Health Council of the Netherlands

The maximum number of children per sperm donor

An evaluation of the current guideline

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : presentation of advisory report *The maximum number of children per sperm donor. An evaluation of the current guideline*
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Dear Minister,

I hereby submit the advisory report entitled The maximum number of children per sperm donor. An evaluation of the current guideline. This advisory report has been prepared by the Standing Committee on Genetics and the Standing Committee on Medical Ethics and Health Law. You have asked the Health Council to critically assess the maximum of 25 children per sperm donor (which is commonly used in current practice) and to determine whether there any grounds for increasing or reducing this number. You indicated that the interests of the donor, the donor child, and the prospective parents, as well as public health interests should be weighed against one another. The Council was also asked to take into account the outcome of the evaluation of the Artificial Insemination (Donor Information) Act being carried out by the Netherlands Organisation for Health Research and Development. This assessment involved a determination of whether the Act is fit for purpose (i.e. does it guarantee the right of a donor child to know the identity of its biological father) and a survey of current practice with regard to donation.

The Standing Committee on Genetics has concluded that a scientifically-based maximum number cannot be established at the present time, as the requisite data are not available. Moreover, in the context of non-anonymous donation, a number like this cannot be determined by a purely scientific approach. Nevertheless, in everyday practice, there is a need for a nationally uniform maximum. The standing committee therefore, proposes that the current maximum be maintained until more is known about the psychosocial effects of

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non-anonymous donation. However, measures to reduce the risks of sperm donation are still justified. The standing committee has made several specific recommendations to that end.

I endorse the standing committee's conclusions and recommendations.

Yours sincerely,
(signed)
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to:

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No. 2013/18E, The Hague, September 3, 2013

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

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Executive summary

Time for a reconsideration

Since 1992, medical practitioners involved in artificial insemination with donor sperm have adopted a maximum number of children per donor. In that year, the limit was set at twenty-five children per donor per donor region. In practice, this is taken to mean the maximum per donor.

The main criterion for determining this limit was the risk (albeit a very small one) that half-brothers and half-sisters, unaware of their kinship, might develop a relationship with one another, and have children. As a result of their parents' blood kinship (also referred to as consanguinity), such children would be at greater risk of hereditary diseases. It was decided in 1992 that this risk must be no greater than it is in the general population, where consanguineous relationships also occur (between first cousins, for example).

Today, well over twenty years later, a great deal has changed. The main change was the introduction of the Artificial Insemination (Donor Information) Act, in 2004. The Act specified that children over the age of sixteen have the right to know the identity of their donor father. Assuming that the parents tell their child about the insemination, the child can decide to request details of the donor's identity, and may then contact him.

This development will further reduce the already small chance that the individuals in question might unwittingly become involved in a consanguineous relationship, with the associated risk of hereditary diseases for their offspring.

This raises the question of whether the current maximum number is still relevant. That question is at the heart of this advisory report. The recent evaluation of the Act is another reason for advising on this subject.

Medical assessment

In 1992, the risk of consanguineous relationships between donor children was a pivotal consideration when deciding on the maximum number of children per donor. In theory, the same approach could be used today. However, further reflection shows that this standard is no longer viable.

Firstly, an analysis carried out for the purpose of this report has shown that calculation of the risk is not possible. The data used for the calculation in the early 1990s were not up to date, even at that time. Any attempt to produce a new, accurate calculation would be hampered by the large number of variables involved. Secondly, the 2004 Act gave rise to an entirely new situation. The end of anonymous donation will further reduce the already minor risk of consanguineous relationships, which in turn will mean a smaller risk of medical problems in the offspring. As a result, consanguinity as a standard has become increasingly irrelevant.

This raises the question whether there is any other quantifiable medical standard that might be used to replace the old standard. One option might be to focus on incidental genetic risks, such as the risk of a donor carrying a dominantly inherited disorder that only manifests itself after children have been conceived using his sperm. These children are at a high risk of developing the same disorder. However, these clusters of risks are of no use when attempting to calculate a maximum number. If a low maximum number were to be adopted then fewer children would be affected per incident. In this situation, however, additional donors would be needed, which increases the risk that the donor population will contain genetically affected individuals.

In conclusion, on medical grounds, no quantifiable conclusions can be drawn concerning the appropriate maximum number of children per sperm donor.

Assessment on other grounds

This conclusion leads to the question whether there are any other criteria on which to base a recommended maximum number. The first criterion is the possibility of psychosocial effects. Under the new Act, from their sixteenth birthday onwards, any children who are aware that they were conceived by artificial insemination have the right to contact their donor father. It is anticipated

that lesbian and single mothers (currently a large proportion of the group using artificial insemination with donor sperm) will be very likely to inform their children of the circumstances of their birth. There is less certainty concerning the degree of openness on this issue among heterosexual couples.

In the case of children who seek out the donor and any half-brothers and half-sisters, a maximum of twenty-five means that extensive kinship networks can develop. As yet, there is no empirical evidence about how those involved will experience this. There is some evidence to suggest that donor children enjoy getting to know their half-sisters and half-brothers, but it is conceivable that a tipping point will be reached when this network reaches a given size. On socio-cultural grounds, neighbouring countries have generally opted for a lower number than the Dutch limit.

The second criterion to consider is the effect of shortages. At present, four of the eight sperm banks in the Netherlands have waiting lists. A reduction of the maximum number would lead to greater shortages and this might incite people to look into alternative avenues. This in turn would result in the loss of certain safeguards, such as a reliable medical anamnesis, registration of donor identity, and the limit on the number of children.

Incidentally, current practice is unable to provide guarantees with respect to the latter safeguard, due to the lack of a national registration system. This means that in practice the number of children born to individual donors may exceed the current limit. However, as some clinics adopt a lower maximum, the actual number may also be lower. Donors may also specify a lower maximum number themselves.

A third criterion that can be taken into account when evaluating the current maximum is the concern caused when donors are retrospectively found to be suffering from a severe, dominantly inherited disorder. If many children are affected at the same time it will have a greater societal impact than when the same number of incidents occurs in different places at different times. In a recent case in Denmark, a clustered incident of this kind led to the maximum number of children per donor being reduced from twenty-five to twelve.

Advice on the maximum number and recommendations

There are no quantifiable medical reasons on which to base the maximum number of children per donor. Scientific knowledge regarding the psychosocial aspects is also very limited. The first children to be born under the new Act will have the opportunity to know their donor starting from 2021. Only then will it

become apparent how many of them actually want to do so, and what impact this will have.

Those who are deeply concerned about the potentially adverse aspects of large kinship networks may well favour a lower maximum number. Incidents involving multiple donor children who are found to have a hereditary disorder may also point in that direction. On the other hand, a lower maximum can lead to shortages, with all of the associated drawbacks.

In conclusion, there are no decisive arguments to amend the guideline at the present time. For pragmatic reasons, it makes sense to maintain the maximum number of twenty-five children per donor. In addition, this advisory report contains a number of recommendations on how current practice could be improved.

