Anterior Pituitary Function in Women with Postpartum Hemorrhage

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Received March 7, 1977

Thirteen asymptomatic women with postpartum blood loss of at least 500 cc were evaluated for anterior pituitary endocrine function. Insulin tolerance tests and TRH stimulation tests were done and determinations made for serum growth hormone, cortisol, thyrotropin, and prolactin. There was no laboratory evidence of pituitary dysfunction in this group of 13 patients. Subclinical hypopituitarism in women with previous postpartum hemorrhage would appear to be uncommon.

Spontaneous anterior pituitary insufficiency occurs most commonly in women who have hemorrhaged during the postpartum period (Sheehan's Syndrome) [1]. Sheehan's Syndrome becomes clinically apparent in the puerperium with failure of lactation followed by absent or scanty menses, loss of pubic and axillary hair, atrophy of breasts and genitals, pallor, infertility, and signs of adrenal and thyroid insufficiency. However, Sheehan's Syndrome often emerges insidiously and may not fully develop for several years [2]. Patients with long-standing Sheehan's Syndrome are exposed to considerable risk especially during times of stress [3]. Since the onset of clinically apparent disease may be delayed for several years, there may be a number of apparently normal women who have experienced postpartum blood loss and who may have impaired pituitary function. With increasing refinements in the testing of pituitary function it might be possible to identify these women before they develop clinical hypopituitarism. Anterior pituitary function was evaluated in thirteen asymptomatic women who had postpartum hemorrhage.

METHODS AND PROCEDURES

Patient Selection

All patients at the Yale-New Haven Hospital with a discharge diagnosis of postpartum hemorrhage within the past ten years were identified through chart review of the medical records. Postpartum hemorrhage was defined as a minimum estimated blood loss of 500 cc for purposes of the study. One hundred and forty patients were identified; only 38 of these patients could be contacted by letter or telephone call. After obtaining their obstetricians' consent, each patient was contacted and their participation was solicited. Four patients were excluded from the study because of pregnancy (two patients) and breastfeeding (two patients). Twelve patients from the initial group of 38 agreed to participate. Three of these patients...
were taking estrogens: Orthonovum 1/80<sup>®</sup> for contraception (two patients) and Premarin<sup>®</sup> 1.25 mg as replacement therapy (one patient status-post bilateral oophorectomy). These three patients will be discussed separately. A thirteenth patient volunteered to participate, met the criteria for inclusion in the study, and was accepted. Patients were not selected according to age, parity, obstetrical or medical history, amount of estimated blood loss in excess of 500 cc, duration of hemorrhage, presence of hypotension or shock, or obstetrical cause of hemorrhage. The thirteen patients ranged in age from 23 to 40 years with an estimated postpartum blood loss of 500 to 2000 cc (mean 1000 cc ± 130 cc {± SEM}) occurring from 1 to 10 years prior to the initiation of this study. The nature of the study was discussed in detail with each patient and all subjects gave informed written consent. This research was approved by the Human Investigation Committee of the Yale-New Haven Hospital.

**Protocol**

All patients had a routine medical history and physical examination, formal fields of vision examination (Goldmann perimetry), x-ray examination of the sella turcica, 24 hour urine collection for 17-hydroxycorticosteroids (170HCS) and 17-ketosteroids (17KS), and determinations of fasting blood glucose, 8 AM and 8 PM serum cortisols, 8 AM serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and thyroid function tests. All patients underwent an insulin tolerance test with 0.1 units of regular insulin/kg body weight injected IV over 30 seconds. Two patients required 0.15 units of regular insulin/kg body weight to obtain an adequate level of hypoglycemia. Serum samples were obtained at 30 minute intervals for glucose, cortisol, growth hormone, and prolactin for two hours. All patients had a fall in blood glucose of greater than 50 percent to levels below 40 mg/dl with a mean minimal glucose of 27 mg/dl.

All patients underwent a thyrotropin-releasing hormone (TRH) stimulation test with 100 micrograms of TRH injected IV over 30 seconds. Serum samples were obtained at 15 minute intervals for prolactin and thyrotropin over two hours. One patient who failed to have a cortisol response to insulin hypoglycemia underwent a metapyrone test and an ACTH stimulation test. Metapyrone 750 mgs q4h was given orally for 24 hours. Twenty-four hour urine samples for 17-OHCS, 17-KS, and compound S were obtained the day before, the day of, and the day after metapyrone administration. An ACTH test was performed with IV Cortrosyn<sup>®</sup> 0.5 mg infused over 8 hours from 9 AM to 5 PM. Twenty-four hour urine collections for 17-OHCS, 17-KS, and compound S as well as serum cortisols at 8 AM, 4 PM, and 6 PM were obtained.

**Assays**

Radioimmunoassay determination of serum growth hormone, prolactin, and TSH were performed according to standard procedures. Antisera for prolactin was provided by the National Institutes of Health. Serum LH and FSH assays were performed by Bio-Science Laboratories.

