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Pharmacological treatment of asthma and allergic diseases in pregnancy

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Abstract

Allergy incidence in pregnancy is about 20% and frequently observed as rhinitis and asthma. Asthma often coexists with allergic rhinitis in adults, and severe nasal findings are present in one out of every three pregnant women. Asthma and allergic rhinitis may worsen or remain unchanged in pregnancy. Allergic reactions can also worsen the course of pregnancy. Appropriate drug selection should be made for asthma and other allergic diseases, and possible risks should be explained to the pregnant woman. Increased risk perception of drug use may cause the pregnant woman to stop taking the drug suddenly and the disease to worsen. The purpose of the treatment in pregnancy is controlling the mother's disease while ensuring a normal course of fetal development. Treatment should be started with the least number of drugs and the lowest dose possible. Inhaled beta-2 adrenergic agonists and theophylline can be used as bronchodilators during pregnancy. Chlorpheniramine, loratadine and cetirizine may be preferred in allergic conditions requiring antihistamine use. Prednisone and also pseudoephedrine can be used during pregnancy, if necessary. The use of alpha-adrenergic drugs other than pseudoephedrine and epinephrine should be avoided except for anaphylaxis.

Keywords: Asthma, Allergic Rhinitis, Anaphylaxis, Drug, Pregnancy

Introduction

Allergy is an immune-system-mediated hypersensitivity reaction of the body to foreign substances. Allergy incidence in pregnancy is about 20% and frequently observed as rhinitis and asthma [1,2]. Drug and food allergies, acute urticaria, allergic conjunctivitis and anaphylaxis are also allergic reactions that may occur in pregnancy. Allergic reactions can worsen the course of pregnancy. Similarly, pregnancy can worsen or trigger pre-existing allergic disease. Therefore, follow-up care is important for allergic conditions during pregnancy.

Hormonal changes due to pregnancy cause some physiological changes in the respiratory system. Respiratory volume (tidal volume), minute volume, alveolar-arterial oxygen gradient, oxygen partial pressure and partial blood pH (to respiratory alkalosis) increase during pregnancy, while functional residual capacity, residual volume, diffusing capacity and partial carbon dioxide pressure decrease. Respiratory rate generally does not change [3]. Therefore, respiratory symptoms in pregnant women with previous asthma may worsen gradually or remain unchanged [4].

Similar to asthma, allergic rhinitis may worsen or remain unchanged as a result of hormonal changes during pregnancy [5]. Severe nasal findings are present in one out of every three pregnant women [6]. Allergic rhinitis in adults often coexists with asthma. 80% of adults with asthma have allergic rhinitis, and 20-50% of adults with allergic rhinitis have asthma [7].

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Appropriate drug selection should be made for asthma and other allergic diseases, and possible risks should be explained to the pregnant woman. There may be an increased risk perception in pregnant women in terms of adverse drug-related consequences. Increased risk perception of drug use may cause the pregnant woman to stop taking the drug suddenly and the disease to worsen. For this reason, the most accurate treatment choice should be made for both pregnant women and the baby, and detailed up-to-date data on the possible effects of drugs on pregnancy should be known [8].

Asthma treatment in pregnancy

The purpose of the treatment of asthma during pregnancy is controlling the mother's disease while ensuring a normal course of fetal development. It is aimed that asthma symptoms and acute attacks do not occur, the daily activities of the pregnant are not limited and the quality of life does not decrease, and the lungs reach a respiratory capacity close to normal. Uncontrolled asthma during pregnancy will impair maternal lung functions and reduce the amount of oxygen in the blood, so it will have a greater effect on fetal development than asthma drugs. Therefore, treated asthma during pregnancy is considered a safer condition than untreated asthma with avoided drug use.

It is important to follow up the asthmatic pregnant during her pregnancy. It is recommended to evaluate the lung functions of pregnant women by performing a spirometry test with monthly follow-up. It should be ensured that the pregnant woman avoids allergens and especially smoking that may worsen asthma symptoms or cause attacks. The patient must be informed and educated about the control and treatment of asthma, its effects on pregnancy and fetal development, and the correct use of drugs. Treatment should be started with the least number of drugs and the lowest dose possible, and the dose and amount of the drug should be adjusted according to the clinical picture.

