Recent Advances in

OBSTETRICS AND GYNAECOLOGY

EDITED BY

JOHN BONNAR

NUMBER SIXTEEN

ecent Advances in
BSTETRICS AND
YNAECOLOGY

ITED BY

OHN BONNAR

NUMBER SIXTEEN

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1990

CHURCHILL LIVINGSTONE
Medical Division of Longman Group UK Limited

Distributed in the United States of America by Churchill Livingstone Inc., 1560 Broadway, New York, N.Y. 10036, and by associated companies, branches and representatives throughout the world.

First published 1990

ISBN 0 443 0 4117 2

British Library Cataloguing in Publication Data
Recent advances in obstetrics and gynaecology.
16
1. Gynecology——Periodicals 2. Obstetrics
——Periodicals
618'.05 RG1

Library of Congress Cataloguing in Publication Data
Recent advances in obstetrics and gynaecology.—
— Edinburgh; New York: Churchill Livingstone;
Distributed in the U.S. of America by Longman Inc.,
v.: ill.; 24 cm.
Began in 1926.
Description based on: no. 12 (1977).
ISSN 0143-6848 = Recent advances in obstetrics and gynaecology.
1. Gynecology—Collected works. 2. Obstetrics—Collected works.
DNLM: W1 RE105YJ

RG1.R42 618'.05 81-644212
AACR 2 MARC-S

Printed in Great Britain at The Bath Press, Avon

Preface

This 16th issue of *Recent Advances in Obstetrics and gynaecology* follows within three years of the 15th issue which marked the 60th Anniversary of the publication. The demand for the book is such that Churchill Livingstone are planning publication of a new issue every two years. The book is for the Registrar and Consultant to keep abreast of the main developments in obstetric and gynaecological practice in both the developed and developing countries. As Editor, I have selected authors who are recognized internationally as experts in their particular field. The contributors have been asked to provide a distillation of their knowledge and experience of a particular topic and the relevance of new information for the practising obstetrician and gynaecologist.

The obstetrics section starts off with Professor Ho-Kei Ma and her team in Hong Kong who have extensive experience in the management of trophoblastic disease. The immunology of recurrent abortion is an area of some confusion and the subject is reviewed by Professor David Clark of Ontario. A new development in assessing the feto-placental unit is the use of Doppler to measure umbilical and uteroplacental blood flow. The present position is critically examined by Mr Peter McParland and Mr Malcolm Pearce from St George's Hospital, London. Of major concern for the obstetrician practising all over the world is the patient with the acquired immune deficiency syndrome; Dr George Kinghorn of Sheffield provides a balanced assessment of this ever-increasing problem in the pregnant woman and neonate. A major problem in the developing countries is a rapid growth of urban populations which can overwhelm the maternity services. This has led to the development of community obstetric care with midwife delivery units working as an integral part of the obstetric service. Dr Herman van Coeverden de Groot has pioneered this community service in Cape Town and he and Dr Ronald Howland describe in detail the organization of midwife delivery units.

Regrettably litigation against obstetricians and gynaecologists has been rising exponentially over the last five years. Dr Chris Orr, an experienced Obstetrician and Gynaecologist now with the Medical Protection Society, provides an analysis of the present trends, the key areas of practice where litigation is likely to arise and the steps to be taken to prevent claims.

In the gynaecology section, the first two chapters deal with cervical carcinoma. Professor Allan Templeton and his team have a major research programme in cervical screening and their critical analysis of the present position for cervical screening is important information for every gynaecologist. A sad fact of life is the increasing incidence of cervical carcinoma in young women. Mr John Shepherd at St Bartholomew's Hospital, London, has extensive experience of this problem and he examines the options which are now available in the treatment of the young woman with cervical

cancer. In both the developed and developing world, acute pelvic inflammatory disease is a common gynaecological emergency. Professor Hein Odendaal at the University Department of Stellenbosch, South Africa, has extensive experience of acute pelvic inflammatory disease and he describes the current medical and surgical management. For definitive diagnosis and treatment of intrauterine abnormalities, hysteroscopy is now becoming more and more accepted. Jacques Hamou from Paris and Victor Lewis from Watford, Hertfordshire, have pioneered the use of hysteroscopy and they provide a careful appraisal of this development in endoscopy. The complex area of infertility is examined by Professor Harrison of Dublin.

