GENDER BARRIERS IN POLICY AND REGULATION

Martha Nolan

Vice President, Public Policy, Society for Women's Health Research, Washington, D.C.

Corresponding Author: martha@swhr.org

Symposium presented at the American Society of Pharmacology and Experimental Biology & Canadian Society of Pharmacology and Therapeutics Conference: "Women and Pregnancy: Safety, Efficacy, Ethics and Research Needs", April 23, 2013, Boston, Massachusetts. Sponsored by: Pregmedic, The Canadian Alliance for Safe and Effective Use of Medications in Pregnancy and Breastfeeding (www.pregmedic.org)

ABSTRACT

The Society for Women's Health Research (SWHR) has been a driving force in the U.S. for ensuring that biomedical research is conducted on women and for raising awareness about the biological and physiological differences between men and women. SWHR is a Washington, DC-based patient/research advocacy organization that has successfully advocated for the inclusion of women in clinical trials for more than two decades. It has lobbied successfully for research into women's health and sex differences and continues to recommend a number of actions to government, lawmakers and organizations as part of a comprehensive effort to transform science and improve the quality of medical care.

Key Words: *Women, pregnancy, advocacy, policy barriers, government, research*

For more than two decades, the Society for Women's Health Research (SWHR; http://www.swhr.org) has been a driving force for ensuring that biomedical research is conducted on women and for raising awareness about the biological and physiological differences between men and women. The SWHR is the Washington, DC-based patient/research advocacy organization that successfully advocated for the inclusion of women and minorities in clinical trials and is the thought leader on sex differences research today.

HISTORY

Today, we regularly speak about women's health or men's health and sex and gender differences, but that was not the case until recently. It may surprise many people that until the 1990s, scientists believed that women were biologically the same as men, except for our unique reproductive capabilities. It is now known, but not sufficiently understood by all physicians, that there are many conditions that affect women solely, predominantly, or differently than men.

Enormous scientific advances have been gained in the 20 years since the advent of the 1993 mandate of the National Institutes of Health (NIH), which was advocated for by SWHR.[1] This mandate required the inclusion of women and minorities in clinical trials funded by the NIH. Also in 1993, the U.S. Food and Drug Administration (FDA) lifted its prohibition on inclusion in clinical trials of women during their reproductive years. Unfortunately, despite legal and scientific advances, gender barriers in biomedical research policy and regulation still exist. These barriers go beyond pregnant women and their unique challenges.

We are all asking what can be done to enable more research on women who are pregnant, because there is a tremendous need in medical practice to be able to treat pregnant women who get sick and sick women who get pregnant.

It is important to understand what it took to accomplish the first changes for women, and the subsequent incremental steps, in order to identify what might be needed to change policy and to remove barriers to involving pregnant women in study populations. The question that initiated change back in 1988 was triggered by the Physicians' Health Study, where we were told that

if you had a risk of heart disease you should take an aspirin a day.[2] A group of women scientists, physicians and lobbyists asked, "Is this true for women?" This simple question ended up causing quite a stir, as there were no women in the study – only about 22,000 male physicians.[2] The answer, obtained nearly 20 years later was, "No, aspirin does not seem to work for women with heart disease."[3]

It is now known, for example, that heart disease is the number one killer of women in the United States.[4] Furthermore, women and men can differ in their presenting symptoms of heart attack, which can confuse diagnosis and treatment. Unfortunately, disparities in diagnosis continue, often leading to under-diagnosis and improper or less aggressive treatment in women, resulting in worse outcomes than should be the norm. And this is for a disease that is now studied in women.

Until recently, women generally did not know that there were important differences in their health as compared to men, and that they may not be getting the right diagnosis or treatment. Many women still don't understand that there may be a discrepancy between their health management and a man's, although we are trying to change this. This symposium, together with other conferences and publications, indicates that there is a great deal that needs to be learned about the health care of women in general, and particularly of pregnant women.

Most pregnant women, those considering pregnancy, or those postpartum who are breastfeeding, are unaware of how little research has been done on the medicines they need because they have become ill or have a chronic disease. It isn't until a woman asks the question, "Was this tested in someone like me: a pregnant woman?" that she discovers the truth and the tough decisions that healthcare professionals are faced with. This needs to change, and that is why we are here today. How do we change the protective policies that unnecessarily prevent researchers from being able to study pregnant women to vastly expand our data capital?