1. Bronchodilators (beta agonists)

Short acting bronchodilators are used in acute attacks and situations where a quick effect is desired. Albuterol (salbutamol), terbutaline, metaproterenol are among the drugs in this group and their use by inhalation is recommended during pregnancy. Studies conducted to date on its use in pregnancy suggest that short-acting bronchodilators are safe. An increased risk in terms of congenital defects or other pregnancy problems has not been detected in pregnant women using short-acting bronchodilators compared to those who do not use these drugs [9- 11].

Long-acting beta agonists such as salmeterol and formoterol are used in the long-term control of asthma and are generally preferred in combination with inhaled glucocorticoids. Having less information about their use in pregnancy than other asthma medications, these drugs are recommended to be used only when necessary. It can have tocolytic effects when used near birth. Additionally, it may have betamimetic effects such as tachycardia, tremor, tremor, and hypoglycemia in the newborn. Since their chemical structures are similar to short-acting beta mimetics but they have a long effect, it is thought that their benefits in asthma control during pregnancy are higher than the possible risk.

The United States National Institute of Health (NIH) reported that the use of beta agonists during pregnancy was safe in its 2004 report, in which the treatment of asthma during pregnancy was evaluated in detail [12]. Although some studies conducted in recent years have reported that it may be associated with fetal cardiac defects [13] and cleft palate development [14], researchers have stated that this may be due to medication, asthma or other reasons, and that there are some limitations in the studies.

2. Glucocorticoids

Glucocorticoids are used in asthma and in many conditions other than asthma. Studies on their use during pregnancy indicate that they do not create an increased risk for fetal development. Glucocorticoids used by inhalation such as beclomethasone, budesonide and fluticasone are among the drugs that can be preferred in pregnant women in the treatment of asthma [15]. Budesonide and fluticasone are the safest ones and beclomethasone is widely used during pregnancy.

Regarding the systemic (e.g. oral) use of glucocorticoids in pregnancy, some studies have concluded that first trimester exposures may be associated with slight increases in the risk of cleft palate and cleft lip [16]. There are also few studies reporting an increased risk of preterm birth and low birth weight. However, in these studies, it could not be concluded as to whether the severity of asthma in pregnant women or drugs caused this correlation. On the other hand, it is thought that a severe asthma picture during pregnancy will bring more risk than drug use.

Since gestational diabetes and hypertension are more common in pregnant women using oral glucocorticoids, it is important to follow-up them. Uncontrolled diabetes and high blood pressure during pregnancy are risky conditions for both mother and fetal development.

3. Theophylline

Theophylline is a drug that can be used orally in the treatment of asthma and chronic obstructive pulmonary disease during pregnancy; however, it has now been replaced by more effective inhaled glucocorticoids. There are case reports reporting cardiovascular defects, otocephaly (not developing lower jaw and joining ears below) and extremity anomalies following theophylline use during pregnancy [17-19]. However, case reports are not sufficient to assess drug-related risks and determine a correlation. Studies on the use of theophylline in pregnancy have not found a relationship with stillbirth or congenital defects [20-22]. On the other hand, it is stated that an increase in fetal respiratory movements may be observed due to the use of theophylline during pregnancy [23].

Due to the changes that may occur in theophylline pharmacokinetics during pregnancy, the drug level in the blood should be monitored in patients using theophylline. Especially drug-drug interactions (for example when used with beta agonists) and theophylline toxicity are among the factors that limit the use of theophylline in pregnancy. It is recommended to keep serum theophylline concentrations at 5-12 mcg / ml. It has been reported that theophylline toxicity findings such as tremor, tachycardia and vomiting can be observed in babies born to mothers using theophylline [24, 25], and these findings are

detected in pregnancies with theophylline concentrations above 10 mcg / ml [26,27].

4. Leukotriene receptor antagonists

Leukotriene receptor antagonists, such as montelukast and zafirlukast, are recommended as alternative drugs in the treatment and control of chronic asthma. In a study examining pregnant women who used montelukast during their pregnancy, the pregnancy outcomes of 180 pregnant women, 166 of which were in the first trimester, were compared with those with asthma and non-asthmatic pregnant women who did not use montelukast [28]. Although no difference was observed between the babies of the pregnant women using other asthma medications, it was reported that the babies of the pregnant women using montelukast had a lower weight than the babies of the pregnant women who did not receive asthma treatment. This result indicates that asthma rather than drugs may cause low birth weight during pregnancy. In this study, an increase in the risk of birth defects in pregnant women using montelukast was not identified. In another study, 96 pregnant women with asthma using montelukast or zafirlukast were followed up, congenital defects (clubfoot / pes equinovarus, neurofibromatosis, imperforate anus) were found in three babies, and no increase in the risk of congenital defects was identified [29]. In the national studies conducted in Switzerland and Denmark, an increase in the risk of congenital defects was not identified in pregnant women using montelukast, while the increases in preterm birth and preeclampsia rates were linked to the asthma diseases of pregnant women [13, 30].

