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REVIEW ARTICLE

Treating common ear problems in pregnancy: what is safe?

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Abstract In everyday practise, more than 80% of pregnant women receive one at least medication, often for ENT causes. The aim of the present paper is to review the literature on safety and administration of medical treatment for ear diseases, in pregnant women. The literature review includes Medline and database sources. Electronic links, related books and written guidelines were also included. The study selection was as follows: controlled clinical trials, prospective trials, case-control studies, laboratory studies, clinical reviews, systematic reviews, metanalyses, and case reports. The following drugs are considered relatively safe: beta-lactam antibiotics (with dose adjustment), macrolides (although the use of erythromycin and clarithromycin carries a certain risk), and acyclovir. Non-selective NSAIDs (until the 32nd week), nasal decongestants (with caution and up to 7 days), intranasal corticosteroids, with budesonide as the treatment of choice, first generation antihistamines, or cetirizine (third trimester) and loratadine (second and third trimester) from the second generation, H_2 receptor antagonists (except nizatidine) and proton pump inhibitors (except omeprazole), can be used to relieve patients from the related symptoms. Meclizine and dimenhydrinate, as antiemetics in vertigo attacks; metoclopramide, vitamin B_6 and ginger rhizome, alternatively. Low-dose diazepam and diuretics in severe cases of Meniere's disease (with caution). Systemic administration of prednisone and prednisolone can be considered in selected cases. By contrast, selective COX-2 inhibitors, betahistine and vasodilating agents are contraindicated in pregnancy. Since otologic and neurotologic manifestations during pregnancy tend to seriously affect the quality of life of the expectant mothers, ENT surgeons should familiarise themselves with the basic guidelines and safety precautions for any related medication, in order to provide appropriate treatment.

Keywords Pregnancy · Ear · Drugs · Safety · Teratogenicity

Introduction

Pregnancy is not a disease, but a special period in woman's life, when the well being of the mother is closely related to the well being of the foetus. In other words, for any medical intervention to the mother for pregnancy related or unrelated diseases, the possible sequelae to the child should be taken into account.

During pregnancy the ideal would be to abstain from any drug administration, especially during the first 3 months. However, in practice, approximately 85% of women will have at least one medical prescription during their gestation [1], whereas the typical gravid woman takes three to four different drugs, excluding vitamins and mineral supplements [2]. Moreover, 6% of pregnant women receive at least one drug during the first trimester [3].

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Various metabolic, endocrinologic, and physiologic changes during the gestational period can present as otolaryngologic conditions, affecting the ear and the sense of hearing. Furthermore, pregnancy does not exclude the appearance of other concomitant, but unrelated conditions. However, most ENT surgeons are completely unaware of safety guidelines, regarding drug administration to pregnant women, and usually refer patients to gynaecologists, who, in turn, are usually unaware of proper treatment for ENT diseases.

The aim of the present paper is to review the current knowledge on the appropriate management of otologic and neurotologic diseases that may be encountered during pregnancy, and assess the possible effect of medical treatment to the foetus and mother.

Materials and methods

An extensive search of the literature was performed in Medline and other available database sources, using the keywords "pregnancy", "otolaryngology", "antibiotics", "decongestants", "corticosteroids", "allergy" "vertigo", "safety", and "teratogenicity". Information from electronic links, related books, and written guidelines were also included in the analysis of data.

Results

Nine controlled clinical trials, seven case-control studies, two prospective trials, two retrospective studies, two laboratory studies, 57 clinical reviews, 15 systematic reviews, three metanalyses, and three case reports met the defined criteria and were included in study selection.

Discussion

Teratogenicity

Potential teratogenesis, which is defined as structural or functional dysgenesis of the foetal organs [4], is the major consideration when prescribing drugs to pregnant women. Total foetal exposure and gestational age at first exposure are the main parameters that should be evaluated. Thus, exposure to a teratogenic drug around the time of conception or implantation is more likely to result in spontaneous abortion, while structural defects can occur after exposure between the third and tenth week of gestation. More delayed exposure is more likely to incur functional abnormalities, especially when the exposure is prolonged.

