possibility that selective elimination of B cells and alloantibodies might foster acceptance of partner-matched organs in multiparous women.

Incredibly, we lack compelling evidence to support the notion that anti-paternal antibodies which arise during healthy pregnancy and compromise subsequent transplant either harm or contribute positively to fetomaternal tolerance. Perhaps they are best conceptualized as an "epiphenomenon of any pregnancy", as was previously suggested (96). However, as detailed in sections below on rejection, exceptional fetal and placental antigens elicit pathogenic maternal antibody responses or are targeted by pre-existing maternal autoantibodies. Both situations unequivocally mediate harm to pregnancy. Moreover, as I also describe below, it is possible that anti-paternal antibodies participate in several enigmatic placental pathologies associated with significant adverse outcomes. A better understanding of how pregnancy can proceed unharmed in experimental situations where robust cytotoxic anti-paternal antibodies are present could shed light on where along the tolerance pathway breakdowns occur and how this causes disease.

Humoral mechanisms of rejection

The remainder of this review explores uncommon scenarios where breakdown of B cell fetomaternal tolerance results in adverse pregnancy outcomes (**Figure 3**). Throughout, I attempt to highlight and speculate upon features that distinguish the pathogenic antigens, B cell, and antibody responses detailed below from the harmless responses described above.

Hemolytic disease of the fetus and newborn (HDFN)

Written descriptions of a condition matching the disease we now call Hemolytic Disease of the Fetus and Newborn (HDFN) trace back to 400 BC (97). It was then that Hippocrates used the term "fetus carnosus" to describe stillborn fetuses with an edematous appearance. Many centuries later, clinicians established HDFN as a disease caused by maternal IgG which recognize paternal alloantigens on fetal red blood cells (RBCs) and elicit RBC destruction (98; 99). Most cases involved women who lacked the gene for RhD antigen and carried pregnancies with paternal inheritance of the RhD allele (100). Exposure of maternal B cells to RhD^{+} fetal RBCs occurs in late gestation when minor disruptions in the syncytiotrophoblast layer and fetal endothelium leak fetal blood into maternal circulation, and again at delivery when tearing of fetal vessels results in larger quantities of "fetomaternal hemorrhage". During subsequent pregnancies, maternal RhD-specific IgG are passively transferred across the placenta, bind to and mediate destruction of any RhD^{+} fetal RBCs. Severity of disease ranges widely. More severe anemia results in high output fetal cardiac failure leading to an accumulation of interstitial fluid and the edematous appearance that was historically noted (97). Prior to the development of an immunotherapy that prevents generation of maternal RhD-specific IgG, clinically significant sensitization occurred in approximately 16% of pregnancies where RhD^{neg} women carried RhD^{+} fetuses (100). Estimates suggest that HDFN used to affect approximately 1% of all pregnancies and was thus a major driver of fetal and neonatal morbidity and mortality (101).

The specific humoral pathways and cell types leading to generation of RhD-specific IgG in pregnant women have not been experimentally defined. It is reasonable to hypothesize that fetal RBCs are engulfed by maternal splenic DCs which process and present peptides on MHCII, providing initial activation of alloantigen-specific CD4 T cells. Alloantigen-specific B cells also interact with, process, and present peptides from RBC alloantigens on MHCII, and could

subsequently receive survival signals from follicular helper T (Tfh) cells in GCs or CD4 T cells in an extrafollicular location. Either trajectory could generate long-lived antibody producing plasma cells and memory B cells. Older work shows that Rh blood group-specific IgG rarely fix complement (102). Thus, it is presumed that after anti-RBC IgG are passively transferred across the placenta, they bind fetal RBCs, destruction of which proceeds via FcR-mediated removal by myeloid cells of the reticuloendothelial system in the fetal spleen and liver (**Figure 3*a***).

