

0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

Contents

	List of contributors	page xv
	Preface	xvii
	Foreword	xix
	List of abbreviations	xxi
1	Pathophysiology of the alloimmune cytopenias	1
	Andrew G Hadley and Craig Turner	
	1.1 Maternal alloimmunization	1
	1.1.1 Some key events in the humoral immune response	1
	1.1.2 The maternal alloimmune response to fetal red cells	4
	1.1.3 The maternal alloimmune response to fetal platelets	5
	1.1.4 The maternal alloimmune response to fetal neutrophils	6
	1.2 Transfer of IgG to the fetus	6
	1.3 The immune destruction of blood cells in the fetus	7
	1.3.1 IgG and Fc γ receptors	8
	1.3.2 The immune destruction of fetal red cells	8
	1.3.3 The immune destruction of fetal platelets	12
	1.3.4 The immune destruction of fetal neutrophils	14
	1.4 Conclusions	14
	1.5 References	14
2	Blood group antibodies in haemolytic disease of the	
	fetus and newborn	21
	Geoff Daniels	
	2.1 Introduction	21
	2.2 Blood group terminology	21
	2.3 The genetics of blood groups	24
	2.4 The effect of antigen expression on the pathogenicity and severity of HDFN	25
	2.5 Antibodies that most commonly cause moderate or severe HDFN	27

V



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

vi	Contents	
	2.5.1 Anti-D	27
	2.5.2 Other antibodies to Rh-system antigens	30
	2.5.3 Anti-K	3
	2.5.4 Other antibodies to Kell-system antigens	32
	2.6 Antibodies that most commonly cause mild HDFN	33
	2.6.1 The ABO system	33
	2.7 Antibodies that rarely cause HDFN	34
	2.7.1 MNS system	34
	2.7.2 Duffy system	3.5
	2.7.3 Kidd system	35
	2.7.4 Diego system	3.5
	2.7.5 Colton system	30
	2.7.6 Other antigens	30
	2.8 Antibodies that do not cause HDFN	30
	2.9 Conclusions	37
	2.10 References	37
	Geoff Poole	
	3.1 Introduction	4
	3.2 The basis of screening for HDFN	4
	3.3 Antenatal screening tests performed in the blood transfusion laboratory	42
	3.3.1 Antiglobulin methods	42
	3.3.2 Enzyme methods	40
	3.3.3 The choice of red cells for screening tests	47
	3.3.4 Manual versus automated methods	48
	3.3.5 Timing of screening tests	49
	3.4 The identification of red cell alloantibodies	50
	3.4.1 Methods	50
	3.4.2 The principles of antibody identification	5
	3.4.3 Difficulties encountered in antibody identification	54
	3.4.4 Implications of detecting a red cell alloantibody during pregnancy	55
	3.5 Paternal and fetal phenotyping	50
	3.5.1 Paternal phenotype	50
	3.5.2 Fetal phenotype	57
	3.6 Laboratory tests immediately following delivery	58

3.7 References



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

vii Contents

4	Epidemiology and screening for alloimmune thrombocytopenia Lorna M Williamson and Michael F Murphy	61
		61
	4.1 Background4.2 Epidemiology and the natural history of alloimmune thrombocytopenia	62
	4.2.1 The incidence of maternal alloimmunization	62
	4.2.2 The incidence of maternal anomination 4.2.2 The incidence of fetal thrombocytopenia due to maternal	02
	alloimmunization	62
	4.2.3 The incidence of intracranial haemorrhage and other sequelae	63
	4.2.4 The influence of obstetric history on clinical outcome	63
	4.3 Criteria for antenatal screening for alloimmune thrombocytopenia	64
	4.3.1 The condition should be an important health problem	64
	4.3.2 The epidemiology of the condition should be known	65
	4.3.3 The natural history of the condition should be understood	65
	4.3.4 There should be a recognized latent period or early asymptomatic stage	65
	4.3.5 All the cost-effective primary prevention interventions should have been	03
	implemented as far as practicable	66
	4.3.6 There should be a simple, safe, precise and validated screening test	66
	4.3.7 The distribution of test values in the target population should be known	00
	and a suitable cut-off level defined and agreed	66
	4.3.8 The test should be acceptable to the population	67
	4.3.9 There should be an agreed policy on the further diagnostic investigation	07
	of individuals with a positive result and on the choices available to those	
	individuals	67
	4.3.10 There should be an effective treatment or intervention for patients	0,
	identified through early detection	67
	4.3.11 There should be agreed evidence-based policies covering which	0,
	individuals should be offered treatment and the appropriate treatment	
	to be offered	69
	4.3.12 Clinical management of the condition and patient outcomes should be	0,
	optimized by all health providers prior to participation in a screening	
	programme	69
	4.4 The cost-effectiveness of a screening programme	69
	4.5 Conclusions	70
	4.6 References	70
		, 0
5	Principles of antibody-mediated immune suppression and the	
	prevention of maternal RhD alloimmunization	73
	Belinda Kumpel	
	5.1 Haemolytic disease of the fetus and newborn due to anti-D	73
	5.2 Experimental studies on the prevention of RhD immunization	74



