GENETIC DISEASES IN PREGNANCY

Maternal Effects and Fetal Outcome

Edited by

Joseph D. Schulman

— and —

Joe Leigh Simpson

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ACADEMIC PRESS
A Subsidiary of Harcourt Brace Jovanovich, Publishers
NEW YORK LONDON TORONTO SYDNEY SAN FRANCISCO 1981

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data
Main entry under title:

Genetic diseases in pregnancy.

Includes bibliographies and index.
1. Pregnancy, Complications of--Genetic aspects.
2. Medical genetics. I. Schulman, Joseph D.
II. Simpson, Joe Leigh. [DNLM: 1. Hereditary Diseases--
Complications. 2. Pregnancy complications. WQ 240 G328]
RG580.G45G46 618.3'042 80-68562
ISBN 0-12-630940-X AACR2

PRINTED IN THE UNITED STATES OF AMERICA

81 82 83 84 9 8 7 6 5 4 3 2 1

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Preface

With improving care, an increasing number of women with genetic diseases survive until the reproductive age. Many genetic defects compatible with reduced or normal levels of female reproduction are modified in their expression by gestation. Furthermore, in some heritable disorders, gestation may be altered by direct or indirect effects of the disease on the mother or fetus. Women with genetic diseases may thus pose particularly complicated problems when reproduction is contemplated, both with respect to medical problems and to genetic counseling.

This volume represents the first attempt to review comprehensively the interactions of genetic disorders with pregnancy. We have attempted to summarize current knowledge on this subject after scanning thousands of articles selected by conventional and computer-assisted methods and by soliciting information regarding relevant cases from our colleagues. The editors and contributors believe the present work will meet a need long felt by those involved with caring for pregnant patients with heritable diseases.

In the first chapter, Joel M. Lamon, Roger R. Lenke, Harvey L. Levy, Joseph D. Schulman, and Vivian Shih discuss selected metabolic disorders affecting a variety of organ systems. A particularly detailed section is devoted to a discussion of the major problem of maternal phenylketonuria. Judith G. Hall next summarizes the complex disorders of connective tissue and skeletal dysplasias, which may give rise to problems during pregnancy. This review is followed by three chapters on the genetic hematological disorders of pregnancy, all written by outstanding authorities: Mitchell S. Golbus and Russell Laros discuss hemoglobinopathies and hereditary red cell defects; Connie Miller and Margaret Hilgartner systematically analyze genetic disorders of hemostasis; and John T. Queenan summarizes current knowledge about Rh and other blood group incompatibilities.

Sherman Elias and Ruth Yanagi next review genetic defects of the cardiovascular system, and in the subsequent chapter Dr. Elias examines disorders of the respiratory system. Stanley A. Mendoza, Clyde H. Beck, Jr., and William R. Griswold summarize important aspects of renal pathophysiology

during pregnancy as a background to a lucid discussion of genetic defects that may affect the maternal kidney. Jerome I. Rotter, an expert on the genetics of gastrointestinal disorders, discusses their relationship to pregnancy.

Endocrine disorders are reviewed in two chapters: Menachem Nitzan discusses diabetes mellitus, and James R. Schreiber and Robert W. Rebar systematically review endocrine genetic disorders other than diabetes mellitus and provide a comprehensive discussion of this diverse subject. In the penultimate chapter, Steven P. Targum and Elliott S. Gershon examine the interaction of pregnancy and psychiatric disorders that are genetic in etiology. This chapter is of a special value because of its treatment of the genetics of the major psychiatric diseases, a subject on which the authors are acknowledged authorities.

Finally, Simpson exhaustively reviews current knowledge about pregnancies in women with chromosomal abnormalities. This chapter includes a clear discussion of the mechanisms by which such abnormalities may arise and be transmitted.

Despite efforts by the editors and contributors to be comprehensive, many genetic disorders occurring in adult women are nevertheless not discussed in this volume. In some cases this is because there appears to be no interaction of the disease with gestation, but in other instances failure to discuss a disorder merely indicates that no satisfactory data are currently available.

