Original Article

A review of clinical studies involving pregnant women registered in the Clinical Trials Registry of India

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Abstract

Context and Aims: Pregnant women undergo physiological changes which influence the efficacy as well as safety of medications used. Very few drugs are tested and approved for medical conditions during pregnancy, and less pharmacokinetic data are available to form clinical treatment guidelines. There was no data available regarding the type of research studies conducted in pregnancy in India. Hence, we conducted this study to analyze the type of research studies in pregnancy registered in the Clinical Trials Registry of India (CTRI).

Subjects and Methods: Following exemption from review by the Institutional Ethics Committee, all studies in pregnant women registered in CTRI from its inception in July 2007 to June 2018 were reviewed. Data were captured with respect to geographical distribution, trimester of pregnancy, study designs used, therapy area, and funding.

Statistical Analysis Used: The variables were analyzed using descriptive statistics using SPSS version 16.0.

Results: Out of a total of 14,911 studies in CTRI, a total of 285 (1.91%) studies involved pregnant women. Of these studies, 199 (69.8%) were interventional, whereas 86 (30.1%) were observational. Of all the interventional studies, 119 (60%) tested drugs, 47 (24%) tested a nondrug intervention, and the rest were nutraceuticals, Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy, and vaccines. Postgraduate theses constituted 140 (49.1%) studies, 79 (27.7%) were academic projects, 27 (9.4%) were government-funded studies, and only 16 (5.6%) were pharmaceutical-sponsored studies. The most commonly studied therapy area was anesthesia, followed by hypertension and induction of labor.

Conclusions: This study depicts underrepresentation of pregnant women in clinical studies and more evidence needs to be generated with respect to drug safety and pharmacokinetics.

Keywords: Pregnancy, research, trial registry

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INTRODUCTION

Pregnancy represents a special physiological condition. The physiological changes associated with pregnancy influence the efficacy as well as safety of any medication used during pregnancy. There is a need for using drugs for a variety of medical conditions during pregnancy, yet we find that the evidence for their safety and efficacy specifically during pregnancy is not generated. Management decisions regarding drug use in pregnant women cannot be based on

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the data available in nonpregnant women. A study revealed that India accounts for almost 17% of the global maternal deaths.[1] Another study revealed that about 8%–27% of women were hospitalized at least once during pregnancy for reasons such as preterm labor, vomiting, genitourinary complications, and hypertensive disorders.[2]

Very few drugs are tested and approved for the use of medical conditions during pregnancy, and we find that little pharmacokinetic data are available to form clinical treatment guidelines. A review of literature showed that a number of studies have highlighted the dearth of evidence related to drug use in pregnancy. Safety concerns, both for the mother and the fetus, are paramount due to which pregnant women are excluded from clinical trials. The major hurdle is when new drugs are available, there are no data regarding the safety and doses in pregnancy which can be generated, and the benefits of new treatment cannot be extended to pregnant women.[3] In this era of evidence-based medicine, several attempts have been made to link the clinical research and practice to provide the best possible care to the pregnant women.[4] Despite this, shortages of new medications approved for safe use during pregnancy[5,6] create a significant barrier in treatment of women during pregnancy.

Previously, the Food and Drug Administration (FDA) used the five pregnancy categories for denoting the risk of drug use in pregnant women, but after much evaluation, it has now been replaced by the Pregnancy and Lactation Labeling Rule.[7] This was intended to improve risk versus benefit assessment of drugs used in pregnant and nursing women. However, it also led to the observation that very little clinical data were existed for most drugs that were available in the United States and that almost 93% of drugs obtained pregnancy data from preclinical studies with only 5.2% having human pregnancy data. The new labeling may provide added incentives for the development and conduction of more clinical research in pregnant women, according to some researchers.[8]

Scaffidi *et al*. conducted a global survey on pregnancy drug trials (PDT) and found that only 0.32% of all the trials involved pregnant women. Furthermore, they noted a high prevalence of off-label use of medications by the pregnant women.[9] Even though the data pertaining to the Indian registry were included in the above-quoted study by Scaffidi *et al*., the details were limited and the study considered only active trials during 2013–2014. Therefore, in an attempt to get a complete picture on the type of clinical studies in pregnancy conducted in India, we decided to compile data on the studies registered in the Clinical Trials Registry of India (CTRI). The present study objectives were to analyze the type of studies done and therapy areas considered in the research studies. We also looked at drug interventional and observational studies specifically.

