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Proceedings of the EUCROMIC Workshop on Prenatal Diagnosis

Paris, May 23–24, 1996

Key Words
Prenatal diagnosis · Europe · Amniocentesis · CVS · Screening · Funding · Legislation

Registration of prenatal diagnostic (PND) procedures, abnormal and ambiguous diagnoses, and outcome of pregnancy is of importance to genetic centres as well as policy-makers. In European countries, this registration varies considerably: some countries compile detailed data from all centres each year, while in others there is no central registration. Within these extremes, there are various levels of registration.

One of EUCROMIC goals is to obtain an overview of the PND activity in Europe for the project period 1993–1995. The data reported from the participating 78 centres represent, but do not cover the entire activity. Consistent with the EUCROMIC goals, the intentions for a workshop on PND in Europe was (1) to increase the level of information on PND between the EU countries; (2) to create a forum for exchange of experience with national registers; (3) to unveil the present state: what are we actually doing? and (4) to support the start of new registers, revive prior registers and increase the efficiency of existing registers; could we do better?

In Amsterdam, November 6, 1995, an organising committee consisting of Segolène Aymé, Nico J. Leschot, Gordon Lowther and Lars O. Vejerslev decided to pursue the goals through a closed workshop in Paris, May 23–24, 1996. The invited participants, selected according to scientific criteria and active involvement in PND, were one geneticist and one gynaecologist/obstetrician from each of the EU countries. Besides, observers from non-EU European countries and related concerted actions were encouraged to participate and contribute. The delegates (table 1) were asked to prepare a paper addressing the following questions at the workshop and in the proceedings:

(1) What sources of information are available at the local, regional, or national level? What data relevant to PND are systematically collected?

(2) What is the impact of prenatal diagnosis on the prevalence of chromosomal disorders and severe malformations?

(3) Which diagnostic procedures are available for fetal karyotyping, biochemical serum screening, ultrasound screening/diagnosis, and molecular diagnosis?

(4) What are the current methods in use for PND (amniocentesis, chorionic villus sampling, cordocentesis), and what are the professional guidelines?

(5) What areas are under development (interphase cytogenetics, fetal cells in maternal circulation, first-trimester biochemical screening, others)?

(6) What are the funding arrangements for PND?

(7) What is the current legislation surrounding PND for termination of pregnancy and for pre-implantation diagnosis?

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Table 1. Participants in EUCROMIC workshop on PND, Paris 1996

Country	Genetics	Gynaecology
Austria	Hannelore Zierler	
Belgium	Esther Vamos	Kamiel Vandenberghe
Denmark	Claes Lundsteen	Lars O. Vejerslev
Finland	Riitta Salonen	Pirkko Ammala
France	Ségolène Aymé	
	Nicole Morichon	
Germany	Rolf-Dieter Wegner	Rolf Becker
UK	Gordon Lowther	Martin Whittle
Greece	Ariadni Mavrou	Aris Antsaklis
Italy	Emilio Donti	Graziano Clerici
Luxembourg	François Schneider	
Netherlands	Nico Leschot	Maarten D. Kloosterman
Portugal	A.M. Tavares Fortuna	
	Maximina Pinto	
Spain	Joaquina Gabarron	
	Carmen Ramos	
Sweden	Ulf Kristoffersson	The-Hung Bui
Non-EU participants		
Norway	Kåre Berg	
Switzerland	Célia DeLozier-Blanchet	Josef Wisser
EU, BIOMED I	Heikki Kallasvaara	
CA CAGSE	Rodney Harris	
CA DADA	Theresa Marteau	

(8) What are the problems you have to face in the future in your own country, and how do you see the future?

For the proceedings, the authors were furthermore asked to include an introduction on the national organisation of PND, a list of indications for PND, the psychosocial impact of PND, and the topic of counselling. They were also asked to give the name of a third person, who could act as independent reviewer of the information given in the paper.

Evidently, it has been a tremendous task for the authors to collect this amount of data on a nation-wide scale. None of the papers provide complete information on all topics, which is mainly due to lack of central registration or considerable variation between countries and regions.

