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# منابع اطلاعاتی

1) www.motherisk.org (Canada)

2) Gerald G. Briggs, Roger K. Freeman, Sumner J. Yaffe.
Briggs' Drugs in Pregnancy and Lactation

3) FDA (Pregnancy risk categories : A → X)

| | |
|---|---|
| A | Controlled studies in women fail to demonstrate risk to the fetus. |
| B | **Either** :<br>Animal studies have **not** demonstrated a risk and no controlled studies have been done in women, OR<br>Animal studies have shown a risk that has not been confirmed in humans. |
| C | **Either** :<br>Studies in animals have shown an adverse effect on the fetus and no controlled studies have been done in women, OR<br>**No studies in women or animals are available.** |
| D | There is evidence of fetal harm, but the benefit of the medication may outweigh the risk. |
| X | There is evidence of fetal harm, and **no benefit** of the medication outweighs the risk. |

Pharmacodynamics

# Relative Infant Dose (RID)

The maximum percentage of the maternal dose, in milligrams per kilogram, received by the infant during a 24-hour period.

By convention, a relative infant dose of less than **10 percent** is considered to be safe.

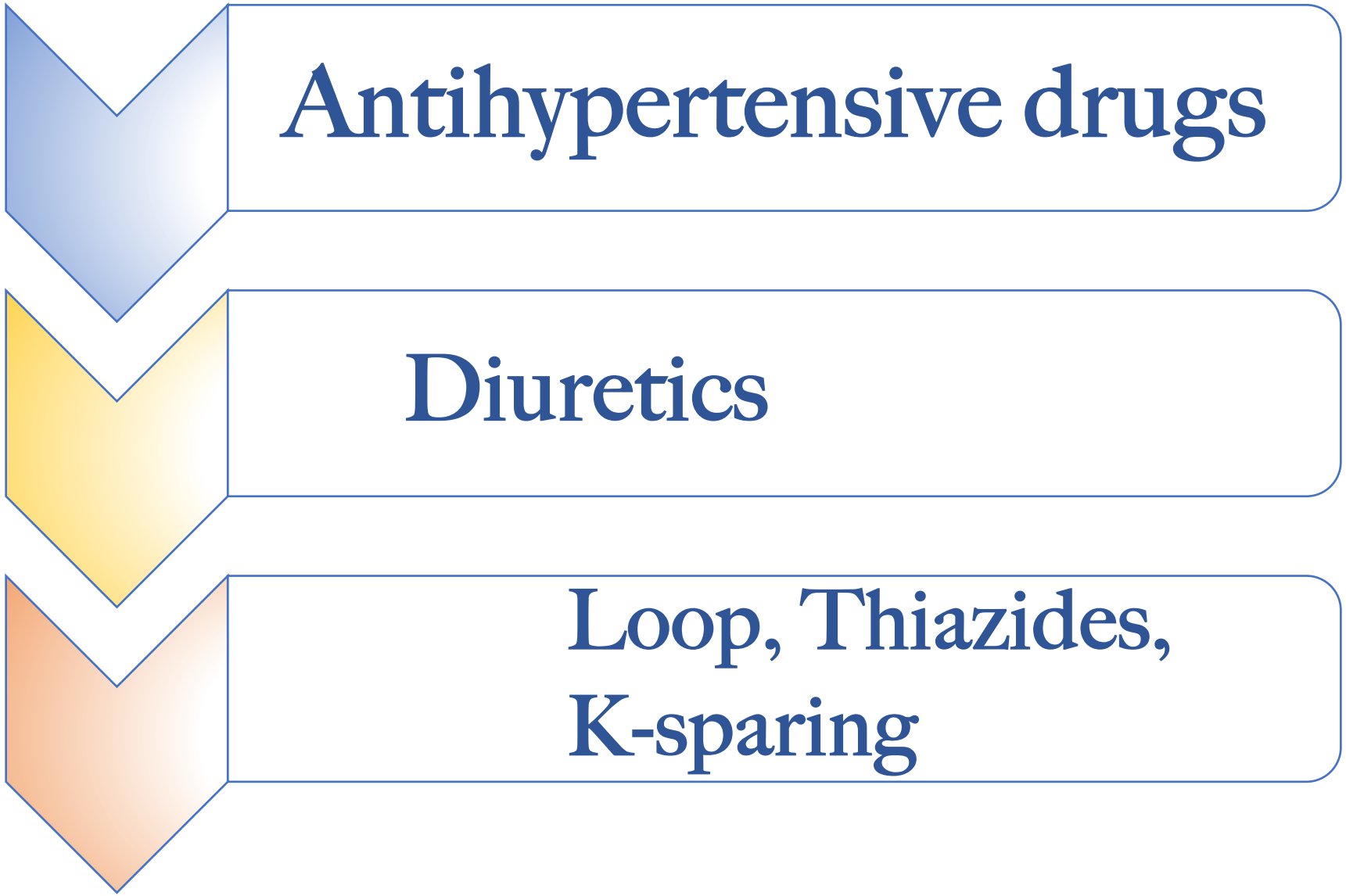
While the relative infant dose reflects the quantity of drug ingested, it does not account for the pharmacodynamics of the drug in the infant.

Hence, the convention that a relative infant dose of less than 10% is "safe" should be applied with caution to **preterm** or **sick infants** (or for psychotropic agents).

Data on the milk/plasma ratio and relative infant dose for maternal medications are derived from pharmacokinetic studies and published in books on medication use during lactation.

Pregnancy

Lactation


Antihypertensive drugs
Diuretics
Loop, Thiazides,
K-sparing

# Furosemide

## Reproductive Considerations

When diuretics are used for the treatment of heart failure in patients planning to become pregnant, adjust dose prior to conception to minimize risk of placental hypoperfusion (AHA/ACC/HFSA [Heidenreich 2022]).

## Pregnancy Considerations

Furosemide crosses the placenta (Beerman 1978; Gonçalves 2020; Riva 1978).

Monitor fetal growth if used during pregnancy (ESC [Regitz-Zagrosek 2018]).

Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of furosemide may be altered. Following administration of a single oral dose of furosemide to patients prior to cesarean delivery, the $V_d$ and clearance were increased, and the $C_{max}$ was lower compared to nonpregnant, healthy individuals (Gonçalves 2020).

Heart failure in pregnancy is associated with adverse maternal and fetal outcomes, including premature birth, infants born small-for-gestational-age, increased risk of maternal and fetal death (Bright 2021). Furosemide may be used for symptom management in pregnant patients with heart failure complicated by pulmonary congestion; closely monitor volume status and adjust dose to minimize risk of placental hypoperfusion (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]).

Short-term postpartum use of furosemide is being evaluated to reduce the risk of persistent hypertension in patients who had hypertensive disorders of pregnancy (Lopes Perdigao 2021, Veena 2017); additional data needed (Malhamé 2023).

## Breastfeeding Considerations

Furosemide is present in breast milk.

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. In general, large doses of loop diuretics have the potential to decrease milk volume and suppress lactation; use should be avoided when possible (WHO 2002). When used for the treatment of heart failure, furosemide may be considered with close neonatal monitoring (AHA/ACC/HFSA [Heidenreich 2022]).

# Hydrochlorothiazide

## Reproductive Considerations

When diuretics are used for the treatment of heart failure in patients planning to become pregnant, adjust dose prior to conception to minimize risk of placental hypoperfusion (AHA/ACC/HFSA [Heidenreich 2022]).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Hydrochlorothiazide is a second-line agent for the treatment of hypertension in pregnant patients (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019; SOGC [Magee 2022]).

## Pregnancy Considerations

Hydrochlorothiazide crosses the placenta (Beerman 1980).

Maternal use may cause fetal or neonatal jaundice, thrombocytopenia, or other adverse events observed in adults.

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke and myocardial infarction (ACOG 2019). Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). Hydrochlorothiazide is a second-line agent for the treatment of hypertension in pregnant patients (ACOG 2019; SOGC [Magee 2022]).

Use of thiazide diuretics during pregnancy may be considered to treat edema due to pathologic causes (as in the nonpregnant patient); monitor.

Heart failure in pregnancy is associated with adverse maternal and fetal outcomes, including premature birth, infants born small-for-gestational-age, increased risk of maternal and fetal death (Bright 2021). Thiazide diuretics may be used for symptom management in pregnant patients with heart failure complicated by pulmonary congestion; closely monitor volume status and adjust dose to minimize risk of placental hypoperfusion (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]).

A case report describes the use of hydrochlorothiazide for the treatment of nephrogenic diabetes insipidus during pregnancy (Gala-Błądzińska 2018).

## Breastfeeding Considerations

Hydrochlorothiazide is present in breast milk.

Data related to the presence of hydrochlorothiazide in breast milk are available from one mother taking hydrochlorothiazide 50 mg once daily for 3.5 years. The study was conducted 28 days postpartum; breast milk was sampled prior to and at intervals for ~23 hours after the dose. Trough breast milk concentrations were ~50 ng/mL and the mean breast milk concentration was 80 ng/mL. The highest breast milk concentrations of hydrochlorothiazide occurred between ~4 to 10 hours after the dose. Hydrochlorothiazide was not detected in the infant serum (limit of detection 20 ng/mL) (Miller 1982).

- Using a mean milk concentration of 80 ng/mL, the estimated exposure of hydrochlorothiazide to the breastfeeding infant would be 0.012 mg/kg/day (relative infant dose [RID] 0.6% to 1.2% when compared to an infant therapeutic dose of 1 to 2 mg/kg/day).
- In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000).

Due to the potential for serious adverse reactions in the breastfeeding infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother. Hydrochlorothiazide is considered compatible with breastfeeding (WHO 2002). However, thiazide diuretics have the potential to decrease milk volume and suppress lactation; use should be avoided when possible (ACOG 2019; WHO 2002).

# Indapamide

## Reproductive Considerations

When diuretics are used for the treatment of heart failure in patients planning to become pregnant, adjust dose prior to conception to minimize risk of placental hypoperfusion (AHA/ACC/HFSA [Heidenreich 2022]); agents other than indapamide may be preferred (ESC [Regitz-Zagrosek 2018]).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Diuretics are second-line agents for the treatment of hypertension in pregnant patients (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019; SOGC [Magee 2022]).

## Pregnancy Considerations

Diuretics cross the placenta and are found in cord blood.

Maternal use may cause fetal or neonatal jaundice, thrombocytopenia, or other adverse events observed in adults.

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Use of thiazide diuretics during pregnancy may be considered to treat edema due to pathologic causes (as in the nonpregnant patient); monitor.

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). Diuretics are second-line agents for the treatment of hypertension in pregnant patients (ACOG 2019; SOGC [Magee 2022]); however, data related to the use of indapamide in pregnancy are insufficient and other agents may be preferred (ESC [Regitz-Zagrosek 2018]).

Heart failure in pregnancy is associated with adverse maternal and fetal outcomes, including premature birth, infants born small for gestational age, and increased risk of maternal and fetal death (Bright 2021). Thiazide diuretics may be used for symptom management in pregnant patients with heart failure complicated by pulmonary congestion; closely monitor volume status and adjust dose to minimize risk of placental hypoperfusion (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]); however, data related to the use of indapamide in pregnancy are insufficient and other agents may be preferred (ESC [Regitz-Zagrosek 2018]).

## Breastfeeding Considerations

It is not known if indapamide is present in breast milk.

If indapamide is needed, the manufacturer recommends that breastfeeding be discontinued.

# Spironolactone

## Reproductive Considerations

Spironolactone is associated with dose-dependent menstrual irregularities (AAD [Zaenglein 2016]; ES [Funder 2016]; ES [Martin 2018]; Kallistratos 2018). Some guidelines recommend use of combination oral contraception in premenopausal patients to regulate menses and prevent pregnancy (AAD [Zaenglein 2016], ES [Martin 2018]). Decreasing the dose or switching to an alternative mineralocorticoid receptor antagonist may be appropriate for some indications (ES [Funder 2016]; Kallistratos 2018).

Spironolactone is associated with dose-dependent erectile dysfunction (AAD [Zaenglein 2016]; ES [Funder 2016]; ES [Martin 2018]; Kallistratos 2018). Decreasing the dose or switching to an alternative mineralocorticoid receptor antagonist may be appropriate for some indications (ES [Funder 2016]; Kallistratos 2018). The antiandrogen blocking activity of spironolactone results in decreased spontaneous erections, sperm production, and testicular volume in transgender patients undergoing feminizing therapy (ES [Hembree 2017]).

