Use of ophthalmic medications during pregnancy

Key words: Administration, oral; Anti-bacterial agents; Ophthalmology; Pregnancy complications, infectious/ drug therapy; Teratogens

Objectives. To review potential risks of eye medications to the mother and her foetus.


Study selection. All types of publication that documented potential risks of eye medications during pregnancy. The following key words were used: pregnancy, fetus, teratogenicity, eye, ocular, ophthalmic, glaucoma, antibiotics, anti-inflammatory, and corticosteroids.

Data extraction. All relevant articles including original articles, review papers, case studies, and relevant book chapters were extracted and reviewed.

Data synthesis. Whether ophthalmic medications can be used during pregnancy is a very important issue; yet, limited information on the subject exists in the literature. Topically applied eye medications that give rise to systemic side-effects are of particular concern to both patients and doctors. Various ophthalmic anti-infective preparations and ophthalmic corticosteroids have shown to cause teratogenicity in animal studies. Furthermore, anti-glaucoma drugs pose potential risks to the foetus if they are absorbed systemically. This article examines the association between the main groups of ophthalmic medication and their possible adverse effects on the mother and the foetus. Recommendations for the treatment of pregnant patients with eye diseases are also discussed.

Conclusion. The risk of giving ophthalmic drugs to pregnant women is low. Doctors should be cautious when prescribing drugs for pregnant women and consult experts in the field when in doubt.

Introduction

“Doctor, I am pregnant. Can I still use this eye drop?” This is probably one of the most common questions asked by pregnant women when they visit not only their ophthalmologist, but also their obstetrician or even family physician. Perhaps it is also one of the few questions that doctors of various specialties might have difficulty in answering, especially when they have to present evidence to convince their patients.

Limited data have been published regarding the potential risks of eye medications to the mother and the foetus. This article summarises the main published...
findings to provide physicians with a brief guide on the use of common eye treatments during pregnancy. We conducted a PubMed search from 1966 to 2003, using the following key words: pregnancy, fetus, teratogenicity, eye, ocular, ophthalmic, glaucoma, antibiotics, anti-inflammatory, and corticosteroids. Two search formulas were used: the first was (ophthal* OR ocular OR eye*) AND (pregn* OR foetus OR teratogen*) AND (group name of drug or name of individual drug), and the second was (name of eye disease) AND (treat* OR manage*) AND (ophthal* OR ocular OR eye*). Additional information sources were obtained from the bibliographies of the selected articles.

This article covers five important groups of eye medication: anti-infection preparations, anti-allergy preparations, anti-inflammatory preparations, corticosteroids, and anti-glaucoma drugs. Within each group, specific drugs are highlighted to describe their documented risks during pregnancy.

Anti-infection preparations

Topical chloramphenicol is used widely to treat superficial eye infections because of its broad spectrum of effectiveness and low cost. Many concerns, however, have been documented about this drug’s serious side-effects—namely aplastic anaemia and ‘grey baby’ syndrome (a potentially fatal condition seen in neonates due to reaction to chloramphenicol, characterised by an ashen grey cyanosis, weakness, and hypotension). A review article in 2002 concluded that the risk of these serious side-effects is low and they are unlikely to occur if patients adhere to the prescribed dose and duration of treatment. Furthermore, expert opinion suggests that chloramphenicol is safe to use during pregnancy as long as treatment is stopped at the time of delivery. A case-control study also showed that chloramphenicol poses minimal teratogenic risk to a foetus whose mother has received the drug orally, even during early pregnancy.

Quinolone, gentamicin, and erythromycin are very important ophthalmic antibiotics that are used against various infective eye diseases. There is no conclusive evidence to prove that the use of these drugs contributes to an elevated rate of congenital abnormality or foetal death.

The antiviral drug acyclovir is indicated in herpes simplex infections, such as herpetic keratitis and dendritic corneal ulceration. In animal studies, the use of acyclovir was not associated with any teratogenic effects. Acyclovir is generally well tolerated in pregnant women. Treatment with clinically recommended doses have low toxic potential, and no adverse effects have been reported regarding its use during pregnancy.

