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Editorial Letter

Is Maternal Aspirin Intake Truly Safe in The Long Run?

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Sir,

Aspirin is now an important part of modern obstetrics for high-risk pregnancies. It is used to prevent pre-eclampsia and recurrent pregnancy loss (RPL), as well as to relieve pain [1]. Existing evidence supports the protective effect of low-dose aspirin (LDA) in a daily dose of 75-150 mg against the risk of pre-eclampsia (PE), which shows a reduced risk of 60% [1-3]. Additionally, it reduces the risk of FGR and perinatal death if initiated before 16 weeks' gestation. For women with RPL, especially in antiphospholipid syndrome (APS), aspirin is crucial as an antithrombotic drug that increases live birth rate by inhibiting micro-thrombosis at the maternal/fetal interface, which represents the root of the placental insufficiency underlying the pathology of PE and FGR [3,4]. Nevertheless, with the increased use of LDA in high-risk groups, the focus is now shifted to its long-term safety and the developmental outcome of the offspring, which needs to be addressed. Currently the gap in existing knowledge is about a thorough assessment of developmental safety over the long term rather than showing off aspirin efficacy [5]. As a prophylactic agent, aspirin's role is well established by many health communities; still, a careful clinical application is needed, especially in terms of patient selection and dosage regimes. The endorsed time for aspirin discontinuation is around 36 weeks of gestation, keeping a delicate balance between the continued prevention of late-onset preeclampsia vs. the possible risks of maternal postpartum bleeding and fetal ductus arteriosus closure [1]. LDA is contraindicated in pregnant women with documented salicylate hypersensitivity and active peptic ulcer disease and in those with severe hepatic insufficiency. Even in low doses, aspirin can trigger a life-threatening bronchospasm in patients with "aspirin-exacerbated respiratory disease," which requires a careful pre-prescription screening [6]. The immediate neonatal effects of aspirin, although rare at today's low doses, remain a point of caution for the prescribing physician; early observational reports indicated that salicylates seemed to be linked with neonatal transient platelet dysfunction or intraventricular hemorrhage, particularly in the extremely preterm infant who suffers from fragile blood vessels [7,8]. These concerns from historical data concerning higher doses of aspirin emphasized the necessity of careful safety validation of any pharmaceutical intervention; however, in today's world, these short-term threats seem to be falling off in significance. Many meta-analyses of randomized control trials have examined the effect of prophylactic LDA on intraventricular hemorrhage or major bleeding events, but none have shown a significant increase [2,3]. This reassuring evidence has led to the investigation of the remaining critical gaps, which are long-term neurodevelopmental and somatic safety outcomes [5]. This synthesis of data over the long term through 2026 gives us a strong, though incomplete, story of safety. The strongest evidence so far comes from follow-up to the APRIL trial, which looked at children 4 years after their mothers had taken 80 mg of aspirin during pregnancy. No evidence of harm, behavior, growth, or general health was observed in the study [2]; the result confirmed that the children taking aspirin had higher overall Ages and Stages Questionnaire (ASQ-3) scores than those taking placebos (mean 259.3 *vs*. 248.3; MD 10.96, 95% CI 0.17–21.76) and that the difference was most apparent in fine and gross motor domains [2]. These results imply that there is a clear and apparent improved developmental outcome for the offspring. Although the small sample size may limit the generalization of their findings, there may be developmental dividends from the mitigation of placental pathology. The follow-up of the multinational ASPIRIN trial, which evaluated more than 300 children at age three, shows consistent results; there was no evidence to support a claim of subtle cognitive or behavioral toxicity, as antenatal LDA (81 mg) did not affect neurodevelopmental outcomes when compared to placebo [5,9]. This finding has got clinical relevance; it indicates that the protection of a normal placenta with its attendant neuro-inflammatory stressors does not negatively impact the child's cognitive architecture. Moreover, the historical cohort data from the Collaborative Perinatal Project, which included the use of various aspirin dosages, actually showed an 8–16% decrease in the risk of abnormal or lower cognitive scores in age-7 children [10]. These protective associations were strongest with

