



A Practical Guide to the Pregnant and Breastfeeding Patient with Glaucoma

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Glaucoma is mostly associated with an older population; however, it does occur in women of childbearing potential. In a survey of UK consultant ophthalmologists, more than one-quarter of respondents reported on having to deal with glaucoma management in the pregnant patient, and 31% of these were unsure about how they would deal with the situation.¹ This highlights that glaucoma in the pregnant patient is an issue of significant prevalence and that guidelines to assist with delivery of care are needed. There are multiple challenges and uncertainties related to the management of women planning a pregnancy, during pregnancy, and during the breastfeeding period. The approach to treatment must consider the risks of treatment to both the mother and the fetus versus the risk of vision loss for the mother. It is important to have a coordinated team approach when caring for the pregnant patient with glaucoma, and the family physician, obstetrician and other healthcare providers ideally should be included in the decision-making process. This review is meant to present a practical approach to managing the pregnant and breastfeeding patient with glaucoma and to serve as a quick reference guide facilitating simple clinical application.

Intraocular Pressure during Pregnancy

Effective intraocular pressure (IOP) management during pregnancy is facilitated by a proper understanding of how IOP is likely to vary from the start of pregnancy, through delivery, and to the postpartum period. In this section, IOP changes over the course of pregnancy are reviewed for patients with and without glaucoma. Additionally, possible mechanisms of IOP change are discussed, as are behaviors and medical treatments that might influence IOP during pregnancy.

Intraocular Pressure Changes in Pregnant Women without Glaucoma

Numerous studies have demonstrated lower IOP in pregnant women without preexisting glaucoma when compared with similarly aged nonpregnant women.²⁻⁴ The IOP in the pregnant group is generally reported to be lower than in the nonpregnant control group at later stages of pregnancy.⁵⁻¹⁰

Decline in IOP starts at approximately 18 weeks gestation,⁶ reaching a nadir of 1 to 4 mmHg below baseline during the third trimester and early postpartum period.¹¹ It then begins its increase back to normal as early as 6 weeks postpartum.⁹

Thus, IOP changes during pregnancy in women without preexisting glaucoma are benign, with IOP generally decreasing, and none of the above studies²⁻¹¹ reporting any women with significant IOP increases. Unlike other conditions that are more prone to appear de novo during pregnancy,¹¹ there should be little concern of new glaucoma appearing in normal women during pregnancy, with some exceptions in cases of individuals strongly predisposed to glaucoma, that is, a family history of juvenile open-angle glaucoma (JOAG).¹²

Mechanisms Underlying Typical Intraocular Pressure Changes in Pregnancy

No reason has been firmly established for the cause of IOP lowering during pregnancy, but several theories have been put forth. It is clear that pregnancy-related IOP lowering is the result of increased aqueous outflow facility^{5,13} and not downregulation of aqueous production.^{5,14} Although many authors have invoked hormonal changes as a likely explanation for better aqueous outflow, evidence supporting this theory is mixed. Several lines of evidence suggest that lower lifetime estrogen increases the risk of glaucoma,¹⁵ but parity has not been reported to protect against glaucoma, nor is it likely that a lower IOP over 2 trimesters of pregnancy would significantly alter the likelihood of glaucoma. Intramuscular administration of both progesterone and relaxin has been noted to slightly lower IOP,¹³ but neither IOP nor aqueous outflow has been noted to vary with progesterone changes related to the menstrual cycle.^{16,17} Moreover, although progesterone has been found to be associated with lower IOP, it was not found to be associated with outflow facility.⁵

An alternate explanation for improved aqueous outflow is lower episcleral venous pressure, with lower episcleral venous pressures noted in pregnant women compared with nonpregnant women.¹⁸ A second alternative explanation is that choroidal expansion plays a role in increasing IOP, a mechanism suggested to be etiologic in various secondary

angle-closure glaucomas.¹⁹ Several studies have shown increased choroidal thickness in pregnant women,^{3,20,21} including highly myopic women.²² However, one study found no association between choroidal thickness and IOP in a group of normal pregnant women, suggesting that this increase in thickness has minimal clinical implications.³

It has been suggested that IOP is only apparently decreased in pregnancy as a result of corneal stromal hydration, resulting in increased central corneal thickness (CCT) and lowered measured (but not actual) IOP. Indeed, estrogen has been observed to increase CCT in experimental systems.²³ Additionally, several studies have noted increased CCT in pregnant women compared with nonpregnant women,²⁴ as well as in late pregnancy versus the nonpregnant state.^{5,8} However, other studies found no difference in CCT between pregnant and nonpregnant women^{2-4,25} and no changes in CCT over the course of pregnancy and the postpartum period.²⁶ In one study of pregnant women, CCT was not associated with lower IOP, suggesting that it may not explain the lower IOPs encountered in pregnancy.²⁴ Also of note, other corneal factors relevant to glaucoma, such as hysteresis or corneal resistance factor, do not seem to be affected significantly by pregnancy.^{4,7}

The mechanism for IOP lowering during pregnancy in normal women remains uncertain, and few clinically meaningful insights are obtained by past studies aimed at elucidating the mechanism for pregnancy-related IOP changes.

