

## **MEDICAL THERAPY TO THE FETUS**

The human fetus has for centuries remained a medical recluse in an opaque womb. The concept of the fetus as a patient is alarmingly modern, as in earlier days there were no diagnostic or therapeutic measures available to assess the severity of fetal involvement, until after delivery. Experience in the management of fetal disorders is limited and the optimal management of each disorder is still in evolution. Opinion about the treatment of each fetal problem must hence be tentative and open to revision in relation to rapidly growing knowledge and experience.

For decades drugs and other agents have been administered to pregnant women for treatment of fetal disorders in the hope of improving postnatal adaptation(1). The Rhesus iso-immunization model provides a successful illustration of medical intervention in the developing fetus(2). This article highlights some of the established modes of medical therapy for the fetus.

### **1. Prevention of Respiratory Distress Syndrome (RDS)**

The pioneering work of Francis Moog led to the observation that glucocorticoids were capable of accelerating developmental process in the mammalian lung. Liggins observed that when glucocorticoids triggered the onset of labor in pregnant sheep, the

lamb born prematurely had well aerated lungs, while a large number of control animals died of RDS. Subsequently, a number of prospective studies(3-5) were unanimous in their observation that exogenously administered glucocorticoids significantly decreased the incidence of RDS in preterms below 34 weeks gestation. The mode of glucocorticoid action is believed to be either increased release of surfactant from granules in alveolar type II cells or by increasing lecithin synthesis.

In a study recently concluded by us at the Wadia Maternity Hospital in Bombay (data under publication), cord blood cortisol levels were estimated in preterms (<34 weeks gestation) whose mothers had or had not received antenatal glucocorticoid therapy. A significant reduction in the incidence of RDS was noted in those neonates whose mothers had received at least two doses of 12 mg IM dexamethasone administered at least 24 hours before delivery.

### **2. Maternal Treatment with Phenobarbitone for Prevention of Neonatal Jaundice**

Interest in using phenobarbitone to decrease neonatal hyperbilirubinemia was generated following the retrospective study by Trolle(6) who reported a diminished incidence of neonatal jaundice among the offsprings of epileptic women who were treated with phenobarbitone during pregnancy.

The daily administration of 60 to 100 mg of phenobarbitone to the mother for more than 10 days before delivery reduces the mean serum bilirubin level on the fourth postnatal day by approximately half. The combination of antenatal and postnatal

(total dose 25-50 mg over 3 to 5 days) is the most effective schedule in neonates without hemolytic disease(7). From the practical viewpoint this schedule may be suitable for the management of preterm labor and threatened delivery. No significant difference in neonatal behavior pattern has been reported following intrapartum exposure to this drug(8).

### **3. Prevention of Fetal Growth Retardation with Low Dose Aspirin Therapy**

The efficacy of aspirin in the prevention of arterial thrombosis has been known for many years. Several studies have shown that low dose aspirin (50-150 mg/day) can prevent eclampsia and fetal growth retardation(9, 10). This effect of aspirin is linked to its action of inhibiting thromboxane production in the human placenta. Results of the EPREDA trial(9) revealed that the mean birth weight of neonates born to mothers who received low dose aspirin from 20 weeks gestation till delivery was 200-225 g higher than those whose mothers had received a placebo.

Aspirin does not increase the overall risk of fetal malformations, nor increases the risk to abnormal bleeding in the neonate or the risk to premature closure of fetal ductus arteriosus(11). Thus, there has been no evidence as yet that low dose aspirin poses any risk to the mother or fetus. Although preliminary data with this drug is encouraging, only large multicentric study data will finally ascertain both the safety and efficacy of this modality of therapy.

### **4. Prenatal Vitamin K Supplementation to Prevent Neonatal Hemorrhagic Disease**

Newborns, particularly preterms and those exposed to anticonvulsant or antitu-

berculous therapy *in utero* show a bleeding tendency because of vitamin K deficiency. Recent reports(12,13) have suggested that vitamin K<sub>1</sub>, (phyloquinone) crosses the placenta. Thus adequate dosage and duration of oral vitamin K<sub>1</sub> therapy to pregnant women could replace prophylaxis with vitamin K injection at birth and may be effective in the prevention of both early (within 48 hours of birth) and classic hemorrhagic disease. Oral vitamin K<sub>1</sub> prenatally administered in daily doses of 10 mg for 10-15 days activates vitamin K dependant coagulation factors for atleast the first 5 days of postnatal life. Thus, oral prenatal vitamin K<sub>1</sub> therapy may replace prophylaxis with parenteral vitamin K to the newborn.