Chapter 1

Introduction

1.1 Current guideline for the maximum number of children per donor

Since the 1970s, many hospitals and private clinics in the Netherlands have provided an artificial insemination service, using sperm provided by donors. Artificial insemination with donor sperm (Dutch abbreviation = KID, *Kunstmatige inseminatie met donorsperma*) is used to assist heterosexual couples to have children in cases where the man is infertile or where he is at significant risk of passing on a hereditary disorder. This service is also available to lesbian couples and single women.

Initially, each institution pursued its own policy on ethical and medical-technical issues. Over the course of time, however, general guidelines were drawn up at the initiative of the Dutch-Belgian Society for Artificial Insemination. (NBVKI). Together with the Dutch Institute for Healthcare Improvement (CBO), the former founded the Working Group on Artificial Insemination with Donor Sperm. In 1992, a report was published entitled "*Advies medisch-technische aspecten van kunstmatige donorinseminatie*" (Advisory report on medical-technical aspects of artificial insemination with donor sperm), which addressed issues about donor recruitment, donor selection, needs assessment, and matching donors and prospective mothers. The report was endorsed by every clinic in this field.

The Dutch Institute for Healthcare Improvement's guideline devotes an entire chapter to the genetic risks of allowing donors to father an unlimited

number of children.[1] A single sperm donor can potentially father a large number of offspring. Children fathered by the same donor are half-brothers and half-sisters. If they are ignorant of their origins and are not acquainted with one another, there is a risk (albeit a very small one) that these blood relatives will enter into a sexual partnership with one another. Any children resulting from such consanguineous relationships would be at increased risk of suffering from recessively inherited genetic disorders. Annex C contains a comprehensive explanation of this issue.

At that time, these genetic risks were the main argument in support of limiting the maximum number of children per sperm donor in the Netherlands. For the purposes of arriving at a number, the criterion chosen was that the percentage of consanguineous sexual partnerships in the population of donor children should be no greater than that in the Dutch population as a whole. It was concluded that, if there are no more than twenty-five KID children per donor per donor region, this percentage would not be expected to increase. The current maximum was therefore selected to prevent an increase in the frequency of genetic disorders in the population as a result of anonymous sperm donation.

Incidentally, in practice the maximum of twenty-five children per donor per donor region is taken to mean the maximum per donor, regardless of region or institution.[2] In keeping with this interpretation, this advisory report also refers to the maximum number of children per donor.

The maximum number adopted by the Netherlands is high in comparison to other countries. Elsewhere, limits are usually based on local socio-cultural considerations. An example of such a criterion is that the maximum number must not deviate too far from the number of children that a man could reasonably be expected to father without the use of artificial insemination. In Germany the limit is fifteen children per donor, in France it is ten, in Switzerland eight, in Spain six, and in Denmark twelve (until recently this was still twenty-five).[3] Some countries have limited the number of families to which a donor may donate. These are Britain (ten), Belgium (six), and Austria (three).

1.2 Reason for a re-evaluation

Much has changed since 1992. The most important development was the elimination of the anonymous donation option in medical settings when the Artificial Insemination (Donor Information) Act was adopted in 2004. This means that, from their sixteenth birthday onwards, all children conceived by donor insemination can request details of their donor father's identity. They also have the right to contact him. The first eligible cohort of children will reach the

age of sixteen in 2021. Various aspects of the Act were recently evaluated by the Netherlands Organisation for Health Research and Development.[2]

Aside from the technical evaluation of this legislation, there is the issue of whether the Dutch Institute for Healthcare Improvement's guideline (which was published more than twenty years ago) needs to be updated. For instance, should the maximum number of children conceived through artificial insemination be amended in the light of current scientific knowledge?

This question prompted the Minister of Health, Welfare and Sport to ask the Health Council to produce an advisory report. The text of the request for advice can be found in Annex A.

In response to the Minister's request for advice, the President of the Council has asked one of the Health Council's permanent advisory bodies, the Standing Committee on Genetics, to act as an advisory committee in this matter. Details of the make-up of the standing committee are given in Annex B. The advisory report has also been extensively reviewed by the Standing Committee on Medical Ethics and Health Law.

1.3 Question posed and design

The questions addressed by the standing committee in this advisory report are as follows:

- At the present time, are there any medical reasons for modifying the 1992 guideline of a maximum number of twenty-five children per donor?
- At the present time, are there any other reasons for modifying the guideline?
- What is the recommended maximum number of children per donor?
- What recommendations can be made to further reduce the risk of medical and psychosocial problems in donor children themselves and in any offspring that they might have?

Chapter 2 explores the medical aspects of a maximum number of children per donor. Chapter 3 is devoted to psychosocial effects and to the importance of an adequate supply of donor sperm. Finally, in Chapter 4, an assessment is made and the question concerning the maximum number is answered. This chapter also contains a number of recommendations by the standing committee.

Chapter 2

Medical assessment

In this chapter, the standing committee assesses the current level of knowledge regarding the medical risks to which donor children and their offspring are exposed, in relation to the maximum number of children per donor.

2.1 The risk of consanguinity

The 1992 guideline for the maximum number of children per donor was based on a calculation of the risk that children fathered by the same donor might unwittingly become involved in a sexual partnership with one another and have children who, due to their parents' consanguinity, would be at greater risk of hereditary disorders. It was decided that this risk must be no greater than it is in the rest of the population, where consanguinity between parents also occurs (relationships between first cousins, for example).

The goal of this calculation was to provide an objective criterion for a maximum number. Accordingly, the present assessment could review that risk among the general population. However, further reflection shows that the options in this regard are limited and, furthermore, that this criterion is no longer relevant in the current situation.

Limited and outdated data

An analysis of the calculation carried out by the standing committee shows that the data on which the Dutch Institute for Healthcare Improvement's guideline was based are no longer in keeping with the current situation. Indeed, it indicates that they were already outdated when the guideline was produced. Details of this analysis are given in Annex C.

A 1979 estimate was used for the purposes of comparison. This, in turn, was based on unpublished Statistics Netherlands data on the number of marriages between first cousins, uncles and nieces, and aunts and nephews in the period from 1956 to 1965. This was an attempt to determine the risk of hereditary disorders occurring in children in the general population as a result of consanguinity between their parents.

Other data used at that time stem from 1989. This concerns the number of marriages and births per year, the average number of children per individual, and the average age difference between partners. Some of the other data sets used were just estimates, as it was not possible to calculate them. No account was taken of the effect of ethnicity or socio-economic status on the choice of partner, both of which are important factors in this context. The fact that these parameters are used to match donors to prospective parents tends to increase the risk that offspring of the same donor will select one another as partners. Even so, the risk involved is still a very small one.

The data used were already outdated in 1992, and are now even more so. Major demographic changes have taken place in the Netherlands since the maximum number of children per donor was set at twenty-five. The Dutch population has grown by one and a half million, and its make-up has also changed.

These changes are highly relevant in epidemiological terms. This is because the limit is based on the criterion that the risk of hereditary disorders in the offspring (due to consanguinity between parents) must be the same in the general population as in those conceived following artificial insemination with donor sperm. However, given the large number of variables involved (which would still have to be partly based on estimates), it is difficult to assess the impact of adjusting and recalculating these data.

