Alloimmune disorders of pregnancy

Anaemia, thrombocytopenia and neutropenia in the fetus and newborn

Collectively known as the alloimmune cytopenias, haemolytic disease of the fetus and newborn, alloimmune thrombocytopenia and alloimmune neutropenia are all consequences of maternal immunization to fetal blood cells. The effective prevention, diagnosis and management of these disorders has become a team effort involving haematologists, obstetricians, paediatricians, immunologists, laboratory technicians, midwives and research scientists. This book has been written by experts in their respective fields to bring together the issues of pathogenesis, epidemiology, prevention, diagnosis and clinical management. This comprehensive but accessible account is extensively cross-referenced to emphasize the links between pathogenesis and clinical sequelae, between epidemiology and the rationale for screening programmes, and between diagnosis and therapeutic intervention.

This is an authoritative overview suitable for trainees in obstetrics, maternal and fetal medicine, transfusion medicine and clinical immunology.

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Alloimmune disorders of pregnancy

Anaemia, thrombocytopenia and neutropenia in the fetus and newborn

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Contents

List of contributors 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 Fcγ 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
3 Basis and practice of screening for haemolytic disease of the fetus and newborn

Geoff Poole

3.1 Introduction

3.2 The basis of screening for HDFN

3.3 Antenatal screening tests performed in the blood transfusion laboratory

3.3.1 Antiglobulin methods

3.3.2 Enzyme methods

3.3.3 The choice of red cells for screening tests

3.3.4 Manual versus automated methods

3.3.5 Timing of screening tests

3.4 The identification of red cell alloantibodies

3.4.1 Methods

3.4.2 The principles of antibody identification

3.4.3 Difficulties encountered in antibody identification

3.4.4 Implications of detecting a red cell alloantibody during pregnancy

3.5 Paternal and fetal phenotyping

3.5.1 Paternal phenotype

3.5.2 Fetal phenotype

3.6 Laboratory tests immediately following delivery

3.7 References
### 4 Epidemiology and screening for alloimmune thrombocytopenia

**Lorna M Williamson and Michael F Murphy**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Background</td>
<td>61</td>
</tr>
<tr>
<td>4.2 Epidemiology and the natural history of alloimmune thrombocytopenia</td>
<td>62</td>
</tr>
<tr>
<td>4.2.1 The incidence of maternal alloimmunization</td>
<td>62</td>
</tr>
<tr>
<td>4.2.2 The incidence of fetal thrombocytopenia due to maternal</td>
<td>62</td>
</tr>
<tr>
<td>alloimmunization</td>
<td></td>
</tr>
<tr>
<td>4.2.3 The incidence of intracranial haemorrhage and other sequelae</td>
<td>63</td>
</tr>
<tr>
<td>4.2.4 The influence of obstetric history on clinical outcome</td>
<td>63</td>
</tr>
<tr>
<td>4.3 Criteria for antenatal screening for alloimmune thrombocytopenia</td>
<td>64</td>
</tr>
<tr>
<td>4.3.1 The condition should be an important health problem</td>
<td>64</td>
</tr>
<tr>
<td>4.3.2 The epidemiology of the condition should be known</td>
<td>65</td>
</tr>
<tr>
<td>4.3.3 The natural history of the condition should be understood</td>
<td>65</td>
</tr>
<tr>
<td>4.3.4 There should be a recognized latent period or early asymptomatic stage</td>
<td>65</td>
</tr>
<tr>
<td>4.3.5 All the cost-effective primary prevention interventions should have been implemented as far as practicable</td>
<td>66</td>
</tr>
<tr>
<td>4.3.6 There should be a simple, safe, precise and validated screening test</td>
<td>66</td>
</tr>
<tr>
<td>4.3.7 The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed</td>
<td>66</td>
</tr>
<tr>
<td>4.3.8 The test should be acceptable to the population</td>
<td>67</td>
</tr>
<tr>
<td>4.3.9 There should be an agreed policy on the further diagnostic investigation of individuals with a positive result and on the choices available to those individuals</td>
<td>67</td>
</tr>
<tr>
<td>4.3.10 There should be an effective treatment or intervention for patients identified through early detection</td>
<td>67</td>
</tr>
<tr>
<td>4.3.11 There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered</td>
<td>69</td>
</tr>
<tr>
<td>4.3.12 Clinical management of the condition and patient outcomes should be optimized by all health providers prior to participation in a screening programme</td>
<td>69</td>
</tr>
<tr>
<td>4.4 The cost-effectiveness of a screening programme</td>
<td>69</td>
</tr>
<tr>
<td>4.5 Conclusions</td>
<td>70</td>
</tr>
<tr>
<td>4.6 References</td>
<td>70</td>
</tr>
</tbody>
</table>