After reviewing all manuscripts, we have designed a number of tables in order to summarise some of the many data. These tables were sent to the authors for corrections/completion. Unfortunately, Austria though present at the workshop, was unable to prepare a formal manuscript.

Table 2 illustrates the great variety of the number of genetic centres in relation to the total population in each country. Since the definition of a 'genetic centre' differs between the different countries, this is only a very rough estimate. At the extreme ends of the spectrum are Finland/Luxembourg each with 1 centre for every 400,000 people and the Netherlands with 1 centre for every 1,900,000 people. In 9 countries there are only public genetic centres, in the other 6 countries private laboratories exist in addition to public centres.

Some form of central data collection of diagnostic prenatal chromosome studies exists in 8 countries (table 3). For prenatal molecular studies such a registration exists in only 5 countries. The registration of the invasive obstetrical procedures and of ultrasound screening is only carried out in a minority of the 15 countries. Biochemical maternal serum screening seems not to be registered at a national level at all.

In table 4, the number of pregnancies that were actually examined by an invasive obstetrical procedure (i.e. amniocentesis and chorionic villus sampling) is compared with the total number of pregnancies in each country for the years 1993–1995. Again, great difference among the 15 countries are evident. This time, the extreme ends of the spectrum are Norway/Portugal each with 2.3% invasive procedures and Italy with 14.2% invasive procedures (including a number of cordocenteses). In all countries, the annual number of amniocenteses that was carried out exceeded the number of chorionic villus sampling.

The national screening strategies are summarised in table 5. Even for the almost 'classical' maternal age indication for the detection of fetal Down syndrome, there are differences between the 15 countries, varying from ≥ 35 years to >38 years in most countries to an unspecified 'advanced' maternal age in the UK. Maternal serum screening is organised as a local programme in 3 countries, and widely (but not universally) available in the UK, France and Italy. The number of ultrasound examinations per pregnancy is listed in this table too and varies from 0 to 3 to 'unlimited'.

There is more or less consensus over the indications for PND by an invasive procedure as is illustrated in table 6. It is interesting to note that in 12 of the 15 countries an abnormal result after maternal serum screening is an indication for invasive prenatal chromosome studies. In 14 of the 15 countries, an indication for prenatal chromosome studies exists if ultrasound examination has revealed a fetal anomaly. In some countries, a chromosomal or monogenic disease among close relatives is an indication for PND. In other countries, additional examinations are

Table 2. Population and number of public and private genetic centres

Country	Population millions	Public centres	Private centres	Total centres	Population per center millions
Belgium	10	8	0	8	1.25
Denmark	5.5	5	0	5	1.1
Finland	5.1	9	3	12	0.4
France	58			70[a]	0.8
Germany	81.5	82	47	129[b]	0.6
Greece	10.5	5	3	8	1.3
Italy	58	73	27	100	0.6
Luxembourg	0.4	1	0	1	0.4
Netherlands	15	8	0	8	1.9
Norway	4.4	3	0	3	1.5
Portugal	10	12[c]	2	14	0.7
Spain	39	28	19	47	0.8
Sweden	8.8	7	0	7	1.3
Switzerland	7	5	3	8	0.9
United Kingdom	58.4	42	1	43	1.4

[a] Cytogenetic labs only.
[b] Minimum estimate.
[c] Some of these partial service only.

Table 3. Central registration of PND and screening

Country	Cytogenetic diagnoses	Molecular diagnoses	Invasive procedure	Ultrasound screening	Serum screening
Belgium	–	–	–	–	–
Denmark	+	+	+	–	–
Finland[a]	(+)	–	–	–	–
France	+	+	+	+	+
Germany	–	–	–	–	–
Greece	–	–	–	–	–
Italy	–	–	–	–	–
Luxembourg[b]	(+)	–	(+)	–	–
Netherlands	+	+	+	–	–
Norway[b]	(+)	(+)	–	–	–
Portugal	+	+	+	–	–
Spain[c]	–	–	–	(+)[d]	–
Sweden[d]	(+)[e]	–	–	–	–
Switzerland	–	–	–	–	–
United Kingdom	+	+	+	–	–

[a] Partial information in Malformation Register after termination of pregnancy and Medical Birth Register with information on prenatal diagnoses.
[b] Local register in the one centre performing ≥ 80% of PND.
[c] Partial, not including private centres
[d] Partial, under introduction.
[e] Only autosomal aberrations.

