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Second and third trimester FMH testing and anti-D prophylaxis: Review of routine administration and special situations

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Faculty Disclosure

In compliance with CPD policy, Temerty Faculty of Medicine requires the following disclosures to the session audience

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I have no conflicts of interest

Objectives

Describe the frequency of FMH testing and repeat RhIg dosing for a patient with recurrent vaginal bleeding

Discuss if RhIg prophylaxis is necessary when immune vs. passive anti-D is uncertain

Discuss the dose and frequency of RhIg following medical events after the first trimester

29 year old G1P0 at 12 weeks gestation

Blood group and screen

A –

She does not have antibodies

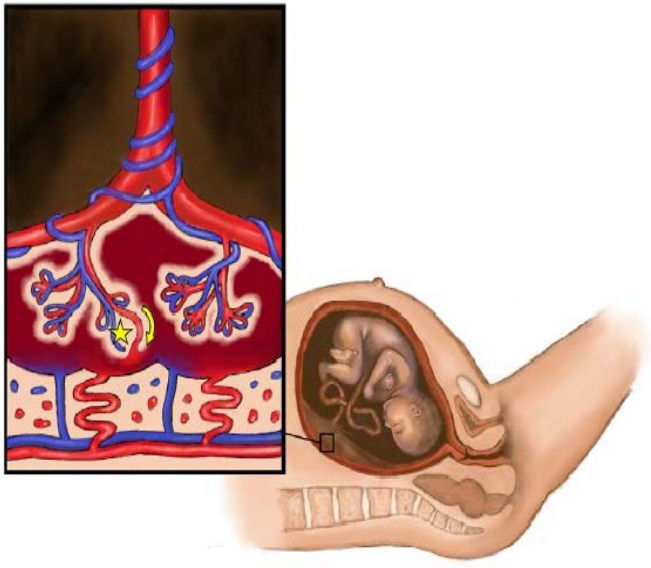
Counselled about the need RhIg

Transplacental Hemorrhage

Entry of fetal erythrocytes from the higher pressure fetal circulation into the intervillous space where they are ultimately returned to the maternal circulation

Frequency and volume depends on gestational age

Low and infrequent in 1st and 2nd trimester unless there is trauma

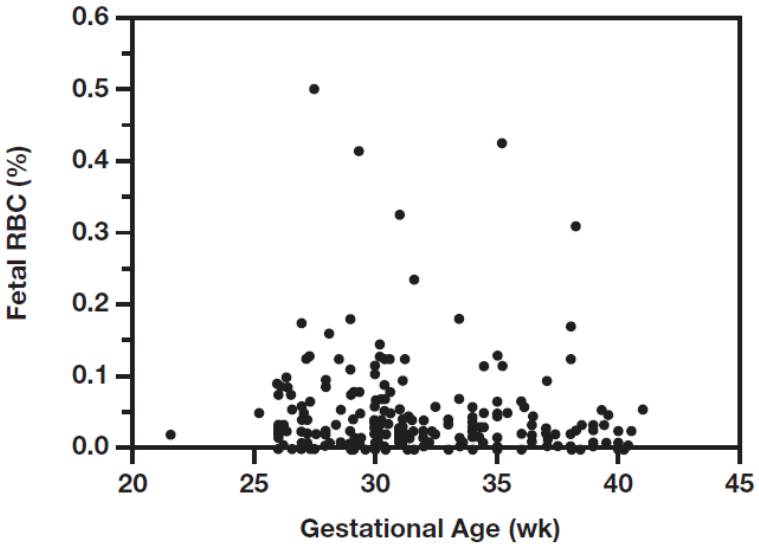


Wylie B, D'Alton M, Obstet Gynecol 2010;115:1039–51

Boller MJ, AJOG 2021: 225,, e1-540.e8

Transplacental hemorrhage is more frequent in the 3rd trimester and postpartum

Increasing size, gradual deterioration in the placental blood barrier in the latter weeks of gestation



Range: 0-0.125%
30 % ≤0.01 mL

De Wit H et al. Am J Clin Pathol 2011;136:631-636. Sebring,ES, Polesky F. Transfusion I0 N 1990-Vol. 30. Zipursky, Lionels CMAJ1967:97:1245

Allo anti-D is detectable in a first pregnancy

D-ABO compatible

1% detectable postpartum

50% detectable 34-40 weeks gestation

4-9% detected at 6 months post-delivery

TABLE 18 *Anti-D antibody detected in first and subsequent pregnancies of RhD-negative women delivered of an RhD-positive infant (RAADP given to the treatment group in the first pregnancy only)*[133]

First pregnancy		Second pregnancy		Third pregnancy		Fourth pregnancy	
Treatment group ($n = 1234$)	Control group ($n = 1881$)	Treatment group ($n = 604$)	Control group ($n = 582$)	Treatment group ($n = 167$)	Control group ($n = 121$)	Treatment group ($n = 32$)	Control group ($n = 18$)
4 (0.32%)	19 (1%)	1 (0.17%)	9 (1.5%)	0 (0%)	3 (2.5%)	1 (3.1%)	1 (5.5%)

Contreras M. BJOG 1998 Nov;105 Suppl 18:7-10.

