



## Placental transfer and vascular effects of pharmaceutical drugs in the human placenta *ex vivo*: A review

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### ABSTRACT

At least 80% of pregnant woman in Europe use at least one medication during their pregnancy. The majority of these drugs are prescribed off-label. A better understanding of drug transport and effects in the placenta can provide an improved pharmacological basis to rationalize drug and dose selection for prescription. Here we provide a narrative review of studies that used the *ex vivo* placenta perfusion model to study placental drug transport and vascular effects of pharmaceuticals. For studies on placental transfer, we found that the methodology used varied substantially between studies as well as the way in which data was reported. Across the different therapeutic groups, *ex vivo* measurements of transfer generally corresponded well to *in vivo* findings. Still, further standardization of the perfusion technique would facilitate a broader use of perfusion data, e.g. in the context of quantitative systems pharmacology models as has been explored in recent years. Only few studies investigated the effects of drugs on the vascular tone using the *ex vivo* dual-side perfusion model. The model was particularly applied to study vasodilatory effects of pharmaceuticals in the fetoplacental circulation. In conclusion, the *ex vivo* dually perfused human cotyledon provides a relevant system to gain insights in placental drug disposition and study effects on the fetoplacental vasculature.

### 1. Introduction

During pregnancy it is not always possible to avoid maternal therapy, as pre-existing or novel medical conditions may require ongoing or episodic treatment [1–3]. It is therefore not surprising that around 80% of pregnant women in Europe have been reported to use at least one medication at some point during their pregnancy [4,5].

Most drugs administered to counteract maternal disease exhibit extensive placental transfer, with the consequence of potential fetal exposure to undesirable, pharmacologically active drug concentrations. Of course, in specific situations fetal exposure may be beneficial, e.g. when treating fetal or placental disorders *in utero*. In any case, the extent of fetal exposure to a drug is rarely studied. This hampers risk assessment and weighing of fetal safety versus potential maternal benefit that

may be obtained by treatment. Apart from the fetoplacental drug disposition, there is a lack of knowledge on potential placental effects of pharmaceuticals, which further impedes evidence-based drug dosing and selection during pregnancy [6].

Maternal drug dosing, fetal exposure and drug safety in pregnancy, are usually studied in the form of post-marketing observational studies. In an earlier phase, non-clinical studies may be applied to estimate fetal exposure and toxicity, mostly in reproductive toxicology studies in animals [7,8]. As interspecies translation of results is problematic, e.g. due to differences in placental structure and development, it is essential to explore how human *in vitro* and *ex vivo* systems may contribute to improve pharmacological and toxicological profiling of drugs administered during pregnancy.

Fetal exposure and pharmacokinetics of the human term placental

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barrier can be studied using the *ex vivo* dually perfused placenta as it closely resembles the human *in vivo* situation. The structural integrity of the tissue is retained with this technique, and physiological conditions during experimentation can be controlled. Many studies have been published since the first publication of the dually perfused cotyledon study on amino acid transfer by Schneider et al. in 1972 [9]; the majority of these studies focus on placental transfer of pharmaceuticals. However, the technique can contribute more knowledge than solely on drug transfer. In this manuscript we review the term *ex vivo* dually perfused human placental cotyledon with respect to drug transfer and distribution, as well as the use of this model to study placental vascular effects.

## 2. Literature search strategy

We focused our narrative review on the most common indications for pharmacological treatments during pregnancy: HIV/AIDS, psychiatric disorders, diabetes, infections, cancer, epilepsy, and other diseases of the immune and vascular system. Only research on the human placenta cotyledon method was included in this review, covering the period from 1979 up to and including October 2021. Only papers that could be accessed by the authors were included and are presented in Tables 1 and 2.

## 3. Placental transfer

We reviewed studies on the *ex vivo* transfer of small molecule pharmaceutical drugs (Table 1). Although from a mechanistic perspective placental transfer depends on physicochemical drug properties and interactions of a compound with drug transporters and drug metabolizing enzymes, we now chose to categorise compounds per pharmacotherapeutic area and highlight differences in placental drug disposition and effects within a given therapeutic class. Table 1 provides an overview of placental drug transfer. Where possible we reported clinical data on placental drug transfer as well, to allow a qualitative or semi-quantitative comparison between *ex vivo* and *in vivo* findings. We noted that in the reviewed literature *ex vivo* perfusion conditions differed substantially between laboratories. We therefore included brief statements on the employed perfusion protocol and, if reported by the authors, the starting drug concentrations that were added to the maternal reservoir. When perfusions were also performed in the fetomaternal direction, the starting concentrations in the fetal reservoir are included as well. When detailed information on possible mechanisms of transfer were provided, we also mentioned those in the table. Reviewed studies expressed placental transfer in a diverse number of ways; e.g., by reporting changes in drug concentrations in the maternal and fetal reservoir, concentration ratios, transfer rates, absolute cotyledon clearances or clearance indices (usually normalized to antipyrine transfer). Parameters were included as reported in the papers.

As can be seen in Table 1, the majority of studies were on antiretroviral agents, followed by studies on antidepressants and anxiolytics, which together comprise approximately half of the studies reviewed. The other half of studies encompass a diversity of therapeutics, including vaso-active drugs, anti-epileptics, antidiabetics, antibiotics, chemotherapeutic agents, immunosuppressive drugs, anticoagulants, antipyretic/analgesic drugs and one phosphodiesterase-inhibiting agent. Below we discuss the studies on placental transfer of drugs belonging to the antiviral, anti-epileptic, vaso-active, or psychopharmacological therapeutics, in more detail.

### 3.1. Transfer of anti(retro)viral drugs

We found that anti(retro)viral agents are well-represented in perfusion experiments. Indeed, the benefits of HIV treatment with antiretrovirals has been well established, since it can reduce the chance of mother-to-child transmission of HIV from 20% to less than 1% [10]. Given the large number of studies we do not go into detail with regard to

disposition mechanisms of all the individual compounds, but it can be clearly noted that differences exist in the *ex vivo* placental transfer of the various antiretroviral agents. For example, ritonavir, enfuvirtide and saquinavir display a very low maternal-to-fetal placental transfer *ex vivo*, which also corresponds to clinical findings [11–17]. Most compounds, however, do exhibit placental transfer *in vivo*, but also this is generally captured well by the *ex vivo* model (see Table 1). For indinavir and raltegravir, the correlation between *in vivo* and *ex vivo* data appears to be indistinct. Indinavir displays a good degree of *ex vivo* transfer, while it was reported undetectable in cord blood *in vivo* [12,18]. For raltegravir the opposite appears to be the case, as median *in vivo* cord-to-maternal blood concentration ratios were reported to be higher than 1. At the extreme, a cord blood concentration of 4 times the concentration found in the mother was reported. An *ex vivo* study, however, reported a maternal-to-fetal clearance index of 0.3 and a similar value in the opposite direction, which does not appear to be in line with clinically observed data [19,20].

In the reviewed literature, it is suggested that several of the antiretroviral drugs exhibit active transport in the fetal to maternal direction. Often this is evidenced by observations of asymmetric compound clearances across the placental barrier. Few perfusion studies with anti (retro)viral agents used co-perfusion with pharmacological inhibitors of transporters to confirm transporter involvement. Such studies showed that, indinavir, saquinavir and lopinavir were likely to interact with ATP-Binding Cassette efflux transporters [17,18,21]. Apart from transfer, several of the antiretroviral agents in Table 1 appear to accumulate within placenta tissue, e.g. via ion-trapping or extensive protein binding. It is unclear whether for the anti(retro)viral agents this high level of placental exposure has toxicological meaning or whether it may be of pharmacotherapeutic relevance for inhibiting vertical viral transmission.

### 3.2. Transfer of psychopharmacological and anti-epileptic drugs

#### 3.2.1. Benzodiazepines and benzamides

Early *ex vivo* perfusion studies from the late 1970s and early 80s examined the transplacental transfer of different benzodiazepines and benzamides. These are anxiolytic agents and anti-emetics, widely used during pregnancy and labor to induce sedation and muscle relaxation, and in the treatment of eclampsia and severe pre-eclampsia. The neonatal symptomatology includes hypothermia, respiratory depression and withdrawal symptoms (floppy baby syndrome). The benzodiazepines studied transferred rapidly across the placental barrier at levels of 79–93% of antipyrine, except for the hydrophilic clorazepate, which had a relative transfer of 20%. This would favor clorazepate use in pregnancy and labor, but as the substance metabolizes to the more lipophilic nordiazepam at low pH, the maternal administration should be parental. The less protein bound and less lipid-soluble fosazepam showed reduced placental uptake, but no difference in transplacental transfer, which suggests higher maternal extraction. The benzamides displayed a transplacental transfer of 34–44% compared to antipyrine with negligible tissue retention and plasma protein binding. Their placental clearance correlated with their coefficient of free diffusion in water, suggestive of transplacental transfer through water-filled pores in the placental tissue [22–25].

