CHAPTER 35

Glucagon and Pregnancy

C. KÜHL and J.J. HOLST

A. Introduction

The interest in obtaining knowledge of glucagon secretion in pregnancy emanates from two characteristic features of this state. First, pregnancy is known to exert a diabetogenic stress on carbohydrate metabolism and second, the metabolic responses to starvation and food intake are characteristically modified by gestation. Evaluation of the possible contributory role of glucagon in bringing about these metabolic changes in pregnancy is obviously of interest.

I. Impaired Glucose Tolerance in Pregnancy

In normal pregnancy, several physiologic changes take place, the sum of which tends to reset glucose homeostasis in the direction of diabetes. Thus, glucose tolerance gradually deteriorates (LIND et al. 1973; KÜHL 1975) for which reason pregnancy is often called “diabetogenic”. The reason for the deterioration of glucose tolerance in pregnancy is still not fully understood (KÜHL 1977). Theoretically, any one of the mechanisms outlined in Table 1, or any combination of these mechanisms, might be involved. This chapter will mainly focus on the role of glucagon in the first of these possibilities, i.e., A-cell function in human and animal pregnancy.

II. Metabolic Adaptations to Pregnancy

During intrauterine life, the human fetus is completely dependent upon maternal supply of glucose, free fatty acids, and amino acids. The increasing demands of the growing fetus are met by certain changes in the metabolic responses to caloric deprivation in the pregnant mother in order to ensure a continuous supply of fuels for energy metabolism for the mother and the fetus.

Pregnancy is associated with a conversion from a glucose-utilizing fuel economy to catabolism of mainly lipids and protein, and with a drain of maternal en-

Table 1. Possible pathophysiologic mechanisms for the diabetogenicity of pregnancy

- a) Secretory function of endocrine pancreas altered by pregnancy
- b) Changed blood levels of hormones and other constituents with anti-insulin effect
- c) Changes in insulin metabolism
- d) Changes at the receptor level in target organs of insulin
- e) Diminished potentiation of insulin secretion by insulinotropic gastrointestinal hormones
ergy products, nutrients being mobilized for the fetus at the expense of the mother. Maternal adaptations to dietary deprivation result in a metabolic profile (e.g., increase in fasting plasma free fatty acid levels and in production of ketone bodies, but a decrease in fasting plasma glucose and amino acid levels) which has been designated “accelerated starvation” (FREINKEL et al. 1972). Contrariwise, when the mother is fed, mechanisms are evoked which favor maternal anabolism (e.g., the conversion of a larger proportion of ingested glucose into circulating triglyceride, a mechanism which, in view of the relative impermeability of the placenta to esterified lipids, would assure retention of some of the carbohydrate excess in the mother for later mobilization). Therefore, “accelerated starvation” in the fasting state and a compensating “facilitated anabolism” in the fed state would seem to be present at the same time in late pregnancy (FREINKEL et al. 1973). The possible contributory role of glucagon in the induction of the metabolic adaptation to pregnancy is the subject of this chapter.

B. Plasma Glucagon in the Fasted State

I. Changes After Overnight Fasting

There is some uncertainty about the influence of pregnancy on overnight fasting plasma glucagon levels. In normal human pregnancy, the plasma glucagon concentration in the fasting state has been reported to be decreased (KÜHL and HOLST 1976) or increased (LUYCKX et al. 1975) in midpregnancy, whereas both unchanged (LUYCKX et al. 1975; LEBLANC et al. 1976; LORRAIN et al. 1977) and elevated (DANIEL et al. 1974; KÜHL and HOLST 1976; KÜHL et al. 1977; METZGER et al. 1977; HORNNES and KÜHL 1980; KITZMILLER et al. 1980; HORNNES et al. 1981 a, b) glucagon levels have been reported in late pregnancy.

In late gestational diabetic pregnancy, fasting plasma glucagon is reported to be either unchanged (KÜHL and HOLST 1976; LORRAIN et al. 1977; KITZMILLER et al. 1980) or enhanced (DANIEL et al. 1974; HORNNES et al. 1981 a). In insulin-dependent diabetic women in the last trimester of pregnancy, data on fasting plasma glucagon are sparse and contradictory; both unchanged (KITZMILLER et al. 1980) and increased (FALLUCCA et al. 1979) levels have been reported. Data on fasting plasma glucagon concentrations in animal pregnancy are no less confusing. Thus, decreased (METZGER et al. 1974) or unchanged (SAUDEK et al. 1975) levels have been found in rats, whereas, in the rhesus monkey, fasting glucagon levels were unaffected by pregnancy (CHEZ et al. 1974).

The discrepant results concerning fasting plasma glucagon levels in gestation are probably due to the fact that, compared with postpartum, changes in fasting plasma glucagon concentrations in pregnancy, if any, are small. Detection of small differences in plasma glucagon levels makes heavy demands on the specificity and accuracy of the glucagon assay and, furthermore, it is mandatory that the pregnant women serve as their own nonpregnant controls. With these reservations in mind, it is probably permissible to conclude that the available evidence is for an enhancing effect of late human pregnancy on fasting plasma glucagon concentrations. As regards other stages of pregnancy and pregnancy in gestational diabetics and in-