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Advances in CLINICAL CHEMISTRY

Edited by

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PREFACE

As has been the tradition with past volumes, the Editors have attempted to assemble a balanced volume with material related to the latest methodological and technical developments in the field and articles that review the clinical biochemistry of newer developments in our understanding of disease. Inherently, clinical chemistry is based on a close relationship between these two kinds of knowledge. The Editors firmly believe that all advances in clinical chemistry are directly related to the introduction of analytical techniques that permit more sensitive and more precise measurement of smaller and smaller concentrations of biologically important components.

In this volume Hartwick and Brown have elegantly reviewed the use of high pressure liquid chromatography in the measurement of both therapeutic drugs and drugs of abuse. They have also described techniques for the assay of many endogenous metabolites including enzymes, steroids, vitamins, biogenic amines, and other components. In keeping with the ever increasing interest in the genetic control of serum proteins, Tárnoky has reviewed the pathophysiology of genetically controlled variants of serum albumin. Barbara E. Clayton has reviewed the clinical importance and the physiological role in health and disease of trace metals, particularly in children. Zinc and copper are most extensively reviewed with additional sections on molybdenum, chromium, cobalt, manganese, and selenium. An area often overlooked by clinical chemists, the clinical chemistry of pregnancy, is reviewed by Lind. This "normal" state often results in laboratory data that are difficult to interpret.

Bloom and Polak have reviewed the chemistry, physiology, and pathology of gut hormones. As the authors point out, knowledge of these hormones has created a new medical field, gut endocrinology. In addition to a consideration of the more traditional hormones such as gastrin and secretin, the role of vasoactive intestinal peptide, substance P, bombesin, and endorphins is described.

The volume represents the first assembled without the guiding hand of Oscar Bodansky. We thank the contributors and publisher for their patience and understanding during the transition and hope that the readers will conclude that the quality of the volume has maintained the excellence of previous entries in this publication.

A. L. Latner
M. K. Schwartz

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CLINICAL CHEMISTRY OF PREGNANCY

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1. Introduction

The modern clinician relies increasingly upon the results obtained from laboratory tests for the management of his patients; for some the stage has been reached when deviation from an accepted range of values is in itself sufficient to justify treatment. The principle is not intrinsically unreasonable, but clinical management that rests solely on this basis implies a confidence in the "normality" of any given range of laboratory values that is seldom justified.

Pregnancy is a time during which the physiological status of the mother changes progressively as gestation advances. Pregnant women have biochemical measurements that deviate conspicuously from what is regarded as normal for males and nonpregnant females, and the accepted range of normality for such women is inevitably wider and even more arbitrary.

Normal values can only be defined as those occurring in manifestly healthy women who have trouble-free pregnancies resulting in healthy, well-grown infants. But even this may not be sufficient, because optimum maternal adaptations must contain a margin of safety sufficient to allow for possible hostile circumstances occurring during the 9 months of fetal development. Such circumstances will arise infrequently in a westernized society, and their effect cannot therefore be tested with any accuracy. Tests of normality will therefore be partly statistical. Ideally, a normal range for all values will be based upon a large number of measurements made at all stages of gestation under standardized conditions, by reliable techniques, upon young, healthy, well-nourished, pregnant women living in good social circumstances. Needless to say, such information is rarely available; what is presently regarded as normal for pregnancy is usually the same physiological range of values determined for males and nonpregnant females.

Every major system is influenced by pregnancy, and it would be impossible to describe all these changes in a chapter. Books have been

devoted to the hormonal changes alone (F6), and the information obtained from analysis of amniotic fluid has almost founded a subspeciality (F2, N1). Four major groups of changes will be discussed, chosen because of their relevence to clinical management: (*a*) volume and composition of the blood; (*b*) renal function; (*c*) carbohydrate metabolism; (*d*) tests reported to determine placental function. But it must be emphasized again that every major system is affected, and pregnancy-appropriate values must be defined.

2. Changes in Blood Volume and Composition

Before describing changes in the composition of blood, it is first necessary to deal with changes in blood volume. It has been appreciated for some years that plasma volume increases during pregnancy, and this has given rise to a concept of "dilution," as though volume expansion was achieved by the simple addition of water. The concept is fallacious: some constituents of the plasma decrease in concentration while others increase, arguing for specific controlling mechanisms meeting specific needs.