### 5 Principles of antibody-mediated immune suppression and the prevention of maternal RhD alloimmunization

**Belinda Kumpel**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Haemolytic disease of the fetus and newborn due to anti-D</td>
<td>73</td>
</tr>
<tr>
<td>5.2 Experimental studies on the prevention of RhD immunization</td>
<td>74</td>
</tr>
</tbody>
</table>
### 5.3 Clinical studies on the efficacy of RhD prophylaxis

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3.1 Dose of anti-D</td>
<td>76</td>
</tr>
<tr>
<td>5.3.2 The current situation</td>
<td>77</td>
</tr>
</tbody>
</table>

### 5.4 Characteristics and requirements of RhD prophylaxis

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4.1 Ratio of antibody to antigen required for suppression</td>
<td>78</td>
</tr>
<tr>
<td>5.4.2 Relationship of red cell clearance to antibody-mediated immune suppression</td>
<td>78</td>
</tr>
<tr>
<td>5.4.3 Protection afforded by ABO antibodies</td>
<td>79</td>
</tr>
<tr>
<td>5.4.4 Role of the spleen in RhD prophylaxis</td>
<td>79</td>
</tr>
<tr>
<td>5.4.5 Timing of passive anti-D</td>
<td>79</td>
</tr>
<tr>
<td>5.4.6 Time of detection of anti-D response</td>
<td>79</td>
</tr>
<tr>
<td>5.4.7 Effect of passive anti-D on subsequent immunization</td>
<td>80</td>
</tr>
<tr>
<td>5.4.8 Effect of passive anti-D on an established primary response</td>
<td>80</td>
</tr>
<tr>
<td>5.4.9 Role of anti-D Fc fragments</td>
<td>80</td>
</tr>
<tr>
<td>5.4.10 Epitope specificity</td>
<td>80</td>
</tr>
</tbody>
</table>

### 5.5 Theories of the mechanism of action of prophylactic anti-D

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5.1 Inhibition of B cells by crosslinking heterologous receptors</td>
<td>81</td>
</tr>
<tr>
<td>5.5.2 Anti-idiotypic antibodies</td>
<td>83</td>
</tr>
<tr>
<td>5.5.3 Masking of antigen sites</td>
<td>84</td>
</tr>
<tr>
<td>5.5.4 Clearance and destruction of D-positive red cells</td>
<td>84</td>
</tr>
</tbody>
</table>

### 5.6 Development of monoclonal anti-D for RhD prophylaxis

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6.1 Production of monoclonal anti-D</td>
<td>85</td>
</tr>
<tr>
<td>5.6.2 Half-lives of monoclonal anti-D</td>
<td>85</td>
</tr>
<tr>
<td>5.6.3 In vitro functional activity of monoclonal anti-D</td>
<td>86</td>
</tr>
<tr>
<td>5.6.4 In vivo red cell clearance mediated by monoclonal anti-D</td>
<td>86</td>
</tr>
<tr>
<td>5.6.5 Suppression of the anti-D response by monoclonal anti-D</td>
<td>88</td>
</tr>
</tbody>
</table>

### 5.7 References

<table>
<thead>
<tr>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
</tr>
</tbody>
</table>
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
6.8 References 116

7 Fetal genotyping 121

Neil D Avent

7.1 Introduction 121
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
7.3 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
8 Laboratory assays to determine the severity of haemolytic disease of the fetus and newborn

Andrew G Hadley

8.1 Introduction
8.2 Serological assays
8.3 Quantitative assays
8.4 Cellular assays
  8.4.1 The K lymphocyte-mediated ADCC assay
  8.4.2 The monocyte-mediated ADCC assay
  8.4.3 The monocyte monolayer assay
  8.4.4 The chemiluminescence test
8.5 A strategy for antenatal testing
8.6 References

9 Assessing the severity of haemolytic disease of the fetus and newborn: clinical aspects

Sherif Abdel-Fattah and Peter Soothill

9.1 Introduction
9.2 Noninvasive assessment
  9.2.1 Previous obstetric history
  9.2.2 Antibody levels
  9.2.3 Ultrasound findings
  9.2.4 Fetal heart rate monitoring
  9.2.5 Fetal Doppler ultrasonography
9.3 Invasive testing
  9.3.1 Amniocentesis
  9.3.2 Fetal blood sampling
9.4 Conclusions
9.5 References
## Contents

