Editorial

Use of glaucoma medications during pregnancy and breastfeeding☆

Uso de fármacos antiglaucomatosos durante el embarazo y lactancia

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There is an abundance of literature on treatment options for glaucoma in pregnant women. Even so, the doubts about the safest medical treatment and the adequate management of glaucoma during pregnancy have not yet been resolved. In a survey published in 2007 by Eye, 26% of respondents referred having treated a pregnant woman with glaucoma. This theoretically infrequent situation is becoming increasingly common as in daily clinical practice we find women in childbearing age with glaucoma expressing their concerns about the treatment for the disease and complications during pregnancy and lactation. Developments in the medical and surgical treatment of congenital and childhood glaucoma have contributed to this situation by enabling patients to reach the adult age with good visual function.

It is estimated that during pregnancy IOP diminishes up to 10%, with this reduction being stronger in the third quarter. The causes for this reduction appear to be multiple, with hormonal change being the main cause as it influences an increase in aqueous humor outflow and a reduction in episcleral venous pressure. However, the evolution of glaucoma during pregnancy is variable despite said theoretical hormonal protecting factor. Most patients remain stable during pregnancy although a small percentage (about 10%) have increased IOP or progression of the disease.

The impossibility of carrying out studies obliges ophthalmologists to refer to clinical case series to obtain more information about glaucoma management during pregnancy. In a retrospective study on 28 eyes of 15 women published 6 years ago, 57.1% of studied eyes (a total of 16) experienced no progression, with IOP remaining stable during pregnancy. An addition, despite the natural tendency toward diminished IOP, cases have been described in which the disease progressed during pregnancy. Many of said women were diagnosed with congenital, infant or adolescent glaucoma. Others have inflammatory or pigmentary glaucoma. In many cases we found women who had undergone several surgeries exhibiting a significantly diminished visual field in at least one of the eyes. It is possible that in these types of glaucoma, which appear most frequently in childbearing age, IOP does not vary as in open angle primary glaucoma or in healthy women in whom IOP variations has been analyzed during pregnancy.

One of the difficulties in the treatment of glaucoma during pregnancy is the need to maintain the visual function of patients who exhibit advanced campimetric defects vis-à-vis the potential risks of medical or surgical treatment for the mother as well as the fetus.

The decision to treat or not to treat and the type of medication to be used should be taken on an individual basis. Available treatment options for glaucoma (medical, laser trabeculoplasty or surgery) are more limited in these cases. It would be recommendable to anticipate pregnancy as far as possible and to explain to the patient the importance of reporting pregnancy at the earliest possible date to allow the

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Table 1 – FDA drug classification based on teratogenesis risk.

<table>
<thead>
<tr>
<th>Category</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Risk for the fetus in controlled studies in humans has not been demonstrated</td>
</tr>
<tr>
<td>B</td>
<td>Risk for the fetus in gestating animal studies has not been demonstrated, or the risks which were demonstrated were not confirmed in studies on humans</td>
</tr>
<tr>
<td>C</td>
<td>Teratogenic effect on the fetus has been demonstrated in gestating animal studies. Only to be used if the benefits for the mother exceed potential risks for the fetus</td>
</tr>
<tr>
<td>D</td>
<td>Clear evidence of teratogenic risk. Benefits could make its use acceptable during pregnancy despite risk in the case of severe disease and in the absence of alternative treatments</td>
</tr>
<tr>
<td>X</td>
<td>Anomalies have been demonstrated in the fetus of human beings or animals. The drugs in this group are contraindicated during pregnancy</td>
</tr>
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ophthalmologist to control IOP with the lowest possible use of eyedrops.

None of the analyzed studies provide full guarantees of safety for the fetus. For this reason, it is recommended to suspend medical treatments in the first quarter of pregnancy when the risk of fetal malformations is higher.

In cases in which it is necessary to establish medical treatment, the side effects which could arise due to the passage of the drug to the fetus through the blood-placental barrier should be considered together with possible effects on uterine motility and the ensuing risk of premature labor or miscarriage. According to the FDA safety classification based on experimental models (Table 1), brimonidine belongs to category B, i.e., no adverse effects have been demonstrated in the fetus of animal studies. No studies have been carried out on humans. The rest of anti-glaucoma drugs (prostaglandin, β-blockers, carbonic anhydrase inhibitors, collinergics, among others) are in category C, which means that adverse effects have been demonstrated in the fetus in controlled animal studies even though there are no studies or evidence in human beings. Brimonidine could be considered as the safest medication during pregnancy due to being the only drug included in category B. However, brimonidine not only goes through the hematonecathelic barrier producing CNS depression and apnea in infants, but can also pass through the hematopoietic barrier. The potential risk involved in its use excludes its acceptance as a safe option and should be avoided during the entire pregnancy due to the absence of information about its safety, even though some authors consider it as a treatment option for the second and third quarters thereof.

