



IVF and human evolution

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ABSTRACT: Humans are shaped by evolution through natural selection, as are all species. While evolution is central to all biological processes, the key stage for competition and selection is reproduction, which encompasses various events from courtship and mating to fertilization and pregnancy. In humans, IVF is used to aid the intrinsically inefficient reproduction by coitus, and in several countries, the proportion of children born after IVF is increasing. While IVF is an enabling technology for infertile patients, it also circumvents reproductive barriers and changes selection pressures. This grand theme review describes the systematic differences between IVF and coitus in selection pressures on reproducing cells, individuals and populations. At the cellular unit of selection, for example, IVF favours different traits in spermatozoa (fast swimmers over short distances) than coitus does (forward mobility over longer distances). Similarly, a male with low sperm quality and a female who decides to delay her first birth to an advanced age, can both increase their reproductive fitness by IVF compared to if reproduction by coitus is their only option. In as much as delayed reproduction is a cultural trait, IVF thus enables cultural practices that may in their turn affect human evolution. A main point in this review is to discuss the interactive effects of biological and

cultural traits in the context of IVF, and how they act in concert as drivers towards increased demand for IVF. It is not the aim of this review to argue against IVF, which no doubt is a major medical advancement, but rather to examine IVF and human evolution from a broad perspective, including potential longer-term impacts. Since IVF is a young technology, the empirical data indicative of evolutionary effects of IVF in humans are sparse. In general, we argue that IVF facilitates the redirection of resources away from reproduction in humans, since reproduction by IVF bypasses some of the resource-demanding processes that reproduction by coitus entails. Hence, IVF sets the evolutionary stage for a human species increasingly reliant on, and adapted to, technological means of reproduction.

Key words: evolution / Darwin / human / assisted reproduction / IVF / cultural evolution / sexual selection / phenotype / adaptation / life history

Introduction

Of all the stages in an organism's life cycle, reproduction contains the most intense selection pressures and is thus essential in evolution. Recent reports from various countries of decreased birth rates (Collins and Page, 2019; Beaujouan, 2020), increased prevalence of infertility (Skakkebaek et al., 2006; Te Velde et al., 2012) and increased use of assisted reproductive technology (WVyns et al., 2020), such as IVF, make it timely to review the joint cultural and biological drivers behind these trends. Moreover, since IVF circumvents or changes selection pressures in human reproduction (Hanevik et al., 2016; Jiang et al., 2017), we also ask if there is an impact of IVF on human evolution mediated by increased demand for IVF.

One of Charles Darwin's great insights was that evolution is inextricably linked to reproduction (Darwin, 1859). From a biological point of view, the ultimate reason for an individual to reproduce is the transfer and proliferation of heritable information to subsequent generations, while the individual's proximate reason to engage in reproduction is hormonally determined desire (Tinbergen, 1963; Bateson and Laland, 2013). As reproduction and survival are biological imperatives, and since biological evolution acts to maximize the transfer of genes to coming generations, one perspective of the individual is as 'a survival machine' for the genes (Dawkins, 1976). Evolution is undoubtedly geared towards reproduction in humans also, yet there is certainly more to human life than simply passing on genes, and human reproduction is also moulded by cultural influences (Henrich and McElreath, 2003). Hence, both cultural and biological drivers affect human reproductive fitness at different steps in the reproductive cycle, from the so-called sexual selection of detecting and seducing a mate (Fisher et al., 2006; Bode and Kushnick, 2021) to several pre- and postzygotic arenas for selection.

The selection of an oocyte for ovulation in a menstrual cycle, the fierce competition and selection between spermatozoa to fertilize that oocyte, and the selection of embryonic traits that confer the optimal chance of implanting and developing in that month's endometrium are key selection pressures to evolution in many species (Servedio and Saetre, 2003). Throughout human history, these selection arenas and others have served as an efficient screen to determine which traits were passed on to subsequent generations. With IVF now increasingly used to aid the intrinsically inefficient (Wilcox et al., 1995) reproduction of humans, selection pressures on gametes, embryos and even infertile patients have to some degree changed, with putative effects on human evolution (Hanevik et al., 2016). Phenotypes are not determined by genes alone, and evolutionary biology has lately explored

how traits could be modified by epigenetic and environmental modification of gene expression (Varki et al., 2008; Laland et al., 2010; Wei et al., 2015; Jablonka, 2017; Skúlason et al., 2019). Moreover, interactions between biological and cultural influences on individuals' reproductive decisions have gained further significance in a contemporary lifestyle in which young people often embrace other means of success than reproductive output (Mills et al., 2011; Schmidt et al., 2011; Neels et al., 2017; Pennings, 2021). A main component of the decreasing lifetime number of offspring born to couples in several developed countries is increased female age at first birth (Sobotka, 2004; Rendall et al., 2005). Advanced female age at first birth is also associated with an increase in female involuntary childlessness and a widening gap between desired and achieved lifetime number of offspring (Leridon and Slama, 2008; Te Velde et al., 2012). This is partly mediated by the biological constraints on the female reproductive period (Te Velde and Pearson, 2002), but see also Smarr et al. (2017) for a discussion about knowledge gaps in this area. Regarding males, there is increasing, but not uniform, evidence of declining quality of semen samples in some developed countries (Bonde and Te Velde, 2017; Levine et al., 2017). The reasons for this decline are likely complex, though ambient factors, such as environmental pollutants, likely play a key role (Bloom et al., 2015; Le Moal et al., 2021). In addition, males increasingly postpone fatherhood to a later age across the developed world (Schmidt et al., 2011; Nilsen et al., 2013), and sperm quality has been shown to decline with increasing male age (Kühnert and Nieschlag, 2004; Stone et al., 2013; Collodel et al., 2021). At the same time, demand for IVF has increased in the countries affected by these trends (WVyns et al., 2020). Although the underlying reasons for this demand vary locally (Te Velde et al., 2017; Calhaz-Jorge et al., 2020), there can be no doubt that the development and uptake of IVF and other medically assisted reproduction since its inception has been formidable (Niederberger et al., 2018), to the point where over 5% of all children born every year in some countries are now conceived after medically assisted reproduction (WVyns et al., 2020).

In light of these trends, we herein review and discuss the evolutionary implications of IVF in humans within a broad frame of reference. Our aim is to provide a wider interdisciplinary perspective on how biological (genetic) evolution and cultural evolution interact in this context, where a suite of biological and cultural traits under selection act in concert as drivers towards increased demand for and use of IVF. When IVF is more widely applied, it also becomes relevant to address the potential biological evolutionary outcomes of IVF *per se*. We start by presenting some of the underlying concepts and notions, notably the differences and similarities between biological evolution, cultural

evolution and the concept of enabling technologies in this context, before addressing the process of IVF itself and how it influences selection at various steps of the human reproductive cycle. We stress that we provide no normative bearings or judgments of IVF itself, which no doubt represents a formidable medical advancement, but aim at providing a neutral description and discussion of IVF from the perspective of human evolution.

Evolution is relevant to all aspects of life

Evolution is a fundamental principle of life (Benner, 2010) that in essence deals with the variation, selection and replication of information over time (Mayr, 1982; Smith and Szathmari, 1995). Historically, evolutionary theory was predominantly applied to biology, famously captured by the phrase 'nothing in biology makes sense except in the light of evolution' (Dobzhansky, 1973). Yet, evolutionary theory not only applies to biology but also penetrates a broad range of fields that imply selection of one trait or idea over another (Dennett, 1996; Aldrich *et al.*, 2008), spanning from medicine (Attolini and Michor, 2009; Gluckman, 2016) and linguistics (Nowak and Krakauer, 1999; Newberry *et al.*, 2017) to culture (Boyd and Richerson, 2009) and computation (Reddy and Kumar, 2012). While the application of evolutionary theory to human biology is largely uncontroversial, the scientific concept of human cultural evolution is more recent, perhaps not as well known (Cavalli-Sforza and Feldman, 1973; Richerson and Boyd, 2005; Creanza *et al.*, 2012, 2017; Mesoudi, 2017; Whitehead *et al.*, 2019), and still contested (Aldrich *et al.*, 2008; Nettle, 2020). Some of the key terms used in studies of both biological and cultural evolution are outlined in the glossary (Table I). Although differences between cultural and biological evolution exist as outlined below (Smolla *et al.*, 2021), the fundamental principle of evolution applies to all aspects of life, including culture. It can be explained in terms of variation, selection and replication of information.

