THE SURFACTANT SYSTEM OF THE LUNG

The Surfactant System of the Lung

Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome

Edited by

E. V. Cosmi

*Second Institute of Gynaecology and Obstetrics
University La Sapienza
Rome, Italy*

G. C. Di Renzo

*Institute of Gynaecology and Obstetrics
University of Perugia
Policlinico Monteluce
Perugia, Italy*

and

M. M. Anceschi

*Second Institute of Gynaecology and Obstetrics
University La Sapienza
Rome, Italy*

M

**MACMILLAN
PRESS
Scientific & Medical**

© Macmillan Academic and Professional Ltd 1991
Softcover reprint of the hardcover 1st edition 1991

All rights reserved. No reproduction, copy or transmission
of this publication may be made without written permission.

No paragraph of this publication may be reproduced, copied or
transmitted save with written permission or in accordance with
the provisions of the Copyright, Designs and Patents Act 1988,
or under the terms of any licence permitting limited copying
issued by the Copyright Licensing Agency, 33–4 Alfred Place,
London WC1E 7DP.

Any person who does any unauthorised act in relation to
this publication may be liable to criminal prosecution and
civil claims for damages.

First published 1991

Published by
MACMILLAN ACADEMIC AND PROFESSIONAL LTD
Houndmills, Basingstoke, Hampshire RG21 2XS
and London
Companies and representatives
throughout the world

Typeset by Wearside Tradespools,
Fulwell, Sunderland

British Library Cataloguing in Publication Data
The surfactant system of the lung: prevention and treatment of neonatal and adult
respiratory distress syndrome.
1. Man. respiratory system. Disorders. Role of surface-active agents
I. Cosmi, E. V.
616.20047
ISBN 978-1-349-12555-5 ISBN 978-1-349-12553-1 (eBook)
DOI 10.1007/978-1-349-12553-1

Contents

The Contributors

ix

Preface

xvii

1. Gene structure of the pulmonary surfactant proteins SP-A, SP-B and SP-C <i>J. A. Whitsett</i>	1
2. Pulmonary surfactant-associated proteins: their role in surface tension reduction <i>F. Possmayer, A. Cockshutt and S.-H. Yu</i>	7
3. Mesenchymal–epithelial interactions during late fetal lung development <i>I. Caniggia and M. Post</i>	18
4. Effects of corticosteroids on fetal lung maturation <i>M. M. Anceschi, P. Luzi, L. Broccucci, G. C. Di Renzo and E. V. Cosmi</i>	23
5. Biological approaches to the prevention of RDS <i>B. T. Smith</i>	28
6. Surfactant disorders in infants and vitamin D deficiency <i>E. M. Lukyanova</i>	34
7. Relevance of surfactant inactivation by anti-surfactant antibodies to the evaluation of therapies for neonatal RDS <i>D. S. Strayer</i>	39
8. Risk factors for RDS in preterm newborns <i>M. Luerti, G. Bevilacqua, A. Agarossi and M. Rocchetti</i>	49
9. Development, indication and present status of ‘late’ amniocentesis in pregnancy <i>W. Schmidt, R. Boos and J. Gnirs</i>	57
10. Determination of fetal lung maturity by the comparison of one-dimensional L/S ratio, enzymatic lecithin and S/A ratio <i>V. Ragosch, U. Lorenz, B. Arabin, S. Jürgens and H. Weitzel</i>	64
11. Antenatal glucocorticoid treatment in the prevention of neonatal RDS <i>V. Ragosch, U. Lorenz, B. Arabin, S. Jürgens and H. Weitzel</i>	69
12. Induction of fetal pulmonary maturity with Ambroxol: side effects and therapeutic effectiveness <i>A. Revelli, M. G. Oliveri, G. Molina, P. Parolini, M. Mascher and M. Massobrio</i>	74

