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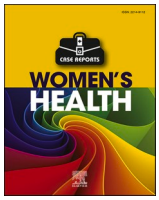

Balancing health and safety: Cardiovascular medications during pregnancy and lactation

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Cardiovascular disease (CVD) is the leading cause of indirect maternal mortality during pregnancy, accounting for 15.5 % of maternal deaths in the United States [1]. The risk of CVD during pregnancy has increased in the Western world due to a higher number of women with congenital heart disease reaching childbearing age [2], as well as rising maternal age at first pregnancy and an increase in pregnant women with cardiometabolic risk factors such as obesity, hypertension, and diabetes [3]. Data on the prevalence of pharmacological therapy use during pregnancy is scarce; however, the Registry of Pregnancy and Cardiac Disease reports that 32 % of pregnant women with CVD use cardiac medication [4]. Most of these women were treated for congenital heart disease, with beta-blockers and antiplatelet agents being the most commonly used cardiac medications. The use of cardiac medication during pregnancy was associated with an increased rate of adverse fetal events [4]. Information on medication use specifically for ischemic heart disease in pregnancy is limited. In this editorial, we focus on women with a history of ischemic heart disease and evaluate the safety and efficacy of the "golden five" classes of medication for secondary prevention during pregnancy and lactation following a prior acute coronary event. The "golden five" include angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), aspirin, P2Y12 inhibitors, beta-blockers, and statins [5].

ACE inhibitors and ARBs are contraindicated in pregnancy and should be discontinued during the preconception period [6]. These medications have been associated with fetal abnormalities, including lung hypoplasia, skeletal malformations, and impaired fetal renal function, particularly when used in the second and third trimesters [7]. Discontinuation of ACE inhibitors should occur under supervision of a cardiologist due to the potential risk of a decrease in left ventricular ejection fraction [8]. In patients with proteinuria, ACE inhibitors may be considered, under strict regulation, until a positive pregnancy test, to ensure renal protection during this period. While some ACE inhibitors, such as enalapril, may be considered safe for use in the postpartum period with careful monitoring of the infant's weight, manufacturers recommend against use of other agents during lactation [6]. Among ACE inhibitors, enalapril is preferred based on limited data suggesting negligible levels in breast milk [9]. No data are available on the use of ARBs during lactation; therefore, they should be avoided [6].

Low-dose aspirin (50 to 150 mg daily) is commonly used for the prevention of preeclampsia and has not been shown to increase the risk of maternal or fetal bleeding or to cause congenital anomalies [10]. In contrast, high-dose aspirin (>150 mg daily) is associated with risks such as premature closure of the patent ductus arteriosus and should be avoided [6]. Low-dose aspirin can also be used for secondary prevention of atherosclerotic cardiovascular disease (ASCVD), providing similar preventive effects as higher doses [11]. Low-dose aspirin (75 to 150 mg daily) passes into breast milk in negligible amounts, with infants ingesting only a very small quantity [12]. No adverse effects have been reported in infants exposed to low doses of aspirin via breast milk. However, aspirin use should be avoided if the infant has symptoms of a viral infection or fever due to the potential risk of Reye's syndrome [13].

Data on the safety of P2Y12 inhibitors during pregnancy are limited [6]. A systematic review of 37 pregnancies suggests reassuring outcomes for both mothers taking clopidogrel and neonates exposed to the drug [14]. Evidence for other P2Y12 inhibitors is sparse. To minimize the risk of postpartum hemorrhage, clopidogrel should be discontinued seven days before a scheduled delivery [15]. Women who have taken clopidogrel within seven days should consider alternative pain management strategies during labor, as neuraxial anesthesia poses a high risk for complications, making general anesthesia preferable for cesarean deliveries [15]. To mitigate these risks while maintaining the benefits of antithrombotic therapy, switching from clopidogrel to low-dose aspirin in the seven days before planned labor may be considered. No published information is available on the use of P2Y12 inhibitors during breastfeeding. Manufacturers report no adverse effects in breastfed infants from mothers using clopidogrel in a small number of post-marketing cases.

Beta-blockers are commonly used to treat various cardiovascular conditions during pregnancy, including hypertension, arrhythmias, and heart failure [16]. As a result, their safety for both mother and child has

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Table 1
"Golden-five" classes of medication used during pregnancy and lactation.