Variation

Evolution requires variation upon which selection may act. In the context of biology, the prime source of variation is genetic mutation. Mutations can be larger genomic rearrangements, such as duplications (Hessen, 2015), but in their simplest form, mutations are changes in single nucleotides that may or may not change a trait. For example, one spermatozoon may have the trait of 'slow swimmer' and another that of 'fast swimmer'. Human culture, defined herein as human behaviour, knowledge or constructed artefacts, also varies both within and between populations (Creanza *et al.*, 2017; Mesoudi, 2017). An example of variation in constructed artefacts is the shape and size of hand-axes used by early humans (Wynn and Gowlett, 2018). As for human behaviour, one example is how initiation and maintenance of aggressive behaviour varies between individuals (de Almeida *et al.*, 2015).

Selection

As different variants of biological and cultural traits compete for limited resources, such as energy and attention, over time some proliferate while others disappear. One of Darwin's key insights was that there is always variation in biology, and since in general resources are limited, only some individuals have offspring that survive to reproductive age. Those who leave most surviving offspring behind are, statistically speaking, the fittest, and accordingly there is 'survival of the fittest' (Darwin, 1859), with some traits being selected instead of others. In cultural evolution, selection of traits occurs when a variant in behaviour, knowledge or artefact is systematically preferred over a competing alternative. A smaller hand-axe is easier to handle and could thus be preferred (Wynn and Gowlett, 2018). An individual who behaves aggressively under certain conditions pays the costs and reaps the benefits of that behaviour, with implications for behaviour the next time those conditions occur (Georgiev *et al.*, 2013; Simon and Hessen, 2019).

Replication

The ability to replicate—or copy—information is fundamental in all living systems, and information is replicated both within and across generations. One key carrier of information across generations is DNA. The human brain is another, as social learning leads to transmission of cultural traits both within and across generations in humans (Henrich and Broesch, 2011; Simon and Hessen, 2019; Branje *et al.*, 2020; Miu *et al.*, 2020; Kronfeldner, 2021). Fidelity of neither biological nor cultural copying is absolute, and minor copy errors, such as *de novo* mutations in germ-line DNA (Sasani *et al.*, 2019) and trial-and-error copying of behaviour by young brains (Legare and Nielsen, 2015), are examples of sources of new variation upon which selection may act.

Biological and cultural evolution

Evolution, both biological and cultural, works by iterative cycles of variation, selection and replication, as shown in Fig. 1. Although evolution often leads to change over time, it has no 'purpose' in the sense of planning, but merely selects between available variants. What we in this manuscript label biological evolution reflects genomic changes with phenotypic consequences, and the unit of selection can be the gene or genome *per se*, the organism or even the population as reflected by the term 'multilevel selection' (Traulsen and Nowak, 2006). In biological evolution, evolutionary success is labelled fitness. A well-adapted individual has, in relative terms, a good chance of survival and reproduction in its environment, and thus by definition a higher fitness than its competitors (Peck and Waxman, 2018). Yet adaptation is a moving target. As outlined in Fig. 1, environments often change, and the very trait that gives a fitness advantage either in terms of reproduction or survival in one environment might confer a disadvantage when environmental changes occur. In other words, biological evolution does not take place in isolation, but in an environmental scene that proffers rich feedback from other parts of the biota, as well as from the inorganic environment (climate, water, atmosphere, radiation and nutrients). In the context of this review, it is important to note that culture can also pose feedbacks to fitness, as we will discuss in the context of IVF. As the environment is not constant, humans keep evolving, as do all other

Table 1 Glossary of selected terms in IVF and evolution.

Biological evolution	Change in genotype caused by iterative cycles of variation, selection and replication of genotype
Cultural evolution	Change in culture caused by iterative cycles of variation, selection and replication of culture
Culture	Behaviour, knowledge or constructed artefacts
Evolution	Change caused by iterative cycles of variation, selection and replication. The theory of evolution applies to a range of fields that imply selection of one trait or idea over another
Fecundability	The probability of a pregnancy, during a single menstrual cycle, in a woman with adequate exposure to sperm and no contraception, culminating in a live birth
Gene-culture co-evolution	Cultural processes shape biological evolution by affecting the selection of genes, often entailing reciprocal interactions and feedback
Genotype	All information carried by the genome in the unit of selection
Infertility/subfertility	Used interchangeably to denominate a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner
Phenotype	All traits displayed by the unit of selection
Phenotypic plasticity	The ability of a given genotype to produce different phenotypes in different environments
Reproductive fitness	The relative ability of a unit of selection to pass on its phenotype to subsequent generations. Proportional to its chances of surviving and reproducing in the current environment
Trait	A variant of a characteristic in a unit of selection
Unit of selection	Depending on the level of analysis, can be either a gene or any part of the genome, a cell, an embryo, an individual or a population

For terms in studies of cultural and biological evolution (see [Mesoudi, 2017](#); [Whitehead et al., 2019](#)) and in IVF (see [Zegers-Hochschild et al., 2017](#)).

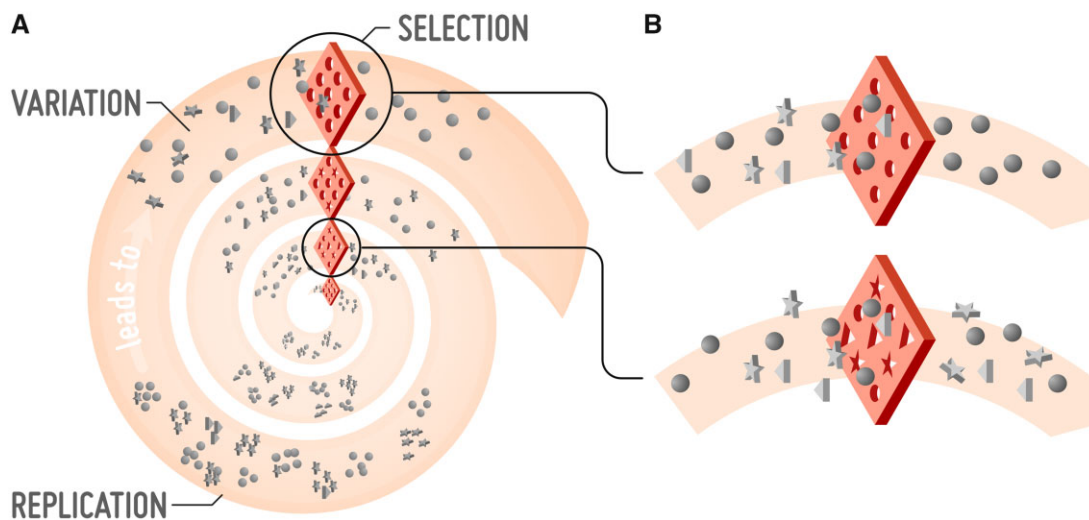


Figure 1. Evolution deals with variation, selection and replication of information over time. Evolution works by cycles of variation, selection and replication as outlined in (A). In biology, each round of the cycle typically takes one generation. The grey shapes that move through the cycles represent traits under selection, and their replication is one source of variation in traits. (B) Zooms in on the selection step of evolution and shows how differences between selective barriers have consequences for traits. The reasons behind differences in selective barriers between cycles are, most often, environmental changes. Traits to the right of the selective barrier may thus be seen as adaptive to the present environment.

species (Stearns *et al.*, 2010; Troup *et al.*, 2015; Valge *et al.*, 2021). When environments change, biological evolution can act surprisingly fast on modern humans (Keinan and Clark, 2012), even considering our long intergeneration interval (Kong *et al.*, 2017). Molecular evolution of proteins with a role in mammalian reproduction can be particularly speedy (Swanson *et al.*, 2001; Hart *et al.*, 2018).

Cultural evolution is similar to biological evolution in that the prevalence of cultural traits in a population changes over time and in different environments (Mesoudi, 2021). Cultural traits could include everything from technological innovations, music, fashion and behaviours to sexual signals and attributes (Lambert *et al.*, 2020), and in addition to the hand-axes and aggression mentioned earlier there is an almost endless list of cultural aspects, from words, habits and fashion to technology and tools that typically change rapidly over time due to a preference over competing alternatives. Two trivial but illustrative examples are how the names given to newborns change with time, reflecting the varying popularity that selects 'winners' and thus proliferation of certain names over others (Hahn and Bentley, 2003), and how different dog breeds have varied in popularity as pets over time (Ghirlanda *et al.*, 2013). In general, selection between cultural traits is affected by factors such as the perceived prestige of the individual displaying the cultural trait in question (Chudek *et al.*, 2012; Bond and Gaoue, 2020), as well as other factors such as conformity pressures (Muthukrishna *et al.*, 2016) and the benefit-to-cost ratio for a certain behaviour in a specific environment (Georgiev *et al.*, 2013; Glowacki and Wrangham, 2015). In this context, it is important to emphasize that there are at least two different, yet not mutually exclusive, ways of conceptualizing cultural evolution (Mesoudi, 2021), where one sees cultural evolution as an analogue to population genetics with a competition and selection between culturally transmitted traits, while the other views cultural evolution as directional transformation of information in a non-random manner that over time cause a cultural change (Mesoudi, 2021). Another notable difference between cultural and biological evolution is that at present there is no widely accepted analogue in cultural evolution to the concept of fitness (Ramsey and Block, 2017; Smolla *et al.*, 2021). As the above examples show, biological traits increase their presence in a population by having a positive impact on the number of fertile offspring that an individual displaying that trait produces, but this is not necessarily the case for cultural traits, at least not in humans (Whitehead *et al.*, 2019). In fact, certain cultural traits in humans may decrease the reproductive fitness of an individual, but still persist over time and in different environments. One extreme example of a cultural trait that impedes the reproductive fitness of an individual is religious celibacy. Another notable example is how having few children increases the socio-economic position of the child, which is culturally beneficial, yet is detrimental to the long-term biological fitness of the parent (Goodman *et al.*, 2012).

