Placenta (2006), **27**, 468–474
doi:10.1016/j.placenta.2005.04.010

Villous Histomorphometry and Placental Bed Biopsy Investigation in Type I Diabetic Pregnancies

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Paper accepted 26 April 2005

Insulin-dependent diabetes mellitus (Type I) is associated with disregulation of the glucose and oxygen metabolic pathways during pregnancy, both of which affect placental villous development. Term complete placentas and placental bed biopsies, between 37 and 40 weeks, from 12 singleton pregnancies complicated by Type I diabetes were collected following delivery by elective Caesarean section. The controls consisted of 10 term placentas from uncomplicated pregnancies delivered by elective Caesarean section. Villous morphology was investigated using unbiased histomorphometric techniques, in relation to the degree of transformation of the spiral arteries and the presence of fetal macrosomia. A significant increase in fetal and placental weights, placental volume, volumes of the intervillous space and the trophoblast was found in the diabetic group compared to the controls. A significant reduction in the villous membrane specific diffusing capacity was observed between the diabetic and control groups (1.32 vs 1.72 $cm^3\,min^{-1}\,mmHg^{-1}\,kg^{-1}$, $P = 0.032$). A significant increase in the volume of the intermediate and terminal villi, the surface area of the villi and of the fetal capillaries, and the harmonic thickness of the villous membrane was found in the macrosomic subgroup compared to the controls. There were no differences between the hypertensive subgroup with histological evidence of partial transformation of the spiral arteries and the controls. These data indicate that placental development in insulin-dependent diabetic pregnancies is affected differentially when pregnancies complicated by fetal macrosomia are separated from those complicated by maternal hypertensive disorders with partial transformation of the spiral arteries. The reduction in the specific diffusing capacity of the villous membrane may contribute to the fetal hypoxia and increased fetal and neonatal morbidity associated with diabetes.

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Keywords: Diabetes; Placenta; Histomorphometry; Bed biopsy; Pregnancy

INTRODUCTION

A physiological state of insulin resistance is required during pregnancy to preferentially direct maternal nutrients toward the feto-placental unit, allowing adequate growth of the fetus. Type I diabetes mellitus during pregnancy is associated with disregulation of the glucose and oxygen metabolic pathways, both of which affect placental villous growth and function [1,2]. Alteration of placental development may contribute to the associated increased risk of complications of pregnancy associated with diabetes, such as preeclampsia, macrosomia, or fetal growth restriction, and to the state of relative fetal hypoxia [3].

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0143–4004/$–see front matter

Classical morphologic investigations of placental structure in diabetic pregnancies have shown a varying degree of changes in the syncytiotrophoblast, cytotrophoblast, trophoblastic basement membrane, and fetal vessels [4–7]. Some authors found no major differences in microscopic villous changes [8], in particular in women with good glycaemic control [9]. Overall, most authors reported a relative placental immaturity, due probably to a high proportion of villi with stromal oedema [4,5,7,10,11], and focal fibrinoid necrosis [5,11,12]. More detailed ultrastructural and ultrahistochemical studies of placentas from women with established diabetes before the onset of pregnancy but no hypertensive complications have shown patchy focal syncytiotrophoblastic necrosis with marked cytotrophoblastic hyperplasia and focal thickening of the villous trophoblastic basement membrane [6,13].

The findings of histomorphometric studies have been more controversial due to major differences in study design. Early studies demonstrated that the average surface area in the placenta from diabetic mothers is greater than that in the

