Patterns of Serum Immunoreactive Human Placental Lactogen (IR-HPL) and Chorionic Gonadotropin (IR-HCG) in Diabetic Pregnancy

Herbert A. Selenkow, M.D., Kamlesh Varma, M.B.B.S., D.G.O., M.S., Donna Younger, M.D., Priscilla White, M.D., and Kendall Emerson, Jr., M.D., Boston

SUMMARY

Serum levels of immunoreactive human placental lactogen (IR-HPL) and chorionic gonadotropin (IR-HCG) were evaluated in eighty-four diabetic patients classified according to White. All patients in this group were treated with estrogen/progesterone therapy throughout pregnancy and were compared with a small group of twenty-seven diabetic patients not receiving hormonal therapy. In 164 normal pregnancies, serum IR-HPL is detected first at about six weeks and rises steadily to plateau levels of 6.2 ± 1.4 μg./ml. at thirty-five to thirty-seven weeks. In eighty-four diabetic pregnancies, the pattern of steady rise in IR-HPL levels simulates normal but the mean values are significantly greater than normal with peak values of 10.3 ± 4.7 μg./ml. at thirty-five to thirty-seven weeks. Serum IR-HCG is first measured in normal pregnancy at about five to seven weeks by this assay, rises rapidly to peak levels of 163 ± 60 IU./ml. at eight to ten weeks and then falls to a nadir of 12.0 ± 2.0 IU./ml. at seventeen to nineteen weeks. Thereafter, there is a gradual secondary rise to a lesser mean peak value of 63 ± 19 IU./ml. at thirty-five to thirty-nine weeks. In diabetic pregnancy, the pattern of serum IR-HCG is similar to normal but with striking quantitative differences. The mean values in the second and third trimesters are significantly higher than normal with extreme variations among different pregnant individuals. The clinical implications of these abnormalities are not clear but suggest that the excessive secretion of HCG may mollify the diabetic imposition of early pregnancy whereas HPL contributes to the exaggerated glucose intolerance in late pregnancy. DIABETES *20*:696-706, October, 1971.

Pregnancy has long been known to impose some degree of carbohydrate intolerance in nondiabetic women.[1] Impaired glucose metabolism in pregnancy generally increases to term and is often more evident in successive pregnancies. The primary metabolic abnormalities responsible for this diabetogenic phenomenon are not yet fully understood. The characteristic deviations from normal which have been identified in nondiabetic pregnancy include some impairment of glucose utilization associated with a corresponding insulin resistance. These occur despite serum insulin responses to appropriate stimuli which are usually greater than normal. The glucose response to intravenous tolbutamide

Presented in part at the Thirtieth Annual Meeting of the American Diabetes Association, June 13-14, 1970, in St. Louis.

From the Department of Medicine, Harvard Medical School, the Peter Bent Brigham Hospital, the Boston Hospital for Women (Lying-In Division) and the Joslin Clinic, Boston, Massachusetts.

in late normal pregnancy is not infrequently in the diabetic range despite supranormal secretion of insulin. Thus, normal pregnancy induces a state of insulin resistance and consequently some impairment of glucose utilization despite enhanced pancreatic insulin responsiveness.[2-4] This state of insulin-resistant glucose intolerance in pregnancy disappears rapidly postpartum with a return to normal insulin-glucose relationships in the nondiabetic subject and an amelioration of carbohydrate intolerance in diabetic patients. These observations bear a striking resemblance to the metabolic alterations following growth hormone excess or induced by adrenal glucocorticoids or, to some extent, estrogenic steroids.

Two polypeptide hormones of placental origin are of particular interest in the diabetogenic imposition of pregnancy. Human chorionic gonadotropin (HCG) is known to be secreted in excess during diabetic pregnancy,[1,5-8] but the extent and nature of this secretory abundance has not been characterized with certainty. More recently, human placental lactogen (HPL) has been shown to have distinct diabetogenic properties similar to human growth hormone (HGH).[9-14] HPL given in concert with HGH may enhance this effect.[15] The feasibility of measuring polypeptide hormones by sensitive radioimmunoassay technics permitted the present investigation, designed to characterize the secretory patterns of serum immunoreactive HCG (IR-HCG) and HPL (IR-HPL) during normal and diabetic pregnancy.

MATERIAL AND METHODS

The eighty-four diabetic patients in the Joslin Clinic portion of this study attended that clinic and were under the medical supervision of Dr. Priscilla White and her associates. Each patient had known diabetes in the nonpregnant state and the extent of this was designated according to White's classification.[16] Once the diagnosis of pregnancy was established, each patient was started on a prescribed program including 1-2 ml. of a combination of ethinyl estradiol valerate 5.0 mg./ml. and hydroxyprogesterone caproate 250 mg./ml. intramuscularly in castor oil. This estrogen/progesterone therapy was continued each week to term and all patients were delivered by the thirty-seventh week of gestation. The present study includes patients selected randomly from Classes A, B, C, D and R. Class R refers to patients with proliferative diabetic retinopathy developed prior to or during the course of pregnancy.

In order to characterize serum IR-HCG and IR-HPL levels in patients not receiving estrogen/progesterone therapy, a group of twenty-seven diabetic pregnant women (the BLI group) were selected at random from the clinic population at the Boston Hospital for Women (Lying-In Division). These patients were under the medical care of Dr. Kendall Emerson, Jr. The number and distribution of the BLI patients in the various diabetic groups differed significantly from the Joslin Clinic group and thus, no direct comparisons could be made.

Serum samples for IR-HCG and IR-HPL were obtained from each patient at weekly intervals. Radioimmunoassays of IR-HCG and IR-HPL were performed by a rapid, pre-incubated double antibody, charcoal-dextran method developed in this laboratory.[17,18] Placental weights were determined after removal of the umbilical cord, extraplacental membranes and clots according to the procedure described in another publication.[18a] Patterns of serum hormone concentrations in normal subjects have been reported previously for these assays[11,17-19] and were used in this study for comparison with results obtained in diabetic patients. Statistical analyses were performed according to standard methods (Snedecor and Cochran, sixth edition, Iowa State University Press, 1967).