Table 4. PND by amniocentesis (AC) or chorionic villus sampling (CVS) related to births per year[a, b]

Country	Year	Births total	AC	CVS	Tot.	AC %	CVS %	Tot. %
Belgium	1995	125,000	10,569	820	11,389	8.4	0.7	9.1
Denmark	1993	67,371	5,390	3,256	8,646	8.0	4.8	12.8
Finland	1995	65,000	4,053	1,389	5,442	6.2	2.1	8.3
France	1994	760,000	28,420	2,240	49,771	3.7[c]	0.3	6.6
Germany[d]	1994	693,648	45,300	3,100	48,400	6.5	0.4	6.9
Greece	1995	100,000	–	–	6,500			6.5
Italy	1993	560,000	–	–	80,000	–	–	14.2[e]
Luxembourg		5,000						
Netherlands	1995	200,000	8,209	3,686	11,895	4.1	1.8	5.9
Norway	1994	60,092	1,360	40	1,400[f]	2.3	0.06	2.3
Portugal	1993	115,000	2,625	27	2,652	2.3	<0.1	2.3
Spain	1995	357,197						
Sweden	1995	103,326	5,875	435	6,310	5.7	0.4	6.1
Switzerland	1994	82,890	7,900	2,500	10,400	9.5	3.0	12.5
United Kingdom	1994	726,382	31,887	3,882	35,769	4.4	0.5	4.9

[a] When data from central registers were not available, the figures were collected from local centres.
[b] Information on fetal blood sampling was scarce and not included in the present table (see also: c and e).
[c] Including 19,111 cordocenteses.
[d] Procedures in patients with public insurances only.
[e] Including cordocenteses.
[f] 80% = 1,151.

Table 5. National screening strategies in each country

Country	Ultra-sound[a]	Maternal serum[b]	Age indication for invasive procedure
Belgium	3	local	>35
Denmark	no	no	≥35 (at LMPB)
Finland	1–2	yes/no	35–40 (depending on county)
France	≥3	yes	≥38
Germany	3	no	≥35
Greece	2	no	≥35
Italy	3	yes	>35
Luxembourg	3	no	>35
Netherlands	0	no	≥36 (at 18th week of GA)
Norway	2→	no	>38 (at delivery)
Portugal	1→	no	≥35 or 38 (depending on centre)
Spain	3	local	35 or 38 (depending on county)
Sweden	1	no	≥35–37 (depending on county)
Switzerland	2→	no	≥35
United Kingdom	1	yes[c]	advanced

[a] Ultrasound scans offered or recommended. → = unlimited when indicated.
[b] Official programme for screening of biochemical markers in maternal serum.
[c] Widely, but not universally.

Table 6. Indications for prenatal diagnosis by invasive procedure

Indication	B[a]	DK	FIN[b]	F	D[c]	GR	I	L	NL	N	P	E	S	CH	GB
Maternal age	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Previous child chromosomal aberration		+	+	+	+	+	+		+	+	+	+	+	+	+
Parent carrier of chromosomal aberration	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Previous child monogenic disease	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Parent carrier of monogenic disease	+	+	+	+	+		+		+	+	+	+	+	+	+
Chromosomal disease among close relatives	–		–		–			+	–	+			–		+
Monogenic disease among close relatives	±	+	–		+		+		+	+			–	+	+
Material obtained on other indications[d]			+		+				+			+	+	+	+
Positive serum screening	+		+	+	+	+	+	+	+		–	+	+	+	+
Ultrasound anomaly	+		+	+	+	+	+	+	+	+	+	+	+	+	+

[a] No official guidelines.
[b] Indications besides maternal age listed as 'special risk'.
[c] Not specified.
[d] Chromosome studies in addition to molecular or metabolic studies or α-fetoprotein estimation.