#### 3.2.2. Tricyclic antidepressants (TCAs), atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs)

From the year 2000 and onwards, *ex vivo* perfusion publications include tricyclic antidepressants (TCAs), atypical antipsychotics and selective serotonin reuptake inhibitors (SSRIs). TCAs are widely prescribed for depression and panic disorder during pregnancy. The transplacental transfer of two TCAs, amitriptyline and nortriptyline, was studied in open-circuit 2 h placental perfusion experiments and showed rapid transfer of 81% and 62% of antipyrine diffusion, respectively [26].

The best documented antidepressants for use during pregnancy are

**Table 1**  
Transplacental transfer of drugs studied in *ex vivo* placental perfusion, categorized per therapeutic area.

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Anti(retro)viral agents (29 references)</b>						
<b>Zidovudine - NRTI</b>	Closed 120 min. cannulae: 2. <i>Krebs-Ringer</i>	M: 1 g/L	N=2 placentas. 1: M120 and F120: 156,8 vs 79.7 ng/mL 2: 133.6 vs 172.8 ng/mL F concentration range: 2.3 ± 0.4 to 2.5 ± 0.4 mM at 250 min F/M at 250 min was ~ 1			[64]
	Closed 840 min. cannulae: 2. Flow: F: 3 mL/min M119, glucose 2 g/L, dextran- 40 7.5 g/L F: M119, glucose 2 g/L, dextran- 40 30 g/L	M: 3.8 mM 3 sequential administrations			It is suggested that AZT is metabolized by the placenta [65]	[66]
<b>Dideoxy-inosine (Didanosine) - NRTI</b>	Open 90 min, Closed 240 min. Flow: M: 10, F: 3 mL/min <i>Heparinized Krebs-Ringer</i> , HSA 2 g/L		Open: CI <sub>MTF</sub> : 0.315 ± 0.126, CI <sub>FTM</sub> : 0.246 ± 0.100, Closed: CI <sub>MTF</sub> : 0.234 ± 0.054, CI <sub>FTM</sub> : 0.295 ± 0.107		Structural analogues (inosine, uric acid) did not influence transfer	[67]
<b>Lamivudine - NRTI</b>	Closed 60 min. cannulae: 2 Flow: M: 17; F: 3 mL/min <i>Earle's</i> , 3% HSA	M: 1.39 µg/mL M: 14.68 µg/mL	1.39 µg/mL; CI <sub>MTF</sub> : 0.23 ± 0.14, CI <sub>FTM</sub> : 0.14 ± 0.06. 14.68 µg/mL; F60: 0.24 ± 0.20 µg/ mL, F60: 1.44 ± 0.80 µg/mL		Non-saturable transport mechanism, transport not affected by AZT	[68]
<b>Emtricitabine – NRTI</b>	Closed 150 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 30 g/L (M) or HSA 40 g/L (F)		Emtricitabine FTR: 24.3 ± 6.4 %, CI: 0.53 ± 0.17 Tenofovir: FTR: 21.0 ± 5.7 %, CI: 0.39 ± 0.11	Emtricitabine: 1.63 (0.46–1.82) [69] Tenofovir: 0.60 (0 – 1.97) (dose 600 mg) or 0.59 (0–3.06) (dose 900 mg) [70]. 0.82 (0.64–1.10) [69], 0.88 (0.76–1.03) [71]		[58]
<b>Tenofovir - NRTI</b>						
<b>Abacavir - NRTI</b>	Closed 60 min. <i>Heparinized Earle's minimal</i> <i>essential medium</i>	M: Abacavir: peak: 10 µg/ mL, trough: 1 µg/mL, Amprenavir: peak: 6.7 µg/ mL, trough: 1.3 µg/mL	Peak concentrations CI <sub>Abacavir</sub> : 0.47 ± 0.19, CI <sub>Amprenavir</sub> : 0.38 ± 0.09. Trough concentrations: CI <sub>Abacavir</sub> : 0.50 ± 0.07 CI <sub>Amprenavir</sub> : 0.14 ± 0.08	Abacavir: 1.0 (0.7–1.0) [72], 1.06 (90% CI, 0.9–1.2) [73], Amprenavir: 0.267 (0.241–0.297) [74]		[75]
<b>Ritonavir - PI</b>	Open 60 min. cannulae: 2. Flow: M: 17; F: 3–4.5 mL/min M: <i>Earle's</i> , zidovudine: 1 mg/L or <i>Earle's</i> , zidovudine: 10 mg/L F: <i>Earle's</i>	M: 1-2, 20 or 100 mg/L	CI <sub>20 mg/L</sub> : 0.085 ± 0.05, CI <sub>100 mg/L</sub> : 0.30 ± 0.11	In most clinical studies ritonavir was undetectable in cord blood [12, 13]. Others report a C/M ratio of 0.28 [76].	No tissue accumulation detected. Transfer was unaffected by zidovudine	[11]
<b>Indinavir - PI</b>	Open 90 min. cannulae: 2. Flow: M: 14, F: 7 mL/min M: <i>Krebs-Ringer</i> , 3% dextran, 0.1% glucose, vinblastine 0.03 mg/L	M: 7.6 mg/L M: 0 F: 7.6 mg/L	MTF: 0.39 ± 0.09, FTM: 0.97 ± 0.12		P-gp and MRP1 were involved in transfer [77, 78]	[79]
<b>Darunavir - PI</b>	Open 90 min. cannulae: 2. Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L Open 150 min. cannulae: 4 Flow: M: 12, F: 6 mL/min <i>Krebs-Henseleit</i> , 11.1 mM glucose, HSA 30 g/L, ritonavir 0.5mg/L	M: 1 mg/L F: 0 M: 6 mg/L F: 0 M: 0 F: 6 mg/L	CI: 40.3% ± 5.8%, Steady state: 15.0% ± 2.1% Cotyledon CL FTM: 1.6 ± 0.03 mL/min, MTF: 0.91 ± 0.11 mL/min	C/M ratios were in range 0.10 to 0.24 [80] and 0.08 – 0.35 [81]		[82]
				0.13 (0.08–0.35) [83] 0.11–0.18 [84]	Ritonavir is a P-gp inhibitor [79, 85]	[61]
<b>Nelfinavir – PI</b>	Open 85 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L		CI: 0.31 ± 0.18 (0–0.54), F/M at steady state: 11.1 ± 6.3% (0–18.7%)	0.27 (0.07–0.43) [86]		[87]