The standing committee concludes that the figure of twenty-five cited in the Dutch Institute for Healthcare Improvement's guideline is not well founded, and that, at the present time, it is not possible to make an accurate calculation based on the same criterion.

New Act based on different criterion

A second problem with the use of degree of consanguinity as a criterion for the maximum number of children per donor is the Artificial Insemination (Donor Information) Act, which came into effect in 2004. This Act gives children conceived with donor sperm the right to request details of their biological father's identity from their sixteenth birthday onwards. Armed with this knowledge, they will be able to find out whether they are related to potential partners.

Even though it will take until 2021, when the first eligible cohort of children will reach the age of sixteen, to determine how many children will actually want to discover their donor's identity, this will still have the effect of nullifying a major criterion on which the calculation is based. After all, it had been assumed that donors would remain anonymous with the associated risk that people conceived by artificial insemination with donor sperm might unwittingly become involved in partnerships and have children with blood relatives. That anonymity has now been lifted.

As a result, KID children are now much more likely to discover their donor father's identity (and those of any half-brothers and half-sisters) than was the case under the old legal regime. A number of factors determine whether or not children actually acquire this information.

1 Information provided by the parents

The first and most crucial factor is whether parents inform their child of the circumstances of its birth. The standing committee takes the view that parents have a *prima facie* responsibility to inform their child that it was conceived using artificial insemination, however they are under no legal obligation to do so. If they fail to do so, then the child will take no further steps to discover the identity of its donor father, and the lifting of anonymity will have had no effect.

What is known about the information that KID children get from their parents? Until the 1990s, the standard approach was to observe confidentiality, and it was in this spirit that parents were counselled. As part of the recent review of the Act, a questionnaire-based survey was carried out among prospective parents and the parents of donor children.[2] This included an investigation of the extent to which parents inform their child about the circumstances of its birth. More than 90 per cent of the parents who participated in the survey and who had a child using artificial insemination with donor sperm before 2004 had informed

the child of the circumstances of its birth. Among parents whose child was born after 2004 and which was above the age of three at the time of the survey, the corresponding figure was 85 per cent. Of those parents who had not yet informed their child, 95 per cent indicated that this was because the child was still too young. Only 3 per cent indicated that they were still unsure about whether or not they would inform the child of the circumstances of its birth.

There is one further comment to make with regard to these results. Given the way in which the survey was carried out, parents who favour openness were quite probably overrepresented. Some follow-up studies described in the international literature found different results[4-6], i.e. that a significant proportion of heterosexual parents who have had a child using donor conception do not inform their child about how it was conceived.

However, it is reasonable to assume that there is now more openness on this matter than in the past. This is because the composition of the group of prospective parents making use of artificial insemination with donor sperm has changed. The proportion of heterosexual couples has fallen, while the percentage of lesbian couples and single women has increased.[2] The latter two groups are more likely to inform their children of the circumstances of their birth. The institutions involved assign this decline in the number of heterosexual prospective parent couples to the development of new reproductive technologies, which offer further options for establishing a pregnancy using the male partner's own sperm.

2 Obtaining details about the donor, half-brothers and half-sisters, and contacting them

Once children have been told that they were conceived in a medical setting, by artificial insemination with donor sperm, they can make up their own minds about how they use that knowledge. As the first cohort of children born under the new Act have not yet reached the age of sixteen, at the present time it is not known what proportion of them will request details of the donor's identity. However, it is quite likely that a substantial proportion of the donor children will want to know the identity of their biological father. The logical consequence of this is that they will also try to contact him.[7]

Another question is whether these children will also want to get in touch with any half-brothers and half-sisters. It is more difficult to estimate what proportion of children will take this step, primarily because many more people are involved. Clearly, however, such children are likely to inform their future partners about the circumstances of their birth. If it turns out that the partners were also born by

means of artificial insemination with donor sperm, then it is likely that the couple will check whether they are related to one another.

The new situation offers many possibilities to further reduce the already minimal risk of consanguineous relationships and that of any associated medical problems in offspring from these relationships. However, it is not yet known how many of those who were born by means of artificial insemination with donor sperm will actually make use of this knowledge. Nevertheless, these new possibilities mean that the earlier method of determining a maximum number of children per donor is no longer appropriate for the current situation.

This was a second reason for the standing committee to abandon attempts to formulate a recommendation based on the degree of consanguinity.

The medical significance of consanguinity

Finally, it is highly questionable whether the degree of consanguinity is an appropriate medical criterion on which to base a maximum number of children per donor.

Firstly, the degree of consanguinity in the population is not fixed. The make-up of the population is continually changing, both in place and time, and this is reflected by the degree of consanguinity. For instance, the degree of kinship between individuals living in Amsterdam differs from that between the residents of a traditional Dutch village like Volendam. Moreover, the degree of kinship in Amsterdam during the 1950s was different from that in the 1990s.

Secondly, the concept of consanguinity is only of medical significance because kinship between parents involves a risk that recessive inherited disorders will be transmitted to their children. Where tests are available to identify carriers and to prevent these disorders from being transmitted, consanguinity is no longer a major factor. With the emergence of low-cost techniques for analysing large sections of an individual's DNA (next generation sequencing) this is now becoming a realistic option. In the context of generally accessible, elective, preconception health care, couples wanting to have children could be screened for the most common hereditary disorders. In such cases, it would also seem reasonable to screen donors and prospective mothers.

However, no such screening is yet available, nor is it certain that this will be supported by society at large. If genetic screening were to be used specifically for donors, this would entail ethical issues with regard to privacy and to donors' (and their families') right not to know. In addition, genetic screening prior to artificial insemination with donor sperm might greatly amplify the differences with natural forms of conception. On the other hand, medical intervention does

involve a duty of care. Whatever the case, the screening of donors remains a point of reflection and debate.

The standing committee concludes that the degree of consanguinity is not a suitable guiding principle for determining a maximum number of children per donor on medical grounds. This is because it is not an unvarying feature of the population, and because various new developments are making it increasingly irrelevant. This is yet another reason not to adopt a maximum number based on this criterion.

2.2 The risk of dominantly inherited disorders

Another way of determining a maximum number of children per donor, based on quantifiable medical criteria, is to consider risks that may occasionally increase. That could happen if a sperm donor carries a dominantly inherited disorder that has not yet clinically manifested itself. One such case in the Netherlands involved a donor who was found to be suffering from spinocerebellar ataxia, a serious, dominantly inherited brain disease.[8] Before this became known, more than ten children had been conceived using his sperm. About half of them will develop the same disorder as the donor.

Is the risk of dominantly inherited disorders sufficient reason for modifying the limit? Based on purely medical criteria, the answer is “No”. This is based on the principle of equal risks for the donor children and for children who were not conceived by artificial insemination with donor sperm. After all, there is no reason to suppose that the donor population is any different, in genetic terms, to non-donors. Accordingly, with regard to the absolute number of children affected, it makes no difference whether the maximum number is larger or smaller.[9]

In cases where a small maximum number is used and a donor has a dominantly inherited disorder, fewer children will be affected. However, the use of smaller maximum numbers means that more donors will be needed. This larger group may include more men with dominantly inherited disorders (of varying kinds).