Behaviors, Events, and Treatments that May Affect Intraocular Pressure during Pregnancy

Pregnant patients with or at risk for glaucoma will often inquire about specific behaviors or events that might elevate IOP. However, little evidence exists to suggest any unsafe behaviors or events in glaucoma. For example, postural changes do not affect IOP differently in pregnancy than might be expected in normal adults. IOP was noted to decrease approximately 3 mmHg while sitting compared with lying positions.²⁷ However, no differences in IOP were noted in the supine, left, or right lateral decubitus positions, suggesting that there are no deleterious sleeping positions in pregnancy with regard to IOP.²⁷ These mild increases in IOP are probably inconsequential, even in cases of prolonged bed rest.

Concerns are also frequently cited as delivery approaches with regard to the dangers of IOP elevation at the time of childbirth. However, in women without glaucoma, IOP has not been observed to change significantly over the course of normal vaginal delivery.²⁸ IOP was noted to increase during the fundal pressure stage of Caesarian section, but the increase was mild (3-4 mmHg),²⁹ and there is likely no clinical significance to this small degree of IOP elevation over a limited time period.

Another set of concerns focus on concurrent medical issues occurring during pregnancy, which may pose a particular danger with regard to IOP elevation. IOP has

been found to be statistically higher in hypertensive pregnant women compared with nonhypertensive women, but the differences were small (<1 mmHg).³⁰ Limited data are available regarding the impact of steroid treatments during pregnancy, but such treatments are occasionally necessary for uveitis or other conditions such as diabetic macular edema. In one small case series, 5 pregnant women without preexisting glaucoma received intravitreal slow-release dexamethasone for diabetic macular edema. In 3 of 8 treated eyes, IOP was noted to increase, but increases were mild (IOP elevation to 22-24 mmHg), and none required IOP-lowering medicine.³¹ The limited numbers and lack of a comparison group preclude conclusions about the relative risk of steroid-induced IOP increases in pregnant patients versus nonpregnant patients.

Intraocular Pressure Changes in Pregnant Women with or at Risk for Glaucoma

Although prior research has heavily focused on IOP changes in normal eyes, practical clinical concerns more typically center on how to deal with patients with glaucoma or at high risk for glaucoma as a result of ocular hypertension or a family history of early-onset glaucoma.

In a series of 32 ocular hypertensive pregnant women, IOP was noted to be significantly lower than baseline IOP starting at 24 weeks gestation, with an average IOP lowering of 24%, most of this manifesting between the 24th and 30th week of gestation.⁶ Many patients were even noted to have their IOP lowered into the normal range.

However, the infrequency of IOP increases in persons without glaucoma should not be used to conclude that women with known glaucoma will demonstrate a benign IOP course during pregnancy.^{12,32,33} In one case series of 8 patients with a variety of diagnoses (3 with primary congenital glaucoma, 2 with developmental glaucoma, 3 with other conditions), 7 demonstrated stable IOPs and no visual field progression despite a lowering of medication burden from a mean of 1.7 to 0.8 medications per eye.³³ One patient, however, had IOP elevation to 44 mmHg during the third trimester, with concomitant visual field progression. In another series of 15 pregnant females with preexisting glaucoma (JOAG in 3 patients, uveitic glaucoma secondary to juvenile rheumatoid arthritis in 3 patients, pigmentary glaucoma in 2 patients, and aniridia in 2 patients), IOP elevation of 5 mmHg or more was noted in approximately half of patients (7/15).³² Additionally, 5 eyes of 4 patients were observed to have visual field progression that did not reverse in the postpartum period. Finally, in one series of 3 patients with medically uncontrolled glaucoma during pregnancy, 2 patients demonstrated severe bilateral IOP elevation before the third trimester after entering pregnancy on 3 or more antiglaucoma medications.¹² The third patient had no diagnosis of glaucoma before pregnancy but did have a family history of JOAG. She presented with new-onset bilateral IOP elevation during the second trimester. Her

IOP could not be controlled medically, necessitating bilateral surgery.¹²

Together, these case series suggest that the benign IOP course during pregnancy in women without glaucoma may not extend to patients with preexisting glaucoma. These patients, whether as a result of their pregnancy or their underlying disease, have a moderate risk of IOP elevation and disease progression during pregnancy and should be followed carefully (i.e., every 1–3 months).

