Pregnancy outcomes in 188 French cases of prenatally diagnosed Klinefelter syndrome


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BACKGROUND: Klinefelter syndrome (KS), a common sex chromosome aneuploidy (47,XXY) is diagnosed prenatally with an incidence of 0.15%. The diagnosis is generally incidental, since there are no typical malformations on ultrasound (US). Once detected, genetic counseling is often difficult and the parents’ decision to continue or terminate the pregnancy is greatly dependent on the amount and nature of the information provided. We sought to assess the pregnancy outcomes (i.e. continuation versus termination) and the influence of multidisciplinary centers for prenatal diagnosis on parental decisions in cases of KS.

METHODS: From 1985 to 2009, 188 prenatal diagnoses of KS were made by 11 participating laboratories in mainland France. In each case, the karyotype indication, parental ages, year of prenatal testing, sampling procedure, karyotype, associated US findings and outcome were recorded.

RESULTS AND CONCLUSIONS: The pregnancy termination rate declined markedly over time, from 46.9% before 1997 to 11.6% thereafter, in line with the introduction of new legislation on prenatal diagnosis for medical reasons and, more specifically, the creation of multidisciplinary prenatal diagnosis centers. However, an additional microdeletion in one KS infant who exhibited echogenic bowel on US was unfortunately diagnosed postnatally. This raises the question as to whether array comparative genomic hybridization should be prenatally advised when US abnormalities are detected, in line with advice for fetuses with a normal karyotype.

Key words: prenatal diagnosis / Klinefelter syndrome / outcome / multidisciplinary centers

Introduction

Sex chromosome abnormalities (SCAs) are the most frequent chromosomal abnormalities encountered in prenatal diagnoses, accounting for 0.3% of viable fetuses (Perrotin et al., 2000). This diagnosis usually comes as an unexpected, incidental result of a test carried out for other reasons. Klinefelter syndrome (KS) is an SCA (47,XXY) that occurs with an incidence of ~0.15% in prenatal diagnosis series (Lanfranco et al., 2004). The syndrome was first described in 1942 by Klinefelter as an endocrine disorder characterized by small, firm testes, gynecomastia, hypogonadism and increased concentrations of FSH. Adults are generally infertile, due to severe alterations in spermatogenesis (azoospermia or severe oligospermia). The information about KS given to couples has changed considerably over time. The understanding of KS has moved on from the stereotypes encountered in the 1960s (largely based on biased studies of individuals in mental and penal institutions) to that of a subclinical condition, since the majority of individuals with KS will go through life unaware of their condition (Abramsky et al., 2001). Following a prenatal diagnosis of KS, we have observed a change over time in parents’ decisions to...
terminate or continue the pregnancy. Parents are now more likely to choose to continue with the pregnancy and so the termination of pregnancy (TOP) rate following prenatal diagnosis of KS has fallen in recent years (Christian et al., 2000). This change may be a worldwide trend but may differ from one country or region to another.

France’s Bioethics Bill (which became law in 1994 and was revised in 2004) states that TOP—for medical reasons—is legally justified if the fetus presents a very severe, untreatable disease at the time of diagnosis. In order to provide solid information for justifying (or not) TOP, multidisciplinary prenatal diagnosis centers (MPDCs) were created in 1997 in accordance with the legislation. The centers’ specialists in prenatal diagnosis (obstetricians, experts in ultrasound (US), geneticists, etc.) give advice on possible pregnancy outcomes and prognoses to parents considering TOP. Next, a multidisciplinary care team meets to discuss these well-documented, severe fetal conditions, while taking into account the parental and psychosocial context. This procedure has profoundly modified the management of prenatal diagnosis and TOP procedure in France, which is no longer approved by a single physician. After the multidisciplinary discussion, couples receive counseling from one of the MPDC’s specialists.

Although many published studies have focused on the outcomes of prenatally diagnosed SCAs, most have included only a few cases of KS. The present, 25 years, retrospective study focused on KS and described the changes in pregnancy outcome in France after prenatal diagnosis and a correlated karyotype indication. We therefore sought to assess parental decisions over the years and the MPDC’s influence on pregnancy outcomes.

## Materials and Methods

### Patients

In 1985, five French cytogenetics laboratories started to collect information on prenatal diagnoses of KS. By the end of the study in 2009, six additional investigating centers had joined the network. The study centers made a total of 106 000 prenatal diagnoses and detected 188 cases of KS. For each case, the following data were available: karyotype indication, maternal and paternal age, year of prenatal testing, sampling procedure (amniotic fluid, chorionic villi or fetal blood), karyotype, US findings and the parents’ decision to continue or terminate the pregnancy and pregnancy outcome.

