Published in final edited form as:

Semin Perinatol. 2015 November ; 39(7): 508–511. doi:10.1053/j.semperi.2015.08.002.

Epidemiology of Medications Use in Pregnancy

Martina Ayad, MD and

Fellow, Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, The University of Texas Medical Branch, Galveston, TX

Maged M. Costantine, MD

Associate Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, The University of Texas Medical Branch, Galveston, TX

Abstract

The use of prescribed and over-the-counter medications in pregnancy is on the rise. Many women become pregnant at an older age and with pre-existing medical conditions that require pharmacotherapy. In addition, pregnancy is associated with profound changes in the physiology of virtually every organ in the body, which affect medications' pharmacokinetics and pharmacodynamics. Despite all of these, pregnant women are still considered therapeutic orphans as the majority of current therapeutics were never studied in pregnancy. The goals of this review are to synthesize the available information regarding the epidemiology of medications use and the state of drug research in pregnancy, in an effort to highlight the need for pharmacologic research in pregnancy.

Epidemiology of Medications Use in Pregnancy

The use of medications in pregnancy has been progressively increasing over the past 3–4 decades. (1) This is predominantly due to changing in the demographics of pregnant women, the prevalence of preexisting medical comorbidities and the development of obstetric conditions that require pharmacotherapy during pregnancy. (1) Despite this, pregnant women are still considered therapeutic orphans as the majority of therapeutics and biologics were never studied in them during development. The pregnancy-induced changes in maternal physiology affect medications' pharmacokinetic and secondary pharmacodynamic properties. The purpose of this paper is to provide a general overview on the epidemiology of medications use and the state of drug research in pregnancy, in an effort to highlight the need for the latter.

Corresponding author: Maged M. Costantine, MD, Department of Obstetrics and Gynecology, The University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-0587, Phone 409-772-1571, Fax 409-772-5297, mmcostan@utmb.edu.

Conflicts of interests: The authors have nothing to disclose

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Medications use in pregnancy

The use of medications in pregnancy has been increasing over the past 3–4 decades both in the US and other developed countries. (1,2) In a recent review from the US, the average number of medications used by pregnant women increased by 68%, from 2.6 in 1976–1978 to 4.2 in 2006–2008. Currently, almost half of pregnant women use 4 or more drugs at some point during their pregnancy. (1) These numbers are not very different from studies in other developed countries. Using a web-based online questionnaire, Lupattelli and others showed that more than 80% of pregnant women in Europe, Australia and the Americas use at least one medication during pregnancy. (2) In addition to prescriptions medications, pregnant women are also self-medicating themselves with over-the-counter drugs and herbal products for which there are limited information in pregnancy. (3) Moreover, pregnant women use medications from across all the Federal Drug Administration (FDA) drug classification risk categories. In a review of more than 150 thousand pregnancies, Andrade et al found that while the majority (78%) of pregnant women are exposed to either class B or C drug, 1.1% and 3.4 % are exposed to either a class X or D. (4–6) (Class D indicates that there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; whereas class X indicates that studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.).

This increase in the use of medications is also predominant in the first trimester, where the average number of medications used increased by 62.5%, from 1.6 in 1976–1978 to 2.6 in 2006–2008; and almost one third of pregnant women use at least 4 medications. (1) This is concerning since the first trimester is a crucial period for organogenesis and placental development including trophoblast invasion, vascular remodeling and chorionic villi development; in addition many women are unaware of their pregnancy status. (1,5,7)

While there is no doubt that more pregnant women are using more medications, this is thought to be predominantly due to changing in the demographics of pregnant women. More women enter pregnancy at a later age (1,2) with increasing prevalence of preexisting chronic medical comorbidities (such as diabetes, hypertension, asthma, depression, and others) and increased risk of obstetric complications (e.g. nausea and vomiting of pregnancy, gestational diabetes, cholestasis of pregnancy, preeclampsia, etc...) that require pharmacotherapy. (4, 6, 8–13). For example, while less than 1% of pregnant women used an antidepressant in the late 1980's, it is estimated that almost 10% of pregnant women are currently prescribed psychotropic medicines, with antidepressants being the most common ones (7.5%). Moreover, 1.6% of pregnant women are using 2 or more different categories of psychotropic medications, most often a combination of an antidepressant and an anxiolytic. (8, 11) Similarly, the use of antihypertensive medications almost doubled from 1.7% in 1996 to 3.1% in 2005, with the most commonly used ones being calcium channel blockers, whereas the use of lipid lowering agents (e.g. statins) increased from 0.03% to 0.11% in the same

time period. (9, 10, 13) These examples highlight a pattern of the increase in medications use by pregnant women.