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Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Lopinavir - PI Ritonavir - PI/ booster</b>	Open 83 ± 6 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 or 10 or 40 g/L		<i>HSA 2 g/L</i> : Lopinavir: 0.73 ± 0.16, Ritonavir: 0.28 ± 0.30. Lopinavir + Ritonavir, <i>HSA 10 g/L</i> , <i>CLLopinavir</i> : 0.57 ± 0.07, <i>CIRitonavir</i> : 0.19 ± 0.17, <i>HSA 40 g/L</i> , <i>CLLopinavir</i> : 0.10 ± 0.01, <i>CIRitonavir</i> : 0. F/M at steady state: <i>HSA 2 g/L</i> : Lopinavir: 30.4% ± 9.3%, Ritonavir: 12 ± 15.6. <i>HSA 10</i> <i>g/L</i> : Lopinavir: 20.7%±10%, Ritonavir: 8.3 ±8.5. <i>HSA 40 g/L</i> : Lopinavir: 3.3% ± 0.5% Ritonavir: 0. FTR: 14.0% ± 8.9%, CI: 27% ± 10%	0.16 – 0.20 [76]	Placental accumulation was observed for lopinavir and ritonavir	[88]
<b>Saquinavir - PI</b>	Open 120 min. cannulae: 4 Flow: M: 10, F: 3 mL/min <i>Krebs-Ringer</i> , HSA 30 g/L Open 120 min. cannulae: 4. Flow: M: 10, F: 3 mL/min <i>Krebs-Ringer</i> , HSA 30 g/L  Open 75 ± 5 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L	M: 6.67 µg/mL F: 0 µg/mL M: 0 µg/mL F: 6.67 µg/mL	MTF 0.29 ± 0.12, M120: 5541 ± 583 ng/ mL, F120: undetectable. FTM 23.1 ± 19.1, M120: undetectable, F120: 5589 ± 438 ng/ mL CI: 0.05 ± 0.05, M: range 322 – 2197 ng/mL, F: range <5 – 118 ng/mL, F/M at steady state: 1.8% ± 1.6%	Concentration in cord blood samples (128 - 357) ng/ml [89]	P-gp active transport [90]	[16]
<b>Lopinavir - PI Ritonavir - PI</b>	Open 95 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle medium</i> , BSA 10, 30 or 40 g/L	Lopinavir: 6 mg/L Ritonavir: 3 mg/L ciclosporin A: 10 µM	M95: lopinavir: 6.121 ± 1.824 mg/L, ritonavir: 3.318 ± 1.134 mg/L		P-gp active transport	[17]
<b>Dolutegravir - INSTI</b>	Closed 180 min. cannulae: 4 Flow: M: 12, F: 6 mL/min <i>Krebs-Henseleit</i> , 10.1 mM glucose, HSA 30 g/L Closed 180 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L Open 180 min. cannulae: 4 Flow: M: 12, F: 6 mL/min M: <i>Krebs-Henseleit</i> , 11.1 mM glucose, HSA 29 g/L F: <i>Krebs-Henseleit</i> , 11.1 mM glucose, HSA 34 g/L	M: 4.2 mg/L  M: 3 mg per experiment  M: 4 µg/mL F: 0 M: 0 F: 4 µg/mL	M180: 2.3 ± 0.4 mg/L, F180: 1.3 ± 0.3 mg/L, FTM: 0.6 ± 0.2  CI: 79% ± 23%, M180: 2450 ± 286 µg/L, F180: 715 ± 369 µg/L, F/M at steady state: 34% ± 18% Cotyledon CL: MTF: 1.03 ± 0.06 mL/min, FTM: 1.03 ± 0.23 mL/min	C/M ratios in range of 0.64–1.81 [94], 0.68–1.68 [95] and 1.07–1.40 [96]	No tissue accumulation detected	[97]
<b>Elvitegravir - INSTI Cobicistat -booster</b>	1. Closed 180 min 2. Open 180 min 3. Closed 180 min 4. Open 180 min. <i>Earle's</i> , HSA 2 g/L		1: M: 771 ± 237 µg/L, F: 149 ± 84 µg/L, F/ M: 20 ± 10 % 2: CI: 0.46 ± 0.21, M: 3340 ± 2150 µg/L, F: 602 ± 552 µg/L, F/M: 19 ± 13 % 3: M: 2070 ± 731 µg/L, F: 428 ± 229 µg/L, F/M: 21 ± 11 % 4: CI: 0.63 ± 0.34, M: 5850 ± 4990 µg/L, F: 964 ± 518 µg/L, F/M: 23 ± 13 % CI <sub>MTF</sub> : 0.28 ± 0.05 ; CI <sub>FTM</sub> : 0.31 ± 0.09, MTF: 9.1% ± 1.4%	Undetectable in infants after delivery [99]	1: AI: 12.28 ± 5.57 2: AI: 8.19 ± 4.26 3: AI: 3.46 ± 2.19 4: AI: 5.78 ± 3.6	[100]
<b>Raltegravir - INSTI</b>	Open 90 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i>			1.48 (range: 0.32–4.33) [20] 1.50 [101]	Substrate and inducer of P-gp, SLC22A6 and SLC15A1 [102, 103]	[19]
<b>Cabotegravir - INSTI Bictegravir - INSTI</b>	Open 90 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L	Cabotegravir 660 ng/mL Bictegravir 2576 ng/mL	Cabotegravir: CI: 19–28 %, M: 344–788 µg/ L, F: 37–54 µg/L, F/M: 5–16 %. Bictegravir: CI: 17–29 %, M: 1455–1960 µg/ L, F: 112 – 142 µg/L, F/M: 6–9.5 %		Accumulation in placenta tissue was observed for cabotegravir and bictegravir	[104]

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Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Enfuvirtide - fusion inhibitor</b>	Open 90 min. Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L	M: 10 mg/L	F90: undetectable	Peripheral blood sample concentration after delivery: M: 4135 and 3647 ng/mL F: undetectable [15]		[14]
<b>Maraviroc – entry inhibitor</b>	Open 90 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i>	600 ng/mL	CI <sub>MTF</sub> : 0.26 ± 0.07, CI <sub>FTM</sub> : 0.52 ± 0.23, F/M: 8.0% ± 3.0%	0.33 (0.03–0.56) [105]	High-affinity P-gp substrate [106]	[107]
<b>Doravirine - NNRTI</b>	Open 90 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's Balanced Salt Solution</i> , HSA 2 g/L	M: 250 ng/mL	CI: 48%, F/M: 16%		Doravirine probably accumulated in the placental lobule (39%)	[108]
<b>Rilpivirine – NNRTI</b>	Open 90 min. cannulae: 2 Flow: M: 12, F: 6 mL/min <i>Earle's</i> , HSA 2 g/L		CI: 61% ± 20%. M90: 401 ± 31 µg/L F90: 101 ± 38 µg/L, F/M: 26% ± 8%	0.74 [109]. 0.55 (0.4–0.8) [110].		[111]
<b>Daclatasvir Sofosbuvir main metabolite, GS-331007</b>	Closed 180 min. cannulae: 4 Flow: M: 12, F: 6 mL/min <i>Krebs-Henseleit</i> , 11.1 mM glucose, HSA M: 29 g/L, F: 34 g/L	Daclatasvir M: 1534 ng/mL. GS-331007 M: 582 ng/mL	Daclatasvir F180: 250 ± 110 ng/mL, F/M: 0.41 ± 0.14. GS-331007 F180: 120 ± 50 ng/mL, F/M: 0.38 ± 0.15.		Placental accumulation of daclatasvir: 1483 ± 292 ng/g. GS-331007 does not readily accumulate in placental tissue: 223 ± 27 ng/g.	[112]
<b>Oseltamivir phosphate</b>	Closed 180 min. cannulae: 2 Flow: M: 12, F: 3 mL/min	M: 65.2 ng/ml M: 348 ng/ml			Oseltamivir phosphate but not Oseltamivir carboxylate is a substrate of P-gp, and the influx transporter PEPT1 [113, 114]	[115]
<b>Oseltamivir carboxylate (active metabolite)</b>						
<b>Oseltamivir phosphate</b>	Open 60 min combined with closed 60 min. cannulae: 3 Flow: M: 17, F: 4.5 – 5 mL/min <i>Eagle's minimal essential media</i> , BSA 3%	M: 320 to 54000 µg/L	CI: 0.13 ± 0.08 for concentrations > 400 µg/L. Undetectable in the fetal compartment when levels in the maternal perfusate were below 400 µg/L.		Oseltamivir phosphate is extensively metabolized to oseltamivir carboxylate	[116]
<b>Psychopharmacological drugs (9 references)</b>						
<b>Paroxetine - SSRI</b>	Closed 60 min + drug free for 180 min. <i>Krebs-Ringer</i> , Dextran 40 1 g/L, HSA 2 g/L.	M: 41.5, 128 or 149 ng/mL	% of AP: 40%	Cord blood concentrations: (26 ng/ml) [117] Serum paroxetine cord blood: 368 nmol/L [118] 0.51 (0.05-0.91) [119]		[28]
<b>Bupropion – anti-depressant</b>	Closed 240 min. cannulae: 2 Flow: M: 12, F: 2.8 mL/min <i>M199 medium</i> , Dextran 40 30 g/L (F) or 7.5 g/L (M), HSA 30 g/L.	M: 150ng/mL and 450ng/mL	% of AP: 1, CI: 20% to fetal circuit	0.53 [120] 1.14 (0.3-5.08) [121]	48% in placental tissue	[29]
<b>Quetiapine - Atypical antipsychotic drug</b>	Open 180 min. cannulae: 4 Flow: M: 10, F: 3 mL/min <i>Krebs-Ringer</i> , BSA 30g/L.	M: 75 ng/ml	% of AP: 80%	0.24	No effect of P-gp inhibitors	[30]

