Historic Recommendations to Increase Scientific Evidence on Safe and Effective Therapies for Pregnant & Lactating Women

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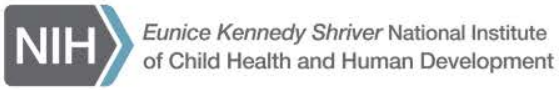


Overview

- Methods
  - Publications identified in course of search for articles to inform Task Force of *types* of research on therapies (drugs, supplements & vaccines) for medical management of 16 classes of disorders in pregnant and lactating women
  - Additional publications identified in search for articles on ethical issues in research with pregnant and lactating participants

Overview

- Methods
  - Reviewed publications that reported recommendations/opinions of expert panels (e.g. IOM), research workshops, & similar activity
  - 15 publications (1994-2018) yielded recommendations in topical areas:
    - Research strategies, methods, & topics
    - Research infrastructure & resources (includes registries, research training)
    - Ethical, legal &/or regulatory issues
    - Communication

Sources of Recommendations

1994
IOM report
Women & health research
PMID 25144026

2007
ACOG opinion
Research involving women
PMID 17766625

2008/9
2nd Wave initiative
Inclusion of pregnant women in research
PMID 19774226

2010
ORWH Work-shop
Clinical research in pregnant women
PMID 23312713

2011/13
NIAID Work-shops
Clinical research: vaccines, antimicro-bials & pregnant women
PMIDs 25425719, 25425722, 25425720, 25425721, 25425718

2015
ACOG opinion
Women research participants
PMID 26488521
SMFM Work shop
Drugs in pregnancy & lactation
PMID 28142152

2016
FDA Work-shop
Drugs, biologicals & lactation
PMID 28510297
ASCPT Expert panel
Pregnant, lactating women in research
PMID 28925019
NVAC
Maternal immuniz.
PMID 28379782

General observations

- Trend: From generally urging “more clinical research in women” to:
  - Research including pregnant women &
  - Specific research approaches (e.g. PK/PD, large (EHR) opportunistic studies) and topics (e.g. preclinical and early clinical vaccine research on immune response in pregnancy)
- Only recent recognition of lactation research needs

General observations

Among possible recommendations the Task Force has considered, the following were rare or not seen in prior recommendations:

- Highlight (in communications) impacts of not taking medication during pregnancy or lactation; include impacts of not breastfeeding
- Develop research infrastructure (investigators, networks) & methods; leverage large studies (e.g. PregSource) to collect data
- Distinguish between new drug development & approved drugs already used in pregnancy and/or lactation, in research considerations
- Develop incentives for industry & agencies & to facilitate collaboration

1985

Women's Health

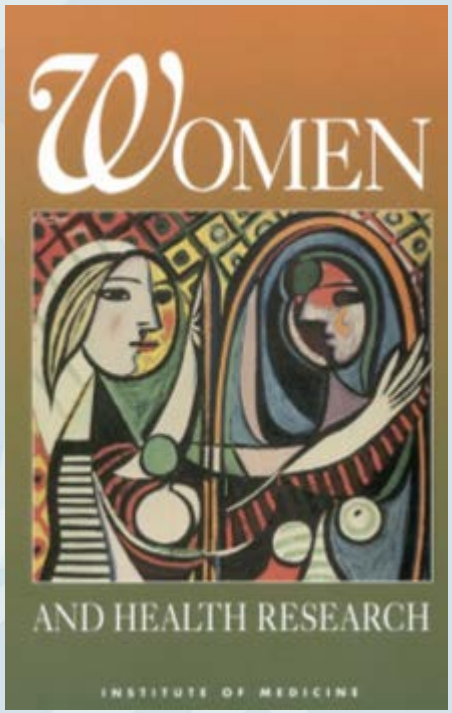
Report of the Public Health Service Task Force on Women's Health Issues

Volume I

- the issuance of a Public Health Service-wide policy directing all operating units to review their research guidelines to ensure that sex differences are routinely studied, wherever feasible. Such instructions should be included in grant application kits.
- the requirement that postmarketing surveillance of all prescription drugs should include reporting of the adverse effects in women of drug interactions with alcohol, commonly used psychotherapeutic drugs, and drugs commonly used in relation to hormonal changes in women.
- the requirement that adequate numbers of women be included in clinical trials of drugs that will be used by women, and of all new drugs that are to be recommended for use by women.
- the commissioning of an interdisciplinary panel of senior scientists, including women, to review existing research and research protocols or methodologies and to develop a comprehensive plan for addressing any gender bias identified in research in general, but in particular in alcohol, drug abuse, and mental health research.
- the establishment of a task force to review mental health issues related to women and to make recommendations for changes in the Fourth Revision of the Diagnostic and Statistical Manual (DSM IV) of the American

1985: HHS Report of PHS Task Force on Women's Health Issues

1994



The committee also struggled with how to accommodate within its support for the shift of the presumption to *inclusion* of pregnant women (from that of exclusion) a role for conscience and an individual investigator's moral commitments. It was agreed that, at a minimum, such a mechanism would require that the investigator provide the IRB with a written explanation of his or her concerns of conscience and that the IRB review any such requests in light of a presumption that favors the inclusion of pregnant women in clinical studies. It is because of the potential for abuse of a "conscience" exemption that the committee could not resolve whether or under what conditions such an exemption should be constructed.

