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Postmaturity and Placental Dysfunction Syndrome were studied by Ralph H. Kunstadter and Sidney E. Schnitz[1] (Michael Reese Hosp.). The terms are not synonymous. Postmaturity, defined by various authors as a gestation exceeding the normal by from 7 to 20 days, is considered here to mean a gestational age of 294 days or more. Postmaturity occurred 247 times among 2,877 deliveries and was over 299 days in 132 of the babies. Clifford first described the syndrome and divided it into 3 stages. In the 1st stage, the infants are long and thin with dry, cracking, parchment-like skin; the 2d stage is more severe, and the infants show green staining of the skin and umbilical cord; in the 3d and most severe stage, the infants show yellow staining. He suggested that the term "placental dysfunction syndrome" is better than "postmaturity syndrome" because the condition is not entirely limited to postmature infants and most postmature infants do not have the syndrome.

Of the 247 infants, 11 had the signs described by Clifford; 6 showed respiratory difficulties. One neonatal death occurred among the group with the syndrome; among the entire group of 247 postmature babies, perinatal mortality was 5 (2.02%). All perinatal deaths occurred in babies of mothers aged 26 or over. Of 252 controls, only 1, with a gestational age of 280 days had the syndrome. The postmature and control infants did not differ significantly in average weight and length.

Experiments in animals and human beings suggest that after term, the placenta is no longer able to provide adequate nutrition to the fetus. If pregnancy is prolonged, the fetus may be forced to live off its own tissues, and some authors believe that if a baby is postmature 20 days or more, it begins to lose weight. Diminished permeability of the placenta reduces fetal oxygenation. Oxygen content decreases significantly in the umbilical vein by the 43d week of pregnancy; the fetus at this time is able to receive just enough oxygen

(1) J.A.M.A. 161:1551-1554, Aug. 18, 1956.

from the blood for its resting needs and returns little or no oxygen to the placenta. Increased activity or infection of the mother may lead to insufficient oxygen saturation of the blood supplying the fetal brain and may produce such symptoms as relaxation of the anal sphincter (with passage of meconium), postnatal dyspnea and ultimate death. A reduced amount of vernix leads to maceration, dryness and peeling of the skin after birth. Meconium stains the skin and umbilical cord.

A higher perinatal mortality in postmature infants is reported by some authors than by this study. In Clifford's group of postmature infants, 90% of the mortalities occurred in infants born of women with only 1 delivery in 10 years. In this group postmaturity ranked second only to prematurity as a cause of fetal and neonatal mortality. In Clifford's series of postmature infants born to multiparas, mortality did not increase significantly. As many obstetricians do not recognize the concept of postmaturity or the placental dysfunction syndrome, induction of labor or cesarean section is not often done in a woman with prolonged pregnancy. Obviously, these are the main ways of reducing incidence of the disease.

► [The authors agree with previous investigators that the clinical picture called the "placental dysfunction syndrome" occurs more frequently in postmature infants than in infants born at term. However, they find no higher mortality rate in the postmature infant. This point needs further study, for if there is no greater risk for the postmature than the full term infant, the obstetrician's failure to "recognize or accept the concept of postmaturity" is a sound one, unalterable by any debate by the pediatrician.

If the mortality rate proves to be higher, then we must determine whether or not interference with pregnancy lowers the rate.

Dr. Stewart H. Clifford was asked if he could reconcile the authors' findings with his own in which he recorded a higher mortality rate for postmature infants (see 1954-55 YEAR BOOK, p. 28).

"We both agree on the incidence rate of postmaturity; they agree on the occurrence of a placental dysfunction syndrome as I described and found the incidence of the condition to be 11%. We agree that the length and weight are of little significance unless associated with placental dysfunction and then the weights are low for length and age.