RBC antigen systems do not naturally cause transfusion reactions in mice and obtaining transgenic surface expression of the genetically complex human Rh antigens in mice has proven to be difficult (103). Ten years ago, however, researchers circumvented these challenges and successfully modeled HDFN by mating wildtype females to male mice carrying a single copy of the human *KEL2* gene under the beta-globin promoter (104). Notably, KEL, a polymorphic human RBC transmembrane glycoprotein implicated in rare HDFN cases, is absent in mice. In the mouse model, KEL was expressed on fetal RBC precursors, KEL^+ fetal RBCs were detected in maternal circulation after delivery, and maternal anti-KEL IgM and IgG (of all subclasses) were variably detected in mothers after two KEL pregnancies (104). Pathology became evident during the third pregnancy and was manifested by litters with markedly fewer than 50% KEL^+ pups at birth, and anemia in KEL^+ pups that did survive.

Much is known about mechanisms of alloimmunization to blood transfusion in non-pregnant mice and humans (105). Aside from the observation that pathology is abrogated by maternal B cell and antibody deficiency, additional features that exacerbate or attenuate generation of KEL-specific IgG and modulate their effector functions have not been directly studied in the setting of pregnancy. The complex physiology of pregnancy, including the global changes in maternal B cells and IgG glycans, and distinct characteristics of fetal antigen and

mode of exposure, implies that mechanisms may be pregnancy specific. For instance, there is a noteworthy elevation in serum C3 levels during pregnancy (106). Considering that C3 exerts complex regulation over alloantibody formation to transfused RBCs in non-pregnant mice (107), it will be important to investigate mechanisms specifically in the pregnant host.

Determining the exact cellular and molecular pathways by which fetal RBC antigens elicit HDFN could thus illuminate important facets of fetomaternal tolerance. It is possible that inherent features of RhD foster its immunogenicity and help to explain why this alloantigen results in pathology while other paternal antigens rarely do. For example, among the cell surface proteome, RhD stands out for its distinctiveness in lacking glycans (108; 109). Consequently, this antigen would not be able to engage the suppressive sialic acid/Siglec axis that facilitates maternal B cell tolerance. More broadly, might some conceptus-derived antigens elicit GC responses while others elicit extrafollicular responses? Is this dependent upon the quality of T cell help (i.e. Tfh versus lack thereof)? Clinical observations raise further questions, particularly with regards to the fact that the incidence of clinically relevant HDFN in cases of genetic mismatch is only 16%, but it is unknown where along the path from sensitization to IgG effector function that tolerance dominates. Are some pregnancies protected because fetomaternal hemorrhage results in antigenic doses too low to elicit responses? Or is there a pathway that generates active B cell tolerance to fetal RBCs in the at-risk women who fail to develop anti-RhD IgG? At present, circumstantial evidence suggests that maternal/fetal ABO incompatibility decreases the risk of the sensitization to RhD, raising the possibility that pre-existing ABO antibodies facilitate so-called “antibody-mediated immunosuppression” (AMIS)(110).

AMIS is a phenomenon whereby experimental introduction of antigen-specific IgG in the absence of cellular immunity prevents de novo formation of humoral responses in the recipient

(111). Historic studies in the 1960s showed that administration of antisera to a non-self antigen prior to vaccination sometimes blocked generation of immune memory in the recipient (112; 113). Based upon this knowledge, the first immunotherapy was created to prevent RhD immunization in pregnancy. Pooled total IgG from sera of RhD-antigen sensitized RhD^{neg} donors was formulated for intramuscular injection and remains standard of care today. The current protocol involves two doses of 300 micrograms total IgG, first at 28 weeks of gestation and again within 72 hours of delivery (101).

