

# BIOETHICS NEWS



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## News

### Assisted reproduction results for Europe, 2009

The European Society of Human Reproduction and Embryology (ESHRE) has published the results for assisted reproduction for the year 2009. The study included data from 34 countries, 1,005 clinics and 537,463 treatment cycles: 135,621 in-vitro fertilisation (IVF) and 266,084 intracytoplasmic sperm injection (ICSI).

In 21 countries where all clinics reported to assisted reproduction registers, a total of 399,020 cycles were performed. The total population of these 21 countries is 373.8 million inhabitants, so the prevalence is 1,067 cycles per million inhabitants.

The pregnancy rate for IVF was 28.9% per cycle commenced and 32.9% per transfer. These percent-

ages for ICSI were 28.7% and 32.0%, respectively.

When frozen embryos were thawed and transferred, the pregnancy rate was 20.9%.

The percentage of singleton, twin and triplet deliveries when IVF and ICSI were considered jointly was 79.8%, 19.4% and 0.8%, respectively. These results are similar to those obtained in the four previous years.

We consider it of interest to present these data (considered official in Europe), since in our opinion the low efficacy of both IVF and ICSI is not sufficient to disseminate data from some assisted reproduction centres that do not match those reported here.

### Is the earth overpopulated?

The problem of overpopulation of the Earth is often raised in different social settings and especially in some media, often resulting in the promotion of antinatalist policies. But is our planet really overpopulated?

This is a complex issue that is impossible to address here, but we would like to provide some information extracted from an article by Norbert Treitz, professor of physics at the University of Duisburg-Essen (Germany), published in *Investigación y Ciencia* (July 2014, pages 86-89).

Treitz provides some interesting facts on the heterogeneous distribution of the population in different regions of the world.

On average, 13 persons per square kilometre live on the surface of the planet, around 50 on terra fir-



ma. In view of the extensive unpopulated regions on Earth, this is a huge number. We humans are very unevenly distributed in the different regions and countries. Moreover, the closer we look at the situation, the more deviations we find with respect to the average.

Among the European countries, Holland holds the record, with 402 inhabitants per square kilometre, although it is surpassed by the German region of North Rhine-Westphalia, with 523. Topping the world list is Bangladesh, with around 1,000 inhabitants per square kilometre. However, it is overshadowed by tiny countries like Monaco and the Vatican, and particularly districts with no parks in major cities; around 40,000 people per square metre live in the 11th arrondissement.

ment (district) of Paris, between the metro stations of Bastille, Nation and République. If they all lived at ground level, the average distance between two individuals would be around five metres.

However, the fact that most drew our attention in Treitz's article refers to Lake Victoria, in Africa. Treitz states, "We now consider Lake Victoria, with its 69,000 square kilometres - all of mankind could go swimming there. This would cause the water level to rise by 4 millimetres, with a density of bathers of more than 100,000 per square kilometre. This would be equivalent to a network of people about

three metres apart, so carrying out the experiment would not be too inconvenient (except having to travel several hundred kilometres on the surface of the water, which would be costly and would have to be well planned). In other words, according to Treitz "all the inhabitants of the earth could splash around at the same time in Lake Victoria at a comfortable distance of 3 metres apart". Clearly this is not a definitive piece of information, but it does make us think about whether our planet Earth really cannot possibly accommodate any more people, or if could be a comfortable habitat for new inhabitants.

## **Cristiano Ronaldo was born thanks to a conscientious objector**

On 25th July this year, Cristiano Ronaldo's mother, Dolores Aveiro, published her autobiography in a book entitled "Mother Courage" with her son's permission.

