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.
- Evangelia Vlachodimitropoulou has no conflict of interest.

Objectives

- Discuss whether regular anti-K titrations should be performed for an alloimmunized patient.

- Know when patients should be referred to high-risk maternal-fetal medicine specialists.

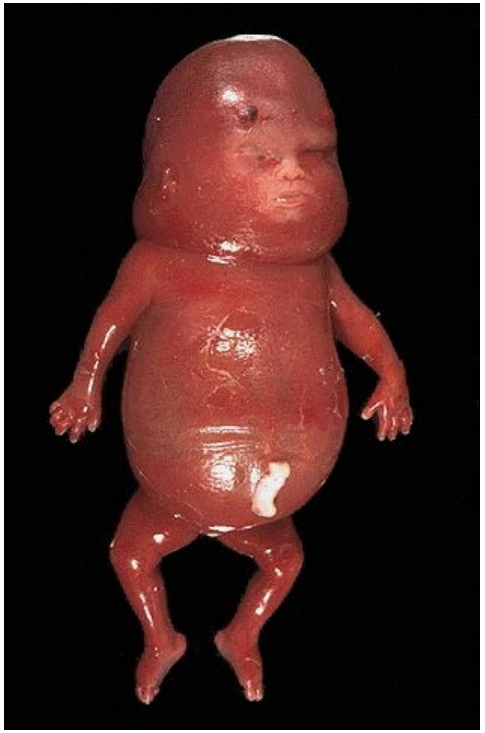
- Review the critical titre that would be used to follow immunized patients with anti-K .

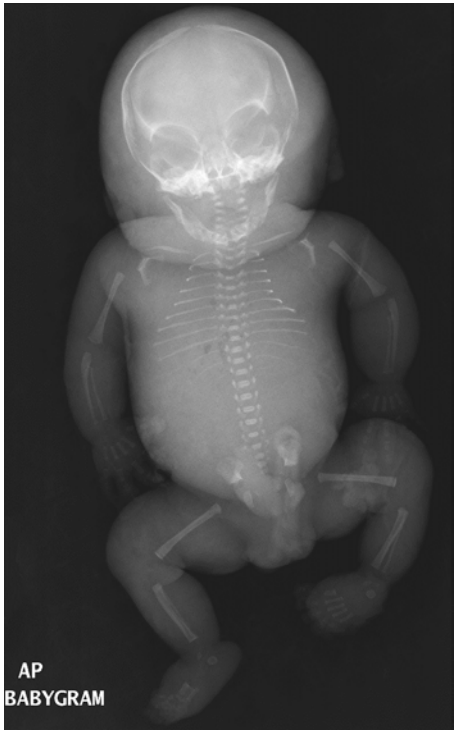
Background

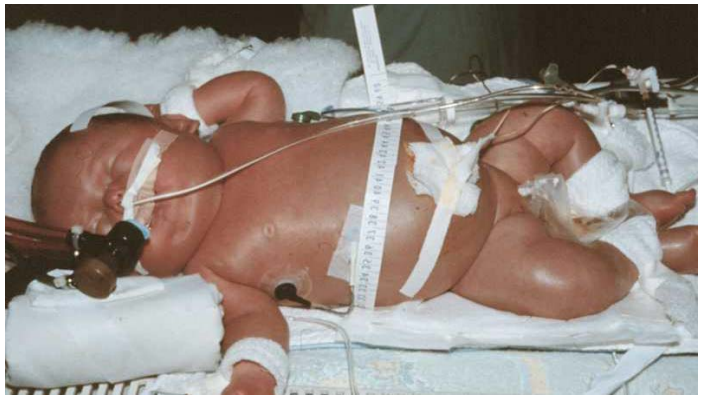
- HDFN: Destruction of fetal/newborn RBCs by maternal antibodies (IgG)
- Anti-K antibodies are the second most common cause of severe HDFN after Anti-D
- Anti-K antibodies cause anemia by
  a) haemolysis
  b) suppression of fetal erythropoiesis
- K/k antigen expression begins as early as 6-7 week's gestation

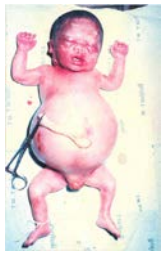
Complications

Hydrops fetalis/IUD/NND – high output cardiac failure with ascites, effusions, oedema

