Drug Therapy during Pregnancy

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Drug therapy in pregnancy may cause anxiety to both physicians and patients due to uncertainty regarding dosing and safety. Nevertheless, the need for medication is high given that maternal chronic illnesses such as hypertension or diabetes are on the rise[1]. In a national study in the United States over 33 years, the prevalence of prescription medication use by pregnant women in the first trimester increased by 62.5% between the first 2 years of the study and the last 2 years[2]. Furthermore, the average number of medications used anytime in pregnancy has increased two-fold [2]. More recent research from different countries has found that medications are widely used in pregnancy, with the prevalence of using at least one drug ranging from 60 to 90 percent, excluding vitamins and minerals [3-5]. Prescription of drugs with potential teratogenicity has also increased in pregnancy, including folate antagonists or angiotensin converting enzyme inhibitors[3,4]. This suggests that many women go into pregnancy with chronic conditions that require medications, including those may pose some degrees of risk to the fetus, since the maternal benefit may outweigh the risk or if the pregnancy is unplanned. Successful treatment of pregnant patients requires a correct diagnosis and providing treatment that not only is effective but also balances risks and benefits, as maternal health is the best defense for fetal health. However, concomitant health conditions, and the intrinsic complex physiological changes associated to pregnancy can make prescribing in this population a particularly challenging balancing act. Very few drugs have specific pregnancy dosing regimens supported by scientific evidence in spite of well-known pharmacokinetics changes during pregnancy affecting a large proportion of medications (Table 1)[6-10]. Data on drug efficacy and safety is sorely lacking for pregnant women, even for drugs that have been available for decades. Pregnant patients are commonly excluded from clinical trials during the drug development process due to ethical and safety concerns, which implies that the majority of drug therapy data in pregnancy have been extrapolated from males and to a much lesser extent, from non-pregnant females[11]. However, using extrapolated data in pregnancy has a number of major drawbacks such as that the extrapolation commonly fails to account for the changes in drug metabolism related to pregnancy [6]. Multiple physiological changes in pregnancy, including those affecting pharmacokinetics, must be considered when prescribing. Furthermore, these changes can also be affected by genetic variability[10]. Some drugs need to be used at higher doses in pregnancy due to increasing metabolic demand. A classic example is thyroid hormone, which requires a 30 to 45 percent higher dose in order to maintain euthyroid state due to limited compensation in pregnant patients with underlying thyroid disease [12]. One of the biggest physiologic changes in pregnancy is the expansion of plasma volume by approximately 50 percent due to hormone-mediated vasodilation, leading to activation of the renin-angiotensin-aldosterone system[10]. This change results in and increased volume of distribution for hydrophilic drugs and reduced peak concentrations [6]. Increased glomerular filtration rate in pregnancy also increases elimination of renally cleared drugs; a classic example of this effect is lithium[13]. Changes in hepatic enzyme activity in pregnancy, including upregulation of cytochrome P450 and glucuronidation, are another cause of increased metabolism and elimination of drugs[14]. Increased metabolism of lamotrigine by glucuronidation results in low drug levels in pregnancy and this can be further affected by polymorphism of UDP-glucuronosyltransferases [15]. One strategy to address changes in drug metabolism is to use therapeutic drug monitoring (TDM) with blood levels; however, TDM analysis is not readily available for the majority of

