Does anonymous sperm donation increase the risk for unions between relatives and the incidence of autosomal recessive diseases due to consanguinity?

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ABSTRACT: In France gamete donation and notably sperm donation are anonymous. It has been claimed that anonymous artificial insemination by donor (AID) could highly contribute to an increase in the level of consanguinity and the incidence of autosomal recessive diseases, due to the unions between offspring of anonymous donors, unaware of their biological kinship, with the special case of unions between half-siblings. The actual incidence of consanguinity due to AID was compared with that resulting from the two other main sources of consanguinity and recessive diseases, i.e. voluntary unions between related individuals or inadvertent unions between the offspring of a common unknown male ancestor (false paternity). From these data, we estimated that expected unions in France between half sibs per year are 0.12 between offspring of sperm donors (1.2 every 10 years) and 0.5 between offspring of common male ancestors through false paternity (5 every 10 years). More generally, the inadvertent unions between false paternity offspring are roughly four times more frequent than those resulting from anonymous AID. We estimated that in the future, when AID has been in practice for several generations, out the 820 000 annual births in France, respectively, 6 and 25 births will be consanguineous through an unknown common ancestor related to anonymous AID and to a false paternity, both of which are negligible when compared with the 1256 children born from first-degree cousins. About 672 children per year are born with a recessive genetic disease due to the panmictic risk and additional affected cases due to consanguinity would be 34.54 for first-cousin offspring, 0.33 for offspring of individuals related due to false paternity and 0.079 for offspring of individuals related due to anonymous AID. Anonymous AID would therefore be responsible for 0.46% of consanguineous births and for 0.01% of recessive diseases. Therefore, the effect of anonymous AID on half-sibling unions, consanguinity and recessive disease incidence can be regarded as marginal.

Key words: gamete donation / genetic disorders / assisted reproduction / epidemiology / ethics

Introduction

In France, sperm and oocyte donations are anonymous, and considered as the donation of a human body element, similarly to blood or organ donations. Furthermore, donations are unremunerated and considered as purely altruist.

As far as sperm donation is concerned, the collection and distribution of the samples is organized by the CECOS (Centre d’Etudes et de Conservation des Oeufs et du Sperme humains), which is organized in a national network (Fédération Française des CECOS) within the framework of the state public health system. At the present time, according to legal rules in France, artificial inseminations by donor (AID) are only conducted in the medical context of male factor sterility or for a genetic indication, and for heterosexual couples only. It is worth noting that the number of children conceived from one donor varies among countries practising gamete donation (Janssens et al., 2011). The present French legislation set the limit of 10 children per donor, which is comparable to other countries in which gamete donation is still anonymous.

Recently, the legal rules about assisted reproductive technology were debated in France and anonymity of gamete donation was particularly discussed. Indeed, similarly to the conflicting debates concerning the right of any woman in France to give birth anonymously, donor anonymity has
been challenged, owing to the right for anybody to know his or her biological origins. In Europe, several countries have allowed the access to gamete donor identity while others have maintained the principle of anonymous gamete donation. In France, in contrast to the conclusions of recent publications in this field (Daniels, 2007; Greenfeld, 2008), donor anonymity was guaranteed by the Bioethics Law revised in 2011 and recently confirmed in 2013. Jurisprudence about the subject has so far been in favour of preserving the anonymity of sperm donors and considering gamete donation as a human product donation, similarly to blood or organs, and therefore anonymous and unremunerated.

Using a different approach, supporters of non-anonymous gamete donation recently raised new ethical and sanitary considerations. First, they evoked the risk of inadvertent half-sibling unions between the offspring of anonymous donors, unaware of their biological kinship. Secondly, they mentioned the risk of an increased consanguinity rate in a given population, and its consequences on public health, with an increased incidence of hereditary recessive diseases (Curie-Cohen, 1980; Wang et al., 2007), although this risk had already been considered to be very low (Jacquard and Schoevaert, 1976).

It is well established that two related individuals may have inherited from a common ancestor two identical copies of a mutated gene and therefore may conceive, with a one out of four risk, a child homozygous for this mutated gene. This can lead, depending on the gene and type of mutation, to an autosomal recessive genetic disease, although this risk had already been considered to be very low (Jacquard and Schoevaert, 1976).