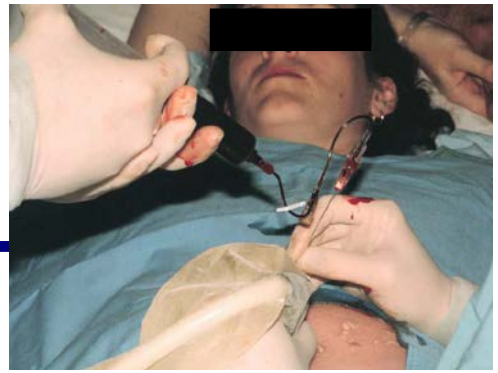






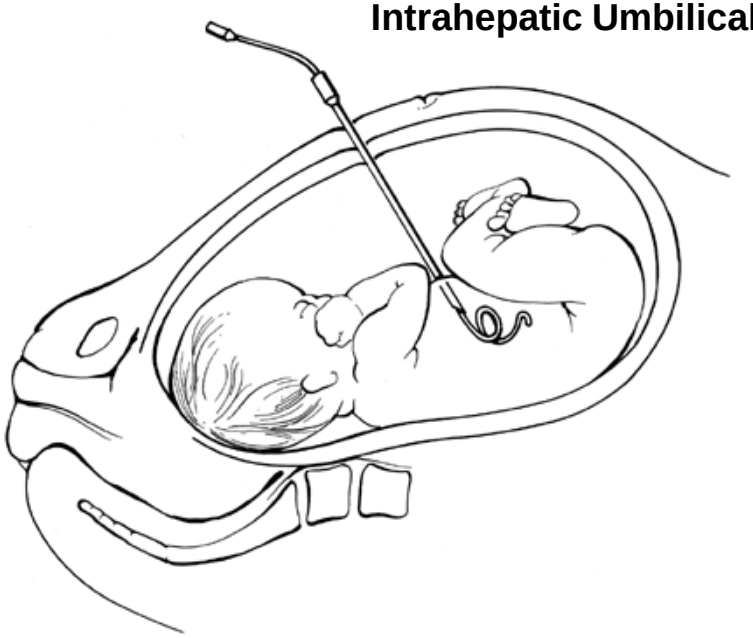


Treatment

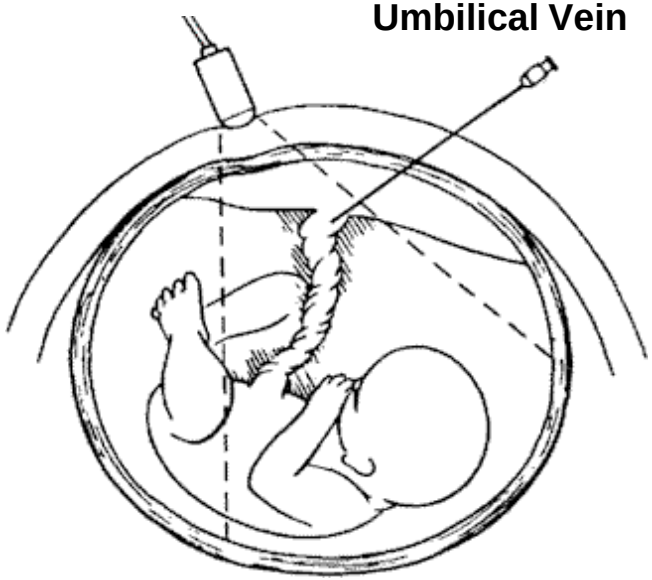


Intrauterine transfusion (IUT) of packed red cells have improved neonatal survival

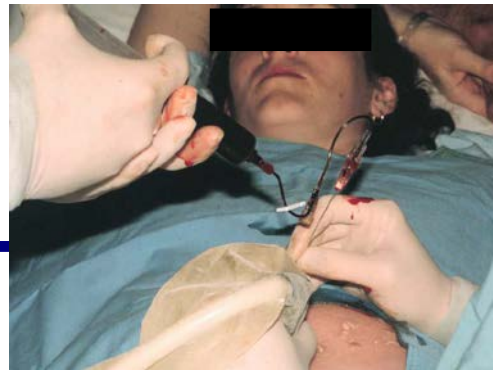
Intrahepatic Umbilical Vein



Umbilical Vein



Treatment



Intrauterine transfusion (IUT) of packed red cells have improved neonatal survival

Objectives

- Discuss whether regular anti-K titrations should be performed for an alloimmunized patient.
- Know when patients should be referred to high-risk maternal-fetal medicine specialists.
- Review the critical titre that would be used to follow immunized patients with anti-K .

