

Three year national survey of prenatal cytogenetic activity in France 1998-2000

Jean-Michel Dupont and Elisabeth Carles, on behalf of ACLF

National regulations and training of cytogeneticists

In France several laws govern cytogenetic activity for prenatal diagnoses. Most cytogeneticists are either MDs qualified in Biology or Genetics, or Pharmacists qualified in Biology. Both groups then specialise further in cytogenetics. After a minimum of two years experience, this leads to a diploma. This diploma, combined with proven activity for three or four more years in cytogenetic prenatal diagnosis lab, is required to obtain national accreditation to be able to work in this field and authorise results. This accreditation is renewed every five years.

Each laboratory must also be accredited by the ministry of Health before being authorized to run a cytogenetic unit. The purpose of this control is to verify that the lab has adequate facilities for Cytogenetic investigations. Renewal of laboratory accreditation is decided by the national commission, which requires the lab to have followed the approved national guidelines published by the ACLF (Association des Cytogénéticiens de Langue Française, French speaking cytogeneticists association). These guidelines deal with the general organisation of cytogenetic laboratories and the cytogenetic procedure to be followed (number of cells to be analysed, banding techniques, items to include in the final report etc...). All laboratories have to send a yearly activity report to the Health ministry including various items such as total number of diagnoses performed, number of abnormal results, reasons for referral, number of termination of pregnancies, number of errors and failures etc...

However, the accreditation procedure does not control the quality of the cytogenetic analyses (number of cells analysed, quality of banding etc...). For this reason, a national quality control system is to be organised by the ACLF to control these technical points.

Prenatal cytogenetic investigations, either amniocentesis, chorionic villus sampling or foetal blood sampling are free of charge for all the patients from the following categories

- Maternal age ≥ 38 years on the day of the sampling
- Patient with increased risk after bio-chemical testing (Risk $\geq 1/250$)
- Pregnancies with abnormal ultrasound
- Patient having a previous child with a chromosomal disorder
- Parents carrying a chromosomal rearrangement
- Sexing for X-linked disorders

Table 1 : Distribution of activity in the French cytogenetic laboratories

Number of karyotypes/Year	Number of laboratories (1998)	Number of laboratories (2000)
<200	4	2
200 - 500	10	12
500 - 1000	21	25
1000 - 1500	11	10
1500 - 2000	11	7
> 2000	6	8

missing

Map of France including details for the center Ile de France and the oversea departments showing the distribution of cytogenetic laboratories with authorization for prenatal diagnosis.

Distribution of laboratory activity

There were 79 authorised laboratories in 1998 and 72 after the renewal of 1999 (47 in public hospitals and 25 private laboratories).

Of these, we could obtain the official activity report for more than 60 giving an overview of the cytogenetic activity in France for the years 1998 – 2000.

There was no change in overall activity during this three-year period (see Tables 1 and 2), however there was a slight decrease in the overall activity per lab reflecting a change in the size of the laboratories (1267 fetuses analysed / laboratory in 1998, 1226 / laboratory in 1999 and 1217 in 2000). The majority of the laboratories have a prenatal diagnosis activity in the range of 500 – 1000 karyotypes per year.

Table 2 : Changes in indications for karyotyping 1998-2000

	1998	1999	2000
Maternal Age > 38	26316	27896	26583
Parent with abnormal karyotype	708	769	775
Previous child with chromosomal abnormality	1871	2108	1813
Abnormal ultrasound	16475	14454	13059
Biochemical screening	28308	32100	31055
Others	7429	6754	5045
Total KT	81107	84567	78330

In the « Others » category are found prenatal diagnoses conducted for reasons other than increased risk of chromosomal abnormality (either genetic or infectious disease).

The majority of the karyotypes are from amniotic fluid (see Table 3); chorionic villus sampling represents less than 10% of the activity for all the laboratories in 2000, except for 6 which work only with amniotic fluid (11 in 1998) and two that work mainly with chorionic villi (77 % and 52 % of their activity).

Table 3 : Distribution of the activity by sampling category

	1998	1999	2000
Amniotic fluid	94 %	94 %	93 %
Chorionic Villi	5 %	5 %	6 %
Fetal blood	1 %	1 %	1 %

During this three-year period, reasons for referral did not alter except for a slight increase of karyotyping for increased risk after maternal serum screening. Despite a lower predictive positive value than that of maternal age (1/63 versus 1/40 respectively), this indication is increasing since 1997 when the test was offered free of charge to all pregnant women. This situation will probably be affected in the future by combining the main risk factors (maternal age, biochemical serum screening and nuchal thickness measure), giving an integrated risk estimate. However, after genetic counselling, a high percentage of women still choose to have an amniocentesis when the biochemical serum screening shows an elevated risk because of the high degree of anxiety generated.

Results of prenatal diagnoses

The rate of failure of cell culture is stable, between 0.4 and 0.5 %.

The overall rate of chromosomal abnormality is stable at 4 %, 0.8 % of balanced and 3.2 % of unbalanced abnormalities (with a predictive positive value of 1/28).

As expected, the rate of chromosomal abnormality is highest for abnormal ultrasound (9.5 %) and in the progeny of a parent with a chromosomal abnormality (31.3 %).

