Haemolytic diseases of the foetus and newborn

Prof Omondi-Ogutu

2020

Learning objectives

- To be able to define and understand the different types of HDFN
- To be able to differenciate the timing of onset of heamolysis in the types of HDFN
- understand the presentations in the different groups
- Understand the scientific basis of the diagnostic tests
- The different management approaches in the 2 groups
- Complications and prevention

Difination- HDFN

- Is a condition in which the lifespan of the fetal or newborn infants red cells is shortened by the action of maternal antibodies against antigens present on the infants red cells.
- The most common routes of maternal sensitization are via blood transfusion or feto-maternal hemorrhage.

Causes of HDFN

Major

- **ABO incompatibility**
- **Rhesus incompatibility**

MINOR

- **drugs**
- **Infections**
- **Prematurity**
- **Heavy metal poisoning**

Common causes

Major

- **ABO incompatibility**
- **Rhesus incompatibility**

MINOR

- **drugs**
- **Infections**
- **Prematurity**
- **Heavy metal poisoning**

Incidental

- Early pregnancy with no anti-D in Rh –Neg mother, Ectopic pregnancy, abortion
- Transfusion of un matched blood (where correct group is not done)

“Other” Hemolytic Disease

- Uncommon, occurs in ~0.8% of pregnant women.
- Immune alloantibodies usually due to anti-E, -c, -Kell, -Kidd or -Duffy.
- Anti-K
  - disease ranges from mild to severe
  - over half of the cases are caused by multiple blood transfusions
  - *is the second most common form of severe HDN*
- Anti-M very rare

historical

- A French midwife was the first to report hemolytic disease of the newborn (HDN) in a set of twins in 1609.
- In 1932, Diamond and colleagues described the relationship among fetal **hydrops**, **jaundice**, **anemia**, and erythroblasts in the circulation, a condition later called **erythroblastosis fetalis**.

ABO haemolytic disease

DIFFERNTIAL DIAGNOSIS

- RBC enzyme disorders (e.g., G6PD, pyruvate kinase deficiency) -Hemoglobin synthesis disorders (e.g., alpha-thalassemias)
- -RBC membrane abnormalities (e.g., hereditary spherocytosis, elliptocytosis) -Hemangiomas (Kasabach Merritt syndrome)
  -Acquired conditions, such as sepsis, infections with TORCH or Parvovirus B19 (anemia due to RBC aplasia) and hemolysis secondary to drugs.

defination

- ABO incompartibility occurs when the mother is blood group O positive and the New born is either A,B,AB positive . There is new borns blood destruction within 24 hrs of delivery

physiology

- The major blood types are:
- A,-41% B,- 9% O,-47% & AB,-3% (in Caucasians).
- The antigens types A & B occur on the surfaces of the red blood cells in a large proportion of human beings
- Types A & B cause strong agglutination on the cells
- The type O gene is either functionless or almost functionless.

physiology

- 20-25% of all infants have an ABO maternal blood group incompatibility
- But only in 5-10 % show signs of overt haemolysis.
- Mothers are usually blood group O,
- The babies with group A are the most affected
- Nearly ½ occur in the first born

pathogenesis

- Onset of haemolysis is within 24 hours after birth.
- There maybe a rapid rise in the bilirubin levels.
- Majority tend to be self limiting.
- Only in few cases will exchange transfusion be required.-1%

Why not in utero

- Iso antibodies to A & B are IgM which does not cross the placenta
- Foetal erythrocytes have a diminished number of A & B antigenic sites

Clinical features

- Jaundice
- Foetal irritability
- Hepato-splenomegally
- Anaemia
- Kernicterus

diagnosis

- Mother gp O, with anti-A & B in her serum. Foetus is gp A, B, or AB.
- Onset of jaundice within first 24 hrs.
- Rapid increase in bilirubin levels in the baby leading to
- Anaemia, erythroblastosis, reticulocytosis
- Exclusion of other causes of haemolysis
- Indirect bilirubin levels tend to be negative.,

- Seen in primigravida
- Tend to recur in up to 30 % of cases.

management

This will depend on the clinical state of the baby

- Reassurance to the mother
- Phototherapy
- Exchange transfusion using blood gp O negative

Rhesus haemolytic disease

history

- 1892- Ballantyne established the criteria for diagnosis of hydrops fetalis
- 1940- Landsteiner & wiener,
- 1941- Levine

  confirmed that erythroblastosis was due to maternal issoimunisationwith paternal inherited foetal factors.
- 1961 Fin-UK. 1963 Freda-USA. Development of the Ati-D

introduction

- There are more than forty antigens in the Rh system including weak D (formerly called Du variant). Mothers typed as weak D appear to be Rh negative on blood screening.
- The majority of mothers with weak D are Rh (D) positive. However, the presence of the C allele causes the D antigen to be weakly expressed
  - Mothers or infants typed as weak D are usually treated as Rh positive.

Rh Hemolytic Disease

- Anti-D is the commonest form of severe HDN. The disease varies from mild to severe.
- Anti-E is a mild disease
- Anti-c can range from a mild to severe disease - is the *third most common form of severe HDN*
- Anti-e - rare
- Anti-C - rare
- antibody combinations (ie anti-c and anti-E antibodies occurring together) - can be severe

- The Rh alleles (D,Cc, Ee) are inherited as a complex of three loci .One set from each parent.
- A person is Rh-positive if they possess the D allele and Rh negative if it is absent.
- The hypothetical "d" allele has not been identified

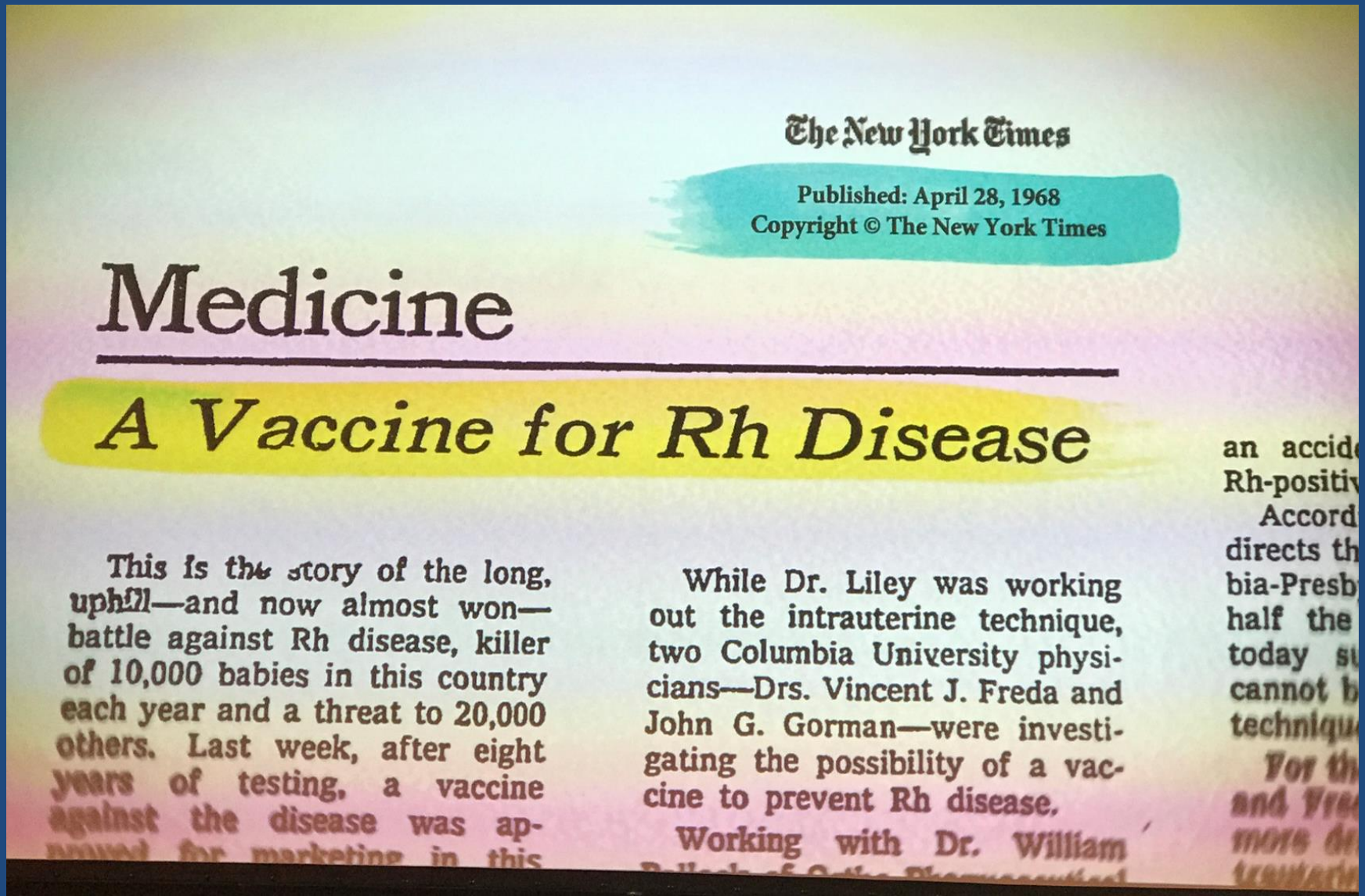
investigations

- MCA Doppler studies can be started as early as 18 weeks' gestation but are not reliable after 35 weeks' gestation.

First Description

- French midwife, Louise Bourgeois worked at the royal court of King Henry IV and Queen Marie de Medicis
- 1609 - Described the birth of twins
  - First had hydrops and died immediately
  - Second, rapidly became jaundiced and, than developed neurological symptoms (kernicterus), died 3 days after being born.

