ORBCoN
Ontario Regional Blood Coordinating Network

Inspiring and facilitating best transfusion practices in Ontario.

First Trimester Anti-D Prophylaxis

What is the evidence?

What Guidelines do we have?

What can we agree on?

Faculty Disclosure

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

- This program has received no financial external support

- Speaker disclosure none

- Acknowledgement:
  - Dr. Lani Leiberman
  - Dr. Jeannie Callum

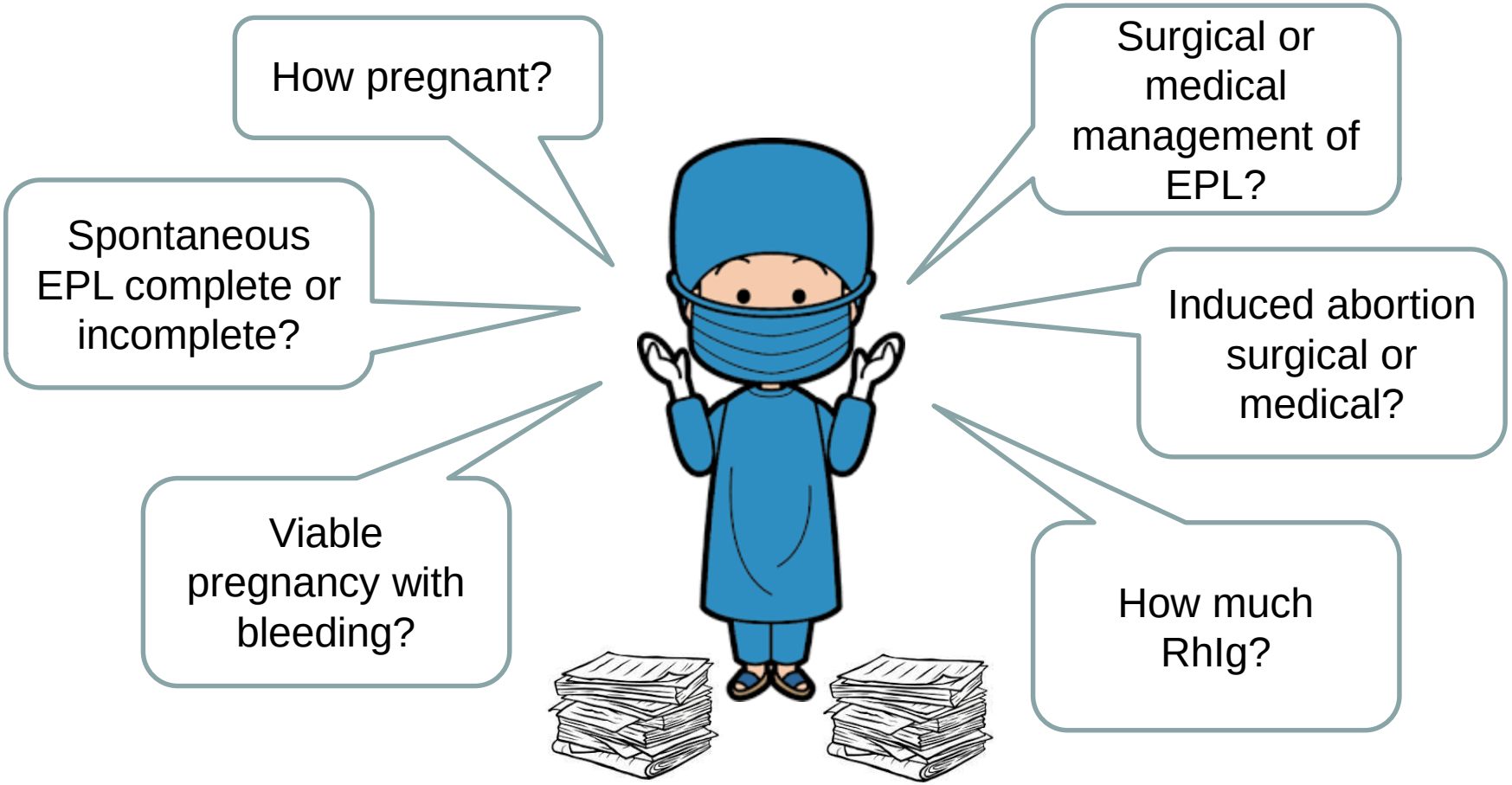
Objectives

- Discuss clinical situations that occur during the first trimester where the need for anti-D prophylaxis (RhIg) is uncertain: Focus on first trimester intrauterine pregnancies
- Consider clinical scenarios in the first trimester when it is:

    a) safe to withhold RhIg

    b) optimal to provide RhIg

??Questions??



EPL = early pregnancy loss

What We Know

- Alloimmune hemolytic disease of the fetus and newborn (HDFN) can pose significant health risks in pregnancy
- Rh Immunoglobulin (RhIg) significantly reduces the risk of HDFN
- D antigen has been detected as early as 52 days after LMP (7 3/7 wks gestation)
- Many countries, start Rh testing at 8 wks

What Don’t We Know

- What gestational age the presence of fetal blood cells in the maternal circulation correlates with the development of Rh alloimmunization

What We Know

- Data is lacking to support evidence based recommendations
- Result: expert opinion and guidelines vary
- Best practice not clearly defined
- Guidelines acknowledge this gap when making recommendations about gestational age when RhIg should be given

Fetal Placental Volume (FPV)

- FPV <12 wks is < 5 cc, <2.5 cc fetal RBCs
- FPV at 20 wks is 30 cc, 15 cc fetal RBCs
- Canadian Blood Services:
  - 120 ug RhIG covers 6 cc of fetal RBC's, cost $35.42
  - 300 ug RhIG covers 15 cc fetal RBC's, cost $88.54
- Plus cost of the Group and screen $20-22

CASE ONE

- 29-year-old, living in a remote community, presents with a spontaneous early pregnancy loss at 7-8 weeks gestation
- The community has no access to Rh antigen testing or RhIg
- Considerations for management

Barrier: Group and Screen and RhIg

- Many remote sites cannot do G&S

- RhIg
  - Freeze Dried Pooled Blood product
  - Storage: needs to be at a site that can maintain temperature and quality

Barrier: Travel and Patient Impact

- Cost of Travel:
  - Patient to RhIg or RhIg to patient
- Patient Impact:
  - If patient to RhIg, distanced from community and family support
  - Delay in access, increased wait time

Economics

- If evidence does not support RhIg, cost saved include:
  - Cost of G&S
  - Cost of RhIg
  - Cost of travel
  - Cost of human resource time at each step

Early Pregnancy Complications

- No clear literature to guide different approached for:
  - Viable Early Pregnancy Bleeding
  - Early pregnancy loss – spontaneous
  - Early pregnancy loss – medically managed
- Surgical management carries a higher risk of FMH than Medical or spontaneous
  - Early pregnancy loss – surgical management

Summary of Guidelines

	NICE (2012/2019)	**SOGC** (2018)	**CBS** (2018)	**ACOG** (2017)	**BCSH** (2014)
Spont. incomplete or complete preg loss < 12 wks	NO	YES	YES	?**	NO
First trimester bleeding < 12 wks	NO	YES	YES*	?***	NO****
Medical management of preg loss < 12 wks	NO	YES	YES	----	----
Surg management of preg loss < 12 wks	YES	YES	YES	YES	YES

SOGC 2018 Guidelines: Transplacental hemorrhage can affect women with threatened/complete/incomplete abortions from 8 weeks GA

Table 1.—Incidence of Transplacental Hemorrhage and Mean Fetal Cell Score Among 98 Aborting Patients

	Threatened	Complete	Incomplete	Total
Patients (No.)	23	25	50	98
Positive (No.)*	11 (48%)	9 (36%)	11 (22%)	31 (32%)
Fetal cell score				
Mean	7	4	3	4
Range	2-40	1-7	1-34	1-40

*Positive = fetal cell score ≧1.