Patients taking spironolactone for primary aldosteronism (PA) who are planning to become pregnant should be switched to other agents prior to conception when possible (Forestiero 2022). Patients who require use of spironolactone for the treatment of PA should use the lowest effective dose prior to a planned pregnancy, then stop treatment once their pregnancy is confirmed (Riester 2015).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. The use of mineralocorticoid receptor antagonists is not recommended for the treatment of chronic hypertension in pregnant patients (ACOG 2019). Consider transitioning to an agent preferred for use during pregnancy in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

Patients with heart failure who are planning to become pregnant should discontinue mineralocorticoid receptor antagonists prior to conception (AHA/ACC/HFSA [Heidenreich 2022]).

## Pregnancy Considerations

Spironolactone crosses the placenta (ESC [Regitz-Zagrosek 2018]).

Based on the mechanism of action and data from animal reproduction studies, in utero exposure to spironolactone during the period of embryogenesis may cause feminization of a male fetus (limited human data; Liszewski 2019). High doses late in pregnancy may be associated with intrauterine growth restriction (Riester 2015).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019). Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of chronic hypertension during pregnancy is indicated, the use of mineralocorticoid receptor antagonists is generally not recommended (ACOG 2019).

Data specific to the treatment of primary aldosteronism (PA) in pregnancy are limited. Patients with PA should stop spironolactone before conception or during the first trimester once the pregnancy is confirmed (Riester 2015). If spironolactone is stopped and PA is not controlled, agents other than spironolactone are recommended for the adjunctive treatment of PA during pregnancy (Forestiero 2022; Sanga 2022).

Heart failure in pregnancy is associated with adverse maternal and fetal outcomes, including premature birth, infants born small for gestational age, and increased risk of maternal and fetal death (Bright 2021). When treatment of heart failure during pregnancy is needed, the use of an agent other than a mineralocorticoid receptor antagonist is recommended (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]).

Case reports describe the use of potassium-sparing diuretics such as spironolactone for the adjunctive treatment of Gitleman syndrome during pregnancy (Calò 2012; Moustakakis 2012; Shahzad 2019).

## Breastfeeding Considerations

The active metabolite of spironolactone (canrenone) is present in breast milk.

Data are available from a case report following maternal use of spironolactone 25 mg twice daily throughout pregnancy, then 4 times daily after delivery. Milk and maternal serum samples were obtained 17 days after birth. Two hours after the maternal dose, canrenone concentrations were ~144 ng/mL (serum) and ~104 ng/mL (milk). When measured 14.5 hours after the dose, canrenone concentrations were ~92 ng/mL (serum) and ~47 ng/mL (milk). The authors calculated the estimated maximum amount of canrenone to the breastfeeding infant to be ~0.2% of the maternal dose of spironolactone (Phelps 1977).

Spironolactone is considered compatible with breastfeeding (WHO 2002). According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

# Eplerenone

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## Reproductive Considerations

Eplerenone may be preferred for the treatment of primary aldosteronism (PA) in patients who are planning to become pregnant and require treatment with a mineralocorticoid receptor antagonist (Forestiero 2022; Riester 2015). Use of eplerenone may be considered for patients experiencing menstrual irregularities or erectile dysfunction with other mineralocorticoid receptor antagonists during treatment for PA or resistant hypertension (ACC/AHA [Whelton 2018]; ES [Funder 2016]; Kallistratos 2018).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. The use of mineralocorticoid receptor antagonists is not recommended for the treatment of chronic hypertension in pregnant patients (ACOG 2019). Consider transitioning to an agent preferred for use during pregnancy in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

Patients with heart failure who are planning to become pregnant should discontinue mineralocorticoid receptor antagonists prior to conception (AHA/ACC/HFSA [Heidenreich 2022]).

## Pregnancy Considerations

Eplerenone crosses the placenta (Saito 2021).

Data related to eplerenone use in pregnancy are limited (Cabassi 2012; Gehlert 2021; Gunganah 2015; Hutter 2006; Morton 2011; Morton 2017).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019). Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of chronic hypertension during pregnancy is indicated, the use of mineralocorticoid receptor antagonists is generally not recommended (ACOG 2019).

Data specific to the treatment of primary aldosteronism (PA) in pregnancy are limited. Patients with PA should stop eplerenone before conception if possible. If treatment is stopped and PA is not controlled, eplerenone can be restarted in the second or third trimester (ES [Funder 2016]; Forestiero 2022; Riester 2015; Sanga 2022).

Heart failure in pregnancy is associated with adverse maternal and fetal outcomes, including premature birth, infants born small for gestational age, and increased risk of maternal and fetal death (Bright 2021). When treatment of heart failure during pregnancy is needed, the use of an agent other than a mineralocorticoid receptor antagonist is recommended (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]).

Case reports describe the use of potassium sparing diuretics such as eplerenone for the adjunctive treatment of Gitleman syndrome during pregnancy (Calò 2012; Moustakakis 2012; Shahzad 2019).

## Breastfeeding Considerations

Eplerenone is present in breast milk.

Data related to the presence of eplerenone in breast milk are available from a case report. Eplerenone 50 mg once daily was initiated during pregnancy and continued postpartum. Multiple breast milk samples were obtained on postpartum days 7 and 35. The highest breast milk concentration observed was 161.2 ng/mL, obtained 4 hours after the dose on postpartum day 35. Using a milk concentration of 161.2 ng/mL, authors of the study calculated the estimated daily infant dose via breast milk to be 0.024 mg/kg/day, providing a relative infant dose of 3% based on the weight adjusted maternal dose. The infant was partially breastfed (over 50%); no adverse reactions were reported, and normal development was observed at 1 and 3 months (Saito 2021).

# Triamterene

## Pregnancy Considerations

Triamterene crosses the placenta and is found in cord blood. Use of triamterene to treat edema during normal pregnancies is not appropriate; use may be considered when edema is due to pathologic causes (as in the nonpregnant patient); monitor.

## Breastfeeding Considerations

It is not known if triamterene is present in breast milk. Breastfeeding is not recommended by the manufacturer.

# Antihypertensive drugs

## ACEIs

## ARBs

# Enalapril

## Reproductive Considerations

Avoid use of angiotensin-converting enzyme (ACE) inhibitor therapy in patients who may become pregnant and who are not using effective contraception (ADA 2021).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Angiotensin-converting enzyme (ACE) inhibitors are fetotoxic. Transition patients prior to conception to an agent preferred for use during pregnancy unless treatment with an ACE inhibitor is absolutely necessary (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019). Closely monitor pregnant patients on ACE inhibitors with serial ultrasounds.

When ACE inhibitors are used for the treatment of proteinuric chronic kidney disease in patients who could become pregnant, discontinue use at the first positive pregnancy test (ADA 2021; Fakhouri 2022).

ACE inhibitors are not recommended for the treatment of heart failure in patients planning to become pregnant (AHA/ACC/HFSA [Heidenreich 2022]).

## Pregnancy Considerations

Enalapril crosses the placenta; the active metabolite enalaprilat can be detected in the newborn (Schubiger 1988).

Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Exposure to an angiotensin-converting enzyme (ACE) inhibitor during the first trimester of pregnancy may be associated with an increased risk of fetal malformations (ACOG 2019; ESC [Regitz-Zagrosek 2018]). Following exposure during the second or third trimesters, drugs that act on the renin-angiotensin system are associated with oligohydramnios. Oligohydramnios, due to decreased fetal renal function, may lead to fetal lung hypoplasia and skeletal malformations. Oligohydramnios may not appear until after an irreversible fetal injury has occurred. ACE inhibitor use during pregnancy is also associated with anuria, hypotension, renal failure, skull hypoplasia, and death in the fetus/neonate. Monitor infants exposed to an ACE inhibitor in utero for hyperkalemia, hypotension, and oliguria. Exchange transfusions or dialysis may be required to reverse hypotension or improve renal function.

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Discontinue ACE inhibitors as soon as possible once pregnancy is detected. Agents other than ACE inhibitors are recommended for the treatment of chronic hypertension during pregnancy (ACOG 2019; ESC [Cífková 2020]; SOGC [Magee 2022]). Consider the use of ACE inhibitors only for pregnant patients with hypertension refractory to other medications (ACOG 2019). Closely monitor pregnant patients on ACE inhibitors with serial ultrasounds.

ACE inhibitors are not recommended for the treatment of heart failure or proteinuric chronic kidney disease during pregnancy (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]; Fakhouri 2022).

## Breastfeeding Considerations

Enalapril and enalaprilat are present in breast milk.

Data related to the presence of enalapril and enalaprilat in breast milk are available from multiple reports.

- Enalapril and enalaprilat breast milk concentrations were evaluated in one patient who was 12 months' postpartum following administration of enalapril 10 mg/day for 11 months. The highest level of enalapril was 2.05 ng/mL at 4 hours after the dose. The highest level of enalaprilat was 0.75 ng/mL at 8.75 hours after the dose (Rush 1991).
- The presence of enalaprilat in breast milk was evaluated in three patients, one treated with enalapril 5 mg for chronic glomerulonephritis and two treated with enalapril 10 mg for hypertension. Enalaprilat was not detected in breast milk (<0.2 ng/mL) of any patient 4 hours after the maternal dose. Serum concentrations of enalaprilat were significantly greater (179 ng/mL) in the first woman, who also had renal impairment, when compared to the two patients treated for hypertension (48 ng/mL, 23.9 ng/mL). Enalapril concentrations were not evaluated (Huttunen 1989).
- Breast milk concentrations of enalapril and enalaprilat were evaluated in five lactating patients treated for hypertension. Following a single dose of enalapril 20 mg, breast milk was sampled over 24 hours; serum samples were obtained at 2 and 4 hours. Breast milk concentrations of enalapril ranged from 0 to 5.9 mcg/mL with the highest concentration observed 6 hours after the dose (maximum maternal serum concentrations: 92 to 151 ng/mL). Enalapril was not detectable in the breast milk of one patient over the 24-hour dosing interval (maternal serum concentration: 151 ng/mL). Concentrations of enalaprilat ranged from 0 to 2.3 ng/mL (maximum maternal serum concentrations: 39 to 112 ng/mL). Peak breast milk concentrations of the metabolite occurred 6 hours after the dose in one patient and at 24 hours in two others; the metabolite was only measurable in a third patient at 24 hours. Mean peak breast milk concentrations for enalapril and enalaprilat were 1.74 ng/mL and 1.72 ng/mL, respectively (Redman 1990). Using the highest breast milk concentration of 5.9 ng/mL, the estimated exposure of enalapril to the breastfeeding infant would be 0.00089 mg/kg/day (relative infant dose: 1.1% based on a therapeutic infant dose of 0.08 mg/kg/day).
- In general, breastfeeding is considered acceptable when the RID of a medication is <10% (Anderson 2016; Ito 2000).

Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer. When postpartum treatment with an ACE inhibitor is needed, available guidelines consider enalapril to be acceptable for use (AHA/ACC/HFSA [Heidenreich 2022], ESC [Cífková 2020]). Avoid breastfeeding if high maternal doses of an ACE inhibitor are needed (ACOG 2019).

# Captopril

## Reproductive Considerations

Avoid use of angiotensin-converting enzyme (ACE) inhibitor therapy in patients who may become pregnant and who are not using effective contraception (ADA 2021).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. ACE inhibitors are fetotoxic. Transition patients prior to conception to an agent preferred for use during pregnancy unless treatment with an ACE inhibitor is absolutely necessary (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

When ACE inhibitors are used for the treatment of proteinuric chronic kidney disease in patients who could become pregnant, discontinue use at the first positive pregnancy test (ADA 2021; Fakhouri 2022).

ACE inhibitors are not recommended for the treatment of heart failure in patients planning to become pregnant (AHA/ACC/HFSA [Heidenreich 2022]).

## Pregnancy Considerations

Captopril crosses the placenta (Hurault de Ligny 1987).

Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Exposure to an angiotensin-converting enzyme (ACE) inhibitor during the first trimester of pregnancy may be associated with an increased risk of fetal malformations (ACOG 2019; ESC [Regitz-Zagrosek 2018]). Following exposure during the second or third trimesters, drugs that act on the renin-angiotensin system are associated with oligohydramnios. Oligohydramnios, due to decreased fetal renal function, may lead to fetal lung hypoplasia and skeletal malformations. Oligohydramnios may not appear until after an irreversible fetal injury has occurred. ACE inhibitor use during pregnancy is also associated with anuria, hypotension, renal failure, skull hypoplasia, and death in the fetus/neonate. Monitor infants exposed to an ACE inhibitor in utero for hyperkalemia, hypotension, and oliguria. Exchange transfusions or dialysis may be required to reverse hypotension or improve renal function

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

ACE inhibitors should be discontinued as soon as possible once pregnancy is detected. When treatment of chronic hypertension in pregnancy is indicated, agents other than ACE inhibitors are recommended (ACOG 2019; ESC [Cífková 2020]; SOGC [Magee 2022]). Use during pregnancy should only be considered for cases of hypertension refractory to other medications (ACOG 2019). Closely monitor pregnant patients on ACE inhibitors with serial ultrasounds.