In the context of this review, a trait of particular interest is delayed reproduction, i.e. some females may have their first child at 20 years of age, while an increasing share of women in developed countries delay their onset of reproduction until reaching nearly 40 years of age (Beaujouan, 2020). Similar to the example of aggression mentioned above, we consider delayed reproduction in humans to be primarily a cultural trait (Rijken and Liefbroer, 2009; Bernardi, 2016; Riise *et al.*,

2016), with biological underpinnings (Barban *et al.*, 2016; Day *et al.*, 2016; Lynch *et al.*, 2020). Delayed reproduction increases the risk of female and male infertility at the time of intended reproduction (Ford *et al.*, 2000; Te Velde and Pearson, 2002; Hassan and Killick, 2003; Verweij *et al.*, 2019; Collodel *et al.*, 2021), and decreases the lifetime number of offspring compared with peers of lower age at first offspring (Sobotka, 2004; Troup *et al.*, 2015). Faced with the negative consequences of delayed reproduction on reproductive fitness, we see IVF as an enabling technology that offers individuals the possibility of, to some extent, circumventing the negative consequences of postponed reproduction on fecundability (Habbema *et al.*, 2015) and lifetime number of offspring (Gershoni and Low, 2021), although not completely so (Leridon, 2004; Horta *et al.*, 2019). In short, IVF lessens the negative consequences on fecundability and lifetime number of offspring that postponement of reproduction to a later age would otherwise have had, particularly so for females. One empirical indication of this effect of IVF on fecundability and lifetime number of offspring in females is that the share of IVF offspring born to older females is substantially higher than it is for offspring born to younger females, reflecting the fact that the contribution of IVF to lifetime number of offspring in females increases with female age (Goisis *et al.*, 2020). Thus, we ask if IVF is a technology that influences human cultural evolution. Also, when coitus is replaced by IVF in human reproduction, the IVF treatment *per se* constitutes a fundamental change in the environment in which human reproduction occurs (Jiang *et al.*, 2017), meaning that IVF could also influence human biological evolution. In addition to reviewing how IVF could in itself constrain the chances of reproduction by coitus in future generations by affecting or circumventing several pre- and postzygotic selection pressures (Hanevik *et al.*, 2016), we discuss in this review how both cultural evolution and biological evolution in humans work in concert to generate increased demand for IVF. In other words, the confluence of human biological and cultural evolution in the human reproductive cycle demands that a review of IVF and human evolution considers both cultural and biological traits that are affected by IVF. To structure the discussion of how IVF constitutes a different selective environment for human reproduction compared with reproduction by coitus, we have divided the human reproductive cycle into steps, as shown in Fig. 2.

IVF changes selection pressures on gametes

Spermatozoa

Selection acts on phenotypes, and each individual spermatozoon has a phenotype that is determined by its genotype in interaction with environmental, epigenetic and other influences (Marcho *et al.*, 2020). For example, the mRNA content of an ejaculate differs markedly between fertile and infertile males (Garcia-Herrero *et al.*, 2010), and examination of gene transcription profiles between sperm subpopulations in individual semen samples has revealed transcriptional differences between these subpopulations related to sperm physiology and capacity for reproduction (Caballero-Campo *et al.*, 2020; Stimpfel and Vrtacnik-Bokal, 2020). In nearly all imaginable semen samples, IVF selects for another phenotype of spermatozoon to fertilize the oocyte

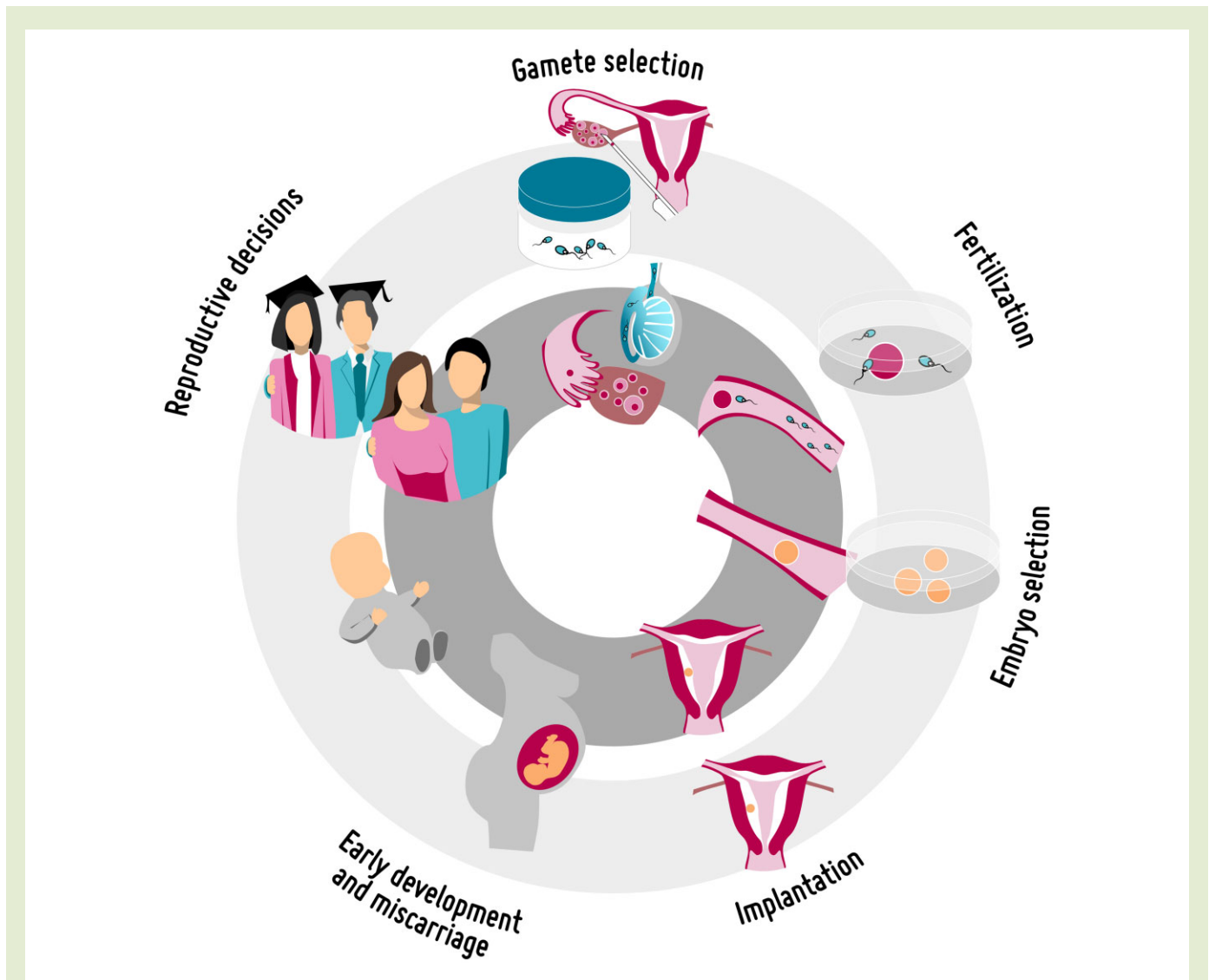


Figure 2. Key steps in the human reproductive cycle affected by IVF. Differences in selection pressures between reproduction by coitus (inner circle) and IVF (outer circle) are indicated. Starting on top and moving clockwise, selection between spermatozoa and oocytes differs between IVF and coitus, as does fertilization and embryo selection. During implantation and early pregnancy, IVF affects the environment in which the foetus develops. At later steps, though it is in the evolutionary interest of the individual to maximize its long-term reproductive fitness, a suite of cultural drivers affected by IVF could influence reproductive strategies.

