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Urinary excretion of prostaglandin E and $F_{2\alpha}$ in healthy newborn infants and in infants with hyaline membrane disease

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Urinary PGE and $PGF_{2\alpha}$ excretion was estimated in 11 healthy full-term (mean birth weight, 3327 g; mean gestational age, 39.2 weeks), 15 healthy preterm (mean birth weight, 1722 g; mean gestational age, 32.1 weeks) and in 9 preterm infants suffering from hyaline membrane disease (HMD) (mean birth weight: 1454 g, mean gestational age: 31 weeks).

Measurements were carried out on the 1st, 3rd and 5th days of life by radioimmunoassay, using Clinical Assays Inc. RIA kits.

Urinary PGE excretion on the first day of life was 3.76 ± 0.41 ng/day, 2.43 ± 0.65 ng/day and 1.19 ± 0.27 ng/day for healthy full-term, healthy premature and premature infants with HMD, respectively. The differences were significant at the level of $p < 0.05$. With advancing postnatal age urinary PGE excretion markedly increased in each group ($p < 0.05$).

Urinary $PGF_{2\alpha}$ excretion on the first day was 10.8 ± 2.0 ng/day in full-term, 6.6 ± 2.2 ng/day in healthy premature and 4.35 ± 1.9 ng/day in premature infants with HMD. Then an inconsistent rise could be observed without statistically significant difference between the individual groups of various postnatal age and between the different groups of the same postnatal age.

The decreased renal PGE production is suggested to be involved in the pathomechanism of HMD.

The prostaglandins (PG) are well-known to be involved in the regulation of a number of biological processes, but their importance in perinatal pathophysiology is not well understood.

High plasma PGE and $F_{2\alpha}$ levels were found in pregnant women [5, 7], and the level rose further during labour and delivery [17, 22, 26]. PGs cross the placenta freely and their concentration is higher in cord blood than in the blood of young infants, children or adults [30, 34, 35]. The increased PG production seems to have an important role in maintaining fetal circulation in utero [20, 31, 32, 33] and also in normal postnatal cardiopulmonary adaptation [8, 9, 14, 21, 27, 28].

As about 90% of PGE and F is metabolized in the lung during one circulation through the pulmonary vasculature [12] the maternal PGs may only have a short-term effect on the neonate, and after the immedi-

ate postnatal period the plasma level is governed mainly by the newborn's own PG production.

In an attempt to provide information on the role of PGs in neonatal adaptation, a study was made to assess neonatal PG production by measuring urinary excretion of PGE and $F_{2\alpha}$ in full-term and healthy preterm infants and also in those with hyaline membrane disease (HMD).

Material and Methods

Three groups of male newborn infants were selected for the study.

Group I comprised 11 healthy full-term newborn infants with a mean birth weight of 3327 g (range, 2750—4400 g) and mean gestational age of 39.2 (range, 37—41) weeks.

Group II consisted of 15 healthy preterm infants with birth weight and gestational age varying between 980 and 2350 g (mean, 1722 g) and between 29 and 34 weeks (mean, 32.1 weeks), respectively.

The infants of groups I and II after a normal pregnancy were delivered vaginally; their one-minute Agpar score was more than 7.

Group III included 9 preterm infants with HMD. Their mean birth weight and mean gestational age was 1454 g and 31 weeks (ranges, 850—2580 g and 26—36 weeks), respectively.

The diagnosis of HMD was based on clinical evaluation (tachypnea, retractions, expiratory grunting and the need of increased inspiratory oxygen concentration to maintain arterial oxygen tension above 50 mm Hg) and confirmed by chest X-ray examination. Five infants survived, 4 died on the 2nd, 3rd and 4th days of life; autopsy revealed HMD and intraventicular haemorrhage in all of the latters.

Urinary PG E and $F_{2\alpha}$ excretion was determined on the 1st, 3rd and 5th days of life. Urine was fractionally collected for 24 hours. The specimens were refrigerated, pooled and stored at −20 °C until analysis. Immunoreactive PGE and $PGF_{2\alpha}$ were measured by radioimmunoassay using Clinical Assays Inc. RIA kits. Each sample was assayed in duplicate and the mean was calculated.

The extraction and assay procedure followed the method of Jaffe et al. [25] and Gutierrez—Cernosek et al. [19] with some modifications. Ten ml urine was used for analysis. Neutral lipids were removed with petroleum ether and PGs extracted with ethyl acetate: isopropanol : 0.2 NHCl 3 : 3 : 1. PGs were fractionated using silicic acid column chromatography and the fractions were eluted with a mixture of benzene — ethyl acetate — methanol. For PGE determination the extract was converted to PGB by 1 N NaOH and radioimmunoassayed with PGB antibody.