ACE inhibitors are not recommended for the treatment of heart failure or proteinuric chronic kidney disease during pregnancy (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]; Fakhouri 2022).

## Breastfeeding Considerations

Captopril is present in breast milk.

Data related to the presence of captopril in breast milk are available following maternal administration captopril 100 mg 3 times a day for 7 doses to 11 normotensive lactating patients. The mean peak milk concentration of captopril was 4.7 ng/mL. The maximum milk concentrations occurred 3.8 hours after the maternal dose. Captopril was not detected in all milk samples. Concentrations of captopril in breast milk were ~1% of those in maternal blood (Devlin 1981).

- Using a milk concentration of 4.7 ng/mL, the estimated daily infant dose via breast milk is 705 ng/kg/day providing a relative infant dose (RID) of 0.01% to 0.02% compared to an infant therapeutic dose of 3 to 6 mg/kg/day.
- In general, breastfeeding is considered acceptable when the RID of a medication is <10% (Anderson 2016; Ito 2000).

According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of exposure to the infant and the benefits of treatment to the mother. When postpartum treatment with an angiotensin-converting enzyme (ACE) inhibitor is needed, available guidelines consider captopril to be acceptable for use in lactating patients (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Cífková 2020]; WHO 2002). Avoid breastfeeding if high maternal doses of an ACE inhibitor are needed (ACOG 2019).

# Lisinopril

## Reproductive Considerations

Avoid use of angiotensin-converting enzyme (ACE) inhibitor therapy in patients who may become pregnant and who are not using effective contraception (ADA 2023).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Angiotensin-converting enzyme (ACE) inhibitors are fetotoxic. Transition patients prior to conception to an agent preferred for use during pregnancy unless treatment with an ACE inhibitor is absolutely necessary (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

When ACE inhibitors are used for the treatment of proteinuric chronic kidney disease in patients who could become pregnant, discontinue use at the first positive pregnancy test (ADA 2023; Fakhouri 2023).

ACE inhibitors are not recommended for the treatment of heart failure in patients planning to become pregnant (AHA/ACC/HFSA [Heidenreich 2022]).

Lisinopril may be effective for prevention of migraines. In general, preventive treatment for migraine in patients trying to become pregnant should be avoided. Options for patients planning a pregnancy should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data and needs of the patient should pregnancy occur. A gradual discontinuation of preventive medications is generally preferred when the decision is made to stop treatment prior to conception (ACOG 2022; AHS [Ailani 2021]). When lisinopril is used for migraine prevention, treatment should be discontinued prior to attempting to conceive (ACOG 2022).

## Pregnancy Considerations

Lisinopril crosses the placenta (Bhatt-Mehta 1993; Filler 2003).

Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Exposure to an angiotensin-converting enzyme (ACE) inhibitor during the first trimester of pregnancy may be associated with an increased risk of fetal malformations (ACOG 2019; ESC [Regitz-Zagrosek 2018]). Following exposure during the second or third trimesters, drugs that act on the renin-angiotensin system are associated with oligohydramnios. Oligohydramnios, due to decreased fetal renal function, may lead to fetal lung hypoplasia and skeletal malformations. Oligohydramnios may not appear until after an irreversible fetal injury has occurred. ACE inhibitor use during pregnancy is also associated with anuria, hypotension, renal failure, skull hypoplasia, and death in the fetus/neonate. Monitor infants exposed to an ACE inhibitor in utero for hyperkalemia, hypotension, and oliguria. Exchange transfusions or dialysis may be required to reverse hypotension or improve renal function.

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, pre-eclampsia, delivery complications, stroke and myocardial infarction (ACOG 2019).

Discontinue ACE inhibitors as soon as possible once pregnancy is detected. Agents other than ACE inhibitors are recommended for the treatment of chronic hypertension during pregnancy (ACOG 2019; ESC [Cífková 2020]; SOGC [Magee 2022]). Consider the use of ACE inhibitors only for pregnant patients with hypertension refractory to other medications (ACOG 2019). Closely monitor pregnant patients on ACE inhibitors with serial ultrasounds.

ACE inhibitors are not recommended for the treatment of heart failure or proteinuric chronic kidney disease during pregnancy (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]; Fakhouri 2023).

In general, preventive treatment for migraine should be avoided during pregnancy. Options for pregnant patients should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data, the potential for adverse maternal and fetal events, and needs of the patient (ACOG 2022; AHS [Ailani 2021]). Lisinopril is not recommended for migraine prevention during pregnancy (ACOG 2022).

## Breastfeeding Considerations

It is not known if lisinopril is present in breast milk.

Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue lisinopril.

In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient (AHS [Ailani 2021]). When postpartum treatment with an ACE inhibitor is needed, consider use of an agent other than lisinopril (ESC [Cífková 2020]). Avoid breastfeeding if high maternal doses of an ACE inhibitor are needed (ACOG 2019).

# Losartan

## Reproductive Considerations

Avoid use of an angiotensin II receptor blocker (ARB) in patients who may become pregnant and who are not using effective contraception (ADA 2023).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. ARBs are fetotoxic. Transition patients prior to conception to an agent preferred for use during pregnancy unless treatment with an ARB is absolutely necessary (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

When an ARB is used for the treatment of proteinuric chronic kidney disease in patients who could become pregnant, discontinue use at the first positive pregnancy test (ADA 2023; Fakhouri 2023)

## Pregnancy Considerations

Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Exposure to an angiotensin II receptor blocker (ARB) during the first trimester of pregnancy may be associated with an increased risk of fetal malformations (ACOG 2019; ESC [Regitz-Zagrosek 2018]).Following exposure during the second or third trimesters, drugs that act on the renin-angiotensin system are associated with oligohydramnios. Oligohydramnios, due to decreased fetal kidney function, may lead to fetal lung hypoplasia and skeletal malformations. Oligohydramnios may not appear until after an irreversible fetal injury has occurred. ARB use during pregnancy is also associated with anuria, hypotension, kidney failure, skull hypoplasia, and death in the fetus/neonate. Monitor infants exposed to an ARB in utero for hyperkalemia, hypotension, and oliguria. Exchange transfusions or dialysis may be required to reverse hypotension or improve renal function.

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Discontinue ARBs as soon as possible once pregnancy is detected. Agents other than an ARB are recommended for the treatment of chronic hypertension during pregnancy (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]). Closely monitor patients exposed to an ARB during pregnancy with serial ultrasounds.

ARBs are not recommended for the treatment of proteinuric chronic kidney disease during pregnancy (Fakhouri 2023).

## Breastfeeding Considerations

It is not known if losartan is present in breast milk.

Due to the potential for serious adverse reactions in the breastfeeding infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother. When treatment for hypertension is needed in a breastfeeding patient, consider use of an agent other than an angiotensin II receptor blocker (ESC [Cífková 2020]; NICE 2019).

# Valsartan

## Reproductive Considerations

Avoid use of an angiotensin II receptor blocker (ARB) in patients who may become pregnant and who are not using effective contraception (ADA 2021).

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. ARBs are fetotoxic. Transition patients prior to conception to an agent preferred for use during pregnancy (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

When an ARB is used for the treatment of proteinuric chronic kidney disease in patients who could become pregnant, discontinue use at the first positive pregnancy test (ADA 2021; Fakhouri 2022).

ARBs are not recommended for the treatment of heart failure in patients planning to become pregnant (AHA/ACC/HFSA [Heidenreich 2022]).

## Pregnancy Considerations

Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Exposure to an angiotensin II receptor blocker (ARB) during the first trimester of pregnancy may be associated with an increased risk of fetal malformations (ACOG 2019; ESC [Regitz-Zagrosek 2018]). Following exposure during the second or third trimesters, drugs that act on the renin-angiotensin system are associated with oligohydramnios. Oligohydramnios, due to decreased fetal kidney function, may lead to fetal lung hypoplasia and skeletal malformations. Oligohydramnios may not appear until after an irreversible fetal injury has occurred. ARB use during pregnancy is also associated with anuria, hypotension, kidney failure, skull hypoplasia, and death in the fetus/neonate. Monitor infants exposed to an ARB in utero for hyperkalemia, hypotension, and oliguria. Exchange transfusions or dialysis may be required to reverse hypotension or improve renal function.

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, preterm delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated hypertension may also increase the risk of adverse maternal outcomes, including gestational diabetes, myocardial infarction, preeclampsia, stroke, and delivery complications (ACOG 2019).

Discontinue ARBs as soon as possible once pregnancy is detected. Agents other than an ARB are recommended for the treatment of chronic hypertension during pregnancy (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]). Closely monitor patients exposed to an ARB during pregnancy with serial ultrasounds.

ARBs are not recommended for the treatment of heart failure or proteinuric chronic kidney disease during pregnancy (AHA/ACC/HFSA [Heidenreich 2022]; ESC [Regitz-Zagrosek 2018]; Fakhouri 2022).

## Breastfeeding Considerations

It is not known if valsartan is present in breast milk.

Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer. When treatment for hypertension is needed in a breastfeeding patient, consider use of an agent other than an angiotensin II receptor blocker (ESC [Cífková 2020]; NICE 2019).

# Telmisartan

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Angiotensin II receptor blockers (ARBs) are fetotoxic. Transition patients prior to conception to an agent preferred for use during pregnancy unless treatment with an ARB is absolutely necessary (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

## Pregnancy Considerations

Drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus. Exposure to an angiotensin II receptor blocker (ARB) during the first trimester of pregnancy may be associated with an increased risk of fetal malformations (ACOG 2019; ESC [Regitz-Zagrosek 2018]). Following exposure during the second or third trimesters, drugs that act on the renin-angiotensin system are associated with oligohydramnios. Oligohydramnios, due to decreased fetal kidney function, may lead to fetal lung hypoplasia and skeletal malformations. Oligohydramnios may not appear until after an irreversible fetal injury has occurred. ARB use during pregnancy is also associated with anuria, hypotension, kidney failure, skull hypoplasia, and death in the fetus/neonate. Monitor infants exposed to an ARB in utero for hyperkalemia, hypotension, and oliguria. Exchange transfusions or dialysis may be required to reverse hypotension or improve renal function.

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Discontinue ARBs as soon as possible once pregnancy is detected. Agents other than an ARB are recommended for the treatment of chronic hypertension during pregnancy (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]). Closely monitor patients exposed to an ARB during pregnancy with serial ultrasounds.

## Breastfeeding Considerations

It is not known if telmisartan is present in breast milk.

Due to the potential for serious adverse reactions in the breastfeeding infant, breastfeeding is not recommended by the manufacturer. When treatment for hypertension is needed in a breastfeeding patient, consider use of an agent other than an angiotensin II receptor blocker (ESC [Cífková 2020]; NICE 2019).

# Antihypertensive drugs

## CCBs

# Amlodipine

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Amlodipine is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

## Pregnancy Considerations

Amlodipine crosses the placenta. Cord blood concentrations were ~40% of maternal serum at delivery, and concentrations in the newborn were below the limit of quantification (< 0.1 ng/mL) when measured in eight infants within 48 hours of delivery (Morgan 2017; Morgan 2018).

Due to pregnancy-induced pharmacologic changes, amlodipine pharmacokinetics may be altered immediately postpartum (Morgan 2018; Naito 2015b; Taguchi 2019).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than amlodipine may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]).

## Breastfeeding Considerations

Amlodipine is present in breast milk.

