

Management of glaucoma in pregnancy – balancing safety with efficacy

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Abstract: Glaucoma and pregnancy is an uncommon combination, but it constitutes a very challenging situation for the treating doctor. The challenge is not only controlling the intraocular pressure and preventing glaucoma progression in the mother, but also having to deal with her mental stress and anxiety regarding the safety of her child. The situation is further worsened by the lack of definite guidelines as to how to deal with such patients. Relative rarity of glaucoma in this population restricts any large prospective randomized clinical trials or any large systematic studies. Moreover, none of the existing anti-glaucoma medications is absolutely safe in pregnancy. Current practice patterns depend on some case reports, a few observational studies and a few animal studies that attempt at determining the safety and efficacy of the available medicines. These are then prescribed on the basis of their relative safety in any particular stage of pregnancy or lactation. Newer medications that were released recently in 2018, such as Vyzulta and Rhopressa, presently have limited data to support their safety for use during pregnancy. Laser trabeculoplasty, conventional filtration surgery (of course without anti-metabolites), and minimally invasive glaucoma surgery represent a few non-pharmacological management options. Surgical procedures such as trabeculectomy and tube-shunts or collagen matrix implants, and newer minimally invasive glaucoma surgery procedures such as the gelatin stents are currently being explored and may prove to be viable solutions for severe glaucoma during pregnancy, although they too have their own inherent drawbacks. Management of glaucoma during pregnancy and lactation requires careful consideration of the disease status, gestational stage, US Food and Drug Administration classification and guidelines, and potential benefits and limitations of the various therapeutic modalities. This review focuses on the importance of a multidisciplinary team approach, starting with preconception planning and counseling, determining the treatment options depending on the stage of glaucoma and of pregnancy, and emphasizes the involvement of the patients, their obstetrician, and pediatrician through active discussion regarding the various medical, laser, or surgical modalities currently available or under exploration for use during pregnancy and lactation. The ultimate aim is to achieve an optimal balance between the risks and benefits of any type of intervention, and to customize treatment on an individual basis in order to achieve the best outcomes for both mother and fetus.

Keywords: anti-glaucoma medications, glaucoma in pregnancy, glaucoma surgery in pregnancy, iridoplasty, laser iridotomy, laser surgeries in pregnancy, laser trabeculoplasty, Rhopressa, Vyzulta, XEN Gel Implant

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Introduction

Glaucoma is a slowly progressing, potentially blinding disease, usually of the elderly population but may occasionally be seen in females of the

child-bearing age.¹ The availability of new diagnostic tools, the increased clinical awareness of the disease, along with advances in reproductive technology that enables women to conceive at

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increasingly older ages, has increased the chances of ophthalmologists facing the challenging situation of glaucoma during pregnancy.² The problem lies in the fact that glaucoma detected in the child-bearing age is likely to be a variant of pre-existing childhood glaucoma (anterior segment dysgenesis or congenital glaucoma), juvenile open-angle glaucoma (JOAG) or glaucoma secondary to uveitis, diabetes, or trauma, and these conditions are known to be mostly refractory to the conventional treatment.

The prevalence of glaucoma increases appreciably with age for all races and ethnicities. Hence data for the child-bearing age, that is from 18- to 40-years age is very scarce. In a study from Japan, the prevalence of open-angle glaucoma (defined by the presence of typical visual field defects along with corroborating optic nerve head changes) was 0.48%, 0.42%, and 0.73% among women aged 15–24, 25–34, and 35–44 years, respectively.³ A similar study in Germany reported its prevalence as being 0.16% in the age group of 18–40 years, in their primarily White-Caucasian population, with 49% being females.⁴ The relatively uncommon coincidence of glaucoma and pregnancy makes it challenging to conduct few adequately powered clinical trials or any systematic studies which need large sample size. Our current knowledge is derived only from a few published case reports and from certain observational animal studies or trials. Resultant paucity of information and lack of definite guidelines regarding the optimal medical, laser, or surgical treatments in this clinical situation, renders most ophthalmologists uncertain about their management of pregnant or breast-feeding glaucoma patients. In a survey conducted by Vaideanu and Fraser, only 26% of ophthalmologists had experience in treating pregnant women, and 31% admitted that they were not sure how to handle such cases.⁵ To deal with this problem, our present review aims at summarizing the current literature available regarding the different management options of glaucoma in the pregnant and lactating patients. We also discuss some recent updates, suggesting protocols for the judicious and timely intervention in each stage of pregnancy, starting from the preconception period, to the different trimesters of gestation, to labor then the postpartum and lactational period as well.