At least a technical amendment to Subpart A, sec. 46.111(a)(3), eliminating the reference to pregnant women as a "vulnerable population" will be required by the recommended revision to Subpart B.

The committee recommends that OPRR revise and reissue subpart B of the DHHS regulations for the Protection of Human Subjects, titled "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human

IOM Study: Women and Health Research
Ethical and Legal Issues of Including Women in Clinical Studies, Volume 1 (1994)

Research strategy: Inclusion of pregnant and lactating women in clinical research

- IOM: “The committee recommends that pregnant women be presumed to be eligible for participation in clinical studies…”
  - With “adequate risk-benefit” information
  - If risk evidence “unknown or ambiguous,” a woman should decide about acceptability of risk…as part of informed consent.
- “…the lack of proven safe treatment options for ill pregnant women carries its own set of concerns and risks.”
- “…investigators and IRBs [should] not exclude women who are lactating from…clinical studies.”

Research strategy: Inclusion of pregnant/lactating women in clinical research

- ACOG opinion (2007): Presume women eligible for clinical studies & don't automatically exclude because of "potential for pregnancy" though may require contraception. "Consent of pregnant woman alone is sufficient for most research."
- Second Wave*:* "…progress will not happen until we shift the burden of justification"…to inclusion…"
- ORWH workshop: NIH should "consider adopting a policy of inclusion and a need to justify exclusion of pregnant women."
- ACOG opinion (2015): Presume women eligible (as in 2007 opinion)
- NVAC recommendations "[R]evise the current exclusionary climate of research in pregnancy…"

Research methods

- Recruitment
  - NIAID workshops: “Leverage influence of prenatal providers”
  - ACOG opinion (2015): “…address [obstacles specific to women such as] lack of…child care…while participating in research”
  - FDA workshop: Recruit for lactation studies through pregnancy exposure registries…NICUS, milk banks

Research methods

- ORWH workshop: Develop “scientific models that address the [birth defects] baseline rate and attribution of causation…”
- ASCPT panel: Improve existing animal models…”to address…mechanisms of actions of drugs and drug toxicity during pregnancy”
- NIAID workshops: Standardize research methods on vaccines administered during pregnancy

Topic: Research methods

- FDA workshop: Physiologically-based and population PK modeling of drug concentration in milk potentially useful to ID & prioritize “drugs of concern” but need further development and refinement to predict…human exposure.

- ASCPT panel: Big data from electronic medical records “reflect routine daily practice” and there is “good correlation between observational studies and clinical trials…” but refinement needed

Research infrastructure & resources

- IOM: “review…existing birth defects monitoring programs to critically define what they are capable of doing and suggest improvements & reasonable expectations for their use.”

- NVAC: Expand “pharmacovigilance systems” that “link maternal and infant electronic health records and safety surveillance systems”

- ASCPT: Prospective pregnancy registers “require continuous commitment to enrollment, recruitment…retention…prespecification of a similar comparator group”

Research infrastructure & resources

- ASCPT: “…establish well-trained researchers and clinicians specialized in obstetric clinical pharmacology.”

- 2nd Wave: “Expand [NICHD’s OPRU network] and other groups to perform opportunistic studies involving women already taking medication during pregnancy”

Research topics

- 2nd Wave: "…public health impact of the current lack of knowledge around medications in pregnancy."
- NVAC: "…the public health burden of diseases prevented by maternal immunization…[also] "Prioritize preclinical and early clinical vaccine research on immune response during pregnancy…evaluat[e] maternal…& neonatal outcomes."
- ORWH workshop: "Identify questions that can be addressed with existing studies and resources (e.g. opportunistic pharmacokinetic studies and pregnancy registries"
- FDA workshop: Priority drugs for lactation studies: "Products commonly used by women of reproductive age [categories listed], drugs [with] potential risk for exposed infant that…have no…data in the literature…[d]rugs for which…assays have been developed…and drugs used commonly in women with no…lactation data and presumed low risk to nursing infant based on nonclinical data"

Ethical, legal, & regulatory issues

- ORWH workshop: Opportunistic studies may ethically "[e]nroll pregnant women already using medication…prescribed for therapeutic purposes."

- FDA workshop: Distinguish maternal decision to use medically necessary drug for illness during lactation [not a research-related risk] and taking a new drug in research setting [& if research risk for infant, discontinue unless greater risk in switch to formula]

Ethical, legal, & regulatory issues

- IOM report: "…OPRR [OHRP predecessor] should revise and reissue Subpart B
- ORWH workshop: Clarify existing regulations and focus on IRB behavior; ambiguities in regulations and conservative and variable IRB interpretations are problems, especially interpretation of minimal risk.
- NVAC recommendations: Clarify & standardize definitions of minimal risk

Ethical, legal, & regulatory issues

- IOM: NIH should "…review…compensation for research injury…consideration of implementation of any compensation scheme include attention to prenatal and preconceptual injuries to children resulting from a parent's participation in a clinical trial"
  - But no recommendation to adopt compensation scheme because of "especially difficult problems [of] establishing causation" & many "questionable recoveries."