Medication Class	Common drugs	Use during Pregnancy	Use during Lactation
ACE inhibitors / ARBs	Benazepril, Captopril, Enalapril, Valsartan	Generally contraindicated due to risk of fetal abnormalities	Limited evidence, milk levels of ACE inhibitors are negligible. Enalapril is the preferred choice No information on ARBs
Aspirin	Low-dose aspirin (50–150 mg)	Safe during pregnancy, regarding maternal or fetal bleeding or to cause congenital anomalies	Limited evidence, milk levels of low-dose aspirin are negligible. Caution when infant is having viral symptoms
P2Y12 inhibitors	Clopidogrel, Prasugrel, Ticagrelor	Limited data on clopidogrel during pregnancy. It appears to be safe. Stop 7 days before labor	Limited data, a few postmarketing cases. No fetal adverse effects of maternal clopidogrel usage
Beta-blockers	Atenolol, Bisoprolol, Carvedilol, Labetalol, Metoprolol, Propranolol	Atenolol should be avoided Other beta-blockers seem safe to use, with labetalol posing the lowest risk for intrauterine growth restriction	Limited evidence, milk levels of beta-blockers are negligible. Labetalol, metoprolol and propranolol are first choice
Statins	Atorvastatin, Pravastatin, Rosuvastatin, Simvastatin	May be safe, advised only in specific cases	Lack of evidence

ACE = Angiotensin-converting enzyme; ARBs = Angiotensin II receptor blockers.

been studied more extensively and prospectively. In the Registry of Pregnancy and Cardiac Disease, metoprolol and bisoprolol were the most frequently used beta-blockers [17]. All beta-blockers in pregnancy are associated with risks such as torsades de pointes, fetal bradycardia, hypoglycemia, and reduced birth weight [6]. Atenolol, a hydrophilic drug with renal elimination, has been particularly linked to significant intrauterine growth restriction and is therefore contraindicated during pregnancy [16]. Other beta-blockers are generally considered safe with respect to fetal malformations [6], with labetalol presenting the lowest risk for intrauterine growth restriction [17]. Labetalol, a nonselective α, β-1, and β-2 receptor blocker, is used as a first-line treatment for both acute and chronic hypertension in pregnancy, showing similar outcomes to nifedipine and methyldopa [18]. Labetalol, metoprolol, and propranolol are the beta-blockers of choice during breastfeeding, as they transfer into breast milk in very small amounts and have shorter half-lives, leading to a lower risk of accumulation in the breastfed infant [19–21].

Historically, statins were contraindicated during pregnancy due to concerns about an increased risk of congenital anomalies [6]. However, in July 2021, the Food and Drug Administration (FDA) removed its strongest warning against statin use during pregnancy, based on new observational studies that found no association with birth defects [22]. Despite this update, the FDA still recommends discontinuing statins upon confirmation of pregnancy for most patients. Statins may be used in women with familial hypercholesterolemia, severe LDL-C increases, or prior ASCVD when the benefits outweigh the risks [22]. The European Medicines Agency and European Society of Cardiology guidelines have not updated their recommendations on statin use during pregnancy. Based on the ESC/EAS guidelines no lipid-lowering drugs should be administered during breastfeeding [23], because data on possible adverse effects are lacking.

Low-dose aspirin (<150 mg), clopidogrel, beta-blockers (preferably labetalol), and statins appear safe for use during pregnancy, while enalapril, low-dose aspirin, clopidogrel, and certain beta-blockers (labetalol, metoprolol, propranolol) are considered safe during breastfeeding (Table 1). However, these recommendations are largely based on limited evidence. Most of the European Society of Cardiology guidelines for managing cardiovascular disease in pregnancy rely on level C evidence, comprising 90 % of recommendations [3]. The lack of high-quality evidence results from the exclusion of pregnant and lactating women from cardiovascular trials, following a "protection by exclusion" approach [24]. This approach aims to protect the mother and, to a larger extent, the fetus from potential harm. Nevertheless, it is crucial to gather data on efficacy and safety in this population, as findings from non-pregnant individuals may not be generalizable to pregnant women due to alterations in pharmacodynamics and pharmacokinetics [25]. In addition to ensuring maternal safety, fetal safety is also crucial.

The exclusion of these pregnant and lactating women from trials should be based on biological probability, preclinical data, or clinical evidence, and follow established criteria [26]. Carefully monitored trial participation may offer improved safety for both women and their offspring compared to the risks of untested or less effective therapies in clinical practice. Moreover, improved registries are needed to assess the long-term risks of non-treatment during pregnancy. Finally, pregnancy and lactation should not be treated as a single exclusion criterion, as they are distinct states, and combining them may lead to unnecessary exclusion from research [24].

Contributors

Marte F. van der Bijl contributed to the conception, drafting and editing of the manuscript, and performed the literature review for the editorial.

Koen Verdonk contributed to the clinical interpretation of the literature, drafting and editing of the manuscript.

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References

[1] A.A. Creanga, C. Syverson, K. Seed, W.M. Callaghan, Pregnancy-related mortality in the United States, 2011-2013, Obstet. Gynecol. 130 (2) (2017) 366–373.
[2] U. Elkayam, S. Goland, P.G. Pieper, C.K. Silverside, High-risk cardiac disease in pregnancy: part I, J. Am. Coll. Cardiol. 68 (4) (2016) 396–410.
[3] V. Regitz-Zagrosek, J.W. Roos-Hesselink, J. Bauersachs, C. Blomström-Lundqvist, R. Cífková, M. De Bonis, et al., 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy, Eur. Heart J. 39 (34) (2018) 3165–3241.
[4] T.P. Ruys, A. Maggioni, M.R. Johnson, K. Sliwa, L. Tavazzi, M. Schwerzmann, et al., Cardiac medication during pregnancy, data from the ROPAC, Int. J. Cardiol. 177 (1) (2014) 124–128.
[5] R.A. Byrne, X. Rossello, J.J. Coughlan, E. Barbato, C. Berry, A. Chieffo, et al., 2023 ESC guidelines for the management of acute coronary syndromes, Eur. Heart J. 44 (38) (2023) 3720–3826.

