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Prenatal Diagnosis in Sweden: Organisation and Current Issues

Key Words

Prenatal diagnosis
Sweden
Organisation

Abstract

Invasive prenatal diagnosis was introduced in Sweden in the early 1970s and is an integral part of the public health care system. Funding is provided by taxation; the patient only pays a consultation fee. Genetic analyses on a broad range of cytogenetic and molecular disorders are performed at the 6 university-affiliated hospitals and in 1 county hospital. About 6% of all newborns have been cytogenetically screened during pregnancy, and about 90% of the analyses are performed after amniocentesis. The main indication is chromosome analysis because of advanced maternal age.

Introduction

Sweden covers 450,000 km² and stretches 1,650 km in north-south direction from above the polar circle. The population was just below 9 million (8,837,496 at the end of 1995; 20 inhabitants/km²), of whom 10.5% are first-generation immigrants mainly from the other Scandinavian countries, the Mediterranean region, and the Middle East. The population is concentrated in the south and middle of the country and the coastal part of the northern region. For health care purposes, the county councils are organised in 6 health care regions (fig. 1).

Invasive prenatal diagnosis was introduced in Sweden in the early 1970s. A short account of the organisation and current issues of prenatal diagnosis in this country is given below.

Departments of Clinical Genetics in Sweden

They are found at the university hospitals in (the number of specialists in clinical genetics is given in parentheses) Gothenburg (2); Linköping (1); Lund (4); Stockholm (4); Umeå (2) and Uppsala (3). In Linköping, the genetics unit consists of a cytogenetic laboratory for pre- and post-natal constitutional investigations and a small counselling clinic; the remaining 5 have a broad competence in molecular genetics and cytogenetics as well as in genetic counselling. A small cytogenetic and molecular laboratory is connected with the Department of Pathology at the District Hospital in Skövde (Western region). The other departments have good research facilities. In Lund, Stockholm, and Umeå, the heads of the departments are also professors in clinical genetics at the Medical School. Addresses to the genetics units mentioned here are found in appendix 2, and table 1 provides some information about their activities.

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Partly due to the long distances to the genetic centres, but also because of the limited numbers of clinical geneticists, much of genetic counselling has to be provided by other specialists at the local or district hospitals, e.g., paediatricians or gynaecologists and midwives. Clinical geneticists mainly provide the counsellor with up-to-date information. There are no national standards for how the information should be provided but the National Board of Health and Welfare has published recommendations (ref. 3 in appendix 1). All the clinical genetic units have issued information leaflets about prenatal diagnosis (PND) which are used by midwives and gynaecologists in their respective region. Some lay organisations provide information sheets on the specific disorders they represent.

The Swedish Society for Medical Genetics has brought forward a quality assessment document for clinical genetic units including guidelines for cytogenetic and molecular analysis as well as for genetic counselling. This document has been adopted by all the university departments of clinical genetics as a minimum standard for quality. When a specific analysis is performed by only a single department, external assessment is available by laboratories in other countries. These contacts are mostly informal and based on research collaboration.

Sources of Information on Prenatal Diagnosis

The National Board of Health and Welfare administers 5 registries to which reporting is compulsory and of relevance to PND. They are: the Medical Birth Registry, the Registry of Congenital Malformations, the Central Cytogenetic Registry (only including unbalanced *autosomal aberrations* detected prenatally or before 1 year of age), the Paediatric Cardiac Malformation Registry, and the Prenatal Malformation Registry (under introduction). In addition, listing of permission to terminate pregnancy after 18 weeks gestational age assumed by this authority as a result of PND can be retrieved.

One national newsgroup relevant to PND, the Planning Group for New Molecular Methods in Clinical Medicine, sponsored by the Swedish Medical Research Council, has existed for 10 years and is a forum for exchange of experience in new molecular diagnostic procedures. Within each of the hospital regions there are informal newsgroups involving different interested specialists. However, no formal listing exists.