Overall, major congenital malformations occur in 2–4% of all newborns [5, 6], 1% of which can be attributed to medication in general. The overall incidence of minor malformations is estimated to 9% [7].

The potential detrimental effect of drugs administered to pregnant women has led FDA in establishing five risk categories for medication use during pregnancy (Table 1). The present paper discusses the management of common ear problems in pregnant women, taking also into account the category, in which each of the proposed medication falls.

Specific diseases

Otologic manifestations

The oedema of the respiratory mucosa, commonly seen in pregnant women, or following a related infection, may lead to hypoventilation of the middle ear cavity and otitis media. The usual treatment in non-pregnant humans consists of antibiotic administration, along with nasal decongestants

Table 1 FDA classification for medication risk during pregnancy

Category	Risk
A	Controlled human studies have failed to demonstrate a risk to the foetus and the possibility of foetal harm appears remote
B	(a) Animal studies have not demonstrated a foetal risk but no results of controlled human studies are available, or (b) animal studies have shown an adverse effect (other than decreased fertility) that has not been confirmed in controlled human studies
C	(a) Animal studies have revealed adverse effects (i.e. teratogenic or other) but controlled human studies are lacking, or (b) Studies in women and/or animals are not available. Drug use is justified only if the potential benefit outweighs the potential risk to the foetus
D	There is positive evidence of human foetal risk; however the benefits from use in pregnant women may be acceptable despite the risk. These drugs should be reserved for a life-threatening situation or a serious disease, in which safer drugs cannot be used or are ineffective
X	(a) Animal or human studies have demonstrated foetal abnormalities, and/or (b) there is evidence of foetal risk based on human experience. The drug is contraindicated in women, who are or may become pregnant, because the risk by its use clearly outweighs any potential benefit

and/or H_1 receptor antagonists (antihistamines), if allergy or serious nasal symptoms are involved.

Beta-lactam antibiotics are the safest choice in pregnancy (category B) and can be taken throughout the three trimesters of gestation [8–16]. However, due to the potential alteration in their pharmacokinetics, their dosage may need to be adjusted, in order to avoid undertreatment [17–19]. In case of allergy, the macrolides (also belonging to category B) can be used as alternatives [9, 10, 13, 16, 20, 21]. It should be mentioned, however, that although these antibiotics are generally considered safe in pregnancy as a group [22], various reports suggest an increased risk of congenital malformations, largely attributed to cardiovascular defects, after erythromycin therapy [23, 24]. This adverse outcome not only involves erythromycin exposure in early pregnancy [23, 24], but may also occur with regard to erythromycin use during any part of gestation [25-Table 3]. In addition, a possible association between prenatal erythromycin administration and infant pyloric stenosis was observed following early pregnancy exposure [23], but this finding does not seem to be consistent among studies [26]. Therefore, not only should erythromycin be avoided during the first trimester, but it may also not be safe throughout pregnancy altogether. The use of clarithromycin is also not recommended, as it is a category C drug [27]. Hence, the newer macrolide members, such as roxithromycin, may be used as valid therapeutic alternatives, although larger studies are necessary to fully evaluate their safety [28].

Frequent irrigation of nostrils using normal saline solutions can be helpful and is considered harmless. Nasal decongestants can be used to relieve congestion and facilitate the introduction of other topical therapy, such as nasal corticosteroids [29–31]; however, their use should be limited to less than seven days, due to the potential rhinitis medicamentosa caused by their prolonged administration. Although the use of nasal decongestants in pregnant women has been recommended in several articles [17, 29–33], the studies assessing their safety in pregnancy are very few. Schatz found no statistical association between major congenital malformations of the foetus and the use of nasal oxymetazoline or phenylephrine [34]. Until there is more and conclusive evidence, they should be used with caution. In addition, oral decongestants are not advised, because of their proven teratogenicity in animals [35–37]. Even though a position statement, adopted by both the American College of Obstetrics and Gynaecology and the American College of Allergy, Asthma, and Immunology, recommended pseudoephedrine as the oral decongestant of choice [38], caution in the prescription of this particular drug is warranted, as not only it carries a category C listing, but, additionally, case control studies have established a consistent association of pseudoephedrine to gastroschisis [39], especially with regard to first-trimester exposure [40–42].

