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REVIEW ARTICLE

Hepatic Elimination of Drugs in Gestational Diabetes

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Abstract: ***Background*:** The liver is the major metabolic clearance organ for chemical agents from the human body.

Pregnancy is associated with several physiological changes that may affect one or more of these factors, and also induces changes in the hepatic clearance of certain drugs. The aim of this paper was to review some of the currently available information in the field to provide some insights about the relevance of these changes on the clearance of some drugs.

***Methods*:** A comprehensive literature search was carried out to identify eligible studies from MEDLINE/PubMed, EMBASE and SCIELO databases through 1970 first semester.

***Results*:** Gestational Diabetes Mellitus (GDM) is a frequent disease commonly associated with other entities as obesity, hypertension, dyslipidemia, non-alcoholic fatty liver disease, prothrombotic conditions, changes in intestinal microbiome. These entities, together with the glycemic fluctuations associated with GDM might affect the determinants of the hepatic clearance (hepatic blood flow, the unbound fraction of drugs, and the hepatic intrinsic clearance).

GDM is frequently associated with multi-drug treatments. While many of these drugs are cleared by the liver, little is known about the clinical relevance of these GDM associated pharmacokinetic changes.

***Conclusion*:** Considering the frequency of the disease and the effects that these pharmacokinetic changes might have on the mother and child, the need for further research seems advisable. In the meantime, cautious clinical judgment in the management of drug administration in women affected by this disease is recommended.

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1. INTRODUCTION

The liver is the major metabolic clearance organ for many endogenous and exogenous chemical agents from the human body. Many drugs are extensively metabolized (biotransformed) within the liver, generating more polar or *hydrophilic* compounds that can be more easily eliminated from the organism. These metabolites may be completely inactive, less equally, or more active than the parent compound. The liver's ability to effectively eliminate drugs from the organism can be measured through the determination of the hepatic clearance. The hepatic clearance of a pharmacological agent is the volume of plasma from which a drug is completely removed during its passage through the liver per unit of time [1, 2].

The hepatic clearance of a specific drug with first-order elimination kinetic relies on three factors: 1) the hepatic blood flow, 2) the fraction of drug in the blood that is not bound to proteins, and 3) the ability of the hepatic enzymes to metabolize or bio-transform the drug, which is commonly defined as the hepatic "intrinsic clearance" (CLint) [1-3].

When a drug is to be removed by the liver, hepatocytes only uptake the free (unbound) drug that circulates in the hepatic bloodstream.The total hepatic blood flow results from the sum of the portal plus the hepatic arterial blood flow. Different enzymatic systems located within hepatocytes metabolize the agents with a determined drug-metabolizing capacity. CLint is thus characterized as the ability of the liver to remove an agent in the absence of flow limitations or binding to cells or proteins in the blood [1-3].

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For some drugs (*e.g*., propranolol, morphine), hepatic elimination is mainly (or only) limited by the degree of hepatic perfusion (high extraction rate drugs). In other cases (*e.g*., diazepam), the depuration rate is limited by the intrinsic capacity of the liver metabolizing enzymes and the unbound fraction of the drug [1-3]. The extraction ratio (ER) refers to the fraction of a substance taken up from the hepatic circulation into hepatocytes, making it available for biotransformation.

Pregnancy is associated with several physiological changes that may affect one or more of these factors, and also induces changes in the hepatic clearance of certain drugs [4]. These alterations may result in altered therapeutic or toxic effects of some drugs and/or may necessitate dosing modifications to achieve the desired therapeutic doses [4].

