Prenatal RhoGAM for Rh Negative Mothers

NOTE - Although RhoGAM in the United States used to be preserved with thimerosol, a mercury derivative, most of the RhoGAM in the United States is now preservative free, so there are no mercury derivatives in it. It doesn't hurt to ask about it, though, just to be sure!

Fetal Rh Genotyping from the mother's blood is now available!

The SensiGene™ Fetal RHD Genotyping test is a highly-specific direct detection test for fetal RHD status from a simple blood sample from the mother.

Here's the information for patients.

For about 38% of women, this means they would not need the 28-week RhoGAM shot!

Fetal Nucleic Acid Technology - SEQureDxTM, a Sequenom Technology is a revolutionary approach to genetic screening. Rather than harvesting placental tissue cells (as is required for chorionic villus), or entering the uterus to sample the amniotic fluid surrounding the baby (as is done with amniocentesis), SEQureDx Technology extracts DNA material safely and comfortably **from the blood of the mother. The first application is the analysis of fetal RhD, i.e. Rhesus or Rh status.**

Determining Fetal Rh Status from Mother's Blood

Maternal PCR Blood Test Accurately Determines Fetal Rh Status [Medscape registration is free]

Noninvasive prenatal RHD genotyping by real-time polymerase chain reaction using plasma from D-negative pregnant women.
Zhou L, Thorson JA, Nugent C, Davenport RD, Butch SH, Judd WJ.
Am J Obstet Gynecol. 2005 Dec;193(6):1966-71.

CONCLUSION: Fetal RHD genotyping in this study correctly predicted fetal Rh status in 92 of 98 (94%) cases.

Fetal RhD genotyping by maternal serum analysis: a two-year experience.
Gautier E, Benachi A, Giovangrandi Y, Ernault P, Olivi M, Gaillon T, Costa JM.
Am J Obstet Gynecol. 2005 Mar;192(3):666-9.

CONCLUSION: The present report demonstrates that a reliable fetal RHD genotype determination can be achieved with 100% accuracy. It is therefore possible to consider that such an assay could be systematically proposed to all RhD-negative pregnant women in order to more effectively utilize RhD prophylaxis.

An associated editorial.

Management of pregnancies with RhD alloimmunisation. [full text]
Kumar S, Regan F.
BMJ. 2005 May 28;330(7502):1255-8.

"Anti-D immunoglobulin is no longer necessary in women with threatened miscarriage with a viable fetus and cessation of bleeding before 12 weeks' gestation"

If you are really interested in the science, history, and ethics of Rh immune disease, I HIGHLY recommend the book Rh: The intimate history of the conquest of a disease by David Zimmerman. It was published in 1970-something, is out of print, but can still be found at www.abebooks.com.

Rh isoimmunization Guidelines and free full text articles

Metacollection of relevant links

By rights, a Kleihauer should be done on *all* Rh -ve mothers of Rh +ve babies postpartum, although I know that this isn't the standard of care everywhere. The generally accepted figure is that at least 75% of women have some degree of feto-maternal haemorrhage after a birth (usually expressed as a percentage figure in the lab report). Although the Kleihauer is a reasonably accurate test, I'm aware enough of lab errors and the things that can go wrong to be very unwilling to bank on it as a means of determining whether or not someone needs RhIG.

RhIG is expensive. I'm quite confident that if the Kleihauer were sufficient to determine whether or not a woman required RhIG, our health care system up here would have adopted that as policy long ago. However, isoimmunization can be such a disaster, that, understandably, no one would ever take the risk that something didn't go awry in the testing or the report.

We're far enough removed from the times when babies had complete exchange transfusions (sometimes in utero) for hemolytic anemia and when stillbirths from hydrops fetalis caused by isoimmunization were common that we think we can be cavalier about this.

Screening for D (Rh) incompatibility from the National Guideline Clearinghouse

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When mom is Rh negative and dad is Rh positive is there any value to the blind prophylactic RhoGAM shot at 28 weeks? By blind I mean there hasn't been any bloodwork to confirm sensitization or any episodes of bleeding.

The thing that's hanging me up is the postnatal requirement that the mom gets the shot within 72 hours after birth to prevent sensitization, and the fact that the 28 week shot is given in case one of those seemingly mythical *microbleeds* has occurred. If a microbleed has occurred, wouldn't the RhoGAM have to be administered within 72 hours also????

I am not quite understanding your point about a blind prophylactic shot at 28 weeks. No one I know does the shot "blindly" . We always check for antibodies prior to giving RhoGAM. For one reason, it won't do any good to give RhoGAM in the presence of antibodies.

