The significance of sex and gender in clinical pharmacokinetics

Giselle Mirfallah[1]

[1]University of British Columbia, Vancouver, British Columbia, Canada

Abstract The consequences of the historical exclusion of cisgender women and pregnant people from pharmacological clinical trials have resulted in a dangerously low quality of care for these populations. Analyzing and interpreting significant sex- and gender-related differences in drug absorption, distribution, metabolism, and excretion are critical for adjusting dosing regimens and therapeutic drug monitoring. A deep understanding of the impact of these differences is required for practitioners and clinical researchers. This review summarizes the physiological differences between the sexes as they relate to cardiovascular, respiratory, gastrointestinal, and renal variations. A direct examination of the possible effects of these difference on the pharmacokinetics of drugs critically highlights the current knowledge gap. The importance of including all sexes in clinical trials and pharmacokinetic studies is emphasized in this review. Current and future scientists should strive toward reducing health care disparities based on sex and gender in their studies, incorporating sex and gender-specific analysis whenever possible.

INTRODUCTION

It is hardly surprising that sex differences impact the experience and symptomology of diseases. Nevertheless, sex-based biological differences and their influence on drug metabolism are rarely considered when prescribing medications and developing treatment plans (Kim et al., 2010). Based on many existing reports, cisgender women (cis women) experience nearly twice the rate of side effects than cisgender men (cis men) and represent 60% of adverse drug event-related visits to the emergency department (Budnitz et al., 2006). In 1998, the Food and Drug Administration (FDA) mandated that new drug applications must conduct sex-based studies on safety and efficacy. While this was a necessary change, most of the currently available prescription drugs received their approval from the FDA prior to 1993, without sufficient representation of men and women in their clinical trials (Zucker & Prendergast, 2020). Moreover, a 2018 meta-analysis of 107 trials controlled by the National Institutes of Health (NIH) that included cis men and women found that 72% did not perform sex-specific analysis (Zucker & Prendergast, 2020). While cis women are now participating in clinical trials at a higher rate than ever before, the ability to generalize these results is limited by a lack of sex-based analyses on physiological differences, side-effect profiles, and drug efficacy (Soldin & Mattison, 2009).

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Correspondence
Address correspondence to **Giselle Mirfallah** at Ghazal.mirfallah@gmail.com

This review aims to highlight the importance of sex-based analysis in pharmaceutical clinical trials by focusing on the influence of sex on pharmacokinetics: the study of drug absorption, distribution, metabolism, and excretion. The following section describes how, menstruation, pregnancy, and menopause cause variations in human physiology (such as cardiovascular, gastrointestinal, etc.) and could potentially explain the pharmacokinetic differences. Recent literature has begun to explore this theory, however, the capacity to spot these discrepancies has been compromised by the historical exclusion of all populations other than cis men from clinical research studies. Thus, we need to dedicate a tremendous amount of effort to correct previous non-inclusive data. This review should be used as an example to illustrate the importance of including all sexes in scientific data and to remind future scientists to minimize sex-based gaps in their research.

In addition to sex, gender can also influence drug safety and effectiveness. Gender is an individual's internal sense and experience of being male, female, both, or neither, and refers

to the characterizations that are socially constructed (World Health Organization, n.d.). Sex encompasses the biological factors associated with a person's categorization as a male, female, or intersex, and may or may not be aligned with their gender. Throughout this review, the terms female and male will be used to attribute to sex and gender non-conforming will be used as an umbrella term for adults whose gender identity differs from their sex assigned at birth. Pharmacokinetic research on the gender non-conforming population is insufficient, and the extent of generalizability of drug safety from research involving cisgender people to gender non-conforming and intersex populations is unclear (Cirrincione & Huang, 2021). In addition, gender non-conforming adults may elect to do hormone therapy (HT), gonadectomy, mastectomy, and other forms of gender-affirming procedures. While this can result in physiological and hormonal changes, their influence on the disposition of other prescribed medications is poorly understood and research studies are scarce (Cirrincione & Huang, 2021; Yager & Anderson, 2020). Given the population's disproportionate HIV burden, several phase III clinical trials for HIV pre-exposure prophylaxis (PrEP) have prioritized the inclusion of gender non-conforming people, but often lack sub studies on PrEP-HT interactions (Cirrincione et al., 2023). The FDA has failed to shed light on the critical issue of trans and intersex inclusion in their "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" draft (Center for Devices and Radiological Health, 2014). One small but promising success story is the phase III clinical trial for HIV PrEP that is prioritizing the inclusion of transgender people (Cirrincione et al., 2023). While stressing the importance of further research focused on gender non-conforming and intersex populations, this review will focus on summarizing physiological and pharmacokinetic differences of sex during the menstrual cycle, pregnancy, and menopause.