Pregnancy and intraocular pressure

Stormy hormonal changes known to occur during pregnancy are primarily attributed to the

fluctuating levels of certain important hormones, human chorionic gonadotropin (β -hCG), progesterone, estrogen, and other placental hormone. The decrease in intraocular pressure (IOP) that is generally observed during pregnancy is multifactorial and has been attributed to these hormonal changes as well.⁶ Anti-glucocorticoid features of progesterone negate the ocular hypertensive effect of endogenous corticosteroids and causes reduction of IOP.⁷ Estrogen has a dilator effect on the vessels by the production of mediators such as nitric oxide, prostacyclins, endothelin-I, and eicosanoids.⁸ Omoti and colleagues⁹ reported that this vasodilator effect provides a decrease of arterial pressure and thus causes a reduction of aqueous humor production. In pregnancy, there is a general decrease in peripheral vascular resistance. Therefore, episcleral venous pressure also decreases.^{10,11} Due to the increased levels of the β -hCG, progesterone, and general decreased peripheral vascular resistance in this condition aqueous humor outflow is facilitated. Hormone relaxin, released by the high levels of estrogen during pregnancy, has softening properties. It induces elastic changes in the collagen hence decreases the cornea-scleral rigidity as well as the rigidity of Schlemm's canal and the trabecular meshwork.¹² This causes a decrease in IOP by the diminished production of aqueous humor (AH) and enhanced outflow.¹³ It has been estimated that IOP diminishes gradually throughout pregnancy by up to 10%, with this reduction being most marked in the third quarter. In one study of pregnant women, the mean IOP of first trimester patients was on the average 2 mm Hg higher than that of third trimester patients.¹⁴ Qureshi and colleagues¹⁵ found that patients with ocular hypertension also had reduced IOP during pregnancy. Moreover, the reductions persisted for several months postpartum.^{16,17} Patient should be made aware of the fact that transient decrease in IOP during pregnancy or postpartum is due to hormonal changes. Hence follow-up of the patients should not be compromised at any phase. There is a general temptation to withdraw or hold anti-glaucoma medications to minimize the risks to the fetus. However, the behavior of IOP in pregnant glaucoma patients remains unpredictable. Although most patients generally remain stable during pregnancy, approximately 10% experience IOP elevation and progression of the disease.¹⁸ The only modifiable risk factor in pregnancy to stop progression of glaucoma is lowering of IOP.

Table 1. FDA classification for medications in relation to teratogenic risk.

Category A	Controlled studies show no risk. Adequate well-controlled studies in pregnant women have failed to demonstrate risk to the fetus
Category B	No evidence of risk in humans. Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative
Category C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk
Category D	Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk
Category X	Contraindicated in pregnancy. Studies in animals or human have shown definite harm to the fetus

FDA: US Food and Drug Administration.

Treatment options

Medical management

The main challenge in prescribing anti-glaucoma drugs for pregnant women is to maintain the critical balance between drug efficacy in terms of IOP control and its safety to the fetus. None of the anti-glaucoma drugs has been proven to be absolutely safe in such patients. Relative safety of these drugs has been outlined by the US Food and Drug Administration (FDA) according to the pregnancy categories (Table 1). This has been strictly on the basis of animal trials, merely extrapolating the results for clinical application on humans.¹⁹ Lack of adequately powered randomized clinical human trials in such a population limits any drug to qualify as category A at present.^{19,20} Categories B and C are comparatively safer, while category D should be avoided. Category X drugs are absolutely contraindicated due to their definite fetotoxic effect.

The FDA has amended its regulations governing the content and format of the “Pregnancy,” “Labor and delivery,” and “Nursing mothers” sections of the labeling for human prescription drug and biological products.²¹ The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling. Instead it should include a summary of the risks of using a drug during pregnancy and lactation, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. These revisions intend to facilitate prescriber counseling for these populations.

Toxicity of anti-glaucoma medications is attributed not only to the parent compound but also to the added preservative as well, the most common being benzalkonium chloride (BAK). Its concentration in anti-glaucoma medications is reported to be 0.004–0.02%, which is sufficient to cause disruption of the tear film and subsequent ocular surface disturbances.^{22,23} Animal trials have confirmed its fetotoxicity which is dose-related. Although it was not associated with any discernible visceral malformations, minor sternal defects occurred in fetuses exposed to a single dose of 100 and 200 mg/kg.²² Hence reducing topical anti-glaucoma medications to the minimum in pregnant patients is the preferred practice, and every effort should be made to minimize their systemic absorption. Type-IV hypersensitivity reaction has also been noted with BAK when used systemically.²⁴ The concentration of BAK in anti-glaucoma eye drops is miniscule compared to the animal study. Its absorption can be decreased by nasolacrimal occlusion (NLO), punctal plugging, or eyelid closure. Zimmerman and colleagues found that NLO or eyelid closure for 5 min reduced systemic absorption by over 60%; both techniques being safe, simple, and effective in minimizing systemic side effects.^{25,26} The preservative-free forms of the following anti-glaucoma medications are available and seem to be a better choice in pregnant patient than the preservative-containing compounds. Medical record documentation should be carefully maintained, and patients (mother and newborn) should be monitored by the obstetrician and the neonatologist.

