Rh Immune Globulin & Citrus Bioflavonoids: When to Use Them

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**INTRODUCTION**

Rh immune globulin is a blood by-product that is used in the prophylaxis (prevention) of hemolytic disease of the newborn and that currently stands alone as the only available and acceptable deterrent to this disease. Rh immune globulin (often referred to as RhoGAM) owns many names: Anti-Rh agglutinin; Anti-D gamma globulin; Anti-D (Rh) human immune globulin; Anti-D; Rh (D) immune globulin (previously used name); Immunoglobulin D (IgD); Rh immunoglobulin (RhIG); Rh immunoglobin (RhIG); and Rh immune globulin (RhIgG). Such variety of names is due to the fact that the words agglutinin, gamma globulin, immune globulin, and antibody are synonyms. Trade names include Gamulin Rh, Hydro-D, MicRhOgam, HypRho-D, WinRho SDF, and of course, RhoGAM (which is the most commonly used name and anti-D solution). For convenience, the name anti-D will refer to any **Rh immune globulin (RhIgG)**. (Words in bold appear in the glossary).

Anti-D is a sterile solution that contains concentrated antibodies to the Rh factor and that originates from human plasma (the liquid part of blood). The discovery of anti-D was the completion of a puzzle whose individual pieces include colorful particulars, such as the search for a safe diphtheria vaccine; research into butterfly mimicry; Indian monkeys; and Sing Sing prison inmates.

This paper seeks to give parents / midwives / doctors the information they need to make an informed choice regarding the use of anti-D &/or citrus bioflavonoids. The reader will also be exposed to the reasoning behind various positions regarding the use of anti-D. A Biblical view will be considered. Understanding various viewpoints will aid parents and health care professionals to interrelate and cooperate as much as possible. The intent of this paper is to prove that vital information (the use of citrus bioflavonoids and the management of the third stage of labor) has been overlooked, causing current statistics on the incidence of isoimmunization to be higher than they should be and overlooking a possible preventive treatment for women who have been isoimmunized.

The following paper stems from over 40 recently-published medical reports, including well-documented case reports; documented and supported research; retrospective audits; inquiries; surveys (one such covered over 3,500 institutions); retrospective and prospective studies (two covered a 10-year period); established parameters from recognized medical societies; a consensus conference from the Royal Colleges in Britain; as well as primary research. The doctors and medical journals represent 12 countries: Australia, Canada, China, Denmark, France, India, Ireland, Israel, New Zealand, Switzerland, the United States, and the United Kingdom. Several articles from midwifery journals include testimonies; surveys; and secondary and primary research and offer paradigmatic counterbalance. Various midwifery, nursing, and medical textbooks also shed light into the report.

An understanding of certain vocabulary is beneficial. In this context, an **antigen** is a protein marker that is found on the surface of a red blood cell (RBC). While the RBC remains in its owner’s body, the body recognizes the antigen and “accepts” the presence of the RBC. However, if the RBC is placed in another person’s body, his body can recognize the antigen as foreign and reject (destroy) the RBC. For this destruction to take place, the body produces another protein, called an **antibody**, that bonds to the foreign antigen and marks the RBC for destruction. **Isoimmunization** occurs when the blood of one person enters the circulation of another person and causes the recognition and destruction of foreign RBCs. **Hemolytic disease of the newborn (HDN)** occurs when a mother’s antibodies enter the fetus and destroy the baby’s RBCs.

Some weaknesses present with this type of paper, one being the inability to do one’s own primary research. Many published studies refer extensively to studies that date back 25-35 years. While research has continued through the present, resultant statistics stem from similar setting, i.e., standard obstetric practice. The shortcoming is exhibited by the lack of statistics related to birth in a non-medical setting. Each resource is weaker than it could be, due to the fact that each one is written by, and speaks only to, those who hold a given opinion; each study is not counterbalanced by research into opposing views.
Decisions regarding the use of anti-D can entail far-reaching consequences. Knowing the drug’s history will aid in dispelling fears that arise from a lack of information and will help in eliminating misconceptions related to the drug’s origin. Facts about isoimmunization offer the opportunity to evaluate the need for anti-D and to make well-informed choices. An understanding of blood issues calls for early testing that can relieve unnecessary fears and treatment. One will find the answers to common questions regarding anti-D (dosages, risks, etc.). Such foundational factors prepare the reader to consider and evaluate when anti-D should be used. Most people approach this question from one of three perspectives: scientific, intuitive, or Biblical.

HISTORY
The first known description of hemolytic disease of the newborn (HDN) dates back to 1609. Though scientists made anti-D available in 1969, its discovery stemmed from many others. In 1909, Theobald Smith, a professor at Harvard, was searching for a safe diphtheria vaccine. He injected guinea pigs with neutralized mixtures of diphtheria toxin and antitoxin. His research unveiled a principle of immunology: an antigen will not usually cause isoimmunization in the presence of excess passively acquired antibody. Since HDN was not well understood at the time, fifty years would pass before scientists would apply passive immunity to this disease.

The 1940s produced three vital discoveries. In 1940, Landstein and Wiener mixed the blood of rhesus monkeys with the serum (liquid part of blood) of rabbits and discovered an agglutinable (clumping) factor which would agglutinate the red blood cells of 85% of Caucasians. In 1941, Levine and colleagues associated hemolytic disease of the newborn (HDN) to the presence of the anti-Rh factor (Rh antibody, or anti-D) in the mother’s blood during pregnancy. In 1943, Levine observed that infants suffering from HDN had fewer ABO incompatibilities, suggesting that ABO incompatibility could reduce the incidence of isoimmunization.

The 1950s saw research change from observation to testing and benefited society with four discoveries. In 1952, Cyril Clarke, a physician who studied butterflies, found that blood group (ABO) inheritance was similar to the heredity of wing patterns in some butterflies. Clarke and Sheppard also found a prevalence of HDN among ABO compatible mothers and infants. In 1956, Stern et al. injected 39 Rh-negative male volunteers with Rh-positive red blood cells (RBCs) and clearly demonstrated that ABO incompatibility affords substantial protection against isoimmunization. In 1957, Jandl et al. coated Rh-positive RBCs with anti-D and injected them into Rh-negative male volunteers. The volunteers cleared the coated RBCs from their circulations in two hours, forty minutes, vs. 12 days for noncoated RBCs. In 1957, the Kleihauer Betke test received recognition as a method of detecting fetal RBCs in the mother’s blood.

Then the 1960s ushered in trials and testing that would produce an anti-D solution ready for use by postpartum women. In 1960, Finn suggested administering an anti-D solution to postpartum women to help them clear the Rh-positive fetal cells from their circulations before they could cause isoimmunization. In 1961, Finn et al. determined the incidence and amount of fetal RBCs among 256 Rh-negative postpartum mothers. In 1962, Hamilton (in the St. Louis area) treated the first postpartum mother ever to receive anti-D. He administered “raw” plasma from immunized mothers who had given birth to stillborn infants due to HDN. In 1963 and ‘64, three clinical groups reported protection against isoimmunization in men and nonpregnant women treated with anti-D. During this time, Freda et al. performed a trial involving Sing Sing prison inmates and confirmed that anti-D could prevent isoimmunization even if given after the entry of Rh-positive RBCs into the circulation. They had planned to administer the anti-D at 24 hours after the RBC injection. However, the warden’s concerns that such a schedule could encourage the possibility of a planned prison break caused the researchers to inject the anti-D at 72 hours following the RBC injections. This time limit formed the basis for our present-day, 72-hour protocol. Freda et al. also produced the first high-titer (higher concentration) anti-D preparation in 1963.

By using cord blood (vs. adult blood) in volunteers, Schneider showed that fetal RBCs are even more sensitive to anti-D than adult RBCs (1963). A parenthetical note of interest is that Hamilton
and Pilla were the first physicians in St. Louis to perform a successful intrauterine transfusion on a fetus with HDN (1964). In 1965, researchers first reported successful prophylaxis in Rh-negative postpartum mothers. In 1966, Woodrow and Finn determined through prenatal blood tests that fetal-maternal hemorrhage (FMH) was occurring during pregnancy. This finding led to the Winnipeg, Manitoba (Canada) group’s commencement of the first clinical trials of prenatal anti-D injections in 1968. Also in 1968, the United States licensed Rh immune globulin for postpartum use. The year 1969 is the official starting line for the routine use of postpartum anti-D given to mothers after the completion of each pregnancy.

