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SYMPOSIUM: REPRODUCTIVE TECHNOLOGIES AND THE CONCEPTUALISATION OF THE BIOLOGICAL CLOCK
ORIGINAL ARTICLE

The making of 'old eggs': the science of reproductive ageing between fertility and anti-ageing technologies

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Abstract This article proposes going back in the history of reproductive medicine to shed light on the role of assisted reproductive technology (ART) in the making of 'old eggs'. Focusing on two key technologies — egg donation and cytoplasmic transfer — both of which contributed significantly to the production of scientific knowledge about reproductive ageing, the article suggests that ART can be analysed as 'in-vivo models' playing a pivotal role in the shift from age as a demographic variable to ageing understood in biological terms. It will shed light on the role of ART in locating age in the eggs and producing a cellular understanding of fertility decline. It argues that ART not only offers new means of reconfiguring the biological clock by extending fertility, but also reconfigures the biology of reproductive ageing itself. This becomes both the target and the means for new technological interventions, imaginaries and norms, anchored in women's bodies and a more plastic biology, and thereby illuminates hitherto underexplored aspects of the encounter between the science and technology of reproduction and anti-ageing.

KEYWORDS: ageing, biological clock, biologization, fertility decline, reproduction, reproductive technology

Introduction

A quick Internet search on egg freezing leads to a visual repertoire of eggs on ice, in ice cubes, made of gold, tenderly protected or ready to hatch a happy baby into the light. Within reproductive biomedicine, freezing or vitrification technology represents a new strategy for extending or preserving fertility for women undergoing cancer treatment and those anticipating age-related fertility decline (Cobo et al., 2013) or gamete exhaustion (Stoop et al., 2014). With

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the promise of solving the problem of the 'biological clock', the procedure has become more visible since its experimental label was removed in 2013 (ASRM and SART, 2013). A similar visual repertoire of eggs is also used in the public sphere to refer to egg quality. This concept is often presented as key to age-related infertility, with egg freezing being one of the main ways to preserve it (ColoCRM, n.d.; Extend Fertility, 2019; Sekhon, 2020). However, egg quality, sometimes used synonymously for 'healthy strong eggs' (Holland, 2018), and differentiated from the complementary notion of 'egg quantity' (Sekhon, 2020), takes centre stage along with the promotion of less medicalized and low-tech solutions.

In blogs by natural therapists, biomedical practitioners and women themselves, eggs are often represented on a timeline as changing shape, colour and matter with age (Holland, 2018), in the opposing categories of young and old (MacIsaac, 2018), or with a cracked shell in need of repair (PremamaWellness, n.d.). These images are rooted in a concern for fertility decline with ageing. However, more than chronological age itself, it is the quality of eggs which stands out. If age cannot be changed and there is 'no way to turn back the clock,' it can be 'slowed down' (Sekhon, 2020) and egg quality 'boosted' (Caroline, 2019), 'improved' (Jacqueline, 2017) or 'influenced' to 'make eggs younger' (Sumner, 2017). To counter the 'walking time bomb about to tilt', the quality of eggs is seen as the factor that 'women have the power to change' (Bolton, 2020). This empowering narrative contrasts sharply with popular notions of the 'biological clock' as ineluctable and fertility decline as irreversible.

It is also in contrast to the empowering narrative of highly medicalized assisted reproductive technology (ART), such as egg freezing. Intervention here is imagined without technological mediation; it is seen as being in the hands of women capable of influencing biology directly through their use of appropriate health services (e.g. acupuncture and medical coaching) or products (e.g. hormones, vitamins and antioxidants), but also by their acquisition of the right expertise through recommended articles such as 'It starts with the egg: how the science of egg quality can help you get pregnant naturally' (Fett, 2019) advertised in blogs (Caroline, 2019).

In order to understand the origin of the idea of egg quality and how it relates to different understandings of age-related fertility decline, I propose illuminating the underexplored role of ART in the making of 'old' and 'healthy' eggs. Although reproductive biomedicine has, since its inception, held the promise of technical solutions to fertility decline, it was only in the 1990s, with the use of egg donation in women in their 40s and after menopause, that the possibility of extending fertility technologically came to the fore. Based on a substitution principle — 'young' eggs for 'old' — and the logic of 'catching up' once infertility is diagnosed, egg donation remains the most widely used ART in circumventing the effects of age on women's fertility (see, for example, the European Society of Human Reproduction and Embryology factsheet on egg donation, 2017). Egg freezing, in contrast, is based on the idea of suspending time and making life 'latent' (Radin, 2013). It allows fertility to be extended according to an anticipatory logic to prevent the unwanted absence of genetically related children (Martin, 2010; van de Wiel, 2015).

