Transplacental Distribution of Lidocaine and Its Metabolite in Peridural Anesthesia Administered to Patients With Gestational Diabetes Mellitus

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Abstract

Background: Neonatal effects of drugs administered to mothers before delivery depend on the quantity that crosses the placental barrier, which is determined by the pharmacokinetics of the drug in the mother, fetus, and placenta. Diabetes mellitus can alter the kinetic disposition and the metabolism of drugs. This study investigated the placental transfer of lidocaine and its metabolite monoethylglycinexylidide (MEGX) in pregnant women with gestational diabetes mellitus (GDM) submitted to peridural anesthesia. **Patients and Methods:** A total of 10 normal pregnant women (group 1) and 6 pregnant women with GDM (group 2) were studied, all at term. The patients received 200 mg 2% lidocaine hydrochloride by the peridural locoregional route. Maternal blood samples were collected at the time of delivery and, after placental expulsion, blood samples were collected from the intervillous space, umbilical artery, and vein for determination of lidocaine and MEGX concentrations and analysis of the placental transfer of the drug. **Results:** The following respective lidocaine ratios between the maternal and the fetal compartments were obtained for groups 1 and 2: umbilical vein/maternal peripheral blood, 0.60 and 0.46; intervillous space/maternal blood, 1.01 and 0.88; umbilical artery/umbilical vein, 0.77 and 0.91; and umbilical vein/intervillous space, 0.53 and 0.51. The following MEGX ratios for groups 1 and 2 were, respectively, fetal/maternal, 0.43 and 0.97; intervillous space/maternal blood, 0.64 and 0.90; umbilical artery/umbilical vein, 1.09 and 0.99; and umbilical vein/intervillous space, 0.55 and 0.78. **Conclusion:** Gestational diabetes mellitus did not affect the transplacental transfer of lidocaine but interfered with the transfer of MEGX, acting as a mechanism facilitating the transport of the metabolite.

Keywords

pregnancy, gestational diabetes mellitus, lidocaine, monoethylglycinexylidide, placental transfer

Introduction

Diabetes mellitus (DM) can alter the kinetic disposition and the metabolism of drugs depending on the type and duration of the disease, on the drug investigated, and on its metabolic and excretion pathways.^{1,2} Diabetes mellitus may interfere with the placental capillarization index, causing delays in the mature placenta. Theoretically, these changes in placentation can directly influence the rate of transplacental transfer of drugs used during pregnancy.³ The influence of gestational DM (GDM) on the placental transfer of drugs used in clinical practice has not been extensively studied in the literature.

The placenta is a metabolic organ, which, therefore, follows the principles of a metabolic barrier. Many drugs are transported through the placental barrier by simple diffusion without energy expenditure, depending on the concentration of the free drug and on the ratio and extent of the placental exchange barrier.⁴

Protein-bound drug fractions and drugs of high molecular weight do not cross the placental barrier. Because of their physical characteristics, practically all anesthetic agents used for labor anesthesia pass freely through the placental barrier,

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except for neuromuscular blockers. However, fetal exposure to the drugs administered to the mother will be determined by the placental and fetal ability to metabolize the drugs, by the intrinsic physiological factors of the mother–placenta–fetus unit and by the ability of the drug to cross the placental barrier.⁵

Lidocaine is a local anesthetic of the amide type used for anesthetic infiltration and/or regional blockade which acts by inhibiting the ion flows necessary for the conduction of impulses from pain sensation fibers. Its elimination half-life is 1 to 2 hours. *N*-Deethylation of this anesthetic occurs in the liver under the action of CYP1A2 and CYP3A4, resulting in the formation of the main active metabolite monoethylglycinexylidide (MEGX).^{6,7} A secondary metabolic form derived from a second deethylation of MEGX is glycinexylidide. Hydroxylation of the aromatic ring occurs by the action of CYP1A2, giving origin to 3-hydroxy-lidocaine.^{8,9}

Lidocaine is a drug with a medium to high rate of hepatic extraction (0.6–0.8), with its clearance being influenced by changes in hepatic function or by variations in blood flow in the liver.¹⁰ Approximately 90% of the lidocaine administered is excreted in the form of metabolites and less than 10% is excreted unchanged through the kidneys.^{6,11} Therefore, the aim of this study was to investigate the placental transfer of lidocaine and its metabolite MEGX in pregnant women with GDM submitted to peridural anesthesia.