"The only issue I could take with the authors is their comparing perinatal mortality (294 days or over—20/1,000; 300 days or over—30/1,000) with figures 'for infants of all gestational ages' and concluding that 'perinatal mortality does not appear to be significantly higher in postmature babies than in full-term babies'. In the first place, the recorded mortality may be low due to the small total series of 2,877 deliveries. In 4,633 deliveries, I found the perinatal mortality for 290-299 days to be 27/1,000

and for 300-339 days to be 68/1,000. Arne Lindell (Prolonged pregnancy, Acta obst. et gynec. scandinav. 35:136, 1956) found the perinatal mortality for 294 days and over in 21,281 cases from Stockholm to be 39/1,000 and for 25,100 cases from Uppsala to be 36/1,000. In the second place, it would seem more reasonable to compare results with the perinatal mortality for gestational ages 280 days ± 2 weeks rather than that for 'all gestational ages' that begin at 28 weeks or 400 Gm. and include this early high mortality premature group. Our perinatal mortality for 270-289 days was 12/1,000; Lindell's for 40 ± 2 weeks was 12/1,000 for both the Stockholm and Uppsala series. If this latter type comparison had been used by the authors, their conclusions might have been that in their series postmature infants of over 294 days had twice, and those over 300 days had three times the perinatal mortality to be expected in term babies."—Ed.]

Meconium Staining of Newborn Infants was studied by Murdina M. Desmond, John E. Lindley, Jack Moore and Clarence A. Brown[2] (Houston), who analyzed incidence of meconium-stained amniotic fluid at delivery and prognosis for infants with this classic sign of fetal distress. The characteristic appearance of infants exposed to such fluid, the nature of the pigments involved, and factors concerned in staining of the skin and nails by the pigment are also discussed. Clifford contends that yellow vernix is the result of prolonged exposure to amniotic fluid containing meconium. This, in turn, is related to fetal anoxia secondary to placental dysfunction. According to Van Liere, the sequence in hypoxia is hyperperistalsis followed by ileus and ultimately relaxation of the sphincter concomitant with shock and flaccidity.

Among 3,865 consecutive deliveries, meconium-stained amniotic fluid was present in 407 or 10.9%. With correction for infants with blood incompatibility, high intestinal obstruction and breech delivery, incidence is reduced to 9.6% which is almost twice the highest reported incidence in the literature (5%) and much higher than the 0.5 and 3% given in various reports. Most of these infants were of term weight. The percentage of premature infants was actually less than in the controls. However, neonatal mortality was much increased—3.4% opposed to 1.5% in controls. Morbidity was also increased. In the affected group, 13.4% had apnea neonatorum (3.2% in controls), and 78 infants in the meconium-stained group had some difficulties in the neonatal period, against 25 in controls.

(2) J. Pediat. 49:540-549, November, 1956.

Meconium derives its color from biliverdin and bilirubin excreted by the fetal biliary tract. It is first found in the gastrointestinal tract after the 4th or 5th gestational month. Color ranges from a mustard yellow to green-black. Spectrophotometry of amniotic fluid with meconium showed a uniform peak at 460 mμ, typical of commercial bilirubin. Vernix and nails are stained yellow, regardless of the color of the meconium-containing amniotic fluid, but the umbilical cord and superficial skin assume the same color as the fluid, yellow, green or bronze. The feet of normal newborns were covered with rubber gloves and immersed in meconium-containing solution; it was found that a minimum of 4-6 hours was required for staining the nails. Vernix acquires a yellow stain after 12-14 hours' exposure to meconium in vitro. The capacity of bilirubin to bind to protein may explain the yellow color of skin and nails following exposure to meconium. The placenta also tends to assume the color of the amniotic fluid. The pigment is deposited on the fetal surface and washes off readily under running water.

The authors found a long wave Wood's light helpful in detecting meconium-stained infants, whose skin would show a dull orange-red fluorescence at the free nail borders, periungual tissues and over desquamating or macerated skin. Yellow vernix may not show this phenomenon. Normal skin appears purple. The degree of fluorescence begins to fade in a few hours, usually disappearing after 24. During such examinations, the eyes of the infant must be protected. Caution in interpretation is advised, for a glowing yellow-green fluorescence may be found if the mother has been given vitamin B complex or a tetracycline shortly before delivery.

Hyaline Membrane Disease: Preclinical Roentgen Diagnosis; Planned Study. S. B. Feinberg and M. E. Goldberg[3] tried to evaluate early x-ray lung changes occurring before manifestation of respiratory distress by taking chest films routinely of premature newborn infants, those delivered by section and those born of diabetic mothers. The first film was taken as soon after delivery as possible, or at least with-

(3) Radiology 68:185-192, February, 1957.

in the first hour of life. The follow-up films were taken at 2, 4, 8 and 24-hour intervals. If necessary, further examinations were done. In all, 89 infants were followed.

