An Approach to Glaucoma Treatment in Pregnant and Lactating Women

Minimize medications and dosing frequency to limit the risks to the mother, fetus, and breastfed infant.

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The treatment of glaucoma during pregnancy and lactation requires physicians' careful consideration of the stage of pregnancy, the therapeutic agent(s) to be administered, and the status of the disease. When treating glaucoma during the patient's pregnancy and lactation, the potential benefits of therapy and the visual goals of the mother must be weighed against the risks of treatment to the fetus or infant, which are often poorly defined. Each class of glaucoma medication has its own set of potential side effects that may be problematic at various stages of pregnancy and lactation, making therapeutic decisions difficult.

PLAN EARLY

The potential for medications to cause a teratogenic effect is greatest during the process of organogenesis, which begins 3 to 8 weeks after conception, when many women are unaware of their pregnancy. Therefore, discussions about how glaucoma may be managed during pregnancy are best held well in advance of conception. Because women may not always inform their ophthalmologist about their desire to become pregnant, physicians should initiate discussions with all women of childbearing age who require medical treatment for glaucoma.

There are many benefits associated with discussing a plan for glaucoma care before conception occurs. First, untreated IOP can be recorded. Additionally, optic nerve imaging and visual function examinations can be performed to assess the baseline status of the disease and to determine the risk of observation off treatment or with fewer medications. In women who demonstrate unacceptably high IOPs off treatment and who are reluctant to use medications during pregnancy, laser trabeculoplasty or surgical procedures can be performed before conception, thus avoiding the potential risks of surgical anesthesia during pregnancy.

Surgical options include standard trabeculectomy and aqueous drainage devices. In addition, newer surgical modalities that target the physiological outflow system, such as the Trabectome (NeoMedix Corporation), canaloplasty (iTrack microcatheter; iScience Interventional), or the iStent (Glaukos Corporation; not available in the United States) may be considered in such cases. Physicians must keep in mind, however, that many of these women will have underlying diagnoses of primary congenital glaucoma, juvenile open-angle glaucoma, or secondary glaucoma due to aphakia, uveitis, anterior segment neovascularization, or anterior segment dysgenesis. In general, the efficacy of the aforementioned newer glaucoma procedures for these conditions is not well established.

WILL GLAUCOMA WORSEN DURING PREGNANCY?

A common concern of patients and treating physicians regards the uncertainty of the IOP's behavior and disease course during the pregnancy. IOP in normal females typically decreases during pregnancy[1] as a result of reduced episcleral venous pressure, hormonal

TABLE 1. FDA'S CLASSIFICATION OF GLAUCOMA MEDICATIONS

FDA Class	Description	Glaucoma Medications
A	Strong evidence of safety based on human studies	None
B	Varying and/or contradictory human and animal study data	Brimonidine
C	Side effects shown in animal models but few or no human studies	β-blockers Carbonic anhydrase inhibitors Prostaglandin analogues
D	Human studies showing risk to fetus	None
X	Strong evidence of birth defects in humans	None

TABLE 2. SIDE EFFECTS OF GLAUCOMA MEDICATIONS USED DURING PREGNANCY AND LACTATION

Medication Class	Secreted Into Breast Milk?	Potential Side Effects	Notes
β-blockers	Yes, at low concentrations	Fetal arrhythmia Fetal bradycardia	Side effects specific to oral β-blockers
α-adrenergic agonists	Unknown	Neonatal apnea Neonatal hypotension	Side effects reported for drops instilled in infants
Prostaglandin analogues	Unknown	Uterine contractions Premature labor Limb defects	Side effects associated with oral or vaginal prostaglandin use
Carbonic anhydrase inhibitors	Yes, at low concentrations	Low fetal body weight Vertebral malformations Renal tubular acidosis	All side effects noted for oral carbonic anhydrase inhibitors only

changes, and gestational metabolic acidosis.[2,3] However, a small study performed on 28 eyes of 15 pregnant women found visual field progression in nearly one in five eyes and elevated IOP in an additional one in five eyes, suggesting that the risk for additional damage may be significant.[4] Therefore, careful follow-up during pregnancy is warranted.

DRUG DELIVERY

When medical treatment is required, physicians should minimize the dosage of medicine and limit systemic absorption. Many medications, including β-blockers, α-agonists, and prostaglandin analogues, are available in different concentrations, with little to no difference in efficacy with the lower concentration. In one study, a minimal change in efficacy was observed for once- versus twice-daily timolol, offering another mechanism to decrease overall drug load.[5]

The systemic absorption of eye drops can also be significantly reduced with nasolacrimal duct occlusion or punctal plugs. In one study, the plasma levels of timolol decreased by approximately 65% with either nasolacrimal duct occlusion or eyelid closure.[6] To date, the efficacy of reducing the systemic absorption of medication with punctal plugs has not been studied, although similar effects to those achieved with nasolacrimal occlusion might be expected.

