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Bridging the Gaps between Aspirin Guidelines and Pregnancy Outcomes

Matthew K. Hoffman, MD, MPH

Department of Obstetrics & Gynecology, Christiana Care

Abstract

Currently birth outcomes in the United States lag other industrialized countries and are driven predominantly by adverse pregnancy outcomes including preeclampsia, spontaneous preterm birth, stillbirth and fetal growth restriction. In aggregate these conditions are termed adverse pregnancy outcomes (APOs) and are complex in their origin, but largely reflect placentally mediated conditions that begin in early pregnancy. Low-dose aspirin (LDA) has been shown to lower the risk of APOs, but questions about the optimal dose, patient population to receive it, and barriers to prescribing and adherence have limited the impact of LDA on a population level. Multiple investigations unfortunately have shown that uptake is low and often biased in its provision. To address these inequities in care, the Delaware Perinatal Quality Collaborative (DPQC) organized efforts around standardizing screening all patients, providing hospital level feedback and enhanced patient education. With this effort, the rate of appropriate LDA prescription increased from 10% to 65%. Further studies and thoughtful conversations around additional barriers to care must be addressed jointly by researchers, providers, public health officials, patients and the community at large if the full promise shown in randomized controlled trials is to be realized.

Current Status of Obstetrical Outcomes

Little change has occurred in obstetrical outcomes in the last several decades, with most gains in outcomes being attributable to antenatal corticosteroids, improved neonatal care and guidelines limiting iatrogenic late preterm birth.[1,2] In 2024, the March of Dimes deemed the US as having a grade of "D+" for preterm birth, noting that preterm birth rates have steadily increased, with the state of Delaware similarly receiving a D+.[3] The predominant drivers of preterm birth are spontaneous preterm birth and iatrogenic delivery, mostly the result of preeclampsia, fetal growth restriction and maternal medical conditions associated with higher risks of stillbirth.

Of ongoing and growing concern is the issue of preeclampsia, which has been increasing across the United States over the last decade, approaching a rate of 1 in 10 pregnancies.[4] This increase is thought to be the result of a birthing population that is getting older, having a higher body mass index, and having more associated medical disorders. From a mechanistic standpoint, the underlying causes of preeclampsia are increasingly being understood in that it is probably at least two separate disease processes that converge on a common phenotype of high blood pressure occurring after 20 weeks. Researchers have now begun to divide preeclampsia into two different forms of preeclampsia: early onset preeclampsia (EOPE) which occurs before 34 weeks, results in higher rates of fetal growth restriction, and more maternal/neonatal complications; and late onset preeclampsia (LOPE) which is comparatively benign with fewer maternal/neonatal complications.[5] EOPE has been clearly associated with early placental development between 10 and 16 weeks while LOPE appears to be linked to metabolic stress on the placenta.

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LDA for the Prevention of Preeclampsia

Given the importance of preeclampsia, increasingly efforts have pivoted to the prevention of preeclampsia. In 1978, three obstetricians in California published a case report in the Lancet of an individual who had repetitive cases of preeclampsia and poor outcomes followed by a successful pregnancy after being treated with daily low-dose aspirin.[6] This case report study was followed up a year later by a case control study, wherein women delivering at a UK hospital were asked if they had taken aspirin in the prior fortnight, and those who did not have preeclampsia were more likely to report that they had been taking LDA.[7]

Subsequently, this has led to numerous randomized trials in both high and low-risk populations for the prevention of preeclampsia. To date, over 60,000 pregnancies have been randomized to LDA with a consistent treatment effect being seen that LDA lowers the overall rate of preeclampsia by approximately 10%.[8,9] This effect appears to be greatest when LDA is begun before 16 weeks, a time of active placental development.[10] Though these effects appear to be modest, when examined more closely, LDA has a profound reduction on the rate of EOPE (62% reduction prior to 34 weeks and 30% reduction in less than 37 weeks).[11,12] This echoes the concept that LDA may only be effective if given before 16 weeks when poor placental development results in EOPE. It thus appears that the principal benefit of LDA may not be in the prevention of preeclampsia but rather in delaying its onset to a time frame when neonatal outcomes are markedly better.