DISCUSSION/LITERATURE REVIEW

Hormonal variation within the menstrual cycle, pregnancy, and menopause

Pharmacokinetics can be considerably influenced by factors such as genetics, diet, age, and lifestyle; however, this review will specifically explore how the menstrual cycle, pregnancy, and menopause affect drug pharmacokinetics (Jamei et al., 2009). In order to evaluate this effect, it is important to understand the influence of each condition in the absence of pharmacological intervention. The following are some of the highlighted factors of these complex phenomena.

The menstrual cycle is commonly divided into three phases: follicular, ovulatory, and luteal. Plasma hormone concentrations, including estrogen, progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH), respectively, vary significantly between different phases. During the early days of the follicular phase (known as menses), estrogen, progesterone, FSH, and LH concentrations are at a minimum (Oertelt-Prigione, 2012). In the remainder of the follicular phase, estrogen is secreted by the ovaries and will reach maximum concentration during the mid to late follicular phase. This triggers peak concentrations and subsequent ovulation (Oertelt-Prigione, 2012). During the early days of the luteal phase, the dominant follicle that released the matured egg transforms into the corpus luteum, and estrogen concentration decreases as progesterone secretion increases. Estrogen concentration peaks during the mid-luteal phase as progesterone concentration plateaus (Thiyagarajan et al., 2021). Close to the end of the luteal phase, both estrogen and progesterone concentrations decrease while FSH secretions increase (Oertelt-Prigione, 2012).

During the first 10 weeks of gestation, estrogen and progesterone are largely produced by the corpus luteum (Csapo et al., 1973). However, as the placenta develops, the corpus luteum degenerates and the placenta mainly contributes to the production of these essential hormones. Estrogen levels skyrocket throughout the pregnancy, increasing 30-fold by the time of childbirth (Betts et al., n.d.). During the 32nd week, a gradual increase of progesterone production by the placenta is observable (Rothchild, 1983). Progesterone decreases during late gestation, allowing for uterus contractions and eventually labor. Some of the other influential hormones that increase during pregnancy and require close observation are prolactin, relaxin, human chorionic gonadotropin (HCG), and human placental lactogen (hPL) (Kumar & Magon, 2012).

Menopause occurs slowly and at an average age of 51 years in females (Al-Azzawi & Palacios, 2009). Menopause is accompanied by a gradual decline in estrogen and consequently an increase in FSH. In the absence of ovulation, progesterone is only found at basal levels and secreted by the adrenal glands due to the lack of corpus luteum synthesis in menopausal people (Al-Azzawi & Palacios, 2009).

Physiological differences between sexes

Cardiovascular variations across menstrual cycle phases have been consistently documented. Those who menstruate have higher heart rates, lower diastolic blood pressure, and higher systolic blood pressure during the luteal phase (Kharitonov et al., 1994). While these factors could influence pharmacokinetics, more research is needed to determine their clinical relevance (Woodward, 2019). Gastrointestinal (GI) motility can be a rate-limiting factor for pharmacokinetics and is coordinated by the central nervous system and multiple hormones (Kashuba & Nafziger, 1998). Some researchers suggest that endogenous sex hormones can lead to slower gastric emptying in females (Hutson et al., 1989). Gastrointestinal sex differences influence all orally administered medication by impacting drug absorption and bioavailability. For example, progesterone can induce relaxation on the intestinal smooth muscles, increasing gastric emptying time (Kashuba & Nafziger, 1998).

Research focused on the menstrual cycle found that higher kidney secretions (renin activity) along with certain plasma concentrations (vasopressin and aldosterone) are higher in the luteal phase than in the follicular phase of the menstrual cycle (Forsling et al., 1981). In addition, the increase of estrogen during ovulation correlates with decreased sodium excretion (Parboosingh et al., 1974). These factors could potentially have a significant influence on the distribution and excretion processes of pharmacokinetics (Kashuba & Nafziger, 1998). Fluctuations in body weight, body temperature, and electrolytes during different phases of the menstrual cycle have been well established and can influence pharmacokinetics at different rates (Dadlani et al.,1982).

The influence of sex on pharmacokinetics

Absorption is the first step in pharmacokinetics. It is the movement of drug from the administration site into the bloodstream. This step is bypassed when the drug is administered through intravenous (IV) injection. Several factors can influence a

drug's absorption rate, including gastric acid secretion, gastric emptying time, gastrointestinal surface area, blood flow, and presystemic hepatic and gut metabolism and transport (Martinez & Amidon, 2002). The influence of sex hormones on GI motility implies that there are variations in drug absorption between menopausal, pregnant, and premenopausal persons. Gastric emptying time differences have been consistently observed during pregnancy and are slower in females than males in general (Hutson et al., 1989; Singer & Brandt, 1991).