13.	The combination of betamethasone and Ambroxol for the prophylaxis of neonatal RDS <i>F. Zullo, N. Colacurci, G. Rota, I. Strina, A. Scarcella, M. Stanzone and G. De Placido</i>	81
14.	Prevention of HMD and survival in low-birth-weight infants <i>A. Scarcella, M. Stanzone, F. Zullo, G. Rota and F. Ciccimarra</i>	86
15.	RDS and the use of corticosteroids <i>J. G. Koppe and H. Smolders-de Haas</i>	91
16.	Surfactant function: is it influenced by artificial ventilation? <i>J. Bos and B. Lachmann</i>	96
17.	Experiences with Curosurf in Europe <i>B. Robertson</i>	107
18.	Further experiences with Curosurf in Europe <i>H. L. Halliday and T. R. J. Tubman</i>	112
19.	Curosurf for therapy in neonatal RDS: an Italian randomized clinical trial <i>G. Bevilacqua</i>	122
20.	Early experiences with Curosurf therapy for severe neonatal RDS <i>G. Dévai and B. Büky</i>	128
21.	Preliminary results in the use of a natural surfactant (Curosurf) in four infants with severe RDS <i>B. Foresti and G. Marraro</i>	131
22.	Incidence and outcome of persistent ductus arteriosus in premature babies treated with surfactant for severe RDS <i>T. Troester, C. Roll, U. Neudorf, F. Hentrich and L. Hanssler</i>	139
23.	The effect of natural porcine surfactant (Curosurf) on the phagocytosis-associated functions of human neutrophils <i>C. P. Speer, B. Götz, B. Robertson and T. Curstedt</i>	142
24.	Surfactant replacement in severe RDS: effects of perinatal acidosis on therapeutic response <i>E. Herting, K. Harms, C. P. Speer, T. Curstedt and B. Robertson</i>	151
25.	Surfactant therapy and IgE levels in the neonatal period <i>M. Amato, P. Hüppi and D. Markus</i>	156
26.	Pulmonary function in mechanically ventilated surfactant-treated preterm infants <i>F. Mosca, C. Farina, M. R. Colnaghi and A. Marini</i>	159
27.	Development of antioxidant defences in preterm infants <i>R. Bracci, G. Buonocore, S. Berni, G. De Nisi and D. Gioia</i>	168
28.	A computerized method of pulmonary function evaluation in preterm infants <i>S. Parmigiani and G. Bevilacqua</i>	175

Contents

vii

29.	Pharmacotherapy in bronchopulmonary dysplasia <i>F. Rubaltelli and F. Benini</i>	177
30.	Pathophysiology of adults RDS <i>A. Grossi and P. P. Giomarelli</i>	183
31.	Pulmonary epithelial permeability in adult RDS <i>T. Todisco and M. Dottorini</i>	191
32.	Respiratory emergencies and supplementary surfactant in the treatment of severe RDS in leukaemic adolescents <i>G. Marraro</i>	198
33.	Adult RDS: its possible role in burn disease—a case report <i>A. F. Sabato, A. Borgognone, M. B. Silvi, G. Gherardini, M. Dauri and P. Palombo</i>	207
	<i>Index</i>	213

The Contributors

A. Agarossi

VII Department of Obstetrics and
Gynaecology
University of Milan
Milan
Italy

M. Amato

Division of Neonatology
Universitäts-Frauenklinik
3012 Berne
Switzerland

M. M. Anceschi

Second Institute of Gynaecology and
Obstetrics
University *La Sapienza*
Rome
Italy

B. Arabin

Klinikum Steglitz
Freien Universität Berlin
Hindenburgdamm 30
1000 Berlin 45
Germany

F. Benini

Department of Paediatrics
University of Padua
Via Giustiniani 3
35128 Padua
Italy

S. Berni

Division of Neonatology
University of Siena
Via P. Mascagni 46
53100 Siena
Italy

G. Bevilacqua

Institute of Child Health and Neonatal
Medicine
University of Parma
Via Gramsci 14
43100 Parma
Italy

R. Boos

Department of Obstetrics and
Gynaecology
University of Homburg/Saar
Oscar-Orth-Strasse
6650 Homburg/Saar
Germany

A. Borgognone

Dipartimento di Chirurgia, Anaesthesia
Generale e Speciale
Odontostomatologica
2a Università *Tor Vergata*
Via O. di Raimondo, 8
00173 Rome
Italy

