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OVER THE COUNTER DRUGS DURING PREGNANCY- TIPS FOR A CORRECT APPROACH

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Abstract. From the viewpoint of pharmaco-therapeutic approach, pregnancy is a period that deserves special consideration. Health care providers face concerns regarding the safety and efficiency of drugs for both mother and fetus. Ethical considerations limit clinical testing during pregnancy, so there is an important lack in safety data. There is a general misconception that all drugs are harmful to the fetus, therefore mothers expose themselves to high risks refusing medication in life threatening medical conditions. On the other hand, although they are readily available, over-the-counter (OTC) drugs should not be used by pregnant women without the physician's advice. While there is a fairly good safety record for some commonly used OTC medication like short-acting NSAIDs, calcium based antacids, Chlorpheniramine, or PPIs, the misuse of others can be harmful to the fetus. Therefore it is very important to always assess that benefits overweight the risks while using OTC drugs during pregnancy.

Introduction

Pregnancy is a physiological condition characterized by multiple pharmacological particularities for the embryo, fetus and mother. The use of drugs during pregnancy and lactation remains a controversial issue, with serious medical and emotional implications. Health care providers deal with concerns related to the safety and efficiency of therapy, both for the mother and for the fetus. [1,2]

The unfortunate experience with thalidomide in the early 60's had multiple consequences, among which: development of clinical pharmacology as a discipline, reconsidering the way drugs are used during pregnancy and preclinical testing of new drugs for both efficacy and toxicity.[3]

Preclinical studies are without doubt a powerful tool, minimizing drugs' toxic effects on patients. Animal reproductive studies are extremely useful in preventing the release of drugs with significant pregnancy risks, but they have certain limitations due to pharmacokinetic and pharmacodynamic differences between humans and animals. Therefore clinical testing of drugs is also mandatory, providing vital data regarding safety and efficacy. [4, 5]

The risk of toxic effects on both mother and fetus led to serious limitation of clinical testing during pregnancy. Therefore, due to ethical consideration, a significant number of drugs are marketed without relevant information of their use in pregnant women.[6]

On the other hand, medical conditions can occur at any time during pregnancy. Acute or chronic underlying diseases require adequate control to ensure optimal health of both mother and fetus, cases in which the use of drugs will be necessary. A study by Andrade and colleagues in 2004 showed that a pregnant woman is prescribed 3-5 drugs during pregnancy, and 64% of pregnant women receive at least one drug during pregnancy: antibiotics, antiemetics, tranquilizers, analgesics, etc.[7] Numerous other studies on this topic also underline the frequent use of medication in pregnancy.[1,8,9,10]

Unfortunately not only drugs prescribed by doctors are used by pregnant women, but also self chosen OTC medication, herbals and dietary supplements, which they consider to be totally safe and therefore misuse.[11,12] At the opposite side, fearing side effects, a number of pregnant women stop their chronic treatment without medical advice, sometimes with serious life threatening consequences.[13]

Overall, if medical conditions require it, medication should be used during pregnancy and lactation only under strict medical supervision, with systematic monitoring pre, intra and post-partum.

Pharmacokinetic and pharmacodynamic changes in pregnancy

As a study by Loebstein and collaborators underlines, absorption, distribution, biotransformation, clearance, and especially adherence to therapy strongly influence the outcome of medication during pregnancy.14 Since classical methods like collecting repetitive blood samples

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for assessing pharmacokinetic changes is not suitable during this delicate period, new investigative methods like hair analysis are being studied.[15, 16]

Absorption of drugs can be affected due to decreased intestinal motility and delayed gastric emptying time. Another limiting factor is the gastric acidity, which decreases on average by 40% during pregnancy. Nausea and vomiting can cause delayed or incomplete absorption of nutrients and medication. Evening doses can partially overcome this. Underlying chronic conditions like inflammatory bowel disease can also lead to decreased absorption.[17]

