YEAR BOOK®

YEAR BOOK OF OBSTETRICS AND GYNECOLOGY® 1990

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The Year Book of OBSTETRICS AND GYNECOLOGY®

Editors

Daniel R. Mishell, Jr., M.D.
Lyle G. McNeile Professor and Chairman, Department of Obstetrics and Gynecology, University of Southern California School of Medicine

Thomas H. Kirschbaum, M.D.
Professor, Department of Obstetrics and Gynecology, University of Southern California School of Medicine

C. Paul Morrow, M.D.
Professor, Department of Obstetrics and Gynecology, and Director, Gynecologic Oncology, University of Southern California School of Medicine

Contributing Editor

William H. Hindle, M.D.
Associate Clinical Professor, Department of Obstetrics and Gynecology, University of Southern California School of Medicine; Director, Breast Diagnostic Center, Women's Hospital

Editorial Assistant

Laurel D. Howat

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Journals Represented

Year Book Medical Publishers subscribes to and surveys nearly 850 U.S. and foreign medical and allied health journals. From these journals, the Editors select the articles to be abstracted. Journals represented in this YEAR BOOK are listed below.

Acta Cytologica
Acta Endocrinologica
Acta Obstetricia et Gynecologica Scandinavica
American Heart Journal
American Journal of Diseases of Children
American Journal of Epidemiology
American Journal of Human Genetics
American Journal of Industrial Medicine
American Journal of Medicine
American Journal of Obstetrics and Gynecology
American Journal of Perinatology
American Journal of Physiology
American Journal of Public Health
American Journal of Surgical Pathology
Andrologia
Anesthesia and Analgesia
Annales Chirurgiae et Gynaecologiae
Annals of Clinical Biochemistry
Annals of Internal Medicine
Archives of Internal Medicine
Australian and New Zealand Journal of Obstetrics and Gynaecology
Blood
Bone
British Journal of Family Planning
British Journal of Industrial Medicine
British Journal of Obstetrics and Gynaecology
British Journal of Psychiatry
British Journal of Surgery
British Journal of Urology
British Medical Journal
Canadian Journal of Surgery
Cancer
Chest
Clinical Chemistry
Clinical Endocrinology
Clinical Genetics
Clinical Nephrology
Clinical and Laboratory Haematology
Contraception
Diabetes
Diabetic Medicine
Diseases of the Colon and Rectum
Early Human Development
Endocrinology
European Journal of Obstetrics, Gynecology and Reproductive Biology
Family Planning Perspectives
Fertility and Sterility
Fetal Therapy

Gynecologic Oncology
Gynecologic and Obstetric Investigation
Health Physics
Human Pathology
International Journal of Cancer
International Journal of Cardiology
International Journal of Fertility
International Journal of Gynaecology and Obstetrics
International Journal of Gynecological Pathology
Israel Journal of Medical Sciences
Journal of Applied Physiology
Journal of Bone and Joint Surgery (British volume)
Journal of Clinical Endocrinology and Metabolism
Journal of Clinical Investigation
Journal of Clinical Microbiology
Journal of Clinical Pathology
Journal of Computer Assisted Tomography
Journal of Endocrinology
Journal of Epidemiology and Community Health
Journal of Family Practice
Journal of Infectious Diseases
Journal of Nuclear Medicine
Journal of Obstetrics and Gynaecology
Journal of Pathology
Journal of Pediatric Surgery
Journal of Pediatrics
Journal of Psychosomatic Research
Journal of Reproductive Immunology
Journal of Reproductive Medicine
Journal of Urology
Journal of Vascular Surgery
Journal of the American Academy of Dermatology
Journal of the American Geriatrics Society
Journal of the American Medical Association
Journal of the Canadian Association of Radiologists
Journal of the Royal College of General Practitioners
Journal of the Royal College of Surgeons of Edinburgh
Lancet
Life Sciences
Maturitas
Medical Journal of Australia
Medicine
New England Journal of Medicine
New York State Journal of Medicine
New Zealand Medical Journal
Obstetrics and Gynecology
Paediatric and Perinatal Epidemiology
Pediatric Research
Physical Therapy Journal
Prenatal Diagnosis
Prostaglandins
Public Health Reports

