5.2.7. Renin–angiotensin–aldosterone system inhibitors

Angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), angiotensin receptor/neprilysin inhibitors (ARNIs), and renin inhibitors can cause foetal malformations, IUGR and death, and are contraindicated in pregnancy. Caution should be recommended to childbearing women, especially in the absence of effective contraception. Captopril, enalapril, and benazepril are safe during lactation,[146] whereas ARBs are not recommended. Candesartan may be an exception.[256] Aldosterone antagonists, canrenone, and spironolactone can have antiandrogenetic effects and are contraindicated in pregnancy. Spironolactone is considered safe during lactation because of extensive metabolism to canrenone, thus the infant would receive less than 1% of the mother's daily dosage of canrenone.[257] Case reports of eplerenone in pregnant women with resistant hypertension identified no adverse effects.[258–261]

5.2.8. Lipid-lowering agents

Diagnosis of maternal hypercholesterolaemia at the first trimester or familial hypercholesterolaemia have adverse consequences for both foetus and mother.[262] Low-density lipoprotein (LDL) levels increase by ~30%–50%, high-density lipoprotein cholesterol by 20%–40%, and triglycerides by 50%–100% during pregnancy[262], so referring to reference range as for routine testing is of limited clinical use. Previously, lipid-lowering treatment was usually discontinued during pregnancy because of limited safety data.[43] Having been contraindicated in pregnancy since 1987, statins now remain contraindicated only during lactation. In July 2021 the United States Food and Drug Administration (FDA)[263] stated that the evidence was insufficient to conclude that a risk of miscarriage is increased with statins and requested removal of the contraindication.[264] Continuing with statins may therefore be considered during pregnancy in women with familial hypercholesterolaemia or established atherosclerotic cardiovascular disease (ASCVD) (see *Section 12.2*).[265] Furthermore, inadvertent conception during statin therapy does not require pregnancy termination but should prompt close follow-up. Bile acid binding sequestrants[265] and LDL apheresis[265] can be considered in women with familial hypercholesterolaemia. PCSK9 inhibitors and ezetimibe are not recommended during pregnancy due to lack of clinical data.[266] Bempedoic acid has a strong contraindication and therefore women are recommended contraception during its use.

5.2.9. Beta-adrenergic blocking agents

Beta-blocker use during early pregnancy has not been associated with an increased risk of congenital malformations.[250,267,268] Recent data from ROPAC indicate higher SGA rates in women with beta-blocker exposure (15.3% vs 9.3%, $P < .001$). With metoprolol as reference, labetalol (0.2, 95% CI 0.1–0.4) was the least likely to cause SGA, and atenolol (2.3, 95% CI 1.1–4.9) the most.[12] Labetalol and lipophilic drugs (metoprolol, propranolol, carvedilol) are preferred due to high first-pass metabolism, as well as beta-1-selective drugs (bisoprolol, metoprolol), which reduce the risk of hypoglycaemia in addition to reduced IUGR. Nadolol and pindolol are also safe in the case of arrhythmic events in cardiomyopathies and channelopathies (see *Section 6*).[269–271] Of note, the metabolism of metoprolol (and perhaps other oral lipophilic beta-blockers) was significantly higher in mid and late pregnancy than post-partum, likely due to enzymatic induction during pregnancy.[272] Changes in dosage (dose and frequency) are likely required if inadequate clinical responses are encountered.[272]

Atenolol causes severe growth restriction, bradycardia, and hypoglycaemia and is not recommended.[250,268,272,273]

Propranolol, metoprolol (combined with hydralazine), and labetalol had the lowest and sotalol the highest risk of neonatal bradycardia during lactation.[274] For the lipophilic beta-blockers, milk level was <1% of the maternal weight-adjusted dose, thus reducing the risks associated with neonatal exposure during lactation.[272]

5.2.10. Immunosuppressants

The balance between maternal and foetal safety is challenging for immunosuppressant therapy, especially for women with heart transplantation. Medication can pass to the milk and expose neonates and infants to adverse drug effects. Changes in maternal physiology impact the pharmacokinetics of immunosuppressant drugs (see *Section 3.2*).[275] Calcineurin inhibitors (e.g. cyclosporine, tacrolimus), mammalian target of rapamycin inhibitors (e.g. everolimus, sirolimus), and azathioprine are the drugs of choice during pregnancy and lactation, which should not be discouraged. Mycophenolate derivatives increase the risk of miscarriage and foetal malformations especially during the first trimester and should be discontinued at least 6 weeks before conception.[276,277]

5.2.11. Neuroactive drugs

Selective serotonin reuptake inhibitors, including sertraline, can be taken safely during pregnancy and lactation.[278] Zuranolone, a synthetic form of the neurosteroid allopregnanolone, has recently been approved for the treatment of post-partum depression. No information is available on its safety in patients with CVD. Zuranolone is excreted in the milk and lactation should be avoided in the absence of safety data.[279]

5.2.12. Obstetric drugs in patients with cardiovascular disease

Drugs for inducing ovulation, including follicle-stimulating hormone and luteinizing hormone or combinations, are associated with an increased risk of deep vein thrombosis (DVT) and PE, due to the sharp rise in oestrogen levels during follicle recruitment,[280] but no other immediate cardiovascular side effects are known.

5.3. Internet databases

See Supplementary data online, Internet databases.

5.4. List of drugs

See Supplementary data online, *Table S4*.