The present study aims to evaluate the effects of anonymous gamete donation first on expected unions between related individuals, especially half-sibling ones, and secondly on the level of consanguinity and public health issues resulting from these unions. This analysis will only cover sperm donation, within the general context of natality in France, where other causes of consanguinity exist, such as voluntary unions between first-degree cousins or false biological paternity. These consequences of these true legal and educative paternities can be compared with that of anonymous AID.

### Expected number of half-sibling and other consanguineous unions

France cannot be considered as a single population unit because of its large size and because most unions occur inside restricted geographic areas. Therefore, in our study, we have taken into account six independent subpopulations (West, North, East, South-East, South-West and Paris), which are roughly equal in terms of size and parameters related to AID or false paternity.

Using the model developed by Wang et al. (2007) (http://homepage.ntu.edu.tw/~ckhsiao/ARTweb/maximum_k.htm), it is possible to evaluate, in a subpopulation, the expected number of various kinds of consanguineous mating (Table I).

The parameters used in Wang’s model were defined in relation to the actual situation in France for AID or false paternity, as follows:

(i) Maximum number of living births per donor (k): 10 for AID and or 1.5 for false paternity.
(ii) Fertility rate (f): 2.
(iii) Average number of child per donor in one pregnancy (n): 1.
(iv) Success rate (S): 100%, that is the maximum value in the Wang model, corresponding to the fact that all donors have an equal success rate in AID (this hypothesis maximizes the expected numbers of unions between relatives).
(v) Factor of assortative mating for phenotype (C): 9. Different values for assortative unions (i.e. unions between phenotypically similar individuals) are possible and a median value was chosen. It takes into account 18 different factors (e.g. stature, ear length, IQ, etc . . .) to measure phenotypic similarity.
(vi) Average number of new borns in a year (A): 136 667.
(vii) Numbers of donors per year (D): 50 for AID and 4100 for false paternity. Indeed, the rate of false paternity is usually estimated

#### Table I Types and expected numbers of consanguineous unions between offspring issued from either anonymous AID or false paternity (using the model developed by Wang et al. 2007, with the parameters for the French population) within a single panmictic subpopulation and the whole French population under the hypothesis of six large independent subpopulations (see text).

<table>
<thead>
<tr>
<th>Type and expected number of each kind of consanguineous union (inbreeding value of offspring)</th>
<th>Half-sibs (1/8)</th>
<th>Half-uncle–niece half-aunt–nephew (1/16)</th>
<th>Half first-degree cousins (1/32)</th>
<th>Half first-degree cousins once removed (1/64)</th>
<th>Total or mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within offspring of anonymous AID</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected number within a single subpopulation per year</td>
<td>0.020</td>
<td>0.078</td>
<td>0.078</td>
<td>0.313</td>
<td>0.49</td>
</tr>
<tr>
<td>Expected number within the whole French population per year</td>
<td>0.12</td>
<td>0.47</td>
<td>0.47</td>
<td>1.88</td>
<td>2.94</td>
</tr>
<tr>
<td><strong>Within offspring of false paternities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected number within a single subpopulation per year</td>
<td>0.083</td>
<td>0.33</td>
<td>0.33</td>
<td>1.33</td>
<td>2.07</td>
</tr>
<tr>
<td>Expected number within the whole French population per year</td>
<td>0.500</td>
<td>1.98</td>
<td>1.98</td>
<td>7.98</td>
<td>12.42</td>
</tr>
</tbody>
</table>

AID, artificial insemination by donor.
to range between 3 and 6% (personal communication from the French Blood Donation Agency ‘Etablissement Français du Sang’) and our analysis was conducted with the conservative estimate of 3% representing 24,600 births out of a total of 820,000 (INSEE census in 2012) that is a ratio of 30/1000 and 4100 for any subpopulation.

The expected numbers of consanguineous unions per year \( Y = \text{DmSP} \) are reported in Table I either for a subpopulation or for the whole French population for which the expected values are six times higher. The \( Y \) value calculated on the website (0.532) was corrected to be 0.49, because we did not consider, either for AID or false paternities, any of the full relationships (biological father or mother, uncle–niece or aunt–nephew, first cousins and first cousin once removed) that were considered by Wang et al. (2007). In any case, this does not change the overall expected number of inadvertent consanguineous couples since the excluded couples are rare (see website).