2.1. Plasma Volume

Plasma volume increases from an average nonpregnant value of 2600 ml to about 3850 ml during a healthy pregnancy. The exact pattern of this change is not certain; there is probably little change during the first 10 weeks of gestation, then a progressive rise thereafter to a plateau value at about 35 weeks (H8). Interestingly, the extent of the volume increase is related to reproductive performance; the greater the rise in plasma volume, the heavier the infant (H8); there is a bigger increase in volume during twin pregnancies (F7); and preeclampsia is associated with a considerably smaller than average volume change (C1).

2.2. Total Erythrocyte Volume

Without iron supplementation the total red cell volume increases by about 180 ml from an average nonpregnant value of about 1240 ml to 1420 ml. When hematopoiesis is stimulated by giving oral iron, however, the red cell mass may increase by about 350 ml, or 20% above the non-

pregnant value (T2). Again reproductive performance appears to have some effect: the volume is undoubtedly increased in multiple pregnancies but does not appear to be affected by preeclampsia (C1).

2.3. Hematocrit

Plasma volume bears no fixed relation to total erythrocyte volume. The amount of circulating hemoglobin is governed by complex mechanisms that ensure sufficient oxygen-carrying capacity; the plasma volume is governed by quite separate mechanisms ensuring a sufficient circulating volume. Thus a normal woman living at sea level happens to have an erythrocyte volume forming about 40% of the circulating blood. In a hot climate the same woman would increase her plasma volume to provide a greater peripheral circulation for heat loss, and the ratio, or hematocrit, would decrease. At high altitudes the same woman would increase her oxygen-carrying capacity by increasing her hemoglobin mass without the need to increase her circulating volume, and the hematocrit would increase. In pregnancy both the plasma volume and erythrocyte volume *increase*, but because the *proportional* increase is greater for plasma volume than for erythrocyte volume the hematocrit falls. The average nonpregnant value of 0.379 ± 0.0215 (liter/liter) decreases to 0.3385 ± 0.0268 at term in those not taking iron, but is 0.3709 ± 0.0263 in those taking iron supplementation.

2.4. Erythrocyte Count

The count falls from an average nonpregnant value of 4.35 ± 0.28 (SD) (expressed × 10^{12}/liter) to a value of 3.93 ± 0.35 × 10^{12}/liter at term if no iron supplements are prescribed. If oral iron is taken, the average term value would increase to about 4.16 ± 0.34 × 10^{12}/liter.

2.5. Hemoglobin Concentration

The concentration decreases from an average nonpregnant value of 12.95 ± 0.85 (SD) g/dl to 11.22 ± 0.7 g/dl by 26 weeks of gestation whether or not iron is given. However, the concentration will continue to fall to an average value of 11.05 g/dl at term if no iron supplements are given, whereas with such supplements the value will rise after 26 weeks to a term value of 12.22 ± 1.34 g/dl, i.e., similar to the starting, or nonpregnant, value. As stated earlier, those women with a "low" hemoglobin concentration still have a significantly greater amount of total circulating hemoglobin, and the increase is exaggerated in those given oral iron.

2.6. Erythrocyte Volume

By term the value in women not taking iron is 86.2 ± 5.57 (fl) which is not much different from the average nonpregnant value of 87.18 ± 4.00. However in women given iron the value at term is 89.6 ± 4.49 (fl), which is significantly greater than the term value for unsupplemented women.

All these data are from Taylor and Lind (T1).

