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Trends and geographic inequalities in the prevalence of Down syndrome in Europe, 1980-1999

Tendances temporelles et inégalités géographiques pour la prévalence du syndrome de Down en Europe, 1980-1999

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Background: EUROCAT is a network of population-based registries for the epidemiologic surveillance of congenital anomalies covering approximately one quarter of births in the European Union. Down syndrome constitutes approximately 8% of cases of registered congenital anomaly in Europe, with over 7 000 affected pregnancies in the 15 current member states of the European Union each year. In this paper, we aim to examine trends in the live birth prevalence of Down syndrome in Europe in the light of trends in maternal age and in prenatal diagnosis.

Methods: Descriptive analysis of data from 24 EUROCAT registries, covering 8.3 million births 1980-99. Cases include live births, stillbirths and terminations of pregnancy following prenatal diagnosis.

Results: Since 1980, the proportion of births to mothers of 35 years of age and over has risen quite dramatically from 8 to 14% for the European Union as a whole, with steeper rises in some regions. By 1995-1999, the proportion of "older" mothers varied between regions from 10% to 25%, and the total prevalence (including terminations of pregnancy) of Down syndrome varied from 1 to 3 per 1 000 births. Some European regions have shown a more than twofold increase in total prevalence of Down syndrome since 1980. The proportion of cases of Down syndrome which were prenatally diagnosed followed by termination of pregnancy in 1995-1999 varied from 0% in the three regions of Ireland and Malta where termination of pregnancy is illegal, to less than 50% in 14 further regions, to 77% in Paris. The extent to which terminations of pregnancy were concen-

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trated among older mothers varied between regions. The live birth prevalence has since 1980 increasingly diverged from the rising total prevalence, in some areas remaining approximately stable, in others decreasing over time.

Conclusion: The rise in average maternal age in Europe has brought with it an increase in the number of pregnancies affected by Down syndrome. The widespread practice of prenatal screening and termination of pregnancy has in most of the regions covered by EUROCAT counteracted the effect of maternal age in its effect on live birth prevalence. Under the joint influences of maternal age and prenatal screening the pattern of geographic inequalities in Down syndrome live birth prevalence in Europe has also been changed.

Down syndrome. Maternal age. Prenatal diagnosis. Termination of pregnancy.

Contexte : Eurocat est un réseau de registres de surveillance des anomalies congénitales couvrant approximativement un quart des naissances de l'Union Européenne. Le syndrome de Down représente environ 8 % des cas de malformations congénitales enregistrées, avec plus de 7 000 grossesses affectées dans les pays de l'Europe des 15 chaque année. Dans cet article, notre objectif est d'examiner les tendances dans la prévalence du syndrome de Down à la naissance en Europe, à la lumière des tendances de l'âge maternel et du diagnostic prénatal.

Méthodes : Analyse descriptive des données de 24 registres Eurocat, couvrant 8,3 millions de naissances entre 1980 et 1999. Les cas incluent les naissances vivantes, les mort-nés et les interruptions de grossesse suivant un diagnostic prénatal.

Résultats : Depuis 1980, la proportion de naissances chez des mères de 35 ans et plus a augmenté de façon très importante, passant de 8 à 14 % pour l'ensemble de l'Europe des quinze, avec des augmentations plus fortes dans certaines régions. Dans la période 1995-1999, la proportion de naissances chez les mères de 35 ans et plus variait de 10 à 25 % selon les régions, et la prévalence totale du syndrome de Down (incluant les interruptions de grossesse) variait de 1 à 3 pour 1 000 naissances. Certaines régions européennes ont connu une multiplication par plus de 2 de la prévalence totale du syndrome de Down depuis 1980. La proportion de cas de syndrome de Down diagnostiqués avant la naissance et suivis d'une interruption de grossesse en 1995-1999 variait de 0 % dans les 3 régions d'Irlande et de Malte où l'interruption de grossesse est illégale, à moins de 50 % dans 14 autres régions, pour atteindre 77 % à Paris. La proportion de femmes de 35 ans et plus parmi celles ayant recours à l'interruption de grossesse variait entre les régions. Depuis 1980, la prévalence du syndrome de Down à la naissance suit une tendance divergeant de la prévalence totale, restant approximativement stable dans certaines régions et diminuant au cours du temps dans d'autres.