Managing Glaucoma in the Pregnant Patient

Pregnancy and Current Glaucoma Medications

The 2 main challenges facing the ophthalmologist medically treating glaucoma in pregnancy are the lack of good clinical data and the apprehension of the pregnant patient and her healthcare providers to introduce any medication with a risk of fetotoxicity, no matter how small. This can lead to noncompliance even in the face of firm clinical recommendations, making good communication essential.

In 2015, the Food and Drug Administration adopted a new labeling system for pregnant women needing prescription medication that is being phased in for drugs approved as of June 30, 2001. The new system requires labels to include potential risks and risk summary for pregnancy and lactation and pregnancy exposure registries. Drugs approved before June 30, 2001, are not required to use the new system and instead use the previous 5-letter system that was introduced in 1979: category A, deemed safe; category B, possibly safe to 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.³⁴ Most glaucoma medications in this classification system are category C. There are no glaucoma medications in category D or X. Many excellent reviews have been written on the topic of glaucoma medications and the pregnant patient that outline the paucity of good basic science and clinical data.^{35–38} The following is a description of the different medications by group, followed by a review of known clinical experience, and ending with general recommendations for treating the pregnant patient with glaucoma.

Beta-Blockers: Category C

Wagenvoort et al³⁹ described bradycardia and arrhythmia in a healthy fetus at 21 weeks of gestation whose mother was receiving topical timolol 0.5%. The fetal heart rate improved when the dosage of the topical timolol was reduced from 0.5% to 0.25%. The slow pulse completely resolved with discontinuation of timolol. Apart from this single report, there are no reports of fetal harm due to the use of topical beta-blocker in humans, and a case series from Taiwan including 189 woman prescribed topical beta-blockers during pregnancy indicated that the risk of low birth weight is similar to that of the control cohort.⁴⁰ Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to

50 mg/kg/day (7000 times the systemic exposure after the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations.⁴¹ As for systemic beta-blockers, case reports have described their adverse effects to include apnea, intrauterine growth retardation, neonatal depression at birth (low Apgar scores), postnatal hypoglycemia, and bradycardia.⁴² Frishman and Chesner⁴³ reviewed the available literature on systemic beta-blockers in pregnancy and concluded that beta-blockers are relatively safe. The authors comment that because definitive data were lacking, systemic beta-blockers should be (1) avoided during the first trimester, (2) used in the lowest dose possible during pregnancy, and (3) discontinued 2 to 3 days before delivery to limit the effects of beta-blocker therapy on uterine contractility and to avoid possible neonatal complications. Despite these systemic concerns, beta-blockers are used systemically when needed in pregnancy.⁴⁴

Oral Carbonic Anhydrase Inhibitors: Category C

Oral carbonic anhydrase inhibitors (CAIs) have shown teratogenic effects (forelimb anomalies) in mice.^{45–47} The activity of carbonic anhydrase enzymes was found to be less in a primate monkey fetus study, suggesting there may be less effect in humans versus mice.⁴⁸ Worsham et al⁴⁹ reported 1 case of a teratoma in the neonate of a patient treated with oral acetazolamide in the first 19 weeks of pregnancy. Another case report demonstrated the trans-placental transfer of acetazolamide and its subsequent induction of electrolyte imbalance in a neonate. A pregnant mother was treated with oral acetazolamide (750 mg/day) for glaucoma for 3 successive days before a Caesarean section delivery at 34 weeks of gestation for fetal distress. The newborn was noted to have renal tubular acidosis and measurable serum levels of acetazolamide, demonstrating the trans-placental passage.^{50,51}

On the other hand, a case series of 24 patients with idiopathic intracranial hypertension were treated with acetazolamide during pregnancy without adverse events.⁵² The National Collaborative Perinatal Project reported no increase in major or minor fetal abnormalities in the infants of 1024 women exposed anytime in pregnancy to acetazolamide, including 12 infants exposed during the first trimester.⁵³ The number of infants with malformations was less than expected.