The 1-2 hour interval x-rays were of the greatest diagnostic value. In 7 of the 8 proved cases of hyaline membrane

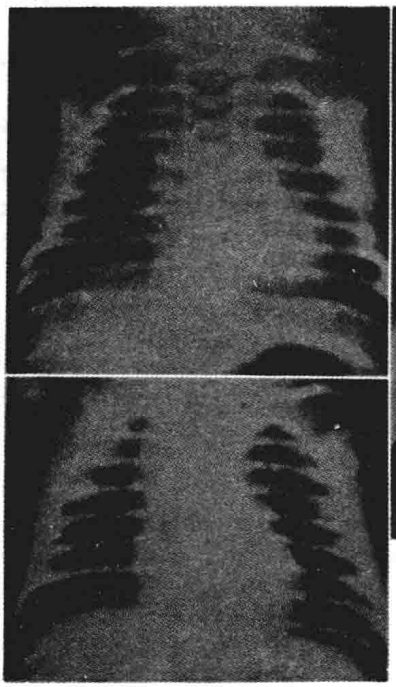

Fig. 1 (above left).—In infant, 5 lb. 10 oz., born by section at 40 weeks and normal at birth, 45-minute film shows bilateral granularity suggesting hyaline membrane disease.

Fig. 2 (above).—Enlargement of right lower lung field showing diffuse granularity. At 6 hours respiratory rate began to increase, until at 24 hours it reached 60/minute. No cyanosis developed.

Fig. 3 (left).—Film showing improvement after respiratory rate began to slow at 48 hours.

(Courtesy of Feinberg, S. B., and Goldberg, M. E.: Radiology 68:185-192, February, 1957.)

disease unequivocal abnormality was demonstrable on the initial film (Figs. 1-3).

Early diagnosis of hyaline membrane disease may be fostered by institution of a simple chest x-ray routine. This should include at least one examination within the first hour as well as a second hour follow-up film in premature infants,

those born of diabetic mothers and those delivered by section.

The descriptions of earlier granularity and later eventual frank generalized atelectasis, especially in fatal cases, are reliable diagnostic criteria for advanced hyaline membrane disease. If the finely granular and increased bronchovascular pattern were recognized before the development of physical signs, the diagnosis might be anticipated earlier.

► [The authors' findings confirm earlier observations that pulmonary hyaline membranes may be diagnosed by roentgenograms. We are not convinced that these infants show no respiratory distress soon after birth; careful observation immediately following delivery together with respiratory rates will show that air exchange is not completely normal.—Ed.]

Occurrence of Anemia of the Newborn in Association with Appearance of Fetal Hemoglobin in Maternal Circulation was demonstrated by Walter J. O'Connor, George Shields, Schuyler Kohl and Marvin Sussman[4] and constitutes evidence for hemorrhage of the fetus into the maternal circulation. Spectrophotometric hemoglobin determinations were made on capillary blood of infants who appeared pale in the nursery, and blood samples of these infants' mothers were analyzed for fetal hemoglobin by the alkali denaturation technic. Controls were 8 normal adults. The initial hemoglobin level in 17 pale infants was 10-18 Gm./100 ml. Mothers of these babies showed fetal hemoglobin in the blood. By comparison, 24 infants used as controls whose mothers showed no fetal hemoglobin had 13.5-24.6 Gm. hemoglobin/100 ml., a statistically significant difference. Of the 17 infants whose mothers had fetal hemoglobin in their circulation, 7 were premature by weight.

The clinical aspect of infants whose mothers had circulating fetal hemoglobin varied from pallor to acute hemorrhagic shock, severe enough to require blood transfusions in 1. Fetal hemorrhage into the maternal circulation or into the uterine cavity may be a cause of fetal death and may resemble asphyxia pallida. Cervical blood collected from 9 women with vaginal bleeding during the last trimester of pregnancy showed fetal hemoglobin in 7; of these, 4 gave birth to stillborn infants. Of the 2 women without fetal hemoglobin in the circulation, 1 delivered a stillborn infant.

(4) Am. J. Obst. & Gynec. 73:768-776, April, 1957.