The state of drug research in pregnancy

Despite the above, pregnant women are still considered therapeutic orphans as the majority of current therapeutics were never studied in pregnancy during development. (14–18) Instead, their safety and toxicity data were obtained from either post-marketing surveillance or late stage retrospective studies. Similarly, their efficacy and dosing data were extrapolated from studies conducted in men or non-pregnant women. In a review of the labeling data of 213 new pharmaceuticals approved by the FDA between 2003 and 2012, only 5% of them included human data in their pregnancy section, and almost half did not have any breastfeeding data at all. (18)

The lack of pregnancy data from the majority of therapeutics is a result of multitude of factors. Traditionally, pregnant women and women of child bearing age were prohibited from being enrolled in phase I testing studies, and it was not until the early 1990's that the FDA started requesting gender specific analysis of safety and efficacy data on all new drug applications, and the National Institute of Health started requesting the inclusion of women in human subjects research. (19) Additionally, there is a lack of interest from pharmaceutical companies to include pregnant women in their drug development studies due to several medico-legal risks and ethical concerns, as well as, a lack of enthusiasm as pregnant women represent a small percentage of the patient population that these companies target. These and other factors led pregnant women to being excluded from research studies in general and pharmacological studies specifically. In a review of all protocols submitted to a single institutional review board (IRB), Schonfeld et al found that pregnant women were excluded from more than 75% of all research protocols, and from more than 90% of all protocols involving drug studies. For the majority of these protocols, women were required to either have a negative pregnancy test or to be on a contraceptive method before consideration for enrollment in research studies. (17) Similarly, in a review of all phase IV interventional studies involving medications that were not thought to be teratogenic, enrolling women of childbearing potential in the US, and posted on www.ClinicalTrials.gov between October 2011 and January 2012, Shields et al, found that more than 95% of these studies excluded pregnant women. (16)

Need for pharmacokinetic studies in pregnancy

Given the dearth of research on drug therapies in pregnant women, physicians are faced with the dilemma of treating medical conditions with insufficient efficacy and safety information to make an evidence-based recommendation or decision regarding treatment options. (20–22) While teratogenicity is usually at the center of every decision regarding medications use in pregnancy, it should not be the only concern. In a recent review of the literature, less than 2% of all pharmacokinetic studies conducted in the US involved pregnant women. (23) The lack of pregnancy specific pharmacokinetic and dosing data leads physicians to extrapolate drug dosage regimens from non-pregnant subjects or men. This may lead to over or under dosing and may reduce efficacy or increase risk of toxicity.

The need for pregnancy specific pharmacokinetic data stems from the complex physiologic changes that occur in pregnancy and which affect a drug's pharmacokinetic profile. Pregnancy is characterized by significant changes in the anatomy and physiology of almost all systems, which affect medications pharmacokinetic and pharmacodynamic properties. Pharmacokinetics generally refers to —what the body does to the drug, and is usually described using the drug's absorption, distribution, metabolism and elimination; whereas pharmacodynamics refers to —what the drug does to the body and usually influences the drug's efficacy and safety. (15, 20, 24–27) For instance, absorption of orally administered drugs may be affected by changes in the gastrointestinal system such as delayed gastric emptying and decrease in gastrointestinal motility. This leads to decrease in maximum concentration and time to maximum concentration. (26, 28) During pregnancy, maternal blood volume increases by 40–50%, and total body water increases to almost 8.5 liters by the end of pregnancy. In addition, maternal fat stores and fat mass increase by almost 10 fold. The increase in blood volume and water within the body expands the volume of distribution of hydrophilic substances. On the other hand, the increase in fat mass leads to a larger volume of distribution of lipophilic drugs. For some drugs, a larger volume of distribution could lead to decreased peak serum concentration, which may necessitate a higher initial and maintenance dose to obtain therapeutic plasma concentrations. (24, 25, 29) Additionally, because of the decrease in serum albumin during pregnancy, highly protein bound compounds (such as digoxin, midazolam, and phenytoin) may display higher free levels, which increases their peak plasma concentrations, and thus risks of drug related side effects. (26, 29) Drug elimination, especially for renally cleared medications, is enhanced by the increased renal blood flow and glomerular filtration rate (40–65% increase) in pregnancy. (25, 26, 29) This can lead to significant increase (20 – 60%) in the elimination rates of renally cleared medications, leading to shorter half-lives, and risk of sub-therapeutic concentrations. Examples of these medications include lithium, ampicillin, cefuroxime, cefazolin, atenolol, and digoxin. Lastly, drug metabolism is also affected by the changes (increase and decrease) in the expression and activity of various metabolizing enzymes. (30–32) A more comprehensive review of pregnancy induced physiologic changes and their effects on medications pharmacokinetics is discussed elsewhere. (25–27, 29)

