The Need to Consider Pregnancy As a Biological Variable to Reduce Preventable Suffering Related to Pregnancy

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Abstract

Maternal morbidity and mortality constitute a national health crisis, and pain is a significant component of maternal morbidity. One important way to reduce maternal morbidity is to reduce the pain associated with pregnancy. Unfortunately, our understanding of how to reduce pain in women is hampered because, historically, mostly male subjects have been used in the study of pain. However, more recently, females increasingly have been included in pain research studies, and astounding differences in how males and females process pain have been uncovered. Moreover, pain in nonpregnant women differs in many ways from pain experienced by pregnant women. We argue here that to better address maternal morbidity, we must better address the pain associated with pregnancy. Furthermore, just as it is important to include both men and women in pain research to better understand pain in both sexes, conducting pain research in pregnant women is essential to finding ways to reduce pain in pregnant women.

Keywords: pain, pregnancy, analgesia, maternal morbidity

Introduction

HISTORICALLY, BIOMEDICAL RESEARCH has focused on the study of males, and clinical trial subjects predominantly have been males because of a misconception that males and females were essentially the same, except that female hormones could interfere with the interpretation of the data. This misconception has not only led to erroneous conclusions about the health of women but also has been proven to be a grossly incorrect assumption.¹

Despite the passage of legislation that mandates the inclusion of women in clinical studies, this issue still pervades the scientific community. For example, from the 120 journal articles published in the *New England Journal of Medicine* in 2001, only 24.6% of the participants enrolled were women.² In addition, pregnant women traditionally have been excluded from clinical trials because they were deemed a vulnerable population and became a protected class of human subjects by the Common Rule,³ which—although protective—also means that research that could lead to reducing diseases and suffering in pregnant women often is not conducted.

In 2016, to advance biomedical research that would promote the health of males and females, the National Institutes of Health (NIH) adopted the Sex As a Biological Variable (SABV) policy (<https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable>), which mandated the inclusion of both sexes in research, with some exceptions. The policy states that “NIH expects that SABV will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.”

The SABV policy applies across the spectrum of biomedical research and is making a significant difference, but it is especially needed in the field of pain research. Chronic pain affects about 100 million Americans and costs our society between \$550 billion and \$650 billion annually,⁴ more than any other health condition. Pain is more prevalent in women than in men,⁵ and in almost all studies, females have been found to be more sensitive to pain than males.⁶ Despite the impact of pain, especially in women, we still struggle to manage it effectively because pain is often difficult and

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expensive to treat, and the overprescribing of opioids as a “quick fix” to alleviate pain has set the foundation for the opioid crisis in the United States. We need to do better for men and women in pain.

Why are we not better able to treat pain? Part of the reason is that we historically have done most of the preclinical pain research on males and unsuccessfully have tried to apply these findings to females. Between 1996 and 2005, 79% of the preclinical research studies with rodent subjects published in the journal *Pain* tested male rats or male mice only,⁷ and although more females are being used in pain research since the implementation of the NIH SABV policy, nearly half of the animal studies published in *Pain* in 2019 were still male-only studies.⁸

Despite a historical bias toward conducting pain research (and biomedical research, in general) predominantly in males, leading to a “male-based literature,”⁸ more recent research is making it dramatically clear that males and females have very different pain-processing systems that are sensitive to different treatment approaches.

One recent review by Jeffery Mogil,⁸ a leader in this field, highlighted many of these differences. Mogil presents almost 50 articles that report sex differences in genetics related to pain processing. For example, Smith et al.⁹ found a genetic predictor of temporomandibular joint disorder (TMJD) that is predictive of TMJD only in males. Mogil also presents the findings from about 30 articles addressing sex differences in the neural mediation of pain. This includes the work of Anne Murphy and colleagues who have discovered that the descending pain control system—first described in the 1970s^{10,11} and extensively studied since—works very differently in males than in females, for example, opioids are far less effective at inducing pain relief using this pain control system in females than in males.^{12–14}

The documentation of this pain control system is largely of the male system, and we do not know what the female system looks like because, for the most part, we simply have not been looking for it. In addition, Mogil describes extensive literature on sex differences in the neuroimmune mediation of pain. It is becoming increasingly clear that the immune system is involved critically in pain processing; the work by Mogil and collaborators shows that different components of the immune system are more involved with the pain of females (e.g., significant T cell involvement) than males (e.g., significant glial cell involvement).¹⁵ Last, Mogil covers sex differences between cognitive, environmental, and social factors of pain in males and females.