Prostaglandin analogs. This class of anti-glaucoma medicines comprising of latanoprost, travoprost,

bimatoprost, and tafluprost, are basically prostaglandin-F2 analogs. They are otherwise a very effective group of topical anti-glaucoma medicines and are preferred as first-line therapy in normal glaucoma patients with raised IOP. But because they can cross the blood-placental barrier, this class of medications may stimulate uterine contractions, resulting in premature labor or spontaneous abortion. These act by binding to the prostaglandin F2 α receptor and stimulates both luteolytic activity and the release of oxytocin.²⁷ It can cause an abortion by degrading the corpus luteum, which nourishes the fetus in the womb. This contractile function has been demonstrated specifically with latanoprost, travoprost, and bimatoprost in the non-pregnant uterus in rat models, but there are no reports of premature labor in humans. This can be attributed to the remarkable difference in doses between human and animal studies. Embryocidal effect of PGF2 alpha analogues in rodent studies was elicited when administered at extremely high doses (15–97 times the human dose). Travoprost is teratogenic in rats at intravenous doses that correspond to exposure levels up to 250 times the human exposure at the maximum recommended human ocular dose.²⁸ The prostaglandin misoprostol is commonly used as an abortifacient when used within the first 10 weeks of gestation. Although the prenatal use of oral and vaginal misoprostol has been associated with birth defects like Moebius syndrome and terminal transverse limb defect, it is unclear whether the very low drug concentrations used in ophthalmic prostaglandin formulations are sufficient enough to elicit this side effect.²⁹ De Santis and colleagues³⁰ reported no adverse events on pregnancy nor on the neonate with exposure to latanoprost in a small series of 11 pregnant women. Low birth weight (LBW) was found to be more common in latanoprost-exposed babies than in the non-exposed controls; however, no other differences were observed between groups. There are no published data regarding the use of bimatoprost or travoprost in pregnancy. Still being members of prostaglandin analogues, risk of premature delivery prohibits their use in all stages of pregnancy and they belong to FDA category C.³¹ This class is considered a reasonable option during lactation though it has been shown that prostaglandin analogs are excreted in the breast milk of animals but human studies are lacking such results. Newer and modified prostaglandin-F2 analog, Vyzulta (Latanoprostene bunod 0.024%) is another option which has been approved recently.³² It is metabolized into latanoprost, a familiar and established component and a moiety that donates nitric oxide once the medication is in the eye. Latanoprost works

primarily by increasing uveo-scleral outflow, while nitric oxide increases trabecular outflow, which is a novel mechanism of action. Because of these complementary mechanisms, combining the two molecules offers favorable reduction in IOP that is even better than latanoprost alone in primary open-angle glaucoma (POAG) and ocular hypertension cases, but their efficacy and safety in pregnancy are not established.^{33,34} However, certain studies suggest that nitric oxide is an important pro-gestational molecule in normal human physiology. Hence nitric oxide donors may have a positive impact on pregnancy by enhancing fetal and uterine blood flow.²⁵ Early safety studies have demonstrated very low systemic concentrations of latanoprostene bunod. On the contrary, concentration of latanoprost acid in the commercially approved formulation of latanoprostene bunod (Vyzulta) is four-fold higher than that of latanoprost, making it a poor choice in pregnant patients. Moreover the efficacy of the former is only better than that of latanoprost by 1 mmHg. In a nutshell, Vyzulta does not seem to have any added advantage as compared to other prostaglandinoids and should be considered a member of category C.

Beta-blockers. Topical beta-blockers that are commonly used in glaucoma include timolol maleate, timolol hemihydrate, betaxolol, carteolol, levobunolol, and metipranolol. All of these except betaxolol are non-selective beta-antagonists, that is, these agents have both beta-1 and beta-2 antagonistic activities.³⁵ Betaxolol is a beta-1-selective antagonist; therefore, it avoids some of the systemic effects of the non-selective agents, although for IOP reduction, it is less efficacious than the non-selective medications.³⁶ All the beta-blockers, whether systemic or topical, reduce IOP by decreasing aqueous humor production through the inhibition of cAMP in the ciliary epithelium. Obstetricians frequently use systemic beta-blockers in managing pregnancy-induced hypertension. Many neurological complications like lethargy, confusion, and depression in the mother and growth restriction in the newborns have been reported.^{37,38}

Beta-blockers are one of the first-line treatment options for glaucoma patients, but are considered FDA pregnancy category C because of these anticipated complications.³⁹

To study the safety of topical drops in pregnancy, Ho and colleagues⁴⁰ conducted a large population-based study and concluded that although there was no significant difference in the risk of having LBW

infants in mothers prescribed beta-blockers, yet a significantly higher risk was associated with other topical anti-glaucoma medications as compared with the control group. A similar result with timolol was published by Brauner and colleagues,⁴¹ though punctal occlusion after drug instillation was instructed to all. But in contrast, Razeghinejad and Nowroozzadeh reported significant reduction in the birth weight in infants born to mothers on topical beta-blockers. However, the sample size was very small and patients were on combination therapy.⁴² Regarding cardiac complications, Wagenvoort and colleagues⁴³ reported a case of fetal bradycardia and arrhythmia while the mother was on topical timolol, but these side effects improved with reduction in the drug concentration. On the contrary, studies by Pellegrino and colleagues reported no effect of timolol on fetal heart rate. Once-daily topical timolol 0.1% gel has been suggested as a safer alternative during pregnancy.