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

viii Contents

	5.3 Clinical studies on the efficacy of RhD prophylaxis	75
	5.3.1 Dose of anti-D	76
	5.3.2 The current situation	77
	5.4 Characteristics and requirements of RhD prophylaxis	78
	5.4.1 Ratio of antibody to antigen required for suppression	78
	5.4.2 Relationship of red cell clearance to antibody-mediated immune	
	suppression	78
	5.4.3 Protection afforded by ABO antibodies	79
	5.4.4 Role of the spleen in RhD prophylaxis	79
	5.4.5 Timing of passive anti-D	79
	5.4.6 Time of detection of anti-D response	79
	5.4.7 Effect of passive anti-D on subsequent immunization	80
	5.4.8 Effect of passive anti-D on an established primary response	80
	5.4.9 Role of anti-D Fc fragments	80
	5.4.10 Epitope specificity	80
	5.5 Theories of the mechanism of action of prophylactic anti-D	81
	5.5.1 Inhibition of B cells by crosslinking heterologous receptors	81
	5.5.2 Anti-idiotypic antibodies	83
	5.5.3 Masking of antigen sites	84
	5.5.4 Clearance and destruction of D-positive red cells	84
	5.6 Development of monoclonal anti-D for RhD prophylaxis	84
	5.6.1 Production of monoclonal anti-D	85
	5.6.2 Half-lives of monoclonal anti-D	85
	5.6.3 In vitro functional activity of monoclonal anti-D	86
	5.6.4 In vivo red cell clearance mediated by monoclonal anti-D	86
	5.6.5 Suppression of the anti-D response by monoclonal anti-D	88
	5.7 References	88
6	The clinical application of anti-D prophylaxis	97
	Stan Urbaniak	
	6.1 Epidemiology	97
	6.1.1 Causes and incidence of alloimmunization	97
	6.1.2 Ethnic groups	97
	6.1.3 Use of D-negative transfusions for young women	97
	6.1.4 Relative importance of anti-D before and after the introduction of	
	anti-D prophylaxis programmes	98
	6.2 Prophylaxis programmes	98
	6.2.1 Suppression of the immune response	98
	6.2.2 Recommendations and guidelines	99
	6.2.3 Effectiveness in Caucasian populations	101



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

ix Contents

	6.2.4 Reasons for continued failures	101
	6.2.5 Anti-D immunization during pregnancy	102
	6.2.6 Antenatal administration of anti-D immunoglobulin	102
	6.2.7 Anti-D immunoglobulin use on women with weak D or partial D	104
	6.2.8 Anti-D immunoglobulin use after the accidental transfusion of	
	D-positive red cells	104
(6.3 Detection of fetal red cells in the maternal circulation	105
	6.3.1 The Kleihauer–Betke acid-elution test	106
	6.3.2 Flow cytometry	106
	6.3.3 Serological tests of fetomaternal haemorrhage	107
	6.3.4 Calculating the size of fetomaternal haemorrhage	107
(6.4 Fetomaternal haemorrhage and dose of anti-D immunoglobulin	108
	6.4.1 Fetomaternal haemorrhage at delivery	108
	6.4.2 Bleeding during pregnancy	108
	6.4.3 Spontaneous fetomaternal haemorrhage during first, second and third	
	trimesters	109
	6.4.4 Other significant events during pregnancy	110
	6.4.5 Fetomaternal haemorrhage due to medical procedures	110
	6.4.6 Calculation of the required dose of anti-D	111
(6.5 Procurement of hyperimmune anti-D	112
	6.5.1 Identification, recruitment, boosting and accreditation of donors	112
	6.5.2 Manufacture of anti-D immunoglobulin and safety considerations	113
(6.6 Economics of prophylaxis programmes	114
	6.6.1 Cost-effectiveness of antenatal versus postnatal prophylaxis	114
	6.7 Future developments	115
(5.8 References	116
_	atal assatississ	101
	etal genotyping	121
IN	eil D Avent	
	7.1 Introduction	121
7	7.2 The polymerase chain reaction	121
	7.2.1 Principle of the polymerase chain reaction	121
	7.2.2 Polymerase chain reaction – restriction fragment length polymorphism	
	analysis	122
_	7.2.3 Allele-specific primer amplification	122
7	7.3 PCR-based typing for clinically significant blood groups	124
	7.3.1 The Rh system	125
	7.3.2 Kell system	130
	7.3.3 Duffy system	131
	7.3.4 Kidd system	132
	7.3.5 ABO system	132



