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Contribution of the *ex vivo* placental perfusion model in understanding transplacental immunoglobulin G transfer

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A B S T R A C T

Introduction: The acquisition of humoral immunity *in utero* is essential for the fetus. The crucial protein, which is responsible for this part of immunity, is immunoglobulin-G (IgG). Immune functions of IgGs are mediated via the interaction of the crystallizable fragment (Fc) region of IgG with specific Fc γ receptors (FcγRs). However, an atypical FcγR, the neonatal Fc receptor (FcRn), is a key regulator of IgG transfer across the human placenta. During the last four decades *ex vivo* placental perfusion studies have contributed significantly to the study of mechanisms of IgG transfer across the multicellular placental barrier.
Method: A PubMed search was conducted by using specific keywords: placenta, perfusion and IgG to review manuscripts using human placental perfusion to study the transplacental transfer of IgG. Relevant studies found in reference lists of these manuscripts were also added to the review, and references were included that supported or gave nuance to the discussion of the mechanisms of IgG kinetics in the placenta.
Results and Discussion: We found twenty publications on the study of transplacental transfer of IgG using human *ex vivo* placental perfusion, by research groups with partly different settings. This review summarizes knowledge about placental IgG transfer, with a strong focus on the contributions from *ex vivo* placental perfusion studies.

1. Introduction

A crucial role of the human placenta is the selective barrier function between mother and child. Macromolecules are generally not transported via the placenta; the essential exception is IgG, which is transferred across the placental membranes [1]. Studies in rabbits and rodents first described IgG transport *in utero* already in the 1950s and 60s [2,3]. In a human study from 1964, women in the last trimester of pregnancy were injected with radioiodinated IgG, and high levels of labeled IgG were detected in the newborn, showing that the same mechanism was at play in humans [4]. The selective transport of IgG from mother to fetus provides the fetus and newborn with humoral immunity in the early vulnerable stage of life. The receptor responsible was later shown to be the neonatal Fc receptor (FcRn), which was cloned from human placenta in 1989 [5,6]. Since then, it has become clear that FcRn is expressed throughout life in most cells of the body and has a range of important functions, including regulation of IgG serum half-life, IgG transport across epithelial cell surfaces, and regulation of antigen presentation in immune cells, as reviewed elsewhere [7].

The aim of this review is to provide insight into the contribution of the dual *ex vivo* perfusion model in studying IgG transfer and critically appraise the different placental perfusion approaches. Besides cellular models, the *ex vivo* placental perfusion model [8] has provided insights into the mechanism of passive humoral immunity acquisition *in utero* [9–27]. The strength of the perfusion model lies in the functional integrity of the tissue and its cellular barrier function. In fact, essential differences in IgG processing were identified between cell culture and placental perfusion [24,26], and gestational age related transplacental IgG transfer capability in humans was identified from the first trimester onwards [4,28].

This review provides insights into all aspects of IgG transfer in the placenta, with a particular focus on the importance of the *ex vivo* perfusion model. Therefore, we conducted a targeted time-independent PubMed search for primary literature references with *ex vivo* placental

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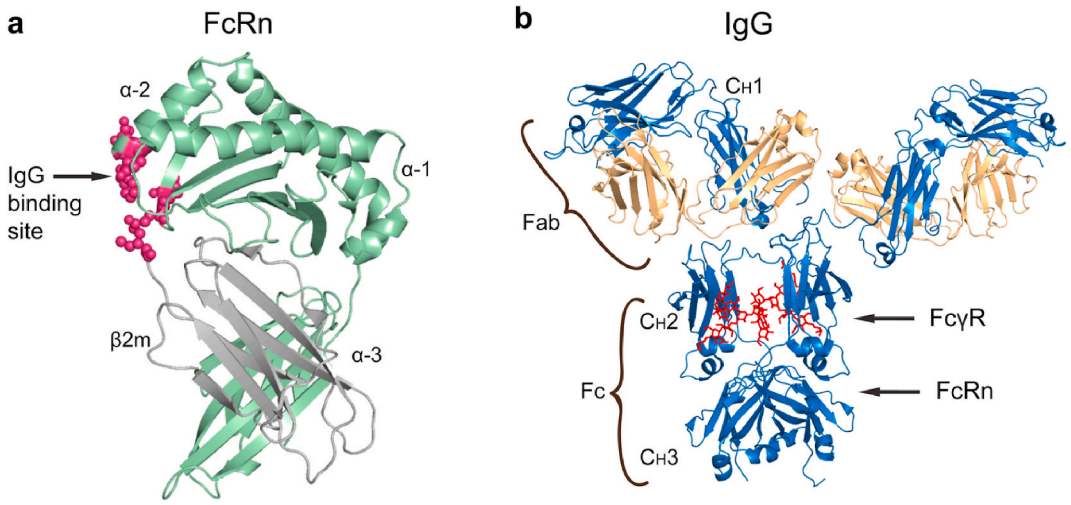

Fig. 1. The structure of FcRn and IgG. Left: Structure of the FcRn heavy chain (green), in complex with β2-microglobulin (B2M) (gray). The binding site for IgG is marked in red. The figure was made using PyMol, and crystal structure data from PDB file 4N0U [38]. Right: Structure of an IgG1 molecule showing the constant (C) heavy chain (H) domains 1–3, and the light chain (yellow). The N-linked glycans are shown in red, and binding site for FcγRs in the upper CH2, and the FcRn binding site in the CH2–CH3 interface of the Fc fragment are indicated. The figure was made using PyMol, and crystal structure data from PDB file 1HZH [[41].

perfusion reference. The used keywords were: placenta, IgG and perfusion. References found in the reviewed literature revealed further studies using the placenta perfusion, which were then included in the review. Furthermore, we supplemented the review with *ex vivo* perfusion-independent literature contributing to the understanding of IgG transfer across the placenta. Importantly, the perfusion studies are carried out using different experimental conditions, depending on the question asked, as well as the preferences of the laboratory where the experiments are being conducted. Thus, we also present methodological approaches and research results that differ between laboratories.