Distribution is another process that can be modified under this particular condition. Increased body weight, plasmatic volume and cardiac output during pregnancy can lead to a relative decrease in plasma concentration. During the third trimester the serum albumin concentration decreases, causing an increase in free form of the drugs that extensively bind to it. This can ultimately result in higher efficacy, but also possible toxic effects of such medication.[18]

Metabolic changes have also been noticed during pregnancy, but their mechanism remains partially unknown. The hepatic metabolism of drugs can be influenced by the increased level of hormones and also by the modified activity of cytochrome enzymes, which can be increased (CYP3A4, CYP2D6, and CYP2A6) or decreased (CYP1A2, CYP2C19) in pregnant women. [19] During pregnancy higher clearance rate for drugs which are renally excreted can be noticed. This is due to increased glomerular filtration (up to 50%) and can require dose adjustment.[18] As the pregnancy advances, the placental barrier's permeability increases up to ten times. Therefore most drugs administrated to the mother, cross into the fetal circulation, raising safety concerns. For better understanding and predicting this process, placental perfusion models are currently under study.[20]

Adherence to therapy has been suggested as an important limiting factor, since a number of pregnant women refuse to follow prescribed therapies fearing side effects. The consequences are serious, sometimes even lethal.[15]

Pharmacodynamic modifications can also occur during this period due to decreased immunity, increased risk of nausea and vomiting, depression, acute condition induced by pregnancy, etc. Therefore, clinical studies that have not been conducted on pregnant women may not be relevant to them, and therapeutic regimens can require adjustment. [15, 19]

Concluding, knowledge on pharmacokinetic changes together with pharmacodynamic variability and eventual underlying medical conditions, should be integrated for designing an optimal individualized therapeutic plan for each pregnant patient.

Selection of drugs in pregnancy

Although a number of drugs have been proven to have teratogenic effects, so unnecessary exposure should be avoided, this shouldn't limit the correct use of medication during pregnancy. As discussed above, when medical conditions require it, drugs should be given even during pregnancy. A study by Brent showed that exposure to drugs during pregnancy is responsible for producing congenital malformations in less than 1% of cases.[21] Therefore patients should be informed that not all medication can cause birth defects, and in correctly chosen cases the benefit outweighs the risks.1

Some factors are very relevant and should be carefully considered for an optimal therapeutic plan. Beside the drug itself, the route of administration, dosage, posology and gestational age can influence the safety profile of medication.[22] During the first 2 weeks pregnancy goes by the law "all or nothing", so if the embryo undergoes teratogenic changes due to drug exposure, it is spontaneously eliminated. Between 18 and 60 days after conception (organogenesis stage), improper medication can cause structural abnormalities such as growth impairment, CNS abnormalities, or even death. Different classes of drugs are known to have these risks: chemotherapeutic agents (methotrexate, cyclophosphamide), sex hormones (diethylstilbestrol), lithium, retinoids, thalidomide, some antiepileptics, coumarin derivatives, etc. On the other hand, drugs considered safe in the first trimester, can be contraindicated in the third. This is the case of the most used OTC medication, NSAIDs.[23, 24]

A review by Lo and Friedman showed that in 2002 teratogenic information was still unknown for more than 90% of the medication approved by the FDA between 1980 and 2000.[25] Even when information is available, the access to it is still, many times, delayed due to the lack of a common data base or proper labeling containing all relevant data.[8] These indicate that accessible and up-to-date drug information should be available to health care providers and also to women. This would decrease the exposure to unnecessary toxic risks, and pregnant women with medical conditions that require drug therapy wouldn't refuse to follow it due to the fear of unknown teratogenic effects.[8, 26]

A first step in this direction was taken in 1979 by the Food and Drug Administration (FDA), whom at that time introduced specific regulations regarding the administration of drugs in pregnancy and lactation, as response to the 1962' thalidomide cases. This has lead to a classification according to the presence or absence of data on the effect of drugs in pregnancy, source of such data (animal or human), and results of studies (positive or negative). The five categories that drugs were classified in are shown in the table below.[28]