Recommendations

- RCOG, UK, 2014
- BCSH, UK, 2016
- ACOG, USA, 2018
- CBS, Canada, 2018

RCOG, UK, 2014

Royal College of Obstetricians & Gynaecologists

The Management of Women with Red Cell Antibodies during Pregnancy

Green-top Guideline No. 65
May 2014

RCOG UK, 2014

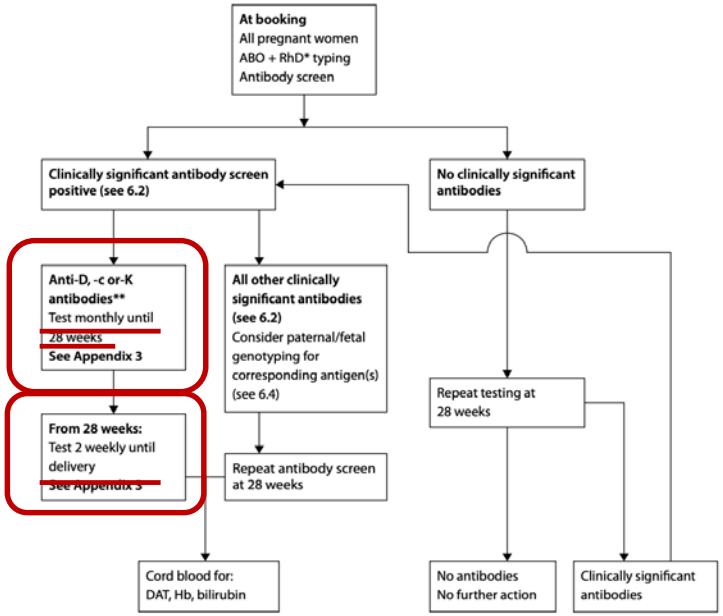
Appendix I: Red cell antibodies showing published clinical significance

Antibody	HDFN	Haemolytic transfusion reaction
D	Severe in fetus and neonate	Severe
c	Severe in fetus and neonate	Severe
K	Severe in fetus and neonate	Severe
c+E	Severe in fetus and neonate*	Severe
E	Yes in neonate*[39,40]	Yes
C	Yes in neonate*	Yes
e	Yes in neonate	Yes
Ce	Yes in neonate	Yes
Fy^a	Yes in neonate*[6]	Yes
Fy^b	Yes in neonate	Yes
Fy^3	No	Yes
Jk^a	Yes in neonate*	Yes
Jk^b	No	Yes
S	Yes in neonate	Yes
s	Yes in neonate	Yes
U	Yes in neonate*	Yes
M	Yes (occasionally)*[41]	Yes (if active at 37°C)
N	Mild (1 case)	Yes
H (Bombay)	Yes in neonate*	Yes
G	Yes in neonate	Yes
k	Yes in neonate*[42]	Yes
Kp^a	Yes (in neonate occasionally)	No
C^w	Yes (in neonate occasionally)	No
Vel	No	Yes

Anti-D, -c and -K are the three main antibodies that have been reported to cause severe anaemia, jaundice or death in the fetus or neonate. Many other antibodies (*) can cause anaemia or jaundice predominantly in the neonatal period but there have also been occasional case reports of the **fetus** being severely affected.