RESULTS

The characteristic patterns of serum IR-HPL and HCG in normal, nondiabetic women obtained by radioimmunoassay in this laboratory are shown as shaded areas in figures 1-7 and the data are listed in tables 1 and 2. Serum IR-HPL is detectable at five to seven weeks by this assay and the levels increase gradually throughout pregnancy to reach a peak at thirty-five to thirty-seven weeks. Thereafter levels plateau or decrease slightly. Serum IR-HCG was first assayed at about five to seven weeks since most patients in this study were not seen earlier. There is a rapid rise of serum IR-HCG in early pregnancy which reaches a high peak at eight to ten weeks, falls to a nadir at seventeen to nineteen weeks and then rises gradually to a second lesser plateau at about thirty-five to thirty-seven weeks.

Patterns of serum IR-HPL and IR-HCG in diabetic pregnancy are generally qualitatively similar to nondiabetic pregnancy but differ strikingly in their quantitative aspects. In the eighty-four diabetic patients of the Joslin group (figure 1) all of whom received estrogen/progesterone therapy throughout pregnancy, mean levels of IR-HPL were significantly above the normal range throughout the last trimester with markedly broad variations about the mean. At thirty-five to thirty-seven weeks, IR-HPL levels of 10.3 ± 4.7 (SD) μg./ml. in the diabetic group differed significantly from levels of 6.2 ± 1.4 (SD) μg./ml. in the nondiabetic group. More strikingly, serum IR-HCG levels were generally

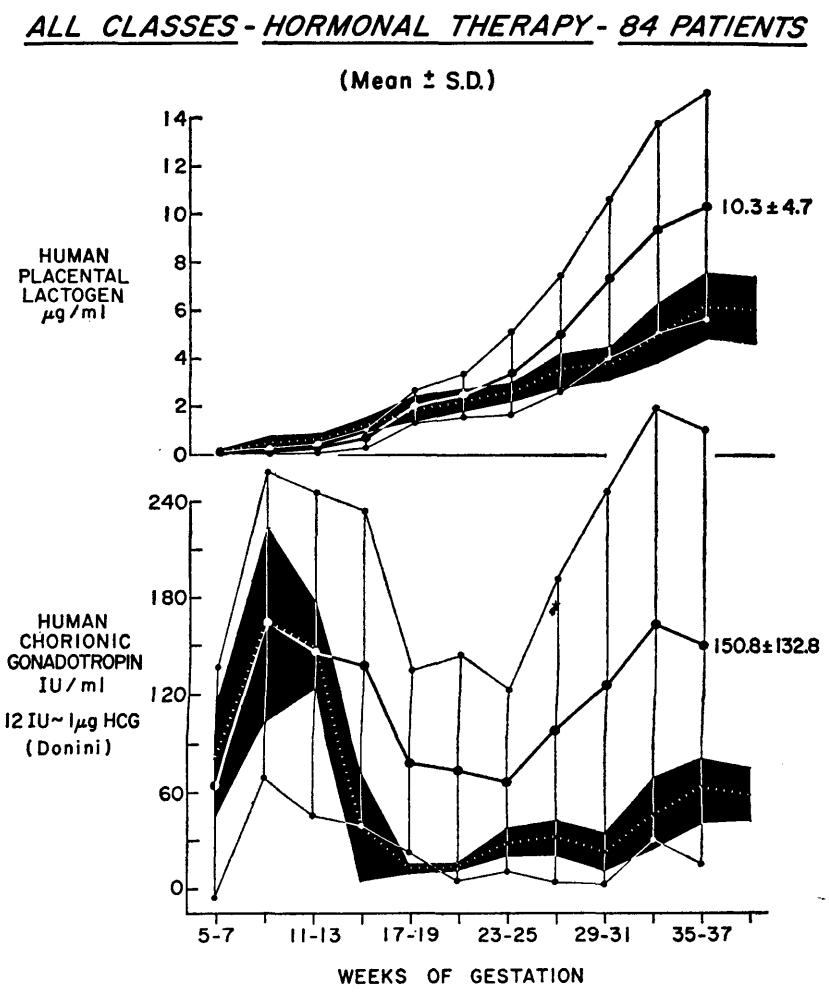

FIG. 1.

Patterns of serum IR-HPL and IR-HCG in eighty-four diabetic pregnancies (total of all classes) followed at the Joslin Clinic. All patients were given estrogen/progesterone therapy and were delivered around thirty-five to thirty-seven weeks. In this and in all subsequent figures, shaded areas indicate the mean ± S.D. for each three-week interval in nondiabetic patients studied in this laboratory. The solid curves represent the mean values in the diabetic group with upper and lower limits representing ± S.D.

elevated above normal but with marked variability about the mean value throughout gestation. Although the mean value of 163 ± 97 (SD) IU./ml. at ten to twelve weeks in the diabetic group was not significantly different from that in the nondiabetic group (163 ± 60), values later in pregnancy were generally quite elevated.

TABLE 1

Values of serum IR-HCG (IU./ml.) in normal and diabetic pregnancy

Patient group	Number of patients	Weeks of gestation* 5-7	8-10	11-13	14-16	17-19	20-22
Normal	98 (104)	81±37 (10)	163±60 (16)	150± 27 (7)	38±35 (5)	12± 2 (5)	13± 2 (5)
BLI (total)	12 (52)	112 (2)	—	—	—	56.2 (2)	64± 41 (5)
Joslin (total)	84 (557)	65±71 (4)	163±97 (12)	146±110 (27)	138±99 (33)	79±57 (40)	74± 41 (45)
Joslin A	3 (25)	—	—	—	—	—	—
Joslin B	15 (127)	—	182 (2)	76± 63 (3)	73±60 (3)	75±57 (9)	72± 98 (10)
Joslin C	30 (224)	—	114±73 (12)	168±121 (15)	128±85 (21)	76±56 (20)	63± 37 (19)
Joslin D	27 (185)	—	160±115 (6)	163± 48 (9)	156±128 (11)	84±58 (14)	57± 47 (10)
Joslin R	9 (47)	—	—	192 (1)	240 (2)	132 (1)	63± 22 (7)

* Numbers in parentheses indicate the number of samples. Each value represents the mean ± S.D.