Conclusion : L'élévation de l'âge maternel en Europe a entraîné une augmentation dans le nombre de grossesses affectées par le syndrome de Down. La généralisation du dépistage prénatal et de l'interruption de grossesse a, dans la plupart des régions couvertes par Eurocat, contrebalancé l'effet de l'augmentation de l'âge maternel sur la prévalence du syndrome de Down à la naissance. Les influences simultanées de l'âge maternel et du dépistage prénatal ont modifié les inégalités géographiques de la prévalence du syndrome de Down à la naissance en Europe.

Syndrome de Down. Âge maternel. Diagnostic prénatal. Interruption de grossesse.

INTRODUCTION

EUROCAT is a network of population-based registries for the epidemiologic surveillance of congenital anomalies which started in 1979 [1]. Thirty six registries in 18 countries were participating in the network in 2002, covering together more than 1 million births per year, and approximately one quarter of births in the European Union. Down syndrome constitutes approximately 8% of cases of registered congenital anomaly in Europe, with over 7 000 affected pregnancies estimated in the 15 current member states of the European Union each year. Over the last two

decades there have been two strongly changing influences on the prevalence of Down syndrome in Europe. One is the increasing average maternal age at childbirth, the other the increasingly widespread use of prenatal screening [2], with the offer of termination of pregnancy where this leads to a Down syndrome diagnosis.

In this paper, we aim to examine trends in the live birth prevalence of Down syndrome in Europe in the light of trends in maternal age and in prenatal diagnosis.

METHODS

We include here data from 24 EUROCAT registries from 1980-1999 *(table I)*. These registries ascertain cases of Down syndrome in live births, stillbirths and terminations of pregnancy following prenatal diagnosis, and could provide data for the numbers of births by maternal age in their region. Descriptions of the methods registries use to ascertain cases are published elsewhere [1, 3]. Many registries *(table I)* are notified of all Down syndrome cases by cytogenetic laboratories as one of multiple sources of information.

EUROCAT Central Registry holds a standardised anonymised database on individual cases of congenital anomaly, including year of birth, maternal age at delivery, type of birth and gestational age at delivery/abortion [4]. We include in this study all live births, fetal deaths from 20 weeks gestation, and terminations of pregnancy of any gestational age following prenatal diagnosis.

Denominators for all births by 5 year maternal age group in the geographic areas covered by the registries were obtained by each registry from hospital or regional statistics. EUROSTAT figures were also obtained for the 15 EU member countries in 2002, except Germany for which no maternal age distribution for births was available.

Total prevalence is defined here as the number of Down syndrome cases (live births, fetal deaths from 20 weeks, terminations of pregnancy of any gestational age) divided by the total number of births (live and still).

Live birth prevalence is defined here as the number of live born cases of Down syndrome divided by the total number of live births.

RESULTS

The 24 registries surveyed a total of 8.3 million births during 1980-1999, recording a total of 7 185 cases of Down syndrome in this period *(table I)*.

The average maternal age-specific total prevalence rates of Down syndrome in these registries (1980-1999) rise from 7.0 per 10 000 births for the less than 25 age group, to 8.6 per 10 000 in the 25-29 year age group, to 14.8 per 10 000 in the 30-34 year age group, to 62.8 per 10 000 in the age group 35 years or more. Mothers over 35 years of age thus have an average 8 to 9 fold higher prevalence compared to mothers of less than 25 years of age, while the prevalence among mothers of 30-34 is approximately double that of those under 25.

Figure 1 indicates the rising proportion of mothers aged 35 or over in the birth populations surveyed by these registries, for all registries with data going back at least as far as 1990. EUROSTAT data for 14 countries of Europe show a rising proportion of older mothers from 8% 1980-1984 to 14% 1995-1999. We show wide regional variation in this trend, even within countries *(fig. 1)*. By 1995-1999 almost one quarter of all births were to mothers of 35 and over in Paris and the Basque Country, compared to only 10% in Styria, Zagreb and Antwerp *(fig. 2)*. The average across registries for 1995-1999 was 16%, close to the European average.