"At that time I was 30 years old and I had three children. It didn't seem right to deal with a new arrival and enlarge the family, so I went to a doctor, but he refused to do anything", she explained. It was a far from rosy time at home: feeding her children Hugo, Elma and Cátia Liliana became more of a challenge every day with her husband José Dinis out of work (he died in 2005 due to alcoholism) and with little savings". But the doctors reticence and attempts to discourage her from aborting did not stop her from trying to terminate the pregnancy anyway, which she attempted with a "homemade remedy" suggested by a friend: "She told me to drink warm



ale. That way, the child would die" ('we don't give the devil ideas', readers note ffd). However, the beer couldn't stop the vital energy of the heart that beat in Dolores's womb. A few hours after taking the "potentially fatal" drink, peace continued to reign in

Ronaldo's mother's womb, as a sign that the "homemade remedy" hadn't worked. Little by little, Dolores (already used to feedings, nappies and night-time crying) decided to have her fourth child. "If it's the will of God that this child be born, then so be it", was her innermost thought.

On 5 February 1985, in a city on the Savage Islands, a small archipelago in the Atlantic Ocean closer to the African coast than to Portugal, Cristiano Rolando was born. A strong healthy boy who became world famous because of his singular football talent.

## **Number of human embryos lost due to the use of Preimplantation Genetic Diagnosis**

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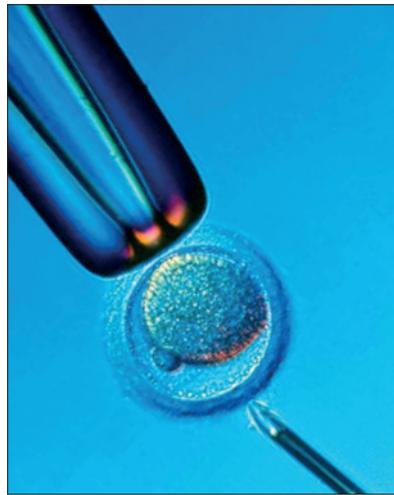
suggested by a friend: “She told me to drink warm ale. That way, the child would die” (‘we don’t give the devil ideas’, readers note ffd). However, the beer couldn’t stop the vital energy of the heart that beat in Dolores’s womb. A few hours after taking the “potentially fatal” drink, peace continued to reign in Ronaldo’s mother’s womb, as a sign that the “home-made remedy” hadn’t worked. Little by little, Dolores (already used to feedings, nappies and night-

time crying) decided to have her fourth child. “If it’s the will of God that this child be born, then so be it”, was her innermost thought.

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## Negative medical effects of in-vitro fertilisation

There is growing medical evidence of the presence adverse outcomes following the use of assisted reproduction techniques. There is no doubt that most perinatal morbidity associated with in-vitro fertilisation (IVF) can be attributed to multiple pregnancies. The latest data from the United States shows that the incidence of twin pregnancies after IVF is 29%, and for triplet pregnancies is 3.7%, 14 and 57 times higher, respectively, than those that occur in natural conception. It is widely agreed that multiple pregnancies have much higher risks than singleton pregnancies. For example, more than 60% of twins are born prematurely, and 50% have low birth weight, when these percentages are 14% and 9%, respectively, in singleton pregnancies, i.e. it seems obvious that the negative side effects associ-



ated with multiple pregnancies are increased by the use of assisted reproduction.

However, the adverse effects are not limited to multiple pregnancies. Although most singleton pregnancies that result from IVF are uncomplicated, various studies indicate that they are associated with an increase in premature births, low birth weight, congenital abnormalities and perinatal complications, when compared with naturally-conceived singleton pregnancies.

These data were evaluated in detail in a study published in *Fertility and Sterility* (95; 1887-1889, 2011), confirming that described above on the existence of an increase in negative effects associated with assisted procreation.

## Reports

### Freezing embryos and in-vitro fertilisation: New findings

#### Introduction

In its July 2014 edition, the journal *Fertility and Sterility* published three studies that analysed the different circumstances that affect the complicated process of obtaining embryos and their use in in-vitro fertilisation (IVF) cycles.

They analysed the ovarian stimulation procedures used to obtain oocytes for subsequent fertilisation in the laboratory, and the advantage of transferring the embryos obtained in the same cycle in which they were obtained, or freezing them by different methods and transferring them in subsequent cycles.

In view of the findings of these studies, it seems that the likelihood of success for achieving a pregnancy varies according to whether one or other method is used. The neonate’s health can also be affected by the IVF method selected, all factors that pose not only a clinical, but also an ethical dilemma.