Especially because of the incompleteness of present information on this subject, we hope that the present volume will lead to increasing attention by physicians and investigators to interactions between genetic diseases and pregnancy. Inadequate and highly selected reporting of cases in the medical literature should be replaced by a growing awareness of the need to evaluate critically and to describe relevant observations. Scholarly reviews of genetic diseases should pay more attention to interactions with pregnancy, a subject often neglected even in otherwise outstanding contributions. We are convinced that understanding the interactions of pregnancy and genetic diseases is important both clinically and scientifically. The subject is worthy of future thought, synthesis, and investigation.

This book is not intended as a substitute for standard reference works on human genetics, genetic counseling, or prenatal diagnosis. Its perspective is different, and as such should satisfy many additional requirements of geneticists, obstetricians, pediatricians, internists, family practitioners, and others who must provide help to women with genetic diseases.

The editors and authors would be most grateful for information supplied to them providing new data and pointing out their omissions and errors.

Joseph D. Schulman
Joe Leigh Simpson

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Selected Metabolic Diseases

JOEL M. LAMON, ROGER R. LENKE, HARVEY L. LEVY,
JOSEPH D. SCHULMAN, AND VIVIAN E. SHIH

ISBN 0-12-630940-X

I. PHENYLKETONURIA

Phenylketonuria (PKU) is a metabolic disorder in which the conversion (hydroxylation) of phenylalanine (Phe) to tyrosine is impaired due to reduction in activity of the enzyme phenylalanine hydroxylase. Discovered by Fölling (1934), this disease may cause mental retardation and other manifestations of brain damage (e.g., seizures, hyperactivity, behavior disturbances, increased deep tendon reflexes). The major biochemical findings include increased concentrations of Phe and secondary phenolic metabolites (e.g., phenylpyruvate, phenylacetate) in blood and urine.

Newborn screening for PKU begun in the 1960s has led to the recognition that there is heterogeneity in this disorder. In addition to "classical" PKU in which the blood Phe concentration is usually greater than 20 mg/dl, patients with milder degrees of hyperphenylalaninemia have been discovered. Those with persistent hyperphenylalaninemia of 12 mg/dl or less are asymptomatic, whereas those whose blood Phe level is 12–20 mg/dl (sometime referred to as "atypical" PKU) may show intellectual deficit. In addition to the above primary defects in phenylalanine hydroxylase, occasional hyperphenylalaninemic patients have defects in the synthesis of the specific pteridine cofactor for this enzyme with secondary deficiencies in hydroxylation of Phe, tyrosine, and tryptophan. These latter two amino acids are precursors of brain neurotransmitters. Such patients, representing approximately 1% of hyperphenylalaninemic newborns, have a severe and progressive neurologic course sometimes culminating in death at 4–6 years of age. There is no effective therapy for patients with defects in pteridine synthesis.

If begun in early infancy, a low-phenylalanine diet that controls the biochemical abnormalities prevents mental retardation and most of the other neurologic sequelae of PKU. As a result of routine newborn screening, there are now thousands of children and adolescents with PKU who have received this therapy and who are of normal intelligence. Since PKU is an autosomal recessively inherited disorder, approximately one-half of these individuals are female and will potentially be subject to the maternal PKU syndrome.

The problem of maternal PKU first came to attention in 1957 when Dent recorded the occurrence of severe mental retardation in all offspring of a woman with PKU. Subsequently, Mabry and colleagues described several mothers with PKU whose non-PKU children were retarded (Mabry *et al.*, 1963, 1966; Dennis-ton, 1963). Perhaps the most convincing evidence that PKU in the mother during pregnancy produces fetal damage is a family studied by Mabry *et al.* (1966) in which the mother with PKU had three mentally retarded non-PKU children; one of these children subsequently had three mentally normal offspring by a retarded non-PKU man. Biochemical evidence of this relationship between maternal PKU and fetal brain damage has been supplied by Menkes and Aeberhard (1969) who found the abnormalities of cerebral lipids in a non-PKU offspring of a PKU woman to be similar to the abnormalities in patients with PKU. These findings suggest that the fetal damage is related to prenatal exposure to the high concentrations of Phe and/or Phe metabolites in the mother.

The maternal PKU syndrome is now a defined complication of pregnancy. Several reviews on this subject have been published (Mabry *et al.*, 1966; MacCready and Levy, 1972; Hansen, 1978; Mabry, 1978), the most recent and most extensive by Lenke and Levy (1980). The latter information includes 524 pregnancies in 155 mothers with PKU or some degree of hyperphenylalaninemia. Readers are referred to the above reviews for detailed information.