Patients and Methods

The study was approved by the Research Ethics Committee of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo. All patients who participated in the study signed a term of informed consent. It should be pointed out that the study did not interfere with the clinical conduct adopted for the patients.

The sample size calculation was performed using the parameters of placental transfer of lidocaine in women treated with averaged dose 4.0 ± 1.7 mg/kg. The significance level was set at 5% and the power of the test in 80%, the difference between mean fetal/maternal ratio was fixed in 50% of 0.52 (0.26) and the standard deviation within the group in 0.18. A score of 6 patients per group was obtained.

The series consisted of 2 groups, that is, pregnant women with no diagnosed diseases and patients with GDM admitted to the Obstetrical Center of MATER—Maternidade do Complexo Aeroporto or to the Obstetrical Center of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo. The parturients were submitted to resolution of pregnancy by cesarean section due to medical indication and were selected in an aleatory manner without randomization. The patients in the 2 groups were not matched but had similar characteristics.

All patients were submitted to the 75-g 2-hour oral glucose tolerance test. Patients diagnosed as having GDM according to the recommendations of the World Health Organization, which were included in this study, did not use insulin and oral anti-diabetic agents as therapy. They were submitted to nutritional

guidance and evaluation of fasting plasma glucose and postprandial plasma glucose once a week to obtain an adequate glycemic control.

Inclusion criteria were normal pregnant women or women with GDM, term singleton pregnancy, delivery by cesarean section, and anesthetic assistance with epidural blockade. Exclusion criteria were delivery performed due to obstetrical urgency/emergency situations, presence of maternal diseases except GDM, chronic use of medications except polyvitamin supplements, altered prenatal subsidiary exams, and refusal to participate in the study or to sign the informed consent form. Criteria for discontinuation were patients who ceased to participate during the study, need to change the anesthetic procedure to rachianesthesia, continuous epidural or general (intravenous and/or inhalatory) anesthesia, and pregnant women who needed to receive drugs that would interfere with the pharmacokinetics of lidocaine during the anesthetic surgical procedure.

Epidemiological data were collected using a standard protocol form, including age, life habits, use of medications, anthropometric data, parity, gestational age, and ultrasound information about fetal and/or placental changes. Systolic and diastolic arterial pressure and heart rate were monitored throughout the collection process.

The pregnant women were submitted to peridural locoregional anesthesia with 2% lidocaine hydrochloride without a vasoconstrictor (Xylestesin, Cristália, lot 02030982) at the dose of 5 mL for skin and subcutaneous blockade and at the dose of 10 mL in the peridural space, 0.05 mg/mL fentanyl citrate (Fentanest, Cristália, lot 02041393) at the dose of 2 mL in the peridural space, and 0.5% bupivacaine hydrochloride with 1:200 000 epinephrine (Neocaina, Cristália, lot 53200809) at the dose of 15 mL in the peridural space.

Before the administration of the anesthetic drugs, a maternal blood sample was collected for hematologic and biochemical laboratory tests in order to detect possible undiagnosed diseases.

Maternal blood samples were collected into heparinized syringes at the time of delivery and, after placental expulsion, blood samples were obtained from the umbilical artery and vein and from the intervillous space according to the technique described by Camelo et al¹² in order to determine lidocaine and MEGX concentrations and the rate of placental transfer of the drug.

Determination of Lidocaine and MEGX

A stock lidocaine solution was prepared in methanol (chromatography grade; EM Science, Merck, Darmstadt, Germany) at the concentration of 1 mg/mL and diluted to working solutions at the concentrations of 200, 100, 70, 50, 40, and 20 µg/mL in methanol. The stock solution of MEGX (Astra Pharmaceuticals, Södertälje, Sweden) was prepared at the concentration of 8 µg/mL methanol and diluted to concentrations of 3.2, 1.6, 1.0, 0.8, 0.4, and 0.32 µg/mL. Sodium chloride (analytical grade), sodium hydroxide (analytical grade), hexane (chromatography grade), and dichloromethane (chromatography grade), used in the extraction procedure, were from Merck.

Chromatographic Analysis of Lidocaine and MEGX in Plasma

Lidocaine and MEGX were separated from the endogenous constituents of plasma through a reverse-phase $4 \times 50 \text{ mm}^2$ Lichrospher 60 RP-Select B column (Merck) in internal diameter with 5- μm particles, with a similar $4 \times 4 \text{ mm}^2$ precolumn. The mobile phase, consisting of a mixture of 25 mmol/L phosphate buffer, pH 4.5, and acetonitrile (82:18, v/v), was used at a rate of 1 mL/min.

