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Hormonal monitoring of the first trimester of pregnancy

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The hormonal changes and maternal adaptations of human pregnancy are among the most remarkable phenomena in nature. Endocrinologic parameters in the early gestation period have been used to predict abnormal pregnancies and to identify fetuses that have chromosomal aberrations. This article focuses on the changes in hormones that are secreted by the maternal-fetal-placental unit that are unique for the first trimester of pregnancy and their impact on clinical outcome.

Progesterone and 17 α -hydroxyprogesterone

The principal source of progesterone during pregnancy is the placenta, although the corpus luteum is the major source during the first 6 to 8 weeks of gestation when progesterone is essential for the development of a secretory endometrium to receive and implant a blastocyst [1]. By 8 weeks' gestation, the developing trophoblasts take over as the principal producers of progesterone because removal of the corpus luteum before this time leads to abortion [2]. After 8 weeks' gestation, the corpus luteum contributes only a fraction of the progesterone that is secreted. Maternal progesterone plasma levels increase from 25 ng/mL during the late luteal phase to 40 ng/mL near the end of the first trimester to 150 ng/mL at term. Because progesterone has a shorter half-life than

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human chorionic gonadotropin (hCG), it is expected to reflect any change in the dynamics of the pregnancy more accurately.

17 α -Hydroxyprogesterone (17OHP) is a steroid that is secreted in parallel to progesterone from the corpus luteum. 17OHP may be a better marker of corpus luteum function in early pregnancy than progesterone because there is limited placental hydroxylation at this stage.

A single measurement of serum progesterone level has been used to distinguish a normal pregnancy from a nonviable or an ectopic one. A value of 25 ng/mL or more is associated with a normal intrauterine pregnancy 98% of the time, whereas a value of less than 5 ng/mL identifies a nonviable pregnancy, regardless of the location [3]. Most patients, however, have a progesterone level that is between 10 ng/mL and 20 ng/mL at presentation; this significantly limits the clinical usefulness of the progesterone measurement. The value of 25 ng/mL as an indicator of a normal intrauterine pregnancy was established in women who had spontaneous ovulation and pregnancies. The appropriate number for women who receive medication for the induction of ovulation is probably higher; this further limiting its use as a diagnostic tool in these cases. Therefore, a single measurement of serum progesterone level must be viewed as an adjunct to hCG levels and ultrasonography.

Estrogen

The corpus luteum of pregnancy is the principal source of estrogen during the first few weeks. Subsequently, nearly all of the estrogen is formed by the trophoblast of the placenta. Estrogen production and plasma estrogen level increase markedly and lead to a 1000-fold increase in urinary estriol.

Human chorionic gonadotropin

hCG is a glycoprotein with a molecular mass of 38 kd which consists of two noncovalently-linked subunits— α and β [4]. The α unit is shared by follicle-stimulating hormone and luteinizing hormone but the β subunit (β -hCG) is specific to hCG. β -hCG has been used extensively as a pregnancy test and can be detected in the serum as early as 6 to 8 days after ovulation. The most widely accepted theory regarding the role of hCG in pregnancy is the maintenance of the early corpus luteum to ensure continued progesterone and, possibly, relaxin secretion by the ovary until this function is taken over by the growing syncytiotrophoblasts.

hCG that is secreted by the syncytiotrophoblast of the placenta is released into the fetal and maternal circulation and is excreted in maternal urine. Human embryos secrete hCG into the culture medium 5 to 8 days after fertilization; pregnancy-specific β -hCG is detectable in peripheral maternal blood 1 week after conception. β -hCG can be detected in 5% of ovulatory cycles on the eighth

day; in 16% on the ninth day; in 53% on the 10th day; and in all cycles on the 11th day after the preovulatory luteinizing hormone surge [5]. Most commercially available monoclonal antibody-based urine pregnancy tests can detect β -hCG at a level that is greater than 25 IU/L; this corresponds to the 24th or 25th day of a regular 28-day cycle.

