Eur Arch Otorhinolaryngol (2008) 265:499–508
DOI 10.1007/s00405-008-0601-4

REVIEW ARTICLE

Treating common problems of the nose and throat in pregnancy: what is safe?

Petros V. Vlastarakos · Leonidas Manolopoulos · Eleftherios Ferekidis · Aris Antsaklis · Thomas P. Nikolopoulos

Received: 30 November 2007 / Accepted: 24 January 2008 / Published online: 12 February 2008

Abstract Although all kinds of medications should be avoided during pregnancy, the majority of pregnant women receive at least one drug and 6% of them during the high-risk period of the first trimester. The aim of the present paper is to discuss the appropriate management of rhinologic and laryngeal conditions that may be encountered during pregnancy. A literature review from Medline and database sources was carried out. Related books and written guidelines were also included. Controlled clinical trials, prospective and retrospective studies, case–control studies, laboratory studies, clinical and systematic reviews, meta-analyses, and case reports were analysed. 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), clindamycin, metronidazole (better avoided in the first trimester), amphotericin-B (especially in immunocompromised situations during the second and third trimester) and acyclovir. First-line antituberculous agents isoniazid, ethambutol, pyrazinamide, and ciprofloxacine in drug-resistant tuberculosis can be also used. 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, second generation antihistamines (cetirizine in the third trimester, or loratadine in the second and third trimester), H2 receptor antagonists (except nizatidine) and proton pump inhibitors (except omeprazole) can be used to relieve patients from the related symptoms. In cases of emergencies, epinephrine, prednisone, prednisolone, methylprednisolone, dimetindene and nebulised b_2 agonists can be used with extreme caution. By contrast, selective COX-2 inhibitors and BCG vaccination are contraindicated in pregnancy. When prescribing to a pregnant woman, the safety of the materno-foetal unit is considered paramount. Although medications are potentially hazardous, misconceptions and suboptimal treatment of the mother might be more harmful to the unborn child. Knowledge update is necessary to avoid unjustified hesitations and provide appropriate counselling and treatment for pregnant women.

Keywords Pregnancy · Nose · Throat · Drugs · Safety · Teratogenicity

P. V. Vlastarakos (✉) · L. Manolopoulos · E. Ferekidis
ENT Department, Hippokrateion General Hospital of Athens,
29 Dardanellion str., Glyfada-Athens, 16562 Athens, Greece
e-mail: pevlast@hotmail.com; pevlast@yahoo.gr

A. Antsaklis
OBG Department, Atticon University Hospital,
Athens, Greece

T. P. Nikolopoulos
ENT Department, Atticon University Hospital,
Athens, Greece

P. V. Vlastarakos
114 Vas. Sofias Av, 11527 Athens, Greece

Introduction

The pregnant woman represents a unique situation for medicine, because, during gestation, close attention should be given to the materno-foetal unit as a whole. Therefore, physicians should always consider possible sequelae to the unborn child when prescribing to a pregnant woman.

Although expectant mothers are usually healthy young women, recent advances in fertility clinics have increased the probability of older women getting pregnant, who by definition have more diseases than the younger ones. Large

cohort studies have demonstrated that as much as 85% of women will receive at least one medical prescription during their gestation [1, 2], with a median value of three drugs, even when vitamins and mineral supplements are excluded [1]. Moreover, 6% of pregnant women take at least one drug during the critical first trimester [3], although this is the time period that all physicians try to avoid prescribing medications.

Rhinologic disorders, which are commonly observed in otherwise healthy individuals, exhibit an increased prevalence in pregnancy [4]. In addition, a broad spectrum of laryngeal diseases may become life threatening and require emergency intervention, either medical or surgical. However, being unfamiliar with safety guidelines regarding drug administration, most ENT surgeons are quite reluctant to treat pregnant women and feel safer referring these patients to gynaecologists, who in turn are usually unaware of proper treatment for ENT diseases [5].

The aim of the present paper is to review the current knowledge on the appropriate management of rhinologic and laryngeal conditions 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 establishing two main categories of outcomes:

(a) identification of specific rhinologic, pharyngeal and laryngeal disorders that may be encountered, or exaggerated during pregnancy. Symptoms and signs referring to these anatomical sites from other primary origins were also evaluated, (b) establishment and support of recommendations, regarding both optimal and safe treatment of the materno-foetal unit.

During the search, the keywords “pregnancy”, “otolaryngology”, “nose”, “throat”, “antibiotics”, “decongestants”, “corticosteroids”, “allergy”, “safety”, and “teratogenicity” were utilised. The keyword “pregnancy” was considered primary and was either combined to each of the other keywords individually, or used in groups of three.

Case reports were excluded from the analysis of data, unless they referred either to large groups of cases, or reflected the clinical experience of the authors in managing life-threatening situations. Information from related books and written guidelines were included in the analysis of data. Electronic links not relating to formally indexed journals were only cited in the text.

Results

Seven controlled clinical trials, nine case–control studies, two prospective cohort studies, nine retrospective cohort studies, two laboratory studies, seven metanalyses, 21 systematic reviews, 42 clinical reviews and seven case reports met the defined criteria and were included in study selection. The classification of evidence and the respective recommendations, with regard to the most commonly used drugs for nose and throat problems in pregnancy, are illustrated in Tables 1, 2, and 3 [6].