Figure 3 shows the increase in the total prevalence of Down syndrome in 12 registries with data going back at least as far as 1990, reflecting the increase in maternal age. By 1995 to 1999, the total prevalence of Down syndrome varied threefold between the 24 regions *(table I)*, from 1 to 3 per 1 000 births.

The proportion of cases of Down syndrome which were prenatally diagnosed followed by termination of pregnancy in 1995-1999 varied from 0% in the three regions of Ireland and Malta where termination of pregnancy is illegal, to less than 50% in 14 further regions, to 77% in Paris *(table I)*. This resulted in quite a different pattern of geographic variation in live birth prevalence of Down Syndrome compared to the total prevalence *(table I)*. With the exception of Ireland and

TABLE I. — *Down Syndrome in 24 Regions of European 1995-99: Number of cases, proportion of terminations of pregnancy (TOP), total and live birth prevalence per 10 000 births.*

Registry	Years	1980-1999 Tot DS cases	1995-1999 Tot DS cases	1995-99 : % 35+/All births	1995-99 : % 35+/DS cases	1995-99 : % < 35 years DS cases/TOP	1995-99 : % ≥ 35 years DS cases/TOP	1995-99 : % All ages % DS cases/TOP	1995-99 DS total prev / 10 000 births	1995-99 DS LB prev / 10 000 births
Paris* (F)	1981-99	1779	652	24.1	61.0	67.2	83.2	76.8	34.61	7.53
Basque Country* (S)	1990-99	382	226	23.8	55.8	29.0	73.0	53.5	27.94	12.91
Cork & Kerry (I)	1996-99	78	78	21.1	60.3	0.0	0.0	0.0	25.67	25.51
Vaud* (Switz)	1989-99	192	93	15.8	45.2	58.8	83.3	69.9	24.54	6.62
Barcelona*[1] (S)	1992-99	190	118	22.1	61.0	44.4	61.1	54.2	24.49	6.46
Mainz (Germany)	1990-99	77	40	14.3	37.5	20.0	60.0	35.0	22.39	14.61
Strasbourg* (F)	1982-98	376	114	12.5	52.6	50.0	81.7	66.7	21.35	6.77
Dublin (I)	1980-99	825	212	18.7	51.4	0.0	0.0	0.0	21.26	20.26
Asturias* (S)	1990-99	118	66	18.2	51.5	12.5	61.8	37.9	20.40	12.73
Merseyside* (UK)	1995-99	264	264	13.2	48.1	37.0	54.3	43.6	18.87	10.13
Wales* (UK)	1998-99	123	123	14.9	44.7	29.4	58.2	42.3	18.67	10.38
Trent* (UK)	1998-99	209	209	12.5	43.1	45.4	55.6	47.4	17.87	8.77
Galway (I)	1981-99	123	23	23.5	56.5	0.0	0.0	0.0	17.75	17.83
Odense* (Den)	1980-99	156	49	11.6	40.8	6.9	65.0	30.6	16.93	10.77
Glasgow (UK)	1980-99	351	90	14.3	51.1	27.3	45.7	36.7	16.93	10.6
Tuscany (I)	1980-99	458	211	18.0	47.9	37.4	76.2	55.9	16.90	7.21
Malta	1986-99	126	37	14.4	54.1	0.0	0.0	0.0	15.86	15.53
N Netherlands	1981-99	413	154	14.1	48.7	7.6	54.7	30.5	15.74	10.48
Emilia Romagna* (I)	1995-99	181	181	17.0	37.0	18.1	56.7	38.7	14.03	8.63
Styria* (A)	1990-99	169	80	9.9	46.3	22.2	54.1	42.5	13.71	7.57
Campania (I)	1996-99	265	265	12.4	44.9	31.0	59.7	43.0	13.51	7.68
Zagreb (Croa)	1983-99	134	40	9.7	35.0	0.0	21.4	7.5	12.80	11.58
Antwerp[2] (B)	1990-99	122	81	9.7	32.1	31.5	69.2	43.2	10.68	
S Portugal[3]	1990-99	74	60	11.3	41.7	2.9	32.0	16.7	7.50	6.15
Total		7185	3466	15.9	50.1	32.9	60.0	46.5	19.01	10.14

* Registry which includes notifications from cytogenetic laboratories among multiple sources of notification (in N Netherlands subject to parental consent).
** Registries listed in order of the proportion of all births to mothers 35 years and over *(fig. 2)*.
[1] Barcelona data excludes year 1997.
[2] Antwerp live birth prevalence rate calculated with total births as denominator instead of live births.
[3] S Portugal data excludes years 1993-94.

