<u>Diagnosis and management of</u> FETAL ANEMIA

(Essay)

Submitted for Partial Fulfilment of Master Degree in Obstetrics and Gynecology

 $\mathbf{B}\mathbf{y}$

Zeinab Mehrize AL dosuky Hegazy

M. B., BCh, 1988

Faculty of Medicin- Alazhar university Medical sector of people assembly

Supervised By

Prof. Dr. Ali Elyan Khalfallah

Professor of Obstetrics and Gynecology Faculty of Medicine Ain Shams University

Prof. Dr. Hassan Tawfik Khairy

Professor of Obstetrics and Gynecology Faculty of Medicine Ain Shams University

Dr.Ahmed Mohamed Ibrahim

Lecturer in Obstetrics and Gynecology Faculty of Medicine Ain Shams University (2005) To the memory of my father and my sister

Acknowledgment

First and foremost, thanks to God, the most beneficial and most merciful.

It is my pleasure to express my sincerest acknowledgment to **DR. ALY ELYAN KHALAF ALLAH**, professor of obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University, for his generous support and valuable supervision which enriched the work by his great knowledge and experience.

I wish to express my deepest appreciation and gratefulness to **DR. HASSAN TAWFIK KHAIRY** Gynecology, Faculty of Medicine, Ain-Shams University, for his almost help, kind indispensable support, cooperation and continuous encouragement in performing this work.

I Also, owe a particular dept of gratitude to **DR. AHMED MOHAMED IBRAHIM**, lecturer in Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University, for his constructive guidance and general help in accomplishing this work.

Last but not least, I gratefully acknowledge the sincere help and support of my husband Refaat and my kids Ramy & Radwa for them patiency all that time

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكُ لاعِلْمَ كَنَا إلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيمر سورة البقرة الآية 32

DIAGNOSIS AND MANAGEMENT OF INTRAUTERINE FETAL ANEMIA

Essay

Submitted for Partial Fulfilment of Master Degree in Obstetrics and Gynecology

By
Zeinab Mehrize AL dosuky Hegazy
M. B., Bch, 1988

Supervised By

Prof. Dr. Ali Elyan Khalfallah

Professor of Obstetrics and Gynecology Faculty of Medicine Ain Shams University

Prof. Dr. Hassan Tawfik Khairy

Professor of Obstetrics and Gynecology Faculty of Medicine Ain Shams University

Dr.Ahmed Mohamed Ibrahim

Lecturer of Obstetrics and Gynecology Faculty of Medicine Ain Shams University

(2004)

INTRODUCTION

Fetal anemia is defind as hematocrit or hemoglobin conecentration >2SD below the mean for gestational age.(Harrington and Fayyad 2002)

With the dawn of the new millennium, medical science has made little impact on the major complication of pregnancy. The one notable exception is rhesus alloimmunization and its associated fetal / neonatal consequence. (Lokeshwar et al 2003)

Antenatal serology screening and the widespread use of anti-D immunoglobulin has dramatically reduced the incidence of immune anemia . (Kumpel 2002)

Consequently, less common causes, such as parovirus infection, are now becoming relatively more common causes of this serious condition.

Despite these developments, fetal anemia is an important cause of perinatal morbidity and mortality. The following facts remain an true: fetal anemia can be caused by immune, non-immune and idiopathic causes and up to 50% of patients referred with red blood cell antibodies have those directed against an antigen other than D. (Lehmann et al 2003)

Etiological factoer of fetal anemia can be caused by immune, non immune, and idiopathic causes. Among the immune causes, anti-D Rhesus antibodies are the most common. The administration of the anti-D Ig to all pregnant women at risk has dramatically decreased the incidence of Rh

-hemolytic disease. However, the use of anti-D has not eliminated the problem of alloimmunization, since more than 50 Red blood cell irregular antigens will continue to be a problem. Currently, there are no routine method to measure the levels of non-D antibodies, and even the titres of these antibodies are not reliable predictor of the severity. In addition, immunoprophylaxis is not available to prevent these causes . (Moise 2002)

Non-immune causes of fetal anemia include hemolytic causes (alpha-thalassemia,red blood cells enzymes membrane defects, microangiopathic and others), aplastic (parvovirus B-19 infection, other congenital causes infections, Diamond -Blackfan anemia, Fanconi s anemia and hemorrhagic others) and causes (FMH.FP twin-twin chorioangioma, transfusion, vasa previa and internal hemorrage). Again, no routine accurate screening test exists, and the diagnosis is often late when hydrops has occurred. Accordingly in spite of the modern advancement in maternofetal medicine, fetal anemia remains an important cause of perinatal mortality and morbidity. (Leung et al 2002)

Diagnostic approaches: Initially, the diagnosis in case of Rh isoimmunization begins with past obstetric history and maternal antibody titre measurement. If the titre is negative, it should be repeated monthly up till the time of delivery, and the woman given anti-D Ig. On the other hand, once the critical level of antibody titre is exceeded, the patient should be regarded at risk and other forms of fetal evaluation are needed. The diagnosis of other causes of fetal anemia depends on the

underlying etiology e. g. fetal and maternal DNA samples are used to diagnosis alpha-thalassemia, and parvovirus infection is diagnosed by detection of its DNA in maternal orfetal tissues using the PCR technique .(Opkes 2000)

