Pharmacological Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Does poor fetal growth influence the extent of fetal exposure to maternal medications?

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ARTICLE INFO

Article history:
Received 30 October 2017
Received in revised form
18 December 2017
Accepted 1 February 2018
Available online xxx

Keywords:
Drug metabolism
Drug transporter
Complicated pregnancy

ABSTRACT

A large proportion of women are prescribed a medication during pregnancy, and the conditions requiring treatment with these medicines are often also associated with placental dysfunction and abnormal fetal growth. For the fetus, exposure to maternal illness or medications can alter fetal growth trajectory, which is a key indicator of fetal and postnatal wellbeing. There is a large amount of human and animal evidence highlighting the hormonal and/or metabolic changes that occur in both the mother and the fetus as a result of maternal illness or either excessive or restricted fetal growth. These changes can affect the expression of drug metabolising enzymes and drug transporters in the both the mother and her fetus, and may ultimately alter fetal drug exposure. This review aims to explore the complex and multidirectional interplay between maternal illness, fetal growth trajectory, maternal drug treatment, and fetal drug exposure.

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Abbreviations: 11βHSD, 11β-Hydroxysteroid dehydrogenase; ABC, ATP-binding cassette; AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; BCRP, breast cancer resistance protein; CAR, constitutive androstane receptor; CYP, cytochrome P450; DME, drug metabolising enzymes; DT, drug transporter; ER, estrogen receptor; ERE, estrogen response elements; GDM, gestational diabetes mellitus; GFR, glomerular filtration rate; GRE, glucocorticoid receptor response elements; HNF, hepatocyte nuclear factor; hsp, heat shock proteins; IL, interleukin; IUGR, intrauterine growth restriction; MRP, multidrug resistance-associated protein; OATP, Organic anion-transporting polypeptide; OCT, organic cation transport proteins; P-gp, p-glycoprotein; PPAR, peroxisome proliferator-activated receptor; PR, placental restriction; PXR, pregnane X receptor; SLC, solute carrier; SSRI, selective serotonin reuptake inhibitor; UGT, uridine 5′-diphospho-glucuronosyltransferase; Vd, volume of distribution; XAP, X-associated protein; XRE, xenobiotic response element.

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https://doi.org/10.1016/j.phrs.2018.02.001
1043-6618/

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Funding 00
Conflict of interest 00
References 00

1. Introduction

Optimising maternal and fetal health during the course of pregnancy often requires prescription or over the counter medication, with 70–99% of women receiving and/or filling a prescription during pregnancy [1,2]. These medications treat illnesses that may be pre-existing or that occur during pregnancy, including hypertension, asthma, psychiatric illnesses, gestational diabetes, and morning sickness [3–5]. These medications can be used either as a single dose, intermittently, or throughout pregnancy. Despite the rising use of medications during pregnancy, few clinical trials include women, particularly women who are of reproductive age or pregnant [6], which limits our understanding of the effects of medication on the mother and fetus.

Population based data linkage studies, which involve data collection about an individual from different sources, have been suggested as a method of identifying effects of maternal medications on key pregnancy outcomes such as fetal growth and weight in childhood [4,7–10]. However, this approach has limited ability to differentiate between the effect of the disease requiring treatment, the effect of the medication and the effect of gestational age at the time of medication exposure on later outcomes or elucidate the physiological mechanisms that are involved.

Drug transporters (DT) and drug metabolising enzymes (DME) are key regulators of drug concentration in the body. Hormonal changes that occur as part of normal pregnancy, such as increases in plasma progesterone and estrogen concentration, can also affect the expression and activity of DME and DT in the mother, the placenta and the fetus [11]. In addition, many medical conditions during pregnancy, such as depression and gestational diabetes, have direct effects on fetal growth (a powerful measure of overall fetal well-being) independent of any additional effects of medication exposure [12,13].

Fetal growth is also a key indicator for postnatal outcomes because babies with restricted or excessive growth are at increased risk of both adverse neonatal outcomes and long-term neurodevelopmental, cardiovascular and metabolic problems [14–17]. However, the impact of fetal weight on the offspring's later health outcomes is 'U' shaped with both excessively low and high birth weight are associated with adverse cardio-metabolic outcomes in later life [18–22]. Furthermore, studies in humans and animals provide evidence that maternal illness and abnormal fetal growth can lead to hormonal and metabolic changes in both the mother and the fetus [23,24]. Thus, maternal illness, medication use or complications resulting in a smaller or larger baby may affect maternal, placental or fetal expression of DME and DT and hence alter medication exposure in both fetal and postnatal life. Hence, the focus of this review is to explore the potential interactions between fetal growth and its effect on medication exposure in fetal and postnatal life.

2. Pharmacokinetics in pregnancy

The efficacy and duration of the pharmacological effect of a medication are determined by the drug concentration at the site of action, and this can be influenced by a variety of factors related to its pharmacokinetics. These can essentially be classified as effects on the extent of drug absorption, distribution into tissues, metabolism and excretion. In pregnancy, there are three compartments to consider: maternal, placental and fetal (Fig. 1), and the relationships between these compartments are highly dynamic. For example, in addition to the effect the mother's endocrine, hormonal and medication status has on her own metabolism of medications, the functional capacity of placental and fetal DME and DT changes across gestation and may vary according to maternal, placental and fetal wellbeing. Similarly, the fetal endocrine and hormonal status may affect the response to any maternal medication and/or metabolites that enter the fetal circulation.

3. The mother

3.1. Absorption of medication by the maternal gastrointestinal tract

Medication absorption from the gut is influenced by several factors including gastric pH, rate of gastric emptying, and small intestine motility. In pregnancy, gastric acid secretion, gastric emptying time and small intestine motility are reduced [26–28]. However, current data indicates that there is little significant effect of these changes in pregnancy on absorption of orally administered medication [29]. In addition, efflux DT such as P-glycoprotein (P-gp, ABCB1) and DME are expressed in the small intestine where they modulate drug bioavailability [30]. In animal models, pregnancy does not appear to affect the small intestine expression of efflux transporter P-gp [31] or multi drug resistant protein (MRP) 2 [32]. Similarly, small intestine expression and activity of DME is unchanged during pregnancy [11].

3.2. Distribution of medications in the mother

After absorption to the systemic circulation, drugs rapidly flow through the body and distribute into tissues such as fat, muscle and brain. Volume of distribution (V_d) is a theoretical value that represents the volume of fluid required for a medication to be diluted in order to produce the observed plasma concentration. The V_d of a medication is determined by many factors, including plasma and tissue protein binding, lipophilicity and degree of ionization. During pregnancy, there is a decrease in plasma proteins, including albumin, alpha-1 acid glycoprotein and corticosteroid hormone binding protein, which may increase the fraction of medication that is not bound to plasma proteins and hence more medication may be available for distribution into tissues [33,34]. Furthermore, pregnancy is usually accompanied by increased fat stores, which may in turn increase the proportion of an administered dose of medication that is distributed to adipose tissue, particularly for lipophilic medications. Overall, compared to the non-pregnant state, V_d is expected to increase for many drugs in pregnancy due to a decrease in plasma protein concentration and increase in fat mass [35].

3.3. Maternal hepatic metabolism of medication in pregnancy

The liver is the primary site of drug metabolism, although other organs, including the gut, lungs and kidney also have some capacity

Please cite this article in press as: J.Y. Soo, et al., Does poor fetal growth influence the extent of fetal exposure to maternal medications? Pharmacol Res (2018), https://doi.org/10.1016/j.phrs.2018.02.001