RCOG UK, 2014

Appendix II: Timing and frequency of antibody screening in pregnancy



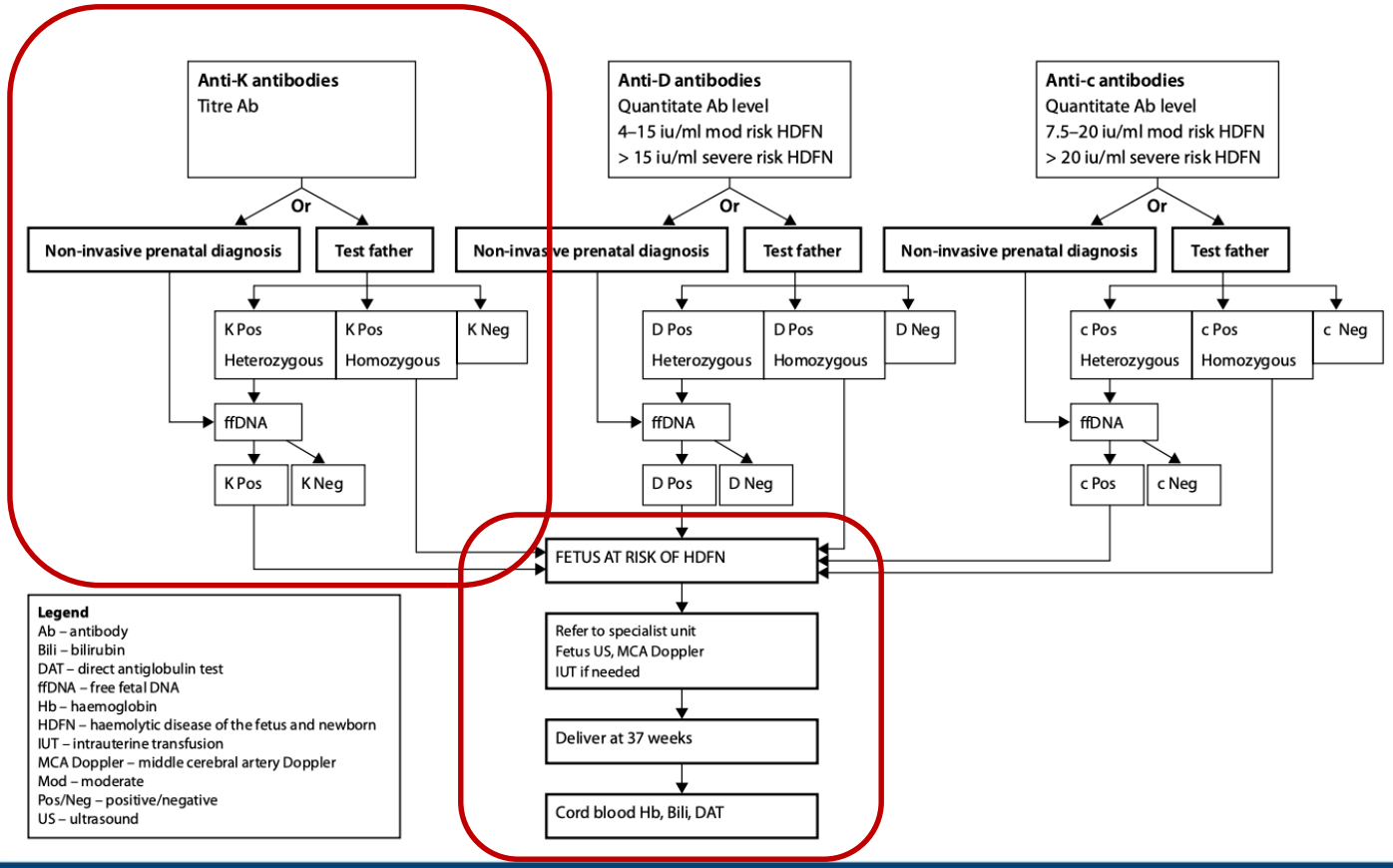
*If RhD-negative mother with no immune anti-D antibodies then advise anti-D prophylaxis for any potentially sensitising events in pregnancy and give routine antenatal anti-D prophylaxis either RAADP single dose or two doses (see RCOG anti-D guidelines); after delivery check cord sample for RhD type and maternal sample for fetomaternal haemorrhage (e.g. Kleihauer) testing to check if further anti-D needed in addition to the standard dose which should be given in the first instance after delivery.

**Pregnancies with immune anti-D, -K or -c are at particular risk of severe fetal HDFN so further early assessment and referral to fetal medicine specialist is indicated (see 6.7).

Legend
DAT – direct antiglobulin test; Hb – haemoglobin; RAADP – routine antenatal anti-D prophylaxis

RCOG UK, 2014

Appendix III: Management algorithm for pregnancies complicated with anti-D, anti-K or anti-c alloimmunisation



RCOG UK, 2014

Although anti-K titres do not correlate well with either the development or severity of fetal anaemia, titres should nevertheless be measured every 4 weeks up to 28 weeks of gestation, then every 2 weeks until delivery.

6.7 What thresholds should be used for the various antibodies that could cause fetal anaemia to trigge referral for further investigation or monitoring?

For anti-K antibodies, referral should take place once detected, as severe fetal anaemia can occur even with low titres.

BCSH, 2016

TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
British Blood Transfusion Society
Transfusion Medicine | GUIDELINES

Guideline for blood grouping and red cell antibody testing in pregnancy

White, J[1] Qureshi, H[2] Massey, E[3] Needs, M[4] Byrne, G[5] Daniels, G[6] Allard S[7] & British Committee for Standards in Haematology

[1]UK National External Quality Assessment Scheme for Blood Transfusion Laboratory Practice, Watford, [2]Department of Haematology, University Hospitals of Leicester, [3]NHS Blood and Transplant & University Hospitals Bristol NHS Foundation Trust, [4]Institute of Biomedical Scientists and NHS Blood and Transplant, [5]Department of Haematology, University Hospitals of Leicester, [6]International Blood Group Reference Laboratory, NHS Blood and Transplant, and [7]Barts Health NHS Trust and NHS Blood and Transplant