In our laboratory the normal value for adults ranged from 55 to 115 ng/day (mean, 75 ng/day) for PGE, and from 82 to 195 ng/day (mean, 132 ng/day) for $PGF_{2\alpha}$.

Statistical evaluation was done by Student's t test.

Results

Postnatal urinary PGE excretion in the three groups is shown in Fig. 1. On the first day of life, PGE excretion in group I was 3.76 ± 0.41 ng/day, in group II 2.43 ± 0.65 ng/day ($p < 0.05$), and in group III 1.19 ± 0.27 ng/day ($p < 0.05$). With advancing age, PGE excretion increased in each group ($p < 0.05$), but most rapidly in infants recovering from HMD.

On the 3rd and 5th days of life, there was no significant difference between the three groups.

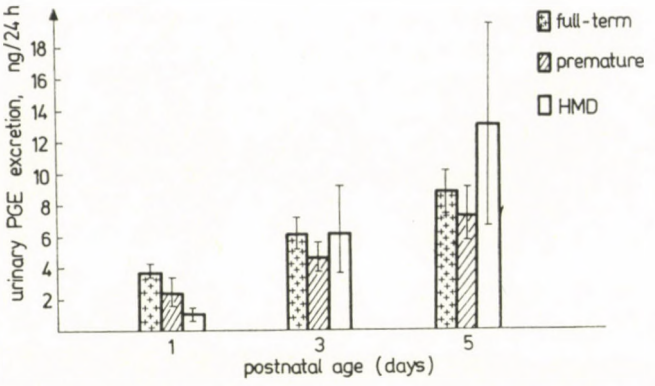

FIG. 1. Urinary PGE excretion in healthy term and healthy preterm infants and in preterm infants with HMD during the first week of life

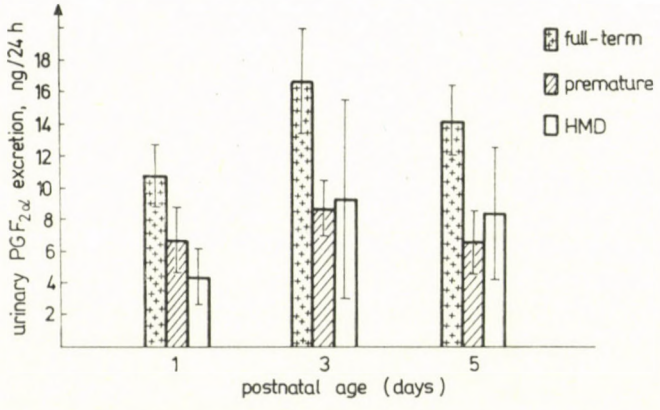

FIG. 2. Urinary $PGF_{2\alpha}$ excretion in healthy term and healthy preterm infants and in preterm infants with HMD during the first week of life

Fig. 2 shows urinary $PGF_{2\alpha}$ excretion as a function of postnatal age. In group I the mean was 10.8 ± 2.0 ng/day; in group II, 6.6 ± 2.2 ng/day; and in group III, 4.36 ± 1.9 ng/day, much higher than the respective values for PGE excretion on the first day of life.

Subsequently, an inconsistent rise in $PGF_{2\alpha}$ excretion was observed without significant differences among the different groups.

As a result of these changes, the ratio PGE to $PGF_{2\alpha}$ excretion was low during the first day, followed by a gradual rise parallel with age; this pattern was particularly pronounced in group III.

Discussion

PGs have been shown to have a role in the cardiopulmonary adaptation of the neonate. Infants born to moth-

ers on indomethacin treatment developed a syndrome of persistent fetal circulation [8, 9, 28]. Indomethacin, an inhibitor of PG synthesis, has successfully been used to induce closure of the patent ductus arteriosus complicating the respiratory distress syndrome in premature infants [14, 21, 27]. There is also evidence to suggest that PGs may be involved in the pathogenesis of HMD. In support of this, the following findings should be considered.

1. PGs of the E series are potent vasodilatators, while PGF's are vasoconstrictor substances. An increase in PGF and a decrease in PGE concentration or both may result in a fall in the PGE to PGF ratio and lead to increased pulmonary vascular resistance and subsequent pulmonary hypoperfusion [29].

2. PG's are known to enhance adrenal steroid production [13, 24]. Increased cortisol output by the fetal adrenals may be a mechanism by which normal maturation of pulmonary surfactant occurs [10, 11].