Gynaecologists are expected to be conversant with methods of contraception. New information on hormonal contraception relevant to clinical practice is provided by Dr Dorothy Tacchi from Newcastle. In current practice, the request for hormone replacement therapy after the menopause continues to grow. The role of hormone replacement therapy in the prevention of osteoporosis is examined by Mr David Purdie of Leeds and the new delivery systems which are being researched are described by Mr Malcolm Whitehead's group from King's Hospital in London.

The contributors to the 16th issue are all experts who are busy in research and clinical practice. I would like to express my gratitude and indebtedness to them for accepting the invitation to write a chapter and to adhere to a strict time schedule. I am sure that you the readers will be equally grateful to them for examining the growing edges of the speciality and so assisting you to provide the best and most up-to-date treatment for the patients in your care.

Dublin 1990 J.B.

Contributors

DAVID A. CLARK MD PhD FRCPC
Professor, and MRC Scientist, Departments of Medicine and Obstetrics and Gynaecology, McMaster University, Hamilton, Ontario, Canada

DAVID CROOK PhD
Laboratory Director, Cavendish Clinic, London, UK

MICHAEL P. CUST MB BS MRCOG
Clinical Research Fellow, Academic Department of Obstetrics and Gynaecology, King's College School of Medicine and Dentistry, and Cavendish Clinic, London, UK

LESLEY A. FENTON MB BS
Research Fellow in Pathology and Obstetrics and Gynaecology, University of Aberdeen, Aberdeen, UK

P. M. FISHER MB ChB DObst MRCOG
Consultant Gynaecologist, Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen, UK

KEVIN F. GANGAR MA MB BChir FRCS MRCOG
Clinical Research Fellow, Academic Department of Obstetrics and Gynaecology, King's College School of Medicine and Dentistry, London, UK

JACQUES HAMOU
Chargé de Cours à la Faculté de Médécine de Paris, Attaché à la Maternité de Tenon et Port Royal, Paris

ROBERT F. HARRISON MA MD FRCS (Edin.) FRCOG FRCPI
Professor of Obstetrics and Gynaecology, Royal College of Surgeons in Ireland, Rotunda Hospital, Dublin, Ireland

RONALD C. HOWLAND MB CHB (Cape Town)
Principal Medical Officer, Midwife Obstetric Units, University of Cape Town and Cape Provincial Administration, Cape Town, South Africa

G. R. KINGHORN MD FRCP
Consultant Physician in Genitourinary Medicine, Royal Hallamshire Hospital, Sheffield, UK

B. V. LEWIS MD FRCS FRCOG
Consultant Gynaecological Surgeon, Watford General Hospital, Watford, Hertfordshire, UK

H. K. Ma MB BS MRCOG
Professor and Head, Department of Obstetrics and Gynaecology, University of Hong Kong

J. ELIZABETH MACGREGOR OBE BSc MD FRCPath FRCOG
Honorary Director, Harris Birthright Research Centre, University of Aberdeen, Aberdeen, UK

PETER McPARLAND MRCPI MRCOG
Research Fellow, Fetal Welfare Laboratory, St George's Hospital Medical School, London, UK

HEXTAN Y. S. NGAN MB BS MRCOG
Lecturer, Department of Obstetrics and Gynaecology, University of Hong Kong

H. J. ODENDAAL MB ChB MD FCOG (SA) FRCOG
Professor and Head, Department of Obstetrics and Gynaecology, University of Stellenbosch, Tygerberg, South Africa

CHRISTOPHER J. B. ORR BA MB BCh MAO FACS FRCOG
Member of Secretariat, Medical Protection Society, London; Examiner in Obstetrics and Gynaecology, Worshipful Society of Apothecaries, London, UK

J. MALCOLM PEARCE MD FRCS MRCOG
Senior Lecturer, Fetal Welfare Laboratory, St George's Hospital Medical School, London, UK

DAVID W. PURDIE MB FRCOG
Senior Lecturer, Department of Obstetrics and Gynaecology, University of Leeds, Leeds, UK

JOHN H. SHEPHERD MB FRCS MRCOG FACOG
Consultant Gynaecological Surgeon and Oncologist, St Bartholomew's and The Royal Marsden Hospitals, London, UK

DOROTHY A. TACCHI MB BS
Senior Medical Officer, Family Planning and Well Woman Service, Newcastle upon Tyne, UK

ALLAN TEMPLETON MD FRCOG
Professor, Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen, UK