Topical Carbonic Anhydrase Inhibitors: Category C

Dorzolamide in rabbits at 37 times the human dose caused fetal vertebral body malformation and decreased fetal weight.⁵⁴ Brinzolamide was shown to cross the placenta in rats and was toxic at 125 times the human dose, causing fetal malformations.⁵⁵

Alpha Adrenergic Agents: Brimonidine (Category B) and Apraclonidine (Category C)

There are studies demonstrating the fetal safety of brimonidine; thus, this drug is categorized as B.^{56,57} Reproductive

studies using brimonidine tartrate given orally to rats at 375 times the human dose revealed no evidence of harm to the fetus, from day 6 to 15. In rabbits, a dose of 19 times that of humans caused no teratogenesis in days 6 to 18. Regarding apraclonidine, 60 times the human dose was embryocidal, and it is labeled category C.⁵⁸ There is less clinical experience with this medication than brimonidine.

Prostaglandin Analogues: Category C and D

Prostaglandins play a role in both the maintenance of pregnancy and birth. Prostaglandins are known to stimulate uterine smooth muscle, causing uterine contractions, and animal studies have suggested an increased risk of abortion or preterm delivery with the administration of prostaglandin.⁵⁹ Some human data corroborate this.⁶⁰ Prostaglandin F2 alpha was not found to be toxic to rabbit fetus at doses up to 80 times human dosing. There is limited clinical experience with this medication class. In a survey of British ophthalmologists, this was the second-line medicine choice for pregnant patients with glaucoma after topical beta-blocker treatment.¹

Latanoprostene bunod 0.24%, Vyzulta (Bausch & Lomb, Bridgewater, NJ), is a new prostaglandin analogue (PGA) with no human data. However, in rabbits fetal toxicity was noted starting at intravitreal doses over 0.28 times the clinical dose.⁶¹ These data suggest great caution for its use in pregnant patients with glaucoma, because this is a rather narrow therapeutic margin compared with most drop therapy. It is classified category D by one of the authors (S.M.J.).

Rho Kinase Inhibitors

Netarsudil 0.2%, known as Rhopressa (Aerie Pharmaceuticals, Irvine, CA), is a new category of glaucoma drops. There are no human studies available. In rabbits, 214-fold the human clinical dose did not cause adverse events to the fetus.⁶² On the basis of the prior Food and Drug Administration classification, this drug is likely C or even B, pending more clinical information.

Miotics: Category C

Pilocarpine is known not to traverse membranes well, and little was shown to traverse the placenta in rats in a study by Omori et al.⁶³ Clinical information was provided by Kooner and Zimmerman⁶⁴ for the use of this drug in the first 4 months of pregnancy without fetal defects.⁴

Combination Drugs

When deciding on a combination glaucoma medication, consideration of the individual classes of drugs in the solution is important. Also, combination drops may come in different concentrations and formulations than the comparative individual medication. There will be more absorption of timolol in a fixed-dose combination with dorzolamide or brimonidine compared with using a gel-forming formulation. There will be a higher dose of brimonidine in Combigan (brimonidine

tartrate 0.2% and timolol maleate 0.5%, Allergan, Irvine, CA) than Alphagan P (brimonidine tartrate 0.15%, Allergan).

Clinical Experience in Pregnant Patients with Glaucoma

Because most of the animal studies use very high concentrations of drug, it is hard to translate this to the human experience. At this time, much of what is relied on are case reports and small case series. Caution should be taken in interpreting such data, because it could provide false assurance on the one hand or an unjustified sense of alarm on the other. Johnson et al³⁵ described the use of timolol maleate gel-forming solution 0.5% in a pregnant woman throughout the course of pregnancy. The patient was also started on dorzolamide 2% and brimonidine 0.2% in the seventh month of gestation, and the patient delivered a healthy infant. Another patient reportedly took latanoprost, a PGA, during her entire pregnancy with a healthy baby born. An Iranian group reported on 6 pregnant patients with glaucoma who all took timolol during pregnancy and oral acetazolamide during the last month.⁶⁵ In addition, 3 were exposed to brimonidine. Three of the 6 pregnancies had low birth weight infants, although all 6 infants were otherwise normal. A series from Spain⁵³ looked at 8 patients on timolol with 1 taking a PGA for 3 months and 1 taking fixed-dose timolol dorzolamide who experienced intrauterine growth retardation. Prostaglandin use was reported in a series of 10 women without adverse effects in 9.⁶⁶ One, with older maternal age, had a miscarriage; however, it was considered unlikely that the PGA played a role. Brauner et al³² reported 13 successfully medicated (11 taking a beta-blocker, 4 using a topical CAI, and 5 taking brimonidine/apraclonidine) pregnant patients with glaucoma with no adverse effects noted in the patients or offspring.