than coitus does. IVF practitioners and researchers alike have long since acknowledged the differences between the selection of sperm in coitus compared with that in IVF, and they have used these differences to inspire research into how to select the most competent sperm for assisted reproduction (Jeyendran *et al.*, 2019) and how to engineer methods for selection of spermatozoa in the IVF lab that mimics sperm selection after coitus (Vaughan and Sakkas, 2019). When reviewing that field of study, Sakkas *et al.* (2015) included a section on evolutionary mechanisms used to promote sperm selection after coitus. The spermatozoa ejaculated into the vagina first swim through the uterus and a fallopian tube, in close contact and interaction with female cells and secretions, and perhaps influenced by female peristalsis

(Kunz *et al.*, 1996; Fitzpatrick and Lupold, 2014; Gasparini *et al.*, 2020; Jokiniemi *et al.*, 2020; Kekäläinen, 2021). Upon reaching the vicinity of the oocyte, spermatozoa are attracted to the oocyte by chemotaxis before penetrating the zona pellucida by applying a variety of means, both kinetic and chemical (Ikawa *et al.*, 2010). In contrast, the phenotype of a spermatozoon selected for fertilizing the oocyte in IVF is one that swims fast over the shorter distances required by various sperm-preparation methods used in the IVF lab (Oehninger *et al.*, 1990; World Health Organization, 2010). In the case of ICSI, the demanding step of penetrating the oocyte is performed by the ICSI operator, and even an almost immotile spermatozoon may be selected (Ortega *et al.*, 2011). ICSI also removes the selection pressure on the

spermatozoon to localize an oocyte in its immediate surroundings and overruns the selection of sperm that occurs after coitus by factors secreted from the oocyte (Fitzpatrick *et al.*, 2020).

Oocytes

The physiology of recruitment and selection of ovarian follicles, reviewed recently from an evolutionary perspective (Laisk *et al.*, 2019), is complex (Zeleznik, 2004; Baerwald *et al.*, 2012; Kerr *et al.*, 2013; Hsueh *et al.*, 2015). Still, the selection of one growing follicle for ovulation in a menstrual cycle amongst several available candidates must be based on follicular phenotype. Since all follicles carry genotypically unique oocytes, and as there is strong interplay between the oocytes and the granulosa cells in the follicles (Eppig, 2001; Gilchrist *et al.*, 2008; Gosden and Lee, 2010; Alam and Miyano, 2020), there are likely to be genetic or epigenetic (Wei *et al.*, 2015; Olsen *et al.*, 2020) differences between follicles that influence their growth and selection for ovulation. Oocyte development is also influenced by follicular content (Uyar *et al.*, 2013), yet initial recruitment of follicles into follicular waves is thought to occur at random (Baerwald *et al.*, 2003), but see also Schmidt *et al.* (2003) and Noble (2017). To become selected for ovulation, a growing follicle must display a certain sensitivity to the relevant endocrine signals when the pituitary signals for final maturation and ovulation (Zeleznik, 2004). The principle of controlled ovarian stimulation for IVF, in which FSH analogues are injected to rescue growing follicles otherwise doomed to atresia, selects for a different phenotype of follicular sensitivity to endocrine signals prior to oocyte retrieval than that of the ovulatory follicle in a non-IVF cycle. Effectively, no oocytes from follicles with a size of 12 mm across or less at the time of the endogenous surge of LH become fertilized after coitus. In IVF, oocytes from even the smallest punctured follicles will undergo an attempt at fertilization and, if further development is normal, will be used for later embryo transfer (Wittmaack *et al.*, 1994; Wirleitner *et al.*, 2018), though the molecular and metabolic profile of the follicles correlates with later oocyte fate (Gioacchini *et al.*, 2018). Following selection on follicular phenotype, further differences occur in the selection on oocyte phenotype between the two modes of reproduction as a result of factors in the IVF laboratory. There, plastic dishes, light and pipettes constitute what is in effect a selective environment for oocytes that is entirely different from the interior female genital organs. In ICSI, the oocyte must even allocate resources to cope with being punctured. In contrast, the coital setting requires the oocyte to be transported through the female fallopian tubes and interact with them before fertilization (Lyons *et al.*, 2006; Jackson-Bey *et al.*, 2020). IVF, on the other hand, favours the oocyte that is robust in the face of external stimuli and manipulation.

IVF changes selection pressures on embryos and fetuses

Embryos

Again, a primary difference between IVF and coitus in terms of selection pressures is the handling of embryos by pipettes and their

exposure to light and growth media in IVF compared with transportation through the interior of a female in reproduction by coitus (Gardner and Lane, 1997). IVF embryos bypass the fallopian tubes and, like IVF gametes, are indifferent to the selection pressures conferred by this complex environment. A further difference arises from the minimal biological variation in embryo morphology and timing of early cellular events that is accepted in an IVF lab. In coital reproduction, we expect there to be considerable variation in morphology of embryos that arrive in the uterus (Graham *et al.*, 2010). In principle, such variation accommodates the embryo's adjustment to its environment in the fallopian tubes and the uterus, and offers the endometrium variation from month to month in terms of the phenotype of the arriving embryo. In IVF, this variation in embryo morphology is minimized by the use of laboratory criteria to select embryos for transfer into the uterus (Montag *et al.*, 2013; Apter *et al.*, 2020). Furthermore, in many IVF clinics, the selection of embryos is assisted by the computerized assessment of embryo morphology and kinetics, including by machine learning and artificial intelligence (Zaninovic and Rosenwaks, 2020; Riegler *et al.*, 2021). Accordingly, algorithms increasingly represent a selection barrier for IVF embryos, favouring those embryos that conform to the algorithm's standards. Finally, embryo cryopreservation has become routine practice in IVF laboratories, and some patients even have all their embryos cryopreserved initially to lower the risk of complications (Devroey *et al.*, 2011). Cryopreservation represents a novel selection barrier for embryos, as surviving a freeze-thaw cycle is crucial for the fitness of the thus treated embryo.

Implantation

After Brosens *et al.* (2014) showed how the endometrium acts as a biosensor towards the embryo and how developmentally competent embryos emit signals to the endometrium that activates its contribution to implantation, the endometrium can no longer be considered to have only a passive role in implantation (Lessey and Young, 2019). Whether the endometrial biosensor function is altered in IVF is unknown, yet variation in IVF protocols has an impact on endometrial gene expression and timing (Humaidan *et al.*, 2012; Zapantis *et al.*, 2013; Hernández-Vargas *et al.*, 2020). Endometrial decidualization could also function as a modulator of implantation, possibly mediated through hormonal levels (Lucas *et al.*, 2013). The endometrium thus constitutes a selective environment for arriving embryos, and phenotypic differences between embryos determine whether they are accepted for further development or discarded. One recent paper examined whether prenatal adversity, such as famine, causes selection on embryo phenotype *in utero*, and concluded that what occurs in this situation is indeed maternal selection between embryos, rather than a physiological reaction in the embryo in response to the current intra-uterine conditions (Tobi *et al.*, 2018).

Early development and miscarriage

Though it is unlikely that the intrauterine environment from about Week 12 of pregnancy onwards differs systematically between the two modes of reproduction, the opposite is the case from the time of

transfer of the embryo into the uterus and until Week 12 of pregnancy. The impact of this early intrauterine environment on the developmental trajectory of a therein implanted embryo has been investigated intensely in recent years. Though it did not focus specifically on evolution, a recent review of developmental origins of health and disease by Fleming *et al.* (2018) asserted that '(...) assisted reproductive treatments can change the phenotype and potential of gametes and early embryos, with enduring consequences across the lifespan'. For the developmental effects acquired during early pregnancy to persist into adulthood, the affected embryos must pass the 'quality control' system of miscarriage. Miscarriage has been conceptualized as a safety valve to ensure that whatever happens upstream in the reproductive process, the continued maternal investment in an embryo depends on it passing maternal quality control; as many as 30–40% of all implanted embryos fail to develop into an ongoing pregnancy (Macklon *et al.*, 2002). The available data on miscarriages after IVF and reproduction by coitus indicate that IVF pregnancies are miscarried at the same rate and for the same reasons as in reproduction by coitus (Farr *et al.*, 2007). Considering the profound differences between IVF and coital reproduction upstream of the selective hurdle that early pregnancy loss represents, this quality control might be very favourable to IVF practice in that many of the most unwanted consequences that one could fear from IVF practice, such as a grossly increased risk of genetically or epigenetically mediated diseases in IVF children, have not materialized.