2.7. Serum Iron Concentration

In a recent study 21 women were given oral iron supplements (325 mg daily) throughout pregnancy, and 24 were not. At 36 weeks of gestation the serum iron concentration in the treated group had increased from a nonpregnant level of 15.9 ± 4.9 to 19.4 ± 6.7 μmol/liter while in the untreated group it decreased from 19.8 ± 5.6 to 10.9 ± 4.5 μmol/liter (D. J. Taylor and T. Lind, unpublished). The nonpregnant values had been derived from samples obtained 6 months postpartum. These findings agree with those of Morgan (M7), who had suggested that serum iron concentration decreased during pregnancy and this fall could be modified though not completely prevented by oral iron supplements. Such findings have led some to believe that pregnancy is therefore a time of iron deficiency; such an inference must be made with great caution because the reasons for fluctuations in serum iron levels are not completely understood and may reflect a change in hormonal status. It has been reported that decreases in iron concentration equivalent to those described during pregnancy can occur during normal menstrual cycles (Z1). As discussed above for hemoglobin, it should be remembered that expressing serum iron as a concentration can be misleading. The mean plasma volume in the above series of women increased from a nonpregnant level of 2336 ml to 3384 ml at 36 weeks in the treated group and from 2340 ml to 3478 ml in the untreated group. Thus the total serum iron increased from a nonpregnant value of 37.21 μmol to 65.57 μmol in those given iron whereas it only fell from 46.33 μmol to 37.91 μmol in those not given iron.

2.8. Serum Transferrin and Transferrin Saturation

The concentration of the specific β-globulin transferrin is increased during pregnancy along with that of ceruloplasmin and some other carrier proteins. In the series quoted above, the 21 women treated with iron increased their serum concentration of transferrin from a mean nonpregnant value of 43.18 ± 5.89 to 62.46 ± 9.04 μmol/liter at 36 weeks of

gestation; however, the 24 untreated women increased their concentrations by a similar amount, i.e., from 43.01 ± 5.6 to 68.91 ± 10.5 μmol/liter.

As would be expected from the foregoing data, the percentage saturation of transferrin decreased from 22.8 ± 7.5% to 8.3 ± 3.9% in the women not given iron, whereas those given iron hardly decreased from a nonpregnant mean of 18.6 ± 5.9% to 16.3 ± 6.9% at 36 weeks of gestation.

2.9. Concept of Anemia

The significance of these changes lies in the concept of diagnosing anemia during pregnancy from the usual hematological values derived from males and nonpregnant females. Some women with a significant increase in their total red cell volume may have an even bigger increase in their plasma volume resulting in a hemoglobin concentration of 9.0 g/dl; despite the fact that such women are active and do not display symptoms after exercise, "anemia" may be diagnosed. Conversely, a less than average rise in plasma volume could lead to the maintenance of a "normal" hemoglobin concentration in women who are demonstrably iron deficient.

The *response to iron* has long been the keystone to the argument that a fall in hemoglobin concentration is due to iron deficiency. Many of the changes outlined above can be modified or reversed by the giving of oral iron; this suggests cure by replacement, always the classic test of deficiency. But what is anemia? Many animals, including the meat-eating dog, show pronounced falls in hemoglobin concentration during pregnancy, but could hardly be classed as iron deficient. Physiologically, the only meaningful criterion of "anemia" is a reduction in the adequacy of oxygen-carrying capacity. The average woman experiences a rise of 18% in this capacity against a rise in oxygen consumption of only 15%. This margin of safety is reflected in the strikingly reduced arteriovenous oxygen difference of the blood returned to the heart (H7).

It should not be concluded that iron deficiency does not occur during pregnancy. Genuine iron-deficiency anemia is more common in pregnant women, and even in the absence of defined anemia iron stores are probably reduced. However, in a normal Western society an average dietary intake together with these stores is probably sufficient to cope with pregnancy demands, and the stores will be replenished between pregnancies. As we cannot be certain that the giving of iron to an otherwise iron-sufficient pregnant woman is entirely without risk to the fetus, it would

seem prudent to reserve iron medication for those with a proven deficiency.

2.10. Leukocyte Count

The total count increases from an average nonpregnant value of 6.08 ± 1.25 (expressed × 10^9/liter ± SD) to a value at term of 9.98 ± 2.08 × 10^9/liter. Oral iron medication does not influence this change (T1).

2.11. Electrolytes

During normal pregnancy there is a small but consistent fall in the concentration of most of the serum electrolytes. The actual values recorded depend upon the method used for their determination and the conditions under which the samples were obtained. Because of this, the following data indicate only the order of any change; with the exception of bicarbonate the mean values remain well within the "normal" clinical range for males and nonpregnant females.