(Table 1 continued on top of next page)

TABLE 1 (continued)

Values of serum IR-HCG (IU./ml.) in normal and diabetic pregnancy

Patient group	Number of patients	Weeks of gestation* 23-25	26-28	29-31	32-34	35-39	38-40
Normal	98 (104)	28±10 (6)	31±12 (9)	23± 12 (7)	46± 22 (7)	63± 19 (18)	58±17 (11)
BLI (total)	12 (52)	72±42 (6)	101±43 (8)	104± 53 (8)	124± 54 (12)	173± 77 (9)	—
Joslin (total)	84 (557)	66±56 (46)	98±93 (77)	126±123 (100)	165±134 (109)	151±133 (64)	—
Joslin A	3 (25)	41±34 (4)	46±33 (3)	97± 82 (7)	73± 37 (7)	57± 22 (4)	—
Joslin B	15 (127)	48±22 (10)	134±144 (18)	170±201 (24)	174±119 (26)	117± 92 (22)	—
Joslin C	30 (224)	62±32 (19)	94±63 (26)	125± 75 (35)	171±119 (32)	177±126 (25)	—
Joslin D	27 (185)	85±73 (23)	85±63 (26)	115± 87 (35)	172±132 (36)	137±101 (15)	—
Joslin R	9 (47)	43±20 (6)	72±57 (10)	100± 70 (6)	125± 65 (8)	137± 52 (6)	—

* Numbers in parentheses indicate the number of samples. Each value represents the mean ± S.D.

At thirty-five to thirty-seven weeks, the mean of the diabetic group was 151 ± 133 (SD) compared to a normal of 63 ± 19 (SD).

Although there are insufficient data for meaningful comparisons, the patterns in the individual diabetic classes (figures 2-5) were similar to the over-all group.

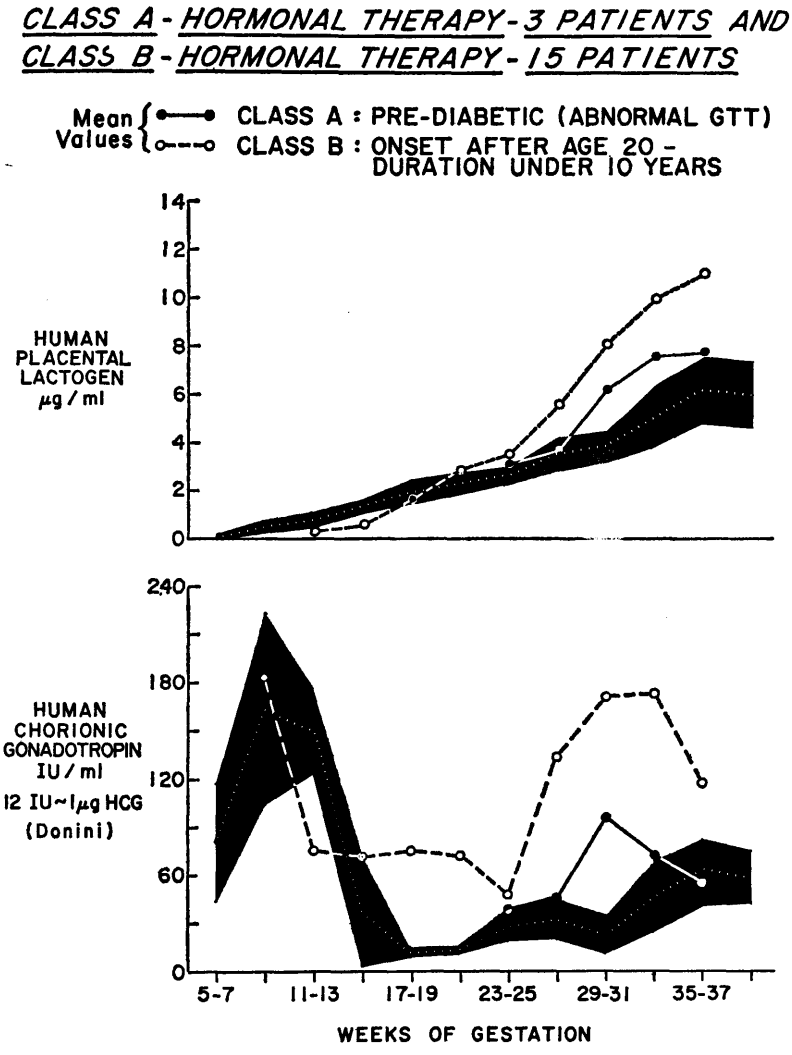

FIG. 2.

Patterns of serum IR-HPL and IR-HCG in three Class A and fifteen Class B patients of the Joslin group. See legend figure 1 for explanation of symbols.

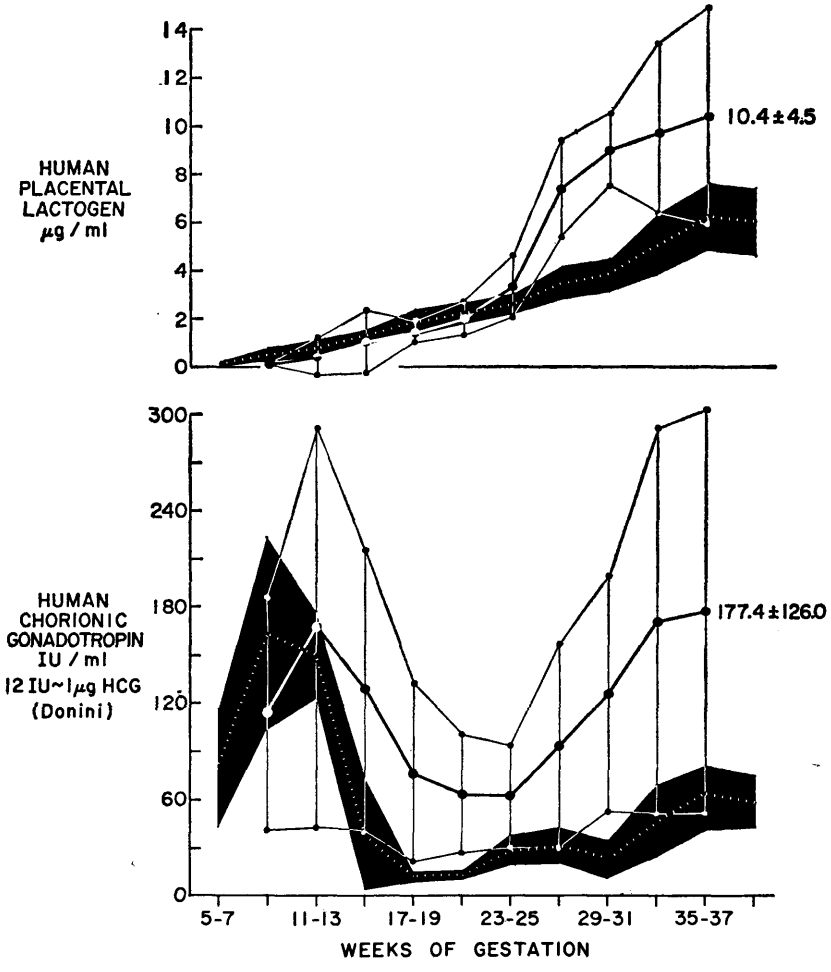

FIG. 3.