#### Ovarian stimulation

The first step in the IVF process consists of obtaining oocytes, either from the future mother or from a donor, for subsequent fertilisation in the laboratory.

The need to work with several of these to increase

the probability of success in the assisted fertilisation process requires stimulation of multiple ovulation in the woman, by administering drugs such as clomiphene. These treatments not only cause the proliferation of several ovarian follicles, in which many oocytes will mature (the objective pursued), but they will activate a series of changes that will influence the subsequent implantation process, compromising its success. They also have potentially serious side effects, such as thromboembolic disorders, some types of cancers and even death. These changes are,



basically, elevated oestrogen levels and increases in the plasma progesterone concentration during the super-ovulation. These will cause changes in the endometrial receptivity, the expression of certain genes involved in the progression of the implantation process and pregnancy, and in vascular endothelial growth factor (VEGF)-mediated vascular proliferation of the endometrium, altering the period in which the endometrium will be receptive to implantation of the blastocyst. Likewise, a relationship has also been described between the progesterone levels and the establishment of a maternal-foetal immune tolerant environment, which will be critical for the progression of the implantation process and the pregnancy, in which multiple factors are involved. The natural killer (NK) cells have a notable role here, secreting interleukin-15, which converts them into uterine NK cells; these in turn secrete VEGF, cytokines and leukaemia inhibitory factor (LIF). The number of these uterine NK cells is significantly reduced in the case of women undergoing ovarian stimulation treatment compared to levels in normal cycles.

Studies in mice have also shown that there are epigenetic changes in the embryo itself that will remain after birth, as a result of the ovarian hyper-stimulation.

Some of these studies suggest that performing the embryo transfer in a later cycle (after the one in which the oocytes were obtained following stimulation) may increase the possibilities of success in

achieving a pregnancy, thus making it necessary to cryopreserve the embryo, an outcome that poses new dilemmas.

### **Embryo cryopreservation.**

If the fresh embryo is not transferred after its creation in the laboratory, it must be frozen for subsequent use. There are basically two freezing techniques that are currently used: slow freezing and vitrification, or ultra-rapid freezing. The first has been used since 1984, and in 1990 the first child was born from an embryo that had been vitrified and thawed. The differences between both methods lie, as well as in the rate at which the freezing/thawing cycles occur, in the concentrations of the Cryoprotective Agents (CPAs) used, which are lower in the slow methods; these act as drying agents, at both intra- and extracellular level.

Although cryopreservation allows embryo transfer a posteriori, it also has the major disadvantage of causing abnormalities in the frozen embryos, which can compromise their subsequent viability. Various studies have examined the viability of these embryos, in an attempt to establish selection criteria after they have been thawed, to increase the chances of success in their subsequent transfer and implantation in the uterus. Some of the studies have stated that embryos in which at least half of the blastomeres are intact after thawing should be considered viable.

Microscopic examination of the embryo after thawing is the screening method used to determine those that will or will not be transferred. We understand that embryos that have been thawed and discarded are definitively eliminated, which is extremely important from an ethical point of view.



This embryo selection after cryopreservation and thawing appears to increase the success rates as regards the number of full-term pregnancies achieved per embryo transferred, but it reduces the number of embryos available (many are discarded) and prolongs the IVF process, making it more expensive.

Nevertheless, some studies have suggested that freezing of all embryos obtained could be indicated, instead of trying to transfer fresh ones. They argue that the endometrium is more receptive in women who have not undergone ovarian stimulation treatment in the same menstrual cycle in which the embryo transfer is performed, children born from embryos transferred after cryopreservation with respect to those from fresh cycles have better health, and there is a greater increase in the transfer success rates of cryopreserved embryos with respect to fresh embryos. Unlike previously, today both methods are equally successful.

### Ethical assessment

The production of embryos in the laboratory, outside the natural setting where this should take place, already presents ethical difficulties. These are worsened if more embryos are produced that can be expected to transfer. Surplus embryos will be frozen

for later transfer (or not), or to be used for other purposes, such as for obtaining stem cells.