The major clinical manifestations in non-PKU offspring of women with PKU are mental retardation, microcephaly, congenital heart disease, and low birth weight. Neurologic problems such as convulsions and spasticity may develop in childhood (Mabry, 1978). Women with PKU may have an increased frequency of spontaneous abortions.

When the mother has a blood Phe concentration of 20 mg/dl (1.2 μmole/ml) or greater and increased urinary excretion of abnormal phenolic metabolites (positive ferric chloride test in urine) brain damage in her offspring is the rule (Table I). When the maternal blood Phe concentration is in the range of 16 to 19 mg/dl (1.0–1.1 μmole/ml) the fate of the fetus is less predictable. Approximately ¾ of the offspring from such women are mentally retarded and about ⅔ have microcephaly (Table I). The risk of effects on the fetus is far less when the maternal blood phenylalanine concentration is between 11 and 15 mg/dl and may be no greater than normally expected with lower levels (10 mg/dl or less) of maternal hyperphenylalaninemia.

Congenital cardiac defects in the offspring follow a similar pattern though are less frequent (Table I). These defects are often major and result in neonatal death. No particular cardiac lesion seems to predominate. Anomalies of the skeletal system, gastrointestinal tract, eye, spleen, and lung have occasionally been reported (Mabry, 1978) but seem not to be particularly frequent. An exception to this may be esophageal atresia (Lenke and Levy, 1980). A surprisingly large number of offspring have themselves had PKU or a lesser degree of hyper-

TABLE I
Frequency of Spontaneous Abortions and Offspring Abnormalities among Untreated Pregnancies of Women with PKU or Hyperphenylalaninemia

	Maternal blood phenylalanine (mg/dl)			
	⩾ 20	16–19	11–15	3–10
Abortions (spontaneous)	24% (72/297)	30% (20/66)	0 (0/33)	8% (4/48)
Offspring[a]				
Mental Retardation[b]	92% (158/172)	73% (27/37)	22% (5/23)	18% (5/28)
Microcephaly[c]	73% (100/138)	68% (30/44)	54% (7/13)	24% (5/21)
Congenital Heart Disease	10% (22/225)	11% (5/46)	6% (2/33)	0 (0/44)
Birth Weight <2500 g	40% (36/89)	50% (14/28)	56% (5/9)	13% (2/16)

[a]Offspring with PKU or hyperphenylalaninemia are excluded.
[b]IQ < 75, or observed "mental retardation."
[c]Head circumference > 2 S.D. below the mean.

phenylalaninemia (Lenke and Levy, 1980) but whether this represents a truly increased frequency or is due to ascertainment bias remains to be seen.

It should be emphasized that most of this information is from retrospective studies. The reported values of blood Phe in these women were obtained at the time of investigation and may not reflect their metabolic status during pregnancy. These values were also obtained with different analytical methods, some perhaps more accurately quantitative than others. Consequently, correlation between these blood levels and effects on the fetus may be subject to error, particularly at maternal blood Phe concentrations of 10–20 mg/dl.

Treatment with a low-phenylalanine diet has been given during 30 pregnancies, the majority in women with pretreatment blood Phe levels 20 mg/dl or greater. The blood Phe concentration during treatment was generally maintained within the range of 4 to 12 mg/dl with some levels as low as <1 mg/dl or as high as 16 mg/dl. Data from these pregnancies are summarized in Table II, catagorized according to the time of gestation when therapy was initiated. In over 80% of the cases treatment was started in the first or second trimester. It appears that treatment begun in the first trimester results in better intellectual development of offspring than when the treatment is begun later in pregnancy. Even with first trimester treatment, however, there was no clearly beneficial effect in preventing microcephaly or congenital heart disease. That four of the 11 offspring from these mothers died of congenital heart disease is disconcerting (Bush *et al.*, 1979; Buist *et al.*, 1979; Smith *et al.*, 1979; Bovier-Lapierre *et al.*, 1974). Furthermore, the outcome of a treated pregnancy cannot be predicted solely on the basis of the degree of biochemical control, as reflected by periodic maternal blood Phe levels. Two equally well-treated pregnancies resulted in one case in a normal child (Farquhar, 1979) and in the other in an infant who died at 17 days of age with a severe cardiac defect (Smith *et al.*, 1979).