Introduction

In women predisposed to diabetes mellitus and in insulin-dependent diabetic women abnormalities of glucose metabolism following intake of oral contraceptives (OCs) obviously attract special attention. Previously there has been a negative attitude towards the use of OCs in these women due to the enhanced risk of unfavourable clinical events. As a consequence of the rapidly accumulating amount of scientific data available on the undesirable metabolic effects of contraceptive steroids it has become evident that the pharmacokinetic properties of the hormonal constituents and the amount, and type, of steroid are of fundamental significance for the observed effects. This chapter summarizes the influence on glucose metabolism of combined OCs with differences in the steroid content when administered to women with previous gestational diabetes mellitus (GDM) and to women with insulin-dependent diabetes mellitus (IDDM).

The Pharmacological Profile of Sex Steroids in Oral Contraceptives

In contraceptive compounds the oestrogens marketed today are either ethinylestradiol or mestranol. Unconjugated ethinylestradiol is the active substance in both compounds. Ethinylestradiol undergoes enterohepatic recirculation and reabsorption. Approximately 30% of a given dose can be recovered in the faeces and the faecal/urine ratio is about 2:3. The half-life in plasma varies from 6 to 20 h (Orme et al. 1983).
Genuine or non-alkylated oestrogens, oestrone, 17-β-oestradiol and oestriol are not used in commercially available contraceptive compounds, whereas they have been used extensively for substitution therapy in climacteric women. Compared with artificial oestrogens higher doses of oestradiol must be used in oral compounds due to higher rates of metabolism in the gut wall and to first-pass effects in the liver. The use of microcrystalline forms, however, improves the absorption.

Most of the progestational components used in the combined contraceptive pills are 17-α-ethyl derivatives of the reduced form of testosterone (19-nortestosterone). The 19-nortestosterone derivatives are classified in oestranes and gonanes. All progestogens of the oestrane type are converted to norethisterone after oral intake (Orme et al. 1983). The gonanes differ from other 19-nortestosterone products in having a beta-ethyl group at carbon 13 instead of the one-carbon chain unit present in the products, and thus, the pharmacokinetic properties are markedly different. The most widely used gonane is norgestrel or the active D-isomer, levonorgestrel. The bioavailability of oestranes is approximately 60% (Okerholm et al. 1978) whereas no first-pass effect seems to occur with the gonanes. The half-life of oestranes varies from 5 to 14 h compared with 10 to 24 h for the gonanes (Orme et al. 1983).

Oral Contraceptives and Glucose Metabolism in Women with Previous Gestational Diabetes Mellitus

It is well established that intake of OCs may decrease glucose tolerance and cause a rise in insulin levels in healthy non-diabetic women. Such changes have become evident in both intravenous and oral glucose tolerance tests (Kalkhoff 1975). The relative effects of oestrogens and progestogens on glucose metabolism have been debated from the very beginning of the OC period but today the consensus is that the progestogens are mainly responsible for the diabetogenic effect of the combined compounds (Spellacy et al. 1972) although the artificial oestrogens may modulate this effect. A possible decreased insulin sensitivity at cellular level in peripheral tissues has been suggested as the mechanism behind the altered glucose metabolism (De Pirro et al. 1978; Skouby et al. 1987).

Despite these adverse effects on glucose tolerance no risk of developing clinical diabetes has been found in epidemiological studies (Wingrave et al. 1979). However, in women with previous GDM an overall incidence of 44% of deterioration of glucose tolerance has been registered during intake of the traditional brands of OCs (Beck and Wells 1969; Szabo et al. 1970). Only a limited number of studies has been published on the effect of previously used low-dose OCs on glucose metabolism in pregnancy in women with previous GDM. We have previously reported the effects of a monophasic low-dose ethinyl estradiol/levonorgestrel preparation (Skouby et al. 1982). Before treatment the women with previous GDM displayed significantly elevated glucose values compared to non-diabetic controls. After hormonal intake for 6 months the insulin response to oral glucose increased significantly, but no deterioration of