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human reproduction **OPINION**

Can IVF influence human evolution?

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ABSTRACT: IVF, a procedure in which pharmacological and technological manipulation is used to promote pregnancy, offers help to infertile couples by circumventing selection at the most fundamental level. Fertility is clearly one of the key fitness-promoting drivers in all forms of sexually reproducing life, and fertilization and pregnancy are fundamental evolutionary processes that involve a range of pre- and post-zygotic screening mechanisms. Here, we discuss the various selection and screening factors involved in fertilization and pregnancy and assess IVF practices in light of these factors. We then focus on the possible consequences of these differences in selection pressures, mainly at the individual but also at the population level, to evaluate whether changes in the reproducing genotype can affect human evolution. The aim of the article is not to argue for or against IVF, but to address aspects of assisted reproduction in an evolutionary context.

Key words: assisted reproduction / evolution / human / selection / infertility

Introduction

Reproduction defines the start of the human life cycle and is subject to intense selection. Not only is sexual selection in relation to choosing a mate a crucial evolutionary barrier, but so too is the selection of individual gametes for fertilization, the implantation of the blastocyst into the endometrium and the development of the embryo. These pre- and post-zygotic barriers are well described in the literature on speciation (Seehausen *et al.*, 2014) and, in principle, the same barriers apply within a species.

From this evolutionary perspective, it is of interest that our generation is able to circumvent these fundamental evolutionary barriers. Assisted reproduction by IVF, and by the more advanced technique of ICSI, has become an established service in modern health care (IVF is used in this paper as a collective term). Many people who in historical contexts would have been unable to reproduce can today obtain treatments that specifically bypass most obstacles to reproduction. Perhaps most significantly, as gametes are united *in vitro*, fertilization no longer depends on sexual intercourse. Embryos can, in principle, be designed, stored, exchanged and implanted in just about any womb, and reproduction is increasingly independent of age, gender, sexual orientation and other aspects of the human body.

Assisted reproduction is redefining human society and biology (Ramm, 2014) and, in the face of profound ethical issues, it is important to understand the technical and conceptual principles that underlie this new paradigm. In this theoretical analysis, we therefore explore the implications of assisted reproduction from the perspective of evolution: What are the selection criteria of IVF? How do these criteria differ from the natural selection process, and to what extent will assisted reproduction affect the genetic composition of future generations?

Infertility and assisted reproduction

The World Health Organization defines infertility as 'failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse' (Zegers-Hochschild *et al.*, 2009). On the basis of this definition, infertility is estimated to affect ~10% of couples in developed societies (Gnoth *et al.*, 2003). The natural fecundity rate in humans—the chance of pregnancy per menstrual cycle with regular intercourse—is on average about 20%, which is low compared with that of other species. For women in their early twenties it is somewhat higher, but it begins to decline in the mid-thirties (Larsen and Yan, 2000; Baird *et al.*, 2005). From ~10 years before menopause, most women are for all practical purposes sterile (Dolleman *et al.*, 2013).

The genetic quality of human gametes and embryos is also low compared with that of other species. Aneuploidies in sperm cells (Templado *et al.*, 2013) and oocytes (Pacchierotti *et al.*, 2007) are relatively frequent, and even in morphologically good-looking embryos with normal developmental kinetics, the frequency of aneuploidy is as high as 70% (Mertzanidou *et al.*, 2013). Similarly, chromosomal instability is frequent in human embryos, resulting not only in aneuploidies, but also in deletions, inversions, duplications, amplifications and uniparental disomy (Vanneste *et al.*, 2009). For these and other reasons couples may

undergo IVF and in some countries 4% of all newborns are now conceived by IVF (Kupka et al., 2014).

IVF systematically changes selection pressures

IVF implies that gametes from a selected group of infertile couples are chemically induced to develop and are harvested, screened and subsequently selected for fertilization by using a set of defined morphological and functional criteria. The resulting embryos are then subjected to *in vitro* culturing, additional screening and embryo selection before being transferred into the uterus for implantation, or frozen for thawing and transfer in a later cycle. Accordingly, IVF involves a combination of artificial environments and selection criteria that are distinctively different from those of natural reproduction. The differences in preferred traits between IVF and natural reproduction may be grouped by the steps of the reproductive cycle in which traits can be favoured or disfavoured, as shown below and summarized in Table I.

