Human Placental Lactogen and Other Placental Proteins as Indicators of Fetal Well-Being

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The knowledge that sera from pregnant women contain pregnancy-specific hormones is not new. Ascheim and Zondek discovered chorionic gonadotropin in 1927.[1] However, it was not until 1962 that a second hormone, namely, human placental lactogen (hPL), was isolated.[2] Both of these substances are glycoproteins produced by the syncytiotrophoblast and released predominantly into the maternal circulation. Human placental lactogen in particular has been widely employed for clinical fetoplacental assessment.[3]

Although it has long been suspected that other hormones are present in the sera of pregnant women, it has only been within the past decade that improved laboratory techniques plus increased interest have resulted in the isolation of numerous other pregnancy-associated and/or trophoblast-specific hormones. The purpose of this article will be to review the role of hPL and the newer hormones as indicators of fetal well-being.

Human Placental Lactogen

As mentioned, the isolation and purification of hPL was accomplished in 1962 by Josimovich and MacLaren.[2] Human placental lactogen is a single-chain protein of 190 amino acids with two interchain disulfide bonds and a molecular weight of 21-23 K. The chemical characterization and primary sequencing as described by Sherwood and Handwerger[4] have confirmed an 84% homology between the amino acid sequence of hPL and human growth hormone (hGH). More recently, Shine et al. and Seeburg et al.[5,6] were able to reconstruct the complementary DNA nucleotide sequence

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TABLE 1. Alternative Nomenclature of Pregnancy Hormones*

I.	Schwangerschaftsspecifiche beta$_1$-glycoprotein (SP1)
	Pregnancy-specific beta$_1$-glycoprotein (PSBG)
	Pregnancy-associated plasma protein C (PAPP-C)
	Trophoblast-specific beta$_1$-globulin (TSG)
II.	Human placental lactogen (hPL)
	Human chorionic somatomammotropin (hCS)
	Pregnancy-associated plasma protein D (PAPP-D)
III.	Pregnancy-associated alpha$_2$-glycoprotein (α_2-PAG)
	Pregnancy zone protein (PZP)
	Pregnancy-associated alpha$_2$-globulin
	Alpha$_2$-pregnoglobulin

*Other hormones are commonly referred to by a single name.

for hPL and reconfirmed its extensive homology with hGH. As might be anticipated from its structural homologies, hPL resembles both prolactin and hGH in its bioactivity. In both traditional bioassays and in receptor-binding studies, hPL is cross-reactive with both hGH and prolactin. Human placental lactogen shows a high degree of binding with lactogenic receptors, and its activity at these receptors is equal to that of hGH. A weaker cross-reactivity is seen with lymphocyte receptors for hGH (0.03% specific binding). Human prolactin, by contrast, showed no activity in this system.[7] Specific hPL receptors have not been isolated in humans, and the biologic activity of hPL is presumed to be mediated through prolactin and hGH receptors.

Human placental lactogen is synthesized through a precursor called pro-hPL, which is larger by some 25 amino acids than the mature hormone. The precursor is cleaved on the endoplasmic membrane prior to secretion.[8,9] Synthesized by the syncytiotrophoblast, hPL can be isolated from maternal and fetal serum, maternal urine, and amniotic fluid. Both maternal and neonatal serum levels drop rapidly following delivery but maternal levels remain unchanged if selective fetectomy is performed and the placenta left in situ. A serum half-life of 30 minutes has been derived by Samaan.[10] Human placental lactogen secretion at term may reach 3 g/24 hr in normal pregnancies, and it is a major protein synthetic product of the human placenta near term.

Human placental lactogen secretion is largely autonomous. The serum levels show no circadian rhythm and no consistent variation with changes in maternal posture, activity level, smoking, the onset of labor, or brief periods of hypoglycemia.[11-13] The hPL concentration in maternal serum is some 300 times greater than the level in umbilical venous blood. HPL enters amniotic fluid by simple diffusion[14]; and its levels in amniotic fluid, are parallel to, but much lower than, maternal levels.[15] The function of the small quantities of hPL found in amniotic fluid and fetal serum is unknown.