Multiple reports have evaluated the presence of amlodipine in breast milk:

- Amlodipine was not detected in the colostrum of 6 women taking amlodipine 5 mg daily during pregnancy for chronic hypertension and continuing after delivery. Breast milk was sampled at intervals between 4 and 24 hours after the maternal dose on postpartum day 2. Although detectable in maternal serum, amlodipine was not present in breast milk (limit of detection 0.1 ng/mL). This same study evaluated cord blood concentrations; although amlodipine was present in cord blood, it was not detected in the newborn serum at 24 to 48 hours of life (Morgan 2018).
- In a case report, amlodipine was not detected in the blood of an exclusively breastfed infant. The infant was born at 32 weeks' gestation. The mother started amlodipine postpartum (dose not noted). Breastfeeding was initiated on postpartum day 7 and amlodipine levels were obtained 4 days later (Vasa 2013). In a second case report, adverse events were not observed in an exclusively breastfed infant. Maternal amlodipine 5 mg/day was initiated at 2 weeks' postpartum. The baby had normal growth and development at 3 months of age (Ahn 2007).
- In a study of 8 lactating mothers and their 9 breastfeeding infants, peak breast milk concentrations of amlodipine (6.5 to 19.7 ng/mL) occurred 8 hours after the maternal dose (5 mg/day n = 7; 2.5 mg/day n = 1). In this study, 6 mothers started therapy 1 to 2 days postpartum and 2 were taking amlodipine throughout pregnancy; sampling of foremilk occurred 5 to 7 days' postpartum. Plasma concentrations of amlodipine in the infants were lower than the limit of quantification (< 0.4 ng/mL). Authors of this study calculated the relative infant dose (RID) of amlodipine to be 1.56% to 4.32% of the weight-adjusted maternal dose (Aoki 2018).
- Amlodipine was detected in the breast milk of 31 lactating women when sampled ~3 weeks postpartum. Patients in the study were initiated on amlodipine 5 mg/day with the dose adjusted as needed (median daily dose of 6.01 mg ± 2.31 mg). Sampling occurred prior to a dose and ~10 days after treatment initiation. The median predose milk concentration of amlodipine was 11.5 ng/mL (interquartile range [IQR] 9.84 to 18 ng/mL). Authors of the study calculated the estimated daily infant dose of amlodipine via breast milk to be 4.17 mcg/kg/day (IQR 3.05 to 6.32 mcg/kg/day) and the median RID to be 4.18% (IQR 3.12 to 7.25%). The maximum reported RID was 15.2%. Adverse events were not observed in the breastfed infants (Naito 2015a).
- In general, breastfeeding is considered acceptable when the RID is < 10%; when a RID is > 25%, breastfeeding should generally be avoided. Additional considerations can include the gestational and postnatal age of the infant, the actual amount of milk being ingested (less in the first couple days of life and when weaning), properties of the specific maternal medication, medical conditions of the infant, and medications the infant is receiving therapeutically (Anderson 2016; Ito 2000).

Use of a calcium channel blocker other than amlodipine may be preferred in lactating patients (ESC [Cífková 2020]).

# Diltiazem

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Diltiazem is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

## Pregnancy Considerations

Outcome data following maternal use of diltiazem during pregnancy are available; a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes has not been identified (El-Sayed 1998; Khandelwal 2002; Lechner 1991; Lubbe 1987; Magee 1996; Wang 2024; Weber-Schoendorfer 2008; manufacturer's labeling).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of chronic hypertension during pregnancy is indicated, agents other than diltiazem may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]).

## Breastfeeding Considerations

Diltiazem is present in breast milk.

Data related to the presence of diltiazem in breast milk are available from a case report. Oral diltiazem 60 mg four times a day was started in a mother on postpartum day 14 for arrythmia. Four days later maternal blood and breast milk were sampled. Peak breast milk concentrations of diltiazem were 200 ng/mL, similar to those in the maternal serum. Breast milk concentrations decreased to <50 mg/mL 22 hours after the final diltiazem dose (Okada 1985).

Diltiazem is compatible for use in patients who are breastfeeding (ESC [Cífková 2020]). According to the manufacturer, a shared decision-making approach should be used to determine whether to discontinue breastfeeding or discontinue diltiazem. The decision should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

# Verapamil

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## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Verapamil is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

Verapamil may be effective for prevention of migraines. In general, preventive treatment for migraine in patients trying to become pregnant should be avoided. Options for patients planning a pregnancy should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data and needs of the patient should pregnancy occur. A gradual discontinuation of preventive medications is generally preferred when the decision is made to stop treatment prior to conception (ACOG 2022; AHS [Ailani 2021]).

## Pregnancy Considerations

Verapamil crosses the placenta.

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than verapamil may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]).

Verapamil may be used IV for the acute treatment of supraventricular tachycardia (SVT) in patients who are pregnant when adenosine or beta-blockers are ineffective or contraindicated. Verapamil may also be used for the ongoing management of SVT in highly symptomatic patients. The lowest effective dose is recommended; avoid use during the first trimester if possible (ACC/AHA/HRS [Page 2016]). Additional guidelines are available for management of cardiovascular diseases during pregnancy (ESC [Regitz-Zagrosek 2018]).

In general, preventive treatment for migraine should be avoided during pregnancy. Options for pregnant patients should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data, the potential for adverse maternal and fetal events, and needs of the patient (ACOG 2022; AHS [Ailani 2021]). If preventive therapy is needed, verapamil may be used (ACOG 2022).

Verapamil is used for the prevention of cluster headache (AHS [Robbins 2016]). Verapamil may be used when prophylaxis is needed in pregnant patients; however, use should be avoided during the third trimester if possible (Bjørk 2021).

## Breastfeeding Considerations

Verapamil and norverapamil are present in breast milk (Anderson 1987; Miller 1986).

Data related to the presence of verapamil in breast milk are available from multiple case reports. Following maternal use of verapamil 80 to 120 mg three times daily in patients ≤3 months postpartum, the relative infant dose (RID) of verapamil was calculated to be ≤1% of the weight-adjusted maternal dose. Adverse events were not observed in breastfed infants (Andersen 1983; Anderson 1987; Inoue 1984; Miller 1986). In general, breastfeeding is considered acceptable when the RID of a medication is <10% (Anderson 2016; Ito 2000).

Although breastfeeding is not recommended by some manufacturers (consider the risk of infant exposure), other sources consider verapamil compatible for use in patients who are breastfeeding (ESC [Cífková 2020]; WHO 2002).

In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient (AHS [Ailani 2021]). If preventive therapy is needed, verapamil may be considered (CHS [Pringsheim 2012]). Verapamil is likely compatible if prophylaxis for cluster headache is needed when breastfeeding infants are >2 months of age (limited data) (Bjørk 2021).

# Antihypertensive drugs

## Beta-blockers

## Beta(alpha)-blockers

# Propranolol

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Propranolol is generally not a preferred agent for use in pregnant patients (ACC/AHA [Whelton 2018]; ACOG 2019); however, use may be considered (SOGC [Magee 2022]).

Propranolol is approved for prevention of migraines. In general, preventive treatment for migraine in patients trying to become pregnant should be avoided. Options for patients planning a pregnancy should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data and needs of the patient should pregnancy occur. A gradual discontinuation of preventive medications is generally preferred when the decision is made to stop treatment prior to conception (ACOG 2022; AHS [Ailani 2021]).

Erectile dysfunction and male impotence are noted in product labeling following use of propranolol. As a class, outcomes from available studies evaluating beta-blockers and sexual dysfunction are inconsistent, and the negative effects on erectile function and libido are considered controversial. A clear relationship between use of beta-blockers and erectile dysfunction has not been established. Hypertension itself is associated with erectile dysfunction. Patients on a beta-blocker presenting with sexual dysfunction should be evaluated for underlying disease (Farmakis 2021; Levine 2012; Semet 2017; Terentes-Printzios 2022; Viigimaa 2020).

## Pregnancy Considerations

Propranolol crosses the placenta.

Exposure to beta-blockers during the third trimester of pregnancy may increase the risk for bradycardia, hypoglycemia, hypotension, and respiratory depression in the neonate. Newborns should be monitored and managed accordingly. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression (ESC [Regitz-Zagrosek 2018]).

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

The pharmacokinetics of propranolol are not significantly changed by pregnancy (Livingstone 1983; O'Hare 1984; Rubin 1987; Smith 1983).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than propranolol may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]); however, use may be considered (SOGC [Magee 2022]).

Propranolol may be used for the treatment of maternal ventricular arrhythmias, atrial fibrillation/atrial flutter, or supraventricular tachycardia during pregnancy; consult current guidelines for specific recommendations (ACC/AHA/HRS [Page 2016]; ESC [Regitz-Zagrosek 2018]).

Propranolol is recommended for use in controlling hypermetabolic symptoms of thyrotoxicosis in pregnancy (ATA [Alexander 2017]).

In general, preventive treatment for migraine should be avoided during pregnancy. Options for pregnant patients should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data, the potential for adverse maternal and fetal events, and needs of the patient (ACOG 2022; AHS [Ailani 2021]). If preventive therapy is needed, beta-blockers may be considered (ACOG 2022). Based on available data, propranolol may be used if prophylaxis of migraine is needed in pregnant patients; it should be discontinued 2 to 3 days prior to delivery to decrease the risk of adverse events to the fetus/neonate and potential reductions in uterine contraction (CHS [Pringsheim 2012]).

## Breastfeeding Considerations

Propranolol and its inactive metabolites are present in breast milk (Smith 1983).

Data related to the presence of propranolol in breast milk are available from 3 lactating patients 1-week postpartum receiving propranolol for hypertension. Breast milk was sampled ~3, 4, 6, and 8 hours after the maternal dose. The first 2 patients received propranolol 1.2 mg/kg/day and the third received propranolol 2.6 mg/kg/day. The highest propranolol milk concentration was 74.9 ng/mL observed in the first patient ~3 hours after the dose. The lowest propranolol milk concentration was 13.5 ng/mL in the second patient, observed ~8 hours after the dose. The overall half-life of propranolol in breast milk was 6.5 ± 3.4 hours. In comparison, the overall half-life in the maternal plasma was 2.6 ± 1.2 hours (Smith 1983). Peak milk concentrations are reported to occur between 2 to 3 hours after an oral dose (Bauer 1979).

Bradycardia was reported in an infant exposed to propranolol via breast milk (Soussan 2014).

In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient (AHS [Ailani 2021]). Based on available data, propranolol may be used if prophylaxis of migraine is needed in lactating patients (CHS [Pringsheim 2012]).

When used for hypertension, propranolol is compatible for use in patients who are breastfeeding (ACOG 2019; ESC [Cífková 2020]).

In general, propranolol may be compatible with breastfeeding when used at usual doses. Breastfeeding infants should be monitored for bradycardia, cyanosis, and hypoglycemia (WHO 2002).

# Metoprolol

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Metoprolol is generally not a preferred agent for use in pregnant patients (ACC/AHA [Whelton 2018]; ACOG 2019); however, use may be considered (ESC [Cífková 2020]; SOGC [Magee 2022]).

Metoprolol may be continued for the treatment of heart failure in patients planning to become pregnant; treatment should be made as part of a shared decision-making process (AHA/ACC/HFSA [Heidenreich 2022]).

Metoprolol is effective for prevention of migraines. In general, preventive treatment for migraine in patients trying to become pregnant should be avoided. Options for patients planning a pregnancy should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data and needs of the patient should pregnancy occur. A gradual discontinuation of preventive medications is generally preferred when the decision is made to stop treatment prior to conception (ACOG 2022; AHS [Ailani 2021]).

Erectile dysfunction and inhibition of sperm motility are noted in product labeling following use of metoprolol. As a class, outcomes from available studies evaluating beta-blockers and sexual dysfunction are inconsistent, and the negative effects on erectile function and libido are considered controversial. A clear relationship between use of beta-blockers and erectile dysfunction has not been established. Hypertension itself is associated with erectile dysfunction. Patients on a beta-blocker presenting with sexual dysfunction should be evaluated for underlying disease (Farmakis 2021; Levine 2012; Semet 2017; Terentes-Printzios 2022; Viigimaa 2020).

## Pregnancy Considerations

Metoprolol and the metabolite alpha-hydroxymetoprolol cross the placenta (Lindeberg 1987; Ryu 2016).

Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression (ESC [Regitz-Zagrosek 2018]).

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

The pharmacokinetics of metoprolol may be changed during pregnancy; the degree of changes may be dependent upon maternal CYP2D6 genotype (Ryu 2016).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than metoprolol may be preferred (ACOG 2019); however, use may be considered (ESC [Cífková 2020]; SOGC [Magee 2022]). Metoprolol may be continued for the treatment of heart failure in pregnant patients; treatment should be made as part of a shared decision-making process (AHA/ACC/HFSA [Heidenreich 2022]). Metoprolol may be used for the treatment of maternal ventricular arrhythmias, atrial fibrillation/atrial flutter, or supraventricular tachycardia during pregnancy; consult current guidelines for specific recommendations (ACC/AHA/HRS [Page 2016]; ESC [Regitz-Zagrosek 2018]).

In general, preventive treatment for migraine should be avoided during pregnancy. Options for pregnant patients should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data, the potential for adverse maternal and fetal events, and needs of the patient (ACOG 2022; AHS [Ailani 2021]). If preventive therapy is needed, beta-blockers may be considered (ACOG 2022). Based on available data, metoprolol may be used if prophylaxis of migraine is needed in pregnant patients; it should be discontinued 2 to 3 days prior to delivery to decrease the risk of adverse events to the fetus/neonate and potential reductions in uterine contraction (CHS [Pringsheim 2012]).