Selection of oocytes for fertilization

In a natural menstrual cycle, the differential growth and maturation of ovarian follicles is a fine-tuned physiological event. It is orchestrated mainly by pituitary gonadotrophins, but a plethora of local and paracrine regulatory factors are also involved (Gougeon, 1996). The follicle that undergoes ovulation has met a range of physiological demands such as high and increasing expression of receptors for FSH during the FSH-dependent phase of growth, and expression of LH receptors around the time of the LH surge. The follicles that undergo ovulation have, more accurately than their sister follicles that undergo atresia, timed these and other physiological events to coincide with varying concentrations in the pituitary hormones.

In IVF, these naturally occurring selection pressures on oocyte traits are changed by controlled ovarian stimulation (COS). COS is used to retrieve the multiple oocytes needed for IVF and builds on the FSH threshold concept of pharmacologically establishing a serum FSH plateau above the threshold level for multiple developing follicles (Brown, 1978). Later, an injection of hCG mimics the mid-cycle LH peak in a spontaneous menstrual cycle, and about 36 h after the hCG injection, oocytes are aspirated from all follicles above a certain size. In many fertility clinics, the threshold is set to ~8 mm diameter, in contrast to the ovulatory follicle in a natural cycle, which is typically 20 mm diameter or more. The oocyte yield after COS is highly variable and the range of 5–14 oocytes is considered clinically optimal (Popovic-Todorovic et al., 2003). With the exception of oocytes that are clearly immature (likely originating from small follicles), it is common to use all harvested specimens in the subsequent procedures.

With respect to preferred traits, the selection pressure towards high follicular FSH sensitivity is much less under IVF than it is with natural reproduction. In addition, natural selection favours a large follicle with many LH receptors that respond to the LH signal from the pituitary (Zeleznik, 2004), whereas in IVF all but the smallest follicles are aspirated at oocyte retrieval. Under natural reproduction, one oocyte is selected as 'the chosen one' that undergoes ovulation, whereas for the IVF oocyte, it suffices to be one of the many that undergo further treatment in the laboratory. There, plastic surfaces, light, mechanical manipulation, various growth media and abrupt temperature changes in themselves represent selective barriers that must be overcome. In ICSI, oocytes also undergo needle puncture, some of their cytoplasm being aspirated before the spermatozoon enters.

Selection of spermatozoa for fertilization

In natural reproduction, the spermatozoon that fertilizes an oocyte is ejaculated into the vagina during intercourse, after which it swims through the uterus and Fallopian tubes in close contact with female cells and secretions before it is attracted to the egg by a mechanism that is probably chemotactic. Some data showed this journey to be influenced by female endocrinology (Kunz et al., 1996), and sperm selection in natural conception was recently reviewed by Sakkas et al. (2015). In a highly competitive race, likely one of the strongest selective forces in nature (Fitzpatrick and Lupold, 2014), the spermatozoon must not only reach the oocyte, but must also penetrate the zona pellucida by energetic movements and chemical means (Ikawa et al., 2010).

In IVF, the spermatozoa are subjected to chemicals and environments other than those of the female reproductive tract. Sperm preparation methods, such as the 'swim-up', favour fast movement over comparatively short distances, as does fertilization in droplets. IVF thus selects for spermatozoa that swim fast for a short distance and, arguably, genetic traits that confer this ability. The natural process, on the other hand, favours long-distance swimmers that are able to navigate the female reproductive tract. Accordingly, IVF is likely to favour

Table I Theoretical differences in favoured traits between natural reproduction and IVF/ICSI, grouped by the step in the reproductive cycle where they may be selected.