However, this advocated cryopreservation has an added difficulty, namely the damage inflicted on the embryo, which will be subjected to various freezing/thawing processes, resulting in many of them having to be discarded in the process.

If we recognise, as science very clearly confirms, that each of these embryos is an individual of the human species, it seems that treating these embryos as simple cell clusters that can be tested, selected and discarded, is an attack on their dignity, against which the voices of well-founded ethics should be raised up, the ethics that respects life and seeks its good.



Julio Tudela

## Which biological entity can be considered a human embryo?

Defining which biological entity can be considered a human embryo is a hugely important bioethical issue, since it can be manipulated depending on whether it is recognised as so or not. This affects a great many biomedical practices, especially in the ethical assessment of the use of embryonic stem cells.

There are essentially three biological entities to which the condition of human embryo may be attributed: those obtained by natural fertilisation, those derived from human cloning, and the “parthenotes”, which are generated by activating the division of a non-fertilised ovum.

The requirement in order for each of the aforementioned biological entities to be considered as a human embryo, is that a living human being can be derived from it.

That this is the case with those obtained by natural fertilisation is beyond doubt. There is a larger question with respect to those obtained by cloning (somatic nuclear transfer), since although they have the complete genetic makeup characteristic of human beings, it has not hitherto

been possible to confirm whether living human beings can be produced from them. This has, however, been achieved in various types of mammals (we need only remember Dolly the sheep) and non-human primates, such as those achieved by Mitalipov’s team in Oregon (USA). It even appeared that in April 2013, this same team managed to produce human blastocysts, from which they were able to derive functioning human embryo stem cell lines,



although for obvious ethical reasons, the blastocysts obtained were not transferred to a woman to see if a pregnancy and birth of a child could be achieved. In any case, after Mitalipov’s experiments it appears, at least due to a prudent ethical decision, that the blastocysts obtained could be considered as human embryos, and as such should be treated with the respect that their potential human dignity merits.

The issue of “parthenotes”, human ova asexually activated to their division into cells is more complex. According to Nicolas Jouve, dean of Genetics at the University of Alcalá (Cívica 27-IX-2014), an unfertilised egg in which cell division is stimulated

until it reaches the blastocyst stage should not be considered an embryo. The fact that it proliferates and resembles a human embryo does not confer it with the biological nature of a human being in an embryonic state. Since it has not been fertilised, the entity, which has been termed “parthenote”, lacks the genetic information necessary to develop, as it has only half of the chromosomes and genes necessary for development. There are no human beings with 23 chromosomes - developed human beings have 46 (23 paternal and 23 maternal). An embryo with half its chromosomes (more so if it is from a single parent) is in principle, biologically non-viable. On the other hand, when talking about a human embryo, we are talking about higher beings with sexual reproduction in which parthenogenesis does

not exist as an alternative. Thus far has been stated by Jouve.

In summary, in essence, we believe that the naturally conceived embryo is undoubtedly a human embryo. The embryo obtained by cloning, while we cannot be absolutely certain, on a principle of prudence must be considered as such, and finally, we believe that “parthenotes” cannot be considered human embryos.



*Justo Aznar MD, PhD,  
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## Do genes influence man's liberty?

Debate is still raging in a philosophical-legal-scientific field, although it was back in 2009 that an Italian court reduced a murderer's sentence by one year because experts identified that the person concerned had a gene called MAOA (monoamine oxidase A), which is associated with a violent nature and anti-social behaviour. Evidently, a person's actions depend on factors such as their personality, genes, circumstances and social circles. How much room is left for individual liberty? The dilemma is as old as man himself: destiny against personal choice, determinism against self-control. Violent people and delinquents always have reasons for their crimes: revenge, necessity, obfuscation, justice, etc. The social contract, norms of coexistence, and that natural law inscribed in the human heart establish limits, judgments and punishments. But if this illegal behaviour is predetermined, does it merit better legal and social understanding? “The major mistake the people make is to think that if you've identified a cause, it must mean that people are excused or mitigated” stated Stephen Morse, a professor of Law at the University of Pennsylvania, in *The Verge*.