Despite now decades of clinical experience with anti-RhD prophylaxis, there is lack of consensus on exactly how this prevents formation of RhD-specific IgG in at-risk pregnancies. Unfortunately, this lack of understanding appears to have hampered the development of a monoclonal anti-RhD IgG to replace pooled donor IgG. The term AMIS itself is somewhat misleading, since in some instances pre-existing antibodies can mediate enhancement of active immunity rather than suppression (114). For many years, the prevailing theory was that pre-existing RhD-specific IgG prevented maternal B cell responses by mediating extravascular clearance of fetal RBCs prior to any interaction with B cells. However, studies testing prophylaxis with monoclonal antibodies showed poor correlation between RBC clearance and effectiveness (111; 114). Research in non-pregnant mice given RBC transfusions also argues against a role for active tolerance induction in antigen-specific B cells via engagement of the inhibitory receptor FcγRIIb by immune complexes (115; 116). Instead, the dominant mechanism of AMIS appears to be “antigen modulation”, which required recipient C3 and FcγRs to presumably result in extraction of alloantigen from the RBC (trogocytosis) (117). Perhaps pooled anti-RhD IgG engages a variety of suppressive pathways, and research to identify these should consider prioritizing the use of pregnant, rather than non-pregnant animal models for reasons

outlined above. Nevertheless, anti-Rh(D) IgG as currently produced and used has been incredibly successful: incidence of Rh(D) in at risk pregnancies treated with anti-Rh(D) IgG has fallen to below 1% (100).

Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by maternal IgG antibodies which recognize paternal-derived human platelet antigens (HPA) on fetal platelets. HPA comprise approximately 35 antigenic determinants present on exposed regions of platelet transmembrane glycoprotein complexes (118). FNAIT is relatively rare and affects between 1 in 1000 and 1 in 2000 pregnancies (119). Morbidity ranges widely from mild to severe fetal thrombocytopenia, the latter of which risks triggering intracranial hemorrhage and stillbirth. Another complication is low birth weight (120), which most likely results from placental dysfunction. Unlike HDFN, where the placenta is unharmed, maternal anti-HPA IgG might damage placental cells which share expression of the antigen, as elaborated below. Additionally, unlike HDFN, there is currently no screening program or prophylactic therapy to prevent the formation of anti-HPA IgG. To prevent recurrence of severe FNAIT in a second pregnancy, current regimens include generalized maternal immunosuppression with IVIg and prednisone (121).

Research on mechanisms of FNAIT has focused on the HPA-1a antigen located in β3-integrin (122-125). β3-integrin is a component of the fibronectin receptor, highly expressed on platelets, as well as the vitronectin receptor, expressed on some trophoblasts (125) and fetal endothelial cells (124). Maternal β3-integrin-specific IgG not only trigger fetal

thrombocytopenia but also demonstrate an affinity for invasive trophoblasts. A mouse model of FNAIT was developed over a decade ago and involves immunizing β3-integrin deficient female mice with wildtype platelets prior to mating with wildtype males (122; 123). Immunization was necessary because β3-integrin deficient female mice mated to wildtype males do not develop β3-integrin-specific IgG, even after multiple pregnancies. Without considering all conceivable reasons for why this mating fails to elicit FNAIT, perhaps disrupting tolerance to an antigen common to both the placenta and fetus necessitates an additional disturbance in checkpoints that maintain fetomaternal tolerance. Nevertheless, immunizing β3-integrin deficient female mice with wildtype platelets prior to mating with wildtype males, or passive administration of mouse or human β3-integrin-specific IgG, caused significant fetal loss, and thrombocytopenia, hemorrhage, and growth restriction in surviving pups (122; 123). When β3-integrin deficient female mice were bred to heterozygous males, selective pathology in the β3-integrin^{+} fetuses was observed (125).

In the FNAIT mouse model, β3-integrin-specific IgG led to an accumulation of maternal NK cells in the decidua at E14.5 (125). This timepoint is well after uterine NK cells have typically declined in normal implantation sites. In E14.5 FNAIT pregnancies, NK cells showed an NKp46^{+}CD107^{+} activated phenotype, surrounded maternal spiral arteries which supply the placenta, and appeared to induce apoptosis of β3-integrin^{+} invasive and endovascular trophoblasts (125) (**Figure 3*b***). Optimal maternal placental perfusion requires trophoblast invasion and then successful remodeling of spiral arteries such that they become lined by endovascular trophoblasts. Poor perfusion in these pregnancies thus likely contributed to poor fetal growth. In addition to the placental pathology, fetuses exhibited defects in brain vascular development due to antibody-mediated dysfunction of β3-integrin^{+} vascular endothelial cells