A small number of cases have been reported with limb anomalies following the use of montelukast during pregnancy. In the post-marketing research conducted by the manufacturer company, 271 pregnancies using montelukast were examined, 221 of the pregnant women were reported to have first trimester exposure and 9 of the babies born had congenital defects. While no increase in the risk of congenital defects due to montelukast use during pregnancy was identified, amniotic band deformity, polydactyly, foot deviation, hypospadias and penile curvature, thoracoabdominal syndrome, cystic kidney, hydrocele, and bifid tongue have been reported among congenital defects [31-33]. No causal relationship was found between the use of montelukast during pregnancy and fetal limb anomalies [34].

5. Zileuton/5-Lipoxygenase inhibitors

Since there is insufficient data on the use of Zileuton in pregnancy, it is recommended for use in the treatment of severe asthma that does not respond to other drugs. In patients receiving zileuton therapy, regular monitoring of liver function is required, and if an alternative drug can be used, the use of zileuton can be discontinued during pregnancy.

6. Omalizumab

Omalizumab is an immunomodulator used in the control of severe asthma. This monoclonal antibody treatment (anti-Ig E), which is applied once or twice a month, should be performed in a place with emergency medical intervention and by health personnel due to the risk of anaphylaxis. In case reports about its use during pregnancy, it was reported that asthma treatment was successful, and no pregnancy complication or fetal anomaly was observed [35-37]. According to the results of the reports on the use of omalizumab in pregnancy, 20 out of 169 births, most of whom had first trimester exposure, had congenital defects, of which 7 had major defects (hypospadias, arteriovenous malformation, bilateral renal pelvis dilatation, cutaneous mastocytosis, patent foramen ovale, vesicoureteral reflux) have been described [38]. Since the major defects observed did not show a pattern, it was not thought to be associated with omalizumab use during pregnancy. In the same study, preterm birth rates are around 15%, and researchers think this may be related to asthma. When the structural defects seen in babies were examined in detail, the researchers who reported that 6 out of 20 infants with congenital defects had ankyloglossia, did not include any comments regarding this anomaly in their studies, and underlined the need to investigate the effect of omalizumab in pregnancy in detail with controlled studies. Consequently, data on omalizumab use in pregnancy are not sufficient to make a risk assessment.

Treatment of allergic diseases in pregnancy

Apart from asthma, allergic rhinitis is one of the other allergic conditions that may worsen or need treatment in pregnancy. Treatment of allergic rhinitis during pregnancy is no different from treatment for non-pregnant patients. Due to their low systemic effects, intranasal drugs (such as intranasal steroid and montelukast) are preferred in pregnancy. Second-generation antihistamines (such as loratadine, cetirizine) can also be used during pregnancy, if necessary [39].

1. Antihistamines (H-1 receptor blockers)

First generation antihistamines (such as dexchlorpheniramine, chlorpheniramine, diphenhydramine, hydroxyzine, clemastine) used in allergy treatment are drugs with sedative side effects. Sedative effect does not occur in second generation antihistamines such as loratadine, cetirizine, levocetirizine, fexofenadine, ebastine, rupatadine. Although data on ebastine, desloratadine, fexofenadine and levocetirizine are very limited, there is sufficient data on the use of loratadine and cetirizine in pregnancy. In studies conducted on the use of cetirizine during pregnancy, the results of more than 1000 pregnant women were evaluated and an increase risk of congenital defects was not identified [40, 41].

Some studies conducted on pregnant women using loratadine suggest that the use of loratadine during pregnancy increases the risk of hypospadias [42-45]. However, other prospective studies and many systematic analyzes revealed that the use of loratadine in pregnancy is not associated with the development of hypospadias [46]. Loratadine, as a non-sedating antihistamine, is one of the most preferred drugs in the treatment of allergies in pregnancy today.

