Review Article

Glaucoma Management During Pregnancy and Lactation

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Abstract

Glaucoma is a chronic, progressive disease of advancing age which is relatively uncommon in childbearing age. However, with increasing professionalism among women, late pregnancies are becoming more common. This combined with early onset of ageing diseases in India, including glaucoma, more and more cases of glaucoma are being seen among pregnant women. Management of glaucoma in and around pregnancy is a unique challenge of balancing the risk of vision loss to the mother as against the potential harm to the foetus or newborn. During pregnancy, there is physiological reduction in intraocular pressure (IOP). However, some women with pre-existing glaucoma have elevated IOP requiring enhanced medical treatment. The only anti-glaucoma medication categorized in Category B is brimonidine, all others being in Category C. Laser trabeculoplasty is an alternative treatment that can be performed in all trimesters. In selected pregnant glaucoma patients with medically uncontrolled and progressive glaucoma, surgery with caution may lead to good outcomes for the patient with no additional risk for the foetus, especially in second trimester. Beta blockers and carbonic anhydrase inhibitors are preferred for use during lactation when brimonidine is an absolute contraindication due to its ability to cross blood brain barrier. Possible options for glaucoma management and their risks should be discussed with pregnant and lactating patients and optimum treatment given so as to prevent any further deterioration in progressive vision loss and quality of life.

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Introduction

Glaucoma, primarily a disease of the older population, may affect women of childbearing age. Although Quigley and Broman in 2006 estimated that by 2020 women will comprise 59 % of all glaucoma patients (55% POAG and 70 % PACG), studies on Indian population speak differently.[1] A population based study on Indian Singaporeans in 2013 reported incidence of glaucoma to be 2.58% among males and 2.01% among females.[2] Similarly, Paul et al, in 2016, in a population survey, found that among patients 'of glaucoma - 53.42 to 55.31% were males.[3] In pregnant women, incidence of glaucoma is increasing due to the growing tendency to start families late and with advances in medical and obstetric care ensuring safe birth in older and career conscious women. With increasing awareness and due to availability of new diagnostic techniques, glaucoma is being detected early as well. Most of these women are 'un-aware' of the possible risk of birth defects associated with anti-glaucoma drugs leading to reduced adherence during pregnancy. Although intraocular pressure (IOP) is known to reduce, physiologically during pregnancy, in some cases it can increase, necessitating enhanced medical, laser, or surgical intervention.[4-6] Treating glaucoma during the patient's pregnancy and lactation requires weighing the potential benefits of therapy and the visual goals of the mother against the risks of treatment to the foetus or infant. Due to ethical and legal constraints on conducting clinical trials in these groups, there is paucity of literature and there are no evidence based guidelines for managing this clinical situation. In this review, we aim to collect the array of available data from observational studies and case reports to provide the reader with guidance and context for the safety of glaucoma management during pregnancy and lactation.

Medical Management

The FDA has classified drugs according to their safety in pregnancy as under:[7]

- 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
- Category X- drugs with known risks to the foetus that cannot be outweighed by possible benefits.

Prostaglandin Analogues

Prostaglandin analogues such as latanoprost, bimatoprost, travoprost and tafluprost reduce the IOP by increasing the uveoscleral outflow. They are classified as category C drugs. Being oxytocic, they can increase the uterine tone and stimulate uterine contractions producing premature labor.[8-11] Latanoprost exposure has not been associated with any increased risk of congenital malformations or spontaneous abortion during pregnancy but low birth weight was found to be common in these babies than the non-exposed ones.[9] There are no published data regarding the use of bimatoprost, travoprost or tafluorost in pregnancy.

Latanoprostene bunod 0.24% (Vyzulta) is a new prostaglandin analogue with no human data. However in rabbits, fetal toxicity was noted starting at intravitreal dose of over 0.28 times the clinical dose. It is classified as category D drug.[12]

Beta Blockers

Oral beta blockers are categorized as class C medications in pregnancy. No categorization is available for topical medications. Topical beta blockers like timolol, betaxolol, carteolol, levobunol and metipranolol decrease the IOP by

reducing the aqueous humour production. A population based study of 244 pregnant women on topical antiglaucoma medications showed that the risk of low birth weight infant was higher in mothers using anti-glaucoma medication other than beta blockers.[13] Topical beta blockers can be considered as the first line drugs in the medical treatment of glaucoma in pregnant women. Systemic use of beta blockers close to delivery may results in foetal and neonatal bradyarrythmia, hypotension and hypoglycaemia.[14,15] Respiratory distress and apnoea have been reported following in-utero exposure. Neonatal symptoms due to the beta blockers are usually mild and resolve within 48 hours. However, none of the side effects have been reported with low dose timolol 0.1% in gel formulation. In contrast to adults, this group of drugs is more effective than PG analogues among children.