Some recent official publications related to prenatal diagnosis are listed in appendix 1.

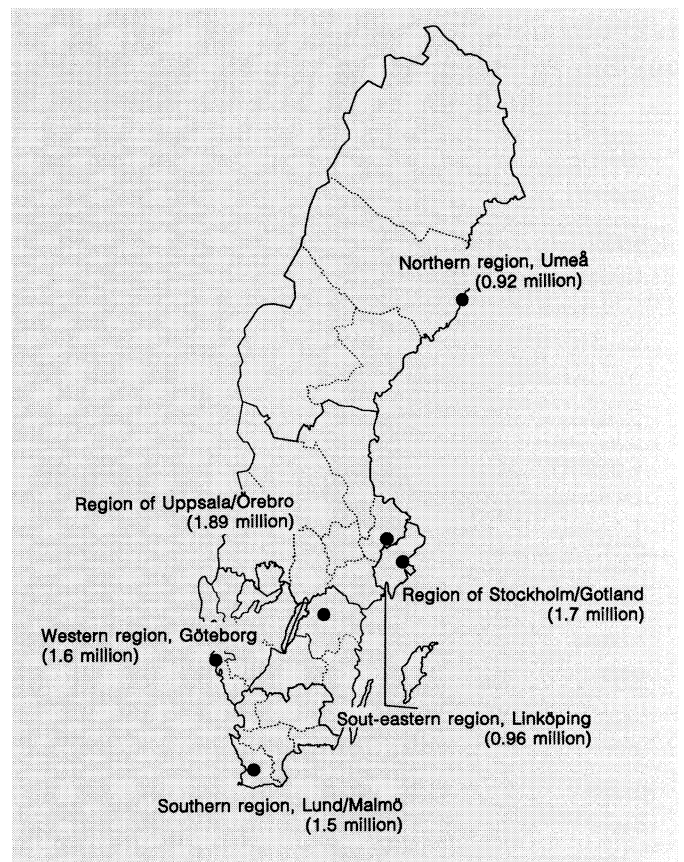


Fig. 1. Map of Sweden showing the health care regions (population on December 31, 1991). The locations of the regional hospitals are indicated by a black dot. The different regions are delineated by a full line and the districts, which are equal to counties, are separated by dotted lines. The number of inhabitants in the regions is indicated in parentheses.

Available Diagnostic Procedures for Prenatal Diagnosis

Almost all (>99%) pregnancies are followed by 5–10 regular visits to midwives in maternity health care clinics or to gynaecologists. Ultrasound investigations are offered to all pregnant women either in late first trimester or, more frequently, around the 16th–18th week of gestation for pregnancy ‘dating’, combined in some units also with malformation screening. Targeted ultrasound (malformation scan) in specialised centres are available for pregnancies identified as high-risk for recurrence because of previous affected offspring or by family history.

Amniocenteses are often performed early in the 13th–14th week of gestation for cytogenetic investigations. For molecular and biochemical analysis, chorionic villus sam-

Table 1. Number of clinical samples in the 7 genetic laboratories in Sweden 1995

Genetic centre	Gothenburg	Linköping	Lund	Skövde	Stockholm	Umeå	Uppsala	Total
<i>Cytogenetic analyses</i>								
Amniocentesis	967	583	998	164	2,279	419	465	5,875
CVS	77	6	21	34	72	32	193	435
Total prenatal	1,044	589	1,019	198	2,351	451	658	6,310
Blood ¹	788	187	579	200	887	496	545	3,619
Bone marrow ²	–	–	352	68	374	291	407	1,492
Solid tumours	–	–	172	60	7	–	11	250
<i>Molecular analyses</i>								
Total ³	435	–	170	72	708	446	674	2,505
thereof prenatal	15	–	12	–	38	2	16	83

¹ Constitutional analyses.

² Leukaemia/lymphoma.

