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Medical Management of Glaucoma for the Pregnant and Breastfeeding Patient

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Background

Glaucoma is a progressive optic neuropathy which is relatively uncommon in childbearing age, with a reported prevalence of 0.16% between the ages of 18-40 years.[1] Glaucoma management among pregnant patients presents a challenging scenario to the treating physician. Even with its low prevalence in the United Kingdom, a country-wide survey has revealed that approximately 26% of ophthalmologists reported having treated a pregnant patient with glaucoma.[2] Perhaps due to this low prevalence, 31% of these ophthalmologists reported uncertainty about managing glaucoma in this population.[2] When treating pregnant or breastfeeding patients, one must consider the benefit of treatment for the mother while weighing this against the risks the treatment may pose for the mother and fetus/child. This highlights the importance of having a review which can serve as a reference for physicians when managing glaucoma in pregnant and/or breastfeeding patients.

Glaucoma Progression and Pregnancy

Intraocular pressure (IOP) is the only modifiable risk factor in patients with glaucoma. In pregnancy, the aqueous humor formation rate stays constant, whereas the outflow facility increases, resulting in a decrease in IOP.[3] Accordingly, IOP declines at 18 weeks gestation; it decreases dramatically during the third trimester and early post-partum period, prior to rising back to normal levels as early as 6 weeks post-partum.[4,5] Furthermore, the central corneal thickness (CCT) is found to increase during the second and third trimester of pregnancy. The increased CCT can potentially elicit falsely high IOP measurements.[6] Nonetheless, IOP fluctuations are unpredictable in patients with glaucoma and in those at high risk for developing glaucoma (e.g., family history of juvenile open-angle glaucoma). In light of this, approximately 10% of glaucoma patients experience IOP elevation and disease progression during pregnancy. Therefore, it is important that these patients be followed on a regular basis to capture any potential IOP elevation or visual field progression.[7,8]

FDA Classification and Teratogenicity of Glaucoma Medications

Clinicians managing glaucoma in pregnancy must balance the risk of disease progression and the potential harm to the fetus or newborn. The Food and Drug Administration (FDA) has two labelling systems to aid clinicians in decision-making. Drugs that were approved prior to June 30, 2001 have been classified according to a five-letter system: Category A (deemed safe); Category B (possibly safe for use in pregnancy); Category C (adverse effects reported in animal studies); Category D (definite risks but possible benefits); and Category X (drugs with known risks to the fetus that cannot be outweighed by possible benefits).[4,9] This system, however, was overly simplistic, and had the potential for misinterpretation as a grading system. Therefore, the FDA has introduced a new labelling system for drugs approved as of June 30, 2001 which includes potential risks and risk summaries for pregnancy and lactation, as well as pregnancy exposure registries.[4]

Medical Management of Glaucoma During Pregnancy

Beta-blockers

Systemic

Beta-blockers are FDA Category C drugs that work by decreasing aqueous humor production through inhibition of cyclic adenosine monophosphate (cAMP) in the ciliary epithelium. Systemically, beta-blockers are the most used class of medication to treat cardiac conditions in pregnant women; however, data supporting their safety is limited.[10] The most recent review on systemic beta-blockers was conducted in 1988 by Frishman and Chesner who recommended that systemic beta-blockers be 1) avoided during the first trimester; 2) used at the lowest possible dose during pregnancy; and 3) discontinued two to three days prior to delivery to limit the effects on uterine contractility and to avoid possible neonatal complications.[11] Since then, a large case control study by Bergman et al demonstrated that beta-blockers were not associated with a higher risk of specific congenital anomalies.[12] However, Peterson et al did show an association of beta-blockers with small gestational age in infants, preterm birth and perinatal mortality.[13]

Topical

Ho et al conducted a large population-based study on ophthalmic preparations in which 77.5% of women were prescribed topical beta-blockers and found that there was no significant difference in the risk of low-birth-weight infants between mothers prescribed beta-blockers and the comparison cohort.[14] Moreover, Pellegrino et al followed pregnant females through a series of telephone interviews and did not find any negative impact of beta-blockers on pregnancy/fetal or neonatal outcomes.[15] Conversely, a smaller study of six females using topical beta-blocker therapy showed an increased risk of low-birth-weight infants.[16] Furthermore, Wagenvoort et al described a case of a pregnant female with 21-week gestation with a fetal cardiac arrhythmia.[17]

In the survey of British ophthalmologists cited above, 45% stated that they would utilize topical beta-blockers as first-line therapy,[2] most likely because systemic beta-blockers are frequently used during pregnancy. After reviewing the literature on both systemic and topical preparations, beta-blockers appear to be a relatively safe category of drugs when accompanied by frequent monitoring and co-management with maternal fetal medicine and obstetric colleagues in consideration of the risk of fetal arrhythmia and uterine contractility.