Still, maternal control over offspring has its limits, and the embryo is not a passive bystander in early development. To the contrary, at this step of the reproductive cycle the fundamental conflict between the interests of the foetus and those of the mother become evident (Haig, 1993). In short, the interest of the foetus is to extract as many resources as possible from the mother to maximize its chance of conveying its own set of genes to future generations. The mother, on the other hand, is inclined to 'hedge her bets' (Simons, 2011), limiting her investment in the individual foetus to maximize her own long-term reproductive fitness by having more children later on (Vitzthum, 2009; Trivers, 2015). In this respect, the fact that human preimplantation embryos possess mechanisms that affect their own chances of implantation (Berkhout *et al.*, 2018) and successful early development (Vinketova *et al.*, 2016) could be considered an early sign of the widespread ability in organisms to manipulate the ambient environment to their own benefit. In general, traits that enable the individual to manipulate or modulate the environment to promote its own survival and reproductive fitness are highly beneficial to the individual. Such manipulation of the environment to one's own benefit is a central feature in Dawkins' concept of the extended phenotype (Dawkins, 1982) and is fundamental to the evolutionary phenomenon of niche construction (Laland *et al.*, 2016). Lately, a broader evolutionary theory called the extended evolutionary synthesis was proposed, wherein various aspects of the extended phenotype and niche construction play a more central role (Laland *et al.*, 2014), and there have been efforts to link the extended phenotype to aspects of culture in both humans and animals by analysing culture as an extension of biology (Whiten *et al.*, 2017). Clearly, the influence between the individual and the environment is reciprocal (Cronk, 1991; Kaplan and Lancaster, 2003; Sear

et al., 2016), and the study of how the environment in turn influences human fitness pertains to the scientific field of human reproductive ecology (Ellison, 2001; Vallengia and Núñez-de la Mora, 2015). The processes whereby embryos promote own fitness by manipulating the maternal environment have, as other traits, evolved by iterative cycles of variation, selection and replication, and promotion of own fitness continues throughout the lifespan of the individual. It is particularly prominent in the next step of the reproductive cycle, that of competing for a mate with whom to reproduce.

IVF changes selection pressures on adults

Sexual selection and partnership formation

The competition for a mate with whom to have sex and offspring is likely the one step in the human reproductive cycle in which biological and cultural evolution interact most clearly, and this is also true for other animal species (Whitehead *et al.*, 2019). Different species have specific traits that serve as proxies of fitness and thus are strongly selected for by so-called sexual selection in both males and females (Jones and Ratterman, 2009; Tobias *et al.*, 2012; Alonzo and Servodio, 2019). Darwin himself acknowledged the strong selective powers of sexual selection that 'depend not on a struggle for existence, but on a struggle between the males for possession of the females; the result is not death to the unsuccessful competitor, but few or no offspring' (Darwin, 1859). The struggle to become the selected partner for reproduction amongst a variety of potential mates may come with large costs in terms of energy expenditure or survival (Promislow, 1992). While surviving to reproductive age is a requirement for reproduction, reproductive fitness in several species also depends heavily on signalling high genetic quality by status-related physical attributes, such as large antlers, striking colours or the peacock's tail, anatomical features that are sometimes, paradoxically, detrimental to survival. Perhaps even more striking than the physical organs used to attract a partner are courtship behaviours such as birdsong, ritualized dances and object display (Martin *et al.*, 2008; Buss and Schmitt, 2019). Displaying these signals makes the individual more attractive for a potential partner. Yet they remain only signals, and some traits that are interpreted as attractive could in fact be detrimental to the survival and fertility of offspring in the long term (Harvey and Arnold, 1982; Jones and Ratterman, 2009; Goodman *et al.*, 2012).

Compared with those of other species, human survival and resource acquisition require a high level of cognitive (Hill *et al.*, 2009) and social skills (Adolphs, 1999). Accordingly, the selection for such abilities has been intense in humans (Kaplan and Robson, 2002; Richerson and Boyd, 2020). When deliberating between mates, humans judge the reproductive fitness of potential mating partners not only by physical traits such as facial attractiveness (Barber, 1995), female breast size (Dixson *et al.*, 2015) and male grip strength (Skirbekk *et al.*, 2018) but also by consideration of traits on display that are primarily cognitive, such as the perceived ability of the other to acquire resources (Buss, 1989; Miller, 2000; Buss and Schmitt, 2019). It is hypothesized that

sexual selection for cognitive traits was instrumental to the historical rapid increase of brain size in humans, yet exactly which cognitive traits are preferred in human sexual selection is debated (De Block and Dewitte, 2007). One possibility is that human resource acquisition is increasingly dependent on spending several potentially high-fecundability years obtaining a formalized and lengthy education (Kc et al., 2010), and higher education is also associated with, though perhaps not causal in, survival and longevity (Pettay et al., 2005; Case and Deaton, 2021). While beneficial for resource acquisition, mate value (Jonason and Antoon, 2019) and survival (Strand et al., 2010), extended education was also shown to be associated with decreased fertility (Rindfuss et al., 1980), mediated in part by delayed reproduction (Ní Bhrolcháin and Beaujouan, 2012; Nitsche and Brückner, 2021). Thus, while a lengthy education could be beneficial for wooing a desired long-term mate in a knowledge-based economy (De Hauw et al., 2017), the associated delayed reproduction is detrimental to fecundability and lifetime number of offspring (Leridon, 2008; Mills et al., 2011; Hayward et al., 2015). In other words, some individuals in modern societies find themselves in a squeeze between the pressure from sexual selection to delay reproduction on the one hand and the resulting reduced lifetime number of offspring on the other. Faced with this trade-off, IVF could offer a third way out by increasing the reproductive fitness of the delayed reproducers to the level of their early reproducing peers, thus enabling individuals to circumvent the dilemma between attractiveness and number of offspring. While this attractiveness argument may have a gender bias (Buss and Schmitt, 2019) and clearly should not be stretched too far (Verweij et al., 2020), it is one of several cultural-biological interactions in human reproduction in which IVF is an enabling technology to circumvent otherwise inescapable trade-offs between cultural and biological influences on human reproductive decisions. In fact, some studies from the Nordic countries, where income disparity is low and IVF is often subsidized by the state, show that IVF parents score well above average on markers of cognitive ability (Bratsberg et al., 2020), socio-economic status (Goisis et al., 2020) and extended education (Goisis et al., 2020). Assortative mating, the tendency of individuals to form a partnership with other individuals from similar backgrounds, will likely sharpen these differences (Mare, 1991; Greenwood et al., 2014). Furthermore, children born to older mothers in some studies show improved educational performance (Barclay and Myrskylä, 2016), and IVF children score slightly better on measures of cognitive development according to some data (Barbuscia and Mills, 2017). Thus, while the causes underlying the educational and socio-economic gradients in IVF usage are of course not limited to sexual selection (Greely, 2016; Te Velde et al., 2017), how the selection for and replication of the primarily cultural trait of postponement of reproduction increases the demand for IVF should not be overlooked. By enabling individuals that are culturally inclined to postpone reproduction to increase their lifetime number of offspring to the level of their peers, IVF influences human cultural evolution. Simultaneously, due to the differences in pre- and postzygotic selection pressures between the two modes of reproduction outlined above, the cultural trait of postponed reproduction by IVF conveys feedback on biological evolution, as outlined in Fig. 3. Such gene-culture co-evolution is well documented in humans in other fields, such as metabolism (Laland

et al., 2010; Richerson et al., 2010; Laland et al., 2016), as well as in other animal species (Whitehead et al., 2019).

Female reproductive decisions

While formation of partnerships is important for human reproduction, reproductive decisions within a couple also constitute a crucial step in the human reproductive cycle (McAllister et al., 2016). Reproductive decisions within a partnership are of increasing importance for lifetime fertility and timing of births in modern societies (Stein et al., 2014; Boivin et al., 2018), and more often than not it is the female who has the final say in these decisions in modern couples (Stein et al., 2014). The timing of first reproduction varies between females and, when considered together with interbirth intervals, is often referred to as a female reproductive strategy (Benagiano, 2002; Cornwell et al., 2006; von Rueden and Jaeggi, 2016). There is selection between and inter-generational replication of reproductive strategies in humans (Pluzhnikov et al., 2007; Kolk et al., 2014; Zietsch et al., 2014; Branje et al., 2020), and the genetic basis of human reproductive strategies was investigated in recent studies on the genetics of infertility and lifetime number of offspring (Barban et al., 2016; Day et al., 2016; Mills