More recently, the experimental and controversial Augment technique (Fakih, 2015; Gosden and Johnson, 2016) has added to the spectrum of technologies aimed at medical treatment of age-related fertility decline through direct intervention on 'egg health' by supplementing 'energy' via the mitochondria of immature egg cells found in the ovarian lining (Woods and Tilly, 2015). This new technology rests on the prospect of regeneration and is embedded in the promissory logic of hype and expectations (Brown, 2003; Brown and Michael, 2003). The idea of egg quality at the core of popular and medical understandings of age-related fertility decline is associated with all these technologies. It is also central in promoting behavioural, nutritional or pharmaceutical techniques seen either as complementary to high-tech biomedical solutions or as replacements, thereby extending the anticipatory logic (Adams et al., 2009) at work when women try to conceive.

If these developments are recent, rejuvenation and reproductive technologies are historically rooted in the same project of 'improving the bodily bases of human life' (Squier, 2004: 148) through technological and chemical intervention that took place in the first decades of the 20th century (Squier, 2004). The 'postmenopausal mother' is the striking result of this ongoing traffic between reproductive and anti-aging technologies, and illustrates how some ART may decouple age and fertility or even 'queer' motherhood (Pridmore-Brown, 2009). It also indicates a shift from the original goal of 'improving the human product' to the broader goal of 'reconfiguring the human life span' (Squier, 2004: 166), as Squier expresses very well:

> Dedicated to blurring its [the life span] constitutive categories — those fixed biological life stages of parenthood and generationality — both projects [reproduction and age extension] may now serve a new construction of birth and aging, as exemplified in the notion of the postmenopausal mother (Squier, 2004: 166).

ART provides thus a relevant site to examine how 'the biological is remade' (Franklin, 2013) when reproduction meets ageing.

The development of fertility extension technologies can be read as an example of the biomedicalization (Baldwin, 2019a; Clarke et al., 2010) and biologization of social anxieties about changing gender relations and the heteronormative family order (Amir, 2007). In this article, I ask what is the biology at the core of these processes? What happens when it is technologized? When the life course — birth, ageing and death — becomes located in oocytes? I focus on the upstream relationship between ART and the biology of fertility decline by showing that biologization is not a straightforward process of turning the political or the social into the biological; it is rather the case that different versions of the biological, which allow more or less space to the social, are produced in the process. I argue that ART not only offers new ways to reconfigure the biological clock by extending fertility, but also reconfigures the biology of reproductive ageing itself, which becomes both the target and the means for new technological interventions, imaginaries and norms, anchored in women's bodies and a more plastic biology. For

the purpose of this article, I will focus on two technologies — egg donation and cytoplasmic transfer — both of which have contributed significantly to the production of scientific knowledge about reproductive ageing.

Drawing on a feminist science and technology studies approach and the concept of ontological choreography (Thompson, 2013, 2005), I analyse scientific settings which use these technologies as not only producing scientific knowledge but also as 'materializing' (Barad, 2007) specific and situated realities or ontologies of reproductive ageing. The article suggests that ART can be analysed as 'in-vivo models' and plays a pivotal role in the production of a biological and cellular understanding of age-related fertility decline. It will shed light on the role of ART in producing distinct ontologies of this biology, depending on the ART involved, focusing mainly on egg donation and cytoplasmic or mitochondrial transfer. I will highlight how egg donation tends to locate age in the eggs, producing a fixed understanding of age as resistant to technological intervention which can also be substituted following the logic of organ replacement. However, by situating the locus of age in eggs, egg donation also draws scientific attention to egg quality, which is at the centre of the second set of technologies involved namely cytoplasmic or mitochondrial transfer. The article goes on to show how these produce a more plastic understanding of age-related fertility decline, based on scientific knowledge of the ageing processes themselves. It thereby illuminates neglected aspects of the 'traffic' (Squier, 2004) between reproductive and anti-ageing science and technology.