Intranasal corticosteroids appear to be safe, and could be used during pregnancy [17, 43], although data on pregnancy outcomes after maternal exposure are limited [30, 44]. However, no association between intranasal corticosteroids and an increase in congenital malformations in humans has been found [32]. Budesonide, which holds a category B listing, both as an intranasal, and as an inhaled corticosteroid, is the treatment of choice [44, 45].

H_1 receptor antagonists are typically prescribed to facilitate nasal decongestion; however, their use is not recommended during the first trimester of pregnancy [46]. First generation antihistamines are favoured over second generation ones, based on their longevity, which has led to more conclusive evidence of safety [21, 30]. In a meta-analysis examining the safety of first generation antihistamines in pregnancy, 200,000 first trimester exposures failed to show increased teratogenic risk [32]. In pregnant women, who cannot tolerate first generation antihistamines, the use of a second generation agent, either cetirizine (third trimester) or loratadine (second and third trimester), both listed as category B drugs, should be considered [32, 33, 43, 47].

Otitis externa might also occur in pregnancy, especially during the summer. Even though scarce information is available about the use of local aminoglycosides in gestation, with the exception of streptomycin, which is strictly contraindicated [48, 49], local treatment with gentamycin, with or without the use of an ear wick, could be considered in serious cases [49]. Nevertheless, experiments in animals have proven the potential systematic absorption of local aminoglycosides in the ear canal. Therefore, they should be given only when the expected benefit outweighs the potential risk. Orally given NSAIDs can also be used, as most of their potential adverse effects (i.e. constriction of the ductus arteriosus, persistent foetal circulation, and impairment of renal function, or prolongation of gestation and labour and bleeding) [50–56] can be prevented, if they are stopped for the last 8 weeks prior to delivery [50, 54, 55, 57–61]. However, even though there is no evidence for teratogenicity of classic non-selective NSAIDs, including low-dose aspirin in humans [50, 53, 55, 57], the use of ibuprofen should be avoided, as the issue of its potential association with gastroschisis still remains controversial [41, 42, 52]. With regard to the latter, an increased risk for gastroschisis has also been reported after aspirin use in early pregnancy [41, 62].

In addition, interesting drug specificity for the development of orofacial clefts has been observed after naproxen administration in the first trimester of cyesis. Indeed, Ericson and Kallen reported that the absolute risk of having an infant with an orofacial cleft after the use of naproxen may be as high as 1/200 [63]. With regard to selective COX-2 inhibitors, their use is contraindicated in pregnancy [64], as COX-2 activities are necessary to support all stages of

reproduction, from ovulation to implantation to decidualisation and delivery [65]. Paracetamol (acetaminophen) can be given alternatively as an analgesic [66], throughout pregnancy; however, it lacks any anti-inflammatory properties. When antibiotic medication is required, the combination of amoxicillin and clavulanic acid (category B) should be considered [67–69].

Otomycosis can also occur in pregnancy, and requires frequent removal of fungal hyphas, using fine suction. Clotrimazol drops (http://www.canesten.com) can also be used with safety during gestation, for topical treatment.

Neurotologic manifestations

It is sometimes difficult to distinguish vertigo attacks from the bouts of nausea and vomiting, which are quite common, especially in the first trimester of pregnancy [70]; seeking for nystagmus might be proven helpful towards this direction.