Patterns of serum IR-HPL and IR-HCG in thirty Class C diabetic patients of the Joslin group. See legend figure 1 for explanation of symbols.

TABLE 2

Values of serum IR-HPL (μg./ml.) in normal and diabetic pregnancy

Patient group	Number of patients	Weeks of gestation* 5-7	8-10	11-13	14-16	17-19	20-22
Normal	164 (155)	0.1±0.1 (7)	0.6±0.2 (23)	0.8±0.3 (18)	1.3±0.3 (11)	1.9±0.6 (12)	2.2±0.5 (9)
BLI (total)	27 (136)	—	0.4 (1)	0.8 (1)	2.4 (1)	1.4±0.6 (4)	1.8±0.8 (7)
Joslin (total)	84 (660)	0.1±0.1 (7)	0.1±0.1 (24)	0.3±0.2 (42)	0.7±0.4 (40)	2.0±0.6 (46)	2.5±0.9 (56)
Joslin A	3 (33)	—	—	—	—	—	1.3 (2)
Joslin B	15 (131)	—	0.4 (2)	0.3±0.2 (6)	0.6±0.3 (3)	1.7±0.8 (10)	2.8±1.2 (10)
Joslin C	30 (272)	—	0.1±0.1 (13)	0.5±0.8 (21)	1.0±1.3 (26)	1.4±0.5 (21)	2.0±0.7 (26)
Joslin D	27 (226)	—	0.1±0.2 (9)	0.3±0.2 (10)	0.7±0.4 (12)	1.4±0.8 (16)	2.0±0.9 (19)
Joslin R	9 (56)	—	0.1 (1)	0.8 (1)	0.6±0.1 (3)	1.2±0.2 (3)	1.9±0.7 (9)

* Numbers in parentheses indicate the number of samples. Each value represents the mean ± S.D.

(Table 2 continued on top of next page)

TABLE 2 (continued)

Values of serum IR-HPL (μg./ml.) in normal and diabetic pregnancy

Patient group	Number of patients	Weeks of gestation* 23-25	26-28	29-31	32-34	35-37	38-40
Normal	164 (155)	2.6±0.4 (8)	3.5±0.7 (11)	3.8±0.7 (5)	5.1±1.3 (18)	6.2±1.4 (21)	6.0±1.4 (12)
BLI (total)	27 (136)	3.1±1.1 (10)	3.6±1.5 (21)	4.7±2.2 (17)	5.9±2.6 (31)	7.4±2.5 (35)	6.9±1.6 (8)
Joslin (total)	84 (660)	3.3±1.7 (54)	5.0±2.4 (88)	7.4±3.3(112)	9.4±4.4 (121)	10.3±4.7 (70)	—
Joslin A	3 (33)	3.2±1.1 (5)	3.7±0.5 (3)	6.4±2.0 (8)	7.6±1.1 (9)	7.8±2.0 (6)	—
Joslin B	15 (131)	3.5±1.1 (10)	5.6±3.1 (18)	8.1±1.0 (24)	10.0±5.3 (26)	11.0±4.1 (22)	—
Joslin C	30 (272)	3.3±1.3 (22)	7.4±2.0 (38)	9.0±1.5 (39)	9.7±3.7 (37)	10.4±4.5 (29)	—
Joslin D	27 (226)	4.2±2.4 (28)	5.4±2.3 (34)	7.3±3.3 (40)	9.0±4.1 (42)	10.1±5.3 (16)	—
Joslin R	9 (56)	2.5±1.2 (8)	5.2±2.3 (11)	6.0±1.8 (6)	9.3±3.0 (8)	15.8±7.2 (6)	—

* Numbers in parentheses indicate the number of samples. Each value represents the mean ± S.D.

No difference among the classes appeared evident from gross inspection.

In an effort to assess the effects of estrogen/progesterone therapy on serum levels of IR-HPL and IR-HCG, a randomly selected group of twenty-seven patients from the Boston Hospital for Women (Lying-In Division) were studied who did not receive estrogen/progesterone therapy (figure 6). The general patterns

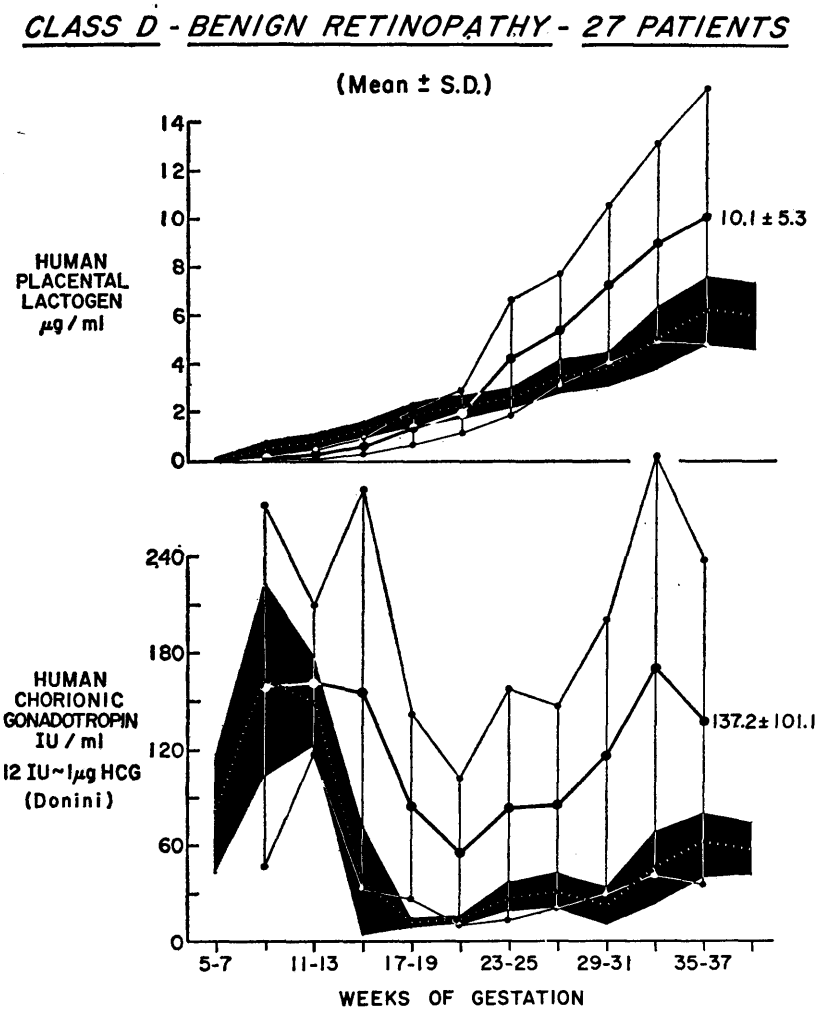

FIG. 4.