## Breastfeeding Considerations

Metoprolol is present in breast milk.

Data related to the presence of metoprolol in breast milk are available from 3 lactating patients, 4 to 6 months postpartum. They were administered oral metoprolol after they stopped breastfeeding, but lactation was maintained via breast pumping. Metoprolol 50 mg twice daily was administered on day 1, 100 mg twice daily on days 2 and 3, and 100 mg on day 4. Blood and milk samples were obtained immediately prior to the dose on day 4, then at intervals from 3 to 12 hours later. The maximum maternal metoprolol blood concentrations ranged from 27 to 259 ng/mL, and the maximum milk concentrations ranged from 102 to 690 ng/mL (Liedholm 1981). Using the highest milk concentration reported (690 ng/mL), the estimated exposure to the breastfeeding infant would be 0.1 mg/kg/day (relative infant dose [RID] 7%) compared to a weight-adjusted maternal dose of 100 mg/day. In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000).

A case report also notes the presence of the α-OH-metoprolol metabolite in breast milk (Grundman 2011). Metoprolol is measurable in the serum of some breastfed infants (Sandström 1983). Adverse events were not reported in 6 infants exposed to metoprolol via breast milk (Ho 1999).

The manufacturer recommends monitoring the breastfed infant for adverse events such as bradycardia; constipation; diarrhea; and dry mouth, skin, or eyes when metoprolol is administered to a mother who is a slow metabolizer.

When treatment for hypertension is needed in a breastfeeding patient, consider use of an agent other than metoprolol (ACOG 2019). Metoprolol may be continued for the treatment of heart failure in lactating patients; treatment should be made as part of a shared decision-making process (AHA/ACC/HFSA [Heidenreich 2022]). In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient (AHS [Ailani 2021]).

# Atenolol

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Atenolol is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019).

Atenolol is effective for prevention of migraines. In general, preventive treatment for migraine in patients trying to become pregnant should be avoided. Options for patients planning a pregnancy should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data and needs of the patient should pregnancy occur. A gradual discontinuation of preventive medications is generally preferred when the decision is made to stop treatment prior to conception (ACOG 2022; AHS [Ailani 2021]).

Impotence is noted in product labeling following postmarketing use of atenolol. As a class, outcomes from available studies evaluating beta-blockers and sexual dysfunction are inconsistent, and the negative effects on erectile function and libido are considered controversial. A clear relationship between use of beta-blockers and erectile dysfunction has not been established. Hypertension itself is associated with erectile dysfunction. Patients on a beta-blocker presenting with sexual dysfunction should be evaluated for underlying disease (Farmakis 2021; Levine 2012; Semet 2017; Terentes-Printzios 2022; Viigimaa 2020).

## Pregnancy Considerations

Atenolol crosses the placenta and is found in cord blood.

Maternal use of atenolol may cause harm to the fetus. Adverse events, such as bradycardia, hypoglycemia and reduced birth weight, have been observed following in utero exposure to atenolol. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression (ESC [Regitz-Zagrosek 2018]).

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

The maternal pharmacokinetic parameters of atenolol during the second and third trimesters are within the ranges reported in nonpregnant patients (Hebert 2005).

When treatment of chronic hypertension during pregnancy is indicated, atenolol is not recommended due to adverse fetal/neonatal events (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]). Atenolol is also not recommended for the treatment of atrial fibrillation or supraventricular tachycardia during pregnancy; consult current guidelines for specific recommendations (ESC [Regitz-Zagrosek 2018]).

In general, preventive treatment for migraine should be avoided during pregnancy. Options for pregnant patients should be considered as part of a shared decision-making process. Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data, the potential for adverse maternal and fetal events, and needs of the patient (ACOG 2022; AHS [Ailani 2021]). If preventive therapy is needed, beta-blockers may be considered (ACOG 2022) however agents other than atenolol may be preferred (CHS [Pringsheim 2012]).

## Breastfeeding Considerations

Atenolol is present in breast milk.

Bradycardia has been observed in some breastfeeding infants and neonates may also be at risk for hypoglycemia. Adverse events may be more likely in premature infants or infants with impaired renal function.

Atenolol can be detected in the plasma of breastfeeding infants not previously exposed during pregnancy (Lwin 2018). Per the manufacturer, the milk/plasma ratio of atenolol is 1.5 to 6.8; however, larger ranges have been reported and ratios have been shown to vary within the same patient (Holt 1982; Lwin 2018). Beta-blockers with higher M/P ratios, such as atenolol, should be avoided while breastfeeding (Beardmore 2002). The relative infant dose (RID) of atenolol has also been calculated by authors of various studies, providing a large variability in ranges (~3% to ~35%) which may also reflect postpartum age and maternal dose (Atkinson 1988; Eyal 2010; Lwin 2018). In general, breastfeeding is considered acceptable when the RID of a medication is <10%; when the RID is >25% breastfeeding should generally be avoided (Anderson 2016; Ito 2000). Additional considerations can include the gestational and postnatal age of the infant, the actual amount of milk being ingested (less in the first couple days of life and when weaning), properties of the specific maternal medication, medical conditions of the infant, and medications the infant is receiving therapeutically.

The manufacturer recommends that caution be exercised when administering atenolol to patients who are breastfeeding. Use of a beta-blocker other than atenolol may be preferred in patients who are breastfeeding (ESC [Cífková 2020]).

In general, preventive treatment for migraine in lactating patients should be avoided. When needed, therapy should be individualized considering the available safety data and needs of the patient (AHS [Ailani 2021]).

# Bisoprolol

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Bisoprolol is generally not a preferred agent for use in pregnant patients (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019); however, use may be considered (ESC [Cífková 2020]).

Impotence is noted in product labeling following use of bisoprolol. As a class, outcomes from available studies evaluating beta-blockers and sexual dysfunction are inconsistent, and the negative effects on erectile function are considered controversial. A clear relationship between use of beta-blockers and erectile dysfunction has not been established. Hypertension itself is associated with erectile dysfunction. Patients on a beta-blocker presenting with sexual dysfunction should be evaluated for underlying disease (Farmakis 2022; Levine 2012; Semet 2017; Terentes-Printzios 2022; Viigimaa 2020).

## Pregnancy Considerations

Outcome data following maternal use of bisoprolol during pregnancy are limited compared to other beta-1 selective beta-blockers (Hoeltzenbein 2018; Kayser 2020).

Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression (ESC [Regitz-Zagrosek 2018]).

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than bisoprolol may be preferred (ACOG 2019; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]); however, use of bisoprolol may be considered (ESC [Cífková 2020]).

## Breastfeeding Considerations

It is not known if bisoprolol is present in breast milk.

Bisoprolol 5 mg/day was initiated in one patient 5 days postpartum. Bisoprolol was not detected in breast milk sampled 11 and 18 days later (lower limit of quantification 1 ng/mL) (Khurana 2014).

The manufacturer recommends that caution be exercised when administering bisoprolol to breastfeeding patients. Use of a beta-blocker other than bisoprolol may be preferred in lactating patients (ESC [Cífková 2020]).

# Carvedilol

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Carvedilol is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

Impotence is noted in product labeling following use of carvedilol. As a class, outcomes from available studies evaluating beta-blockers and sexual dysfunction are inconsistent, and the negative effects on erectile function are considered controversial. A clear relationship between use of beta-blockers and erectile dysfunction has not been established. Hypertension itself is associated with erectile dysfunction. Patients on a beta-blocker presenting with sexual dysfunction should be evaluated for underlying disease (Farmakis 2022; Levine 2012; Semet 2017; Terentes-Printzios 2022; Viigimaa 2020).

## Pregnancy Considerations

Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression (ESC [Regitz-Zagrosek 2018]).

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than carvedilol may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]). Carvedilol may be considered for use in pregnant patients with heart failure (ESC [Regitz-Zagrosek 2018]).

## Breastfeeding Considerations

It is not known if carvedilol is present in breast milk.

According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Use of a beta-blocker other than carvedilol may be preferred in lactating patients (ESC [Cífková 2020]).

# Antihypertensive drugs

# Alpha$_1$-antagonists

# Prazosin

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Prazosin is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

## Pregnancy Considerations

Prazosin crosses the placenta (Bourget 1995).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of prazosin may be altered (Bourget 1995; Rubin 1983).

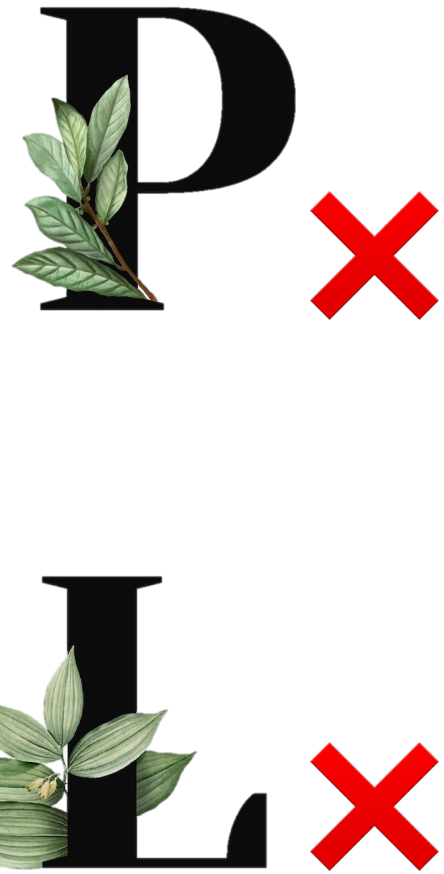
Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of chronic hypertension during pregnancy is initiated during pregnancy, agents other than prazosin may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]); if needed, use of prazosin should be considered in consult with subspecialists (ACOG 2019).

Untreated hypertension due to a pheochromocytoma during pregnancy is associated with a high rate of maternal and fetal mortality therefore treatment is recommended (ESC [Cífková 2020]). Case reports describe the use of prazosin as part of combination therapy for the treatment of hypertension due to pheochromocytoma in pregnant patients (Agrawal 2022). Prazosin may be an alternative option for the treatment of hypertension due to pheochromocytoma during pregnancy (Pacu 2021).

## Breastfeeding Considerations

Prazosin is present in breast milk.

The manufacturer recommends that caution be exercised when administering prazosin to lactating patients.



# Terazosin

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Terazosin is not considered a preferred agent for use in pregnant patients; consider transitioning to a preferred agent in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

## Pregnancy Considerations

Chronic maternal hypertension is also associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

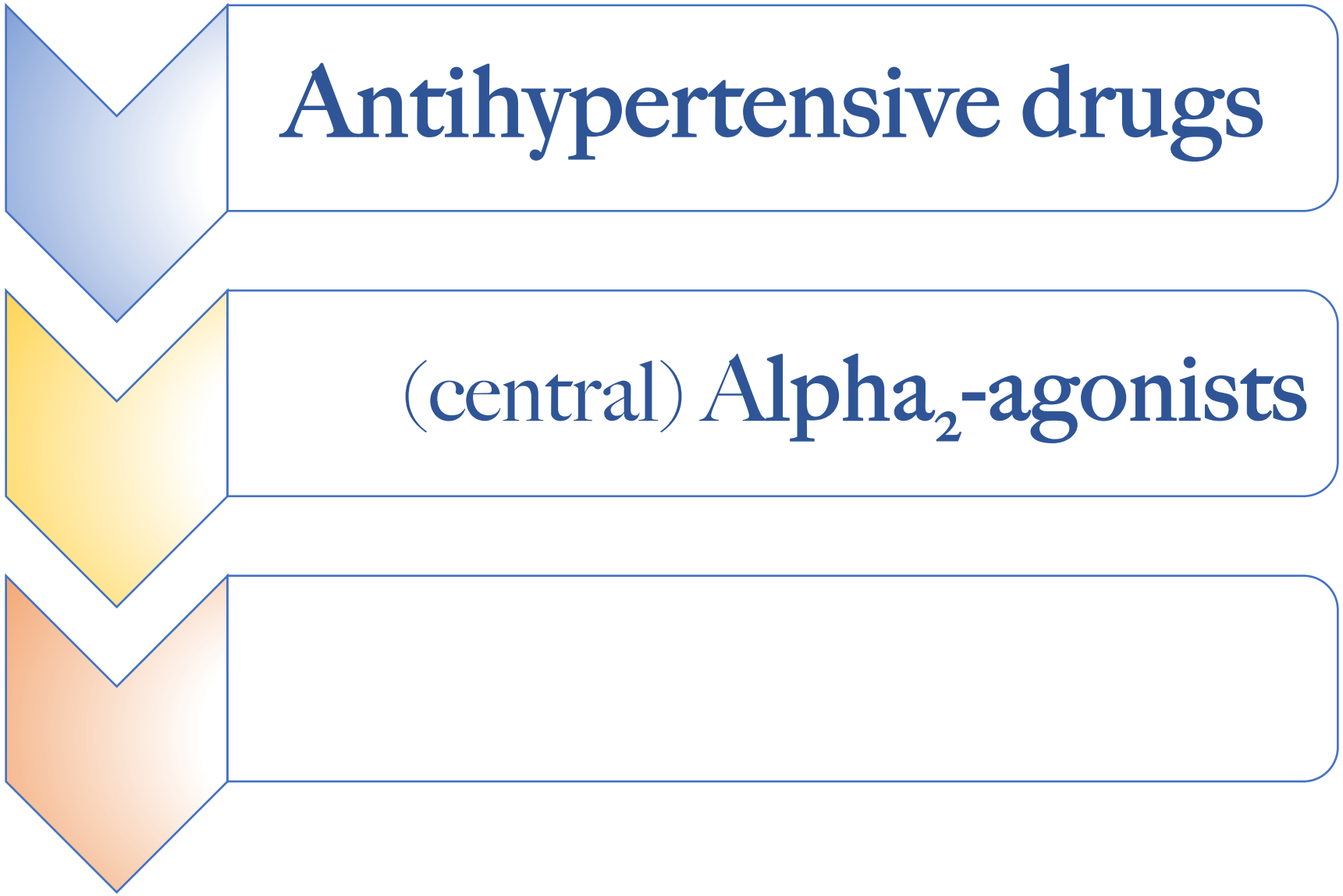
Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of chronic hypertension during pregnancy is indicated, agents other than terazosin may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]).