There is no literature information on the possible effects of azelastine and olopatadine, which are used intranasally, during pregnancy. However, considering that the systemic effects of these drugs are negligible in terms of administration routes, it is not thought that they may affect fetal development.

2. Decongestants

Although decongestants are not used in the treatment of asthma, they are preferred for symptomatic treatment of upper respiratory tract allergies. Among the decongestants used orally or intranasally, pseudoephedrine is the most well-known, and oxymetazoline, phenylephrine and phenylpropanolamine are among these drugs. Because of vasoconstrictive effects, they

should not be used in pregnant women with high blood pressure and placental problems. Although some studies on decongestants' effects on pregnancy have shown associations with congenital defects such as extremity anomalies, gastroschisis, intestinal atresia and hemifacial microsomia, these findings have not been confirmed by other studies [47-49]. On the other hand, the absolute risk is considered quite low, since the defects mentioned in the studies are observed very rare. There is no conclusive evidence that decongestants are teratogenic.

Studies on the use of decongestants in pregnancy are rather limited and contain conflicting results. Therefore, until more detailed data are available, it is recommended to use pseudoephedrine as a nasal spray and not exceeding three days, if it is necessary to use it in the first trimester, which is important for organ development, It is not expected to cause problems in pregnant women who do not have high blood pressure and placental anomaly in the later stages of pregnancy. However, it should be kept in mind that nasal decongestants may lead to addiction in long-term use.

3. Corticosteroids

Corticosteroids such as triamnisolone, mometasone, budenoside, fluticasone can be used in pregnancy either intranasally or by inhalation. It may be preferred to use intranasal corticosteroids before the use of decongestants, especially in the treatment of allergic rhinitis. Similarly, since the systemic effects are unlikely when used at recommended doses, topical use of corticosteroids may also be required in the treatment of allergic dermatitis in pregnancy. However, applications on large surfaces should be avoided since it increases the possibility of systemic effects of glucocorticoids used topically.

Anaphylaxis treatment in pregnancy

Anaphylaxis is a life-threatening condition and therefore pregnant women should be treated like non-pregnant women; otherwise, fetal and maternal problems may occur. Oxygenation and volume replacement should be done primarily. In hypotensive conditions, the pregnant woman should be placed on her left side to eliminate possible vena cava inferior pressure [50]. Epinephrine can reduce uteroplacental blood flow; it can be used only if needed in the treatment of anaphylaxis. Systemic glucocorticoid therapy can be selected primarily in cases of life-threatening anaphylaxis. Intubation and tracheotomy may be required in cases with laryngeal spasm.

In a study on epinephrine use in the first trimester of pregnancy, several major and minor anomalies were observed. However, it has been reported that only the formation of inguinal hernia may be specifically related to the drug [51]. On the other hand, in a study examining 259 pregnant women with asthma using various sympathomimetics including epinephrine, no increase in congenital defects or adverse pregnancy outcomes was observed [52].

Although the prevalence of anaphylaxis during pregnancy is not known exactly, it can be said to be a rare condition [53]. Specific Ig-E antibodies are not expected to reach the fetus, since they do not pass through the placenta [54]. It is mainly maternal hypoxia or hypotension secondary to anaphylaxis that affects the fetus. In anaphylaxis, uteroplacental flow is disrupted and it may cause a series of complications that can lead to fetal distress, brain damage and death [55-57].

Conclusion

Inhaled beta-2 adrenergic agonists and theophylline can be used as bronchodilators during pregnancy. Chlorpheniramine, loratadine and cetirizine may be preferred in allergic conditions requiring antihistamine use. Prednisone and also pseudoephedrine can be used during pregnancy, if necessary. It is recommended that the use of alpha-adrenergic drugs other than pseudoephedrine and epinephrine should be avoided except for anaphylaxis.