J. Bos

Department of Anaesthesiology
Erasmus University
Postbox 1738
3000 DR Rotterdam
The Netherlands

R. Bracci

Division of Neonatology
University of Siena
Via P. Mascagni 46
53100 Siena
Italy

L. Broccucci

Institute of Gynaecology and
Obstetrics
University of Perugia
Policlinico Montelucente
06100 Perugia
Italy

B. Büky

2nd Department of Obstetrics and
Gynaecology
Semmelweis Medical University
Üllői ut 78/a
1082 Budapest
Hungary

G. Buonocore

Division of Neonatology
University of Siena
Via P. Mascagni 46
53100 Siena
Italy

I. Caniggia

Neonatal Research Division
Hospital for Sick Children
555 University Avenue
Toronto
Canada M5G 1X8

F. Ciccimarra

National Intensive Care Unit
Department of Paediatrics
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

A. Cockshutt

Department of Obstetrics and
Gynaecology
University Hospital
London
Ontario
Canada N6A 5A5

N. Colacurci

Institute of Obstetrics and
Gynaecology
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

M. R. Colnaghi

Department of Obstetrics and
Gynaecology
University of Milan
Milan
Italy

E. V. Cosmi

Second Institute of Gynaecology and
Obstetrics
University *La Sapienza*
Clinico Umberto I
00161 Rome
Italy

T. Curstedt

Department of Pathology
St Göran's Hospital
11281 Stockholm
Sweden

M. Dauri

Department of Plastic and
Reconstructive Surgery
St Eugenio Hospital
00144 Rome
Italy

G. De Nisi

Division of Neonatology
University of Siena
Via P. Mascagni 46
53100 Siena
Italy

G. De Placido

Institute of Obstetrics and
Gynaecology
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

G. Dévai

2nd Department of Obstetrics and
Gynaecology
Semmelweis Medical University
Üllői ut 78/a
1082 Budapest
Hungary

G. C. Di Renzo

Institute of Gynaecology and
Obstetrics
University of Perugia
Policlinico Montelucente
06100 Perugia
Italy

M. Dottorini

Institute of Medical Semeiotics
University of Perugia
Via Enrico dal Pozzo
06100 Perugia
Italy

C. Farina

Department of Obstetrics and
Gynaecology
Istituto Mangiagalli
University of Milan
Milan
Italy

B. Foresti

Anaesthesia and Intensive Care
Department
L. Mandic Hospital
Merate (CO)
Italy

G. Gherardini

Department of Surgery
II University of Rome
Tor Vergata
Rome
Italy

D. Gioia

Division of Neonatology
University of Siena
Via P. Mascagni 46
53100 Siena
Italy

P. P. Giomarelli

Department of Intensive Therapy
University of Siena
53100 Siena
Italy

J. Gnirs

Department of Obstetrics and
Gynaecology
University of Homburg/Saar
Oscar-Orth-Strasse
6650 Homburg/Saar
Germany

B. Götze

Department of Paediatrics
University of Göttingen
3400 Göttingen
Germany

A. Grossi

Department of Cardiac Surgery
Istituto Scientifico Ospedale
'S. Raafele'
Milan
Italy

H. L. Halliday

Department of Child Health
Queen's University of Belfast
Grosvenor Road
Belfast
UK

L. Hanssler

Klinik für Kinder- und Jugendmedizin
Universität (GHS) Essen
Essen
Germany

K. Harms

Department of Paediatrics
University of Göttingen
3400 Göttingen
Germany

F. Hentrich

Klinik für Kinder- und Jugendmedizin
Universität (GHS) Essen
Essen
Germany

E. Herting

Department of Paediatrics
University of Göttingen
3400 Göttingen
Germany

P. Hüppi

Division of Neonatology
Universitäts-Frauenklinik
3012 Berne
Switzerland

S. Jürgens

Klinikum Steglitz
Freien Universität Berlin
Hindenburgdamm 30
1000 Berlin 45
Germany

J. G. Koppe

Department of Neonatology
University of Amsterdam
Meibergdreef 9
1102 AZ Amsterdam
The Netherlands