Pilgrim H et al. Health Technology Assessment 2009; Vol. 13: No. 10

ABO incompatibility reduces frequency of sensitization

TABLE 19 *ABO compatibility and incidence of sensitisation in RhD-negative women not treated with routine antenatal anti-D prophylaxis*[129]

ABO compatibility	*n*	*r*	% Sensitised (95% CI)
Primigravidae	2768	45	1.6 (1.2–2.1)
Compatible	2257	44	1.9 (1.4–2.5)
Incompatible	511	1	0.2 (–0.2 to 0.6)
Multigravidae	765	17	2.2 (1.2–3.3)
Compatible	602	14	2.3 (1.4–3.5)
Incompatible	163	3	1.8 (–0.2 to 3.9)

CI, confidence interval; *n*, number of deliveries of RhD-positive babies to RhD-negative women; *r*, number of sensitised RhD-negative women.

Pilgrim H et al. Health Technology Assessment 2009; Vol. 13: No. 10

RhIg prophylaxis administered once before 40 weeks gestation

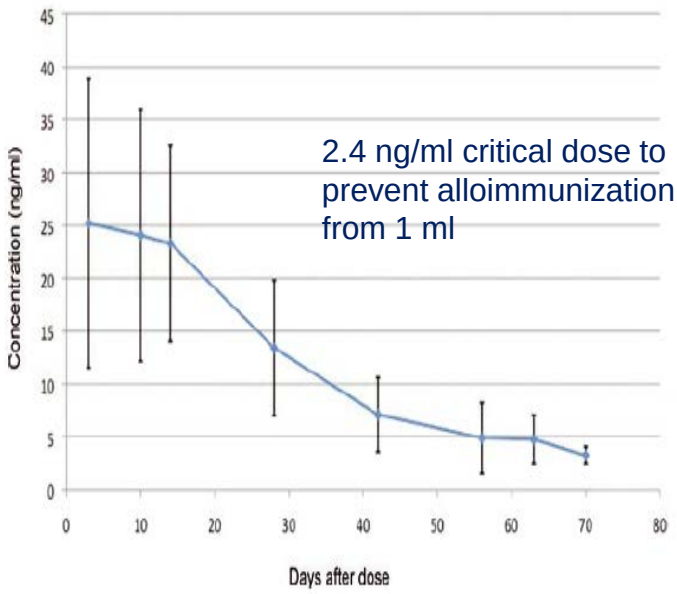
Reduces sensitisation from

0.95% (95% CI 0.18–1.71)

to 0.35% (95% CI 0.29–0.40)

Pilgrim H et al. Health Technology Assessment 2009; Vol. 13: No. 10

Does RhIg need to be repeated at 40 weeks?



Mean plasma concentrations of anti-D IgG days after intramuscular injection (in nanograms/milliliter ±SD).

T ½= 21-23 days

Median anti-D 3–10 days post injection = 25 ng/mL

Detectable levels of anti-D IgG within 2 weeks of parturition in 11/12 women

Lower than critical dose

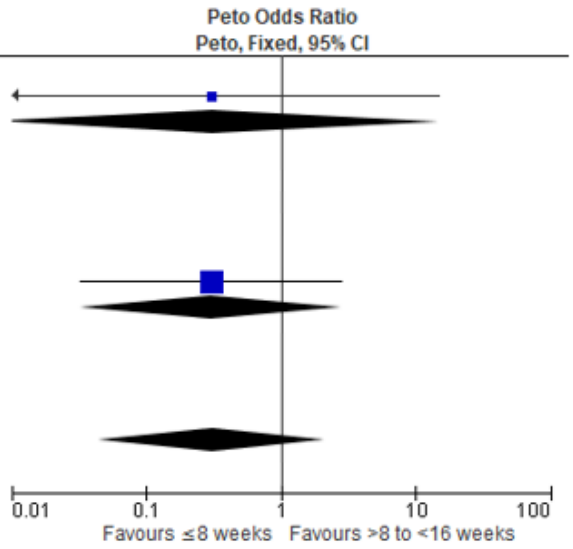
None had detectable antibodies >14 weeks (n=150 women)

Tibbald E et al. Acta Obstet Gynecol Scand 2012;91:587–592. Rudensky B et al. EJOGRB 2003 Mar 26;107(1):45-6. MacKenzie IZ et al BJOG 2006; 113:97–101.