Policy Barriers

One of the major policy barriers when SWHR took on the issue of researching women 20 years ago was a 1977 FDA prohibition on women being included in clinical trials during their reproductive years. This was attributable to the diethylstilboestrol (DES) and thalidomide tragedies. Furthermore, it was easier for scientists to study men and extrapolate the data to women, as women subjects were considered to be more costly to include in trials due to their hormonal cycles and the variation to those cycles.

And despite the 1985 report from the U.S. Public Health Service Task Force on Women's Health Issues, that the lack of research on women had compromised quality of information and care for women,[5] the NIH did not include women in clinical trials.

So, when the Aspirin study results were released to great fanfare, a dedicated group of scientists (lead by Dr. Florence Haseltine of NIH), advocates, providers and patients came together around that question of whether this was true for women. They created SWHR and began to fight.

The Society for Women's Health Research (SWHR)

To succeed in changing attitudes and policy, SWHR knew early on that it needed to be a broadly based and diverse group.

I am very thankful that I did not face the question, "Was this tested in someone like me: a pregnant woman?" while I was pregnant. However, I did face the issue while in the emergency room (ER) with bad case of pneumonia, shortly after giving birth in 1997. I overheard the ER doctor talking to my doctor on the phone about what drug therapy options they might consider, and, since I was breastfeeding, what information they had regarding the safety of the baby. I did ask questions, but even so, did not at that time understand how little they knew.

They were able to pull together physicians and researchers specializing in areas such as cardiology, mental health, obstetrics and gynecology, as well as nurses, lawyers and public policy advocates - men and women. Similar initiatives will be needed today to change pregnancy research policy.

To gain visibility and media attention, SWHR sought support from the Congressional Caucus for Women's Issues (women members of congress) and from other powerful Members of Congress to request hearings and to persuade the Government Accountability Office (GAO) to investigate NIH's policies and practices regarding the inclusion of women and minorities in clinical trials. This was a key step. When high level members of Congress request a formal audit or investigation, it moves more quickly in priority and scale, but also, Congress governs the budget and authority over NIH as it does over all the federal agencies. Federal agencies pay attention to these reports for they often result in congressional hearings.

Timing worked to the advantage of SWHR because congressional hearings on the NIH were scheduled in June, 1990, and the GAO audit was released just in time for the hearings. The report concluded that the NIH's policy (1986):

- to encourage the inclusion of women in clinical trials, had not been well communicated or understood or enforced within NIH or the research community;
- was applied inconsistently across institutes, and;
- was only applied to extramural research, if at all.

These dramatic hearings created great media coverage and general outrage. As a result, within months, policy changes began to happen. The NIH, feeling the pressure from the Congressional hearings, published guidelines that required women and minorities to be included in clinical research and established the Office of Research in Women's Health (ORWH).

But no matter how well intentioned these steps by NIH, more needed to be done, as changes were not occurring within the NIH. The advocates would need Congress to take steps to mandate change. And they would need a legislative vehicle.

Congress used to follow a more regular order of business than today. This included somewhat routinely reauthorizing the existence of federal agencies. Reauthorization allows Congress to review, and sometimes redirect or eliminate, the responsibilities, focus, priorities, of an agency. They do this carefully, because it opens up the statute for the agency to proposed amendments, which can be time-consuming to consider and agree upon.

Thankfully, as a result of the efforts of SWHR, in 1993 Congress brought the NIH statute forward for reauthorization, creating an opportunity and a legislative vehicle to mandate a policy change, and thus to require the NIH to include women in all clinical trials, where appropriate, and

- for phase III clinical trials, to have sufficient numbers of women to be able to analyze the data by sex, and
- to permanently establish the Office of Research on Women's Health.

Not to be slowed down, SWHR quickly turned its advocacy attention to the FDA, knowing that its prohibition needed to change. Again Congress was asked to request a GAO audit of the agency. The GAO's 1993 FDA report, not surprisingly, found:

- Women were underrepresented in drug trials.
- Even if women were included, data were not analyzed to determine if women's responses to drugs differed from those of men.
- Insufficient numbers of women were included in pre-approval clinical drug trials.