In view of the gaps in the scientific knowledge regarding medications pharmacokinetics and short- and long-term safety in pregnancy, lies the need to study the pharmacokinetic properties of many medications currently used for various obstetric indications (e.g. magnesium sulfate), as well as ones with potential impact in targeting molecular pathways involved in the pathophysiology of various obstetrical complications (e.g. statins) (22), or novel therapeutics for common medical conditions experienced by pregnant women (e.g. new anti-hepatitis C medications, newer oral anticoagulants, anti-epileptic medications, etc). (33) This will lead to more effective treatment of pregnant women, while reducing the risks of adverse events.

Conclusion

Despite the continuous rise in the proportion of women using medications in pregnancy, pregnant women remain excluded from drug trials, and a large scientific gap exists necessitating significant increase in drug research in pregnancy. However, there are vast

challenges in conducting these medications trials in pregnancy. These include low patient enrollment and unwillingness of many pregnant women to consent when healthy, the physiologic adaptations of pregnancy, the perceived risk of medications to pregnant women and their fetuses/infants, the lack of interest from pharmaceutical companies, and the lack of strong legislative support. (34) In order to circumvent these obstacles, potential solutions may include the development of better sampling strategies and pharmacokinetic/pharmacodynamic modeling techniques rendering the conduct of pharmacokinetic trials more feasible. Additionally, there is an urgent need to increase the support of pharmacokinetic trials in pregnancy through private/government-funding organizations, and to support current existing (or future) networks charged to perform obstetric-fetal pharmacology studies. More importantly, there is immediate need for legislative reform in order to encourage pharmaceutical companies to include pregnant women in their studies. We hope that the new FDA rule regarding drug classification represents a huge first step in encouraging research in this field. (35)

References

1. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs, 1976–2008. *Am J Obstet Gynecol*. 2011; 205:51.e1–8. [PubMed: 21514558]
2. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ*. 2014; 4:e004365.
3. Glover DD, Amonkar M, Rybeck BF, et al. Prescription, over-the-counter, and herbal medicine use in a rural obstetric population. *Am J Obstet Gynecol*. 2003; 188:1039–45. [PubMed: 12712107]
4. Andrade SE, Raebel MA, Morse AN, Davis RL, Chan KA, et al. 2006 Use of prescription medications with a potential for fetal harm among pregnant women. *Pharmacoepidemiol Drug Saf*. 2008; 15:546–54. [PubMed: 16586470]
5. Andrade SE, Gurwitz JH, Davis RL. Prescription drug use in pregnancy. *Am J Obstet Gynecol*. 2004; 191:398–7. [PubMed: 15343213]
6. Kao LT, Chen YH, Lin HC, Chung SD. Prescriptions for category D and X drugs during pregnancy in Taiwan: a population-based study. *pharmacoepidemiology and drug safety*. 2014; 23:1029–1034. [PubMed: 24578346]
7. Mitchell AA, Hernandez-Diaz S, Louik C, Werler MM. Medication use in pregnancy. *Pharmacoepidemiol Drug Saf*. 2001; 10:S146.
8. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol*. 2008; 198:94 e1–e5. [PubMed: 18166318]
9. Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D, Rolnick SJ, Roblin D, Smith DH, Dal Pan GJ, Scott PE, Platt R. Outpatient use of cardiovascular drugs during pregnancy. *pharmacoepidemiology and drug safety*. 2008; 17:240–247. [PubMed: 18200619]
10. van den Bosch EA, Ruys PET, Roos-Hesselink JW. Use and impact of cardiac medication during pregnancy. *Future Cardiol*. 2015; 11(1):89–100. [PubMed: 25606705]
11. Hanley and Mintzes: Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. *BMC Pregnancy and Childbirth*. 2014; 14:242. [PubMed: 25048574]
12. Pasternak B, Hviid A. Use of Proton-Pump Inhibitors in Early Pregnancy and the Risk of Birth Defects. *N Engl J Med*. 2010; 363:2114–23. [PubMed: 21105793]
13. Soriano LC, Bateman BT, García Rodríguez LA, Hernández-Díaz S. Prescription of antihypertensive medications during pregnancy in the UK. *pharmacoepidemiology and drug safety*. 2014; 23:1051–1058. [PubMed: 24797728]
14. Koren G. Sex Dependent Pharmacokinetics and Bioequivalence – Time for change. *J Popul Ther Clin Pharmacol*. 2013; 20:e358–e361. [PubMed: 24214491]

