Supplementary Information

Autumn – September 2026

Maternal Influenza Vaccination

In Ireland, the seasonal influenza (flu) vaccine is recommended for **all pregnant women, from October to the end of April each year, free of charge**.[1] Pregnant women are more susceptible to influenza infection than the general population and upon infection are at increased risk of severe illness and associated adverse pregnancy outcomes.[1–3] Maternal flu vaccination is the most effective strategy to protect both the mother and infant, providing passive immunity to the new-born during the first months of life. Although vaccination is recommended as early as possible during pregnancy, the flu vaccine can be administered safely at any stage of pregnancy and may be given concurrently with other recommended maternal vaccines, including pertussis (whooping cough) and COVID-19 vaccines.[1]

Despite extensive evidence supporting the safety and effectiveness of flu vaccination during pregnancy, uptake is often suboptimal and varies considerably across different countries and healthcare settings.[2–5] Ongoing public discussion surrounding maternal vaccination recommendations in some jurisdictions may contribute to uncertainty, potentially influencing vaccine confidence and uptake. Consequently, there remains a need to address concerns, support informed decision-making, and promote confidence in maternal influenza vaccination.

Building on the current evidence supporting the safety of maternal flu vaccination, a systematic review and meta-analysis published in May this year, concluded that **flu vaccination in early pregnancy did not increase the risk for birth defects (BDs)**. In total, 31 studies involving 1,223,024 pregnant individuals were included in this study. Compared to the control group (unvaccinated or those who received flu vaccination during second or third trimester), no increased risk of **total BDs** (28 studies, unadjusted OR 1.15, 95% CI 0.97–1.36; 10 studies, adjusted OR 1.03, 95% CI 0.98–1.07) or **major BDs** (16 studies, unadjusted OR 1.11, 95% CI 0.97–1.25; 6 studies, adjusted OR 1.03, 95% CI 0.98–1.09) was observed among those vaccinated during the first trimester. Additionally, no potential risks were observed based on different vaccine type, the use of adjuvants, the assessment of BDs or control type. Results were consistent across sensitivity analyses for primary results.[2]

To further support pregnant women, the Health Service Executive (HSE) and National Immunisation Advisory Committee (NIAC) have published an updated **information leaflet for pregnant women** on the flu vaccine for the 2026/2027 season, available on the HSE website.[1]

Medication Safety – Renin angiotensin inhibiting drugs

Earlier this year, a **Prevention of Future Deaths report** from the United Kingdom (UK) was published following a tragic neonatal death arising from complications after **candesartan**, an angiotensin receptor blocker (ARB) was prescribed before pregnancy for maternal migraine prevention and subsequently continued throughout pregnancy. The report found that the mother was unaware of the risks associated with continuing candesartan in pregnancy, following a series of missed opportunities to identify and address the continued prescription of candesartan.[6]

Medicines that inhibit the renin-angiotensin system (RAS), including ARBs, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor-neprilysin inhibitors (ARNIs), are not recommended during the first trimester of pregnancy and are contraindicated during the second and third trimesters.[7,8] Use beyond the first trimester has been associated with a potentially severe fetopathy resulting from inhibition of the fetal RAS, an important modulator of umbilical-placental circulation, fetal blood pressure, and cardiovascular function.[9,10]

A 2012 systematic review described the spectrum of **serious and potentially fatal complications associated with prenatal exposure to RAS inhibitors**, collectively referred to as *fetal renin-angiotensin system blockade syndrome* (RAS blockade syndrome). These complications are summarised in **Figure 1**. The authors reported that the syndrome appeared to occur more frequently and with greater severity following exposure to ARBs (grey bars) than after exposure to ACE inhibitors (black bars).[10]