Noninvasive tests (ultrasound assessment and fetal Doppler measurement of fetal circulation) to predict fetal anemia are of value not only in avoiding unnecessary invasive procedures but also in deciding on the appropriate timing of itervention (Roberts et al 2002)

Doppler blood velocity studies (especially fetal middle cerebral artery –of peak systolic velocity) appear to be the most valuable single noninvasive test .When sonographers are appropriately trained .(Zimmerman et al 2002)

Therapeutic Modalities: intrauterine transfusion is the most effective treatment in the management of most causes of fetl anemia. In cases of previous perinatal loss in the early second trimester Intravenous Immunoglobulin alone or in combination with plasmapheresis may enable the fetus to reach a gestation at which intravenous transfusion becomes feasible

Possible future advances in therapy include selective immunotherapy to block or suppress maternal anti-red cell antibodies.

(Marie et al 2004)

Aim of work : spots lights on these types of fetal anemia and trials of the intervention or prevention .

References

- (1) Harrington K and Fayyad A. Prediction of fetal anemia. Curr Opin in Obestet Gynecol. 2002;14:177- 185.
- (2) Kumpel B. Principles of antibody-mediated immune suppression and the prevention of maternal RhD alloimmunization. In Alloimune disorders of pregnancy, Cambridge University Prees. 2002; Chapter 5:73-96.
- (3) Lokeshwar Mr, Singhal T, and Shah N.Anemia in the newborn.India J Pediatr.20032;70 (11):893-90
- (4) Leung WC, Oepkes D, Seaward G et al serial sonographic finding of four fetuses with homozygous alpha-thalassemia-1 from 21 weeks onwards. Ultrasound Obstet Gynecol. 2002;19:56-59.
- (5) Lehmann HW,Von Landenberg P ,Modrow S .Parvovirus B19 infection and autoimmune Rev. 2003;2:218-223.
- (6) Marie HP, Olivier P, Yves B etal.Intra venous exchange transfusion before 22 weeks of gestation in early and severe red cell fetomaternal alloimmunization.Obstet Gynecol. 2004;59(5):327-8.
- (7) MoiseJr Management of rhesus rhesus alloimmunization in regnancy. Obstet Gynecol.2002;100:600-11.
- (8) Opkes D. Invasive versus non-invasive testing in red-cell alluimmunized pregnancy. Eur J Obstet Gynecol Reprod Biol.2000; 92:83-93.

- (9) Roberts AB , Mitchll JM , Lake Ypattison NS. Ultrasonographic surveillance in red blood cell alloimmunization. AMJ Obstet Gynecol .2002; 184:1251-1255.
- (10) Zimmerman R , Durig P , Carpenter RJ , etal. longitudinal mea surement of peak systolic velocity in the fetal middle cerebral artery for monitoring pregnancies complication by red blood cell alloimmunization:a prospective multicentre trial with intention-to treat. Br J Obstet Gynecol.2002;109:746-752.

Index Review of literature

Introduction	1
Aim of work	4
Chpater 1 - Embryological background	5
Developmental hematopoiesis occurs in three	5
anatomic stages:	
Erythropoiesis	6
Hemoglobin (Hb)	6
Changes in Hb and erythroid cells during	7
pregnancy:	
Fetal anemia (fa)	9
Classifications of fetal anemia	10
Chapter 2 - alloimmune fetal anemia	13
Blood group terminology	13
The genetics of blood groups	14
Identification of paternal zygosity	15
Identification of fetal blood type	15
Effects of Antigen Expression on Pathogenicity	17
and Severity of HDFN	1.0
Antibodies cousing HDFN	18
Antibodies that most commonly cause 1 - moderate or severe HDFN	18
	22
2 - Antibodies that most commonly cause mild HDFN	22
(abo system)	22
Antibodies that rarely cause HDFN 3- Antibodies that do not cause HDFN 4-	22
Third outes that do not eause Tibit	22
PATHOPHYSIOLOGY OF ALLOIMMUNE	23
FETAL ANEMIA	22
Maternal exposure to the Antigens	23
Maternal immune Response:	24
Fetal Effects	25

N 4 LECC 4	26
Neonatal Effects	26
Prevention of RhD Immunization	27
(Immunoprophylaxis)	20
Possible mechanisms of action	28
Doses and indications of immunoprophylaxis	29
I) Antenatal prophylaxis administration	29
II) Postpartum immunoprophylaxis administration	33
Risks of anti-D Ig immunoprophylaxis	36
Non-invasive diagnosis of Alloimmune Fetal Anemia	37
Past obstetric history	37
Maternal Antibody levels	38
Methods used in measuring maternal antibody levels	39
Other red cell antibodies	40
Ultrasound Findings	40
Fetal Hydrops	40
Fetal liver and spleen size	42
Fetal cardiac morphology	42
Fetal Heart rate Monitoring	43
Fetal Doppler Ultrasonography	43
Middle Cerebral Artery (MCA)	44
MCA-PSV as a predictor of FA and monitoring	46
patients at risk	
Effect of correction of fa on MCA-PSV	47
Use of MCA-PSV for timing the second transfusion	48
Fetal Aorta	48
Splenic Artery	49
Invasive Siagnosis of Fetal Anemia	49
Background	49
Amniocentesis	49
Fetal blood sampling	53
Technique blood sampling	54
Fetal blood indices	54
A- fetal hemoglobin and hematocrit	54
B- fetal blood reticulocyte, erthropoietin &	55
erythoblast count	
Fetal Bilirubin levels	55