### Statistical analysis

A $\chi^2$ test was used to assess trends in yearly TOP rates throughout the study period. Pearson’s $\chi^2$ test was used to compare the TOP rates for isolated KS before and after the creation of the MPDCs. The threshold for statistical significance was set to $P < 0.05$.

### Results

Prenatally diagnosed KS accounted for 0.17% of all prenatal diagnoses (188 out of 106 000) made in the participating laboratories. The main karyotype indication was maternal age over 38 (110 out of 188: 58.5%). The other main indications were abnormal second trimester results for Down’s syndrome in double [alpha fetoprotein (AFP) and HCG] or triple (AFP and HCG and unconjugated estriol) screening tests (36 out of 188: 19.1%) and abnormalities on US (35 out of 188: 18.6%). Fetal karyotyping was performed because of parental chromosomal abnormalities in two cases (1.1%). A few other indications were reported only once (Table I).

The mean maternal and paternal ages at diagnosis were 36.6 and 37.2, respectively.

The main invasive procedure used for prenatal diagnosis was amniocentesis (92.5%), followed far less frequently by chorionic villus sampling (6.9%) and fetal blood sampling (0.6%).

A 47,XXY karyotype was reported in most cases (172 out of 188: 91.5%). There were 10 cases of mosaicism with a 46,XY cell line (5.3%) and one case of mosaicism with a 46,XX cell line (0.5%). Additional chromosomal abnormalities were observed in five cases (2.7%); with one inherited balanced t(4;8)(q35;q22) reciprocal translocation and four unbalanced karyotypes (Table II).

One case with a prenatal diagnosis of 47,XXY and an echogenic bowel on US was reclassified postnatally as an 8 Mb 14q11.2 microdeletion after array comparative genomic hybridization (CGH; Bluegnome, Cambridge, UK) prompted by hypotonia, facial dysmorphism and hyperinsulinemia.

The outcomes of these 188 pregnancies are shown in Fig. 1. Information was unavailable for nine fetuses (4.8%), two of which had increased nuchal translucency (NT). There were two (1.1%) unexpected fetal deaths with a 47,XXY karyotype, with one fetus

### Table I Indications for karyotyping.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced maternal age (&gt;38)</td>
<td>110</td>
<td>58.5</td>
</tr>
<tr>
<td>Abnormal maternal serum screening results</td>
<td>36</td>
<td>19.1</td>
</tr>
<tr>
<td>Abnormalities on ultrasound</td>
<td>35</td>
<td>18.6</td>
</tr>
<tr>
<td>Previous chromosomal abnormality</td>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>Other indications</td>
<td>5</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>188</td>
<td>100</td>
</tr>
</tbody>
</table>

*One case was prenatally diagnosed as 47,XXY but then postnatally diagnosed through array CGH as a microdeletion: 47,XXYarr 14q11.2q12(19,650,000–27,615,000) × 1.*

### Table II Karyotypes.

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>47,XXY*</td>
<td>172</td>
<td>91.5</td>
</tr>
<tr>
<td>mos 47,XXY/46,XY</td>
<td>10</td>
<td>5.5</td>
</tr>
<tr>
<td>mos 47,XXY/46,XX</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>48,XXY,+21</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>48,XXY,+18</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>47,XXY,t(4;8)(q35;q22)</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>mos 47,XY,+mar/47,XXY/46,XY</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>188</td>
<td>100</td>
</tr>
</tbody>
</table>
exhibiting hydrops fetalis, and the other one a dolichocephaly. For the remaining 177 cases, the TOP frequency was 24.3% (43 cases). Nine mosaic cases were carried to term (100%). Of the cases with an additional abnormality, pregnancies were terminated in three cases (two cases of 48,XXY, +21 one of which had increased NT, and one case of 48,XXX, +18 which had in utero growth retardation and exomphalos) and maintained in two cases (a benign mosaic marker chromosome with moderate intrauterine growth retard (IUGR) and an inherited balanced reciprocal translocation). In the 163 remaining 47,XXY cases, 28 cases (17%) displayed US abnormalities (Table III), of which 7 (25%) were terminated, while 33 (24%) of the 135 pregnancies with non-mosaic, isolated KS (i.e. in the absence of US abnormalities) were terminated.