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

X	Contents	
	7.4 Noninvasive testing	133
	7.4.1 Detection of fetal RHD targets in genomic DNA extracted from fetal	
	leukocytes in maternal blood	133
	7.4.2 The detection of fetal RhD cDNA derived from RNA extracted from	
	maternal blood	133
	7.4.3 Detection of fetal RHD targets in genomic DNA extracted from	
	maternal plasma	134
	7.5 Future perspectives	134
	7.6 References	135
8	Laboratory assays to determine the severity of haemolytic	
	disease of the fetus and newborn	141
	Andrew G Hadley	
	8.1 Introduction	141
	8.2 Serological assays	141
	8.3 Quantitative assays	144
	8.4 Cellular assays	144
	8.4.1 The K lymphocyte-mediated ADCC assay	145
	8.4.2 The monocyte-mediated ADCC assay	146
	8.4.3 The monocyte monolayer assay	146
	8.4.4 The chemiluminescence test	147
	8.5 A strategy for antenatal testing	148
	8.6 References	149
9	Assessing the severity of haemolytic disease of the fetus and	
	newborn: clinical aspects	153
	Sherif Abdel-Fattah and Peter Soothill	
	9.1 Introduction	153
	9.2 Noninvasive assessment	153
	9.2.1 Previous obstetric history	153
	9.2.2 Antibody levels	154
	9.2.3 Ultrasound findings	156
	9.2.4 Fetal heart rate monitoring	158
	9.2.5 Fetal Doppler ultrasonography	159
	9.3 Invasive testing	163
	9.3.1 Amniocentesis	163
	9.3.2 Fetal blood sampling	165
	9.4 Conclusions	167
	9.5 References	167



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

xi Contents

10	Antenatal therapy for haemolytic disease of the fetus and newborn	173
	Kenneth J Moise Jr and Paul W Whitecar	
	10.1 Introduction	173
	10.2 Plasmapheresis and intravenous immune globulin	173
	10.2.1 Plasmapheresis	173
	10.2.2 Intravenous immunoglobulin	175
	10.3 Intrauterine transfusion	178
	10.3.1 History	178
	10.3.2 Access site	179
	10.3.3 Method of transfusion	180
	10.3.4 Amount to transfuse	181
	10.3.5 The severely anaemic fetus	183
	10.3.6 Adjunctive measures	183
	10.3.7 Outcome	184
	10.4 Red cells for transfusion	188
	10.5 Experimental therapy	190
	10.5.1 Immunoabsorption	190
	10.5.2 Oral tolerance	191
	10.5.3 Chemotherapeutic agents	191
	10.5.4 Sensitization to paternal leukocyte antigens	192
	10.6 Timing of delivery	193
	10.7 Conclusion	193
	10.8 References	193
11	Neonatal therapy for haemolytic disease of the newborn Glynn Russell and Nic Goulden	203
	11.1 Features of haemolytic disease in the neonate	203
	11.1.1 Hydrops	203
	11.1.2 Neonatal jaundice	204
	11.1.3 Persistent anaemia	204
	11.2 Laboratory diagnosis	204
	11.3 General neonatal management	205
	11.3.1 Communication	205
	11.3.2 Resuscitation	205
	11.4 Treatment of hydrops	206
	11.5 Treatment of anaemia	206
	11.5.1 Blood transfusion	206
	11.5.2 Influence of fetal transfusions	209