Table 2.—Incidence of Transplacental Hemorrhage, According to Gravidity

Gravida	Cases (No.)*	Positive		Fetal Cell Score	
		No.	%	Mean	Range
1	24	9	38	4	1-8
2	26	15	58	5	1-40
Subtotal	50	24	48		
3	12	2	17	2.5	2-3
4	11	1	9	4	...
5	7	1	14	4	...
≧6 and more	14	4	29	5	4-9
Subtotal	44	8	18		

*No information about gravidity of four patients.

Table 3.—Incidence of Transplacental Hemorrhage, According to Duration of Gestation

Gestation (Weeks)	Cases (No.)	Positive		Fetal Cell Score	
		No.	%	Mean	Range
8-10	42	9	21	3	1-8
11-13	30	11	37	9	1-40
14-16	9	4	44	2	1-2
17-20	17	7	41	7	1-34

- Risk of FMH increases with instrumentation use
- FMH (>0.05 mL fetal RBCs) found in 26% of women with spontaneous abortions
- No evidence to guide decision making before 8 weeks gestation

Fetal RBCs express D antigen 52 days from LMP

Litwak et al., JAMA, 1970

Back to the Case

- Would our management change if our patient had a viable pregnancy at 7-8 weeks gestation and desired a medical abortion?
- What about a surgical abortion?
  - Risk of RhD alloimmunization is estimated btw 1.5-2% in susceptible women after spontaneous loss and 4-5 % after D&C

Summary: Abortion Guidelines

	Medical Abortion	Surgical Abortion
SOGC (2016)	< 49 days (can offer earlier)	SOGC (2018) Yes
SOGC (Pandemic)	< 70 days < 56 days * 57-70 days ** expert opinion	----
WHO (2022)	< 12 wks (84 days) No	< 12 wks (84 days) No
ACOG (2017)	Yes	Yes
NAF (2020)	< 56 days *** < 70 days (may consider)	----
BCSH (2014)	Yes	Yes
CBS (2018)	Yes	Yes

Summary: Ectopic Pregnancy

	NICE (2012/2019)	**SOGC** (2018)	**CBS** (2018)	**ACOG** (2017)	**BCSH** (2014)
ECTOPIC	Medical – NO Surgical – YES	YES	YES	YES	YES

Emerging Evidence

	Netherlands	Canada
RhIg EPL < 10 wks (70 days)	NO	YES
RhIg Induced abortion < 49 days medical or surgical	NO	YES
Prevalence of clinically significant antibodies	4.21 (95% CI4.12-4.30)	4.03 (95% CI3.93-4.12)
Rh negativity rate	14.5 %	13.0 %