[6] D.G. Halpern, C.R. Weinberg, R. Pinnelas, S. Mehta-Lee, K.E. Economy, A. M. Valente, Use of medication for cardiovascular disease during pregnancy: JACC state-of-the-art review, J. Am. Coll. Cardiol. 73 (4) (2019) 457–476.
[7] S. Tabacova, R. Little, Y. Tsong, A. Vega, C.A. Kimmel, Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment, Pharmacoepidemiol. Drug Saf. 12 (8) (2003) 633–646.
[8] M.A. Konstam, M.F. Rousseau, M.W. Kronenberg, J.E. Udelson, J. Melin, D. Stewart, et al., Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure, SOLVD Investig. Circulat. 86 (2) (1992) 431–438.
[9] C.W. Redman, J.G. Kelly, W.D. Cooper, The excretion of enalapril and enalaprilat in human breast milk, Eur. J. Clin. Pharmacol. 38 (1) (1990) 99.
[10] L.M. Askie, L. Duley, D.J. Henderson-Smart, L.A. Stewart, P.C. Group, Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data, Lancet 369 (9575) (2007) 1791–1798.
[11] W.S. Jones, H. Mulder, L.M. Wruck, M.J. Pencina, S. Kripalani, D. Muñoz, et al., Comparative effectiveness of aspirin dosing in cardiovascular disease, N. Engl. J. Med. 384 (21) (2021) 1981–1990.
[12] P. Datta, K. Rewers-Felkins, R.R. Kallem, T. Baker, T.W. Hale, Transfer of low dose aspirin into human milk, J. Hum. Lact. 33 (2) (2017) 296–299.
[13] J. Chapman, J.K. Arnold, Reye syndrome, in: Ineligible Companies. Disclosure: Justin Arnold Declares no Relevant Financial Relationships with Ineligible Companies, StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC, Treasure Island (FL), 2024.
[14] M. Nana, H. Morgan, S. Moore, Z.X. Lee, E. Ang, C. Nelson-Piercy, Antiplatelet therapy in pregnancy: a systematic review, Pharmacol. Res. 168 (2021) 105547.
[15] C.D. Yarrington, A.M. Valente, K.E. Economy, Cardiovascular Management in Pregnancy: antithrombotic agents and antiplatelet agents, Circulation 132 (14) (2015) 1354–1364.
[16] V. Regitz-Zagrosek, J.W. Roos-Hesselink, J. Bauersachs, C. Blomström-Lundqvist, R. Cífková, M. De Bonis, et al., 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy, Eur. Heart J. 39 (34) (2018) 3165–3241.
[17] K.P. Ramlakhan, J.W. Roos-Hesselink, T. Basso, J. Greenslade, R.B. Flint, E. V. Krieger, et al., Perinatal outcomes after in-utero exposure to beta-blockers in women with heart disease: data from the ESC EORP registry of pregnancy and cardiac disease (ROPAC), Int. J. Cardiol. 410 (2024) 132234.
[18] Hypertension in pregnancy, Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy, Obstet. Gynecol. 122 (5) (2013) 1122–1131.
[19] B. Sandström, C.G. Regårdh, Metoprolol excretion into breast milk, Br. J. Clin. Pharmacol. 9 (5) (1980) 518–519.
[20] J.H. Bauer, B. Pape, J. Zajicek, T. Groshong, Propranolol in human plasma and breast milk, Am. J. Cardiol. 43 (4) (1979) 860–862.
[21] N.O. Lunell, J. Kulas, A. Rane, Transfer of labetalol into amniotic fluid and breast milk in lactating women, Eur. J. Clin. Pharmacol. 28 (5) (1985) 597–599.
[22] US Food and Drug Administration, FDA requests removal of strongest warning against using cholesterol-lowering statins during pregnancy; still advises most pregnant patients should stop taking statins, 2021. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-removal-strongest-warning-against-using-cholesterol-lowering-statins-during-pregnancy.
[23] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, et al., 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), Eur. Heart J. 41 (1) (2019) 111–188.
[24] E. Assadpour, H.G.C. Van Spall, Pregnant and lactating women should be included in clinical trials for cardiovascular disease, Nat. Med. 29 (8) (2023) 1897–1899.
[25] E.A. Pinheiro, C.S. Stika, Drugs in pregnancy: pharmacologic and physiologic changes that affect clinical care, Semin. Perinatol. 44 (3) (2020) 151221.
[26] L. Filbey, M.S. Khan, H.G.C. Van Spall, Protection by inclusion: increasing enrollment of women in cardiovascular trials, Am. Heart J. Plus 13 (2022) 100091.

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