Ideally, extensive medical case histories should be obtained for all prospective donors. In this way, any applicants with a family history of dominant hereditary disorders can be excluded, thus giving the donor children a slightly better start in life.

In conclusion, it is not possible to determine a maximum number based on the medical risk of dominantly inherited disorders in donors. In the next chapter, the standing committee discusses the psychosocial aspects of dominantly

inherited disorders in donors. This relates to the social effects of clustered incidents.

2.3 Conclusion

The standing committee concludes that it is not feasible, based on quantifiable medical criteria, to determine a maximum number of children per donor. Firstly, if consanguinity is to be the criterion, there is insufficient reliable data to calculate a maximum with any degree of accuracy. Secondly, the introduction of the Artificial Insemination (Donor Information) Act in 2004 is giving rise to a new situation in which fewer donor children will be ignorant of the circumstances of their birth, but the extent of this change cannot be quantified. Thirdly, given the changes in the make-up of the population, combined with developments in the field of genetic screening, the relevance of consanguinity as a criterion for the maximum number of children per donor is highly questionable. Nor do the medical risks posed by sperm donors with a dominantly inherited disorder provide any basis for determining a number on medical grounds.

Chapter 3

Assessment of other considerations

Medical risks are not the only considerations to be taken into account when attempting to determine a maximum number of children per donor. Given that the possibility of arriving at a number based on scientific medical criteria has now been ruled out, the question is whether these other considerations can justify an adjustment of the current number of twenty-five. This is the topic of this particular chapter.

3.1 Effects of large kinship networks

The psychosocial effects of non-anonymous donation are an important consideration when attempting to determine a maximum number. In theory, under the new Act, donors may find themselves in situations in which a large number of children (possibly as many as twenty-five) want to get in touch with them. In addition to the donors themselves, this will also have an impact on members of their immediate family and other relatives.

All sperm banks consult their donors about the maximum number of children that may be conceived using their sperm. The donors are entitled to give their views regarding what they consider to be an appropriate maximum number of children.[2] The survey carried out in the context of this legislative evaluation showed that nearly half of the participating donors made use of this option. On average, they opted for a maximum of twenty children. Almost half went with the maximum of twenty-five.

The vast majority of sperm donors surveyed (90 per cent) feel that details of their identity should be made available to any children conceived with their sperm. A clear majority are also prepared to honor requests for contact. The present system, therefore, protects donors by giving them a say in the process of determining a limit. The donors' ability to foresee the consequences of their decision will be put to the test after 2021. At that time the first cohort of donor children to be born since the Artificial Insemination (Donor Information) Act came into effect will reach the age of sixteen, and will be entitled to contact their donor.

Only then will it be possible to find out how the children themselves feel about contacting their donor father, and what it means for them to be part of potentially extensive kinship networks together with other children of the same donor. Will such children want to get in touch with their half-brothers and half-sisters? Will they see their kinship network as good, bad, or both? And how will their parents deal with this?

The evidence suggests that many donor children like having half-brothers and half-sisters.[7] Yet this advantage could conceivably turn into a drawback where very large numbers are involved. The sense of being a unique and wanted child might be turned upside down by the discovery that one's biological father has twenty-four other children. Having a large number of half-sisters and half-brothers, all of about the same age, could conceivably create a family experience that is quite unlike anything encountered by the rest of the population.

All of these questions are still clouded in uncertainty, as very few scientific studies have tackled the psychosocial effects of the large kinship networks created by donation.[6,7,10] In the Netherlands, the task of collecting data in this area will have to wait until 2021.

3.2 Effects on waiting lists

Another consideration when attempting to determine a maximum number of children per donor is the availability of sperm. Before the Artificial Insemination (Donor Information) Act came into effect in 2004, and immediately afterwards, there was a drop in the number of donors.[2] The legislative evaluation ascribed this fall partly to the lifting of donor anonymity and partly to the years of uncertainty while the legislative proposal was pending.

A few years after the Act came into effect there was actually a slight increase in the number of donors, although it has never returned to the level of the early 1990s. Aside from the lifting of anonymity, the long-term decline in the number

of donors may be related to other factors, such as changes in medical procedures, which make donation a more complicated process.

Around the start of 2012, four of the eight sperm banks had waiting lists. At two of these institutions, prospective parents spend up to three years on the waiting list. The other two each have a waiting list of around eighteen months. There are various ways for prospective parents to avoid the waiting lists. One way is to try to find a private donor, such as a family member or a friend. Alternatively, they can locate an unknown donor on the internet, who they will then introduce as an acquaintance when applying to a relevant institution. They may also opt for home insemination. According to the legislative evaluation, some institutions estimate that more than half of all pregnancies resulting from home insemination with donor sperm involved donors who had been located via the internet. The institutions also indicate that the length of the waiting lists is not the only reason why individuals opt for home insemination. These prospective parents also find the procedures in medical settings very time-consuming, due to the mandatory safety requirements involved. According to the institutions, some parents simply prefer to use an anonymous donor and try to locate one outside the usual channels.

In medical terms, home insemination can have some drawbacks. The donors registered at sperm banks have been medically and psychologically screened. Safety measures have also been taken to preclude infectious diseases. In addition, the process of informing parents is fully in keeping with the provisions of the Artificial Insemination (Donor Information) Act, and the donor's personal data are recorded for the benefit of the child. Outside the medical setting, there are far fewer guarantees. It is also conceivable that some of those donors who fail the institutions' screening process will offer their services on the internet. Moreover, there is no way of checking that they are limiting themselves to any maximum number of children.

The legislative evaluation concludes that there is a hidden shortage of donors, as the clinics' waiting lists cause some prospective parents to resort to informal arrangements. The effect of reducing the maximum number of children per donor would be to exacerbate the existing shortages still further. That might well result in waiting lists at all eight institutions. This might conceivably induce even more prospective parents to resort to home insemination by unknown donors. That still leaves the option for the prospective parents to find a donor themselves and to introduce him to the institution. In many cases, however, prospective parents only resort to sperm banks because they themselves have been unable to find a suitable donor.

Another issue is that, in professional practice, the maximum number guideline is not always strictly observed.[2] All institutions keep track of the number of children fathered by each sperm donor. In practice, some fertility clinics take the view that the maximum of twenty-five is too high. As a result, they limit themselves to a lower number, such as five children or families. This indicates that, in practice, intuitive objections can play a greater part in determining the limit than the recommended maximum. In some cases, the number of children per donor may exceed the guideline, as some individuals donate at several institutions. This is made possible by the fact that the sperm banks' registration systems are not linked, so they cannot check whether their donors are also registered with other clinics.

While the *Stichting Donorgegevens Kunstmatige Bevruchting* (Foundation for Data on Artificial Insemination Donors), the central registration authority, does record the number of children fathered by each donor in medical settings, it has no statutory duty to actively supervise the number of donations per donor. The legislative evaluation has also revealed that a number of individuals probably donate both at sperm banks and in the context of informal arrangements.