1.1. *FcRn structure, substrate binding, and other FcγRs in the placenta*

FcRn is a non-classical Fc γ receptor (FcγR), which is structurally related to major histocompatibility class I (MHC I) with a 40 kDa heavy chain that is non-covalently associated with the 12 kDa light chain, β2 microglobulin [5,29,30]. The FcRn heavy chain consists of three domains (α1, α2 and α3) followed by a transmembrane domain and a cytoplasmic tail (Fig. 1a). The α1 and α2 domains form a platform of eight antiparallel β-strands with two α-helices forming a groove on top, but unlike MHC I, FcRn is not able to bind antigenic peptides for presentation to T cells because of a narrow groove [29,31]. The receptor is mainly located intracellularly, and FcRn mediated transport across cells is dependent on a pH regulated mechanism, where binding of ligand occurs in endosomes at and below pH 6, but not at neutral pH, favoring release at the cell surface [31–35]. Binding of IgG is dependent on protonation of histidine residues, which occurs at mildly acidic pH. Binding studies following site-directed mutagenesis and inspection of co-crystal structures have revealed that residues Ile253, His310 and His435 in the CH2–CH3 interface of the IgG Fc are crucial for binding (Fig. 1b), and that mutating these residues abrogates FcRn binding at acidic pH [36–38] as well as FcRn mediated transport [39,40].

FcRn with bound IgG are sorted intracellularly, and the two main pathways taken are recycling and transcytosis. The recycling pathway prevents intracellular degradation of bound IgG in lysosomes, and this rescue mechanism forms the basis for the long serum half-life of IgG [34,42–44]. Transcytosis on the other hand, ensures transport across polarized epithelial cell layers, such as placenta, intestine and lung epithelium [39,45–51]. Monomeric IgG and IgG immune complexes can be transported from either the apical or the basolateral side into acidified endosomes, and efficient release from the receptor at the opposite cell surface in response to extracellular neutral pH, is crucial to ensure

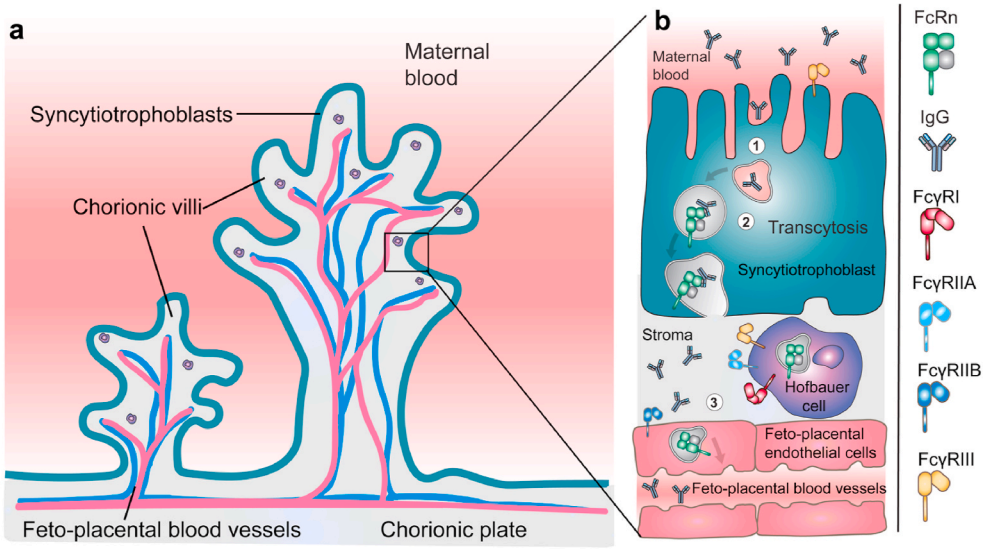

Fig. 2. The cellular barrier of the placenta for IgG transfer. The chorionic villi of the placenta are surrounded by maternal blood, and contain fetal blood vessels. The outermost cell layer of the villi consists of syncytiotrophoblast. Underneath is stroma with Hofbauer cells and the feto-placental endothelium. For IgG to transfer from maternal to fetal circulation it needs to be internalized by the syncytiotrophoblast through pinocytosis (1). Binding to FcRn takes place in acidified endosomes (pH 6.5-5.5) (2). FcRn mediated transcytosis ensures delivery of IgG to the opposite cell surface, where neutral pH triggers release of IgG. The IgG crosses the stroma and is transcytosed also across the feto-placental endothelial cell layer before it enters the fetal circulation (3).

directional transport [52,53]. Molecular details of how transport across the epithelium is regulated have been revealed by studies mainly in model cell lines. Here, transport is regulated by calmodulin, Rab25 and Myosin Vb as well as by N-glycosylation of FcRn [54–56].

Transport from mother to fetus requires that IgG crosses the epithelial cell layer: the multinucleated syncytiotrophoblast formed by cytotrophoblasts fusing, the villous stroma, as well as fetal endothelial cells (Fig. 2). FcRn mediated transcytosis of IgG has been studied *in vitro* using the choriocarcinoma cell line BeWo, cultivated on microporous inserts to achieve cell polarization, which is a model cell line for placenta trophoblasts, and revealed transport in the apical to basolateral direction [45]. Also transcytosis across human placental endothelial cells has been studied *in vitro*, and showed transport preferentially in the basolateral to apical direction [51]. Less is known about how IgG crosses the stroma, which separates these two cell layers. *Ex vivo* placental perfusions provide an important tool for studies on how IgG is transported in intact tissue containing all cell types.

The chorionic villus regulates the exchange of substances in the placenta. This composite structure consists of syncytiotrophoblasts, which are directly in contact with maternal blood, stroma cells, and a highly branched feto-placental vasculature. The stroma is penetrated with tissue resident macrophages, called Hofbauer cells, and capillaries consisting of endothelial cells (Fig. 2a). Functional studies with the *ex vivo* placental perfusion approach carried out in the 1990s showed reduced transfer of bovine IgG compared to human IgG [9,10], and decrease in placental transfer of specific antibodies in the presence of rising levels of human IgG. Together, these set of *ex vivo* studies suggested a shared and saturable transfer mechanism of IgG that was later proven to be mediated by FcRn [13,15–17].

FcγRs are also expressed in the placenta, and their involvement in transplacental transport of IgG has been addressed in several studies [57–61]. FcγRI, FcγRII and FcγRIII are all expressed in Hofbauer cells [62,63]. In addition, FcγRIII is expressed in syncytiotrophoblasts, and the inhibitory FcγRIIB in fetal endothelium [62,63]. In contrast to FcRn, FcγRs are expressed on the cell surface, bind IgG at neutral pH, thus actively internalizing IgG. IgG variants that lack FcγR binding are transported from maternal to fetal circulation in *ex vivo* placental perfusion studies, demonstrating FcγR binding independent transport to the fetus [24].