LDA and Other APOs

Though initially thought to be a preventative strategy for preeclampsia, others have put forward that other placentally mediated conditions such as preterm birth, fetal growth restriction, and still birth may be also lessened by LDA. Improvement in these outcomes has now been documented in meta-analyses and large trials.[13,14] In 2020, Hoffman and colleagues published the ASPIRIN trial that randomized 11,976 nulliparous women with a singleton pregnancy to either aspirin 81 mg or placebo early in in pregnancy (6-14 weeks). This study not surprisingly found a decrease in overall preeclampsia (11%), preeclampsia before 34 weeks of 62% but also preterm birth less than 37 weeks (11%), preterm birth before 34 weeks (25%), stillbirth (14%), and fetal growth restriction associated with preeclampsia (88%); fundamentally confirming all the findings of the meta-analyses.[9,11] Though these benefits have been shown consistently across trials, from a public policy standpoint LDA remains mostly focused as a preventative strategy for preeclampsia because of its near 50-year history of being framed as a preventative strategy for preeclampsia. If we are to improve birth outcomes, it will be important to continue to bring forward all of these potential benefits.

Dose and Adherence and its Impact on Birth Outcomes

As a lingering question, the issue of dose has piqued the intrigue of investigators following the publication of the ASPRE trial that utilized a dose of 150mg.[12] Both small prospective trials[15] and meta-analyses[10] have suggested that higher doses are more impactful in preventing poor outcomes. For example, a meta-analysis examining dose in low-risk women, found that the risk of preterm birth was markedly lower in women randomized to a dose of 100mg or greater (RR 0.39, 95% CI 0.31-0.48) compared to those randomized to a lower dose.[16] Currently, several large trials are currently directly comparing higher doses (150mg-162mg) vs. lower doses (75-81mg), which will hopefully further inform guidelines.

In addition to the question of does is the question of adherence. In a large prospective RCT, Rolnik and colleagues found a lack of benefit when adherence was less than 90% (Rolnik et al., 2017). Unfortunately, typical use in clinical circumstances is often much lower than it is research trials.

Barriers to Realizing the Full Benefit of LDA in Clinical Use

Inefficient Screening Guidelines

One of the greatest challenges in realizing the benefits of LDA in clinical practice is the ability of screening guidelines to identify at risk pregnancies. Such guidelines can be cumbersome to implement in clinical care and provider uptake can be variable. The prior American College of Obstetricians and Gynecologists (ACOG) guidelines suggested that the detection rate was poor.[17] In 2021, these guidelines were amended to consider LDA in pregnancies associated with low-socioeconomic status or in black pregnancies. These changes potentially result in over-half of US pregnancies being potentially eligible for LDA, and further analyses suggest that universal recommendations may be the most cost-effective strategy.[18]

Provider Behavior

A second clear barrier is provider adoption. Vendelbo and colleagues in a study examining the behavior of providers following a 2012 guideline recommending LDA in high-risk pregnancies found that only 12% of at-risk pregnancies were receiving aspirin four years after the guidelines were implemented.[19] Not surprisingly, the impact on perinatal outcomes was noted to be modest. Further complicating the issue, a number of studies have demonstrated that providers are frequently biased in their prescription of LDA, creating further barriers to achieving equity.[20]

Patient Factors

Beyond both the screening guidelines and provider prescribing behavior, patient factors associated with low-rates of adherence have been well documented. From the literature, factors such as health literacy, lack of trust in the health care system, socioeconomic drivers (housing instability), lack of peer support, perceived risks and psychological factors have all been shown to affect adherence.[21] Of particular concern for many pregnant people is the potential long-term effects on the newborn.

This is in part triggered by the current FDA black-box warning about NSAIDs in pregnancy. Though the black box warning notes that 81mg of LDA is an exception, because of the warning, concerns for risk may be inferred. Nonetheless, well conducted follow-up trials have suggested no difference in either neurodevelopment or improved outcomes.[22,23] It should be noted that LDA adherence is uniquely understudied, and if the promise of LDA is to occur on a population level understanding, patient factors and potential remedies must be undertaken. Key to this effort will be community engagement and listening to fully understand barriers. In addition, trialing potential solutions such as digital engagement,[24] social media and other novel approaches must be undertaken.