Searching for age in reproduction

When I started my research on reproductive biomedicine in 2011, I was struck by the omnipresence of age in clinical practice, in the experiences of women undergoing fertility treatment and in the media as soon as ART is mentioned. If empirically, the relationship between age and fertility was very much present, I found them underexplored when I started to research their treatment in the social scientific literature on ART. While ageing studies tended to focus on later life, conceived as non-reproductive, and gave little attention to the transformations of a 'new middle age' (Hepworth and Featherstone, 1982), social studies of reproduction did not usually focus on age and ageing. However, there was extensive literature on the timing of motherhood and the reasons why women embark on it (Benzies et al., 2006; Sevón, 2005; Welles-Nyström, 1997). The experiences of older mothers and late parenthood (Carolan, 2003; Dillaway, 2006; Perrier, 2013; Shelton and Johnson, 2006; Windridge and Berryman, 1999) and their media portrayal (e.g. Mills et al., 2015) were also studied. If these studies focused on age in relation to fertility and motherhood/parenthood, the importance of ART and reproductive biomedicine tended to remain in the shadows.

Although age itself was not at the centre of the analysis, the potential of egg donation to disrupt the normative order of the biological clock was recognized (Pridmore-Brown, 2009) in that it could undermine the biologically anchored distinction between ageless men with unlimited fertility and infertile ageing women (Löwy, 2009), and '[break] down some of the more oppressive aspects for women of the ''biological clock"' (Thompson, 2005: 174). The way the technology was used with postmenopausal women challenged ontological, epistemological, international, gender and responsibility boundaries and furthered ethical and social debates (Campbell, 2011), as is shown in the abundance of ethical and medical literature on age limits (Heffner, 2004; Kocourková et al., 2015; Smajdor, 2008).

An exception to the lack of engagement with biology is the pioneering work by Friese et al. (2008) which focused on how egg donation changed the meaning of middle age and the life course and, more importantly for this article, what the 'biological clock' (Friese et al., 2006) actually means. In their earlier work, Friese et al. show how, in reproductive biomedicine, the metaphor of 'old eggs' designates a 'diminished ovarian reserve' and age-related fertility decline, and has become a new referent for the biological clock discourse, replacing in this way the symbolic and material frontier of the menopause. A further exception is the work by Amir (2007) who draws on Foucault, Deleuze and Butler in discussing a new biopolitical regime which regulates sexualities and gender identities in the name of the specific temporality of the female body and its 'biological clock'. Amir recalls that these new ways of regulating reproduction and population are genealogically linked to the eugenic discourses of the turn of the 20th century, and emerge in a period when the institution of the family is losing its regulatory power. In this context, Amir argues, reproductive biomedicine can be seen as a way of shoring up the heteronormative order by anchoring gender differences in women's biological temporality, as well as promoting normative futures based on ideal notions of the nuclear family and the life course.

This situation changed radically during my project due to the possibility of cryopreserving one's own oocytes, and thereby extending the fertility timespan without recourse to the oocytes of another woman in egg donation. As with any new biotechnology, egg freezing sparked many medical, ethical and social debates; there is a flourishing literature on the topic in relation to reproductive rights and choices, the biomedicalization of women's bodies, and issues related to the reconciliation of work and family (Almeling et al., 2014; Baldwin, 2019b; Cattapan et al., 2014; Lockwood, 2011). Whilst the risk of increased pressure on women to anticipate their reproductive futures (Martin, 2010), together with the illusory technological fix it promises, are to be criticized, the empowering dimension of egg freezing in enabling women to synchronize conflicting timescales is also stressed (Goold and Savulescu, 2009; Mertes and Pennings, 2011; Rybak and Lieman, 2009; Waldby, 2014). Although this literature discusses age very much in relation to ART and its impact on women's 'reproductive navigation' (van der Sijpt, 2014), studies engaging more directly with the biology of age-related fertility decline and the upstream traffic rendering fertility extension possible have been left out of the account. What happens when age enters the domain of reproduction? What is reproductive ageing in the first place? How does ART help to produce its specific realities?