(124). Remarkably, the placental pathology, but not fetal thrombocytopenia or intracranial hemorrhage, can be prevented by administering antibodies to deplete NK cells at E11.5 or antibodies to block the activating receptor FcγRIIIa (125). Unfortunately, translating a NK cell depletion strategy to human pregnancy would be risky since uterine NK cells are important for pathogen defense and necessary in early gestation for optimal spiral artery remodeling (126). Nonetheless, the mouse work thus far raises the possibility that immunotherapies which are more selective than IVIg and prednisone could alleviate FNAIT pathology with significantly fewer side effects.

Analyzing clinical studies and placental pathology in cases of human FNAIT illuminates additional interesting facets of fetomaternal tolerance and breaks therein. Why do β3-integrin-specific IgG cause pathology during pregnancy, but anti-HLA antibodies do not? Curiously, anti-HLA antibodies commonly mediate transfusion reactions to platelets in non-pregnant individuals yet anti-HLA antibodies are very rarely implicated in FNAIT (118). Since most pregnant women develop anti-HLA antibodies, it remains a conundrum why these do not mediate significant destruction of fetal platelets or endovascular trophoblasts. It may be the case that the broader fetal tissue distribution of HLA dilutes antibody density, thereby reducing effector functionality (118). Or it could be that anti-HLA antibodies are effectively absorbed and destroyed within the placenta, as mentioned previously. Frustratingly, at present, we lack an understanding of the factors that shield HLA^+ endovascular trophoblasts in mice hyperimmunized to paternal strain splenocytes before pregnancy, preventing them from experiencing a fate like that of β3-$integrin^+$ trophoblasts in the mouse FNAIT model.

As speculated earlier, antibody glycosylation could alter the effector functionality of certain anti-paternal antibodies. This hypothesis was somewhat indirectly evaluated in a recent

study attempting to correlate anti-HPA IgG Fc glycans with disease severity (127), which otherwise does not tightly correlate with anti-HPA IgG levels. The Fc region of anti-HPA-1a-specific IgG was found to be modified by glycans that contain significantly less core fucosylation than the glycans attached to total IgG (127). Decreased core fucosylation increased Fc affinity for activating FcγRIIIa and FcγRIIIb receptors, enhancing the antibody-dependent phagocytic activity of monocytes. While literature describing placental pathology in human FNAIT pregnancies is relatively sparse, comparison of placentas from FNAIT and control healthy pregnancies showed an increased frequency of chronic inflammatory lesions in FNAIT specimens (120; 128; 129). These included chronic histiocytic intervillous (CHIV), a disease characterized by an accumulation of maternal monocytes in the intervillous space, as discussed further below. Considering these observations and mouse findings, collective evidence suggests the hypothesis that glycan modification of an anti-paternal antibody may disrupt fetomaternal tolerance by imparting pathogenic Fc-mediated effector functionality.

Anti-phospholipid antibody syndrome (APS)

Anti-phospholipid (aPL) antibodies are a class of autoantibodies present in women prior to pregnancy which elicit complications largely by their ability to activate complement and cause inflammation in the placenta and uterus. Primary anti-phospholipid antibody syndrome (APS) is characterized by serologic evidence of aPL in the setting of recurrent venous and arterial blood clots and/or adverse pregnancy outcomes (130). Secondary APS refers to when these characteristics are seen in a patient with an autoimmune disorder (e.g., 50% of patients with systemic lupus erythematosus (SLE) have APS). Adverse pregnancy outcomes seen in patients