While normal pregnancy is associated with these pharmacokinetic changes, pregnancy-associated diseases might be linked to even more pronounced alterations that may result in damaging effects for the mother, the fetus, or even the newborn [5]. Gestational diabetes mellitus (GDM) is a frequent complication observed in pregnancy. It is usually defined as a type of diabetes with onset or first recognition during pregnancy. Its prevalence varies according to the diagnostic criteria applied, ethnicity, personal and family history, and other factors, and may result in relevant additional changes in the hepatic clearance of several drugs. According to data from the Center for Disease Control and Prevention (CDC) of the United States, GDM might affect close to 10% of all pregnancies [6], whereas other countries report prevalence rates of up to 15% [7]. GDM accounts for 85% to 90% of all cases of diabetes in pregnancy [7]. Diabetes is *per se* associated with some changes in the general pharmacokinetic behavior of some drugs and their hepatic clearance. Several mechanisms, such as the glycosylation of proteins (plasma proteins, receptors, enzymes and other), oxidative stress, and the effects of some cytokines and growth factors might explain some of these changes [8, 9]. Nevertheless, many questions related to diabetes-induced kinetic modifications remain unanswered.

Likewise, limited evidence is available regarding the GDM-associated changes that can affect the hepatic clearance of drugs, as well as its consequences in the clinical arena. The aim of this paper is to review some of the currently available information in the field, as well as to provide some insights about the potential importance of these GDM-associated changes on the hepatic clearance of some relevant drugs frequently used in clinical practice.

2. MATERIALS AND METHODS

A comprehensive literature search was carried out to identify eligible studies from MEDLINE/PubMed, EMBASE and SCIELO databases through 1970 first semester. Two review authors independently selected studies and extracted relevant data from included studies. The keywords used and their combinations can be divided into two groups: disease related section search ('gestational diabetes', 'pregnancy and diabetes', 'obesity and pregnancy', 'fatty liver disease and pregnancy', 'hypertension and pregnancy'), and pharmacology section search ('pharmacokinetics and pregnancy', 'pharmacokinetics and diabetes', 'pharmacokinetics and obesity', 'pharmacokinetics and hypertension', 'drug metabolism and diabetes', drug metabolism and pregnancy', 'drug metabolism and obesity', 'drug metabolism and fatty liver disease').

3. PREGNANCY-ASSOCIATED FACTORS THAT MODIFY HEPATIC CLEARANCE UNDER NORMAL CONDITIONS

Normal pregnancy is associated with several physiological changes that may affect the hepatic clearance of some drugs. These changes can affect some of the key factors that determine the hepatic clearance in a drug-dependent manner.

3.1. Changes in Hepatic Perfusion

Pregnancy is associated with an increase in total body water, as well as extracellular fluid expansion [10]. As a result, the distribution volume of hydrosoluble drugs is enhanced (in addition, an increase in the fat mass may also affect the distribution volume of lipophilic agents). The plasma volume also increases by approximately 40%. In parallel, an increase in cardiac output is commonly observed. This increase in heart output reaches its steady state by the 16th week of gestation [11], persisting at nearly 7 liters until the end of the pregnancy. The stroke volume starts to augment at the 20th week of gestation and the maternal heart rate may reach a mean of 90 beats/min at rest in the third trimester [12]. The hepatic blood flow also seems to be augmented. This effect might result in an increased elimination of perfusion-dependent drugs. Nakai *et al*. [13] found that liver blood flow is increased during the third trimester of pregnancy, mainly driven by an increased flow through the portal vein (up to 150%), with smaller changes in flow through the hepatic artery. Higher values of flow velocity have been observed in the portal vein during pregnancy, with a significant decrease postpartum [11]. Some factors may explain these changes, including modifications in cardiac output as well as a significantly decreased systemic vascular resistance during pregnancy [11]. The hepatic artery resistance indices seem to be decreased during the third trimester of pregnancy. This finding may be the expression of a systemic arterial vasodilatation occurring in normal pregnancy [14]. Nevertheless, some other authors have failed to detect any relevant changes in the hepatic blood flow [14].