Discussion

Materno-foetal physiology

Changes in the maternal physiology (distribution volume, serum albumin levels, renal excretion, and hepatic metabolism) can adversely influence patient management, by altering the pharmacodynamics of administered drugs. Indeed, during pregnancy, maternal blood volume increases by approximately 50%; a marked increase in the extracellular water is also observed. Fat stores also increase and thus the distribution volumes of all drugs expand and their plasma concentrations are reduced; polar drugs may be more susceptible to these changes than lipophilic ones [7]. However, the gradual decrease in the maternal serum albumin leads to diminished binding of drugs to serum proteins. As a consequence, more drug is circulating as an

Table 1 Evidence-based categorisation of medical studies

Category of evidence	Origin of evidence
Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 2 Strength of recommendation by category of evidence for guideline development

Strength of recommendation	Category of evidence
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Table 3 Evidence-based recommendations for medication prescription in pregnancy

Category of commonly used medication	Category of evidence	Strength of recommendation	FDA classification
H_1-receptor antagonists			
1st generation	Ia	A	B[a]
2nd generation	IIb	B	B[b]
Corticosteroids			
Intranasal	III	C	B[c]
Systemic	Ia	B	C
Decongestants			
Nasal	IIa	C	C
Oral	III	C	C
Antibiotics			
b-Lactams	Ib	A	B
Macrolides	IIa	B	B[d]
NSAIDs			
B_2-agonists	III	C	C[e]
Protectants of the gastric mucosa	III	C	C[f]
Proton pump inhibitors	Ib	A	B[g]
H_2 receptor antagonists	IIa	B	B[g]

[a] Data referring to chlorpheniramine and diphenhydramine

[b] Data referring to loratadine and cetirizine

[c] Data referring to budesonide

[d] Erythromycin estolate (category D) and clarithromycin (category C) are excluded

[e] Diclofenac belongs to category B

[f] Terbutaline belongs to category B

[g] Omeprazole and nizatidine belong to category C

unbound fraction. This fraction readily crosses the placenta by diffusing along a concentration gradient to establish and maintain equilibrium [8]. The terms "complete", "incomplete" and "exceeding" are used to describe the extent of placental transfer, with low molecular weight, lipid-soluble, un-ionised drugs achieving more rapid transfer rates.

An increased renal function is also present during pregnancy, having as a result the accelerated elimination of polar drugs, while the elimination of lipophilic drugs may be retarded, and the effect on intermediate drugs is variable. The hepatic metabolism of drugs shows a less consistent pattern and the consequent drug elimination varies among different drug categories.

Finally, foetal physiologic mechanisms also contribute to some extent to the eliminating process of an administered drug, mainly by sulphate conjugation in the liver and renal excretion [7], and the placenta also displays a marginal eliminating capacity through drug metabolism.

Teratogenicity–risk classification

Potential teratogenesis is the major consideration when prescribing drugs to pregnant women. The main reason is that two equally true facts seem to apply in this period, even though few drugs have definitely proven teratogenic in humans, no drug can actually be considered as completely safe [9]. Hence, the use of drugs during pregnancy requires maintenance of a fine balance (or a "terror" equilibrium) between risk to the foetus and necessity of the mother.

This reality has led several countries in establishing risk classification systems to summarise the limited data on drug safety during pregnancy. These systems, however, often result in ambiguous statements and may prove difficult in patient counselling. The most widely used risk assessment systems have been proposed by the US Food and Drug Administration (FDA), the Australian Drug Evaluation Committee (ADEC) and the Swedish Committee for Drugs (FASS). However, the significant variability that exists between these systems results not only in limiting the

number of common drugs included, but also, more alarmingly, in an even smaller percentage of drugs classified in the same risk factor category (26%). These discrepancies are not only attributable to the different definitions of the categories used, but also depend on how the available scientific literature is handled. This situation obviously contributes to an increasing confusion and limits the usefulness of risk classification systems [10]. Indeed, it cannot be considered irrelevant that 20% of pregnant women in a large cohort study had used at least one drug classified as potentially harmful during pregnancy, and 3.4% had used at least one drug classified as clearly harmful [11].

Fortunately, despite the relatively high consumption rates of potentially or clearly harmful drugs, only 1% of major congenital malformations can be attributed to medication in general [12]. The overall incidence of the former ranges from 2 to 4% for all newborns [12, 13], whilst the respective percentage of minor deformities is estimated at 9% [14].

Under this perspective, the management of potential nose and throat problems in pregnancy, which is discussed in the present paper, takes into account the respective FDA classification, although every case should be treated individually (Table 4).

Specific disorders

Nose and paranasal cavities

Rhinologic diseases are very common in the general population and their frequency further increases during pregnancy; approximately 30% of gravid women suffer from nasal disorders [15]. Especially in pregnant women there is a specific rhinogic disease, the so called "pregnancy rhinitis" that may occur in as much as 20% of them [16], fortunately most often during the last six or more weeks of pregnancy. This situation is not associated with any symptoms or signs of respiratory tract infection or known allergic cause, and disappears completely within 2 weeks after delivery. Nasal saline mist, antihistamines and topical corticosteroids are recommended [16, 17].

Intranasal corticosteroids appear to be safe, and could be used during pregnancy [16, 18], although data referring to their impact after gestational exposure are limited [19, 20]. However, this form of administration has not been associated with an increase in congenital malformations in humans [21]. Budesonide, carrying a category B listing, both as an intranasal and inhaled formulation is considered as the treatment of choice [19, 22]. It should be noted, however, that even though maternal exposure to orally inhaled budesonide during pregnancy was not associated with adverse foetal outcomes in studies of more than 6,600 infants, and its pharmacodynamics actually show much lower systemic exposure after intranasal administration [19], Kallen and Olausson report a nearly significant increased risk for cardiovascular defects, albeit less severe, or unspecified, after the use of a nasal budesonide preparation but not of an inhaled one [23].

H_1 receptor antagonists are not recommended during the first 3 months of pregnancy [15]. Although the longer existence of first generation antihistamines has led to more conclusive evidence of safety [20, 24], the use of second generation ones, either cetirizine (third trimester) or loratadine (second and third trimester), both listed as category B drugs, should be considered [18, 21, 25, 26], as the commonly occurring tiredness that is associated with the use of the former generation, seems to exaggerate similar pregnancy-related phenomena. Moreover the clinical effect of first generation antihistamines compared to their second-generation counterparts is actually proven inferior. Loratadine is the most studied second-generation agent and did not appear to increase the risk of major congenital malfor-

Table 4 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 others) 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.

mations in a patient cohort of 2,147 pregnant women who were exposed [21].