Production of hPL during gestation can first be detected by radioimmunoassay at 20-40 days after implantation and shows a gradual rise until 37 weeks' gestation. Beyond this time a slight but progressive decline occurs, and by 42 weeks' gestation a significant decrease can be demonstrated.[16]

The rise in maternal serum hPL levels parallels the increase in placental volume during pregnancy. As might be expected, clinical conditions resulting in larger placental mass, such as multiple pregnancy, erythroblastosis, and poorly controlled maternal diabetes mellitus, are associated with higher maternal serum hPL values.

The action of hPL on human tissue and its proposed physiologic role in pregnancy have been extensively investigated. While hPL does have growth hormone-like activities, these activities are weak. Doses 200 times those of hGH are necessary to show equivalent growth stimulation.[17] Human placental lactogen can also stimulate production of somatomedins in both pregnant and nonpregnant subjects. By the action of maternal somatomedins at specific placental receptors, it has been suggested, hPL may contribute to the regulation of substrate availability to the growing fetus.[18]

The lactogenic activity of hPL has been documented in animal models.[19] However,

current evidence from human studies does not support a role for hPL in preparation for human lactation. In addition, hPL is not luteotropic in human studies.[20] An immunosuppressive effect has been demonstrated for hPL[21,22]

Human placental lactogen also has effects on fat metabolism. Administration of hPL to nonpregnant hypopituitary dwarfs in concentrations adequate to achieve blood levels seen in late pregnancy increases serum free fatty acids and glycerol.[23] It also stimulates lipolysis in adipose tissue in both gravid and nongravid women.[24] It has been suggested that this increased lipolytic activity is due to the action of a hormone-sensitive lipase.[25]

The effect of hPL on carbohydrate metabolism has also been extensively studied. With hPL infusions, impaired glucose tolerance in nonpregnant women has been demonstrated despite augmented insulin responses.[26] In hypophysectomized nonpregnant diabetics, hPL influsion increased fasting glucose and urinary glucose excretion and decrease glucose tolerance.[27] Human placental lactogen is postulated to contribute to this relative insulin resistance and glucose-sparing as a result of its actions on adipose cells, causing increased intracellular free fatty acid levels, which then block peripheral uptake and utilization of glucose. Such increases in free fatty acids can inhibit the enzymatic reactions necessary for glycolysis. As previously stated, accelerated lipolysis also increases serum free fatty acid and triglyceride levels, allowing the transfer of triglycerides and free fatty acids to the liver for gluconeogenesis, further facilitating glucose availability.

The presence of high hPL levels in maternal serum and its described physiologic effects on fatty acid and carbohydrate metabolism have led to speculation that hPL functions as a major physiologic regulator of intermediary metabolism in late pregnancy. Through its glucose-sparing and free-fatty-acid-mobilizing acitivites, hPL helps assure a constant supply of glucose to the developing fetus. Although such statements imply a definite requirement for hPL during normal pregnancy, it is worth noting that it is apparently possible to complete normal pregnancies in the absence of hPL secretion,[28–31] as an increasing number of case reports document. No sex linkage has been confirmed,[28] and no associated placental or maternal abnormalities have been found with hPL deficiency.

As previously mentioned, the major determinant of maternal serum hPL concentration is the volume of functional syncytiotrophoblast. Human placental lactogen has, therefore, been evaluated extensively in an attempt to monitor placental function and thereby assess fetal well-being. Numerous studies have evaluated hPL values in early complications of pregnancy. In patients with first-trimester threatened abortion, low maternal serum hPL values have correlated with an increased risk of subsequent miscarriage.[32–34] However, such correlations are far from perfect, and it seems generally agreed that therapeutic intervention of nonintervention should not be based on hPL values alone.