B. Lachmann

Department of Anaesthesiology
Erasmus University
Postbox 1738
3000 DR Rotterdam
The Netherlands

U. Lorenz

Klinikum Steglitz
Freien Universität Berlin
Hindenburgdamm 30
1000 Berlin 45
Germany

M. Luerti

Department of Obstetrics and
Gynaecology
Luini Confalonieri Hospital
Luino (VA)
Italy

E. M. Lukyanova

Kiev Research Institute of Paediatrics
and Obstetrics & Gynaecology
Manil'skogo St. 8
Kiev 252050
USSR

P. Luzi

Second Institute of Gynaecology and
Obstetrics
University *La Sapienza*
Policlinico Umberto I
00161 Rome
Italy

A. Marini

Department of Obstetrics and
Gynaecology
University of Milan
Milan
Italy

D. Markus

Division of Neonatology
Universitäts-Frauenklinik
3012 Berne
Switzerland

G. Marraro

Anaesthesia and Intensive Care
Department
L. Mandic Hospital
Merate (CO)
Italy

M. Mascher

Department of Obstetrics and
Gynaecology
Mauriziano 'Umberto I' Hospital
Largo Turati 62
10128 Turin
Italy

M. Massobrio

Department of Obstetrics and
Gynaecology
Mauriziano 'Umberto I' Hospital
Largo Turati 62
10128 Turin
Italy

G. Molina

Department of Obstetrics and
Gynaecology
Mauriziano 'Umberto I' Hospital
Largo Turati 62
10128 Turin
Italy

F. Mosca

Department of Obstetrics and
Gynaecology
Istituto Mangiagalli
University of Milan
Milan
Italy

U. Neudorf

Klinik für Kinder- und Jugendmedizin
Universität (GHS) Essen
Essen
Germany

M. G. Oliveri

Department of Obstetrics and
Gynaecology
Mauriziano 'Umberto I' Hospital
Largo Turati 62
10128 Turin
Italy

P. Palombo

Department of Plastic and
Reconstructive Surgery
St Eugenio Hospital
00144 Rome
Italy

S. Parmigiani

Institute of Child Health and Neonatal
Medicine
University of Parma
Via Gramsci 14
43100 Parma
Italy

P. Parolini

Department of Obstetrics and
Gynaecology
Mauriziano 'Umberto I' Hospital
Largo Turati 62
10128 Turin
Italy

F. Possmayer

Department of Obstetrics and
Gynecology
University Hospital
London
Ontario
Canada N6A 5A5

M. Post

Neonatal Research Division
Hospital for Sick Children
555 University Avenue
Toronto
Canada M5G 1X8

V. Ragosch

Klinikum Steglitz
Freien Universität Berlin
Hindenburgdamm 30
1000 Berlin 45
Germany

A. Revelli

Department of Obstetrics and
Gynaecology
Mauriziano 'Umberto I' Hospital
Largo Turati 62
10128 Turin
Italy

B. Robertson

Research Unit for Experimental
Perinatal Pathology
St Göran's Hospital
11281 Stockholm
Sweden

M. Rocchetti

Division of Biomathematics and
Biostatistics
M. Negri Pharmacological Institute
Milan
Italy

C. Roll

Klinik für Kinder- und Jugendmedizin
Universität (GHS) Essen
Essen
Germany

G. Rota

Institute of Obstetrics and
Gynaecology
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

F. Rubaltelli

Department of Paediatrics
University of Padua
Via Giustiniani 3
35128 Padua
Italy

A. F. Sabato

Department of Surgery
II University of Rome
Tor Vergata
S. Eugenio Hospital
00144 Rome
Italy

A. Scarcella

Neonatal Intensive Care Unit
Department of Paediatrics
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

W. Schmidt

Department of Obstetrics and
Gynaecology
University of Homburg/Saar
Oscar-Orth-Strasse
6650 Homburg/Saar
Germany

M. B. Silvi

Department of Surgery
II University of Rome
Tor Vergata
S. Eugenio Hospital
00144 Rome
Italy