drugs used in pregnancy, limiting the usefulness of this strategy in clinical practice. Furthermore, lower total drug levels do not necessarily translate to less free drug due to volume expansion in pregnancy leading to relative hypoalbuminemia [6]. For some drugs, many clinicians modify the dosing regimen on their own based on limited pharmacokinetic data. For example, labelatol, a common antihypertensive used in pregnancy, has a half-life of only 1.7 ± 0.27 hours in patients in the 3rd trimester of pregnancy, compared to 6-8 hours outside of pregnancy[16]. This difference leads many clinicians to prescribe labelatol three times per day based on patient response instead of twice-per-day as per drug monograph[16]. However, there is considerable variation among clinicians due to lack of scientific evidence. For example, in patients diagnosed with acute pulmonary embolism, twice-per-day dosing and once-per-day dosing of low molecular weight heparin are both commonly used [17]. Enoxaparin once-per-day versus twice-per-day in a population pharmacokinetics study both achieved target plasma concentration in pregnancy[18]; however, once daily regimen has not been universally adopted in clinical practice and no similar data are available for other low molecular weight heparins. Pregnancy is also a vulnerable period for the occurrence of cardiac events. In particular consideration must be given to patients known to have long QT syndrome or on QT prolonging drugs. The adrenergic nature of labor and delivery may lead to catecholaminergic polymorphic ventricular tachycardia in these patients. Furthermore, patients with congenital long QT syndrome are also at risk during a nine-month post-partum period [19]. Treatment with beta-blockers are the mainstay of therapy during pregnancy and in the post-partum period[19]. There is a lack of data for therapeutics that may be urgently needed intrapartum that may prolong the QT interval in susceptible patients. For example, oxytocin and carbetocin are both known to prolong the QT interval but may be required for prevention or treatment of postpartum hemorrhage[20,21]. Clinical guidelines for using oxytocin for augmentation or induction of labour are lacking and some obstetricians may choose to do an elective Caesarian section to avoid prolonged oxytocin in these patients although this is not evidence based due to lack of studies. In addition to the challenges in proper prescribing in pregnancy, the information on teratogenicity of drugs is also limited. Management of the care of a pregnant patient must balance the benefits of treating the maternal medical condition with possible adverse effects on the fetus. Clinicians must rely on animal data, data from pregnancy registries, and published case control studies and case reports to make these risk/benefit assessments. These resources are by no means ideal as results are confounded by recall bias, selection bias, and inconsistency, as well as lack of ability to extrapolate safety between species [22]. Other than a few specific drugs with clear evidence of harm, many drugs have limited information, leading to variable practice among clinicians and inconsistent information provided to patients. For example, while angiotensin-converting enzyme inhibitor induced fetopathy has been described since the 1990s and accepted by medical community consistently[23], the risk of maternal corticosteroid use with increased risk of cleft lip and palate has not been consistent among studies[24,25]. In addition, long term corticosteroid use is also linked to increased risk of preeclampsia which needs to be taken into consideration for treatment and monitoring[26]. The US Food and Drug Administration recognized the limitation of the prior FDA classifications for medication use in pregnancy (A, B, C, D, X category system). Thus, the "Pregnancy and Lactation Labeling Rule" went into effect by the FDA in June 2015, requesting manufacturers to provide available information regarding risks in pregnancy and lactation in a narrative summary; however, according to a recent survey, less than 50 percent of prescribers were aware of this change, while more than half deemed the narrative summary not helpful [27]. Lack of quality data is one of the barriers identified in this survey. In addition to the rating systems used in various jurisdictions, an evidence-based medicine classification system has been developed by toxicologists, which can be used to assist clinical decision making. Unfortunately, all of the currently available systems are of limited utility due to reliance on small studies and inability to be updated frequently with new data[22]. Since the thalidomide story in the 1960s, much advancement has been made in medical therapy in pregnant women. However there remains a significant knowledge gap in pharmacological information which may expose patients to either toxicity or under treatment with reduced efficacy. In addition, numerous commonly used medications lack concrete data on teratogenicity. Supported by the NIH, the Pediatric Trials Network is currently conducting a multicentre trial studying the pharmacokinetics and safety of commonly used drugs in lactating women and breastfeeding infants in North America (NCT03511118); similar studies in pregnancy are also warranted to guide appropriate dosing. Long term data on children with fetal exposure for developmental toxicity are also urgently needed, and while some data for newer medications is systematically

collected by international registries, in general information on fetal risks of maternal exposures is limited to incidental data obtained from accidental exposures. Finally, making all up-to-date information readily available to clinicians should also be a priority.

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