Revolution in 1968



The New York Times

Published: April 28, 1968

Medicine

A Vaccine for Rh Disease

This is the story of the long, uphill—and now almost won—battle against Rh disease, killer of 10,000 babies in this country each year and a threat to 20,000 others. Last week, after eight years of testing, a vaccine against the disease was ap-

While Dr. Liley was working out the intrauterine technique, two Columbia University physicians—Drs. Vincent J. Freda and John G. Gorman—were investigating the possibility of a vaccine to prevent Rh disease.

Working with Dr. William

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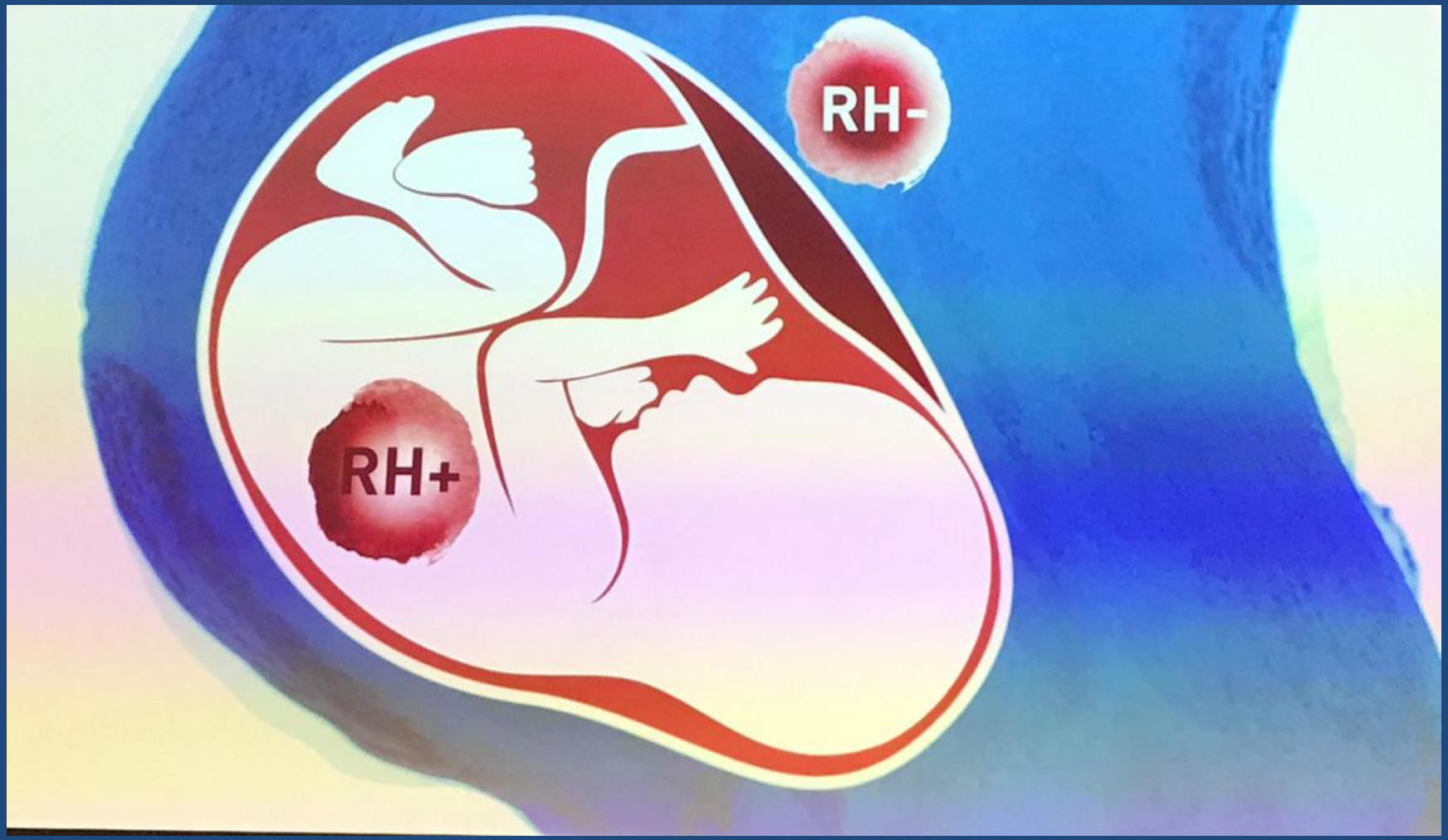
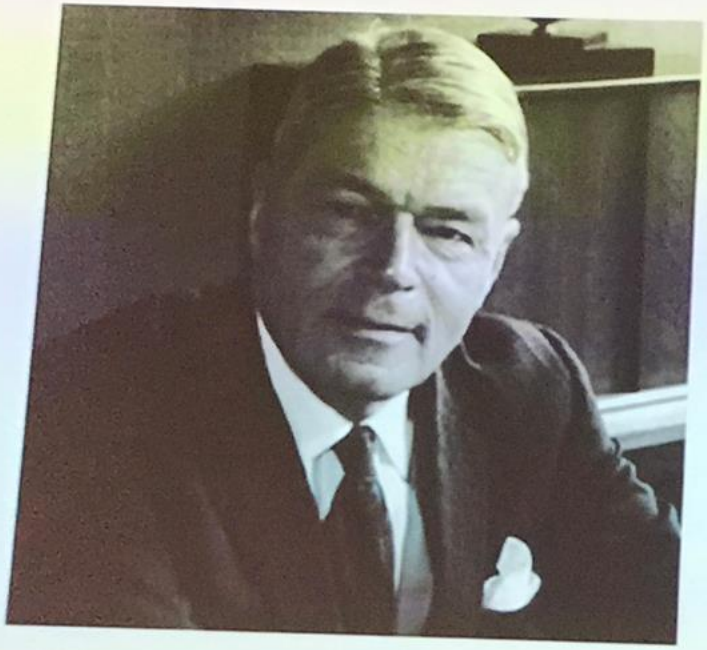
Pregnant mother





Cyril A. Clarke

The University of Liverpool

Ronald Finn

Royal Liverpool Hospital

Vincenta Freda:: William Pollack

- The true genetic Du variant is an incomplete form of D antigen and may rarely become D immunized.

- The rare occurrence of a D immunized true genetic Du mother may be sufficient reason to treat a weak D mother with RhIg when the nature of the Du variant is in doubt.

epidemiology

- Chinese and Japanese 1%
- North American Indian and Inuit1 2%
- Indo-Eurasian 2%
- African American 4 - 8%
- Caucasian 15 - 16%
- Basque 30 - 35%
- KNH 4.5%

physiology

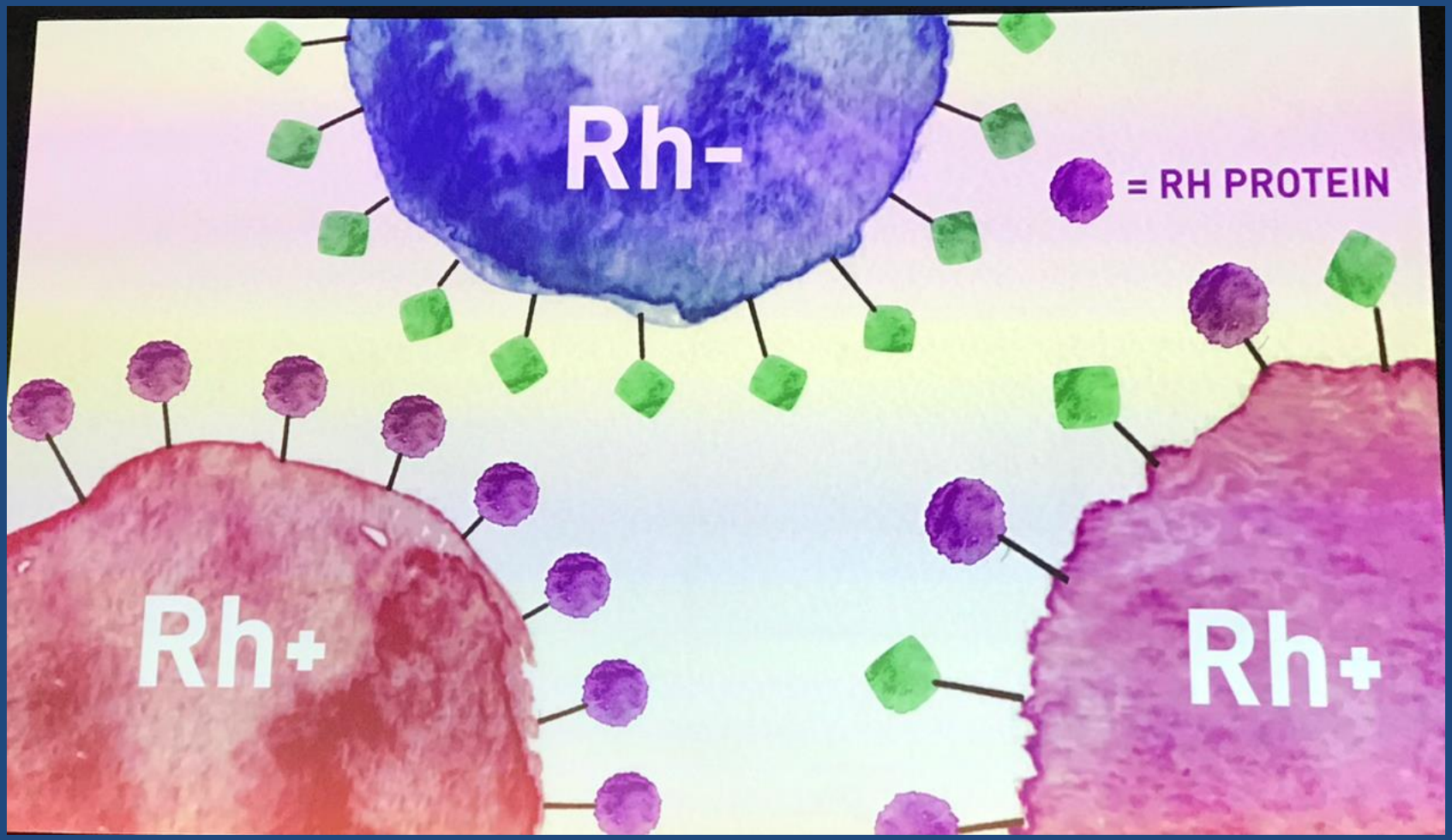
- Rhesus blood group is the most complex

  Dd, Cc, Ee.
- > 400 other red cell antigens have been identified
- Racial factor .highest in the Basque community-34%. Lowest in the Chinese and Asians -1%.

pathogenesis

- Blood production in the fetus begins at about 3 weeks' and Rh antigen has been identified in the red cell membrane bas early as 38 days after conception.