CHOOSE AN IOP-LOWERING AGENT

The risks of most IOP-lowering medications are not well established in the human fetus or infant and must often be inferred from animal studies (Table 1) or the medication's mechanism of action. Additionally, the classification of drugs is often based on findings regarding their oral form rather than the topical formulation (Table 2). The risks of medications also depend on the mother's stage of pregnancy and lactation (Table 3).

β-Blockers

The risk of topical β-blockers is generally inferred from the described risks of oral β-blockers, which are classified as class C medications by the FDA. β-blockers have been known to cross the placental barrier, producing fetal bradycardia and cardiac arrhythmia. These agents are also secreted into breast milk and may cause systemic effects in breastfeeding infants.[7]

TABLE 3. APPROACH TO MEDICAL TREATMENT OF GLAUCOMA BY STAGE OF PREGNANCY

Stage	Specific Concerns	Medical Approach
Preconception	None	Counsel patient about the status of the disease and various therapeutic options
First trimester	Organogenesis, highest risk of teratogenic effects	Minimize medications Minimize concentration and dosing frequency of medications Consider punctal plugs, nasolacrimal duct occlusion, or eyelid closure
Second trimester	Growth or developmental defects from medicines' crossing the blood-placenta barrier	Minimize medications Minimize concentration and dosing frequency of medications Consider punctal plugs, nasolacrimal duct occlusion, or eyelid closure
Third trimester	Induction of premature delivery (theoretical side effect of prostaglandin analogues) Side effects in newborn from medicines taken around time of delivery (α-adrenergic agonists)	Minimize medications Minimize concentration and dosing frequency of medications Consider punctal plugs, nasolacrimal duct occlusion, or eyelid closure Stop α-adrenergic agonists as delivery approaches
Lactation	Low concentrations of β-blockers and oral carbonic anhydrase inhibitors found in breast milk Secretion of α-adrenergic agonists into breast milk unknown	Avoid α-adrenergic agonists given gravity of potential side effects Topical carbonic anhydrase inhibitors and prostaglandins likely safe

α-adrenergic Agonists

The FDA classifies brimonidine as a class B medication, although no studies in humans have been conducted to demonstrate its safety. Although brimonidine may be safe during pregnancy, it is known to cause potentially fatal central apnea in infants. It is not known whether the drug crosses the blood-placenta barrier or if it is secreted into breast milk. Brimonidine should be used with considerable caution in breastfeeding mothers or in the peripartum period.

Prostaglandin Analogues

Prostaglandin analogues are classified as class C medications by the FDA based on a high rate of miscarriage in animal studies and reports of birth defects with oral and vaginal prostaglandins.[8] Additionally, prostaglandin analogues are known to stimulate uterine contractions, which could lead to premature delivery. The likelihood of these side effects with the topical administration of these drugs, however, is unknown. In a prospective series of 10 pregnant women who used latanoprost during the first trimester, nine experienced normal delivery without any noted congenital defects, with one spontaneous abortion in a 46-year-old woman.[9] Given the theoretical risk of premature delivery associated with prostaglandin analogues, however, clinicians should consider discontinuing the agents late in pregnancy or if any signs of premature delivery arise.

Carbonic Anhydrase Inhibitors

The risks of carbonic anhydrase inhibitors (CAIs) have mostly been evaluated in studies of animals who received systemic CAIs; lower birth weights and occasional birth defects have been described. As such, oral and topical CAIs are all class C medications. No adverse effects were found in 12 pregnant women using oral acetazolamide to treat their idiopathic intracranial hypertension,[10] although one case of renal tubular acidosis was reported in the child of a woman who took oral acetazolamide during pregnancy.[11]

SURGICAL TREATMENT DURING PREGNANCY

The surgical treatment of glaucoma should be avoided during pregnancy if possible due to the risk surgical anesthesia poses to both the mother and fetus. The surgical risk to the mother increases as the fetus enlarges during the second and third trimesters of pregnancy. Supine

positioning can compress the aorta and/or vena cava and lead to hypotension. Therefore, uterine displacement should be performed as necessary. Additional risks to the mother include hypoxia, gastric acid aspiration, and increased difficulty with airway management.

In cases where the visual benefit to the mother outweighs the potential risks to the infant, intraoperative fetal monitoring should be considered for fetuses of viable gestational age. In addition, a fetal ultrasound should be performed before and after surgery to confirm the fetus' well-being.

CONCLUSION

Women of childbearing age with glaucoma who require medical therapy should be made aware of treatment issues that may arise before conception. The physician and patient should formulate a plan together to avoid or minimize the use of medications over the course of pregnancy and lactation. When choosing glaucoma medications, clinicians should take into consideration the stage of pregnancy or lactation and the FDA's guidelines. It is important to reduce the concentration or dosing frequency of medications when possible. Systemic absorption of the medications can be minimized with nasolacrimal duct occlusion, eyelid closure, or punctal plugs. ■

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