Sodium. Sodium falls by about 2–3 mEq/liter from 139 ± 3.9 mEq/liter to 136 ± 5.9 mEq/liter (L6).

Potassium. Potassium falls by about 0.3 mEq/liter but can achieve nonpregnant levels by term (H3, M1).

Calcium. Differences in methodology for the determination of total and ionized calcium make it difficult to give absolute values, but there is general agreement that total calcium falls to about 10% below the nonpregnant value by term [5.03 to 4.54 mEq/liter by 36 weeks (M4)]; there is a small decrease in the ionized calcium.

Magnesium. Magnesium appears to fall slowly and progressively to about 10% below the nonpregnant value [e.g., 1.61 to 1.48 mEq/liter (M4)].

Chloride. Chloride falls little, if at all, during normal pregnancy (M3, N3).

Bicarbonate. Bicarbonate falls by a small amount during early pregnancy consistent with the fall in pCo_2 thus preventing development of respiratory alkalosis (H7).

Phosphate. Most reports suggest that no significant change occurs, but one group has reported a small but significant fall in concentration during pregnancy (W1).

Osmolality. During the first trimester, osmolality falls by about 10 mos/kg owing largely to the change in electrolyte composition. The colloid osmotic pressure also falls over the same interval (L6).

2.12. Proteins

Total Proteins. Despite differences in the sampling techniques and the laboratory methods for determining protein concentration, there is broad agreement that the total concentration decreases by about 1 g/dl. This new level is usually attained during the first trimester and maintained throughout the remainder of pregnancy (D2, S7).

There are two levels of published data concerning the protein fractions: that obtained by simple electrophoresis distinguishing five main components, and the more sophisticated immunoelectrophoretic techniques in which over 40 fractions can be defined. The main fractions will be discussed here and specific carrier proteins and enzymes later. The data given are summarized from Hytten and Lind (H7):

Albumin. There is a rapid fall in concentration over the first 12 weeks of gestation amounting to 0.5 g/dl or more. Thereafter a further slow decrease in concentration occurs leading to a total fall of about 0.75 g/dl.

α_1-globulin. A gradual rise occurs to an average value about 0.1 g/dl above the nonpregnant norm.

α_2-globulin. α_2-globulin behaves similarly to α_1-globulin, again increasing by about 0.1 g/dl toward term.

β-globulin. Most reports indicate a progressive rise of β-globulin through pregnancy of about 0.3 g/dl above nonpregnant levels.

γ-globulin. There appears to be a fall in concentration of the IgG fraction of the order of 0.1 g/dl while IgA and IgM remain unchanged.

Pregnancy-Specific Proteins. Using antisera derived by immunizing rabbits with proteins derived from human placentas, four "pregnancy proteins" have been described. Two, placental lactogen and a β_1-glycoprotein, are specific for pregnancy; a further β_1-glycoprotein and an α_2-glycoprotein can be detected during pregnancy but have also been described in nonpregnant women taking oral contraceptives. The α_2-glycoprotein is a macroglobin apparently identical with the serum factor XL and can be easily identified from the common α_2-macroglobin by radial immunodiffusion methods (H4). A clinically useful role for the determination of the pregnancy-specific proteins has yet to be confirmed.

α-Fetoprotein. α-Fetoprotein is an α_1-glycoprotein synthesized in the fetal liver and yolk sac. It appears in increasing amounts in maternal serum and can achieve massive concentrations when the fetus has died *in utero;* levels of 9000 μg/liter have been recorded (S2). The determination of maternal α-fetoprotein concentration as a method of screening for fetuses with an open neural-tube defect is "in vogue" but still requires validation as a clinically useful procedure; there is a "gray zone" of values between the unequivocally normal and the obviously abnormal, as has been found by several workers (M6).

2.13. Erythrocyte Sedimentation Rate

The range of normal values is much increased during normal pregnancy: for whole blood the mean is 78 mm/hour with a range of 44–114 mm/hour; for citrated blood the mean is 56 mm/hour, range 30–98 mm/hour. This is caused by the increased levels of plasma globulins and fibrinogens, which are normally raised during pregnancy; this means the ESR is of little or no diagnostic value during this time (H7).