The 0.15-N sodium hydroxide solution of 50 μL were added to 1-mL plasma samples, which were then extracted with 4 mL hexane dichloromethane (82:18, v/v) after saturation of the aqueous phase with 500 mg sodium chloride. Lidocaine and MEGX were extracted by shaking at 220 ± 10 cycles/min for 45 minutes in a horizontal shaker, followed by centrifugation at 1800 rpm for 10 minutes, and concentration of the organic extracts at room temperature under an air flow, and 20- μL aliquots were analyzed by high-performance liquid chromatography.

The HPLC system (Shimadzu, Kyoto, Japan) used for chromatographic analysis consisted of an LC-10AS pump, an SPD-10A ultraviolet detector operating at 205 nm, and a C-R6A integrator. The Rheodyne injection system (Cotati, California), model 7125, was used with a 20- μL sampler.

For the construction of the calibration curves, 1-mL aliquots of blank plasma obtained from healthy volunteers receiving no medications for the last 10 days were enriched with 25 μL each of the standard solutions of lidocaine (0.5-5.0 $\mu\text{g/mL}$) and MEGX (8-80 ng/mL) and submitted to the extraction and chromatography procedures described previously. Linear regression equations and correlation coefficients were calculated on the basis of the ratios of the peak areas obtained (standard/internal standard) as a function of plasma concentration. The calibration curves for lidocaine and MEGX had the following linear regression equations, respectively: $1911.71 + 41527.46 \times$ (coefficient of determination = 0.99718) and $7.8185 + 44.4046 \times$ (coefficient of determination = 0.99771).

The recovery of plasma lidocaine and MEGX was determined by comparing the height of the peaks obtained after plasma extraction to the height of the peaks obtained after direct injection of the standard solutions. Recovery was evaluated in triplicate at concentrations of 5, 1, and 0.5 $\mu\text{g/mL}$ plasma for lidocaine and of 80, 20, and 8 ng/mL plasma for MEGX. Linearity was evaluated by analysis of plasma samples enriched with increasing concentrations of standard solutions compared to those used for the construction of the calibration curve. Samples enriched with concentrations up to 20 $\mu\text{g/mL}$ plasma (0.5-20.0 $\mu\text{g/mL}$) for lidocaine and 640 ng/mL plasma (8.0-640.0 ng/mL) for MEGX were evaluated. Precision and accuracy were determined by analysis of plasma samples enriched with lidocaine (0.4 and 2.8 $\mu\text{g/mL}$) and MEGX (8 and 45 ng/mL). Plasma samples were analyzed in triplicate ($n = 10$), using a single calibration curve for the intra-assay evaluation and in duplicate for 5 consecutive days for the interassay

Table 1. Median Values and 25th and 75th Percentiles of the Maternal Demographic Data.

Parameters	Control Group	Diabetic Group
Age, years	28.50 ^a (22.5-32.00)	34.00 ^a (30.00-37.00)
Gestational age, days	271.50 (266.50-286.00)	270.50 (266.50-272.50)
Weight, kg	69.25 ^a (66.55-77.65)	81.55 ^a (75.00-90.15)
Height, m	1.61 (1.54-1.66)	1.58 (1.54-1.61)
Body mass index, kg/m ²	27.20 ^a (24.20-30.10)	31.86 ^a (31.20-35.70)

^a $P < .05$.

evaluations. The coefficients of variation obtained in the study of intra- and interassay precision for low and high lidocaine and MEGX concentrations were lower than 15%.

Statistical Analysis

The GraphPad Prism 3 software, through the Mann-Whitney test, was used to calculate the measures of position and dispersal of each variable and to carry out the statistical analysis for comparison of normal and GDM pregnant women, with the level of significance set at 5%.

Results

The study was conducted on 10 parturients with no base disease (group 1) and on 6 parturients with GDM (group 2). The median and 25th (P25) and 75th (P75) percentiles for maternal age, gestational age, body weight, height, and body mass index (BMI) are listed in Table 1. The laboratory tests carried out for functional evaluation of the hematologic, renal, hepatic, and endocrine systems/organs did not reveal important differences, except for carbohydrate metabolism in the diabetic group.