Fetomaternal Transfusion: Another Cause of Posthemorrhagic Anemia in Newborn. Although erythroblastosis fetalis accounts for about 95% of cases of anemia occurring during the first 2 days of life, failure properly to diagnose the other 5% may cause delayed or improper treatment. Virtually all nonhemolytic anemias at this age are caused by hemorrhage and rarely by syphilis, neoplasms, leukemia or infection, John H. Colebatch, David Pitt and T. G. Maddison[5] (Melbourne) recognize at least 6 mechanisms by which hemorrhage may arise from the region of the placenta: placenta previa, placenta previa cesarea, abruptio placentae, vasa previa, rupture of the cord and ruptured vessels in the fetal aspect of the placenta. To these are added intracranial hemorrhage, trauma, slipped cord ligature and hemorrhagic disease. At the authors' hospital, stillbirth or neonatal death occurs in 17% of cases of placenta previa. Generally, the mother requires transfusion though the infant rarely has much anemia if delivered per vaginam. Damage to the placenta at section may lead to rapid exsanguination of the infant. Abruptio placentae more often causes fetal anoxia than posthemorrhagic anemia. Vasa previa, a rare condition, is usually associated with velamentous insertion or other placental anomaly. Rupture of the unprotected vessels is associated with at least 50% risk of stillbirth or neonatal death.

Another mechanism of posthemorrhagic anemia, first suggested by Wiener, involves hemorrhage from the fetal surface of the placenta, through ruptured blood vessels, into the mother's circulation. Wiener described 3 cases in which the infant was extremely pale at birth, with weak cord pulsations and a hemoglobin level less than 9 Gm./100 ml. Three similar cases are presented by the authors, in which evidence of fetomaternal transfusion is adduced from elevated concentrations of fetal hemoglobin in the mother's blood post partum, which declined significantly during subsequent weeks.

The usual clinical features by which posthemorrhagic anemia may be recognized in the first 2 or 3 days of life are: pallor, weakness, loss of tone, tachycardia, no undue jaun-

(5) M. J. Australia 2:209-212, Aug. 11, 1956.

dice, no hepatosplenomegaly, little benefit from oxygen and dramatic effect of transfusion.

► [We were not very impressed by the percentages of fetal hemoglobin in the maternal blood and hesitated to accept these cases as proven instances of the fetus bleeding into the mother. Dr. Bruce Chown commented that "while these may well have been cases of fetal bleeding, I cannot accept them as proved."—Ed.]

Kernicterus Not Associated with Hemolytic Disease is reported by Wong Hock Boon[6] (Gen'l Hosp., Singapore). During 10 months, 96 infants, under age 1, were hospitalized for jaundice. All were tested for Rh and A-B-O antibodies and the Coombs antiglobulin test was done, but only twice was jaundice caused by isoimmunization (once due to Rh incompatibility and once to A-B-O incompatibility). There were, however, 26 patients with symptoms, signs or pathologic lesions of kernicterus. These infants were all full term, under age 15 days, and showed no evidence of isoimmunization. The criteria for diagnosis were a high serum bilirubin level with or without severe jaundice, with neurologic signs, and evidence of bile staining in the brain nuclei at autopsy in patients who died. The clinical features of these 26 closely resembled each other.

CASE 1.—Girl, aged 6 days, was hospitalized with history of fever with jaundice for 1 day. She was a second child, born at full term by normal delivery, and had a birth weight of 7 lb. The first child was well. Temperature was 101 F. Serum bilirubin level was 32.5 mg./100 ml. The jaundice disappeared completely after 4 months, but the limbs were still slightly stiff.

CASE 2.—Boy, aged 10 days, had jaundice from the 3d day of life and diarrhea for 4 days before hospitalization. He was a third child, born at full term by a normal delivery. The throat was injected and the umbilicus was septic. The liver was palpable 1½ fingerbreadths, but the spleen was not felt. He died the next day. Autopsy showed bright yellow staining of the basal nuclei. (The same autopsy findings were seen in another infant with jaundice and a septic umbilicus.)

All 26 patients refused food, 73% showed fever, 42.3% vomiting, 19.2% breathlessness and 15.4% convulsions. All had jaundice, 73% were drowsy, 61.5% had manifest concomitant infection, 46.1% had stiffness of the limbs or neck and 7.7% had different degrees of dehydration. Kernicterus occurred when the serum bilirubin level was definitely high.