N-glycosylation of IgG, at N297, is required for binding of classical FcγRs, and the attached N-glycans participate in binding [64]. Recent work revealed that FcγRs are selecting the fetal transported IgGs depending on attached N-glycan structures. Jennewein et al. used systems serology to define IgG Fc features associated with antibody transfer [59]. In particular, they revealed a transport preference for antibodies that activate NK cells due to increased affinity for FcγRIII and FcRn, explained by IgG Fc N-glycosylation patterns. In particular, digalactosylated IgGs showed increased transplacental transport. In line with this are reports describing higher concentration of digalactosylated IgG in infants [65–67]. Interestingly, other studies have concluded that there are no links between IgG N-glycosylation and placental transport [61,68,69]. Borghi et al., studied paired maternal-fetal samples and reported no differences in IgG1 and minimal differences in IgG2 Fc N-glycan profiles. They also found that galactose on the Fc N-glycan on IgG1 did not alter FcRn or FcγRIIIa binding [61]. Bakchoul et al. showed that complete absence of N-glycosylation did not affect transplacental transport in mice [68]. Einarsdottir et al. performed glycoanalysis of fetal IgG molecules and could not find accumulation of a specific glycoform [69]. Fc N-glycosylation may modulate FcRn binding through inducing structural changes of the Fc, and digalactosylated IgG were shown to have increased binding compared to deglycosylated IgG [59,70]. Although FcRn is the only receptor that is indispensable for IgG transplacental transport, it is interesting that classical FcγRs may modulate transport. Clearly, conflicting data exist, and future studies should continue to address how these receptors orchestrate passive immunization and shape the immune system of the fetus and newborn.

1.2. Transplacental transfer of IgG

Placental transfer of IgG progresses throughout the pregnancy with little transfer in the first trimester [71]. IgG levels may be as low as 5–10% of maternal levels at the onset of the second trimester, but rises to 50% before the beginning of third trimester [72]. The rate of IgG transfer is high in the third trimester, and particularly from gestational week 36 onwards. At term, infant IgG level typically exceeds the maternal level [1,72,73]. Lozano et al. recently reported that IgG transport correlates well with FcRn expression by studying IgG concentration in maternal and fetal serum samples and comparing these to immunohistochemistry analysis of FcRn expression in the placenta [74].

IgG is the only class of antibodies that is transported across the placenta [1]. Of note, maternal IgG antibody levels negatively correlate with maternal to fetal transfer ratios of IgG subclasses and neonatal levels of total IgG and IgG subclasses seems largely unaffected by maternal factors [75]. The relative serum abundance is roughly 60% IgG1, 32% IgG2, 5% IgG3 and 3% IgG4, and of the four IgG subclasses IgG1 and IgG4 are transported readily, whereas IgG2 and IgG3 show somewhat less transplacental passage in *ex vivo* perfusion [14]. For IgG3, the lower transplacental transport can be explained by reduced FcRn binding due to an arginine in position 435 for most allotypes. An IgG3 allotype with a histidine in position 435 shows half-life similar to that of IgG1, and is efficiently transported across the placenta [76,77]. For IgG2 however, the lower concentration found in cord blood cannot be explained solely by FcRn binding properties, as IgG2 has similar affinity for FcRn as IgG1 [78]. A recent report showed that IgG2 is transcytosed less efficiently by FcRn [79]. The reduced transport is due to a missing glycine (G236) which gives IgG2 a shorter and less flexible hinge compared to IgG1 and IgG3. Recent work has also shown that FcRn binding is modulated by the Fab regions of IgG [80–84], which could lead to different FcRn mediated transport properties of IgGs with various V regions.

Placental transfer in *ex vivo* perfusion of the Fab fragment abicimab was reported [18], which is in contrast to a study with the PEGylated Fab fragment certolizumab [25]. How Fab fragment transfer across the placenta could be mediated has so far not been studied. Furthermore, IgG1 antibodies that were mutated so as to show reduced binding to FcγRs and C1q, also show reduced FcRn binding and transplacental transport properties [19,26]. As such, these are examples of how IgG Fc mutations can affect FcRn binding and placental transport even if the amino acid substitutions are distant from the actual FcRn binding site.

To what extent IgG immune complexes cross the placenta has been less studied, but Malek et al. reported that concentrations of tetanus antigen and tetanus specific IgG in fetal blood closely fit the ratios found in the mother, which suggests transport of the complexes [85]. With subsequent experiments, they confirmed the placental passage of tetanus antigen in the presence of tetanus specific IgG [12]. In line with this, *Plasmodium falciparum* merozoite surface protein 1 could be detected in complex with IgG in cord blood, and the complex was transported from maternal to fetal circulation in *ex vivo* placental perfusion studies [11].

Of note, mimicking maternal-fetal transport in FcγR/FcRn humanized mice confirmed that only FcRn contributed to transplacental transport of IgGs [61]. These findings argue conclusively against a dominant role for FcγRs in IgG transplacental transfer, suggesting Fc engineering of maternally administered IgG antibody to enhance only FcRn binding as a means to improve maternal-fetal transport of IgG.

1.3. The contribution of the ex vivo placental perfusion model

The human *ex vivo* placental perfusion studies included in this review are presented in Table 1. These studies demonstrate the use of placental perfusion to study transplacental transfer of wild type IgG antibodies (n = 11), therapeutic IgG antibodies (n = 5), and antibody fragments (n = 4).

Table 1
Perfusion methods used to study the transfer of antibodies and derived fragments. Unless otherwise stated, the method used was dually perfused placental lobule in closed loop perfusion.

