Is there an extrathyroidal source of calcitonin during pregnancy?

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Abstract. Calcitonin (CT) and ionic calcium (Ca++) were measured in paired serum samples from the umbilical artery and vein of 47 normal term babies (28 females and 19 males). In the whole group, we found higher CT levels in the vein than in the artery (P < 0.01). Considered by sex, significant CT (P < 0.01) and Ca++ (P < 0.05) gradients existed only in the female group. CT and Ca++ were also measured in serum samples from a group of 26 normal babies (16 females and 10 males) at 2 days of life and in a group of 25 normal babies (12 females and 13 males) at 30 days of life. At 2 days we found a significant increase of CT (P < 0.001) (females P < 0.001 and males P < 0.05), and a significant decrease of Ca++ (P < 0.001) (females P < 0.001 and males P < 0.001), in umbilical artery blood levels at 30 days. Our data show more CT coming from the placenta to the foetus than vice versa, more evident in the females, suggesting an extrathyroidal source of CT, which may be the human placenta. The increase of CT at 2 days, opposing the release of calcium from bone, may contribute in part to the decrease in Ca++ levels observed at that time.

The term foetal skeleton acquires 80% of its 25 g of calcium during the last trimester of pregnancy (Heaney & Skillman et al. 1971). Calcium and phosphorus required for the formation of hydroxyapatite are actively transferred across placenta by way of the so-called 'placental calcium pump' (Shami & Radle 1971; Fuchs & Fuchs 1957). The mother's calcitrophic hormone status at delivery in comparison with that of non-pregnant women is as follows: high (Drake et al. 1979; Pitkin et al. 1979; Cushard et al. 1972; Reitz et al. 1977) or normal (Wieland et al. 1980; Hillman et al. 1978; Whitehead et al. 1981) parathyroid hormone (PTH), high calcitonin (CT) (Drake et al. 1979; Wieland et al. 1980; Whitehead et al. 1981; Samaan et al. 1975), high 1,25 dihydroxy vitamin D (1,25 (OH)2 D) (Wieland et al. 1980; Whitehead et al. 1981; Kumar et al. 1979) and normal (Wieland et al. 1980; Delvin et al. 1982) or low (Weisman et al. 1978) 25 hydroxyvitamin D (25 (OH) D) and 24,25 dihydroxy vitamin D (24,25 (OH)2 D) levels. The foetal calcitrophic hormone status at birth in comparison with that of the mother is characterized by high CT (Wieland et al. 1980; Hillman et al. 1978; Samaan et al. 1975), low (Reitz et al. 1977; Wieland et al. 1980; Hillman et al. 1978) or normal (Delvin et al. 1982; Pitkin et al. 1980) PTH and low vitamin D metabolites (Wieland et al. 1980; Delvin et al. 1982; Weisman et al. 1978).

Although almost everybody agrees about the hypercalcitoinaemic status of the foetus, there are discrepancies in the umbilical artery and vein CT levels (Wieland et al. 1980; Samaan et al. 1975; Pitkin et al. 1980). Consequently, the source of this hypercalcitoninaemia is not clear. After finding extraultimobranchial gland localizations of immunoreactive CT (iCT) in submammalian species (Galán Galán et al. 1981a,b) one of us (F.G.G.) studied human placenta tissue extracts, finding a concentration of iCT of 5.5 ± 1.3 ng/g wet tissue (mean ± se) (unpublished data). These results motivated us to carry out the present study, looking for the existence of an umbilical arteriovenous gradient of CT in normal term newborn infants in
order to investigate the possibility of placental CT production. We also studied the ionic calcium (Ca++) and CT status at 2 and 30 days of life, looking for sex differences such as have been reported in adult life (Hillyard et al. 1978).

Material and Methods

We carried out a cross-sectional study of three groups of normal full-term babies, appropriate for gestational age. The ante-partum course was uncomplicated. All deliveries were vaginal and the babies were non-asphyxiated as evidenced by Agar scores of 7 or more.

First group: Blood was collected from the umbilical artery and vein of the clamped cord immediately after delivery in 47 babies (28 females and 19 males).

Second group: Blood was obtained by heel stick from 26 normal babies (16 females and 10 males) 48 h after delivery.

Third group: Twenty-five normal babies (12 females and 13 males) 1 month old were studied. Blood was obtained from each one by heel prick. Informed consent was obtained from parents of all babies.

After collecting, samples were allowed to clot at room temperature for 1 h, then centrifuged and stored frozen at −20°C. Serum was reequilibrated with 5.2% CO₂ (40 mm p CO₂) (Schwartz 1976) before measurement of ionized calcium by the ICA-1 flow-through electrode (Radiometer, Copenhagen). Ionic calcium concentration (cCa++) is corrected automatically to pH = 7.4 by the equation: 1 g cCa++ (pH = 7.4) = 1 g cCa++ (pH = X) − 0.24 · (7.4 − X). So, all the Ca++ values we present in this paper are referred to a standard pH of 7.4. Inadequate volume of serum samples prevented us from determining serum ionic calcium in some babies. Calcitonin concentrations were measured in serum by direct radioimmunoassay (7 days of incubation) (Coombes et al. 1974) with a detection limit of 20 pg per ml and an intra-assay variation of under 10%. All the samples were assayed at the same time. All chemical determinations were done in duplicate.

