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Prostaglandin E_2 Concentration in Gastric Secretions of Critically Ill, Full-Term, and Premature Infants

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Summary

Critically ill, full-term, and premature infants are at increased risk to develop gastric mucosal ulceration. The cytoprotective effects of prostaglandin E_2 (PGE_2) may be important in the preservation of gastric mucosal integrity in these patients. PGE_2 concentrations in the gastric secretions of seven full-term and 16 premature infants with severe pulmonary disease were measured by radioimmunoassay. The mean PGE_2 concentration was significantly greater in the full-term infants (460 ± 94 pg/ml), (mean ± S.E.M.) than in the premature infants (190 ± 35 pg/ml), $P < 0.01$. There was a linear correlation between gestational age and PGE_2 concentration, $r = 0.70$, $P < 0.001$. In the 11 infants ≥35 wk gestational age there was a linear correlation between gastric pH and PGE_2 concentration, $r = 0.69$, $P < 0.01$.

Critically ill newborns are often hypoxic, acidotic and hypotensive, and have decreased gastrointestinal blood flow as a consequence. This low-flow state can cause breakdown in the mucosal barrier and loss of mucosal integrity throughout the gastrointestinal tract. Such mucosal insults may result in inflammation, ulceration, and blood loss (10, 14). The most common complication described, due to this low-flow state, is necrotizing enterocolitis (22); however, upper gastrointestinal hemorrhage can also be a complication (1, 6, 8, 10, 19). Most infants who have upper gastrointestinal hemorrhage in the immediate newborn period have gastric or prepyloric ulcerations (19). As expected, there is a significantly higher incidence of these bleeding episodes in seriously ill, full-term and premature infants (1, 8, 11, 19).

Prostaglandin E_2 protects the gastric mucosa against noxious insults (16). In animal studies, administration of prostaglandin analogues prevents gastric mucosal injury produced by aspirin, indomethacin, ethanol, and acid (17). Recent work by Wright *et al.*, (25) in humans with benign and malignant gastric ulcers, has shown significant differences in mucosal prostaglandin production in patients with disease.

Critically ill, premature infants are at greatest risk for developing gastric ulcerations and gastrointestinal hemorrhage. In the present study, we have evaluated the intraluminal concentration of gastric PGE_2 in critically ill, premature, and full-term infants in order to assess their capacity to produce this cytoprotective compound.

MATERIALS AND METHODS

Infants who were evaluated were admitted to the neonatal intensive care unit at Rainbow Babies and Childrens Hospital during October and November 1981. Seriously ill, full-term infants served as a comparison group. Premature and full-term infants eligible for enrollment into the study fit the following criteria: (*1*) pulmonary disease that required oxygen and either continuous positive-airway pressure or ventilator support; (*2*) birth weight appropriate for gestational age; (*3*) postnatal age ≤10 days; (*4*) normal abdominal examination and stool examination negative for blood; (*5*) normal arterial blood pressure, arterial blood gas, and serum electrolytes; (*6*) intravenous alimentation with dextrose and electrolyte solutions that excluded protein and lipid emulsion; and (*7*) no medications other than antibiotics.

Permission for this study was granted by the Institutional Review Board of University Hospitals. Informed consent was obtained at the time of admission. Gastric secretions were obtained via nasogastric tubes placed as part of routine care. Tube placement was checked by abdominal radiographs. Secretions were obtained with minimal disturbance to the infants between 8:00 a.m. and 3:00 p.m. The stomach was initially emptied, and 15 min later, secretions were removed by single aspiration with a plastic syringe and placed on ice.

Volume and pH of all samples were recorded. Samples were extracted with ethyl-acetate alone in a 5:1 (volume:volume) ratio. The organic layer was dried under nitrogen and the residue was resuspended with phosphate-buffered saline (15). The extracted and resuspended samples were then stored at −20°C for maximum of 2 wk before assay. PGE_2 was then measured by radioimmunoassay (5). Each sample was run on two separate assays and in triplicate for each assay. The intraassay coefficient of variation was 5.0%. The interassay coefficient of variation for the samples was 8.5%. Ligand was purchased from New England Nuclear, Boston, MA; prostaglandin standard from the Upjohn Company, Kalamazoo, MI; and PGE_2 antiserum from Sigma Chemical Company, St. Louis, MO. The antiserum had a cross reactivity with PGE_1 of 2.7%. The sensitivity at 50% displacement of radioligand was 10–20 pg.

Statistical analysis was performed using the Student *t* test and linear regression (3).