SUBJECTS AND METHODS

The study was granted exemption from review by the Institutional Ethics Committee. All the studies conducted in pregnant women registered under CTRI since its inception in July 2007 to June 2018 were reviewed and analyzed. The studies were searched in the "Trial Search" section with the "pregnant" keyword. Out of all the search results obtained, the studies being conducted in pregnant women and mentioning pregnancy as inclusion criterion were chosen for further analysis. The variables for capturing data were geographical distribution of studies, trimester of pregnancy in which the study was being conducted, types of study designs used whether observational or interventional, status of study whether ongoing or completed, therapy area, and type of intervention tested whether pharmaceutical sponsored/academic/government funded. The variables were analyzed using descriptive statistics using SPSS for Windows, Version 16.0. Chicago, SPSS Inc.

RESULTS

Out of a total of 14,911 studies registered in CTRI from 2007 to June 2018, a total of 285 (1.91%) studies involved pregnant women. Among the 285 studies, 145 studies were ongoing at the time of analysis. Out of all the studies, 199 (69.8%) were interventional, whereas 86 (30.1%) were observational. Ninety-eight studies involved women in their first trimester, 114 in their second trimester, and 240 in their third trimester. Out of the 98 studies carried out in the first trimester, 49 were interventional. The distribution of the types of interventions used in different studies has been shown in Figure 1. Of all the interventional studies, 119 studies (60%) tested drugs, 47 (24%) tested a nondrug intervention, and the rest were nutraceuticals, Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy (AYUSH) interventions, and vaccines. The nondrug interventions tested included devices such as intrauterine device, Doppler and cardiotocograph, and different techniques and positions for spinal anesthesia. They also included behavioral interventions such as music therapy, exercises, maternal and fetal health-related and breastfeeding-related counseling, and cognitive behavioral therapy. The AYUSH interventions included breathing exercises, yoga and ayurvedic drugs, and procedures such as Basti, Yonipurana, Nasya, and Unani medicines. There were only two vaccine-related studies, one evaluating respiratory

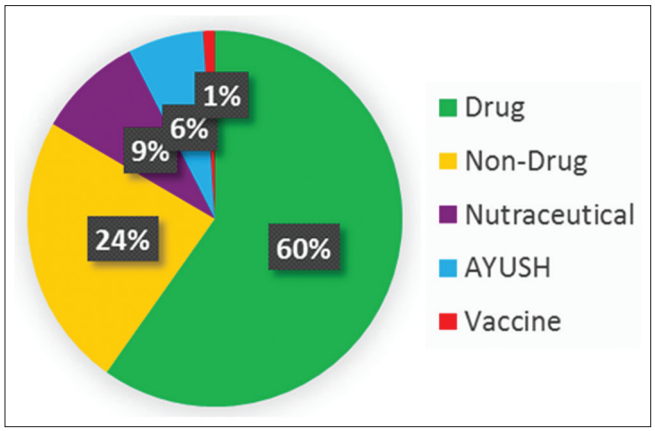

Figure 1: Types of interventional studies in pregnant women

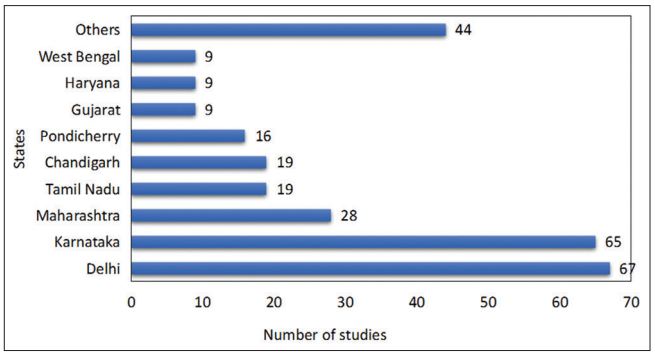

Figure 2: Distribution of studies across various states in India

syncytial virus (RSV) vaccine and the other being influenza vaccine. The nutraceuticals studied were docosahexaenoic acid, vitamin D, and protein supplementation.

On analyzing the therapy areas, we found maximum observational studies in anesthesia and hypertension, whereas very few studies in infections (n = 4). We also noted that out of all observational studies, only three were observing effects of drugs which included an influenza vaccine and anesthetic agents (n = 2). Thirty-five studies had a sample size of 100 or less, whereas 37 had a sample size between 100 and 500. Five studies had a sample size between 500 and 1000. One study which aimed to estimate the maternal mortality ratio included a sample size of 400,000 women, whereas another evaluating birth outcomes included 5000 women.

Out of all the studies, 278 (97.5%) were Indian while the remaining 7 (2.5%) were part of global studies. In India, a maximum number of studies were carried out in Delhi followed by Karnataka and Maharashtra. Figure 2 gives the distribution of studies across various states. There were very few studies (<5) being conducted in Rajasthan, Uttar Pradesh, Bihar, Andhra Pradesh, and Orissa. Postgraduate theses constituted 140 (49.1%) studies, 79 (27.7%) were academic projects, 27 (9.4%) were government-funded studies, and only 16 (5.6%) were pharmaceutical-sponsored studies.