Human placental lactogen has been studied in patients with molar pregnancy and trophoblastic tumors. In general, hPL values are substantially lower than would be expected in normal pregnancies of similar duration.[35] Human chorionic gonadotropin levels are considered to be of more value in the monitoring of such patients. Goldstein has also shown that hPL levels are lower when the trophoblastic tissue appears malignant.[36] Human placental lactogen has also been isolated from the sera of patients with nontrophoblastic tumors,[37] including lung and liver tumors, lymphoma, and pheochromocytoma.

As mentioned, normative studies have demonstrated a progressive rise in maternal serum hPL values until 37 weeks' gestation, after which time levels remain constant or decline slightly.[16,38–41] Mean values near term are in the range of 5.4–7.0μg/ml, with those values below 4μg/ml generally be-

lieved to represent a small placenta and, therefore, an increased probability of fetoplacental compromise. Values of less than 4 μg/ml beyond 30 weeks' gestation have been designated as being within the "fetal danger" zone,[42] with consistently low values being as ominous as values that decrease from the normal range. Spellacy has reported that the risk to the fetus progressively increases with progressive decreases in maternal serum hPL values.[43]

Maternal serum hPL has been advocated as a screening procedure for all pregnant patients.[44-47] However, other studies,[48-52] the majority of which have been in recent years, have questioned the efficacy of this approach and have suggested that hPL determinations be reserved for specific clinically identifiable high-risk pregnancies.

The incidence and degree of fetoplacental macrosomia with maternal diabetes mellitus has progressively diminished as closer attention has been directed toward careful blood glucose control. In spite of this, the placentas in diabetic pregnancies are often large, and most investigators report normal to high hPL levels in diabetic pregnancies.[41,53-56] In spite of suggestions that the fetal danger zone be revised upward, hPL determinations have been of limited value in the management of diabetic pregnancy, because many diabetic stillbirths occur as acute events unrelated to chronic and/or progressive placental insufficiency.

The incidence of pregnancies complicated anti-D isoimmunization has diminished because of passive immunization techniques as well as improved blood crossmatching procedures. However, a persistent number of isoimmunized patients are still encountered. Because significantly involved gestations are associated with large placentas, hPL values might be expected to be in or above the normal range. Several reviews have found this to be the case.[41,54,57-59] Like those related to diabetes, isoimmunization-related stillbirths often occur as a result of acute or subacute fetal disease unrelated to chronic and/or progressive placental insufficiency. Human placental lactogen is thus of little value in the monitoring of pregnancies complicated by isoimmunization.

Multiple gestation remains a significant contributor to perinatal wastage, partially because of an increase risk of preeclampsia and premature delivery and partially because of a persistent clinical inability to diagnose the condition early enough in pregnancy to allow early monitoring or therapy for complications of pregnancy. Because of the increased syncytiotrophoblast mass associated with multiple gestation, maternal serum hPL concentrations might be expected to be elevated in all three trimesters. This has been documented by several investigators.[60-62] Maternal serum hPL screening, with follow-up ultrasound examination of elevated values, has been reported and has both improved the incidence of diagnosis and permitted the diagnosis to be made earlier in pregnancy.[63]

In the past two decades the importance of adequate fetal growth for duration of gestation has been recognized. Inadequate fetal growth for duration of gestation, commonly called intrauterine growth retardation (IUGR) is a clinically important corollary. IUGR may be the result of any combination of maternal, fetal, or placental diseases and has repetitively been shown to be associated with increased perinatal morbidity and mortality.[64,65] Most attempts to detect IUGR by clinical parameters alone have been disappointing, identifying only about 30% of those infants in the lowest 10th percentile of weight for gestational age.[66] Because IUGR is frequently associated with a reduction in functional placental tissue, maternal serum hPL values have been extensively evaluated in an attempt to improve the antenatal detection and treatment of IUGR. The results are inconclusive; some studies have been extremely optimistic,[67,68] others have been pessimistic,[69] and the majority report low maternal serum hPL values in 32%[70] to 60%[41] of IUGR pregnancies. The predictive ability of hPL alone thus is not good.