### 10 Antenatal therapy for haemolytic disease of the fetus and newborn

Kenneth J Moise Jr and Paul W Whitecar

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.1 Introduction</td>
<td>173</td>
</tr>
<tr>
<td>10.2 Plasmapheresis and intravenous immune globulin</td>
<td>173</td>
</tr>
<tr>
<td>10.2.1 Plasmapheresis</td>
<td>173</td>
</tr>
<tr>
<td>10.2.2 Intravenous immunoglobulin</td>
<td>175</td>
</tr>
<tr>
<td>10.3 Intrauterine transfusion</td>
<td>178</td>
</tr>
<tr>
<td>10.3.1 History</td>
<td>178</td>
</tr>
<tr>
<td>10.3.2 Access site</td>
<td>179</td>
</tr>
<tr>
<td>10.3.3 Method of transfusion</td>
<td>180</td>
</tr>
<tr>
<td>10.3.4 Amount to transfuse</td>
<td>181</td>
</tr>
<tr>
<td>10.3.5 The severely anaemic fetus</td>
<td>183</td>
</tr>
<tr>
<td>10.3.6 Adjunctive measures</td>
<td>183</td>
</tr>
<tr>
<td>10.3.7 Outcome</td>
<td>184</td>
</tr>
<tr>
<td>10.4 Red cells for transfusion</td>
<td>188</td>
</tr>
<tr>
<td>10.5 Experimental therapy</td>
<td>190</td>
</tr>
<tr>
<td>10.5.1 Immunoabsorption</td>
<td>190</td>
</tr>
<tr>
<td>10.5.2 Oral tolerance</td>
<td>191</td>
</tr>
<tr>
<td>10.5.3 Chemotherapeutic agents</td>
<td>191</td>
</tr>
<tr>
<td>10.5.4 Sensitization to paternal leukocyte antigens</td>
<td>192</td>
</tr>
<tr>
<td>10.6 Timing of delivery</td>
<td>193</td>
</tr>
<tr>
<td>10.7 Conclusion</td>
<td>193</td>
</tr>
<tr>
<td>10.8 References</td>
<td>193</td>
</tr>
</tbody>
</table>

### 11 Neonatal therapy for haemolytic disease of the newborn

Glynn Russell and Nic Goulden

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1 Features of haemolytic disease in the neonate</td>
<td>203</td>
</tr>
<tr>
<td>11.1.1 Hydrops</td>
<td>203</td>
</tr>
<tr>
<td>11.1.2 Neonatal jaundice</td>
<td>204</td>
</tr>
<tr>
<td>11.1.3 Persistent anaemia</td>
<td>204</td>
</tr>
<tr>
<td>11.2 Laboratory diagnosis</td>
<td>204</td>
</tr>
<tr>
<td>11.3 General neonatal management</td>
<td>205</td>
</tr>
<tr>
<td>11.3.1 Communication</td>
<td>205</td>
</tr>
<tr>
<td>11.3.2 Resuscitation</td>
<td>205</td>
</tr>
<tr>
<td>11.4 Treatment of hydrops</td>
<td>206</td>
</tr>
<tr>
<td>11.5 Treatment of anaemia</td>
<td>206</td>
</tr>
<tr>
<td>11.5.1 Blood transfusion</td>
<td>206</td>
</tr>
<tr>
<td>11.5.2 Influence of fetal transfusions</td>
<td>209</td>
</tr>
</tbody>
</table>
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 219
Andrew G Hadley
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 235
Geoff Lucas
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 245
## Contents

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 253

Michael F Murphy, Rachel Rayment, David Allen and David Roberts

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 early intracranial haemorrhage 269

14.4 Preparation of platelet concentrates for transfusion in cases of alloimmune thrombocytopenia 270  
14.4.1 Provision of HPA-typed platelets for neonates with alloimmune thrombocytopenia 270  
14.4.2 Identification and recruitment of HPA-1a-negative and HPA-5b-negative donors 270  
14.4.3 Preparation of platelet concentrates for fetal transfusions 271

14.5 Future directions 272  
14.6 References 274

Index 279
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Preface

Definitions and terminology

The alloimmune cytopenias are a group of conditions in which the life span of fetal blood cells or their precursors is shortened by the action of antibodies derived from the mother by placental transfer. Three conditions are recognized: antibodies to fetal red cells, platelets or neutrophils, or their precursors, cause alloimmune anaemia, thrombocytopenia or neutropenia, respectively. Various terms are in common usage for these disorders, many of them inappropriate. For example, alloimmune anaemia is sometimes referred to as Rhesus disease, erythroblastosis fetalis or haemolytic disease of the newborn and all three are misnomers. It is incorrect to use ‘Rhesus’ to refer to the Rh system, fetal haemolysis may be caused by antibodies outside the Rh system, anaemia is not always associated with erythroblastosis and, finally, the disorder primarily affects the fetus rather than the newborn. Therefore, throughout this book, alloimmune anaemia (perhaps the best term) will be referred to as haemolytic disease of the fetus and newborn (HDFN). For similar reasons, alloimmune thrombocytopenia and alloimmune neutropenia will be used in preference to other terms, such as neonatal alloimmune thrombocytopenia, fetomaternal alloimmune thrombocytopenia and neonatal alloimmune neutropenia, while, at the same time, acknowledging that these terms are also commonly used.

