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## Advancing Maternal-Fetal Immunology by Unlocking New Insights into Immune Pathways

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**N**ew insights into immune pathways are unlocking opportunities to revolutionize maternal-fetal immunology, including how hemolytic disease of the fetus and newborn (HDFN) is addressed. The primary etiopathogenesis of HDFN, a maternal immune response against fetal red blood cells (RBCs), is well characterized.<sup>1,2</sup> However, by teasing out the elegant molecular factors at work in this disease, immunology researchers anticipate both improving the therapy for HDFN as well as developing diagnostic tests to identify women for whom HDFN might be an issue during pregnancy.

At Janssen Pharmaceutical Companies of Johnson & Johnson, our focus on HDFN is informed by nearly a quarter-century of foundational immunology expertise. We are currently evaluating a novel therapy that may interrupt the immune processes in HDFN by focusing on molecules that mediate the normal functions of the immune system. At Janssen, immune targets of interest are often selected from natural regulatory mechanisms that our bodies use to balance immune activation with control. We are not narrowly focused on HDFN in this task. Rather, we believe much is to be gained by examining immune pathways across various inflammatory diseases, leveraging insights from Janssen's years of research in these areas. The lessons learned from these pathway-driven scientific approaches to both our basic and clinical investigations provide a scale and efficiency of discovery not typically available for rare diseases like HDFN. A closer look at HDFN reveals the opportunities that these lessons provide.

### About HDFN

HDFN is a rare, but potentially devastating, immune-mediated illness. The maternal immune response to fetal RBCs leads to destruction of fetal RBCs after specific maternal alloantibodies travel across the placenta. This intrauterine immune cascade may result in fetal injury ranging from anemia to hydrops fetalis, with associated organ damage, heart failure, or even death.<sup>1,2</sup> Infants who survive and are born after exposure to these maternal alloantibodies may exhibit hyperbilirubinemia with jaundice and/or neurotoxicity; they may also suffer from hyporegenerative anemia.<sup>1,2</sup>

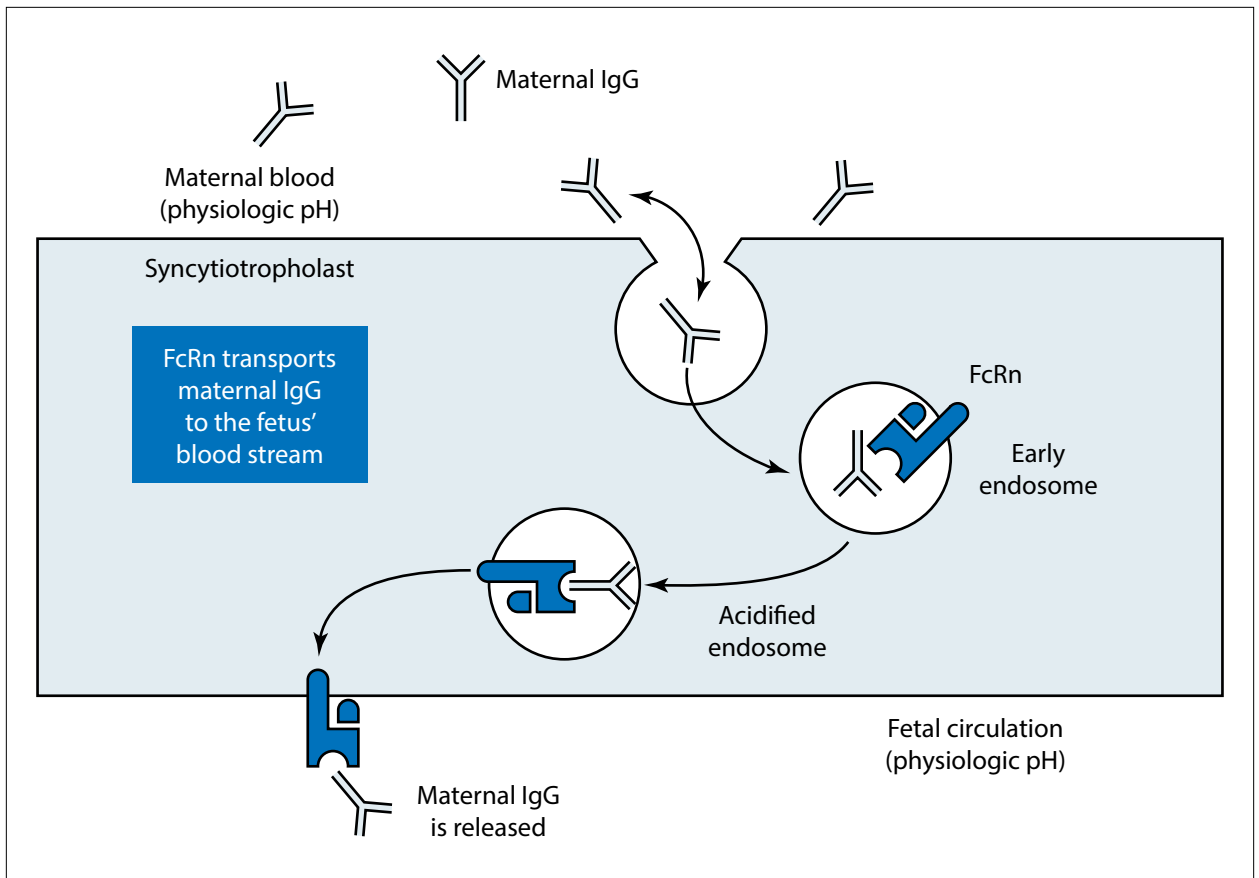
The recognition that HDFN results from a maternal antibody-led immune assault dates back to the 1930s, when 1% of babies had the disease and about 50% of all babies with HDFN died.<sup>3</sup> Pathologist Ruth Darrow correctly postulated the role of maternal antibodies as the cause of HDFN, but the immune antigen on fetal RBCs was not identified until 1940, when the recognition of Rhesus blood groups led to the discovery of the Rhesus D (RhD) molecule on fetal RBCs as the target.<sup>4</sup>