3.2. Changes in the Unbound (Free) Fraction of Drugs

Pregnancy is associated with profound modifications in plasma protein concentrations. It is widely recognized that albumin and alpha-1 acid glycoprotein concentrations decrease during the pregnancy; especially from the second trimester [10]. These decreased concentrations are also associated with a reduction in protein binding for highly bound drugs. An increased concentration of unbound drug may be registered for high ER agents. Under usual conditions, only the unbound drug is active: this augmented free fraction may result in an increased pharmacological effect for some of these high ER drugs [10]. In the case of low ER drugs, the total plasma concentrations may underestimate unbound or free drug concentrations, as demonstrated for some antiepileptics, like phenytoin and valproic acid. As only the free fraction is active, the monitoring of these drugs based on

total plasma concentrations may misestimate their pharmacological effect [5, 15].

3.3. Variation in Enzyme Mass and Activity During Pregnancy

As mentioned, pregnancy is associated with relevant changes in plasma volume, glomerular filtration rate, body water and fat mass (and fat mass distribution). All these factors induce modifications into the distribution volume of drugs. As the total clearance of a pharmacological agent results from the product of the distribution volume and the elimination constant of the drug, it is always difficult to attribute any change in the clearance value to just one of these individual factors. Then, the assessment of the contribution of the pregnancy-induced changes on the hepatic CLint assumes relevance, even when these modifications were of difficult exploration and interpretation. Variations in the expression of hepatic metabolizing enzymes and in their respective activities during pregnancy have been detected, although their effect on pharmacokinetics and on clinical practice still requires further clarification [5, 10].

Changes in the cytochrome P450 (CYP) system in pregnancy have been reported by several authors [5, 15, 16]. CYP families and subfamilies constitute the predominant oxidative enzyme system involved in the removal of xenobiotic compounds in humans. In mice, the activity of CYP3A1 (evaluated through changes in roxithromycin concentrations over time) seems to be increased in pregnant mice on the 16th day of gestation. The level of CYP3A1 was significantly lower in fetal liver compared with that in the maternal liver [17]. In women, reduced CYP1A2 activity has been reported during pregnancy compared to postpartum values [16], with a reduction of 33% at the first trimester and reductions of 48% and 63% for the second and third trimesters, respectively. An increase in CYP2D6 activity has been reported compared to postpartum levels: an increase of 26% between 14-18 weeks of pregnancy and increases of 35% at 24–28 weeks and 48%over the 36–40 week period [16]. Also in women, CYP3A4 activity seems to consistently increase by 35% to 38% overall trimesters. CYP3A4 is the most important enzyme isoform for drug metabolism in humans. CYP2D9 activity is also clearly incremented, which results in reduced concentrations of several drugs, like phenytoin, some anti-inflammatory agents, metoprolol, and antidepressants, such as glipizide and glibenclamide [5, 16] (Table **1**). The salivary clearance of caffeine was used as a measure of CYP1A2 activity and the dextromethorphan O- and N-demethylations were used to document CYP2D6 and CYP3A activity, respectively [16]. Enzyme induction by estrogen and progesterone has been postulated as a basic and general mechanism for the positive changes observed in some of the CYP enzyme families. The glucocorticoid receptor, the pregnane X receptor (PXR), and the constitutive androstane receptor mediate CYP2C9 gene induction in humans; both dehydroepiandrosterone (DHEA) and dexamethasone have been demonstrated as active CYP2C9 inducers [18]. Nevertheless, CYP2D6 seems to be resistant to the inductive effect of many xenobiotics (*e.g*., rifampin, phenobarbital, dexamethasone) and it is unclear whether the hormonal environment during pregnancy may contribute at least in part to this phenomenon. Similarly, the behavior of CYP1A2 is difficult to explain based on the inducing effect of steroidal hormones during pregnancy.