Nasal decongestants can also be used to reduce congestion and facilitate the introduction of other topical therapy, such as nasal corticosteroids [20, 27, 28]; however, their administration should not exceed a period of 7 days, because prolonged use might lead to the appearance of rhinitis medicamentosa. It is worth mentioning that even though the use of nasal decongestants in gravid women has been suggested in several articles [16, 20, 21, 25, 27, 28], the studies assessing their safety in cyesis are actually quite few. Nevertheless, no statistically significant association between major congenital malformations of the foetus and first trimester, or any maternal exposure to nasal oxymetazoline or phenylephrine was identified in a cohort of 253 pregnant women in the study of Schatz et al. [29]. Until the related evidence is more conclusive, nasal decongestants should be used with caution. Moreover, oral decongestants should be avoided altogether because of their proven teratogenicity in animals [30–32]. Hence, 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 [33], caution in the prescription of this particular drug should be exercised, as not only it is listed as a category C drug, but case–control studies have also established a consistent association between pseudoephedrine and gastroschisis [34], especially with regard to first-trimester exposure [35–37].

In severe cases, invasive methods of turbinate reduction may be effective, but are not usually recommended in this self-limiting condition, because of potential side effects [16]. In addition, environmental changes to avoid allergens, moderate exercise (that the gynaecologists allow), and mechanical alar dilators (i.e. nasal strips for subjective relief) are also safe, although optimal and definite treatment still does not exist [16].

Allergic rhinitis, one of the most frequent diseases in the general population, is also a common problem in pregnancy. Naturally, the ideal first-line approach would be to avoid potential allergens. If environmental modification is ineffective, women with allergic rhinitis can be treated with a number of pharmacological agents, without concern of untoward effects on their unborn child [20]; at least one drug from each major class can be safely utilised to control symptoms as analysed below [30].

Efficient control of allergic rhinitis has proven valuable for the adequate control of asthma exacerbations [19], which carry a significant risk to adversely affect both the mother and the foetus; therefore, aggressive management may be necessary. Long-term control during high pollen-load periods can be achieved with the use intranasal sodium cromoglycate or nedocromil (both considered to be in category B) [12, 20, 22, 24, 25, 28, 38, 39]. Leukotriene receptor antagonists, zafirlukast and montelukast (both also considered to be in category B, although conclusive literature is limited) [18, 20, 38, 40, 41] should be reserved for special circumstances (i.e. in combination with asthma therapy in severe asthmatic gravid women). Second generation antihistamines can be given, as discussed earlier. Intranasal steroids (preferably budesonide) [16, 18, 19] can be added to reverse severe nasal obstruction. It has been suggested that, based on their efficacy and their limited systemic absorption, they must be favoured as first-line treatment over all agents [21], however, the number of controlled trials in pregnancy is still limited to undoubtedly support this notion.

Systemic corticosteroids (category C) are generally contraindicated for the treatment of allergic rhinitis during pregnancy, due to their association with the development of oral clefts [42]. This association, however, was only proven relevant in the first trimester of gestation [43, 44], whereas most experts agree that systemic administration of corticosteroids is possible during the second and especially the third trimester of cyesis [45].

Local decongestants can be considered as second line therapy for short-term relief with the reservations discussed earlier [21, 25], whereas oral decongestants are not advised. Pregnancy is not a contraindication for specific immunotherapy, which appears to be the only disease modifying treatment for allergic rhinitis [18, 25, 28, 30]. However, such therapy should not be initiated during gestation, and we should also take into account the related complications encountered in the general population [46].

Evidence-based management of acute rhino-sinusitis requires the combined use of oral antibiotics and topical corticosteroids. The bacteriology of acute rhino-sinusitis usually includes aerobic microbes; therefore, a beta-lactam antibiotic, prescribed for a time period of approximately 2 weeks, is sufficient and actually represents the safest choice in cyesis [47–51] (category B). Beta-lactams can be administered throughout the three trimesters of gestation [52], however, increased dosage may be required during pregnancy, due to the faster elimination and the concomitant lowered plasma concentrations of these antibiotics [8, 16, 53]. In case of allergy, the macrolides (also belonging to category B) can be used as alternatives [24, 44, 45, 48, 51, 54]. It should be pointed out, however, that though these antibiotics are generally considered as safe in pregnancy as a group [55], various reports suggest an increased risk of congenital malformations, largely attributed to cardiovascular defects, after erythromycin therapy [23, 56]. This adverse outcome not only involves erythromycin exposure in early pregnancy [23, 56], but may also occur with regard to erythromycin use during any part of gestation ([57]-Table 3). Furthermore, it has also been suggested

that erythromycin therapy might actually be considered as weakly teratogenic for the cardiovascular system [56]. In addition, a possible association between maternal use of erythromycin and infant pyloric stenosis was observed following early pregnancy exposure [56], though this finding does not seem to be undoubtedly accepted [58]. Therefore, not only is it best to avoid erythromycin administration during the first trimester of cyesis, but also its use may not be safe throughout the entire pregnancy. The use of clarithromycin is also not recommended, as it is a category C drug [59]. Thus, newer macrolides, such as roxithromycin, may be safer as treatment alternatives, although larger series are needed, in order for more conclusive evidence about their safety to be drawn upon [60]. The use of a topical decongestant (taking into account the reservations expressed earlier) for a period not exceeding 7 days (due to the potential rhinitis medicamentosa) is considered beneficial only as a symptomatic relief (therefore could be avoided). Oral antihistamines are considered helpful only in patients with a history of allergic rhinitis [61]; second generation antihistamines are usually preferred (as discussed earlier).

