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Can we safely stop testing for Rh status and immunizing Rh-negative women having early abortions? A comparison of Rh alloimmunization in Canada and the Netherlands☆,☆☆

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ABSTRACT

Objective: The objective of this study was to compare Rh alloimmunization rates in two countries (Canada and the Netherlands) with completely different policies regarding abortion-related use of anti-D immunoglobulin to ultimately determine any benefit in use. In the Netherlands, the policy is to offer anti-D immunoglobulin to Rh-negative women having spontaneous abortions over 10 weeks 0 days gestation and induced abortions over 7 weeks 0 days. In Canada, it is recommended to offer all Rh-negative women having induced or spontaneous abortions anti-D immunoglobulin.
Methods: We used public databases to obtain the population data, the number of births, the abortion rates (the percentage of women having induced abortions in one year) and the Rh-negativity rates (percentage of Rh negative women) in Canada and the Netherlands. Both countries do routine prenatal blood screening and we obtained the rates of clinically significant antibodies from public databases.
Results: In nearly 2 million blood samples from pregnant women in both Canada and the Netherlands, the prevalence of clinically significant antibodies was statistically lower in the Netherlands: 4.21 (95% CI: 4.12 to 4.30) and 4.03 (95% CI: 3.93 to 4.12) per 1000, respectively. Canada and the Netherlands had small differences in rates of abortion (1.9 per 100 vs 1.2 per 100) and of Rh negativity (13.0% vs 14.5%).
Conclusion: Despite different anti-D Ig treatment policies, we found a similar prevalence of clinically significant perinatal antibodies among women in Canada and the Netherlands.
Implications: Our findings suggest that The Dutch policy of not treating Rh-negative women having spontaneous abortions under 10 weeks' or induced abortions under 7 weeks' gestation can be safely adopted by other countries.

1. Introduction

The D-antigen, a member of the family of Rh-antigens, is an immunogenic protein associated with red blood cell (RBC) membrane complexes. As a result, Rh-negative people can develop circulating antibodies of anti-D IgG following exposure to Rh-positive RBCs. In a subsequent pregnancy among sensitized women, maternal anti-D may react with D-antigens from a Rh-positive fetus, leading to the destruction of fetal Rh-positive RBCs. Rh alloimmunization increases the risk for hemolytic disease of the fetus and the newborn. While Rh alloimmunization may harm subsequent pregnancies, there is a lack of evidence that this occurs in early gestations. Canada and many other countries recommend offering anti-D IgG to all Rh-negative women at the time of a spontaneous or an induced abortion in order to block alloimmunization [1,2].

Although fetal RBCs can express the D-antigen as early as 52 days after the last menstrual period (LMP) [3], we lack convincing evidence for the benefit of using anti-D in the first trimester [4].

One argument in favour of anti-D IgG administration comes from a 1979 study that used the Kleihauer-Betke (KB) test to detect fetal cells in the maternal circulation. The study found that 2.6% of patients undergoing elective abortions at gestational periods of less than 8 weeks LMP exhibited a positive KB test before the procedure, and 15.5% of patients had a positive KB test after the procedure. Also, it appeared that the number of patients with a positive KB test after the procedure increased

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with the gestational age at abortion [5]. However, these results are difficult to interpret due to imprecise methods used to determine gestational age (i.e. the date of LMP and physical examination). More importantly, it remains to be shown that a positive KB test translates to subsequent development of Rh alloimmunization.

Another argument in favour of anti-D IgG administration within 72 hours of a spontaneous abortion, regardless of gestational age, is that there is risk of fetomaternal hemorrhage (FMH) due to breach of the choriodecidual space. The only randomized, double-blind, controlled study to evaluate the benefit of anti-D IgG in the first trimester of pregnancy found that the incidence of Rh alloimmunization was zero, with (0/19) or without (0/38) anti-D IgG treatment [6]. Thus, even though some studies indicate the presence of fetal blood in Rh-negative women at early gestational periods [3], this does not necessarily correlate with the development of Rh alloimmunization.

In an experimental study in 1956, Rh-negative incarcerated men were injected with Rh-positive blood and the minimum dose of 7.5 mL did not produce a titre above 16 in any of the 39 men; multiple additional doses were required [7]. In a 2002 report, the volume of fetal blood at 8 weeks' gestation was estimated to be 0.33 mL and at 12 weeks to be 4.2 mL [8]. Since approximately half of the fetal blood volume is in the placenta, less than 7.5 mL of fetal blood is available to potentially enter the maternal circulation and pose a sensitization risk under 12 weeks LMP.