3.3 Psychosocial effects of clustered incidents

Another factor that could affect any decision concerning the maximum number of children per donor, is the distribution of medical incidents between institutions and over time. This relates to risks associated with a given donor's dominantly inherited disorders, such as the above-mentioned case of the donor with spinocerebellar ataxia.

People generally find a cluster of events to be more disturbing than a similar number of more widely distributed incidents. Similarly, any incident that affects a large number of donor children at the same time will cause greater social disquiet than the sum of a number of smaller incidents, spread over several clinics and at more widely-spaced intervals. Suppose that five children are affected once every 100 years, then – for the above reason – this might be preferable to 25 children once every 500 years.

In a recent case in Denmark, a clustered incident of this kind led to the maximum number of children per donor being greatly reduced. In October 2012, following the discovery of neurofibromatosis (NF1-1; an hereditary disorder) in several children of the same donor, the number was reduced from twenty-five to twelve.[11]

3.4 Conclusion

Medical aspects, which do not lead to a quantifiable criterion, are not the only considerations to be taken into account when attempting to determine a maximum number of children per donor.

The first consideration is the psychosocial effect of the current situation of non-anonymous donation on donors, children and parents. These effects will not become visible until after 2021, when the first children conceived under the Artificial Insemination (Donor Information) Act will be able to contact their donor, together with any half-brothers and half-sisters. Only then will it be possible to see how those directly involved will deal with their role as part of a large kinship network.

Existing donor shortages also need to be taken into account. Any further increase in the waiting lists would be most unhelpful, as this might prompt more prospective parents to opt for home insemination with an unknown donor. That setting lacks certain guarantees, such as protection against infectious diseases, and a full medical and genetic case history. Also, it makes no allowance for the child's right to make the acquaintance of its donor father, once it has turned sixteen.

Finally, clustered incidents involving dominantly inherited disorders in donors have a relatively large social impact. This also needs to be taken into account when determining a maximum number.

Chapter 4

Conclusions and recommendations

4.1 Conclusion concerning the maximum number

A calculation is not possible

In 1992, the maximum number of children per sperm donor was set at twenty-five, based on medical criteria. This was based on the criterion that the offspring of donor children should not be at greater risk of hereditary disorders than others in the general population due to the fact that their parents were blood relatives (unbeknownst to them).

The standing committee concludes that it is not feasible to come to a decision about modifying the current maximum number of twenty-five children per donor based on quantifiable medical criteria for the current situation. The available data are outdated and limited, so it is not possible to reliably calculate the risk of consanguineous relationships between donor children. Moreover, this risk has become irrelevant to the determination of a maximum number, primarily due the end of anonymous donation.

Taking other considerations into account

Accordingly, any opinion on the maximum number must be based on other considerations.

The first consideration is the psychosocial effect of non-anonymous donation on those directly involved. As yet, little is known about the psychosocial effects that being part of a large kinship network might have on the donor, the children and their parents. Only after 2021, when the first sixteen-year-olds will be able to contact their donor father, together with any half-brothers and half-sisters, will it be possible to gather such data for the Netherlands. The evidence suggests that donor children appreciate being in contact with their donor and their half-brothers and half-sisters[7], but does this also apply when a large number of siblings are involved? For some, it could raise issues of identity. This is one argument, at any rate, for not raising the maximum number above twenty-five.

A second consideration is that of shortages. We know that, at the present time, there are not enough donors to meet the demand for sperm. On the basis of potential psychosocial effects, it would not be reasonable to increase the maximum number. Indeed, consideration could even be given to reducing it, as a precaution.[12] However, in view of the number of donors that are currently available, this would mean extending waiting lists and waiting times. This would have various adverse knock-on effects for the prospective parents, the children themselves, and for public health.

A final relevant consideration is the impact of clustered incidents, where several of a donor's children are found to have inherited a serious disorder. This may be sufficient reason for reducing the maximum number of children per donor, as happened recently in Denmark following an incident of this kind.

Weighing up the options

Because of the lack of scientific evidence concerning the maximum number of children per donor, the standing committee is unable to propose a substantiated number.

It is not feasible to perform a calculation on the grounds of medical risk. At the present time, other considerations tend to generate a mixed picture. The results obtained depend on the weight assigned to one factor or the other. Those who attach great importance to the prevention of potentially adverse psychosocial effects in adult donor children will push for the number to be reduced, purely as a precaution. Those who attach great importance to preventing the adverse effects of long waiting lists, will want the maximum to be increased, or, at the very least, kept at the same level. Conversely, any incidents involving a dominantly inherited disorder in a number of children from the same donor may cause people to consider a reduction.

It is still very difficult to weigh these issues in a way that is sufficiently substantiated. Accordingly, for purely pragmatic reasons, the standing committee recommends that the current maximum number used in practice be maintained at the present time. Indeed, there are no decisive arguments for adjusting the number either up or down.

4.2 Recommendations aimed at reducing risks still further

This is not to say that there is no room for improvement in current practice. To this end, the standing committee has included a number of recommendations here.

Determining the maximum number of families per donor

There are two possible ways of limiting the number of offspring a sperm donor is permitted to father. One involves limiting the number of children per donor and the other is to limit the number of families to which a donor may donate. The advantage of opting for a limited number of families is that this reduces the slight risk of consanguineous relationships between donor children even further. After all, children within a single family grow up as brother and sister. This measure also slightly reduces the potential psychosocial risks of large kinship networks, as it reduces the number of families in the network around each donor. The standing committee therefore recommends setting a maximum number of families per donor. If there are a maximum of twenty-five children per donor and an average of two or three children per family, there will be between eight and twelve families per donor.

Donor registration

The legislative evaluation shows that some donors have donated in several different clinics. This can result in a much higher number of children per donor than the agreed maximum. This problem can be overcome by giving clinics feedback about donor registrations, notifying them when potential donors are already registered elsewhere. The standing committee therefore recommends establishing a system for the exchange of registration details. If it is legally possible, this system could be linked to the statutory donor registry at the Foundation for Data on Artificial Insemination Donors (SDKB). Otherwise, a separate system will need to be set up.

Distribution of donor sperm

The standing committee also recommends that samples of donated sperm be distributed over several regions. One advantage of this approach is that it reduces the risk of consanguineous relationships between donor children. Another is that it evens up the waiting times in the various donor regions. Exchanging samples like this should pose no problems for hospitals, but a separate arrangement will have to be made for private clinics.

Genetic counselling for donors and prospective parents

Genetic counselling can help to detect hereditary disorders in donors, by asking about their family history and the names of their four grandparents, and comparing these with that of the prospective mother. As has often been stated, genetic counselling for donors and prospective parents must be carried out by an appropriately trained individual, i.e. a clinical geneticist or genetic counsellor. The standing committee recommends that a checklist be drawn up, listing the items to be covered. This will guarantee that the medical testing of donors is as rigorous as possible, and that no detail is omitted from the information they are given. During the information session, it should also be explained to donors why it is important for them to comply with the regulations. Without exception, it is vital to confirm that donors are making an informed decision. The standing committee also recommends that donors be kept informed about the number of children who have been conceived using their sperm. Parents also benefit from effective information sessions. By this means, they can also be motivated to fulfil their responsibilities and inform their child of the circumstances of its birth.