During blood sample collection for the determination of lidocaine and MEGX concentrations in maternal plasma, maternal systolic and diastolic arterial pressure and heart rate were monitored, demonstrating hemodynamic stability throughout the study, with no significant differences between the groups.

None of the newborn infants presented diseases diagnosed at birth. Median birth weight was 3170 and 3710 g and median length was 47 and 48.75 cm for the 2 groups, respectively. Only 1 newborn in each group presented an Apgar score of less than 7 at the first minute and all presented an Apgar score of 10 at the fifth minute. All newborns had a favorable postnatal course and were discharged from the hospital on the same day as their mothers. Median placental weight was 540 g for normal patients and 550 g for diabetic patients and no relevant macroscopic changes were observed in any placenta.

Median latency between administration of the drug and birth was 28.5 minutes for the control group and 28 minutes for the diabetic group. At delivery, mean maternal plasma concentrations of lidocaine and MEGX were 1034.55 and 75.1 ng/mL for the control group and 1280.46 and 37.60 ng/mL for the GDM group, respectively. Median fetal plasma concentrations of

Table 2. Median Values and 25th and 75th Percentiles of the Lidocaine Concentrations (ng/mL) in Maternal Plasma, in the Fetal Arterial and Venous Plasma of Umbilical Vessels, and in the Placental Intervillous Space, Fetal/Maternal Ratio, Intervillous Space/Maternal Ratio, Umbilical Artery/Umbilical Vein Ratio, and Umbilical Vein/Intervillous Space Ratio.

Parameter	Unit	Control Group	Diabetic Group	P
Latency	minutes	28.50 (22.50-32.50)	28.00 (25.00-35.00)	.79
Maternal concentration	ng/mL	1034.55 (882.00-1275.15)	1280.46 (1138.09-1968.74)	.03
UV concentration	ng/mL	653.10 (283.10-726.85)	615.46 (465.42-769.26)	.87
UA concentration	ng/mL	445.60 (313.70-591.10)	527.75 (435.85-664.65)	.21
PIVS concentration	ng/mL	1079.90 (795.90-1328.65)	1411.41 (965.37-1587.33)	.07
F–M ratio	–	0.60 (0.31-0.69)	0.46 (0.29-0.63)	.36
Artery–vein ratio	–	0.77 (0.58-1.23)	0.91 (0.71-1.09)	.63
V–PIVS ratio	–	0.53 (0.39-0.74)	0.51 (0.36-0.57)	.56
PIVS–M ratio	–	1.01 (0.65-1.27)	0.88 (0.70-1.23)	.79

Abbreviations: UA, umbilical artery; UV, umbilical vein; PIVS, placental intervillous space; V–PIVS ratio, vein–placental intervillous space ratio; F–M ratio, fetal–maternal ratio (umbilical vein/maternal peripheral blood); PIVS–M ratio, intervillous space–maternal ratio.

Table 3. Median Values and 25th and 75th Percentiles of the MEGX Concentrations (ng/mL) in Maternal Plasma, in the Fetal Arterial and Venous Plasma of Umbilical Vessels, and in the Placental Intervillous Space, Fetal/Maternal Ratio, Intervillous Space/Maternal Ratio, Umbilical Artery/Umbilical Vein Ratio, and Umbilical Vein/Intervillous Space Ratio.

Parameter	Unit	Control Group	Diabetic Group	P
Latency	minutes	28.50 (22.50-32.50)	28.00 (25.00-35.00)	.79
Maternal concentration	ng/mL	75.10 (46.50-106.40)	37.60 (23.49-55.19)	.01
UV concentration	ng/mL	27.70 (17.15-47.45)	39.36 (23.06-54.37)	.36
UA concentration	ng/mL	49.45 (18.00-104.10)	33.94 (17.11-55.90)	.42
PIVS concentration	ng/mL	65.00 (29.65-75.80)	37.30 (29.19-61.49)	.42
F–M ratio	–	0.43 (0.20-0.53)	0.97 (0.59-1.79)	.004
Artery–vein ratio	–	1.09 (0.63-4.71)	0.99 (0.62-1.24)	.63
V–PIVS ratio	–	0.55 (0.36-0.73)	0.78 (0.69-1.36)	.02
PIVS–M ratio	–	0.64 (0.45-1.30)	0.90 (0.66-2.35)	.26