3. Augmentation of cAMP concentration in the fetal lung has been associated with accelerated pulmonary maturation [2, 3]. PGs have been shown to increase the tissue cAMP concentration by increasing adenylate cyclase activity [4, 23], thus PGs may be supposed to contribute to the acceleration of fetal lung maturation. Recent findings indicate, however, that PG E and F act antagonistically in respect to cAMP and cortisol output, stressing the importance of PGE in surfactant formation [24].

4. Both PGE_2 and $F_{2\alpha}$ stimulate the incorporation of ^{3}H-choline and ^{14}C-palmitate into dipalmitoyl lecithin; in this, PGE_2 is much more effective than $PGF_{2\alpha}$ [6].

The present study provided further evidence that PGs may be implicated in the aetiology of HMD, by demonstrating a decreased urinary PGE to $PGF_{2\alpha}$ ratio in preterm infants with HMD. The decrease of this ratio was due to the low rate of urinary PGE excretion. With increasing postnatal age, urinary PGE excretion increased rapidly; the increase was due either to the recovery from HMD or to the routinely administered furosemide which is known to enhance renal production and release of PGE [1]. At the same time, significantly elevated plasma PGE and PGF levels were found in the acute phase of RDS, while in agreement with our results, the ratio PGE to PGF in plasma was significantly reduced [15].

As far as urinary PGE and $F_{2\alpha}$ excretion reflects their endogenous production rate [16], the high plasma concentration of PGE and $PGF_{2\alpha}$ as compared to the normal ($F_{2\alpha}$) or even reduced (E) urinary PG excretion can be regarded to indicate either a decreased metabolic clearance in the lung tissue, or a diversion of circulating PGs through right to left shunts from their pulmonary catabolic sites.

The reason for the limited renal PGE excretion in HMD is not clear. It might be a result of the decreased renal function in infants suffering from respiratory distress syndrome

[18], but the normal value of renal $PGF_{2\alpha}$ excretion speaks against this assumption. Whatever the cause of the decreased urinary PGE excretion in HMD, it may be of great importance in influencing the pathological processes leading to HMD.

References

1. Abe, K., Yasujima, M., Chiba, J., Irokawa, N., Itoh, T., Yoshinaga, K., Saito, T.: Effects of furosemide on urinary excretion of prostaglandin E in normal volunteers and patients with essential hypertension. Prostaglandins **14,** 513 (1977).
2. Barrett, C. T., Sevanian, A., Lavin, N., Kaplan, S. A.: Role of adenosine 3',5'-monophosphate in maturation of fetal lungs. Pediat. Res. **10,** 621 (1976).
3. Barrett, C. T., Sevanian, A., Phelps, D. L., Gilden, C., Kaplan, S. A.: Effects of cortisol and aminophylline upon survival, pulmonary mechanics, and secreted phosphatidyl choline of prematurely delivered rabbits. Pediat. Res. **12,** 38 (1978).
4. Butcher, R. W., Baird, C. E.: Effects of prostaglandin on adenosine 3',5'--monophosphate levels in fat and other tissues. J. biol. Chem. **243,** 1713 (1968).
5. Coats, P., Walker, E., Youssefnepadian, E., Craft, I. L.: Variations in plasma steroid and prostaglandin concentrations during human pregnancy. Acta obstet. gynaec. scand. **56,** 453 (1977).
6. Colaccico, G., Baju, M. K., Ray, A. K., Wittner, M., Rosenbaum, R. M.: Effects of prostaglandins E_2 and $F_{2\alpha}$ on lecithin biosynthesis by cultured lung cells. Prostaglandins **14,** 283 (1977).
7. Craft, I. L., Scrievener, R., Dewhurst, C. J.: Prostaglandin $F_{2\alpha}$ levels in the maternal and fetal circulations in late pregnancy. J. Obstet. Gynaec. Brit. Cwlth **80,** 616 (1973).
8. Csaba, I. F., Sulyok, E., Hadnagy, J.: Caesarean section and respiratory distress syndrome. Brit. med. J. **1,** 977 (1977).
9. Csaba, I. F., Sulyok, E., Ertl, T.: Relationship of maternal treatment with indomethacin to the persistence of fetal circulation syndrome. J. Pediat. **92,** 484 (1978).
10. Farell, P. M., Avery, M. E.: Hyaline membrane disease. Amer. Rev. resp. Dis. **111,** 657 (1975).
11. Fencl, M. de M., Tulchinsky, D.: Total cortisol in amniotic fluid and fetal lung maturation. New. Engl. J. Med. **292,** 133 (1975).
12. Ferreira, S. H., Vane, J. R.: Prostaglandins: their disappearance from and release into the circulation. Nature (Lond.) **216,** 868 (1967).
13. Flack, J. D., Jessup, R., Ramwell, P. W.: Prostaglandin stimulation of rat corticosteroidogenesis. Science **163,** 691 (1969).
14. Friedman, W. F., Hirschklau, M. J., Printz, M. P., Pitlick, P. T., Kirkpatrick, S. E.: Pharmacologic closure of patient ductus arteriosus in the premature infant. New. Engl. J. Med. **295,** 526 (1976).
15. Friedman, Z., Demers, L. M.: Essential fatty acids, prostaglandins and respiratory distress syndrome of the newborn. Pediatrics **61,** 341 (1978).
16. Frölich, F. C., Wilson, T. W., Sweetman, B. J.: Urinary prostaglandin; identification and origin. J. clin. Invest. **55,** 763 (1975).
17. Green, K., Bygdeman, M., Foppozada, M., Wiquist, N.: The role of prostaglandin $F_{2\alpha}$ in human parturition. Amer. J. Obstet. Gynec. **120,** 25 (1974).
18. Guignard, J. P., Torrado, A., Mazzoni, S. M., Gautier, E.: Renal function in respiratory distress syndrome. J. Pediat. **88,** 845 (1976).
19. Gutierrez-Cernosek, R. M., Morill, L. M., Levine, L.: Prostaglandin $F_{2\alpha}$ levels in peripheral sera of man. Prostaglandins **1,** 71 (1972).
20. Heynemann, M. A., Rudolph, A. M.: Effects of acetylsalicylic acid on the ductus arteriosus and circulation in fetal lambs in utero. Circulat. Res. **38,** 418 (1976).
21. Heynemann, M. A., Rudolph, A. M., Silvermann, N. H.: Closure of the ductus arteriosus in premature infants by inhibition of prostaglandin synthesis. N. Engl. J. Med. **295,** 530 (1976).
22. Hillier, K., Calder, A. A., Embrey, M. P.: Concentrations of prostaglandin $F_{2\alpha}$ in amniotic fluid and plasma in spontaneous and induced labours. J. Obstet. Gynae. Brit. Cwlth **81,** 257 (1974).
23. Hinman, J. W.: Prostaglandins. Amer. Rev. Biochem. **41,** 161 (1972).
24. Hohn, K. V., Chavin, W.: Temporal