As far as chronic rhino-sinusitis is concerned, patients with and without nasal polyps usually require certain modifications in their therapeutic approach. Hence, frequent saline washings and long-term intranasal steroid administration, in combination with long-term antibiotic treatment, when indicated, are advised for the conservative management of the former category of patients. Clindamycin (category B) as single-treatment covering aerobic and anaerobic bacteria [54, 62], or the combination of beta-lactams and metronidazole can be considered, as earlier fears of teratogenic effects of the latter on humans have not been confirmed by recent data [63, 64]. However, it should be administered with caution, as no definite conclusions exist. Oral corticosteroids (that cross the placenta poorly and with the reservations expressed earlier) and oral antihistamines (in allergic patients) can be added to the therapeutic regimen in the presence of nasal polyps [61]. Finally, endoscopic sinus surgery may be required for effective management; however, such interventions are obviously contraindicated in pregnancy.

Management of fungal sinusitis may be quite difficult, especially when it concerns immunosuppressed expectant mothers. Administration of amphotericin-B as a first choice drug is advised in these situations (category B), although with extreme caution, especially during the first trimester, due to its maternal–foetal side effects [65, 66]. The latter may include hypokalemia in the mother and increased creatinine level in the foetus [67]. Itraconazole could also be used; however, it holds a category C listing [62]. Washings with solutions containing amphotericine-B and water for injection may also prove useful, along with topical decongestants (taking into account the reservations discussed earlier). Corticosteroids are generally not indicated in fungal infections. Endoscopic sinus surgery should be reserved for very advanced disease or life-threatening situations.

The increased vascular congestion, along with the alterations of the nasal mucosa during pregnancy, predispose to spontaneous incidents of nose bleeding. Epistaxis is usually transient and self-limited; however, haemodynamic imbalance, associated with excessive blood loss, may pose significant danger, both to the mother and foetus. Treatment should include prophylactic measures such as humid environment and application of Vaseline gel in the nostrils. In case that the bleeding vessel is visible, diathermy can be considered. Anterior and/or posterior packing can be performed, when needed; however, caution is warranted in the case of bilateral anterior or posterior packing, due to the related distress and the theoretical possibility of decreased partial pressure of oxygen [68]. Nonetheless, when packing is performed, prophylactic antibiotics are recommended (usually b-lactams).

Pharynx

A large number of pregnant women present to ENT specialists with symptoms and signs of pharyngitis and/or tonsilitis. When the suspected cause is viral, orally given non-steroidal anti-inflammatory agents (NSAIDs), mouthwash solutions, and gastrointestinal agents (if necessary) are usually considered for therapy.

Orally given non-selective NSAIDs can 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) [69–75] can be prevented by avoiding their consumption in the last 8 weeks, prior to delivery [69, 73, 74, 76, 77]. Even though the classic non-selective NSAIDs including low-dose aspirin do not increase the risk of congenital malformations in humans [69, 72, 74, 76], the use of ibuprofen should be avoided, as there still remains a controversial issue with regard to its potential association with gastroschisis [36, 37, 71]. An increased risk for the latter malformation has also been reported in case–control studies that evaluated aspirin use in early pregnancy [36, 78].

In addition, apparent drug specificity for the development of orofacial clefts has been observed after naproxen consumption in the first trimester of cyesis. Indeed, Ericson and Kallen [79] 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, even though they argued that due to low exposure rate, the attributable risk in the general population does not exceed three cases per 100,000 births.

By contrast, selective COX-2 inhibitors are strictly contraindicated in pregnancy [80], as COX-2 activities are

necessary to support all stages of reproduction, from ovulation to implantation to decidualisation and delivery [81]. Paracetamol (acetaminophen), on the other hand, can be considered as an alternative throughout pregnancy, mainly due to its analgesic and antipyretic effects [82], as it basically lacks any antiinflammatory properties.

Gargle washings with camomile tea can be used. However, gargles with hexetidine have not been assessed for safety (http://www.netdoctor.co.uk), and povidone iodine solutions are generally not indicated for regular use, because the foetal thyroid gland is considered susceptible [83].

When the suspected cause is microbial, antibiotics should also be prescribed. Beta-lactam antibiotics are the safest choice in pregnancy (as discussed earlier in this paper), whereas in cases of allergy a macrolide could be prescribed (taking into account the reservations also discussed earlier).

The management of peritonsilar abscess requires drainage, hospitalisation and intravenous administration of antibiotics. Clindamycin (category B) as single-treatment [54, 62], or a combination of beta-lactams and metronidazole (category B) [63, 64] can be used, as all of these drugs are now considered safe.

In case of severe simple herpes infections, acyclovir administration (category B) has proven quite helpful [84, 85], without increased side effects related to its use in pregnancy [86]; however, the dosage scheme requires modification towards decreased doses for both intravenous and oral administration [87]. Newer agents such as valacyclovir and famciclovir can also be administered [84], as they belong to category B too. However, one should consider that all these drugs in theory have antiDNA properties.

Larynx

Laryngeal manifestations may be life threatening and require appropriate and timely management in order to secure a patent airway. Acute laryngitis is usually viral. Voice rest, humid environment, steamy inhalations of menthol or eucalyptus, and plenty of water are helpful in very mild cases. In more serious cases, epinephrine (systemic and nebulised) [24], nebulised b_2 agonists [12, 24, 39, 41, 44, 88–90], and systemic steroids may be required to sustain a patent airway. Due to the urgent nature of the situation, there are limited options, other than administration of even potentially hazardous medications. However, existing observational cohort data do not associate an increased risk of total congenital malformations with maternal exposures to inhaled b-agonists [44]. With regard to epinephrine, the data is insufficient for any robust safety conclusion. When systemic corticosteroid treatment is necessary, clinical experience suggests that both prednisone and prednisolone can be considered as drugs of choice, due to the minimal foetal exposure. This, at least partially, may be attributed to the inability of the foetal liver to convert prednisone into its active metabolite and the ability of the placenta to convert prednisolone into inactive prednisone [74, 91, 92]. The protection of the gastric mucosa in these cases usually requires the use of either H_2 receptor antagonists, or proton pump inhibitors. Both H_2 receptor antagonists and proton pump inhibitors can be safely given [93–99], as they are category B listed drugs. Nizatidine and omeprazole represent the only members of these drug categories that carry a category C listing; however, large cohort studies have not confirmed an elevated risk of congenital malformations after their administration [93, 96, 100, 101].