Although only 1.0% to 4.5% of the total hepatic CYP content, the CYP2D6 isoform metabolizes over 160 drugs [19]. In another study on pregnant women, a decreased area under the plasma concentration-time curve and total exposure to ondansetron across gestation was attributed to increased activity of CYP3A4 and CYP2D6 during pregnancy [20]. Other changes in CYP enzymatic activity have been reported, for example CYP2A6 activity seems to be increased in pregnancy, whereas there is a reduction in the activity of CYP2C19 [5].

Pregnancy is also associated with changes in other hepatic metabolizing systems. Uridinediphosphate-glucuronosyltransferases (UGT) activity seems to be notably altered during pregnancy. Changes in the pharmacokinetic profile of lamotrigine suggest that an increase in the activity of UGT1A4 favors an augmented formation rate of glucuronide conjugates [5]. While the increment in UGT1A4 activity seems to be consistent among different studies, variable results have been reported with regard to changes in

Table 1. Modifications of CLint associated with pregnany and diabetes. Selected examples.

	Changes in Enzymes	Other Relevant Changes	CLint	Refs.
Glibenclamide	↑ CYP2A9	↑ Unbound Fraction (?)	↑	[5, 16, 37, 38, 41, 42]
Metoprolol	↑ CYP2D6	↑ Unbound fraction	↑	[15]
Labetalol	↑ UGT1A1	Deeper changes on one of the stereoisomers (?)	↑	[31, 32]
Nifedipine	↑ CYP3A4 in pregnancy ↓ CYP3A4 in diabetes (?)		Unknown	[34, 35]
Phenytoin	↑ CYP2C9	↑ Unbound fraction	↑	[15]
Lamotrigine	↑ UGT1A4		↑	[15]
Cortisol	↑ CYP3A4		↑	[15]
Proguanil	↓ CYP2C19		Unknown	[15]

UGT2B7 activity, which is involved in the biotransformation of morphine, zidovudine, and other agents during pregnancy [5]. Very limited data are available for N-acetyltransferase 2(NAT2) activity in pregnancy [5].

In summary, available data suggest that pregnancy is associated with an increased enzymatic activity of CYP3A4, CYP2D6, CYP2C9, CYP2A6, UGT1A4, and UGT2B7; whereas, the activity of CYP1A2 and CYP2C19 seems to be consistently reduced.

3.4. Pregnancy-induced Modifications of Concentration-time Curves

In a systematic review of a total of 198 studies involving 121 different medications, pregnancy-associated changes in different pharmacokinetic parameters and concentration-time curve indicators were extensively explored [4]. Studies on the following drug classes were included: antiretroviral agents (54 studies), antiepileptic drugs (27 studies), antibiotics (23 studies), antimalarial drugs (22 studies), and cardiovascular drugs (17 studies). An enhanced drug elimination and decreased exposure to total drugs (bound and unbound to plasma proteins) were the most relevant findings for many of these studies, which is consistent, as expected, with the changes due to altered distribution or elimination at a given dose [4]. A very high variability in elimination rates was noticed for most of the agents. In addition, the association of these alterations with concentration/time curves and clinical responses, effects, and outcomes remains unknown.

4. GESTATIONAL DIABETES-ASSOCIATED CHANGES IN THE HEPATIC ELIMINATION OF DRUGS

GDM and its comorbid conditions may intrinsically affect the hepatic clearance of some pharmacological agents. GMD is linked to overweight/obesity, non-alcoholic fatty liver disease, an altered intestinal microbiome, systemic inflammation, pregnancy-associated hypertension, and glycemic alterations (among other factors).