Beta-blockers have a controversial safety profile when used during lactation, as they are actively secreted into breast milk and may have potential adverse effects in breastfed infants. According to studies by Lustgarten and Podos, the concentration of timolol in breast milk was found to be six times that of the plasma within one and a half hours after topical ophthalmic use. However, Madadi and colleagues did not report any such finding.^{44,45} Yet another study found betaxolol to be three times more concentrated in breast milk than in the plasma.⁴⁶ In conclusion, breastfed babies of mothers on beta blockers should be monitored for signs of beta blockade, especially those with pre-existing cardiopulmonary disease.

Sympathomimetics. Brimonidine tartrate is the only topical anti-glaucoma medications classified as category B.

Other counterparts like clonidine and apraclonidine are avoided as they have side effects with chronic use, such as nausea, vomiting, palpitations, and difficulty in micturition.^{47,48} Animal studies suggest brimonidine to be safer and well tolerated for use on a long-term basis. But, since it crosses the blood–brain barrier, it might cause central nervous system (CNS) depression and apnea in infants and hence should be discontinued close to the time of delivery.⁴⁹ Although considered relatively safe to be used in pregnancy, brimonidine is thought to be secreted in breast milk, so the general consensus is to avoid it in nursing mothers.

Carbonic anhydrase inhibitors. This group of anti-glaucoma medications is used widely in both oral as well as topical forms.

Acetazolamide and methazolamide are oral while dorzolamide and brinzolamide are the topical forms of CAI used for glaucoma management. Systemic absorption of the topically administered carbonic anhydrase inhibitors (CAIs) may rarely cause systemic side effects in contrast to oral administration. This is especially true in patients with chronic kidney disease, where CAI elimination may be compromised. A rare case report documented occurrence of fatigue, metabolic acidosis, and normocytic anemia with topical dorzolamide, in a patient with impaired renal function.⁵⁰ These agents are category C for use during pregnancy. While some reports suggest definite associated LBW or birth defects in animals, human studies are controversial. Sacrococcygeal teratoma and transient renal tubular acidosis have been reported in neonates with the use of oral acetazolamide during pregnancy.^{51,52} A case of normal anion gap metabolic acidosis in a premature neonate who was on topical dorzolamide, betaxolol, and latanoprost for bilateral congenital glaucoma has also been reported.⁵³ Although upon discontinuation of the dorzolamide ophthalmic solution, the metabolic acidosis gradually resolved. Thus dorzolamide was suspected to be the primary cause of a normal gap acidosis. There is no evidence of occurrence of such metabolic acidosis in neonate of glaucoma patient who were administered dorzolamide during pregnancy. An isolated incidence of limb anomalies like ectrodactyly, syndactyly, and oligodontia in a 12-year-old Saudi boy who was exposed to maternal acetazolamide (1,000 mg/day) for treatment of idiopathic intracranial hypertension (IIH) before pregnancy, during the first trimester, and throughout the pregnancy, has been found in the literature.⁵⁴ Although Falardeau and colleagues,⁵⁵ in their study on the use of acetazolamide in IIH, reported no adverse effects in any participant, but the outcome was insufficiently powered to rely on its results to conclude its use is safe during pregnancy. Owing to high incidence of limb deformities in animal studies and few case reports of limb deformities in humans as a result of fetal exposure, in our opinion this class should better be avoided in the first trimester of pregnancy. If the clinical situation warrants, the strategy should be to use topical CAI with punctal occlusion only after consulting the maternal fetal medicine experts. Patient's

should be well informed consent about the effect of these drugs. Since very low levels of acetazolamide have been reported in the plasma of infants exposed to the medication through breast milk, CAI's have been approved by the American Academy of Pediatrics for use by breastfeeding mothers, but certainly with close monitoring.⁵⁶

Parasympathomimetics. Cholinergic receptors are found on the placenta, and it is thought that they are linked to myometrial and placental prostaglandin release and regulation of placental perfusion.⁵⁷ Parasympathomimetics, or cholinergic agents, are classified as FDA category-C drugs. Although Kooner and colleagues did not find any association between congenital abnormalities and the use of topical cholinergic agents during the first 4 months of gestation in humans, they are generally avoided in pregnancy due to poor tolerance and documented teratogenic effects in animals.^{58,59} There are reports of hyperthermia, seizures, or restlessness in neonates, and therefore, these medications are generally avoided in the postpartum period.

