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# The management of glaucoma during pregnancy

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*Abstract*

*The prevalence of open angle glaucoma increases with age, being relatively uncommon under the age of 40. It may though affect women of childbearing age. Although the intraocular pressure tends to decrease during pregnancy, there are still patients that require surgical or medical treatment to prevent further glaucomatous optic nerve damage. The treatment should therefore be individualized, balancing the potential risks to the fetus versus the risk of vision loss for the mother. We must take into consideration not only the systemic side effects on the mother of both medical and surgical treatment, but also any potentially teratogenic effects on the developing fetus. No topical ophthalmic drugs are placed in category A or X. Most topical glaucoma medications are labeled in pregnancy category C. The present review summarises the therapeutic options and their potential side effects in pregnant women diagnosed with glaucoma.*

***Keywords:*** *glaucoma, anti-glaucoma medications, intraocular pressure, pregnancy*

## Introduction

The prevalence of primary open-angle glaucoma increases with age and it is a disease that is more frequent in adults over the age of 40. It may affect occasionally pregnant women, but there are no studies to date that demonstrate the frequency of glaucoma during pregnancy[1,2]. The glaucoma onset in females of childbearing age is more frequent during childhood (congenital glaucoma, anterior segment dysgenesis) or it manifests as a secondary glaucoma (associated with diabetes, uveitis). Usually these types of glaucoma are more severe and must receive a more aggressive treatment. The management of glaucoma during pregnancy presents unique challenges and requires consideration of potential side or teratogenic effects to the fetus or newborn of anti-glaucoma medication or surgery.

## Intraocular pressure changes during pregnancy

There are studies that demonstrate that the intraocular pressure (IOP) decreases spontaneous during pregnancy and stays decreased for several months postpartum[3,4]. In healthy eyes, pregnancy has been associated with a decrease of 10% in IOP[5], while in pregnant women with ocular hypertension, studies demonstrated a more pronounced decrease in IOP compared to pregnant women without intraocular hypertension[6]. The IOP declines statistically significant as pregnancy progresses (from the first to the last trimester)[6,7,8] with a lower diurnal IOP fluctuation as compared to non-pregnant women[9].

There are many mechanisms that have been proposed to explain the reasons for the IOP decrease during pregnancy. Studies have demonstrated that the formation rate for the aqueous humor does not change during pregnancy, but there is an increase in the outflow facility via the uveoscleral pathway[10-12]. Apparently, this is due to the fluctuation of the hormonal levels during pregnancy, such as estrogen, progesterone, relaxin or ß-human chorionic gonadotrophin[10,11,13,14]. Also, the slight metabolic acidosis[15] induced by pregnancy and the decreased episcleral venous pressure due to an overall reduction of venous pressure in the upper extremities could contribute to the IOP lowering during this period[16]. The physiological softening of the cornea and sclera[17] as well as the increased corneal thickness due to the increased water retention during pregnancy[5] might lead to an underestimated IOP even with 10-30 mmHg[18].

Despite all these studies that demonstrate that the IOP decreases during pregnancy, a great number of patients with glaucoma may still need treatment or we can face the progression of glaucoma in pregnant women[19]. Thus, it is very important to keep a careful monitoring on glaucoma during pregnancy because some of the patients may present with a decrease in the IOP, while other individual cases may develop glaucomatous disease progression and vision loss.

## Medical treatment

Drug treatment of glaucoma at any stage of pregnancy is controversial, thus it is important to establish a balance between the treatment's risks to the mother and the potential side effects on the fetus. It is recognized that after topical administration of eye drops (including anti-glaucoma medications), 80% of the volume drains through the nasolacrimal duct and it is absorbed systemically because of the high blood flow in this area, bypassing the hepatic metabolism[20]. Therefore, the substance can cross the placental barrier and is able to enter the fetal circulation unmetabolized (the length of fetal exposure may be much longer than in the mother because of the recirculation of fluids in the fetal system)[21]. Also, the teratogenic effects of medication are more severe if they are administered during the first 12 weeks of gestation, when the organogenesis occurs[22]. The safety of glaucoma medications in pregnancy has been classified by Food and Drug Administration (FDA) based on evidence available from human and animal studies (Table 1). Most of the topical glaucoma medications (beta-blockers, prostaglandin analogues, carbonic anhydrase inhibitors) are labeld in pregnancy category C; animal studies have shown evidence

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**Table 1** Food and drug administration drug risk categories in pregnancy

| Category | Description |
|---|---|
| A | These drugs are the safest for pregnant patients. Well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities. |
| B | Animal studies have not shown evidence of harm to the fetus and there are no adequate and well-controlled studies in pregnant patients; OR there is evidence of adverse effects on the fetus in animal studies, but studies in pregnant women have failed to demonstrate fetal risk. |
| C | Animal studies have shown evidence of harm to the fetus and there are no adequate and well-controlled studies in pregnant women; OR lack of any animal studies, and no adequate and well-controlled studies in pregnant patients. |
| D | Risk to the fetus has been demonstrated in well-controlled or observational studies in pregnant patients. However, the benefits of therapy may outweigh the potential risk. |
| X | Evidence of fetal abnormalities in well-controlled or observational studies in animals or pregnant patients. The drug is contraindicated in pregnancy. |

of harm to the fetus, but there are no adequate studies in humans. Brimonidine and dipivefrin are included in category B, which implies safety in administration based only on animal studies. None of the topical ophthalmic drugs are placed in category A or X[23].

