NOTE

Serum Relaxin in Patients with Invasive Mole, Choriocarcinoma and Persistent Trophoblastic Disease

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Human chorionic gonadotropin (hCG) is considered to be one of the factors which regulate relaxin secretion in humans. Serum immunoreactive relaxin levels are increased and are detectable by radioimmunoassay both in normal and molar pregnancy. Circulating hCG levels are increased in trophoblastic disease. In the present study, relaxin and hCG levels were sequentially measured in patients with invasive mole, choriocarcinoma and persistent trophoblastic disease. Serum relaxin levels were detectable by radioimmunoassay in these patients before treatment, though they were significantly lower than in normal pregnancy. The corpus luteum of pregnancy is the main source of circulating relaxin in normal pregnancy. The existence of a corpus luteum was confirmed in the 2 patients who underwent laparotomy. Consequently, the corpus luteum may also be the main source of circulating relaxin in trophoblastic disease. Parallel changes in hCG and relaxin levels were observed during the courses of trophoblastic disease. The finding suggests that relaxin secretion is dependent on hCG stimulation in trophoblastic disease in the presence of corpus luteum.

Human chorionic gonadotropin (hCG) is considered to be one of the factors which regulate relaxin secretion in humans (Quagliarello *et al.*, 1979; Quagliarello *et al.*, 1980; Weiss *et al.*, 1976). Serum immunoreactive relaxin levels are increased and detectable by radioimmunoassay (RIA) both in normal (O'Byrne *et al.*, 1978) and molar pregnancy (Seki *et al.*, 1986). Circulating levels of hCG are increased in patients with invasive mole or choriocarcinoma as in patients with hydatidiform mole. Consequently, the amount of serum relaxin may also be increased in such patients. We now report circulating levels of relaxin and hCG

sequentially measured in patients with invasive mole, choriocarcinoma and persistent trophoblastic disease.

Materials and Methods

The subjects of this study were 2 patients with invasive mole, 2 patients with choriocarcinoma and 2 patients with persistent trophoblastic disease. Luteal cysts were detected in none of them. In 5 of the 6 patients, serum relaxin and hCG levels were sequentially measured by RIA before and after the initiation of therapy. In the remaining 1 patients with invasive mole, relaxin and hCG levels were measured only before therapy. Relaxin was measured by RIA (Sherwood *et al.*, 1975; O'Byrne and

Steinetz, 1976) as previously described (Seki *et al.*, 1985). hCG was measured with RIA kits obtained from Commissariat à l'Energie Atomique, France. The sensitivity of the hCG assay was 2.0 mIU/ml. Statistical analysis was performed using signed rank test. Serum hCG and relaxin concentrations in patients with invasive mole,

choriocarcinoma and persistent trophoblastic disease were compared with those in 31 normal women during the first trimester of pregnancy (average 11.2 weeks of pregnancy; range nine to 14) or with those in 7 patients with hydatidiform mole, which had previously been reported elsewhere (Seki *et al.*, 1986).

Table 1. Serum concentrations of relaxin and hCG (median and range) in patients with invasive mole, choriocarcinoma and persistent trophoblastic disease before treatment (n=6), patients with hydatidiform mole (n=7) and normal women during the first trimester of pregnancy (n=31).

	Invasive Mole Choriocarcinoma Persistent Trophoblastic Disease	Hydatidiform Mole	Normal Pregnancy
Relaxin (ng/ml)	0.31 (0.20-0.46)	0.70 (0.60-1.03)*	0.73 (0.49-0.97)*
hCG (IU/ml)	3.5 (1.1-340)	420 (290-650)*	76 (25-166)*

* $p < 0.01$ vs patients with invasive mole, choriocarcinoma and persistent trophoblastic disease.

Fig. 1. A 33-year-old woman, gravida 2, para 2, underwent evacuation of a hydatidiform mole in June, 1984. Because of the rising hCG titers, she was referred to us on September 14, 1984. She underwent a total hysterectomy and right salpingo-oophorectomy (TAH-RSO) on October 15, 1984. Pathologic examination revealed invasive mole in the uterus and a corpus luteum in the right ovary. The shaded area represents an undetectable level. hCG=open circle, relaxin=closed circle.

Results

Relaxin and hCG levels before treatment

Serum relaxin was detectable before treatment in all 6 patients. The relaxin and hCG concentrations were lower in these patients than in normal women during the first trimester of pregnancy or in patients with hydatidiform mole (Table 1). There was an overlap in the range of hCG values, but not in that of relaxin values between these patients and those with hydatidiform mole (Table 1).

Case Reports

Invasive mole

In a patient with invasive mole, relaxin

levels decreased to an undetectable level 3 days after a total hysterectomy and right salpingo-oophorectomy (Fig. 1). hCG levels also rapidly decreased, though they were still detectable 3 weeks after operation. A corpus luteum was confirmed by histology in the right ovary.