From the results reported in Table I, one may conclude that unions between anonymous AID descendants are four times less numerous than those between false paternities descendants (0.49 versus 2.07 in each subpopulation or 2.94 versus 12.42 for the whole population). Within these consanguineous unions, those between half-siblings are very rare since there would be only 1 every 10 years for anonymous AID descent and 1 every 2 years for false paternity descent although, in that case, the actual number could be lower due to the possible interference of the mothers, and possibly the fathers, who should be aware of the false paternity.

Moreover, AID in France is only a 40-year-old practice. Consequently, only the first generation of children born after AID are currently having their own children and the actual values for relationships more remote than half-siblings (e.g. half first cousins and almost half first cousins once removed) are therefore very low today. The number of these relationships would only increase after several generations following the first generation of AID children, thus leading to higher and higher numbers of descendants from a single donor but with a rapidly decreasing level of kinship. Finally, one might expect a stable and low level of consanguinity in the general population, mostly related to sporadic unions between first cousins (Cavalli-Sforza and Bodmer, 1971).

It is noteworthy that the risk for half-sibling unions would remain very low even if the whole French population was to be divided into even smaller parts than those obtained by partitioning it into six large subpopulations. However, one can assert that the more divided the general population, the greater is this risk, emphasizing the need for a small number of large banks instead of numerous smaller institutions.

### Number of consanguineous births in France and mean consanguinity values

Even if the risk of unions between half-siblings after AID can be considered as marginal, another concern about anonymous gamete donation is the potential increase of the mean rate of consanguinity in the general population that could result from a long-term practice of AID (i.e. over several decades) and all types of recurrent unions between relatives.

### Causes of consanguinity and values of the coefficient of consanguinity

In order to estimate the medical consequences of consanguinity, the number of consanguineous births must be evaluated together with their respective level of consanguinity (Fig. 1). A first cause is represented

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**Figure 1** The values of kinship coefficients of relatives issued from a gamete donor (half sibs, half avuncular, half first cousins, half first cousins once removed) are equal to half that of relatives issued from a couple. AID, artificial insemination by donor.
by the voluntary unions between close biological kin, most often first cousins, for cultural or socio-economic reasons. In this case, the level of consanguinity, measured by the consanguinity coefficient, is equal to 1/16 (6.25%). A second cause of consanguineous births is the occurrence of unions between individuals sharing an unknown common ancestor, mostly due to false paternities or anonymous AID. In that case, the mean consanguinity value is equal to the addition of the consanguinity coefficient values of each kind of union (Table I), weighted by their relative frequencies in the 1-4-4-16 sequence, either for the offspring from AID or from false paternity (see Wang formula). The mean consanguinity value will therefore be equal to (1/8)/1/25 + (1/16)4/25 + (1/32)4/25 + (1/64)16/25 = 0.03.

**Births from voluntary first-cousin couples**

First-cousin unions are quite rare in France except in recently immigrated populations that are still observing the matrimonial customs of their countries of origin, mostly of the Mediterranean Basin and the Indian Peninsula.

For these specific subpopulations, representing roughly 3% of births (http://www.insee.fr/), unions between cousins are much less common than within their populations of origin, where they can reach 10–15% of the total number of unions (Bittles, 2012). In the absence of reliable data on the subject, we will consider that the rate of first-degree cousin unions within this immigrant population is not higher than 2–4%, and a rate of 2% will be used for the calculations in order to avoid overstating this rate compared with other sources of consanguinity. Therefore, out of the 820 000 annual births in France, 3% occur within these populations, 2% of which (492 children) have a consanguinity coefficient of 1/16 (0.0625).

In the remaining, 97% of births, the fraction g issued from first-cousin parents may be estimated using the study of Sutter and Tabah (1948). Using the $F$ statistics of Wright representing the average consanguinity equal to $0.0625 \times g$ (the frequency of first-cousin unions), these authors showed that the $F$ value decreased from the 19th to the 20th century to reach a plateau comprised between 0.0005 and 0.0007, in the rural France of the 1930s and 1940s. Since rurality was then divided by two (Bergouignan et al., 2005) while the educational level rose from 5% high-school graduates in 1954 to 65% in 2008 (www.education.gouv.fr), one can consider that $F$ followed a drastic decrease and we will estimate its value to 0.00006, ten times lower than in 1954.