Rho-kinase inhibitors. This new class of anti-glaucoma medication which has recently been introduced and is thought to have distinctive mechanisms of action, the most common being an increase in trabecular meshwork aqueous outflow, has gotten FDA approval.⁶⁰ The small guanosine triphosphatase RhoA/Rho-kinase cascade has been implicated in uterine contraction and evaluation of rho-kinase inhibitors in mice model has suggested its tocolytic effects.⁶¹ During the development of Rhopressa (netarsudil) (Aerie Pharmaceuticals, Irvine, CA, USA), a novel rho-kinase inhibitor, testing revealed no clear teratogenicity when used at physiologic concentrations in animal studies.⁶² However, in view of the diverse targets of action, the possibility of fetal malformations or demise cannot be overlooked.⁶³ The lack of enough data of use in humans eyes, and owing to the potential teratogenic risks, netarsudil should be avoided in pregnancy, especially the first trimester (Table 2).⁶⁴ Also, its safety during breastfeeding is not clear.

Laser management

Laser surgery seems to be a safer option of managing glaucoma during pregnancy in terms of safety to the mother as well as the fetus. Being non-invasive, no infiltration anesthesia is needed, and hence there is no risk of their systemic toxicity.

Laser procedures are done in sitting position so risk of postural hypotension due to venacaval compression is omitted. It can be offered as the sole therapy in case all medicines are contraindicated or ineffective, or as an adjunct to other drugs to minimize their number thereby decreasing systemic toxicity. Laser peripheral iridotomy (LPI) or laser iridoplasty are safe for the treatment and prophylaxis of acute angle closure in pregnant women. Laser trabeculoplasty can be a part of pre-conceptional planning where it eliminates the need of anti-glaucoma medicines and their side effects during pregnancy. This was suggested in a case series of selective laser trabeculoplasty (SLT) in 12 patients of child-bearing ages.⁶⁵ Argon laser trabeculoplasty (ALT) nowadays has been replaced by SLT, as the latter induces minimal thermal damage with similar efficacy.⁶⁶ Using the micropulse diode laser, the thermal spread of laser energy, and consequent coagulative damage can further be avoided.⁶⁷ One major limitation is its reduced efficacy in younger patients, as their pathology is mostly a variant of congenital glaucoma, such as Axenfeld-Reiger syndrome, Sturge Weber syndrome, Peter's anomaly or aniridia, or of JOAG that are more likely to be seen in younger women of child-bearing age and represents set of refractory glaucomas.⁶⁸ Moreover, IOP lowering with laser is not instant and takes time. Beside laser trabeculoplasty, cyclophotocoagulation with the diode laser under peribulbar anesthesia has been reported to benefit a pregnant woman with aphakic glaucoma or refractory glaucoma and could also be considered as an alternative to traditional incisional glaucoma surgery.⁶⁹

Incisional surgery in glaucoma

Glaucoma surgery is another alternative when the disease is progressive and IOP is not adequately controlled with maximum glaucoma medication or laser treatment. However, surgical intervention presents its own unique set of challenges during pregnancy, including anesthesia concerns, postural concerns, teratogenicity of antimetabolites, and postoperative medications.⁷⁰ Glaucoma surgeries are mostly done under local anesthesia, but available data show variations in safety profile. In a large multicentric trial, Heinonen and colleagues⁷¹ reported no increased incidence of fetal malformations with the use of local anesthetics, while Moore⁷² reported the occurrence of fetal bradycardia due to local bupivacaine, while lidocaine did not show any side-effects. Peribulbar or sub-Tenon lidocaine seems to be a safer option

Table 2. Adverse effects of glaucoma pharmacotherapy toward fetus and infant.

Pregnancy			Humans		
Medication	FDA category	Animals	Theoretical risk	Documented cases	Lactation
Sympathomimetics (i.e. Brimonidine)	B	No effect	Uterine hypotony/ delayed labor	None reported	CNS depression, hypotension, and apnea
Beta-blockers	C	Fetal resorption and delayed fetal ossification	Teratogenicity (in first trimester), cardiac rhythm changes, and respiratory changes	Arrhythmia, bradycardia, and impaired respiratory control in newborn	Controversy over concentrations in breast milk. Can cause apnea and bradycardia
Topical CA Inhibitors	C	Decreased weight gain and vertebral body malformation	Low birth weight, metabolic acidosis, and newborn lassitude	None reported	None reported
Systemic CA Inhibitors	C	Forelimb anomalies	Limb malformations	One case of teratoma	None reported
Prostaglandin analogs	C	High incidence of miscarriage	Uterine contraction	One case of miscarriage	None reported
Parasympathomimetics	C	Teratogenic	Teratogenicity and dysregulation of placental perfusion	Meningism in the newborn	Seizures, fever, and diaphoresis
Prostaglandin β nitric oxide (i.e. Vyzulta), teratogenic		Fetal resorption, high incidence of miscarriage	Uterine contraction or Uterine hypotony/ delayed labor	No data	Unknown concentration in breast milk. Likely very low
Rho kinase inhibitors (i.e. Rhopressa)		None reported	Undetectable to very-low systemic concentrations Uterine hypotony/ delayed labor	No data	Unknown concentration in breast milk. Likely very low