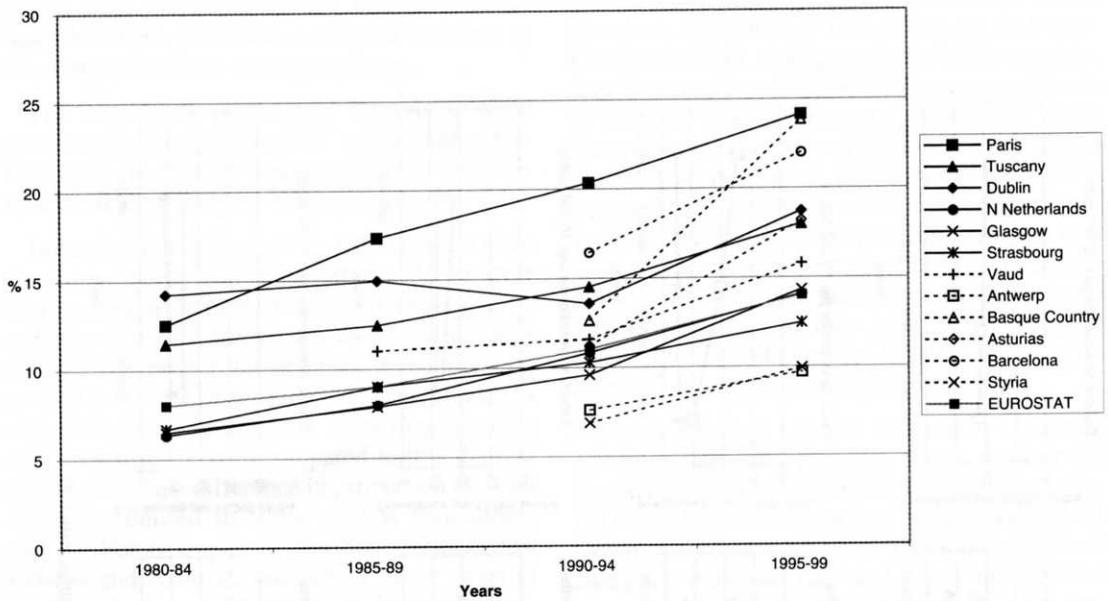

FIG. 1. — Trend in proportion of births to women of 35 years and over, 1980-1999, in 12 EUROCAT registries and EUROSTAT (14 countries).
EUROSTAT data is for 14 out of the 15 member states of European Union (excluding Germany).