The most commonly studied therapy area was anesthesia, followed by hypertension and induction of labor as evident from Figure 3. The other lesser studied therapy areas were Vitamin D (9), thyroid disorders (3), cardiovascular diseases (1), hematological abnormalities (2), urological conditions (3) and oncology (1). Among the studies in analgesia, majority dealt with the management of postoperative pharmacological pain after cesarean section, and rest involved analgesia following instrumental vaginal delivery and nondrug behavioral interventions such as music therapy for pain relief. The studies conducted for induction of labor mainly dealt with misoprostol or mifepristone administration and some involved the use of balloon catheters for cervical ripening. In the area of diabetes in pregnancy, majority of the studies were evaluating the use of insulin and oral hypoglycemic drugs, and others were assessing fetal outcomes, awareness and compliance in women, and associations with obesity. The anti-infective studies were mainly carried out in the domain of HIV and malaria, followed by bacterial vaginosis, sepsis, and influenza in pregnancy.

Out of the 140 postgraduate theses, 42 were observational studies, whereas the remaining 98 were interventional studies. The studies were most commonly in the therapy areas of anesthesia, analgesia, and induction of labor, followed by hypertension and preterm labor. The drug interventions were randomized controlled trials carried out mostly in the area of anesthesia.

DISCUSSION

Ever since the thalidomide tragedy, stricter rules and regulations have been put in place with respect to research in pregnancy. This has led to the exclusion of women from clinical studies. However, pregnancy is not devoid of medical disease conditions, and research shows that a healthy woman's pregnancy is most commonly complicated by diseases such as psychiatric illness, hypertension, and cancer.[10] A study showed that up to 64% of pregnant women receive at least one prescription for medical needs.[10] Along with increasing age for pregnancy, there is an increase in complex medical problems, subsequently increasing the use of prescription medications by pregnant women. A study conducted in 2011 revealed that of all medications approved by the FDA from 1980 to 2010, 91% did not have enough data on safety, efficacy, and fetal risk of medication taken during pregnancy.[3] Thus, treatments

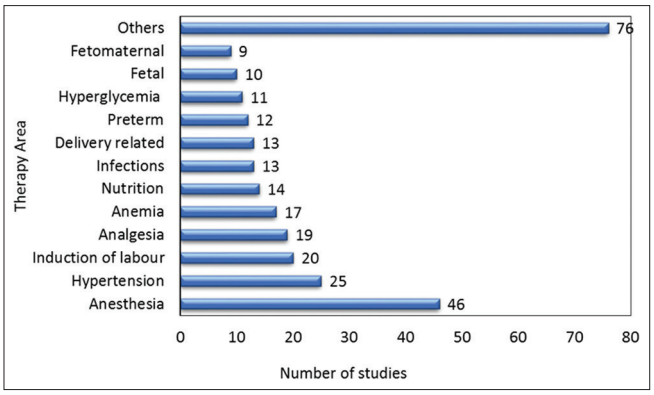

Figure 3: Therapy areas in clinical studies in pregnancy

in pregnancy are mainly empirical and not evidence based, simply due to the lack of sufficient studies in pregnant women.

Our study results indicate that there are very few pharmaceutical-sponsored drug intervention studies in areas other than pregnancy-associated conditions. Most of the studies are related to analgesia, hypertension, and anemia which are directly related conditions. The need of the time would be to have more number of observational studies in general medical illnesses as well as pregnancy- and labor-associated indications. Although lower down in the hierarchy of evidence, observational studies if conducted rigorously can pave a way for controlled clinical studies to allow generation of higher level of evidence. We also find that very less number of studies are done in the first and second trimesters wherein compared to the third trimester. The total number (30%) of observational studies indicates that there is a lack of drive to conduct more studies or they are not registered in large number in the CTRI.

Scaffidi *et al.* conducted a similar study where they analyzed trials involving pregnant women registered on 16 different trial registries in the year 2013–2014. Their analysis also revealed that <0.5% of all registered clinical trials investigate pharmacological therapies in pregnancy.[9] Our study supports this as <2% of all the studies registered on CTRI involved pregnant women. Out of all these studies, only 1% were testing pharmacological interventions. Our study also revealed that there are very few pharmaceutical industry-sponsored studies undertaken in pregnant women. Similar to Scaffidi *et al.*, who found that only 7% of pharmaceutical-funded studies, our study also showed that only 5.6% of studies were sponsored by pharmaceutical industry. This figure is markedly lower than for other areas of medicine, where rates are typically 30%–60%.[9] This might be due to the stringent regulations as well as lack of incentives for companies to conduct studies in pregnant women. An RSV vaccine was the only new drug that was being studied. It is expected that new drugs will not be tested initially in pregnant women due to safety concerns. However, it is possible to generate evidence through observational studies whenever new drugs and therapies are tested as clinically indicated. Our study also revealed lack of observational studies for monitoring safety and evaluating pharmacokinetics of drugs in pregnant women. This shows that pregnancy is indeed a research area that needs to be explored, and perceived lack of profit must be one of the reasons for this deficit.