The process



pathogenesis

- The initial response to D antigen is slow sometimes taking as long as 6 months to develop.
- Re-exposure to the antigen produces a rapid immunological response usually measured in days.
- **The sensitized mother produces IgG anti-D (antibody) that crosses the placenta and coats D-positive fetal red cells which are then destroyed in the foetal spleen.**

.

pathogenesis

- Severe haemolysis leads to red blood cell production by the spleen and liver.

- Subsequently, hepatic circulatory obstruction (portal hypertension) with placental oedema interferes with placental perfusion and ascites develops.

pathogenesis

- **Hepatomegaly, increased placental thickness, and polyhydramnios often precede the development of hydrops (foetal heart failure).**

- As liver damage progresses decreased albumin production results in the development of anasarca, and effusions

Sensitized

- **Overall, 16% of Rh-negative women will become sensitized after their first pregnancy if not given Rhogam.**
- ABO incompatibility reduces this risk to 4-5%. The reduced risk of Rh sensitization with ABO incompatibility may result from the rapid clearance of incompatible red cells thus reducing the overall exposure to D antigen.

pathogenesis

- Mild to moderate hemolysis (red cell destruction) manifests as increased indirect bilirubin (red cell pigment).

- Severe hemolysis leads to red blood cell production by the spleen and liver

causes

- Maternal transfusion with a positive blood group.
- Significant ante partum haemorrhage
- Foetal maternal transfusion

- 1932 Diamond

Erythroblastosis secondary to severe haemolysis, cause was still unknown.

- 1938 Ruth Darrow from W&CH, Chicago

Identified the (antibody-related) pathogenesis of HDN

- 1940 Landsteiner and Wiener
- Discovery of the Rhesus blood group system

pathology

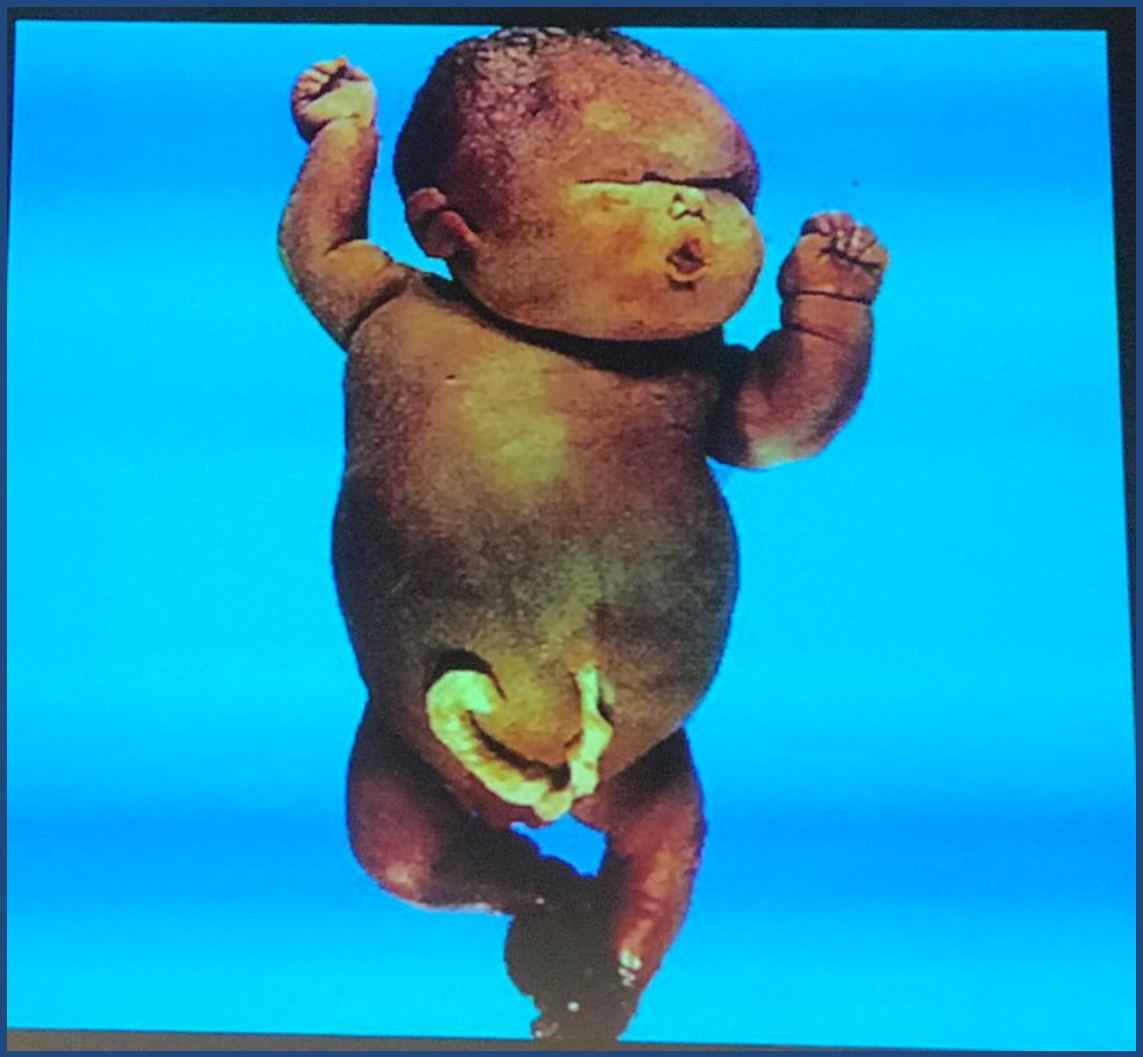
- The maternal red cells adsorb the fetal cells and crosses the placenta to exist as unbound and bound, thus acting as haemolysin. Causing accelerated rate of RBC destruction.

- Detected by the direct Coombs test

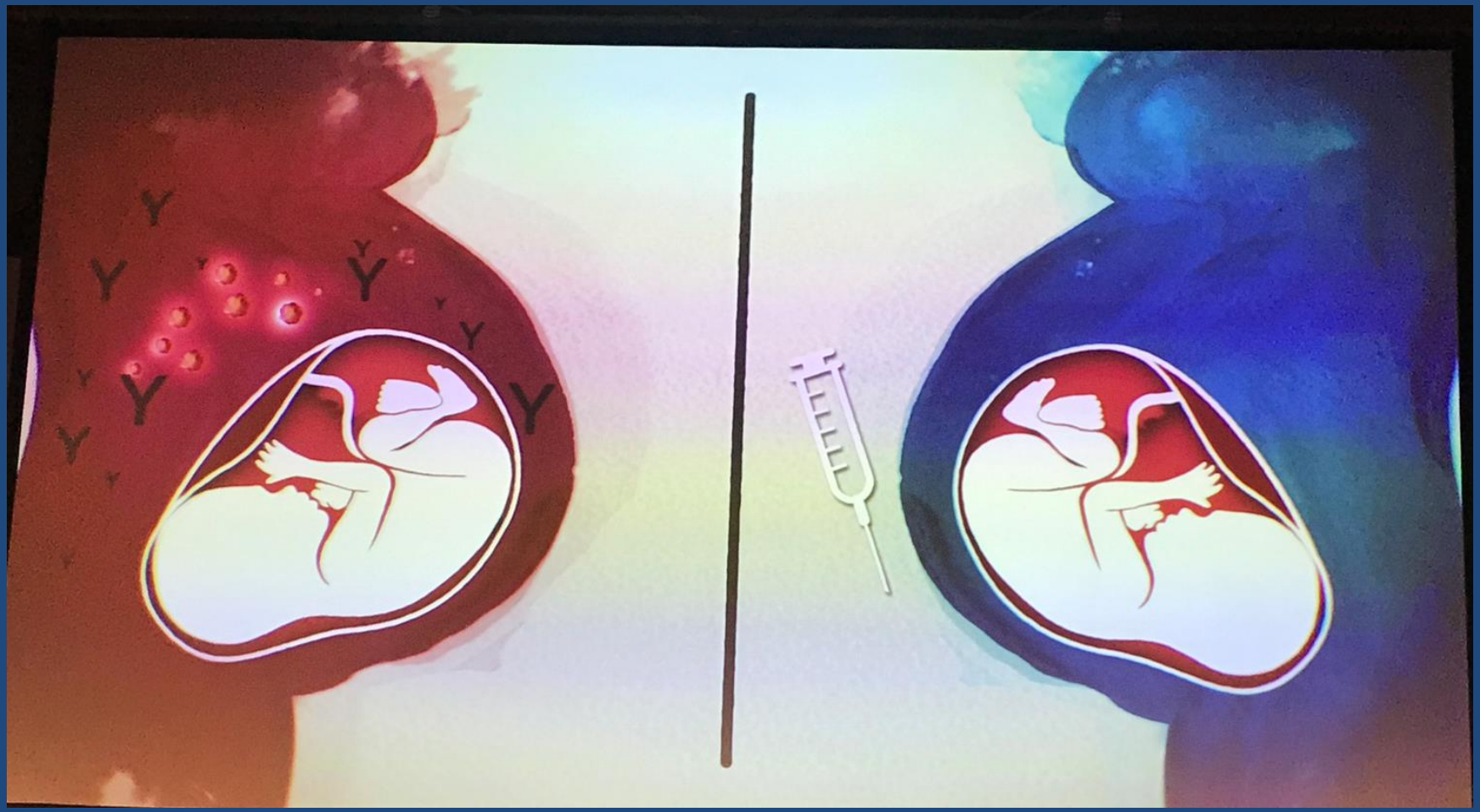
Immune hydrops

- Subcutaneous oedema with effusion into the serous cavities-hydrops fetalis.
- Oedematous placenta
- Fatty degeneration of the liver.
- In these sever cases death tends to occur in utero.