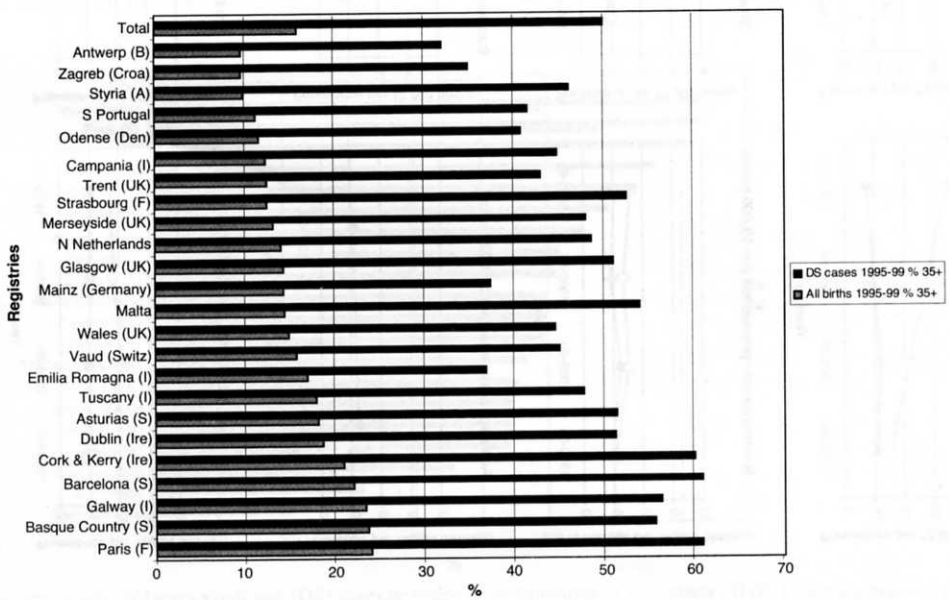

FIG. 2. — Proportion of all births and of Down syndrome (DS) cases to mothers aged 35 +, 24 registries, 1995-1999.