The FDA was charged with improving women's representation. All of this again created significant pressure on the agency and resulted in the FDA reversing its 1977 guidelines and issuing new "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" that same year. These new guidelines[6]:

- encouraged the inclusion of women in Phase I and II (safety and dosing) studies
- required inclusion in efficacy studies, and
- required analysis of data on sex differences as well as those based on race and ethnicity.

These exciting changes to federal law, regulation, and guidance truly broke the barriers for women's health research, but policy and practice did not change overnight. Nor will it today for the efforts regarding research in pregnant women.

SWHR has had to keep the pressure on over the last two decades to transform the views of the scientific community, i.e., that studying women is important.

Since 1993, SWHR has held annual scientific meetings around the country. The SWHR now holds its annual scientific conference in Washington, DC, entitled What a Difference and X Makes.[i] The conference focuses on research in women's health and the biology of sex differences. SWHR has also created scientific research networks that focus on sex differences in a particular disease or organ system, and established a scientific society, the Organization for the Study of Sex Differences (OSSD), as well as a scientific journal, the Biology of Sex Differences (BSD).

SWHR obtained congressional support and funding for ORWH at NIH in order for ORWH to create a unique program entitled "Building Interdisciplinary Research Careers in Women's Health (BIRCWH)" (http://www.bircwh.psu.edu/). This highly successful program is designed to advance research into women's health and continues to this day.

Further, SWHR frequently runs public education campaigns encouraging women to participate in clinical trials and to know more about their health, encouraging them to ask questions of their health care provider about their treatment.

SWHR raised the funds for a ground breaking report from the Institute of Medicine, Exploring the Biological Contributions to Human Health: Does Sex Matter?[7] "Yes!" was the answer, from bench to bedside. IOM's well respected scientific position helped to make this result quite visible in the scientific community and has since been widely used to fight for women's health and sex differences' research. It validated this need and continues to do so to this day.

SWHR also went back to Congress to request additional GAO investigations and reports to prove lack of sufficient policy enforcement. Several useful examples of SWHR requests resulted in the following actions.

- In 2000, the GAO audited NIH again and determined that, although changes were instituted, not enough progress was made on women's health.
- A 2001 GAO audit of FDA records on drugs withdrawn from the market found that 8 out of the 10 withdrawn drugs had posed greater health risks for women than for men.

Then in 2010, at the request of Congress, the Institute of Medicine (IOM) published the report, Women's Health Research: Progress, Pitfalls, and Promise.[8] One of the recommendations in this status report was for the FDA to enforce its own regulations and guidelines with respect to reporting and analysis of sex, race and ethnicity.

These details emphasize what it took to not only change policy, but to change perspectives at all levels. This has allowed us to gain significant information about women's health in just two decades, yet many barriers still exist as regards studying females in all stages of research, from the bench to phase III clinical trials.

Pregnancy

So what does this history now mean for policies and barriers for pregnant women, since there are many parallels? What needs to happen, and when do we need congressional action, if at all?

Unlike the situation in 1990, today the scientific research community has come together, as have providers, to make the point that there needs to be research on pregnant women, and that regulations need to change. Unfortunately, pregnancy policy has not changed very much since the 1994 IOM report which created the presumption of exclusion of pregnant women. Yet, there is no requirement to justify such exclusion.

In the regulatory arena, two major regulations and guidelines continue to govern the landscape of research on pregnant women. And

[i] What a Differences an X Makes is the name of the annual SWHR congress held in Washington, DC.

there are others. The FDA's 2004 Guidance for Industry, Pharmacokinetics in Pregnancy[9], still provides the guiding principles followed by the research community and still leads to a persistent presumption of exclusion of pregnant women from clinical research.

I understand that the FDA is in the process of developing guidance on the additional ethical and scientific complexities associated with studying pregnant women in the setting of a clinical trial. It is very important for all constituencies to weigh in with the agency and comment on the guidance. While guidances do not have the force of law as do regulations, they still have powerful effects and are a policy change opportunity and, more so than changing the view of the NIH, changing the view of the FDA will be important to all our efforts.