Hydrops foetalis



Vaccinated vs not vaccinated



Took too long!

New York Times editorial October 29, 1967

An End to Rh Disease?

For tens of thousands of couples each year the future is clouded by physicians' warnings that the life of a baby they are expecting is threatened by Rh disease the result of a specific difference in the blood types of the prospective father and mother.

Now there is mounting evidence that a technique may have been found to prevent Rh disease from developing. Babies that suffer from this ailment are victims of the fact that their mothers, who have Rh negative blood, have become immunized and manufacture antibodies against Rh positive blood.

Researchers have apparently found an effective and safe means of preventing an Rh negative mother from developing the dangerous antibodies. **The original observation from which this new technique derives was made long ago as 1909** by a researcher in basic medical science, Theobald Smith. **Not until 1960 was it realized that Smith's findings were relevant to this problem.**

Once again the value of basic research has been dramatically proved. But laymen must wonder why a half century had to pass before Smith's work would begin to be applied to save lives.

52 Years

Again, a good idea, entirely 'doable' in 1941 when Levine discovered the cause of Rh Hemolytic Disease - *It just didn't occur to anyone for 19 years.*

19 Years

Journey by Freda

RhoGAM® ORIGINS

In 1958, I became the first resident in Clinical Pathology at Presbyterian Hospital. The blood bank was one of my rotations. One day in 1959 I was in the pathology microscopic lab with the medical students, and the Saunders book salesman presented me with a free copy of *Florey's General Pathology* - in the hope that I would recommend it to the students. One chapter, by Gladstone and Abrahams, caught my interest – it was devoted entirely to multiple studies showing passive antibody preventing active immunity. This chapter demonstrated clearly that passive antibody suppressed active immunity reliably in a wide ranging manner. I realized it would work for Rh.

RhoGAM® ORIGINS

What is notable and ironic is that RhIg is exactly the same agent that was killing babies. And, the more dangerous the antibody, the more effective it is in preventing sensitization. In 1960, **there it was**, a fully optimized molecule, in plentiful supply from the legions of Rh mothers already Rh sensitized. No need for clever chemists to synthesize, fine tune and test, a novel molecule, as is the case with most new drugs. In fact, 50 years of efforts to develop a monoclonal RhIg that prevents Rh sensitization have failed so far.

The New York Times

Published: April 28, 1968

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This is the story of the long, uphill—and now almost won—battle against Rh disease, killer of 10,000 babies in this country each year and a threat to 20,000 others. Last week, after eight years of testing, a vaccine against the disease was approved for marketing in this country.

The story began with the discovery in 1939 that a factor known as Rh was present in the blood of some persons (designated as Rh-positive) but not in others (Rh-negative).

It was followed soon after by the realization that Rh disease

While Dr. Liley was working out the intrauterine technique, two Columbia University physicians—Drs. Vincent J. Freda and John G. Gorman—were investigating the possibility of a vaccine to prevent Rh disease.

Working with Dr. William Pollack of Ortho Pharmaceutical Corporation in Raritan, N. J., Drs. Freda and Gorman developed a vaccine that consisted of the very substance that caused Rh disease—anti-Rh antibodies.

Conclusions

The researchers found that when an Rh negative person

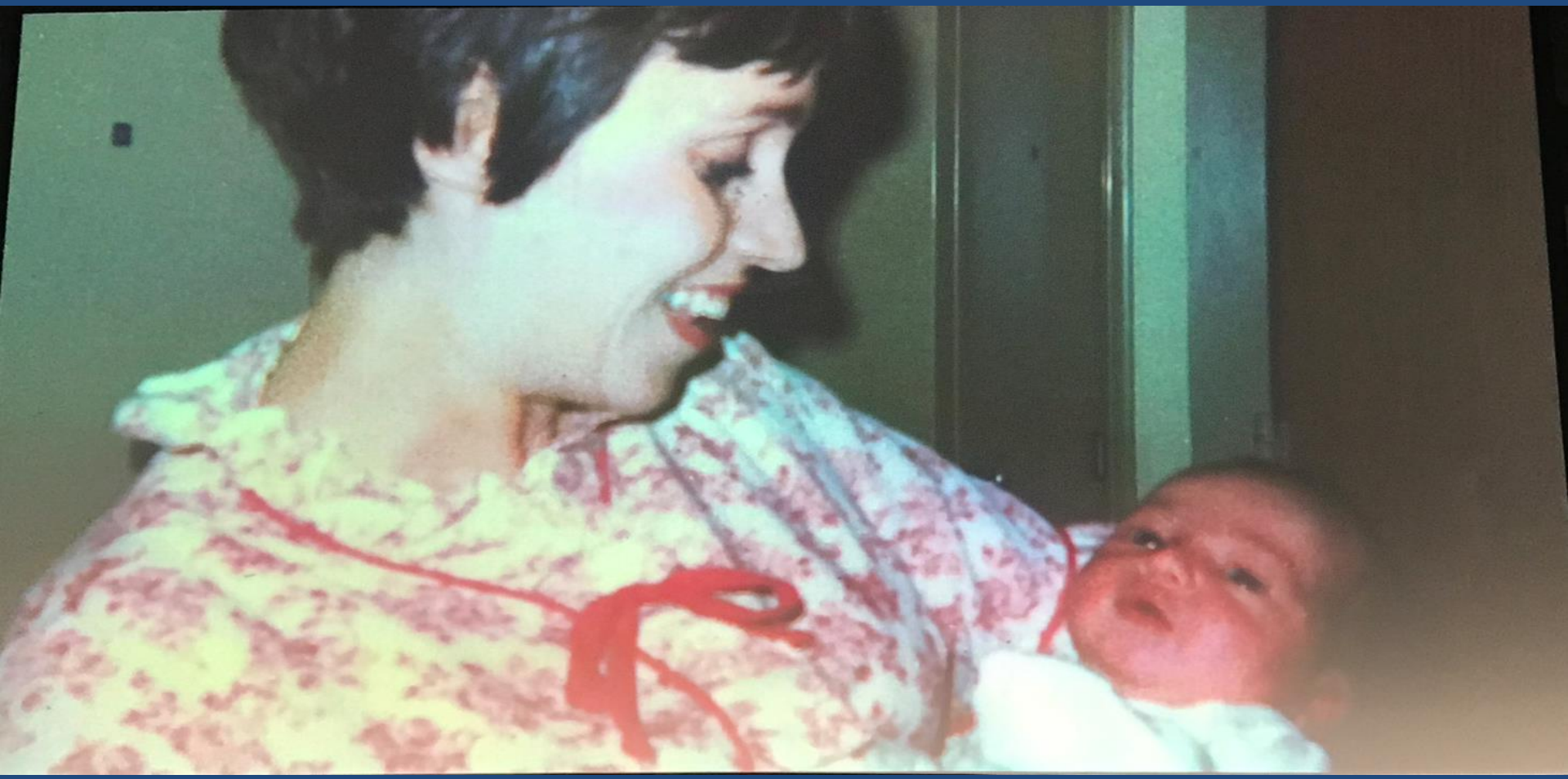
an accidental transfusion with Rh-positive blood.

According to Dr. Gorman, who directs the blood bank at Columbia-Presbyterian Hospital, about half the women whose babies today succumb to Rh disease cannot be helped by any known technique.

For these women, Drs. Gorman and Freda hope to try an even more drastic technique than intrauterine transfusion. Starting at the 18th week of pregnancy, they propose to remove four pints of the woman's blood a day, take out the anti-body-containing plasma and return to her own red blood cells plus normal plasma.

The procedure would be repeated until the 32d week of pregnancy, when it is considered

First Rh vaccine baby



The babies

Marianne Cummins

1st vaccinated Patient 1968 and the Dr

- 1977

1.8% of Rh negative women, despite post-natal prophylaxis, continued to develop anti-D antibodies due to small transplacental hemorrhages during pregnancy