Given the lack of evidence that anti-D IgG prevents Rh alloimmunization at low gestational ages, a number of countries have stopped testing for Rh status and treating Rh-negative women having abortions at early gestations. In the Netherlands, the policy for over 20 years has been to not treat Rh-negative women having spontaneous abortions under 10 weeks' gestation or induced abortions (medication-induced or aspiration) under 7 weeks' gestation [9]. In the United Kingdom, the 2012 National Institute for Health and Care Excellence (NICE) guidelines recommended no anti-D IgG be given for spontaneous or ectopic pregnancies treated medically at any gestational age [10]. In contrast, the Canadian Blood Services and the Society of Obstetricians and Gynecologists of Canada recommend giving all Rh-negative women having induced or spontaneous abortions anti-D IgG [2].

A randomized controlled trial with sufficient statistical power would be difficult to conduct due to ethical, logistical, and financial reasons. As a result, other means of determining the value of anti-D IgG administration to women having early abortions need to be explored. In this analysis, we chose to compare the clinically significant Rh alloimmunization rates in Canada and the Netherlands to explore whether the Dutch policy could be safely adopted by other countries, including Canada.

2. Methods

In addition to comparing alloimmunization rates, we needed to compare other factors in the two countries that might influence these rates. These include the total number of pregnancies in each country: those that end in birth (known), those that end in abortion (known), those that end in miscarriage (not known, but can be estimated). Miscarriage estimates need to account for pregnancies that would have ended in both birth and abortion, had they continued. These numbers can be mathematically estimated. The purpose of estimating miscarriages in addition to births and induced abortions is to show how many opportunities there were for alloimmunization to occur. We retrieved data on the rates of abortions, births, and the prevalence of Rh negativity among reproductive-aged women from public databases in Canada between January 1, 2006 and December 31, 2016, and the Netherlands between January 1, 2006 and December 31, 2015. Government websites provided the information on the number of births and populations [11,12] as well as the number of induced abortions [13–15]. We estimated the number of spontaneous abortions by multiplying births by 1.278 and induced abortions by 1.116 to get the total number of pregnancies from which the number of spontaneous abortions can be calculated using the Hammerslough method [16]. We calculated the total fertility rates (the average number of children born to a womanover her reproductive lifetime). We determined the Rh negativity proportions (percentage of Rh negative women) among reproductive-aged women in Canada and the Netherlands by consulting publications from each country [15,17].

Canada and the Netherlands do routine prenatal blood screening and publish the total numbers of clinically significant perinatal antibodies in the first trimester of pregnancy [15,18]. In both countries, antibodies are considered clinically significant in causing hemolytic disease of the fetus and the newborn if they meet the following criteria:

1. They are predominantly IgG antibodies (and therefore can cross the placenta).
2. The antigen is present on fetal RBCs.
3. The antibody is known to bind to the fetal antigen resulting in anemia (either due to hemolysis of fetal RBCs or fetal bone marrow erythroid suppression).
4. The titre of the antibody is above 16.

We calculated the prevalence of significant antibodies per 1000 women by dividing the total number of tests with significant antibodies by the total number of samples tested, multiplied by 1000. Exact confidence intervals were calculated using the Clopper-Pearson method. Because Canada provided the number of significant antibodies rather than the number of women with significant antibodies from 2006 to 2013, we estimated the number of women with antibodies as follows. Because we had data for both the number of significant tests and the number of significant antibodies in 2014, 2015, and 2016, we used the average ratio of the number of significant tests/number of significant antibodies (0.847) to 'correct' the counts in the previous years to provide an estimate of the number of significant tests in those years, as follows:

2.1. Sensitivity analysis for prevalence

The estimates of isoimmunization prevalence assume that the compliance with policy in each country is 100%. We do not know if compliance with policy in Canada and the Netherlands is less than 100%; thus, we constructed simulations to assess the effect of changing the rate of compliance on the estimates of prevalence of significant antibodies using the following steps:

1. Using the numbers of pregnancies estimated in Table 1, we calculated that the proportion of pregnancies ending in induced abortions were approximately 16% in Canada and 12% in the Netherlands.
2. We assume that the proportion of women who had blood tests during pregnancy, and who also had a previous induced abortion should be similar to the rates of induced abortion in each country.
3. Within Canada, if actual compliance was 80% instead of 100%, we could expect that up to 20% of the women with significant antibodies and who had a previous induced abortion had not actually received treatment. If so, the isoimmunization rate would be lower if compliance were actually 100%.
4. Corrected number of tests with significant antibodies = number of tests with significant antibodies – (number of tests with significant antibodies * 0.16 * 0.2)
5. Within the Netherlands, the opposite would be true. The number of antibodies in the raw data would be too low if compliance was not actually 100%. Assuming the raw estimates came from data where 20% of the women were treated, the number of tests with significant antibodies would be increased if compliance were actually 100%:

   Corrected number of tests with significant antibodies = number of tests with significant antibodies – (number of tests with significant antibodies * 0.12 * 0.2)

6. Simulations were run using these corrected estimates for significant antibodies. The simulations drew 150,000 random samples

Table 1
The total fertility rates and the total number of pregnancies, births, induced and spontaneous abortions in Canada and the Netherlands between 2006 and 2015.

Year(s)	Canada					The Netherlands				
	Total number of induced abortions	Estimated total number of spontaneous abortions*	Total number of births	Estimated total number of pregnancies*	Total fertility rate	Total number of induced abortions	Estimated total number of spontaneous abortions*	Total number of births	Estimated total number of pregnancies*	Total fertility rate
2006	91,377	109,183	354,617	555,177	1.59	32,992	55,273	185,057	273,322	1.72
2007	98,758	113,722	367,864	580,344	1.66	33,148	54,257	181,336	268,741	1.718
2008	95,876	116,174	377,886	589,936	1.68	32,983	55,154	184,634	272,771	1.773
2009	93,755	116,755	380,863	591,373	1.67	32,427	55,168	184,915	272,510	1.79
2010	90,747	115,392	377,213	583,352	1.63	30,984	54,857	184,397	270,238	1.796
2011	92,524	115,716	377,636	585,876	1.61	31,707	53,735	180,060	265,502	1.759
2012	83,708	115,870	381,869	581,447	1.61	30,577	52,464	175,959	259,000	1.723
2013	83,689	115,438	380,323	579,450	1.59	30,601	51,183	171,341	253,125	1.679
2014	81,897	116,280	384,100	582,277	1.58	30,361	52,222	175,181	257,764	1.713
2015	100,104	117,917	382,392	600,413	1.56	30,803	50,975	170,510	252,288	1.658
2006-2015	912,435	1,152,447	3,764,763	5,829,645	1.62	316,583	535,286	1,793,390	2,645,259	1.73

* We estimated the rate of spontaneous abortions multiplying births by 1.278 and induced abortions by 1.116 to get the total number of pregnancies from which the number of spontaneous abortions can be inferred (using calculations in Hammerslough 1992) [18].

from a binomial distribution with probability of success equal to the corrected prevalence of significant antibodies. This sampling procedure was repeated 1000 times for each country. We calculated the proportion of the 1000 iterations where the p-value for the test of differences in prevalence was < 0.05.

7. We repeated the above steps of the simulation for compliance = 90% and 80% in each country.

3. Results

Table 1 presents the total number of induced abortions, the estimated number of spontaneous abortions, the number of births, the estimated number of pregnancies and the calculated fertility rates in the two countries between 2006 and 2015. We also calculated the abortion rates (number of abortions in women 15-44 per 100). For Canada, the total fertility rate was 1.62 and the abortion rate was 1.6 per 100. For the Netherlands, the total fertility rate was 1.73 and the abortion rate was 1.2 per 100. Between 2006 and 2015, the estimated number of spontaneous abortions was 1,152,447 in Canada and 535,286 in the Netherlands; the number of reported induced abortions were 5,521,394 in Canada and 2,500,309 in the Netherlands. The proportion of Rh negativity reported between 2011 and 2015 was 13.0% in Canada and 14.5% in the Netherlands.

Table 2 presents the numbers of women tested and those with clinically significant perinatal antibodies. In Canada, out of 1,964,229 samples tested in pregnant women, 4.21 (95% CI 4.12 to 4.30) per 1000 had clinically significant perinatal antibodies and in the Netherlands, out of 1,816,457 samples tested, 4.03 (95% CI 3.93 to 4.12) per 1000 had clinically significant perinatal antibodies.