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Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>PSC833</b>						
<b>(valsopodar) - P-gp inhibitor</b>						
<b>GG918 - P-gp inhibitor</b>						
Citalopram – SSRI	Open 180 min. cannulae: 4	M (nmol/L): citalopram:	% of AP: citalopram: 86%, metabolite C:	Citalopram: 0.71 (0.17–1.42) [119],		[27]
Fluoxetine – SSRI metabolites C & F - SSRI	Flow: M: 10, F: 3 mL/min <i>Krebs-Ringer</i> , BSA 30 g/L	1230, fluoxetine: 1455, metabolite C: 600, metabolite F: 525.	50%, fluoxetine: 88%, metabolite F: 91%	0.78 (0.46–1.66) [122] Fluoxetine: 0.64 (0.32–0.36) [119], 0.67 (0.61–0.74) [123]		
Amitriptyline – TCA	Open 180 min. cannulae: 4	M (ng/mL):	% of AP: amitriptyline: 81%, nortriptyline:	Nortriptyline: 0.68 ± 0.40 active metabolite, cis-10-		[26]
Nortriptyline - TCA	Flow: M: 10, F: 3 mL/min	amitriptyline:200, nortriptyline: 150	62%	hydroxynortriptyline:1.40 ±2.40		
Sulpride - APP	Open 60 min.	M: 2µg/mL each	% of AP: 34-44%		High degree of ionization at physiological pH.	[25]
Sulpride tiapride - APP						
Clobazam - benzodiazepine	<i>In vitro</i> . Open 60 min.	M: 2µg/mL each	Clobazam 86%, norclobazam 93% of tritiated water			[24]
Norclobazam - benzodiazepine						
Diazepam - benzodiazepine	Open 60 min. <i>Earle's</i> , without or with adult plasma (25g/l, HSA 15g/l) Open	M: 2µg/mL each  M: 2000 ng/mL each	% of AP: Diazepam 84% fosazepam 79% in protein free medium	0.82 (0.19–1.67)[124] 0.84 (0.49–1.43) [125] 1.2 (0.73–2.5) [126]		[23]  [22]
<b>Antiepileptic and mood stabilizers (5 references)</b>						
Valproic acid	Closed 180 min. cannulae: 3 Flow: M: 10 – 12, F:6–8 mL/min <i>M199</i> , HSA 30mg/ml. After perfusion a bolus of prostaglandin E2 added to fetal arterial side	M: 42, 83 or 166µg/mL		1.43 [127] 1.7 [128]	Maybe a substrate for P-gp	[39]
	Closed 150 min. cannulae: 2 Flow: M: 14, F: 3.8mL/min <i>M199/HBSS</i>	M: 75 or 225 µg/mL.	% of AP: 84.3-97%		No accumulation of drug in the placenta	[38]
Lamotrigine	Closed 120 min. Flow: M: 9, F: 5 mL/min <i>Krebs-Ringer-phosphate-bicarbonate buffer</i> , glucose 1 g/L, dextran-F:40 30, M: 8.4 g/L	M: 2.5 mg/L or 10 mg/L	2.5 mg/L: FTR: 28,9 ± 10,7%, CI: 0,83 ± 0,41 10 mg/L: FTR: 37,8 ± 3,2%, CI: 1,26 ± 0,20.	1.02 in one pair and 1.55 in the other		[40]
Oxcarbazepine	120-180 min. <i>Protein-free buffer</i>	M: 50 µg/mL for both drugs	Carbamazepine: CI: 1.1 Oxcarbazepine: CI:1.24-1.47	Carbamazepine (pg/mL): 3.7-5.0 in maternal and 2.9-4.3 in cord blood. Oxcarbazepine (µg/mL): 0.04-0.37 in maternal and 0.04-0.29 in cord blood	Accumulation of the drugs in the placenta was seen	[34, 35]
Carbamazepine						
Phenytoin	Closed 240 min. Flow: M: 15-16, F: 3-3.5 mL/min <i>M199</i> , glucose 1g/L, sodium bicarbonate 7,5%, dextran-40 F: 30 or M: 7.5 g/L		At the end of perfusion fetal reservoir concentration is 73% of the maternal reservoir concentration		Accumulation of the drugs in the placenta. No parahydroxylation, oxidation or conjugation of the drug was found.	[129]

(continued on next page)



Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Anticoagulants (3 references)</b>						
<b>Dabigatran</b>	Closed 180 min.	Dabigatran: 35, dabitragan	Dabigatran: F/M: 0.33 (IQR 0.29–0.38),			[130]
<b>Dabigatran</b>	Flow: M: 13–14, F: 2–3 mL/min	etexilate mesylate: 3.5 ng/ mL	dabigatran etexilate mesylate: F/M: 0.17 (IQR 0.15–0.17)			
<b>Etexilate Mesylate</b>	<i>M199 tissue culture medium</i> , dextran 40 M: 7.5, F 30 g/L, glucose 1.0 g/L					
<b>Apixaban</b>	Closed 180 min. Flow: M: 12–15, F: 2–3 mL/min <i>M199 tissue culture medium</i> , dextran 40 M: 7.5, F 30 g/L, glucose 1.0 g/L	M: 150 ng/mL	F180: 39.0 ng/mL, FTM concentration ratio: 0.77			[131]
<b>Rivaroxaban</b>	Closed 180 min. Flow: M: 13–15, F: 2–3 mL/ min <i>M199 tissue culture medium</i> , dextran 40 M: 7.5, F 30 g/L, glucose 1.0 g/L	M: 250 ng/mL F: 0 M: 0 F: 250 ng/mL	MTF: 0.69 (IQR, 0.58–0.73), FTM: 0.69 (IQR, 0.67–0.71)			[132]
<b>Chemotherapeutic agents (5 references)</b>						
<b>Paclitaxel</b>	Closed 120 min Flow: M: 12, F: 3 mL/min <i>Medium 199</i> with Earle's salts (11 mg/mL), dextran M: 3, F 12 mg/mL, HSA 30 mg/mL Open 180 min. <i>Earle medium</i> , BSA 40 g/L	M: 20 µg/mL  M: 1530 ng/mL	F/M: 7%  F180: 36.6 ± 2.2 ng/mL, F/M: 3.9 ± 0.3%		Persistence in fetal blood obtained less than 3 weeks after the last maternal infusion of chemotherapy	[133]  [134]
<b>Carboplatin</b>	Closed and open 120 min. cannulae: 3 Flow: M: 17, F: 4.5 mL/min <i>Eagle's mini-mum essential medium</i> , BSA 30 g/L	M: 1 mg/L, M: 5 mg/L, M: 11 mg/L	1 mg/L CI: 0.22 ± 0.01, 5 mg/L: 0.14 ± 0.08, 11 mg/L: 0.50 ± 0.07			[135]
<b>Crizotinib</b>	Closed 180 min. cannulae: 4 Flow: M: 12, F: 6 mL/min <i>Krebs-Henseleit buffer</i> , HSA 30 g/L, 10.1 mM glucose	M: 1 µM	M rapid initial decrease. M180: 0.2 ± 0.05 µM, F180: 0.08 ± 0.01 µM		Crizotinib accumulates in placental tissue. Total crizotinib recovery 83 ± 11%; 59 ± 8% in perfused cotyledon	[136]
<b>Gefitinib</b>	Open 90 min. cannulae: 2	Gefitinib: 500, Imatinib:	Gefitinib CI: 0.59, F/M: 16.8%, Imatinib CI:	Gefitinib: 0.20 [137]	Placental uptake in cotyledon (%):	[141]
<b>Imatinib</b>	Flow: M: 12, F: 6 mL/min	1000, Erlotinib: 1500 ng/mL	0.48, F/M: 10.6%, Erlotinib CI: 0.93, F/M:	Imatinib: 0.064 [138] crossed the	Gefitinib: 0.030, Imatinib: 0.010	
<b>Erlotinib</b>	<i>Earle medium</i> , BSA 30 g/L		31.4%	mature placenta poorly [139]	Erlotinib: 0.003	
				Erlotinib: 0.25 [140]		
<b>Antibiotics (6 references)</b>						
<b>Trovafloxacin</b>	Open 60 min. followed by Closed 60 min. Flow: M: 17, F: 4 mL/min <i>Eagle's MEM</i>	M: 1.0 µg/mL M: 7.0 µg/mL	1 µg/mL: CI: 0.19 ± 0.13, 7 µg/mL: CI: 0.16 ± 0.10		Trovafloxacin crosses the placenta by simple diffusion, no accumulation in media or placenta	[142]
<b>Meropenem</b>	Open 60 min. followed by Closed. cannulae: 2 Flow: M: 17, F: 4.5–5 mL/min <i>Eagles minimal essential medium</i> , BSA 3%		Peak: CI: 0.077 ± 0.007, M: 54.3 ± 3.3 µg/ mL, F: 2.2 ± 1.8 µg/mL Trough: CI: 0.052 ± 0.015, M: 12.7 ± 1.3 µg/mL, F: 0.44 ± 0.10 µg/mL			[143]
<b>Vancomycin</b>	Open 120 min. followed by Closed. cannulae: 2 Flow: M: 17, F: 4.5–5 mL/min <i>Eagles minimal essential medium</i> , BSA 3%	M: 37.2 g/L (peak) M: 11.7 g/L (trough)	Peak: CI: 0.000–0.080, Trough: CI: 0.00–0.17		No accumulation. A vancomycin-heparin complex may have formed, decreasing vancomycin's transplacental passage	[144]