Antibody/Substrate	Results	Method	Medium	Control parameters	Publication
Wildtype IgG antibodies					
^{125}I-human or bovine IgG. 0.5 mg, cpm: 2.04 ± 0.96x 10^7 or 7.51 ± 0.13x 10^7.	2.5-fold difference in human (n = 6) and bovine (n = 5) IgG transfer (0.25% and 0.1%/2h)	Five maternal cannulae. 2h perfusion.	Fetal blood and Earle's solution adjusted to hematocrit 20%.	pH and pO_2 and pCO_2 kept within physiological range.	Contractor 1983 [10]
[^{3}H]-IgG: 1.4 × 10^3cpm	The transfer of IgG showed a rapid initial uptake, and levelled out after 30 min in both entrance in and exit from villous capillary bed (n = not reported). Receptor binding kinetics calculated.	One maternal cannula. 1h open circuit perfusion.	Buffered saline, 2 mM PMSF to protect ligand against proteolysis. Flow rate F5 and M2.5 ml/min,	Fetal arterial pressure 40–50 mmHg.	Lubega 1990 [20]
IgG-HRP: **1 mg/ml.**	Uptake and intracellular routing of IgG suggests a receptor mediated pathway through syncityotrophoblast (n = 2 for each condition). Perfusion with bovine IgG-HRP: No reaction product observed on microvilli or intermicrovillous spaces after 10 min and no uptake.	Isolated lobule fixed in perfusion chamber, maternal perfusion clamped 2.5 cm not restricting the fetal perfusion. 30 min preperfusion. 10, 20, 30 or 60 min perfusion. Examined ultrastructuraly. 2 per experimental condition.	TC199, 8 g/l dextran, dye (0.5 mg/ml Evan's blue-albumin complex). Flow rate 5.0 ml/min. Gas 95%O_2/5%CO_2.	Fetal arterial pressure <30 mmHg	Leach 1990 [21]
IgG **5–10 g/l,** IgG including anti-PI^{A1} 1:4 5 g/l, IVIG 5 and 20 g/l. Washout procedures reduced the IgG levels in the maternal and fetal circulations to 0 pg/ml at time 0 h.	IgG transfer rate 6–7 μg/h, lag time 2–3 h. IVIG transfer rate 5–6 μg/h, lag time 3–4 h, no difference between initial concentration 5 or 10 g/l or 5 and 20 g/l. No transfer of IgG anti-PI^{A1} 5 g/l with simultaneous perfusion of IVIG 20 g/l. The IgG transferred was entirely IgG1 subclass (n = 2 for each condition). Endogenous IgG rapid rise in fetal circulation in the first 2h with plateau after 3h at 5–16 pg/ml.	Placenta mounted in perfusion apparatus. Two maternal cannulae, Experimental phase 6h.	M 199, heparin (25 IU/ml), glucose (2 g/l) and dextran (fetal 29 g/l, maternal 7.5 g/l). M150mL, F100mL. Flow rate F3.0 and M25.0 ml/min Gas M 95%O_2/5%CO_2, F95% N_2/5%CO_2.	Placental consumption of glucose and oxygen and the production of lactate and human placental lactogen. The initial oxygen tension in Fv/Fa of 90 mmHg.	Morgan 1991 [15]
IgG four subclasses: **6-9 g/l.** Endogenous IgG washed out during preperfusion.	All IgG subclasses transferred. Preferential transfer for IgG1. **0.5%/6h** (n = 4). Endogenous IgG reached M60-80 mg/l F29 mg/l during control phase.	Placenta mounted in perfusion apparatus. Three or four maternal cannulae. 30 min open flushing phase, 2h preperfusion. 2–5 h perfusion.	NCTC-135 with Earl's balanced salt solution (2:1) 130 ml, glucose (2 g/l), dextran 40 (10 g/l) heparin (2500 IU/l) clamoxyl (250 mg/l)^{14}C-BSA (10,000–30,000 disintegrations/min per ml) 6 g/l. Flow rate F4-6.0 and M12.0 ml/min. G gas M + F95%O_2/5%CO_2.	Fetal volume loss <4 ml/h, low fetal arterial pressure <20 mmHg indicated intact cotyledon, creatinine and antipyrine permeability.	Malek 1995 [14]
Anti-D IgG 6.7 g/l, IVIG 12.77 g/l, Anti-D IgG + IVIG 32.23 g/l	The two forms of IgG antibody interfered with the movement of the other (n = 3 for Anti-D and n = 5 for IVIG).	Placenta mounted in perfusion apparatus. Four maternal glass cannulae. 1h open preperfusion. 5 h perfusion	Phenol red and L-glutamin free RPMI, 3% dextran, gentamycine 12 mg/l, co-trimoxazole 80 mg/l, in fetal circuit; 10UI heparin, 2% BSA after 60 min Flow rate F6.0 and M20.0 ml/min. Gas M 95%O_2/5%CO_2, F95% N_2/5%CO_2.	High degree of fetal venous return, glucose consumption, progesterone production.	Duncan 1995 [13]
IgG anti-D therapeutic levels: **6.5 g/l (n = 4), 11.2 g/l (n = 3), 26.2 g/l (n = 4).** IVIG 4.5g, 6g. Total IgG level within physiological range. Corrected for release of endogenous IgG.	Transport rate of IgG characterized in mathematical models. IgG complexing with perfusate materials is described. IgG: 18.3 ± 8.6 mg/l (n = 4), 58.4 ± 27.0 mg/l (n = 3), 66.0 ± 35.0 mg/l (n = 4), **(0.28, 0.52, 0.25%/5h)** Most endogenous IgG washed out in 1h open preperfusion.	Placenta mounted in perfusion apparatus. Four maternal cannulae. 1h open preperfusion. 5 h perfusion	RPMI 200 ml, L-glutamin, 3% dextran, gentamicin 12 mg/l, co-trimoxazole 80 mg/l, 10UI heparin. 12.9 g/l BSA in fetal circuit Flow rate F6.0 and M20.0 ml/min. Gas M 95%O_2/5%CO_2, F95% N_2/5%CO_2.	High degree of fetal venous return, glucose consumption, progesterone production.	Urbaniak 1997 [16]
IgG: 6–10 g/l incl: anti-TT-IgG: 21–25 mg/l, TT-AG: 0.19–0.24 mg/l, IgA:	Maternal levels 85–90% of starting concentration. Fetal concentration of IgG linear	Placenta mounted in perfusion apparatus. Three or four maternal	NCTC-135 tissue culture medium with Earl's balanced salt solution (2:1) 130 ml	Fetal volume loss <4 ml/h, low fetal arterial pressure <20 mmHg,	Malek 1997 [12]

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Table 1 (*continued*)