An Italian series⁶⁷ reviewed 27 women taking timolol during pregnancy and an additional 48 also using a topical CAI or PGA. They concluded that their pregnant glaucoma cohort did not exhibit different morbidity or an increase in low birth weight babies than the general Italian pregnancy statistics. One woman, who used bimatoprost, had a preterm baby who died. This occurrence was thought to be among expected statistics and not due to the glaucoma medication. A larger study in Taiwan observed 244 pregnant patients with glaucoma with 189 on topical beta-blockers and reported no cases of low birth weight babies.⁴⁰ However, 2 of 7 patients (28.6%) using a topical CAI, 2 of 16 (12.5%) taking PGAs, and 2 of 20 (10%) taking brimonidine had low birth weight babies, all over the expected rate of 6.2%. By pooling these results with the prior studies cited,^{32,33,65-67} the rates are 23% for CAI, 7.1% for PGAs, and 8% for brimonidine, which are closer to the statistics cited in the series from Italy.⁶⁷ Cases from Iran were not included because that was a multidrug study. The synthesis of the information provided by these studies is shown in Table 1 and in the summary recommendations next.

Summary Recommendations

Consultation with the obstetrician may be advisable for the pregnant patient with glaucoma. Punctal occlusion should

Table 1. Summary of Pregnancy Categories for Glaucoma Medications

Class	Category	Recommended Trimester
Alpha-adrenergic agonist: Brimonidine	B	First and second (avoid close to delivery because of neonatal effects)
Alpha-adrenergic agonist: apraclonidine	C	All 3
Beta-blockers	C	First and second (avoid close to delivery because of neonatal effects)
PGAs (excluding latanoprostene bunod 0.24%; Vyzulta, Bausch & Lomb, Bridgewater, NJ)	C	Third and possibly second (because of risk of early labor) Avoid Vyzulta
CAI	C	Late second and early third
Pilocarpine	C	All 3
Rho kinase inhibitor	No category	Possibly all 3 based on limited animal studies

CAI = carbonic anhydrase inhibitor; PGA = prostaglandin analogue.

also be emphasized in the care of pregnant patients with glaucoma on drop therapy.⁶⁸ Until we have large databases of patients who have been exposed to glaucoma drops during pregnancy, clinicians must interpret the cases and data we have critically and approach each pregnant patient with glaucoma with a risk–benefit ratio and make an informed decision with the patient. The small available dataset becomes even smaller when attempting to consider medications by trimester, although the timing of the medication during gestation may play an important role in its safety. It may also be helpful to consider the diminished return with the addition of a third or fourth class of medication, possibly altering the risk–benefit profile.

Timolol is the glaucoma drug with the longest track record of use in pregnant patients with glaucoma. In a survey sent to 605 British ophthalmologists, 282 responded with 26% having experience with glaucoma and pregnancy. Seventy-one percent continued patients on their medical regimens, and overall 45% considered timolol the first-line therapy in pregnancy.¹ Ho et al⁴⁰ reported on a group of 244 pregnant women treated for glaucoma during pregnancy. Of these, 77.5% were prescribed a topical beta-blocker. There was no correlation between beta-blocker use and low birth weight, and the authors conclude that topical beta-blockers can be used as first-line therapy in this scenario. Timolol is available in a gel-forming formulation with less systemic absorption for greater safety.⁶⁹ The pediatrician caring for the newborn should be made aware if a mother is on a beta-blocker, so appropriate surveillance is used for the neonate. The twice-daily 0.25% formulation should be weighed against the once-daily 0.5% formulation, but there are currently no data to support the use of one over the other.

Brimonidine may be used in the first 2 trimesters and is labeled category B in the original Food and Drug Administration classification system based on animal studies. However, as the pregnancy reaches term, brimonidine should be discontinued because of the risk of central nervous system depression.⁷⁰ Consideration can be made to change to apraclonidine, which unlike brimonidine is not lipophilic and should not cross the blood brain barrier of the neonate, thereby reducing, but not eliminating, the risk. Limited cases of use of this drug have been reported, and this drug is category C, indicating that fetal toxicity has been shown in animal studies.⁵⁸

Topical CAIs may be safe according to the small case series, but awareness should be undertaken for possible risk of low birth weight, based on the cases cited above.^{33,40,67} Caution should be taken with oral CAIs given the mixed literature. Perhaps it can be used mid-pregnancy when limbs are already formed but not close to birth because of concerns of acidosis and metabolic problems in the neonate.^{50,51} Again, the neonatology team should be aware of use of this medication in the mother. Prostaglandin analogues are sometimes avoided in pregnancy because of concern over inducing labor and are best considered in the later stages of pregnancy when any inducement of labor is safe.⁷¹ Pilocarpine has been used successfully in the first 4 months of pregnancy.