The above classification is far from an optimal one, with many weak points among which:

- One could assume that classification of drugs in the same category implies that all carry the same type, severity or incidence of fetal anomalies, which is not the case
- In class B there is no clear difference in relevance if the data is collected from animals or humans
- Categories are seen as a scale for risk increase, without looking into the risk/benefit balance.[28, 29]

These lacks were underlined during the FDA public hearing in 1997, leading to the Proposed Rule for Pregnancy and Lactation Labeling in 2008. It was concluded that dividing into categories wouldn't be the optimal solution, but a narrative labeling model, with the separation of clinical information from animal data.

Labeling for pregnancy and lactation would stipulate drug data referring to:

- fetal risk (for both systemically and not systemically absorbed drugs, based on animal data and, when available, human data)
- clinical considerations (inadvertent exposure, risk for pregnant and the fetus due to the medical condition or to the drug, effects of exposure, dose and duration of treatment, potential neonatal complications effects during labor and birth)
- data (human data first, than animal data, including description of the study) [28, 29]

Since this is not a labeling law yet, and there is no complete source that gathers all available information on correct management of medication for pregnant women, doctors should consult multiple sources, besides the drug label. Reliable and up to date for this purpose are case reports and follow-up case-control studies presented during conference meetings, medical literature (Sheppard's Catalog of Teratogenic Agents, REPROTOX), on-line data bases (REPROTEX, TERIS), and different informatics systems REPRORISK, etc.[8]

General recommendations for over-the-counter drugs (OTCs) during pregnancy

Self-care and active participation are becoming issues of awareness in many of life's aspects, including pharmacotherapy. For this mater, in the last decades OTC's have been gaining territory over prescription drugs. A lot of previously prescribed medication is now marketed over-the-counter. As a result, approximately 60 percent of the drugs on the United States' market are OTC's.[30]

This is valid also for pregnant women, studies showing that 80% of them take at least one OTC drug during the gestational period.[31] Around 60 % of them use nonprescription drugs as advised by a physician, but the rest use auto medication, which can result in adverse effects for both mother and fetus.[23]

Among OTC drugs pregnant women most frequently use non, steroidal anti-inflammatory drugs (NSAIDs) rank among the first positions, these including aspirin, mostly for pain relive.[23] Available data concerning their safety during this delicate period lacks consensus. For example, regarding the risk of miscarriage, a clinical study by Li concluded that the use of aspirin increases this risk, while one published three years later by Keim proved the opposite.[32, 33]

Although so far NSAIDs are not known to have teratogenic effects on humans, due to the maternal and fetal possible risks they should be used in the lowest effective doses, and discontinued in the last 6-8 weeks of pregnancy. Different studies indicate as possible fetal risks premature closure of the ductus arteriosus, intracranial bleeding, renal dysfunction, and oligohydramnios. Especially in high doses (over 3g of aspirin) these drugs increase the risk of maternal anemia, prolonged gestations by inhibiting uterine contractions, and peri partum hemorrhage. [23, 24, 34]

Used in small doses for its antiplatelet effect, acetylsalicylic acid (eventually in combination with heparin) is the most effective therapy in patients with anti-phospholipid syndrome and a history of spontaneous abortion.[24,35,36] Clinical studies have proved that in low doses aspirin is also beneficial for preventing preeclampsia and intrauterine growth restriction.[24,37]

Acetaminophen is an analgesic frequently used during pregnancy due to its good safety profile. It does not increase the risk of miscarriage, fetal intracranial hemorrhage, or maternal bleeding (no antiplatelet effect), but maternal abuse or chronic over dosage can lead to acute liver failure. Some studies suggest that short-acting NSAIDs, with inactive metabolites, such as diclofenac and ibuprofen, are safer for pregnant women. [23, 24]

Nausea and vomiting are common conditions during pregnancy. Although they are regarded as normal problems especially during the first trimester, selected cases can require therapy. Therapeutic options go from lifestyle changes, to antiemetic drugs, severe cases requiring hospitalization.