3.1. Results from sensitivity analysis

We estimated corrected prevalence in each country as shown in Table 3. The corrected prevalence estimates represent what the prevalence would be under theoretical 100% compliance with policy in each country with the assumption that the actual data came from populations with 80 to 90% compliance. With realistic levels of compliance (80-90%), only 5 to 6% of 1000 random simulations would have produced estimates that were significantly different between the countries. This is displayed graphically in Fig. 1.

4. Discussion

Clinically significant perinatal antibodies do not occur at a rate that is significantly higher in the Netherlands than in Canada, despite a higher rate of Rh negativity in the Netherlands (14.5% compared to 13.0%) and far less frequent anti-D IgG administration. Any factors that might

Table 2
The number of women with clinically significant perinatal antibodies identified in six Canadian provinces and territories (British Columbia/Yukon, Alberta/Northwest Territories, Saskatchewan, and Manitoba*) and the Netherlands between 2006 and 2015.

Year	Canada			The Netherlands	
	Number of pregnant women tested	Number of women with clinically significant perinatal antibodies	Total number of clinically significant perinatal antibodies	Number of pregnant women tested	Number of women with clinically significant perinatal antibodies
2006/2007**	158,118	512***	605	188,435	454
2007/2008**	177,796	631	745	183,777	671
2008/2009**	120,562	454	536	186,209	683
2009/2010**	177,105	660	779	186,644	661
2010	179,596	772	911	187,529	936
2011	181,304	842	994	182,259	864
2012	184,891	820	968	174,037	1,093
2013	191,362	973	1,149	176,602	710
2014	197,693	1,006	1,183	174,819	638
2015	198,377	841	993	176,146	606
2016	197,425	761	903		
2006-2015	1,964,229	8,272		1,816,457	7,316

* Manitoba data was not available for 2006/2007.
** 2006 to 2009 Canadian data was recorded in fiscal years (April 1-March 31) instead of calendar years.
*** 2006 to 2013 Canadian data was recorded as total number of antibodies rather than number of women with antibodies, so those years are estimates based on data from 2014-2016 where the average ratio of women with antibodies to total antibodies was equal to 0.847.

Table 3
Sensitivity simulation results.

	Corrected prevalence per 1000		Mean prevalence from simulations (95%CI)		
Compliance	Canada	Netherlands	Canada	Netherlands	% of simulations with significant difference
90%	4.14	4.08	4.15 (4.14-4.16)	4.09 (4.08-4.10)	5.5%
80%	4.08	4.13	4.11 (4.10-4.12)	4.13 (4.11-4.14)	6.1%

The corrected prevalences were calculated using the formula in the text and represent what the prevalence would be if compliance were 100% assuming that compliance in the raw data corresponded to 90%, or 80%. These corrected prevalences were used as the probability of significant antibodies in the simulation runs for each level of compliance. Mean prevalence is the average of the prevalences estimated from the 1000 simulation runs per country. The % simulations with a significant difference were calculated as the number of simulation runs in which there was a significant difference by Chi-square test ($p<0.05$) between the Canadian and Netherland estimates, divided by 1000. The population size for each simulation run was set at 150,000 per country.

influence the antibody rates, other than the different policies of testing and treating Rh-negative pregnant women having induced or spontaneous abortions, will now be considered. There are small differences in the birth rates, abortion rates, and total fertility rates between the two countries, but there is no evidence that these factors would affect the rates of alloimmunization.

There is no evidence that medication-induced or spontaneous abortions pose less risk of Rh alloimmunization than surgical abortions at the same gestations. The rate of spontaneous abortion is assumed to be the same in both countries, but the rate of medication induced abortions was much higher in the Netherlands. This is because mifepristone (the standard medication used for medical abortions) has been available in the Netherlands since 1999 and only became available in Canada in 2017 We know that 27% of induced abortions in the Netherlands occurred at less than 6.5 weeks' gestation and did not qualify for treatment with anti-D IgG [19]. The Dutch policy requires testing and treatment only above 7 weeks' gestation for both medication-induced and surgical abortions, so many Rh-negative women would not have been tested or treated. It is possible that some alloimmunization would have been missed in these women.