Ethical, legal, & regulatory issues

- 2nd Wave: [A]ddressing the liability concerns that animate so much of the behavior around research and drug development during pregnancy will require substantial efforts at both state and Federal levels."

Communication

- NIAID workshops: There is need for “effective communication of providers and patients on current recommendations” for vaccines during pregnancy and postpartum”
- FDA workshop: There are needs for a“[c]ontemporary common [information] resource [for lactating women] that is…easily accessed by or integrated into internet and social media,” as well as “trusted sources” of drug safety information
- FDA workshop: Electronic medical record platforms should “disseminate best available information” at point of decision-making for lactating patients

Communication

- SMFM panel: Develop approaches to improve provider-patient communications about risks and benefits of medication use in perinatal period.
- NVAC recommendations: Professional societies should…increase provider awareness of the importance of research
- ASCPT panel: Publish all CT.gov obstetrics study results: “Dissemination of all available obstetric clinical pharmacology knowledge is fundamental.”

You are standing and building on the hard work and efforts of others as you make PRGLAC recommendations

Sources of Recommendations

- IOM Report: Mastroianni AC, Faden R, Federman R. *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies.* Institute of Medicine, Committee on Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies. 1994 PMID25144026.
- ACOG Opinion: Committee on Ethics, American College of Obstetricians and Gynecologists. *ACOG Committee Opinion No. 377: Research Involving Women.* Obstet Gynecol 2007;110:731-16. PMID 17766625. (withdrawn/no longer available; see 2015 opinion)
- 2nd Wave Initiative: Lyerly AD, Little MO, Faden R. *The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research.* Int. J Fem Approaches to Bioeth 2008; 1:5-22. PMID19774226. (Initiative launched at Georgetown University, 2009; currently at University of North Carolina; http://bioethics.unc.edu/second-wave-initiative/)
- ORWH Workshop: Blehar MC, Spong C, Grady C et al. *Enrolling Pregnant Women: Issues in Clinical Research.* Womens Health Issues 2013; 23:e39-e45. PMID 23312713. (Workshop occurred in 2010; its first publication was Foulkes MA, Grady C, Spong CY et al. *Clinical Research Enrolling Pregnant Women: A Workshop Summary.* Journal of Women's Health 2011;10:1429-1432 PMID 21819233)

Sources of Recommendations

NIAID Workshops: A series of workshops, 2011-13, focused on clinical research in vaccines and antimicrobials, with regard to pregnant women. Publications include:

- Beigi RH, Fortner KB, Muniz FM et al. *Maternal Immunization: Opportunities for Scientific Advancement.* Clin Infect Dis 2014; 59 Suppl 7:S408-2414. PMID 25425719
- Sheffield JS, Siegel D, Mirochnick M et al. *Designing Drug Trials: Considerations for Pregnant Women.* Clin Infect Dis 2014; 59 Suppl 7;S437-S444.
- Frew PM, Saint-Victor DS, Isaacs MB et al. *Recruitment and Retention of Pregnant Women into Clinical Research Trials: An Overview of Challenges, Facilitators, and Best Practices.* Clin Infect Dis 2014; 59 Suppl 7: S400-407 PMID 25425718

ACOG Opinion: Committee on Ethics, American College of Obstetricians and Gynecologists. *Ethical Considerations for Including Women as Research Participants.* Obstet Gyencol 2015; 126:e100-107. PMID 26488521

Sources of Recommendations

SMFM et al. workshop: Riley LE, Cahill AG, Beigi R et al. *Improving Safe and Effective Use of Drugs in Pregnancy and Lactation: Workshop Summary.* Am J Perinatol 2017; 34:826-832. PMID 28142152 (Workshop at February, 2015 annual meeting of the Society for Maternal-Fetal Medicine and sponsored by NICHD, the Society, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics)

FDA workshop: Wang j, Johnson T, Sahin L et al. *Evaluation of the Safety of Drugs and Biological Products Used during Lactation: Workshop Summary.* Clin Pharmacol Ther 2017; 101:736-744. PMID 28510297.

ASCPT expert panel: Illamola SM, Bucci-Rechtweg C, Costantine MM et al. *Inclusion of Pregnant and Breastfeeding Women in Research – Efforts and Initiatives.* Br J. Clin Pharmacol 2018; 84:215-222. PMID 28925019 (Expert panel at March 2016 annual meeting of the American Society for Clinical Pharmacology & Therapeutics).

Sources of Recommendations

NVAC: *Overcoming Barriers and Identifying Opportunities for Developing Maternal Immunizations: Recommendations from the National Vaccine Advisory Committee.* Public Health Reports 2017;132:271-284. (Recommendations of the Maternal Immunization Working Group of the Committee, as approved by the Committee September, 2016.