Supraglottic infections may require hospitalisation, supply of oxygen, humid environment, intravenous administration of fluids to ensure adequate hydration, and intravenous antibiotics. Early intubation and aggressive airway management should be considered in life-threatening situations [102]. Intravenous antibiotic administration using a third generation cephalosporin (ceftriaxone), a second generation cephalosporin, or the combination of ampicillin and sulbactam should be considered, as they all belong to category B [62]. Systemic corticosteroids (as discussed earlier) may also be required, and should be tapered, as signs and symptoms of laryngeal obstruction resolve. Oral cefixime [64] or the combination of amoxicillin and clavoulanic acid [103, 104] can be used, as outpatient treatment, following discharge. In case of allergy, intravenous chloramphenicol (category C) could be administered with extreme caution, and only in life-threatening situations, as it was formerly strictly contraindicated during pregnancy [50]. Later reports, however, consider its use in severe cases during pregnancy, provided that it is not circulating at the time of delivery [105], as it falls into category D near that period.

Laryngeal tuberculosis is no longer associated with advanced active lung disease. Physical examination can reveal nodular or ulcerative lesions, primarily affecting the true vocal cords, along with diffused laryngeal oedema, especially in the posterior third of the larynx. Tuberculin testing is safe and can be used for diagnosis [106]. Treatment with first-line agents, isoniazid and ethambutol, is considered safe [106–108] and should be continued for 9 months, with the ethambutol being stopped after 2 months of treatment [107]. For safety reasons rifampicin (category C) [62] should be included only in case of severe or extensive disease, preferably after the first trimester of cyesis [107, 108]. B_6 vitamin should also be added to the drug treatment of tuberculosis in all pregnant women taking isoniazid [106]. With regard to the other first-line agents, pyrazinamide is reported to have excellent safety record [105], whereas streptomycin is contraindicated in pregnancy [106, 108]. Ciprofloxacine has the best safety profile

among second-line drugs in the treatment of drug-resistant tuberculosis (category C) [62, 106]. By contrast, BCG vaccination should be avoided in pregnancy [106].

In the case of anaphylaxis and laryngeal oedema, the use of epinephrine is indicated as discussed earlier [24, 109]. Parenteral administration of a corticosteroid that crosses the placenta poorly, such as methylprednisone, should also be considered. Intravenous antihistamines diluted in normal saline could also be considered [110], although safety data are missing. Finally, nebulised b_2 agonists could be used (as also discussed earlier).

Besides common laryngeal problems, pregnant women may have additional physiological disorders, presented as single acute or recurrent episodes. The acute form is usually presented just prior to delivery, with dyspnoeic and painful phenomena. Laryngeal oedema, possibly related to submucosal inflammation, may be present, mainly in the arytenoids and false vocal cords. In the chronic form, symptoms may be more persistent, but usually occur earlier in pregnancy. Treatment of both situations may involve only reassurance [67].

Other common disorders

Gastroesophageal reflux is a common situation in pregnancy, especially during the third trimester. Atypical manifestations, such as swallowing difficulties, sore throat and/or dyspnoea, may lead pregnant women to ENT specialists. Physical examination usually reveals redness and/or swelling in the arytenoid area. Initial nonpharmaceutical treatment includes lifestyle modifications and dietary changes. Antacids (preferably magnesium-containing or aluminum-containing antacids) can be used as a first-line therapy, as, at least in theory, pose minimal risk for the foetus. When these interventions are not successful, sucralfate, a mucosal protectant with little to no systemic absorption, should be considered next. Therapy with H_2 receptor antagonists or proton pump inhibitors (as discussed earlier) can be considered in patients with refractory symptoms [94, 95, 97, 100], whereas prokinetic agents should be used with extreme caution or avoided altogether in the pregnant patient [95]. Although widely used, some of the above medications have no FDA listing for pregnancy.

Conclusions

The safety of the materno-foetal unit in pregnancy is considered paramount; hence, drug administration should be based both on safety and comparative efficacy. Rhinologic and laryngeal disorders are very common in pregnant women and may become challenging to both ENT surgeons and gynaecologists. Yet, many drugs in common ENT practice are not teratogenic, according to current evidence, and the available armamentarium for effective disease management with regard to the welfare of the foetus is actually not that restricted. Nevertheless, ENT surgeons usually hesitate to prescribe any medication to pregnant women, often leading to suboptimal treatment, which in turn might mean less protection for the unborn child. Furthermore, quality-of-life issues of the expectant mothers should also be taken into account. ENT surgeons should, thus, familiarise themselves with the basic guidelines and safety precautions for any related medication and modify their practice accordingly, in order to avoid unjustified hesitations and provide appropriate counselling and treatment for pregnant women.