CNS: central nervous system; FDA: US Food and Drug Administration.

during pregnancy, but surgery should preferably be deferred in the first trimester. With increasing gestational age, the weight of the fetus increases and lying supine for any surgery induces profound hypotension through compression by the heavy uterus of the aorta and/or vena cava, resulting in maternal hypotension and compromise of the fetal circulation. There can also be problems related to gastroesophageal reflux and difficulty in intubation due to increasing maternal and fetal weight with increasing gestational age. Hence, the second trimester is relatively safer for surgical intervention. The antimetabolites mitomycin-C (MMC) and 5-Fluorouracil (5-FU), which are commonly used adjuncts for glaucoma filtering procedures, are FDA category-X owing to their

teratogenic potential and hence contraindicated in pregnancy.⁷³

With the advent of newer minimally invasive glaucoma surgical (MIGS) devices and techniques, the scope of surgical glaucoma treatment has increased and can even be extended for pre-conceptional planning. The advantages of shorter operating time and smaller incisions make procedures such as ab-interno trabeculotomy, trabecular meshwork bypass devices, and gel stents worth considering. Only one case of XEN Gel Stent (Allergan, Irvine, CA, USA) implantation without antimetabolite has been reported, with favorable IOP reduction when used bilaterally in a sequential fashion for a pregnant patient with

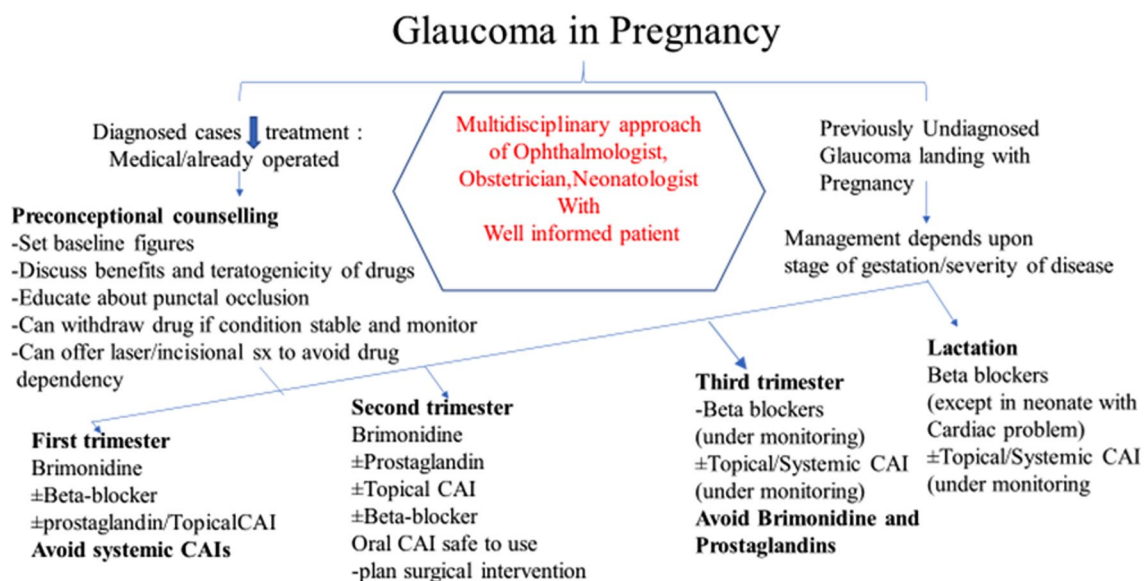


Figure 1. Systematic approach for managing glaucoma in pregnancy.

glaucoma.⁷⁴ These procedures are typically not time-consuming, spare the conjunctiva for additional surgery postpartum if needed, and are minimally invasive due to a smaller corneal incision, which could be sutured if necessary, in anticipation of the labor-induced positive pressure.