It was shown that maternal serum hCG levels double over 1.4 to 1.6 days from the time of first detection to the 35th day of pregnancy and then doubles over 2.0 to 2.7 days from the 35th to the 42nd day [6]. Plasma levels continue to increase rapidly during normal pregnancy and reach a peak between 60 and 90 days of gestation. Thereafter, the maternal serum hCG concentration plateaus and declines until delivery [7]. With the development of accurate and rapid quantitative measurements of β -hCG in serum, these tests have been used extensively to confirm a normally-developing embryo and trophoblasts. A doubling of the β -hCG levels at 48-hour intervals usually signifies a normal viable intrauterine pregnancy [8], whereas decreased or decreasing levels are associated with an inevitable abortion or an ectopic pregnancy [9].

Activin

Activins are homodimers that consist of $\beta A\beta A$ (activin-A), $\beta A\beta B$ (activin-AB), and $\beta B\beta B$ (activin-B) subunits that are linked by disulphide bonds. The fetoplacental unit is the main source of activin A in early pregnancy, although an ovarian contribution also was suggested [10]. Maternal serum activin-A that is measured in first trimester does not predict pregnancy outcome.

Carcinoembryonic antigen-125 (CA-125)

In normal pregnancies, maternal CA-125 serum values in the first trimester are elevated as compared with nonpregnant levels. In pregnant women who present with intact fetal heartbeat and vaginal bleeding, maternal CA-125 levels increase beyond those that are found in women who have uncomplicated pregnancies [11]. Similarly, women who have ectopic pregnancies—ruptured or unruptured—are more likely to have elevated levels of serum CA-125 compared with women who have intrauterine pregnancies [12]. An elevation in maternal CA-125 serum is dependent on the extent of decidual disruption. A single CA-125 measurement does not have a prognostic value in most cases; however, sequential determinations of increased maternal CA-125 measurements seem to be highly predictive for subsequent abortion [11]. Among aborters, CA-125 levels that are measured 5 to 7 days apart remain high or increased, whereas nonaborters have constantly low or steeply declining CA-125 measures.

Insulin growth factor binding protein–1

Insulin growth factor binding protein (IGFBP)-1—also known as placental protein 12—is one of the six proteins that specifically binds insulin like growth factors (IGFs) in body fluids and tissues [13]. IGFBP-1 contains 234 amino acids and has a molecular mass of 25 kd. The human IGFBP-1 gene is located on chromosome 7. IGFBP-1 is synthesized in large amounts by the decidua in early pregnancy [14] and its concentration is increased in the maternal circulation. It also is the predominant IGFBP in amniotic fluid and the major IGFBP in fetal plasma [15]. IGFBP-1 also is a local modulator of IGF action that regulates fetal growth and is able to interact independently with cytotrophoblast cells.

Pregnancy-associated plasma protein–a

Pregnancy-associated plasma protein–A (PAPP-A) is a 187-kd macromolecular glycoprotein that is produced by the trophoblast; its serum levels increase during pregnancy. This glycoprotein circulates as a complex with the proform of eosinophil major basic protein (pro-MBP) [16]. The pro-MBP also binds to the complement component, C3, and to angiotensinogen [17]. Because polyclonal antibodies against PAPP-A also recognize pro-MBP, these antibodies cross-react partially with C3 and angiotensinogen [18].

The biologic function of PAPP-A is not clear. PAPP-A is a protease for IGFBP-4 and -5 [19]. Following cleavage, the affinity of IGFBPs for IGF-I and -II is reduced. Variables that regulate the amount of proteolysis regulate the action of the IGFs [20]. Locally-synthesized IGFs promote cellular mitosis and differentiation and probably are important in embryogenesis and the regulation of fetal and placental growth [20,21]. At term, cord blood concentration of IGF-I correlates positively—whereas that of IGFBP-1 correlates inversely—with birth weight [22]. The level of PAPP-A in maternal serum might reflect the local level of PAPP-A and the availability of IGFs. Decreased levels of PAPP-A might indicate low levels of IGFs and poorer fetal or placental growth. It is not known whether poor fetal growth is a consequence of poor placental function or if fetal growth and placental function are poorer because of the influence of the same factors (eg, decreased levels of growth factors such as IGFs).