15. Briggs, GG.; Freeman, RK.; Yaffe, SJ. Drugs in pregnancy and lactation. [S.l.]. Lippincott Williams & Wilkins; 2011.
16. Shields KE, Lyster AD. Exclusion of pregnant women from industry-sponsored clinical trials. *Obstet Gynecol.* 2013; 122:1077–81. [PubMed: 24104789]
17. Schonfeld T, Schmid KK, Brown JS, et al. A Pregnancy Testing Policy for Women Enrolled in Clinical Trials. *Ethics & Human Research.* 2013; 35:9–15. [PubMed: 24437001]
18. Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, et al. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. *Am J Obstet Gynecol.* 2014; 211:690.e1–11. [PubMed: 24912093]
19. National Institutes of Health. National Institutes of Health Revitalization Act of 1993. Available at: <http://orwh.od.nih.gov/about/pdf/NIH-Revitalization-Act-1993.pdf>. Retrieved March 29, 2015
20. Anger GJ, Piquette-Miller M. Pharmacokinetic studies in pregnant women. *Clin Pharmacol Ther.* 2008; 83:184–7. [PubMed: 17882157]
21. Chen ML, Lee SC, Ng MJ, et al. Pharmacokinetic analysis of bioequivalence trials: implications for sex-related issues in clinical pharmacology and biopharmaceutics. *Clin Pharmacol Ther.* 2000; 68:510–21. [PubMed: 11103754]
22. Cleary KL, Roney K, Costantine M. Challenges of studying drugs in pregnancy for off-label indications: Pravastatin for preeclampsia prevention. *Semin Perinatol.* 2014; 38:523–7. [PubMed: 25315293]
23. McCormack SA, Best BM. Obstetric pharmacokinetic dosing studies are urgently needed. *Front Pediatr.* 2014; 2:9. [PubMed: 24575394]
24. Anderson GD. Pregnancy-Induced Changes in Pharmacokinetics: A Mechanistic-Based Approach. *Clin Pharmacokinet.* 2005; 44:989–1008. [PubMed: 16176115]
25. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. *Front Pharmacol.* 2014; 5:65. [PubMed: 24772083]
26. Pacheco, L.; Costantine, MM.; Hankins, GDV. Physiologic changes during pregnancy. In: Mattison, DR., editor. *Clinical Pharmacology During Pregnancy*. San Diego: Academic Press; 2013. p. 5-14.
27. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med.* 1998; 338(16):1128–1137. [PubMed: 9545362]
28. Parry E, Shields R, Turnbull AC. Transit time in the small intestine in pregnancy. *J Obstet Gynaecol Br Commonw.* 1970; 77:900–901. [PubMed: 5473321]
29. Frederiksen MC. Physiologic changes in pregnancy and their effect on drug disposition. *Semin Perinatol.* 2001; 25:120. [PubMed: 11453606]
30. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science.* 1999; 286:487–91. [PubMed: 10521338]
31. Helldén A, Madadi P. Pregnancy and pharmacogenomics in the context of drug metabolism and response. *Pharmacogenomics.* 2013; 14:1779–91. [PubMed: 24192125]
32. Ke AB1, Rostami-Hodjegan A, Zhao P, Unadkat JD. Pharmacometrics in pregnancy: An unmet need. *Annu Rev Pharmacol Toxicol.* 2014; 54:53–69. [PubMed: 24392692]
33. Chung RT, Baumert TF. Curing Chronic Hepatitis C — The Arc of a Medical Triumph. *N Engl J Med.* 2014; 370:1576–1578. [PubMed: 24720678]
34. Gonzalez D, Boggess KA, Cohen-Wolkowicz M. lessons learned in pediatric clinical research to evaluate safe and effective use of drugs in pregnancy. *Obstet Gynecol.* 2015; 125:953–8. [PubMed: 25751205]
35. U.S. Food and Drug Administration. Pregnancy and lactation labeling final rule. Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>. Retrieved march 29, 2015