CYP pathways seem to be modulated by changes in glycemia. In micro patterned co-cultures of primary human hepatocytes, hypo- and hyperglycemic states were associated with changes in expression and activity of some CYP isoforms [21]. After several days of exposure to *hypoglycemic* culture medium, CYP1A2, CYP2B6, CYP2C19, and CYP3A4 gene expression were increased by 2- to 4-fold as compared to normoglycemic controls after a 10-day incubation period [21]. After 18 days, an increased expression of CYP2D6 and CYP2E1 were also observed [21]. Accordingly, CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activities were increased by a factor of 1.3 to 1.6 under prolonged hypoglycemic-like conditions [21]. Instead, under hyperglycemia-like conditions, an increase in CYP2A6 transcripts at day 10 was observed, while at day 18, up-regulations of CYP1A2 and CYP2D6gene expression were observed, with a reduction in CYP21E expression when compared to controls [21]. Nevertheless, CYP3A4 activity was reduced by 40 % after 4 days of hyperglycemic exposure [21]. An important message from these experimental results is that chronic hypoglycemic-like environments seem to be associated with increased CYP3A4 expression and activity, whereas conditions mimicking hyperglycemia seem to be correlated with a reduction in CYP3A4 activity. Gestational diabetes is frequently associated with relevant variations in glycaemia that could be linked to significant changes in the liver enzymatic activity. Nevertheless, caution should be exercised in extrapolating these *in vitro* results to human beings. Time-of-exposure to hypo or hyperglycemic conditions in humans is unknown, and the influence of other co-variates frequently associated with gestational diabetes (for instance, inflammatory microenvironment, hepatic lipid accumulation, pregnancy hormone effects,changes in hepatic blood flow) are still to be elucidated.

The increase in expression of different CYP enzymes under hypoglycemia might be explained by the up-regulation of the expression of nuclear receptor subfamilies (NR), more specifically, that of the constitutive androstane receptor, the pregnane X receptor, and the aryl hydrocarbon receptor [21]. NRs are sensitive to the cellular energy status and their activities might vary accordingly. In the above-mentioned experimental model, hyperglycemic conditions were associated with a relevant accumulation of neutral lipids including triglycerides and cholesterol esters. An increased expression of FASN and SREBP1 genes may represent a potential explanation underlying this phenomenon [21].

As mentioned before, hyper and hypoglycemic episodes are frequent in GDM; nevertheless, the intensity and duration required to translate into CYP changes remain obscure. Fluctuations on these effects on CYP might be also expected.

Obesity and non-alcoholic fatty liver disease are frequently present in patients with GDM as pre-existing conditions. In a guinea pig model, high fat diet plus high fructose or glucose was associated with a reduction in CYP3A4 expression and mass [22]. Primary human hepatocyte cultures from steatotic livers showed a 50% reduction in CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2E1, and CYP3A4 activities [23]. In human steatotic liver samples, CYP3A4 reflected a similar reduction in activity [23]. In a more advanced stage of non-alcoholic fatty liver disease, the inflammatory component might play a relevant role. A possible inflammation-associated induction of the pregnane X receptor has been suggested [23]. Nevertheless, this effect seems to be minor and its relevance warrants further clarification.

Overweight and obesity are associated with changes in the intestinal microbiome. This altered microflora composition ("dysbiosis") may result in mild inflammation, alterations in the intestine-endocrine and gut-liver axes, energy yield and utilization, immunity, *etc*. [24]. In obese and overweight pregnant women, insulin concentration was positively correlated with microbes of the *Coriobacteriaceae* family (more specifically, the genus *Collinsella*) [25]. Similar positive correlations were found for C-peptide and the insulin resistance index (HOMA-IR). The abundance of *Collinsella* was also reported in non-pregnant diabetic subjects [25]. Maternal triglycerides and very-low-density lipoprotein (VLDL) cholesterol were positively correlated with the presence of this genus [25]. In parallel, the presence of excessive levels of members of the *Ruminococcaceae*family

in early pregnancy might be also related to adverse metabolic health [25]. These changes might promote a systemic pro-inflammatory environment as well as several modifications in the expression of CYP and other enzymatic systems at the intestinal wall and in microsomes of hepatic cells [26]. CYP3A, CYP2C9, CYP1A, and CYP2D6 are expressed in the intestinal wall and microbial metabolites can either induce or inhibit these enzymes, or act as substrates of these metabolic systems [26]. The composition of the microbiome has a clear influence on entero-hepatic cycling of many molecules, as has been demonstrated for contraceptives. Substances cleared by glucuronidation, sulfation, or conjugation to taurine or glycine (*e.g*., estrogens, digitoxin, morphine) might see their elimination rates modified in correlation with the microbiome composition [26].