The multidisciplinary approach to the management of the alloimmune cytopenias

The last 10 years of the 20th century saw significant advances in the management of alloimmunized pregnant women; immunologists made progress characterizing the molecular basis of the alloimmune response; molecular biologists solved the genetic basis for all the clinically important blood groups and developed DNA-based fetal typing assays; epidemiologists and health care economists developed a better understanding of the natural history of the alloimmune cytopenias and the
cost-effectiveness of preventative programmes; obstetricians and fetal medicine specialists progressed the use of noninvasive fetal monitoring techniques; and haematologists improved the safety and efficacy of the various fetal transfusion therapies. With significant advances being made on so many fronts, the optimal prevention, diagnosis and management of alloimmunized pregnant women has become a team effort involving haematologists, obstetricians, paediatricians, immunologists, laboratory technicians in hospitals and transfusion centres, midwives and research scientists. However, it is rare for the individuals who contribute to this team effort to have a comprehensive overview of all the laboratory and clinical aspects associated with the alloimmune cytopenias.

Our intention in producing this book has been to bring the issues of pathogenesis, epidemiology, prevention, diagnosis and management together in a way which is both comprehensive and relevant to the various professionals involved. To this end, we have tried to avoid subspecialty jargon and to limit the use of abbreviations as far as possible because those used daily by laboratory scientists may be less familiar to clinicians and vice versa.

Andrew G Hadley
Peter Soothill
This book is a very good idea. It brings together all the different aspects of the alloimmune cytopenias that are needed to understand them. The two most important are the red cell and the platelet cytopenias and they have features in common as well as characteristics that sharply differentiate them. For each condition, consideration is given to the genetics, the pathophysiology, the evidence for the efficacy and cost-effectiveness of screening and prevention, and to the management of the affected fetus and neonate. To have authoritative chapters on all these topics within the covers of one book is extremely helpful both for those who are new to these clinical problems and for those who, like the author of this foreword, have been grappling with them for over 20 years. The editors and their multidisciplinary team are to be congratulated and thanked for producing this valuable synthesis.

Professor Charles H Rodeck
Department of Obstetrics and Gynaecology
Royal Free and University College London Medical School
Abbreviations

ADCC  Antibody-dependent cell-mediated cytotoxicity
AMIS  Antibody-mediated immune suppression
ARMS  Amplification refractory mutation system
ASPA  Allele-specific primer amplification
C3    Third component of complement
CD    Cluster of differentiation
CLT   Chemiluminescence test
CMV   Cytomegalovirus
CTG   Cardiotocography
DAGT  Direct antiglobulin test
ELISA Enzyme-linked immunosorbent assay
FBS   Fetal blood sampling
FcγR  Fc gamma receptor (receptor for the Fc domain of IgG)
GAT   Granulocyte agglutination test
GIFT  Granulocyte immunofluorescence test
HbsAg Hepatitis B surface antigen
HCV   Hepatitis C virus
HIV   Human immunodeficiency virus
HPA   Human platelet antigen
HTLV  Human lymphotropic virus
IAGT  Indirect antiglobulin test
ICH   Intracranial haemorrhage
IL    Interleukin
Ig    Immunoglobulin
im    Intramuscularly
IU    International Units
IUT   Intrauterine transfusion
iv    Intravenously
IVIG  Intravenous immunoglobulin
Hb    Haemoglobin
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDFN</td>
<td>Haemolytic disease of the fetus and newborn</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen or histocompatibility locus antigen</td>
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<tr>
<td>HPA</td>
<td>Human platelet antigen</td>
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<tr>
<td>HNA</td>
<td>Human neutrophil antigen</td>
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<tr>
<td>kD</td>
<td>Kilodalton</td>
</tr>
<tr>
<td>LISS</td>
<td>Low ionic strength saline</td>
</tr>
<tr>
<td>MAIGA</td>
<td>Monoclonal antibody immobilization of granulocyte antigens assay</td>
</tr>
<tr>
<td>MAIPA</td>
<td>Monoclonal antibody immobilization of platelet antigens assay</td>
</tr>
<tr>
<td>MMA</td>
<td>Monocyte monolayer assay</td>
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<tr>
<td>$\Delta OD_{450}$</td>
<td>Optical density at a wavelength of 450 nm</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PEG</td>
<td>Polyethylene glycol</td>
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<tr>
<td>PIFT</td>
<td>Platelet immunofluorescence test</td>
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<tr>
<td>RFLP</td>
<td>Restriction fragment length polymorphism</td>
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<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
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<tr>
<td>TAV</td>
<td>Time-averaged mean velocity</td>
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<tr>
<td>TPH</td>
<td>Transplacental haemorrhage</td>
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