Step in the reproductive cycle	Favoured trait in natural reproduction	Favoured trait in IVF/ICSI
Oocyte	High follicular sensitivity to FSH and LH	Survive laboratory conditions, including puncture
Spermatozoon	Forward mobility for longer distances in mucus	Fast movement for shorter distances
Embryo	Interaction with Fallopian tube	Conformation to laboratory standards; survive cryopreservation
Implantation and miscarriage	Induce implantation in a non-stimulated endometrium	Induce implantation in an endometrium altered by controlled ovarian stimulation
Opportunity to reproduce	Various sociocultural factors	Legislation; economic resources

spermatozoa that allocate more resources to rapid movement and quick penetration of the zona pellucida, whereas natural reproduction is likely to favour endurance and chemotactic orientation.

In ICSI, the operator subjectively selects a single spermatozoon. In severe cases of oligoasthenozoospermia, this spermatozoon may be more or less immotile and clearly not able to fertilize an oocyte under natural conditions. Subjective selection in ICSI also favours spermatozoa with normal morphological characteristics, whereas little is known about the morphology of the spermatozoa that fertilize oocytes in natural reproduction. Moreover, ICSI completely bypasses the natural selection process of locating the oocyte.

Selection of embryo for transfer into the uterus

Although it is hard to study the timing of cellular events within the embryo in natural reproduction and the data are limited, one may suspect that biological variation occurs in these events in embryos that arrive in the uterus (Graham *et al.*, 2010). At least in principle, this variation in early development could be a way for the embryo to adjust to its environment in the Fallopian tubes and the uterus. In IVF, this variation in embryo morphology is minimized by different laboratory criteria used to select embryos for transfer that have the highest chance of producing a pregnancy (Montag *et al.*, 2013). In many fertility clinics, the selection of an embryo for transfer is assisted by time-lapse photography of developing embryos with simultaneous computerized assessment of cellular morphology and kinetics. Accordingly, the software's algorithm represents another selection barrier for the embryos in IVF (Kovacs, 2014), and the increased use of computer-assisted embryo selection will favour those embryos that conform to the defined standards.

With the increased use of single embryo transfer, cryopreservation has become an important component of IVF programmes. Improved cryopreservation techniques make the selection of the highest quality embryo for fresh transfer less important than it once was (Mastenbroek *et al.*, 2011), and the ability to survive cryopreservation represents a new selection barrier.

Embryos in IVF bypass the Fallopian tubes and, like gametes in IVF, they are indifferent to the selection criteria conferred by this complex environment. Conversely, they must survive a rough environment in the IVF laboratory very different to that in natural reproduction.

Selection in implantation and miscarriage

After arriving in the uterus, the embryo in both natural reproduction and IVF must avoid implantation failure in order to proceed in the reproductive cycle. Recent evidence indicates that the endometrium acts as a biosensor towards the embryo; developmentally competent embryos emit signals to the endometrium, activating its contribution to implantation (Brosens *et al.*, 2014). Whether this biosensor function is altered in IVF is unknown. What is known, however, is that variation in the COS protocols has an impact on endometrial gene expression (Humaidan *et al.*, 2012). A study of cattle indicates that the endometrium tailors its response depending on the embryo's origin (Mansouri-Attia *et al.*, 2009), with possible implications for implantation and early growth.

From the maternal point of view, early detection and expulsion of unviable embryos either by implantation failure or clinically recognizable miscarriage constitutes a long-term fitness advantage that optimizes her number of viable offspring. Yet data on the differences in clinically recognizable miscarriages between natural reproduction and IVF are inconclusive (Farr *et al.*, 2007).

Selection of couples for IVF treatment

The decision about if and when to become pregnant is more often than not taken after careful consideration of a range of factors for both fertile and subfertile couples. As long as IVF remains more regulated, more expensive and more burdensome than natural reproduction; however, the limited availability of IVF treatment is in itself an arena for selection of discernible traits among infertile couples. This selection can be illustrated by two women with a BMI of 25 and 45 kg/m^2, who are both infertile because of tubal occlusion. In Norway, the patient with a BMI of 25 kg/m^2 will receive publically funded IVF, whereas the woman with a BMI of 45 kg/m^2 will be denied such treatment. Although they are both infertile, the slimmer woman will be selected to reproduce and the obese woman will not. The obese patient may of course pay for privately funded IVF, or she may lose weight, but that is expensive and strenuous, and so the selection pressure is not eliminated. Other selection factors that influence subfertile patients' access to IVF include smoking, human immunodeficiency virus/hepatitis infection, psychiatric disease, sex-hormone responsive cancers and a frozen pelvis. Although these factors are also selection pressures in natural reproduction, the limited availability of IVF enhances their importance.