(6) Arch. Dis. Childhood 32:85-90, April, 1957.

The lowest level was 23 mg./100 ml. and the highest 54 mg./100 ml. in patients who had serum bilirubin estimations.

Hemolytic disease was excluded by all available methods. Foci of infection were demonstrable in 61.5% of patients. Such foci may affect the liver, producing a toxic hepatitis. If this is associated with the immature liver of the newborn and the physiologic excessive breakdown of red cells, then an excess of bilirubin will accumulate in the blood. However, onset of jaundice in 14 patients was in the first 2 days of life, which is extremely early for a toxic hepatitis from sepsis.

► [This is an amazing series—26 cases with autopsy findings or clinical signs suggestive of kernicterus in full-term infants, all within a period of 9 months and without evidence of isoimmunization. In most instances there was evidence of infection, but the author says nothing about blood cultures nor is there any mention of lumbar punctures. Most of these patients would appear to have had sepsis, and we submit that this accounted for the hyperbilirubinemia.

Any newborn infant who shows abnormal levels of indirect bilirubin in the absence of isoimmunization must be considered to have sepsis. Immediately after a blood culture and lumbar puncture are made, antibiotic therapy should be started. Obviously there are other possible causes, such as congenital hemolytic anemia, nonspherocytic anemia, etc., but these are rare whereas sepsis is relatively frequent. If sepsis proves to be the wrong diagnosis, no harm will have been done by the antibiotics. On the other hand, success in treating neonatal sepsis is entirely dependent on rapidity of specific therapy.—Ed.]

Kernicterus in the Premature. Marcel Lelong[7] (Paris), reviewed the records and autopsy findings in 13 cases. Kernicterus without fetomaternal blood incompatibility, like retrolental fibroplasia, is a birth complication associated with extreme prematurity. Clinical diagnosis is easy, but problems of causation are still unsolved. Some investigators stress the importance of anoxia as the primary cause with hyperbilirubinemia a secondary factor; others attribute the disease primarily to the toxic effect of hyperbilirubinemia on the newborn and especially on the premature. Pigment found in the gray nuclei, like that of the serum, of premature infants with kernicterus is indirect bilirubin, which is strongly fixed in the brain (in association with a lipid), whereas indirect bilirubin is never retained by the brain. After birth, indirect bilirubin, set free in large quantities in the blood, should normally be converted by the liver into

(7) Ann. paediat. 187:257-262, September, 1956.

direct bilirubin, but if the infant is premature, this conversion is hampered, and the level of indirect bilirubin in the blood remains high. Prematurity thus explains both the high levels of indirect bilirubin resulting from immaturity of the liver and the fragility of the cerebral tissues resulting from immaturity of the nerve cells and anoxia. These and other clinical and experimental findings may be taken as the basis for a fairly coherent combined hypothesis of the origin of kernicterus in the premature and the newborn. Kernicterus is proper to the newborn; the biliary impregnation of the nerve centers is caused by indirect bilirubin and is facilitated by the increased sensitivity of the nerve cells, which, in turn, is due to their immaturity and to anoxia; the flooding of the brain with indirect bilirubin is related to immaturity of the liver. As a practical result of this hypothesis, it should be considered whether exchange transfusion is not indicated in all forms of icterus in the newborn, whatever the cause, as soon as the indirect bilirubin passes a certain limit. Only the difficulties connected with performing this procedure in extremely premature infants should restrict its application.

Effect of Vitamin K Dosage on Plasma Bilirubin Levels in Premature Infants is reported by J. P. Bound and T. P. Telfer[8] (Univ. College Hosp., London), who compare two groups of premature infants. The only significant variable was the dosage of vitamin K analogue, Synkavite®. Plasma bilirubin levels in venous blood were estimated on the 5th day. Among 55 infants who received 30 mg. Synkavite® (10 mg./day for 3 days), the mean 5th-day bilirubin level was 15.4 mg./100 ml., and 21 had levels over 18 mg./100 ml. By contrast, in 51 infants receiving only 1 mg. Synkavite®, the mean plasma bilirubin level on the 5th day was 9.7 mg./100 ml., and only 2 had levels over 18 mg./100 ml. (Fig. 4). Both these differences were statistically significant. Two infants in the high dosage group died of kernicterus, and 3 had transient symptoms of the condition. All 5 of the affected infants had bilirubin levels between 22 and 34 mg./100 ml. In no infant in the low dosage group did kernicterus develop.