B. T. Smith

Hospital for Sick Children
555 University Avenue
Toronto
Ontario
Canada M5G 1X8

H. Smolders-de Haas

Department of Neonatology
University of Amsterdam
Meibergdreef 9
1102 AZ Amsterdam
The Netherlands

C. P. Speer

Department of Paediatrics
University of Göttingen
3400 Göttingen
Germany

M. Stanzione

Neonatal Intensive Care Unit
Department of Paediatrics
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

D. S. Strayer

Department of Pathology
University of Texas Health Science
Center
6431 Fannin Street
Houston
TX 77030
USA

I. Strina

Institute of Obstetrics and
Gynaecology
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

T. Todisco

Pulmonary Division
Ospedale Silvestrini
S. Andrea delle Fratte
06080 Perugia
Italy

T. Troester

Klinik für Kinder- und Jugendmedizin
Universität (GHS) Essen
Essen
Germany

T. R. J. Tubman

Department of Child Health
Queen's University of Belfast
Grosvenor Road
Belfast
UK

H. Weitzel

Klinikum Steglitz
Freien Universität Berlin
Hindenburgdamm 30
1000 Berlin 45
Germany

J. A. Whitsett

Pediatrics/Neonatology Division
University of Cincinnati College of
Medicine
231 Bethesda Avenue
Cincinnati
OH 45267-0541
USA

F. Zullo

Institute of Obstetrics and
Gynaecology
II School of Medicine
University of Naples
Via Pansini 5
Naples
Italy

S.-H. Yu

Department of Obstetrics and
Gynecology
University Hospital
London
Ontario
Canada N6A 5A5

Preface

This volume contains the proceedings of the international symposium entitled "The Surfactant System of the Lung: Prevention and Treatment of Neonatal and Adult Respiratory Distress Syndrome", which was held in Perugia, Italy on November 7-9, 1989. The symposium was in line with other conferences organized in previous years by the Departments of Obstetrics and Gynecology, and Neonatology, of Perugia and Rome, respectively, and under the auspices of the Italian Society of Perinatal Medicine.

Over the last decade there has been an impressive surge of scientific interest in the pathophysiology, diagnosis and treatment of the respiratory distress syndrome, not only of the neonate (RDS), but also of the adult (ARDS). This has resulted in an increased understanding of the function of the surfactant system of the lung, whose deficiency almost invariably causes the onset of RDS.

Over the same period, however, other aspects of the maturation events of the fetal lung (e.g. interaction between mesenchyme and epithelium, and the cell biology of alveolar pneumocytes) have gained increased attention and have been successfully related to the pathophysiology of the syndrome.

The advent of molecular biology, with its powerful tools, has revolutionized the study of the proteins which are strictly associated with lung surfactants. The gene structure and regulation of these molecules, whose functions are not yet completely understood although they are involved in some aspects of the biophysical activity of surfactants, have been elucidated.

In spite of substantial advances and sophistication of neonatal-, child- and intensive-care units, including the use of different settings of mechanical ventilation, the prevention and treatment of RDS and ARDS have remained difficult challenges. Therefore a goal of many clinicians and basic scientists has long been the development of optimal therapeutical regimens for RDS and ARDS.

A large amount of experimental and clinical evidence now indicates the beneficial effects of antenatal administration of steroids on the maturation of the fetal lung, and its use is now widespread. However, room exists for substantial improvements in this field, and therapeutical associations with other drugs are currently being evaluated.

In the last five years, major efforts have been devoted to the development and validation of surfactant replacement therapy for RDS and ARDS. Natural, semi-synthetic and synthetic surfactants have been de-

veloped and tested in a variety of clinical settings. An increasing number of clinical trials has shown the validity of such therapeutical options and has generated enthusiasm among providers. It is very likely that surfactant replacement therapy will be routinely used in the very near future in intensive-care units for the treatment of RDS and ARDS. However, many questions remain to be answered and the need exists for continuing research efforts in this exciting field. The chapters of this book try to address some of these fundamental questions.

Rome and Perugia, 1991

E. V. C.
G. C. Di R.
M. M. A.