Several authors have recommended that IUGR be suspected in all near-term pregnancies in which the maternal serum hPL value is less than 5 μg/ml.[41,71] Certainly any patient thus identified should be carefully monitored with several accepted means of assessing fetal well-being, both during the remaining antepartum period as well as during labor. However, Hobbins and Berkowitz[72] have reported that when hPL is used as the sole identifier of patients at risk for IUGR, approximately one-third of actual IUGR fetuses would not have the benefit of additional fetal surveillance. Since hPL is a placental hormone (and not all cases of IUGR are related to placental insufficiency), it is not unexpected that some cases of IUGR are associated with normal hPL values.

It has long been recognized that hypertension in pregnancy is associated with small placentas, and evidence exists that suggests that the observed lowering of maternal serum hPL values associated with hypertension is proportional to the diminution of placental villous surface area.[73]

In a study of pregnancies complicated by hypertension, Kelly and associates[74] found that hPL most accurately predicted fetal compromise when associated with IUGR. Of perhaps greater significance, only 50% of the adverse outcomes (neonatal asphyxia, fetal distress, or IUGR) were predicted by low hPL values. Morrison and associates[75] also found that hPL values were acceptably sensitive only in those hypertensive pregnancies associated with growth-retarded fetuses.

In preeclampsia, hPL values also tend to be reduced, generally being lowest in multigravidas with severe hypertension.

From these and other reported series, it appears that hPL levels are often subnormal in hypertensive pregnancies. Low values are frequently associated with fetal or neonatal distress, but this is by no means always the case. Conversely, the presence of normal hPL values should not be interpreted as an assurance that complications will not occur. Several studies[76,77] suggest that hPL may provide some additional diagnostic specificity when combined with other parameters of fetoplacental well-being.

Although many postdate obstetric patients are subjected to varying fetoplacental surveillance protocols, a significant number of them will have no evidence of IUGR or fetal compromise and will deliver healthy infants. A frequent explanation can be found in the difficulties associated with the correct assessment of the duration of gestation, especially in women with irregular menses, who become pregnant shortly after discontinuing oral contraceptives or who do not register for prenatal care until late in pregnancy. However, those patients who can reliably be documented to still be pregnant beyond the 42nd week of gestation are at an increased risk of progressive placental insufficiency[78,79] and might be expected to have low or falling serum hPL values. Such results have been reported.[34,54] However, others have subsequently found hPL values to be of little clinical usefulness in this situation.[80]

Several small series[81,82] have suggested that hPL values may be low in association with major fetal congenital anomalies. However, in a larger series of 113 pregnancies complicated by congenital anomalies[83] the investigators were unable to document any significant difference. Such findings might be expected, since low hPL values reflect only functional placental mass.

The preceding literature review suggests that maternal serum hPL values may deviate from normal when the pregnancy is complicated by conditions that diminish functional placental mass. Low hPL values do correlate to some extent with fetal outcome in pregnancies complicated by IUGR and hypertension. While earlier reports suggested that hPL was of value in postmature pregnancies, more recent reports have questioned this recommendation. Elevated hPL values in late-second- or early-third-trimester pregnancies may be helpful in identifying multiple gestations. Human placental

lactogen has not been helpful in identifying those gestations complicated by fetal anomalies. Likewise, hPL values are of little help in diabetes or isoimmunization, where the major fetal risks are unrelated to chronic placental insufficiency.