### **5. Prenatal Management of Immune Fetal Anemia**

Fetal hydrops due to rhesus-isoimmunization induced hemolysis has been successfully treated by transfusing red blood cells into the fetus. The older practice of infusing red cells into the fetal peritoneal cavity(14) has been largely replaced in favor of the physiologically more correct mode of intravascular transfusion. This is done by percutaneous umbilical cord puncture and blood directly injected into the fetal vascular system through the umbilical vein(15-17). The procedure is usually attempted around 24-26 weeks of gestation and repeated at 10-15 days intervals till the fetus reaches a stage of maturity when safe delivery and neonatal survival becomes a reality, which is at an approximate gestational age of 34 weeks(18).

The procedure was first popularized by Rodeck(16) and subsequently with greater success and less fetal trauma by Nicolaides *et al.*(17). 'O' rhesus negative blood packed to a hematocrit of approximately 70-75%

and previously cross matched with mothers' serum is slowly infused into the umbilical vein while a close watch is kept on the fetal heart rate. The exact volume of blood to be transfused is estimated from a normogram which takes into consideration the pretransfusion hematocrit of fetal blood, the donor hematocrit, the expected hematocrit to be achieved, as also the fetal gestation(19).

Our experience at the Wadia Hospital with 8 such severely sensitized 'Rh' negative women whose fetuses had received a total of 28 ultrasound guided intrauterine intravascular transfusions into the umbilical vein between 25 to 33 weeks gestation has been extremely encouraging. The volume of blood we have transfused at a time ranged from 50 to 200 ml and the transfusion time from 30 to 60 minutes. Pre and post transfusion hematocrit was determined in all cases. Procedural problems that we encountered were transient fetal bradycardia in four instances, and difficulty in umbilical vein cannulation on two occasions. All but one baby were delivered by elective cesarean section between 34-36 weeks gestation. One baby delivered spontaneously vaginally at 28 weeks gestation and expired of severe HMD and one expired of DIC. Our procedural mortality was nil, however postnatally 2 of 8 (25%) expired.

## 6. Antenatal Medical Management of Metabolic Defects

(a) *Congenital Adrenal Hyperplasia (CAH)*: Evans *et al.* first demonstrated that the fetal adrenal gland can be suppressed pharmacologically by maternal replacement doses of dexamethasone(20), and that this helped to prevent external genital masculinization of female fetuses affected with severe form of 21 hydroxylase deficient CAH. Several such female infants with CAH who

would have been masculinized have been born with normal female genitalia after this form of fetal therapy. With the availability of a probe for the gene and the advent of first trimester chorionic villus sampling, a definitive diagnosis of an affected fetus is usually possible by DNA analysis of the chorionic villi before initiation of therapy. The current recommended protocol is to start dexamethasone 0.25 mg qid, at 7-8 weeks gestation and to perform fetal sexing and DNA analysis at 9-10 weeks. If the fetus is an affected female, then therapy is continued throughout gestation, whereas if the fetus is a male or is unaffected, then<sup>s</sup> maternal steroids are tapered off(21).

(b) *Multiple Carboxylase Deficiency and Methylmalonic Acidemia*: These metabolic defects related to Biotin and vitamin B<sub>12</sub> deficiency, respectively, are known to cause severe neonatal metabolic acidosis, brain damage and may even be fatal(22). Both these disorders can be diagnosed antenatally and can be treated with large doses of biotin 10 mg/day or vitamin B<sub>12</sub> 10 mg/day for the respective disorders. Whether there is any significant clinical benefit to the fetus by *in utero* treatment cannot be adequately assessed, but it seems likely that reducing the fetal burden should have some beneficial effect on fetal development and possibly reduce risks in the neonatal period(23,24).

(c) *Galactosemia*: An inborn error of galactose metabolism inherited in an autosomal recessive manner that results in cataracts, hepatitis, growth and ovarian failure, U can be diagnosed antenatally by studying is cultured chorionic villi. The disorder is treated postnatally by eliminating galactose from the diet; however, irreversible damage can occur to the ovaries long before birth(25). There has been speculation that

prenatal damage to the galactosemic fetus could contribute to subsequent abnormal CNS development and the female fetus may have higher incidence of amenorrhea and ovarian insufficiency. These observations have led to the speculation that galactose restriction during pregnancy may be desirable if the fetus is affected with galactosemia. Thus, anticipatory treatment in pregnancies at risk for having a galactosemic fetus must be initiated early in gestation or even pre-conceptually(26). There is little reason to believe that galactose restriction would have adverse consequences as the fetus is capable of some endogenous galactose synthesis.

