# Chorion Villus Sampling

EDITED BY

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# Foreword

The reduction of childhood handicap and serious genetic disease is an aim worthy of us all. Increasing knowledge about genetics and about the molecular pathology of inherited disease should provide many families at risk of handicapped children with the benefit of being forewarned, so that they can consider reproductive options. Genetic counselling is the cornerstone of such disease prevention and it is high time that this important service is made more generally available. At present the public are largely denied this knowledge, and so often reproach the medical profession when they learn too late of the help that might have been made available to them.

The most important adjunct of genetic counselling is undoubtedly prenatal diagnosis, which allows the couple at risk of fetal abnormality the opportunity of confirming the normality of their future offspring. Many thousands of couples now have healthy children only because the availability of a prenatal test enabled them to plan a pregnancy. In a comparatively small proportion of prenatal diagnoses the couple learn that their fetus is affected, and that they have to consider the option of termination. Invariably the diagnosis is made in the second trimester of pregnancy which means a late abortion and all its associated trauma and distress. The possibility of an early diagnosis in the first trimester is much more acceptable to the couple, and this explains the current widespread interest in developing first trimester diagnosis by chorion villus sampling (CVS).

The editors of this volume are to be congratulated in choosing a team of experts to produce such a valuable account of this important development. Progress has been dramatic when one considers that it has only been four years since Kazy and his colleagues (1982) re-awakened interest in the possibility of early prenatal diagnosis by reporting successful CVS under the guidance of endoscopy and ultrasound in a substantial series of cases. A year later Simoni indicated the potential for the diagnosis of fetal chromosome aberrations by showing that chromosome preparations could be made directly from rapidly dividing cytotrophoblast in chorion samples. Since then many pregnancies at high risk of metabolic disorders, chromosome abnormalities and disorders detected by DNA analysis have been tested successfully. This progress is covered clearly and comprehensively in the following pages, which not only indicate the current state of CVS, but detail

the outstanding questions and concerns which at present limit the widespread application of the procedure. Chief among these is the question of safety, and an important contribution is made in chapter 16 by Jackson, who has co-ordinated an international collaborative effort to document a worldwide experience of over 13 000 CVS diagnoses, the first 6500 of which have been analyzed in some detail. This suggests that the excess fetal loss due to the procedure in experienced hands may be 0.5–1.5%, which is not too different from published data on amniocentesis. However, a reliable assessment of early and late complications can only be achieved by mounting appropriately controlled trials, and a compelling case is made for randomized trials of CVS versus amniocentesis by Chalmers in chapter 17. The ethics of offering CVS to couples at low risk of fetal abnormality (for increased maternal age, for example) outside the limits of a properly organized randomized trial are certainly debatable.

Experts in prenatal diagnosis will be interested to read the chapters on sampling techniques and laboratory methods. The introduction of the transabdominal approach to CVS shows particular promise in view of its increased patient acceptability and simplicity. It can be undertaken in the ultrasound room, and the avoidance of the transcervical route should reduce any risk of infection and allow greater flexibility at the time of sampling. An important problem for the laboratory is the difficulty in determining the significance of the fortunately rare cases of chromosomal mosaicism (such as normal/trisomy 2, 16 or 20) in trophoblast. The abnormal cell line noted in the trophoblast frequently cannot be confirmed in tissues obtained from the aborted fetus, and continuing pregnancies have been found to be normal on delivery. Until the origin and nature of such mosaicism is further clarified, it would seem wise to confirm findings of mosaicism in chorion by amniocentesis before attempting an interpretation.

If, as is likely, CVS proves to be the important advance that is suggested by the contributions to this volume, its widespread application will require considerable reorganization of obstetric and genetic services. The key is communication about the procedure, not only to the family doctors and obstetricians providing antenatal care, but also to the public, who need to know that the best time to consider prenatal diagnosis is before pregnancy and after genetic counselling. Whether this counselling is best done at combined genetics/obstetric clinics or at pre-pregnancy clinics will have to be determined, but it is already clear that the antenatal clinic is not the appropriate place. Debate on these and other issues relating to first trimester prenatal diagnosis is to be encouraged. It is to be hoped that this book will reach a wider audience than those with a professional interest in prenatal diagnostic services, because it has a most important message about a new technology which could substantially reduce the burden of disease in the community.

