocytopenia.[33]

CONCLUSION

Overall, current evidence supports the safety and effectiveness of LDA in pregnancy when used for appropriate indications. LDA reduces the risk of preeclampsia, may lower rates of preterm birth and fetal growth restriction, and improves outcomes in conditions such as antiphospholipid syndrome and SLE. Major international guidelines endorse its use for high-risk women, particularly when started before 12-16 weeks. Although NSAID-related gastrointestinal symptoms and rare risks such as placental abruption or postpartum haemorrhage have been reported, LDA is generally well tolerated. Large cohort data also show no increased risk of congenital anomalies. In summary, LDA is a safe, beneficial, and widely recommended intervention for improving maternal and fetal outcomes in high-risk pregnancies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kumar M, Gupta NK, Kumari M, Abhishake B, Shah R. Aspirin history and its clinical applications in pregnancy. Int J Reprod Contracept Obstet Gynecol 2026;15:1149-53.