### 7. Treatment of Fetal Cardiac Arrhythmias

Supraventricular tachycardia (SVT) is known to cause cardiac failure *in utero* and may lead to hydrops and death(27). Although an extremely uncommon disorder, it can be successfully treated by administration of digitalis to the mother(28). The drug crosses the placenta into the fetus and converts the SVT into a normal rate and rhythm, thereby salvaging the fetus from a potentially fatal outcome(29). Propranolol has also been used for the same purpose as a second drug of choice; however, it places the fetus at risk for hypoglycemia, bradycardia and depressed Apgar scores(30). Our experience in the treatment of fetal SVT is limited to the management of two cases, both of whom responded dramatically to the administration of maternal digoxin and in whom postnatal digoxin therapy was not required. The etiology of the fetal SVT in both these cases could; however, not be established.

Medical treatment has until now been largely directed at transplacental drug

administration with the aim of creating pharmacological alterations in the fetus. The disadvantages of transplacental treatment are: (a) placental transfer depends on the degree of maternal absorption and excretion of the drug; and (b) direct monitoring of fetal drug level is not feasible.

There is also a subset of fetal states in which something vital to fetal wellbeing is not present in sufficient quantity and supplementing the missing substance would constitute the essence of medical therapy. The list of substances that may be given therapeutically to the fetus *in utero* is certain to grow. For example it may be possible in the near future to treat the growth retarded fetus by instilling nutrients into the amniotic fluid(31) or even to administer thyroid hormone in this fashion.

There has been a considerable sobering of the initial wave of enthusiasm surrounding fetal surgical intervention and medical and pharmacological alterations in the milieu of the fetus now appears to be more promising and ultimately is likely to be the mainstay of fetal therapy(1). Our ability to diagnose a number of fetal disorders has achieved considerable sophistication. The treatment of several of these fetal conditions has now proven feasible and the treatment of more complicated disorders will expand as techniques and our knowledge improves.

The fetus could not be considered a patient until it was demystified and since then it has come a long way from the biblical "seed" to an individual with medical problems that can be diagnosed and treated. Although the fetus seldom complains, he occasionally needs a physician, and the possibility of treating certain fetal disorders before birth gives an entirely new meaning to prenatal diagnosis. The possibility of fetal

therapy raises complex ethical questions about risks and benefits and about the rights of the mother and fetus as patients. We are only beginning to address some of these difficult areas(32).