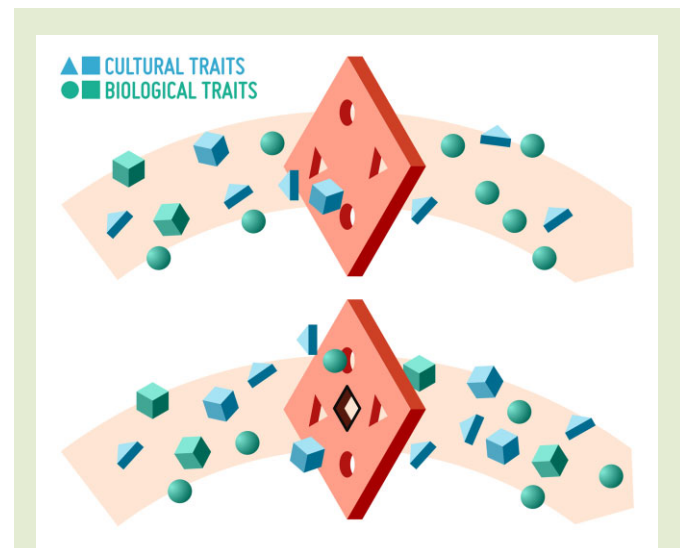


Figure 3. IVF influences the selection of biological and cultural traits. As in Fig. 1, the different shapes in Fig. 3 represent different traits under selection. Green shapes are biological traits such as looking healthy (green spheres) or low semen quality (green cubes). Blue shapes are cultural traits such as being kind to others (blue triangles) or delayed female reproduction (blue cubes). The upper part of the figure shows human reproduction without IVF where no cubes pass the selective barrier. The lower part of the figure shows human reproduction with IVF as an enabling technology, represented by the square opening with black lining. Here IVF allows the cubes, both blue and green, to pass the selective barrier. The evolutionary outcome of this technologically induced change in the barrier's holes is an increased prevalence of the traits represented by cubes.

et al., 2021). As is often the case with complex traits (Holtzman, 2002), the contribution to the phenotype from each of the associated genetical loci was quite small. However, from the perspective of gene-culture co-evolution, it is notable that the genes with the strongest association with reproductive strategies were those that are also known to affect human reproduction at other steps in the reproductive cycle, such as genes involved in FSH signalling and oocyte development (Mills *et al.*, 2021), supporting the notion that biological and cultural factors interact in human reproduction (Verweij *et al.*, 2019; Berg *et al.*, 2020). Another study focused on how genetic influences on reproductive behaviour are modified by the cultural environment (Tropf *et al.*, 2017), concluding that there is large variation in the extent to which the genetic effects that underlie reproductive behaviour in one population are predictive of reproductive behaviour in another population. Although none of these studies explicitly take IVF into account, it seems reasonable to assume that IVF modifies the cultural environment in which reproductive behaviour takes place (Mac Dougall *et al.*, 2013), thus influencing selection pressures on different reproductive strategies. In short, 'a gene for' having children late is probably under less negative selection pressure in populations where IVF is available.

The variation, selection and replication of reproductive strategies in individuals have population-level consequences (Balbo *et al.*, 2013). Throughout most of human history, the dominant reproductive strategy in humans was to maximize the number of offspring permitted by the resources available in the surrounding environment. As with other species, this reproductive strategy demands trade-offs between the number of offspring to support and their likelihood of surviving to proliferate heritable information into the next generation. With high child mortality, a large number of offspring was the default human reproductive strategy. More recently, the preferred reproductive strategy in some human populations started shifting towards having fewer children (Sear *et al.*, 2016). Demographers use the term 'The demographic transition' to describe the general trend in which an increase in economic output is accompanied by a decrease in reproductive output. The transition from a low-income/high-fertility setting into a high-income/low-fertility setting occurs both at the country level and generally for more privileged groups within nations (Lesthaeghe, 2010), but see also (Myrskylä *et al.*, 2009). Given the biological imperative of turning resources into offspring, both the origin and the spread of the demographic transition contains several evolutionary paradoxes (Colleran, 2016; Sear *et al.*, 2016; Stulp and Barrett, 2016), as does the current maintenance of low-fertility behaviour in many rich countries. The demographic transition is one of many examples of what can be considered an evolutionary mismatch between traits that have evolved over human evolutionary history and those favoured by the current environment (Gluckman *et al.*, 2019). The modern obesity epidemic is another oft-cited example of such evolutionary mismatches (Qasim *et al.*, 2018), and maladaptive traits are often a result of the widely different timescales of biological (slow) and cultural (fast) evolution (Gluckman *et al.*, 2019). Apart from maladaptation, another evolutionarily plausible explanation for the origin and spread of the demographic transition concerns the shift in which it confers a long-term fitness advantage for parents to direct their energy investments towards fewer offspring but with a higher investment per child as

societies develop economically and child mortality declines (Lawson and Bergerhoff Mulder, 2016; Stulp *et al.*, 2016). Of particular interest in this regard is how fertility and parental investment has varied in traditional and modern human societies (Kaplan, 1996), how small family sizes evolved (Ihara and Feldman, 2004; Lawson and Mace, 2011), and the evolutionary dynamics of culturally transmitted traits that reduce the number of children that a female gives birth to (Wodarz *et al.*, 2020). In a demographically transitioned society with small families, couples using IVF could be seen as showing adaptation to an environment that favours having children at an advanced age (Aarssen, 2005). In addition, the very fact that IVF is being used by so many removes some of the taboos once associated with needing help to conceive, making IVF more culturally acceptable and a normal part of a country's health service (Inhorn and Birenbaum-Carmeli, 2008). This is not to say that IVF is causal in demographic transitions nor the main reason for maintenance of behaviours that lead to a low number of lifetime offspring in some populations (Stulp and Barrett, 2016). Yet it is clear that also on a population level, IVF is a technology that counteracts the reproductive disadvantages pertaining to the cultural trait of giving birth later, thus offering a technological bypass to the evolutionarily speaking maladaptive strategy of delayed reproduction. In a key example, one recent paper reported data from Israel in which a natural experiment facilitated the study of changes in female reproductive behaviour caused by making IVF more available to the population (Gershoni and Low, 2021). The paper describes how the state-funded policy of free-of-charge IVF in Israel was causative in increasing age at first birth in that country (Gershoni and Low, 2021). In other words, the reproductive timing in females in Israel was affected by the availability of IVF in their environment, an association also found in data from the USA (Machado and Sanz-de-Galdeano, 2015). As there is a tendency for offspring to copy the reproductive strategy of their parents (Pettay *et al.*, 2005; Steenhof and Liefbroer, 2008), we speculate that the longer-term effect of this could again contribute to a self-reinforcing tendency to delayed reproduction by IVF. If so, then Israel's legislation concerning IVF and its' funding, originally put in place to nudge more people into having more children and earlier, might in fact end up giving an opposite effect, in part due to gene-culture interactions.

We reiterate that a tendency for IVF to induce more IVF is, if proven, not necessarily a problem. Clearly, the technological development and expansion of IVF have several positive implications for males and females alike, as IVF to a certain degree (Habbema *et al.*, 2015) alleviates couples from the trade-off between postponing childbirth or postponing their careers. The assisted reproductive technologies that make this possible have also expanded beyond conventional IVF. At the gamete-stage for example, children have now been born after activation of dormant follicles in postmenopausal ovaries (Kawamura *et al.*, 2013). Elective egg freezing, the option for a woman to cryopreserve her oocytes before reaching reproductive senescence, is marketed as another possibility for minimizing the effect of the passage of time on female reproductive output, yet see Bozzaro (2018) and Pennings (2021) for a discussion of the cultural background and implications of this practice. At the embryo-stage, the technology is now in place to screen preimplantation embryos for a number of polygenic

traits, giving patients the possibility to deselect embryos for transfer into the uterus that are genetically predisposed to certain traits (Lello *et al.*, 2019; Turley *et al.*, 2021). Finally, for adults, certain offshoots of IVF technology, such as gamete donation and surrogacy, have enabled a detachment between parenthood and the biological imperative of maximizing the transfer of genes into the coming generations, a development that has a separate evolutionary dynamic (Hamilton, 1964). We recognize that some of these examples apply to very few cases, and some must even be considered experimental and may never become part of routine IVF practice. Yet they are relevant to bring up as illustrative examples of how future technological advances could facilitate further changes in human reproduction, a development that has memorably been suggested as a conduit towards the end of human reproduction by coitus (Greely, 2016).

Environmental hazards

In the cycle of human reproduction shown in Fig. 2, we have now come full circle back to the spermatozoa, and the differences between the individual spermatozoa selected for fertilization in IVF and coitus have already been discussed. Yet IVF affects not only the selection of the phenotype of a spermatozoon in an ejaculate that fertilizes the oocyte but also which phenotype of a male makes a female pregnant. This is so as it is becoming increasingly clear that semen quality is declining, at least in some parts of the world (Levine *et al.*, 2017). The causes of this decline are probably multiple and affect individuals to a varying degree, yet several recent papers point to environmental factors, such as exposure to endocrine-disrupting chemicals either *in utero* or *ex utero*, as major contributors to the decline (Skakkebaek *et al.*, 2016; Sharma *et al.*, 2020; Istvan *et al.*, 2021; Le Moal *et al.*, 2021). Prominent researchers of human semen quality have proposed that a 'tipping point' in semen quality could be on the horizon, after which there would be a gross increase in male factor infertility in the affected populations (Andersson *et al.*, 2008). Since the number of spermatozoa in a human ejaculate is typically very high, there is substantial room for decrease in semen quality before the average semen sample falls below the 20–40 million/ml mark that indicates increased risk of male infertility in reproduction by coitus (Skakkebaek *et al.*, 2016). The threshold for semen quality to reproduce by IVF is far below that of coitus, however, as an experienced ICSI professional may require only some hundred spermatozoa in an ejaculate to fertilize all the oocytes supplied by one typical oocyte retrieval in IVF. Thus, where available and accessible, reproduction by IVF/ICSI markedly lowers the tipping point for what may be considered a semen quality that affects the chance of making a female pregnant compared with reproduction by coitus. In other words, IVF/ICSI allows males to bypass the disadvantages to reproductive fitness accrued by environmental pollution by endocrine disruptive chemicals (Liffner *et al.*, 2021). By doing so, IVF is enabling the maintenance of the environment that led semen quality to decrease in the first place, an effect similar to the case with delayed reproduction in females. The extent to which declining semen quality should be seen as a trait affected by culture can of course be debated. It depends not least on where one draws the line between our cultural and natural environments (Valeggia and Núñez-de la Mora, 2015).

