Hemolytic disease of newborns (HDN) is a serious and often fatal disease caused by incompatibility occurring during pregnancy, mainly between the blood group of an Rh- mother and her Rh+ child.  

During pregnancy, an Rh- woman (from <1 percent up to 15 percent of population, depending on ethnicity) who carries an Rh+ baby may be exposed to fetal blood and become sensitized. This typically occurs after delivery or invasive procedures such as amniocentesis or abortion. At subsequent pregnancy, there will be a rapid immune response of the mother, with a large quantity of antibodies directed against the red blood cells of the fetus (fig 1). As a result, 14 percent of affected pregnancies result in stillbirth; 30 percent of survivors have serious disease (hemolysis and severe anemia); and an additional 30 percent have a moderate disease (accumulation of bilirubin into tissues, particularly into brain with lifelong neurological sequelae).  

Preventing Hemolytic Disease of Newborn (HDN) has been one of the most relevant accomplishment in the struggle against neonatal mortality and childhood disability. In the 1960s, hemolytic disease of newborn was responsible for 10 percent of perinatal deaths in the U.S. The development of Anti-D immunoglobulin (Ig) and its administration after delivery decreased the immunization risk of 90 percent, thus preventing the onset of HDN in subsequent pregnancies.  

No doubt, it can be affirmed that introduction of Anti-D Ig prophylaxis in the 1970s has been one of major milestones in women's and children's health medicine (fig. 2).  

A second accomplishment was the introduction of Anti-D Ig antenatal prophylaxis, based on the finding that a few pregnant women were still immunized in spite of post-partum prophylaxis. It was discovered that immunization can occur even in absence of clinically evident events, such as delivery, trauma, or invasive procedures. Exposure to fetal blood normally occurs during the third trimester (occasionally earlier), and is responsible for
Fig. 1 Pathogenesis of Rh Hemolytic disease of newborn

Fig. 2: Decline in death rate for all causes of HDN in U.S, 1968-75 (modified from 6)
<table>
<thead>
<tr>
<th>EVENT</th>
<th>IMMUNIZATION RATE (PERCENT)</th>
<th>STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>17 %</td>
<td>Post-partum prophylaxis</td>
</tr>
<tr>
<td>Abortion</td>
<td>4-5%</td>
<td>Targeted prophylaxis (within 72 hours)</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>5-7%</td>
<td>Targeted prophylaxis (within 72 hours)</td>
</tr>
<tr>
<td>3rd trimester “occult” fetomaternal hemorrhages</td>
<td>1-2%</td>
<td>Routine Antenatal prophylaxis (28-30 weeks)</td>
</tr>
</tbody>
</table>

Table 1: Strategies to prevent mother's immunization and hemolytic disease.

**KEY WORDS**

**RH OR D ANTIGEN**
Designate same red blood cell group. Women who carry the “D” antigen are designed as positive (Rh+), women who don’t are negative (Rh-).

**HDN**
Hemolytic disease of newborn. Mother’s immunization results in destruction of fetus' red blood cells (hemolysis), accumulation of metabolites of red blood cell in tissues, such as skin (jaundice) or brain (kernicterus)

**ANTI-D IG**
Anti-D Immunoglobulin is human antibody solution, directed against D/Rh antigen. These are obtained from Rh- donors sensitized by Rh+ erythrocyte booster. Dosage is in mcg or IU; depending from the standard adopted in Country. Full dose is typically 200 to 300 mcg (1000-1500 IU). Micro doses (50 mcg /500 IU) are available in some Countries, used for small hemorrhage as in first trimester events.
10 percent of total immunizations. Anti-D Ig prophylaxis during pregnancy was assessed by randomized clinical trials, which clearly demonstrate that this strategy is more effective than the sole postpartum prophylaxis. Risk of immunization was reduced from 2 percent to 0.1 percent (table 1) probably by covering “occult” feto-maternal hemorrhages.

Today, several countries recommend routine antenatal prophylaxis (1 full dose of Ig Anti-D at 28-30 weeks to all pregnant Rh- women) in addition to post-partum prophylaxis (only Rh- women delivering a Rh+ child). The question of cost effectiveness has been raised but the favorable economics of this approach has been demonstrated by different authors.

Anti-D Igs obtained by cold alcohol-fractionation of plasma can claim a long standing record of viral safety, additionally improved by the introduction of specific viral inactivation methods such as nanofiltration, heat or solvent detergent treatments. The industrial process of Anti-D Igs relies on specific pools of sensitized blood donors, who have saved millions of lives with their dedication. Its complexity is a permanent challenge for the plasma derived industry and it works as an example of commitment which entails ethics, even more than industry profit. Despite all this progress, the eradication of HDN is still far from being accomplished.

Today in emerging and low-income countries, there is still limited access to prophylaxis, sometimes complicated by difficulties in point-of-care Rh blood-type testing. It is estimated that the lack of adoption of Anti-D Ig prophylaxis is responsible for more than 100,000 avoidable neonatal deaths per year and a larger burden of infant disability.

In order to eradicate this preventable disorder, a global initiative has been started, also with unrestricted grant from the industry such as Kedrion Biopharma and Eldon Biologics. This initiative is called CURhE (from the acronym Consortium for Universal Rh disease Eradication) and has been prompted by three neonatologists who have devoted most of their professional careers to the struggle against hemolytic diseases and infant brain injury. These are: Giuseppe Buonocore Full Professor at Molecular and Developmental Medicine Dept. Siena University and member of Council of UENPS (Union of European Neonatal & Perinatal Societies); Vinod K. Bhutani Professor of Pediatrics and Neonatology at Stanford University School of Medicine and author of several original studies on this topic; and Alvin Zipursky, Professor Emeritus, Hospital for Sick Children, Centre for Global Child Health in Toronto who pioneered Anti-D prophylaxis.

CURhE goals will be achieved by improving patients’ access, educating health professionals, patients, and maternal child healthcare providers, enhancing the capacity for timely diagnosis and therapeutic networking mostly in emerging countries. “There is a huge gap that we need to fill and resolve; over the last almost 45 years we’ve done a phenomenal job in North America and Europe. But this...
knowledge was not transferred and what we have to do is to implement this knowledge into practice in places which are most at risk for Rh disease hemolysis” says Prof. Bhutani when launching CURhE initiative.

However we cannot forget that also in developed countries Anti-D prophylaxis practice has not been completely implemented. Today in European countries, we have not yet reached the eradication goal, mainly due to the incomplete adoption of antenatal prophylaxis. This issue is neglected and in some way overlooked; sporadic data reported from national registries should be a wake-up call for healthcare professionals and their stakeholders. Reaching the zero disease rate should be a common objective of industry and health decision makers, particularly in case of an avoidable disease such HDN.

Anti-D Ig, with many other plasma derived therapies, is a life-saving drug which has marked the history of a therapeutic area. After 50 years, its role still deserves development in order to save more lives, both in emerging and established countries. Disease awareness, plasma availability, and access to therapy are the keys to accomplish this goal. Industry, healthcare professionals, and stakeholders should work together for improving global access to this pivotal prophylactic tool.

GIOACCHINO DE GIORGI, Global Marketing Manager, Anti-D Franchise, Kedrion Biopharma

References