- 1998

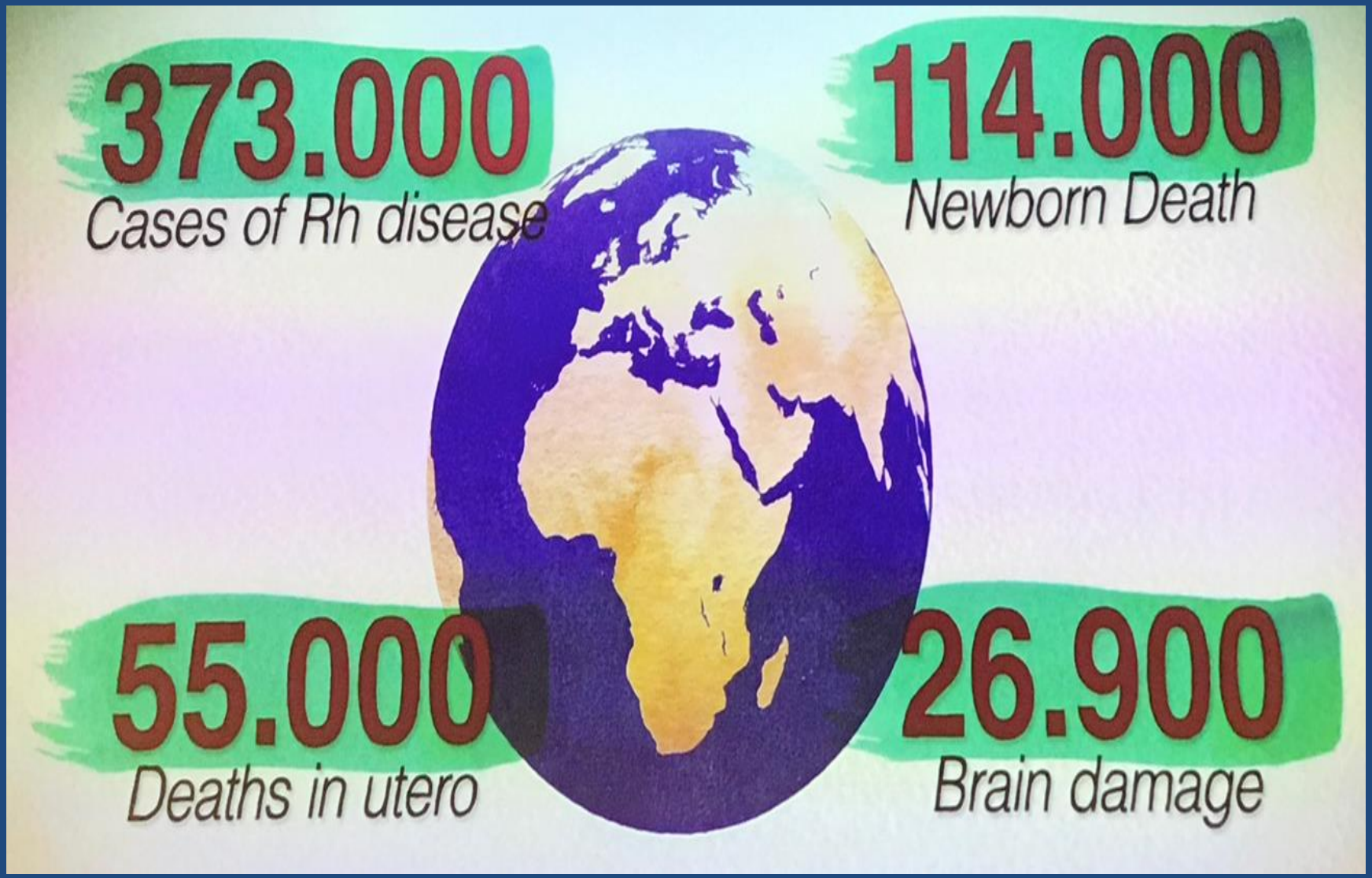
Bowman *et al.* - incidence reduced to 0.1% by prophylaxis with antenatal anti-D IgG, in addition to post-partum prophylaxis

- Currently

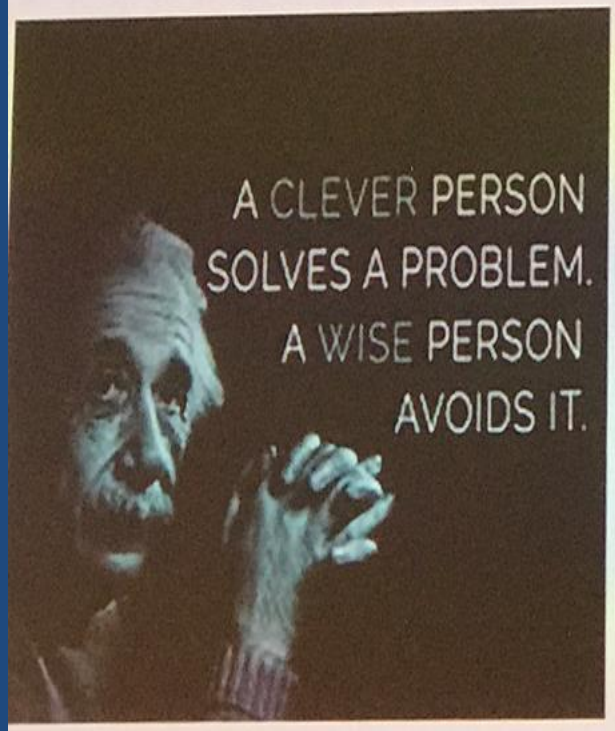
Evidence that antenatal anti-D prophylaxis reduces the risk of Rh immunisation in the next pregnancy to below the level of 0.4%.

The paediatrician

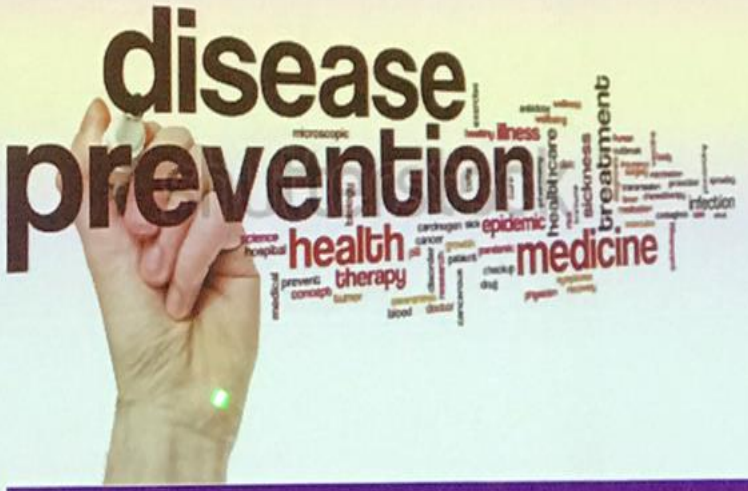
The Rh burden



What is our role



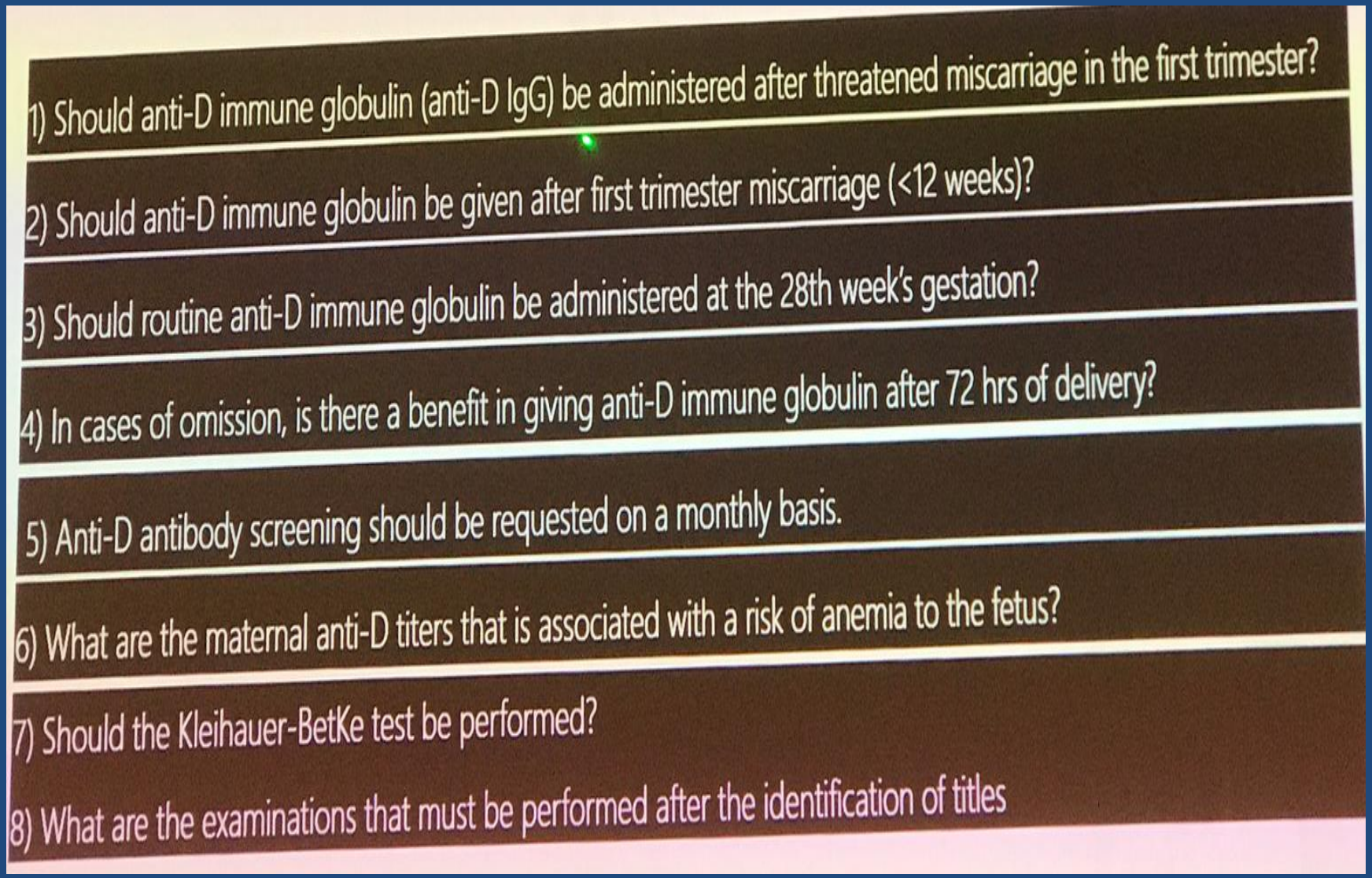
Albert Einstein



Prevention is always better than cure!