Patterns of serum IR-HPL and IR-HCG in twenty-seven Class D diabetic patients of the Joslin group. See legend figure 1 for explanation of symbols.

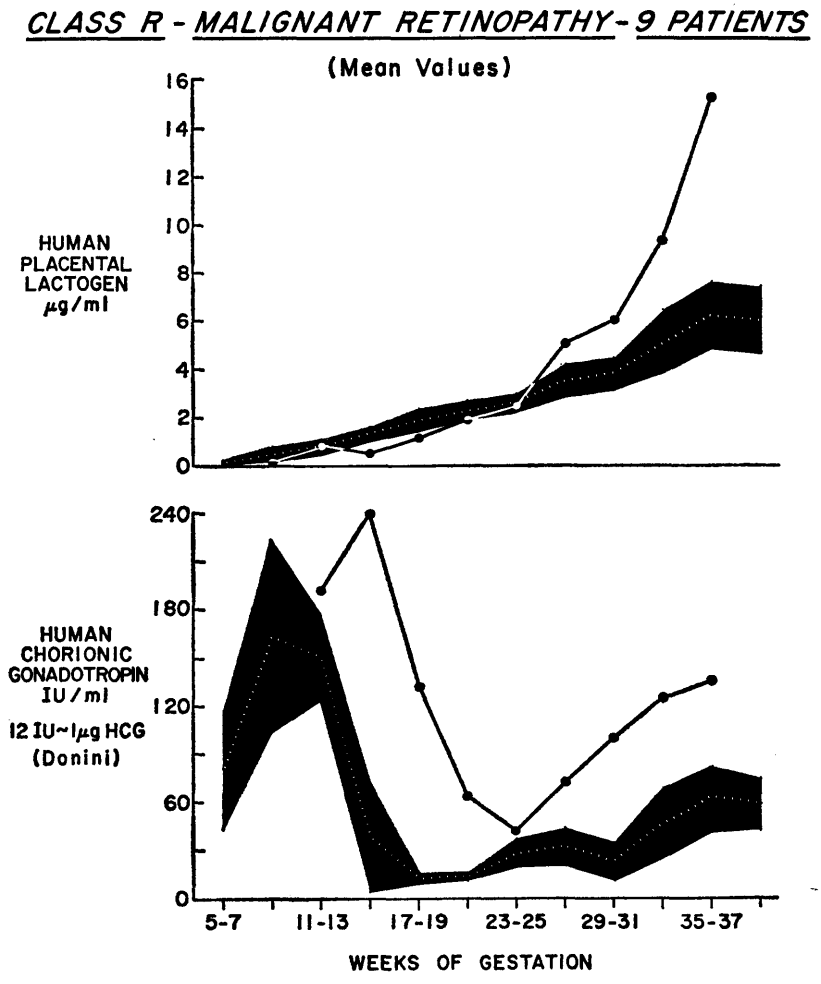

FIG. 5.

Patterns of serum IR-HPL and IR-HCG in nine Class R patients of the Joslin group. See legend figure 1 for explanation of symbols.

and the magnitudes of serum IR-HPL and IR-HCG levels were similar to the hormonally treated Joslin group.

Correlations of serum levels of IR-HPL at term with placental and fetal weights are shown in table 3. As shown previously for nondiabetic pregnancy and confirmed in this study in diabetic pregnancy, serum IR-HPL levels at term correlate significantly with placental weights and, in general, with fetal weights. There did not appear to be such a correlation when serum IR-HCG levels were compared with placental or fetal weights.

DISCUSSION

The patterns of serum IR-HPL and IR-HCG through-

TABLE 3

Correlation of serum IR-HPL levels at term with placental and fetal weights

Groups compared	Number of subjects	Weight (gm.) (Mean ± S.D.)	IR-HPL (µg./ml.)	Correlation coefficient (R)	Significance (p)	Remarks
IR-HPL: P.W.*	36	536.9±119.6†	11.6±6.0	0.5765	< 0.001	Highly significant
IR-HPL: F.W.*	32	3,076 ± 0.51†	11.5±5.7	0.3971	< 0.05	Significant

* P.W.—placental weight; F.W.—fetal weight.

† Approximate weights of nondiabetic placentas at thirty-five to thirty-eight weeks are 410-425 gm. (Beverschke, K. and Driscoll, S. G. The Pathology of the Human Placenta, Springer-Verlag, p. 457, 1967). Approximate nondiabetic fetal weights at thirty-five to thirty-eight weeks are 1,320-1,430 gm.