with APS include recurrent miscarriage, fetal growth restriction, pre-eclampsia, and stillbirth (131). Significantly, aPL are discovered in up to 25% of pregnancies experiencing fetal growth restriction (132) or recurrent miscarriages (133). Adverse outcomes are often associated with the presence of autoantibodies that recognize β2 glycoprotein I (β2GPI), a phospholipid-binding serum protein (134). β2GPI can associate with trophoblast cell surfaces via binding to the low-density lipoprotein receptor family member ApoER2 (135) or to cardiolipin (136), a phospholipid usually present on inner mitochondrial membranes which becomes exposed on the plasma membrane of apoptotic cells. The biochemistry of β2GPI is complex, and there is a role for β2GPI-activity in optimal mouse placental development and function (137) . How anti-β2GPI antibodies interacts with trophoblast cell surfaces to elicit changes to cell fate and function has been comprehensively reviewed elsewhere (138). Briefly, in vitro experiments show β2GPI-specific IgG can inhibit proliferation, hormone production, and invasive properties of trophoblasts (138). In vivo work, however, strongly implicates antibody-mediated effector functions as a key driver of aPL-associated adverse pregnancy outcomes (139-142).

The initial theory explaining the association between aPL and adverse outcomes posited that thrombus formation in maternal uteroplacental circulation compromised placental function (143). However, this hypothesis did not quite align with the frequent lack of thrombi on pathologic examination (144; 145). Instead, results from over two decades of research in pregnant mouse models of APS has significantly shifted the paradigm for how aPL elicit adverse outcomes. Fortuitously, passive administration of human or mouse aPL IgG at various timepoints before and/or during gestation recapitulated many of the adverse outcomes seen in human APS pregnancies (146). Pregnant mice that received aPL showed significant increased fetal resorptions, decreased placental weights and growth restriction in surviving pups when compared

to controls (142; 147; 148). Notably, aPL IgG, C3, and neutrophils appeared to accumulate in placentas and deciduas prior to subsequent tissue necrosis (142). Moreover, C3 deficient pregnant mice were protected from the aPL antibody-induced adverse outcomes (142). Therefore, the hypothesis for how aPL antibodies contribute to adverse pregnancy outcomes was revised to involve maternal complement. Reduced pathology in *C4*$^{-/-}$, *C5*$^{-/-}$ and *C5ar1*$^{-/-}$ pregnant mice administered aPL IgG, as well as an absence of pathology in pregnant mice administered F(ab')$_2$ aPL IgG, indicated a requirement for activation of the classical complement pathway by antibody bound to trophoblasts (140). Remarkably, elimination of maternal neutrophils or complement factor B were also protective and associated with significantly reduced C3 accumulation in the uterus (**Figure 3*c***)(140).

Thus, while antibody-mediated activation of the classical complement pathway appeared to be required for APS disease initiation without further amplification by the alternative pathway of complement, adverse pregnancy outcomes were largely averted. While it is evident that aPL antibodies can cause damage to the placenta, these findings also highlight a notable degree of trophoblast protection against robust activation of the classical pathway. It will also be intriguing to delve deeper into mechanisms by which trophoblasts appear to avert formation and/or membrane insertion of the membrane attack complex. This phenomenon seems absent not only in this APS mouse model, but also in other situations where there is dysregulated activation of the alternative pathway of complement in the placenta (149). Nevertheless, a wealth of evidence indicates that successful pregnancy outcomes necessitate proper placental regulation of complement (87; 149-151) and aPL IgG are a clear example of a maternal antibodies that can override local complement regulatory factors.

Besides fetal loss, APS shows an additional association with pre-eclampsia (152), a syndrome characterized by imbalances in angiogenic growth factors and poor placental development. Normal placentation requires coordinated local expression of growth factors and their receptors on trophoblasts that invade the decidua and participate in remodeling maternal spiral arteries. Remarkably, innate immune cells, attracted to the placenta due to pathologic complement activation, become sources of TNF-α (139) and anti-angiogenic factors(150). That neutrophils and monocytes in mouse models of placental complement activation produce excess anti-angiogenic factors (e.g., sVEGFR-1) is somewhat surprising, since these cells often promote angiogenesis in other contexts. Regardless, local production of anti-angiogenic factors could impair trophoblast invasion and vascular remodeling, a key mechanistic link for the association between maternal autoantibodies and clinical features of pre-eclampsia (153).