HDFN typically develops when an Rh-negative mother is exposed to the RBCs of an Rh-positive fetus. In addition to RhD-mismatch between fetus and mother, HDFN can also result from mismatch of ABO blood types or other maternal-fetal blood incompatibilities.<sup>5</sup> Non-RhD antigens include the fetal Kell (K and k), Duffy (Fya), Kidd (Jka and Jkb), and MNSs (M, N, S, and s) systems.<sup>6</sup> Three of these maternal antibodies have been associated with severe HDFN: anti-RhD, anti-Rhc, and anti-Kell(K1).<sup>7</sup>

Diagnostic tests and preventative medical maneuvers have reduced HDFN incidence and severity, especially for RhD-related cases. However, 1700 in 100,000 newborns in the United States are still affected each year, with most cases resulting from maternal incompatibility with the non-Rh antigens.<sup>5</sup>

HDFN does not require the mother to be previously exposed to large amounts of mismatched blood. Rather, maternal alloimmunization may occur even after exposure to small amounts of fetal blood resulting from asymptomatic fetomaternal hemorrhage. About 75% of pregnancies have such bleeding across the placenta.<sup>7</sup> Maternal abdominal trauma; abortion; ectopic pregnancy; procedures such as external cephalic version; and diagnostic tests involving amniocentesis, chorionic villus sampling, or cordocentesis can raise alloimmunization risk as well.<sup>7</sup>

Following exposure to fetal RBCs, the mother's immune system may target a fetal antigen as "foreign," ultimately leading to the production of maternal immunoglobulin G (IgG).<sup>7</sup> This is important, as IgG is the only type of antibody that can normally cross the placental barrier in significant amounts.<sup>8</sup> For patients at risk of HDFN during pregnancy, monitoring of maternal IgG alloantibodies is warranted. Additional monitoring for fetal anemia can be carried out by measuring fetal peak systolic middle cerebral artery (MCA) velocity, avoiding the need for more invasive maneuvers. Approximately 50% of newborns affected by HDFN have mild disease, but 25% develop severe jaundice after birth, which is overwhelmingly fatal without treatment. The other 25% develop hydrops fetalis *in utero*, which may require interventions with inherent risks, such as intrauterine blood transfusion and/or early delivery.<sup>2,7</sup>