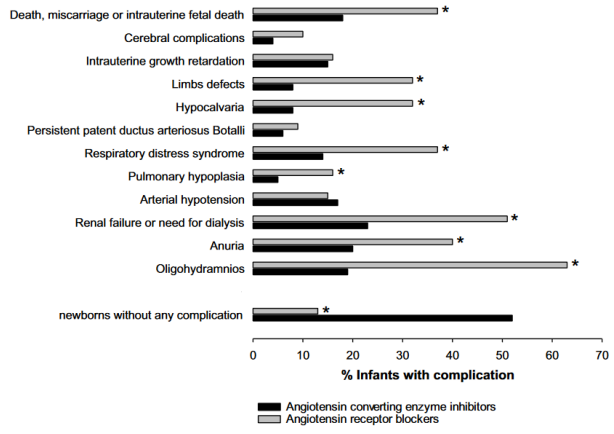


Figure 1: *The complications observed following exposure during pregnancy to drugs that inhibit the renin-angiotensin system (expressed as percentages). The black bar indicates angiotensin-converting enzyme inhibitors: grey bar, angiotensin receptor blockers. *denotes a significant difference between the 2 groups (P<0.05).*[10]

Despite initial warnings of fetal harm emerging in the 1980s and extensive subsequent evidence, cases of fetal exposure to ACE inhibitors and ARBs continue to be reported, including exposure during the second and third trimesters of pregnancy.[7,10] Improving awareness among both healthcare professionals and patients, together with timely preconception counselling, is therefore essential. Discussions should include the potential fetal risks, review of the underlying maternal condition, and consideration of alternative treatment options where appropriate.[9,11]

ACE inhibitors and ARBs are commonly prescribed to women of childbearing age for conditions including hypertension, cardiovascular disease, chronic kidney disease and diabetes mellitus. They may also be used for off-label indications such as migraine prevention. Outside pregnancy, both National Institute for Health and Care Excellence (NICE) and British and Irish Hypertension Society (BIHS) guidelines recommend ACE inhibitors or ARBs as first-line treatment options for hypertension in adults younger than 55 years.[12,13,14] Furthermore, their use in the postpartum period is common, as enalapril and captopril are generally considered compatible with breastfeeding.[14] Consequently, many women may be receiving these medicines at the time of conception, creating an **ongoing risk of inadvertent fetal exposure**. Many women may also be commenced or recommenced on treatment in the postpartum period, presenting renewed opportunity to consider subsequent pregnancies and discuss preconception planning, to reduce future risk of inadvertent exposure to these medications.

As the prevalence of chronic conditions requiring long-term treatment continues to rise, the potential for inadvertent exposure during pregnancy remains an important patient safety concern.[15] **This highlights the need for routine discussions regarding pregnancy intentions and medication safety for all women of child-bearing age who prescribed medicines**.

Statins in Pregnancy

Background

Statins inhibit HMG-CoA reductase, reducing cholesterol synthesis, which is important for fetal development, particularly cell membrane formation and embryogenesis. Early animal studies and case reports raised concerns about possible teratogenicity of statins at high doses, leading to a longstanding contraindication during pregnancy.

With increasing prevalence of hypercholesterolemia and cardiovascular disease among women of reproductive age, questions about the use of statins during pregnancy are increasing.

Reassessing the risk of congenital malformations and other pregnancy outcomes

Over the last decade, substantially larger and methodologically stronger studies have provided evidence on the association between statin exposure in early pregnancy and risk of congenital malformations. Multiple observational cohort studies, systematic reviews and meta-analyses have consistently reported that statin exposure is **not associated with an increased overall risk of major congenital anomalies when compared with unexposed populations.**[16–18]

The largest study to date, a nationwide registry-based cohort study of pregnant women from Norway, involving over 800,000 pregnancies, reported no significant increase in the incidence of major congenital malformations among infants exposed to statins during pregnancy (n=283) compared to those who discontinued (n=1255).[18] These findings were consistent with earlier population-based studies from the United States and South Korea.