References

1. Egen-Lappe V Hasford J (2004) Drug prescription in pregnancy: analysis of a large statutory sickness fund population. Eur J Clin Pharmacol 60(9):659–666. Epub 2004 Oct 7
2. No authors listed (1992) Medication during pregnancy: an intercontinental cooperative study. Collaborative Group on Drug Use in Pregnancy (C.G.D.U.P.). Int J Gynaecol Obstet. 39(3):185–196
3. Rubin PC, Craig GF, Gavin K, Sumner D (1986) Prospective survey of use of therapeutic drugs, alcohol, and cigarettes during pregnancy. BMJ (Clin Res Ed) 292(6513):81–83
4. Wheeler PW, Wheeler SF (2005) Vasomotor rhinitis. AFP 72(6):1057–1062
5. Vlastarakos PV, Nikolopoulos TP, Manolopoulos L, Ferekidis E, Kreatsas G (2008) Treating common ear problems in pregnancy: what is safe? Eur Arch Otorhinolaryngol 265(2):139–145. Epub ahead of print
6. Shekelle PG, Woolf SH, Eccles M, Grimshaw J (1999) Clinical guidelines: developing guidelines. BMJ 318(7183):593–596
7. Reynolds F, Knott C (1989) Pharmacokinetics in pregnancy and placental drug transfer. Oxf Rev Reprod Biol 11:389–449
8. Mucklow JC (1986) The fate of drugs in pregnancy. Clin Obstet Gynaecol 13(2):161–175
9. Shehata H, Nelson-Piercy C (2001) Drugs to avoid. Best Pract Res Clin Obstet Gynaecol 15(6):971–986
10. Addis A Sharabi S Bonati M (2000) Risk classification systems for drug use during pregnancy: are they a reliable source of information? Drug Saf 23(3):245–253
11. Malm H Martikainen J Klaukka T Neuvonen PJ (2004) Prescription of hazardous drugs during pregnancy. Drug Saf 27(12):899–908
12. Schatz M (1997) Asthma treatment during pregnancy. What can be safely taken? Drug Saf 16(5):342–350
13. Ekelund H, Kullander S, Kallen B (1970) Major and minor malformations in newborns and infants up to one year of age. Acta Pediatr Scand 59:297–302
14. Ash P, Vennart J, Carter CO (1977) The incidence of hereditary disease in man. J Med Genet 14:305
15. Gani F, Braida A, Lombardi C, Del Giudice A, Senna GE, Passalacqua G (2003) Rhinitis in pregnancy. Allerg Immunol (Paris) 35(8):306–313
16. Ellegard EK (2004) Clinical and pathogenetic characteristics of pregnancy rhinitis. Clin Rev Allergy Immunol 26(3):149–159
17. Lekas MD (1992) Rhinitis during pregnancy and rhinitis medicamentosa. Otolaryngol Head Neck Surg 107(6 Pt 2):845–848. Discussion 849

18. Blaiss MS, Food, Drug Administration (U.S.); ACAAI-ACOG (American College of Allergy, Asthma, and Immunology and American College of Obstetricians and Gynecologists.) (2003) Management of rhinitis and asthma in pregnancy. Ann Allergy Asthma Immunol 90(6 Suppl 3):16–22
19. Gluck PA, Gluck JC (2005) A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. Curr Med Res Opin 21(7):1075–1084
20. Mazzotta P, Loebstein R, Koren G (1999) Treating allergic rhinitis in pregnancy. Safety considerations. Drug Saf 20(4):361–375
21. Gilbert C, Mazzotta P, Loebstein R, Koren G (2005) Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. Drug Saf 28(8):707–719
22. Osur SL (2005) The management of asthma and rhinitis during pregnancy. J Womens Health (Larchmt) 14(3):263–276
23. Källén BA Otterblad Olausson P (2003) Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol 17(3):255–261
24. Di Lorenzo G, Mansueto P, Melluso M, Purello D'Ambrosio F, Putignano E, Barbagallo Sangiorgi G (1994) Allergy in pregnancy (article in Italian). Clin Ter 145(9):223–229
25. Keles N (2004) Treatment of allergic rhinitis during pregnancy. Am J Rhinol 18(1):23–28
26. Paris-Kohler A, Megret-Gabeaud ML, Fabre C, Mares P, Vincent D (2001) The allergic pregnant woman (article in French). Allerg Immunol (Paris) 33(10):399–403
27. Bogacka E (1999) Decongestants in treatment of nasal obstruction (article in Polish/abstract). Otolaryngol Pol 53(3):347–352
28. Naclerio RM (1998) Optimizing treatment options. Clin Exp Allergy 28 Suppl 6:54–59
29. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D (1997) The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 100(3):301–306
30. Demoly P, Piette V, Daures JP (2003) Treatment of allergic rhinitis during pregnancy. Drugs 63(17):1813–1820
31. Gilbert-Barness E, Drut RM (2000) Association of sympathomimetic drugs with malformations. Vet Hum Toxicol 42(3):168–171
32. Ugen KE, Scott WJ Jr (1987) Reduction of uterine blood flow by phenylephrine, an alpha-adrenergic agonist, in the day 11 pregnant rat: relationship to potentiation of acetazolamide teratogenesis. Teratology 36(1):133–141