effect of prostaglandins E and F on human adrenal cAMP and cortisol output. Life Sci. **22,** 543 (1978).
25. Jaffe, B. M., Behrman, H. R., Parker, C. W.: Radioimmunoassay measurement of prostaglandin E, A and F in human plasma. J. clin. Invest. **52,** 398 (1973).
26. Karim, S. M. M.: Appearance of prostaglandin $F_{2\alpha}$ in human blood during labour. Brit. med. J. **4,** 618 (1968).
27. Lucas, A., Mitchell, M. D.: Plasma prostaglandins in preterm neonates before and after treatment for patent ductus arteriosus. Lancet **2,** 130 (1978).
28. Manchester, D., Margolis, H. S., Sheldon, R. E.: Possible association between maternal indomethacin therapy and primary pulmonary hypoperfusion of the newborn. Amer. J. Obstet. Gynec. **126,** 467 (1976).
29. Mathé, A. A., Hedquist, P., Strandberg, K., Leslie, C. A.: Aspects of prostaglandin function in the lung. New Engl. J. Med. **296,** 850 (1977).
30. Mitchell, M. D., Brunt, J., Bibby, J., Flint, A. P. F., Anderson, A. B. M., Turnbull, A. C.: Prostaglandins in the human umbilical circulation. Brit. J. Obstet. Gynae. **85,** 114 (1978).
31. Novy, M. J., Piasecki, G., Jackson, B. T.: Effect of prostaglandins E_2 and $F_{2\alpha}$ on umbilical blood flow and fetal hemodinamics. Prostaglandins **5,** 543 (1974).
32. Rankin, J. H. G., Phernetton, T. M.: Effect of prostaglandin E_2 on ovine maternal placental blood flow. Amer. J. Physiol. **231,** 754 (1976).
33. Sharpe, G. L., Thalme, B., Larsson, K. S.: Studies on closure of the ductus arteriosus. XI. Ductal closure in utero by a prostaglandin synthetase inhibitor. Prostaglandins **8,** 363 (1974).
34. Siegler, R. L., Walker, M. B., Grouch, R. H., Christenson, P., Jubiz, W.: Plasma prostaglandin E concentrations from birth through childhood. J. Pediat. **91,** 734 (1977).
35. Zuckerman, H., Reiss, U., Atad, J., Lampert, I., Ben Ezra, S., Skland, D.: Prostaglandin $F_{2\alpha}$ in human blood during labor. Obstet. and Gynec. **51,** 311 (1978).

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