Quarterly Journal of Medicine
Radiology
South African Medical Journal
Scandinavian Journal of Primary Health Care
Science
Southern Medical Journal
Surgery, Gynecology and Obstetrics
Ultrasound in Medicine and Biology
Vox Sanguinis
Western Journal of Medicine

Introduction

The editors, with the excellent assistance of the YEAR BOOK staff, have scanned a vast amount of scientific literature written during the past year to select those articles in the field of obstetrics and gynecology believed to be of greatest interest to practicing clinicians. A total of 407 relevant articles chosen from reviewing nearly 111 scientific journals have been abstracted and included in the 1990 YEAR BOOK OF OBSTETRICS AND GYNECOLOGY. We have selected articles that are of particular clinical relevance, and it is our hope that the comments of the editors will assist the clinician in his or her interpretation of the information summarized in the abstract.

The assistance of Drs. Arieh Bergman, David Grimes, and John Schlaerth, with their expertise in the respective areas of gynecologic urology, infectious diseases, and gynecologic oncology, is gratefully acknowledged. This year, Dr. William Hindle, a gynecologist with special interest in breast disease, has reviewed the relevant literature on breast disease and used his expertise in this area to comment on the selected articles. The editors also wish to acknowledge his contributions to this volume. As in the past, suggestions from readers to improve the value of this volume are solicited and would be welcomed.

Daniel R. Mishell, Jr., M.D.

Table of Contents

OBSTETRICS

1 Maternal and Fetal Physiology

Indomethacin in the Treatment of Premature Labor: Effects on the Fetal Ductus Arteriosus

Moise KJ Jr, Huhta JC, Sharif DS, Ou C-N, Kirshon B, Wasserstrum N, Cano L
(Baylor College of Medicine, Houston)
N Engl J Med 319:327–331, Aug 11, 1988 1–1

The use of indomethacin, a potent agent in the treatment of premature labor, has been limited because of concerns about its constrictive effects on the fetal ductus arteriosus. To further investigate these effects, serial fetal echocardiography was done in 13 pregnant women in premature labor who received indomethacin according to 3 different dose schedules, ranging from 100 mg to 175 mg daily for a maximum of 72 hours. One woman carried twins. The gestational ages of the fetuses ranged from 26.5 to 31 weeks.

In 7 of the 14 fetuses detection of ductal constriction by echocardiography led to discontinuation of indomethacin. Three fetuses were found to have tricuspid regurgitation as well. No significant difference was observed between the mean gestational age of the fetuses with ductal constriction and that of those without constriction. There was no relationship between serum indomethacin levels in the mothers and ductal constriction. Ductal constriction was resolved in all 7 affected fetuses by the time they were restudied 24 hours after discontinuation of the indomethacin. Persistent fetal circulation was not seen in any of the 11 neonates examined after delivery.

Constriction of the ductus arteriosus was detected in 7 of 14 fetuses after their mothers were treated with indomethacin. Thus indomethacin used to treat premature labor apparently causes transient constriction of the ductus arteriosus in some fetuses, even after short-term administration.

▶ Normally, patency of the ductus arteriosus is maintained by high rates of production of prostaglandin species by its endothelial and muscular layers. The ductus is important in maintaining the high cardiac output in fetal life that, because of parallel coupling of the ventricles, equals the sum of the output of the right and left ventricles, minus pulmonary blood flow. The latter is small because the relative hypoxemia of fetal pulmonary arterial blood holds the pulmonary bed in vasoconstriction, maintaining high pulmonary vascular resistance. In the normal transition from fetus to neonate, the ductus constricts as fetal blood Po_2 increases by virtue of pulmonary rather than placental O_2 acquisition, but it

does not close until the increase in pulmonary blood O_2 has led to vasodilatation of the pulmonary vascular bed. This, plus some other changes, reduces cardiac output because the right and left ventricles are now linked in series and because cardiac output equals the lesser of the 2 cardiac ventricular outputs, not their sum.

Evidence is produced here that inhibiting ductus prostaglandin production without a change in fetal Po_2 may constrict the ductus arteriosus without expanding the pulmonary vascular lung bed, causing dilatation of the right heart and incompetence of the tricuspid valve through widening of the atrioventricular annulus of the heart. Reduced cardiac output would result.