Antibody/Substrate	Results	Method	Medium	Control parameters	Publication
0.13–0.19 g/l. IgG-BT 2 g/l and ^{14}C-BSA: 30–40 nCi/ml. Control experiments studying washout of IgG and IgA from placenta.	rise, IgA and ^{14}C-BSA no increase in last 3–4 h. Fetal IgG-BT different from IgG and resembled curve for ^{14}C-BSA. TT-AG showed similar transport to anti-TT-IgG. FM-ratio: IgG: **0.46**–**0.49%**, IgA: 0.01%, ^{14}C-BSA: 0.12%, TT-AG: 0.48% (n = 8). Washout with stable levels after 2 h: IgG: M = 115 mg/l and IgA: M = 25 mg/l in fetal system levels 5 (IgG) and 1000 (IgA) times lower.	cannulae. 2h preperfusion. 4–6h perfusion.	glucose (2 g/l), dextran 40 (10 g/l) heparin (2500 IU/l) clamoxyl (250 mg/l)' BSA 4%. Flow rate F4-6.0 and M12.0 ml/min. Gas M atmospheric gas F95% O_2/5%CO_2.	glucose consumption, lactate production, hormone release (HPL and HCG).	
HIVIG, IVIG, Endogenous IgG washout.	Maternofetal HIVIG transfer inhibited by 1h perfusion with IVIG. Majority of endogenous IgG washed out of the placenta in 30 min (N = 9)	Lobule placed maternal side up. Two maternal catheters. Closed circuit perfusion 1–5h or open circuit 1h.	Phenol red free tissue culture medium 100 ml, sodium bicarbonate pH M7.4 F7.35, heparin (20u/ml), glucose(2 g/l), dextran (M7.5 g/L F30 g/l). Flow rate F3.0 and M15.0 ml/min. Gas F95%O_2/5%CO_2 M 95% N_2/5%CO_2.	Perfusion within 20 min of delivery. Fetal volume loss <2 ml/h, fetal arterial pressure <70 mmHg, pO2 difference Fv/Fa >60 mmHg, biometric measures within range.	Landor 1998 [17]
I^{125} IgG1 H435A lower affinity for FcRn 3 mg/150 ml medium: **20 μg/ml**. 400-fold excess (1.2g) unlabeled human IgG.	Transfer rate of IgG1 H435A decreased from 0.41 to 0.04%/h by excess unlabeled IgG (3h). Labeled IgG1 transfer **1%/3h** (n = 2) **0.3%/3h** (n = 2).	Three maternal catheters. 15–30 min preperfusion, 1h open perfusion with antipyrine. 3h perfusion with I^{125}IgG, unlabeled IgG added after 90 min.	EMEM 150 ml, 3% BSA. Flow rate F4.5 and M17.0 mL/min.	Antipyrine 5 mM 40% transfer rate in open loop perfusion.	Firan 2001 [22]
10 or 25% immune plasma containing anti-MSP1 IgG antibodies. malaria antigen rMSP1$_{42}$ **1 μg/ml**.	**0.3**–**0.5%** of total MSP1 transferred across placenta when adding immune plasma. No transfer when IgG antibodies not present (n = 6).	Placenta mounted in perfusion apparatus. Three maternal catheters. 30 min open washing phase, 1h pre-perfusion. Three phases perfusion 120 min each, 30 min washout before each.	NCTC 135 in Earls buffer (1:3) 140 ml, 4% albumin, 0.2% glucose, 1% dextran 40, 2500 u/l heparin 250 mg/l clamoxyl. Flow rate F4 and M12 ml/min. Gas F95%O_2/5%CO_2 M atmospheric gas.	Fetal volume loss <4 ml/h, fetal arterial pressure 25–40 mmHg, glucose consumption, lactate production, hCG release, creatinine, erythropoietin permeability. Antipyrine permeability >0.04 ml/min x g.	May 2009 [11]
Therapeutic IgG **antibodies**					
Monoclonal anti-D (Fog1G1), or (Fog1G1 Δ nab) with modified Fc region to abrogate FcγRI, II and III binding, FcRn binding intact. **5 mg** in maternal circuit.	%Tf for Fog1G1 **0.36 ± 0.17** and for Fog1G1 Δ nab 0.06 ± 0.02 (n = 8, mean ± SEM, respectively). The hourly increase in Tf was significantly lower for Fog1G1 Δ nab.	Placenta mounted in perfusion apparatus. Four maternal glass cannulae. 1h open preperfusion. 5 h perfusion for endogenouse IgG washout	Phenol red and L-glutamin free RPMI, 3% dextran, gentamycine 12 mg/l, co-trimoxazole 80 mg/l, in fetal circuit; 10UI heparin, 2% BSA after 60 min Flow rate F6.0 and M20.0 ml/min. Gas M 95%O_2/5%CO_2, F95% N_2/5%CO_2.	High degree of fetal venous return, glucose consumption, progesterone production.	Armstrong-Fisher 2004 [19]
Two nicotine specific IgG antibodies (mouse monoclonal Nic, K_d 60 nM, rabbit Nic-IgG, K_d 1.6 nM): **50 μg/ml.**	Placental transfer mouse-Nic (0.07 μg/mL = **0.14% 4h**, n = 6) and rabbit-Nic-IgG (0.06 μg/ml = **0.12% 4h**, n = 3) IgG antibodies bound nicotine, reducing fetal nicotine exposure.	Lobule placed maternal side up. Two maternal catheters. 2h pre-perfusion. 4h perfusion.	M199, sodium bicarbonate pH M7.4 F7.35, 40 mg/l gentamicin sulfate, 80 mg/l sulfamethoxazole, 16 mg/l trimethoprim, M7.5 g/l F30 g/l dextran. Flow rate F2.8 and M12.0 ml/min. Gas F95%O_2/5%CO_2 M 95% N_2/5%CO_2,	Fetal volume loss <2 ml/h, fetal arterial pressure <50 mmHg, pO2 difference Fv/Fa >60 mmHg, hCG release. Antipyrine 20 μg/mL F50% 4h.	Nekhayeva 2005 [9]
I^{125} or biotinylated wild type IgG1 and HN-mutant (H433K/N434F, higher affinity for FcRn): 3 mg/150 ml medium: **20 μg/ml**.	HN-mutant improved transport relative to wild type IgG1 in assays of human FcRn function: placental transfer rate: 0.091/h vs **0.051/h** (n = 3).	Three maternal catheters. 15–30 min preperfusion, 1h open perfusion with antipyrine. 4h perfusion.	EMEM 150 ml, 3% BSA. Flow rate F4.5 and M17.0 mL/min.	Antipyrine 5 mM 40% transfer rate in open loop perfusion.	Vaccaro 2006 [23]
2 mutated human IgG3 antibodies: IgG3ΔHinge (hinge deletion and C131S point mutation eliminate complement activation and binding to FcγRs and C1q, IgG3ΔHinge:R435H added single point	Placenta perfusions: IgG3ΔHinge: R435H = wild type IgG1 = wild type IgG3>>>IgG3ΔHinge. Wild type transport: **0.1%/6h.** Endogenous IgG in maternal and fetal systems: 800 and 30 μg/ml (n = 16).	Lobule placed maternal side up. Two maternal catheters. 300 ml maternal open washing phase, 1h closed pre-perfusion. 6 h perfusion.	RPMI 100 ml, L-glutamin 200 mM, penicillin 200 IU/ml, streptomycin to 0.05 mg/ml, heparin to 25 IU/ml, HSA M 30 g/l and F 40 g/l. FITC dextran 40kD in fetal reservoir. Flow rate F3.0 and M12.0 ml/	Fetal volume loss <3 ml/h Antipyrine 100 μg/ml transfer FM ratio >0.75 2h.	Mathiesen 2013 [24]