Successful outcomes were reported recently in a case series of pregnant patients with JOAG, who were managed surgically during the second trimester with bilateral procedures of orphan trabeculectomy or with drainage devices, either Ahmed glaucoma device (New World Medical, Rancho Cucamonga, CA, USA), or Baerveldt glaucoma device (Johnson & Johnson Surgical Vision, Santa Ana, CA, USA).⁷⁵ In view of pregnancy, the choice of trabeculectomy *versus* Ahmed or Baerveldt needs certain considerations. Ideally, for such patients, rapid and sustained IOP reduction is needed, in order to reduce or discontinue altogether anti-glaucoma medications postoperatively. It is well known that there is a significant risk of IOP elevation during the hypertensive phase following Baerveldt implantation with tube ligation, as well as with other tube-shunt procedures.^{76,77} Trabeculectomy with nonpharmacologic adjuvants provides an alternative for pregnant patients undergoing this procedure.⁷⁸ In a case report of a pregnant patient with iridocorneal endothelial (ICE) syndrome-associated glaucoma, trabeculectomy with Ex PRESS mini-shunt (Alcon Laboratories Inc, FortWorth, TX,

USA) and Ologen Collagen Matrix (Eon Astron Europe, the Netherlands), implantation was done. At 6 months, IOP was 9 mmHg with no need for hypotensive treatment. The cornea was transparent, and the patient maintained her left eye visual acuity. It was concluded that Ex-PRESS mini-shunt can be considered a surgical option for ICE syndrome.

Stage-wise management plan

Preconception counseling

Women of the child-bearing age who give a history of glaucoma most likely will already be on anti-glaucoma medications (Figure 1). There are chances that they might have undergone trabeculectomy/trabeculectomy or both in one or both eyes since this category of patients mostly have pathology which is a variant of childhood glaucoma. Here comes the importance of proper counseling of the patient regarding the benefits and risks of anti-glaucoma medications on the fetus, the importance of punctal occlusion, the establishment of a baseline IOP and visual field examination, the effect of pregnancy per se on IOP, and the need for frequent follow-ups. This will ultimately help in determining the best possible course of management of glaucoma during pregnancy. The situation becomes difficult when the pregnancy is unplanned or undiagnosed, as it exposes the fetus to the risk of teratogenicity

Table 3. Stage wise choice of anti-glaucoma medicines.

Medication	First trimester	Second trimester	Third trimester	Lactation
Brimonidine	First line		Discontinue in late phase	
Beta-blockers	First line/ second line	Second line	Continue, close monitoring fetal growth, and HR	First line (but avoid in heart disease)
Prostaglandins	Third line	Second line		First line
Topical CAIs	Third line	Second line	Continue, monitoring for neonatal acidosis	First line
Systemic CAIs	Limited time, for acute need only	PRN uncontrolled on topical therapy		First line

CAI: carbonic anhydrase inhibitor; PRN: pro re nata.

caused by anti-glaucoma medicines, the first trimester being the period of organogenesis.⁷⁹ If the glaucoma is well controlled, one can afford to discontinue medical treatment and observe for any changes during the course of pregnancy, or else the number and frequency of medications may be reduced. This stage is ideal for any intervention, either laser trabeculoplasty or surgical intervention in uncontrolled cases, as part of preparing the patient for pregnancy.

First trimester

The first 8 weeks of pregnancy are very crucial, as they constitute the phase of organogenesis and high susceptibility to drug teratogenesis. If pressure can be kept under control without treatment during this critical period, close monitoring of the IOP and visual fields would be the ideal approach. We believe, after baseline investigations, follow-up protocol should be followed at least once in every trimester in mild to moderate cases. But in advanced glaucoma cases, it should be more frequent preferably monthly if possible. Should medical treatment become inevitable, brimonidine, a category-B drug, is the safest option as a first-line drug. Beta blockers may be added, if need be, although they fall into category C, and they may also be used as first-line along with brimonidine (Table 3).

The prostaglandin misoprostol is commonly used as an abortifacient when used within the first 10 weeks of gestation. To date, only a single case of miscarriage in the setting of latanoprost exposure has been reported. So being a pregnancy category-C drug, it is not recommended routinely, but can be prescribed as a third-line drug, as part of maximal medical therapy. The status of topical

CAI's is similar to that of PG analogs as third-line drugs. With all categories of drugs, it is always safer to practice punctal occlusion. However, systemic CAI's with well-documented teratogenic effects in animal models are restricted to those patients who have an urgent need of short-term IOP reduction in the first trimester. Surgery is best avoided in the first trimester, but the consideration of surgical management in patients who may otherwise require extended treatment with systemic CAI's becomes justifiable.

Second trimester

The risk of serious fetal malformations due to medical treatment decreases in the second trimester. Brimonidine remains safe to be used as a first-line agent. Beta-blockers may be used, if needed, but while carefully monitoring fetal growth and heart rate. Prostaglandin analogues, including latanoprostene bunod, and topical CAI's may also be used, but it is probably safer to resort to them only as second-line drugs. Patients should be warned to be on the lookout for symptoms of premature labor if topical prostaglandin analogs are used. The use of systemic acetazolamide may be indicated in selected refractory or severe cases and is probably safer as compared to first trimester. This trimester is also the best phase for undergoing any surgical intervention if planned.