Glaucoma Medications and Breastfeeding

Glaucoma medications taken by nursing mothers can be found in breast milk, which can potentially harm newborns. Newborns and infants are particularly vulnerable to undesirable systemic effects of these glaucoma medications, because infants have reduced drug metabolism⁷² and an immature blood–brain barrier,⁷³ which makes them more susceptible to systemic side effects from these ingested medications. When a patient instills glaucoma drops to the eye, up to 80% of the glaucoma drop may diffuse into the systemic circulation.^{74,75} Of that percentage, some may bypass the mother's first metabolism in the liver, and if the hepatic cytochrome P450 system has no chance to degrade the drug to inactive metabolites, some active drug will be secreted into the breast milk and ingested by the newborn.⁷⁵ When treating a nursing woman, it is imperative to use only the minimal amount of medication possible to achieve IOP control and to reinforce the implementation of punctal occlusion to reduce systemic absorption. Because eye drop levels in breast milk are highest at 30 to 120 minutes after instillation, some authors advise that medications should be administered just after nursing whenever possible.^{75,76}

Beta-blockers

Although studies have shown that topical beta-blockers have been found in human milk,^{76,77} one of these studies

Table 2. Recommendations for Glaucoma Medications during Breastfeeding

Class	Safety	Comment
Alpha-adrenergic agonist: brimonidine	Contraindicated	• Risk of CNS depression, apnea, lethargy, bradycardia
Beta-blockers	Safe	• Caution in infants with cardiopulmonary disease
PGAs (excluding latanoprostene bunod 0.24%; Vyzulta)	Likely safe	• Short half-life
CAIs	Safe	
Pilocarpine	Unknown	• Short half-life • Risk of cholinergic symptoms
Rho kinase inhibitor	Unknown	• No data available

PGA = prostaglandin analogue; CAI = carbonic anhydrase inhibitor; CNS = central nervous system.
Safe refers to being deemed compatible with lactation by the American Academy of Pediatrics. Likely safe refers to assessment by authors given available data.

suggested that timolol levels in breast milk are too low to impose a health risk to breastfed infants;⁷⁷ therefore, this class of drug is approved by the American Academy of Pediatrics for use during nursing,⁷⁸ but there is still a theoretical risk of bronchoconstriction, bradycardia, and cardiac arrhythmia in infants. This is due to the lipophilic nature of beta-blockers, which allows for high systemic bioavailability and rapid maximum plasma concentrations.^{74,79} Despite being considered a safe option when mothers are using beta-blocker eye drops, their infants should be closely monitored, especially the ones with cardiopulmonary disease.

Carbonic Anhydrase Inhibitors

Although teratogenic effects, such as limb and kidney defects, have been implicated with use of high doses of oral CAI in animal studies,^{46,80} and a case report has shown a possible relationship between the use of acetazolamide by a pregnant woman and congenital malformations,⁸¹ no reports of adverse effects associated with topical CAI use during pregnancy and postpartum were found. Oral (acetazolamide, methazolamide) and topical (dorzolamide, brinzolamide) CAIs are also considered safe and compatible with lactation by the American Academy of Pediatrics.⁷⁸ Although a case report has shown that acetazolamide can be found in human breast milk, the resulting plasma levels in infants were too low to be considered harmful.⁸² To date, it is still unknown if brinzolamide and dorzolamide are excreted in breast milk; however, both were found in rat milk after administration.⁵⁵ The potential side effects for a newborn would be respiratory problems or impairment of renal and hepatic function.

Prostaglandin Analogs

There are reports of the presence of prostaglandin analogs in breast milk in animal studies,⁸³⁻⁸⁵ but it remains unknown if prostaglandins are excreted in human milk. It is unlikely that prostaglandins would cause unwanted systemic side effects for the infant, because once in the mother's bloodstream, the half-life of these eye drops is approximately 17 minutes. Taking care not to breastfeed closely after the time of drop application should virtually eliminate the risk of side effects.