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#### REFERENCES

1. Evans MI, Schulman JD. Biochemical Fetal therapy. *Clin Obstet Gynecol* 1986, 29: 523-530.
2. Bowman JM. The management of Rh-immunization. *Obstet Gynecol* 1978, 52: 1-15.
3. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of RDS in premature infants. *Pediatrics* 1972, 50: 515-525.
4. Caspi E, Schreyer P, Weinraub Z, *et al.* Prevention of respiratory distress syndrome in premature infants by antepartum glucocorticoid therapy. *Br J Obstet Gynecol* 1976, 83: 187-193.
5. Doren TA, Swyer P, McMurray A, *et al.* Results of double blind controlled study on the use of betamethasone in the prevention of RDS. *Am J Obstet Gynecol* 1980, 136: 313-320.
6. Trolle D. Phenobarbitone and neonatal jaundice. *Lancet* 1968, 1: 251-252.
7. Wallin A, Boreus LO. Phenobarbital prophylaxis for hyperbilirubinemia in preterm infants. *Acta Paediatr Scand* 1984, 73: 488-490.
8. Valaes T, Kipouros K, Petmezaki S, *et al.* Effectiveness and safety of prenatal phenobarbital for the prevention of neonatal jaundice. *Pediatr Res* 1980, 14: 947-950.
9. Uzan S, Beaufils M, Breart G, Bazin B, Capitant C, Paris J. Prevention of fetal growth retardation with low dose aspirin. Findings of the EPREDA trial. *Lancet* 1991, 337: 1427-1431.
10. Trudinger BJ, Cook CM, Thompson RS, Giles WB, Connelly A. Low dose aspirin therapy improves fetal weight in umbilical placental insufficiency. *Am J Obstet Gynecol* 1988, 159: 681-684.
11. Sibai BM, Mirro R, Chesney CM, Leffler C. Low dose aspirin in pregnancy. *Obstet Gynecol* 1989, 74:551-557.
12. Anai T, Hirota Y, Yoshimatsu J, Oga M, Miyakawa I. Can prenatal vitamin K<sub>1</sub> (Phylloquinone) supplementation replace prophylaxis at birth? *Obstet Gynecol* 1993, 81: 251-254.
13. Lane PA, Hathaway WE. Vitamin K in infancy. *J Pediatr* 1985, 106: 351-359.
14. Liley AW. Intrauterine transfusion of fetus in hemolytic disease. *Br Med J* 1963, 2: 1107-1109.
15. Berkowitz RL, Hobbins JC. Intrauterine transfusion utilizing ultrasound. *Obstet Gynecol* 1981, 57: 33-35.
16. Rodeck CH, Nicolaidis KH, Warsof SL, Fysh WJ, Gamsu HR, Kemp JR. The management of severe rhesus isoimmunization by fetoscopic intravascular transfusions. *Am J Obstet Gynecol* 1984, 150: 769-774.
17. Nicolaidis KH, Rodeck CH, Mibashan RS, Kemp RJ. Have Liley's charts outlived their usefulness? *Am J Obstet Gynecol* 1986, 155: 90-94.
18. Whittle MJ. Rhesus hemolytic disease: Obstetrics for Pediatricians. *Arch Dis Child* 1992, 67: 65-68.
19. Parer JT. Severe Rh isoimmunization. Current methods of *in utero* diagnosis and treatment. *Am J Obstet Gynecol* 1988, 158: 1323-1329.
20. Evans MI, Chrousos GP, Mann DL, *et al.*

- Pharmacologic suppression of the fetal adrenal gland. Attempted prevention of 21 hydroxylase insufficiency congenital adrenal hyperplasia *in utero*. JAMA 1985, 253: 1015-1021.
21. Forrest M, David M. Prenatal treatment of congenital adrenal hyperplasia due to 21 hydroxylase deficiency. Seventh International Congress of Endocrinology. Abst No. 911. Quebec, Canada, 1984.
  22. Packman S. Approach to inherited metabolic disorders presenting in the newborn period. *In: Pediatrics*, 17<sup>th</sup> edn. Eds Rudolph AM, Haffman JCE, Norwalk, CT. Appleton-Century-Crofts, 1982, pp 256-259.
  23. Nyhan WL. Prenatal treatment of methylmalonic aciduria. N Engl J Med 1975, 293: 353-354.
  24. Packman S, Cowan MJ, Golbus MS, *et al*. Prenatal treatment of biotin responsive multiple carboxylase deficiency. Lancet 1982, 1: 1435-1439.
  25. Chen YT, Mattison DR, Feigenbaum L, *et al*. Reduction in oocyte number following prenatal exposure to a high galactose diet. Science 1981, 214: 1145-1147.
  26. Segal SS. Disorders of galactose metabolism. *In: The Metabolic Basis of Inherited Disease*, 5th edn. Eds Stanbury JB, Wyngarden JB, Frederickson DS. New York, McGraw Hill, 1983, p 167.
  27. Holzgreve W, Curry CJR, Golbus MS, *et al*. Investigations of non immune hydrops fetalis. Am J Obstet Gynecol 1984, 150: 805-812.
  28. Kleinman CS, Copel JA, Weinstein EM, *et al*. *In utero* diagnosis and treatment of fetal supraventricular tachycardia. Semin Perinatol 1985, 9: 113-129.
  29. Gough JD, Keeling JW, Caste B, Iliff PJ. The obstetric management of non immunological hydrops. Br J Obstet Gynecol 1986, 93: 226-234.
  30. Gladstone GR, Hardorf A, Gersony WM. Propranolol administration during pregnancy: Effect on fetus. J Pediatr 1975, 86: 962-964.
  31. Saling E, Kynast G. A new way for the paraplacental supply of substances to the fetus. J Perinat Med Suppl 1981, 1: 144-145.
  32. Harrison MR, Filly RA, Golbus MS. Management of the fetus with a correctable congenital defect. JAMA 1981, 246: 774-780.
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