What constitutes the most cautious approach for a pregnant person with weak D type 4.0?

A recent *CMAJ* Practice article[1] on modern Rhesus (Rh) typing in transfusion and pregnancy and its associated correspondence[2] prompted a productive discussion on safe recommendations for pregnant patients with a weak D type 4.0 allele, originally described in 2000.[3] The differing approaches[1,2] represent the personal views of the respective authors. Based on our review of 20 years' worth of literature on this specialized topic, we have agreed on the following 5 statements:

1. No published case reports have documented adverse clinical effects, such as hemolysis, among pregnant people with weak D type 4.0 caused by an allo- or auto-anti–D.
2. Similarly, no published case reports have documented adverse clinical effects, such as anemia or jaundice, among fetuses or newborns caused by such a mother's allo- or auto-anti–D.
3. No published evidence has shown that Rh immunoglobulin (RhIg) is clinically effective in an individual with weak D type 4.0 (e.g., for preventing anti-D formation); RhIg can cause a positive direct antiglobulin test, which does not imply clinical harm.
4. The weak D type 4.0 phenotype may be associated with a proportionately larger number of anti-D than most other weak D types.[4–6] The nature of these antibodies has not been well characterized (i.e., allo- v. auto-antibody).[6] A fraction of all people with a weak D type 4.0 are routinely typed as normal RhD-positive and do not receive RhIg.[3,7,8]
5. The decision of whether or not to use RhIg or RhD-negative transfusion in such mothers should be based on national guidelines.[9] Both approaches have been adopted by expert groups[2,6,8–10] and are considered safe. The decision may still depend on an individual patient's circumstances.[11] If providers are unsure, consultation with a transfusion medicine physician or perinatal immunohematology reference laboratory is recommended.[1,10]

Willy Albert Flegel MD
Transfusion medicine specialist, chief of Laboratory Services section, NIH Clinical Center, National Institutes of Health, Bethesda, Md.
Melanie Bodnar MD
Hematopathologist, transfusion medicine specialist, Canadian Blood Services, Edmonton, Alta.
Gwen Clarke MD
Hematopathologist, transfusion medicine specialist, associate medical director of Donor and Clinical Services, Canadian Blood Services, Edmonton, Alta.
Judith Hannon MD
Hematopathologist, transfusion medicine specialist, chair of Perinatal Advisory Council, Canadian Blood Services, Edmonton, Alta.
Lani Lieberman MD
Pediatric hematologist, transfusion medicine specialist, chair of Canadian Obstetric and Pediatric Transfusion Network, University Health Network, Toronto, Ont.

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References

1. Flegel WA. Modern Rhesus (Rh) typing in transfusion and pregnancy. *CMAJ* 2021;193:E124.
2. Bodnar M, Hannon J, Lieberman LRE. Modern Rhesus (Rh) typing in transfusion and pregnancy [letter]. *CMAJ* 2021 Apr. 06. Available: www.cmaj.ca/content/193/4/E124/tab-e-letters#re-modern-rhesus-rh-typing-in-transfusion-and-pregnancy (accessed 2021 Apr. 26)
3. Wagner FF, Frohmajer A, Ladewig B, et al. Weak D alleles express distinct phenotypes. *Blood* 2000;95:2699-708.
4. Flegel WA. How I manage donors and patients with a weak D phenotype. *Curr Opin Hematol* 2006;13:476-83.
5. Pham BN, Roussel M, Gien D, et al. Molecular analysis of patients with weak D and serologic analysis of those with anti-D (excluding type 1 and type 2). *Immunohematology* 2013;29:55-62.
6. Westhoff CM, Nance S, Lomas-Francis C, et al. Experience with RHD*weak D type 4.0 in the USA. *Blood Transfus* 2019;17:91-3.
7. Yu X, Wagner FF, Witter B, et al. Outliers in RhD membrane integration are explained by variant RH haplotypes. *Transfusion* 2006;46:1343-51.
8. Ouchari M, Srivastava K, Romdhane H, et al. Transfusion strategy for weak D Type 4.0 based on RHD alleles and RH haplotypes in Tunisia. *Transfusion* 2018;58:306-12.
9. Flegel WA, Peyrard T, Chiaroni J, et al. A proposal for a rational transfusion strategy in patients of European and North African descent with weak D type 4.0 and 4.1 phenotypes. *Blood Transfus* 2019;17:89-90.
10. Flegel WA, Denomme GA, Queenan JT, et al. It's time to phase out "serologic weak D phenotype" and resolve D types with RHD genotyping including weak D type 4. *Transfusion* 2020;60:855-9.
11. Yin Q, Srivastava K, Brust DG, et al. Transfusion support during childbirth for a woman with anti-U and the RHD*weak D type 4.0 allele. *Immunohematology* 2021;37:1-4.

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