To answer the questions at the core of this article, there is a need to turn to social scientific work focusing on and

problematizing biology itself in relation to reproduction or ageing. Following advances made in the life sciences with the advent of ART and the Human Genome Project, other science and technology studies scholars have undertaken foundational work to understand the transformations and the politics of life itself when it is technologized and molecular (Franklin, 2003, 2000; Franklin and Lock, 2003; Rose, 2007). By definition, technology materializes human intervention in nature, whether in agriculture or in the life sciences and biomedicine. It is part of a history where tools and techniques have been developed by humankind to control, benefit from and exploit natural resources (Franklin, 2013). In the life sciences, similar processes are at work, as life itself becomes something that can be controlled, re-engineered and capitalized. The development of contemporary biomedicine with its molecular and genetic tools in particular entails a molecularization of life (Rose, 2007).

The idea that cellular time is reversible and open to technological intervention and control has been explored in relation to reproduction in the domains of embryonic stem cells, regenerative medicine (Bharadwaj, 2007; Franklin, 2013; Thompson, 2013; Waldby and Mitchell, 2006), cloning techniques (Franklin, 2007; Friese, 2013) and, more recently, social egg freezing (Wiel, 2020). The domain of biogerontology, anti-ageing science and medicine also provides a site to observe how targeting ageing processes at the cellular level blurs the boundary between the biological and the social, as well as the normal and the pathological towards open-ended optimization logics (Cardona, 2008; Higgs et al., 2009; Katz and Gish, 2015; Katz and Marshall, 2004; Lafontaine, 2009; Mykytyn, 2009, 2008; Pickard, 2014; Vincent et al., 2008).

Drawing on these insights, Bock von Wülfingen et al. (2015) show how temporality is at the core of knowledge about reproduction in the life sciences, whether it be chronological, linear, circular or reversible. As an example, by going back to early work in embryology around 1800, Wellmann (2017) proposes that 'rhythm' becomes a central epistemological category in understanding life development. She turns to molecular biology, genetics, stem cell research and epigenetics to further examine the temporalization of nature (Wellmann, 2015), and highlights contrasting versions of temporality when it becomes biological. Whereas in genetics, DNA emerges as a timeless entity, with postgenomics returning to the cell and its development to understand how DNA is expressed, the idea that cellular time is reversible and open to technological intervention and control has come to the fore. In the same vein, Landecker's work on apoptosis or programmed cell death (Landecker, 2003), cell cultures (Landecker, 2007) and epigenetics (Lappé and Landecker, 2015; Landecker and Panofsky, 2013) highlights the biological and social implications when life and death become cellular. In stating that 'before changing what it is to be human, [...], biotechnology changes what it is to be biological' (Landecker, 2007: 232), she also recalls that biological norms and the scientific work performed in the laboratory need to be taken seriously in order to understand how the manipulation of time frames and the reversibility of life processes operate in the life sciences. In the field of ART, Wiel focuses on the emergence of a new gendered politics of ageing predicated on reproductive ability. She shows how egg freezing, and also time-lapse embryo imaging technology, produce new understandings of cellular time and reshape understandings of age-related reproductive processes. The technological instrumentalization of eggs, embodying reproductive loss and bodily finitude, produces more plastic understandings of cellular temporality (van de Wiel, 2014, 2018).

The exploration of the remaking of life and death in reproductive biomedicine highlights the centrality of the ART platform in dissolving the distinction between the biological and the technical (Franklin, 2013), and in contributing to increasingly fuse research and therapeutic purposes. This article contributes to this scholarship by examining the hitherto neglected encounter between reproduction and ageing and the role of ART, especially egg donation and cytoplasmic transfer, in producing knowledge about reproductive ageing.

Methods and data

In order to study the role of ART in the making of 'old eggs', I draw on material collected and analysed in the context of my PhD project between 2011 and 2016 and updated for this article. I focus on part of this material, which consists of a corpus of scientific and medical articles collected through the databases PubMed, Web of Science and Google Scholar. I started by using keywords such as 'age-related fertility decline', 'ovarian ageing' and 'reproductive ageing', and following up these sources turned out to be a valuable complementary strategy. While going back into the history of reproductive ageing took me to the end of the 19th century, my analysis in this article draws mainly on scientific data published between approximately 1990 and 2020, a period marked by the rise of ART, especially technology enabling the extension of fertility, as well as by developments in biological research on reproductive ageing, fostered by advances in the field of cell biology and (post)genomics. Among the corpus of articles collected, I identified key milestones in the history of reproductive ageing through systematically cross-checking and following sources. Next, I studied some benchmark articles I found relevant for the broader picture in highlighting the crucial aspect of the role of ART in reproductive ageing in greater depth, and these are presented in more detail in this article.