Third trimester

Fetal exposures during the third trimester, especially in the last half of this period, have direct bearing upon the neonatal complications after birth. Brimonidine is absolutely contraindicated late in the third trimester, for fear of life-threatening CNS

depression in the newborn. Beta blockers and CAI's are the ideal medications to be used in this period, though the former can cause fetal arrhythmias, bradycardia, hypotension, and CNS depression. It is recommended that fetal growth and heart rate be closely monitored if beta blockers are continued into the peripartum period. Case reports document incidence of metabolic acidosis in neonates with congenital glaucoma when treated with dorzolamide. However, no such complication has been mentioned when it is used during pregnancy.⁸⁰ Although the chances of fetal acidosis seem very unlikely, topical and systemic CAI's during the peripartum period should be used with utmost caution. Newer anti-glaucoma medicines, such as the PG F2 analog latanoprostene bunod and netarsudil (rhokinase inhibitor) can theoretically impair the progression of normal labor, and hence are probably better avoided in the peripartum period.

Labor

Labor-associated Valsalva, as in the process of normal delivery, seems to be a matter of concern especially in patients with advanced glaucoma, where the elevated IOP can accentuate glaucoma damage or may result in damage of thin blebs in trabeculectomy operated patients. Variations in IOP during the different stages of labor was investigated in 64 healthy females by Avasthi and colleagues,⁸¹ with the conclusion that after an initial significant increase, the IOP drops immediately after delivery and returns to pre-labor values in all patients by 72 hours. However, a more recent study by Meshi and colleagues⁸² negates any significant variation in IOP during the various stages of labor and suggests that patient positioning definitely does have an effect on IOP. But since the investigators did not measure IOP while the laboring patients were pushing and engaged in Valsalva, episodes of raised IOP and its consequent effects on the optic nerve cannot be denied in normal delivery. Condition can worsen if the labor is prolonged when C-section seems to be safer. Although it has been found that fundal pressure, in order to facilitate delivery during C-section, does cause a small increase in maternal IOP.⁸³ This is contrary to what was believed earlier, but there is no clinical evidence in support of these findings.

Lactation

Both beta-blockers and CAI's may be used during lactation, although beta-blockers are best avoided if the baby has congenital heart diseases

or any pre-existing cardiac problems. Because of their short half-lives, prostaglandins, including latanoprostene bunod, are unlikely to cause any harm in breastfed infants if applied immediately after breastfeeding. The use of topical and systemic CAI's is also thought to be safe for breastfed infants with no reported complications. Brimonidine is contraindicated during breastfeeding because of the known complications of CNS depression. Laser trabeculectomy, preferably selective laser may be considered if the IOP remains uncontrolled with medical treatment.

Conclusion

Glaucoma management in the child-bearing age group, specifically during pregnancy and lactation, is a challenge for both the patient and the ophthalmologist. Physiological changes in eyes during pregnancy provide natural protection in the majority of cases by lowering IOP, but one has to be vigilant, as some patients are always at risk of progression. In known cases of glaucoma, pre-conceptional planning widens the range of treatment options that can be offered to the patient as compared to those which can be offered to an already pregnant woman. The treatment plan depends on the stage of pregnancy, severity of the disease, and on a thorough knowledge of the safety profile of the various medical, laser and surgical options. It is sort of a tug of war between the risk of glaucoma progression and visual loss in the mother and the risk of fetal toxicity. No anti-glaucoma medication is considered absolutely safe. Therefore, every drug should be chosen considering its relative safety in accordance with the FDA pregnancy guidelines. Every effort should be made to minimize systemic absorption of medications by practicing nasolacrimal duct occlusion, eyelid closure, or punctal plugging. Filtration surgery with tube-shunts or with collagen matrix implants, minimally invasive glaucoma surgery and laser trabeculectomy have increased the feasibility of non-pharmacological management options in this set of population. With the combined efforts of the ophthalmologist, obstetrician, and the neonatologist, any treatment algorithm should be offered with the aim of minimizing potential harm to the fetus throughout gestation, along with preserving vision by controlling glaucoma progression in the mother.

Methods of literature search

In preparing this review, a thorough literature search was conducted in PubMed, Medline, the

Cochrane Library Database, EMBASE, Scopus, and Google Scholar until December 2020 using the following key words in various peer reviewed journals: glaucoma in pregnancy, anti glaucoma medications, laser trabeculoplasty, laser surgeries in pregnancy, glaucoma surgery in pregnancy, laser iridotomy, iridoplasty, cyclophotocoagulation Micropulse Diode laser, and titanium-sapphire laser trabeculoplasty. From literature search, all articles pertaining to the relevant topics were included in this review. No constraints were placed on publication date or publication journal. Only articles or abstracts in English were cited.

Conflict of interest statement

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