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Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Vancomycin</b> <b>Telavancin</b>	Closed 240 min. cannulae: 2 Flow: M: 12, F: 2.8 mL/min <i>M199 tissue culture medium</i> , dextran-40 M: 7.5, F 30 g/L, HSA 30 g/L	Vancomycin: 25 mg/L Telavancin 25 mg/L	Vancomycin: MTF: $9.6 \pm 4\%$ , FTM: $5 \pm 2\%$ . Telavancin: MTF: $6.5 \pm 2\%$ , FTM: $5 \pm 1\%$	Transplacental passage occurs with fetal levels equaling maternal levels, but is somewhat slow in both directions [145]	Telavancin was reported as an inhibitor of P-gp-mediated digoxin transport	[146]
<b>Solithromycin</b>	Closed 180 min. Flow: M: 10, F: 4 mL/min <i>phenol red-free medium-199 cell culture medium</i> , glucose 2 g/L, BSA 3 g/L	M: 10 µg/mL	CI: 87%, F/M: $40.3 \pm 23.6\%$		No inhibition of IL-6 and TNF- $\alpha$ production at non-toxic pharmacological concentrations of Solithromycin ( $\leq 11$ µg/mL)	[147]
<b>Rifampin</b> <b>Rifabutin</b>	Open followed by Closed 60 min. Flow: M: 17, F: 3–4 mL/min <i>Eagle's medium</i>	Rifampin: 1.0 mg/L, 10.0 mg/L Rifabutin: 1.0 mg/L, 10.0 mg/L	Rifampin 1 and 10 mg/L: $0.12 \pm 0.05$ and $0.12 \pm 0.11$ Rifabutin 1 and 10 mg/L: $0.44 \pm 0.11$ and $0.37 \pm 0.15$			[148]
<b>Analgesics and antipyretic agents (2 references)</b>						
<b>Paracetamol</b> <b>PCM-S</b> <b>PCM-G</b>	Closed 210 and 360 min. cannulae: 5 Flow: M: 14, F: 6 mL/min <i>Krebs buffer</i> , glucose 2.61 g/L BSA: M:30, F: 40 g/L	PCM: 30 µg/mL PCM: 10 µg/mL PCM-S and PCM-G: 10 µg/mL and 25 µg/mL PCM-S and PCM-G 5 µg/mL and 12.5 µg/mL	PCM 30 MTF: $0.96 \pm 0.07$ , PCM 10 MTF: $0.97 \pm 0.08$ , FTM: $0.82 \pm 0.07$ . MTF: PCM-S 10: $0.79 \pm 0.10$ , PCM-G 25: $0.67 \pm 0.03$ . MTF: PCM-S 5: $0.81 \pm 0.01$ , PCM-G: 12.5: $0.60 \pm 0.11$ . FTM: PCM-S 5: $0.33 \pm 0.01$ , PCM-G 12.5: $0.26 \pm 0.01$		No formation of PCM-S nor PCM-G was seen during the perfusions with PCM. No tissue accumulation of PCM.	[149]
<b>Buprenorphine</b>	Closed 240 min. cannulae: 2 Flow: M: 10–12, F: 2.8–3.2 mL/min <i>M199 tissue culture medium</i> , glucose 1 g/L, 25 IU/mL heparin, gentamicin sulfate 40 mg/L, sulfamethoxazole 80 mg/L, trimethoprim 16 mg/L dextran-40: M: 7.5, F: 30 g/L	M: range 0.5 to 30 ng/mL	F/M: $0.29 \pm 0.007$	0.5	The concentration ratios of the drug in tissue/maternal and tissue/fetal were $13 \pm 6.5$ and $27.4 \pm 0.4$ . Less than 5% was metabolized to norbuprenorphine.	[150]
<b>Immunosuppressive agents (1 reference)</b>						
<b>Tacrolimus</b>	Closed 180 min. cannulae: 4 Flow: M: 12, F: 6 mL/min <i>Krebs-Henseleit buffer</i> , glucose 11.1 mM, HSA 30 g/L	M: 10 ng/mL	M180: $1.9 \pm 0.4$ ng/mL, F180: undetectable	In 2 cases venous umbilical cord blood concentration 4.8 and 6.2 ng/mL. Placental tissue concentrations of patients (55–82) ng/g.	Tissue-to-maternal perfusate concentration ratio of $113 \pm 49$ . Tacrolimus was distributed non-homogeneously in cotyledon.	[57]
<b>Phosphodiesterase (PDE) inhibitors (2 references)</b>						
<b>Sildenafil</b>	Closed 180 min. cannulae: 4 Flow: M: 12, F: 3–6 mL/min <i>Krebs-Henseleit buffer</i> , glucose 8.3 mM	M: 500 ng/mL	F/M: Healthy placenta: $0.37 \pm 0.03$ PE placenta: 0.66 and 0.47	Clinical studies reported inconclusive results with sildenafil in the treatment of PE [151–156]	~45% of sildenafil adhered to tubing, no metabolism or significant accumulation of sildenafil in tissue	[157]
	Closed 180 min. cannulae: 5 Flow: M: 14, F: 6 mL/min <i>Earle's balanced salt solution</i> , glucose 1.6 g/L, BSA 30 g/L maternal and 40 g/L fetal	M: 500 ng/mL M: 50 ng/mL	500: F180: 70 (67–86) ng/mL 50: F180: 10 (7–10) ng/mL		~45% of sildenafil adhered to tubing, no metabolism, significant accumulation in tissue (30-fold higher than maternal compartment)	[158]
<b>Therapeutic antibodies (3 references)</b>						
<b>Infliximab</b> <b>Etanercept</b>	Closed 360 min. cannulae: 4 Flow: M: 12, F: 6 mL/min <i>RPMI 1640 culture medium</i> , HSA M29, F34 g/L	Infliximab M: 100 µg/mL Etanercept: M: 100 µg/mL	Infliximab: F360: $0.3 \pm 0.3$ µg/mL Etanercept: F360: $0.2 \pm 0.2$ µg/mL	Infliximab levels in cord blood exceeded the maternal levels. Etanercept 0.04	Infliximab: Homogeneously distributed in all placentas of patients. Placenta-to-maternal ratios $0.34 \pm 0.11$ Etanercept: placenta-to-maternal ratio 0.03 - administered 4 days before delivery	[159]

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Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CL relative to AP CL)	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Certolizumab</b>	Closed 240-360 min. Flow: M: 20, F: 6 mL/min <i>RPMI-1640 medium</i> , BSA F1.8 g/L	M: 200 mg/L	F/M: Anti-D IgG: $0.41 \pm 0.24\%$ , Certolizumab undetectable		No apparent inhibitory effect of certolizumab on the placental transfer of IgG	[160]
<b>Adalimumab M281</b>	Closed 240-360 min. cannulae: 2 Flow: M: 12, F: 3 mL/min <i>M199 medium</i> , glucose 1 g/L, dextran-40 F30, M7.5 g/L, BSA 3 g/L	Adalimumab: 270 mg/L,+ M281:10 mg/L,+M281: 200 mg/L	FTR: 270 mg/mL: $0.23\% \pm 0.21\%$ , +M281 10mg/L: $0.07 \pm 0.01\%$ , +M281 200mg/L: $0.06 \pm 0.01\%$		Transfer rate of M281 was approximately 100-fold lower than that of adalimumab	[161]
<b>Antidiabetic agents (8 references)</b>						
<b>Rosiglitazone</b>	Open 60 min combined with Closed 60 min. cannulae: 2 Flow: M: 17, F: 4.5–5 mL/min <i>Eagle's minimal essential medium</i> , BSA 30 g/L	M: ranged from 216 ng/mL to 692 ng/mL	CI: 216 ng/mL $0.14 \pm 0.04$ , CI: 692 ng/mL $0.20 \pm 0.08$		Fetal accumulation:1 of 5 placentas at 16.4 ng/mL (5%) (low dose). 2 of 5 placentas ranging from 0 to 74 ng/mL (5% to 8%) (higher doses)	[162]
<b>Metformin</b>	Closed 180 min. cannulae: 4 Flow: M: 10-12, F: 4–6 mL/min <i>M199 tissue culture medium</i> , glucose 1 g/L, BSA 3 g/L,	M: 1 mg/L	CI: $0.34 \pm 0.05$ , F/M: $10.61 \pm 2.85\%$	Concentrations in umbilical vein and artery higher than in maternal venous blood [163]	Metformin has been shown to act as a substrate for three organic cation transporters OCT1, OCT2, and OCT3	[164]
	Closed 180 min. cannulae: 4 Flow: M: 10-12, F: 4–6 mL/min <i>M199 tissue culture medium</i> , glucose 1 g/L, BSA 3 g/L,	10 mg/L 1000 mg/L	F/M: 10 mg/L: $11 \pm 1.32\%$ , 1000 mg/L: $16.92 \pm 0.98\%$		Metformin does not cross by passive diffusion	[165]
	Closed - open, 240 min. cannulae: 2 Flow: M:10–12 F: 2.8–3.2 mL/min <i>M199 tissue culture medium</i> , glucose 1 g/L, 25 IU/mL heparin, gentamicin sulfate 40 mg/L, sulfamethoxazole 80 mg/L, trimethoprim 16 mg/L dextran-40: M 7.5, F: 30 g/L	M: 5 mg/L	% of AP: 50%. M: $56 \pm 5.3\%$ of initial concentration, F: $26 \pm 7.6\%$ of initial concentration		Transfer and distribution of metformin in healthy placentas was not different from diabetic placentas Placental tissue retained low amounts of metformin (<20% of that in the maternal circuit)	[166]
	Open 120 min. cannulae: 4 Flow: M: 10, F: 3mL/min <i>Krebs-Ringer bicarbonate buffer</i> , BSA 30 g/L	M: 2 mg/L, F: 0 or M: 0, F: 2 mg/L	MTF: 3.7%, FTM: 15.5%		OCT transporters not likely the transfer mechanism, - cimetidine (OCT inhibitor, 100 mg/L) no effect on the transfer of metformin	[167]
<b>Repaglinide</b>	Open 120 min. cannulae: 4 Flow: M: 10, F: 3mL/min <i>Krebs-Ringer bicarbonate buffer</i> , BSA 30 g/L	M: 10 mg/L, F: 0 or M: 0, F: 10 mg/L	MTF: 1.5%, FTM: 6.7%			[168]
<b>Glargine Insulin</b>	Closed 180 min. cannulae: 4 Flow: M: 10–12, F: 4–6 mL/min <i>M199 tissue culture medium</i> , glucose 1 g/L, BSA 3 g/L	M: 50 mU/L or 200 mU/L	M: 50% of initial starting concentration, F: undetectable		Reduced maternal steady state concentrations may suggest insulin uptake by the placenta	[169]
<b>Glyburide</b>	Closed 180 min. buffer with kanamycin 100 mg/L, glucose 1 g/L, dextran-40 F:30, M: 7,5 g/L	200 µg/L or 200 µg/L nicardipine: 20 µM	F/M: 200 µg/L: $0.32 \pm 0.06$ , +nicardipine 20 µM: $0.56 \pm 0.06$	97% cord samples glyburide levels< 10 ng/mL. 37% higher than corresponding maternal samples [170]. $0.62 (0.50-0.74)$ [171]	BCRP actively transports glyburide	[172]