The 1970s confirmed the benefits of anti-D and saw the introduction of prenatal prophylaxis. In 1970, researchers standardized anti-D preparations. By 1971, reports were revealing that postpartum anti-D was about 90% or more effective. In 1971, Pollack et al. determined how much anti-D was needed to protect against a given amount of Rh-positive blood. By 1977, Bowman (Winnipeg) reported that their trial of prenatal anti-D had been almost 100% effective in preventing isoimmunization.

The 1980s and ‘90s have served to confirm previous findings. Schneider and Brehens (1992) underlined that routine prenatal anti-D would reduce the incidence of isoimmunization by a factor of 10. In 1995, the United States approved an anti-D preparation for intravenous use. In 1997, a Consensus Conference held in the U.K. agreed strongly in favor of prenatal use of anti-D.

With the advent of effective anti-D in 1969, scientists paid no more attention to a remarkable discovery made in the late 1950s to early 1960s. Researchers had endeavored to find a cure or preventive to HDN and had succeeded in identifying a readily-available and easily-useable preventive--citrus bioflavonoids. Understandably, doctors and parents welcomed anti-D, and the bioflavonoid studies--which would still be benefiting many women today--sunk into oblivion.

ISOIMMUNIZATION

Isoimmunization is the normal immune system’s response that occurs in an Rh-negative mother when Rh-positive blood enters her circulation. (The opposite--an Rh-positive mother carrying an Rh-negative fetus--does not cause isoimmunization). The Rh factor is an antigen (a protein marker, often called D) which is found on the surface of RBCs of about 85% of Caucasians. When the Rh factor is present, the person’s blood is Rh-positive. If the Rh factor is absent, the individual’s blood is Rh-negative.

When exposed to fetal Rh-positive RBCs, an Rh-negative mother can develop anti-D (anti Rh-positive) antibodies to destroy those RBCs, much in the same way that an individual develops antibodies to destroy a virus. B lymphocytes (B cells) found in the spleen respond to foreign antigens by becoming plasma cells and producing antibodies. In isoimmunization, splenic B cells recognize Rh-positive RBCs as foreign and produce anti-D antibodies. This process can take days or weeks. The antibodies do not immediately destroy the foreign (Rh-positive) antigens, but rather label them for destruction. The RBCs dissolve as the antibodies agglutinate (clump) and rupture them.

Hemolysis (destruction of fetal RBCs) does not usually cause any symptoms in the mother, but the Rh-positive fetus is at risk for hemolytic fetal anemia and HDN. The affected fetus experiences RBC destruction that ranges from minimal to extreme. Maternal IgG (anti-D) antibodies cross the placental barrier by attaching to placental receptor sites and enter fetal circulation. Maternal anti-D then clumps and ruptures the fetal RBCs. The fetus can develop varying degrees of jaundice as the body eliminates the destroyed RBCs. Loss of RBCs can lead to anemia, for which the fetus compensates by increasing splenic erythropoesis (RBC production), which can cause splenomegaly (large spleen). Severe hemolysis leads to profound anemia, which can cause a large spleen and liver, severe swelling, congestive heart failure, fetal death, neonatal death, and kernicterus. Kernicterus is a serious complication of severe jaundice which causes 70% of affected infants to die; those who live will have permanent brain damage.
The first maternal isoimmunization does not usually cause fetal damage because antibody production is slow and in small amounts the first time. Unless the initial exposure is massive, it usually takes two exposures to cause HDN. Since the antibody response generally increases with each exposure, the prognosis (outcome) for each subsequent pregnancy is generally worse. However, antibody production varies from person to person. If a mother bears two or three babies with mild HDN, the disease will generally remain at that level for subsequent pregnancies. If a mother bears a severely-affected baby, she is 90% to 100% likely to have another severely-affected baby.43

What circumstances lead to isoimmunization? An Rh-negative woman can develop antibodies in various situations. Causes include a wrongly-typed/matched blood transfusion (which can be more likely in foreign or underdeveloped countries);22 miscarriage; abortion; ceremonial blood pacts;53 human error (wrongly-typed mom); and fetal-maternal hemorrhage. A note of interest is that one study showed a 2% to 3% incidence of error in blood typing when mothers were tested at delivery before anti-D administration.6 Two theories about the cause of isoimmunization also exist, one being the “grandmother” theory, which states that an Rh-negative woman could be isoimmunized at birth by receiving Rh-positive RBCs from her mother. The other theory suggests that isoimmunization could occur in a twin-to-twin transfusion where one fetus has Rh-positive blood and the other has Rh-negative blood.43 Isoimmunization occurring during pregnancy is probably due to the edges of the placenta coming loose from the uterus and bleeding slightly.55

Without the use of anti-D (RhGAM), 13-16% of Rh-negative mothers delivering Rh-positive babies are isoimmunized.55 Rh-negative women who are pregnant for the first time and who have uncomplicated deliveries have a 10% rate of isoimmunization if not treated with anti-D. The overall incidence of isoimmunization during uneventful first pregnancies is between 1% to 10%, with half occurring during the third trimester.40,56 However, the antibodies formed during the primary isoimmunization are often not detectable serologically (by blood test) until after the second exposure to Rh-positive blood. The risk of isoimmunization in both spontaneous and induced abortion is about 3% to 5.5% (varies with length of gestation), and one study reported an isoimmunization rate of up to 15% after induced abortion.31 One study reported that 15 obstetric units in England experienced a decrease in HDN from 1:170 births in 1969 to 1:500 births in 1988. Their mortality rate in 1953 was 1:2,000, decreasing to 1:65,000 in 1989 (due not only to anti-D, but also to advanced prenatal care, intrauterine transfusion, and improvements in neonatal care, making early planned delivery safer).9 Routine administration of prenatal (vs. only postpartum) anti-D in Britain decreased the isoimmunization rate from 1.3% to 0.4-0.2%, corresponding to studies done in 1978, 1983, and 1987.10 A study of 147 cases of isoimmunization showed that 22% of cases had occurred during the first pregnancy or at delivery; 39% during the second pregnancy; and 28% during the third pregnancy. In half of these cases, the mothers had experienced no potential immunizing event other than delivery. The three most common isoimmunizing events were delivery, abortion, and miscarriage.9

Volunteers have proven that isoimmunization can occur through exposure to as little as 0.1 ml of Rh-positive RBCs.6 Up to 3% of women who experience a fetal-maternal hemorrhage (FMH) of less than 0.1 ml RBCs can be isoimmunized.13 However, the chance of isoimmunization is usually related to the magnitude of FMH.40 About two to three fetal RBCs are equal to about 0.1 ml of blood.48

Approximately one-third of FMHs cause isoimmunization. About 30% of Rh-negative people are never isoimmunized, even when challenged with large volumes of Rh-positive blood.54 The balancing truth is that some women respond to tiny amounts of Rh-positive blood with high levels of antibodies. Researchers have named volunteers who do not form antibodies within six months nonresponders.40 A study in Taiwan showed that Asian women who have Rh-negative blood usually do not become isoimmunized.36

One study injected male volunteers monthly with small volumes (<10 ml) of RBCs (equivalent to <20 ml whole blood) until they produced anti-D. The responders equaled 68% of the entire group.
However, immunization rates rose to 85% in one study (1971) when volunteers received 200-250 ml RBCs. Another study (1981) showed a 93% immunization rate when researchers injected 200 ml RBCs as a primary immunization, allowed a waiting period of six months, and then followed with monthly booster injections of 0.5 to 1.0 ml RBCs. The response was 93% after the first boost. The study showed that the rate of isoimmunization among mothers varies according to the volume of FMH. Therefore, about 83% of Rh-negative women do not become isoimmunized during pregnancy with an Rh-positive, ABO-compatible infant, partly because the volume of cells to cross the placenta is often too small to induce isoimmunization.

Isoimmunized mothers produce varying amounts of antibodies, which causes varying degrees of illness among their infants. In one study, 17 already-isoimmunized mothers delivered Rh-positive babies. Of the 17 infants, 12 had maternal antibodies in their blood. Seven of the 12 affected babies needed prompt medical attention (41% of the 17 babies). Please refer to Appendix One.

FMH can theoretically occur at six to eight weeks gestation. The Rh-positive antigen has been identified on fetal RBCs as early as 38 days of gestation. The majority of FMHs occur during the third trimester and at delivery. Isoimmunization takes place at or after 28 weeks gestation in 92% of cases. In normal pregnancies with ABO-compatible fetuses, women have the following rate of FMH: 3% in the first trimester; 12% in the second; 45% in the third; and 50% at delivery.

Prenatal antibody titer levels (indirect coomb’s) indicate the degree of maternal isoimmunization, but they do not accurately convey fetal status. To perform an indirect coomb’s, the laboratory mixes maternal blood serum with Rh-positive RBCs. The RBCs agglutinate if maternal antibodies are present. The dilution of the maternal blood at which clumping takes place establishes the titer of maternal antibodies. The indirect coomb’s is negative if the titer is <1:4. Though prenatal anti-D causes a positive antibody screen, it will not usually cause a titer greater than 1:4. A result over 1:4 means that isoimmunization is likely.