**Beta-blockers**

They can cross the placental barrier and thus they have been associated with fetal bradycardia and arrhythmia[20]. That is why, newborns exposed in utero to beta-blockers should be closely monitoried during the first 24-48 hours after birth. There have also been reported neurologic complications of the newborn (lethargy, confusion)[24]. Furthermore, beta-blockers can be secreted into breast milk[25] with the appearance of potential systemic side effects to the breastfed infant.

**Carbonic Anhydrase Inhibitors (CAIs)**

There are no reports of any fetal complications following topical use of CAIs in pregnant women nor side effects in nursing infants. It has been demonstrated in clinical studies that the amount of systemic carbonic anhydrase inhibition caused by topical dorzolamide is insufficient to produce disturbance in hematologic an urinary tests[24].

Systemic high dose carbonic anhydrase inhibitors in rats can result in forelimb anomalies[26]. Although, there is a single case report of sacrococcygeal teratoma in a new born after the mother had been treated with acetazolamide until the 19th week of pregnancy[27].

**Prostaglandin analogues**

They represent a class of medication that is used systemically to induce labor by stimulating smooth muscle contraction. Therefore, these medication should be used with caution because it is not clear yet whether the very low concentration of prostaglandin analogues used in topical antiglaucoma formulations is considered enough to induce any side effects on the pregnancy or the fetus[28]. Taking into consideration the theoretical risk of premature delivery, the prostaglandin analogues should not be used as first line treatment for glaucoma in pregnant women.

**Alpha 2 agonists**

Animal studies have not demonstrated potential teratogenic effects to the fetus when alpha 2 agonists (brimonidine) are administred in pregnant women. However, there is a lack of well-controlled human studies to confirm this hypothesis. These drugs are secreted in breast milk[29] and central nervous system effects (apnea) have been reported in new born as the result of penetration of the blood-brain barrier[30]. Thus, if these drugs are being used as antiglaucoma treatment during pregnancy, it should be discontinued before labor and during breastfeeding to prevent potential fetal side effects[24].

## Laser trabeculoplasty

Both Argon Laser Trabeculoplasty (ALT) and Selective Laser Trabeculoplasty (SLT) may be taken into consideration in pregnant women to eliminate or reduce the number of necessary medications, without complications[31,32]. The effect of these procedures, although temporary, may be sufficient to lower the IOP to an acceptable level until the end of the pregnancy and breast feeding when other treatments become an option[22]. As far as we know, there is one study that demonstrated successful IOP lowering and the decrease in the number of anti-glaucoma medications in 40 pregnant and lactating women[32]. Unfortunately though, laser trabeculoplasty is less effective in young patients in controlling the IOP[33].

## Surgical treatment

Glaucoma surgery should be taken into consideration during pregnancy when, despite the use of maximum medications, glaucoma progresses. Even then, there are specific risks that must be considered in pregnant women who undergo filtering surgery: the risks of local or general anesthesia and the need for post-operative medications. The risk of failure for glaucoma surgery in this group of patients is higher because of the young patient age (34) and contraindicated antimetabolite usage due to their teratogeic properties[35,36]. Also, it should be considered

the patient's positioning during surgery because in the second and third trimester of gestation, the supine position which can induce profound systemic hypotension due to aortic and caval compression by the uterus.

## Anesthesia in pregnancy

When using anesthesia for pregnant women, it is important to use the minimal effective dosage and avoid unnecessary medications. Most local anesthetics are labeld in pregnancy category B (lidocaine, etidocaine), with no teratogenic effects in humans. Bupivicaine and mepivicaine are placed in category C and according to animal studies they may lead to fetal bradycardia[37]. Anterior sub-Tenon's anesthesia during glaucoma surgery is preferable to retrobulbar anesthesia because it allows less systemic absorbtion of medication. No known contraindications exist to using topical anesthetic drops in pregnancy or in mothers who are breastfeeding[24]. In cases where general anesthesia is indicated, narcotics, paralyzing and inhaling agents can influence fetal development[38].

## Postoperative medications

Topical antibiotics are commonly used after glaucoma surgery. Erythromycin is placed in category B of pregnancy and it is considered of first choice in pregnant and breastfeeding women[38]. Tetracyclines and aminoglycosides are labeld in category D (they cross the placenta quickly), fluoroquinolones are classified as category C medications and chloramphenicol is contraindicated because it has been linked with the gray baby syndrome[38,39].

Corticosteroids, used almost always after glaucoma surgery, are classified as category C medications. When administred systemically, they cross the placenta, but with topical administration, they may be prescribed during pregnancy with no known side effects[40].

Atropine, occasionally used postoperatively in glaucoma surgery, is placed in pregnancy category C. When administred systemically, it may affect fetal heart rate, though the effect may be less likely with ophthalmic dose[38].

## Conclusions and future research

Management of glaucoma during pregnancy presents unique challenges. Although the IOP tends to decrease during pregnancy, there are still patients that require surgical or medical treatment to prevent further glaucomatous optic nerve damage. The treatment should therefore be individualized, balancing the potential risks to the fetus versus the risk of vision loss for the mother. Though, it is better to use the minimal effective dosage of medication and precautions to limit systemic absorption after topical administration: eyelids closure, nasolacrimal occlusion or blotting excess drops away during administration. Also, a multidisciplinary approach is needed, in collaboration with the obstetrician, to ensure the safety of the mother and the fetus.

Until present, only few studies have approaches the management of glaucoma during pregnancy and there is still a lack of meta-analyses and randomised controlled trials in this area. Most of the available evidence is based only on individual case reports and animal studies. ■

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