The clinical usefulness of PAPP-A measurements during pregnancy was investigated [23]. Several studies found an association between decreased maternal serum PAPP-A at 10 to 14 gestational weeks and the delivery of babies who are small for gestational age [24–26]. The predictive value of maternal PAPP-A levels seems to be weaker after adjustment for smoking [26]. A 15% reduction in the level of PAPP-A in smokers was reported [27,28]; the explanation was that smoking inhibits apoptosis of the syncytiotrophoblasts which results in disturbed fetoplacental exchange [28]. Additionally, the direct influence of smoking on reduced PAPP-A production may cause decreased levels in maternal serum and, probably more importantly, in levels of intrauterine

PAPP-A. It is well-known that smoking negatively affects the placental vessels and nutrient supply to the fetus; it also affects PAPP-A production and decreases IGFs that may have synergistic effects on fetal growth.

In women who delivered babies who were large for gestational age (LGA), the PAPP-A level at 10 to 14 gestational weeks was significantly increased when compared with women who delivered babies who were appropriate for gestational age, after adjustment for free β -hCG, inhibin-A, nuchal translucency, maternal age, smoking, gravidity, and gestational diabetes mellitus (GDM) [26]. PAPP-A levels at 10 to 14 gestational weeks are decreased in women who have pre-existing diabetes mellitus or GDM [24,29], including those who delivered LGA babies [26]. It seems that PAPP-A is not responsible for increased fetal growth in the latter cases and increased fetal growth that is associated with diabetes is likely due to maternal hyperglycemia.

In ectopic pregnancies, the specificity of PAPP-A measurements has been the subject of debate. Some investigators reported that PAPP-A was depressed or even undetectable in ectopic pregnancies [30], whereas others found only slightly depressed PAPP-A levels [31]. In an on-going pregnancy, decreased PAPP-A levels—as a result of abnormal placentation or abnormal placental function—is a precedent to fetal death in utero. In a series of 5297 patients who had a miscarriage rate of 1%, Ong et al [24] found 20.4% of miscarriages were associated with PAPP-A levels that were less than the 10th percentile. Similarly, Ruge et al [32] found that 25% of miscarriages were associated with PAPP-A levels that were less than the 10th percentile. In first trimester pregnancies with an ultrasonically-proven live fetus, Kwik and Morris [33] confirmed the association between decreased maternal serum PAPP-A levels that were measured at 11–13 weeks' gestation, fetal death in utero, and birth weight that was less than the 10th percentile. PAPP-A levels had a 49% predictive value of fetal demise with a sensitivity of 89% [34]. The association between decreased PAPP-A level and miscarriage is not limited to pregnancies with fetal chromosomal aberrations. Yaron et al [25] reported a relative risk of 8.76 for subsequent spontaneous miscarriage with PAPP-A levels of less than 0.25 multiples of the median (MoM) that were measured between 10 and 13 weeks' gestation, after excluding fetuses that had chromosome aberrations or anomalies.

Other studies that examined the correlation between first trimester PAPP-A levels and adverse fetal outcomes have not produced consistent results. In one study, reduced circulating PAPP-A concentrations during the first trimester was associated with preterm labor and low birth weight [35]; however, this was not confirmed by other studies [36]. Yaron et al [25] reported that PAPP-A was diminished in women who had proteinuric pregnancy-induced hypertension (PIH), but not in those who had nonproteinuric PIH. Again, this finding was not confirmed by other investigators [26].

Discrepant findings about measurements of PAPP-A in normal and abnormal pregnancies were attributed, in part, to the cross-reaction between polyclonal antibodies against PAPP-A and pro-MBP [18], the immunologic heterogeneity of PAPP-A [37], and the use of different reagents by the various investigators

[38]. Recently, selected monoclonal antibodies that do not recognize pro-MBP, have been raised against PAPP-A and were evaluated for Down's syndrome screening [39]. This screening test had a significantly increased specificity and sensitivity over the methods that use polyclonal antibodies; however, the use of monoclonal antibodies to measure PAPP-A levels did not improve the performances of this test significantly in the diagnosis of pregnancy failure [40].