³ Representing 68 different conditions.

pling (CVS) specimens at the 10th–11th week of gestation are preferentially obtained. CVS is mainly used for cytogenetic purposes when a malformation was found by ultrasound at some centres, whereas it is offered as a first-trimester alternative to midtrimester genetic amniocentesis at others. Amniocentesis is performed at about 30 centres, whereas CVS is only available at the university hospitals and one county hospital. Fetal blood sampling is rarely used for rapid karyotyping, except in Stockholm and Linköping. No professional guidelines exist on the different invasive procedures: the choice between different sampling methods rests to a large extent on local expertise, indication for genetic test, gestational age at sampling, and patient's preference.

Current Methods in Use for Prenatal Diagnosis

Fetal karyotyping is offered on a routine basis to women >35–37 years. Other indications include previous child/fetus with a chromosomal aberration, parent carrier of a balanced structural chromosomal rearrangement, parental mosaicism, fetal malformation(s) found at ultrasound examination, and severe anxiety.

Maternal biochemical serum marker testing for fetal aneuploidy is under introduction, and will probably be offered to selected groups of women since there is, as yet, no general consensus for introduction of a general screening of all pregnant women.

Biochemical and molecular genetic analysis are performed when appropriate for the most common disorders

in Sweden. For rarer disorders, samples are, if necessary, sent worldwide for analysis. Presently, some 70 different monogenic disorders can be diagnosed prenatally in Sweden. Most biochemical analyses for genetic metabolic disorders are performed in one laboratory at the Hospital of Mölndal outside the city of Gothenburg. DNA analyses are performed by most clinical genetics units, and to allow the availability for services for rare genetic conditions collaboration between the different units is well established. Although the number of conditions amenable to DNA analysis is ever growing, quantitatively the number of PND using this approach is low (table 1). A regularly updated list of disorders which can be detected by DNA analyses and available in Sweden can be retrieved from the European Directory of DNA laboratories on the Internet (<http://www.EDDNAL.com/>).

Impact of Prenatal Diagnosis

Prenatal diagnosis for cytogenetic disorders has reduced the number of chromosomally abnormal children born to women older than 35 years (fig. 2). However, as only 50–70% of all women in this group request prenatal cytogenetic analysis, the impact on the total birth rate of cytogenetically abnormal children is limited [2, 8, 9]. A slow increase of children with Down's syndrome, from about 120 per 100,000 life-births to 170 per 100,000, was expected from the early 1970s and onward as a consequence of delayed motherhood in Sweden [2]. The essentially unchanged incidence of Down's syndrome during

Fig. 2. Maternal-age-specific risk to have an infant with Down's syndrome, trisomy 18 or trisomy 13 for the period 1978–1993 [2]. Estimated risks for each maternal age is marked with an asterisk. A smoothed curved has been drawn (whole line) based on 3-year averages. The risk function determined for Down's syndrome for the period 1968–1977 [8] is also shown (dashes and dots).

