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Short Communication

Research conducted on gestating women globally during trials

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ABSTRACT

The aim of clinical research is to impart knowledge that will improve human health or improve understanding of human physiology. Although, till the end of 20^{th} century pregnancy was always under exclusion criteria, now pervasive exclusion of pregnant women in clinical trials is currently not justified. Pregnancy brings in an array of anatomical, physiological and biochemical changes that can impact the pharmacokinetics of important medications. Pregnancy is often accompanied by chronic diseases like diabetes, hypertension, tuberculosis, HIV, depression which can require long term therapy. This indicates a need for studies being conducted exclusively in pregnant women. Current communication narrates ethical and regulatory aspects of inclusion of pregnant women in clinical trials.

1. Introduction

Ethical guidelines for clinical research were formulated only after discovery of inhumane behaviour with participants during research experiments. (Tuskegee Syphilis Study). The Indian Council of Medical Research (ICMR), in February 1980, released a 'Policy Statement on Ethical Considerations involved in Research on Human Subjects". Its latest edition was published in 2017 as "National Ethical Guidelines for Biomedical and Health Research".[1] Although not a law, these guidelines have been incorporated in the New Drugs and Clinical Trials Rules 2019(NDCTR).[1] The Informed Consent Form (ICF) with participant/patient information sheet should be approved by the Ethics committee (EC) before initiating any study.

A checklist of essential elements are to be included in the study subject's informed consent document as well as a format for the ICF (inform consent form) for study Subjects inclusion is provided in Table 3 of the 3^{rd} Schedule of NDCTR 2019.[1] The ICF should have the signature or thumb impression of the prospective participant before start of the experiment. If the participant or legally acceptable representative is unable to read/write, then an impartial witness should be present during the entire informed consent process and must sign the consent form.[1–9]

1.1. Defining vulnerable population and conduct of trials

Persons who cannot protect their own interests are termed vulnerable research population. Children, pregnant women, foetuses, terminally ill or comatose patients, some psychiatric conditions, illiterate, economically challenged, and elderly all fall under this category.[10] Focus on pregnancy and its related issues will be discussed here.

1.2. Crucial trials in pregnancy

Pregnancy brings in an array of anatomical, physiological and biochemical changes that can impact the pharmacokinetics of some important medications.

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Absorption could be altered due to dietary changes, nausea, vomiting and prolonged gastric transit time. During pregnancy there is a change in body composition, blood volume, protein binding and expression of transporters leading to altered distribution patterns. Activity of metabolising enzymes like CYP3Aor UTG1A4 may increase, or CYP2C19 may decrease affecting clearance of the products. Elimination of renally cleared drugs may increase due to increase in cardiac output, renal blood flow and glomerular filtration rate.[8]

The behaviour of drugs in pregnancy will be different from the normal population and the pharmacokinetic parameters set based on healthy population may not apply. Pregnancy is often accompanied by chronic diseases like diabetes, hypertension, tuberculosis, HIV, depression which will require long term therapy. This indicates a need for studies being conducted exclusively in pregnant women.

1.3. Studies during gestation

Pregnancy: Most of labelling information in 20^{th} century discouraged use of drugs during pregnancy. Some investigator driven studies on pregnant women were available with certain drugs like Acarbose, Metformin, SGL T2 inhibitors eg dapagliflozin on basis of experience and requirement to control glycaemic condition. Antimalarials were used cautiously in pregnancy though they are not recommended. The fact remained that sick women could get pregnant or pregnant women could get sick, both needing treatment for the condition. The physician in this case was be obliged to treat the patient not with evidence-based therapy but empirically. This only underlined the need for establishing the effects of not only new but also current commonly used medicines during pregnancy. On this topic, two preventive trials stirred a lot of debate. Folic acid which is considered safe in pregnancy was used in higher doses prenatally. It was shown to reduce the incidence of recurrent and primary neural tube defect. The second study involved Azidothymidine, a drug with known toxic effects, that was used in pregnant women with HIV infection to prevent mother to child transmission. The conduct of this trial broke new ethical ground.[5]

lopinavir–ritonavir has been used extensively worldwide for pregnant women with HIV infection to prevent mother-to-child transmission of HIV. Birth defects are not altered in women taking this medication.[6]

1.4. Research in women, guidance statements

Women should not automatically be excluded from research because of the possibility that they could become pregnant.

CIOMS (Council for International Organizations of Medical Sciences) allows for research with pregnant women under restricted conditions.