Abbreviations: UA, umbilical artery; UV, umbilical vein; PIVS, placental intervillous space; V–PIVS ratio, vein–intervillous space ratio; F–M ratio, fetal–maternal ratio (umbilical vein/maternal peripheral blood); PIVS–M ratio, intervillous space–maternal ratio; MEGX, monoethylglycineylidide.

lidocaine and MEGX were 653.1 and 27.7 ng/mL for the control group and 615.46 and 39.36 ng/mL for the GDM group, respectively. The median fetal/maternal ratios of lidocaine and MEGX were 0.60 and 0.43 for the control group and 0.46 and 0.97 for the GDM group, respectively. The median intervillous space–maternal ratios for lidocaine and MEGX were 1.01 and 0.64 for the control group and 0.88 and 0.90 for the GDM group, respectively (Tables 2 and 3). We emphasize that the group of diabetic patients differed significantly from the control group only regarding the increased placental transfer of MEGX (fetal–maternal ratios and umbilical vein–intervillous space ratio).

Discussion

The 2 groups studied in the present investigation differed in some clinical data. Diabetic women were older than controls, and their weight and BMI were also higher than those of control women, characteristics usually observed in patients with GDM. However, Kleinbloesem et al¹³ reported that age does not affect the activity of the enzymatic system responsible for the metabolism of lidocaine. Braid and Scott¹⁴ demonstrated a poor correlation between maximum lidocaine concentration

and BMI in a population of nonpregnant women. In turn, Downing et al,¹⁵ in a study of pregnant women, also did not observe a correlation between maximum lidocaine concentration and BMI. Thus, these factors are considered not to directly affect the data obtained.

Placental and fetal factors that might interfere with the evaluation of the rate of lidocaine transfer were examined in the present study. Placental weight was homogeneous within the groups studied and no significant macroscopic changes that might alter drug transport were observed. Gestational age might affect the rate of drug transfer to the fetus, since the thickness of the trophoblastic epithelium is reduced during the course of pregnancy.¹⁶ However, the effect of this variable was controlled since all patients in the study were at term.

The biotransformation of anesthetic drugs by the placenta may also reduce the rate of transfer of these agents to the fetus. However, according to Santos et al,¹⁶ there is no evidence suggesting that the placenta has the capacity to metabolize any of the agents commonly used for obstetrical anesthesia. Studies have demonstrated that messenger RNA, but not the protein, of various isoforms of the CYP enzymatic system can be detected in placental tissue during the third trimester of pregnancy although at extremely low levels compared to maternal

hepatic levels.^{17,18} Thus, MEGX metabolism at the placental level is considered to be irrelevant.

The fetal hepatic metabolism, the effect of progressive dilutions in the fetal circulation, and the presence of morphofunctional fetal diseases may influence the pharmacodynamic and pharmacokinetic processes of the drug, altering its concentration.^{4,19} Nonetheless, analysis of ratios between the various compartments revealed no statistically significant difference between the groups, showing that GDM had no significant effect on lidocaine transfer. Fetal metabolism was evaluated by comparing the lidocaine concentrations in the umbilical artery and vein. The values were 0.77 and 0.91 in the normal and diabetic group, respectively, showing low fetal metabolism of lidocaine, probably due to relative hepatic immaturity during this phase of development.

The values detected here indicate plasma lidocaine concentrations of about 60% in the control group and 46% in the diabetic group compared to maternal concentration at delivery. This serves as an alert to the considerable transfer of this drug through the placental barrier, which may act on the fetus by causing arrhythmias when the drug is administered at high doses. This complication was not observed in the groups studied here, but we emphasize that caution should be taken when administering high doses of this drug to pregnant women due to the high rate of transplacental transfer and a possible consequent action on the fetus and/or the newborn.

The data about the fetal–maternal ratio agree with those reported in the literature for normal patients, although there are no reports about them regarding diabetic women. In a study on healthy pregnant women at term submitted to elective cesarean delivery after epidural anesthesia, Ala-Kokko et al²⁰ reported a 0.49 fetal–maternal ratio for lidocaine at delivery. In a study on term pregnant women with no base diseases, Downing et al¹⁵ reported a fetal–maternal lidocaine ratio of 0.43. Sakuma et al²¹ reported a 0.52 rate of placental transfer in normal pregnant women, whereas Ramanathan et al²² detected a higher rate of placental transfer, with a fetal–maternal ratio reaching 0.73 in a group of normal pregnant women.