I am going to quote from Susan Blackburn's book, Maternal, Fetal and Neonatal Physiology in order to help answer your questions:

Normally during pregnancy, the small amounts of fetal blood (<0.05 ml) that cross the placental and enter the maternal circulation are too small to trigger production of antibodies by the mother's immune system. In a few women however, as little as 0.01 ml of fetal blood has been reported to cause maternal immunization (sensitization). Approximately 1 to 2% of Rh-Negative women develop anti-D antibodies during their first pregnancy.
With delivery and placental separation or with other traumatic events, larger quantities of fetal blood (>0.5 ml) may enter the maternal circulation. This amount of fetal blood (if the fetus is Rho(D) positive) is sufficient to stimulate formation of both anti-D antibody and memory cells in many women. Formation of memory cells results in immunization [sensitization]. Once a woman is immunized, she is immunized for life. During subsequent pregnancies even a very small amount of blood from a Rho(D) positive ferus entering her system may be enough to trigger memory cells to produce antibodies against the D antigen on the fetal RBC. The antibodies that are produced in this secondary response are predominantly of the IgG class and are thus able to cross the placental to the fetal circulation and hemolyze fetal RBC's. With each subsequent exposure.... the immune system's response is as intense as previous responses, and ....may respond more rapidly and intensely with each subsequent pregnancy.

If an event such as bleeding has occurred, a miscarriage, ectopic pregnancy or version which could cause bleeding occurs, then RhoGAM should be given as soon as possible after the event. In other words you wouldn't wait till 28 weeks. The 28 wk shot is given to prevent sensitization from an unknown bleed, and does seem to significantly reduce the rate of overall sensitization compared with only giving RhoGAM postpartum. [With no administration of RhoGAM postpartum in the presence of an RH+ fetus, 10 to 14% of all Rh- mothers may become sensitized. This is reduced to less than 2% with postpartum RhoGAM and less than 0.2% with antenatal RhoGAM in addition at 28-29 weeks].

The mechanism of RhoGAM in preventing sensitization may be due to:

1. clearance of antigen from the mother's system
2. blocking of the antigen brought about by the attachment of RhoGAM to the antigenic sites of fetal cells in the mother's circulation, or
3. some sort of more central type (systemic) inhibition of antibody formation

The 72 hour rule emerged from the original trials with Rh IG. Since it can take several weeks for the body to mount a full antibody response, it is possible that RhoGAM could be given much later than 72 hours after an exposure and remain effective.

However, the parameters for how long it would be possible to wait are not known. Obviously, if it is known that an exposure has occurred, then it would seem prudent to give the RhoGAM as soon as possible. But in terms of your question, it is probable that if an *unknown* exposure occurred more than 72 hours prior to giving the injection at 28 weeks, and antibodies have not yet developed, then potentially that RhoGAM would offer protection against the development of those antibodies.

There is evidence that giving the RhoGAM up to 13 days after birth still confers some protection.

Regardless of what seems like it *ought* to be true, we have hard empirical evidence that the 28-week shot does reduce the incidence of Rh immunization from 1.8% to 0.1%.

For both of these factoids and many, many others on this subject, see the amazingly thorough discussion in chapter 70 of one of my favorite OB books, Albert Reece's "Medicine of the Fetus and Mother" (Lippincott 1992).

Actually, RhoGAM is not given at 28 weeks to prevent isoimmunization from bleeds that *already have occurred*, but to prevent isoimmunization from bleeds which might occur from 28 weeks - delivery.

And the reason for the 28 week time is that RhoGAM is supposed to be effective for approximately 12 weeks.

My memory of the stats around prenatal RhoGAM is that 2% of women will be sensitized prenatally if they don't receive RhoGAM and the routine administration of RhoGAM at 28 weeks to all non-sensitized women with Rh pos FOBs reduces that to almost zero.

The truth about RhoGAM is that no one knows what the window period of effectiveness is. For all we know, the postpartum shot from the previous baby might still be operating several years later. The 72 hour window was established by the man who first developed RhoGAM (At Columbia Presbyterian Hospital in New York, using some NYS prison). He tested it on prisoners several hours away from his laboratory. He and the warden picked out three days after exposure for administration

kinda out of a hat and he never (nor did anyone else, as far as I know) did any research on what the limits are. All we know is that it works when given within 72 hours, but no one knows what the upper limit of effective time period is.

We also know that the vast majority of sensitization occurs at birth.

Previous sensitization with Antibody M already puts the baby somewhat at risk, I can only assume that your doctor is thinking to take prenatal RhoGAM to reduce your chances of developing yet another type of sensitization, thus compounding your problems in any future pregnancies, since it would have no impact on your current anti-M status. I still feel that RhoGAM during pregnancy is controversial and perhaps quite ill advised and encourage you to use one of the newly available preservative free types available in the US if you decide to go with it. call 1-800-344-6087 to find out how to get it in your area.

I have a client who is 9+ weeks, Rh-, and bleeding enough to have clots. She has done this with her other 2 viable pregnancies -- don't know yet if this pregnancy is viable. Regardless -- should she have RhoGAM now? (She's had 28 week RhoGAM with the other 2, and 72 hour RhoGAM) And, is this early, prenatal RhoGAM protecting THIS baby, or the next one?

I just updated our OB Guidelines. I am forwarding the info on RH Negative mothers. Any questions let me know. Hope this is helpful.