Inhibins

Inhibins are glycoproteins that belong to the transforming growth factor (TGF)- β superfamily [41]. They consist of an 18-kd α -subunit and a 32-kd β_A (inhibin-A) or a 14-kd β_B subunit (inhibin-B) that are linked by disulphide bonds. Only the dimeric forms of inhibin are bioactive, although the α -subunits circulate in vast excess as biologically-inert monomers.

Corpus luteum is the major site of inhibin production during the luteal phase in a normal menstrual cycle [42]. Immunoreactive inhibin concentrations increase after conception in early pregnancy [43]. Numerous studies have attempted to identify the predominant site of inhibin-A production during pregnancy. Lockwood et al [44] investigated the source of inhibins in early pregnancies that were conceived in vitro with and without corpus luteum function. Comparable inhibin-A concentrations were found in pregnancies that were conceived spontaneously or following in vitro fertilization that involved the transfer of fresh or frozen embryos. This suggested that the main source of dimeric inhibin-A in early pregnancy is the fetoplacental unit. In another study that used a donor-egg model in conjunction with ELISA specific for inhibin-A, the concentrations of inhibin-A in the first trimester of human pregnancy were not significantly different in the women who did or did not have corpora lutea; this again suggested a fetoplacental origin [45]. In contrast, other investigators suggested that the corpus luteum is a major source of circulating inhibin-A in early pregnancy, based on inhibin-A concentrations that were significantly decreased in women who conceived with donor oocyte as compared with women who conceived after ovarian stimulation. Furthermore, inhibin-A concentrations were not significantly different between singleton and multiple pregnancies in the ovarian stimulation protocol; this suggested that the size of the early trophoblast does not seem to influence the secretion of inhibin-A [46].

The physiologic role of inhibins in humans is unclear. Inhibin-A suppresses hCG release; this suppression is gestation-dependent with no effect in the first trimester [47]. Animal studies suggest a role for inhibin-A in the maintenance of luteal progesterone output [48]. It also is believed that inhibin-A plays a part in the cell signaling, and therefore, possibly in trophoblast invasion.

Inhibin-A concentrations increase throughout the first trimester, whereas inhibin-B concentrations in circulation are unaltered in early pregnancy [42,49]. After the completed 10 weeks gestation, inhibin-A levels start to decrease

with gestation [50]. Regulation of placental expression of inhibin-A is not clear; however, it was showed that hCG, prostaglandins, and epidermal growth factor stimulate—whereas activin and TGF- α suppress—placental inhibin production [50].

Inhibin-A has a shorter half-life than hCG or progesterone; therefore, it may be more sensitive to changes in the trophoblasts [51]. Decreased inhibin-A levels in early pregnancy have been associated with biochemical pregnancies and missed miscarriages [49]; however, inhibin-A levels were not decreased in women who were sampled 3 or more weeks before a miscarriage. For this reason, some investigators do not consider inhibin-A to be a useful marker to predict subsequent miscarriage in a currently viable pregnancy [52,53]. Al-Azemi et al [54] disagreed with this view. Women who had a history of recurrent spontaneous miscarriage (at least three previous consecutive first-trimester pregnancy losses) had consistently lower concentrations of inhibin-A in the serum as early as 6 weeks' gestation if the current pregnancy was destined to miscarry.

Inhibins also are elevated in pregnant women who have PIH [26,55]; however, the differences in inhibin-A levels between hypertensive and normotensive women are small and hinders its clinical usefulness. Petraglia [55] proposed that the trophoblast increases the production of inhibin-A as an adaptive response to pathologic conditions. Impaired placental perfusion or placental damage may be followed by a regenerative process with increased synthesis of placental products; however, the spillage into maternal circulation as a consequence of placental damage after impaired placentation also could be the reason for increased levels of markers [56].

Inhibin pro- α C

Inhibin pro- α C circulates as a functionally inactive monomer and as part of high-molecular weight functional dimers [49]. Inhibin pro- α C levels peak at 4 weeks of gestation and then decrease until 11 weeks of gestation. Inhibin pro- α C is believed to play a role as a paracrine and endocrine regulator of placental function. Maternal serum inhibin pro- α C concentrations are decreased in failed intrauterine pregnancies. Interruption of the hormonal activity of the corpus luteum by administration of mifepristone in women who underwent induced termination of pregnancy led to a decrease in pro- α C levels [13]. Elson et al [57] evaluated numerous biomarkers, including β -hCG, progesterone, 17OHP, IGFBP-1, inhibin-A, and inhibin pro- α C, for successful expectant management of incomplete miscarriage. Inhibin-A levels of less than 3.9 pmol/L, IGFBP-1 levels of greater than 15 mg/L, and inhibin pro- α C levels of less than 400 pmol/L were associated significantly with successful expectant management of miscarriage. Nevertheless, β -hCG was the best predictor for pregnancies that resolved spontaneously.