controls, due to increased branching of peripheral villi in the diabetic group [14]. In non-insulin dependent diabetic mothers (Class A), the placenta has significantly more parenchymal and villous tissues, a higher cellular content and more surface area for exchange between mother and fetus, in terms of peripheral and villous capillary surface areas and intervillous space volume [15]. In insulin-dependent diabetic mothers (Classes B and C) the placental changes are related to fetal growth [16,17]. The placenta of the fetuses of appropriate size for gestational age infants are morphologically very similar to those of normal controls except for a well-developed villous vascularization. The placentas of the large-for-gestational age infants differ from the controls by being heavier, due mainly to an increase in non-parenchymal and parenchymal tissues. By contrast, Boyd et al. [18] found that the volume of parenchymatous tissue in the placentas from diabetic mothers is significantly increased while the volume of nonparenchyma is decreased. More recent morphometric studies on pregnancies complicated by gestational diabetes mellitus have shown that although the mean placental weights are similar in controls and diabetic groups, diabetic placentas have a more voluminous fetal capillary bed of greater length, diameter and surface area [19]. These changes can affect the placentas of appropriate-for-age as well as large-for-age babies and currently there is no evidence that they increase with the severity or duration of the diabetes.

Diabetes is a state of chronic oxidative stress, and the responses of the fetal–placental vasculature of diabetic placentas to vasoconstrictor and vasodilator agents are significantly attenuated when compared to those in normal control placentas [1]. Gestational diabetes produces an enhancement of the observed relaxation caused by hypoxia and the contraction produced by reoxygenation or hydrogen peroxide [20]. These data suggest that in patients with vasculopathy, the pathophysiology of the placental changes is secondary to a phenomenon of hypoxia–reoxygenation similar to that found in preeclampsia [21]. There have been few investigations of the utero-placental circulation in diabetic pregnancies. The aim of this study was to study the villous morphology in insulin-dependent diabetic pregnancies, using unbiased histomorphometric techniques, in relation to the degree of transformation of the spiral arteries.

METHODS

Term placentas, between 37 and 40 weeks delivered by elective Caesarean section, from 12 singleton pregnancies complicated by insulin-dependent diabetes (Type I) were collected at delivery (King's College Hospital, London). The clinical data of the study group are summarised in Table 1. Cases 4, 6 and 11 had pre-existing nephropathy, and case 4 also had pre-existing retinopathy. Five women had poor glycaemic control i.e. glycohemoglobin A1 levels $>7\%$ and post-prandial glucose level ranging between 7 and 10 mmol/L throughout pregnancy. All patients were followed at a joint diabetic–antenatal clinic at King's College Hospital. Their glucose levels were monitored continuously throughout pregnancy using a home glucometer.

The controls consisted of 10 term placentas delivered by elective caesarean section, either because of a history of previous caesarean section ($n = 6$) or for breech presentation ($n = 4$), and sampled using the same methodology. In addition, in each case of the study group, biopsies from the placental bed ($n = 5$), at the level of the superficial myometrium were collected during the surgical procedure using biopsy forceps. Informed consent was obtained from each woman before the surgical procedure and the collection of placental tissue and bed biopsies was approved by the local ethical committee.

The placental sampling and stereological techniques have been described in detail previously [22]. In brief, two types of samples were taken and analysed: biopsy samples of peripheral villi obtained immediately after delivery and embedded in

Table 1. Clinical data and results of the histological examination of the bed biopsies for the 12 diabetic pregnancies

Case	Gestation at delivery (weeks)	Diabetic control	Obstetric complications	Fetal weight (g)	Placental weight (g)	Spiral artery conversion
1	39	Poor	Macrosomia, PH	5080	677	Completed
2	37	Poor	Macrosomia, PH	4660	766	Completed
3	37	Good	None	3900	638	Completed
4	38	Good	PH, CHT & preeclampsia	3240	405	Partial
5	37	Good	PH	3760	613	Completed
6	37	Poor	Macrosomia, CHT	4460	747	Partial
7	37	Good	None	3980	450	Completed
8	37	Good	Macrosomia, PH	4280	667	Completed
9	37	Poor	Macrosomia, PH	4830	690	Completed
10	41	Poor	Macrosomia, PH	4840	667	Completed
11	38	Good	CHT	3600	553	Absent
12	37	Good	Preeclampsia	3200	482	Partial

PH, polyhydramnios; CHT, chronic hypertension.