**FIGURE** Prenatal acquisition of immunoglobulin G in humans is mediated by the neonatal Fc receptor (FcRn), expressed in the placental syncytiotrophoblast. As part of its normal role, the syncytiotrophoblast takes samples of maternal blood into endosomes. As these endosomes become acidified, FcRn binds tightly to maternal IgG, protecting it from degradation. These complexes are transcytosed across the cellular barrier where FcRn dissociates from IgG at physiologic pH, releasing IgG to the fetal circulation.<sup>16</sup>

## HDFN Interception

Janssen is pioneering a disease interception approach to change the course of HDFN. This involves an understanding of the transplacental journey of maternal IgG alloantibodies, along with the normal regulation of this process. A successful therapy could disrupt the transport of these antibodies without widely suppressing the mother's immune system or the developing fetal immune system.

One promising target is a protein called the neonatal fragment crystallizable (Fc) receptor (FcRn), which normally binds to and transports IgG. This receptor normally protects IgG in our bloodstreams from rapid destruction by safely transporting it across cell membranes and enabling IgG "recycling" for multiple uses.<sup>8,9</sup> During pregnancy, this receptor is also expressed in maternal syncytiotrophoblasts. Thus, FcRn acts like an antibody chaperone in the placenta, mediating the passage of IgG from the mother's blood to the fetal circulation.<sup>8</sup>

Preclinical studies suggest that blocking FcRn may disrupt the progression of various autoimmune diseases that are driven by IgG.<sup>10-14</sup> One potent candidate for this type of intervention is a monoclonal antibody (mAb) designed to bind to FcRn and block its ability to transport IgG molecules. Thus, an effective FcRn-blocking mAb might be able to be given to pregnant women to prevent maternal IgG from transferring to the fetus and causing HDFN.

## Detection of Risk for HDFN

Whether a mother's pregnancy will be affected by HDFN is not always known. Women who have had prior pregnancies with HDFN are monitored carefully during their subsequent pregnancies. However, it would be ideal to prevent HDFN from occurring in the first place. Ideally, one would be able to stratify women at risk for HDFN with a sensitive and specific blood test *prior* to or very early in pregnancy, so that therapy options might be considered before intervention is needed urgently.

Developing such a prognostic tool is challenging. In other diseases, one can test for a gene mutation or examine tissue histopathology directly from a biopsy. However, for HDFN, we still need to understand the differences between various maternal IgG alloantibodies, their ability to cross the placenta, the impact of binding to different fetal RBC antigens, and the resulting influence on fetal immune functions. Answers to these questions may help us to understand why some fetuses and newborns are more severely affected by HDFN than others. With current research tools, we can begin to dissect which maternal IgG alloantibodies are pathogenic in HDFN and which are not.

Developing an accurate and useful test also requires robust clinical data, which are challenging to obtain in a

rare disease. One approach to understanding HDFN is to study other immune-mediated disorders in which transfer of maternal IgG might harm fetuses or newborns. These diseases include autoimmune thrombocytopenia, Sjogren syndrome, systemic lupus erythematosus, and antiphospholipid syndrome.<sup>15</sup> Data from mothers with such autoimmune disorders may help to inform studies of HDFN and enable better understanding of the mechanisms whereby maternal IgG mediate fetal or neonatal disease. The richness of Janssen's clinical datasets could thus facilitate evaluation of immune outcomes among women with various types of IgG antibodies.

As we use and improve the tools at our disposal to better understand the drivers of maternal-fetal immune diseases, we aim to identify highly informative biomarkers and new molecular targets for therapeutic intervention. With active research in maternal-fetal immunology, we strive toward the day when high-risk HDFN and related immune diseases of pregnancy are historical footnotes, with increased well-being for mothers and babies.

## DISCLAIMERS

This promotional article was developed in conjunction with and sponsored by The Janssen Pharmaceutical Companies of Johnson & Johnson. The views expressed are those of the author; it is the sole responsibility of the medical professional to determine which techniques or protocols are appropriate for their patients.

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