(8) Lancet 1:720-722, May 19, 1956.

The mechanism of Synkavite® in increasing blood bilirubin in premature infants is uncertain although it may be a cause of actual hemolysis or may interfere with the capacity of the liver to handle bilirubin. With these and other reports indicating a toxic action of excessive dosages of this material, the practice of giving inordinate amounts of Synkavite® should be abandoned. Doses of 0.5-1 mg. are adequate for

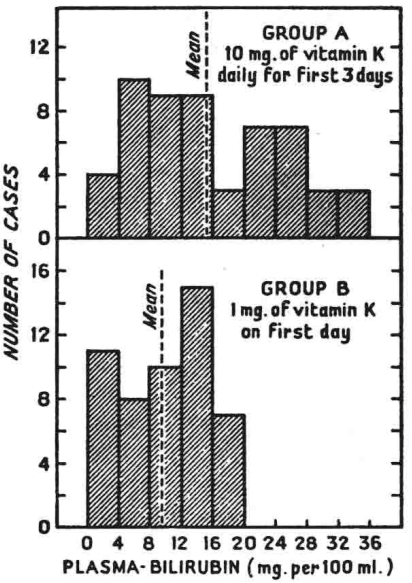

Fig. 4.—Distribution of 5th-day plasma bilirubin levels in premature infants according to vitamin K dosage. (Courtesy of Bound, J. P., and Telfer, T. P.: Lancet 1:720-722, May 19, 1956.)

prevention of postnatal hypoprothrombinemia, and adoption of this dosage is encouraged.

Effect of Large Doses of Synkavite® in the Newborn appears to be increased bilirubinemia and development of kernicterus in susceptible infants, according to Thomas C. Meyer and Joan Angus[9] (Birmingham, England). During the past 4 years, various reports have tended to incriminate this synthetic vitamin K analogue as a contributing factor to kernicterus. Nurseries have noted increased incidence of

(9) Arch. Dis. Childhood 31:212-215, June, 1956.

the disease concurrent with increased routine doses of Synkavite® in newborns. Hemoglobinemia has been produced in experimental rats with vitamin E deficiency by administration of vitamin K in massive doses.

Bilirubin levels were determined in infants of various weight groups, half of whom were given Synkavite®. Full-term babies were given 10 mg. once only; prematures were given daily doses of 10 mg. until feeding was begun, with average total dose of 30 mg. Venous blood was taken for bilirubin determinations. The mean serum bilirubin level

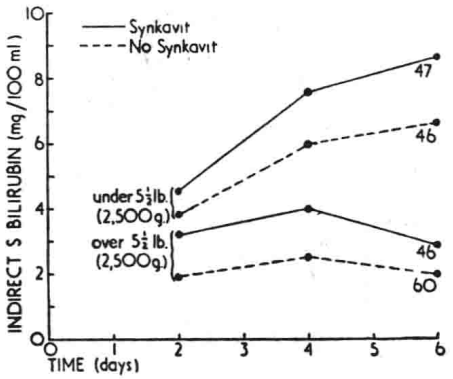

Fig. 5.—Bilirubin levels in 106 full-term babies and 93 prematures with and without Synkavite®. (Courtesy of Meyer, T. C., and Angus, J.: Arch. Dis. Childhood 31:212-215, June, 1956.)

was higher in both weight groups (Fig. 5) although there was wide overlap. Breakdown into various weight groups showed consistently higher levels in those given Synkavite®, except in the 2,000-2,500 Gm. group, in which there was little difference. Crosse observed a concomitant increase in incidence of kernicterus with increasing Synkavite® dosage over 10 years when composition of the nursery studied did not materially change (table).

The mode of action of Synkavite® appears to be hepatotoxic and/or hemolytic, but whatever the mechanism, there is little doubt that intramuscular Synkavite® in large doses causes some elevation of serum bilirubin levels. In a premature infant with poor liver function, this may be sufficient to