The GI enzymes responsible for drug metabolism are also influenced by sex (Freire et al., 2011). A commonly studied enzyme with significant variation between sexes is gastric alcohol dehydrogenase. Cis men typically have a larger quantity of this enzyme, leading to lower blood concentrations of ethanol after consuming the same amount of alcohol as cis women (Frezza et al., 1990). The peak of this sex-based difference in blood alcohol concentration has been found in the premenstrual period (days 21-28) rather than during menstruation (days 1-3) and intermenstrual periods (days 13-18) (Jones & Jones, 1976). Pharmacokinetics research has revealed significant sex differences in the absorption and bioavailability of certain drugs. One example of this is verapamil, a calcium channel blocker primarily used for high blood pressure (Singh et al., 1978). When administered orally, this drug is cleared more slowly in cis women than in cis men, but this trend is not observed following IV administration (Krecic-Shepard et al., 2000). These differences suggest that the underlying variation is due to sex differences in intestinal absorption processes.

The second step of pharmacokinetics is distribution, the process by which the drug leaves the bloodstream, moves between body compartments, and typically reaches the receptors. The distribution of a drug is affected by many factors, including the extent of reversible binding between a drug and plasma proteins, body mass and composition, organ blood flow, and plasma volume (Spaanderman et al., 2000). These factors are greatly influenced by sex, with sex hormone concentrations affecting the major plasma proteins responsible for drug binding. Variations in the levels of plasma binding proteins can alter the level of free (unbound) drug. The free fraction is the pharmacologically active form of the drug and it is often the primary focus during therapeutic drug monitoring studies, thus emphasizing the need for further investigation of sex-based differences in protein binding (Anderson, 2005). Alpha-1 acid glycoprotein (AAG), albumin, and alpha-globulins are three of the main plasma binding proteins for drugs. Research shows that AAG levels decrease with endogenous and exogenous estrogen interactions (Brinkman-Van der Linden et al., 1996; Succari et al., 1990; Walle et al., 1994). Some studies suggest that AAG levels may decrease over the course of pregnancy (Aquirre et al., 1998; Wood & Wood 1981), while another study suggests no observable changes in AAG concentration (Chu et al., 1981). A significant decrease in albumin has been consistently documented in pregnant people, reaching 70-80% of baseline levels by the time of delivery (Dean et al., 1980). Moreover, on average, females have more body fat and lower body weights, while males have larger average plasma volumes and higher organ blood flow, demonstrating a clear sex difference in the volume of distribution for various drugs (Nicolson et al., 2010). Volume of distribution (Vd) relates the amount of the drug that was administered and the amount measured in the blood (Smith et al., 2015). Difference in average body fat percentages between the sexes influences the volume of distribution of lipophilic (Greek word for fat loving) versus hydrophilic (Greek word for water loving) drug compounds in cis men and women. Considering the higher average body fat percentage in cis women, there would be a greater volume of distribution for lipophilic drug agents compared to hydrophilic ones (Gandhi et al., 2004). This difference has been demonstrated with lipophilic paralyzing agents such as vecuronium and rocuronium (Takaya et al., 2001; Xue et al., 1997). These drugs often have been found to have a faster onset and longer duration of action in women compared to men (Semple et al., 1994).

The third step of pharmacokinetics is metabolism, the conversion of the original drug to one or more metabolites. Hepatic (liver) clearance is influenced by both hepatic blood flow and hepatic enzymes. Although hepatic blood flow is lower in females than males, hepatic enzymes are the primary determinant underlying sex-based differences in drug metabolism (Gandhi et al., 2004). Two major enzyme-catalyzed processes drive metabolism: phase I includes oxidation, reduction, and hydrolysis, and phase II involves the conjugation of hydrophilic groups with the parent drug or its phase I metabolite. These processes increase the polarity of the drugs to increase their water solubility. Cytochrome P450 enzymes are the key components running phase I drug metabolism and have been studied extensively. The cytochrome P4503A (CYP3A) subfamily is responsible for the initial steps of the hepatic metabolism for most prescription drugs. A prominent member of this subfamily in humans is CYP3A4 (Shimada et al., 1994). Several pharmacokinetic studies revealed that males and females have significant differences in hepatic enzyme expression, where CYP3A4 levels in females is twice as high as in males (Wolbold et al., 2003). These differences stem from endogenous hormone production and variations during pregnancy, menopause, and the use of oral contraceptives (Kashuba & Nafziger, 1998). Research focusing on CYP3A4 metabolites determined that an increase in dose might be necessary to avoid loss of drug efficacy (Anderson, 2005). It has been shown that progesterone can both inhibit and induce hepatic enzymatic activity (Masuyama et al., 2001). On the other hand, estrogen can decrease the rate of oxidation of metabolites by inhibiting certain CYP enzymes (Waxman, 1988). The influence of hormonal fluctuations on phase II metabolism remains unclear; however, a minimal increase in conjugation activity has been documented by the estrogen component of oral contraceptives (Miners et al., 1983). An example of such differences in the metabolism of drugs is erythromycin. This well-studied drug is a substrate of CYP3A4 and clears more rapidly in women than men, aiding the discovery that there is a greater activity of the this enzyme in cis women (Austin et al., 1980). These results suggest that CYP34A metabolism differ by sex, however other pharmacokinetic factors may lead to varying results in overall drug clearance (Gandhi et al., 2004).