Although alpha-blockers may be used to facilitate ureteral stone expulsion, treatments other than terazosin are preferred if stone removal is needed during pregnancy (AUA/ES [Assimos 2016a]; Juliebø-Jones 2022; Lee 2021; Lloyd 2016).

## Breastfeeding Considerations

It is not known if terazosin is present in breast milk.

The manufacturer recommends that caution be exercised when administering terazosin to patients who are breastfeeding.


Antihypertensive drugs
(central) Alpha$_2$-agonists

# Clonidine

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to conceive. Consider transitioning from clonidine to an agent preferred for use during pregnancy in patients planning to become pregnant (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019); clonidine is considered an alternative option due to possible side effects (SOGC [Magee 2022]).

## Pregnancy Considerations

Clonidine crosses the placenta.

Clonidine concentrations in the umbilical cord plasma are similar to those in the maternal serum and concentrations in the amniotic fluid may be 4 times those in the maternal serum.

The pharmacokinetics of clonidine may be altered during pregnancy due to an increase in nonrenal clearance, possibly regulated by maternal CYP2D6 genotype (Buchanan 2009; Claessens 2010).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of chronic hypertension is initiated during pregnancy, agents other than clonidine may be preferred (ACOG 2019; ESC [Cífková 2020]; ESC [Regitz-Zagrosek 2018]; SOGC [Magee 2022]). Clonidine is considered an alternative option due to possible side effects (SOGC [Magee 2022]); use should be considered in consult with subspecialists (ACOG 2019).

Based on outcome data following use for hypertension during pregnancy, clonidine may be used in pregnant patients with attention-deficit/hyperactivity disorder (ADHD) when needed (Ornoy 2021). Data collection to monitor pregnancy and infant outcomes following exposure to ADHD medications is ongoing. Health care providers are encouraged to enroll patients exposed to Kapvay during pregnancy in the National Pregnancy Registry for ADHD Medications (866-961-2388).

Clonidine has been evaluated for use as an adjunctive agent for epidural labor analgesia (Allen 2018; Cavens 2022; Kumari 2018; Xia 2022; Zhang 2015), including patients who are opioid dependent (Hoyt 2018); however, the manufacturer does not recommend epidural clonidine for obstetrical or postpartum pain due to the risk of hemodynamic instability. Severe maternal hypotension may occur following epidural use, which may result in decreased placental perfusion. Potential benefits may outweigh the possible risks in some obstetrical or postpartum patients.

Clonidine has been evaluated for the management of opioid withdrawal; however, withdrawal management using clonidine is not preferred for patients who are pregnant (ASAM 2020).

## Breastfeeding Considerations

Clonidine is present in breast milk.

Data related to the presence of clonidine in breast milk are available.

- Breast milk samples were obtained on the first 3 days postpartum from 3 women administered oral clonidine 0.3 mg/day. Treatment was initiated 1 to 23 days prior to delivery. Clonidine concentrations were 0.8 to 2.8 ng/mL in breast milk and 0.4 to 1.5 ng/mL in the maternal plasma (Boutroy 1988).
- Data are available from a lactating patient, 4 weeks postpartum, taking oral clonidine 0.0.375 mg twice daily. Clonidine concentrations were 0.33 ng/mL in the maternal plasma (1 hour after the dose), 0.6 ng/mL in breast milk (2.5 hours after the dose), and undetectable (< 0.096 ng/mL) in the infant plasma, 1 hour after breastfeeding (Bunjes 1993).
- Clonidine concentrations in breast milk were approximately twice those of the maternal serum in 9 patients treated with clonidine during pregnancy and postpartum. Breast milk and maternal serum were sampled 1 to 5 days, 10 to 14 days, and 45 to 60 days after delivery. Clonidine was also measurable in the breastfed infant serum at each time point (Hartikainen-Sorri 1987).
- Based on available lactation studies, one manufacturer reports the relative infant dose of clonidine to be 4.1% to 8.4% of the weight adjusted maternal dose (maternal dose and milk concentrations not presented).

Adverse events observed in some breastfed infants also exposed in utero include apathy syndrome, hypoglycemia, hypotonia, drowsiness, feeding difficulties, and hyperexcitability (Hartikainen-Sorri 1987; Sevrez 2014).

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. When treatment for hypertension is needed in a breastfeeding patient, clonidine may be acceptable for use (ESC [Cífková 2020]); however, due to adverse events observed in breastfeeding infants, other sources do not recommend use in patients who are breastfeeding (Ornoy 2021) or recommend avoiding use when breastfeeding infants born < 34 weeks' gestation or when large maternal doses are needed (Atkinson 1988).

Infants exposed to clonidine via breast milk should be monitored for symptoms of hypotension and/or bradycardia (eg, sedation, lethargy, tachypnea, poor feeding).

# Methyldopa

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be continued in patients trying to become pregnant. Methyldopa is an option patients can be transitioned to when one of the preferred agents cannot be used (ACC/AHA [Whelton 2018]; ACOG 2019; NICE 2019).

## Pregnancy Considerations

Methyldopa crosses the placenta.

Available data show use during pregnancy does not cause fetal harm and improves fetal outcomes.

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). If treatment for chronic hypertension during pregnancy is needed, oral methyldopa is an option; however, other agents may be preferred due to adverse events and decreased effectiveness when compared to other medications (ACOG 2019; ESC [Cífková 2020]; SOGC [Magee 2022]).

## Breastfeeding Considerations

Methyldopa is present in breast milk.

Data related to the presence of methyldopa in breast milk are available from multiple reports:

- Breast milk was sampled 30 to 60 minutes following delivery in 4 patients taking methyldopa for at least 4 weeks. The highest breast milk concentrations were obtained in 1 patient taking methyldopa 500 mg every 6 hours. Twelve hours after the last dose, free and conjugated concentrations of methyldopa were 0.2 mcg/mL and 0.9 mcg/mL, respectively (Jones 1978).
- Data related to the presence of methyldopa in breast milk are available from a study of 3 patients. The highest breast milk concentration of free methyldopa (1.14 mcg/mL) was observed in 1 patient 8 weeks postpartum taking methyldopa 1,000 mg/day. In this patient, free methyldopa was ~37% of the total methyldopa (free + conjugate) present in breast milk; methyldopa was detected in the breastfed infant's serum. Using data from all 3 patients, peak breast milk concentrations occurred 3 to 6 hours after the maternal dose. Adverse events were not observed in the breastfed infants (White 1985).
- Methyldopa was also detected in the urine of a breastfed infant. Methyldopa 250 mg twice daily for 10 days was initiated 11 days postpartum to a patient following delivery at 38 weeks gestation. Adverse events were not observed in the infant (Hauser 1985).
- Using a milk concentration of 1.14 mcg/mL, the estimated daily infant dose of methyldopa via breast milk is 0.1716 mg/kg/day providing a relative infant dose (RID) of 1.2% compared to a weight adjusted maternal dose of 1,000 mg/day.
- In general, breastfeeding is considered acceptable when the RID of a medication is <10% (Anderson 2016; Ito 2000).

Methyldopa is compatible with breastfeeding (ESC [Cífková 2020]; SOGC [Magee 2022]; WHO 2002). However, because maternal depression has been reported following methyldopa administration, use of methyldopa should be avoided in the postnatal period due to the underlying risk of depression already present in this patient population (ACOG 2019; Regitz-Zagrosek [ESC 2018]).

# Antihypertensive drugs

# Vasodilators

# Hydralazine

## Reproductive Considerations

Medications considered acceptable for the treatment of chronic hypertension during pregnancy may generally be used in patients trying to conceive. Patients planning to become pregnant may continue taking oral hydralazine for the treatment of chronic hypertension when effective (ACC/AHA [Whelton 2018]; NICE 2019; SOGC [Magee 2022]).

## Pregnancy Considerations

Hydralazine crosses the placenta (Lamont 1986; Liedholm 1982).

High and frequent doses of IV hydralazine are associated with adverse events, such as maternal hypotension and fetal tachycardia, compared to other agents (ACOG 2019; ESC [Cífková 2020]; SOGC [Magee 2022]).

Chronic maternal hypertension is associated with adverse events in the fetus/infant. Chronic maternal hypertension may increase the risk of birth defects, low birth weight, premature delivery, stillbirth, and neonatal death. Actual fetal/neonatal risks may be related to the duration and severity of maternal hypertension. Untreated chronic hypertension may also increase the risks of adverse maternal outcomes, including gestational diabetes, preeclampsia, delivery complications, stroke, and myocardial infarction (ACOG 2019).

Due to pregnancy-induced physiologic changes and maternal acetylator status (*NAT2* genotype), some pharmacokinetic properties of oral hydralazine may be altered. Larger studies are needed to evaluate if or how these changes influence safety or efficacy during pregnancy (Han 2019).

Patients with preexisting hypertension may continue their medication during pregnancy unless contraindications exist (ESC [Regitz-Zagrosek 2018]). When treatment of hypertension is initiated during pregnancy, agents other than oral hydralazine may be preferred (ACOG 2019; ESC [Regitz-Zagrosek 2018]); oral hydralazine is considered an alternative option due to possible side effects (SOGC [Magee 2022]).

IV hydralazine is recommended for use in the management of acute onset, severe hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg) with preeclampsia or eclampsia in pregnant and postpartum patients (ACOG 2020; ESC [Cífková 2020]; SOGC [Magee 2022]).

## Breastfeeding Considerations

Hydralazine is present in breast milk.

Data related to the presence of hydralazine in breast milk are available from a patient receiving oral hydralazine 50 mg 3 times a day, initiated prior to delivery. Hydralazine and metabolites were present in breast milk sampled 30 minutes after a midday dose at 8 weeks postpartum (Liedholm 1982). In a study of 4 breastfeeding women, breast milk concentrations of hydralazine were approximately one-half of maternal serum concentrations. Hydralazine was detected in the serum of their breastfeeding infants at a concentration 10 times smaller than concentrations found in a hypertensive infant being treated therapeutically with hydralazine (Lamont 1986).

The manufacturer recommends that caution be used if administered to patients who are breastfeeding. Hydralazine is considered compatible with breastfeeding; however, sufficient data are not available following long-term use (WHO 2002).

# Immunosuppressive drugs

# Cyclosporine

## Reproductive Considerations

Cyclosporine is an acceptable immunosuppressant for use in kidney (EBPG 2002; KDIGO 2009; López 2014), liver (AASLD [Lucey 2013]), or heart (ISHLT [Velleca 2022]) transplant recipients planning a pregnancy. Conception may be considered for patients on a stable/low maintenance dose for ≥1 year following transplant (AASLD [Lucey 2013]; EBPG 2002; ISHLT [Velleca 2022]; López 2014).