RhIg prophylaxis administered once before 40 weeks gestation

Comparison: Shorter interval (≤ 8 week) vs Longer interval (>8 and <16 weeks) between RhIg and delivery

Study or Subgroup	≤8 week interval Events	Total	>8 and <16 weeks interval Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
11.1.1 Women who received RhIG ante- and postnatally in all previous Rh+						
Bowman & Pollack 1978	0	163	2	923	24.8%	0.31 [0.01, 14.95]
Subtotal (95% CI)		**163**		**923**	**24.8%**	**0.31 [0.01, 14.95]**
Total events	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
11.1.2 Women who did not receive RhIG ante- and posntally in all previous Rh+						
Bowman & Pollack 1978	0	110	6	609	75.2%	0.30 [0.03, 2.83]
Subtotal (95% CI)		**110**		**609**	**75.2%**	**0.30 [0.03, 2.83]**
Total events	0		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Total (95% CI)		**273**		**1532**	**100.0%**	**0.31 [0.04, 2.11]**
Total events	0		8			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



Hamel C et al. PLoS One 2020; 15(9): e0238844.

Antepartum Prophylaxis

- Anti-D 300 µg at 28 weeks
- Repeat antibody screening at 28 weeks
- Routine paternal testing
- Anti-D for "weak D" (e.g., ou)
- Repeat anti-D at 40 weeks

Postpartum Prophylaxis

- Anti-D 120–300 µg within 72 hours of delivery
- Anti-D up to 28 days after delivery
- Routine FMH testing after delivery

SOGC JOGC 2018;40(1):e1–e10

- Anti-D Ig 300 µg IM or IV should be given within 72 hours of delivery to a postpartum nonsensitized Rh-negative woman delivering an Rh-positive infant. Additional anti-D Ig may be required for FMH greater than 15 mL offetal red blood cells (about 30 mL of fetal blood). Alternatively, anti-D Ig 120 µg IM or IV may be given within 72 hours of delivery, with testing and additional anti-D Ig given for FMH over 6 mL of fetal red blood cells (12 mL fetal blood) (I-A).
- If anti-Dis not given within 72 hours of delivery or other potentially sensitizing event, anti-D should be given as soon as the need is recognized, for up to 28 days after delivery or other potentially sensitizing event (III-B).
- There is poor evidence regarding inclusion or exclusion of routine testing for postpartum FMH, as the cost-benefit of such testing in Rh mothers at risk has not been determined[34,35] (III-C).

SOGC JOGC 2018;40(1):e1–e10

29 year old G1P0 at 12 weeks gestation

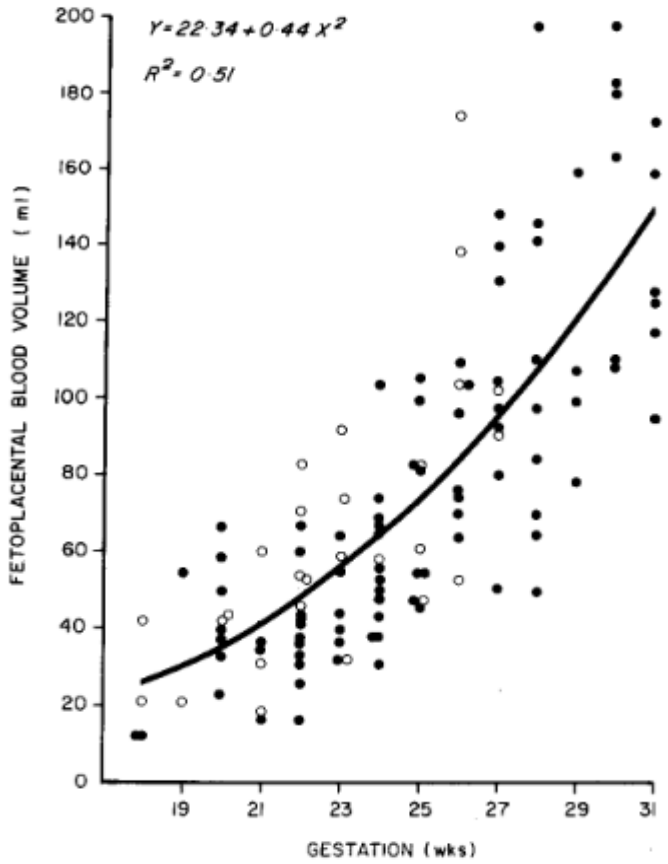
A –

She does not have antibodies

Consents to prophylaxis

At 14 weeks gestation, she has vaginal spotting

Should an FMH test be done?