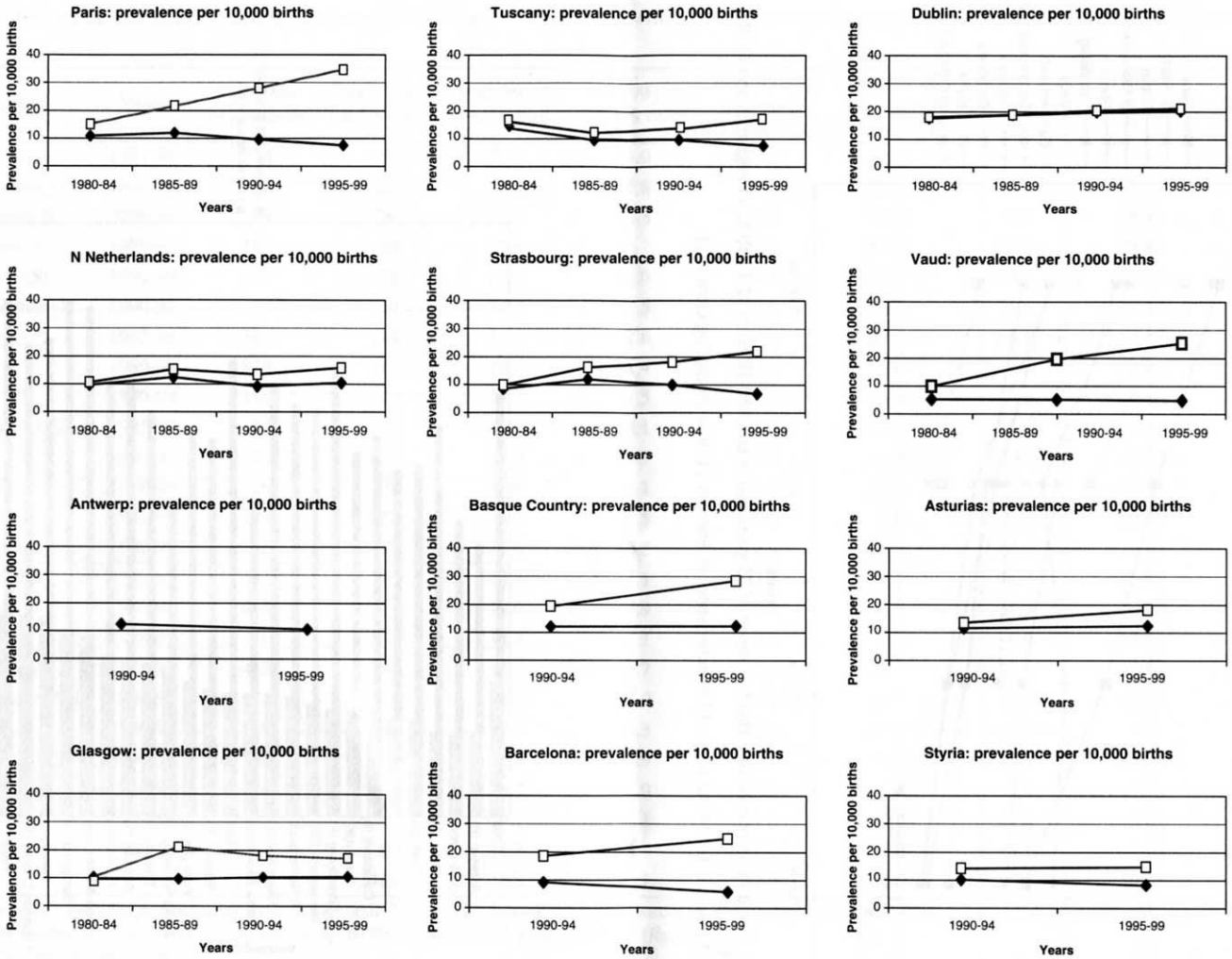

FIG. 3. — Trend in total and live birth prevalence of Down syndrome in 12 EUROCAT registries, 1980-99.
Live birth prevalence = –□–.
Total prevalence = –◆–.

Malta, with much higher live birth prevalence than elsewhere, there was a twofold variation in live birth prevalence among registries.

The live birth prevalence has since 1980 increasingly diverged from the rising total prevalence *(fig. 3)*, in some areas remaining approximately stable, in others decreasing over time.

In ten of the 24 registries 1995-1999, Down syndrome cases with maternal age 35 or over represented more than 50% of all cases *(fig. 2)* and the average across all 24 registries was 50.9%. The proportion of cases prenatally diagnosed followed by termination of pregnancy is higher where maternal age is 35 or over (average of 24 registries 60.0%) compared to less than 35 (32.9%), but this difference in proportion is much more pronounced in some regions than others *(fig. 4)*. For example, in Northern Netherlands, Odense and Asturias, less than 15% of cases to mothers less than 35 years are prenatally diagnosed followed by termination of pregnancy, compared to over 50% of cases to mothers over 35 years of age *(fig. 4)*.

DISCUSSION

The rise in average maternal age in Europe has brought with it an increase in the number of pregnancies affected by Down syndrome. Some European regions have shown a more than twofold increase in total prevalence of Down syndrome since 1980. EUROCAT began surveillance in 1980 [4] when average maternal age in many European countries was at its lowest point [5], so the total prevalence of Down syndrome can be assumed to be returning to levels experienced previously. The fact that it is particularly age at first birth which has been increasing [5] might very slightly lower the total prevalence of Down syndrome — studies to date have shown either a weak positive relationship between parity and Down syndrome risk or no effect at all [6].

The widespread practice of prenatal screening and termination of pregnancy has in most of the regions covered by EUROCAT resulted in a stable or slightly decreasing live birth prevalence of Down syndrome over time. The joint picture of changing maternal age and changing prenatal screening has led to significant and changing geographic inequalities in Down syndrome live birth prevalence in Europe. Liveborn prevalence 1995-1999 varied twofold in countries which practise screening from 6-8 per 10 000 (Strasbourg, Paris, Vaud, Barcelona, Tuscany, Styria, Campania, S Portugal) to 13-15 per 10 000 (Asturias, Basque Country and Mainz). Differences in the proportion of terminations may reflect both screening