There are some flaws in the evidence, however. The ductus was not seen to constrict, but constriction was inferred from Doppler signals indicating increased mean velocity in 7 of 14 fetuses. There is no necessary relationship between the velocity of blood flow and blood volume flow, unless vessel diameter is measured. No relationship between change in velocity and the fetal blood indomethacin concentration was noted. Tricuspid regurgitation helps to confirm ductile vasoconstriction, but this was seen in only 3 of 14 cases. The diagnosis of preterm labor was questionable because it was based on as few as 6 uterine contractions with "minimal cervical dilatation." The 100% effectiveness of indomethacin in stopping preterm labor as defined here makes it likely that not all patients were truly in labor.

The high fetal cardiac output per unit fetal weight is an important factor in fetal cardiovascular homeostasis. Reducing it by constriction of the ductus arteriosus might not put the fetus in immediate jeopardy but would certainly reduce its tolerance to physiologic insult in labor. These data are compatible with, but do not prove that, ductus constriction occurs with indomethacin given to the mother in this dosage. Nonetheless, the potential risk to the fetus should be kept in mind when using this agent in pregnancy.—T.H. Kirschbaum, M.D.

Characterization and Gestational Regulation of Corticotropin-Releasing Hormone Messenger RNA in Human Placenta

Frim DM, Emanuel RL, Robinson BG, Smas CM, Adler GK, Majzoub JA (Brigham and Women's Hosp, Boston; Harvard Med School)

J Clin Invest 82:287–292, July 1988 1–2

Corticotropin-releasing hormone (CRH), a neuropeptide, is synthesized by the hypothalamus and released in response to stress. Antisera to human CRH have detected a related molecule in human placenta and fetal plasma. To determine whether the placenta synthesizes CRH, total RNA was isolated from human placenta and hybridized with radioactive nucleic acid probes homologous to the human CRH gene.

A 1,700-nucleotide-long RNA species appeared to comigrate with the rat hypothalamic CRH mRNA. The 5′ transcriptional initiation site, determined by primer extension analysis, appeared to be the same as that of hypothalamic CRH. Total RNA was extracted from placentas aged 7–40 weeks. Northern blot analysis demonstrated low levels of CRH

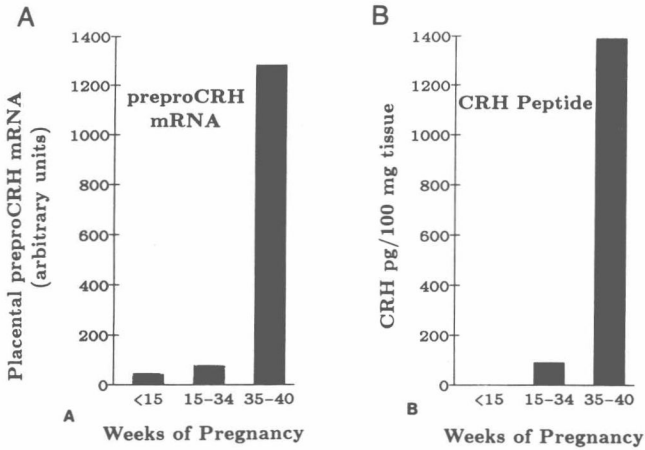

Fig 1–1.—Changes in placental human CRH mRNA (**A**) and hCRH peptide (**B**) during gestation. (Courtesy of Frim DM, Emanuel RL, Robinson BG, et al: *J Clin Invest* 82:287–292, July 1988.)

mRNA at 7–19 week's gestation, which increased by more than 20-fold (Fig 1–1) during the last 5 weeks of pregnancy.

These results demonstrate that CRH mRNA is present in the human placenta. Its level is low initially, but it increases dramatically in the last few weeks before birth, in parallel with the previously demonstrated increase in CRH peptide in the placenta.