33. No authors listed (2000) The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI). Ann Allergy Asthma Immunol 84(5):475–480
34. No authors listed (2004) Gastroschisis and pseudoephedrine during pregnancy. Prescrire Int 13(72):141–143
35. Werler MM (2006) Teratogen update: pseudoephedrine. Birth Defects Res A Clin Mol Teratol 76(6):445–452
36. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ (1996) Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 54(2):84–92
37. Werler MM, Mitchell AA, Shapiro S (1992) First trimester maternal medication use in relation to gastroschisis. Teratology 45(4):361–367
38. Powrie RO, Larson L, Miller M (2006) Managing asthma in expectant mothers. Treat Respir Med 5(1):1–10
39. Ukena D, Koper I, Sybrecht GW (1990) Therapy of bronchial asthma during pregnancy (article in German). Z Geburtshilfe Perinatol 194(5):188–199
40. Gluck JC, Gluck PA (2005) Asthma controller therapy during pregnancy. Am J Obstet Gynecol 192(2):369–380
41. Beck SA (2001) Asthma in the female: hormonal effect and pregnancy. Allergy Asthma Proc 22(1):1–4
42. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, Diav-Citrin O, Chitayat D, Nulman I, Einarson TR, Koren G (2000) Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis. Teratology 62(6):385–392
43. Oren D, Nulman I, Makhija M, Ito S, Koren G (2004) Using corticosteroids during pregnancy. Are topical, inhaled, or systemic agents associated with risk? Can Fam Physician 50:1083–1085
44. Schatz M (2001) The efficacy and safety of asthma medications during pregnancy. Semin Perinatol 25(3):145–152
45. Ambro BT, Scheid SC, Pribitkin EA (2003) Prescribing guidelines for ENT medications during pregnancy ENT J 82(8):565–568
46. Prieto Lastra L, Perez Pimiento A, Gonzalez Sanchez LA, Rodriguez Cabreros MI, Rodriguez Mosquera M, Garcia Cubero JA (2005) Treatment strategies in rhinoconjunctivitis and asthma during pregnancy (article in Spanish/abstract). Allergol Immunopathol (Madr) 33(3):162–168
47. Sa del Fiol F, Gerenutti M, Groppo FC (2005) Antibiotics and pregnancy. Pharmazie 60(7):483–493
48. Miller EL (2002) The penicillins: a review and update. J Midwifery Womens Health 47(6):426–434
49. Cavenee MR, Farris JR, Spalding TR, Barnes DL, Castaneda YS, Wendel GD Jr (1993) Treatment of gonorrhea in pregnancy. Obstet Gynecol 81(1):33–38
50. Friese K (1993) Antibiotic therapy in pregnancy (article in German). Immun Infekt 21(4):111–114
51. Leophonte P (1988) Antibiotics during pregnancy and breast feeding: consequences for the treatment of respiratory infections. Rev Mal Respir 5(3):293–298
52. Garland SM, O'Reilly MA (1995) The risks and benefits of antimicrobial therapy in pregnancy. Drug Saf 13(3):188–205
53. Heikkila A, Erkkola R (1994) Review of beta-lactam antibiotics in pregnancy. The need for adjustment of dosage schedules. Clin Pharmacokinet 27(1):49–62
54. Brocklehurst P (2002) Antibiotics for gonorrhoea in pregnancy Cochrane Database Syst Rev (2):CD000098
55. Sarkar M, Woodland C, Koren G, Einarson AR (2006) Pregnancy outcome following gestational exposure to azithromycin. BMC Pregnancy Childbirth 6:18
56. Källén BA, Otterblad Olausson P, Danielsson BR (2005) Is erythromycin therapy teratogenic in humans? Reprod Toxicol 20(2):209–214
57. Czeizel A, Rockenbauer M, Sørensen HT, Olsen J (1999) A population-based case-control teratologic study of oral erythromycin treatment during pregnancy. Reprod Toxicol 13(6):531–536
58. Louik C, Werler MM, Mitchell AA (2002) Erythromycin use during pregnancy in relation to pyloric stenosis. Am J Obstet Gynecol 186(2):288–290
59. Amsden GW (1996) Erythromycin, clarithromycin, and azithromycin: are the differences real? Clin Ther 18(1):56–72; discussion 55
60. Chun JY, Han JY, Ahn HK, Choi JS, Koong MK, Nava-Ocampo AA, Koren G (2006) Fetal outcome following roxithromycin exposure in early pregnancy. J Matern Fetal Neonatal Med 19(3):189–192
61. Fokkens W, Lund V, Mullol J; European Position Paper on Rhinosinusitis and Nasal Polyps group (2007) European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl (20):1–136
62. Fairbanks DNF (2003) Pocket guide to antimicrobial therapy in otolaryngology-head and neck surgery, 11th edn, American Academy of Otolaryngology-Head and Neck Surgery Foundation
63. Ferrero S, Ragni N (2004) Inflammatory bowel disease: management issues during pregnancy. Arch Gynecol Obstet 270(2):79–85. Epub 30 April 2003
64. Donders GG (2000) Treatment of sexually transmitted bacterial diseases in pregnant women. Drugs 59(3):477–485