**RESULTS**

All patients except one had unremarkable medical histories and physical examinations; one patient had idiopathic galactorrhea. There were no abnormal sella turcicas by x-ray or abnormal fields of vision by Goldmann perimetry. Serum determinations of thyroxine, thyroxine binding capacity, estimated free thyroxine, 8 AM and 8 PM serum cortisol, fasting blood glucose levels, and basal serum FSH and LH levels were
all within normal limits. All patients had normal 24 hour urine collections of 17-OHCS and 17-KS except for the one patient with idiopathic galactorrhea who had a low 17-OHCS value.

Figures 1 through 5 show the individual cortisol, growth hormone, and prolactin responses to insulin hypoglycemia and the TSH and prolactin responses to TRH stimulation for the ten patients not receiving estrogens. Each figure also compares the mean peak responses for these ten patients with the mean peak responses for normal patients obtained from previous reports [4-12]. Mean peak responses derived from these reports represent the grand mean and the standard error of the grand mean obtained from a series of normal control groups not taking estrogens.

For the ten patients not receiving estrogens, insulin hypoglycemia resulted in a mean peak cortisol of 30.1 ± 2.2 μg/ml (Fig. 1), while the mean peak growth hormone after insulin was 41.1 ± 6.6 μg/ml (Fig. 2), and the mean peak prolactin was 25 ± 4.4 ng/ml (Fig. 3). TRH stimulation produced a mean peak TSH of 16.1 ± 2.7 μU/ml (Fig. 4) and a mean peak prolactin of 28.1 ± 4.4 ng/ml (Fig. 5).

For the three patients receiving estrogens, insulin hypoglycemia produced a mean peak cortisol of 58 ± 5.3 μg/ml, a mean peak growth hormone of 53 ± 14.6 μg/ml, and a mean peak prolactin of 35.3 ± 7.7 ng/ml; TRH stimulation produced a mean peak TSH of 15.7 ± 9.2 μU/ml and a mean peak prolactin of 23 ± 3.8 ng/ml. Only the cortisol value was significantly higher than in the patients not receiving estrogens (P < .0001).

The patient with galactorrhea had a baseline 24 hour urine 17-OHCS of 2.3 mg/total volume and a subnormal cortisol response to insulin hypoglycemia (14 μg/dl). This patient was a 23 year old black female gravida two para two whose second delivery was complicated by a post partum hemorrhage with an estimated blood loss of 1000 cc. The patient did not elect to breastfeed either child. Normal menses resumed after the second pregnancy, and the patient took oral contraceptives.

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**FIG. 1. Cortisol response to insulin hypoglycemia.** Baseline and peak responses for individual patients (10) not receiving estrogens. Comparison of mean peak responses for patients not receiving estrogens and for normal patients reported in the literature.
from 1969 to 1970. Galactorrhea began in early 1973. She denied menstrual irregularity, physical stimulation, or the use of any medications. Physical examination revealed moderate obesity and galactorrhea but was otherwise unremarkable. Her baseline serum prolactin was 12 ng/ml and rose to a peak of 28 ng/ml after
FIG. 4. Thyrotropin response in TRH. Baseline and peak responses for individual patients (10) not receiving estrogens. Comparison of mean peak responses for patients not receiving estrogens and for normal patients reported in the literature.

TRH. Skull films and fields of vision by Goldmann perimetry were normal. All the tests of endocrine function performed in this study were normal with the exception of her cortisol response to insulin hypoglycemia and her subnormal 24 hour 17-OHCS excretion. Her pituitary-adrenal axis was further evaluated with a metapyrone test and an ACTH test which were both normal. The cause of her galactorrhea could not be determined.

No evidence of anterior pituitary insufficiency was observed in these thirteen patients.

FIG. 5. Prolactin response to TRH. Baseline and peak responses for individual patients (10) not receiving estrogens. Comparison of mean peak responses for patients not receiving estrogens and for normal patients reported in the literature.
DISCUSSION

Sheehan's Syndrome is the major cause of spontaneous anterior pituitary insufficiency [1]. This clinical entity is often overlooked and exposes the patient to considerable risk particularly during periods of stress. Since the onset of clinically apparent disease is often delayed for several years, there could be a significant number of asymptomatic women who have had postpartum hemorrhages with some impairment of pituitary function. As Sheehan's Syndrome can be readily treated with hormonal replacement therapy, it would be important to know the prevalence among asymptomatic patients with previous postpartum hemorrhage of laboratory evidence of anterior pituitary insufficiency and to identify these patients before they develop overt clinical disease.

Sheehan's Syndrome is typified by failure of lactation in the postpartum period, scant or absent menses, loss of axillary and pubic hair, atrophy of the breasts and genitals, pallor, cold intolerance, lethargy and hypersomnolence, slow monotonous speech, apathy, infertility, deep hoarse voice, thick coarse or waxy skin, macroGLOSSIA, generalized body hair loss, decreased libido, and chronic constipation. Although severe pituitary necrosis usually causes total loss of anterior pituitary function, isolated or partial deficiencies of pituitary hormones may occur [2], and there is no definite sequence of loss of hormone function [13]. There have been numerous reports of patients with Sheehan's Syndrome having normal pregnancies and deliveries [2].