Desiderius Erasmus

What to consider in use of Anti-D



Rh-immunoglobulin - sources

Rh-immunoglobulin is γ-globulin preparation made from plasma containing high concentration of anti-D antibodies

Polyclonal antibodies:
potential risk of blood-borne infections – rare, but …

Women with Rh-conflict in the past (*this source is disappearing due to prevention programs*)

Rh-negative male volunteers (after immunization of D-positive erythrocytes) – *not permitted in some European countries*

Monoclonal antibodies studies 2000-2008: promising, but not finished results

*The Moscow study
**The Bristol study
*** The Bern study

Monoclonal antibodies studies 2010+

Rozrolimubab
(*25 different monoclonal antibodies*)****
Roledumab*****

No laboratory has yet produced a proven effective monoclonal anti-D antibody

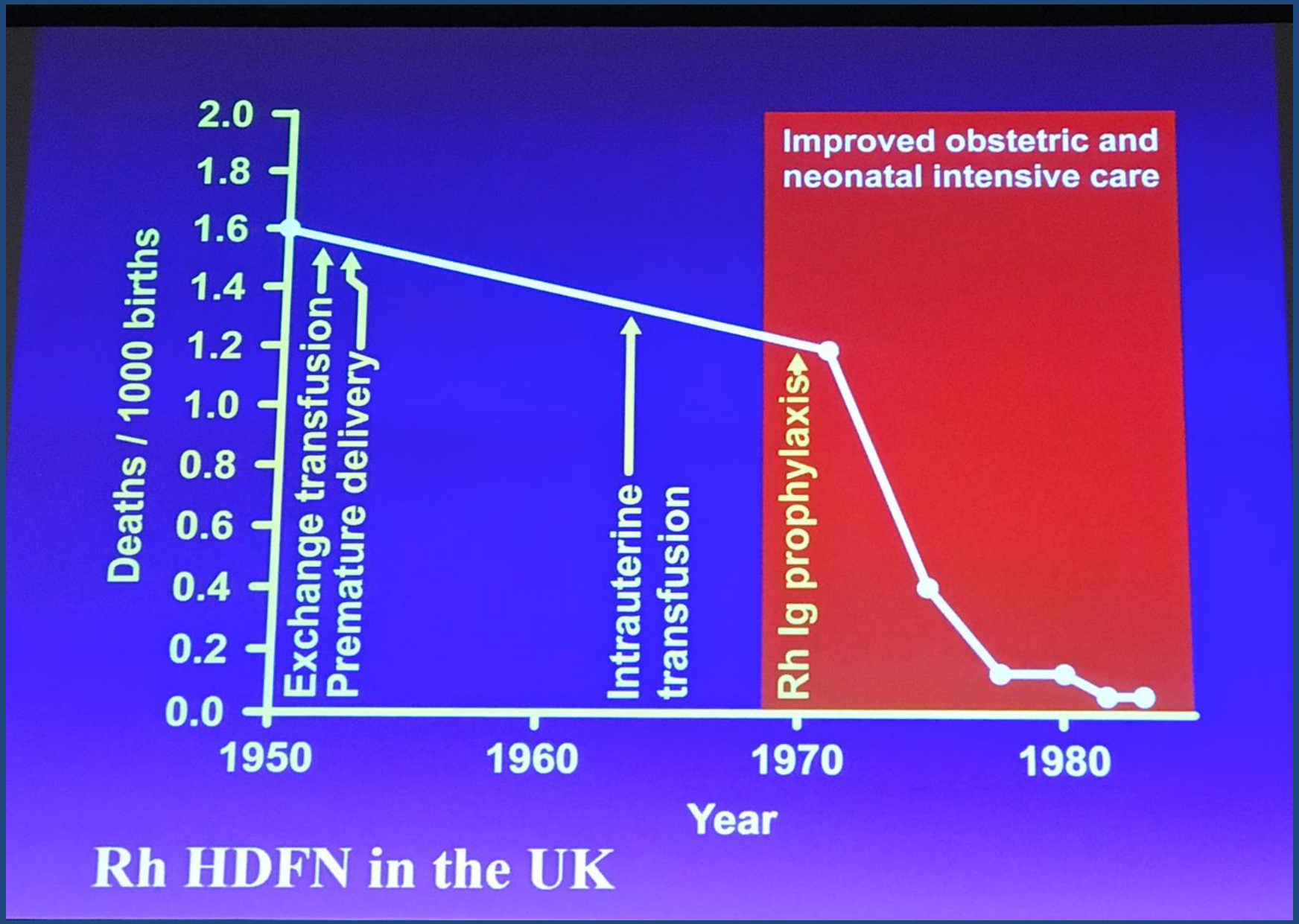
*Olovnikova NI, et al. J Exp Biol Med 2000; 129:77-81; **Kumpel BM, et al. Clin Exp Immunol 2008;154:1-5; ***Miescher S, et al. Blood 4004;103:4028-35. ****Stasi R. Curr Opin Mol Ther 2010;12:734-40; *****Yver A, et al. Vox Sanguinus 2012;103:213-22.

Causes of **non immune hydrops fetalis:**

- Cardiac – 17-35%
- Chromosomal – 7-16%
- Hematologic – 4-12%
- Infections – 5-7%
- Thorax abnormalities – 6%
- Abdominal abnormalities – 0.5-5%
- Lymphatic duct abnormalities – 5-6%
- Tumors – 2-3%
- Idiopathic – 15-25%

The **mortality rate** in non-immune hydrops fetalis – **80-90%**

Bellini C., et al. Am J Med Genet A 2009; 149: 5: 844—851



Rh HDFN in the UK

Anti-D

- Give within 72 hours ideally
- Usually 300ug, but in delivery upto 500ug recommended
- Give in large foetal maternal bleed. Do klei Huer test
- Need in abortions, ectopic gestation is debatable.
- When in doubt give it.
- Regime, give at 28 weeks and at delivery if not sensitized

Why is Rh HDFN still a burden?

- Some countries started using anti-D Ig too late (eg Russia)
- Many countries do not have guidelines or do not supply anti-D Ig for all women who need it (several countries in Latin America, Asia and Africa).
- Most countries do not use antenatal prophylaxis
- In countries where there are guidelines for Rh prophylaxis, anti-D might be given too late or too little or might not be given at all, by mistake.

Mechanism of action of Anti-D

Exact mechanism of suppression of RhD immunisation by anti-D Ig UNKNOWN.

Postulates:1. anti-D clears fetal D+ cells from maternal circulation, through interaction with FcγIIIA receptors on mononuclear phagocytic cells in the spleen. 2. anti-D coating the D+ cells, adheres simultaneously to the BCR and to the FcγIIA receptor on B cells, suppressing the IR. 3. Anti-D complexed with D antigen inhibits dendritic cell maturation, leading to tolerance. 4. Anti-D would target an inhibitory receptor on APCs, inhibiting T-cell dependent B cell responses.

All these mechanisms influenced by the glycosylation pattern of the Fc fragment of IgG anti-D

- 1941 Philip Levine

Discovery of the Rh(D) antigen

- 1960 Stern.K

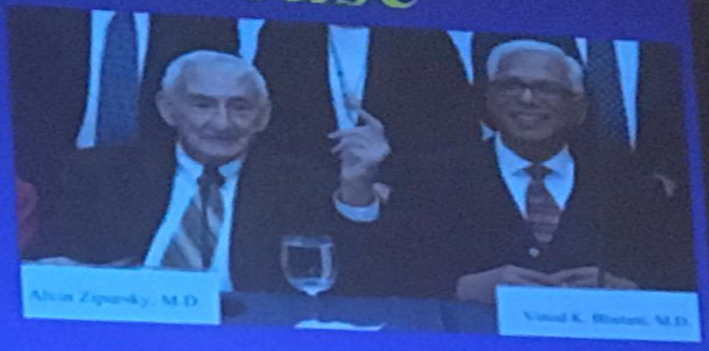
Introduction of anti-D immunoprophylaxis

- 1960

Disease could be accurately diagnosed and treated as it is today.

The eradication of Rh Disease

But NOT everywhere:



Current burden of the disease:

- 50.000 stilbirths
- 114.000 neonatal deaths
- 40.000 kernicterus and cerebral palsy
- 60.000 kernicterus and hearing loss

CUR(h)E; Bhutani, Zipursky et al, Ped Res, 2013

But NOT everywhere:

Current burden of the disease:

- 5(
- 1
- 4(
- 6(

In 50 y, only a 50% reduction in mortality/morbidity

CUR(h)E; Bhutani, Zipursky et al, Ped Res, 2013

Why??

- Forgotten to give
- Forgotten to give after abortion etc
- No access to anti-D globulin (China)
- Too expensive (in some African countries price 8 times higher than in Europe)
- Some anti- D products may be rather ineffective

And do not forget:

Preventive medicine is much more efficient than spending money on expensive modern technology

Continued Occurrence of Disease - LMIC Countries

Care in perspective of HDFN

- Huge populations
- Poverty
- Lack of antenatal care
- Lack of skilled care at birth
- High prevalence of anemia
- Greater incidence of blood transfusions
- Lack of effective protocols and implementation
- Lack of emphasis on quality of care and patient safety

Continued Occurrence of Disease

- Lack of testing
- Possible errors in the typing of the pregnant woman or neonate
- Possible errors in the transfusion treatment of females of childbearing potential (transfusion of red blood cell concentrates with mismatched RhD antigen).
- Lack of administration of immune prophylaxis

Continued Occurrence of Disease

- Occult foetal-maternal haemorrhage, usually after the 28th week of gestation, which affects about 1% of Rh negative mothers
- Unquantified bleeding during pregnancy and at the time of delivery
- Ineffective IP because the amount administered was not sufficient for the volume of the FMH

Recommendations - Immunoprophylaxis following potentially immunising events during pregnancy.

In circumstances that can promote the passage of foetal red blood cells into the maternal circulation, it is **suggested** that prophylaxis with anti-D Ig is offered to all non-immunised RhD negative women.