I analyse the scientific settings described in the scientific sources as 'ontological choreographies' (Thompson, 2005) producing specific realities of reproductive ageing, which illuminate how different ontological orders are assembled (or not). This concept '[...] refers to the dynamic coordination of the technical, scientific, gender, emotional, legal, political, and financial aspects of ART clinics. What might appear to be an undifferentiated mess is actually a deftly balanced coming together of things that are generally considered part of different ontological orders (part of nature, part of the self, part of society). These elements have to be coordinated in highly staged ways as to get on with the task at hand [...]' (Thompson, 2005: 8). Although Thompson uses this concept to examine the making of parents and children in the clinic (Thompson, 2005), and also to describe the different ethics at stake in the making of 'good science' in the context of stem cell research (Thompson, 2013), I suggest that it is

also useful in examining the making of 'old eggs' in the science and medicine of reproduction.

From age to ageing, or when ART comes into play

Although, in the context of reproductive biomedicine, the biological clock discourse has increasingly been rooted in the metaphor of 'old eggs' (Friese et al., 2006), the idea of 'ageing ovaries' is not new and can be found in the work of pioneer embryologists at the turn of the 19th—20th century, drawing mainly on histomorphological methods and working with non-human animal models, especially rodents (Flemming, 1885; King, 1916; Mandl and Zuckerman, 1950, 1951a,b, 1952; Rolle and Charipper, 1949). At stake in these early works is the extent to which the birth, life and death of oocytes is dependent upon and synchronized with the development of women, setting in this way some epistemological foundations for the distinction between the biological and chronological age of women, but also between the biological age of reproduction and the ageing of the rest of the body [see Wellmann (2017) for a deeper exploration of cellular temporality]. Research on the human 'ageing ovary' started in the post-war period but remained limited to biological material removed after elective surgery or autopsy (Block, 1952; Hertig, 1944). A few studies on ovarian and reproductive ageing were published after this experimental work, but their overall number remained relatively low.

This is in contrast to the increase observed in the 1990s. Research conducted with PubMed with the keywords 'ovarian ageing' and 'reproductive ageing' indicates that the number of publications with 'reproductive ageing' as their topic increased from six articles (including two on humans) indexed in the 1970s, to 180 articles (including 103 on humans) in the 2000s, and 183 articles (including 117 on humans) between 2010 and 2015. Using 'ovarian ageing' as a keyword, results show a similar trend, with one article in the 1970s, 82 articles (including 73 on humans) in the 2000s, and 149 articles (including 92 on humans) between 2010 and 2015. This increase needs to be situated in the social context of growing concern about the demographic trend to delay first childbirth and declining fertility rates in the population, making reproductive ageing a 'growing public health problem' (Bentov and Casper, 2013), 'an age-related disease' (Tatone and Amicarelli, 2013) and a 'therapeutic challenge' (Klein and Sauer, 2001).

Another paper would be needed to tease out the complex relationship between demography and biology. The statistical correlations between age and fertility of population studies are limited to differentiating what comes from biology and what comes from the social. They cannot answer the question whether fertility decline, calculated demographically, comes from women's ageing biology rather than from behavioural factors such as frequency of sexual intercourse, the male partner, and other cultural beliefs and socio-economic factors. For this reason, the complementarity of demography and biology as 'auxiliary sciences' has already been invoked by the post-war French demographer Henry (1961). Moreover, the idea of reproduction as a universal biological phenomenon is one of the epistemological conditions allowing demography to develop (Lettow, 2015). ART, starting with sperm donation, provides a means of answering questions left open by demographic knowledge, and also contributes to an understanding of the fertility decline located in women's biology — more precisely, in their eggs. However, these new understandings are not a substitute for statistical knowledge; I would rather argue that demographic and biological knowledge of the fertility decline constitute both an epistemological and technological condition for the other to exist. In order to shed light on how the development of ART has played a crucial role in the co-production of age — chronological and statistical — and ageing, as a biological and cellular process, I want to turn to egg donation and cytoplasmic transfer.