September 1986 *M. A. Ferguson-Smith*

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# Contents

## Section I

# STRUCTURE AND FUNCTION

# 1

# Embryology and physiopathology of early pregnancy trophoblast

*D. Ian Rushton*

Chorion villus sampling provides the promise of the prenatal diagnosis of certain chromosomal, genetic and metabolic disorders before the end of the first trimester, thus allowing termination at an earlier gestation than is currently possible with most other prenatal diagnostic techniques. It is intended to limit this discussion of the normal and abnormal placenta to the first twelve to fourteen weeks of pregnancy.

During the first trimester rapid changes occur affecting the development, growth and maturation of the tissues of both the embryo and placenta. The vast majority of the biological wastage associated with reproduction also occurs during this period though much passes unnoticed by mother and doctor alike (Miller *et al.*, 1980; Whittaker *et al.*, 1983). Though the greater part of this wastage occurs prior to the gestation at which villus sampling is currently carried out, some abnormal pregnancies destined to abort spontaneously will inevitably be encountered in any population subject to villus sampling. Indeed even with current techniques carried out at about the sixteenth week of pregnancy, it is known there is a significant loss of chromosomally abnormal conceptuses that are not terminated because of parental refusal after intra-uterine diagnosis (Hook, 1978). The same is almost certainly true of spontaneous abortions of different aetiologies with normal karyotypes. Certain characteristic patterns of villous pathology have been described in the placentae of spontaneous abortions (Rushton, 1978; 1984) but, as will become apparent, these changes mimic or are closely allied to those occurring in the normal placenta in the junctional zone between the chorion frondosum and chorion laeve. It is therefore of paramount importance that tissue samples should be obtained from appropriate areas within

the placenta since it is not a homogeneous structure. The risk of obtaining villi from the junctional zone is greatest when the placenta is approached from the lateral margin parallel to the chorionic plate (i.e. the usual situation using the transcervical route) and is least if the approach is at 90 degrees to the chorionic plate (i.e. the usual situation using the transabdominal route) (Fig. 1.1).

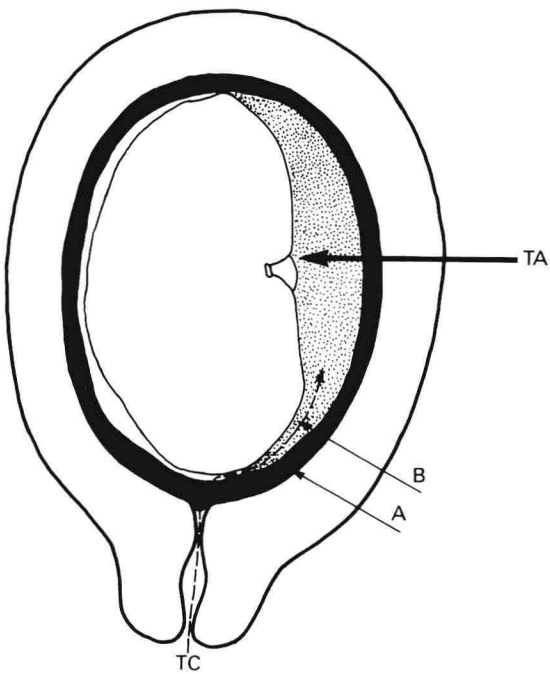


**Figure 1.1** Diagrammatic representation of uterus at 10–12 weeks gestation. A – zone of villi showing microscopic hydatidiform change. B – zone of villi showing stromal fibrosis. TA – transabdominal route for sampling. TC – transcervical route for sampling.

## 1.1 NORMAL DEVELOPMENT

Fertilization generally occurs either in the fimbrial end of the fallopian tube or within the peritoneal cavity. Within three days the fertilized ovum consists of about 60 cells of which approximately 10% are destined to form the embryo while 90% will form the trophoblast (Wynn, 1975). During the next two days the conceptus completes its journey along the tube and enters the uterine cavity, where in a normal woman the secretory endometrium will be approximately 0.5 cm in thickness, the conceptus being only 0.2 mm in diameter.