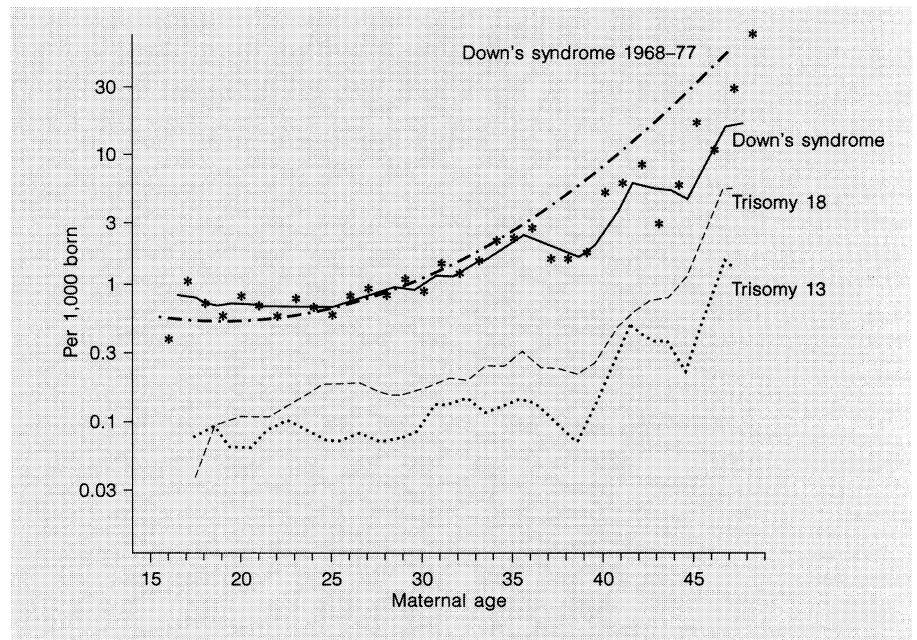
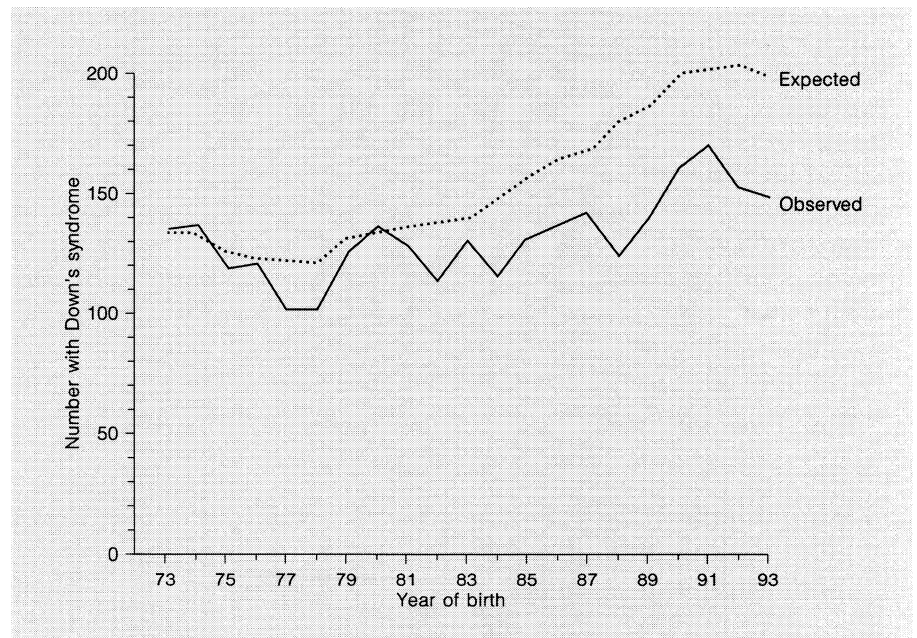


Fig. 3. Expected and observed number of Down's syndrome stratified for maternal age distribution and number of births during 1973–1993 in Sweden [2]. Expected numbers are calculated from the risk function determined from the period 1968–1977 [8].



this period can be ascribed to selective terminations of pregnancies after PND (fig. 3) [2]. Overall about 25% of cases of Down's syndrome are diagnosed prenatally.

For trisomy 13 and 18 there has been a remarkable increase in the number of postnatally registered cases from the early 1980s (fig. 4) [2]. This is most certainly due to better ascertainment and reporting. A significant determinant of this should be the associated malformations found at ultrasound scans late in pregnancy and subse-

quent prenatal cytogenetic diagnosis to manage delivery and aid in genetic counselling.

Since late in the 1980s, almost all pregnancies are routinely monitored by at least one ultrasound scan, usually in the early second trimester. This has reduced the birth of children with anencephaly to almost null, but has had only slight impact on the frequency of children with spina bifida. The overall incidence of major malformations remains, however, unchanged because a large number of



Fig. 4. Yearly rates of registered infants with trisomy 18 or trisomy 13 per 100,000 infants born for the period 1973–1993 in Sweden [2].

these malformations are detected late in pregnancy or do not warrant termination of pregnancy when they are found at earlier gestational age, or are simply missed at routine ultrasound scans.