HERMAN A. VAN COEVERDEN DE GROOT FRCOG
Associate Professor of Community Obstetrics, University of Cape Town and Cape Provincial Administration, Cape Town, South Africa

MALCOLM I. WHITEHEAD MB BS FRCOG
Senior Lecturer/Consultant Gynaecologist, Academic Department of Obstetrics and Gynaecology, King's College School of Medicine and Dentistry, London, UK

L. C. WONG MB BS FRCOG
Reader, Department of Obstetrics and Gynaecology, University of Hong Kong

Contents

Obstetrics

1. The modern management of trophoblastic disease

Ho-Kei Ma L. C. Wong H. Y. S. Ngan

INTRODUCTION

Over the last 30 years major advances have taken place in our understanding and management of gestational trophoblastic disease. It is now possible to diagnose a hydatidiform mole by ultrasonography in a matter of minutes, to prevent the occurrence of metastatic sequelae in the majority of patients with moles, and to achieve a high remission rate in patients with advanced metastatic disease. Patients who were in moribund condition have been treated successfully and have remained well, leading full and healthy lives for many years. Indeed, there are few cancers where treatment can claim equal success.

Research on the cytogenetic profile of complete and partial mole has thrown light on the aetiology of the disease. Subunit assays have been devised in the hope of improving both the accuracy of prediction of the development of metastases, and the monitoring of the tumour response to chemotheraphy. New combinations of chemotherapeutic agents and new drugs have been discovered. These advances notwithstanding, hydatidiform mole and gestational trophoblastic disease are still prevalent in many countries where couples have many children, and where there are many elderly pregnant women. In these countries the results of treatment are still poor due mainly to lack of adequate health care of patients with hydatidiform mole.

TERMINOLOGY

There is no universally accepted classification of gestational trophoblastic disease. Ideally a classification should be simple, easy to remember and used prospectively. Expensive laboratory tests should not be needed for classification and the classified status should indicate the extent and prognosis of the disease. The staging and prognostic scoring system proposed by the WHO in 1983, which is in current use, does indicate the extent of the disease and the prognosis of the patient. Some centres are using modified versions of the WHO classification, while in Japan, histopathology classification is still commonly used. To avoid confusion, the terms used in this chapter are defined.

In Hong Kong, we have used a prospective clinical classification (Table 1.1) and a modified Bagshawe's prognostic score (Table 1.2). We use the term 'residual trophoblastic disease (RTD)' in a mole patient who has a persistently raised level of human chorionic gonadotrophin (HCG) without detectable metastasis. Such patients may have vaginal bleeding and an enlarged uterus. The word 'residual' indicates that in many such patients the trophoblastic activity may regress spontaneously and that they probably do not have a malignant condition. Others use the term 'persistent trophoblastic disease' for similar conditions (Bagshawe 1973). We label a mole patient

as suffering from RTD when her HCG value remains the same for 4 weeks or whose HCG rises for 3 consecutive weeks. A change of HCG level of less than twofold is disregarded. Many of these patients have positive pelvic arteriographic signs of invasive mole, but since hysterectomy is rarely performed, there is no histological diagnosis. Therefore our RTD patients probably have a milder form of the disease and have a better prognosis than those with persistent disease described by others (Bagshawe 1973, Parazzini 1988, Khazaeli 1986).

Table 1.1 Clinical classification of gestational trophoblastic disease (GTD) used in Hong Kong

I	Hydatidiform mole
	Partial
	Complete
II	Residual gestational trophoblastic disease (RTD)
III	Non-metastatic malignant gestational trophoblastic disease (NMTD) (low risk GTD)
IV	Metastatic malignant gestational trophoblastic disease (MTD)
	Low risk
	High risk

Table 1.2 Prognostic score used in Hong Kong

	Score			
	0	1	2	3
Antecedent pregnancy	Hydatidiform mole	Non-mole abortion	Term pregnancy	
Interval between antecedent pregnancy* and initial therapy (months)	<3	3–6	7–12	>12
HCG value at start of therapy†	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Blood group of patient	—	—	B AB	—
Largest tumour (cm)‡	<2	—	2–5	>5
Site of metastases	—	—	GI tract Kidney Spleen	Brain Liver
No. of metastases	—	1–4	4–8	>8
Previous chemotherapy	—	—	Prophylactic	Therapeutic

* When antecedent pregnancy cannot be identified, use interval from onset of symptom.
† Plasma-HCG in m.i.u./ml
‡ Mean of the longest and shortest diameter of the largest tumour

The terms 'invasive mole' 'metastatic mole' and 'choriocarcinoma' are used in this chapter only when there is histological proof of the condition. 'Non-metastatic trophoblastic disease' (NMTD) indicates that the patient's HCG has returned to and remained normal for at least one month and then rises and that pregnancy has been excluded. There is no detectable metastasis. A low risk gestational trophoblastic disease

(GTD) patient would have a total prognostic score of four or less, and a high risk patient has a total score of more than four (Table 1.2).