During a first isoimmunized pregnancy, a low titer does mean that there is a low risk of fetal involvement (<10% incidence of fetal anemia and swelling). In such a case, the health care professional should perform monthly titers. If the titers remain low, the mother can probably carry the fetus to near term without other testing or intervention. However, in subsequent Rh-incompatible pregnancies, maternal titers are poorly predictive of fetal health. Amniocentesis can determine the amount of bilirubin in the amniotic fluid and can determine the severity of fetal hemolytic anemia. Some institutions will order an amniocentesis when a titer rises to 1:8. A level of ≥1:16 in most centers will demand an amniocentesis.

While anti-D prevents isoimmunization after FMH, citrus bioflavonoids work to prevent FMH altogether. Fetal blood can only enter the mother’s circulation through a “break” in the placental capillary system. During pregnancy, varying degrees of decidual (uterine lining) bleeding are normal. Causes include capillary dilatation, engorgement, and stretching which cause breakage. By strengthening the capillaries, bioflavonoids reduce breakage and thereby reduce FMH.

**BLOOD**

The presence or absence of A or B antigens on the surface of a person’s RBCs is what determines his blood group: A, B, AB, or O (absence of both A and B antigens). The presence or absence of the Rh (or D) antigen on the surface of a person’s RBCs is what determines his blood type (Rh-positive or negative).

The percentage of individuals with Rh-negative blood varies with race. The overall incidence among Caucasians (North Americans and most European whites) is 13% to 17%. About 8% to 10% of African Americans are Rh-negative. Hispanics have a rate of about 6%, and west Africans have a rate of about 5%. Less than 0.5% to 1% of Asians are Rh-negative. Of the four
million births per year in the United States, 15% (600,000) are from Rh-negative women. About 35% of the babies born to Rh-negative women also have negative blood.

A weak D (Rh) phenotype consists of a person’s having fewer D (Rh) antigen sites on his RBCs. The average Rh-positive RBC normally has a range of 9,900 to 33,000 D antigen sites per RBC. However, an individual with the weak D phenotype has a range of 110 to <9,000 D antigen sites per RBC. When Rh-positive RBCs combine with weak D blood during a blood typing test, the weakly-reacting D (Rh) antigens may not be directly agglutinated, causing the person’s classification as Rh-negative. However, some centers call this blood Rh-positive, and pregnant women in this situation will receive anti-D, but most of them will not have needed it.

Weak D mothers are generally not considered as candidates for anti-D because most of these women are able to tolerate Rh-positive RBCs without forming antibodies. Though rare cases of HDN have been reported in mothers with weak D, these women are usually called Rh-positive for two reasons. First, their RBCs can stimulate the production of anti-D antibodies. Second, they seldom produce anti-D antibodies themselves. However, one study (July, 2000) showed an incidence of 0.8% to 2.1% isoimmunization among patients found positive for the weak D phenotype.

The partial D (or D mosaic) phenotype is a much more unusual phenotype than weak D and differs in that it consists of a person’s having a portion of the D antigen missing. Though this blood type is called Rh-positive, there is a low occurrence of isoimmunization, and anti-D may help prevent it. Protocols concerning the use of anti-D in both weak and partial D are controversial.

Parental blood types determine the fetal blood type. If a couple both have Rh-negative blood, all their children will be Rh-negative, except in the very rare case of genetic mutation. A person is either homozygous for Rh-positive blood (has two positive genes) or is heterozygous for Rh-positive blood (has one negative gene, dominated by one positive gene). In order to have Rh-negative blood, a woman must have two negative genes. If a woman is Rh-negative, and the father of the baby is homozygous for positive blood, all of their children will be Rh-positive. However, if the father is heterozygous, every child has a 50% chance of being Rh-negative. About 40% of Caucasian, Rh-positive men are homozygous, and about 60% are heterozygous.

ABO incompatibility between a mother and fetus affords substantial protection against Rh isoimmunization. In 1956, Stern et al. demonstrated this fact by repeatedly injecting 39 male volunteers with Rh-positive RBCs. Of the 17 men who received ABO-compatible blood, 10 (58.8%) became immunized. However, of the 22 volunteers who received ABO-incompatible RBCs, two (9.1%) became immunized.

In cases of ABO-incompatibility, the mother is usually group O, and the baby is usually group A (or less often, B). The mother’s group O blood contains anti-A and anti-B antibodies (IgM), and her immune system may also produce similar IgG antibodies. If an O-negative mother is pregnant with an A-positive baby and a FMH occurs, there is a strong possibility that her immune system will react to the ABO incompatibility first. Her anti-A and anti-B antibodies will attach themselves to the foreign A or B antigens and destroy the RBCs before she produces antibodies to the Rh antigen.

Fetal blood type can be determined with about 50% accuracy as early as four to five weeks gestation. Amniocentesis, chorionic villus sampling, and cordocentesis can predict fetal blood type. In fact, three rapid and reliable DNA-based tests exist that accurately show fetal blood type by testing the amniotic fluid. However, a safer method also exists. A simple maternal blood test reveals the presence or absence of the Rh gene through reverse transcription by using mRNA rather than DNA. The RNA test excels above the DNA test by producing fewer false positives and false negatives. In a prospective study, blood samples from 96 pregnant women revealed fetal Rh type
with the following rates of accuracy: 48% accurate in the first trimester; 82% accurate in the second trimester; 85% accurate in the third trimester.

Though ABO incompatibility offers protection against isoimmunization, parents in this situation must understand that it does not offer guarantees. If a woman wants to avoid isoimmunization, she must not choose to avoid anti-D based on ABO incompatibility. However, prenatally determining the baby’s blood type to be Rh-negative can be a valid reason for not receiving anti-D or for substituting citrus bioflavonoids.

**ANTI-D**

Anti-D (RhoGAM) is a sterile solution of anti-D (anti-Rh) antibodies prepared from the plasma of individuals who have a high concentration of anti-D antibodies. Volunteers receive antigen (Rh factor) injections. Once they have formed antibodies, professionals draw their blood and concentrate the antibodies into a serum for injection. Endogenous (meaning *produced within*) anti-D is the anti-D that an isoimmunized woman produces herself. Exogenous (meaning *produced outside*) anti-D is the anti-D (RhoGAM) that a woman receives from donors.

How does anti-D prevent isoimmunization? Actually the mechanism of antibody suppression remains unfathomed. Two popular theories are *Antigen Blocking* and *Central Inhibition*. The first theory suggests that exogenous anti-D attaches to Rh-positive antigens and “coats” them, destroying them before the mother’s spleen has time to recognize them as foreign and form antibodies. The weakness of this theory is that the exogenous anti-D only covers a small percentage of the antigen sites.

The second theory suggests that the binding of exogenous anti-D to antigen sites causes the stimulation of lymphatic suppressor cells which inhibit the body’s production of antibodies. The exogenous anti-D would then destroy the foreign RBCs.

Anti-D (RhoGAM) can only prevent primary isoimmunization; once the immune system has produced endogenous antibodies, the body will always contain those antibodies. Since exogenous anti-D is preventative, it has no helpful effect in women who have already been isoimmunized (even weakly).

Anti-D (RhoGAM) does not remain in the body. Studies have shown that its half-life is about 21-30 days. One study reported that anti-D’s half-life is less than 21 days for most women. A half-life of 21 days (three weeks) means that 50% of the original dose remains three weeks after administration. Another three weeks cause the amount to drop to 25%, and so on, meaning that anti-D protects for about 12 weeks (about three months). If a woman receives anti-D at 28-30 weeks gestation, 10% or less of the original dose is present at 40 weeks gestation. Remaining levels are higher at 40 weeks with two doses of 500 IU at 28 and 34 weeks (vs. one dose of 1,500 IU at 28 weeks).

If a mother receives anti-D prenatally within 21 days of delivery (e.g., following amniocentesis, version, etc.), she will not necessarily need postpartum anti-D, as long as excessive FMH is excluded.

The body completely catabolizes (breaks down) anti-D within six months. Therefore, if a woman has anti-D antibodies in her blood after six months following delivery, those antibodies are endogenous, and she is isoimmunized. Since exogenous anti-D breaks down, subsequent Rh-positive pregnancies cause the woman to be subject to possible isoimmunization and the need for anti-D.