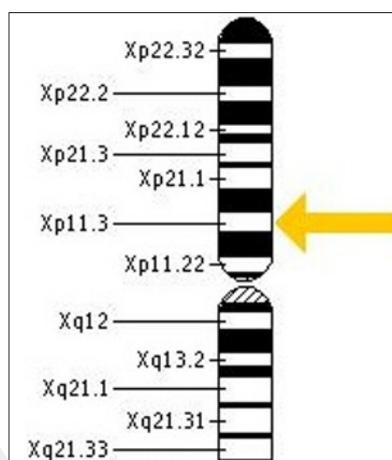
Jorim Tielbeek, a neuroscientist and criminologist at the University of Amsterdam Medical Centre, agrees with Morse: a “higher genetic liability to-

wards committing a crime doesn't necessarily mean a lessened responsibility”. Although scientists have established links, there is “no clear predictive relationship between a single gene and a criminal act — especially since hundreds of genes are involved in criminal behavior, and that each have a very small effect”.

Despite a handful of controversial examples, the use of genetic makeup does not appear to be having a major impact on legal proceedings. A study published in August 2012 in *Science* analysed the effect of genetics on the sentencing of psychopaths,

and found that the average sentence was 13 years when they had a genetic propensity and 14 when they did not. “It's no different than anything that is already being used to reduce sentences”, says Kevin Beaver, a criminologist at Florida State University, such as parents with a history of violence, a violent gang or childhood abuse.

In a study this year in the *Journal of the American Academy of Psychiatry and the Law* (42; 91-100, 2014), Paul Appelbaum, a psychiatrist at the University of Columbia, presented the impact of aggressive genes in homicide cases via a survey administered to 250 people: most were reluctant to accept claims for diminished responsibility or pleas for reduced sentences based



on genetic excuses. And in a trial last month in *Neuron* (82; 946-949, 2014), Appelbaum warned of the risks of the premature introduction of genetic conditions in the courts: “The purported associations [between genetics and behaviour] are not real [...] and can be misinterpreted by [...] jurors”. Except for one adds Morse: “the number one risk factor for violent crime is the Y chromosome”.



*José Ramón Zárate*  
(*Diario Médico* 21/27-VII-2014)

## In Brief

**01** The number of diseases that can be treated by adult stem cell transplant from another person or the patient himself is rising every day. This possibility has now been extended to diffuse cutaneous systemic sclerosis, as a phase 3 clinical trial using autologous stem cells (*JAMA* 311; 2490-2498, 2014) is about to conclude, although at present the results are uncertain.

**02** The Lithuanian Health Minister, Rimante Salaseviciute, has proposed that poor people who do not have access to palliative care units can use euthanasia to end their lives. This measure could reach those people who do not wish to see their family agonise by witnessing their suffering. As if this were not enough, she also proposes to legalise euthanasia in children, which does not necessarily seem odd, since she herself is one of the main promoters of the legalisation of euthanasia in Lithuania (*BioEdge* 29-VII-2014).



**03** Around ten suicides occur daily in Spain. For every death, there are between 10 and 20 suicide attempts. According to the latest recorded data, 3,539 people committed suicide in 2012:

2724 men and 815 women. It is the leading cause of death among men aged 25-34 years old. However, this is perceived to be a much smaller problem than death due to road accidents, which killed 1,915 people in 2012 and 1,128 in 2013. In Spain, 555 people die every year as a result of a work-related accident. Fifty-two persons die per year due to domestic violence and there are 112,390 deaths by abortion. This is by far the leading cause of preventable death .



**04** A recent survey carried out in 47 European countries (*Int J Public Health*, DOI: 10.1007/s00038-013-0461-6) found that euthanasia is accepted in only six countries: Belgium, Holland, Luxemburg, France, Denmark and Switzerland; its acceptance is very low in the remaining 41.

**05** A new bill has been presented in the English Parliament to approve assisted suicide in England and Wales. This bill is very similar to the one in effect in Oregon in the United States, which allows doctors to prescribe a lethal drug to patients who have been given less than six months to live (*BMJ* 2014; 348: g3798).