Pregnancy-Specific Beta$_1$-Glycoprotein

Pregnancy-specific beta$_1$-glycoprotein (also known as Schwangerschaftsspezifisches beta$_1$-glycoprotein, or SP1) is a glycoprotein that can be detected as early as 18–23 days after ovulation.[84] Although suggestions have been made that it is produced in the maternal liver and merely absorbed by the trophoblast[85] or that it is released from disintegrating migrating trophoblastic tissue,[86] most authorities agree that it is produced by the syncytiotrophoblast.[87] Besides being produced by certain tumors, SP1 is also produced by human fibroblast cell strains and human amniotic fluid cell cultures.[88] Maternal serum levels early in pregnancy initially parallel human chorionic gonadotropin (hCG) levels, but SP1 levels continue to rise beyond 8 weeks of pregnancy, suggesting separate synthesis sites in the syncytiotrophoblast.[89] It has a half-life of 30–40 hours.[90] The molecular weight is 90,000 daltons, and approximately 30% of the molecule is carbohydrate. On electrophoresis it moves as a beta$_1$-globulin. Like hPL, it has been found to have a larger form of molecule.[91] It is unclear whether it might be a prohormone. However, currently available radioimmunoassay techniques[92] should minimize this confusion. The smaller molecule is now known as the *beta-form* and was the protein originally described by Tatarinov and Masyukevich in 1970.[93] The larger form is designated the *alpha-form.* Available antisera are reported to vary in their ability to recognize SP1-alpha, and this should always be considered in any clinical situation. In addition, Teisner and associates[91] have also shown that the proportions of SP1-alpha and SP1-beta may vary among patients. Although they report that the ratio of SP1-alpha to SP1-beta remains constant in each patient, Grudzinskas and associates[94] report that the half-life of SP1-alpha is shorter than that of SP1-beta after delivery of the placenta. Maternal serum levels of SP1 gradually rise through pregnancy, in a pattern very similar to the secretion of hPL,[95] although SP1 levels in late pregnancy rise more rapidly than hPL levels. This chronologic similarity is also paralleled by the placental weight curve. SP1 is also present in low concentrations in amniotic fluid, maternal urine, and cord blood.

The biologic action of SP1 is unclear at this time, but it may function in the regulation of maternal carbohydrate metabolism, as a transport protein, as an immunosuppressive, or with some combination of these actions.

Several studies have demonstrated a coefficient of variation in late-pregnancy SP1 values of about 30%.[96] While this might suggest a substantial overlap between normal and abnormal pregnancies, the intrapatient day-to-day variability is remarkably low.[97]

A multitude of papers in the past 6–7 years, primarily in the British literature, have reported on the usefulness of SP1 in monitoring normal and abnormal pregnancy.

SP1 has been reported to be of value in the early diagnosis of pregnancy,[92] although there is no evidence to suggest that it is of any more value than currently available hCG assays.

First-trimester SP1 values are frequently lower in patients who will have spontaneous first-trimester miscarriages. This observation has been applied specifically to the problems of threatened abortion[98] and ectopic pregnancy.[99] Chapman and associates[100] have shown that early-second-trimester values do not correlate with birth weight, placental weight, clinical outcome, or AFP values, although others disagree with this finding.[70,101] However, late-sec-

ond-trimester and early-third-trimester values have been shown to correlate.

Heikinheimo and Unnerus[102] have investigated the usefulness of SP1 assays in preeclamptic pregnancies. Except for those preeclamptic pregnancies complicated by associated intrauterine growth retardation, SP1 values were indistinguishable from those of control patients.

Towler and associates have reported that high SP1 levels can be of help in the diagnosis of multiple gestation.[103] Grudzinskas and associates[104] have shown SP1 levels to be in the normal range in diabetic pregnancies.

High SP1 levels have been reported to be of use in confirming fetal macrosomia,[105] and low values have reportedly been predictive of intrauterine growth retardation,[70,106] although not all authors agree with the latter finding.[107] As with hPL, SP1 values in maternal serum are lower at any duration of pregnancy in women who smoke.[108]

SP1 is produced by trophoblastic tumors[109] and has been utilized as a tumor marker for patient follow-up.[110] It is now known to occur in other tumors as well, including testicular tumors,[105] breast tumors,[111] and lung tumors.[112]