Standard anti-D dosages are based on the results of the injection of volunteers with specific amounts of Rh-positive RBCs, with and without anti-D prophylaxis. Please refer to Appendix Two. Researchers established that 20 mcg protects against one ml RBCs (two ml whole blood). However, not all preparations of anti-D are identical, and it is difficult to measure FMH accurately. For these reasons, the United Kingdom’s standard is to administer 25 mcg (125 IU) intramuscularly per one ml RBCs (two ml whole blood). Intravenous administration can allow a lower dose
because it takes less time to reach its maximum level in plasma than with an intramuscular injection.\textsuperscript{40} In the U.K., the standard postpartum dose is 100 mcg (500 IU), which protects against 5 ml RBCs (10 ml blood), affording protection against 99% of all FMHs. A Kleihauer-Betke test (KBT) then assesses whether the FMH was > 4 ml RBCs and whether additional anti-D is needed. In the U.S., the standard postpartum dose is 250-300 mcg (1,250 - 1,500 IU), which protects against 12 ml RBCs (24 ml blood), affording protection against about 99.8% of all FMHs. The higher dose virtually makes the KBT screening unnecessary.\textsuperscript{40} However, some believe that the health care provider should screen all women using the KBT, since 0.3% to 1.0% of all deliveries result in a FMH greater than 30 ml whole blood.\textsuperscript{6} Several studies showed that the majority of FMHs over 30 ml blood were in women who did not have an obvious potential immunizing event.\textsuperscript{6}

Prenatal doses are related to the volume of blood within the entire fetoplacental unit, as well as to anti-D’s half life. The reasons for the routine 300 mcg dose at the beginning of the third trimester (28-30 wks) are that most isoimmunizations occur after that time, and adequate levels of anti-D still remain near the end of pregnancy. However, about 0.4% of women are still not protected by 300 mcg due to larger FMH (>30 ml blood).\textsuperscript{54}

Primiparas are often given priority for financial reasons. The scarce and dwindling supplies of anti-D\textsuperscript{2}\textsuperscript{5} may cause health care professionals to ration prenatal doses when possible. The greatest cost benefits are thought to come from giving primiparas (women having their first child) priority, since many women do not have more than two to three children.\textsuperscript{27} If a woman received anti-D prenatally and postpartally in her first pregnancy, then became isoimmunized in her second pregnancy, her second child would most likely not be affected. Her third child may not be severely affected and may even have Rh-negative blood. Some health care professionals may use this reasoning to avoid offering prenatal anti-D to women in their second or third pregnancies.

Using anti-D can cause some side-effects and also carries risks. Though anti-D is usually well-tolerated, the most common reaction is discomfort (pain and swelling) at the injection site, and in a few cases, low-grade fever.\textsuperscript{6} One case report revealed that WinRho (IV) had lead to generalized urticaria (severe itching).\textsuperscript{18} Women receiving postpartum anti-D should also understand that live virus vaccines (measles, mumps, rubella, varicella) may not be effective for six weeks to three months following the administration of anti-D.\textsuperscript{6} Overdosing does not seem to be severely problematic to the mother, as some individuals have tolerated 3,000 to 7,750 mcg IV, and another person tolerated 17,700 mcg IM. Reactions ranged from minimal, to fever, to hemoglobinuria.\textsuperscript{6}

Allergic reactions are also slightly possible. If a woman is deficient in IgA, she can develop IgA antibodies and have an anaphylactic or severe systemic reaction. Thimerosal, a preservative (sodium ethyl mercurithiosalicylate, or merthiolate) is an antibacterial agent in many topical medications (contact lens solutions, vaccines, etc.). Its presence in anti-D preparations can cause large, temporarily-indurated (hardened) areas on the skin. Thimerosal in other products has caused contact dermatitis, inflammation of the cornea and conjunctiva, widespread inflammatory skin reactions, severe itching, wheezing, and acute laryngeal (throat) obstruction.\textsuperscript{25} Manufacturers are currently working at systematically removing thimerosal and mercury-related agents from vaccines.\textsuperscript{69} WinRho SD (Univax) does not contain thimerosal.\textsuperscript{25}

Women often fear the transmission of viral infection through anti-D. In the U.K. and North America, anti-D claims a 30-year history free of viral transmission.\textsuperscript{40} However, in the late 1970s, Ireland and East Germany saw over 1,000 women (and some children) become infected with the hepatitis C virus (HCV).\textsuperscript{7, 38} HCV was not identified until about 10 years later (1989), and serologic screening for HCV began in 1991.\textsuperscript{7, 38} HCV remains the most common virus to be transmitted by plasma-derived blood products.\textsuperscript{38} As for HIV, over 350,000 women in the U.S. receive anti-D every year, and no case of HIV transmission has been reported since anti-D’s first use in 1968.\textsuperscript{54, 55}

Safety precautions used in the manufacturing of anti-D enable it to be a relatively safe substance. Donors are subject to a full physical exam and medical history, as well as an in-depth questionnaire.\textsuperscript{43} HCV transmission has been linked to a few causes, including a lack of viral
inactivation after cold ethanol fractionation; the use of ion exchange chromatography without a subsequent viral inactivation step (either after or instead of cold ethanol fractionation); or a failure to maintain Good Manufacturing Practice.\textsuperscript{38} A variety of standards and tests exist regarding biological products in the U.S.A. Any anti-D manufacturing process should include at least one validated viral reduction step in addition to alcohol fractionation.\textsuperscript{40} In the U.K., the process includes PCR screening (for HAV and parvovirus B19), a solvent/detergent (S/D) step, virus nanofiltration, and screening for HIV I and II, HCV, and the absence of increased ALAT activity.\textsuperscript{2, 40} Canadian WinRho SD’s preparation includes a solvent/detergent step that inactivates lipid (fat)-enveloped viruses, including HIV, hepatitis B, and hepatitis C.\textsuperscript{6} As of 1994, the U.S. screens for HIV antibodies, hepatitis B surface antigens, hepatitis C antibodies, and elevated serum alanine aminotransferase (ALT, a marker for hepatitis).\textsuperscript{43}

However, risks remain for various reasons. A donor may be infected with HIV, etc. not know it, and donate blood during a seroconversion window period (period of time when infection is present, but antibodies are not yet detectable).\textsuperscript{38} Other risks involve viral mutation, nonresponder donors, viruses that are unknown and thus not tested for, and procedural error.\textsuperscript{38}

No harmful effects of anti-D have been reported regarding the fetus or the lactating infant. When a woman receives prenatal anti-D, small amounts cross the placental barrier and attach to fetal Rh-positive RBCs. This transmission can cause the direct antibody test (Direct Coomb’s) to be weakly positive at birth, meaning that the Rh-positive newborn has anti-Rh antibodies in his blood. Some feel this presence of antibodies carries risk because anti-D’s package insert explicitly warns not to administer anti-D to the infant. However, the standard doses (100-300 mcg) allow only a small volume to enter fetal circulation, volumes which would not be large enough to cause significant RBC destruction.\textsuperscript{40}

Studies from Canada, Denmark, Sweden, and the U.K. show that up to 10\% of anti-D given to the mother can enter the fetus (based on the IgG transfer in isoimmunized women).\textsuperscript{40} Even when women received anti-D before 20 weeks gestation, fetal levels of anti-D were insufficient to cause fetal or neonatal RBC destruction or anemia.\textsuperscript{40} Studies done in 1978 and 1989 also reported no adverse effects after the use of prenatal anti-D.\textsuperscript{6} Researchers assessed six blood factors (Hgb, PCV, MCV, reticulocytes, bilirubin, and direct Coomb’s) in 37 newborns. Of the babies whose mothers had had two prenatal anti-D doses, 20\% had a positive direct Coomb’s. Of the babies whose mothers had had only one prenatal dose, 2.4\% had a positive direct Coomb’s. The six blood factors were not significantly different between the two groups.\textsuperscript{14}

Concerns also exist regarding the effect of anti-D on the fetal immune system.\textsuperscript{62} In one study, children (four to 12 years) received anti-D. There were no immediate or long-term effects reported, but there was some compromise of lymphatic function for four to five months.\textsuperscript{47, 55} The question arises as to the strength of the impact on the immature fetal immune system.