exposures greater than 7 days and were seen in the 2nd trimester, implying a window of opportunity for aspirin to act as a stabilizer to the intrauterine environment during important periods of neurogenesis and synaptogenesis [10,11]. The retrospective nature of the data in addition to other confounders may offer a compelling alternative to the "harm hypothesis" and imply that aspirin's ability to optimize placental perfusion may have long-term effects on the developing brain. Systematic reviews and data from older trials, including the CLASP and ISAP follow-ups, had reinforced aspirin's safety profile; they suggest that LDA can even reduce post-neonatal mortality (RR 0.28, 95% CI 0.08–0.99) and significantly decrease the incidence of gross and fine motor problems at 18 months [12]. This finding is particularly relevant given that motor delays are often the first clinical indicators of subtle neurological compromise. Somatic outcomes are also subject to scrutiny, beyond the brain. Longitudinal assessments of height, BMI, and respiratory health—including the incidence of childhood asthma and hospitalizations—show no deviation from normative data in children exposed to in utero LDA [2,12]. This finding is that LDA does not disrupt the basic physiological programming from which the child derives or the immunological development of the child, both of which are known factors in the development of chronic adult diseases via "fetal programming" [9]. In spite of these reassuring statements, the clinical community has to be vigilant because the standard of care is moving towards higher prophylactic doses. Current recommendations are more strongly recommending doses of between 100 and 150 mg at night to optimize chronotherapeutic effects [3]. There is confirmation from the meta-analyses that 150 mg works better in preventing pre-eclampsia, but there is no increase in maternal or fetal bleeding complications at this specific higher dose, but there is little direct follow-up of the children long-term [3,8]. The existing evidence is overwhelmingly in favor of the 75–81 mg range. Thus, while current conclusions are optimistically positive, they remain "reassuring but not definitive" for the upper limit of the prophylactic spectrum or for more subtle outcomes extending into adolescence and adulthood, such as cardiometabolic health or reproductive potential [2,11]. The “safety ceiling” of aspirin is large but poorly defined, and it cannot be precisely defined with the same precision as its obstetric effectiveness [13]. Finally, the use of low-dose aspirin looks as if it is one of the most effective interventions in contemporary perinatology. Although some women may be cautious about using medications during pregnancy, the current evidence is reassuring. The current data to age 4 should allow clinicians to reassure patients that LDA is not only safe but also potentially beneficial for early childhood development. Clinicians should take an active role in educating patients and giving them evidence-based reassurance about any concerns they may have so that they are proactively informed of the long-term safety of current LDA regimens. While the basic science is evolving to support the efficacy of higher doses, like 150 mg, in reducing maternal inflammation, the data over multiple years is limited for these higher doses; thus, additional and more intensive assessments of higher LDA (150 mg) doses throughout late childhood are critical to fully understanding the developmental and long-term safety and efficacy of these drugs and to developing new dosing guidelines to improve perinatal care (Figure 1). In the meantime, the benefits of taking aspirin in high-risk pregnancies are not just a preventive medicine for the modern obstetrician; it is a secure investment in the health of the future generation.

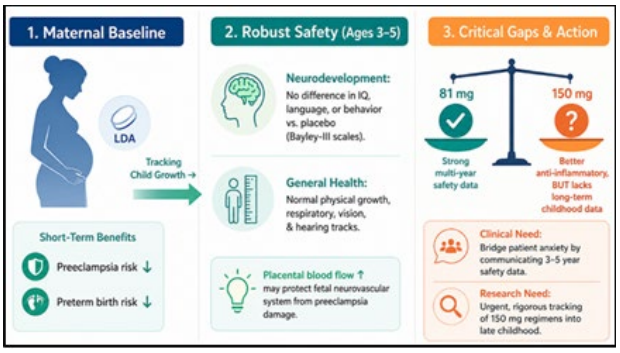

Figure 1:A graphical representaion of common reserch gap and recomndations.

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Conflict of interests

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