Similar values were reported in several other countries such as the USA or Belgium (Curie-Cohen, 1980; Cavalli-Sforza and Bodmer, 1971). Therefore, in order to obtain a value of 0.00006 for $F$, one needs to suppose that a fraction $g$ of 764 births out of 795 400 (97% of 820 000) are from first-degree cousins unions $[(0.00006/0.0625) \times 0.97 \times 820 000 = 764]$. Nowadays, the approximate total number of consanguineous children issued from first cousins would therefore reach 1256 (492 + 764) out of 820 000 births. This would lead to an average consanguinity in the French population of $F = 0.07 \times 0.00006 + 0.03 \times 0.02 \times 0.0625 = 0.000096$. This mean value is 653 times lower than the inbreeding value from first cousins (0.0625).

**Births from couples unaware of their kinship**

The annual numbers of consanguineous unions in the French population have been estimated to be 2.94 (roughly 3) and 12.42 (roughly 12.5) from a long-term practice of AID and false paternities, respectively (Table I). In the future, using a mean fertility rate of 2 for France and considering births as a steady flow, it can hence be expected that there would be 6 and 25 inbred offspring per year with an inbreeding value of 0.03. Thus, the inbred births issued from AID and false paternity would account, respectively, for only 0.46 and 1.94% of the inbred births and 0.0007 and 0.003% of the total number of births, respectively.

<table>
<thead>
<tr>
<th>Recessive diseases</th>
<th>Frequency of the pathologic allele</th>
<th>General panmictic risk</th>
<th>Additional risk related to first cousin induced consanguinity</th>
<th>Additional risk related to false paternity-induced consanguinity</th>
<th>Additional risk related to anonymous AID-induced consanguinity</th>
<th>Total for each disease category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare (2000)</td>
<td>$10^{-4}$</td>
<td>16.4</td>
<td>15.70</td>
<td>0.15</td>
<td>0.036</td>
<td>32.29</td>
</tr>
<tr>
<td>Rare (200)</td>
<td>$10^{-3}$</td>
<td>164</td>
<td>15.70</td>
<td>0.15</td>
<td>0.036</td>
<td>179.88</td>
</tr>
<tr>
<td>Rather common (2)</td>
<td>$10^{-2}$</td>
<td>164</td>
<td>1.57</td>
<td>0.015</td>
<td>0.0036</td>
<td>165.58</td>
</tr>
<tr>
<td>Common (1)</td>
<td>$2.10^{-2}$</td>
<td>328</td>
<td>1.57</td>
<td>0.015</td>
<td>0.0036</td>
<td>329.59</td>
</tr>
<tr>
<td>Total by risk category</td>
<td>672.4</td>
<td>34.54</td>
<td>0.33</td>
<td>0.079</td>
<td>707.34</td>
<td></td>
</tr>
<tr>
<td>Relative weight of the various causes of consanguinity, within the pathology</td>
<td>9506/10 000</td>
<td>488/10 000</td>
<td>5/10 000</td>
<td>1/10 000</td>
<td>10 000/10 000</td>
<td></td>
</tr>
</tbody>
</table>

Values are given for France (see text).

AID, artificial insemination by donor.
Public health consequences according to the various types of consanguineous unions

In order to evaluate the public health consequences of the various causes of inbreeding, an analysis of monogenic autosomal recessive disease frequencies and each type of union is necessary (Table II).

Complex diseases were not considered in our study because the genetic model underlying mental diseases and all the multifactorial traits is still debatable. Moreover, it is noteworthy that Wang et al. underline that calculations cover only the relations between half-sibling, biological father or mother and grandparents because the conditional probabilities of disease status under other kinships are not available.