Studies in which lidocaine was used for perineal blockade have reported a rate of transplacental transfer with a fetal–maternal ratio of about 50%. Philipson et al²³ reported a fetal–maternal ratio of 0.73, while Sakuma et al²¹ and Cavalli et al²⁴ reported a fetal–maternal ratio at birth of 0.45 and 0.46, respectively.

In 1995, Banzai et al²⁵ reported a clinical case involving the treatment of a pregnant woman with cardiac arrhythmia using continuous intravenous infusion of lidocaine. The patient had a twin pregnancy with fetal–fetal transfusion and her arrhythmia was caused by ritodrine. A total of 14.1 g of lidocaine was infused (50 mg/h for 282 hours) and the maternal, umbilical vein, and amniotic fluid concentrations were determined. At delivery, lidocaine concentrations in maternal blood and in the umbilical vein were 1.6 and 0.82 µg/mL, respectively, with a fetal/maternal ratio of 0.52.

In a model of *in vitro* placental perfusion with lidocaine and bupivacaine, a 98.9% rate of maternal–fetal transfer was

observed.²⁰ It should be remembered that an *in vitro* study does not evaluate the protein binding, metabolism, or excretion of these drugs, with higher values being obtained than *in vivo*.

In the present study, the ratio of lidocaine concentrations between maternal peripheral blood and intervillous space revealed equilibrium between the sites of collection. It should be pointed out that the intervillous space is a histofunctional part of the placenta that is divided into compartments by the placental septa, but these compartments communicate freely since the septa do not reach the chorionic plate. Maternal blood fills the entire intervillous space, reaching it from the spiral arteries of the basal decidua of the endometrium, which pass through gaps in the cytotrophoblast sheath. The maternal arterial pressure determines a nonpulsatile blood flow, continuously bathing the branched chorionic villi that project from the stem villi. This blood present in the intervillous space is drained by the endometrial veins, which also cross the cytotrophoblast sheath and are distributed throughout the surface of the basal decidua. Fetal blood maintains an intimate contact with the maternal blood present in the intervillous space, but without a direct contact with it, thus favoring maternal–fetal exchanges. The intervillous space may behave as a deposit for some drugs, showing higher concentrations than in other compartments, enabling late and prolonged fetal effects of drugs administered to the mother during pregnancy and that can accumulate in this space.^{26,27}

When the ratios between the various compartments were evaluated as a whole, no statistically significant difference was observed between the groups, showing that GDM had no significant action on the placental transfer of lidocaine. This result agrees with the study by Calderon et al,³ who evaluated the placentae of women with disorders of carbohydrate metabolism and observed that the placental villi of patients with type 1 and 2 GDM were similar in size and number to those of the controls, with the total villous area being equal for the 2 groups.

Regarding MEGX, when the ratios for the various maternal and fetal compartments were evaluated, a statistically significant difference was observed between the normal and the diabetic groups in MEGX transfer from maternal peripheral blood and also from the intervillous space to fetal blood collected from the umbilical vein. This may indicate the presence of some facilitating mechanism acting on the transplacental transfer of MEGX in the placenta of diabetic women.

Comparison of MEGX concentrations in the umbilical artery and vein revealed a ratio of 1.09 and 0.99 in the normal and diabetic groups, respectively, confirming the low rate of fetal metabolism of lidocaine to MEGX, since the expression of CYP3A4 in the fetal liver is also low as is also the case for CYP1A2.²⁸ The high rates of transplacental MEGX transfer indicate the need for care and caution regarding the doses of lidocaine, the precursor of this metabolite which is an active agent that may have toxic effects on the central nervous system, in order to avoid doses that may reach plasma levels that will cause deleterious maternal, and consequently fetal, effects.

The present study contributed to the knowledge of the effect of anesthetics administered to pregnant women with GDM;

however, further studies are needed in order to clarify the influence of GDM on placental changes that will determine modifications of the mechanisms of maternal–fetal exchanges.

Conclusions

On the basis of the data obtained and analyzed in the present study, we conclude that (1) GDM did not affect the transplacental transfer of lidocaine, (2) there was a significantly higher rate of MEGX transfer from the maternal compartment (peripheral blood and intervillous space blood) to the umbilical vein in the diabetic group compared to the normal group, and (3) there was a nonsignificant rate of fetal metabolism of lidocaine to MEGX and of MEGX to its secondary forms.

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