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Table 1 (*continued*)

Antibody/Substrate	Results	Method	Medium	Control parameters	Publication
mutation (R435H): **10 μg/ml.** Transplacental transport compared with wild type IgG1 and IgG3.			min Gas F95%O_2/5%CO_2 M 80% N_2/20%CO_2,		
G1Δnab (Human IgG1 with reduced binding to FcγRs and C1q): **30 μg/ml.** Transplacental transport compared to wild type IgG1.	Placental perfusion transfer rate lower for G1Δnab than wild type IgG1 (<0.1% vs **0.4%/4h)** (n = 16 and n = 12)**.**	Placenta mounted in perfusion apparatus. 1h open pre-perfusion. 4h perfusion.	RPMI 200 ml, L-glutamin, 3% dextran, gentamicin 12 mg/l, co-trimoxazole 80 mg/l, 10UI heparin. 12.9 g/l BSA in fetal circuit. Flow rate F6 and M20 ml/min Gas F95%O_2/5%CO_2 M 95% N_2/5%CO_2.	Fetal venous return, glucose consumption, progesterone production.	Stapleton 2018 [26]
Antibody-fragments					
ReoPro (abciximab, Fab fragment human-murine chimeric monoclonal antibody) binds to glycoprotein IIb/IIIa receptors on human platelets inhibiting aggregation 3 μg/ml/0.3 μg/ml. IgG (F105) **at trace levels** (100 μg protein)	No ReoPro detected in fetal samples, 6h, >12h (3 × 4h) detection limit 3.9 ng/ml (<0.013% 13.5h n = 4, 6h n = 3).^{125}I-IgG-F105 (**0.55 ± 0.26% 6h** n = 3)	Lobule secured in a plexiglass chamber maternal side up floating on phosphate buffered saline. Two maternal catheters. 2h pre-perfusion. 3 × 4h perfusion or 6h perfusion.	M199 240 ml, sodium bicarbonate pH M7.4 F7.35, glucose 2 g/l, 40 mg/l gentamicin sulfate, 80 mg/l sulfamethoxazole, 16 mg/l trimethoprim, M7.5 g/l F30 g/l dextran. Inulin (5 μl), tritiated water (10 μl). Flow rate F3.0 and M12.0 ml/min. Gas F95%O_2/5%CO_2 M 95% N_2/5%CO_2,	Fetal volume loss <2 ml/h, fetal arterial pressure <70 mmHg, biometric measures within range.	Miller 2003 [18] Centocor Inc. USA
Certolizumab pegol (CZP) (lacks Fc-region): **200 μg/ml.** Control substance anti-D IgG1	CZP placental transfer was below LOQ for 5 out of 6 perfusions, the sixth was 0.46% (with signs of capillary breakdown). Anti-D IgG1 (**0.41 ± 0.24%/4-6h (13h)** n = 6).	Placenta mounted in perfusion apparatus. >30 min open pre-perfusion. 4–6h perfusion, -one 13h.	RPMI L-glutamin 200 ml, dextran, antibiotics, 0.363g/200 ml BSA in fetal circuit. Flow rate F6 and M20 ml/min. Gas F95%O_2/5%CO_2 M 95% N_2/5%CO_2.	Fetal venous return 84–97%, oxygen consumption.	Porter 2016 [25]
Adalimumab (monoclonal IgG1): **270 μg/ml** M281 (IgG1 anti-FcRn blocks FcRn): 10 or 300 μg/ml represent serum levels in phase 1 study.	Transfer rate of adalimumab (**0.23 ± 0.21%/6h**) decreased by adding M281 10 [n = 3] or 300 μg/ml [n = 5] to 0.07 ± 0.01% and 0.06 ± 0.01%. IVIG 6700 μg/ml similar inhibitory effect. [n = 5] Transfer rate of M281 was 0.002 ± 0.02%. [n = 25]	Lobule placed maternal side up. Two maternal catheters. 1h open pre-perfusion. 6h perfusion.	Medium with 3 mg/ml BSA, dextran, gentamicin sulfate, heparin and sodium bicarbonate in materials list. Flow rate F3.0 and M12.0 ml/min. Gas F95%O_2/5%CO_2 M 95% N_2/5%CO_2.	Fetal volume loss <2 ml/h, oxygen transfer. Antipyrine 100 μg/ml transfer 35% in 2h.	Roy 2019 [27] Momenta Pharmaceuticals

Tissue culture medium: RPMI, NCTC, EMEM, M199, TC199.
Abbreviations: anti-TT-IgG: anti tetanus IgG, BSA: bovine serum albumin, cpm: counts per minut, F: fetal, Fv/Fa: Fetal vein/fetal artery, HIVIG: IgG to human immunodeficiency virus, HRP: horseradish peroxidase, HSA: human serum albumin, IgG-BT biotinylated IgG IgG-HRP: horse radish peroxidase labeled IgG, IVIG: intravenous IgG, KI: Potassium iodine, M: maternal, PMSF: phenylmethylsulphonyl fluoride, Tf: transport fraction, TT-AG: tetanus antigen.

The dually perfused placental lobule method has been used to study transplacental antibody transfer since 1983, where radioiodide labeled IgG was studied in human placental term perfusion for 2 h [10]. Since then, around seven different groups in the US, UK, Australia and Denmark have investigated different labeled and unlabeled IgGs, both wild type and mutant monoclonal antibodies as well as Fc-fragments [11,15,21,22]. The placental perfusion model has also been used to study FcRn binding of different pharmaceuticals [18,25–27].