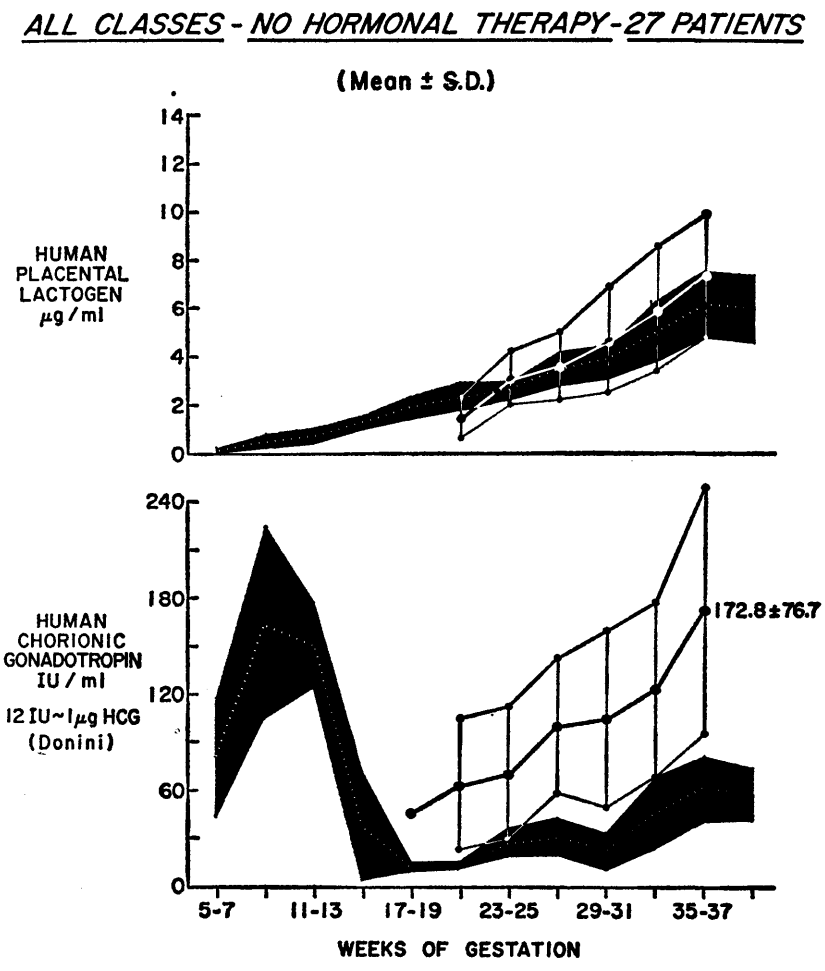

FIG. 6.

Patterns of serum IR-HPL and IR-HCG in twenty-seven diabetic pregnancies (all classes) followed at the Boston Hospital for Women (Lying-In Division). No estrogen/progesterone therapy was given these patients. See legend figure 1 for explanation of symbols.

out diabetic pregnancy are similar qualitatively to normal pregnancy but differ strikingly from normal in magnitude and variability. Although some investigators have not reported significant elevations above normal term values for IR-HPL in diabetic pregnancy,[7,20-23] this has been a consistent finding in our laboratory[8,11,17,19] and has been reported by others.[24,25] The present report confirms and extends these latter observations. There does not appear to be any significant influence on IR-HPL levels of estrogen/progesterone therapy since similar values were also noted in a small group of patients not treated with these hormones. Failure to observe increased serum levels of IR-HPL in some series of diabetic pregnancy probably resulted from insufficient numbers of diabetic patients, the time of sampling prior to delivery, and selectivity [a preponderance of patients with mild diabetes (Class A) would probably not evidence any significant deviation from normal]. Appropriate serial measurements of serum levels of IR-HPL appear to furnish important information to the physician concerning the integrity and viability of the feto-placental unit.

Correlation of serum IR-HPL levels with placental weights has been a consistent finding in our patients[11,17,19] and this relationship is confirmed here for diabetic pregnancy. It is thus evident that serum IR-HPL levels can be interpreted to be a reasonable measure of the integrity of placental mass.[26]

Little information has been available in the past regarding the clinical significance of serum levels of HCG. The recent application of radioimmunoassay to measurements of this important polypeptide hormone now permits more detailed investigations of the secretion and pathophysiologic significance of this placental hormone. Normal patterns of serum IR-HCG levels are similar to those reported using bioassays[27,28] or other immuno-

assays.[29-31] There is a rapid and intense secretion of this hormone in early pregnancy. Maximal placental secretory rates of 5 x 10^5 to 1 x 10^6 I.U./day (about 0.5-1.0 gm.) have been estimated[27] comparable to the extremely high rates for IR-HPL of around 1.0 gm./ day.[32] Because of the longer serum half-life of HCG than HPL, this hormone can be detected in the serum and urine long after parturition.[27,28]

The present observations that serum IR-HCG levels are generally increased in diabetic pregnancy confirms earlier studies by bioassay.[5,6,33] The significance of the striking variability in values for different pregnant diabetics is not yet clear, nor is there adequate data indicating any possible prognostic value to such measurements. Unfortunately, data on serum levels of IR-HCG in the small groups of diabetic patients in this investigation are insufficient to permit adequate conclusions regarding relationship of this hormone to fetal outcome.

The paucity of information regarding the physiologic role of HCG, particularly in late pregnancy, makes it difficult to assign significance to the abnormal patterns in diabetes. However, it is interesting to speculate that placental HCG is a primitive hormone necessary for initial survival of the implanted ovum. It may play only a permissive role once placento-fetal autonomy is achieved. Perhaps this primitive function is reactivated if the conceptus is threatened later in pregnancy. Such a view is consistent with observations[34] that HCG acts to stimulate the androgenic zone of the fetal adrenal preferentially for secretion of dehydroepiandiosterone (DHEA) to provide ample precursors for placental conversion to estrogens. Estriol, or perhaps DHEA, may act as a rate-limiting regulator of placental HCG production. This explanation is supported by the earlier observations of Smith and Smith[5] and White[33] that in diabetic pregnancy, rising urinary HCG levels were accompanied by diminishing levels of progesterone and estrogens.

The data in this report are inadequate for meaningful correlation of serum IR-HPL and IR-HCG levels with the outcome of pregnancy. However, three different patterns of the relationship between serum IR-HPL and IR-HCG were observed which appear to relate significantly with the clinical course of pregnancy. These are shown in figure 7. Pattern I is characterized by normal or low serum IR-HCG levels with disproportionally high serum IR-HPL levels. Pattern II is evidenced by concomitantly elevated levels of both placental hormones, and pattern III by high serum IR-HCG levels despite normal values for IR-HPL. The majority of diabetic pregnancies conform to pattern II and have a relatively uneventful clinical course. Closer observation of patients with pattern I (high IR-HPL) indicates a concurrent disproportionately increasing insulin resistance. The diabetes in these patients is more difficult to control adequately but the pregnancy usually terminates successfully. In patients with pattern III (high IR-HCG), insulin requirements tend to remain stable or, at times, to decrease slightly despite the characteristic insulin resistance of late pregnancy. A sudden marked decrease in insulin requirement is generally considered an ominous sign in late diabetic pregnancy.