The uterus, the ovaries or both? Egg donation and the localization of age

When one speaks today of the biological clock, it seems obvious that one is referring to 'old eggs' and notions of ovarian reserve, rather than the uterus and its endometrial lining, as the visual repertoire presented in the Introduction recalls. However, knowing where to locate age in the body and to understand what part or mechanisms of the reproductive system are responsible for age-related fertility decline in women was not so evident at the beginning of the 1990s. By focusing on a short series of articles published in this decade, this subsection will show how the procedure of egg donation has helped locate age in the eggs by providing new ways of answering the nagging question as to which part of the reproductive system — uterus or oocytes — matters more in terms of age-related fertility decline. This question is driven by a direct concern for clinical efficiency in producing successful reproductive events. A better understanding of which part of the reproductive system most determines age in older women undergoing ART is indeed the key to targeting better medical interventions, and giving this population better advice on their reproductive options (Abdalla et al., 1990, 1993).

Due to their short reproductive lifespan and their age-related decrease in fertility, mice are a favoured animal model for understanding the effects of ageing on reproduction (Brook et al., 1984). Most biological studies of mice revealed the predominance of a 'uterine factor' (Klein and Sauer, 2001; Stein, 1985; Talbert and Krohn, 1966). However, the application of these observations to humans is not so simple, as can be read in the following excerpt from an article on the effects of ageing on the reproductive system by a Spanish team:

> There is an evident decline in human fertility with age. The fundamental physiological question is whether the ovary, the uterus, or both are affected by the changes induced within the body by senescence (Pellicer et al., 1995: 77).

By taking the biological process of conception out of the female body, in-vitro fertilization ((VF) has opened up the possibility of making each step — hormonal stimulation, follicle growth, ovulation triggering, fertilization, embryo development and implantation —independent of the others to some extent. It has also opened up, in unprecedented

ways, the possibility of inducing fertilization between gametes, and thus genetic material that is not from the intended parents, and especially to separate motherhood into different contributions to the making of a child — genetic, ovarian, uterine, gestational, intentional and educative (Kirkman, 2003; Konrad, 2005; Orobitg and Salazar, 2005; Thompson, 2005). The procedure of egg donation results from these possibilities; the main difference with standard IVF being that the oocyte comes from a donor whose reproductive work is to produce oocytes, and that the intended mother undergoes hormonal stimulation to prepare the endometrium and then carries the pregnancy.

The first baby conceived with egg donation was born in Australia at the beginning of the 1980s (Lutjen et al., 1984; Trounson et al., 1983). Although the first medical indications for egg donation are repeated conception failures, inheritable genetic problems, and unexplained or chemotherapy-induced premature ovarian failure, the procedure has been recognized increasingly for its ability to extend fertility and induce pregnancy in women in their 40s and 50s (Sauer and Kavic, 2006). The unexpectedly positive results obtained in this population encouraged medical teams pushing the age limits of pregnancy, successively into the 40s, 50s and 60s (Antinori et al., 1993; Borini et al., 1995a; Flamigni, 1993; Sauer et al., 1990, 1993; Serhal and Craft, 1989). In this way, egg donation has been used increasingly as a fertility extension strategy, resting on a substitution process — 'young' eggs instead of 'old', 'defective' or absent eggs. However, I want to show here how egg donation not only extends fertility and makes older bodies reproductive, but has also helped produce a fixed understanding of age-related fertility decline located and isolated in the eggs.

In the early 1990s, egg donation was proposed as an experimental 'in-vivo' model enabling clinicians and researchers 'to evaluate the relative contribution of oocyte quality and endometrial receptivity to pregnancy outcome' (Navot et al., 1991a), with 'women with ovarian failure who receive donated embryos serv[ing] as a unique model for elucidating the complex interrelations of the ovary, endometrium, and embryo' (Navot et al., 1991a: 408). The choreography of egg donation provides new ways of controlling variables and separating what comes from the donor — the age of the eggs — and what comes from the recipients — the age of the uterus. Egg donation can be used retrospectively, but also prospectively, enabling clinical researchers to test their hypotheses. Initially, retrospective results of first egg donation procedures led to the conclusion that uterine factors are more determining (Abdalla et al., 1990). These results were nuanced when using larger samples of cases and comparing pregnancy and miscarriage rates between recipients of egg donation and women using their own oocytes (Abdalla et al., 1993).