MANAGEMENT OF PARTIAL MOLE

It was recognized long ago that in some moles a fetus was present. In the late 1970s Szulman (1978, 1982), Lawler (1979) and others reported two distinct types of mole based on morphological, histopathological and cytogenetic examination. It is now well accepted that there are two types of mole: complete and partial. A partial mole exhibits focal hydatidiform change of the villi, and hyperplasia of the syncytiotrophoblast, and an embryo/fetus may be present. the fetus usually dies early in the first trimester but some patients with partial mole give birth to live fetuses (Beischer 1966, Jones & Lauerson 1975, Block & Merrill 1982). The fetuses are usually retarded in growth or have multisystem abnormalities. Microscopic examination of the dilated chorionic villi shows the presence of fetal blood vessels and fetal red blood cells in contrast to the villi of the complete mole.

Partial mole has a triploid XXY or XXX or XYY karyotype and seems to develop when a normal egg with 23X haploid set is fertilized by two sperms with haploid set 23X, or one with 23X and another with 23Y, or by one sperm with unreduced genome 46,XY (Szulman 1984). Villi appear to undergo hydatidiform change only when the contribution of the extra haploid set is from the paternal side. If it is from the maternal side, the placenta will not undergo hydatidiform change but the fetus will exhibit abnormality.

The clinical presentation of partial mole does not differ markedly from that of a complete mole, but it tends to present a less florid picture (Szulman 1981, Wong & Ma 1984). The age, parity and symptoms of partial mole patients are similar to those of the complete mole, while the duration of amenorrhoea tends to be longer. Partial moles are frequently misdiagnosed as threatened or missed abortion, because in many patients the uterus is smaller than that of the gestational period. We reported that only 10 of our first 35 partial mole patients (27.6%) had a uterus bigger than that of the gestational period as calculated from the date of the last menstrual period, and 17 patients (49.4%) had a uterus smaller than date (Wong & Ma 1984). Our study was a retrospective review of all the patients with a diagnosis of hydatidiform mole, to reclassify the patients into complete and partial moles. Therefore, the percentage of patients where the uterus was bigger than the reported dates was probably too high. The HCG level in partial mole is usually not as high as that of a complete mole.

The ultrasonographic appearance of partial mole was described by Woo (1983). Recent attempts to use flow cytometry (Fisher 1987) and immunological staining technique (Brescia 1987) to diagnose the condition may simplify the diagnostic procedure. Now that the condition is better known and the use of ultrasonography in all patients who have vaginal bleeding during pregnancy has become standard practice, the diagnosis of partial mole will be increased. Once the diagnosis is made and if there is no live fetus, the treatment is to evacuate the uterus. In the rare situation where there is a live normal fetus, the patient should be warned about the likely adverse fetal outcome.

The post-evacuation HCG regression pattern is no different from that of the complete

mole (Smith 1984). It was previously believed — and some still hold the belief — that persistent or metastatic trophoblastic disease very rarely occurred in partial mole patients. Two of our first 35 patients (5.7%) had RTD and two had MTD (5.7%); in other words, 11.4% of our patients had sequelae. Berkowitz (1985) and Mostoufi-Zadeh (1987) reported that eight of their 81 patients (9.9%) had persistent disease. Therefore, it is important to diagnose partial mole. The ultrasonographer should be acutely alert to the possibility of the condition. If a live fetus is present, chorionic villi biopsy can be done to make the diagnosis. If there is no fetus, evacuated tissue should be sent for cytogenetic study. In spite of the low incidence of metastatic malignant sequelae, partial mole patients should be followed in the same manner as complete mole at least until HCG returns to normal for 3–6 months.