References

1. Incaudo GA. Diagnosis and treatment of allergic rhinitis and sinusitis during pregnancy and lactation. Clin Rev Allergy Immunol. 2004;27:159Y177.
2. Kwon HL, Belanger K, Bracken MB. Asthma prevalence among pregnant and childbearing-aged women in the United States: estimates from national health surveys. Ann Epidemiol. 2003;13:317Y324.
3. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. Am Rev Respir Dis. 1980;121:559Y581.
4. Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, et al. Asthma morbidity during pregnancy can be predicted by severity classification. J Allergy Clin Immunol. 2003;112:283Y288.
5. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy. Safety considerations. Drug Saf. 1999;20:361Y375.
6. Mabry RL. Rhinitis of pregnancy. South Med J. 1986;79:965Y971.
7. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. Allergy. 2003;58:691–706.
8. Pali-Scholl I, Motala C, Jensen-Jarolim E. Asthma and allergic diseases in pregnancy a review. World Allergy Organ J. 2009;2:26–36.
9. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol. 2003;102(4):739–52.
10. Rayburn WF, Atkinson BD, Gilbert K, Turnbull GL. Short-term effects of inhaled albuterol on maternal and fetal circulations. Am J Obstet Gynecol. 1994;171(3):770–3.
11. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D. The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol. 1997;100(3):301–6.
12. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. 2004;1-57. https://www.nhlbi.nih.gov/files/docs/resources/lung/astpreg_full.pdf
13. Kallen B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infants. Eur J Clin Pharmacol. 2007Apr;63(4):383-8.
14. Munsie JPW, Lin S, Browne ML, Campbell KA, Caton AR, Bell EM, et al. Maternal bronchodilator use and the risk of orofacial clefts. Hum Reprod. 2011 Nov;26(11):3147-54.
15. Rahimi, R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Hum Exp Toxicol. 2006 Aug;25:447-52.
16. Xiao W, Liu X, Liu Y, Zhang D, Xue L. The relationship between maternal corticosteroid use and orofacial clefts - a meta-analysis. Reprod Toxicol. 2017;69:99-105.
17. Park JM, Schmer V, Mayers TL. Cardiovascular anomalies associated with prenatal exposure to theophylline. S Med J. 1990;83:1487-8.
18. Gilbert-Barness E, Drut RM. Association of sympathomimetic drugs with malformations. Vet Hum Toxicol. 2000;42(3):168-71.
19. Ibba RM, Zoppi MA, Floris M, et al. Otocephaly: Prenatal diagnosis of a new case and etiopathogenetic considerations. Am J Med Genet. 2000;90:427-9.
20. Heinonen OP, Stone D, Shapiro S. Birth Defects and Drugs in Pregnancy. Littleton:Publishing Sciences Group, 1977. pp. 367-370.
21. Neff RK, Leviton A. Maternal theophylline consumption and the risk of stillbirth. Chest. 1990;97:1266-7.
22. Stenius-Aarniala B, Riikonen S, Teramo K. Slow-release theophylline in pregnant asthmatics. Chest. 1995;107:642-7.
23. Ishikawa M, Yoneyama Y, Power GG, Araki T. Maternal theophylline administration and breathing movements in late-gestation human fetuses. Obstet Gynecol. 1996;88:973-8.
24. Arwood LL, Dasta JF, Friedman C. Placental transfer of theophylline: two case reports. Pediatrics. 1979;63:844-6.
25. Yeh TF, Pildes RS. Transplacental aminophylline toxicity in a neonate. Lancet. 1977;1:910.
26. Horowitz DA, Jablonski WJ, Mehta KA. Apnea associated with theophylline withdrawal in a term neonate. Am J Dis Child. 1982;136:73-4.
27. Ron M, Hochner-Celnikier D, Menczel J, Palti Z, Kidroni G. Maternal-fetal transfer of aminophylline. Acta Obstet Gynecol Scand. 1984;63:217-8.
28. Sarkar M, Koren G, Ying A, Kalra S, Smorlesi C, De Santis M, et al. Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes. Eur J Clin Pharmacol. 2009;65(12):1259-64.
29. Bakhireva LN, Jones KL, Schatz M, Klonoff-Cohen HS, Johnson D, Slymen DJ, et al. Safety of leukotriene receptor antagonists in pregnancy. J Allergy Clin Immunol. 2007;119:618-25.
30. Kallen B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy. 3. Congenital malformations in the infant. Eur J Clin Pharm. 2007;63(4):383-8.
31. Cavero-Carbonell C, Nikel-Hansen A, Rabanque-Hernandez MJ, Martos C, Garne E. Fetal exposure to montelukast and congenital anomialies: A population based study in Denmark. Birth Defects Res. 2017;109(6):452-9.
32. Merck Pregnancy Registry for SINGULAIR (montelukast sodium). Fourtheenth Annual Report Covering the period from U.S. approval (February 20, 1998) Merck Research Labs, West Point, PA. [Cited 2021 June 18]. Available from: http://www.merckpregnancyregistries.com
33. Singulair. Product Labeling. [Cited 2021 June 18]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020829Orig1s068,020830Orig1s070,021409Orig1s045lbl.pdf
34. Nelsen, lM, Shields KE, Cunningham ML, Stoler JM, Barnshad MJ, Eng PM, et al. Congenital malformations among infants born to women receiving montelukast, inhaled corticosteroids and other asthma medications. J Allergy Clin Immunol. 2012;129(1): 251-4.
35. Hirashima J, Hojo M, Iikura M, Hiraishi Y, Nakamichi S, Sugiyama H, et al. A case of an asthma patient receiving omalizumab during pregnancy. Arerugi. 2012;61(11):1683-7.
36. Kuprys-Lipinska I, Tworek D, Kuna P. Omalizumab in pregnant women treated due to severe asthma: two case reports of good outcomes of pregnancies. Postep Derm Alergol. 2014;2:104-7.
37. Ghazanfar MN, Thomsen SF. Successful and safe treatment of chronic spontaneous urticaria with Omalizumab in a woman during two consecutive pregnancies. Case Rep Med. 2015;2015:368053.
38. Namazy J, Cabana MD, Scheuerle AE, Thorp JM Jr, Chen H, Carrigan G, et al. The Xolair pregnancy registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol. 2015;135(2): 407-12.
39. Yawn B, Knudtson M. Treating asthma and comorbid allergic rhinitis in pregnancy. J Am Board Fam Med. 2007;20:289Y298.
40. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational study. Reprod Toxicol. 2008;26:19-23.