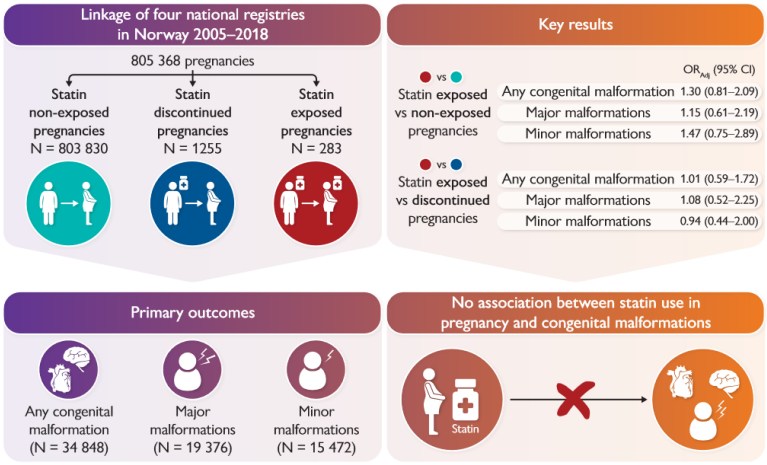


Figure 2: *Statin use in pregnancy and risk of congenital malformations in a nationwide drug safety study in Norway in 2005-2018.*[18]

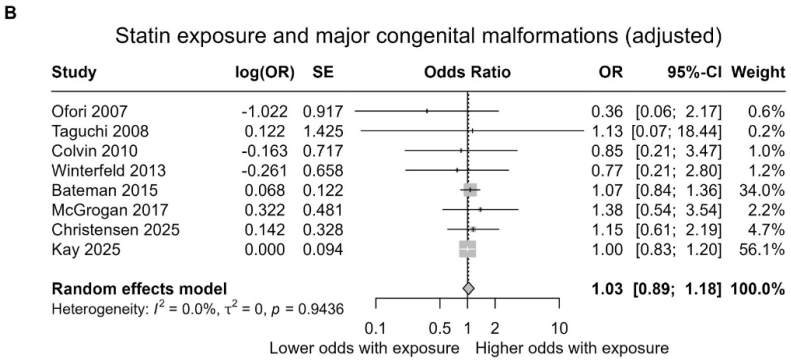


Figure 3: *Meta-analysis of studies on statin exposure and major congenital malformation.*[18]

When incorporated into an updated meta-analysis, Holven et al. found no evidence of an increased overall risk of major congenital malformations among statin-exposed pregnancies, further strengthening the growing body of evidence supporting the fetal safety of inadvertent statin exposure.[18]

Although some studies have reported increased rates of specific congenital cardiac abnormalities, particularly ventricular septal defects, these findings have not been consistent across studies, and in pooled analyses, any apparent association appears largely driven by a small number of observational studies.[17] Potential confounding however, cannot be ruled out and **more data is needed to fully ascertain the risk**.[19]

While data regarding congenital malformations are reassuring, uncertainty remains regarding other pregnancy outcomes. Meta-analyses and large observational studies have reported associations between statin exposure and a trend towards increased risk of miscarriage, preterm birth and low birth weight.[16,17] However, interpretation of these findings is challenging as the indication for statin therapy, including cardiovascular disease, hypertension and diabetes, may independently increase the risk of adverse pregnancy outcomes. **Residual confounding and methodological limitations remain important considerations when assessing the available evidence**.

Maternal considerations

Recent research has also focused on the consequences of discontinuing statin therapy. Recent data from a nationwide South Korean cohort study including 13,374 women who used statins before pregnancy found discontinuation of statins before their last menstrual period was not associated with an increased risk of major maternal cardiovascular and cerebrovascular events, even in high risk women.[20]

While available evidence suggests that temporary discontinuation of statins during pregnancy is not associated with an increased short-term maternal cardiovascular risk for most women, repeated or prolonged periods off treatment related to family planning, pregnancy and breastfeeding may contribute to increased cumulative lifetime cholesterol exposure, particularly among women with familial hypercholesterolaemia (FH).[21]