Prostaglandin analogues

Systemic

Prostaglandin analogues are FDA Category C drugs that increase uveoscleral outflow and are often first-line therapy for the majority of glaucoma patients. In the context of pregnancy, oral prostaglandins have been used to stimulate uterine contractions and terminate pregnancy.[18] Regarding potential risks during pregnancy, prenatal exposure to misoprostol, an oral prostaglandin analogue, has also been associated with increased risk of Mobius sequence and terminal transverse limb defects.[19]

Topical

Santis et al conducted a small observational study on ophthalmic preparations exploring the effects of latanoprost in eleven pregnant women. The study found no evidence of adverse effects of latanoprost on pregnancy or neonatal outcomes.[20] Overall, excluding the third trimester given the possible stimulation of uterine contractions, topical prostaglandin analogues appear to be safe during pregnancy. However, close monitoring of patients is beneficial as there is a paucity of clinical data in this context.

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors (CAIs) are FDA Category C drugs that work by reducing the secretion of aqueous humor. They can be used in oral forms such as acetazolamide and methazolamide, as well as in topical forms such as dorzolamide and brinzolamide. There have been reported cases of teratoma in neonates, as well as renal tubular acidosis and electrolyte imbalance in a neonate born to a mother taking oral acetazolamide.[21-23] Conversely, a questionnaire-based study of 101 women showed no evidence of adverse effects from acetazolamide use during pregnancy.[24] Similar results were also noted in a case series of 12 pregnant women with idiopathic intracranial hypertension receiving oral acetazolamide.[25] Unfortunately, the literature does not contain any clinical studies investigating the use of topical CAIs during pregnancy. Nonetheless, we recommend avoiding oral CAIs during pregnancy due to their potentially high-risk profile. Furthermore, given the lack of clinical studies, if topical CAIs are required during pregnancy, we suggest punctal occlusion and co-management with maternal-fetal medicine experts.

Alpha adrenergic agonists

Brimonidine, a commonly prescribed alpha agonist, lowers IOP by decreasing aqueous humor production.[4] Brimonidine is the only FDA Category B drug available for glaucoma management during pregnancy. Much like the other classes, no well-controlled human studies have been conducted to rule out teratogenic effects. Nonetheless, with close monitoring, this drug can be used safely in early pregnancy. It is important to note that the medication can cross the blood-brain barrier; it should be discontinued close to the time of delivery as it can cause CNS depression and apnea in infants.

Medical Management of Glaucoma During Breastfeeding

Beta-blockers

Beta-blockers have been approved by the American Academy of Pediatrics (AAP) for use during nursing; however, there is inconsistent evidence in the literature.[4,26] Two clinical studies found beta-blockers in breast milk to be at multi-fold concentrations compared to serum levels in nursing mothers using topical beta-blockers.[27,28] On the other hand, a case report by Madadi et al showed that the concentration of timolol was low, and unlikely to cause systemic toxicity to a newborn.[29] Given the conflicting evidence, children of breastfed mothers should be monitored for signs of beta blockade, and extreme caution should be employed in infants with cardiopulmonary disease.

Prostaglandin analogues

There is a paucity of evidence in the literature regarding the use of prostaglandin analogues during breastfeeding. Very low levels are present in breast milk, which are not expected to cause any significant adverse effects in breastfed infants.[7] The half-life of these eye drops is only approximately seventeen minutes; therefore, close care should be taken to avoid breastfeeding following eye drop administration, which should reduce any risks toward the infant.[4]

Carbonic anhydrase inhibitors (CAIs)

Oral and topical CAIs have been approved by the AAP for use during nursing.[4,26] There is limited data on the effects of CAIs in breastfeeding. A case report has shown that acetazolamide does transfer to the infant through breast milk; however, it concluded that in low doses it is unlikely to cause any harmful effects.[30] The rare potential side effects to the infant include respiratory problems and impaired renal and hepatic function.[4] Therefore, both oral and topical carbonic anhydrase inhibitors are considered relatively safe during lactation when accompanied by adequate monitoring for side effects.