65. Figueiro-Filho EA, Duarte G, El-Beitune P, Quintana SM, Maia TL (2004) Visceral leishmaniasis (kala-azar) and pregnancy. Infect Dis Obstet Gynecol 12(1):31–40
66. Pereira CA, Fischman O, Colombo AL, Moron AF, Pignatari AC (1993) Cryptococcal meningitis in pregnancy. Review of the literature. Report of 2 cases (article in Portuguese/abstract). Rev Inst Med Trop Sao Paulo 35(4):367–71
67. Dean JL, Wolf JE, Ranzini AC, Laughlin MA (1994) Use of amphotericin B during pregnancy: case report and review. Clin Infect Dis 18(3):364–368
68. Hansen L, Sobol S, Abelson T (1986) Otolalyngologic manifestations of pregnancy. J Fam Pract 23(2):151–155
69. Ostensen ME, Skomsvoll JF (2004) Anti-inflammatory pharmacotherapy during pregnancy. Expert Opin Pharmacother 5(3):571–580
70. Fardet L, Nizard J, Genereau T (2002) Non-selective and selective non-steroidal anti-inflammatory drugs, administration in pregnancy and breast feeding (article in French). Presse Med 31(31):1462–1468
71. Burdan F, Belzek A (2001) Current opinions on embryotoxic and teratogenic effects of ibuprofen (article in Polish/abstract). Pol Merkur Lekarski 11(63):266–270
72. Ostensen M (1998) Nonsteroidal anti-inflammatory drugs during pregnancy. Scand J Rheumatol Suppl 107:128–132
73. Ostensen M, Ramsey-Goldman R (1998) Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? Drug Saf 19(5):389–410
74. Ostensen M (1994) Optimisation of antirheumatic drug treatment in pregnancy. Clin Pharmacokinet 27(6):486–503
75. Schoenfeld A, Bar Y, Merlob P, Ovadia Y (1992) NSAIDs: maternal and fetal considerations. Am J Reprod Immunol 28(3–4):141–147
76. Burdan F (2001) Prenatal effects of acetylsalicylic acid (article in Polish/abstract). Pol Merkur Lekarski 11(62):182–186
77. De Santis M, Carducci B, Cavaliere AF, De Santis L, Straface G, Caruso A (2001) Drug-induced congenital defects: strategies to reduce the incidence. Drug Saf 24(12):889–901
78. Werler MM, Sheehan JE, Mitchell AA (2002) Maternal medication use and risks of gastroschisis and small intestinal atresia. Am J Epidemiol 155(1):26–31
79. Ericson A, Källén BA (2001) Nonsteroidal anti-inflammatory drugs in early pregnancy. Reprod Toxicol 15(4):371–375
80. Yodfat Y (2004) Is there a future for COX-2 inhibitors (article in Hebrew/abstract)? Harefuah 143(11):820–824, 837
81. Chan VS (2004) A mechanistic perspective on the specificity and extent of COX-2 inhibition in pregnancy. Drug Saf 27(7):421–426
82. Bannwarth B, Pehourcq F (2003) Pharmacologic basis for using paracetamol: pharmacokinetic and pharmacodynamic issues. Drugs 63Spec No 2:5–13
83. Novaes Junior M, Biancalana MM, Garcia SA, Rassi I, Romaldini JH (1994) Elevation of cord blood TSH concentration in newborn infants of mothers exposed to acute povidone iodine during delivery. J Endocrinol Invest 17(10):805–808
84. Baker DA (1998) Antiviral therapy for genital herpes in nonpregnant and pregnant women. Int J Fertil Womens Med 43(5):243–248
85. Greenspoon JS, Wilcox JG, McHutchison LB, Rosen DJ (1994) Acyclovir for disseminated herpes simplex virus in pregnancy. A case report. J Reprod Med 39(4):311–317
86. Tyring SK, Baker D, Snowden W (2002) Valacyclovir for herpes simplex virus infection: long-term safety and sustained efficacy after 20 years' experience with acyclovir. J Infect Dis 186Suppl 1:S40–S46
87. Haddad J, Messer J, Willard D, Ritter J (1989) Acyclovir and pregnancy: current aspects (article in French). J Gynecol Obstet Biol Reprod (Paris) 18(5):679–683
88. Bakhireva LN, Jones KL, Schatz M, Johnson D, Chambers CD, Organization Of Teratology Information Services Research Group (2005) Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol 116(3):503–509
89. Adams BK, Cydulka RK (2003) Asthma evaluation and management. Emerg Med Clin North Am 21(2):315–330
90. Dombrowski MP (1997) Pharmacologic therapy of asthma during pregnancy. Obstet Gynecol Clin North Am 24(3):559–574
91. Lockshin MD, Sammaritano LR (1998) Corticosteroids during pregnancy. Scand J Rheumatol Suppl 107:136–138
92. Guillonneau M, Jacqz-Aigrain E (1996) Maternal corticotherapy. Pharmacology and effect on the fetus (article in French). J Gynecol Obstet Biol Reprod (Paris) 25(2):160–167
93. Garbis H, Elefant E, Diav-Citrin O, Schaefer C, Vial T, Clementi M, Valti E, McElhatton P, Smorlesi C, Rodriguez EP, Robert-Gnansia E, Merlob P, Peiker G, Pexieder T, Schueler L, Ritvanen A, Mathieu-Nolf M (2005) Pregnancy outcome after exposure to ranitidine and other H2-blockers. A collaborative study of the European Network of Teratology Information Services. Reprod Toxicol 19(4):453–458
94. Cappell MS (2003) Gastric and duodenal ulcers during pregnancy. Gastroenterol Clin North Am 32(1):263–308
95. Charan M, Katz PO (2001) Gastroesophageal reflux disease in pregnancy. Curr Treat Options Gastroenterol 4(1):73–81
96. Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, van Tonningen MR, Clementi M, De Santis M, Robert-Gnansia E, Valti E, Malm H, Ornoy A (2005) The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Aliment Pharmacol Ther 21(3):269–275
97. Richter JE (2003) Gastroesophageal reflux disease during pregnancy. Gastroenterol Clin North Am 32(1):235–261
98. Nikfar S, Abdollahi M, Moretti ME, Magee LA, Koren G (2002) Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. Dig Dis Sci 47(7):1526–1529
99. Nielsen GL, Sorensen HT, Thulstrup AM, Tage-Jensen U, Olesen C, Ekbom A (1999) The safety of proton pump inhibitors in pregnancy. Aliment Pharmacol Ther 13(8):1085–1089
100. Nava-Ocampo AA, Velázquez-Armenta EY, Han JY, Koren G (2006) Use of proton pump inhibitors during pregnancy and breastfeeding. Can Fam Physician 52:853–854
101. Källén BA (2001) Use of omeprazole during pregnancy–no hazard demonstrated in 955 infants exposed during pregnancy. Eur J Obstet Gynecol Reprod Biol 96(1):63–68
102. Glock JL, Morales WJ (1993) Acute epiglottitis during pregnancy. South Med J 86(7):836–838
103. Berkovitch M, Diav-Citrin O, Greenberg R, Cohen M, Bulkowstein M, Shechtman S, Bortnik O, Arnon J, Ornoy A (2004) First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study. Br J Clin Pharmacol 58(3):298–302
104. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J (2001) Augmentin treatment during pregnancy and the prevalence of congenital abnormalities: a population-based case-control teratologic study. Eur J Obstet Gynecol Reprod Biol 97(2):188–192
105. Phupong V, Srettakraikul K (2004) Scrub typhus during pregnancy: a case report and review of the literature. Southeast Asian J Trop Med Public Health 35(2):358–360
106. Bothamley G (2001) Drug treatment for tuberculosis during pregnancy: safety considerations. Drug Saf 24(7):553–565
107. Dautzenberg B, Grosset J (1988) Tuberculosis and pregnancy. Rev Mal Respir 5(3):279–283
108. Holdiness MR (1987) Teratology of the antituberculosis drugs. Early Hum Dev 15(2):61–74
109. Gei AF, Pacheco LD, Vanhook JW, Hankins GD (2003) The use of a continuous infusion of epinephrine for anaphylactic shock during labor. Obstet Gynecol 102(6):1332–1335
110. Obenhaus T (1995) Intraoperative anaphylaxis to latex in pregnancy (article in German). Anaesthesist 44(2):119–122