The diabetogenic properties of HPL are now well established and appear to be similar to those of HGH. This is not unexpected, particularly in view of the biologic and molecular similarities of these two polypeptide hormones. Recent evidence suggests some relationship between serum IR-HPL levels and insulin-glucose homeostasis.[35]

The finding of high serum IR-HPL levels in diabetic pregnancy correlating with increasing insulin resistance is thus not surprising. In this regard, it is useful to recall some clinical observations regarding the alterations induced by pregnancy in diabetic patients. Generally, early pregnancy little alters insulin and carbohydrate metabolism. This is true in the nondiabetic as well as the stable diabetic. In some diabetic individuals, however, early pregnancy improves carbohydrate metabolism as reflected by decreased insulin requirements and unexpected hypoglycemia. Early pregnancy is associated with only minimal quantities of serum HPL but with tremendous amounts of HCG, reaching a peak at around eight to ten weeks. As pregnancy progresses beyond the twelfth week, insulin resistance gradually increases along with carbohydrate intolerance. In the last trimester, when there is usually the greatest degree of insulin resistance, serum HPL levels become maximal and plateau around the thirty-sixth week. At this date, there is a marked preponderance of HPL over HCG in contrast to early pregnancy where the converse exists.

The metabolic role of HCG in regulation of carbohydrate metabolism is currently unknown. It may perhaps have an insulin-enhancing action, either directly or indirectly through alterations in steroid secretions or metabolism. On the other hand, the fluctuations in serum IR-HCG levels may merely reflect some general placental dysfunction only remotely related to hormonal action, perhaps vascular in origin. Further clinical studies are currently in progress to assess these correlations in greater detail.

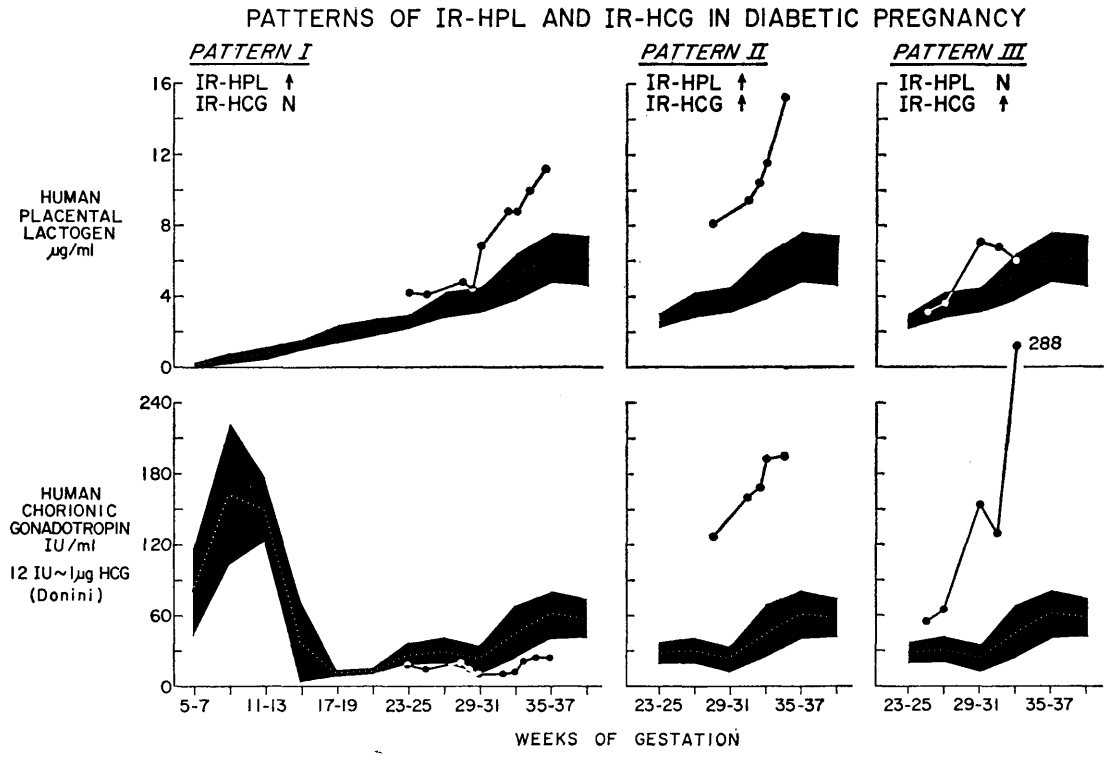

FIG. 7. Three representative characteristic patterns of IR-HPL and IR-HCG in diabetic pregnancy. In pattern I, there is a disproportionately high secretion of serum IR-HPL; in pattern II, both IR-HPL and IR-HCG are increased; and in pattern III, there are disproportionately high levels of IR-HCG. See text for interpretation.

ACKNOWLEDGMENT

The authors are grateful to the physicians of the Joslin Clinic and the Boston Hospital for Women (Lying-In Division) for their generous support in this investigation.

The work was supported in part by a Grant for Immunologic Research from the John A. Hartford Foundation and by a U. S. Public Health Service Grant No. HDO 1793.

REFERENCES

[1] Kyle, G. C.: Diabetes and pregnancy. Ann. Intern. Med. 59 (Suppl. 3):1-82, 1963.

[2] Spellacy, W. N., and Goetz, F. C.: Plasma insulin in normal late pregnancy. New Eng. J. Med. *268*:988-91, 1963.

[3] Kalkhoff, R. K., Schalch, D. S., Walker, J. L., Beck, P., Kipnis, D. M., and Daughaday, W. H.: Diabetogenic factors associated with pregnancy. Trans. Ass. Amer. Physicians 77: 270-79, 1964.

[4] Kalkhoff, R. K., Richardson, B. L., and Beck, P.: Relative effects of pregnancy, HPL and prednisone on carbohydrate tolerance in normal and subclinical diabetic subjects. Diabetes *18*:153-63, 1969.

[5] Smith, O. W., Smith, G. Van S., Joslin, E. P., and White, P.: Prolan and estrin in the serum and urine of diabetic and nondiabetic women during pregnancy, with especial reference to late pregnancy toxemia. Amer. J. Obstet. Gynec. *33*:365-79, 1933.

[6] Loraine, J. A.: The excretion of chorionic gonadotropin by pregnant diabetics. Brit. Med. J. 2:1496-98, 1949.

[7] Samaan, N. A., Bradbury, J. T., and Goplerud, C. P.: Serial hormonal studies in normal and abnormal pregnancy. Amer. J. Obstet. Gynec. *104*:781-94, 1969.