Implementation in Delaware

In the first quarter of 2021, the Delaware Perinatal Quality Collaborative (DPQC), which is composed of birth hospitals, birth centers, obstetrical providers, state government officials, insurance providers, and public advocates, agreed to take on an initiative to increase awareness and screening for LDA. It was agreed that all providers would routinely screen for LDA in all

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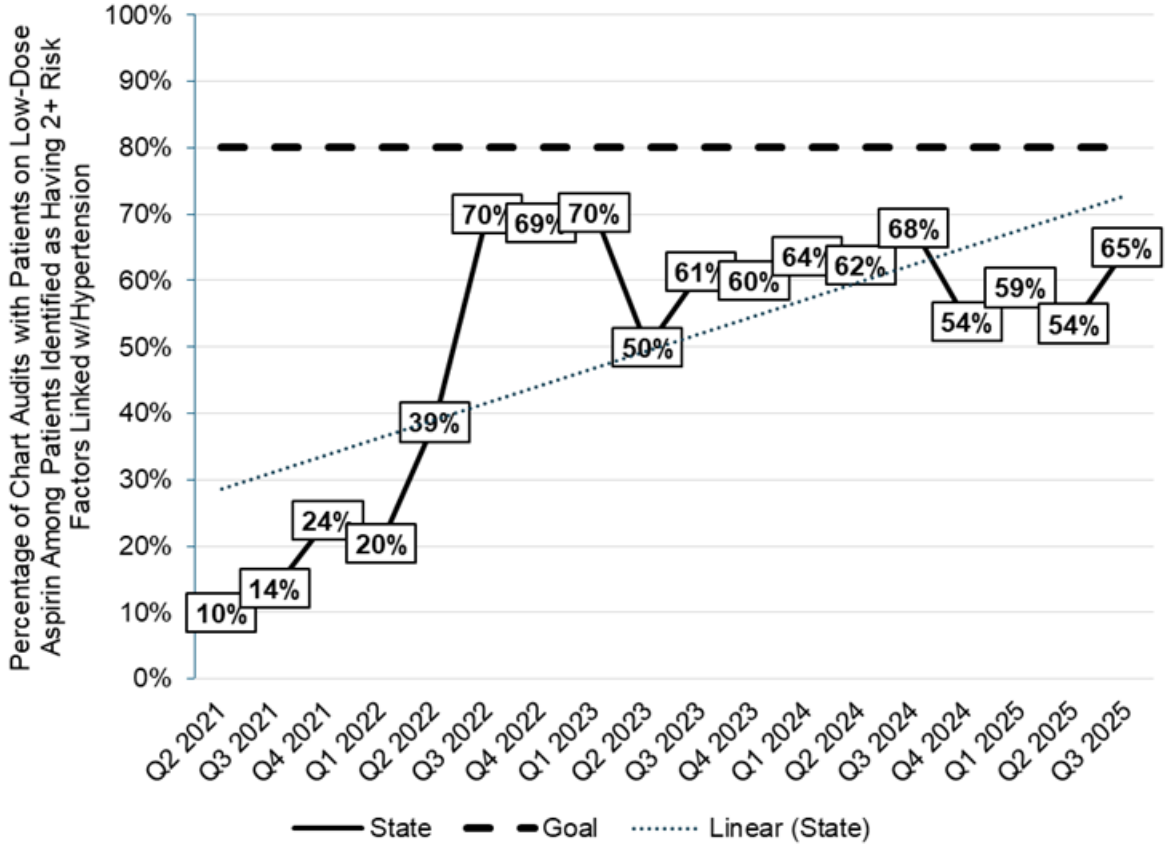
patients using a standardized screening tool. In addition, standardized education using a QR code would be provided. Key to this effort was engaging all obstetrical providers in the state, educating them on the benefits of LDA, and listening to their suggestions to improve uptake and recognition amongst at risk pregnancies.

Meetings were held both at departmental levels and individual practices with episodic return visits to understand how the provided tools were being utilized. Each hospital agreed to ask all patients if they were prescribed LDA during their pregnancy and quarterly audits of 20 charts were made. Each hospital or birth center were provided feedback on their compliance with the recommendations. From a baseline rate of 10% of at-risk pregnancies being prescribed, this rate increased quickly and showed sustained uptake to a rate of approximately 68% (figure 1).

