of these tests were largely ignored. Attempts to educate those who should take action were unsuccessful. Only when steps were taken to draw attention to the results by covering them up were more results followed up. Effective methods are therefore needed to ensure that the results of such profiles are carefully noted and that the implications of the results are fully understood.

LACK OF REFERENCE VALUES

In all biochemical profile studies borderline results constitute a considerable problem, even when the reference ranges are well recognized. In children there is little information about these ranges or on the factors that influence them. For example, several values show a definite trend with age (phosphorus, alkaline phosphatase, SGOT). Thus potentially important abnormalities may easily be overlooked.

In most studies of adults' biochemical profiles[1-3 6-7] the clinician received the profile soon after admission and before all those responsible for the patient discussed his condition. In such studies it is often difficult to decide what proportion of profile abnormalities were truly unexpected and would have remained undiscovered. Probably the number of diagnoses attributed to the profile under these circumstances would be overestimated. Our two trials were designed to avoid this difficulty by using control groups in which either the information was withheld or no profile was constructed. The number of new diagnoses was so small in the test and control groups, however, that it is not possible to say whether withholding information reduced the number of diagnoses attributed to the profile.

Conclusions

The profile made only a small contribution to the overall care of the patient. Nevertheless, the introduction of profiles may be the only way in which a laboratory can cope with its routine work load. We emphasize the importance, in these circumstances, of educating the clinicians to whom the profiles are sent in the use of large quantities of "unsolicited information" and of ensuring that the results are scrutinized carefully.

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Placental Transmission of Thyroid-stimulating Immunoglobulins

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Summary

Long-acting thyroid stimulator (LATS) and LATS protector (LATS-P) were assayed at or near delivery in serum from 18 pregnant women with a history of past or present thyrotoxicosis. The results suggested that neonatal thyrotoxicosis may be predicted prenatally if maternal serum LATS and LATS-P concentrations near delivery are above certain levels.

Introduction

Until recently it was generally considered[1] that neonatal hyperthyroidism was caused by the placental transmission of the long-acting thyroid stimulator (LATS) which is an immunoglobulin G (IgG). The serum of mother and affected infant usually contained detectable LATS activity and the clinical course of the disease seemed to be related to the serum LATS activity in the neonate. The levels of maternal LATS reported, however, have varied widely.

Three recent reports have shown that LATS-protector (LATS-P), an IgG which seems to stimulate only the human thyroid, may also cause neonatal hyperthyroidism. There have been two cases of neonatal thyrotoxicosis in which LATS was undetectable in either mother or infant; LATS-P was detectable in maternal serum two years after the birth of the affected infant in one case[2] and 10 years after in the other.[3 4] Dirmikis *et al.*[5] reported the first case of LATS-negative neonatal hyperthyroidism in which LATS-P was detected in both maternal and cord blood.

We report here the results of simultaneous serum LATS and LATS-P determinations in 18 pregnant women with a history of Graves's disease. In several cases the infant's serum was also assayed.

Patients and Methods

Twenty women were studied, 19 with an unequivocal history of present or past Graves's disease. The remaining patient (case 19) had previously given birth to an infant with neonatal thyrotoxicosis.[3] The clinical diagnosis of Graves's disease was confirmed in all cases by thyroid function tests (including radioiodine uptake, protein bound iodine, and serum T4 estimations, T3 resin uptake, and thyrotrophin releasing hormone test).

Eighteen patients gave birth to infants during this investigation, and two (cases 19 and 20) had previously given birth to infants with neonatal thyrotoxicosis. Five of the 18 infants born during this

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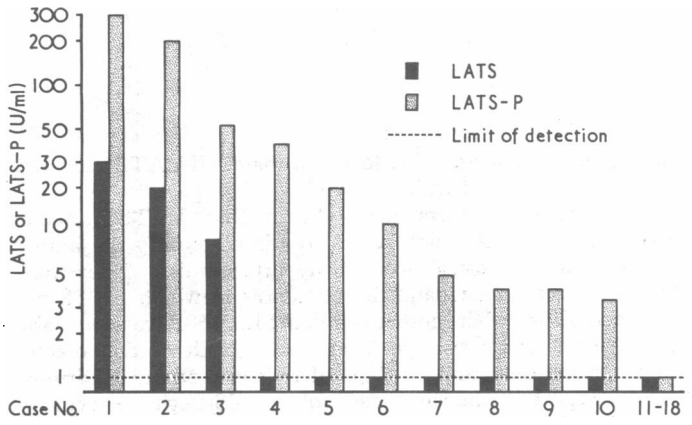
investigation suffered from neonatal hyperthyroidism, and all five were born to mothers (cases 1-5) whose hyperthyroidism was confirmed after delivery. Only one of the remaining 13 mothers (case 6) was shown to be hyperthyroid immediately after delivery, one (case 8) relapsed after four to five months, and 11 (cases 7, and 9-18) remained euthyroid.