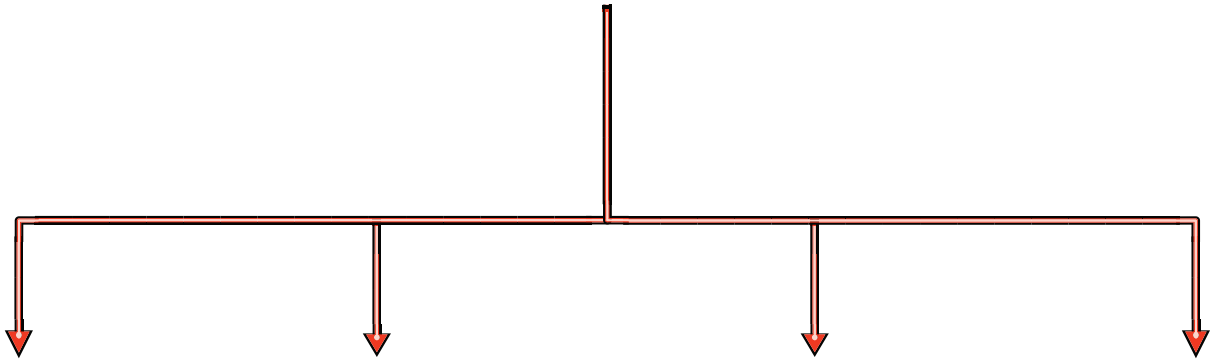
Alpha adrenergic agonists

There is a paucity of data regarding the effects of brimonidine during breastfeeding. However, topical brimonidine is contraindicated in infants and small children due to the risk of CNS depression. Given that brimonidine is secreted in breast milk, it is absolutely contraindicated for use in nursing mothers.

Conclusion

Glaucoma management during pregnancy and breastfeeding presents a challenge to both the treating ophthalmologist and the patient. Based on our review, there is a clear paucity of clinical studies on this topic. Decisions concerning the appropriate medication to use must be individualized for a patient and should consider the stage of pregnancy and severity of disease (**Figure 1**). Ideally, IOP should be optimized at the pre-conception stage with the use of laser, and surgical modalities, if necessary. If topical medications are required, effort must be taken to reduce systemic absorption with the use of punctal occlusion, eyelid closure and punctal plugs. Continued and regular communication between the treating ophthalmologist, obstetrician and pediatrician is paramount in developing a safe treatment plan that is mindful about prioritizing the health of the fetus/baby, along with vision preservation in the mother.

Medical Management of Glaucoma in Pregnancy



First Trimester

Drug	Recommendation
Beta-blocker	Likely safe.
Alpha-agonist (Brimonidine)	Likely safe.
PGA	Likely safe.
Topical CAI	Avoid due to possibility of fetal abnormalities.
Systemic CAI	Avoid due to possibility of fetal abnormalities.

Second Trimester

Drug	Recommendation
Beta-blocker	Likely safe.
Alpha-agonist (Brimonidine)	Likely safe.
PGA	Likely safe.
Topical CAI	Likely safe.
Systemic CAI	Likely safe.

Third Trimester

Drug	Recommendation
Beta-blocker	Likely safe with close monitoring due to neonatal effects.
Alpha-agonist (Brimonidine)	Contraindicated close to delivery due to neonatal effects.
PGA	Avoid due to risk of early labor.
Topical CAI	Likely safe.
Systemic CAI	Likely safe.

Lactation

Drug	Recommendation
Beta-blocker	Likely safe. Caution with cardiac concerns.
Alpha-agonist (Brimonidine)	Contraindicated due to risk of CNS depression, apnea, lethargy, bradycardia.
PGA	Likely safe.
Topical and Systemic CAI	Likely safe. Monitor for respiratory, renal and hepatic function.

Figure 1. An algorithm for the medical management of glaucoma in pregnancy and breastfeeding; courtesy of Gurkaran S. Sarohia, MD; Mathew M. Palakkamanil, MD, MPH, FRCSC

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