Some aspects of the psychological impact of PND have been studied by researchers at the Karolinska hospital [3–7]. One of the conclusions from these studies was the need for education and training in the art of counselling among midwives and gynaecologists.

Areas of Prenatal Diagnosis under Development

Clinical research programmes for pre-implantation diagnosis have recently been started in Gothenburg and Stockholm using both fluorescence in situ hybridisation (FISH) and polymerase chain reaction (PCR) based techniques.

Interphase FISH analysis is operative at most centres. It is presently used as an alternative to repeated amniocentesis when cell cultures failed to grow and for rapid diagnosis (within 24 h) of fetuses with malformations detected by ultrasound investigation.

Second-trimester biochemical serum screening for aneuploidy has recently been introduced in Lund and Stockholm, and it is now available for selected pregnancies.

Funding Arrangements for Prenatal Diagnosis

Funding for PND is provided by local, district and central taxation, and the patient only pays a consultation fee. Investigations associated with the consultation are free for the patient. Mothercare at the maternity wards and health care centres is free. Private health care insurance is practically non-existing. Care for the disabled is also regulated by law and funded in the same way.

Each county council sets its own fees for out-patient care. The fee for consulting a doctor in the primary health care services varies between county councils from SEK 60 to SEK 130. For consulting a specialist at a hospital, the fees vary from SEK 100 to SEK 260. According to current legislation, the fee which patients pay for consulting a private specialist shall be 150% of the fee for a consultation with a family doctor.

To limit the costs incurred by patients, there is a high cost ceiling. A patient who has paid at least SEK 2,200 for medical care and for medication is entitled to free care and free prescription for the remainder of the 12-month period, which is calculated from the first visit to a doctor or the first purchase of medicines. Medication given in hospitals is paid for by the hospitals through tax revenues to the county councils.

Legislation

There is no upper limit of gestational age for abortion in Sweden. Abortions are rarely performed after the 24th week of gestation. However, pregnancies may be interrupted later if the mother's life is threatened, or the fetus has a disorder that is not compatible with extrauterine life, e.g., anencephaly.

The mother can decide herself to have an abortion until the 18th week of gestation in Sweden. Permission to perform abortion from the Abortion Council at the National Board of Health and Welfare is required after the 18th week, but is in practice never denied for genetic disorders or malformations before 22 weeks of gestation.

A new law, encompassing a duty to inform all pregnant women about PND, was passed in 1995. This law requires the attendant to inform on prenatal diagnostic procedures even if the woman does not belong to any risk group. Thus, all women, irrespective of age should be informed about prenatal chromosome analysis even if only women above 35 years of age are offered it.

Problems and Future Perspectives

One method for the county councils to promote rationalisation in the health services has been to introduce a new financial control system [1]. In 1994, 14 county councils had introduced some form of purchaser-provider model in their medical services. Under this model the traditional system of fixed annual allocations to hospitals and primary care services has been abandoned. Instead, payment is made by results or performance, i. e. the funds received by a hospital depend on the number of patients it treats. This model has allowed PND to expend according to needs (table 2). However, there is a shortage of trained cytogeneticists in Sweden. It is still too early to evaluate the total effects of the purchaser-provider model in Swedish medical care. It is clear that it has led to greater interest in the performance of the health services, in the costs of performance, and in the quality of the services provided.