FMH testing is not routinely suggested when the sensitising event < 20 weeks

FBV is insufficient to exceed that covered by 300 µg (300 µg for 30 ml of whole blood)

<12 weeks, FBV is 3 ml (300 µg or 120 µg) can be administered

Nicolaides K et al AJOG 1987:157:50

https://b-s-h.org.uk/media/15705/transfusion-austin-the-estimation-of-fetomaternal-h

External cephalic version	1-6% has FMH
Amniocentesis	5% alloimmunized without D
Chorionic villus sampling	14% FMH
Red cell salvage	Potentially reintroduces a large volume of fetal RBCs

SOGC JOGC 2018;40(1):e1–e10
BSH. Transfusion Medicine, 2007, 17, 252–262

29 year old G1P0 at 12 weeks gestation, A-

At 14 weeks gestation, she has vaginal spotting, administered RhIg

Diagnosed with placenta previa

At 22 weeks she has recurrent vaginal bleeding daily

Group and screen: anti D, too low to titre

Received RhIg 300 µg +FMH

Antibody screens 6-12 weeks after RhIg are positive

19/20 of the mothers (antibody screens within 5 days of delivery) with anti-D, had been given anti-D at 28 weeks as part of routine antenatal prophylaxis

Record of administration of anti-D: anti-D

- Titre every 4 weeks until 28 weeks then every 2 weeks
- Low or decreasing titre suggests RhIg
- Rising titre suggests alloimmunization

Anti-D prophylaxis should continue unless it is established beyond doubt that the anti-D is alloimmune

For continuous vaginal bleeding at least **500iu** anti-D Ig should be administered at a minimum of 6-weekly intervals, irrespective of the presence of detectable anti-D, and a Kleihauer / FMH Test requested every two weeks in case more anti-D is needed

New H, Lancet 2011: 357:1295

BSH. Transfusion Medicine, 2007, 17, 252–262

29 year old G1P0 at 12 weeks gestation, A-

At 14 weeks gestation, she has vaginal spotting, administered RhIg

Diagnosed with placenta previa

At 22 weeks she has recurrent vaginal bleeding daily

Group and screen: anti D, too low to titre

Received RhIg

Offered cffDNA but as she was nearing 28 week received routine prophylaxis 300 µg

Objectives/Summary

Describe the frequency of FMH testing and repeat RhIg dosing for a patient with recurrent vaginal bleeding

Discuss if RhIg prophylaxis is necessary when immune vs. passive anti-D is uncertain

Discuss the dose and frequency of RhIg following medical events after the first trimester

Anti-D immunoglobulin should be given to RhD negative patients with non-anti-D antibodies for routine antenatal prophylaxis, for potential antenatal sensitizing events, and postnatal prophylaxis

When an RhD negative patient experiences an FMH after 20 weeks, routine antenatal anti-D should be administered, as well as additional doses of anti-D providing following an FMH event.

Antenatal anti-D dosing varies depending on gestational age of the fetus at the time of potential FMH:

<12 weeks: 120 (600 IU) should be administered

>12 weeks: 300 micrograms (1500 IU) should be administered

Following delivery an RhD negative patient giving birth to an RhD positive fetus, should receive 120/300 ug of anti-D within 72 hours of delivery (if an error occurs and dose is not administered within 72 hours, RHIG should be given up to 28 days post-delivery) and send for FMH testing.

If the RhD status of the baby cannot be determined within 72 hours anti-D should be administered to the RhD negative patient.

If FMH testing indicates a fetal bleed > 30 mL (15 mL fetal rbc) (for 300ug dose) or > 12 mL (6 mL fetal red cells) (for 120 ug dose) additional anti-D dose should be calculated and administered.

If alloimmune anti-D is detected, prophylaxis is no longer necessary and RhIg should not be administered.

Routine antenatal anti-D prophylaxis, at a dose of 300 micrograms, should be administered to all RhD negative females at around 28 weeks gestation unless cell free fetal DNA assessment from maternal plasma predicts that the fetus is RhD negative.

If the routine dose is missed, it should be given as soon as possible thereafter

In the setting of ongoing or recurrent antepartum bleeding after 20 weeks gestation, FMH testing should be performed with an appropriate dose of RhIg provided at the time of initial bleed.

If bleeding continues, additional RhIg doses of 300ug can be given at three-6- week intervals following the initial dose.

Repeat FMH testing should be performed every 2-3 weeks (if there is a change in the severity of bleeding) and, if FMH is detected, additional anti-D will be required (BCSH 2006a) regardless of the presence or absence of passive anti-D.

When anti D is detected following RhIG administration and immune anti D can not be definitively confirmed,

a. RhIG prophylaxis should be provided for the usual indications;

b. Ongoing titration of the anti D at usual intervals should be performed;

c. Repeat antibody assessment should be/can performed at 6 months post- partum.

Thank you for your attention