Table 7. Quality assessment or demands at the national level

Country	Ultra-sound	Invasive proce-dures	Labora-tory	Med. genet. speciality	Psychosoc. support[a]
Belgium	–	–	+	+	+
Denmark	–	+	+	+	–
Finland	–	–	+	+	–
France	–	–	+	+	+
Germany	+	+[b]	+[c]	+	+[c]
Greece	–	–	–	?	–
Italy	–	–	–	+	–
Luxembourg	–	–	–	–	–
Netherlands	–	+	(–)[e]	+	+
Norway	–	–	–	+	–
Portugal	–	–	(–)[e]	–	+
Spain[d]	+	+	+	–	–
Sweden	–	–	+	+	+
Switzerland	–	–	(–)[e]	(–)[e]	–
United Kingdom	?	+	+	+	–

[a] After termination of pregnancy.
[b] In preparation.
[c] Voluntary.
[d] Recommendations are not carried out.
[e] Under consideration.

indicated in the first place to reveal whether or not the pregnant woman is really at risk for that particular disease.

Quality assessment is summarised in table 7. Only 2 countries have developed criteria for the quality control of ultrasound diagnosis in pregnancy. In 5 countries professional and technical guidelines exist for the application of invasive obstetrical procedures. For the control of the quality of the work in the laboratories, guidelines (or more sophisticated control systems) have been developed in 8 countries. In 10 of the 15 countries Medical Genetics or Clinical Genetics is recognised as an official medical (sub)-speciality. Standard psychological support for women who undergo termination of pregnancy on a genetic indication is available in only 5 of the 15 countries.

The present legislation for termination of pregnancy in the 15 countries is listed in table 8. The application of PND is seriously hampered by the legislation for termination of pregnancy in only one country. In Portugal termination of pregnancy is not allowed after 16 weeks. This is a problem when an abnormal test result is found after second-trimester amniocentesis. Legislation for pre-implantation diagnosis exists in 7 of the 15 countries.

Finally, the funding of PND in the 15 countries is summarised in table 9.

Table 8. Legislation for termination of pregnancy and for pre-implantation diagnosis

Country	Termination			Pre-implantation diagnosis legislation
	allowed	after approval	not allowed	
Belgium	≤12	>12	–	no
Denmark	≤12	>12	–	yes
Finland	≤12	≤20–24	>24	no
France	≤10	>10	–	yes
Germany	≤14[a]	>12	–	no
Greece		≤24	>24	no
Italy	≤12	>12	>24[b]	no
Luxembourg	≤12	>12	–	no
Netherlands	≤24		>24	yes
Norway	≤12	>12	>24	yes
Portugal		≤16	>16	no
Spain		≤22	>22	yes
Sweden	≤18	>18	–	no
Switzerland	≤12	≤22	>22	yes
United Kingdom	–	at any GA	–	yes

[a] Counseling legally required.
[b] Risk for woman's life only.

Table 9. Funding of PND

Country	Funding
Belgium	social security; no funding of analyses performed abroad
Denmark	public health care
Finland	public health care; partly reimbursement of private PND
France	social security for specific indications only
Germany	public and private health insurance
Greece	national and private health insurance on 'valid' indication
Italy	regional law, national health service, private funds
Luxembourg	social security covers tests fulfilling the indications
Netherlands	health insurance companies
Norway	public health care
Portugal	national health system
Spain	national and regional health system and private insurance companies all on valid indications
Sweden	public health service; consultations are free
Switzerland	health insurance on 'valid' indication
United Kingdom	national health service

It is the hope of the organisers of the workshop in Paris that the detailed overview of the situation for PND in Europe, as presented in this supplement issue, can have the function of a basis. This basis can be used as a starting point, both by geneticists and gynaecologists and by the responsible policy-makers, when recommendations are being formulated for this rapidly developing diagnostic field.

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