When taking into account each year of prenatal testing, this percentage of terminations fell markedly over time (from 75 to 0%; \( P < 0.0001 \) in a \( \chi^2 \) test) (Fig. 2). Considering that MPDCs started operating in 1998, the proportion of TOPs for non-mosaic, isolated KS recorded before and after this date differed very significantly (23 out of 49 (46.9%) before 1998 (46.9%) versus 10 out of 86 (11.6%) in 1998 and later; \( P < 0.001 \)).

For the cases as a whole, the proportion of TOPs also varied according to the indication (27%, 25 and 8.3% for US abnormalities, advanced maternal age and abnormal serum screening results, respectively).

### Discussion

Sex chromosomal abnormalities are among the most common disorders encountered in prenatal diagnosis, and they account for ~25% of all chromosomal abnormalities detected after amniocentesis (Crandall et al., 1980). In turn, KS is one of the most frequent SCAs. Diagnosis of KS prompts the question of how to manage the pregnancy and, in particular, whether to terminate or continue it.

Given that the frequency of KS in our cohort (0.17%) was similar to the value observed at birth (0.20%) (Lanfranco et al., 2004), we confirm that miscarriage rarely occurs in this setting (Ljunger et al., 2005). Of the KS cases in our cohort, 91.5% were non-mosaic, which agrees with the values of 89 and 92% from prenatal studies reported by Christian et al. (2000) and Hamamy and Dahoun (2004), respectively.

In KS, the additional sex chromosome is almost as likely to come from the father as it is from the mother (Thomas and Hassold, 2003). The respective impacts of maternal and paternal age on the occurrence of KS are still subject to debate (Lanfranco et al., 2004). Even though we were not able to study the parental origin, we observed mean maternal and paternal ages of 36.6 and 37.2,
respectively. As a great majority of prenatal diagnoses are done for advanced maternal age, increased parental age could be an artifact.

In most cases, a KS genotype is not associated with specific prenatal malformations. The diagnosis of KS was established incidentally in 77.6% of the cases in our cohort. These figures are in accordance with the data from the study by Marteau et al. (2002), in which the fetal karyotyping leading to KS diagnosis was mainly prompted by advanced maternal age (71%).

Although the postnatal features KS are neither life-threatening nor severely disabling, identification of this diagnosis prenatally can result in difficult genetic counseling. As the diagnosis of KS is typically incidental, the parents have to be informed of a condition they did not expect. Children with KS do not have mental retardation, but potentially have delayed language development (Samango-Sprouse, 2001) presenting as dyslexia which can be improved with speech therapy. If gynecomastia occurs at puberty, it can be surgically corrected. Furthermore, testosterone therapy is helpful in that it strengthens psychological and somatic secondary sexual characteristics (Forti et al., 2010). Sexuality in adulthood is usually normal, despite small testes and frequent infertility. The severity of KS depends on the presence of mosaicism associated with the presence of a normal cell line in the testis (Fullerton et al., 2010).

In view of its postnatal phenotypic features, KS cannot be considered to be a particularly severe condition. Hence, TOP for KS is inconsistent with current ethical guidelines and legislation in France, which stipulate that TOP is legally justified only with severe disorders. In all cases, the final decision belongs to the parents after they have received information and advice. If they do not agree with the MPDC’s opinion, they can appeal to another MPDC. If the parents decide to continue pregnancy, stringent follow-up is performed by geneticists, pediatricians and endocrinologists.

To the best of our knowledge, the present study included the largest reported cohort of prenatally diagnosed KS cases (188). Of the 163 non-mosaic KS cases with a known outcome, 135 did not display US abnormalities and were defined as isolated KS; we observed a low TOP rate (24%) over the 25-year study period for these cases. Several other studies with lower numbers of cases (between 6 and 24) have reported values ranging from 42 to 87% (Christian et al., 2000; Perrotin et al., 2000; Sagi et al., 2001; Kim et al., 2002; Forrester and Merz, 2003; Hamamy and Dahoun, 2004; Mezei et al., 2004; Shaw et al., 2008).

The TOP rate recorded in our cohort for the period prior to 1997 (46.9%) is similar to the value of 44% reported by Marteau et al. (2002) for 111 cases in five European countries between 1986 and 1997. We observed that our TOP rate fell after 1997, to a value of 11.6%. This change appears to coincide with the introduction of MPDCs (1997), which probably improved the provision of information to parents, discussed improvements in fertility treatments for KS patients via the use of medically assisted reproductive techniques (Fullerton et al., 2010) and dispelled stereotypes with more recent, optimistic prognoses seen in longitudinal and prenatal studies (Christian et al., 2000; Linden et al., 2002), despite the potential for delayed speech and language skills (Samango-Sprouse, 2001). Long-term follow-up data from these prenatal diagnoses will be useful in determining prognosis of prenatally detected cases.