Anti-D’s effectiveness in preventing isoimmunization depends on when a woman receives it. Postpartum administration of anti-D has caused the original 12-17\% rate of isoimmunization to drop to between 1.5\% and 2\% (decreasing the risk of isoimmunization by 90\%).\textsuperscript{19, 40} Several studies from various countries reveal that of the 1.5\% to 2\%, 0.7\% are isoimmunized due to FMH during pregnancy, and 0.2\% due to FMH during labor and delivery (too large to be covered by the routine dose).\textsuperscript{40, 46} In the U.K., prenatal use of anti-D caused the isoimmunization rate to fall from a mean of 1.12\% in 1988-91 to 0.28\% in 1993-95.\textsuperscript{32} Representing national statistics, one hospital in Michigan reported the following rate of isoimmunization: one woman in 238 (1974, postpartum anti-D only); one woman in 963 (1988, prenatal and postpartum anti-D); and one woman in 1,663 (1992, prenatal and postpartum anti-D).\textsuperscript{40} In one study of 147 cases of isoimmunization, an estimated 86\% could have been prevented through prenatal anti-D.\textsuperscript{9}

Hemolytic disease of the newborn (HDN) and perinatal deaths have also dropped. Between 1970-79, the U.S. saw the incidence of HDN decrease by 65\%.\textsuperscript{43} The U.K. reports a 100-fold decrease in
perinatal deaths since 1969. HDN-related deaths in the U.K. fell from one in 2,180 births (1953), to one in 5,400 births (1977), to one in 62,500 births (1990). Fundamental reasons for administering anti-D prenatally are two-fold. First, in normal pregnancies, 45% of women have fetal RBCs in their circulation by the end of the third trimester. Also, as one review showed, among women who had been isoimmunized, it was only possible to determine the isoimmunizing event in fewer than one in six affected pregnancies. Since one cannot predict isoimmunization, health care providers administer prenatal anti-D.

The only potential, medically acceptable alternative to anti-D is monoclonal anti-D. Produced in vitro, BRAD-5 is the only IgG1 monoclonal anti-D that has been shown to clear Rh-positive RBCs from Rh-negative human volunteers. In one study, a rhesus monkey received RhoGAM and human anti-D monoclonal antibody simultaneously. The RhoGAM’s half-life was 17 days, and the monoclonal’s half-life was 7.9 days. While monoclonal testing seems promising, and researchers completed preliminary trials in 1998, they are still unsure if monoclonal anti-D will be safe, effective, reliable, and affordable. They also do not know in how long it will be available. If monoclonal anti-D succeeded, it would be an unlimited source of anti-D antibodies.

Another possible alternative, citrus bioflavonoids, could be very beneficial in cases where a woman will not or cannot receive anti-D. Some women desire to avoid anti-D due to its potential risks. Others cannot use anti-D because they are already isoimmunized. In either case, citrus bioflavonoids work to prevent FMH and offer substantial protection.

SCIENCE

The medical protocol for the use of anti-D is based on scientific facts and statistics. The foundational reasoning is embedded in the effort to bring the isoimmunization rate down as much as possible.

After a birth, anti-D is given within 72 hours (after the neonate’s blood is typed). However, if the FMH was of a small volume, administering anti-D up to 13 days postpartum still offers some protection and is better than refraining from giving it late. Doctors usually administer anti-D even after a negative KBT (or any other fetal screen) since a negative result does not completely rule out the possibility of FMH.

Health care professionals usually administer routine prenatal anti-D at 28 weeks gestation if the woman has not been isoimmunized. This time frame protects against the highest percentage of FMHs and allows some anti-D to remain near the end of pregnancy. However, two doses of 100 mcg (500 IU) at 28 and 34 weeks (vs. the one dose of 300 mcg [1,500 IU] at 28 weeks) uses less anti-D and gives a higher concentration of circulating anti-D as term approaches.

There is a genuine (and often unrecognized) need for anti-D within 72 hours after potential immunizing events (PIEs). Appendix Three lists recognized PIEs. When vaginal bleeding occurs before 12 weeks gestation, the bleeding usually originates from maternal blood vessels in the decidua (uterine lining) or from the cervix, and not from fetal vessels in the chorionic villi. Since the risks of FMH and isoimmunization are therefore reduced, many health care professionals will not administer anti-D before 12 weeks gestation. Choriodecidual bleeding that occurs during a threatened miscarriage causes an insufficient amount of RBCs (<0.1 ml) to enter the mother’s circulation. However, if the choriodecidual space is breached (as in complete miscarriage and induced abortion), FMH is more likely. One study showed that the rate of FMH doubled after complete miscarriage followed by D&C (dilatation & curettage) and oxytocics, compared to the rate of FMH after threatened or incomplete miscarriage before surgery. After an induced abortion, 4% of women will have had a FMH >0.2 ml RBCs, and 4-5% of these women will become isoimmunized.

Obstetric complications also require anti-D prophylaxis. One exception is after the removal of a hydatidiform mole because no RBCs exist to cause isoimmunization. About 24% of tubal
pregnancies (with rupture) cause FMH. About 2% of amniocenteses (regardless of gestation) can cause FMH of at least 0.1 ml RBCs, even with ultrasound guidance of the needle. Percutaneous umbilical blood sampling and chorionic villus sampling carry an even greater risk of FMH and require a 300 mcg dose of anti-D.

Trauma during pregnancy increases the risk of FMH four to five times. Other situations that multiply the risk of FMH are anterior placement of the placenta, uterine tenderness after trauma, and wearing a seat belt during an automobile accident.

Whether a parent, midwife, or doctor agrees or disagrees with the use of anti-D, the reader should thoroughly understand the potential consequences of avoiding its use. Since anti-D is currently preventing the vast majority of HDN, only history can reveal the extent of suffering experienced before its discovery. Though the U.K. saw one HDN-related death in 2,180 births in 1953, the mother who lost her child experienced a 100% death rate. A mother who had been isoimmunized could experience three different outcomes: An infant with mild to moderate HDN but who survived; a live-born infant who died in the neonatal period in spite of all attempts at therapy (including blood transfusions); or a stillborn infant.

People today who consider not using anti-D may not realize the potential implications. Isoimmunization is irreversible, and subsequent fetuses and infants are often equally or more-severely affected that their older siblings. One must contemplate the pain of a mother who has only given birth to stillborn infants and who has no hope during pregnancy. Between 1940 and 1970, many a mother heard the woeful warning that her baby would probably die. Many a doctor has also fought for the life of an infant and then lost.

Understandably, many parents, midwives, and doctors are uneasy when someone considers not using anti-D. The subject of bioflavonoids may even prove a little irritating, due to their concern for the well-being of infants. Though avoiding anti-D may not be an acceptable option, one can still benefit from information about citrus bioflavonoids as they relate to women who have already been isoimmunized and who cannot receive anti-D.

**ALTERNATIVES**

While the preceding information delineated the scientific viewpoint, the following represents a general perspective that is common among the midwifery community (parents included). However, not all midwives hold each of the philosophies. The word intuition denotes various methods of making decisions, for example, spiritual guidance, intuition, premonition, and feelings. However, not all views held by the general midwifery community stem from intuition. Some perspectives are born from years of experience in physiologic birth (i.e., birth without medical intervention) and also from research.

The general midwifery philosophy about pregnancy and birth is that they are normal, physiologic processes which rarely require medical intervention. Midwives generally believe that science has lost faith in the inherently normal pregnancy and birth processes. In fact, midwives tend to view interventions as potentially causing more harm than good; they question whether or not anti-D is truly an exception, and whether it is causing occult (hidden) problems. When studies show that 15% of women are isoimmunized without anti-D, the midwifery focus tends to remain on the 85% who would not need anti-D and are receiving it (and any of its potential risks) unnecessarily. Therefore, while science admonishes routine anti-D due to occult FMH, midwives often administer routine anti-D without fully accepting its routine use. Many midwives view the structure and physiology of the placenta as “nature’s protection.”

Many people who embrace the general midwifery philosophies also seek enlightenment from various other schools of thought. Often, they express the far-reaching belief that matters of health should be addressed holistically (from a spiritual, emotional, mental, and physical perspective). Their search for enlightenment leads them to sources such as alternative medicines, Eastern religions, New Age, spiritual guidance, intuition, and what they feel or think is right for them. Ultimately, the search for guidance leads to an inward contemplation, a search for inner strength
and wisdom. Trust in one’s self, in one’s own intuition, and in one’s own guidance becomes paramount.

Midwives have several reasons for not agreeing with routine use of anti-D. First, they point out that the medical protocol is based on the medical paradigm (prototype), which is characterized by notions of pathology. In other words, midwives disagree with the concept that pregnancy and birth are illnesses and disasters waiting to happen. Rather, some midwives view FMHs as occasional, accidental events which are often associated with, or caused by, medical intervention. They view physiologic birth as decreasing the need for anti-D, and medical birth as often causing the need for anti-D. Midwives often feel uneasy suggesting anti-D to their clients because of the inability for anyone to tell a woman her chances of isoimmunization and because of the potential risks of anti-D. The midwifery community is often wary of anti-D because laboratories can only screen for known viruses. Other causes for the lack of confidence in anti-D are that medical studies were all conducted on a population of women who experienced managed births and third stages. Also, a lack of conclusive evidence exists regarding the safety of the fetus and infant.