Conventionally, physicians are quite reluctant to prescribe antiemetics, especially before the 12th week of gestation, with the exception of hyperemesis gravidarum [71]. However, quite a few medications are safe and effective for antiemetic use [72]. H_1 antihistamines, very effective in patients with nausea due to vestibular causes, can be administered in vertigo attacks [73]. The available data suggest that meclizine and dimenhydrinate (which belong to category B) are the antiemetics with the lowest risk of teratogenicity [74]. When vomiting is continuous, systemic metoclopramide, which is very efficient and safe (category B), could also be considered [75]. With regard to ondasetron, safety data are insufficient to recommend it as a first-line agent [72], although it is considered to be a category B drug. Therefore, it is preserved for persistent cases. Among newer medications, pyridoxine (vitamin B_6) appears to be effective in reducing the severity of nausea in early pregnancy, without evidence of teratogenicity [76]. Ginger rhizome, which is currently used for the prevention of kinetosis [77], is supposed to be safe and effective for nausea and vomiting in pregnancy; therefore, it can also be considered [78–80]. By contrast, the use of betahistine, which is widely prescribed by ENT doctors in vertigo, is contraindicated during pregnancy [81]. Epley manoeuvres can be performed on pregnant patients with benign positional vertigo; however, caution is advised for the potential appearance of autonomous or psychosomatic sequels, requiring careful monitoring. In any case, non-pharmaceutical vestibular exercises can be used in long term therapy, taking precautions, with regard to the physical and vestibular activities involved.

There are few reports on the course of Meniere's disease during pregnancy. Intramuscular injection of low-dose diazepam (although listed as category D, therefore should be avoided in general) appear to be very effective against vertigo attacks [82]. Although diuretics should be avoided in pregnancy [83], they may be given as maintenance therapy in the first trimester, in reduced doses [84]. However, their administration in more advanced state is not advised, due to the possible hyponatremia, hyperbilirubinemia, thrompocytopenia, placental hypoperfusion, and pre-eclampsia [1, 85]. Therefore, it appears that the combination of dimenhydrinate and B6 (category B) is safer during attacks of Meniere's disease, rather than the above-mentioned drugs that have potential risks for the foetus.

Sudden sensorineural hearing loss is rarely seen in uncomplicated pregnancies. However, toxaemia of pregnancy may be a contributing factor. Treatment of underlying pathologies may be effective in restoring the decreased hearing acuity. When no aetiological factor can be identified, despite a thorough investigation, intravenous administration of systemic corticosteroids can be used, with varying degrees of success.

Systemic corticosteroids (category C) are generally contraindicated in pregnancy, due to their association with the development of oral clefts [86, 87]. This association, however, was only proven relevant in the first trimester of gestation [88], whereas most experts agree that corticosteroids can be safely taken during the second and especially the third trimester of cyesis [89]. It should be noted that both prednisone and prednisolone can be considered, when systemic corticosteroid treatment is imperative, because of the inability of the foetal liver to convert prednisone to its active metabolite and the ability of the placenta to convert prednisolone to inactive prednisone [55, 90, 91].

The protection of the gastric mucosa usually necessitates the use of H_2 receptor antagonists, or proton pump inhibitors, when systemic corticosteroids are administered. Both H_2 receptor antagonists and proton pump inhibitors can be safely given [92–100], as they are category B listed drugs. Nizatidine and omeprazole represent the only members of the above-mentioned categories that carry a category C listing; however, large cohort studies have failed to substantiate any elevated risk of malformations after their administration [92, 97, 101, 102].

Data concerning the safety of vasodilating agents are either lacking, or do not support their use during pregnancy. The administration of acyclovir should be carefully considered, although this agent has been monitored in over a 1,000 pregnancies [103], and it belongs to category B. The dosage scheme during pregnancy requires modification towards decreased doses, for both intravenous and oral administration [104]. It should be mentioned, however, that unless active viral infection is proven, the potential benefit for the mother may not outweigh the potential harm for the foetus, since acyclovir is a drug that has anti-DNA properties.

Idiopathic facial paralysis or Bell's palsy is believed to have an increased incidence in pregnancy, especially during the third trimester [105]. Corticosteroids, as well as B-complex vitamins could be used, along with eye drops of natural tears to avoid xerophthalmia. In the case of Ramsay–Hunt syndrome, acyclovir can be added to the therapeutic regimen. Some ENT surgeons may also consider acyclovir, in any acute facial palsy.

Conclusions

Many drugs in common ENT practice are not teratogenic, according to the current evidence; however, ENT surgeons usually hesitate to prescribe any medication to pregnant women, often leading to suboptimal treatment. Since otologic and/or neurotologic manifestations during pregnancy tend to seriously affect the quality of life of the expectant mothers, ENT surgeons should familiarise themselves with the basic guidelines and safety precautions for any related medication, in order to provide appropriate treatment.

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