MANAGEMENT OF COMPLETE MOLE

It is now known that the classic grape-like complete mole usually has a haploid 46,XX karyotype, but 5–10% of complete moles have a 46,XY karyotype. The 46,XX genome is formed by the fertilization of an empty egg by a normal spermatozoon carrying a 23X set of chromosomes, and this set of paternal chromosomes duplicates to form the homozygous diploid genome. The 46,XX can also be formed by the fertilization of an empty egg by two 23X spermatozoons, resulting in a heterozygous diploid genome. If one of the spermatozoons has 23Y chromosomes, the mole will be a heterozygous 46,XY (Szulman 1978, 1982, Lawler 1979). One of the most consistent findings in epidemiological studies is that the incidence of mole increases with maternal age. Molar pregnancy would appear therefore to be a series of reproductive abnormalities which occur with increasing frequency in older women. However, the search for abormality at chromosomal regions responsible for the occurrence of hydatidiform mole has not produced any positive result.

Ultrasonography, a procedure that is simple, rapid and non-traumatic, has superceded HCG assay as the diagnostic tool for complete mole. HCG assay is now used solely to monitor trophoblastic activity after evacuation of the uterus. All other previous diagnostic tests are obsolete. Attempts were made to find an accurate way to predict which complete mole will become malignant. Potential risk factors have been examined, including maternal and paternal age, parity, age at menarche, age of first pregnancy, previous reproductive performance, uterine size, presence of pre-eclampsia, blood group and use of hormonal contraception. There is general agreement that a patient of 40 years or older with a complete mole, a uterus much bigger than dates, a very high pre-evacuation HCG level and signs of pre-eclampsia or pulmonary hypertension has an increased chance of developing malignant disease. Opinions differ as to the other risk factors. Our experience is similar to the findings of Messerli et al (1985) and Parazzini et al (1988), that paternal age, blood group and contraceptive pill usage are not significant risk factors. When some of the risk factors listed above were used to identify patients for prophylactic chemotherapy, 76.0% of patients were treated (Ma & Wong 1982). Parazzini and his co-workers (1988) could only correctly predict the outcome of 69% of their patients using these risk factors, and only 5% of their 321 patients were identified to be in the high risk group. Goldstein (1971) devised a prognostic score for his mole patients using some of these parameters (Table 1.3) and reported that 8.8% of the high risk mole patients and only 0.6% of the

low risk patients developed MTD. The majority of workers found the risk factors not precise enough in identifying high risk mole patients; the factors are therefore not generally used in the selection of mole patients for chemotherapy.

Table 1.3 Goldstein (1984) mole prognostic score

	Score			
	0	1	2	3
Type	Partial	Classical	Recurrent	
Size of uterus/ gestational month	= or <	> 1 month	> 2 months	> 3 months
HCG level m.i.u./ml	< 50 000	50 000–100 000	10^5–10^6	> 10^6
Theca-lutein cysts	—	< 6 cm	6–10 cm	> 10 cm
Age (years)	—	< 20	> 40 < 50	> 50
Associated factors*	None	One or more present	—	—

Low risk = < 4; high risk = > 4
* Hyperemesis, pre-eclampsia, hyperthyroidism, disseminated intravascular coagulation, trophoblastic embolization

A complete mole ought to be evacuated as soon as diagnosed, and the safest method of evacuation of the uterus is by suction. Medical induction is seldom used as it was found to be associated with a high incidence of persistent disease. Total hysterectomy, when used to terminate the molar pregnancy, did not reduce the incidence of malignant disease (Braga & Chun 1969).

The evacuation of the uterus should be followed by observation of the patient and her HCG level. Different centres adopt different criteria for selection of patients for chemotherapy, and this results in different percentages of patients treated. The reported percentages ranged widely from 5.4 to 100%.

In 1973, Bagshawe reported his results of treatment of patients selected on the grounds of persistent elevated HCG level, persistent uterine haemorrhage and development of metastasis (Bagshawe 1973). Bagshawe advocated treatment only on the following principal grounds:

1. Urinary HCG values of more than 40 000 i.u. HCG/24 hours at more than 4–6 weeks after evacuation, or of more than 25 000 i.u. HCG/24 hours at more than 10 weeks after evacuation of a hydatidiform mole
2. A persistently abnormal value of urinary HCG at 5–7 months after evacuation of a mole
3. Evidence of intracranial or gastrointestinal metastases
4. Evidence of pulmonary metastases with persistently high or rising urinary HCG values
5. Persistent or recurrent uterine haemorrhage requiring transfusions and a persistently raised HCG value in the urine

Using these criteria, Bagshawe treated only 5.4% of his patients, and all the untreated patients as well as the treated did well. During the first 10 years of the United Kingdom