▶ Identification of CRH in the human placenta has always been colored by the chance of contamination by maternal blood. This fine piece of work puts that concern largely to rest. Messenger RNA (mRNA) is an intermediate between gene activation and transcription in the nucleus and protein production by ribosomes in the cytoplasm. Its presence indicates active protein production under gene control in a tissue: Its activity says something about the rate of protein production. Because mRNA is not transferred from mother to fetus, its presence in the placenta proves the placental origin of CRH. Although not fully characterized, human placental and hypothalamic CRH are identical with respect to immunoreactivity, chromatographic behavior, and potency in bioassay. Further, DNA probes show the placental gene locus to be in roughly the same position relative to promoter segments on the gene as in hypothalamic CRH. This is further confirmation that placental mRNA and the resultant change in placental CRH production parallel the twentyfold increase that occurs in available CRH in the last 2 weeks of human pregnancy. Now it becomes important to determine what role this placental gene activation in late pregnancy plays in parturition and the transformation of fetus to neonate.—T.H. Kirschbaum, M.D.

Effects of Somatostatin and Glucose Infusion on Glucose Kinetics in Fetal Sheep

Bloch CA, Menon RK, Sperling MA (Univ of Cincinnati)
Am J Physiol 255:E87–E93, July 1988 1–3

Despite the documented effects of insulin on fetal glucose kinetics, it is not known how glucose affects fetal glucose kinetics independently of insulin. The effects of exogenous glucose infusion to the fetal sheep on fetal glucose turnover while insulin secretion was suppressed by a concomitant infusion of somatostatin (SRIF) were determined.

By infusing SRIF followed by SRIF plus glucose (protocol A) or reversing the initial infusion sequence (protocol B), the contribution of glucose, independently of insulin, on fetal glucose kinetics in the sheep was examined. In protocol A, 8 singleton fetuses were studied at an average gestational age of 129 days and in protocol B, 7 singleton fetuses were studied at a mean gestational age of 126 days.

In protocol A infusion of SRIF at 200 μg/hour decreased mean plasma levels of insulin and blood glucose by 2.8 μU/ml and 1.34 mg/dl from their respective basal concentrations of 6.8 μU/ml and 16.47 mg/dl. No significant changes in plasma levels of glucagon or rates of umbilical glucose uptake or of glucose utilization were found, but mean glucose turnover decreased by 1.77 mg/kg/minute. No effect on plasma levels of insulin or glucagon was found with the addition of glucose at a mean rate of 5.6 mg/kg/minute. Despite suppression of umbilical glucose uptake by 33%, total glucose uptake increased from a mean of 6.37 to a mean of 10.25 mg/kg/minute. Fetal glucose reached a new mean steady state of 23.08 mg/dl; glucose turnover increased by a mean of 4.81 mg/kg/minute from its SRIF-induced nadir.

Because the glucose concentration remained at steady state, the rate of glucose utilization was equivalent to the rate of total glucose uptake, an increase of 60% from basal levels despite suppressed plasma levels of insulin. During combined glucose and SRIF infusion in protocol B the changes in hormone and glucose concentrations, as well as glucose fluxes and kinetics, were quantitatively similar to those in protocol A.

The results suggest that a considerable fraction of glucose utilization in the fetal sheep is largely independent of insulin, both in the basal state as well as during modest hyperglycemia of short duration.

▶ The Danish diabetologist Pederson is responsible for the hypothesis that insulin, coupled with available glucose, serves as a growth factor in the fetus that, if not controlled during diabetic pregnancy, leads to macrosomia. This careful, tightly argued paper makes the point that at least a good part of that relationship is the result of glucose alone operating independent of insulin. Somatostatin is used to produce partial pharmacologic inhibition of fetal pancreatic insulin production and release to a level of 40% reduction from normal. Fetal transfer of glucose and its utilization is unaffected, although the fetal serum glucose concentration declines. The latter, extrapancreatic because the glucagon concentration did not change, may stem from inhibition of growth hormone by somatostatin. Infusion of glucose without somatostatin inhibition of insulin results in an increase in fetal glucose uptake. If these relationships are equally valid in humans, they underline the importance of euglycemia independent of changes in insulin concentration in pregnant diabetic management and alter the Pederson hypothesis a bit.—T.H. Kirschbaum, M.D.

Use of Fetal Streptozotocin Injection to Determine the Role of Normal Levels of Fetal Insulin in Regulating Uteroplacental and Umbilical Glucose Exchange

Hay WW Jr, Meznarich HK (Univ of Colorado)

Pediatr Res 24:312–317, 1988 1–4

Insulin regulates fetal glucose metabolism, and increased concentrations of insulin reduce the glucose concentration and increase fetal uptake and the use of glucose and oxygen. The role of normal fetal concentrations of insulin in regulating placental-fetal glucose exchange was investigated.