Figure 1. Appropriate Low Dose Aspirin Prescriptions in At-Risk Pregnancies Over Time in Delaware



Conclusion

Currently, birth outcomes in the United States and Delaware lag behind our hopes and aspirations. Though complex in its origins, LDA offers at least a partial remedy to improving outcomes. By engaging joint efforts of providers, government, and insurers through the DPQC, the rate of appropriate LDA prescription was able to be markedly improved. Nonetheless, to realize the potential, researchers must continue to investigate the optimal dose of LDA, as well as conduct implementation research studies to understand the barriers to perfect care for both providers and patients. Key to this will be to engage both patients and communities in these discussions to co-develop solutions and, in turn, better outcomes.

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Dr. Hoffman may be contacted at mhoffman@christianacare.org.

References

1. Crowley, P. A. (1995, July). Antenatal corticosteroid therapy: A meta-analysis of the randomized trials, 1972 to 1994. *American Journal of Obstetrics and Gynecology*, *173*(1), 322–335. https://doi.org/10.1016/0002-9378(95)90222-8 PubMed
2. Richardson, D. K., Gray, J. E., Gortmaker, S. L., Goldmann, D. A., Pursley, D. M., & McCormick, M. C. (1998). Declining severity adjusted mortality: Evidence of improving neonatal intensive care. Pediatrics, 102(4 I), 893–899. https://doi.org/10.1542/peds.102.4.893
3. March of Dimes. (n.d.). 2025 March of dimes report card For United States. PeriStats. Retrieved from https://www.marchofdimes.org/peristats/reports/united-states/report-card
4. Ayyash, M. K., McLaren, R., Jr., Shaman, M., & Al-Kouatly, H. B. (2024, July 9). Trends in preeclampsia risk factors in the US From 2010 to 2021. *JAMA*, *332*(2), 167–169. https://doi.org/10.1001/jama.2024.8931 PubMed
5. Jung, E., Romero, R., Yeo, L., Gomez-Lopez, N., Chaemsaithong, P., Jaovisidha, A., . . . Erez, O. (2022, February). The etiology of preeclampsia. *American Journal of Obstetrics and Gynecology*, *226*(2S), S844–S866. https://doi.org/10.1016/j.ajog.2021.11.1356 PubMed
6. Goodlin, R. C., Haesslein, H. O., & Fleming, J. (1978, July 1). Aspirin for the treatment of recurrent toxaemia. *Lancet*, *312*(8079), 51. https://doi.org/10.1016/S0140-6736(78)91367-3 PubMed
7. Crandon, A. J., & Isherwood, D. M. (1979, June 23). Effect of aspirin on incidence of pre-eclampsia. *Lancet*, *313*(8130), 1356. https://doi.org/10.1016/S0140-6736(79)91996-2 PubMed
8. Duley, L., Meher, S., Hunter, K. E., Seidler, A. L., & Askie, L. M. (2019, October 30). Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*, *2019*(10), CD004659. https://doi.org/10.1002/14651858.CD004659.pub3 PubMed
9. Hoffman, M. K., Goudar, S. S., Kodkany, B. S., Metgud, M., Somannavar, M., Okitawutshu, J., . . . Derman, R. J., & the ASPIRIN Study Group. (2020, January 25). Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): A randomised, double-blind, placebo-controlled trial. *Lancet*, *395*(10220), 285–293. https://doi.org/10.1016/S0140-6736(19)32973-3 PubMed
10. Roberge, S., Bujold, E., & Nicolaides, K. H. (2018, May). Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. *American Journal of Obstetrics and Gynecology*, *218*(5), 483–489. https://doi.org/10.1016/j.ajog.2017.12.238 PubMed
11. Kavi, A., Hoffman, M. K., Somannavar, M. S., Metgud, M. C., Goudar, S. S., Moore, J., . . . Derman, R. J. (2023, November). Aspirin delays the onset of hypertensive disorders of

pregnancy among nulliparous pregnant women: A secondary analysis of the ASPIRIN trial. *BJOG*, *130*(Suppl 3), 16–25. https://doi.org/10.1111/1471-0528.17607 PubMed