Midwives often refer to scientific studies which are largely overlooked by the medical community. Such research shows that many interventions increase the likelihood of FMH: oxytocics, fundal pressure, instrumental delivery, cesarean delivery, and managed third stage (cord traction, early clamping, massaging the uterus to cause contractions, and manual removal of the placenta). Certain midwives do believe that the following are indications for anti-D following an otherwise physiologic birth: “dirty” Duncan placental delivery (generally associated with low implantation and separation which starts at the edges); an unusually large placental site; and an abnormal third stage.

Fundal pressure and massaging the uterus can encourage the breakage of delicate capillaries. However, placing the newborn on the mother’s abdomen immediately after birth increases the volume of umbilical cord blood. In other words, the Rh-positive newborn’s best position after birth is on the mother’s abdomen because this position increases blood flow towards the baby (and away from the mother’s circulation).

The type of labor and mode of delivery affect FMH incidence rates. In one study, 18.5% of cesarean patients experienced FMH. These researchers recommend that doctors screen all cesarean patients by KBT because 2.5% of their group experienced FMH >30 ml blood and needed larger doses of anti-D. In India, a study of 100 women showed the following rates of FMH: normal, spontaneous delivery without oxytocics, 0%; normal, spontaneous delivery with oxytocics, 19.05%; forceps delivery, 40%; lower uterine cesarean, 50%; normal delivery with manual removal of the placenta, 100%.

Cord traction significantly increases the incidence of FMH and isoimmunization by causing tears in the vascular structures of the placenta. A study of 153 women tested the affects of not using oxytocics until after the placenta was delivered, and not using cord traction for placental delivery. Only 1.3% of the women experienced isoimmunization (detected by Indirect Coomb’s six weeks to six months postpartum), compared to the expected incidence of 9.2%. In this study, physicians cut the umbilical cord immediately after delivery of the newborn and allowed the maternal end to bleed until the placenta delivered. Contrary to this practice, Dr. Mendelsohn advocates that early clamping actually encourages FMH. He explains that clamping the cord before it stops pulsating causes a back-up of fetal blood (under pressure) into the maternal circulation. Dr. Mendelsohn also reports that those who delay clamping the cord until it stops pulsating report an almost zero incidence of isoimmunization.

In the early 1950s, Jacobs administered 600 mg daily of the citrus bioflavonoids (citrus vitamin P, CVP) to six already-immunized women (beginning at 14 weeks gestation). He noted that capillary fragility was a prominent feature of HDN. One woman’s baby was healthy after a previous hydropic stillbirth. Three women showed no titer rise throughout their pregnancies and gave birth to infants who were unaffected or less affected than previous siblings (clinically and by laboratory
test). The CVP almost eliminated the need for exchange transfusions (though they were done in keeping with protocol).45

In 1960, Jacobs reported the results of a study of 71 already isoimmunized women who did not receive CVP, compared to 32 isoimmunized women who did receive CVP during pregnancy. The women took 400-600 mg daily, from early pregnancy until delivery. The CVP study proved that it is possible to reduce a second FMH. The following table presents the results. Statistically, CVP saved 13 lives in a study of only 32 women.44

<table>
<thead>
<tr>
<th>GROUP 1: Women who had had one or more mildly- to moderately-affected infants who survived.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CVP: 32 babies, 68.8% survived</td>
</tr>
<tr>
<td>Took CVP: 16 babies, 93.7% survived</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP 2: Women who had had one or more live-born infants who died.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CVP: 24 babies, 0% survived</td>
</tr>
<tr>
<td>Took CVP: 6 babies, 50% survived</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GROUP 3: Women who had had one or more stillborn infants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CVP: 15 babies, 0% survived (all stillborn)</td>
</tr>
<tr>
<td>Took CVP: 10 babies, 60% survived</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CVP: 30.9% survival rate</td>
</tr>
<tr>
<td>Took CVP: 75% survival rate</td>
</tr>
</tbody>
</table>

A 10-year study confirmed similar findings,76 (however, due to technical difficulties beyond one’s control, more details will follow in the final draft). :-)

One may wonder if vitamin C (ascorbic acid, VC) is as beneficial as CVP. Clayton et al. (1967) reported that VC alone was less effective than CVP with VC in preventing FMH.70 However, both VC and CVP work synergistically (together) to increase capillary strength, prevent abnormal vascular permeability (prevent hemorrhages and ruptures), and strengthen the utero-placental attachment.43, 71

An expectant woman needs 1,000 to 3,000 mg VC daily.72, 73 Regular and extremely large doses of VC can cause the newborn to experience a deficiency and scurvy-like symptoms.72 Therefore, a woman should not exceed 5,000 mg/day during pregnancy.73 Though high doses of VC act as an antioxidant and are beneficial, they can also lead to the formation of kidney stones.71, 74 In order to prevent stones, the mother should also take daily doses of calcium, magnesium, vitamin B6, and should drink at least 2 liters of water daily.74 The mother should eat natural sources of VC, which include citrus fruits, berries, green and leafy vegetables, tomatoes, cantaloupe, potatoes, sweet bell peppers, and rosehips (richest natural source).72 Based on the references noted, the author recommends that the Rh-negative mother also take supplements: 1,000 mg VC (time release), three times daily.

In CVP, the “P” stands for permeability because CVP is sometimes called the permeability factor. CVP is also named C complex and citruses salts and is composed of citrin, rutin, hesperidin, flavones, and flavonals.74 For every 500 mg of VC, an Rh-negative woman should take at least 100 mg CVP.74 Frequent doses contain 500 mg CVP with 50 mg of rutin and hesperidin. When choosing a supplement, one should know that if the ratio of rutin and hesperidin are not equal, the ratio should be 2 (rutin):1 (hesperidin).74 No known toxicity exists for CVP.71, 74 Natural sources include the white pulp and “skin” of citrus fruits, apricots, blackberries, cherries, rosehips, buckwheat, plums, black currents, soybeans, and alfalfa.71, 74, 75 Based on Jacob’s reports and the references noted, the author recommends 400 mg CVP (with rutin and hesperidin), time release, three times daily (to be taken with the three doses of VC).
Some parents may wonder whether or not the Bible has anything to say that would help them in their decision regarding the use of anti-D and citrus bioflavonoids. Though God’s Word does not directly address the anti-D issue, it does contain principles which a believer can apply to this decision process. In the same way that two believers can have differing practices about food or holidays (Rom.14), two believers may apply Biblical principles and come to different conclusions regarding anti-D. They can find solutions prompted by God’s Spirit and specifically adopted for their individual needs.

It should be noted that humanism and evolution have tainted society’s philosophies. Many people believe that they can disregard the use of technology or medicine because birth and pregnancy are supposed to unfold perfectly. While the design is perfect, humans live in a fallen world and cannot force birth to function perfectly by imposing an unfounded confidence upon it (Rom.8:20-23). One the other hand, the evolutionary thinking process reveals itself in statements that an HDN-affected fetus or baby who dies was perhaps not “meant to live,” and that HDN may be a “self-limiting condition if left alone.”

A survival-of-the-fittest mentality directly opposes the Scriptural principle of caring for and upholding the weak and sickly (Rom.14:1; 15:1; 1 Cor.1:27; 9:22; 1 Thes.5:14). Paul gives the reminder, “I have showed you all things, how that so laboring ye ought to support the weak, and to remember the words of the Lord Jesus, how he said, It is more blessed to give than to receive” (Acts 20:35). David, Jesus, and the apostles exemplified caring for the weak and thereby honored the Godly principle of the sanctity of human life (2 Sam.9:3; Mt.4:23-24; Acts 6:1-4). The sanctity of human life is based on the fact that God made man in His image (Gen.1:27). God commands His children to “. . . choose life, that both thou and thy seed may live” (Dt.30:19).

The Bible offers a strong, threefold “cord” from which to secure one’s decisions. Medicine focuses solely on scientific facts and statistics and ignores intuition and spiritual guidance, producing one strand from which to hang one’s decisions. Midwifery often focuses mostly on intuition, mistrusts scientific answers, and may ignore God’s authority, creating another lone strand from which to suspend one’s choices. However, the Bible encourages the Christian to consider both facts and feelings but then to govern them by the Holy Spirit’s guidance, allowing three strands from which to secure one’s choices. Ecclesiastes 4:12 states, “A threefold cord is not quickly broken.”