Study of psychosocial effects in donor children

Although there is no evidence of adverse psychosocial effects associated with the current maximum number of donor children at the present time, it is important to be prepared for such an eventuality. Children are an inherently vulnerable group, and this is even more true of children who were conceived under unusual circumstances. Unlike donors, prospective parents and physicians, donor children have no control whatsoever over their situation. This is why it is important to find out how the knowledge that they are part of extensive kinship networks affects the children of non-anonymous donors. If these effects are adverse in nature, then that is a strong argument for reducing the maximum.

Pursue an active donor recruitment policy

If a future review concludes that it would be best to reduce the current maximum number, for instance because of psychosocial considerations, this could impact the number of prospective parents that clinics could treat, assuming that the number of donors remains the same. In such an eventuality, more prospective parents might feel compelled to seek assistance in an informal setting. It is vital to maintain capacity in the regular setting, by pursuing a more active donor recruitment policy, for example. This same approach was proposed in the Netherlands Organisation for Health Research and Development's legislative evaluation.[2]

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Annexes

Annex **A**

The request for advice

Letter dated 26 September 2011 (reference PG/E-3075231) from the Minister of Health, Welfare and Sport to the President of the Health Council.

During the preparations for the initial evaluation of the Artificial Insemination (Donor Information) Act, various parties in the field* pointed out that there is no current guideline for the maximum number of children that may be fathered per donor. I strongly support the view that a new guideline should be drawn up, one that is based on an independent advisory report in which all of the interests involved are carefully weighed up.
The 1992 advisory report** by the Dutch Institute for Healthcare Improvement stated that – based on the coefficient of inbreeding – the maximum should be 25 children per donor. The question now is whether, at the present time, the number of 25 children per donor in the Netherlands is still appropriate, relevant and advisable. It is also conceivable that rather than a number of donor children, a maximum number of families be proposed.

The request for recommendations on the appropriateness, relevance and advisability of a maximum for the number of children per donor was prompted by a number of developments.

* These should include the Dutch-Belgian Society for Artificial Insemination and the Foundation for Data on Artificial Insemination Donors.

** Dutch Institute for Healthcare Improvement advisory report (1992) entitled "*Advies medisch-technische aspecten van kunstmatige donorinseminatie*" (Advisory report on medical-technical aspects of artificial insemination with donor sperm).

Firstly, the Netherlands has undergone substantial demographic changes since 1992. The population has grown by one and a half million, the structure and make-up of the population are not what they were 20 years ago, and people are also more mobile. Accordingly, it is quite conceivable that the coefficient of inbreeding may now be lower or possibly higher than when the maximum of 25 half-brothers and half-sisters was established in 1992. The fact that more donor sperm is now being imported from other countries could well be mirrored by changes in the coefficient of inbreeding. One striking fact that should also be pointed out is that several neighbouring countries have a significantly lower maximum permitted number.

Secondly, the lifting of sperm donors' anonymity in 2004 was a major development that may have an impact on the way we view the maximum number of children per donor. Donor children can now get in touch with the man who fathered them and, possibly, with their half-brothers and half-sisters as well. Are the donor's concerns the only issue here, or do the needs of one of the other parties involved require that the maximum be reduced?
In addition, the introduction of the Artificial Insemination (Donor Information) Act, which enshrined in law the lifting of anonymity, resulted in a sharp fall in the number of donors. This, in turn, resulted in long waiting times for artificial insemination with donor sperm. In this situation, increasing the maximum number of children per donor might go some way towards meeting the prospective parents' great need for donor sperm.

The evaluation of the Artificial Insemination (Donor Information) Act that was commissioned by the Netherlands Organisation for Health Research and Development is now getting under way. The evaluation study will provide insight into everyday practices, such as artificial insemination with donor sperm. I would advise you to get in touch with the researchers who are conducting the evaluation.

In conclusion, this issue of the maximum number of children per donor spans a wide range of interests, such as those of public health, of the donor, of the donor child, and of the parents (or prospective parents). Following the inclusion of this topic in the work programme*, and in view of the above-mentioned interests, I would like the Health Council's advice on what constitutes an appropriate maximum number of children or families per sperm donor, as well as recommendations for policy and everyday practice. The Health Council's advisory report will assist parties in the field in drafting a new guideline.
Yours faithfully,
(signed)
the Minister of Health, Welfare and Sport,
Ms E.I. Schippers

* Work Programme 2011 Health Council, p. 20.

Annex **B**

The Committee

- Prof. W.A. van Gool, *chairman*
  President of the Health Council
- Prof. R.A. Wevers, *vice chairman*
  Professor of Clinical Chemistry of Neuromuscular and Neurometabolic Disorders, St Radboud University Medical Centre, Nijmegen
- Prof. D.I. Boomsma
  Professor Professor of Genetic Epidemology and Behaviour Genetics, VU University Amsterdam
- Prof. M.C. Cornel
  Professor of Community Genetics & Public Health Genomics, VU University Medical Centre, Amsterdam
- Prof. J.P.M. Geraedts
  Professor of Genetics and Cell Biology, University Medical Centre Maastricht
- Prof. R.C. Hennekam
  Professor of Paediatrics/Translational Genetics, Academic Medical Centre, Amsterdam
- Prof. R.C. Jansen
  Professor of Bioinformatics, University of Groningen
- Prof. A.C.J.W. Janssens
  Professor of Translational Epidemiology, Emory University, Atlanta GA, USA

- Prof. V.V.A.M. Knoers
  Professor of Clinical Genetics, University Medical Centre, Utrecht
- Prof. G.J.B. van Ommen
  Professor of Human Genetics, Leiden University Medical Centre
- Prof. M. de Visser
  Professor of Neurology, Academic Medical Centre, Amsterdam
- E. van Vliet-Lachotzki
  Senior Policy Officer Genetics and Perinatal Care, Dutch Genetic Alliance, VSOP, Soest
- Prof. G.M.W.R. de Wert
  Professor of Medical Ethics, Maastricht University
- M.S. Prins, *observer*
  Ministry of Health, Welfare and Sport, The Hague
- Dr. V.W.T. Ruiz van Haperen, *scientific secretary*
  Health Council, The Hague
- Dr. G.A.J. Soete, *scientific secretary*
  Health Council, The Hague
- Dr. H.J.W.M. Wijsbek, *scientific secretary until 1st January 2012*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Analysis of the 1992 Dutch Institute for Healthcare Improvement guideline

In every population, i.e. including that of the Netherlands, blood relatives form relationships with one another and have children. The children of related parents are at greater risk of a hereditary disorder than the offspring of unrelated parents. The increased risk involved is proportional to the degree of kinship between the related parents. The more closely related the parents, the higher the child's coefficient of inbreeding and the greater the risk involved. The authors of the 1992 Dutch Institute for Healthcare Improvement's guideline adopted the premise that the average coefficient of inbreeding for the KID population (the children born as a result of artificial insemination with donor sperm) must not exceed that of the population of the Netherlands as a whole. Based on this premise, their mathematical model yielded a maximum of 25 children per donor in a single donor region, on average.[1,13]

Figures quoted in the public debate are far too readily labelled as "hard data". In fact, they are often based on assumptions, choices and estimates, so their reliability is highly questionable. For this reason, any robust assessment of the guideline's worth must determine exactly how it was calculated. In this case that was relatively easy, as the authors had diligently included in the text details of their assumptions, choices and estimates. A familiarity with some basic genetic concepts is needed in order to understand the calculation.