12. Rolnik, D. L., Wright, D., Poon, L. C., O'Gorman, N., Syngelaki, A., de Paco Matallana, C., . . . Nicolaides, K. H. (2017, August 17). Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *The New England Journal of Medicine*, *377*(7), 613–622. https://doi.org/10.1056/NEJMoa1704559 PubMed
13. Roberge, S., Nicolaides, K. H., Demers, S., Villa, P., & Bujold, E. (2013, May). Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: A meta-analysis. *Ultrasound Obstet Gynecol*, *41*(5), 491–499. https://doi.org/10.1002/uog.12421 PubMed
14. Roberge, S., Sibai, B., McCaw-Binns, A., & Bujold, E. (2016, July). Low-dose aspirin in early gestation for prevention of preeclampsia and small-for-gestational-age neonates: Meta-analysis of large randomized trials. *American Journal of Perinatology*, *33*(8), 781–785. https://doi.org/10.1055/s-0036-1572495 PubMed
15. Amro, F. H., Blackwell, S. C., Pedroza, C., Backley, S., Bitar, G., Daye, N., Bartal, M. F., Chauhan, S. P., & Sibai, B. M. (2025). Aspirin 162 mg vs 81 mg for preeclampsia prophylaxis in high-risk obese individuals: a comparative effectiveness open-label randomized trial (ASPREO). American Journal of Obstetrics and Gynecology, 232(3), 315.E1-315.E8. https://doi.org/10.1016/j.ajog.2024.06.038
16. Wodoslawsky, S., Khanuja, K., Saccone, G., Hoffman, M. K., & Berghella, V. (2025, February). Low-dose aspirin use in low-risk nulliparous pregnancies: A systematic review and meta-analysis of randomized controlled trials. *American Journal of Obstetrics & Gynecology MFM*, *7*(2), 101595. https://doi.org/10.1016/j.ajogmf.2024.101595 PubMed
17. O'Gorman, N., Wright, D., Poon, L. C., Rolnik, D. L., Syngelaki, A., de Alvarado, M., . . . Nicolaides, K. H. (2017, June). Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: Comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol*, *49*(6), 756–760. https://doi.org/10.1002/uog.17455 PubMed
18. Wheeler, S. M., Myers, S. O., Swamy, G. K., & Myers, E. R. (2022, January 4). Estimated prevalence of risk factors for preeclampsia among individuals giving birth in the US in 2019. *JAMA Network Open*, *5*(1), e2142343–e2142343. https://doi.org/10.1001/jamanetworkopen.2021.42343 PubMed
19. Vendelbo, J. H., Thunbo, M. Ø., Henriksen, T. B., Liew, Z., Larsen, A., & Pedersen, L. H. (2025, July 7). The nationwide impact of guidelines for prophylactic aspirin treatment for preeclampsia. *Paediatric and Perinatal Epidemiology*. https://doi.org/10.1111/ppe.70046 PubMed
20. Jones Pullins, M., Boggess, K., & Porter, T. F. (2023, December 1). Aspirin in Pregnancy. *Obstetrics and Gynecology*, *142*(6), 1333–1340. https://doi.org/10.1097/AOG.0000000000005429 PubMed
21. Peh, K. Q. E., Kwan, Y. H., Goh, H., Ramchandani, H., Phang, J. K., Lim, Z. Y., . . . Thumboo, J. (2021, September). An adaptable framework for factors contributing to medication adherence: Results from a systematic review of 102 conceptual frameworks. *Journal of General Internal Medicine*, *36*(9), 2784–2795. https://doi.org/10.1007/s11606-021-06648-1 PubMed

22. Hoffman, M. K., Goudar, S., Dhaded, S., Figueroa, L., Mazariegos, M., Krebs, N. F., . . . Derman, R. J. (2024, April 1). Neurodevelopment of children whose mothers were randomized to low-dose aspirin during pregnancy. *Obstetrics and Gynecology*, *143*(4), 554–561. https://doi.org/10.1097/AOG.0000000000005514 PubMed

23. Zhu, J., Gan, Y., Yang, C., Gu, W., Wang, Y., Zhang, J., & Liu, Z. (2024, November). In utero aspirin exposure and child neurocognitive development: A propensity score-matched analysis. *BJOG*, *131*(12), 1630–1639. https://doi.org/10.1111/1471-0528.17871 PubMed

24. Santosa, A., Juniarti, N., Pahria, T., & Susanti, R. D. (2025, November 21). Digital adherence technology to improve medication adherence in tuberculosis patients: A systematic review and meta-analysis randomized control trials. *NPJ Primary Care Respiratory Medicine*, *35*(1), 52. https://doi.org/10.1038/s41533-025-00457-3 PubMed