Among the 820,000 births per year in France, the number of those affected by one of the 2203 known genetic recessive diseases, although the actual number is thought to be close to 3000, may be calculated according to the frequency of the pathologic allele. Those genetic diseases can be classified as ‘very rare’, ‘rare’, ‘rather common’ and ‘common’ diseases. In panmictic conditions, i.e. when there is no consanguinity, the actual number is thought to be close to 3000, may be calculated according to the frequency of each pathologic allele responsible for any one of the 2000 very rare diseases is $10^{-4}$, the frequency of the homozygotes $q^2$ is $10^{-8}$, which corresponds to the birth of 16.4 new cases per year in France [(820,000 × $10^{-8}$) × 2000].

The additional risk related to consanguinity is equal to $F_q$ (Cavalli-Sforza and Bodmer, 1971). It leads to an increased number of affected cases (Table II, following columns) according to the cause of consanguinity (first-cousin unions, false paternity and AID), the number of births and the average consanguinity as estimated above (Table I). Thus, for the 1256 births issued from known first cousins, the additional number of children affected by anyone of the 2000 very rare diseases will be estimated to be 15.7 new cases per year (2000 × 1256 × $F_q = 2000 × 1256 × 0.0625 × 10^{-4}$). Conversely, for the six births issued from related parents through AID, the additional number of children affected by anyone of the 2000 very rare diseases will be estimated to be 0.36 per year (2000 × 6 × $F_q = 2000 × 6 × 0.03 × 10^{-4}$). For common diseases, represented only by cystic fibrosis in Western Europe, the excess in affected children due to AID would be less than 1 case every 250 years (0.0036 per year).

Conclusion

Where they exist, gamete donation legislations show a great variability from one country to the other, even in Europe (Janssens et al., 2011). Our aim was not to make a value judgement on these rules but rather to focus on the situation in France where it is claimed by some people that anonymous gamete donation can increase the risk of inadvertent unions between relatives and, consequently, the rate of consanguinity in the population. Our calculations and conclusions are reassuring on both points and may be extrapolated to any country that practices anonymous gamete. The calculations may also provide information for those countries where the identity of donors is known.

The expected number of unions between related individuals is roughly four times lower among the descendants from anonymous AID than among those descended from false paternities (Table I). Furthermore, it mostly concerns distant relationships under the hypothesis that AID has been practised for several generations. In fact, those distant relationships do not exist at the present time due to the recent introduction of AID in the 1970s.

The estimate of inadvertent unions between half-siblings would be around one every 10 years and it is likely that many factors could limit this even more. Hypothesizing a considerable, although improbable, increase in the number of AID, measures limiting the occurrence of those consanguineous unions could be implemented like exchanges of sperm samples between sperm banks from distant regions, the unification of small banks into a larger one or the limitation of the number of children per donor, such as 10 as in France (Le Lannou et al., 1998). The assertion that AID significantly contributes to half-sibling unions is hence wrong. Such a risk is even low for half-siblings issued from a false-paternity, although they are four times more frequent than those issued from AID. Moreover, whatever the real risk is, it must be emphasized that couples where the individuals are descended from an anonymous AID, and aware of their origin, have the possibility to know whether they have a common direct ancestor by asking for genetic testing before deciding to procreate.

The consequences of consanguinity on public health for recessive genetic diseases (Table II) are insignificant for anonymous AID (1/10 000), as well as for false paternities (5/10 000), when compared with those from chosen first-cousin couples (488/10 000) which nevertheless account for only 5% of the total incidence.

In conclusion, only a significant increase in both the number of AID pregnancies and the number of descendants per donor would lead to significant public health risks when considering autosomal recessive diseases. Even at a 10 times greater frequency, the effects of AID upon consanguineous unions would remain limited and the risk would still be lower than the risk associated with the rare unions between first cousins. However, it must be noted that complex genetic diseases were not considered in this analysis but may contribute a public health risk for consanguineous unions. At this stage, the claim for the disclosure of identity in gamete donation because of a supposed consanguinity increase and public health hazards in the general population appears to be an irrational assertion that can be contested by population genetic calculations. We conclude therefore that sperm donation anonymity versus the disclosure of gamete donor identity to children born from AID is not a genetic matter but a psychosocial issue that should be debated as such (Greenfeld, 2008; Sawyer, 2010).

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Authors’ roles

J.L.S., A.L.L. and J.P.S. did the calculations and wrote the manuscript. M.F., A.B. and A.R. participated in discussing the manuscript and revised the final version.

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Conflict of interest

None declared.

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