Pregnancy-Associated Plasma Protein A

Pregnancy-associated plasma protein A (PAPP-A) was isolated from the serum of pregnant women by Lin and associates in 1974.[113] The molecule is of placental origin, and its concentration increases in parallel with the growth of the placenta.[95] It is produced by the syncytiotrophoblast,[87] although a recent publication suggests that PAPP-A may be present in nonpregnant sera as well.[114] Although not previously detected prior to 12 weeks' gestation, recently reported improved immunoassay techniques[115] allow its reproducible detection as early as the 6th week of pregnancy. Smith and associates[116] report a steady increase in PAPP-A levels throughout the third trimester, the highest levels being reported in patients in early labor. This is a pattern different from that of most of the other placental hormones, which tend to plateau in the latter weeks of pregnancy. Bischof and associates[117] have shown that increasing maternal age and parity, as well as increased maternal body weight, are associated with decreased maternal serum PAPP-A levels, but that increased maternal serum PAPP-A levels were associated with pregnancies carrying male fetuses, Rh-negative fetuses, and infants with Apgar scores higher than 7 at 1 minute. The molecular weight of PAPP-A is approximately 750,000 daltons, and its half-life appears to be 3–4 days. Like other placental proteins, it is found only in trace concentrations in compartments other than the maternal circulation.

Bischof has investigated possible biologic functions of PAPP-A.[118] He demonstrated an in vitro inhibition of the complement system. In addition, evidence of plasmin activation suggested that PAPP-A might play a role in the regulation of fibrinolysis during pregnancy.

The feasibility of using PAPP-A as a screen for pregnancy dysfunction has been evaluated. Hughes and associates[119] evaluated the test in a series of 272 patients at 34 weeks' gestation. They found elevated average values in those patients in whom preeclampsia, premature labor, or antepartum hemorrhage, were destined to develop although there was a wide overlap with normal individuals. Patients with growth-retarded fetuses without a clinically obvious cause had normal PAPP-A values.[150]

Pregnancy-Associated Plasma Protein B

Like PAPP-A, pregnancy-associated plasma protein B (PAPP-B) was first identified by

Lin in 1974.[113] It is also a glycoprotein and has a molecular weight of approximately 1,000,000 daltons. Although it moves as a beta$_1$-globulin on electrophoresis, it is immunochemically unrelated to SP1.[95] PAPP-B appears in the maternal circulation by the early second trimester, increases gradually thereafter until term, has a half-life of less than 24 hours, and has not been detected in either amniotic fluid or cord blood.

Very little information is currently available regarding clinical correlation with PAPP-B levels. Lin, Halbert, and Spellacy[120] found that PAPP-B levels in maternal circulation correlated with placental weight but did not correlate with maternal size, parity, age, blood pressure, or fetal weight. They did find that maternal PAPP-B levels were decreased in preeclampsia and diabetes. It appeared that PAPP-B levels might be increased with multiple gestation, although only a very small number of cases were studied.

Placental Proteins

In 1972, Bohn reported the isolation of a number of proteins in human placenta extracts.[121] These substances have since been named placental proteins (PP) and have been classified by the arbitrary assignment of consecutive numbers 1 through 7. Only two have received significant evaluation: PP2 has been found to be ferritin, and PP5 has been evaluated in an assay of placental function.

PP1 is an alpha$_1$-glycoprotein with a molecular weight of approximately 160,000. It has been localized to both villous stroma and syncytiotrophoblasts but is not specific for either the placenta or pregnancy.[122]

PP3 and PP4 have not been well characterized but do not appear to be specific for the placenta.[123]

PP6 is also an alpha$_1$-glycoprotein that can be found in the nuclei of syncytiotrophoblastic cells.[124] However, it is not specific for the placenta.[125]

PP7 is also a glycoprotein that can be isolated from the placenta but not from the serum of pregnant women.[126]

Placental Protein 5

Placental protein 5 (PP5) is a glycoprotein that contains 20% carbohydrate, moves as a beta$_1$-globulin on electrophoresis, and has a molecular weight of 36,000 daltons.[127] Unlike many of the other placental hormones, PP5 can be localized in the stroma of the placental villi as well as in the syncytiotrophoblast,[124] suggesting that although PP5 appears in the maternal circulation, it is really a tissue protein. This theory would be compatible with the observations that maternal circulating levels of PP5, even at term, are very low.[128] Maternal serum values increase approximately tenfold from 8–10 weeks to 37 weeks, after which time they remain constant or decrease slightly.[129] Postpartum clearance from maternal serum follows a biphasic pattern, with an initial rapid decrease in values over the first postpartum hour, followed by a subsequent slow decrease over the next 6–7 days.[129]