Pregnant women deserve access to effective treatments, and lack of evidence in the clinical research setting leads to uncertainty in the clinical care setting. It is imperative that we not only provide effective treatment to women and adequately assess fetal safety of medications but also should ensure as a matter of justice that pregnant women are offered equitable opportunity to participate in research.[11] Indian Council of Medical Research (ICMR) 2017 guidelines mention that proper justification should be provided for inclusion of pregnant and nursing women in clinical trials designed to address the health needs of such women or their fetuses or nursing infants. Examples for justifiable inclusion are trials designed to test the safety and efficacy of a drug such as reducing perinatal transmission of HIV infection from mother to child, device-related trials for detecting fetal abnormalities, or trials of medical conditions associated with or aggravated by pregnancy, such as vomiting, hypertension, or diabetes.[12] The US Code of Federal Regulations has addressed the risks to pregnant women, according to the which; "the risk to the fetus should be the least possible for achieving the objectives of the research and in research that has no potential individual benefit the risks should not be greater than minimal" (45 CFR 46). Contrarily, the 2015 CIOMS draft guideline states that when the social value of the research for pregnant women or their fetus is compelling, a minor increase above minimal risk might be allowed in research that has no potential for individual benefit.[8]

The limitations of our study were that since CTRI registration is not mandatory for non-regulatory studies, all studies conducted real time may not have been analyzed. This could be a possibility because majority of investigators undertaking academic studies do not register their studies in CTRI. However, we have tried to obtain an overview of the current status of research involving pregnant women based on the registered studies. It is safe to say that though clinical research in pregnant women does pose unique challenges, it is essential for progress in caring for pregnant women and for supplementing and evolving the existing standard of care. Thus, research must be conducted within a thoughtful ethical

framework that takes into account the benefits and risks of both the mother and the fetus.

CONCLUSIONS

This study depicts the marked underrepresentation of pregnant women in clinical studies. The study highlights the need to conduct observational studies for monitoring drug safety and pharmacokinetics which are scarce. Further, conditions such as infections which are common in pregnancy can also be made subject of research for testing drugs which are already approved for adults.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Filippi V, Chou D, Ronsmans C, Graham W, Say L. Levels and causes of maternal mortality and morbidity. In: Black RE, Laxminarayan R, Temmerman M, Walker N, editors. Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities. 3rd ed., Vol. 2. Washington, DC: The International Bank for Reconstruction and Development/The World Bank; 2016.
2. Doke PP. Maternal morbidities and estimates from community studies in India. MGM J Med Sci 2013;1:57-65.
3. van der Graaf R, van der Zande IS, den Ruijter HM, Oudijk MA, van Delden JJ, Oude Rengerink K, *et al*. Fair inclusion of pregnant women in clinical trials: An integrated scientific and ethical approach. Trials 2018;19:78.
4. Maloni JA, Albrecht SA, Thomas KK, Halleran J, Jones R. Implementing evidence-based practice: Reducing risk for low birth weight through pregnancy smoking cessation. J Obstet Gynecol Neonatal Nurs 2003;32:676-82.
5. Norwitz ER, Greenberg JA. FDA approval for use of medications in pregnancy: An uphill battle. Rev Obstet Gynecol 2011;4:39-41.
6. Brandon AR, Shivakumar G, Inrig SJ, Sadler JZ, Craddock Lee SJ. Ethical challenges in designing, conducting, and reporting research to improve the mental health of pregnant women: The voices of investigators and IRB members. AJOB Empir Bioethic 2013;5:25-43.
7. Pernia S, DeMaagd G. The new pregnancy and lactation labeling rule. *P* T 2016;41:713-5.
8. van der Zande IS, van der Graaf R, Oudijk MA, van Delden JJ. A qualitative study on acceptable levels of risk for pregnant women in clinical research. BMC Med Ethics 2017;18:35.
9. Scaffidi J, Mol BW. The pregnant women as a drug orphan : A global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG 2016;124:132-40.
10. Allesee L, Gallagher CM. Pregnancy and protection: The ethics of limiting a pregnant woman's participation in clinical trials. J Clin Res Bioeth 2011;2. pii: 1000108.
11. Little MO, Wickremsinhe MN. Research with pregnant women: A call to action. Reprod Health 2017;14:156.
12. Indian Council of Medical Research. National ethical guidelines for biomedical and health research involving human participants. New Delhi: Indian Council of Medical Research; 2017. Available from: https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf. [Last accessed on 2019 Feb 01].