Proverbs 3:3, 5-6 explains the need to seek a Scriptural solution to the anti-D question. “Let not mercy and truth forsake thee: bind them about thy neck; write them upon the table of thine heart. Trust in the LORD with all thine heart; and lean not unto thine own understanding. In all thy ways acknowledge him, and he shall direct thy paths.” Truth is comparable to scientific fact which has been proven. Mercy means “the exception to the rule” and is comparable to times when one does not follow the anti-D protocol. God commands His children to hold mercy and truth in proper balance and to seek His guidance to do so.

How can parents facing the anti-D option prepare their hearts to seek God’s will? An individual must first have a genuine, personal relationship with God through Jesus Christ. God’s holy and just Word proclaims that, “There is none righteous, no, not one” (Rom.3:10), and that “All have sinned, and come short of the glory of God” (Rom.3:23); and that “The wages of sin is death; but the gift of God is eternal life through Jesus Christ our Lord” (Rom.6:23). God also tells us that Jesus Christ is our only salvation, “Neither is there salvation in any other: for there is none other name under heaven given among men, whereby we must be saved” (Acts 4:12).

The God of love then invites us, “For God so loved the world, that he gave his only begotten Son, that whosoever believeth in him should not perish but have everlasting life” (Jn.3:16) and promises that, “If we confess our sins, he is faithful and just to forgive us our sins, and to cleanse us from all unrighteousness” (1 Jn.1:9). “If thou shalt confess with thy mouth the Lord Jesus, and shalt believe in thine heart that God hath raised him from the dead, thou shalt be saved. For with the heart man believeth unto righteousness; and with the mouth confession is made unto salvation” (Rom.10:9-10). God’s Holy Spirit only guides those whom He indwells and seals for eternity (Jn.14:16-17; Jam.1:5-8; 1 Jn.2:20).
In love, God allows people to make a free choice in all issues, including the use of anti-D and citrus bioflavonoids. Parents are responsible to make the best choices they can. Since they are morally and sometimes legally responsible for the results, they should avoid confidence that borders on presumption. (It could be a presumption that the mother will not contract a new virus from the anti-D, or the presumption that the fetus will be just fine without anti-D). Responsibility should govern freedom. Faith and peace are involved in accepting the results of one’s decision.

CONCLUSION
The discovery of anti-D led to the neglect of citrus bioflavonoids. While anti-D helps prevent isoimmunization, citrus bioflavonoids help prevent FMH and do not carry risks or side effects. Women who are carrying Rh-negative fetuses, and those who have already been isoimmunized, are perfect candidates for trying citrus bioflavonoids and showing (through fetal screening and infant outcome, respectively) that this natural compound can still be helpful to women today. Health care professionals should not miss the opportunity to test the general efficiency of bioflavonoids by testing those women who are carrying Rh-negative fetuses; the fetal screen will reveal the presence or absence of fetal blood regardless of whether or not the fetus is Rh-positive or negative. Citrus bioflavonoids can also help to reduce the risk of FMH in women who have PIH, diabetes, or preeclampsia, even if they will receive anti-D. Citrus bioflavonoids have reduced the incidence of FMH and isoimmunization and have saved as many as 13 lives in only a few studies.

Many studies report that medical interventions (such as the management of the third stage of labor) increase the incidence of FMH and isoimmunization. Combined with the fact that information was gathered from standard obstetric practice, these reports prove that current statistics on the incidence of FMH and isoimmunization are higher than they could be. Various studies have proven the effectiveness of citrus bioflavonoids in preventing FMH and confirm that these compounds are a helpful preventive of isoimmunization, which health care providers should no longer overlook. Citrus bioflavonoids offer an “alternative” to anti-D in that they reduce the incidence of FMH and thereby reduce the need for anti-D in certain cases. Of course, care providers should administer anti-D when needed. This report provides the tools necessary to re-evaluate and re-instate citrus bioflavonoids in the care of Rh-negative women.

Several suggestions follow regarding the use of anti-D. During the initial prenatal visit, the care provider will want to take a thorough patient history, which should include various details: previous pregnancies, miscarriages, abortion, tubal pregnancy, blood pacts, blood transfusions, etc. One will want to chart whether or not the woman received anti-D after these events. The first prenatal visit will also serve to confirm the parents’ blood groups and types and to detect the presence of clinically significant antibodies in the maternal blood.

If the father of the baby has negative blood, then the baby will be Rh-negative also.\(^5\) If the father is homozygous for positive blood, the baby will be Rh-positive. A simple way to know if an Rh-positive father is a carrier of the negative gene is through his family members. If his sibling (born to the same parents) has negative blood, then he is heterozygous for positive blood and carries the Rh-negative gene recessively (see Appendix Two). The care provider may want to include an official copy of the sibling’s blood type in the mother’s chart. The father’s blood should otherwise be tested directly.

The midwife or doctor may then take a sample of maternal blood for the assessment of fetal blood type.\(^4\) Though accuracy is low in the first trimester, the first result can serve as a “confirmation” or contrast to subsequent testings. Doctors and midwives may want to consider administering anti-D later than 28 weeks to primiparas and women who have a history of going past their due date. If this factor is not taken into account, a woman may be left without anti-D prophylaxis in the week or so before delivering—a time when the mother is more prone to FMH, and when postpartum anti-D may prove too late. An alternative would be to administer a second dose near term, with or without postpartum anti-D, depending on a fetal screen.
After birth, the care giver will want to send cord blood to a laboratory for the assessment of blood group and type and weak D status. At the same time, a sample of maternal blood (refrigerated immediately) will show the presence or absence of fetal RBCs (fetal screen). If the screen is positive, the care provider may order a KBT to determine how much fetal blood is in the maternal circulation and how much anti-D to give.

Before administering anti-D, the care provider should retest for blood type (i.e., in centers where a percentage of error exists) and should document the absence of isoimmunization. Any care giver who administers anti-D is responsible to verify its purity to the best of his or her ability (check with the manufacturer for methods of viral detection and removal). Before administering anti-D, the health care provider should have informed the woman prenatally that anti-D preparations are a blood by-product and of the potential risk of side effects or viral transmission. The care provider should also explain the risks of not receiving anti-D and allow the mother to make a fully-informed consent.

Those who are determined not to use anti-D may benefit from the following suggestions. The care provider and parents may want to discuss using ultrasound to determine placental location. If it is anteriorly placed, one may want to avoid manual palpation. Rather, the care giver could assess fetal lie and position through the location of kicks/movement and PMI (point of maximum intensity of the fetal heart tones). Fundal height can serve as a marker for fetal growth. Patient refusal of anti-D must be documented. (Please refer to Appendix Four).

Avoiding unnecessary anti-D is possible. Following a miscarriage, birth, etc., the mother may choose to wait for the results of a fetal screen before receiving anti-D. In Australia, such a protocol is standard in order to avoid unnecessary use of anti-D. If amniocentesis is performed within 48 hours of delivery (e.g., to determine fetal lung maturity), the care giver can withhold anti-D until after the assessment of the newborn’s blood type. Care givers should be aware that prenatal anti-D and contamination of the cord blood by Wharton’s jelly can cause false positives of the newborn’s blood type. The care giver will use capillary or venous blood for a repeat test.

Parents who refuse anti-D must consider their decision alongside their convictions regarding birth control. Some parents may prefer to accept anti-D rather than face the possibilities of isoimmunization, severely affected infants, and the need for birth control.

Parents will want to avoid potential immunizing events as much as possible. They should avoid amniocentesis, unless the benefits would outweigh the risks. External cephalic version (turning a breech baby prenatally) can cause FMH. If their baby is breech, parents will want to consider having a chiropractor perform the Webster technique before opting for external cephalic version. The care giver attending the birth should leave the cord unclamped and uncut until the placenta delivers, or at least should not cut the cord until after it stops pulsating. The care giver should never pull on the cord (controlled cord traction). The care provider should also avoid touching the uterus to assess placental separation (no fundal massage or fundal pressure), if at all possible.

Though professional health care providers will not encourage women to refuse anti-D, some women will decline it. Once the decision is final, it is the care giver’s responsibility to protect the baby’s health to the best of his/her ability. The care provider can inform the woman of citrus bioflavonoids and encourage her to take them regularly (as well as women who are already isoimmunized). ☺
GLOSSARY

**Amniocentesis**: A doctor inserts a needle through the mother’s abdominal and uterine walls and withdraws some amniotic fluid for testing. Performed after the 14th gestational week.

**Antibody**: A protein molecule that is made in the blood and that destroys specific antigens, such as bacteria, toxins, or the Rh antigen by binding to them. After ABO antibodies, the anti-Rh (or anti-D) antibody is the IgG red cell alloantibody found most often in patients.

**Antigen**: A protein found on the surface of cells and that is recognized as foreign when it enters another person’s body.