Discussion

Detectable effects of IVF on human evolution

Putative consequences of IVF in IVF offspring have been a matter of concern and debate for a long time (Engel *et al.*, 1996), and there is a rich and expanding literature regarding the health of IVF offspring (Berntsen *et al.*, 2019). Because of the short time since the first ever baby was born after IVF in 1978 (Steptoe and Edwards, 1978), there is still little data available on the reproductive health and risk of infertility in IVF offspring (Berntsen *et al.*, 2019; Ernst *et al.*, 2019; Rumbold *et al.*, 2019). If long-term monitoring finds evidence of effects of IVF on human reproduction either within or across generations, there could obviously be both biological and cultural reasons for this. What this review adds is a broader view of human evolution in the context of IVF, addressing some of the interactions and self-reinforcing effects in this setting between cultural and biological evolution. However, as IVF is a recent technology, the empirical data available to examine the putative evolutionary outcome of IVF cover, at best, only one generation of alterations in the variation, selection and replication of biological and cultural information.

Consider first the detectable effects of IVF on human evolution conveyed by differential selection of spermatozoa, carriers of paternal information across generations. Paternal effects on children's health are well established (Oldereid *et al.*, 2018), and a recent review concerning health and development in ICSI offspring did show evidence of impaired spermatogenesis in young males born after ICSI (Rumbold *et al.*, 2019). Admittedly, the data showing reduced sperm quality in sons of ICSI fathers are scarce (Belva *et al.*, 2016), and the pathophysiology underlying this association is not established (Belva *et al.*, 2017). Still, a genetic basis for the putative decreased fertility in sons of ICSI fathers, such as transmission of Y-chromosome microdeletions, is one possibility not ruled out by the limited data that does exist (Katagiri *et al.*, 2004). The role of proteins contained in the spermatozoon likely extends beyond motility and the penetration of the oocyte by playing a role in the developing embryo (Jodar *et al.*, 2013; Castillo *et al.*, 2018; Marcho *et al.*, 2020), and there is evidence that epigenetic differences in spermatozoa are associated with different diseases in offspring (Wei *et al.*, 2015; Garrido *et al.*, 2021). Nonetheless, the molecular mechanisms by which sperm RNA conveys heritable information through embryogenesis and early development are unclear (Sciamanna *et al.*, 2019; Zhang *et al.*, 2019).

Regarding detectable effects of IVF on human evolution mediated through differential selection of oocytes, it is well established that IVF follicles are different from non-IVF follicles. Analyses of the cellular and fluid components of follicle fluid from follicles that are punctured after controlled ovarian stimulation for IVF compared with those from the non-IVF cycle show marked differences in terms of intrafollicular concentration of several hormones (von Wolff *et al.*, 2014) and cytokines (Kollmann *et al.*, 2017), as well as differences in the transcriptome of granulosa cells (Zhang *et al.*, 2018). Furthermore, two studies reported that some anthropometric traits, obesity in particular, are associated with changes in oocyte phenotype, such as oocyte size, within an IVF programme (Leary *et al.*, 2015; Weghofer *et al.*, 2019). While this is

indicative of effects of IVF on female gametes, it stops short of showing effects in offspring of the milieu in which oocyte development and selection has taken place. Again, the physiology of oocyte maturation and selection is complex, and research on human oocytes is limited by the lack of available specimens (Brayboy and Wessel, 2016).

Concerning the evolutionary effect of IVF on embryos, early work on the effects of embryo growth media on IVF offspring focused on differences in birthweight (Dumoulin *et al.*, 2010), and subsequent studies established that the retrospectively observed effect on birthweight was also present in prospective studies (Kleijkers *et al.*, 2016), an effect that is likely epigenetically mediated (Kleijkers *et al.*, 2015). Along the same lines, an effect of embryo culture media on pregnancy, birth and child development through parentally imprinted genes in the placenta was postulated, but a recent study reported no difference in mean DNA methylation status between placentae from two different media (Mulder *et al.*, 2020). Regardless of parental or embryological origin, the evidence for epigenetic differences between IVF offspring and coitus offspring is expanding (van Montfoort *et al.*, 2012; Lazaraviciute *et al.*, 2014; Castillo-Fernandez *et al.*, 2017; Novakovic *et al.*, 2019), though the phenotypical implications for the adult IVF offspring are not clear (Magnus *et al.*, 2021).

The detectable evolutionary effects of IVF on early intrauterine development, partnership formation and female reproductive choices were discussed earlier, outlining how the use of IVF is self-reinforcing (Alon *et al.*, 2021). Furthermore, in populations in which IVF is used to increase the reproductive fitness of patients with medical conditions that lead to reduced fecundability, the prevalence of these conditions in the population could increase as long as the medical conditions in question have a heritable component, as is the case for polycystic ovary syndrome (Vink *et al.*, 2006; Charifson and Trumble, 2019) and endometriosis (Montgomery *et al.*, 2020; Dinsdale *et al.*, 2021), for example. This impact of medical care on reproductive fitness is of course not unique for IVF, as survival into reproductive age is an essential component of reproductive fitness, and one that contains selective pressures of its own (Jones, 2009; Jones and Tuljapurkar, 2015). Thus, giving antibiotics to a childless man with pneumonia that would be lethal unless treated also affects his reproductive fitness if he later goes on to have children. IVF is not alone in counteracting selection pressures on humans compared with a situation without efficient health care (Lynch, 2016; Mitteroecker *et al.*, 2017). In some animal populations, such 'shielding' of otherwise deleterious variations resulted in relaxed selection (Lahti *et al.*, 2009), an effect that has also been proposed to occur in humans (Varki *et al.*, 2008; You and Henneberg, 2018). We reiterate that this perspective of modern medical care is merely descriptive and does not imply any normative bearings, as we hold it as obvious that diseases with heritable components should be treated with the best cures available. It is also notable that even in a scenario where IVF use is self-reinforcing, it is perhaps not a likely chain of events that IVF downright outcompetes coitus as a mode for reproduction in humans, for several reasons. One reason is how IVF, for example in age-related female infertility, can be viewed as a method to merely concentrate several months' worth of oocytes, thus simply accelerating a conception that would anyway have occurred later on. After all, the pregnancy rates after IVF in females above

40 years of age that use their own oocytes remain low, and in a computer simulation IVF availability did not have a large impact on when a couple should start building a one child family to have a 50% chance of achieving one (Habbema *et al.*, 2015). Another reason why coitus will probably remain the dominant mode of human reproduction is because evolutionary theory states that traits conferring a high reproductive output will outcompete traits that lead to low reproductive output. Thus, a population composed of individuals with a susceptibility to infertility who need technological assistance in the form of IVF to reproduce is unlikely to reproductively outcompete individuals from other populations. Yet, as Collins and Page (2019) write: 'However, changes in the environment can change the way in which genetically based variation in traits may affect fitness'. One prominent example of such environmental change could be a change in preference for number of lifetime offspring. Finally, when discussing the possible evolutionary outcomes of IVF in humans it is important to keep in mind the distinction between studying selection and predicting evolution (Morrissey *et al.*, 2010). Several methods and equations have been developed to measure the effect of phenotypic and genetic variation on fitness, typically showing that the effect of any single trait on fitness is low (Stearns *et al.*, 2010), and slow (Beauchamp, 2016). Nevertheless, the enabling technology of IVF exerts its' effects on fitness in an unusually direct manner, and at several key steps in reproduction, and could therefore impact human evolution over fewer generations than is usually required.