Leptin

Maternal leptin concentrations increase to levels that are twofold to threefold greater than nonpregnant concentrations; peak levels occur at approximately 28 weeks of gestation [58]. Results from clinical studies suggest that pregnancy-associated increases in maternal plasma leptin may result from an up-regulation of adipocyte leptin synthesis in the presence of increasing insulin resistance and hyperinsulinemia in the second half of pregnancy [59]. The studies that have been published on maternal leptin concentrations in pregnancies that are complicated by GDM reported conflicting results. Festa et al [60] reported that women who had mild GDM presented with relative hypoleptinaemia compared with women who had normal glucose tolerance. In contrast, Kautzky-Willer et al [61] reported that women who had GDM have increased plasma leptin concentrations during and after pregnancy. Elevated maternal serum leptin concentrations in early pregnancy may be a predictor of GDM later in pregnancy. In one study, women who had increased plasma leptin concentrations experienced a 4.7-fold increased risk of GDM as compared with women who had concentrations of 14.3 ng/mL or less [62].

Leptin also may be involved in the pathogenesis of preeclampsia. Increased maternal and cord leptin concentrations in pregnancies that were complicated by preeclampsia were reported [63,64]. It is not known whether increased maternal leptin concentrations that are measured in early pregnancy predict preeclampsia.

Macrophage migration inhibitory factor and macrophage inhibitory cytokine-1

Recent findings indicated possible roles for macrophage migration inhibitory factor (MIF) in a variety of reproductive phenomena (eg, ovulation, blastocyst implantation, and embryogenesis). MIF mRNA and protein have been detected in murine and human ovaries, human follicular fluid, and the murine early embryo [65]. Additionally, it was demonstrated that MIF is expressed in glandular epithelium, stromal and predecidualized stromal cells of the human endometrium, as well as in the decidua [66] and trophoblast [67] of first-trimester placenta. Yamada and colleagues [68] investigated serum concentrations of MIF in pregnant women who had had recurrent miscarriages. They compared serum MIF concentrations in women who had a subsequent miscarriage and normal fetal karyotype with those who had a miscarriage and abnormal karyotype or those who had live births. MIF concentrations were decreased significantly in the serum of women who had subsequent first-trimester miscarriage and normal karyotype compared with women who had pregnancies that ended in live birth. Macrophage inhibitory cytokine (MIC)-1 is a member of the TGF- β superfamily [69]. Maternal serum MIC-1 is decreased in women who miscarry. Furthermore, decreased concentrations of MIC-1 levels precede miscarriage by several weeks [70].

Summary

Measurement of hormonal biomarkers, such as PAPP-A and free β -hCG, between 10 and 14 weeks of gestation are the mainstay of screening strategies for fetal chromosomal anomalies. PAPP-A levels that are determined for such a screening also may be used to alert the obstetrician to potential adverse pregnancy outcomes (eg, poor fetal growth, miscarriage). Although progesterone, inhibin-A, IGFBP-1, inhibin pro- α C, and serial measurements of CA-125 may be used to predict poor fetal development, serial measurement of β -hCG to monitor doubling of its maternal serum level, in combination with ultrasound, remains the most effective strategy to distinguish failed or ectopic pregnancies from normal, early pregnancies. Studies on the association between early pregnancy levels of inhibin-A or PAPP-A and PIH has yielded inconsistent results; further research is warranted. Similarly, more work is needed to establish the role of leptin in GDM and to determine whether it can be clinically useful in the management of patients who have this condition. Efforts to understand early pregnancy endocrinology will shed light on pregnancy physiology and will provide us with tools to manage adverse outcomes more efficiently.

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