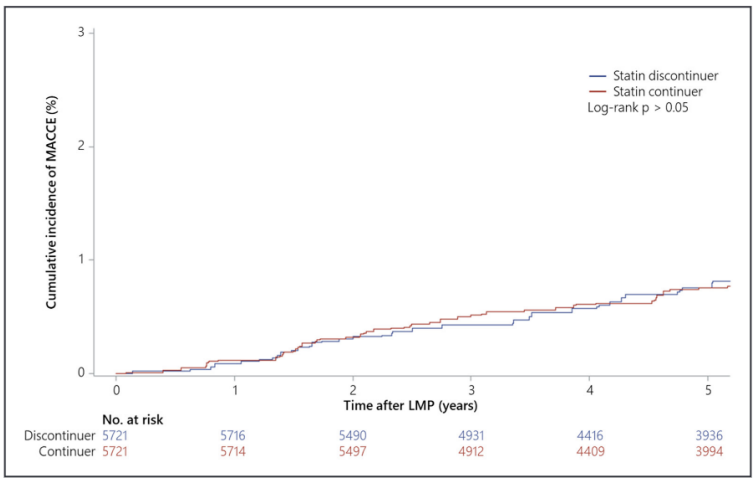


***Figure 4**: Propensity score–weighted cumulative incidence of MACCE (major adverse cardiac and cerebrovascular events) by statin continuation status.*[20]

Despite the evolving evidence, **medicines regulators and international guidelines continue to recommend discontinuation of statins before conception and throughout pregnancy and breastfeeding**.[14,22]

However, emerging **expert consensus increasingly emphasises that pregnancy management should focus on individualised cardiovascular risk assessment rather than general recommendations**. For some women, including those with FH, established vascular disease, previous myocardial infarction or previous stroke, the maternal risks associated with treatment discontinuation may exceed the theoretical fetal risks associated with continued statin exposure.[14,22]

If the benefit of a statin outweighs the potential risk in pregnancy, guidelines consider the use of a hydrophilic statin, such as pravastatin, to be preferable based on results from available clinical trials.[22]

A future role for statins…?

Beyond lipid lowering effects, statins possess anti-inflammatory, antioxidant and endothelial-stabilising properties, prompting interest in their potential role in preventing pre-eclampsia. Several early-phase studies have suggested potential benefits in reducing biomarkers associated with pre-eclampsia and improving placental function. However, larger randomised controlled trials have produced mixed results, and evidence remains insufficient to support routine clinical use for this indication.

References:

1. HSE.ie [Internet]. [cited 2026 Sep 16]. Flu vaccine in pregnancy. Available from: https://www2.hse.ie/conditions/flu/pregnancy-flu-vaccine/

2. Wu Y, Liu C, Qian X, Zhou Y, Xiong Y. Maternal influenza vaccination during the first trimester of pregnancy and risk for birth defects: an updated systematic review and meta-analysis. BMC Pregnancy Childbirth. 2026 May 12;26(1):713. doi:10.1186/s12884-026-09238-3

3. Corbeau M, Mulliez A, Chenaf C, Eschalier B, Lesens O, Vorilhon P. Trends of influenza vaccination coverage in pregnant women: a ten-year analysis from a French healthcare database. Sci Rep. 2022 May 3;12(1):7153. doi:10.1038/s41598-022-11308-3

4. Razzaghi H. Influenza and Tdap Vaccination Coverage Among Pregnant Women — United States, April 2020. MMWR Morb Mortal Wkly Rep. 2020;69. doi:10.15585/mmwr.mm6939a2

5. Seasonal influenza vaccination recommendations and coverage rates in EU/EEA Member States [Internet]. 2023 [cited 2026 Sep 16]. Available from: https://www.ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-recommendations-and-coverage-rates-eueea-member

6. Avery Hall: Prevention of future deaths report. Courts and Tribunals Judiciary [Internet]. 2026 Feb 2 [cited 2026 Feb 20]. Available from: https://www.judiciary.uk/prevention-of-future-death-reports/avery-hall-prevention-of-future-deaths-report/

7. van der Zande JA, Ramlakhan KP, Prokselj K, Muñoz-Ortiz E, Baroutidou A, Lipczynska M, et al. ACE Inhibitor and Angiotensin Receptor Blocker Use During Pregnancy: Data From the ESC Registry Of Pregnancy and Cardiac Disease (ROPAC). Am J Cardiol. 2024 Nov 1;230:27–36. doi:10.1016/j.amjcard.2024.08.004 PubMed PMID: 39122205.