Received 28 September 2015; accepted for publication 1 March 2016

BCSH, 2016

- **Pregnant women with anti-K or other Kell system antibodies (unless the father is confirmed to be negative for the corresponding antigen) should be assessed serologically at monthly intervals to 28 weeks gestation and at fortnightly intervals thereafter until delivery and referred to a fetal medicine specialist when the antibody is first identified (Grade 1B).**

4.4 Pregnant women with immune anti-K or other Kell blood group system antibodies

Where detected, antibodies to other antigens in the Kell blood group system (e.g. anti-k, -Kp^a, -Kp^b, -Js^a, -Js^b) should be investigated and monitored in the same way as anti-K as these have the potential to cause HDFN (Al Riyami *et al.*, 2014).

HDFN due to anti-K is characterised by low haemoglobin concentration, but elevated amniotic and/or cord bilirubin levels are not generally reported. The fetal anaemia associated with anti-K may be due to the inhibition of K-positive erythroid early progenitor cells (Vaughan *et al.*, 1998) and/or to the promotion of their immune destruction (Daniels *et al.*, 2003).

It has been stated in some texts that the severity of HDFN due to anti-K is not correlated with titre of the antibody, and publications prior to 1995 cited occasions where severe HDFN occurred despite low titres of anti-K. More recent case series of affected pregnancies have, however, suggested that severe HDFN is associated with antibodies with a titre of at least 32 (McKenna *et al.*, 1999; Ahaded *et al.*, 2000). Therefore, samples from women with anti-K should be titrated (see Section 2.4.2) when the antibody is first identified in the pregnancy, and serial titration should then be undertaken every 4 weeks until 28 weeks gestation and 2 weekly thereafter until delivery. Once referral to a fetal medicine specialist has been made and serial MCA Dopplers are being performed, the value of undertaking anti-K titration on subsequent samples is doubtful, especially if the titres are already in the high-risk range (RCOG, 2014). The multidisciplinary team, including the laboratory, should be informed of the testing plan to prevent confusion and unnecessary interventions, e.g. the laboratory requesting follow-up samples in cases where the clinical team have decided that they are not required.

ACOG, 2018

INTERIM UPDATE

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 192, MARCH 2018

(Replaces Practice Bulletin Number 75, August 2006)

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics with the assistance of Calla Holmgren, MD, and T. Flint Porter, MD.

INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect a limited, focused change to align with Practice Bulletin No. 181, *Prevention of Rh D Alloimmunization.*

Management of Alloimmunization During Pregnancy

ACOG, 2018

▶ ***At what antibody titer should an additional evaluation be initiated?***

The usefulness of maternal serum antibody titers is determined by the patient's reproductive history. For a woman with a history of a previously affected fetus or neonate, serial titer assessment is inadequate for surveillance of fetal anemia. Titer values are reported as the integer of the greatest tube dilution with a positive agglutination reaction. Variation in titer results from different laboratories is not uncommon, so titers should be obtained in the same laboratory when monitoring a patient, and a change of more than one dilution is significant. A *critical* titer is that titer associated with a significant risk for severe erythroblastosis fetalis and hydrops, and in most centers this is between 1:8 and 1:32. If the initial antibody titer is 1:8 or less, the patient may be monitored with titer assessment every 4 weeks. For patients with alloimmunization involving antigens other than D, similar titer levels should be used to guide care except in Kell-sensitized patients because Kell antibodies do not correlate with fetal status (19).