There is no general agreement about the pathogenesis of Sheehan's Syndrome. The special vulnerability to ischemia of the pituitary gland during pregnancy is probably related to the two to three-fold increase in size of the adenohypophysis during pregnancy, as it is rare for reduced blood flow to cause pituitary necrosis in the non-pregnant female. Indeed, reversible physiologic bitemporal hemianopsia can occur secondary to pituitary enlargement [14]. Sheehan contends that necrosis is produced by local ischemia due to vasospasm in the arterial supply. This results from any severe circulatory collapse at the time of delivery, most commonly due to obstetrical hemorrhage [15]. However, Kopaniky and Cann have found in dogs that as hemorrhage increases, pituitary blood flow falls initially but then increases to levels greater than control [16]. Gotshalk and Tilden have emphasized the importance of the physiologic increase in pituitary size during pregnancy and have noted that a massively enlarged gland confined within the limited volume of the rigid sella turcica would be exposed to considerable pressure and would suffer some degree of vascular compression. In this setting, a sudden drop in blood pressure due to postpartum hemorrhage might allow the increased tissue pressure to cause collapse of the pituitary vasculature and ischemic necrosis. Gotshalk and Tilden described a patient who was found to have a segment of the anterior lobe of the pituitary protruding from the sella at autopsy; no necrosis was found in this area consistent with their hypothesis [17]. Meador and Worrell reported three patients with Sheehan's Syndrome in whom the sella turcica was significantly smaller than in normal controls [18]. An abnormally small sella turcica would further compress the physiologically enlarged gland and might predispose a patient with depleted blood volume to irreversible ischemia and anterior pituitary necrosis.

The three patients receiving estrogens were presented separately because of the known effect of estrogens on some tests of endocrine function. Estrogens elevate total serum cortisol and total serum thyroxine values by increasing transcortin and thyroxine-binding globulin levels. Ramey et al. have shown that oral contraceptives caused a significant increase in TSH response to TRH in normal euthyroid females
[5]. Carlson et al. have shown that estrogens augment the prolactin response to TRH [19]. There are no reports in the medical literature on the effect of estrogens on cortisol, growth hormone, or prolactin response to insulin hypoglycemia. In the present study estrogens caused a significant increase in mean peak cortisol response to insulin hypoglycemia (P < .0001, paired “t” test). The mean peak cortisol response for patients receiving estrogens was 58.0 μg/ml in contrast to a mean peak cortisol response of 30.1 μg/ml for patients not receiving estrogens. This effect of estrogens on cortisol response was not expected and has not been observed previously. Estrogens had no significant effect on prolactin response to TRH or on growth hormone or prolactin response to insulin hypoglycemia. Patients receiving estrogens did not have an increased TSH response to TRH as compared to patients not on estrogens. However, the patients were not tested before receiving estrogens and did not serve as their own controls [5].

All thirteen patients had significant increases in prolactin levels when stimulated with TRH. In contrast, four patients did not have significant increases in prolactin levels when stimulated by insulin hypoglycemia. The mean prolactin baseline value for all thirteen patients was 9.7 ± 1.0 ng/ml (± SEM) in the TRH test and 27.4 ± 3.9 ng/ml (± SEM) in the insulin tolerance test. Both tests appear to be useful in evaluating prolactin secretion and yield remarkably similar results. However, not all patients in the study responded to insulin hypoglycemia. The prolactin response to insulin hypoglycemia has been shown to be a sensitive index of pituitary function [20], and it may be prudent to perform both tests.

The mean blood loss in these patients was estimated to be 1000 cc and it might be argued that this degree of blood loss was too small to cause hypopituitarism. However, there appears to be no correlation between the amount of blood loss and the subsequent development of anterior pituitary insufficiency [2,21]. Effkemann and Muller-Jager found that in a group of 84 patients who lost between 800 and 1600 cc of blood at the time of delivery, 12 of the 20 patients who lost between 1200 and 1600 cc of blood suffered decreased menstrual function and 10 of these 20 patients became permanently sterile [22].

In a survey of 128 females with postpartum hemorrhage, 41 women (32%) had some degree of diminished pituitary function [23]. Thus, out of this current group of 13 women with postpartum hemorrhage, 4 women might have been expected to show diminished pituitary function. Previous studies of pituitary function were done with relatively crude measures of hormone function. The availability of hypothalamic releasing hormones and protein hormone determinations has greatly increased the ability to study pituitary function. However, the small number of patients studied precludes any firm conclusions about the incidence of subclinical pituitary hypofunction or the predictive value of the pituitary function tests.

ACKNOWLEDGEMENTS

This research was supported by Clinical Research Center Grant USPHS #FR-00125. The authors are grateful to Terri Pechinski, R.N., for her assistance in performing this study and to Drs. Philip B. May and Richard K. Donabedian for their valuable advice.

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