Because maternal serum concentrations of PP5 are very low in the first trimester of normal pregnancies, it is unlikely that PP5 levels will be of value in the management of first-trimester complications of pregnancy. Salem and associates have shown a relationship between high midtrimester maternal serum PP5 levels and subsequent premature delivery.[101] Nesbit and associates have also recently reported on PP5 levels in complicated pregnancies.[130] PP5 levels in pregnancies involving intrauterine growth retardation were indistinguishable from control patient values. Patients with preeclampsia and multiple gestation have higher PP5 values than control patients, but a wide overlap exists. Interestingly, diabetic pregnancy was characterized by low maternal serum PP5 values in the first and second trimesters, but high levels in the third trimester. The clinical applicability of such results is unclear at this time.

PP5 values are elevated in patients who subsequently have placental abruption.[131] This may in part explain the increased tendency toward consumptive coagulopathy in these patients, because Bohn and Winckler[127] have previously shown that PP5 is an inhibitor of trypsin and plasmin. Salem and associates have also shown that addition of protamine to pregnancy serum causes an increase in levels of PP5,[132] this finding being less common in diabetic and preeclamptic pregnancies than in normal subjects. They suggest that this provides further evidence that PP5 may be involved in the coagulation system, in particular in abnormal coagulation processes at the placental site.

PP5 has also been found in patients with trophoblastic tumors and certain nontrophoblastic malignancies, including teratomas and breast tumors.

Pregnancy-Associated Alpha$_2$-Glycoprotein

Pregnancy-associated alpha$_2$-glycoprotein (α_2-PAG) is a high-molecular-weight glycoprotein present in pregnancy serum in large amounts. However, it is also present in normal male and nonpregnant female sera, being higher in females than in males and increasing with age.[105] Maternal steroid administration diminishes α_2-PAG levels by more than 50%.[133] This finding may be of significance in high-risk pregnancies treated with steroids to accelerate fetal pulmonary maturity.[134,135]

During pregnancy α_2-PAG levels progressively rise until about 34 weeks,[136] then remain constant or may fall slightly. The half-life of α_2-PAG, as judged by its disappearance rate postpartum, is probably 6–7 days.

The exact site of α_2-PAG synthesis is unclear, but it is probably the result of estrogen-mediated leukocyte stimulation.[137] It is not produced by the trophoblast. Both because of this latter fact and because of a variable distribution of levels, α_2-PAG has not generally been useful in monitoring fetal-placental function.

Damber and associates[137] have shown that women who have spontaneous abortions have lower α_2-PAG levels than do normals, although the degree of overlap is substantial.

Disagreement currently exists as to whether α_2-PAG appears to be of marginal value as a tumor marker.[138–140]

Conclusion

The past few years have seen a progressive decrease in clinical indications for maternal serum hPL determinations. Many institutions no longer employ hPL assays in their fetal surveillance protocols. Although less experience has been accumulated with the other pregnancy-associated hormones covered in this review, many authors—especially those from England and Scotland—are currently quite enthusiastic about their clinical applicability. Such enthusiasm is reminiscent of that encountered with maternal serum hPL determinations during the preceding decade, and it remains to be seen whether these newer pregnancy-associated hormone assays will pass into similar disfavor. These newer hormones have raised several fascinating questions. For example, does PAPP-A really increase more rapidly in those patients destined to become preeclamptic? Does PP5 really increase more rapidly in patients destined for placental abruption? Is the true function of these substances related to immunosuppression? If so, might they hold clues for immunosuppression in nonobstetric areas? Or might they be of value as antigens for immunologic sterilization?

Although such clinically oriented questions are intriguing, a reproducible trend seems obvious as a result of the preparation of this review, namely, that new discoveries are easy prey for immediate clinical correlation studies. While such correlations

may be of considerable value in providing optimal care for our patients, it is only with further understanding of the basic physiologic functions of these substances that we will be able to interpret them in a truly knowledgeable fashion.

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