Alpha adrenergic agonists

Brimonidine is the only ocular hypotensive drug which is classified as category B medication by FDA and is, thus, considered safe in pregnancy. However, it causes central nervous system depression and apnoea in the newborn as it crosses the blood brain barrier and possibly secreted into the breast milk thereby posing substantial risk to the neonate.[16,17] It is contraindicated in infants and children upto 10 years of age because of the propensity of systemic side effects.

Carbonic anhydrase inhibitors

Dorzolamide and brinzolamide are classified as category C drugs. There were malformations of the vertebral bodies in rabbits exposed to dorzolamide during pregnancy, suggesting that brinzolamide may be a better alternative.[18] No controlled reports of brinzolamide or dorzolamide exist in human pregnancy. Studies showed that oral carbonic anhydrase inhibitor acetazolamide is associated with sacrococcygeal teratoma and renal tubular acidosis in neonates.[18,19] They resulted in forelimb anomalies in rats suggesting a possible teratogenic effect.[20-22] Oral acetazolamide is better tolerated in children than adults, however, long term usage can cause growth retardation.[23]

While in first trimester, oral CAIs are absolutely contraindicated, in second and third trimester, they can be used with caution after assessing the risk versus benefit ratio, for IOP not amenable to treatment with topical medications.

Rho kinase Inhibitors

Netarsudil 0.2% is a new category of anti-glaucoma medication. This drug has not been classified yet because of lack of clinical studies. In rabbits, 214 fold the human clinical dose did not cause any adverse events to the foetus. There are no human studies.

Parasympathomimetics

These medications are categorized as group C by FDA for use in pregnancy. Although pilocarpine and carbachol have demonstrated teratogenic and adverse foetal effects in animals, the use of systemic cholinergic drugs found no association between their use during the first four months of gestation and congenital abnormalities. 241 When given near the term, they have been associated with neonatal hyperthermia, restlessness, seizures, diaphoresis and mimicked the signs of meningitis.[25,26]

Osmotic Agents

The osmotic agents viz. mannitol and glycerol have been assigned category C. There are no animal or human studies in pregnancy.

Preference of drugs according to the stage of pregnancy

First trimester

Brimonidine, a category B drug, may be the safest option for the first trimester. Other antiglaucoma medications such as beta blocker, carbonic anhydrase inhibitors and prostaglandins should be avoided in the first trimester to reduce potential teratogenic effects or premature abortion.

Second trimester

Brimonidine can be given and beta blockers can be used with regular foetal heart rate and growth monitoring. Brinzolamide, PGAs and pilocarpine may also be used as second line drug with due cation and monitoring.

Third trimester

Brimonidine, beta blocker or topical carbonic anhydrase can be used with caution. Towards late in third trimester, brimonidine should be discontinued because it can induce central nervous system depression in newborn. Topical carbonic anhydrase inhibitors may be optimal in this period. Prostaglandins should be avoided because of the risk of inducing uterine contraction and labour.

Post partum

Brimonidine is contraindicated for lactating mothers. Beta blockers and carbonic anhydrase inhibitors are certified by the American Academy of Paediatrics as safe during nursing.[27]

Role Of Lasers

Laser trabeculoplasty may be a reasonable alternative management if allowed by the morphology of the angle. Selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT) are equally safe and effective. These can be used in all trimesters. However, benefits of Laser trabeculoplasty are short lived in the form of IOP control. But, they will generally be efficacious until the end of pregnancy and lactation.

Selective laser trabeculoplasty (SLT): The intracellular micro-disruptions caused by this technique are confined to the targeted cells. The laser pulses are so temporary that heat caused within the targeted cells does not spread to the surrounding tissue.[28] As a result, this procedure can be repeated as well, if required. If available and anatomically feasible, this can probably become the most accepted first line treatment during pregnancy and lactation.[29]

Surgical Management

In any female with advanced glaucoma and elevated pressures despite multiple medications, serious consideration should be given to surgery before conception because pre-existin glaucoma can worsen despite medical and laser treatment During pregnancy, surgery is best avoided as it has potential risks for both the mother and foetus. The challenges include

problems with anaesthesia, positioning for surgery, potential risk with antimetabolites and concerns with the management of postoperative complications.