Complications of the Invasive diagnosis of FA	55
Management of Allo Immune Fetal Anemia	56
i- Non-Invasive Treatment of Alloimmune Fetal	56
Anemia	
1 - plasmapheresis	56
2 - Intravenous immunoglobulin (ivig)	57
3 - Oral tolerance	58
4 - Chemotherapeutic agents	59
5 - Sensitization to paternal leukocyte antigens	59
ii- Intrauterine transfusion	60
Routes of intrauterine transfusion	60
Hematological criteria for intrauterine transfusion	61
Blood used during intrauterine transfusion	62
Amount of red cells transfusion	62
Time to repeat the transfusion	63
Timing of delivery	63
Complications of IVT	64
iii- Short-Term Outcome and Neonatal Management	64
III- Short-Term Outcome and Neonatal Management	04
iv- Long-Term Outcome	65
_	
iv- Long-Term Outcome	65
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia	65 66
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia	65 66 66
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background	65 66 66 66
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia	65 66 66 66
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy	65 66 66 66 67
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias	65 66 66 66 67 69
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology	65 66 66 66 67 69 70
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology Diagnosis	65 66 66 66 67 69 70 71
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology Diagnosis Treatment and Prognosis	65 66 66 66 67 69 70 71 71
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology Diagnosis Treatment and Prognosis Fetal Methemoglobinemia (HbM)	65 66 66 66 67 69 70 71 71 72
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology Diagnosis Treatment and Prognosis Fetal Methemoglobinemia (HbM) 2 - Red-Cell Enzyme Defects (Enzymopathies)	65 66 66 66 67 69 70 71 71 72 72
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology Diagnosis Treatment and Prognosis Fetal Methemoglobinemia (HbM) 2 - Red-Cell Enzyme Defects (Enzymopathies) (a) glucose-6-phosphate dehydrogenase	65 66 66 66 67 69 70 71 71 72 72
iv- Long-Term Outcome Chapter 3 - Nonimmune Hemolytic Fetal Anemia i- Nonimmune hemolytic fetal anemia Background Classification non-imune fetal anemia 1 - Hemoglobinopathy Alpha Thalassemias Genetics and pathophysiology Diagnosis Treatment and Prognosis Fetal Methemoglobinemia (HbM) 2 - Red-Cell Enzyme Defects (Enzymopathies) (a) glucose-6-phosphate dehydrogenase deficiency (G-6PD)	65 66 66 66 67 69 70 71 71 72 72 72

4 - Microangiopathic Hemolytic Anemia	75
(a) Kasabach-Merritt Syndrome (KMS)	75
(B) Umbilical Vein Varix	75
(C) placental chorioangioma	75
(5) Iatrogenic Hemolytic Anemia	76
(6) Congenital Malaria	76
ii- Aplastic Fetal Anemia	77
1 - Parvovirus B19 Infection in Pregnancy	77
Clinical manifestations	77
Fetal infection	78
Diagnosis of parovirus B19	79
Management of parvovirus-B-19	80
2 - other congenital infections	80
3 - Congenital Hypoplastic Anemia [Diamond-	81
Blackfan Anemia (DBA)	
4 - Fanconi's Anemia	82
5 - Other Causes Of Aplastic Fetal Anemia	82
iii- Hemorrhagic anemia of the fetus	83
(1) Fetomaternal Hemorrhage (FMH)	83
(2) Feto Placental Hemorrhage (FPH)	85
(3) Twin-Twin Transfusion	85
(4) Placental Chorioangioma	86
(5) Vasa Previa	88
(6) other causes of fetal hemorrhagic anemia	89
Chapter 4 - Neonatal anemia	90
Causes of neonatal anemia	90
Clinical Findings	93
Diagnostic evaluation of neonatal anemia	95
Management	96
Chapter 5 - Recomandation of Diagnosis and	98
Management of fetal Anemia	
i- for Rh Isoimmunization	98
For Non-D Isoimmunization (Other Causes)	99
Summary	100
References	103

Liste of table

Table (1) Reference ranges for feta hemoglobin concentrations as function of gestational age:	
Table (2)Average hematological values in the fetus (Quoted from Lokeshwar e al, 2003)	
Table (3) Some Red Cell Antigens and Their Propensity to Cause Hemolytic Disease in the Fetus-Infant Whose Mother is immunized	c
Table (4) Events following which anti-D Is must be given to all Rh D-negative women with no RhD antibody and/o with antibodies other than anti-D	e
Table(5)Prophylactic anti-D Following abortions to all RhD negative women with no RhD antibody and/or with antibodies other than anti-D	n