Conclusion: Netherlands Policy Safe

Reference: Wiebe et al Contraception:X2019

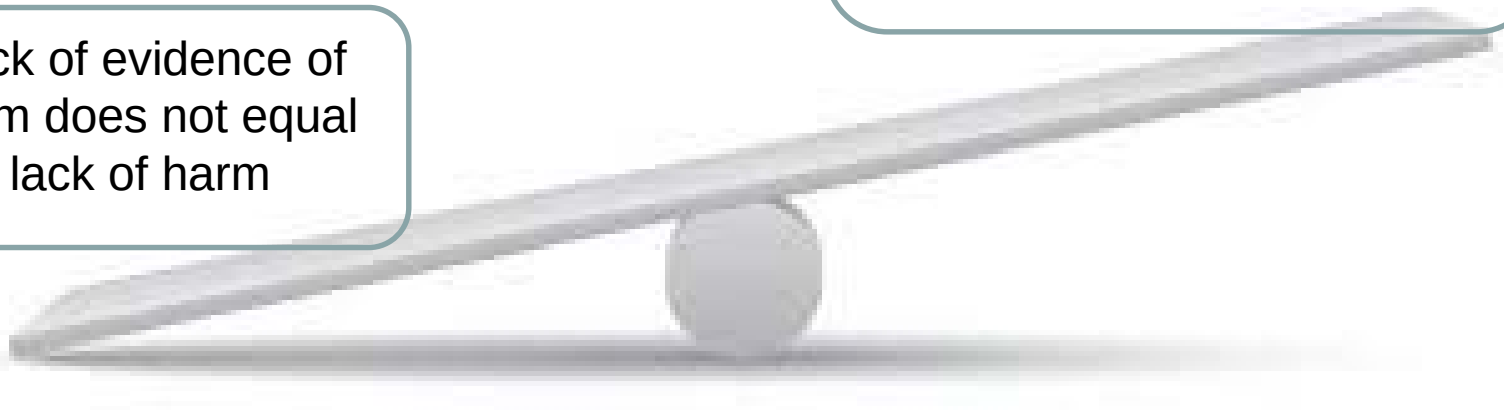
Emerging Evidence

- Horvath et al Contraception 2020
- Pilot study, flow cytometry fetal red blood cell exposure following first trimester uterine aspiration btw 5-12 weeks is well below the calculated threshold for maternal Rh sensitization in cohort studied

Give RhIg:

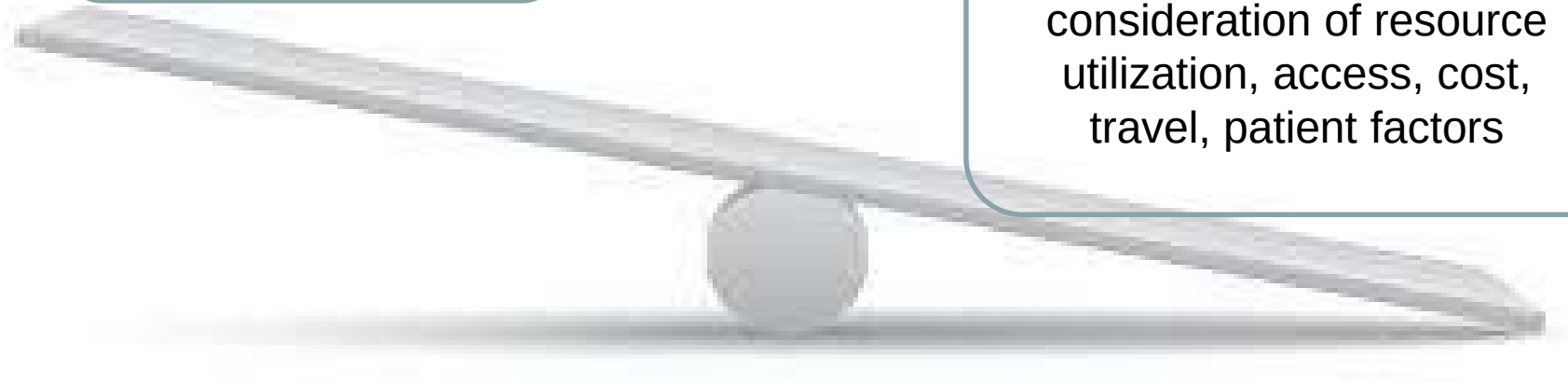
Lack of evidence of benefit – consideration of resource utilization, access, cost, travel, patient factors

Lack of evidence of harm does not equal lack of harm



Do Not Give RhIg:

Lack of evidence of harm does not equal lack of harm



Lack of evidence of benefit – consideration of resource utilization, access, cost, travel, patient factors

Time to reassess when NOT to give RhIg in Canada

Delphi Consensus?

- Current state:
  - After miscarriage, threatened abortion or induced abortion during the first 12 weeks of gestation, non-sensitized D negative women should be given a minimum anti-D of 120 mcg. After 12 weeks they should be given 300mcg.
- Future state:
  - After EPL (spontaneous, medical or surgical management), 1st trimester bleeding viable IUP, induced abortion (medical or surgical) we can safely forego Rh testing and RhIg below 56 days

Delphi Consensus?

- Current State:
  - Anti-D should be given to non-sensitized D negative patients following ectopic pregnancy
- Future State:
  - RhIg – we can forego if ectopic below 56 days and medically or surgically managed except if ruptured ectopic
  - RhIg should be given to non-sensitized D neg patients if ectopic is ruptured