Table 4 : Rate of chromosomal abnormality detection for each indication

	Maternal age > 38	Parent with abnormal KT	Previous child with abnormal KT	Abnormal ultrasound	Biochemical serum screening	Others
Total number of karyotypes (1998-2000)	80795	2252	5792	43988	91463	19228
%	33.2	0.9	2.4	18.1	37.6	7.9
Chromosomal abnormalities, unbalanced AND balanced	2595	706	174	4169	1928	218
%	3.2	31.3	3	9.5	2.1	1.1

The most frequent abnormality is always trisomy 21 (48 % of unbalanced abnormalities). This is true for all indications except when one parent carries a chromosomal abnormality; in this latter case, various abnormalities are found, corresponding to the balanced or unbalanced segregation of the parental chromosomal rearrangements. For the « Others » category, abnormalities of sex chromosomes are as frequent as trisomy 21 due to the low risk of Down syndrome in this group.

The frequency of the other major abnormalities (T18, T13, Turner syndrome and other sex chromosomes aneuploidies) is stable over these three years (14.9 %, 5.9 %, 9.4 %, and 9.2 % respectively).

Table 5 : Frequency of chromosomal abnormalities

	Maternal Age	Parent with abnormal KT	Previous child with abnormal KT	Abnormal ultrasound	Biochemical serum screening	Others
Total number of KT	80795	2252	5792	43988	91463	19228
Unbalanced anomalies	2094 (2.6%)	96 (4.3 %)	76 (1.3 %)	3951(9 %)	1510 (1.7 %)	153 (0.8 %)
T21	1157 (55.2%)	16 (16.7 %)	27 (35.5 %)	1508 (38.2 %)	1035 (68.5 %)	40 (26.1 %)
T18	269 (12.8 %)	4 (4.2)	4 (5.3 %)	845 (21.4 %)	39 (2.6 %)	17 (11.1 %)
T13	86 (4.1 %)	12 (12.5 %)	5 (6.6 %)	318 (8 %)	32 (2.1 %)	10 (6.5 %)
45,X	92 (4.4 %)	1 (1 %)	8 (10.5 %)	552 (14 %)	76 (5 %)	13 (8.5 %)
Sex aneuploidies	325 (15.5 %)	3 (3.1 %)	9 (11.8 %)	182 (4.6 %)	159 (10.5 %)	48 (31.4 %)
Triploidy	6 (0.3 %)	1 (1 %)		196 (5 %)	22 (1.5 %)	1 (0.7 %)
Other abnormality	159 (7.5 %)	59 (61.5 %)	23 (30.3 %)	350 (8.9 %)	147 (9.7 %)	24 (15.7 %)
Balanced anomalies	480 (0.6 %)	610 (27.1 %)	98 (1.7 %)	218 (0.5 %)	418 (0.46 %)	65 (0.3%)

Parental decisions following a diagnosis of sex chromosomes aneuploidy

After genetic counselling the parental decision for continuation or termination of a pregnancy (TOP) with sex chromosome aneuploidy varies according to the aneuploidy involved.

Turner syndrome foetuses are terminated in the vast majority of cases (See table 6), especially if diagnosis is associated with an abnormal ultrasound. The rate of termination was stable in 1999 and 2000 (no data available for 1998). When continuation of pregnancy was chosen, a mosaicism was present in more than half of the cases.

A more conservative picture is apparent for Klinefelter syndrome, with a two fold decrease in TOP between 1999 and 2000. Once again, termination of pregnancy was

chosen mainly when an abnormal ultrasound was present (but in these cases, we do not know whether termination was chosen because of the severity of mal-formations or because of diagnosis of Klinefelter syndrome).

The same pattern was also seen for Triple X syndrome, but in both cases, these results must be confirmed in the upcoming years before conclusions about the impact of genetic counselling can be drawn.

Conclusion

The rate of prenatal diagnosis in France has been stable since 1997 when amniocentesis after biochemical screening was offered free of charge. However, risk assessment as conducted nowadays results in a very high percentage of amniocentesis (about 11 % of all pregnant wom-en in 2000) when compared to the expected rate

of 5 % of amniocentesis for the chosen cut-off levels. Therefore, we hope that the widespread introduction of the combined risk assessment procedure, using correctly measured nuchal thickness, maternal age, and first trimester bio-chemical screening, will increase the efficiency of the detection procedure so that fewer invasive sampling procedures will be necessary.

Table 6 : Parental decision for sex aneuploidies

Cf : <http://www.biologia.uniba.it/eca/NEWSLETTER/NS-13/02-Article.html>

Dr. Jean-Michel DUPONT
Histologie Embryologie Cytogénétique
Hôpital COCHIN
123 Bd Port Royal
75014 Paris
FRANCE
Tel : +33 1 58 41 17 52
Fax : +33 1 58 41 17 55
E-mail: jean-michel.dupont@cch.ap-hop-paris.fr

Dr. Elisabeth Carles
Génétique, cytogénétique
Laboratoire de biologie clinique
20 route de Revel
31400 Toulouse
FRANCE
E-mail: carles.e@voila.fr