Clinical genetics, although a speciality of its own, has a weak position in the medical curriculum. It is also often confused with molecular biology, and thought of only as a subspeciality of laboratory medicine. There are too few positions as clinical geneticists in order to meet the challenge of transforming the results of the Human Genome project to clinical medicine, especially as regards education and predictive testing. Finally, the economic restric-

Table 2. Numbers of live-births, amniocenteses (AC) and chorion villus samplings (CVS) 1990–1995 in Sweden

Year	Live-births	CVS and AC	CVS or AC/ live-births, %
1990	123,938	5,877	4.74
1991	123,737	5,890	4.76
1992	122,848	6,600	5.37
1993	117,846	6,584	5.59
1994	112,257	6,453	5.75
1995	103,326	6,310	6.11

The increased rate of CVS and AC since 1992 is due to a change in policy of offering prenatal chromosome analysis in the Stockholm area; the maternal age limit was then lowered from 37 to 35 years.

tions on the health care system in Sweden are an obvious potential threat to equal access to health care.

Acknowledgments

Anders Ericson, the Swedish National Board of Health and Welfare, kindly provided figures 2–4. We thank the staff of all departments of clinical genetics in Sweden for data on some of their activities.

Appendix 1

Official publications related to genetic services

- (1) Genetic integrity (in Swedish). Genetisk integritet. Betänkande av gen-etikkommittén. SOU 1984:88. Ministry of Health and Social Affairs, Stockholm.
- (2) Prenatal diagnosis. About information and support to parents (in Swedish). Fosterdiagnostik – om att informera och stödja föräldrarna. Socialstyrelsen redovisar 1986:16. The National Board of Health and Welfare, Stockholm.
- (3) Prenatal diagnosis. Facts and problems (in Swedish). Fosterdiagnostik – Fakta och problembeskrivning. Socialstyrelsen redovisar 1988:12. The National Board of Health and Welfare, Stockholm.
- (4) The pregnant woman and her fetus: Two individuals (in Swedish). Den gravida kvinnan och fostret – två individer. Slutbetänkande av utredningen om det ofödda barnet. SOU 1989:51. Ministry of Health and Social Affairs, Stockholm.
- (5) The fetus in focus (in Swedish). Fostret i focus. Medicinska Forskningsrådet, 1991. Medical Research Council, Stockholm.

Appendix 2

Regional Clinical Genetic Centres with Specialist Training

Department of Clinical Genetics
East Hospital
S-416 85 Göteborg
Tel. +46 31 37 40 00; Fax +46 31 55 40 25

Department of Clinical Genetics
University Hospital
S-221 85 Lund
Tel. +46 46 17 33 62; Fax +46 46 13 10 61

Department of Clinical Genetics
Karolinska Hospital
S-171 76 Stockholm
Tel. +46 8 729 20 00 (from March 1, 1997 +46 5177 00 00),
Fax +46 8 32 77 34

Department of Clinical Genetics
University Hospital
S-901 85 Umeå
Tel. +46 90 10 10 00; Fax +46 90 12 81 63

Department of Clinical Genetics
Academic Hospital
S-751 85 Uppsala
Tel. +46 18 66 30 00; Fax +46 18 55 40 25

Clinical Genetic Laboratories with Restricted Services

Cytogenetic Laboratory
Department of Obstetrics and Gynecology
University Hospital
S-581 85 Linköping
Tel. +46 13 22 20 00; Fax +46 13 14 81 56

Cytogenetic Laboratory
Department of Pathology
Central Hospital
S-541 85 Skövde
Tel. +46 500 43 10 00; Fax: +46 500 43 81 56

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- 7 Sjögren B, Uddenberg N: Prenatal diagnosis for psychological reasons: Comparison with other indications, advanced maternal age and known genetic risk. *Prenat Diagn* 1990;10: 111-120.
- 8 Lindsten J, Marsk L, Berglund K, Iselius L, Ryman N, Annerén G, Kjessler B, et al: Incidence of Down's syndrome in Sweden during the years 1968-1977; in Burgio GR, Fraccaro M, Tiepolo L, Wold U (eds): *Trisomy 21. An International Symposium*. Berlin, Springer 1981, pp 195-210.
- 9 Iselius L, Lindsten J: Changes in the incidence of Down syndrome in Sweden during 1968-1982. *Hum Genet* 1986;72:133-139.