Advise against titer monitoring

CBS, Canada, 2018

Canadian Blood Services
BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

Transfusion

Transfusion ▸ Clinical guide

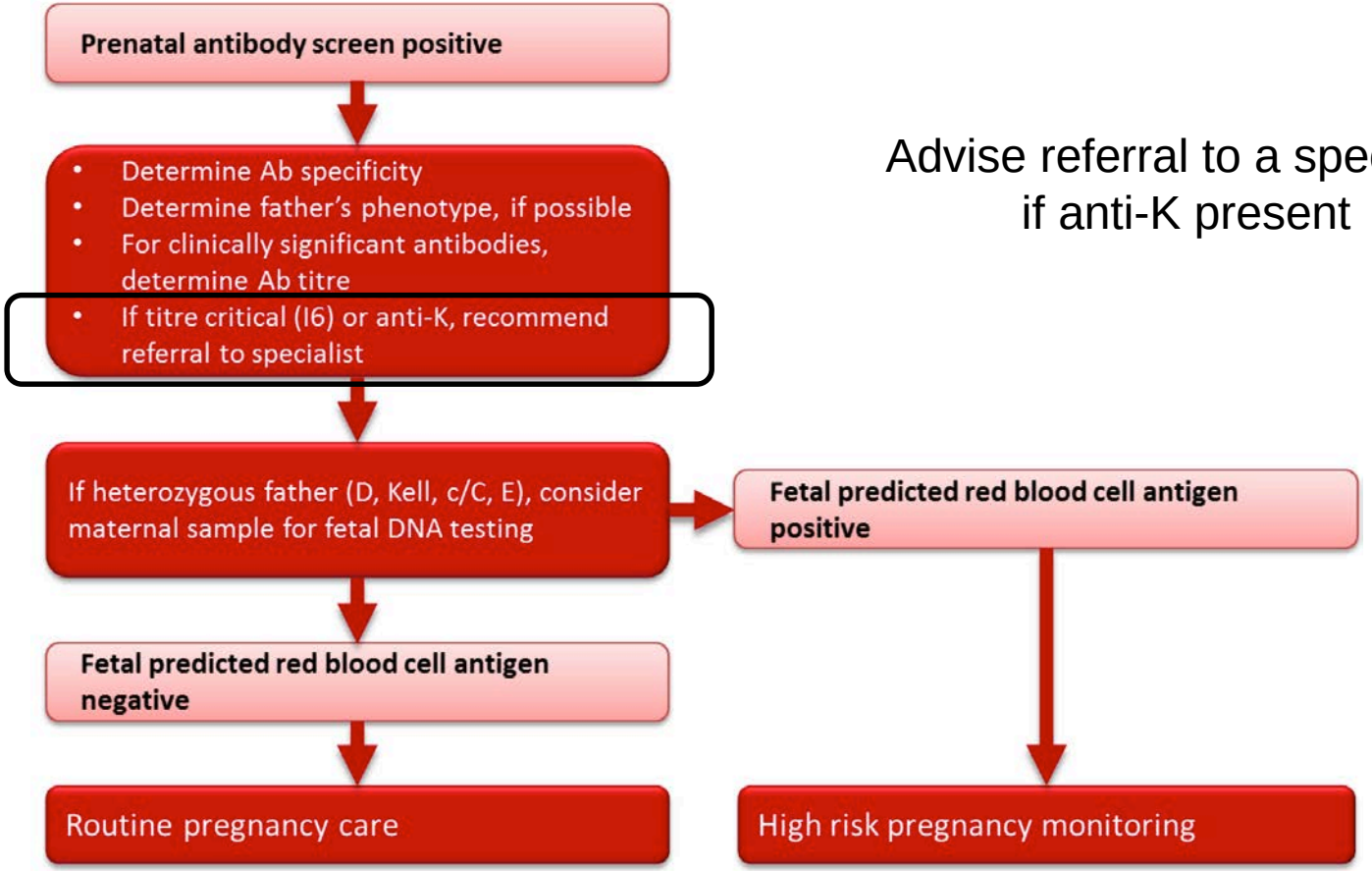
Chapter 12

Hemolytic disease of the fetus and newborn and perinatal immune thrombocytopenia

Author(s)
Gwen Clarke, MD, FRCPC, and Judith Hannon, MD, FRCPC

Date Published
2018-07-20

CBS, Canada, 2018



Advise referral to a specialist if anti-K present

Figure 3. Management of clinically significant red blood cell antibodies in pregnancy.

Overall Statements

- Establish fetal risk to fetus (partner testing/cffDNA)
- Refer to a fetal medicine unit (RCOG, BCSH, ACOG, CBS)
- Follow titre levels monthly until 28 weeks and then every two weeks until delivery (RCOG, BCSH)
- Role of titres doubtful once serial MCAs undertaken (BCSH)
- No role for titre monitoring (ACOG)

Objectives

- Discuss whether regular anti-K titrations should be performed for an alloimmunized patient. Know when patients should be referred to high-risk maternal-fetal medicine specialists.

- Review the critical titre that would be used to follow immunized patients with anti-K .