RESULTS

Seven full-term and 16 premature infants who fit the inclusion criteria were studied. The etiology of their pulmonary disease was meconium aspiration (#4), persistent fetal circulation (#5), or respiratory distress syndrome (#14). Table 1 shows the sex, mean gestational age, and postnatal age of the two groups. The gestational age of the premature infants ranged from 26–37 wk. The postnatal ages of the two groups were not significantly different.

Secretions were obtained without mucosal trauma, as evidenced by the lack of blood in the specimens. The volume collected ranged from 1.0–8.0 ml and the pH between 1.2–4.7.

Figure 1 shows the PGE_2 concentration (pg/ml) for the two groups. The full-term infants had a mean concentration of 460 ± 94 pg/ml (mean ± S.E.M.). Two of the 16 premature infants had no detectable PGE_2 in their gastric secretions. The only clinical factor that differentiated these two infants from the others was that their gestational age was less than 30 wk. Only one infant less than 30 wk gestation had a detectable gastric fluid PGE_2 level.

Table 1. *Clinical information*

Group	(*n*)[1]	Sex M	Sex F	Mean gestational age (week)	Mean postnatal age (days)
Full-term	7	4	3	39	3.8
Premature	16	7	9	33	3.5

[1] (*n*), number.

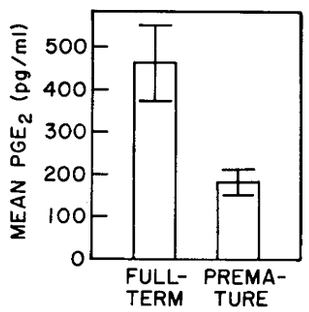

Fig. 1. The mean concentration of PGE_2 in the gastric secretions of full-term and premature infants. The mean PGE_2 concentration of full-term infants was 460 ± 94 pg/ml (mean ± S.E.) and premature infants 190 ± 35 pg/ml. There was a significant difference in mean concentration between the two groups, Student's *t* test comparison $P < 0.01$.

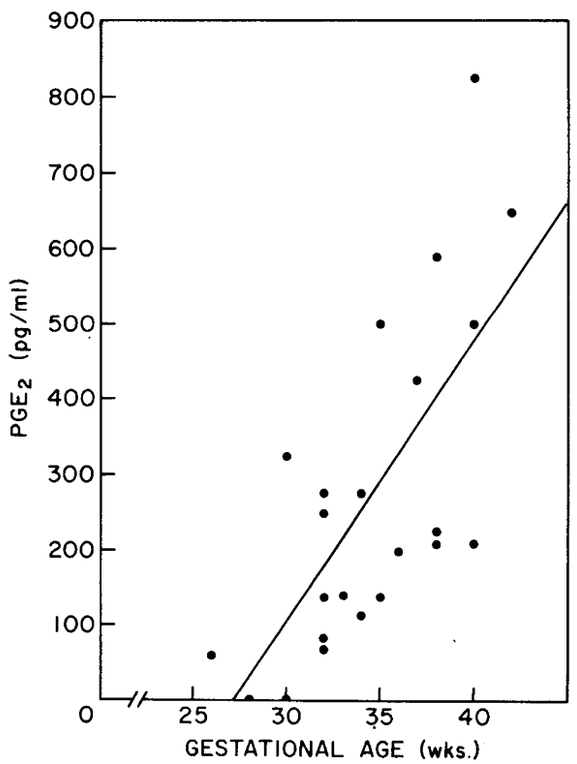

Fig. 2. Relationship between PGE_2 concentration and gestational age for all full-term and premature infants. The x intercept is at 27 wk gestation which suggests that PGE_2 production by the stomach may not occur before this time or that PGE_2 concentrations are below the sensitivity of the radioimmunoassay, 18 pg/ml. The line was drawn from a linear regression analysis, with $r = 0.70$ and $P < 0.001$.

The mean concentration for the 16 premature infants was 190 ± 35 pg/ml. This concentration of PGE_2 was significantly lower ($P < 0.01$) than that observed for full-term infants.

When the relationship between PGE_2 concentration and gestational age was evaluated further, a highly significant correlation ($r = 0.70$, $P < 0.001$) was noted (Fig. 2). From this correlation, it appears that the lack of PGE_2 in the two premature infants less than 30 wk gestation is related to their gestational age. When a similar analysis was performed to compare PGE_2 concentration and postnatal age, no significant correlation was found.

There was no significant difference between the gastric pH of full-term and premature infants. The mean gastric pH for the full-term infants was 2.20 ± 0.40 (mean ± S.E.M.) and for the premature infants 2.34 ± 0.23. Because PGE_2 is known to decrease acid production, (6, 21, 23, 24) the relationship between PGE_2 concentration and pH was evaluated. When infants greater than 35 wk gestation were grouped, there was a linear correlation between PGE_2 concentration and gastric pH, $r = 0.69$, $P < 0.01$ (Fig. 3A). For infants less than 35 wk gestation, no significant relationship between pH and PGE_2 concentration was detected (Fig. 3B).