The last step of pharmacokinetics is excretion, the irreversible process of removal of drugs from the body. This process is mediated by the kidneys (renally) or the liver (via the biliary system). The renal clearance of drugs that are not actively reabsorbed or secreted into bile ducts depends on the glomerular filtration rate (GFR). GFR is proportional to body weight and thus is higher in males on average (Hermann et al., 2003). During pregnancy, a steady increase in renal blood flow and an approximately 50% increase in GRF is observed, followed by a

decrease during the last three weeks of the third trimester (Davison & Dunlop, 1980). These changes have been proposed as a possible explanation for more common adverse events in pregnant people. Due to a decreased rate of drug clearance, the same dose can result in higher drug concentrations and more frequent overdoses (Soldin & Mattison, 2009).

CONCLUSIONS

This review has documented the influences of sex-based physiological and their correlation with different pharmacokinetic processes. For many of these sections, a lack of clinical significance and/or inconsistent results were noted. The lack of adequate sample size, minimal funding, and insufficient data analysis on cis women, intersex, and gender non-conforming adult populations make it difficult to draw concrete and generalizable conclusions (Cirrincione & Huang, 2021). The Canadian Institute of Health Research has made impressive progress by requiring all government-funded research projects to integrate sex and gender into their original study design and analysis (Health Canada, 2023). This review should be used to emphasize the importance of sex based analysis and to remind researchers in all disciplines to be mindful when reviewing commonly cited but not generalizable literature.

A lack of consistency and concrete findings were also documented concerning the influence of the menstrual cycle. There are several possible explanations for these conflicting results, the first of which is inconsistent measurements for the different phases of the cycle. While these studies use semi-consistent vocabulary, some studies assign the phases based on days since menses, while others use urinary measures of hormonal excretion. Some investigations further complicate this by dividing the menstrual cycle into 2 to 5 phases and assigning different definitions to each phase (Kashuba & Nafziger, 1998). Other limiting factors include small sample sizes and limiting clinical investigations to only one cycle. Intra-individual variability and a lack of an established baseline make it difficult to conclude any significant clinical variation. Additionally, most studies only compared values averaged over the entire follicular and luteal phases, which can mask key variations within these phases (Kashuba & Nafziger, 1998). An optimal study design should be more granular in their analysis of the menstrual cycle and include measurements and analysis for menstruation, late follicular, ovulation, and late luteal phases. The first step would be to resolve this lack of agreement in the terminology and develop a gold standard for dividing different menstrual cycle periods (Elliott-Sale et al., 2021). Such standardized categorization will also be important for further research focusing on hormone and drug interactions with individuals going through HT.

Despite 20 years of legal 'enforcement' to include cis women in clinical research, substantial knowledge gaps remain. These gaps are often left for clinicians to fill in, which leaves room for assumptions and/or personal biases that can affect patient care. Gender non-conforming, intersex, and cisgender women populations are victims of this systemic medical naivete. This gap will only be overcome through a fair reallocation of resources to allow for the necessary focus on sex- and gender-based differences in clinical research. Ideally, this research would be paired with continuing physician education on the principles of pharmacokinetics and the mechanism of action of drugs in relation to dosing regimens (Soldin & Mattison, 2009). This will require foundational changes in many different areas of academia, including, but not limited to, pharmacology, medicine, public health, etc. Institutions should view studies that do not conduct sex-specific analyses as incomplete and demand justification for narrowing the sample population to only one sex (e.g. this is justifiable in gynecology research). They should also encourage studies to analyze drug pharmacokinetics during the three trimesters of pregnancy and postpartum, and employ standard definitions and measurements for each phase of the menstrual cycle (Anderson, 2005). In order to address this crisis for existing drugs, stricter and sex-based specific guidelines should be undertaken in order to develop more accurate and consistent dosing regimens for different sexes and genders. Through these measures we will be able to provide comprehensive and evidence-based health care for the members of the population who have been overlooked and under-treated for far too long.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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