Also, these drops are oxidized outside of the eye and eliminated mostly in the urine.^{75,86,87}

Alpha Adrenergic Agonists

Topical brimonidine is contraindicated in infants and small children, because it can cross the blood-brain barrier and therefore cause CNS depression, including lethargy, apnea, and bradycardia.^{86,88-91} Brimonidine is also secreted in breast milk,⁸⁶ and because of the potential severity of its side effects to the infant,⁹² some authors suggest avoiding this class of medication for women who intend to breastfeed.^{37,92,93}

Miotics

To our knowledge, there are no human studies of toxicity with miotic drugs during lactation; therefore, the potential for side effects to breastfed children is unknown. This class of drugs could theoretically cause gastrointestinal over-activity, salivation, sweating, nausea, tremors, and hypotension; however these drugs are rapidly metabolized once they reach the bloodstream, so systemic uptake and cholinergic responses seem unlikely.⁹⁴ Pilocarpine is a weak amine, can cross membranes, and can pass into breast milk,⁹⁵ and there is a case report of maternal pilocarpine use in pregnancy that was associated with signs simulating meningitis, such as hyperemia, restlessness, seizures, and diaphoresis in the newborn.^{96,97}

The management of glaucoma during lactation can be challenging for the ophthalmologist, and it is important to be aware that glaucoma medications can potentially harm breastfed infants even when the concentrations are too low for an IOP-lowering effect. More studies are needed for stronger recommendations. Table 2 shows a summary of this discussion.

Laser Trabeculoplasty

Laser trabeculoplasty (argon laser trabeculoplasty, selective laser trabeculoplasty, and micropulse laser trabeculoplasty) is an attractive alternative to medical management during pregnancy and lactation, because it may lower or eliminate the need of topical medications that inevitably make their

Table 3. Treatment Guide for the Patient with Glaucoma in Preconception, Pregnancy, and Breastfeeding

	Preconception	Pregnancy	Breastfeeding
Medication	<ul style="list-style-type: none"> • Evaluate risk • Consider decreasing medication burden • Nasolacrimal occlusion 	<ul style="list-style-type: none"> • Evaluate risk (Table 1) • Consider decreasing medication burden • Nasolacrimal occlusion 	<ul style="list-style-type: none"> • Evaluate risk (Table 2) • Consider decreasing medication burden • Instill medications immediately after rather than before breastfeeding • Nasolacrimal occlusion
Laser Trabeculoplasty Surgery	Consider performing to decrease medication burden or lower IOP.	Consider if target pressure not achieved using other treatment modalities or to eliminate/decrease medication burden.	

IOP = intraocular pressure.

way into the bloodstream. Laser trabeculoplasty has several important limitations, some of which are of particular relevance to the reproductive age group. First, it requires the anterior chamber angle to be open and physiologic in morphology. Because the proportion of glaucomas secondary to chronic inflammatory processes, previous intraocular surgeries, and anterior segment dysgenesis syndromes is relatively high in this age group, the indications for laser trabeculoplasty may be limited. Second, it has been shown that laser trabeculoplasty tends to be less effective in younger patients.⁹⁸ Because pregnancy has a finite timeline that is short relative to a chronic disease, the temporary nature of this treatment may be a minor issue because it is needed primarily as a bridging measure until medical therapy can be reinstated. To the best of our knowledge, no adverse effects of laser trabeculoplasty to mother or fetus have been recorded in the literature. Vyborny et al⁹⁹ reported on 64 eyes of pregnant patients that had undergone bilateral selective laser trabeculoplasty with the aim of discontinuing all medical treatment for the duration of pregnancy and breastfeeding and found no deterioration of visual function during pregnancy. Although other anecdotal reports exist in the literature,^{12,35} they do not add to our current understanding. The aforementioned advantages of laser trabeculoplasty, especially in view of the limited data regarding the safety of the alternatives (medical therapy and surgery), should prompt the clinician to consider this therapy in pregnant patients, despite reservations regarding its effectiveness.

Surgical Management

Before undertaking surgery in pregnant patients with glaucoma, the clinician should exhaust all available and safe alternatives to IOP lowering. Also, special consideration should be given to the temporary allowance of raised IOP, because the risks of intervention might outweigh the risk of nerve damage in certain patients, especially in those with mild disease. In addition, the risk of failure of filtration surgery is likely higher in this group because of young age, contraindication of anti-metabolites during pregnancy, and possibly a hormone-driven increased wound-healing response.^{100,101} That said, surgical intervention may be

the only way to control IOP and preserve vision in some patients and should be considered on a case-by-case basis.

The main surgical options for pregnant patients are like those for the general population of patients with glaucoma and include subconjunctival bleb-based procedures, glaucoma drainage devices, angle-based procedures, and cycloablation. Anti-metabolite use is currently the standard of care in bleb-based subconjunctival filtering procedures, such as trabeculectomy, the Ex-PRESS (Alcon, Fort Worth, TX), the Xen 45 microstent (Allergan, Dublin, Ireland), and the Preserflo MicroShunt (Santen Pharmaceutical Co, Osaka, Japan), because it has been shown to significantly reduce the failure rate.