ORBCoN
Ontario Regional Blood Coordinating Network

Inspiring and facilitating best transfusion practices in Ontario.

bjh research paper

Outcome predictors for maternal red blood cell alloimmunisation with anti-K and anti-D managed with intrauterine blood transfusion

Evangelia Vlachodimitropoulou,[1,2] Maciej Garbowski,[3] Shelley Anne Solomon,[1] Nimrah Abbasi,[1,2] Gareth Seaward,[1,2] Rory Windrim,[1,2] Johannes Keunen,[1,2] Edmond Kelly,[1,2] Tim Van Mieghem,[1,2] Nadine Shehata[1,2] and Greg Ryan[1,2]

[1]Fetal Medicine Unit, Ontario Fetal Center, Mount Sinai Hospital, [2]University of Toronto, Toronto, Ontario, Canada, and [3]Department of Haematology, University College London Hospital, London, UK

Received 15 August 2021; accepted for publication 30 October 2021

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- Retrospective single-center study at Mount Sinai Hospital (MSH), Ontario Fetal Medicine Center, Toronto, Canada
- 128 pregnancies, 425 IUTS
- Between 1991 - 2018
- 31 pregnancies alloimmunised with anti-K as a single antibody

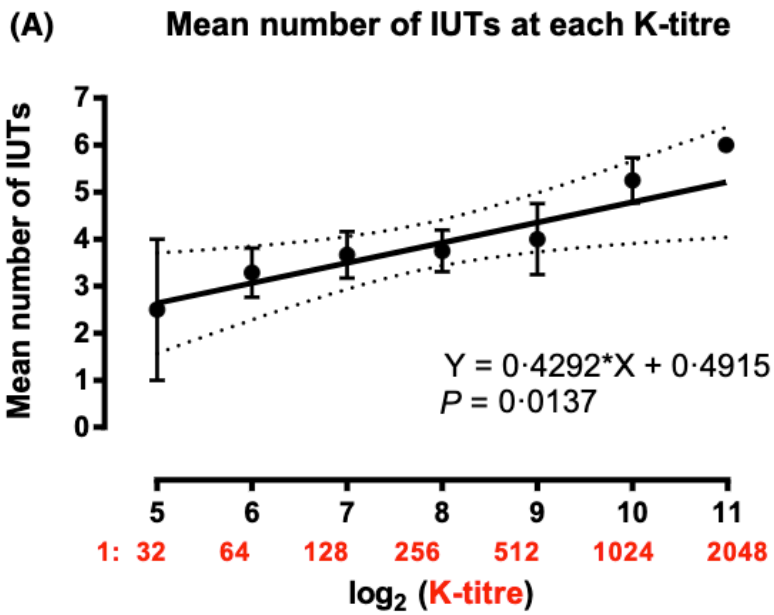
Outcome predictors for maternal red blood cell alloimmunisation with anti-K and anti-D managed with intrauterine blood transfusion

Table I. Baseline characteristics of anti-K and anti-D alloimmunised pregnancies receiving intrauterine transfusions between 1991 and 2018 at Mount Sinai Hospital, Toronto, Canada.

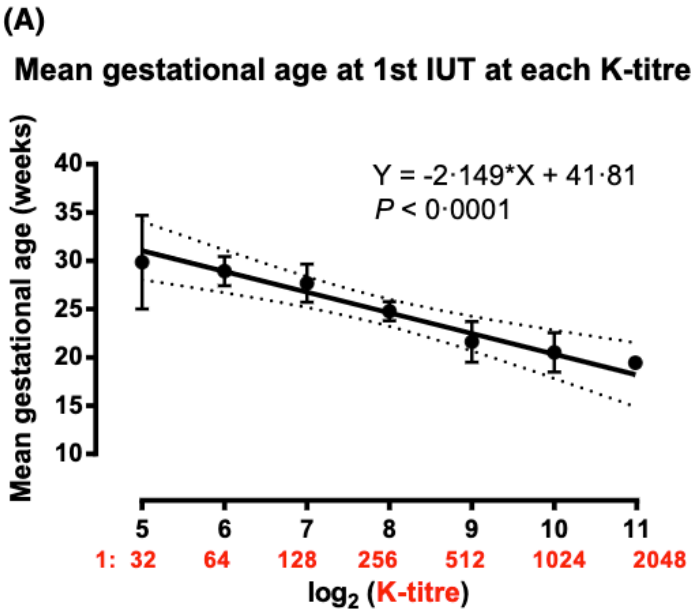
Characteristic	Anti-K $N = 31$	Anti-D $N = 97$	P
Demographics at study entry			
Maternal age, years, median (IQR)	31·00 (27·0–35·0)	32 (23·6–40·6)	0·76
Antibody titre, *n* (%)			
1:32	3 (9·7)	2 (2·1)	
1:64	5 (16·1)	9 (9·3)	
1:128	3 (9·7)	16 (16·5)	
1:256	10 (32·3)	24 (24·7)	
1:512	6 (19·4)	28 (28·9)	
1:1024	2 (6·5)	14 (14·4)	
1:2048	2 (6·5)	5 (5·2)	

No fetus with a titre < 1:32 required an IUT

Outcome predictors for maternal red blood cell alloimmunisation with anti-K and anti-D managed with intrauterine blood transfusion



A greater number of IUTs was required in women with a higher titre.