Fetal insulin deficiency was produced by injecting streptozocin into near-term fetal sheep. Its effects on net uteroplacental glucose uptake and net umbilical glucose uptake were then measured. A dosage of 100 $mg \cdot kg^{-1} \cdot dose^{-1}$ of streptozocin given 2 or 3 times on separate days produced a 97.6% decrease in fetal pancreatic insulin content, a drop in the fetal plasma insulin concentration, an increase in the fetal plasma glucagon concentration, a rise in the fetal blood glucose concentration, and failure of insulin secretion in response to glucose infusion. The fetal blood oxygen content and umbilical oxygen uptake were normal throughout the study. The umbilical uptake of glucose dropped by 66% after streptozocin-induced hypoinsulinemia and hyperglycemia but returned to base levels after insulin infusion into the fetus that reestablished the control maternal to fetal glucose concentration gradient. The net uteroplacental glucose uptake remained the same.

This study provides evidence that, in fetal sheep, streptozocin induces fetal insulin deficiency by decreasing the pancreatic insulin content, insulin secretory capacity, and hypoinsulinemia. Fetal hyperglycemia develops in reaction to fetal hypoinsulinemia, decreasing the maternal-fetal glucose concentration gradient and umbilical glucose uptake. These findings indicate that the normal concentration of insulin in fetal sheep determines uteroplacental-fetal glucose exchange indirectly by regulating the fetal glucose concentration.

▶ This agent is directly cytotoxic to pancreatic beta cells, the liver, and kidneys. A second phase of beta cell injury, dependent on intact immune mechanisms, occurs at times longer than 5–7 days after fetal injection. What resulted in this study was a two thirds increase in the mean fetal blood glucose level, a 50% reduction in the mean fetal insulin concentration, and a compensatory doubling of fetal plasma glucagon. Although the hyperglycemia was probably the result of reduced fetal glucose utilization, increased fetal gluconeogenesis associated with hypoinsulinism or toxic injury to the liver is an alternative explanation. Because replacement fetal insulin reversed the effects, the latter, i.e., toxic injury, is unlikely.

The point here is that the increased fetal blood glucose concentration decreased umbilical glucose transport in a way roughly consonant with facilitated placental diffusion. It's a reasonable conclusion that fetal insulin plays only an indirect role, mediated through fetal blood glucose, on fetal glucose uptake

from the mother. By inference then, the large placental utilization of glucose must depend largely on maternal insulin activity. That is to say, the bulk of maternal insulin and hyperglycemia might reasonably go only to maintaining the high rate of metabolism of the placenta itself.—T.H. Kirschbaum, M.D.

Atrial Natriuretic Factor in the Human Fetus: Effect of Volume Expansion
Robillard JE, Weiner C (Univ of Iowa)
J Pediatr 113:552–555, September 1988 1–5

The control of human atrial natriuretic factor (ANF) in the fetus has not been investigated. To determine whether an increase in intravascular volume load would stimulate ANF secretion in the fetus, as it does in the adult, ANF levels were monitored in 6 human fetuses (21–34 weeks of gestation) as they underwent 12 intravascular transfusions for treatment of immune hemolytic anemia. The ANF levels of 7 normal fetuses (22–26 weeks of gestation) also were monitored.

The mean basal plasma ANF concentration in the fetuses with immune hemolytic anemia was 184 pg/ml as opposed to 90 pg/ml in the controls. During transfusion, the mean plasma ANF concentration increased significantly to 371 pg/ml by midtransfusion and to 528 pg/ml by the end of transfusion. The findings demonstrate that ANF is present as a circulatory hormone in the human fetus by midgestation, at which time fetal release of ANF is increased in response to intravascular volume expansion.