The dependency of placental IgG transfer on FcRn was corroborated by extended perfusion studies where an IgG variant with abrogated binding to the receptor (H435A) failed to cross the tissue [22]. Additionally, transplacental transport could be enhanced in *ex vivo* perfusion experiments by engineering IgG for improved binding to FcRn at acidic pH [23]. It was recently also shown that an anti-FcRn antibody, which blocks the IgG binding site of the receptor can effectively reduce IgG1 transport to the fetal circulation in perfusion experiments [27], which also supports the role of FcRn as the major receptor for IgG transfer across the placenta. In addition, sections of perfused placentas studied with electron microscope showed HRP-labeled antibodies distributed in the syncytium, in proximity to Hofbauer cells and fetal endothelium [21]. Additional analyses confirmed expression of FcRn in syncytiotrophoblasts, fetal endothelium and Hofbauer cells using both biochemical techniques and immunofluorescence on human placental tissue [74,86–89].

The placental perfusion techniques vary with regard to equipment and experimental details. The placement of the placental lobule can either be done by mounting the whole placenta in the perfusion apparatus, or by severing the perfused lobule and placing it with the maternal side up in a smaller perfusion chamber. The medium used in the recent studies is a tissue or cell culture medium, mixed with antibiotics, buffer and dextran or albumin to increase viscosity [8,10,19,21]. Only two earlier studies used buffered saline [6,22]. Some studies have also reported addition of plasma or fetal blood [10,11,16]. To keep physiological oxygen levels, and establish oxygen transfer across the placental membranes from maternal to fetal side, the medium in the fetal and maternal reservoirs is gassed with 95%N_2/5%CO_2 and 95%O_2/5%CO_2 or atmospheric air, respectively. The circulations are re-established in both maternal and fetal tissues with flow rates ranging from 2.8 to 6 ml/min in the fetal and 12–25 ml/min in the maternal circulation, with the use of one to five maternal cannulae. The most frequently used flow rates are fetal flow rate 3 ml/min with maternal flow 12 ml/min [10,13,21] and fetal 6 ml/min with maternal flow rate 20 ml/min [11,12,18].

Before adding IgGs or derived fragments of interest, the placental lobules may comprise endogenous antibodies, which are washed out of maternal, and fetal tissues in open perfusion where the medium is not recirculating. This is reportedly done for 30 min to an hour [14,16,17]. After the washing phase, a pre-perfusion is performed with recirculating media for 30 min to 2 h to establish a stable system with even

temperature, oxygen transfer and placental metabolism. Hereafter, the experimental phase with a closed perfusion of two to six and up to 13 h are performed. In the experimental phase, the test-substances are added, together with substances to control for fetal-maternal perfused tissue overlap, such as antipyrine or creatinine, and some studies have also added a wildtype IgG to compare normal antibody transport to the transport of an engineered pharmaceutical one. Other studies also add excess unlabeled human IgG/intravenous immunoglobulin (IVIG) to study receptor inhibition and receptor binding affinity. In one study investigating FcRn binding kinetics, a 1 h open perfusion was performed [20].

The viability criteria of the perfused placenta, and thus the control for a successful perfusion, also differ between groups. Most often, the quality of the fetal tissue is evaluated by fetal volume loss/fetal leak of <2–4 ml/h. Also, a sufficient overlap of maternal and fetal perfusion measured by the rapid equilibrium of antipyrine in maternal and fetal circulation is required. Some studies also measure fetal arterial back pressure, and report that it should be below 40–60 mmHg, along with fetal oxygen uptake or placental glucose consumption or lactate and hormone production.

The mean transfer of IgG across the placenta in human placental perfusion ranges from 0.1 to 0.5% found in fetal system after two to 13 h, averaging around 0.3% after 5–6 h [12,14,16,18,19,24,25,27]. The transport rate is the fetal concentration as compared to the added concentration in the maternal reservoir. In perfusion studies, a feto-maternal ratio (FM-ratio) can be reported, at each measured time-point throughout the perfusion. When studying transport of antibody or antibody fragments, the transfer is low, as measured in actual numbers (around two per thousand), and small differences in the maternal concentration have a great impact on the FM-ratio, which makes it difficult to interpret the results.

Furthermore, the difference between the highest and lowest amount of a given IgG transported in separate perfusions is large and reflects the biological variability in transport across an intact human organ such as placenta. In line with this, an important finding from these perfusion studies performed at different continents and over decades, using different techniques, is that the intra-study variation is greater than the inter-study variation. However, investigations of mutated antibodies include a control antibody, which enables comparison of IgG1 transfer between different studies and laboratories. Performing transport studies of designed and physiological IgG and their derivatives in undamaged human placental tissue allows for direct interpretation of data from an intact complex human organ. However, complexity, training of highly skilled researchers, and the collaboration with hospitals and access to placentas directly after birth hinders high experimental throughput.

1.4. Transport of maternal vaccination-induced IgG and autoantibodies

Vaccination during pregnancy protects infants from infection due to efficient transplacental transport of maternal vaccination-induced IgG. A number of vaccines including tetanus, pertussis and influenza are now routinely offered to pregnant women in many countries [90]. Randomized controlled trials have shown that infants of influenza vaccinated mothers are 45–63% less likely to have episodes of influenza illness in early infancy (4–6 months of age) [91]. Furthermore, maternal vaccination with a pertussis-containing vaccine results in high disease specific IgG levels in the infant during the first two months of life [92]. SARS-COV-2 vaccinations resulted in sufficient gestational age relevant transferred IgG concentration comparable to states of disease [93,94]. Nevertheless, placental transfer of SARS-COV-2 specific IgG was expected to be higher which may either reflect lack of viremia and/or reduced expression of placental angiotensin-converting enzyme 2, both acting as protective mechanisms against vertical transmission [95,96].