**Chorionic villus sampling (CVS)**: A doctor removes a small tissue specimen from the fetal side of the placenta for genetic studies. Performed between 10-12 weeks of gestation.

**Direct Coomb’s**: A blood test that determines the presence or absence of maternal anti-Rh antibodies on the baby’s RBCs. The newborn’s blood is usually drawn from the umbilical cord.

**Fetal-maternal hemorrhage (FMH)**: The leaking of fetal RBCs across the placental barrier and into the mother’s circulation.

**Fetal screen**: A blood test that determines the presence of fetal RBCs in the mother’s circulation. The Kleihauer-Betke test (KBT) is a fetal screening test which is simple, inexpensive, and can be performed by any hospital laboratory. Other fetal screens are the rosette test, the enzyme-linked antiglobulin test (ELAT), the flow cytometry, and the GAT (gel antiglobulin test).

**Hemolytic disease of the newborn (HDN)**: The result of maternal antibodies entering the fetal circulation, shortening the fetal RBC life span, and destroying the fetal RBCs. HDN is characterized by mild to severe anemia, as well as the consequences of anemia.

**Indirect Coomb’s**: A blood test that detects anti-Rh (or anti-D) antibodies in the mother’s blood. Antibodies are usually detected between six weeks to six months after exposure to Rh antigens.

**Isoimmunisation**: The development of antibodies as a result of exposure to foreign antigens from another human being.

**Passive immunity (artificial, passive, acquired immunity)**: Protection against certain microorganisms (antigens) after receiving an injection of pre-formed antibodies from a donor.

**Percutaneous umbilical blood sampling**: A doctor inserts a needle through the mother’s abdomen and uterine wall, directly into a fetal umbilical blood vessel, and draws 1-4 ml of fetal blood for testing. Performed during the second or third trimesters. Synonym: cordocentesis.

**Rh immune globulin (RhIgG)**: The main antibody found in the human blood. It is capable of moving across the placental barrier.

**Wharton’s jelly**: The white, gelatinous substance that protects the umbilical cord vessels and gives the cord strength.
**A GLANCE**
**AT THE INCIDENCE OF ISOIMMUNIZATION**
**WHEN ANTI-D IS NOT USED**

* In this table, each character (N, T, +, 1) represents one of 100 Rh-negative woman carrying or delivering an *Rh-positive, ABO-compatible* baby.

* The top half (50%) experience FMH. The lower half do not experience FMH.

* N = A Nonresponder (will never produce antibodies).
  T = FMH is *Too small to cause antibody formation, or antibodies are not detectable.*
  + = Women who become isoimmunized.
  1 = Women who do not experience FMH.

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# ANTI-D DOSAGES & EQUIVALENTS

IU = International Unit; mcg = microgram; ml = milliliter; IM = intramuscular; IV = intravenous

<table>
<thead>
<tr>
<th>IU anti-D</th>
<th>mcg anti-D</th>
<th>Route</th>
<th>ml RBCs</th>
<th>ml whole blood</th>
<th>wks gestation</th>
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<tr>
<td>250</td>
<td>50</td>
<td>IM</td>
<td>2.5</td>
<td>5</td>
<td>induced or spontaneous AB &lt;12 wks (unlikely for total fetal blood volume to approach 5 ml, &amp; complete exsanguination unlikely)</td>
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<td>1,250 to 1,500</td>
<td>250-300</td>
<td>IM/ IV*</td>
<td>10-15</td>
<td>30</td>
<td>prenatally at 28 wks; AB, misc., ectopic pg., or other pg complication &gt;12 wks; amniocentesis, CVS &lt;34 weeks; OB complication (e.g. placental abruption, previa)</td>
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<tr>
<td>1,500</td>
<td>300</td>
<td>IM</td>
<td>10-15</td>
<td>30</td>
<td>within 72 hrs pp; amniocentesis, CVS, or other manipulations during pg &gt;34 wks</td>
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<tr>
<td>600</td>
<td>120</td>
<td>IV*</td>
<td>15</td>
<td>30</td>
<td>within 72 hrs pp; amniocentesis, CVS, or other manipulations during pg &gt;34 wks</td>
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* Large FMHS are one indication for IV use, since IM injections of large volumes of anti-D are painful.

--1 ml = 300 mcg (1,500 IU) IM (1 dose or vial)
--1 mcg = one millionth part of a gram (one-thousandth of a milligram)
--20-25 mcg (100-125 IU) IM protect against 1 ml RBCs (2 ml whole blood)
--1 mcg IV = 5 IU IV

* Fetal blood volumes:

  <12 wks = <5 ml
  12 wks = 3 ml (the entire fetoplacental blood volume)
  19 wks = 25 ml
  <20 wks = <30 ml
  31 wks = 150 ml

References:  2, 3, 6, 17, 40, 54, 60, 63
PREGNANCY-RELATED INDICATIONS FOR THE USE OF ANTI-D

Routine:
* Prenatally at 28 (and 34) weeks gestation
* After the delivery of an Rh-positive infant

Miscarriage / Abortion:
* Threatened miscarriage after 12 weeks gestation
* Threatened miscarriage before 12 weeks gestation if bleeding is heavy, repeated or associated with abdominal pain. Intermittent bleeding after 12 weeks gestation should be treated with anti-D at six-week intervals.\(^{13}\)
* Spontaneous complete miscarriage after 12 weeks gestation (especially with D&C)\(^ {41}\)
* Ectopic pregnancy
* Induced abortion--any gestational week

Trauma:
* Abdominal trauma
* Automobile accident or fall
* Invasive prenatal diagnostic procedures (amniocentesis, PUBS, CVS)
* External cephalic version

OB Complication:
* Prenatal vaginal bleeding
* Intrauterine fetal demise
* Stillbirth
* Cesarean delivery
* Placental abruption, placenta previa (often associated with large FMHs)
* Intrauterine manipulations (manual removal of the placenta)
* Placental chorioangioma, choriocarcinoma (often associated with large FMHs)
* Trophoblastic disease or neoplasm
* Preeclampsia, toxemia, PIH

References: 6, 8, 13, 40, 41, 62, 66
INFORMED REFUSAL OF ANTI-D ANTIBODIES

I, ______________________________ refuse to accept an injection of anti-D antibodies (RhoGAM, or an equivalent) after having experienced _______________________________________________________(miscarriage, birth, etc.).

My reason(s) for refusing the anti-D antibodies:

_________________________________________________________________________________

_________________________________________________________________________________

_________________________________________________________________________________

My health care provider has informed me of the potential risks of refusing anti-D, and I have understood these risks. I understand that my refusal could lead to my isoimmunization; fetal hemolytic anemia; medical interventions (such as amniocentesis, intrauterine blood transfusions, induced early labor or cesarean delivery, etc.); hemolytic disease of the newborn, stillbirth, the baby’s need for one or more complete blood transfusions after birth, or neonatal death. I accept full responsibility for any consequences related to my refusal of anti-D antibodies.

Signature: _______________________________

Witness: _______________________________

Signature of health care provider: _______________________________

Date: _____________________________
INFORMED CONSENT FOR THE USE
OF CITRUS BIOFLAVONOIDS

I, _____________________________ have been informed of my state of isoimmunization, which I understand to be irreversible. I understand that the use of citrus bioflavonoids does NOT guarantee a good or better (than previous pregnancies) outcome. I understand that despite my use of citrus bioflavonoids, fetal maternal hemorrhage may still occur, which could lead to fetal hemolytic anemia; medical interventions (such as amniocentesis, intrauterine blood transfusions, induced early labor or cesarean delivery, etc.); hemolytic disease of the newborn, stillbirth, the baby’s need for one or more complete blood transfusions after birth, or neonatal death. I understand that citrus bioflavonoids offer only possible protection.

Signature: ____________________________
Witness: ______________________________

Signature of health care provider: ____________________________
Date: ____________________________
## Record of Consumption of Citrus Bioflavonoids

Name ________________________________ Date __________________

**Vitamin C supplement:**
- Company & Product Name (time release?) ___________________________
- Dosage per tablet ____________ Tablets per day ____________

**Citrus bioflavonoid supplement:**
- Company & Product Name (time release?) ___________________________
- Dosage per tablet ____________ Tablets per day ____________

> “6 / 7” means that the stated dosage was taken six days out of seven for that given week.

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2. Octapharma, Advertisement for WinRhoSD™


55. Gaskin I M, “Is Prenatal Rhogam Dangerous?”


58. The Holy Bible (KJV), New York: American Bible Society.


62. (author and date unknown), “Issues Regarding the Use of Routine Prenatal Rhogam.”