When non-pharmacological options like dietary changes fail to control nausea and vomiting, and they become a health threatening problem, drug therapy becomes mandatory. Since pregnant women have been excluded from most clinical trials, limited data is available on the safety of antiemetics during pregnancy. OTC medication such as vitamin B6 (pyridoxine), antihistamines (diphenhydramine, dimenhydrinate), dopamine antagonists like metoclopramid and phenothiazines (prochlorperazine, chlorpromazine, promethazine) are currently used for these conditions with good results and no reported congenital abnormalities.[38,39,40] Ondansetron, a serotonin antagonist, has also been proven efficient for hyper emesis gravidarum.[41]

Natural therapies such as ginger are also used for their antiemetic effect during pregnancy. Studies which have looked into the safety and efficiency of this traditional remedy, agree on its antiemetic properties, and no teratogenic effects have been noticed so far.[42, 43]

Nausea and vomiting can also be caused by acid reflux and heartburn. In such cases, acid-reducing medication should be considered.[44] Proton-pump inhibitors and H2 blockers are efficient for this matter and so far clinical studies did not show any fetal risks related to them. Antacids can also be used symptomatically and are considered safe, but due to the tocolytic properties of magnesium sulfate and the general concerns about aluminum, the agents containing calcium seem a safer choice. [23, 45, 46]

Due to immunologic changes pregnant women are more susceptible to medical conditions such as common colds. Therapeutic options include OTC drugs such as NSAIDs (already discussed above), antihistamines, decongestants and expectorants.

Antihistamines such as diphenhydramine are used not only for common cold, but also for allergies, nausea, sedation, although few data confirm their safety during pregnancy. Furthermore, in high doses the drug has been shown to have oxytocin-like effects. With a better safety profile, the American College of Obstetricians and Gynecologists recommended chlorpheniramine. [23]

Oral decongestants like pseudoephedrine and phenylephrine, as well as local decongestants like

xylometazoline and oxymetazoline are considered safe during pregnancy, with no malformations reported in clinical studies.[47, 48] Expectorants like guaifenesin are also used during pregnancy, although some studies suggested that their use during the first trimester could increase the risk of neural tube defects.[23, 49]

Conclusion

For the majority of OTC drugs no clinical studies have been conducted on pregnant women, all safety data being initially obtained through animal studies, and further on from case-reports and follow-up studies. Therefore, to correctly assess the risk/benefit, healthcare providers should access all complementary sources that become available once the drugs are marketed, not only the safety data provided by the producing company.

Another aspect to be underlined concerns the fear of medication among pregnant women. They should indeed avoid self medication, but there is no justification for not taking or discontinuing pharmacotherapy when this is being recommended by the physician. This attitude can have serious consequences for both mother and fetus, and should be overcome by offering complete information on the medication that is being prescribed.