Choriocarcinoma

A patient with nonmetastatic choriocarcinoma was characterized by a plateau in both hCG and relaxin levels after evacuation (Fig. 2). A discordant hCG and relaxin profile was noticed. Although relaxin levels later decreased to an undetectable level, low but detectable levels of hCG persisted. Then hCG levels showed a rise, followed by a small rise in relaxin levels. After a total hysterectomy and bilateral salpingo-oophorectomy, hCG levels fell rap-

Fig. 2. A 53-year-old woman, gravida 4, para 2, underwent curetage for a hydatidiform mole in June, 1983. After evacuation, hCG and relaxin levels continued to fall through September, and levelled off thereafter until March, 1984. From April, 1984 on, relaxin levels became undetectable, while low, but detectable levels of hCG continued. From August, 1984 on, hCG levels rose, though relaxin levels remained undetectable. The relaxin level also became detectable on September 9, 1984, and rose to 0.3 ng/ml on September 13, 1984. The patient underwent a total hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) on September 24, 1984. Pathologic examination revealed choriocarcinoma in the uterus and a corpus luteum in the right ovary. The shaded area represents an undetectable level. MAC=methotrexate, actinomycin and cyclophosphamide. hCG=open circle, relaxin=closed circle.

source of circulating immunoreactive relaxin in normal pregnancy (Weiss *et al.*, 1976). In the 2 patients with trophoblastic disease who underwent a total hysterectomy and extirpation of the ovary containing a corpus luteum, relaxin levels promptly fell and became undetectable within 3 days. On the other hand, the disappearance pattern of relaxin was slower in a patient with metastatic choriocarcinoma treated with chemotherapy. In 1 of the 2 patients with persistent trophoblastic disease, serum relaxin levels were still elevated 5 days after the initiation of chemotherapy. Therefore, the corpus luteum may also be the main source of circulating immunoreactive relaxin in trophoblastic disease, though an extraluteal

source of relaxin cannot be excluded. Relaxin was always undetectable after initiation of chemotherapy in a patient with persistent trophoblastic disease. This may be accounted for by the patient's pretreatment relaxin level which was the lowest among the patients studied. Parallel changes in relaxin and hCG levels were, in general, observed during the course of trophoblastic disease. This finding suggests, but does not prove, that relaxin secretion is dependent on hCG stimulation in trophoblastic disease in the presence of corpus luteum. Serum relaxin levels before treatment were significantly lower in trophoblastic disease than in normal or molar pregnancy. This may be accounted for by the significantly lower hCG

Fig. 4. A 34-year-old woman, gravida 4, para 2, underwent evacuation of an hydatidiform mole on April 19, 1983. The titers before evacuation were 650,000 mIU/ml for hCG and 0.8 ng/ml for relaxin. After evacuation, both hCG and relaxin levels fell slowly through September, 1983. However, they plateaued in October, 1983, and increased in November, 1983. Five day courses of methotrexate, actinomycin and cyclophosphamide (MAC) therapy were begun on 5 occasions from December 25, 1983 to April 23, 1984. The shaded area represents an undetectable level.
hCG=open circle, relaxin=closed circle.

level found in our patients with trophoblastic disease compared to normal or molar pregnancy. In a patient with postmolar persistent trophoblastic disease, detectable levels of relaxin were found for 8 months after evacuation of hydatidiform mole. Consequently, the function of the corpus luteum in secreting relaxin may continue as long as stimulation of the corpus luteum by effective hCG persists. While hCG can induce luteal relaxin secretion, constant doses of hCG or luteinizing hormone cannot maintain the nonpregnant corpus luteum for more than 2 additional weeks (Strott *et al.*, 1969; Hanson *et al.*, 1971; Stock *et al.*, 1971). Thus, additional factors may be present to account for the continued function of the corpus luteum in secreting relaxin in trophoblastic disease.

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Fig. 5. A 30-year-old woman, gravida 2, para 1, underwent a laparotomy for a suspected tubal ectopic pregnancy in September, 1983. Postoperatively, the patient continued positive pregnancy tests. Curetage was performed but no molar tissue was obtained. Pathologic examination revealed a secretory endometrium. The patient's previous pregnancy terminated in a spontaneous abortion in August, 1982. A pelvic angiogram revealed a vascular mass in the uterus. Combination chemotherapy (methotrexate, actinomycin and cyclophosphamide, MAC) was begun on November 28, 1983, and the patient received 5 courses. The titers before treatment were 70,000 mIU/ml for hCG and 0.2 ng/ml for relaxin. The shaded area represents an undetectable level.

a spontaneous abortion in August, 1982. A pelvic angiogram revealed a vascular mass in the uterus. Combination chemotherapy (methotrexate, actinomycin and cyclophosphamide, MAC) was begun on November 28, 1983, and the patient received 5 courses. The titers before treatment were 70,000 mIU/ml for hCG and 0.2 ng/ml for relaxin. The shaded area represents an undetectable level.

hCG = open circle, relaxin = closed circle.

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