Cyclosporine is considered acceptable for use in patients with rheumatic and musculoskeletal diseases who are planning to become pregnant and are not able to use alternative therapies; however, blood pressure monitoring is recommended. Conception should be planned during a period of quiescent/low disease activity (ACR [Sammaritano 2020]). Patients treated with cyclosporine for lupus nephritis should continue treatment while planning to become pregnant; conception may be considered after 6 months of inactive disease (EULAR/ERA-EDTA [Bertsias 2012]).

Data related to paternal use of cyclosporine are limited. However, available data have not shown cyclosporine adversely impacts male fertility or increases the risk of adverse pregnancy outcomes when used prior to conception (Mouyis 2019). Potential effects on fertility are associated with higher doses; conception can be attempted once lower serum levels can be maintained and the allograft is functioning (Georgiou 2016). Erectile dysfunction was found to occur more frequently with cyclosporine than other immunosuppressants in a study of renal transplant recipients; consider screening patients with risk factors prior to use (Zakhem 2019). Cyclosporine is considered acceptable for use in patients with rheumatic and musculoskeletal diseases who are planning to father a child (ACR [Sammaritano 2020])

## Pregnancy Considerations

Cyclosporine crosses the placenta (Claris 1993).

In a study of 15 pregnant patients, maternal concentrations did not correlate with those found in the umbilical cord (n = 14). Cyclosporine was detected in the serum of one newborn for several days after birth (Claris 1993).

Cyclosporine is not associated with specific teratogenic effects, but maternal use may be associated with an increased risk of intrauterine growth restriction, small for gestational age babies, maternal hypertension, and preeclampsia (EBPG 2002). Premature births and low birth weight were consistently observed in pregnant transplant recipients (additional pregnancy complications also present). In utero exposure to cyclosporine has not been found to influence renal function or blood pressure in children followed up to 7 years of age (limited data).

Some formulations may contain alcohol; the alcohol content should be taken into consideration prior to prescribing to patients who are pregnant.

Cyclosporine levels decline during pregnancy (KDIGO 2009) and increased monitoring is recommended (AASLD [Lucey 2013]; EBPG 2002; ISHLT [Velleca 2022]; López 2014).

Cyclosporine is an acceptable immunosuppressant for use in patients who become pregnant following a kidney (EBPG 2002; López 2014) or heart transplant (ISHLT [Velleca 2022]). Cyclosporine may also be used when needed in pregnant patients following a liver transplant (AASLD [Lucey 2013]).

For other indications, cyclosporine is not a preferred agent. Cyclosporine is considered acceptable for the treatment of myasthenia gravis in pregnant patients who are not controlled with or unable to tolerate corticosteroids (Sanders 2016). If therapy is needed for psoriasis, other agents are preferred; however, if cyclosporine is used, limit to shortest duration and lowest possible dose (Kaushik 2019). Cyclosporine can be used during pregnancy for refractory cases of lupus nephritis (EULAR/ERA-EDTA [Berstias 2012]) and other rheumatic and musculoskeletal diseases in patients who are not able to use alternative therapies; however, close monitoring of blood pressure is recommended (ACR [Sammaritano 2020]). Cyclosporine may be useful for the treatment of immune thrombocytopenia in pregnant patients who are refractory to preferred agents (Provan 2019). Use of cyclosporine for inflammatory bowel disease is limited to salvage therapy in patients who are pregnant (AGA [Mahadevan 2019]).

The Transplant Pregnancy Registry International (TPR) is a registry that follows pregnancies that occur in maternal transplant recipients or those fathered by male transplant recipients. The TPR encourages reporting of pregnancies following solid organ transplant by contacting them at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

## Breastfeeding Considerations

Cyclosporine is present in breast milk.

Concentrations of cyclosporine in milk vary widely (ACR [Sammaritano 2020]).

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

Recommendations for breastfeeding in patients taking cyclosporine following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses (Constantinescu 2014; EBPG 2002; KDIGO 2009; López 2014). Cyclosporine is considered compatible for use in patients with inflammatory bowel disease who wish to breastfeed (AGA [Mahadevan 2019]). Cyclosporine may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding. Infants should be closely monitored. Infant drug levels should be measured if adverse events such as recurrent infections occur (ACR [Sammaritano 2020]). Some formulations may contain alcohol which may be present in breast milk; the alcohol content should be taken into consideration prior to prescribing to a breastfeeding mother.

# Tacrolimus

## Reproductive Considerations

Family planning and contraceptive options for patients who can become pregnant and patients with partners who can become pregnant should be evaluated prior to starting treatment.

Tacrolimus is an acceptable immunosuppressant for use in kidney, heart, and liver transplant recipients planning a pregnancy. Conception may be considered for patients who can become pregnant who are on a stable/low maintenance dose for ≥1 year following transplant (AASLD [Lucey 2013]; EBPG 2002; ISHLT [Velleca 2023]; López 2014). Tacrolimus has also been used as an immunosuppressant in patients undergoing uterine transplant (Jones 2019).

Based on limited data, tacrolimus may be used in patients with rheumatic and musculoskeletal diseases who are planning to become pregnant and are not able to use alternative therapies; however, BP monitoring is recommended. Conception should be planned during a period of quiescent/low disease activity (ACR [Sammaritano 2020]).

Based on limited data, tacrolimus may be used in patients with rheumatic and musculoskeletal diseases who are planning to father a child (ACR [Sammaritano 2020]).

## Pregnancy Considerations

Tacrolimus crosses the human placenta and is measurable in the cord blood, amniotic fluid, and newborn serum. Tacrolimus also accumulates in the placenta in concentrations that may be higher than the maternal serum (Frériksen 2018; Jain 1997). Infants with lower birth weights have been found to have higher tacrolimus concentrations, possibly due to slower metabolism (Bramham 2013).

Miscarriage, preterm delivery, low birth weight, birth defects (including cardiac, craniofacial, neurologic, renal/urogenital, and skeletal abnormalities), renal dysfunction, transient neonatal hyperkalemia, and fetal distress have been reported following in utero exposure to tacrolimus in infants of organ transplant recipients; however, pregnant patients were also taking a concomitant medication known to cause adverse pregnancy outcomes. Tacrolimus may exacerbate hypertension and hyperglycemia in pregnant patients with preexisting disease. Adverse pregnancy outcomes may also be associated with an organ transplant, including preterm delivery and low birth weight in the infant and hypertension and preeclampsia in the mother. Cholestasis of pregnancy may be increased following liver transplant.

Due to pregnancy-induced physiologic changes, some pharmacokinetic properties of tacrolimus are altered. Increased monitoring of blood levels in the pregnant patient is recommended, and dosage adjustments may be required during pregnancy and immediately postpartum (AASLD [Lucey 2013]; EBPG 2002; ISHLT [Velleca 2023]; López 2014). Whole blood concentrations of tacrolimus decrease as pregnancy progresses; however, unbound tacrolimus concentrations increase. Measuring unbound concentrations may be preferred, especially in patients with anemia or hypoalbuminemia. If unbound concentration measurement is not available, interpretation of whole blood concentrations should account for RBC count and serum albumin concentration (Hebert 2013; Zheng 2012).

Tacrolimus monotherapy is the preferred immunosuppressant in patients who become pregnant following a liver transplant (AASLD [Lucey 2013]). Tacrolimus may also be used in pregnant patients who have had a kidney (EBPG 2002; López 2014), heart (ISHLT [Velleca 2023]), or uterine (Jones 2019; Perni 2022; Richards 2021; Wilson 2023) transplant.

Based on limited data, tacrolimus may be used in pregnant patients with rheumatic and musculoskeletal diseases who are not able to use alternative therapies; however, close monitoring of blood pressure is recommended (ACR [Sammaritano 2020]). Tacrolimus is not one of the recommended agents for the treatment of myasthenia gravis during pregnancy (Sanders 2016).

The Transplant Pregnancy Registry International (TPRI) is a registry that follows pregnancies that occur in maternal transplant recipients or those fathered by male transplant recipients. The TPRI encourages reporting of pregnancies following solid organ transplant by contacting them at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

## Breastfeeding Considerations

Tacrolimus is present in breast milk.

Authors of several small studies and case reports have calculated the relative exposure of tacrolimus to the breastfeeding infant to be in acceptable concentrations (≤0.5% of the weight-adjusted maternal dose) (Akamine 2021; Bramham 2013; French 2003; Gardiner 2006; Hiramatsu 2018; Kociszewska-Najman 2018; Richards 2021; Zheng 2013).

A study describes the course of 15 infants (12 receiving exclusively human milk) exposed to tacrolimus throughout pregnancy and after birth. Serial blood levels evaluated in 13 of the infants over the first 72 hours of life showed a decrease of tacrolimus concentrations over time regardless of breastfeeding status. Although present in cord blood, tacrolimus was undetectable in infant blood between 11 to 22 days after birth (n=8). Breast milk concentrations were variable but correlated with maternal blood levels (Bramham 2013). A second study evaluated tacrolimus concentrations in breast milk and infant serum between 1 and 3 months' postpartum. Although tacrolimus was measurable in breast milk, infant serum concentrations were below the limit of quantification in the 13 infants tested (Hiramatsu 2018). Information is also available from six breastfed children whose mothers were taking tacrolimus. Children were breastfed for 1.5 to 6 months (four exclusively breastfed) and monitored for 2 to 30 months. No adverse outcomes related to tacrolimus exposure were observed (Gouraud 2012).

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the breastfeeding patient. Recommendations for breastfeeding in patients taking tacrolimus following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses (Constantinescu 2014; EBPG 2002; López 2014). Tacrolimus is acceptable for use in lactating patients following a heart transplant (ISHLT [Velleca 2023]) and may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding (ACR [Sammaritano 2020]).

# Sirolimus

## Reproductive Considerations

Patients who could become pregnant should use highly effective contraception prior to initiation of sirolimus, during treatment, and for 12 weeks after sirolimus is discontinued.

Sirolimus may impair fertility. Ovarian cysts, amenorrhea, menorrhagia, azoospermia, or oligospermia have been observed following use of oral sirolimus. Sperm banking prior to sirolimus treatment may be considered (KDIGO 2009).

Agents other than sirolimus may be preferred for patients who have had a kidney transplant and are planning to become pregnant (Agarwal 2021; Cabiddu 2018; EBPG 2002; KDIGO 2009; Longhitano 2021; López 2014).

Sirolimus has been evaluated for the treatment of recurrent implantation failure in patients undergoing in vitro fertilization (Ahmadi 2019; Wang 2021).

## Pregnancy Considerations

Sirolimus crosses the placenta (Barnes 2018; Park 2019).

Based on the mechanism of action and data from animal reproduction studies, in utero exposure to sirolimus may cause fetal harm.

Outcome data following maternal use of sirolimus in pregnant patients who have had organ transplants is limited (Boulay 2021; Framarino dei Malatesta 2011; Sifontis 2006). Although an increased risk of congenital anomalies has not been observed, due to adverse events observed in animal reproduction studies, agents other than sirolimus may be preferred for use in pregnant patients who have had a kidney transplant (Agarwal 2021; Cabiddu 2018; EBPG 2002; KDIGO 2009; Longhitano 2021; López 2014; Ponticelli 2021).

The use of sirolimus for the treatment of lymphangioleiomyomatosis during pregnancy has been reported (Faehling 2015; Shen 2021); however, available data are insufficient to make recommendations (Gupta 2018; McCormack 2016).

Case reports describe maternal administration of sirolimus for the in-utero treatment of fetal cardiac rhabdomyomas that were possibly associated with tuberous sclerosis complex (Barnes 2018; Dagge 2021; Ebrahimi-Fakhari 2021; Park 2019; Pluym 2020; Vachon-Marceau 2019).

The Transplant Pregnancy Registry International (TPR) is a registry that follows pregnancies that occur in maternal transplant recipients or those fathered by male transplant recipients. The TPR encourages reporting of pregnancies following solid organ transplant by contacting them at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

## Breastfeeding Considerations

It is not known if sirolimus is present in breast milk.

According to the manufacturer, the decision to breastfeed during sirolimus therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of sirolimus treatment to the mother.

# Everolimus

## Reproductive Considerations

Verify pregnancy status prior to initiating therapy in patients who could become pregnant. Patients who could become pregnant should be advised to avoid pregnancy and use highly effective birth control during treatment and for 8 weeks after the last everolimus dose. Patients whose partners could become pregnant should use effective contraception during treatment and for 4 weeks after the last everolimus dose.

Everolimus may cause infertility. In females, menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone and follicle-stimulating hormone have occurred. Azoospermia and oligospermia have been observed in males.

## Pregnancy Considerations

Based on the mechanism of action and data from animal reproduction studies, in utero exposure to everolimus may cause fetal harm. Information related to the use of everolimus in pregnancy is limited (Yamamura 2017).