8. HPRA [Internet]. [cited 2026 Sep 25]. HPRA home page. Available from: https://www.hpra.ie

9. USE OF ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs) IN PREGNANCY – UKTIS Toxbase. UK National Poisons Information Service. Accessed online at: Toxbase.org. Last Updated: 11/ 2025. Accessed: 09/2026

10. Pregnancy Outcome Following Exposure to Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists. Hypertension [Internet]. [cited 2026 Sep 8]. Available from: https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.112.196352

11. Recommendations | Hypertension in pregnancy: diagnosis and management | Guidance | NICE [Internet]. NICE; 2019 [cited 2026 Sep 16]. Available from: https://www.nice.org.uk/guidance/ng133/chapter/Recommendations#management-of-chronic-hypertension-in-pregnancy

12. Recommendations | Hypertension in adults: diagnosis and management | Guidance | NICE [Internet]. NICE; 2019 [cited 2026 Sep 16]. Available from: https://www.nice.org.uk/guidance/ng136/chapter/Recommendations#starting-antihypertensive-drug-treatment

13. P L, J G, V K, Nr P, S P, J G, et al. Adult hypertension referral pathway and therapeutic management: British and Irish Hypertension Society position statement. Journal of human hypertension. 2024 Jan;38(1). doi:10.1038/s41371-023-00882-2 PubMed PMID: 38196000.

14. De Backer J, Haugaa KH, Hasselberg NE, de Hosson M, Brida M, Castelletti S, et al. 2025 ESC Guidelines for the management of cardiovascular disease and pregnancy: Developed by the task force on the management of cardiovascular disease and pregnancy of the European Society of Cardiology (ESC) Endorsed by the European Society of Gynecology (ESG). Eur Heart J. 2025 Nov 14;46(43):4462–568. doi:10.1093/eurheartj/ehaf193 PubMed PMID: 40878294.

15. Lovegrove E, Robson J, McGettigan P. Pregnancy protection and pregnancies in women prescribed ACE inhibitors or ARBs: a cross-sectional study in primary care. Br J Gen Pract. 2020 Nov;70(700):e778–84. doi:10.3399/bjgp20X712997

16. Hy K, Hy J, Iw K, Jm O. Pregnancy and neonatal outcomes after fetal exposure to statins among women with dyslipidemia: a nationwide cohort. European journal of pediatrics. 2025 May 14;184(6). doi:10.1007/s00431-025-06119-3 PubMed PMID: 40366447.

17. A H, N T, Dr Z, R R, O A, B HR. The effect of statins exposure during pregnancy on congenital anomalies and spontaneous abortions: A systematic review and meta-analysis. Frontiers in pharmacology. 2022 Sep 29;13. doi:10.3389/fphar.2022.1003060 PubMed PMID: 36249743.

18. Jj C, Kb H, Mp B, K R, Je R van L, Tm M, et al. Statin use in pregnancy and risk of congenital malformations: a Norwegian nationwide study. European heart journal. 2026 Jan 16;47(3). doi:10.1093/eurheartj/ehaf592 PubMed PMID: 40838827.

19. USE OF STATINS IN PREGNANCY – UKTIS. Toxbase. UK National Poisons Information Service. Accessed online at: Toxbase.org Last Updated: 05/ 2023. Accessed: 09/2026

20. Cho Y, Kang D, Lim H, Lee H, Choi EY, Shin JY, et al. Association of Statin Discontinuation in Pregnancy With Maternal Cardiovascular Health and Birth Outcomes: A Nationwide Cohort Study. Circulation. 0(0). doi:10.1161/CIRCULATIONAHA.125.078919

21. Kb H, Fj R, Gf W, Jj C, J R van L. Challenges in the care of women with familial hypercholesterolaemia during the reproductive period - current evidence and practical guidance. Atherosclerosis. 2026 Apr;415. doi:10.1016/j.atherosclerosis.2026.120679 PubMed PMID: 41713387.

22. Rs B, Pb M, M G, Hm J, Ts A, Va B, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2026 May 19;87(19). doi:10.1016/j.jacc.2025.11.016 PubMed PMID: 41824590.