DISCUSSION

Prostaglandin E_2 produces significant changes in gastric physiology. These changes decrease acid production and protect the gastric mucosa from injury, an effect called cytoprotection (16, 17). The cytoprotective effects of prostaglandins are attributed to increased active transport of sodium by the mucosal cell, (2) increased bicarbonate and mucus production (9, 23) and increased mucosal blood flow (7). These mechanisms may be disrupted by acidosis, hypoxia and shock, which decrease gastric blood flow and lead to mucosal ulceration (10, 14).

Our data suggest that there is a significant difference in PGE_2

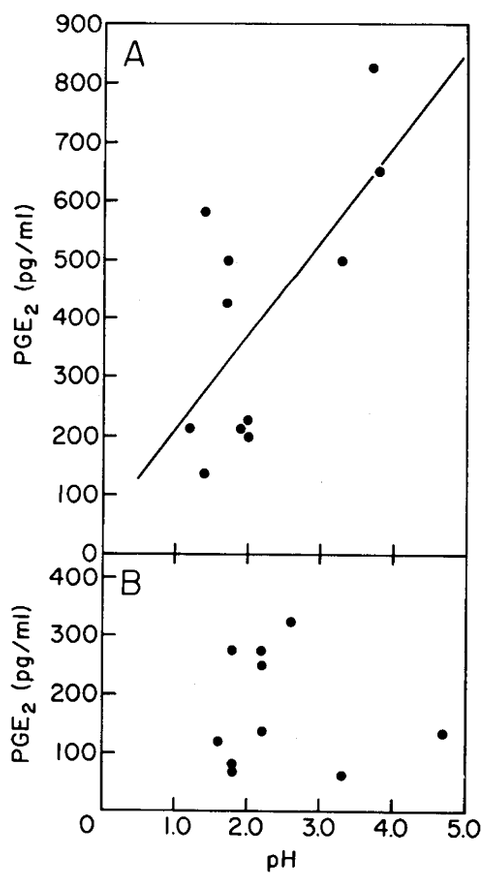

Fig. 3. (A) Relationship between PGE_2 concentration and gastric pH for infants ≥35 wk gestation. The relationship indicates a possible feedback mechanism between pH and PGE_2. The line was drawn from a linear regression analysis, $r = 0.69$, and $P < 0.01$. (B) Relationship between PGE_2 concentration and gastric pH for infants <35 wk gestation. There was no correlation between the values of these infants, suggesting an inability of the immature gastric cells to recognize or respond to stimuli, *i.e.*, hydrogen-ion concentration that increases PGE_2 production.

production between full-term and premature infants (Fig. 1). In addition, there is a linear correlation between PGE_2 concentration and gestational age (Fig. 2). The data in Figure 2 suggest that either PGE_2 is not produced by the fetal stomach until after 27 wk gestation or that the amount produced results in a concentration less than 18 pg/ml, which is the detection limit of the radioimmunoassay.

Because prostaglandin E_2 decreases acid secretion, the linear relationship between gastric pH and PGE_2 concentration in the infants over 35 wk gestation suggests that a feedback mechanism may be in operation. The lack of the correlation between pH and PGE_2 concentration in those infants less than 35 wk gestation probably relates to the inability of the more immature gastric cells to recognize or respond to the stimuli that increase prostaglandin production.

Animal studies have documented developmental differences in prostaglandin production between adult and fetal animals (12, 15). These differences vary in magnitude from lesser to greater quantities in the younger animals. There are specific differences in the amounts of prostaglandin produced and the type produced by specific organs in the same fetal animal. Evaluation of urinary and plasma prostaglandins in human infants has also demonstrated similar complex changes (18, 20). These changes in prostaglandin biosynthesis may represent an alteration in the availability of prostanoid precursors or maturation of the cyclooxygenase enzyme system in the fetus and organ systems and support our findings.

This study documents production of PGE_2 by the stomach of premature and full-term infants and developmental increases in gastric PGE_2 concentration. The data suggest an important correlation between PGE_2 and acid concentration. The cytoprotective effects of PGE_2 make its presence in the gastrointestinal tract important. The critical concentration of PGE_2 necessary for maximum cytoprotection and the stimuli for PGE_2 production must be defined in order to institute possible therapeutic measures that may prevent life-threatening complications. Gastric production of other prostaglandins, such as thromboxane and prostacyclin, must also be evaluated to determine their importance in maintaining normal gastrointestinal function.

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