0521018048 - Alloimmune Disorders of Pregnancy Anaemia, Thrombocytopenia and Neutropenia in the Fetus and Newborn

Edited by Andrew G Hadley and Peter Soothill

Table of Contents

More information

xii	Contents	
	11.5.3 Indications for transfusion	209
	11.6 Treatment of neonatal jaundice	210
	11.6.1 Phototherapy	210
	11.6.2 Exchange blood transfusion	210
	11.6.3 An integrated approach to treating neonatal jaundice	212
	11.7 Experimental treatments	214
	11.8 References	214
12	The diagnosis of alloimmune thrombocytopenia Andrew G Hadley	219
	12.1 Clinical aspects of diagnosis	219
	12.2 Platelet antigen systems	220
	12.2.1 Platelet antigens on glycoprotein IIb/IIIa	220
	12.2.2 Platelet antigens on glycoprotein Ia/IIa	221
	12.2.3 Platelet antigens on glycoprotein Ib/IX/V	221
	12.3 Platelet antibody specificities involved in alloimmune thrombocytopenia	221
	12.4 Laboratory diagnosis of alloimmune thrombocytopenia	224
	12.4.1 Haematology	224
	12.4.2 Assays for the detection of antiplatelet antibodies	225
	12.4.3 DNA-based genotyping	227
	12.4.4 Antibody characteristics and disease severity	228
	12.5 Future perspectives	228
	12.6 References	229
13	The immunological diagnosis of alloimmune neutropenia Geoff Lucas	235
	13.1 Introduction	235
	13.2 Pathophysiology and clinical history	235
	13.2.1 Immunogenicity of fetal neutrophils	235
	13.2.2 Clinical manifestations and haematological findings	235
	13.2.3 Differential diagnosis	236
	13.3 The structure and function of antigens involved in alloimmune neutropenia	238
	13.3.1 Nomenclature	238
	13.3.2 Granulocyte-specific antigens	239
	13.3.3 'Shared' antigens	243
	13.3.4 Antibody specificities involved in alloimmune neutropenia	244
	13.3.5 The function of granulocyte antigens	244
	13.4 Laboratory diagnosis of alloimmune neutropenia	245

13.4.1 Assays for granulocyte antibodies



 ${\tt 0521018048-Alloimmune\ Disorders\ of\ Pregnancy\ Anaemia,\ Thrombocytopenia\ and\ Neutropenia\ in\ the\ Fetus\ and\ Newborn}$

Edited by Andrew G Hadley and Peter Soothill

Contents

Table of Contents

More information

xiii

	13.4.2 Role of crossmatching and parental typing	247
	13.4.3 Granulocyte antigen typing	247
	13.5 References	248
14	Fetal and neonatal treatment of alloimmune thrombocytopenia Michael F Murphy, Rachel Rayment, David Allen and David Roberts	253
	14.1 Introduction	253
	14.2 Neonatal management of alloimmune thrombocytopenia	254
	14.2.1 Platelet transfusion	254
	14.2.2 Intravenous immunoglobulin	256
	14.2.3 Monitoring of the effectiveness of neonatal treatment	257
	14.3 Antenatal management of alloimmune thrombocytopenia	257
	14.3.1 Fetal blood sampling	258
	14.3.2 Maternal treatment	259
	14.3.3 Fetal platelet transfusion	263
	14.3.4 Serial fetal platelet transfusions compared with maternal	
	administration of high-dose intravenous immunoglobulin	267
	14.3.5 Timing of the initial fetal blood sample	268
	14.3.6 Strategy for the antenatal management of pregnancies at risk of very	

14.4 Preparation of platelet concentrates for transfusion in cases of alloimmune

14.4.1 Provision of HPA-typed platelets for neonates with alloimmune

14.4.2 Identification and recruitment of HPA-1a-negative and

14.4.3 Preparation of platelet concentrates for fetal transfusions

early intracranial haemorrhage

thrombocytopenia

14.5 Future directions

14.6 References

Index

thrombocytopenia

HPA-5b-negative donors

269

270

270

270

271

272

274