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Table 1 (continued)

Drug studied in perfusion	Perfusion parameters*: Time, medium, additives	Concentration of drug added	Transplacental transfer: Fetal transfer rate (FTR) and % of AP, Clearance index (CI: drug CI relative to AP (CL))	Clinical data: <i>In vivo</i> cord-to-maternal plasma ratio	Attributes of placental drug disposition: Substrate for enzyme/transporter. Protein/tissue/system binding	Reference
<b>Antihypertensive agents (4 references)</b>						
<b>Labetalol</b>	Open 60 min. cannulae: 6 Flow: M: 12, F: 8 mL/min	( $\mu$ Cl/mmol)	FTR (% MO): Dependent on albumin level (% albumin): Labetalol: 18.1% (0.02%), 15.9% (4%), Propranolol: 14.3% (0.02%), 21.5% (4%), Atenolol: 6.0%, Celiprolol: 3.1%, Timolol: 20.6%	Labetalol: 0.44, Atenolol: 0.89 [173] Celiprolol: 0.25-0.50 [174]	Albumin binding ( <i>ex vivo</i> 4% albumin): Labetalol: <i>ex vivo</i> 55.5%, <i>In vivo</i> : 59-62% [175]. Propranolol: <i>ex vivo</i> 56.4%, Atenolol: <i>ex vivo</i> 4.6%, Celiprolol: <i>ex vivo</i> 4.2%, Timolol: <i>ex vivo</i> 16.7%.	[46]
<b>Propranolol</b>	QC on fetal-venous recovery	Label: <sup>14</sup> C 25, Propan.: <sup>3</sup> H				
<b>Timolol</b>	7.5/8.0 mL/min	16.6, Atenolol: <sup>14</sup> C 32.6,				
<b>Atenolol</b>	Early <i>s</i> bicarbonate buffer: NCTC medium (1:2)	Celiprolol: <sup>14</sup> C 10, Timolol: <sup>3</sup> H 15.3				
<b>Celiprolol</b>	Closed 60 min.	15.1, 115 & 750 $\mu$ g/mL	CI at 60 min (c.f. antipyrine): 57.9; 30.0 & 40.4%, low to high doses, respectively	1.7 [176]	FTM data strongly suggests and active trophoblast uptake or efflux mechanism into the fetal circulation	[177]
<b>Hydralazine</b>	Flow: M: 17, F: 3-5 mL/min			1.0 [178]	11.3% tissue bound at T=120 min	[179]
<b>Clonidine</b>	Eagle's medium	Closed	CI at 120 min (cf antipyrine): 1.04			
	Krebs-Ringer bicarbonate buffer; 200 mg/L HSA; 10K IU/L					
	heparin; 1 g/L dextran					
	Closed 240-360 min.		23% transferred to fetal circulation at 4-6 h; 59% remaining in maternal reservoir.	0.59	18% tissue binding	[180]
<b>Enalapril</b>	Flow: M: 16, F: 3 mL/min					

Abbreviations: % of AP, percentage of antipyrine transport; AI, accumulation index (concentration of the study drug in the cotyledon (ng/mg) multiplied by the tissue density (1.04 g/mL) divided by the mean maternal concentration of the drug); AP, antipyrine; APP, atypical antipsychotic drug; AZT, 3'-azido-3'-deoxythymidine (=zidovudine); BCRP, breast cancer resistance protein; BSA, bovine serum albumin; c.f., corrected for; CI, clearance index; CL, clearance; C/M, cord blood to maternal blood concentration ratio; F, fetal; F90, fetal concentration at 90 min perfusion; F120, fetal concentration at 120 min perfusion; F180, fetal concentration at 180 min perfusion; F/M, fetal/maternal concentration ratio; FTM, fetal-to-maternal; FTR, fetal transfer rate; HSA, human serum albumin; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; M, maternal; M90, maternal concentration at 90 min perfusion; M95, maternal concentration at 95 min perfusion; M120, maternal concentration at 120 min perfusion; M180, maternal concentration at 180 min perfusion; MRRP1, multidrug resistance-associated protein; MTF, maternal-to-fetal; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PCM, paracetamol; PCM-G, paracetamol glucuronide; PCM-S, paracetamol sulfate; PE, preeclampsia; P-gp, P-glycoprotein; PI, protease inhibitor, TCA, tricyclic antidepressant.

\* Closed vs. open circuit perfusions refers to not recirculating vs. recirculating medium in perfusion experiments.

SSRIs. Transfer studies show that citalopram and the active metabolite desmethylcitalopram transferred at 86% and 50%, respectively, and fluoxetine and its active metabolite desmethylfluoxetine at 88% and 91%, respectively. The absence of albumin in the medium reduced transplacental transfer to very low or no transfer. Paroxetine was studied in a closed-circuit perfusion for 1 h followed by a 3 h wash out phase, a design showing 40% fetal-to-maternal transfer, and allowing modelling of the fetal-compartment half-life, to help determine the avoidance of fetal withdrawal syndrome [27,28].

For bupropion, a non-SSRI and non-TCA type antidepressant, transfer studies showed an equilibrium in the fetal and maternal circuits during the perfusion, with 48% of the drug found in placental tissue and 20% in the fetal circuit. It was also found that the placental tissue metabolized bupropion [29]. Transfer of antipsychotics have not been extensively studied in placenta perfusion, however, for the atypical drug quetiapine the transplacental transfer was 80% of antipyrine diffusion, with no noticeable effect of P-glycoprotein (P-gp) inhibitors [30].

### 3.2.3. Anti-epileptics

The most teratogenic medications prescribed to women of child-bearing age are antiepileptic drugs. Epilepsy affects 0.5–1% of pregnant women. In 2015 more than 24 antiepileptic drugs were in clinical use [31]. For some antiepileptics (phenobarbital, phenytoin, diazepam, carbamazepine, oxcarbazepine, valproic acid) human placental perfusion studies exist. When comparing clinical data with the perfusion results two eminent findings emerge. Firstly, significant transfer of all studied antiepileptics is evident, stressing careful clinical selection of the antiepileptic drug in pregnant patients, also taking into account known teratogenic effects [32]. Secondly, human placental perfusion, especially after adjusting for protein binding, reflects the *in vivo* transfer very well in most cases [33], implicating human placental perfusion as a useful tool in preclinical assessment of new antiepileptics.

Carbamazepine (CBZ) and oxcarbazepine (OCBZ) transfer and metabolism have been studied in two series of 2 h human placental perfusions [34,35]. Transfer of CBZ from maternal-to-fetal side in dual recirculating perfusions was similar to the passively diffusing antipyrine, while transfer of OCBZ was faster. OCBZ was metabolized during the perfusion into 10-hydroxy-10,11-dihydro-carbamazepine. No indications of metabolism of CBZ in perfusion could be found. Transfer of the metabolite was studied separately, and it was slower than that of antipyrine. Both OCBZ and the metabolite accumulated in placental tissue during perfusions. However, *in vivo* no accumulation of OCBZ or its metabolites in fetal blood or placental tissue were found in a consequent study [36].