Because the sheer financial cost of IVF is high, infertile patients with a low income are selected against. In countries like Norway, this negative selection is reduced by public subsidies, but in comparison to natural reproduction, there is still a difference on the basis of income. The effect is further enhanced at the macroeconomic level because low-income countries typically have lower IVF availability (Ombelet *et al.*, 2008). Overall, the limited availability of IVF favours healthy subfertile couples in stable relationships who live in high-income societies over other subfertile couples. Whether or not these socio-economic traits are hereditary, and thus genetically selectable, is a controversial question that falls outside the scope of this article.

How IVF may affect human evolution

So far we have discussed the systematic differences in favoured traits between natural reproduction and IVF. IVF pregnancies result from the subjective assessment of gametes and embryos for their suitability to participate in the next step of the reproductive cycle, and these assessments differ from natural reproduction. IVF also favours traits that permit cells to survive and prosper in laboratory conditions. Although we foster no concern per se about the robust gametes and embryos that survive these conditions, the room for phenotypic variation is finite, and so increased robustness comes at the expense of another trait.

Culturally induced changes in the human genome are not a novelty. Throughout human history, the interaction between culture and evolution has been pronounced. One example is the genetic response to

dietary selection, clearly illustrated by the relationship between lactase expression and milk consumption in human populations (Tishkoff *et al.*, 2007). Similarly, a number of traits related both to metabolism and to other physiological systems result from gene-culture co-evolution (Sabeti *et al.*, 2006; Laland *et al.*, 2010). These cases often imply that single gene traits have been persistently and repeatedly selected for in consecutive generations until fixation in the population.

The evolutionary implications of systematically different selection pressures in IVF could be even more influential, as evolutionary theory underlines that selection works through differential reproductive success and not through differential survival. Moreover, and perhaps contrary to popular belief, modern humans are not exempt from evolution, as shown in studies on contemporary human populations in which age at first reproduction and systolic blood pressure were two of the traits influenced by evolution (Byars *et al.*, 2010; Milot *et al.*, 2011). Although these studies were done retrospectively and show rather small effects of evolution in pre-IVF populations, IVF could potentially produce larger effects more quickly as it directly influences reproductive success. The most extreme evolutionary scenario is a subpopulation in which reproduction is entirely dependent on IVF. Although such extreme scenarios are unlikely (Engel *et al.*, 1996), the heritability of the so-called fitness traits, referring to complex measures of fertility and mortality, has also been clearly documented in human populations (Kosova *et al.*, 2010). Accordingly, there are inherited traits that confer varying degrees of infertility or subfertility. Some of this heritability may be genetic and linked to specific diseases that directly influence the process of reproduction. In women, two primary examples include endometriosis, in which scarring may lead to the occlusion of the Fallopian tubes, and polycystic ovary syndrome, in which anovulation and hyperandrogenism are the two central features. Both conditions have a heritable component (Treloar *et al.*, 1999; Vink *et al.*, 2006). The heritable aspects of male subfertility are generally poorly understood. Yet, for this condition, there are also clear indications of a heritable component. As a key example, some cases of oligospermia are related to microdeletions on the Y chromosome and were shown to be propagated from father to son by means of ICSI (Silber, 2011). Hypospadia, a malformation of the penis with implications for fertility, is also more common in boys conceived by using ICSI (Ericson and Källen, 2001). Overall, it seems clear that IVF facilitates the propagation of genetically heritable traits of subfertile couples, and we suspect that ongoing studies of IVF offspring will show an increased risk of subfertility for this group. How subfertility is measured will be of importance in such studies; time-to-pregnancy is increased in many of the conditions described above, but the number of offspring over the entire reproductive career may not be affected.