Inflammation *per se* may be associated with modifications in hepatic clearance. Several changes have been identified in different models of steatohepatitis [23]. Pro-inflammatory cytokines can alter transporter expression and interfere with the access of drugs to hepatocytes and/or their canalicular elimination [23]. Increased levels of the transporter BCRP (Breast cancer resistance protein) were observed in liver samples of patients with non-alcoholic steatohepatitis [23]. Organic cation transporter 1 (OCT1, SLC22A1) is a key transporter responsible for the hepatic uptake of metformin, which is increased in high-fat diet obese animal models [23]. Nevertheless, the clinical implications of these findings remain obscure. Numerous data indicate that an increased expression of multiple efflux transporters on hepatocytes and an altered cellular localization in some individuals with steatohepatitis result in relevant alterations of hepatic elimination of some agents [23]. Chronic inflammation may be associated with fibrosis. It has been reported that the hepatic extraction and liver distribution ratio of metoprolol and atenolol are both increased in animal models of steatohepatitis [23]. Sinusoidal fibrosis may play a role in at least part of these effects [23]. Moreover, epigenetic changes may represent a mechanism involved in the modifications observed in steatohepatitis. More specifically, shifts in DNA methylation seem to be responsible, at least in part, for these metabolic changes [27].

Alterations in the hepatic clearance of certain agents might have implications for the correct dosing of drugs in pregnant women with diabetes. The combined effects of pregnancy diabetes and their co-morbidities on CLintare complex (Table 1), may fluctuate along the disease and might have clinical relevance. Nevertheless, limited data are available regarding the potential pharmacokinetic modifications that might affect the behavior of most drugs frequently used in women with gestational diabetes. In at least one study in patients with steatohepatitis, midazolam concentrations were increased by a factor of 2 when compared with controls [28]. As midazolam is a CYP3A4 substrate, a reduction in CYP3A4 activity due to a proinflammatory environment might explain these changes in concentration.

Metoprolol is a beta-adrenergic blocker agent that is mainly metabolized by CYP2D6. It exhibits a high ER and hepatic blood flow and cytochrome activity affect its altered hepatic clearance during pregnancy [15] (Table **1**). An increased clearance was observed after intravenous administration, whereas peak concentrations of the drug were reduced by a half or less when compared to postpartum values [29]. Hypothetically, the previously described changes in CLint due to hepatic fat accumulation, inflammation and/or hyper- or hypoglycemia might affect its pharmacokinetic profile.

The alpha- and beta-adrenergic blocker labetalol is used to treat hypertension in pregnancy. It is glucuronidated by the liver through the UGT1A1 system [15], which is up regulated by progesterone, but not by estrogen. The oral clearance of labetalol is increased by 30% during the third and second trimesters of pregnancy, and the elimination half-life after an intravenous administration of the drug seems to be significantly reduced at the third trimester when compared with non-pregnant values for adults [30]. This increase in CLint was also observed in women with pregnancy-induced hypertension [31]. Labetalol activity is determined by the combined action of different stereoisomers [32], some displaying more beta-blocking activity whereas others exert more alpha-blocker effects. In patients with GDM, it has been suggested that this augmented hepatic clearance might have a greater influence on the beta-blocking stereoisomer of the racemic mix, which might result in an imbalanced effect on the sympathetic receptors compared to normal conditions [32] (Table 1).The clinical implications of these changes remain unknown. A study conducted on women with well-controlled GDM showed an enantioselective kinetic disposition of metoprolol, with no difference when compared to normal controls [33].