Clearly, many significant qualitative and quantitative differences in the biology of pain exist between males and females, and given the escalating number of recent articles highlighting these differences, we may be just at the beginning stages of this research.

Pregnancy As a “Stress Test”

Pregnancy has been described as a stress test for life,¹⁶ and one must look no further than the maternal morbidity and mortality crisis in the United States to confirm that pregnancy is indeed a stress test. In the United States, we are failing that test. Unlike the rest of the world, from 2000 to 2017, the United States saw a dramatic rise in pregnancy-related deaths, which increased to 19 deaths per 100,000 births in 2017.¹⁷ An estimated 700 women die each year in the United States from conditions related to or associated with pregnancy or childbirth.

Black women die at a rate nearly four times that of white women, and Alaska Native/American Indian women die at nearly three times the rate of white women.¹⁸ In addition, ~50,000 women experience severe maternal morbidity (SMM).¹⁹

A multitude of substantial physiological, anatomical, and behavioral changes occur during pregnancy.^{20–22} During pregnancy, the mother’s body must work harder to meet the demands of the developing fetus. Each maternal organ adapts in a variety of ways over time.²³ Furthermore, the immune system needs to adapt to the presence of the allogeneic fetus to prevent rejection of the fetus.²⁴ Pregnancy and the postpartum period encompass a time of significant biological and psychological change and stress.

Pain and Pregnancy

Pregnant women are propelled into a state that is vastly different from that of nonpregnant women. The immune and nervous systems are very involved with pain regulation and mitigation and changes significantly in pregnancy.^{25–28} Pregnancy causes an increase in oxytocin release, which has been implicated in pain processing.²⁹ Jung et al.³⁰ found a progressive rise in total plasma cortisol, corticosteroid-binding globulin, and 24-hour urinary-free cortisol during pregnancy, peaking during the third trimester, which implicates an upregulation of the maternal hypothalamic/pituitary/adrenal axis that is involved in pain processing. Physical and mechanical changes associated with pregnancy also are associated significantly with pain, for example, carrying the excess weight of pregnancy is associated with lower back pain or pelvic girdle pain^{31,32} and with increased knee and foot pain.^{33,34}

Many disease states associated with maternal morbidity and mortality are painful or have the potential to exasperate existing pain states. Hemorrhage, cardiovascular and coronary conditions, infection, cardiomyopathy, embolism, preeclampsia and eclampsia, and mental health conditions are the leading causes of death associated with pregnancy in the United States.³⁵

Pain commonly is associated with these conditions before death and is a prominent symptom of women with maternal morbidity. Although a consensus has not been developed on the exact definition of SMM,³⁶ the Centers for Disease Control and Prevention has provided a list of 21 indicators it uses to search for instances of SMM among existing electronic health records on hospital visits.³⁷ These indicators include acute myocardial infarction, acute renal failure, adult respiratory distress syndrome, eclampsia, cardiac arrest or ventricular fibrillation, puerperal cerebrovascular disorders, pulmonary edema or acute heart failure, sepsis, sickle cell disease with crisis, and hysterectomy. All of these indicators can have pain associated with them, and in some cases, such as sickle cell disease, the pain can be debilitating.³⁸

However, the news is not all bad. Preclinical and clinical research has demonstrated the existence of pregnancy-associated analgesia, where being pregnant can reduce one’s sensitivity to pain. In animal studies dating back to 1980, studies in rats have shown increases in acute pain tolerance during pregnancy, and such pain tolerance increases across the pregnancy and is opioid receptor mediated.³⁹