The observed difference between placental perfusion and *in vivo* data on transplacental transfer of diazepam [37] diminished significantly after adjusting perfusion data for fetal protein binding and blood pH. In 2 h dual recirculating perfusions with either of two different doses (2  $\mu$ g/mL or 200 ng/mL of diazepam) added to maternal circulation, fetal concentration never reached maternal concentration, while the passively diffusing reference compound added at the same time equilibrated between the circulations in 2 h [37]. Both concentrations also lead to accumulation of diazepam into placental tissue.

*In-utero* exposure to valproic acid (VPA) is associated with major congenital malformations and minor anomalies, as well as an increased risk of autism spectrum disorders and impaired cognitive outcome. In one study it was established in a 2.5 h closed circuit perfusion, that VPA transfer was 84.3–97% depending on the concentration tested. The other study determined that VPA may be a substrate for P-gp, and that at therapeutic concentrations VPA affects placental mRNA levels of major carriers for folic acid, glucose, choline, thyroid hormones and serotonin. These findings indicate consequences such as neural damage, fetal growth restriction and hypoglycemia [38,39]. Thus, in addition to human placental perfusion being able to predict *in vivo* transfer through placenta, provided protein binding and ion trapping are taken into

**Table 2**  
Vascular effects studied in the *ex vivo* placenta perfusion system.

Substance	Perfusion parameters*, time, medium, additives	Effect	Clinical findings	Reference
<b>Anti-Hypertensive</b>				
Labetalol	<p>▲Fetal-side flow rate = 4 mL/min</p> <p>Pre-constriction of fetoplacental circulation with 3.3 nM U46619, or 1.8 nM 5HT to 200–250% of baseline FIHP.</p> <p>Antihypertensive doses given for 10 min following achievement of elevated baseline FIHP.</p> <p>Modified Krebs-Ringer solution 10 IU/mL heparin; 40 mg/mL gentamycin; 1 g/L HSA; 8 g/L pluronic F68.</p>	<p>▲Potentiation of U46619 vasoconstriction response; significant lowest dose = 1 µM.</p>	<p>■Mixed study of beta blockers: labetalol, metoprolol, atenolol: 4.3% incidence of neonatal hypoglycaemia; 1.6% incidence of neonatal bradycardia.</p> <p>○Abnormal fetal CTG and FHR during labour; neonatal bradycardia.</p>	<p>▲ [181]</p> <p>■ [182]</p> <p>○ [183]</p>
Magnesium (Mg <sup>2+</sup> )	<p>▲As above ●Krebs-Ringer bicarbonate buffer.</p> <p>◆Krebs solution; fetal-side flow rate = 5 mL/min; baseline FIHP &lt;60 mmHg. Fetoplacental circulation pre-constricted with PGF<sub>2α</sub>.</p> <p>○Fetal-side flow: 4 mL/min; maternal-side flow: 10 mL/min; tissue medium M199</p>	<p>Reduces FIHP following precontraction with U46619▲○ and PGF<sub>2α</sub>◆.</p> <p>●Attenuates fetoplacental vasoconstriction evoked by peroxide-induced thromboxane B2 release.</p>	<p>■Reduces Apgar scores, increases probability of intubation and admission to special care baby unit after delivery and hypotonia</p>	<p>▲ [181]</p> <p>● [184]</p> <p>◆ [185]</p> <p>○ [186]</p> <p>■ [187]</p>
Dihydralazine	<p>▲As above for labetalol</p>	<p>▲Potentiation of U46619 vasoconstriction response; significant lowest dose = 10 µM.</p>	<p>■Fetal bradycardia and reduced fetal growth.</p> <p>○Antepartum fetal distress.</p>	<p>▲ [181]</p> <p>■ [188]</p> <p>○ [183]</p>
Nifedipine	<p>◆Krebs solution; fetal-side flow rate = 5 mL/min; baseline FIHP &lt;60 mmHg. Fetoplacental circulation pre-constricted with PGF<sub>2α</sub>.</p>	<p>◆Reduces FIHP following precontraction with PGF<sub>2α</sub>.</p>	<p>○No effects on FHR or fetal CTG score</p>	<p>◆ [185]</p> <p>○ [183]</p>
Captopril	<p>▲Tyrode solution; pre-constricted with 0.1–1 nM bradykinin.</p>	<p>▲100 nM captopril significantly potentiated the bradykinin-evoked elevation in FIHP in of the fetoplacental circulation.</p>	<p>●ACEIs are long established teratogens, including associations with oligohydramnios-anuria, neonatal hypotension, renal dysplasia, and hypocalvaria</p>	<p>▲ [189]</p> <p>● [190]</p>
Isradipine	<p>○As above for Magnesium (Mg<sup>2+</sup>)</p>	<p>Reduces FIHP following precontraction with U46619○</p>	<p>▲■No adverse obstetric biometry measurements observed</p>	<p>○ [186]</p> <p>▲ [191]</p> <p>■ [192]</p>
<b>General Anaesthetics</b>				
Propofol	<p>Tyrodes solution; heparin 5,000 IU/L;</p>	<p>Reductions in baseline FIHP; dose dependent reduction in bradykinin constriction, but not against angiotensin-II evoked constriction.</p>	<p>Commonly observed hypotensive effects.</p>	<p>[193]</p>
<b>Fetal growth restriction treatments</b>				
Sildenafil citrate	<p>▲Open; Hank's balanced salt solution; fetal-flow: 4 mL/min; maternal flow: 10 mL/min; two maternal cannulae; 2kU/L sodium heparin; 2 g/L BSA; 5 mg/mL gentamycin</p>	<p>▲10 µM sildenafil reduced FIHP by 42% in 2 nM U46619 pre-constricted cotyledons.</p>	<p>●Sildenafil did no prolong gestation or improve birthweight.</p>	<p>▲ [194]</p> <p>● [52]</p>
<b>Preterm birth treatments</b>				
17-hydroxyprogesterone caproate (17-P)	<p>▲Hank's balanced salt solution; 2 g/L BSA; 2kU/L sodium heparin; fetal flow: 4 mL/min; maternal flow: 10 mL/min</p>	<p>▲200 µL of 200 nM 17-P reduced FIHP by over 50% in cotyledons pre-constricted with U46619</p>	<p>■Risk of preterm delivery is significantly reduced.</p> <p>◆No serious DART effects found in a meta-analysis of animal and human studies at patient prescribed doses.</p>	<p>▲ [195]</p> <p>■ [196]</p> <p>◆ [197]</p>

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; BSA, bovine serum albumin; CTG, cardiotocography; DART, development and reproductive toxicology; FHR, fetal heart rate; FIHP, fetal-side inflow hydrostatic pressure; HSA, human serum albumin.

account, placental perfusion can be used to study placental toxicity of antiepileptics.

Lamotrigine has been used in one human placental perfusion study [40]. Two concentrations, 2.5 and 10  $\mu\text{g}/\text{mL}$ , were used in 2 h perfusions. The mean  $\pm$  SD fetomaternal ratio at the end of perfusions was  $0.83 \pm 0.41$  (range 0.73–1.25) with the lower dose used and  $1.26 \pm 0.20$  (range 1.14–1.56). The individual variation in transfer may reflect genetic differences, as it has been found that a number of single-nucleotide polymorphisms (SNPs) were associated with a higher susceptibility to teratogenicity. Only 4.1–6.3% of the added amount of lamotrigine was found in placental tissue after perfusions indicating no placental accumulation [40].

Challier and colleagues studied transplacental transfer and placental accumulation of the enantiomers of vigabatrin (VGB; gamma-vinyl-GABA) in human placental perfusion [41]. They found that in non-circulating 60 min perfusions of solely the maternal side of the placenta, there was no difference in the transfer of the S (active) and R (inactive) enantiomers (each accounting for 50% of VGB). There was very little interindividual variation in the transfer among the five placentas perfused. From 60 to 150 min, they switched to recirculating perfusion with equimolar concentrations of the drug on both sides to study potential active transport. In contrast to leucine, which was actively transported to the fetal side, there was no concentration gradient for either of the isomers. Perfusion fluid samples were collected frequently ( $n = 40$ ) between 95 and 140 min and the mean FTM-ratio for the S enantiomer was 0.91 and for the R enantiomer 0.89 with no statistically significant difference. However, there was a difference in the uptake and accumulation: a higher uptake of S-enantiomer from perfusion medium during open perfusion and selective accumulation of S-enantiomer in the placental tissue was reported. The authors speculate that this could be due to stereospecific binding to a protein carrier at the maternal-placental interface. The data does not indicate any placental metabolism of VGB [41].

In summary, most antidepressants, anxiolytics and antiepileptic pharmaceuticals studied in the placental perfusion system are studied in 1–2 h perfusion and show rapid transport comparable to free diffusion. Some tissue binding is seen, and some effects on placental tissue and placental tissue metabolism, even in the short perfusion time.