Likewise, FcRn-mediated transplacental transport of IgG can be utilized to deliver therapeutics. One study showed placental transport of an active enzyme to treat lysosomal storage disease *in utero*. This study was performed in mice, and the enzyme fused to the Fc part of IgG alleviated symptoms related to lack of the enzyme [97]. Studies in mice have also shown transplacental delivery of Fc fused to preproinsulin and coagulation factor VIII [98,99], and holds promise for *in utero* delivery of therapeutics also in humans. It should be noted that in rodents the majority of IgG transport *in utero* occurs via the yolk sac, which is different from humans since the yolk sac disappears in the human by circa week 10 and IgG transfer is thereafter only via the chorioallantoic placenta. The differences in placental transport and physiology makes placenta transport studies using human tissue preferable compared to studies in rodents. To transform placental transfer studies from laboratory animals to humans is challenging, which is supported by the fact that numerous species-dependent toxic effects are described in literature [100].

FcRn does not discriminate between IgGs with beneficial and hazardous specificities. Thus, maternal auto- and alloantibodies can be transported across the placenta and be harmful to the fetus. An example is neonatal alloimmune thrombocytopenia where fetal platelets express paternal human platelet antigens that the mother lacks. As a result, maternal IgG directed towards fetal platelets are transported across the placenta and induces severe neonatal thrombocytopenia, which may further lead to major bleeding and particularly intracranial hemorrhage [101,102]. In mothers with systemic lupus erythematosus, autoantibodies directed towards nuclear antigens cross the placenta and causes neonatal lupus erythematosus. The most severe consequence is congenital heart block which is associated with significant morbidity and mortality [103]. In these cases, blocking FcRn mediated transfer of pathogenic antibodies is beneficial. Several FcRn binding molecules that block the IgG binding site of FcRn have been developed and entered clinical trials [104–108]. The concept was proven using the *ex vivo* placental perfusion approach, showing that one such anti-FcRn antibody, M218, could prevent IgG transport to the fetal circulation [27]. Furthermore, Momenta Pharmaceuticals has announced fast track designation for M281, now called nipocalimab, in hemolytic disease of the fetus and the newborn [109].

1.5. Transplacental transfer of therapeutic IgG antibodies

Therapeutic monoclonal antibodies are increasingly used to treat inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. Most of our knowledge concerning the use of therapeutic antibodies during pregnancy comes from anti-tumor necrosis factor α therapy using infliximab. Infliximab is an IgG1, and significant transport of infliximab to the fetus has been reported after week 26 [86]. In most studies investigating the use of infliximab during pregnancy, no adverse pregnancy outcome or increased teratogenicity was observed [110–113]. Also, treatment of pregnant women with eculizumab, a hybrid IgG2/4 designed antibody neutralizing complement factor C5, was shown to be safe and did not affect the complement system of the newborn [114]. In contrast, case reports on trastuzumab, an IgG1 directed against HER2/neu, used for treatment of pregnancy associated breast cancer can lead to severe lethal complications for the newborn [115–117]. Data regarding safety of therapeutic antibody administration during pregnancy are limited, and the general advice is to avoid treatment if possible. Transplacental transport and effects on the fetus or the placenta itself likely depend on the nature of both the antibody and the antigen, and require specific studies. A better understanding of the mechanisms for transplacental antibody transfer will aid future development of antibody-based therapeutics that can provide treatment for women during pregnancy without harming the fetus.

2. Conclusion

The transfer of IgG across the human placenta provides the fetus with humoral immunity. The efficiency of transfer correlates with placental FcRn expression [74], and increases throughout gestational age [71,72].

Of physiological relevance related to the IgG transport are passive immunization effects in the newborn after maternal infections or vaccinations, but also diseases caused by transport of harmful auto- and alloantibodies to the fetus [91–99]. It has been instrumental for our understanding that FcγRs do not contribute the transfer of IgG across human placenta to the same degree as FcRn [24,57–61]. Rather, such receptors may modulate the transfer [59,65–67]. The current understanding of the process of antibody transplacental transport has so far resulted in clinical trials to treat alloimmune mediated pregnancy complications with nipocalimab, which is promising for the treatment of hemolytic diseases.

Dual perfusion of a single placental lobule is the only experimental model to study placental transfer of substances in organized human tissue. In fact, this approach is a highly valuable method for studying IgG transport in fully functional and physiological intact tissue containing all cellular subtypes and receptors, and the best method available to give a clear picture of placental IgG transfer linked to human immunological health and safety testing of IgG therapies. Despite this the published literature shows that different research groups prefer different experimental designs. Our review of the literature on placental perfusion techniques used to study antibody transfer concludes that slight variations in placental perfusion setup have less impact on the magnitude of the actual IgG transfer, compared to modifications of the IgG structure that influence FcRn affinity or pH dependent binding to FcRn. The placental perfusion approach is limited to third trimester tissue, which limits the significance of IgG transfer studies related to the onset of transfer since it already starts in the early second trimester. Another limitation is that the placental tissue can be sustained in the perfusion apparatus under physiological conditions only for a few hours and not days, like cell culture models. Time limitations result from increasing placental barrier damage resulting in increased fetal vascular backpressure and loss of barrier integrity and tissue homeostasis. The *ex vivo* placentap perfusion method will still be important for future studies and the field will benefit from using intact human tissue. Setting methodological standards to facilitate reproducibility and consistency of results should further improve comparability between laboratories [118].

There are many unanswered questions that should be addressed in future studies, as summarized in Table 2. For instance, what is the dominant transfer mechanism in the tissue's sub compartments? What factors determine IgG recycling versus transcytosis? What is the role of IgG N-glycosylation and the IgG Fab region in regulating transport? What is the mechanism of immune complex transfer, the role of placental macrophage Hofbauer cells and the classical FcγRs in the placenta? Answers to these central questions could lead to future therapeutic opportunities with nipocalimab or other therapeutic IgGs, and the development of differently designed therapeutics that can be used for efficient treatment *in utero,* or alternatively lack placental transfer abilities altogether.

Table 2
Unanswered questions and potential tasks for future placental perfusion experiments.

IgG transfer in the placental stroma	Take advantage of labeled IgG and use imaging techniques to get insights in the stroma
Elucidate discriminating factors between IgG recycling and transfer and transfer of immune complexes	Transfer studies of immuno- and allergen complexes with pathogens and toxins
Role of IgG N-glycosylation and the Fab region in placental transfer	Experiments with pools of different N-glycosylated IgGs and various Fab fragments
Role of Hofbauer cells and FcγRs in placental IgG processing	Direct inhibition of FcγRs in perfusion experiments of IgGs may lead to a better understanding of IgG processing and sorting

Declaration of competing interest

All authors declare no conflicts of interest.

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