References

1. **Knoppert D.** Safety and efficacy of drugs in pregnancy. *J Popul Ther Clin Pharmacol.* **2011;18(3):e506-12. Epub 2011 Nov 14.**
2. **Mehta N, Larson L.** Pharmacotherapy in pregnancy and lactation. *Clin Chest Med.* **2011 Mar;32(1):43-52.**
3. **Ward SP.** Thalidomide and Congenital Abnormalities. *Br Med J.* **1962 September 8; 2(5305): 646–647.**
4. **Brent RL.** Utilization of juvenile animal studies to determine the human effects and risks of environmental toxicants during postnatal developmental stages. *Birth Defects Res B Dev Reprod Toxicol.* **2004 Oct;71(5):303-20.**
5. **Suvorov A, Takser L.** Facing the challenge of data transfer from animal models to humans: the case of persistent organohalogens. *Environ Health.* **2008 Nov 13;7:58.**
6. **Domínguez V, Ramos N, Torrents A, García D, Carné X.** Clinical trials during pregnancy: what has been done. *Eur J Clin Pharmacol.* **2011 Nov 11. [Epub ahead of print].**
7. **Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, et al**. Prescription drug use in pregnancy. *Am J Obstet Gynecol.* **2004 Aug;191(2):398-407.**
8. **Lagoy CT, Joshi N, Cragan JD, Rasmussen SA**. Medication Use during Pregnancy and Lactation: An Urgent Call for Public Health Action. *J Womens Health*, **2005 Feb:2:104-109.**
9. **Buhimschi CS, Weiner CP.** Medications in pregnancy and lactation: part 1. Teratology. *Obstet Gynecol.* **2009 Jan;113(1):166-88.**
10. **Lalonde AB.** Drugs indicated for use during pregnancy. *J Popul Ther Clin Pharmacol.* **2011;18(3):e513-5. Epub 2011 Nov 14**.
11. **Low Dog T.** The use of botanicals during pregnancy and lactation. *Altern Ther Health Med.* **2009 Jan-Feb;15(1):54-8.**
12. **Conover E, Buehler BA.** Use of herbal agents by breastfeeding women may affect infants. *Pediatr Ann.* **2004 Apr;33(4):235-40.**
13. **Einarson A.** Abrupt discontinuation of psychotropic drugs following confirmation of pregnancy: a risky practice. *J Obstet Gynaecol Can.* **2005 Nov;27(11):1019-22.**
14. **Loebstein R, Lalkin A, Koren G.** Pharmacokinetic changes during pregnancy and their clinical relevance. *Clin Pharmacokinet.* **1997 Nov;33(5):328-43.**
15. **Koren G.** Pharmacokinetics in pregnancy; clinical significance. *J Popul Ther Clin Pharmacol.* **2011;18(3):e523-7. Epub 2011 Nov 14.**
16. **Gray T, Huestis M.** Bioanalytical procedures for monitoring in utero drug exposure. *Anal Bioanal Chem.* **2007 Aug;388(7):1455-65. Epub 2007 Mar 17.**
17. **Heetun ZS, Byrnes C, Neary P, O'Morain C.** Review article: Reproduction in the patient with inflammatory bowel disease. *Aliment Pharmacol Ther.* **2007 Aug 15;26(4):513-33.**
18. **Pavek P, Ceckova M, Staud F.** Variation of drug kinetics in pregnancy. *Curr Drug Metab.* **2009 Jun;10(5):520-9.**
19. **Anderson GD.** Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *Clin Pharmacokinet.* **2005;44(10):989-1008.**
20. **Hutson JR.** Prediction of placental drug transfer using the human placental perfusion model. *J Popul Ther Clin Pharmacol.* **2011;18(3):e533-43. Epub 2011 Nov 14.**
21. **Brent RL.** Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and post-conception environmental radiation exposures. *33rd Annual Meeting of the National Council on Radiation Protection and Measurements.* **April 2–3, 1997, Arlington, VA. Teratology, 59 (1999), pp. 182–204.**
22. **Buhimschi CS, Weiner CP.** Medications in pregnancy and lactation: Part 2. Drugs with minimal or unknown human teratogenic effect. *Obstet Gynecol.* **2009 Feb;113(2 Pt 1):417-32.**
23. **Black RA, Hill DA.** Over-the-Counter Medication in Pregnancy. *Am Fam Physician.* **2003 Jun; 67(12):2517-2524.**
24. **Janssen MM, Genta MS.** The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med.* **2000 Mar 13;160(5):610-9.**
25. **Lo WY, Friedman JM.** Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol.* **2002 Sep;100(3):465-73.**
26. **Coverdale JH, McCullough LB, Chervenak FA.** The ethics of randomized placebo-controlled trials of antidepressants with pregnant women: a systematic review. *Obstet Gynecol.* **2008 Dec;112(6):1361-8.**
27. **Briggs GG, et al.** Drugs in Pregnancy and Lactation. *7th ed. Philadelphia: Williams & Wilkins*, **2005**.
28. **Feibus KB.** FDA's proposed rule for pregnancy and lactation labeling: improving maternal child health through well-informed medicine use. *J Med Toxicol.* **2008 Dec;4(4):284-8.**
29. **Food and Drug Administration**, HHS. Requirements on content and format of labeling for human prescription drug and biological products. *Final*