The comprehensive follow-up of IVF offspring is making it increasingly clear that heritable effects of IVF cannot be confined to a purely genetic view of heredity. IVF may also induce phenotypical changes by epigenetic mechanisms; gene expression in early embryos, intrauterine growth rate, placental gene expression, birthweight of newborns and body weight at 2 years of age all seem to depend on the media used for culturing embryos *in vitro* (Dumoulin *et al.*, 2010; Eskild *et al.*, 2013; Nelissen *et al.*, 2013; Kleijkers *et al.*, 2014, 2015). As a further example of phenotypical changes, cryopreservation of human embryos is associated with an increase in birthweight and increased frequency of children born large for gestational age (Pinborg *et al.*, 2014; Wennerholm *et al.*, 2013). Furthermore, IVF is associated with changes in cardiometabolic measures, body fat composition, serum levels of hormones and growth factors, initiation of puberty and bone length in children and adolescents (Ceelen *et al.*, 2007, 2008a, b, c, 2009; Miles *et al.*, 2007; Scherrer *et al.*, 2012). All these effects are mainly attributed to epigenetic, not genetic, mechanisms (Kleijkers *et al.*, 2015). It is too early to judge whether these shifts in phenotypes have consequences for the long-term health of IVF offspring. The oldest IVF individual is still in her thirties, leaving unanswered questions about health effects during late adulthood and the fertility profile over the first and future generations of IVF individuals. However, it is noteworthy in the current context that these epigenetic effects may have transgenerational implications along the lines of the effects of nutrition and smoking during pregnancy (Drake and Walker, 2004; Frias and Grove, 2012; Veenendaal *et al.*, 2013; Golding *et al.*, 2014).

Although the present analysis points out systematic differences in selection pressures between IVF and natural reproduction, we are the first to admit that some important selection pressures in human reproduction seem unaltered by IVF. For instance, there is no indication that COS influences the initiation of primordial follicles from the ovarian follicle pool, which in quantitative terms is the most important selection arena for oocytes (Stearns, 2005). Only ~0.005% of oocytes formed are allowed to pass through the 'filter' of oocytic atresia and have the opportunity to be initiated, and this 'filter' is probably not changed by IVF. Moreover, the average number of aspirated oocytes it takes for one live baby to be born has remained stubbornly high at about 25 for young women, even though IVF has developed immensely (Gosden and Lee, 2010). Viewed alongside the low genetic quality of human embryos and gametes described in the introduction, this evidence points to peri- or post-implantation selection pressures that are less likely to be influenced by IVF than those of earlier steps in the reproductive cycle.

Conclusion

In this article, we have demonstrated the selective pressures posed by IVF, the ways in which they differ from natural reproduction, and how this technological intervention may have implications for human evolution. One reason that the potential evolutionary implications of IVF have received limited attention could be resistance against applying an evolutionary perspective to medically induced negative traits. To point out that IVF may favour disease-prone individuals or lead to reduced fitness over generations could surely be provocative, but is nevertheless worth considering. We do, however, strongly emphasize that ours is indeed not a general argument against IVF and that we fully recognize the devastating implications of misinterpreting 'survival of the fittest' as a normative rather than as a descriptive concept.

The purpose of this article is not to judge or impose a set of norms on IVF, but rather to promote a better understanding of how IVF works, not only as a treatment for infertility, but also as a technological intervention at the point in the human life cycle where natural selection operates at its strongest. Although IVF is a great medical achievement, it circumvents a range of pre- and post-zygotic reproductive barriers. It increases the reproductive fitness of subfertile couples by technologically removing several naturally occurring selective barriers and by altering other such barriers. In accordance with the basic principle of evolution, the subsequent generations will thus be genetically and epigenetically adapted to an environment in which reproduction is increasingly dependent on technological intervention. It is our opinion that IVF should be seen as

a primary example of how the human species is becoming not only culturally—but also biologically—dependent on our own technology.

Authors' roles

All authors contributed to idea, planning, data collection, analysis and writing of manuscript.

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Conflict of interest

None declared.

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