In the Code of Federal Regulation on Human Subject Protections - Title 45 CFR46 Subpart B - the burden of inclusion is quite high: requiring that pregnant women or fetuses may be involved in research if ***all*** of the 10 conditions outlined are met.[10] Simply put, clinical research in pregnancy can be conducted only "if there is direct benefit to the fetus or mother,"[10] otherwise, the regulations prohibit research that may cause more than minimal risk to the fetus. The definition of minimal risk is vague, leading to major barriers to be able to proceed. The irony, as with so many laws and regulations, is that while the intent is to provide clarity, it doesn't, and the 10 requirements are subject to much interpretation, to differences of opinion, and are typically determined conservatively by institutional review boards (IRBs) and are not consistently applied across the states.

But efforts to address the barriers to pregnant women in clinical research ***are happening***.

Several months ago I was asked by the American Congress of Obstetricians and Gynecologists (ACOG) if SWHR would work with them, along with several specialty physician associations, on congressional efforts to help transform pregnancy research policy. ACOG is seeking support for a proposed congressional resolution in favor of inclusion of pregnant women in research. Such resolutions help to test the interest and resolve of Congress.

What helps to propel our congressional efforts is the fact that the scientific community has provided strong support and recommendations for us to call upon. In October 2010, the NIH's ORWH convened an important scientific forum, Enrolling Pregnant Women: Issues in Clinical Research.[11] This forum partnered several NIH Institutes and Centers at NIH with ORWH, and the FDA, to address the ethical, IRB and recruitment issues that investigators face in clinical research studies that enroll pregnant women. While for many it provided a forum to present challenges and strategies to overcome barriers to clinical research in pregnant women with chronic or infectious diseases, for advocates it provided solid evidence for policy change, specific recommendations and the clear broad support of the community.

Another major effort is The Second Wave initiative at Georgetown University (http://kennedyinstitute.georgetown.edu/secondwave/). The first wave was 20 years ago, which has already been described. The Second Wave seeks to address the presumption of exclusion of pregnant women from research. This exclusion has led to a troubling lack of knowledge about how to treat pregnant women's illnesses and in understanding how illness during pregnancy affects women`s health across their lifespan.

These two efforts, among many others, are aligning important voices and stakeholders. Advocates and lobbyists cannot influence legal or regulatory policy change without them. To convince policymakers that change is possible and safe, we need data and reports. Getting regulations or guidance issued, let alone changing laws, is difficult and time consuming.

If the FDA sees support and data in the scientific arena, it can help them over the protective hurdle. Perhaps an IOM report addressing that what exists today does not work; how it frustrates clinicians and researchers alike; and how it is actually harmful to pregnant women, could push us forward.

There is still widespread reluctance to include pregnant women in research - memories of DES and thalidomide cases - regardless of the

knowledge gained over the intervening decades. Yet recently, on April 8th, the FDA again approved a drug for morning sickness after it was off the market for 30 years, and caused no proven harm to mother or fetus.[ii] While the FDA is aware of the need to remedy the lack of pregnancy dosing and safety information, and is now more open to considering evidence other than the gold standard randomized controlled clinical trial to inform pregnancy labelling, this does not change the presumption of exclusion and the major hurdles scientists face.

The U.S. Department of Health and Human Services (HHS) must also address its human subject limitations and in a timely manner. In 2011, it asked for input on the common rule for human subject research, understanding that regulations need to keep pace with clinical research as well as the proliferation of multisite clinical trials and observational studies. But HHS did not ask for input on Subpart B.[9]

Fear of Liability

While there is a growing consensus that the exclusion of women from research studies may pose just as much risk of liability as their inclusion, the legal community may not agree. This presents an enormous barrier to changing research policy. Institutional administrators express great concern over exposure to legal liability, even though this may be a rare problem in actual experience. Furthermore, IRBs have a pervasive fear of liability that drives them to adopt conservative policies and practices.

Litigation is expensive and time consuming. Involving and including the IRB and the legal community to consider and reasonably address issues could act as a linchpin in helping to move policy discussions forward and will be very important to any effort. But it must be acknowledged that there are no quick fixes or easy remedies for science-regulatory policies that have become embedded in institutional cultures.