rule. Fed Regist. **2006 Jan 24;71(15):3921-97.**
30. **Jacobs LR.** Prescription to over-the-counter drug reclassification. *Am Fam Physician.* **1998 May 1;57(9):2209-14.**
31. **Matt DW, Borzelleca JF.** Toxic effects on the female reproductive system during pregnancy, parturition, and lactation. *In: Witorsch RJ, ed. Reproductive toxicology. 2nd ed. New York: Raven,* **1995:175-93.**
32. **Li DK, Liu L, Odouli R.** Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ.* **2003 Aug 16;327(7411):368.**
33. **Keim SA, Klebanoff MA.** Aspirin use and miscarriage risk. *Epidemiology.* **2006 Jul;17(4):435-9.**
34. **Ostensen ME, Skomsvoll JF.** Anti-inflammatory pharmacotherapy during pregnancy. *Expert Opin Pharmacother.* **2004 Mar;5(3):571-80.**
35. **Farquharson RG, Quenby S, Greaves M.** Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol.* **2002 Sep;100(3):408-13.**
36. **Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S.** Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database Syst Rev.* **2009 Jan 21;(1):CD004734.**
37. **Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, Forest JC, Giguère Y.** Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol.* **2010 Aug;116(2 Pt 1):402-14.**
38. **Badell ML, Ramin SM, Smith JA.** Treatment Options for Nausea and Vomiting During Pregnancy. *Pharmacotherapy.* **2006;26(9):1273-1287.**
39. **Tan PC, Khine PP, Vallikkannu N, Omar SZ.** Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. *Obstet Gynecol.* **2010 May;115(5):975-81.**
40. **Tan PC, Omar SZ.** Contemporary approaches to hyperemesis during pregnancy. *Curr Opin Obstet Gynecol.* **2011 Apr;23(2):87-93.**
41. **Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G.** The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG.* **2004 Sep;111(9):940-3.**
42. **Tiran D.** Ginger to reduce nausea and vomiting during pregnancy: Evidence of effectiveness is not the same as proof of safety. *Complement Ther Clin Pract.* **2012 Feb;18(1):22-5.**
43. **Boone SA, Shields KM.** Treating pregnancy-related nausea and vomiting with ginger. *Ann Pharmacother.* **2005 Oct;39(10):1710-3. Epub 2005 Aug 30.**
44. **Gill SK, Maltepe C, Mastali K, Koren G.** The effect of Acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy. *Obstet Gynecol Int.* **2009;2009:585269. Epub 2009 Jul 1.**
45. **Matok I, Levy A, Wiznitzer A, Uziel E, Koren G, Gorodischer R.** The Safety of Fetal Exposure to Proton-Pump Inhibitors During Pregnancy. *Dig Dis Sci.* **2011 Oct 30. [Epub ahead of print].**
46. **Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Uziel E, Levy A.** The safety of H(2)-blockers use during pregnancy. *J Clin Pharmacol.* **2010 Jan;50(1):81-7. Epub 2009 Sep 29.**
47. **Kallen BA, Olausson OP.** Use of oral decongestants during pregnancy and delivery outcome. *Am J Obstet Gynecol.* **2006;194(2):480–5.**
48. **Rayburn WF, Anderson JC, Smith CV, Appel LL, Davis SA.** Uterine and fetal Doppler flow changes from a single dose of a long-acting intranasal decongestant. *Obstet Gynecol.* **1990 Aug;76(2):180-2.**
49. **Erebara A, Bozzo P, Einarson A, Koren G.** Treating the common cold during pregnancy. *Can Fam Physician.* **2008 May;54(5):687-9.**