The mouse model used in pregnancy APS work has inherent limitations, shared with the mouse model for FNAIT. A passively administered bolus of high dose IgG does not well mimic the sustained levels of aPL or anti-HPA IgG in patients. This is particularly problematic for experiments where human IgG are given to mice, since alloantibody is rapidly cleared and can induce cross-species immunity. These drawbacks necessitate caution when drawing definitive conclusions about requirements for placental pathology in the setting of anti-placental antibodies. It seems probable that along with the presence of high levels of high affinity, complement-fixing antibodies, the occurrence of a second breakdown in fetomaternal tolerance mechanisms, or the failure of multiple additional mechanisms, is necessary for disease to manifest. For instance, one might hypothesize that anti-placental antibodies become pathogenic when there is an inherited or induced disturbance in trophoblast complement regulatory proteins or cellular damage inflicted via a pathogen. In support of a “double-hit” hypothesis, clinical evidence shows that women with

inherited mutations in complement regulatory factors are at higher risk for pregnancy complications (154).

In total, APS mouse pregnancy studies significantly advanced our understanding of disease pathogenesis and foreshadowed findings from a large prospective study of outcomes in women with SLE. Most important for identifying a high rate of adverse outcome for African and Hispanic American women which now requires additional study, the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study included assessment of serial blood samples for markers of complement activation (155). In women with APS and/or SLE, elevated serum levels of activated factor B (a marker of alternative pathway activation) and C5b-9 (indicative of terminal complement pathway activation) measured at the end of the first trimester were highly predictive of subsequent adverse outcomes (156). These human findings lend strong support to the hypothesis that excessive activation of complement underlies pregnancy complications in APS.

The current clinical approach to prevent adverse APS pregnancy outcomes is based on the outdated idea attributing complications to blood clots, prompting prescriptions of anti-coagulation medicines. Fortuitously, the partial success achieved in patients receiving heparin seems to be based on its ability to inhibit classical complement pathway activation, rather than its anti-coagulant properties (141). Indeed, heparin, but not other anti-coagulants devoid of complement inhibition, uniquely offered some protection against fetal loss in pregnancy APS models (141). Based upon the solid mechanistic framework provided by the mouse studies, the IMPACT (IMProve pregnancy in APS with Certolizumab therapy) clinical trial is currently testing the hypothesis that adding blockade of TNFα to current standard of care will prevent imbalances in angiogenic factors and reduce incidence of pre-eclampsia in APS pregnancies (9).