[ii]Diclegis (doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg) was approved by the FDA on April 8, 2013. Bendectin (doxylamine succinate 10 mg, pyridoxine hydrochloride (Vitamin B_6) 10 mg and dicyclomine hydrochloride 10 mg) was removed from the market by its manufacturer in 1983.

RECOMMENDATIONS

The following are recommendations that have been proposed as part of a comprehensive effort to make progress in this area of research.

1. Particular government-focused efforts at HHS, FDA, IOM, and NIH.

a. Change government guidelines into regulations that presume inclusion of pregnant women and require justification for exclusion.

b. Women should no longer be considered a "vulnerable" population but a "complex" one.

c. Work with the IRB community to create consistency of determinations from state to state.

d. Address the thorny issues of liability.

2. Update the informed consent process. Pregnant women are quite capable of understanding it.

3. Take into consideration new policies on risks vs. benefits from the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) - new provisions in the law that might help or should be applied to pregnant women and their viewpoints as patient stakeholders.

4. Review and update exposure registries' requirements to ensure capture of any and all data possible on pregnant women and drugs and conditions, working with the physician and patient community in designing the approach and parameters.

a. FDA provided authority to require exposure registries, not just encouraging them. We currently have to rely on post-market surveillance and observational studies for most information regarding pregnant women.

b. Privacy issues will need to be reviewed.

5. Consider greater use of the FDA Risk Evaluation and Mitigation Strategy (REMS) in the design of post-marketing studies if an approved drug is likely to be used widely by pregnant women or women of childbearing potential.

6. Encourage the NIH and others to establish a pregnancy research agenda, as was discussed at the 2010 meeting, to address competing priorities and short-and long-term needs, within the realities of funding.

Those of us in the advocacy community will come together to address any and all of these, for in the U.S. alone there are over 500,000 pregnant women facing serious medical illnesses every year; illnesses such as heart disease, diabetes, lupus, and cancer. The number of drugs explicitly approved by the FDA for use in pregnancy is limited, so these women, and all pregnant women, deserve better information.

REFERENCES

1. National Institutes of Health. National Institutes of Health Revitalization Act of 1993. Subtitle B–Clinical Research Equity Regarding Women and Minorities. http://orwh.od.nih.gov/about/pdf/NIH-Revitalization-Act-1993.pdf (July 6, 2013)
2. Physicians' Health Study. http://phs.bwh.harvard.edu/index.html (July 6, 2013)
3. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352(13):1293-304. http://www.nejm.org/doi/full/10.1056/NEJMoa050613 (July 7, 2013)
4. National Heart, Lung, and Blood Institute, National Institutes of Health (NIH). How Does Heart Disease Affect Women? September 26, 2011. http://www.nhlbi.nih.gov/health/health-topics/topics/hdw/ (July 7, 2013)
5. Women's Health. Report of the Public Health Service Task Force on Women's Health Issues. Public Health Rep. 1985;100(1):73-106. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1424718/pdf/pubhealthrep00101-0075.pdf (July 7, 2013)
6. U.S. Department of Health and Human Services, Food and Drug Administration. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs; Notice. Federal Register. 1993;58(139):39406-39416. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126835.pdf (July 7, 2013)
7. Institute of Medicine. Exploring the biological contributions to human health: Does sex matter? Washington, DC: National Academy of Sciences; 2001. http://www.iom.edu/~/media/Files/Report%20Files/2003/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter/DoesSexMatter8pager.pdf (July7, 2013)
8. Institute of Medicine (U.S.). Committee on Women's Health Research, Board on Population Health and Public Health Practice. Women's health research : progress, pitfalls, and promise. Washington, DC: National Academy of Sciences; 2010. http://www.iom.edu/Reports/2010/Womens-Health-Research-Progress-Pitfalls-and-Promise.aspx (July 20, 2013)
9. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). 2004 Guidance for Industry. Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling. April 30, 2009. http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm133348.htm (July 7, 2013)
10. U.S. Department of Health & Human Services. Code of Federal Regulations, Title 45, Public Welfare, Department of Health And Human Services, Part 46 Protection of Human Subjects. July 14, 2009. http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf (July 7, 2013)
11. National Institutes of Health. Enrolling Pregnant Women: Issues in Clinical Research. Webcast. October 18, 2010. http://videocast.nih.gov/Summary.asp?File=16205 (July 7, 2013)