2.14. Serum Enzymes

Lactate Dehydrogenase (LDH), Isocitrate Dehydrogenase (ICDH), and α_1-Hydroxybutyrate Dehydrogenase (HBDH). In a large cross-sectional study it has been shown that each of these enzymes remains within the normal nonpregnant range during pregnancy; a small increase occurs during labor (M3).

17β-Hydroxysteroid Oxidoreductase. This enzyme originates in the placenta and catalyzes the oxidoreduction of estrone and estradiol. It can be detected in maternal serum by about week 12 of gestation.

Monoamine Oxidase. No direct measurements appear to have been made throughout normal pregnancy. However, a dose of 5-HT given to a pregnant woman leads to the excretion of the same amount of 5-HIAA as in the nonpregnant.

Diamine Oxidase (DAO). This oxidase usually increases from a normal nonpregnant level of 0.1 IU/liter to about 0.5 IU/liter by mid-pregnancy and 1–2 IU/liter by term (S6). Much higher values would be recorded if the assay were run at pH 6.9 (optimum) rather than the more usual pH 7.4.

Ceruloplasmin. Ceruloplasmin increases from about 280 to 480 mg/liter or so during pregnancy (O2).

Glutamate Oxaloacetate Transaminase (GOT) and Glutamate-Pyruvate Transaminase (GPT). Numerous studies have shown these enzymes to be well within the average range during normal pregnancy.

Creatinine Kinase. The important feature here is that values *decrease* between 8 and 12 weeks of gestation from an average nonpregnant value of 28 IU/liter to 24 IU/liter; a further decrease occurs until 20 weeks, when values as low as 21 IU/liter may be recorded. Thereafter the concentration rises to nonpregnant levels during the second half of pregnancy. Female carriers of Duchenne muscular dystrophy usually have raised values, but if they seek genetic advice during the early weeks of pregnancy the effect may be to bring them within the "normal" range for nonpregnant subjects (K2).

Lipase. The activity of this enzyme is usually reduced quite con-

siderably from an average value of 40 IU/liter to about 16 IU/liter at term (F1).

Pseudocholinesterase. It seems probably that the serum level is reduced by about 30% during pregnancy (S3). This is of some practical importance, as it implies that some pregnant women will be less efficient at metabolizing muscle relaxants, such as succinylcholine.

Alkaline Phosphatase. This enzyme increases during pregnancy, but the amount by which it increases depends upon the substrate used. The increase is greater if β-glycerophosphate is used (Bodansky units) than if *p*-nitrophenyl phosphate is employed (Bessey–Lowry units). A new fraction, stable at 65°C, is responsible for this pregnancy increase and accounts for between 40% and 65% of the total serum alkaline phosphatase activity during the last trimester; it originates from the placenta (S1).

Acid Phosphatase. There is little change in serum activity throughout pregnancy.

α-Amylase (Diastase). This enzyme is little affected by pregnancy.

Leucine and Cystine Aminopeptidase. The latter enzyme is probably identical with "oxytocinase." Both increase considerably throughout pregnancy (M5).

2.15. Serum Lipids

Triglycerides. The serum concentration increases progressively throughout pregnancy from levels below 100 mg/dl to 200–300 mg/dl (H7).

Cholesterol. The cholesterol concentration seems to fall from a nonpregnant value of 200 mg/dl to about 180 mg/dl during the first 8–12 weeks of gestation, but then rises linearly for the rest of pregnancy, reaching values of 260–300 mg/dl by term (D3, G1).

Phospholipids. The total phospholipid concentration increases from about 250 mg/dl to 350–400 mg/dl.

Nonesterified (Free) Fatty Acids (NEFA, FFA). Because of the wide variations in methodology there is little point in quoting numerical results; there is broad agreement that the concentrations rise from about 600 mEq/liter to 1000 μEq/liter in late pregnancy (B4, N2).

Lipoproteins. During pregnancy there is an increase in the β-lipoprotein fraction. The increase in serum cholesterol and phospholipids occurs mainly in the β-lipoprotein (low-density) fraction (C2).

A detailed account of changes in the various lipid fractions during pregnancy has been published by Knopp, Montes, and Warth (K6).