Strikingly, the TOP rate did not appear to depend on whether the indication for karyotyping was advanced maternal age or abnormal US results (25 versus 27%, respectively). In contrast, the TOP rate after karyotyping prompted by abnormal maternal serum screening for trisomy 21 was only 8.3%. When parents are expecting a possible diagnosis of trisomy 21, the announcement of probable infertility during a genetic counseling session does not seem so worrying.
In our population of 28 cases of non-mosaic 47,XXY cases with US abnormality, the presence of a particularly severe malformation (oligo-hydramnios, bilateral renal agenesis and a congenital heart defect) prompted three TOPs. Enlarged NT (n = 13) and hygroma colli (n = 3) were observed with an unexpectedly high frequency (10%) that has not been reported in other studies (Hamamy and Dahoun, 2004). In this group, we observed four TOPs, one for hygroma colli and three for increased NT. Since screening for trisomy 21 has recently moved to first trimester, it remains to be seen whether an earlier diagnosis of KS will encourage parents to voluntarily terminate pregnancy and if subsequently the TOP rate is likely to increase. It is noteworthy that this difficulty in prenatal counseling prevented a panel of prenatal experts from establishing a consensus on the prenatal diagnosis of KS (Boormans et al., 2010). In the nine remaining 47,XXY cases which displayed only a moderate abnormality on US, the parents decided to continue the pregnancy. Finally, due to a high prevalence of KS in the general population, a diagnosis of this syndrome with associated, abnormal US results is likely to be coincidental (rather than causative) in the great majority of cases.

Strikingly, five cases (2.7%) with another chromosomal unbalance were discovered during the study period (four were prenatal and one was postnatal). The occurrence of double aneuploidy is a relatively rare phenomenon and often leads to miscarriage. Cases that continue beyond the first trimester of pregnancy generally involve a combination of sex chromosome aneuploidy and potentially viable autosomal trisomies (of chromosomes 21, 18 or 13, for example). Numerous cases of 48,XXY,+21 have been reported postnatally (Li et al., 2004; Kovaleva and Mutton, 2005). To the best of our knowledge, only one case of prenatally diagnosed 48,XXY,+21 aneuploidy has been reported (Sanz-Cortés et al., 2006) and 48,XXX,+18 aneuploidy has never been described. Of our five unbalanced cases, one did not have an US abnormality despite having trisomy 21. It is not surprising that of the KS cases with additional chromosomal imbalance and US abnormalities, both double aneuploidies (a case of trisomy 21 and increased NT and a case of trisomy 18 with IUGR and exomphalos) were terminated, whereas the case with a benign mosaic marker chromosome and moderate IUGR was continued. In the case with an additional 14q microdeletion and bowel hyperechogenicity, the abnormality had not been detected with conventional cytogenetic techniques but was identified at birth by array CGH, in view of an abnormal phenotype (combining hypotonia, facial dysmorphism and hyperinsulinemia). There are a few literature reports of microdeletions in association with KS; these include classical Beckwith–Wiedemann and Prader–Willi syndromes (Delicado et al., 2005; Vasudevan and Quarrell, 2007) and, more recently, a 3p duplication diagnosed by array CGH (Stuart et al., 2007). Considering that KS is not associated with a particular prenatal phenotype and that prenatal diagnosis is usually incidentally, US abnormalities could be considered as additional, karyotype-independent features. As in the case for normal 46,XX and 46,XY fetuses, the use of array CGH may be advisable when US abnormalities are observed (as in our case displaying echogenic bowel) as stated by the American College of Obstetrics and Gynecology (ACOG, 2009).

In conclusion, our data (i) reveal a significant decrease in the TOP rate for KS following the creation of MPDCs in France (46.9% before versus 11.6% afterwards) and (ii) raise the question as to whether array CGH should be done when an US abnormality is detected, as for advised fetuses with a normal karyotype. The information obtained would help with genetic counseling.

Authors’ roles
N.L., F.V. and N.G. designed the study. All authors contributed to data collection. Data analysis and manuscript drafting were conducted by N.L., F.V., N.G. and M.D. All authors revised the manuscript and gave a final approval of the version to be published.

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References