- Invasive antenatal diagnosis
- Dilation and curettage
- Abdominal trauma
- External cephalic version

- Antepartum hemorrhage
- Intrauterine fetal death;
- Therapeutic termination of pregnancy
- Spontaneous abortion
- Ectopic pregnancy

Kernicterus per 100.000 live births

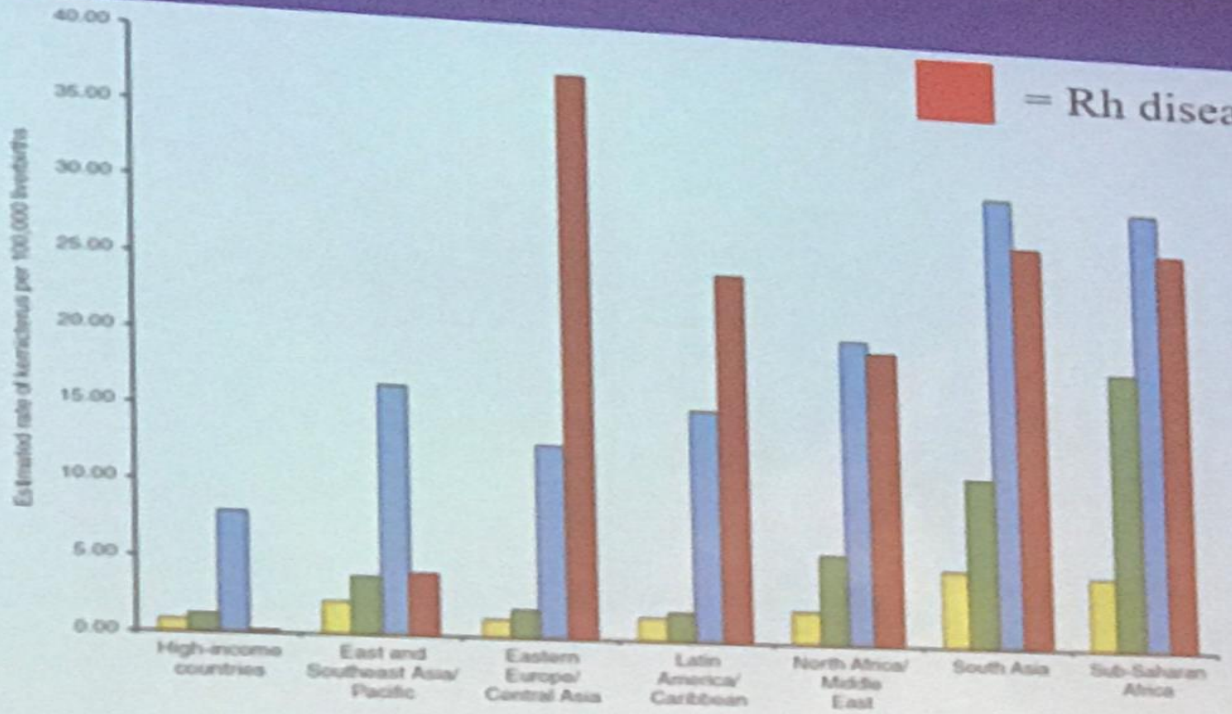


Figure 4. Estimated rates of kernicterus (per 100,000 live births). Data are presented and attributed to cause of hyperbilirubinemia due to prematurity by yellow bars; G6PD deficiency by green; hemolytic and idiopathic conditions by blue; and Rhesus (Rh) disease by red. These are shown for regional geographic distribution worldwide using global burden of diseases (GBD) categorization (54,55).

Bhutani, Zipursky et al, Ped Res 2013

management

- The following information is important
  - Past obstetric history
  - Gestational age
  - Maternal antibody levels
  - Analysis of amniotic fluid by spectrophotometry
  - Paternal blood group and antigen status
  - Any other pregnancy complications

Phototherapy

Fluorescent blue light in the
420-475 nm range

Foetal transfusion

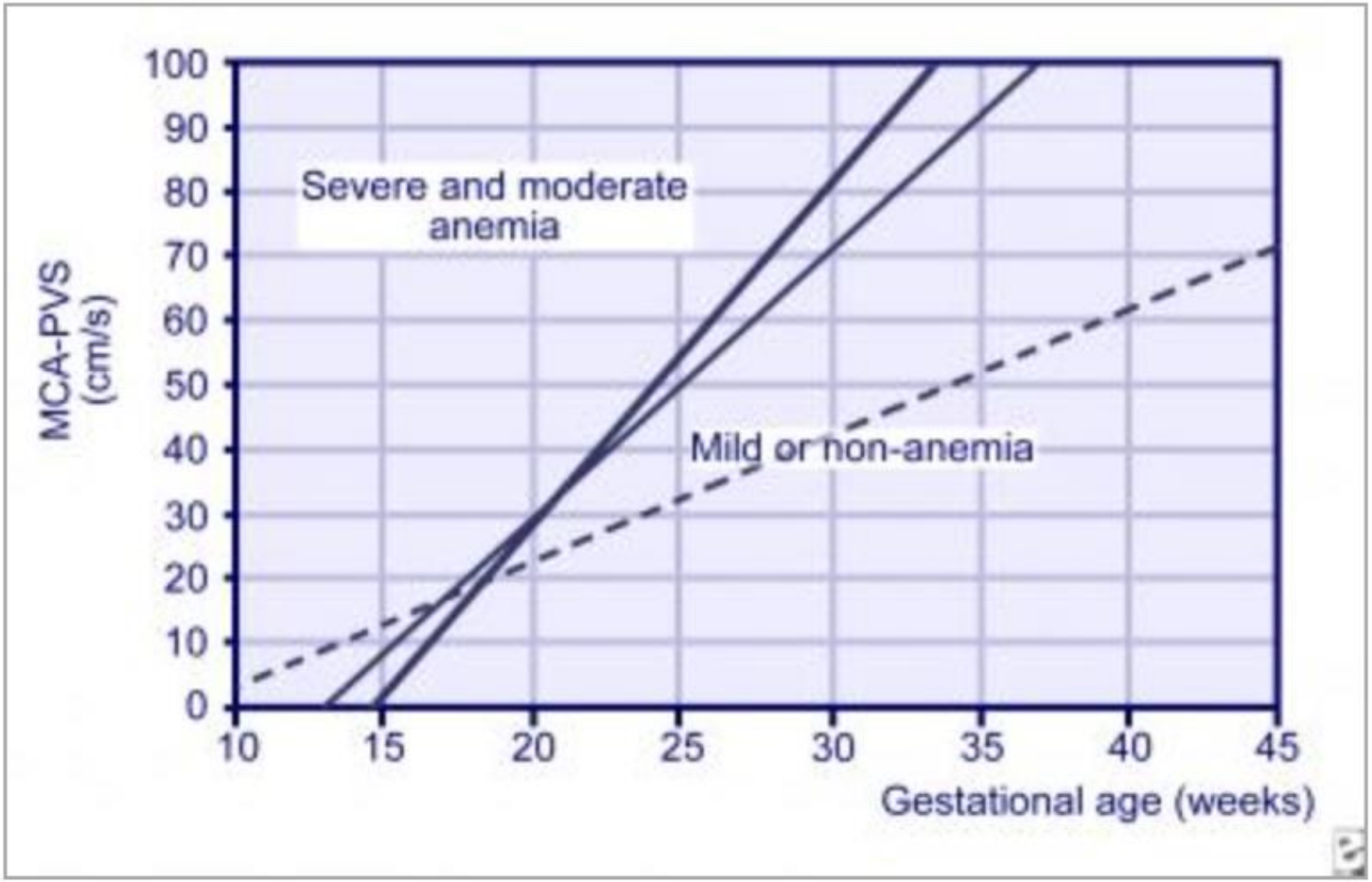
- Intraperitoneal transfusion improves the foetal survival.-1988
- Intravascular transfusion is better-1981

Laboratory findings

Laboratory Findings vary with severity of HDN and include:

Anemia	**Hyperbilirubinemia**†
Reticulocytosis (6 to 40%)	↑ **nucleated RBC count** (>10/100 WBCs)
Thrombocytopenia	**Leucopenia**
+ Direct Antiglobulin Test‡	**Hypoalbuminemia**
Rh negative blood type‡	**Smear:** polychromasia, anisocytosis, no spherocytes

MCA in predicting Anaemia



Slopes for peak systolic velocity in middle cerebral artery (MCA) for normal fetuses (dotted line), mildly anemic fetuses (thin line), and severely anemia fetuses (thick line).

ICT

- Critical titre is 1:16
- Previous done using amniotic fluid
- Now done by sonographically directed foetal blood sampling

Other managements

- Use of steroids?
- Plasmapheresis?
- Promethazine in large doses?
- D- erythrocyte membrane in enteric coated capsules?

Lileys curve

- Foetuses affected by haemolytic disease secrete abnormally high levels of bilirubin into the amniotic fluid.