Altered maternal physiology predisposes pregnant women to hypoxia, hypercapnia, and systemic hypotension, which exposes both mother and foetus to the risk of anaesthesia, more so general anaesthesia. Most local anaesthetics are not teratogenic in humans and are considered relatively safe for use during pregnancy.[30] According to FDA's classification, etidocaine, lidocaine, and prilocaine are categorized in group B while bupivacaine and mepivacaine are placed in group C as they can induce foetal bradycardia. Placental transfer of anaesthetic agents such as narcotics, paralyzing agents, and inhalational agents can cause foetal cardiovascular and central nervous system depression. Reports have shown an increased incidence of low birth weight and neural tube defects with exposure to general anaesthesia in the first trimester.[31] Subconjunctival and anterior sub-tenon anaesthesia combined with a topical anaesthesia for glaucoma surgery may be well tolerated and may allow a less systemic absorption of the medication than a retro bulbar/ peri-bulbar anaesthesia.

It is desirable to defer surgery until the second trimester of pregnancy to reduce the foetus' exposure to the minimum to these potentially teratogenic anaesthetic agents. The supine position in the second and third trimesters of gestation can induce profound systemic hypotension due to aortic and vena caval compression by the conceived uterus. Intraoperative foetal heart rate monitoring using non stress test (NST) could also be done to prevent foetal complications during surgery. As chances of gastroesophageal reflux are high, full stomach should be avoided during surgery under any kind of anaesthesia. There is increased risk of thromboembolic disease during pregnancy. Thus, pregnant patients undergoing longer procedures, like tube surgeries, may benefit from graduated compression stockings or pneumatic compression devices.

Filtration surgery may be at relatively higher risk of failure because of young age, physiological changes during pregnancy and contraindicated antimetabolite usage (both mitomycin C and 5-fluorouracil, are in category X and contraindicated in pregnancy). Using biodegradable, implantable, porous collagen matrix (Ologen) sub-conjunctivally could be an option to modulate wound healing. The presence of tissue oedema, possibly due to hormonal changes, makes scleral and conjunctival suturing difficult. This is likely to affect postoperative tissue healing and bleb morphology. Releasable sutures are preferable for controlled filtration and IOP management in the postoperative period. Valved glaucoma drainage devices seem to be a reasonable alternative to treat refractory glaucoma during pregnancy. Newer minimally invasive glaucoma surgery (MIGS) procedures may also become safer and effective alternative for pregnant patients in future.[32]

Post-Operative Precautions

Topical antibiotics should be used judiciously during post-operative period. Cephalosporins and Penicillin group of drugs fall in category B of US-FDA and are considered safe in pregnancy.[33] Given the absence of clear complications associated with topical steroids, they can be used in pregnant women. Prednisolone and methylprednisolone cross the placenta less than betamethasone and dexamethasone and may have less effect on the foetus. Homatropine hydrochloride 2% eye drops can be used as its ophthalmic dosage is less likely to affect the foetus. Atropine should be avoided as it can cause foetal bradycardia. All topical medications, including ocular hypotensives, should be prescribed with punctal occlusion and eyelid closure to reduce systemic absorption. Patients should be advised to avoid blinking immediately after the instillation of eye drops as blinking can activate the lacrimal pump action and increase systemic absorption.

Summary

To choose to start families later in life is now commonplace for women. Thus, the frequency of glaucoma around pregnancy is on the rise. Physicians should initiate discussions with all women of child-bearing age requiring medical treatment for glaucoma, as women may not always inform their ophthalmologist about their desire to become pregnant. Careful consideration of foetal health in the management of glaucoma during pregnancy and lactation is best done as a part of a multidisciplinary team including obstetrics and neonatology. When medication is necessary, selection of safest agent, using minimal effective dosage and duration and steps to minimize systemic absorption should be employed. Laser trabeculoplasty appears to be safe and effective for lowering the IOP during pregnancy and is a good alternative or adjunct to medications. Surgery, if required, is best performed before planning family. However, those who require surgical management, during pregnancy, second trimester is the safest. The patient may be involved in the therapeutic decision-making process and it is important to emphasize the lack of definitive studies.

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