Toxoplasmosis is an infection caused by the intracellular protozoan *Toxoplasma gondii*. Acute toxoplasmosis during pregnancy can cause stillbirth, severe mental retardation, and ocular disorders in newborn infants. Treatment of the mother aims at preventing foetal infection by reducing the incidence of maternal-foetal transmission of the infective organism. The classic therapy for ocular toxoplasmosis includes the use of pyrimethamine and sulfadiazine. However, pyrimethamine is potentially teratogenic and may lead to bone marrow suppression. Spiramycin is recommended as a safer alternative during pregnancy because of its very low risk of toxicity to foetuses. In a review study, an antibiotic regimen of pyrimethamine and sulfadiazine was as effective in preventing neonatal infection as was continuous treatment with spiramycin alone. Nevertheless, pyrimethamine remains the most commonly used drug in toxoplasmosis management. When this drug is administered, some doctors monitor closely the level of drug in the blood and prescribe folic acid to prevent or reduce its haematological toxicity. Some doctors prefer to refer pregnant women with ocular toxoplasmosis to specialists in that area for treatment.

Anti-allergy preparations

Drugs against allergies are used to treat inflammatory and allergic conjunctivitis. In general, information on ophthalmic antihistamine use during pregnancy is very limited: no epidemiological studies of the effect of this group of drug in human pregnancy have been performed. Similarly, we found no studies on the teratogenic risk posed by the use of an ophthalmic antihistamine during pregnancy. The use of this group of ophthalmic drugs during pregnancy is probably safe.

Anti-inflammatory preparations

Systemic administration of cyclosporin A is commonly used to treat corneal graft rejection and autoimmune uveitis. Because repeated systemic administration of this drug can lead to serious side-effects, such as nephrotoxicity and hypertension, topical therapy is expected to be much safer. Topical cyclosporin A therapy is effective in treating dry-eye syndrome and various immune-related corneal disorders. Corneal deposition and a burning sensation in the conjunctiva have been reported after the use of topical cyclosporin A. Potential adverse effects include foetal growth retardation, foetal prematurity, and congenital malformation. Hence, the use of anti-inflammatory drugs during pregnancy has to be monitored carefully to avoid these adverse outcomes.

Corticosteroids

Topical corticosteroids, such as prednisone and dexamethasone, are effective in the management of red eyes of inflammatory origin. However, they should be given under expert supervision because of serious side-effects,
such as aggravation of herpetic infections, steroid-induced glaucoma, and steroid-induced cataract. Large-scale epidemiological studies have found a positive association between the systemic use of corticosteroids and non-syndromic orofacial clefts. In 1999, the California Birth Defects Monitoring Program described the association between the use of corticosteroids and the delivery of infants with orofacial cleft, conotruncal heart defects, and neural tube defects. Furthermore, multiple types of foetal teratogenicity have occurred during the use of various ophthalmic corticosteroids in rats. Fortunately, no published study has found an association between the administration of ophthalmic corticosteroids and human teratogenicity. The lack of such an association is probably because of the low dosage and small amount of drug used during its ophthalmic application.

**Anti-glaucoma medications**

- **β-Blockers**, such as timolol, can reduce the production of aqueous humour and hence decrease the intra-ocular pressure. A review suggested that β-adrenergic tone affects the foetal heart rate and that β-blockers are potentially harmful to the developing foetus. In 1979, the use of timolol and its association with an episode of apnoea in an 18-month-old child was described. More recently, a case report found a weak association between maternal topical timolol therapy and foetal cardiac arrhythmia. β- Blockers should be avoided during pregnancy, especially in the first trimester, when the risk of teratogenesis is highest. Because of drug passage through the nasolacrimal duct to the nose, the ocular application of timolol will lead to absorption through the nasopharyngeal mucosa and produce a systemic effect, especially if timolol is used in combination with other β-blockers or if a high dose is used.

Acetazolamide is a carbonic anhydrase inhibitor that is used to reduce intra-ocular pressure by reducing aqueous humour production in patients who have glaucoma. In a 1978 report, neonatal teratoma was found to be associated with maternal use of acetazolamide. In 1989, a newborn infant developed metabolic acidosis, hypocalcaemia, and hypomagnesaemia because the mother had been treated with acetazolamide, pilocarpine, and timolol for glaucoma throughout her pregnancy. The blood concentration of acetazolamide is related to the serum carbon dioxide level and chloride ion concentration—which are indicators of metabolic acidosis—especially if patients have renal dysfunction. In 2000, there was another reported case of the transplacental passage of acetazolamide that led to neonatal renal tubular acidosis during the treatment of maternal glaucoma. It has been recommended that the acetazolamide concentration in the blood be monitored as a means of preventing overdose and serious side-effects.