RH Negative Management:
If father of the baby or donor is Rh positive or unknown, the patient is a candidate for RhoGAM prophylaxis in the following cases:

1. Micro RhoGAM - Should only be given if a pregnancy terminates before 13 weeks (TAB, SAB, Ectopic, Molar)
2. Full dose is given:

- Threatened abortion at any stage with confirmed pregnancy
- Abortion, ectopic, or molar pregnancy at or beyond 13 weeks
- Genetic amniocentesis
- Unexplained first, second or third trimester bleeding
- Abdominal trauma 2nd or 3rd trimester

- Third trimester amniocentesis

*if amnio repeated in >21 days another full dose of RhIg should be given
*if amnio is performed and delivery is anticipated within 48 hours, administration of RhIg can be with held until after delivery and determination of the newborn to be Rh positive can be made

- Antepartum prophylaxis at 28 weeks
- External version
- delivery is anticipated within 48 hours, administration of RhIg can be withheld until after delivery and determination of the newborn to be Rh positive can be made
- Post dates pregnancy beyond 40 weeks
- 12 weeks since last RhoGAM, repeat antibody screen and administer RhIg

*if delivery occurs within 21 days of administration of RhIg and examination of maternal blood sample does not reveal an excessive amount of fetal RBC's additional RhIg is not needed

10. Postpartum (if NB Rh Pos)

- If patient elects not to receive RhoGAM at 28 weeks, repeat antibody screen every 4 weeks until delivered.
- If at any time the patient's antibody screen is positive obtain MD consultation.

Intrapartum - Obtain cord blood for Type & Rh and direct coombs

>Postpartum -

- If direct coombs is positive obtain cord bilirubin
- If newborn is Rh positive, have RhIg given to the mother within 72 hours of delivery. (Current recommendations is one vial if fetal RBC's < 25ml and two vials if 25-50 ml and so forth.)
- If mother is a RhoGAM candidate and is also Rubella Non-Immune, administer the RhoGAM and hold the rubella vaccine until 3 months postpartum.

There's a movement towards declining RhoGAM.

anti-d: exploring midwifery knowledge by sara wickham

The above article is incorrect in talking about RhoGAM as a vaccine. Actually, RhoGAM is the opposite; instead of evoking an immune response, it suppresses the immune response.

Back when I was a green apprentice, one of the clients developed Rh sensitization; the midwife never offered her RhoGAM. She was a first-time mom with an uncomplicated labor and birth.

In the early days of Rh research, they found that ABO incompatability is protective against sensitization. (Levine,L. American Journal of Public Health 38:645-651, 1948)(Wiener, A. Proc.Soc.Exp.Biol., Med 58:133-135, 1945)

I have read a few articles stating that there is a theoretical risk that if the woman is carrying an rh- GIRL and she is given prenatal rhogam, the baby girl can be sensitized to all future pregnancies. This hasn't been proven, and I don't know how true it could be, but it does remind us that there may risks of which we are yet still unaware.

Since Rh Immune Globulin is just that -- antibodies, with a lifespan of about 120 days -- I don't know, from a physiological perspective, how that could cause sensitization, which requires an antigen to trigger the immune system response.

RhoGAM for Early Miscarriage

Well, I have the DEFINITIVE answer. On CSI Las Vegas (now this is a credible medical source, right? LOL) Gil Grissom said the babe has circulating blood at 18 days of life. Now, he didn't talk about volume, darn it. However, if that is 18 days after conception, that would be the 32nd cycle day or about 4 weeks. That is pretty darned early.

Blackburn and Loper's text on maternal, fetal, and neonatal physiology states that "the initial RBCs are primitive megaloblasts and appear at 3 to 4 weeks, followed by normative megaloblastic erythropoiesis at 6 weeks." (p. 178).

RBCs appear quite early, but the Rhesus factor doesn't appear until later - I'm not sure exactly when, though. I think the party line is that RhoGAM is "harmless", so they give it anytime there's a possibility of sensitization. Many practitioners won't take a woman's word for when conception occurred, and they don't want to worry about liability risks for not giving RhoGAM when appropriate.

Do Rh-negative women with first trimester spontaneous abortions need Rh immune globulin?
Hannafin B, Lovecchio F, Blackburn P.
Am J Emerg Med. 2006 Jul;24(4):487-9.

CONCLUSION: In summary, there is minimal evidence that administering Rh immune globulin for first trimester vaginal bleeding prevents maternal sensitization or development of hemolytic disease of the newborn. The practice of administering Rh immune globulin to Rh-negative women with a first trimester spontaneous abortion is based on expert opinion and extrapolation from experience with fetomaternal hemorrhage in late pregnancy. **Its use for first trimester bleeding is not evidence-based.**

This article implies that events before 12 weeks' gestation don't warrant RhoGAM:

Management of pregnancies with RhD alloimmunisation. [full text]
Kumar S, Regan F.
BMJ. 2005 May 28;330(7502):1255-8.

"Anti-D immunoglobulin is no longer necessary in women with threatened miscarriage with a viable fetus and cessation of bleeding before 12 weeks' gestation"