The Transplant Pregnancy Registry International (TPR) is a registry that follows pregnancies that occur in maternal transplant recipients or those fathered by male transplant recipients. The TPR encourages reporting of pregnancies following solid organ transplant by contacting them at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

## Breastfeeding Considerations

Everolimus is present in breast milk (Kociszewska-Najman 2017).

Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy (Afinitor, Afinitor Disperz, Zortress) and for 2 weeks following the last dose (Afinitor, Afinitor Disperz).

# Mycophenolate

## Reproductive Considerations

**[US Boxed Warning]: Females of reproductive potential must be counseled regarding pregnancy prevention and planning.** Pregnancy testing, prevention, and planning must be discussed with all females of reproductive potential and male patients with female partners of reproductive potential. Alternative agents should be used whenever possible in patients planning a pregnancy.

Females of reproductive potential (girls who have entered puberty and women with a uterus who have not passed through clinically confirmed menopause) should have a negative pregnancy test with a sensitivity of ≥25 milliunits/mL immediately before mycophenolate therapy and the test should be repeated 8 to 10 days later. Pregnancy tests should then be repeated during routine follow-up visits. Acceptable forms of contraception should be used during treatment and for 6 weeks after therapy is discontinued. An intrauterine device, tubal sterilization, or vasectomy of the female patient's partner are acceptable contraceptive methods that can be used alone. If a hormonal contraceptive is used (eg, combination oral contraceptive pills, transdermal patches, vaginal rings, or progestin only products), then one barrier method must also be used (eg, diaphragm or cervical cap with spermicide, contraceptive sponge, male or female condom). Alternatively, the use of 2 barrier methods is also acceptable (eg, diaphragm or cervical cap with spermicide, or contraceptive sponge **PLUS** male or female condom). Refer to manufacturer's labeling for full details. The effectiveness of hormonal contraceptive agents may be affected by mycophenolate.

Mycophenolate has been used as an immunosuppressant in patients undergoing uterine transplant (limited data); mycophenolate is discontinued and changed to a different agent prior to embryo transfer (Jones 2019).

Mycophenolate should be discontinued, and therapy changed to an appropriate immunosuppressant prior to conception in kidney, liver, and heart transplant recipients who are planning a pregnancy (AASLD [Lucey 2013]); EBPG 2002; ISHLT [Costanzo 2010]; KDIGO 2009; López 2014). Mycophenolate should also be discontinued prior to conception in females treated for other indications who are planning a pregnancy. The Risk Evaluation and Mitigation Strategy (REMS) program recommends discontinuing mycophenolate in females at least 6 weeks before pregnancy is attempted. However, due to the potential for disease flare following discontinuation, women treated for rheumatic and musculoskeletal diseases should consider discontinuing mycophenolate 3 to 6 months prior to attempted pregnancy to allow for disease monitoring and potential change to another immunosuppressant (ACR [Sammaritano 2020]). Women taking mycophenolate for myasthenia gravis are recommended to discontinue therapy at least 4 months prior to planning a pregnancy (Sanders 2016).

When mycophenolate is used for the treatment of rheumatic and musculoskeletal diseases in women undergoing ovarian stimulation for oocyte retrieval or embryo cryopreservation, mycophenolate may be continued in patients whose condition is stable and discontinuation of treatment may lead to uncontrolled disease (ACR [Sammaritano 2020]).

Information related to the mycophenolate and male fertility or pregnancy outcomes following paternal use is limited; however, available data have not suggested safety concerns (Bermas 2019; Mouyis 2019). According to the manufacturer, sexually active male patients and/or their female partners should use effective contraception during treatment of the male patient and for at least 90 days after last dose. In addition, males should not donate semen during mycophenolate therapy and for 90 days following the last mycophenolate dose (recommendation based on animal data). However, use of mycophenolate may be considered for males with rheumatic and musculoskeletal diseases who are planning to father a child (recommendation based on limited human data) (ACR [Sammaritano 2020]; Midtvedt 2017).

## Pregnancy Considerations

**[US Boxed Warning]: Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available.**

Congenital malformations have been reported in 23% to 27% of live births following exposure to mycophenolate during pregnancy. Birth defects include facial malformations (cleft lip, cleft palate, micrognathia, hypertelorism of the orbits); ear and eye abnormalities (abnormally formed or absent external/middle ear, coloboma, microphthalmos); finger malformations (brachydactyly, polydactyly, syndactyly); cardiac abnormalities (atrial and ventricular septal defects); esophageal malformations (esophageal atresia); and CNS malformations (spina bifida). The combination of ear, eye, and lip/palate abnormalities has been identified as mycophenolate embryopathy (Perez-Aytes 2017). The risk of first trimester pregnancy loss may be 45% to 49% following mycophenolate exposure.

Mycophenolate is not an acceptable immunosuppressant for use in patients who become pregnant following a kidney (EBPG 2002; KDIGO 2009; López 2014), liver (AASLD [Lucey 2013]), or heart (ISHLT [Costanzo 2010]) transplant. In addition, mycophenolate should not be used for the treatment of autoimmune hepatitis (AASLD [Mack 2020]), myasthenia gravis (Sanders 2016), or rheumatic and musculoskeletal diseases (ACR [Sammaritano 2020]) during pregnancy.

Data collection to monitor pregnancy and infant outcomes following exposure to mycophenolate is ongoing. Health care providers should report female exposures to mycophenolate during pregnancy or within 6 weeks of discontinuing therapy to the Mycophenolate Pregnancy Registry (800-617-8191).

The Transplant Pregnancy Registry International (TPR) is a registry that follows pregnancies that occur in maternal transplant recipients or those fathered by male transplant recipients. The TPR encourages reporting of pregnancies following solid organ transplant by contacting them at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

## Breastfeeding Considerations

It is not known if mycophenolate is present in breast milk.

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Adverse events were not observed in 7 infants born between 34 and 40 weeks' gestation and exposed to mycophenolate via breast milk for up to 14 months. However, due to the long half-life and lack of information related to mycophenolate and breastfeeding, breastfeeding is not recommended by some guidelines (ACR [Sammaritano 2020]; Constantinescu 2014; López 2014).

# Azathioprine

## Reproductive Considerations

The manufacturer recommends that patients avoid becoming pregnant during treatment. However, additional recommendations are available for use in females and males on azathioprine who are planning a pregnancy.

Azathioprine is an acceptable immunosuppressant for use in kidney transplant recipients planning a pregnancy (EBPG 2002; KDIGO 2009; López 2014). Azathioprine should be substituted for mycophenolate 6 weeks prior to conception. Conception may be considered for females on a stable/low maintenance dose for ≥1 year following transplant (EBPG 2002; López 2014).

Azathioprine may also be acceptable for use in patients with rheumatic and musculoskeletal diseases who are planning to become pregnant. Conception should be planned during a period of quiescent/low disease activity (ACR [Sammaritano 2020]).

Patients with autoimmune hepatitis who are planning to become pregnant should continue use of azathioprine prior to conception to decrease the risk of flare and hepatic decompensation; biological remission is recommended for 1 year prior to conception (AASLD [Mack 2020]).

Data related to paternal use of azathioprine are limited. However, available data have not shown azathioprine adversely impacting male fertility or increasing the risk of adverse pregnancy outcomes when used within 3 months prior to conception (Bermas 2019; Mouyis 2019). Azathioprine is acceptable for use in patients with rheumatic and musculoskeletal diseases who are planning to father a child (ACR [Sammaritano 2020]).

## Pregnancy Considerations

Azathioprine crosses the placenta; the 6-methylmercaptopurine (6-MMP) and 6-thioguanine (6-TGN) metabolites can be detected in cord blood. Infant serum concentrations were undetectable by 6 weeks of age in one study (Flanagan 2021).

An increased risk of stillbirth, preterm birth, and infants large for gestational age may be observed with maternal use of thiopurines (Meyer 2021).

Adverse events, including congenital anomalies, immunosuppression, hematologic toxicities (lymphopenia, pancytopenia), and intrauterine growth retardation have been observed in case reports following maternal use in kidney allograft recipients. Some of these adverse outcomes may be dose-related or a result of maternal disease (ACR [Sammaritano 2020]; EBPG 2002). Adverse pregnancy outcomes may also be associated with a kidney transplant, including preterm delivery and low birth weight in the infant and hypertension and preeclampsia in the mother. Appropriate maternal use of lower risk immunosuppressants may help decrease these risks (KDIGO 2009).

Intrahepatic cholestasis of pregnancy (ICP) has been associated with thiopurine use. In one study, patients with a metabolite ratio of 6-MMP to 6-TGN >11 (referred to as thiopurine shunting) was associated with the risk of ICP (Prentice 2024). The pharmacokinetic properties of thiopurines may be altered by pregnancy. A decrease in 6-TGN and an increase in 6-MMP was observed in the second trimester (Flanagan 2021). Closely monitor liver transaminases and thiopurine metabolites during pregnancy. Split dosing (taking half the total daily dose every 12 hours) may also prevent shunting (Prentice 2024). Patients with symptoms of ICP and elevated bile acid levels should discontinue treatment. Symptoms improve after thiopurine is discontinued (FDA 2024).

Azathioprine can be continued and should be substituted for mycophenolate in patients who become pregnant following a kidney transplant (EBPG 2002; KDIGO 2009; López 2014). Azathioprine may also be used in some pregnant patients who have had a liver (AASLD [Lucey 2013]), heart (ISHLT [Costanzo 2010]) or uterine (Jones 2019 [limited data]) transplant.

Although use for rheumatoid arthritis in pregnant patients is contraindicated by the manufacturer, available guidelines suggest that use of azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy (ACR [Sammaritano 2020]).

Patients with inflammatory bowel disease who are on maintenance therapy with azathioprine monotherapy may continue treatment during pregnancy; initiating treatment during pregnancy is not recommended. Combination therapy with azathioprine should be avoided due to increased risk of newborn infection (AGA [Mahadevan 2019]).

The Transplant Pregnancy Registry International (TPR) is a registry that follows pregnancies that occur in maternal transplant recipients or those fathered by male transplant recipients. The TPR encourages reporting of pregnancies following solid organ transplant by contacting them at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

## Breastfeeding Considerations

The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk.

Azathioprine is a prodrug which is rapidly metabolized to 6-MP. 6-MP is present in breast milk; however, it is inactive until further metabolized to 6-TGN metabolites which are present only within red blood cells (Christensen 2008; Mottet 2016).

Peak breast milk concentrations of 6-MP occurred within 4 hours in a study of eight lactating women (Christensen 2008). Another study measured the active metabolite concentrations in RBCs of four breastfeeding women ≥3 months' postpartum on chronic azathioprine therapy; sampling was conducted at variable times after the dose. Women in the study had normal thiopurine methyltransferase (TPMT) activity. All women had therapeutic concentrations of 6-TGN; however, none of the infants had detectable concentrations (Gardiner 2006). Newborn serum concentrations of 6-MP and 6-TGN were also undetectable in a study which evaluated seven breastfed infants between 1 and 28 days' postpartum. Mothers in this study were taking azathioprine 100 mg/day (Sau 2007).

Information is available from a report of 29 women taking azathioprine 50 to 175 mg/day throughout pregnancy and postpartum and their 30 breastfed newborns. Among 20 infants with blood cell counts evaluated after delivery, one infant was diagnosed with asymptomatic neutropenia on day 15 of life. Neutropenia fluctuated over 1.5 months of breastfeeding, continued for 15 days after breastfeeding was discontinued, and resolved 3.5 months later. No adverse outcomes were observed in the remaining infants who were followed for 1 to 17 months (Bernard 2013). A second study of 11 women taking azathioprine maintenance doses for inflammatory bowel disease (median: 150 mg/day) did not find an increased risk of infection in their 15 breastfed infants. The infants were followed for 6 months to 6 years (Angelberger 2011).

Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. The World Health Organization also recommends breastfeeding be avoided during maternal treatment (WHO 2002).

Recommendations for breastfeeding following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses (Constantinescu 2014; EBPG 2002; KDIGO 2009; López 2014). Azathioprine is considered compatible for use in patients with inflammatory bowel disease who wish to breastfeed (AGA [Mahadevan 2019]). Azathioprine may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding (ACR [Sammaritano 2020]).

Patients who are concerned with the theoretical risks of immunosuppression may consider pumping and discarding breast milk for the first 4 hours after an azathioprine dose to decrease potential exposure to the breastfed infant (ACR [Sammaritano 2020; Christensen 2008). Monitoring infant blood cell count 10 to 15 days after breastfeeding is initiated or in infants with frequent infections may also be considered (ACR [Sammaritano 2020]; Bernard 2013).