The data were analysed by calculation of correlation coefficient (r) and tested for statistical significance by paired and unpaired Student’s t-tests.

Results

Paired umbilical blood samples in normal term babies showed an increase in Ca++ and CT levels in umbilical vein (1.34 ± 0.1 mmol/l; 152.7 ± 106.4 pg/ml) (mean ± SD) over umbilical artery (1.30 ± 0.08; 128.5 ± 103). A significant difference existed only in CT concentrations (P < 0.01). Separating by sex the increase was significant in Ca++ (1.32 ± 0.1 vs 1.27 ± 0.07) (P < 0.01) and CT levels (166 ± 120.6 vs 128 ± 117.0) (P < 0.01) in females but not in males (Fig. 1).

At 48 h after delivery we observed a significant increase of CT levels (255 ± 133) over umbilical artery CT levels (128.5 ± 103) (P < 0.001) and a significant decrease of Ca++ levels (1.03 ± 0.08 vs 1.30 ± 0.08) (P < 0.001). Separating by sex, the increase in CT levels was significant in females and males (P < 0.001 and P < 0.05, respectively). The decrease in Ca++ levels persisted in both sexes (P < 0.001) (Fig. 1).

At 30 days of life CT concentrations returned to umbilical artery levels in both females and males (Fig. 1). Ca++ concentrations rose from 48-h levels, in both sexes, reaching similar concentrations to the umbilical artery, in females. In males there persisted a relative hypocalcaemic state compared to the newborn (P < 0.005) (Fig. 1).

Ca++ and CT levels did not show any significant differences between females and males at each period of life studies. We found no significant correlation in either group between Ca++ and CT levels.

Discussion

The transition from intrauterine to extraterine life requires profound adaptive changes of probably every endocrine system in the newborn organism. Homeostatic control mechanisms involved in the regulation of foetal mineral metabolism must be altered to accomplish the post-natal function of maintaining normal serum mineral concentrations in the face of reduced availability (Schedewie & Fisher 1980).

Our results show that higher Ca++ and CT levels reach the foetus from the placenta than vice versa, being more evident in the female group. All previous reports on ionic calcium agree that there are no significant arteriovenous differences (Pitkin et al. 1980; Schauberger & Pitkin 1979; David & Anast 1974). Our results are in keeping with this but when we take sex, into account, we find a significant difference in favour of the umbilical vein in the female group, reflecting lower Ca++
Fig. 1.
Serum Ca++ at pH 7.4 and CT levels in umbilical vein and artery at delivery, 2 and 30 days of life, in normal term babies, separating by sex.

concentration coming from the foetus to the placenta. Previous reports of CT are discrepant. Samaan et al. (1975) found a gradient in favour of the umbilical artery but Wieland et al. (1980) and Pitkin et al. (1980) found no significant difference; although the latter group reported higher parathyroid hormone concentrations in the umbilical vein than in the umbilical artery. Our results disagree with theirs, demonstrating a significant CT gradient in favour of the umbilical vein, more prominent in the female group.

What is the source of this increment in umbilical vein CT? The 'C' cells appear within the thyroid gland at 14 weeks of gestation in human foetuses. Detectable amounts of immunoreactive CT (iCT) are present after 15 weeks of gestation. The thyroid gland seems to be the main source of foetal CT although no correlation has been found between the thyroid iCT concentration and gestational age (Leroyer-Alizon et al. 1980). As CT does not cross the placenta (Garel et al. 1969) our results suggest CT production by this tissue and agrees with our previous unpublished result described above. Its secretion might be mediated by the Ca++ gradient from the mother to the foetus. The CT coming from the placenta added to that secreted by the thyroid could facilitate Ca++ deposition in bone, being more important in females -- more CT is going into and less Ca++ is coming out -- than in males. Various other peptide and steroid hormones are produced and secreted by the placenta (Osathanondh & Tulchinsky 1980; Ryan 1980).

We corroborate other reports describing CT increase and Ca++ decrease at 48 h of life (Schedewie & Fisher 1980; David & Anast 1974; Hillman et al. 1977). The aetiology of the CT increment is unknown but, as has been suggested, serum glucagon and epinephrine, which are markedly in-
creased shortly after birth, may stimulate CT release (Hillman et al. 1977) and may in part be responsible for the observed CT increase. The deprivation of the placental source of CT after delivery could produce a rebound effect on CT secretion by the newborn thyroid C cells and could contribute to the hypercalcitoninaemia.

Although it is not possible to keep anaerobic conditions during capillary (heelprick) blood collection, we always refer Ca++ concentrations to a standard pH 7.4. In this way, any variation in Ca++ is not due to the pH variation introduced by the aerobic collection. The Ca++ decrease at 48 h may be due to different mechanisms acting together: a) the hypoparathyroidism of the newborn till 72 h (Schedewie & Fisher 1980; David & Anast 1974); b) the deprivation of Ca++ supply by the mother, and c) the increase of CT secretion stopping the bone Ca++ release. The two last mechanisms may be physiological stimuli to the PTH production and secretion observed after the second day of life.

Significantly higher CT concentrations have been found in males than in females during adult life (Hillyard et al. 1978). Immediately after delivery, at 2 and 30 days of life, we do not find any significant sex differences in CT levels, although females have higher values. So, sex differences in CT levels must begin later, but the reason is unknown.

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References


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