The higher the titre, the earlier the GA at which an IUT was required.

Predicting anti-Kell-mediated hemolytic disease of the fetus and newborn: diagnostic accuracy of laboratory management

Yolentha M. Slootweg, MSc; Irene T. Lindenburg, MD, PhD; Joke M. Koelewijn, PhD; Inge L. Van Kamp, MD, PhD; Dick Oepkes, MD, PhD; Masja De Haas, MD, PhD

- Retrospective single center
- Leiden University Medical Center, Netherlands
- 1999-2015
- 93 women with anti-K antibodies and K positive fetuses
- 48 women required an IUT

Predicting anti-Kell-mediated hemolytic disease of the fetus and newborn: diagnostic accuracy of laboratory management

Yolentha M. Slootweg, MSc; Irene T. Lindenburg, MD, PhD; Joke M. Koelewijn, PhD; Inge L. Van Kamp, MD, PhD; Dick Oepkes, MD, PhD; Masja De Haas, MD, PhD

TABLE

Number of positive tests, sensitivity, specificity, and predictive values of Kell-mediated pregnancies without additional antibodies to predict need for transfusion by cut-off first titer (N = 93)

First titer cut-off	Positive tests	Need for transfusion: True positive	Need for transfusion: [a]Missed HDFN cases	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
≥2	81	49	0	100 (91–100)	27 (15–43)	60 (49–71)	100 (70–100)
≥4	77	49	0	100 (91–100)	36 (23–52)	64 (52–74)	100 (76–100)
≥8	70	47	2	96 (85–99)	48 (33–63)	67 (55–78)	91 (70–98)
≥16	62	47	2	96 (85–99)	66 (50–79)	76 (63–85)	94 (77–99)
≥32	57	45	4	92 (80–97)	73 (57–85)	79 (66–88)	89 (73–96)
≥64							
≥128							

CI, confidence interval; *HDF*

[a] Cases with necessity for t

Slootweg et al. Laboratory

CONCLUSION: Early determination of the anti-Kell titer is sufficient to select pregnancies at increased risk for hemolytic disease of the fetus and newborn with need for transfusion therapy. If the Kell status of the fetus is known to be positive, a titer of ≥4 can be used to target intensive clinical monitoring.

The literature..

Publication	Journal	Number of pregnancies	Lowest anti-K titer requiring IUT	Method
Vlachodimitropoulou et al	BJH, 2021	31	1:32	Tube
De Haas et al	AJOG, 2018	48	1:8	Tube
Oepkes et al	Obst & Gyn 2007	41	One 1:2 One 1:4 Thirty-nine > 1:32	Tube
O'Shaughnessy et al	Obst & Gyn 1999	21	1:32	Tube
Caine & Mueller-Heubach	AJOC, 1986	13	1:32 (hydrops, neonatal death, Hb <7.9, heart failure)	Tube

Controversies

In the community, once an anti-K antibody is identified, should the alloimmunized patient be referred to a high-risk obstetric team?

- *Yes*
- *No*

Recommendation: For centers without MFM support, likely best to refer to a center with experience. Anaemia may occur at titers lower than other antibodies and may be confusing.

Controversies

Should we titre anti-K antibodies in pregnancy in the community?

- No

- Yes

If yes, how often should we titre?

- *Every 4 weeks until 28 weeks and then every 2 weeks until delivery, sooner if changes?*

What is the critical titer to trigger referral to MFM?

- 1:4, 1:8 or 1:32 ?

Titers in the community

FOR	AGAINST
Good negative predictive value	No agreed-upon cut off level below which the fetus is safe 1 : 2/4/8/32?
Greater continuity of care/less unnecessary physicians involved	Confusing that anemia could occur at lower titers than other antibodies
Reduced travel time/ expense for patients	Titration is not a primary means of ruling out HDFN
Reduced health care expenses (USS/physician time)	Different techniques for titration in different labs eg ADCC/gel/tube. Hard to compare. Need consistency.

Controversies

Should we titre anti-K antibodies in pregnancy in high-risk centers?

- No, once a critical titre is reached, no further monitoring of titres should be performed
- Yes

- If yes, how often should we titre?

Recommendation: yes, q monthly and if there is an increase q2 weekly with concurrent MCA monitoring. Titers allow planning for subsequent USS.

Controversies

How about subsequent pregnancies? Refer to a high-risk center?

- Yes
- No, manage in the community

Recommendation: yes, refer patients with HDFN early. Serial titer monitoring in the community is not useful.