Some basic genetic concepts

Chromosomes, genes and alleles

Genes are DNA sequences that code for an hereditary trait. The DNA is located on chromosomes, inside the cell nucleus. Humans have 23 pairs of chromosomes, consisting of one pair of sex chromosomes (XX or XY) and 22 pairs of equivalent (homologous) autosomal chromosomes. Each chromosome pair contains one chromosome from the father and one from the mother. The paternal and maternal chromosomes in an autosomal pair contain the same genes, but not necessarily the same variants, or alleles, of these genes, as the exact DNA sequence can vary between alleles. If homologous autosomes carry two different alleles of a given gene, then the carrier of the pair is said to be heterozygous. If both alleles are identical, then the individual in question is homozygous. Alleles are often designated by a letter, such as A and a. So an individual with the alleles Aa is heterozygous, while someone with the alleles AA or aa is homozygous. In fact, both A and a are types that can have a range of sub-variants, such as A_1, A_2, ..., A_m and a_1, a_2, ..., a_n.

In medical practice, alleles are described as being normal or abnormal. Abnormal alleles are involved in disease processes. In autosomal dominant diseases, it is the abnormal allele that is dominant. This means that heterozygotes (who have one normal and one abnormal allele), may become ill. Huntington's disease is an example of an autosomal dominant disease. In autosomal recessive diseases, people only become ill if both alleles are abnormal. So, in the case of autosomal recessive inheritance, heterozygotes do not become ill as they have one normal allele and one abnormal allele. Such heterozygotes are referred to as “carriers”. Accordingly, you will find that patients have two abnormal alleles. A state in which these two alleles are completely identical is described as homozygosity. If different abnormal alleles are involved, this is known as compound heterozygosity. In practice, if the exact nature of the abnormality in the alleles is not known (or not relevant in the context of the discussion) then the compound heterozygotes are treated as homozygotes. Some examples of autosomal recessive diseases are cystic fibrosis and sickle cell disease.

If both parents are heterozygous (Aa) carriers of a disorder, then there is a probability of 1:4 that a child of theirs will inherit a pathogenic allele (a) from each of them. That child will then be homozygous for that gene (aa), and will

have a recessive disorder. The risk that both parents will be carriers of the same disease-causing allele is greater if they are related. This explains why relationships between blood relatives involve an increased risk of recessive genetic disorders for any future children that they may have.

Consanguinity

Consanguinity involves a relationship between individuals who have one or more ancestors in common. In genetics, the degree of kinship is a measure of that part of the genome that, on average, is shared by two individuals who have one or more ancestors in common. If they have half of their genomes in common, they are said to be first-degree relatives. Individuals who share one quarter of their genomes are second-degree relatives, and if it is just one-eighth then they are third-degree relatives.

The coefficient of inbreeding

“F”, the coefficient of inbreeding, is a measure of the probability that a child will have two identical alleles of the same gene, as a result of its ancestry. In other words, the individual in question will have inherited identical alleles from each parent, which have been passed down, via different routes, from a common ancestor. The F coefficient should, therefore, be seen as the probability of an individual being homozygous as a result of his parents' kinship. The higher the value of the coefficient, the greater the probability.

Mathematical model

The authors of the current guideline adopted the premise that the average coefficient of inbreeding for any offspring conceived by artificial insemination with donor sperm must not exceed that of the population of the Netherlands as a whole. The more children conceived per sperm donor, the higher the level of inbreeding in the KID population. Using a mathematical model, they arrived at a maximum of 25 children per donor, on average [1,13]

Box 1 Calculating the coefficient of inbreeding

The approach here is to first count the number of steps, on the father's line and the mother's, between the child and the common ancestor (or ancestors). Let's assume that the child's parents have a grandfather in common. There will be three steps along each of the parents' lines (father's grandfather > father's parent > father > child), giving a value of six for both parents. At each step, there is a 50 per cent (= 1/2) probability of the gene being passed on. The probability of one of the joint grandfather's genes being passed down to the child along both the maternal and paternal lines will be $(1/2)^6$. As the grandfather has two copies of the gene, the total probability that both of the child's alleles are identical (having been passed down from its grandfather) is $2(1/2)^6$. If both parents share not only a grandfather but also a grandmother (as in marriages between first cousins), the probability is doubled: $4(1/2)^6$ or, to put in another way, 1/16. If the parents' common ancestor was "inbred", this will have implications for the child's coefficient of inbreeding, and the calculation involved becomes more complex. When the guideline was being calculated, no account was taken of this complication (that the artificial insemination donor and/or recipient, themselves, were "inbred").

The average in the general population is calculated by multiplying the number of marriages between first cousins, uncles and nieces, and aunts and nephews by the number of children born as a result of those relationships, and then multiplying these products by the coefficient of inbreeding for the children born as a result of those relationships. The sum of these three products gives an estimate of the average coefficient of inbreeding for the general population.

The level of inbreeding in the KID population can be calculated in the same way: by multiplying the expected number of blood-relative relationships of a given type, for example half-brother/half-sister relationships, by the expected average number of children born as a result of such relationships, and then multiplying that product by the coefficient of inbreeding of those children. The same calculation will then have to be performed for all types of relationships between blood relatives where the children have a coefficient of inbreeding of 1/16 or more. At lower levels, the contribution of the KID population to the level of

inbreeding will be much smaller, and is (rightly or wrongly) neglected by the authors. This calculation is then applied to all inseminations resulting in the birth of children with a coefficient of inbreeding greater than 1/16. Finally, all of these products are added up, and the total is the value that was sought, i.e. the coefficient of inbreeding of the KID population. The magnitude of that total will obviously depend on the number of children per sperm donor. It should be noted that the authors use the term "consanguineous relationships" to refer to situations in which the donor and the recipient are related. In terms of the problem of consanguinity in the offspring of donor children, relationships like this are a minor part of the problem.

It is very difficult to calculate the coefficient of inbreeding of the KID population. This is because it is not known how many potential consanguineous relationships result from insemination, so this figure had to be estimated. For this purpose, the authors used a mathematical model that was developed by Curie-Cohen.[14] While the model itself is fairly complicated, its underlying basic concept is not. Calculate the frequency of a given type of relationship between blood relatives by multiplying the number of possible relationships of that type (which is, of course, dependent on the number of relatives involved) by the probability that such relationships will actually develop. Next, multiply the average number of children from these relationships by the coefficient of inbreeding associated with each particular type of relationship, which correlates with the risk of a recessive disorder. The resulting product is the contribution made by this group of children to the level of inbreeding of the KID population. Repeat the calculation for all relationships that can result in the birth of children with a coefficient of inbreeding of 1/16 or more, then add all the products together. Do the same for all possible inseminations and add the product obtained to the previous one. The total is the value that was sought, i.e. the coefficient of inbreeding of the KID population.