It has been suggested that increased CYP3A4 activity may be responsible for the augmented first pass effect observed for nifedipine, a calcium channel blocker, in pregnant women after oral administration of the drug [34]. The clearance of nifedipine seems to be up to 4-fold higher during pregnancy and is associated with a markedly reduced terminal half-life [34]. However, type 2 diabetes may be associated with a reduction in CYP3A4 activity, at least in some patients. A recent study was conducted in 12 hypertensive pregnant women (control group) and 10 hypertensive pregnant women with controlled type 2 diabetes taking slow-release nifedipine. On the 34th week of gestation, this study failed to demonstrate any relevant diabetes-induced alterations in the pharmacokinetic profile of nifedipine [35]. This neutral finding might be the net result of opposite effects. Other calcium channel antagonists are metabolized by CYP3A4 (diltiazem, isradipine), but the influence of pregnancy on the hepatic clearance of these drugs is unknown [15].

Thirty to 50% of women with GDM require drug treatment to keep their glycemic levels under control. Insulin is considered the pharmacological treatment of choice for women affected by GDM. Nevertheless, in recent years and even under off-label indications, the use of oral agents likes glyburide (or glibenclamide) for glycemic control in pregnant women has become more frequent. While it is effective in treating hyperglycemia in GDM, some studies have raised several safety concerns (such as hypoglycemia, higher rates of macrosomia, pre-eclampsia, increased use of neonatal intensive care, *etc*.) [36]. In addition, the pharmacokinetic profile of glibenclamide in GDM is only partially understood. In non-pregnant conditions, glibenclamide is charac-

terized by high plasma protein binding (close to 99.5%) with a total clearance of nearly 1.3 $mL \cdot min^{-1} \cdot Kg^{-1}$, being extensively metabolized by the liver [37,38], and producing both active and non-active metabolites [39]. The CLint of glibenclamide in maternal mice liver microsomes seems to increase as gestation progresses [40]. The total clearance of this drug is also significantly augmented in women with GDM [41,42] (Table **1**). An increased expression of the CYP3A/Cyp3a gene appeared to explain this modification [41]. Glibenclamide crosses the placental barrier achieving fetal concentrations at a term comparable with maternal levels. The fetal hepatic metabolism of the drug seems to be mainly driven by CYP3A7 towards the formation of the M5 metabolite [43]. This partial involvement of the fetus in the pharmacokinetics of glibenclamide provides an indication of the complicated drug metabolism to be expected in women with GDM. Implications of this CLint increase on dosing in pregnant women with GDM are unknown.

CONCLUSION

GDM is a frequent metabolic disease commonly associated with other diseases, such as obesity, hypertension, dyslipidemia, non-alcoholic fatty liver disease, prothrombotic conditions, as well as with some alterations of the intestinal microbiome. All these entities, together with the glycemic variations usually seen in these patients (both hyper- as well as hypoglycemic events) might affect the critical determinants for the hepatic clearance of some drugs (hepatic blood flow, the unbound fraction of drugs, and CLint). Being a highly comorbid condition, GDM is frequently associated with multi-drug treatments. While many of these drugs are cleared by the liver, very little is known about the intensity and clinical relevance of these GDM pharmacokinetic changes for most pharmacological agents. The effect of interactions between the different co-morbidities usually present in this complex condition (GDM) as well as drug-drug (or even food-drug) interactions likely occuring in this context remain unclear for most pharmacological agents. In some cases, the effects on the hepatic clearance may result in modifications of dose or treatment regimens. Taking into account the frequency of the disease, as well as the effects that these pharmacokinetic changes might have on the mother and child, the need for further research seems crucial and advisable. In the meantime, cautious clinical judgment in the management of drug administration in women affected by this multifactorial disease is highly recommended.

DECLARATION OF FINANCIAL / OTHER RELATIONSHIP

The authors have indicated that they have no conflicts of interest regarding the content of this article and have received no payment in the preparation of this manuscript.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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