[8] Varma, K., White, P., Younger, D., Emerson, K., Jr., and Selenkow, H. A.: Patterns of serum immunoreactive human placental lactogen (IR-HPL) and human chorionic gonadotropin (IR-HCG) in diabetic pregnancy. Presented in part at the 30th Annual Meeting of the American Diabetes Association, St. Louis, Missouri, June 13-14, 1970. Diabetes *19* (Suppl. 1):363-64, 1970. Abstract.

[9] Grumbach, M. M., Kaplan, S. L., Sciarra, J. J., and Burr, I. M.: Chorionic growth hormone prolactin (CGP): Secretion, disposition, biologic activity in man, and postulated function as the "growth hormone" of the second half of pregnancy. Ann. N.Y. Acad. Sci. *148*:501-31, 1968.

[10] Samaan, N., Yen, S. C. C., Gonzalez, D., and Pearson,

O. H.: Metabolic effects of placental lactogen (HPL) in man. J. Clin. Endocr. *28*:485-91, 1968.

[11] Selenkow, H. A., Saxena, B. N., Dana, C. L., and Emerson, K., Jr.: Measurement and pathophysiologic significance of human placental lactogen. *In* The Foeto-Placental Unit, Int. Congr. Series No. 183. A. Pecile and C. Finzi, Eds. Excerpta Medica Found., Amsterdam, 1969, p. 340-362.

[12] Spellacy, W. N.: Human placental lactogen (HPL). The review of a protein hormone important to obstetrics and gynecology. Southern Med. J. *62*:1054-57, 1969.

[13] Samaan, N. A., Bradbury, J. T., and Goplerud, C. P.: Serial hormonal studies in normal and abnormal pregnancy. Amer. J. Obstet. Gynec. *104*:781-94, 1969.

[14] Kalkhoff, R. K., Richardson, B. L., Beck, P., and Stoddard, F. J.: Effects of placental lactogen and glucocorticoids on glucose tolerance in normal and diabetic subjects. Clin. Res. *15*:321, 1967. (Abstract).

[15] Josimovich, J. B.: Potentiation of somatotrophic and diabetogenic effects of growth hormone by human placental lactogen (HPL). Endocrinology *78*:707-14, 1966.

[16] White, P.: Pregnancy and diabetes, medical aspects. Med. Clin. N. Amer. *49*:1015-24, 1965.

[17] Saxena, B. N., Refetoff, S., Emerson, K., Jr., and Selenkow, H. A.: A rapid radioimmunoassay for human placental lactogen (HPL) in normal and molar pregnancy. Amer. J. Obstet. Gynec. *101*:874-85, 1968.

[18] Varma, K., Larraga, L., and Selenkow, H. A.: Radioimmunoassay of serum human chorionic gonadotropin during normal pregnancy. Obstet. Gynec. *37*:10-18, 1971.

[18a] Varma, K., Driscoll, S. G., Emerson, K., Jr., and Selenkow, H. A.: Clinical and pathologic evaluation of serum immunoreactive human placental lactogen (IR-HPL) in abnormal pregnancy. Obstet. Gynec. Oct. 1971. In press.

[19] Saxena, B. N., Emerson, K., Jr., and Selenkow, H. A.: Serum placental lactogen (HPL) levels as an index of placental function. New Eng. J. Med. *281*:225-31, 1969.

[20] Beck, P., Parker, M. L., and Daughaday, W. H.: Radioimmunologic measurement of HPL in plasma by double antibody method during normal and diabetic pregnancies. J. Clin. Endocr. *25*:1457-62, 1965.

[21] Gusdon, J. P., Jr.: Improved hemagglutination-inhibition assay: Clinical application to measurement of human placental lactogen. Obstet. Gynec. *33*:397-403, 1969.

[22] Josimovich, J. B., Kosor, B., Boccella, L., Mintz, D. H., and Hutchinson, D. L.: Placental lactogen in maternal serum as an index of fetal health. Obstet. Gynec. *36*:244-49, 1970.

[23] Spellacy, W. N., Teoh, E. S., Buhi, W. C., Birk, S. A., and McCreary, S. A.: Value of human chorionic somatomammotropin in managing high-risk pregnancies. Amer. J. Obstet. Gync. *109*:588-98, 1971.

[24] Zuckerman, J. E., Fallon, V., Tashjian, A. H., Jr., Levine, L., and Friesen, H. G.: Rapid, quantitative estimation of human placental lactogen in maternal serum by complement fixation. J. Clin. Endocr. *30*:769-73, 1970.

[25] Singer, W., Desjardine, P., and Friesen, H. G.: Human placental lactogen. Obstet. Gynec. *36*:222-32, 1970.

[26] Sciarra, J. J., Sherwood, L. M., Varma, A. A., and Lundberg, W. B.: Human placental lactogen (HPL) and placental weight. Amer. J. Obstet. Gynec. *101*:413-16, 1968.

[27] Diczfalusy, E., and Troen, P.: Endocrine functions of the human placenta. Vitamins Hormones (NY) *19*:229-311, 1961.

[28] Fuchs, Fritz: Endocrine factors in the maintenance of pregnancy. Acta Obstet. Gynec. Scand. Suppl. *41*:7-44, 1962.

[29] Brody, S., and Carlstrom, G.: Immunoassay of human chorionic gonadotropin in normal and pathologic pregnancy. J. Clin. Endocr. *22*:564-74, 1962.

[30] Mishell, D. R., Jr., Wide, L., and Gemzell, C. A.: Immunologic determination of human chorionic gonadotropin in serum. J. Clin. Endocr. *23*:125-31, 1963.

[31] McCarthy, C., Pennington, G. W., and Crawford, W. S.: Chorionic gonadotropin excretion in normal and abnormal pregnancy. Clin. Obstet. Gynec. *11*:86-91, 1964.

[32] Kaplan, S. L., Gurpide, E., Sciarra, J. J., and Grumbach, M. M.: Metabolic clearance rate and production rate of chorionic growth hormone prolactin in late pregnancy. J. Clin. Endocr. *28*:1450-60, 1968.

[33] White, P., and Hunt, H.: Pregnancy complicating diabetes. A report of clinical results. J. Clin. Endocr. *3*:500-16, 1943.

[34] Lauritzen, C., and Lehmann, W. D.: Levels of chorionic gonadotrophin in the newborn infant and their relationship to adrenal dehydroepiandrosterone. J. Endocr. *39*:173-82, 1967.

[35] Burt, R. L., Leake, N. H., and Rhyne, A. L.: Human placental lactogen and insulin-blood glucose homeostasis. Obstet. Gynec. *36*:233-37, 1971.