Prostaglandins, the first line medication for glaucoma, belongs to the category C group. Analogs of F2α-prostaglandins display oxytocic and luteolytic activity and could predispose to miscarriages, although in experimental studies in animals no effects on embryos have been found with doses exceeding up to 15 times the therapeutic dose for humans. Even though the literature comprises series of cases in which the use of latanoprost during pregnancy was not associated to premature labor or miscarriage, the ability to pass through the blood-placental barrier and involving ocular motility, with all the risks this implies, excludes this medication from use during pregnancy.

Topical β-blockers can produce bradycardia and arrhythmias in the fetus. However, for many years obstetricians have used β-blockers as antihypertensive drugs for AHT developed during pregnancy. The commercial presentation of this drug in the form of a gel with lower concentration (0.1%) is a safer option for treatment. Due to the greater amount of experience in the use of these drugs during pregnancy, we consider it as the first choice medication.

Oral treatment with carbonic anhydrase inhibitors has been associated to the development of sacrococcygeal teratomas in newborns, although adverse effects with topical treatments have not been described. Recently, intrauterine growth retardation has been described in a woman with congenital glaucoma who maintained topical treatment during pregnancy with a fixed combination of timolol-dorzolamide and required cesarean labor.

In our hospital we endeavor to maintain the patient without topical treatment during the first quarter to avoid the risk of teratogenesis. When it is necessary to treat due to risk of progression, the first therapeutic option is topical β-blocker, preferably timolol in gel form, followed by topical carbonic anhydrase inhibitors. Whenever possible, we maintain the patient under observation and without medical treatment or with the lowest possible number of drugs during the first quarter and the last month of pregnancy. In all cases we discard the use of prostaglandins because, even though retrospective studies have demonstrated the absence of side effects for the fetus, the risk of miscarriage or premature labor is unacceptable and a small amount of bibliography is not enough to consider prostaglandins as a safe drug.

Some authors consider that the scarcity of information about the safety of hypotensor drugs during pregnancy calls for a different therapeutic approach which includes laser treatment or surgery.

Laser trabeculoplasty enables maintaining IOP within normal limits with a lower number of hypotensor drugs. It could be a good treatment option if allowed by the morphology of the angle. This is infrequent in the types of glaucoma exhibited by women in reproductive age. Laser trabeculoplasty is not very effective in these cases due to angular alterations which are inherent to the disease or to the presence of angular synechiae. Inflammatory or congenital glaucoma or those developed during infancy due to anterior chamber deformations such as the Peters-Rieger syndrome or Axenfeld syndrome or aniridia frequently compromise the angle and therefore the results of ALT or SLT are more limited.

Recently, the use of cyclodestruction with diode has been described in pregnancy. The objective of the treatment would be to reduce IOP with the lowest possible number of drugs before planning pregnancy. This treatment can be carried out with local anesthesia and could be repeated if IOP is not sufficiently controlled. Anatomic differences in the morphology and position of the ciliary body must be taken into account in congenital and childhood glaucoma, as well as possible complications in patients with thin sclera or inflammatory glaucoma. In these cases, surgical difficulty is greater because we frequently find patients who were intervened several times and have angular compromise which limits the type
of surgery. In case of hypertension peaks, the risk of visual loss requires taking the decision of filtering surgery with local anesthesia avoiding antimitabolites. On the other hand, it is recommendable to maintain the patient lying on the side to avoid the compression of the vena cava and gastroesophageal reflux, mainly during the third quarter.

In what concerns the use of hypotensor drugs during lactation, we know that the passage of these drugs to the maternal milk has been proved.14,15 As for the safest hypotensor drugs during lactation, we would consider the same therapeutic options as for pregnancy, utilizing timolol in gel form as the first line medication. In order to reduce the amount of the drug to protect the newborn, the drop can be instilled immediately after breast-feeding, occluding the lachrymal points during 5 min, although it is recommendable to suspend lactation if antiglaucoma treatment is necessary.

In summary, when it is necessary to establish medical treatment the pros and cons thereof must be assessed case-by-case, maintaining the patient free of hypotensor treatment during the first quarter and considering only the safest drugs for the mother as well as the fetus, β-blockers and topical carbonic anhydrase inhibitors, occluding the lachrymal points in order to reduce systemic absorption. It is recommendable to suspend medical treatment weeks before the estimated delivery date.

REFERENCES