41. Kallen B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med. 2002;11:146-52.
42. Kallen B, Olausson PO. Monitoring of maternal drug use and infant congenital malformations. Does loratadine cause hypospadias? Int J Risk Saf Med. 2001;14:115-9.
43. Moretti MD, Caprara D, Coutinho CJ, Bar-Oz B, Berkovitch M, Addis A, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. J Allergy Clin Immunol. 2003;111:479-83.
44. Werler M, McCloskey C, Edmonds LD, Olney R, Reefhuis J. Evaluation of an association between loratadine and hypospadias - United States 1997-2001. Morb Mortal Wkly Rep 2004;53(10):219-21.
45. Pedersen L, Nrgaard M, Skriver MV, Olsen J, Srensen HT. Prenatal exposure to loratadine in children with hypospadias: a nested case-control study within the Danish National Birth Cohort. Am J Ther. 2006;13:320-4.
46. Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. Drug Saf. 2008;31(9):775-88.
47. Werler MM, Mitchel AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. Teratology. 1992;45:361-5.
48. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology. 1996;54:84-92.
49. Yau WP, Mitchell AA, Lin KJ, Werler MM, Hernandez-Diaz S. Use of decongestants during pregnancy and the risk of birth defects. Am J Epidemiol. 2013;178(2):198-208.
50. Witter FR, Niebyl JR. Drug intoxication and anaphylactic shock in the obstetric patient. In: Berkowitz RL, editor. Critical care of the obstetric patient. New York: Churchill Livingstone; 1983.
51. Heinonen OP Stone D, Shapiro S. Birth Defects and Drugs in Pregnancy. Littleton, Publishing Sciences Group, 1977, pp 345-56, 439, 477, 492.
52. Schatz M, Zeiger RS, Harden KM, Hoffman CP, Forsythe AB, Chilingar LM, et al. The safety of inhaled (beta)-agonist bronchodilators during pregnancy. J Allergy Clin Immunol 1988;82:686-95.
53. Hayashi RH. Emergency care in pregnancy. In: Queenan JT, editor. Management of high-risk pregnancy. Oxford: Blackwell Science; 1999:377.
54. Baraka A, Sfeir S. Anaphylactic cardiac arrest in a parturient. Response of the newborn. JAMA. 1980;243:1745Y1746.
55. Entman SS, Moise KJ. Anaphylaxis in pregnancy. South Med J. 1984;77:402.
56. Klein VR, Harris AP, Abraham RA, Niebyl JR. Fetal distress during a maternal systemic allergic reaction. Obstet Gynecol. 1984;64:15SY17S.
57. Luciano R, Zuppa AA, Maragliano G, Gallini F, Tortorolo G. Fetal encephalopathy after maternal anaphylaxis. Case report. Biol Neonate. 1997;71:190Y193.

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