However, these agents, namely, mitomycin C and 5 fluorouracil, have shown teratogenicity in animal models.^{102,103} Although, to our knowledge, there are no data on the effects of local ocular use of these agents in pregnancy, and there are anecdotal reports of their use in pregnant patients without detrimental effects on the fetus,¹² the American Academy of Ophthalmology recommends they not be used in the pregnant patient with glaucoma.¹⁰⁴ Trabeculectomy without the use of anti-metabolites is still a valid surgical option, albeit less attractive, especially for surgery in a younger cohort. Glaucoma drainage devices are another surgical option for the pregnant patient. They do not rely on anti-metabolites¹⁰⁵ and arguably allow for a more predictable postoperative course compared with trabeculectomy. There may also be an added benefit to the use of these devices because of the higher proportion of secondary glaucomas in this population. Goniotomy-based procedures, such as the Trabectome (Neomedix, Tustin, CA)¹⁰⁶ and Gonioscopy Assisted Transluminal Trabeculotomy,¹⁰⁷ have shown to be effective in lowering IOP in patients with open-angle glaucoma. Schlemm's canal stenting procedures, such as the iStent Trabecular Micro Bypass devices (Glaukos Inc, San Clemente, CA)¹⁰⁸⁻¹¹⁰ and the Hydrus Microstent (Ivantis, Inc, Irvine, CA),¹¹¹ have shown modest efficacy in IOP and medication load lowering in patients with open-angle glaucoma. Although less effective than bleb-based procedures and glaucoma drainage devices, and with less evidence at the time of writing, angle-based procedures have the advantages of a favorable safety profile, as well as the fact that precious

ocular real estate is preserved for future surgery if needed, which is especially relevant in this young cohort. Of note, the goal of surgery in pregnancy may not be IOP lowering as much as the ability to lower topical medication load (allowing for a postoperative pressure in the high teens or possibly higher), in which case these surgeries may have a role. Cycloablation is also an option for the pregnant patient with glaucoma, especially with the improved safety of micropulsed delivery.¹¹²

In addition to the choice of procedure, there are issues related to anesthesia and postoperative antibiotics and anti-inflammatory drops in the pregnant patient. Because anesthetic drugs affect cell signaling, mitosis, and DNA synthesis,¹¹³⁻¹¹⁵ and thus may affect cellular differentiation and organogenesis, their use, especially in the first trimester, should be avoided if possible. In general, ophthalmic surgery, and specifically glaucoma surgery, can be carried out safely under local or retrobulbar anesthesia. In the Food and Drug Administration's classification, etidocaine, lidocaine, and prilocaine are categorized in group B, and bupivacaine and mepivacaine are placed in group C because of inducing fetal bradycardia.¹¹⁶ The use of topical, subconjunctival or sub-Tenon's anesthesia minimizes systemic absorption while allowing for comfortable surgery in most cases.¹¹⁷ If needed, retrobulbar anesthesia is a reasonable option rather than considering intravenous sedation or general anesthesia. It is important to consult with the patient's obstetrician and anesthesiologist before surgery. Another challenge is the supine position for patients in advanced stages of pregnancy, because the gravid uterus can compress the large blood vessels causing profound hypotension. It is possible to retain a normal head position required for ophthalmic surgery, while rotating the patient's hip, thighs, and abdomen to reduce the risk of compression.

Glaucoma surgery in the pregnant patient is relatively safe and should be discussed with the patient when class B medications and laser trabeculoplasty have failed to adequately control IOP. Careful consideration should be given to the choice of procedure and anesthesia, and to inclusion of the patient and other physicians in the circle of care in the decision process.

Conclusions

The pregnant patient with glaucoma poses a therapeutic challenge. Several important principles are important to consider in this scenario, even before the initiation of treatment as summarized in Table 3. The first is good communication with the patient, including a comprehensive discussion of risks and benefits of the different options, and proper informed consent. There is a high rate of noncompliance in this population, and the physician must make sure the patient is on board with the treatment plan. If there is the opportunity to address the treatment plan during the planning or preconception period, the discussion is best held at that time. The second is the creation of a multidisciplinary care team, in which the patient's obstetrician and later pediatrician are aware of the treatment

and can provide appropriate follow-up. The third is the setting of an appropriate target pressure. Because pregnancy is time limited, a temporary allowance of a higher target pressure may be possible in select cases, allowing for discontinuation of some medications. When a decision has been made to initiate or continue treatment, an understanding of the literature and its many limitations is important in making therapeutic choices. The treating ophthalmologist should know that there are safe options for medical treatment of the pregnant patient with glaucoma, that laser trabeculoplasty is often an option, and that there are a variety of surgical options that can be used in select cases. With judicious use of available therapies, favorable outcomes are expected.

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