More recently, others have found that pregnancy could reduce the pain hypersensitivity produced in the chronic constriction injury model, in which the sciatic nerve is constricted partially with ligature,⁴⁰ during late pregnancy in

rats.⁴¹ Of note, T cells have been found to be involved critically in pain processing in female but not in male mice, whereas glial cells are critical to pain transmission in male but not in female mice.¹⁵ During pregnancy, the dampening of the immune system to protect the fetus⁴² may explain some pregnancy-induced analgesia. Rosen et al.⁴³ have found that T cell-deficient pregnant mice do not exhibit pregnancy-induced analgesia, suggesting that T cells are involved in the mediation of pregnancy-induced analgesia.

In humans, researchers also have looked at pain thresholds in response to experimenter-induced acute pain in pregnant and postpartum women. Cogan and Spinnato⁴⁴ examined the pain thresholds of women in the last few weeks of pregnancy and found that their pain thresholds to pressure stimuli increased (*i.e.*, they experienced less pain sensitivity) as childbirth approached. Pain thresholds of nonpregnant control subjects remained unchanged. In a similar study, Ohel et al.⁴⁵ found that pressure pain thresholds increased during the active phase of labor but not during prelabor, and pain responsiveness returned to normal after childbirth. Furthermore, Kammerer et al.⁴⁶ found a lack of responsiveness to cold pain in women just before giving birth.

Numerous reports indicate that prepregnancy chronic pain becomes diminished during pregnancy. For example, in a prospective study by LeResche et al.,⁴⁷ women with musculoskeletal orofacial pain and pain-free comparison subjects completed a questionnaire assessing pain at the first, second, and third trimesters of pregnancy, as well as 1 year postpartum.

Pain decreased across the course of the pregnancy. Melhado et al.⁴⁸ evaluated the presence of headache in 1,101 pregnant women with a history of headache, conducting interviews with women during the first, second, and third trimesters of pregnancy and immediately after delivery. They found that most of the headaches improved or disappeared during the second and third trimesters. Likewise, Granella et al.⁴⁹ studied 1,300 women who suffered from migraine headaches without aura. Of the 943 patients who became pregnant, 17.4% had complete remission from headaches, and a significant improvement was seen in 49.9% of the pregnant patients.⁴⁹

T cells are implicated in the progression of rheumatoid arthritis (RA), a painful autoimmune disease, so it is not surprising that pregnancy affects RA. A review by Østensen and Villiger⁵⁰ reported that about 75% of patients with RA experience improvement or even remission of arthritis during pregnancy. In terms of RA pain, Barrett et al.⁵¹ found that 66% of pregnant women with RA had decreased pain and 64% had less swelling by the third trimester. de Man et al.⁵² found a similar remission of RA symptoms, including the metrics of pain, but to a lesser extent than Barrett et al.⁵¹

Conclusion

Just as it has been a historical mistake to assume that by studying pain only in males one gets a picture of pain in females as well, it would be a mistake to assume that studying pain in nonpregnant females provides an understanding of pain in pregnant females. A woman's body changes dramatically with pregnancy, and many of these changes help to drive the maternal morbidity and mortality crisis in the United States.

To address the maternal mortality and morbidity crisis comprehensively, much must be done, including improving the treatment of pain during pregnancy. Although in some ways nature may be protecting pregnant women from pain, it is still a significant part of pregnancy. Like nature, we must help protect pregnant women from unnecessary suffering. To do this, we must study pain both during and after pregnancy, rather than exclude pregnant women from pain research altogether, as is too often the case. In pain research and beyond, when appropriate, it is time to consider pregnancy as a key biological variable in biomedical research.

Authors' Contributions

D.A.T., H.E.B., and J.M.W. contributed to the conceptualization of the review topic, the literature review, and writing this article.

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