LATS was measured as described by Smith[6] and LATS-P by a modification[7] of the method of Adams and Kennedy.[8] LATS-P is detected in LATS-negative serum when it blocks the binding of a standard LATS preparation by human thyroid extract. The concentrations of the LATS and the human thyroid extract must be carefully defined by preliminary experiments[7] so that optimal sensitivity for detecting LATS-P is obtained. In LATS-positive serum LATS-P can be detected by assaying serum at a dilution which gives no detectable response to LATS.[9]

We defined units of LATS and LATS-P in terms of our laboratory standard LATS serum. The reference mixture consisted of 20 μl standard LATS serum and human thyroid extract equivalent to 100 mg of wet human thyroid tissue. The LATS activity in 1 μl of the standard LATS serum was defined as 1 unit, and 1 unit of LATS-P activity blocked the binding of 1 unit of standard LATS. In this standard preparation for LATS 1 unit is equivalent to 0·2 unit of M.R.C. research standard B for LATS (code 65/122, Medical Research Council, Division of Biological Standards, National Institute for Medical Research, London).

Results

Serum LATS and LATS-P values for the 18 patients studied during pregnancy or at delivery are shown in the fig. Serum was taken at or near delivery. Infants born to patients with more than 20 units of LATS-P per ml of serum were invariably unequivocally thyrotoxic. Overt neonatal thyrotoxicosis was not seen when maternal serum contained less than 5 units/ml of LATS-P. In three mothers of infants with neonatal thyrotoxicosis some LATS was also detectable (8-30 units/ml) but in each of these patients there was much more LATS-P.



Serum LATS and LATS-P concentrations at or near delivery in women with history of thyrotoxicosis.

Cord blood was tested in infants in cases 1, 3, 4, 6, 11-13, and 15 for both LATS and LATS-P and in infants in cases 2, 5, 19 and 20 for LATS only. In all cases the concentration of serum LATS or LATS-P from cord blood was the same as or slightly less than that in maternal serum at delivery.

Mean birth weights (±S.E. of mean) for infants born at term were lower in the thyrotoxic group (2·57±0·31 kg) than in infants who were not overtly thyrotoxic (3·03±0·11 kg), but the difference was not statistically significant.

The infants in cases 1 and 4 were both unequivocally thyrotoxic; neither mother had received antithyroid drugs during pregnancy. The infant in case 2 was stillborn at term with a definite goitre. Much LATS was present in cord blood, but there was insufficient serum for LATS-P determinations on cord blood; the mother had received antithyroid drugs. One infant (case 3) was not overtly thyrotoxic until the fifth day of life. The mother was treated up till the time of the birth with antithyroid drugs, and these possibly compensated initially for the high concentrations of LATS-P which were found in cord blood. The infant in case 5 was also thyrotoxic, antithyroid drugs having been stopped some days before birth. One infant (case 6) showed no clinical signs of hyperthyroidism at any stage. Antithyroid drugs were gradually reduced and finally discontinued one week before delivery and at this relatively low level of LATS-P (10 units/ml serum) the antithyroid drugs may have compensated completely for the effect of LATS-P.

Serum LATS and LATS-P values for case 19 were obtained almost 10 years after the birth of an infant with LATS-negative neonatal hyperthyroidism[3 4]; values were ≤1 unit LATS/ml: 7 units LATS-P/ml. Possibly the serum LATS-P concentration declined over 10 years, though the patient's clinical condition remained unchanged. This decline was actually observed in the patient in case 20 who gave birth to an infant with neonatal hyperthyroidism when her serum LATS concentration was high (>10 units/ml). Seven years later, in mid-pregnancy, her serum LATS and LATS-P concentrations were both ≤1 unit/ml. At full term the patient was euthyroid (though still on carbimazole treatment) and gave birth to a normal female infant weighing 3·2 kg.

Discussion

All the patients who had detectable serum LATS-P and remained euthyroid (cases 7, 9, and 10) were euthyroid after partial thyroidectomy. The notes of three of the eight patients who had no detectable serum LATS or LATS-P included comments which showed some clinical doubt about whether they were hyperthyroid during pregnancy or not, but all three remained euthyroid after delivery. Mild thyrotoxicosis during pregnancy is notoriously difficult to diagnose clinically, and the usual biochemical tests of thyroid function are almost impossible to interpret until after delivery. Likewise, neonatal hyperthyroidism often remains undetected until some days after birth and may be masked in some cases by the residual effect of antithyroid drugs which have crossed the placenta. We found that maternal serum LATS and LATS-P detected before delivery correlated with maternal hyperthyroidism after delivery and high levels accurately predicted neonatal thyrotoxicosis in the infant.

Clearly, a more extensive prospective study is needed to confirm these findings. Investigations on existing pregnancies are in progress.

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