- The amount of bilirubin can be quantitated by spectrophotometrically measuring absorbance at the 450-nm wavelength in a specimen of amniotic fluid that has been shielded from light

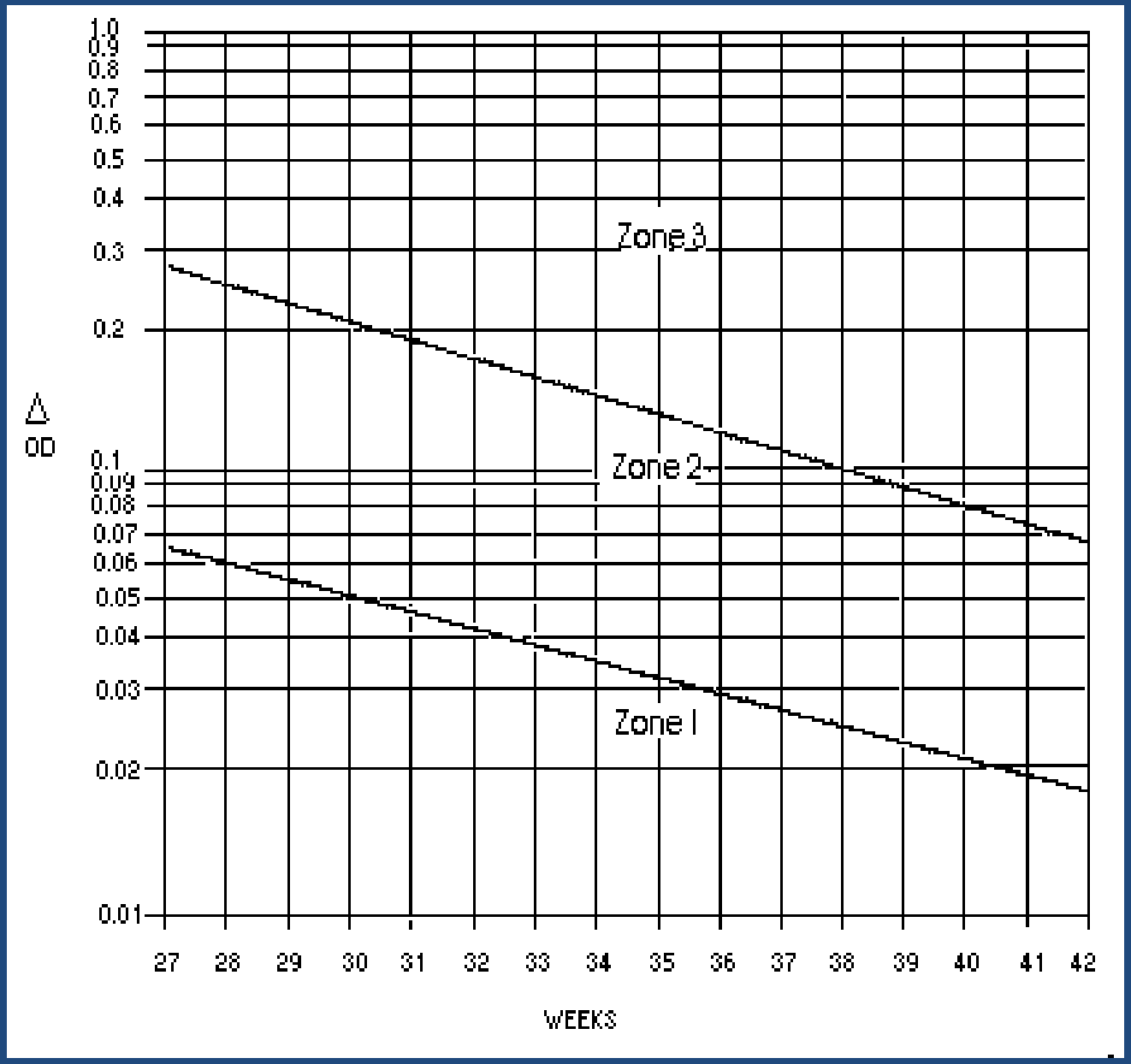
Liley curve

- If amniocentesis is used to monitor the foetus, the results (delta 450) are plotted on a "Liley" curve.

Liley curve

The Liley curve is divided into three zones.

- A result in Zone I indicates mild or no disease. Fetuses in zone I are usually followed with amniocentesis every 3 weeks.
- A result in zone II indicates intermediate disease. Fetuses in low Zone II are usually followed by amniocentesis every 1-2 weeks.
- A result above the middle of Zone II may require transfusion or delivery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0.3
0.2
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
Δ
OD
Zone 3
Zone 2
Zone I
27
28
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30
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40
41
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WEEKS

Calculating KB test

Step 1) stain and count the amount of fetal cells out of 1000 total cells counted

Step 2) calculate the amount of fetal blood in cirulation by multiplying %fetal cells by 50 mL

Step 3) divide mL of fetal blood by 30 (each vial protects against a 30 mL bleed

Step 4) Round the calculated dose up **and** add one more vial for safety

$$\frac{\#\,\text{fetal cells}}{\text{total cells (2000)}}\,x100 = \%\ \text{of fetal cells}$$

$$\text{Required dose of RhIg} = \frac{\%\ \text{fetal cells x 50}}{30}$$

Preventive Measures in the Antenatal Period – Role of Immune prophylaxis

- To predict which pregnancy is at risk
- Immune prophylaxis
  - Antenatal 28 weeks or 28 and 32 weeks
  - Bleeding in pregnancy
  - For Procedures
- An important factor is duration of pregnancy and amount of bleeding
  - Before twelve weeks of pregnancy
  - Quantify bleeding if massive bleeding – Kleihauer- Betke test

Preventive Measures in the Antenatal Period – Immune prophylaxis

Antenatal 28 weeks or 28 and 32 weeks

- Risk of significant FMH before 28 weeks is low
- Antenatal prophylaxis is advised from 28 weeks of gestation onwards
- IP is effective for about 12 weeks.
- All non-immunised RhD negative women are offered systematic antenatal IP with a dose of anti-D Ig of 1,500 IU (300 µg)

Preventive Measures at The Time of Delivery

- 1500 IU or 300 µg within 72 hours following delivery to all non-immunised Rh negative women who have delivered a Rh positive neonate or stillborn baby
- This covers 30 ml of fetal blood leak into maternal circulation.
- If IP is not performed within 72 hours then up to 10 days after the event
- IP can still be attempted even with a delay of as much as 28 days after the sensitising event.

prevention

- All pregnant women to have blood group done and if Rh negative do ICT
- Early prediction of haemolysis
- Need for active management, preterm delivery, in utero transfusion.
- Use of Anti-D

recap

- **List the classifications of Hemolytic Disease of the Newborn and the most antibody specificities involved.**
- **State the testing to perform on the mother to monitor the severity of HDN.**
- **List the laboratory tests and values which indicate that an infant is affected by HDN both in the fetus and newborn.**
- **State the treatment options for intrauterine treatment of HDN.**
- **State the treatment options for HDN in the moderately and severely affected newborn.**
- **State the requirements of blood to be used for transfusion of the fetus and newborn.**


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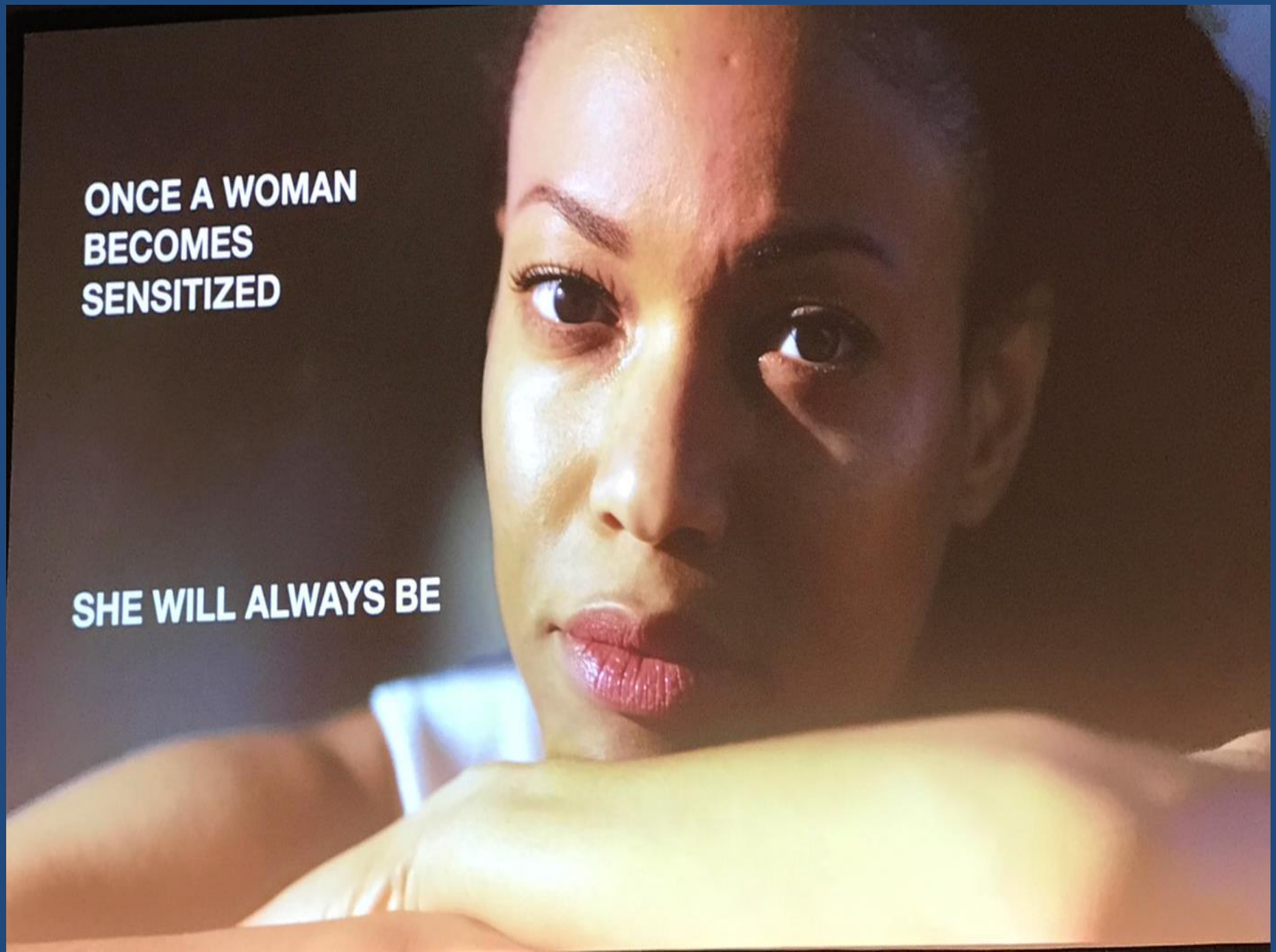
ONCE A WOMAN
BECOMES
SENSITIZED
SHE WILL ALWAYS BE