Comments on "Low-dose aspirin for preventing intrauterine growth restriction and pre-eclampsia in sickle cell pregnancy in Nigeria (PIPSICKLE): a randomised controlled trial"

Sistiana Aiello, Ariela Benigni, Giuseppe Remuzzi

Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Bergamo, Italy

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In the early 1970s, aspirin (acetylsalicylic acid) was shown to inhibit platelet aggregation by irreversibly acetylating platelet cyclooxygenase (COX), thereby suppressing the synthesis of its pro-aggregating product thromboxane A_2 (TxA_2). A major advance toward its therapeutic use as an antithrombotic agent came with the recognition that low doses of aspirin selectively inhibit platelet COX, while largely sparing vascular COX activity and preserving the production of prostacyclin (PGI_2), a potent anti-aggregating and vasodilatory mediator.[1-3] This differential effect provided the pharmacological rationale for the widespread adoption of low-dose aspirin in the prevention of cardiovascular diseases.[4,5]

Disruption of the delicate balance between the opposing COX products, TxA_2 and PGI_2, has been shown to play a significant role in the pathogenesis of pre-eclampsia,[6-9] a disorder of pregnancy characterized by new-onset hypertension, typically accompanied by proteinuria, arising after 20 weeks of gestation. In 1989, Benigni *et al*. reported that low-dose aspirin initiated at the 12th week of gestation in women at risk of pre-eclampsia was associated with prolonged pregnancy duration and increased neonatal birth weight.[10] The proposed protective mechanism involves inhibition of TxA_2 synthesis while preserving PGI_2 production, thereby restoring the TxA_2-PGI_2 balance and improving utero-placental blood flow. At low doses, aspirin was not associated with an increased risk of maternal or neonatal bleeding. Since then, low-dose aspirin prophylaxis in high-risk pregnant women has become a global standard of care for the prevention of pre-eclampsia.[11,12] In women with sickle cell disease (SCD), pregnancy carries approximately a two-fold higher risk of pre-eclampsia, and both maternal and perinatal complications related to pre-eclampsia are frequent. This elevated risk underpinned recommendations from the American College of Obstetricians and Gynecologists and the British Society for Haematology to prescribe low-dose aspirin beginning at 12 weeks' gestation for pregnant women with SCD.[13,14] In contrast, the recent pregnancy guideline from the World Health Organization did not address aspirin use in this population.[15]

To address this gap, Bosede Bukola Afolabi and colleagues conducted the double-blind, randomized PIPSICKLE trial, published in Lancet Global Health.[16,17] The study assessed whether daily low-dose aspirin (100 mg) could reduce downstream complications of pre-eclampsia in pregnant women with SCD. More than 600 women with hemoglobin SS or SC genotypes were screened, and 476 from 16 public health facilities in southwest Nigeria were randomly assigned to aspirin or placebo. There was no significant difference in the composite primary outcome of intrauterine growth restriction, perinatal mortality, or miscarriage. However, interpretation should be tempered by an important limitation: aspirin was initiated relatively late for most participants. Evidence indicates that optimal prevention of pre-eclampsia and growth restriction requires initiation before 16 weeks' gestation.[18] In PIPSICKLE, the mean gestational age at enrolment was 19 weeks, and 75% of participants started treatment after 16 weeks. As such, the trial offers limited insight into the potential benefit of early-initiated aspirin in this high-risk population. Alone, this finding might not discourage aspirin use in SCD pregnancy. However, unexpected findings warrant caution. Aspirin was associated with a small but statistically significant increase in sickle cell crises (32.64 *vs* 30.38 per 100 women) and more deaths (ten *vs* two), most attributable to SCD complications. These findings are particularly concerning in low-resource settings with limited access to multidisciplinary care, pain control, and prophylactic red cell transfusion.

Mechanisms for potential harm remain unclear. Prior studies in SCD did not show similar risks.[19] It is conceivable that in SCD later pregnancy, aspirin adversely affects red cell rheology, mi-

Corresponding author: Sistiana Aiello, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Via Stezzano 87, 24126 Bergamo, Italy.
E-mail: sistiana.aiello@marionegri.it

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crovascular perfusion, or renal function, hypotheses that merit further studies. Importantly, PIPSICKLE study demonstrates what is achievable with coordinated care: nearly 70% of deliveries were by cesarean section and overall maternal mortality was below 3%, which represents a substantial improvement compared with reported maternal death rates of 7% to 12% among pregnant women with SCD in sub-Saharan Africa.[20] Participants benefited from trial enrolment and consistent access to skilled specialist care.

Safe pregnancy for women with SCD requires sustained, multidisciplinary management, an effort that must continue while further studies clarify the role and the safety of aspirin in this population.

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