▶ This hormone affecting sodium and water diuresis in response to atrial distention has been discussed here before (see the 1989 YEAR BOOK OF OBSTETRICS AND GYNECOLOGY, pp 15–17). This study suggests that the human fetus is capable of employing this mechanism as early as 21 weeks' gestation and maintaining plasma volume homeostasis through renal excretion into the amniotic cavity. If so, ANF is one of the determinants of amniotic fluid volume regulation. Certain reservations need to be cited, however. To justify cordocentesis, the observations were made on fetuses with significant immune hemolytic anemia and pretransfusion ANF concentrations tended to be depressed, although intragroup variability in both control and test subjects was wide. Each fetus, in connection with cordocentesis, received pancuronium and furosemide. Neither is likely to cause direct changes in ANF production or its release, but indirect effects of these agents are possible.—T.H. Kirschbaum, M.D.

Effects of Maternal Hyperglycemia on Fetal Renal Function in Sheep
Smith FG, Lumbers ER (Univ of New South Wales, Kensington, Australia)
Am J Physiol 255:F11–F14, July 1988 1–6

The composition of amniotic and allantoic fluids may be regulated by transfer across the membranes, and their volumes may be regulated by

the rate of production of fetal urine. To determine whether fetal hyperglycemia caused by a change in maternal plasma glucose levels affects fetal renal function and to establish the mechanisms underlying any such effect, 10 chronically catheterized fetal sheep were studied after infusion of 100 gm of glucose into the ewe over 30 minutes.

Fetal blood glucose levels increased within 15 minutes of infusion completion from a mean of 15.75 mg/dl to 195.4 mg/dl. A significant elevation in the fetal glomerular filtration rate from a mean of 2.73 ml/minute to 3.65 ml/minute was observed within 1½ hours of infusion completion. The urine flow rate rose from a mean of 0.38 ml/minute to 0.63 ml/minute, and sodium excretion rose from a mean of 18.42 μmol/minute to 38.4 μmol/minute within 2½ hours of infusion completion. The fraction

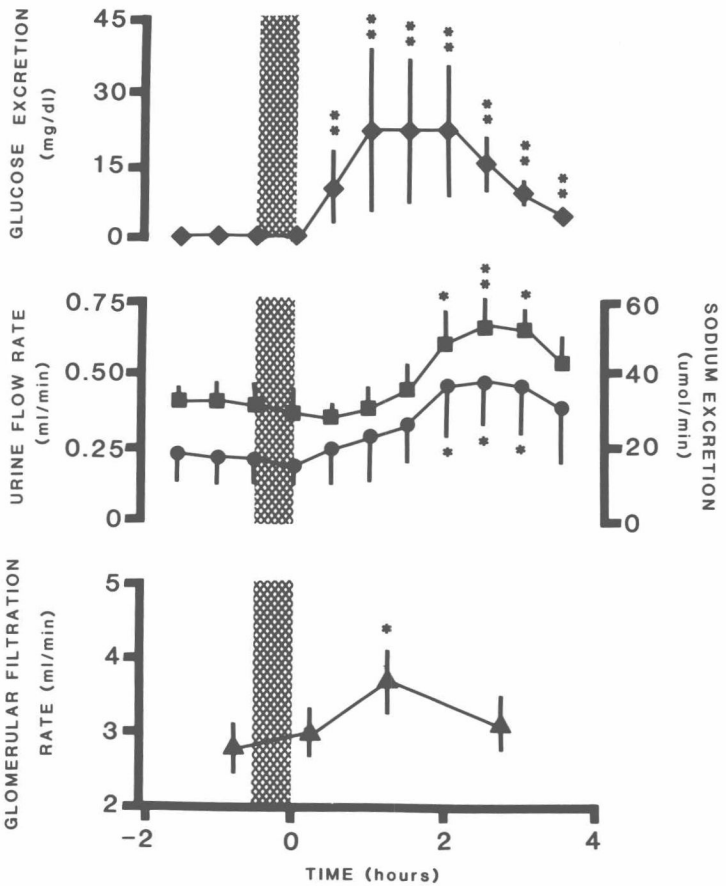

Fig 1–2.—Means ±SE of fetal glomerular filtration rate *(triangles)*, fetal urine flow rate *(squares)* and sodium excretion *(circles)*, and fetal glucose excretion *(diamonds)* before and after infusion of glucose to ewe *(shaded areas)*. Time 0 indicates completion of glucose infusion; * and ** denote significant changes from control levels. (Courtesy of Smith FG, Lumbers ER: *Am J Physiol* 255:F11–F14, July 1988.)