### 3.3. Transfer of antihypertensive drugs

Hypertension complicates 1–2% of pregnancies [42]. Hypertensive pregnant women are at a high risk of having a poor pregnancy outcome, with 47% of them developing pregnancy complications; 18.9% with preterm growth restriction and/or pre-eclampsia and an overall rate of new-borns being small for gestational age (SGA) of 31.2%. Antihypertensive drugs are given to pregnant women with chronic hypertension, gestational hypertension and pre-eclampsia to improve pregnancy outcome [43]. Guidelines on antihypertensive drug use during pregnancy aim to limit dosing of the fetus following placental transfer, which is of particular concern given the number of studies indicating negative effects of maternally prescribed antihypertensive drugs on fetal growth, above and beyond the effects of hypertension *per se* [44,45].

Today, commonly prescribed antihypertensive drugs in pregnancy include non-selective  $\alpha$ -/ $\beta$ -adrenoceptor antagonists, such as labetalol; other  $\beta$ -1 selective adrenoceptor antagonists often prescribed to cardiology cases, such as nebivolol and bisoprolol;  $\alpha$ -2 selective adrenoceptor blockers, such as methyldopa and clonidine; and  $\text{Ca}^{2+}$  channel entry blockers, such as amlodipine and nifedipine. Additionally, these drugs are sometimes used in combination for treatment.

There has largely been a deficiency in the consideration of placental metabolism of these drugs as they cross the placental barrier, or their metabolism occurring in the maternal liver. However, the perfusion data in Table 1 offers refined time-lapse information on drug transfer to the fetal circulation in a controlled environment, which clinical cord-to-maternal plasma ratio studies cannot achieve.

A very thorough comparative study of the transfer of a number of adrenergic receptor blockers, with varying specificity for  $\alpha$ - and  $\beta$ -subtypes was performed by Henning Schneider and Mariette Proegler, published in 1988 [46]. It is clear that transfer of these drugs cannot be generally attributed to the albumin binding of the drugs; and the authors conclude that such binding is only weak and these drugs are readily separated from albumin at the placental barrier. For instance, the adrenergic blockers with the highest transfer rates were labetalol, propranolol and timolol; but albumin binding for these drugs are quite diverse, at 59–62%, 85–96% and 10%, respectively [47]. Also, the degree of lipophilicity is similar for timolol (with high transfer rate) and celiprolol (with a low transfer rate), at 1.8 and 1.92 (LogP octanol: water), respectively [48]. Furthermore, the pKa, indicating the pH-dependency of ionisation of the compound, is pretty similar and too high to elicit much ionisation in compounds that exhibited both low and high transfer rates at the physiological pH of perfusion; propranolol and timolol (high transfer rates) and atenolol and celiprolol (low transfer rates) all have similar pKa values (collective strongest acid pKa range is 13.55–14.09; collective strongest base pKa range is 9.60–9.67) [48]. It therefore appears that tissue binding and specificity of drugs for active transporters offer the most likely explanation for differences in transfer rates of these substance across the placental barrier.

## 4. Vascular effects of pharmaceuticals in *ex vivo* placenta perfusions

Few studies investigated the effects of drugs on the vascular tone in the fetoplacental circulation using the *ex vivo* dual perfusion model of the human placenta. Effects on fetoplacental blood flow could impinge fetal growth, having severe consequences for the health of the baby into its adult life [49,50]. It is also a requirement of drug regulators to assess the effects of medicines on fetal size [51].

In Table 2, an overview is presented of vascular effects of drugs studied in *ex vivo* placenta perfusion studies. Studies were conducted in placentas from healthy pregnancies. Many of the drugs listed have vasodilatory effects on the fetoplacental circulation, including magnesium sulfate nifedipine, isradipine, sildenafil citrate and 17-hydroxyprogesterone caproate. In these vasodilation investigation studies, it is necessary to induce some vascular tone within the villous microcirculation, often using a low continuous dose of the thromboxane A2 mimetic, U46619, which has a useful property of causing a stable elevated baseline resistance to flow. Whilst fetoplacental vasodilation may at first seem beneficial to the fetus, as it ensures a good blood flow to meet the fetal demand for fetal growth and development, the clinical observation of sildenafil citrate failing to show an enhancement of growth (the STRIDER study) suggests otherwise [52]. Perhaps a ubiquitous vasodilation of the fetoplacental circulation by vasoactive agents has the potential to work against patterns of efficient flow matching of fetal and maternal blood in this organ. This phenomenon has been proven to be present in the sheep placenta, where fetal blood flow is thought to be directed to specific villi where maternal PO<sub>2</sub> levels are high [53,54]. Other drugs have been found to potentiate the vasoconstrictor effect of U46619. Of particular interest is the unusual constrictor effect of labetalol in the fetal vessels of the perfused placenta. Labetalol is a commonly accepted first drug of choice to treat maternal hypertension. Whilst the fetoplacental circulation is devoid of sympathetic innervation, there is evidence for adrenoceptor expression in the human placental villous vasculature, which requires further investigation [55].

## 5. Conclusion, discussion and future perspectives

*Ex vivo* placental perfusion studies can provide data on placental drug transfer in the human term placenta. The technique allows characterizing compounds with regard to the extent of placental passage, and generally reflects *in vivo* findings. Sometimes there appears to be a



mismatch between *ex vivo* and *in vivo* observations. However, as illustrated in some of the reviewed works and as also noted by others, taking into account protein binding helps reconcile apparent discrepancies between *ex vivo* and *in vivo* findings [33,37]. In doing so, it should be noted that protein binding in the *ex vivo* setting cannot be assumed to be the same as in plasma, as composition of the fetal and maternal perfusates usually differ from human plasma [56]. Therefore, it is recommended that unbound concentrations are assessed in the fetal and maternal perfusate. Discrepancies between *ex vivo* and *in vivo* placental transfer may also occur when compounds have a high degree of partitioning into erythrocytes, as these are also not present in the perfusion medium [57]. On the other hand, discrepancies can be attributed to uncertainties in the clinical data to which the perfusion studies are compared. Firstly, in perfusion experiments sampling of maternal and fetal circulations can be done simultaneously, whereas in *in vivo* studies timing of maternal blood sampling relative to fetal sampling is not synchronized. Secondly, in clinical studies information on timing of cord blood sampling relative to the time of dosing is often missing. This may also impact the cord-to-maternal concentration ratio, and therefore the degree of *ex vivo-in vivo* correlation that is observed.

In our review we noted the diversity of methodologies used, as well as the ways data are presented. A more standardized approach to performing placenta perfusion experiments would help improve reproducibility and comparison of results between laboratories. It could provide a way to obtain reproducible and reliable information on drug disposition across the placenta already in the early phases of drug development, in a post-marketing phase or at any point in the lifecycle of the drug, when it becomes likely that the drug will be used off-label in pregnant women. Systematically conducting placenta perfusion studies for pharmaceuticals within a therapeutic class could therefore rapidly extend the availability of pharmacokinetic data in the pregnancy domain. In this way, the technique could aid to decide which drug is likely to be safest and/or most effective for pregnant women for a given medical indication. This of course holds true for drugs with dreaded teratogenic effects, as for example outlined above for anti-epileptics. In terms of placental effects, perfusion studies can aid in understanding fetoplacental vascular pharmacology, identify compounds with undesired off-target effects on the fetoplacental vasculature or facilitate drug repurposing/drug development for fetoplacental vascular dysfunction.

A future perspective for the field may also be to combine perfusion data with systems pharmacology approaches. Some of the papers listed in Table 1 already employed perfusion data to parameterize physiologically-based pharmacokinetic (PBPK) models [56,58–61]. In PBPK models, *in vitro* and/or *ex vivo* generated pharmacokinetic data is integrated into a mathematical model describing human anatomy and physiology, thus allowing to extrapolate clinical pharmacokinetics. In contrast to classical pharmacokinetic approaches which derive pharmacokinetic parameters from clinical data and are descriptive of nature, the mechanistic basis of PBPK modeling allows to predict a drug's pharmacokinetic profile, prior to conducting clinical trials. *Ex vivo* placenta perfusion data can take a central place when it comes to parameterizing such models [62]. Moreover, the approach can be extended to include vascular placental effects, as well (pharmacodynamics). Several physiologically-based pharmacokinetic and pharmacodynamic modelling platforms are already employed by pharmaceutical industries, and are also well-accepted by regulators as viable approaches for *in vitro-to-in vivo* extrapolation of drug disposition and effects [63]. Integration of the *ex vivo* placenta perfusion technique with systems pharmacology modeling approaches would therefore offer exciting opportunities to further increase the impact of *ex vivo* placenta perfusions studies and improve rational pharmacotherapy during pregnancy in the coming years.

#### Declaration of competing interest

None.

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