FDA-regulated clinical trials in pregnant women must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR part 56,)

1.5. The following criteria should be met

1. Where scientifically appropriate, nonclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and foetuses.
2. The risk to the foetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the foetus; or, if there is no such prospect of benefit, the risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means
3. The pregnant woman's consent is obtained in accord with the informed consent- provisions of 45 CFR part 46, subpart A (FDA)
4. If the research may benefit only the foetus, consent of the father should also be sought
5. Individuals engaged in the research will have no part in determining the viability of a neonate.[2–7]

1.6. Guidance in India

In case of research in pregnant and nursing women the NDCTR gives the following guidance

1. Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant or nursing women or foetuses or nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.
2. For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.
3. Randomised clinical trials are essential in Pregnant women, they evaluate effects of drugs during pregnancy more effectively.[1,6–9]

1.7. Some issues: ethical and practical

Fair inclusion of pregnant women in research implies that separate trials in pregnant women should be promoted. Inclusion of pregnant women has to be realized at the earliest phases of the research process. In addition to researchers and research ethics committees, scientific advisory councils, funders, drug regulatory agencies, pharmaceutical companies, journal editors and others have a

joint responsibility to further develop the evidence base for drug use in pregnant women. Placebo-controlled trials are not as common in pregnant populations as in non pregnant populations. It is not only important to study the effect of the drug on the mother and foetus but also that of the disease condition itself on them. In such situations placebo controls have been used [3–5]

In case of pregnant women informed consent process has to be very elaborate. She should be given all information about the risks to herself as well as the foetus. In case the study benefits only the foetus she is its representative and has to balance her obligation to protect both herself and the foetus. In such a case paternal consent is also mandatory, but how does one handle a situation where the father disagrees?

Although there are clearly ethical considerations when including pregnant and breastfeeding women in clinical trials, it can also be considered unethical not to test new drugs in pregnant women in a controlled setting. In practice, once new drugs are approved in adults, their use rapidly expands to include pregnant and breastfeeding women, exposing more mothers and infants to these potential risks than would have occurred in the context of a clinical trial.

Hence, it is worthwhile carrying out pharmacokinetic studies during pregnancy when possible [1,7–9]

1.8. Proposed guidelines for research during pregnancy

1. Placental transfer should be studied during the preclinical phases of drug development using techniques such as in vitro–in vivo extrapolations or ex vivo human cotyledon perfusion models.
2. Regulatory authorities and ethics committees should incentivize and support inclusion of pregnant women in premarketing clinical trials for compounds potentially used in pregnancy. As a first step, women enrolled in phase 2 or phase 3 clinical trials should not be removed from the study drug if they become pregnant during the trial. (Provided drug is not under Category X)
3. Antiretroviral, Antidepressants and some Antipsychotics therapeutic groups the clinical pharmacology studies in pregnant and lactating women should be executed according to the highest standards and requirements.
4. Modelling and simulation should be used to facilitate understanding of pregnancy-related clinical pharmacology.
5. Postpartum lactating women should be included in clinical trials and breast milk transfer from mother to infant should be assessed. Precautions are required for more lipophilic drugs.

1.9. Recommendations for the use of psychotropic drugs

1. Fertile women with a psychiatric disease should be advised before pregnancy whether psychotropic drugs are needed during pregnancy. Valproate and Carbamazepine should be avoided for fertile women. (as these come under category X)
2. If antipsychotics are needed, olanzapine is primarily recommended based on the documentation of safety data [5]

2. Conclusion

The inclusion of pregnant women in clinical trials is guided by human subject protection regulations and involves complex risk-benefit assessments that vary depending on the seriousness of the disease, the availability of other treatments, the trial design, and whether the proposed investigation will occur in the premarketing or post marketing setting. In most of trials, complex ethical issues are involved that include pregnant women. However, most therapeutic clinical trials for COVID-19 antiviral therapy excluded pregnant women, though there was no limitation for vaccine trials. Many universities in US and EU are involved in conducting research in Pregnancy with drugs and evaluating their outcome.

3. Source of Funding

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4. Conflict of Interest

None.

References

1. Sanmukhani J, Tripathi CB. Ethics in Clinical Research: The Indian Perspective. *Indian J Pharm Sci*. 2017;73(2):125–30. doi:10.4103/0250-474x.91564.
2. Noah BA. The inclusion of women in clinical research , 2014 Western New England University School of Law; 2014. Available from: https://digitalcommons.law.wne.edu/cgi/viewcontent.cgi?article=1297&context=facschol.
3. Graaf RVD, Ruijter HMD, Oudijk MA. Fair inclusion of pregnant women in clinical trials: an integrated scientific and ethical approach. *Trials*. 2018;19(1):78. doi:10.1186/s13063-017-2402-9.
4. David M. From no to yes: the history and ethics of including pregnant women in clinical trials. *Clin Invest*. 2011;1(10):1349–51. doi:10.4155/CLI.11.125.
5. Centre for Drug Evaluation and Research (CDER)Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry. 2018;Available from: https://www.fda.gov/files/drugs/published/Pregnant-Women--Scientific-and-Ethical-Considerations-for-Inclusion-in-Clinical-Trials.pdf.
6. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States; 2021. Available from: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/appendix-d-dolutegravir-counseling-guide-health-care-providers.
7. Larsen ER. Use of psychotropic drugs during pregnancy and breast-feeding. *Acta Psychiatrica Scandinavica*. 2015;47(3):135–8.
8. Colbers A, Mirochnick M, Schalkwijk S, Penazzato M, Townsend C, Burger D. Importance of Prospective Studies in Pregnant and

Breastfeeding Women Living With Human Immunodeficiency Virus. *Clin Infect Dis*. 2019;69(7):1254–8. doi:10.1093/cid/ciz121.
9. New Drugs and Clinical Trials Rules; 2019. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf.
10. New Drugs and Clinical Trials Rules 2019 GSR 227; 2019. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf.

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