Replication and heritability

This review emphasizes the selection step in the iterative cycles of variation, selection and replication that leads to evolution, and so far in this review, these three steps have been presented as separate processes in evolution to establish conceptual clarity. Yet it is clear that in nature the dynamic between the three steps is more complex. One example is that much genetic variation is in fact the result of imperfect replication, so the two processes of variation and replication are intertwined. It could also be argued that far from all of the selectable variation outlined herein will pass the replication step in evolution. Firstly, even if all individual IVF offspring were born with decreased fecundability (as seems unlikely), this tendency could disappear in the next generation if they form a partnership with someone who is a coitus offspring, and then they themselves reproduce by coitus (as seems likely, as only about 4% of all children born in Norway each year are IVF children, for example). Secondly, there are some reasons to believe that the increase in proportion of children born after IVF each year will soon level off. Although reproduction by IVF has its advantages, it remains a medical treatment with risks of medical complications and side-effects, particularly for females, and IVF incurs financial and emotional costs that are significant, especially when compared to coitus (van Eekelen *et al.*, 2019). Also, historical data point to a prevalence of infertility of only 3–5% given sufficient exposure to coitus (Eijkemans *et al.*, 2014). Third, we have alluded to not only genetic but also to both epigenetic and cultural modes of replication thus far. The effects of epigenetic inheritance, through changes in methylation patterns or otherwise, is as a general rule limited to act on a maximum of three consecutive generations. Cultural inheritance by social learning

may affect even fewer consecutive generations and has a low fidelity of replication over time (Danchin *et al.*, 2019). When considering the replication step in human evolution, it is useful to bear in mind the complexity of inheritance. One intuitive understanding of heritability is that it is what makes offspring resemble their parents (Danchin *et al.*, 2019), yet discernible and oftentimes conflicting concepts of heredity exist. As one example, Helanterä and Uller (2020) outline three concepts of heredity: as transmission, as phenotypic covariance and as a developmental process. While a discussion of the nature of inheritance in humans is beyond the scope of this review, we acknowledge that the replication in future generations of some of the herein proposed effects of IVF on human evolution demands a more inclusive view of heritability than a strictly gene-centred approach (Danchin *et al.*, 2011, 2019; Kronfeldner, 2021), as the evolution of human culture both within and across generations relies heavily on social learning as the mechanism of replication (Olsson *et al.*, 2020; Kuijper *et al.*, 2021; Singh *et al.*, 2021).

Social learning aside, there is evidence to suggest that evolution also operates through epigenetic mechanisms (Jablonka, 2017; Wang *et al.*, 2017; Senaldi and Smith-Raska, 2020; Ashe *et al.*, 2021), but see also (Isbel and Whitelaw, 2015). Selection is not only a matter of the environment strictly selecting the fittest genotype through selection, but it also involves developmental cues operating during ontogeny, some of which are epigenetic (Deans and Maggert, 2015; Skúlason *et al.*, 2019; Baedke *et al.*, 2020). Between generations, replication is affected by epigenetic modification of the genotype with consequences for the phenotype through ontogeny (Sultan, 2017). Epigenetic modifications are known to be replicated across a few generations (Miska and Ferguson-Smith, 2016; Cavalli and Heard, 2019) and may in rarer cases also be fixed (Horsthemke, 2018). Still, an epigenetic change rarely directly affects a genome sequence, and although it may be transmitted for one or two generations, it is generally not fixed in the germ line and should thus not be seen as a Lamarckian way of evolution (Danchin *et al.*, 2019). Yet early life effects, whether they occur *in utero* or in early childhood, leave their mark on the later development of the individual and may span generations, replicating the effects of altered selective environments in IVF into future variants for selection (van Montfoort *et al.*, 2012; Bohacek and Mansuy, 2015; Coall *et al.*, 2016; Danchin *et al.*, 2019; Bar-Sadeh *et al.*, 2020). If we incorporate the cultural dimension into epigenetic inheritance, the information dynamics becomes even more complex (Jablonka, 2016). On the one hand, there is compelling evidence that genetic and epigenetic factors influence the way we think (Day and Sweatt, 2011; Plomin *et al.*, 2013) and behave (Plomin *et al.*, 2016; Liberman *et al.*, 2019). On the other hand, cultural traits, such as diet or cigarette smoking, induce changes in both genes and epigenes in the individual and in the offspring of the pregnant individual (Choi and Friso, 2010; Xavier *et al.*, 2019), with long-lasting effects on offspring lives, as evidenced by twin studies (Bell and Spector, 2011). Thus, instead of one component (e.g. the genome) exerting exclusive control over another (e.g. the phenotype), causation also flows back from more complex levels of organization, such as behaviour, to gene structure and gene expression, and epigenetic change is a mediator that can have wide-ranging consequences for behaviour and physiology (Kuijper *et al.*, 2019).

Different units and timescales of evolution

A fundamental problem often encountered in evolutionary biology is how to deal with different units of selection. This review is no exception, considering the discussion of units of selection as diverse as spermatozoa, males with decreased semen quality, and demographically transitioned females inclined to have children late in life. Clearly, the selective pressures experienced by these varying units come with their own set of assumptions concerning, for example, reproductive fitness. The fitness of a spermatozoon depends on it penetrating an oocyte. The fitness of a male with low semen quality depends on access to a partner, and so on. These varying assumptions limit the generalizability of the findings from one unit of selection to the other, and this issue is not easily solved (Danchin *et al.*, 2019). A further challenge is that, whereas biological evolution typically requires generations and centuries to manifest, cultural evolution often occurs on a timescale of years or decades. Moreover, not all phenotypic plasticity at the cellular or the individual level that occurs due to changing environments directly affects human evolution. Organismal plasticity also includes physiological responses that occur on timescales ranging from milliseconds to years. How human plasticity on different timescales affects human health, long-term fitness and ultimately evolution is a central discussion in modern evolutionary medicine (Wells *et al.*, 2017). Life history theory, another branch of evolutionary biology, provides a framework for understanding how plastic responses to environmental changes are linked to evolution (Stearns, 2000; Vitzthum, 2009; Hochberg and Belsky, 2013; Wells *et al.*, 2016). The interplay between human reproduction and human culture under the lens of evolutionary theory is fundamental in various fields of science such as human behavioural ecology and evolutionary psychology (Brown *et al.*, 2011).

Finally, in emphasizing the selective arenas in human reproduction where the differences between IVF and coital reproduction are most pronounced, we run the risk of overlooking important selective arenas that do not differ between the modes of reproduction. After all, for any oocyte, the most important selective hurdle is to be timely recruited from the pool of dormant primary follicles, and for any spermatozoon, it is to be ejaculated into a vagina or, less commonly, into a cup at an IVF clinic. Although we maintain that there are clear differences between the oocytes selected for reproduction in IVF and coitus, if we consider a reproductive lifespan of the female from age 15 to 45 years, with about 30 years of a maximum 12 ovulations per year, this amounts to 400 mature oocytes being released from the ovary over the female life course, allowing for some duo-ovulatory cycles. In other words, there is a 1 in 1000 chance for an oocyte present in the genital ridge to undergo ovulation, and a 1 in 200 000 chance for the oocyte to contribute to a child if the woman goes on to have two children (Stearns, 2005). These latter numbers are not significantly changed by IVF, and a similar argument could be made for spermatozoa. Thus, randomness remains as an important factor in human reproduction by IVF, though there are indications that the dice of biological randomness are more loaded than is often presumed (Noble, 2017).

Nevertheless, evolution is a defining property of life, and although there are certainly limitations to our current understanding of the mechanisms and drivers of human evolution, these limitations do not

imply that the evolutionary perspective on human reproduction should be ignored. In our view, the methodological and conceptual challenges of viewing human IVF through the lens of evolutionary theory should instead be considered an incentive for further research into how IVF is affecting human evolution.

Conclusions and future perspectives

Reproduction goes to the heart of evolution, and so when we influence reproduction, we influence evolution. Parting from this intuitive principle, this review outlines how reproduction occurs in a framework of populations, couples, individuals and cells, and describes how the evolutionary principles of variation, selection and replication apply to and affect this framework. Thus, to review the interactions between IVF and human evolution is to point out how IVF is different from reproduction by coitus at different levels of analysis, focusing on the differences that influence selection pressures. We underline that the main effect of IVF on human evolution is a systematic change in selection pressures at various stages of the human reproductive cycle, and we show how this leads to a systematic shift in the differential replication of variants of both cultural and biological information. As IVF is a recent technology, little empirical data are yet available to confirm or reject the proposed measurable outcomes of this shift in selection pressures. In sum, we argue that IVF facilitates the redirection of organismal resources from reproduction towards other facets of the human life cycle, since so many of the constraints that coital reproduction entails are affected or even bypassed by IVF. Thus, IVF sets the evolutionary stage for a human species that is increasingly reliant on, and adapted to, technological means of reproduction.

Data availability

No new data were generated or analysed in support of this research.

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Authors' roles

H.I.H. and D.O.H. wrote the manuscript, revised it and approved the final version.

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Conflict of interest

H.I.H. and D.O.H. declare that they have no conflict of interest concerning this review.

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