Travoprost is a prostaglandin analogue that reduces intra-ocular pressure by increasing the uveoscleral outflow. The widespread use of prostaglandin to induce labour, terminate pregnancy, and regulate menstruation has raised concerns of its use in pregnant women. In fact, travoprost is a prodrug that will hydrolyse in the cornea to become fluprostenol—a type of prostaglandin that is highly selective for F₂α receptors, which is used to induce abortion in animals by causing uterine smooth muscle contractions. However, some experts have claimed that latanoprost and travoprost have insufficient active ingredients to cause adverse effects on the foetus. Others believe that the use of prostaglandin is generally contra-indicated in pregnant women.

Because there have been many concerns about medical therapies for glaucoma in pregnant women, one may consider the possibility of surgical treatment, especially for expectant mothers or women planning for pregnancy who have marginal control of glaucoma. However, one must also bear in mind the additional risks of glaucoma surgery in pregnant patients, such as the use of local anaesthetic, postoperative medications, and supine positioning, which may increase the risk of aortic and vena caval compression by the uterus in the second and third trimesters, as well as gastro-oesophageal reflux and its associated complications. Instead of surgery in which the patient is in a supine position, a laser procedure can be considered for suitable cases. The advantage of laser treatment includes its nature as an out-patient procedure, the use of only topical anaesthesia, sitting in an upright posture, faster rehabilitation, and the reduced need for postoperative medication both in dosage and duration.

**Discussion**

To understand about drugs used in ophthalmology and their adverse effects during pregnancy, we must examine the physiology and anatomy of the eye and the pharmacokinetic profiles of these drugs.

The response of the patient to drugs will depend on the concentration of the drug used at the site of action. The corneal epithelium acts as a barrier to the penetration of topical drugs into the eye. Absorption of drugs depends on their solubility: lipophilic substances seem to penetrate readily into the corneal epithelium. Additionally, repeated application of topical eye drops could result in a high intra-ocular level of drugs. To balance the adequacy of drug penetration and the risk of systemic absorption, patients should be instructed to apply only one drop of topical eye medication at one time per squeeze of a bottle. One of the reasons is that the fornix of the lower eyelid can hold only one drop of topical medication, that is, approximately 0.05 mL.

Drug administered topically will drain into the nasolacrimal duct and be absorbed through the epithelial mucosa lining into the systemic circulation. Because punctal patency requires open eyelids, gently closing the eyelids for
1 to 2 minutes may slow down the rate of drainage. The use of nasolacrimal compression through digital pressure over the medial part of the lower eyelid also minimises systemic drug absorption and should be recommended in pregnant women to ensure that the drug is administered at the minimal effective dose.  

Conclusion

Although the topic of this article provides a practical overview for pregnant patients and their doctors, little has been published to evaluate the true risk in the use of eye medications during pregnancy. Several reasons may account for this lack. Firstly, few pregnant patients attribute significant adverse effects on the foetus to the topical administration of ophthalmic medications. Secondly, large-scale population surveillance is needed to detect drug teratogenicity. Finally, researchers may not be willing to invest funds in research that will most likely give a negative association between the two variables studied. Nevertheless, doctors should always be particularly careful when prescribing drugs to pregnant women.

The overall level of evidence for the risk of giving ophthalmic drugs to pregnant women is low. There is a lack of meta-analyses and randomised controlled trials in this area. Most of the available evidence is based on only individual case reports and animal studies.

Opinions from obstetricians, ophthalmologists, and family physicians are essential to ensure that drugs are used safely during pregnancy. Maternal and foetal conditions should be monitored closely throughout the course of treatment. When physicians are in doubt about possible adverse effects of a drug, safer alternatives can be offered. As a general rule, all drugs should be avoided if possible in the first trimester, because the risk of drug-induced foetal teratogenicity is highest during this period than during any other time. Nevertheless, the fear of uncertain drug teratogenicity should not discourage doctors from prescribing treatments when their expected benefits to the mother are thought to outweigh the risk to the foetus. Last but not least, doctors should treat each pregnant woman on an individual basis, and when in doubt, discuss with the patient and experts in the field about possible side-effects of all treatment options.

References


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