The data from the Netherlands are much more complete than the data from Canada. In the Netherlands, reporting of medication-induced and surgical abortions is required and compliance is high. Nevertheless, it is also likely that the Dutch abortion rate is slightly higher than reported, because medication-induced abortions at less than 6.5 weeks' gestation can be done in a family physician's office, where reporting procedures are less consistent than in specialized abortion clinics. Most abortions are done in clinics, not offices, so this would be a small increase in the abortion rate and should not affect our results significantly.

Reporting compliance is poorer in Canada and there were full data from only six of thirteen provinces and territories on Rh alloimmunization. The provinces have different ethno-cultural proportions; for example, there are more people of Chinese heritage living in BC so there may have been a slightly lower Rh negativity rate in our sample compared to all of Canada. [25] Abortion rates vary across the country, but it appears that our sample had a similar rate to the country average [13]. In addition, the Canadian website only reported total number of antibodies, rather than total number of women with antibodies until 2014, so we were required to report estimates. Canadian abortion data are also poor, because many clinics and all private offices do not report medication-induced abortions. Another limitation is that during 10 years, women may have had more than one pregnancy with more than one test in each pregnancy. It seems likely that this was similar in both countries and will not change our outcome significantly. Birth data are accurate and complete in both countries. The sensitivity analysis suggests that even if the data we used for our calculations did not reflect 100% compliance in each country, the estimates of clinically significant antibodies would remain similar to those that we identified using the raw data, and these are similar between the countries.

Strengths of this study include that we were able to employ data collected over the course of a 10-year span, which produced a large sample size. The policies had been consistent in the Netherlands and in Canada for 10 years before the start of our data collection and throughout the study period so data are representative of the individual policies. This report gives evidence that the policy of not treating all Rh negative women with early pregnancy loss or termination may be safe.

We should stop testing Rh status and administering anti-D IgG to women having medication-induced or spontaneous abortions at early gestations, for several reasons. First, in the past, there have been shortages of anti-D IgG in some parts of the world [8]; in developing countries, anti-D IgG is often not available, and availability of future supplies may be a concern. Additionally, there is a cost involved for the government (tax-payers), private insurers, and patients [20]. More importantly, physicians should conduct only indicated Rh testing and anti-D IgG administration because the requirements for routine testing and treatment may prevent abortion access. For remote telemedicine provision of abortions, the need to test and provide anti-D IgG can be challenging [21–24]. Unnecessary treatment also incurs costs for both the health system and the patient. These analyses show that the policy in the Netherlands yields outcomes similar to those in Canada. Based on the amount of blood in first trimester pregnancies and the amount required to induce alloimmunization, it is actually logical to stop testing and treating Rh negative women at gestations even above those in the Netherlands policy (7 weeks for induced and 10 weeks for spontaneous abortions).

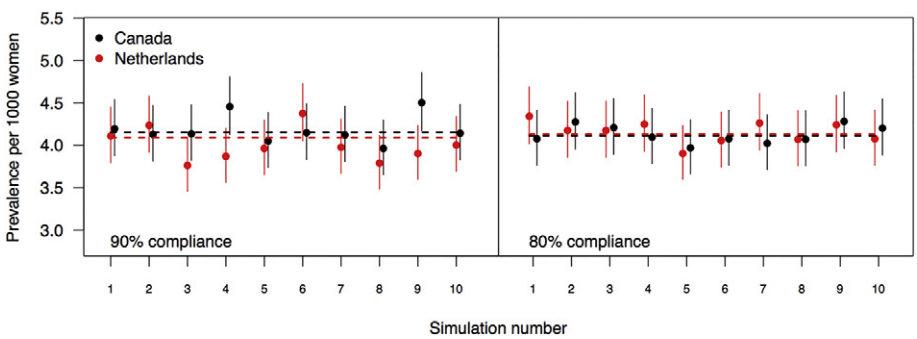

Fig. 1. Sensitivity simulation results.

5. Conclusion

Clinically significant perinatal antibodies do not occur at a rate that is statistically or clinically significantly higher in the Netherlands than in Canada, despite a higher rate of Rh negativity in the Netherlands (14.5% compared to 13.0%) and a policy of not requiring routine administration of anti-D IgG before 10 weeks' gestation in spontaneous and 7 weeks' in induced abortions. These results suggest that it is acceptable for other countries to adopt the policies that have been followed in the Netherlands for the past 20 years. Modifying the guidelines to stop Rh testing at early gestations has the potential to reduce costs and improve access to abortions worldwide.

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