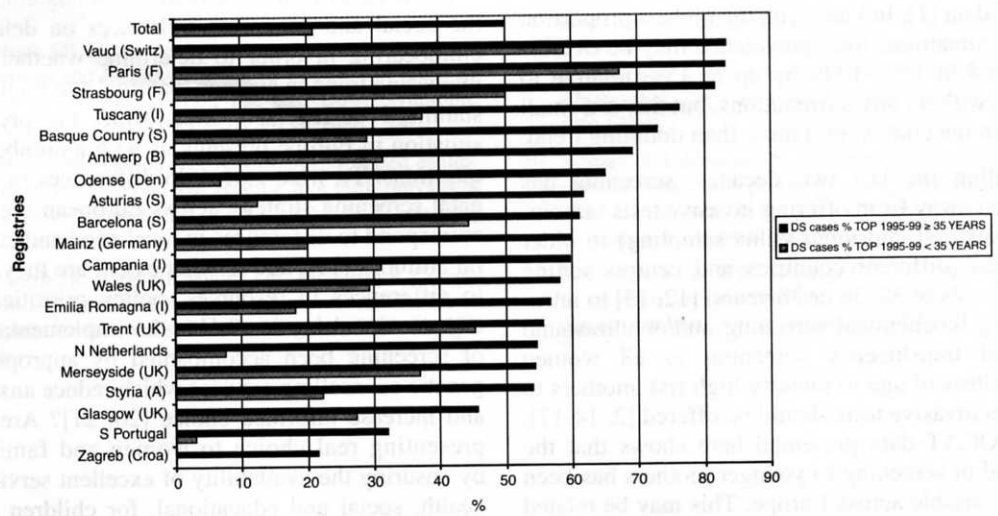

FIG. 4. — Proportion of Down syndrome (DS) cases recorded as terminations of pregnancy (TOP) following prenatal diagnosis among mothers age < 35 years, ≥35 years, 20 registries, 1995-1999.

differences (including whether maternal age is an indication for screening, and gestational age at screening) and cultural factors which influence the frequency with which termination of pregnancy follows prenatal diagnosis, although in most regions over three quarters of prenatally diagnosed cases result in termination of pregnancy [1]. The highest live birth prevalence of Down syndrome was recorded in Ireland (19 to 26 per 10 000) and Malta (16 per 10 000), where termination of pregnancy is illegal.

We have not formally analysed here whether there are any regional differences in maternal age-specific total prevalence of Down syndrome. Very little true variation between human populations has been demonstrated [7]. The average EUROCAT maternal age specific rates for broad age groups are similar to those reported in the literature [8, 9], suggesting generally high levels of ascertainment. However, recent total prevalence rates including many early terminations of pregnancy are overestimated in comparison with rates based on populations with less prenatal screening, since terminations include cases which would otherwise have been lost as spontaneous abortions. For example, it has been estimated that between the time of amniocentesis and term, 23% of pregnancies end in miscarriage or stillbirth [10, 11], while 4% of live births and fetal deaths of 20 weeks gestation or more with Down syndrome are registered as fetal deaths in EUROCAT data [1]. In Paris with the highest proportion of terminations, total prevalence may be overestimated in 1995-1999 by up to 15% relative to years without any terminations, but this is a small bias in the context of a more than doubling trend.

Within the last two decades, screening has moved away from offering invasive tests (amniocentesis and chorionic villus sampling) to older women (different countries and centres setting thresholds of 35, 36 or 38 years) [12, 13] to introducing biochemical screening and/or ultrasound nuchal translucency screening to all women regardless of age to identify high risk mothers to whom invasive tests should be offered [2, 14-17]. EUROCAT data presented here shows that the spread of screening to younger mothers has been very variable across Europe. This may be related to patterns of uptake of screening among women, or to the screening strategies employed by the hospitals (or both). For example, in the Netherlands the Dutch Health Council only recommended moving away from offering invasive tests to women of 36 and over in 2001, after this study period [18].

While a major impetus for expanding Down syndrome screening to all maternal ages was the preponderance of cases born to young mothers, it is ironic that parallel to the development of these new screening methods, the rise in maternal age has meant that concentration of affected pregnancies among older mothers has been increasing. Half of all cases recorded in these EUROCAT data 1995-1999 were to older mothers, more than half in ten of the 24 regions. In comparison only two (both Irish) of the registries with data back to 1980-1984 recorded more than half of cases to older mothers in that earlier period [1]. It is possible that older mothers are resisting the new screening methods in favour of the "certainty" of an invasive procedure, given their own perception of themselves as high risk. While it is generally recommended that less than 5% of pregnant women, or 200 000 women each year in the 15 member states of the European Union, should be undergoing invasive procedures in any screening programme [2], additional demand by the 14% of women 35 years and over would increase this number considerably.

We need to achieve a better understanding of the social and economic influences on delayed childbearing in order to determine whether the increasing trend in average maternal age might be stabilised or reversed. Meanwhile, the present situation in Europe presents us with a number of questions. To what extent do differences in prenatal screening strategy across European regions correspond to differences in local need and cultural attitudes [19], and to what extent are they due to differences in resources, policy priorities or organisational barriers? Has the implementation of screening been accompanied by appropriate genetic counselling services which reduce anxiety and increase informed choice [20, 21]? Are we presenting real choice to women and families by ensuring the availability of excellent services, health, social and educational, for children and adults with Down syndrome and their families in Europe?

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