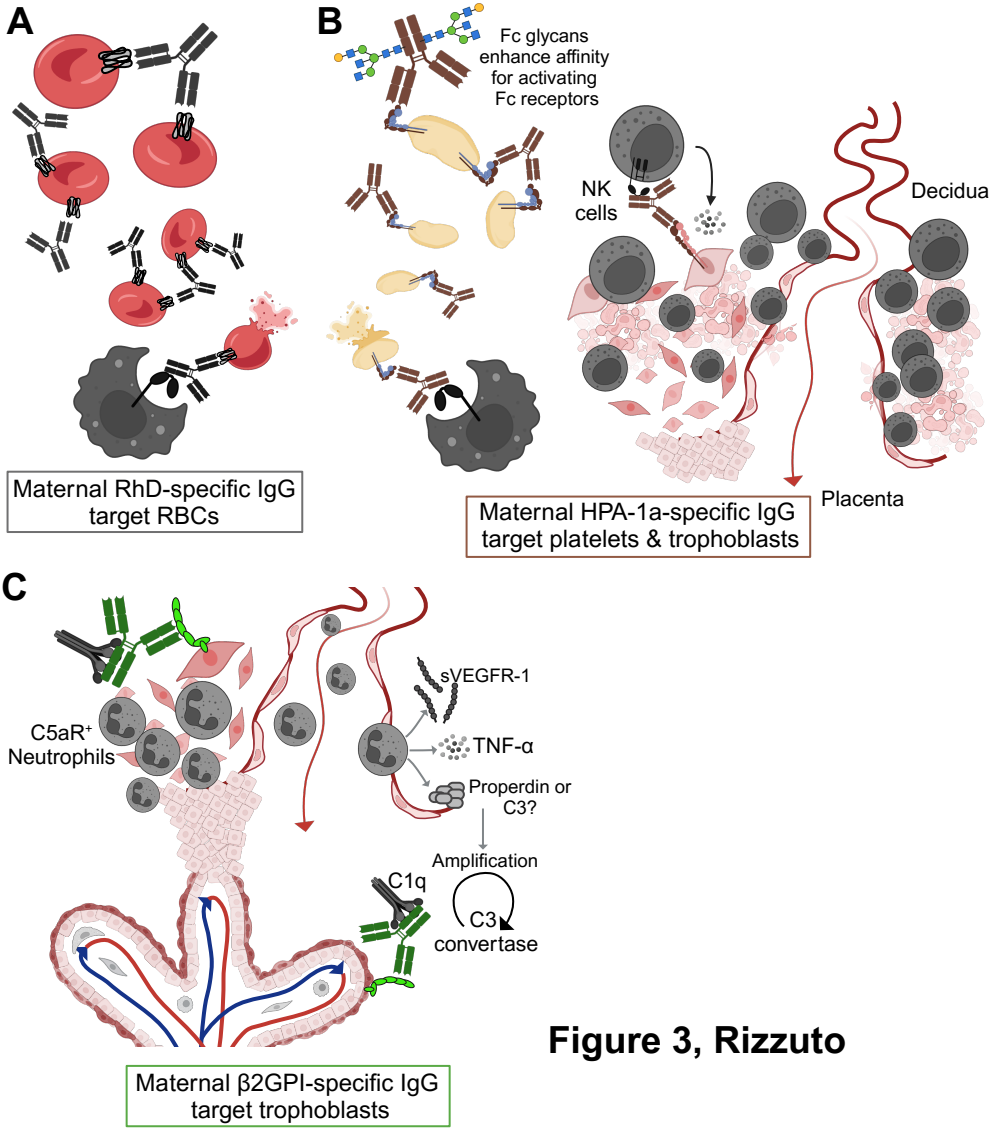

Figure 3, Rizzuto

Figure 3. Pathogenesis of maternal antibody-mediated damage to the placenta and fetus.

(a-c) The three scenarios where breakdown of B cell fetomaternal tolerance results in adverse

pregnancy outcomes. ***(a)*** Hemolytic disease of fetus and newborn (HDFN) is mediated by maternal IgG specific for paternal-derived fetal RBC antigens. After passive transfer across the placenta, anti-RBC IgG mediate extravascular hemolysis of fetal RBCs, as shown. Historically the most common etiology for HDFN was maternal-fetal incompatibility in Rhesus D (RhD) antigen. Note that the specific humoral pathways, including role of CD4 T cell help, leading to the generation of allospecific IgG in pregnancy have not yet been experimentally defined. ***(b)*** Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is commonly mediated by maternal IgG specific for paternal-derived "human platelet antigens" (HPA). The HPA-1a antigen is in β3-integrin which is expressed on platelets, endothelial cells (not shown), and trophoblasts. Thus, antibody-mediated damage is incurred by fetal platelets and placental trophoblasts. Antibody-coated platelets are destroyed via extravascular hemolysis, antibody-coated trophoblasts become targets for maternal NK cells. Engagement of NK cell FcγRIIIa may be enhanced by IgG Fc glycans with decreased core fucose. Activation of NK cells and release of perforin may provoke trophoblast apoptosis. ***(c)*** Anti-phospholipid autoantibodies, including β2GPI-specific IgG, elicit adverse pregnancy outcomes largely by their ability to activate complement and cause inflammation in the placenta and decidua. β2GPI-specific IgG initiate disease by activating the classical pathway of complement. Anaphylatoxin C5a recruits neutrophils which elaborate factors to trigger the alternative pathway and amplify the cascade. Neutrophils, and perhaps other innate immune cells, also produce tumor necrosis factor (TNF-α) and anti-angiogenic factors like soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) which can disrupt remodeling of spiral arteries and maternal vascular perfusion of the placenta.

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