All of the blood relatives in the calculation are those on the biological father's side, as the maternal relatives are already known. Therefore, on average, KID children are just as likely to form relationships with relatives on their mother's side as children who were not conceived by artificial insemination with donor sperm. Thus, the average coefficient of inbreeding resulting from relationships consciously entered into by KID children with relatives on their mother's side will make up half of the national average in the general population. The contribution made by KID children to the coefficient of inbreeding, as a result of relationships unknowingly entered into with relatives from their father's side, depends on the average number of children per donor. At around the time that the Dutch Institute for Healthcare Improvement's guideline was established,

calculations carried out using the model developed by Curie-Cohen showed that, at an average of 25 children or less, that contribution was smaller than the contribution made by children from the general population who knowingly enter into a relationship with a relative. At an average of no more than 25 children per donor, the average coefficient of inbreeding for the KID population remained below that of the general population.

Problems with the current guideline

In view of the demographic and legal developments that have taken place over the last twenty years, would the same criterion (the estimated average level of inbreeding in the general population) and the same mathematical model (Curie-Cohen) still yield a maximum average of 25 children per donor? In the absence of updated data, that question cannot be answered. Moreover, reliable data on the average level of inbreeding in the population and the values of the variables used in the Curie-Cohen formula are not always available. Such data as are available must be re-entered into the model. Nevertheless, some conclusions can still be drawn.

The data

Most of the data on which the calculations are based stem from 1989, so they are now outdated. This applies to the number of marriages and births per year, the average number of children per individual, and the average age difference between partners. Some of the other data sets used are just estimates, as it is not possible to calculate them. The authors adopted Curie-Cohen's estimate of the contribution made by C (appearance) to assortative matings involving half-brother/half-sister relationships. For other relationships, they selected arbitrary values for C, higher in the case of close relatives and lower for distant relatives. The values selected probably exaggerate the effect of appearance on the probability of a relationship developing. Curie-Cohen’s estimate is, in turn, based on research carried out in the 1950s and 1960s. However, the results of more recent research suggest that assortative mating is influenced not only by age, appearance and geographical distance, but (as pointed out by the authors themselves) also by ethnicity, religion and social class. As their effect is difficult to determine, these factors have been excluded from consideration. This approach tends to underestimate the probability of relatives entering into a relationship with one another.

Box 2 The Curie-Cohen mathematical model

The Curie-Cohen mathematical model can best be illustrated using a specific example. To this end, the authors used the contribution made by children born as a result of relationships between half-brothers and half-sisters to the level of inbreeding of the KID population.

(i) N = the number of possible half-brother, half-sister relationships
If 'n' is the number of natural children fathered by a donor, and 'k' is the number of KID children that he has fathered, then a KID child has N = (n + k - 1)/2 half-brothers or half-sisters of the opposite sex. The average number of natural children per donor 'n' is slightly higher than the average number of children per individual, as all sperm donors are known to be fertile. Based on this data, the authors obtained a value for 'n' of 1.87. If there are an average of five KID children, this gives a value for N of 2.93.

(ii) P = the probability of relationship developing between a half-brother and a half-sister
Whether a half-brother and half-sister, who are unaware that they are related, would indeed enter into a relationship, is not only dependent on chance. The probability of this happening is affected by what are known as assortative mating factors: the geographical distance between the two individuals in question (Q_r), age (d) and appearance (C). Furthermore, the probability of a relationship is also dependent on the probability that any given individual will find a partner (l) and on the number of births per year (A). This is expressed by the following formula: $P = 2 \times l \times Q_r \times d \times C / A$. The authors estimated the value of 'l' by dividing the number of marriages per year by half the number of births per year. Given the lack of requisite data in the Netherlands, it is not possible to calculate the probability of any two individuals in the same KID region Q_r entering into a relationship. The authors have, therefore, based their work on data for the United States, derived by Curie-Cohen, which gave a value for Q_r of 0.5. They also adopted the values used by Curie-Cohen for the factors 'd' and 'C'. Both factors are generous estimates, and probably exaggerate the effect of age and appearance on the probability of a relationship developing. The value of P obtained using this formula is 2.15×10^{-5}.

(iii) Children born as a result of half-brother/half-sister relationships have a coefficient of inbreeding (F) of 1/8.

(iv) Assuming that donors father an average five KID children, the contribution of children born as a result of half-brother/half-sister relationships to the coefficient of inbreeding is: N x P x F = 2.93 x 2.15 x 10^{-5} x 1/8 = 7.89 x 10^{-6}. N x P denotes the frequency, the expected number of half-brother/half-sister relationships, while F is related to the risk of a disorder in children born as a result of these relationships. Thus the product (N x P) x F is the contribution made by half-brother/half-sister relationships to the average F by artificial insemination with donor sperm.

To determine the total contribution of artificial insemination with donor sperm to the KID population's average coefficient of inbreeding, the same calculation must be performed for all relationships and inseminations resulting in the birth of children with a coefficient of inbreeding greater than, or equal to, 1/16. The sum of all these products is the total contribution, which of course depends on the number of KID children per donor. As that number increases, the average coefficient of inbreeding will also increase.

Given the lack of requisite data in the Netherlands, it is not possible to calculate the value of Q. Without any further explanation, however, the authors have assigned it a value of 0.5, based on the values derived by Curie-Cohen for the United States. As the population becomes increasingly mobile, the Q parameter will become less and less important.

It is difficult to assess the impact of adjusting and recalculating these data on the permitted maximum number of children per donor. It is less difficult to appreciate that this upper limit is likely to be higher today than it was in 1992. That limit was based on a 1979 estimate of the average level of inbreeding in the Netherlands. That estimate, in turn, was based on unpublished Statistics Netherlands' (CBS) data on the number of marriages between first cousins, uncles and nieces, and aunts and nephews in the period from 1956 to 1965. These data were already outdated in 1992, so by 2012 they were totally obsolete. Prior to 1970, marriages between uncles and nieces and between aunts and nephews

were prohibited, so these will have had a negligible impact on the level of inbreeding before that time. In addition, the immigration of Turkish and Moroccan people coincided with an increase in the number of first-cousin marriages, which are relatively more common in these population groups than in the native Dutch population. This has the effect of undermining the significance of the general average level of inbreeding.

The model does not allow for the fact that some KID children are fully aware of the circumstances of their birth, and that they will make use of this knowledge when choosing a partner. The introduction of the Artificial Insemination (Donor Information) Act, in 2004, means that the probability of these children being aware that they were conceived by artificial insemination with donor sperm will have changed since 1992. This Act gives children conceived with donor sperm the right, from their sixteenth birthday onwards, to request details of their biological father's identity. They will be able to exercise that right from 2021 onwards (assuming that their parents have informed them that they are KID children). This will reduce their risk of unknowingly entering into relationships with relatives.