The importance of ovarian factors was confirmed in 1997 (Abdalla et al., 1997) in other studies using egg donation prospectively as an experimental model. In this clinical research setting, oocytes coming from a single donor are given to women in two distinct age groups: under and over 40 years of age. This setting is especially designed to isolate and control the variable 'egg' and test the variable 'receptivity of the uterus'. It has been used by other teams in Italy (Borini et al., 1995b; Cano et al., 1995) and the USA (Navot et al., 1991a,b). Regardless of the hormonal stimulation protocol the latter research team used to prepare the endometrium for implantation, they observed that this organ could regain morphological integrity and functionality. As pregnancy rates were similar in both age groups and the quality of donated eggs was a controlled factor, they concluded that oocyte quality is more important than the receptivity of the uterus. These observations were confirmed by results of egg donation in women over 50 years of age (Sauer, 1997), showing that the receptivity of the uterus can be maintained way beyond menopause, as long as the oocytes come from a young donor. Therefore, even if the effects of age on the uterus are acknowledged and the uterus also ages (Erel et al., 2005; Pellicer et al., 1995), its ability to regain its morphological structure and sustain implantation when hormonally treated (in other words, its ability to be made functional again) makes it a less important factor in fertility decline.

In this ontological choreography, age emerges as what cannot be made functional medically or technologically, as what resists ART intervention, which helps locate it in the eggs rather than in the uterus. If, in this way, egg donation produces a fixed understanding of reproductive ageing, the more plastic notion of egg quality also emerges from this clinical research choreography. Less than the number of oocytes, it is their quality that matters. But what is quality? How can it be assessed, and is it possible to intervene? This notion is to be understood primarily in relation to chromosomal defects and the rate of miscarriages. However, it concerns more generally everything impacting the reproductive ability of oocytes to develop into an embryo, an ability which is observable *in vitro*. However, attributing pregnancy rate decline or an increase in miscarriages with age to chromosomal defects or genetic problems — old eggs becoming synonymous with defective eggs — occurring during cellular division does not provide explanations about the causes leading to these defects. Correlating them with age, as a chronological variable, is not enough to understand how exactly ageing and/or other external factors might play a role in diminishing egg quality. To explore these questions, I suggest turning to the second choreography which involves ooplasmic transfer and contributes to the production of a more plastic and sensitive version of reproductive ageing which can be manipulated by both low and high technologies.

Ooplasmic transfer: ageing itself and the emergence of egg health

Egg donation programmes contributed significantly to producing a biological understanding of age, thereby drawing attention to the ageing processes in play at the reproductive level. However, another technique is involved in producing knowledge about reproductive ageing *per se*: cytoplasmic or ooplasmic transfer. What I want to show in this section is how, with this cellular level technique which, in a sense, increases the biologization of age, the impact of the environment and lifestyle, initially omitted, are brought back into play in new ways. The question of how reproductive ageing affects egg quality becomes a question of how egg

health can be optimized by high- and low-tech solutions. The biologization of age here tends not to essentialize the biological clock by producing a fixed understanding of it, as in egg donation, but rather to complicate its biology by taking several levels into account — cellular, molecular and epigenetic — and by questioning the impact of general ageing *per se* and of the environment, understood in this context as elements outside the body (e.g. lifestyle, stress, chemical exposure) or as the micro-environment of reproductive cells (Dorland et al., 1998).

While at the clinical level, egg donation allowed age to be located in the eggs, other scientific work performed in the laboratory and using molecular biology tools in the domains of reproductive biology and biogerontology, conducted at the end of the 1990s in the USA, led reproductive clinical researchers to hypothesize that a specific part of the oocyte, and not the reproductive cell as a whole, might be determining in explaining fertility decline. 'Can ooplasmic transfer rescue aged oocytes?' asked two ART gynaecologists in 2019 (Tanaka and Watanabe, 2019). If this question still seems valid today and has even hit the news with the debates around 'three-parent IVF' (Henderson, 2010) involving mitochondrial transfer (Bühler and Herbrand, 2020; Herbrand, 2017), we need to go back to forgotten experiments performed in 1997 in the USA by the embryologist and reproductive scientist Jacques Cohen and colleagues. Published in the prestigious medical journal *The Lancet*, they announced that a child was born after being conceived with the experimental technique of ooplasmic transfer (Cohen et al., 1997). Ooplasm or egg cytoplasm is the liquid contained in the gamete, distinguished from the nucleus containing genetic material, and in which most cellular activities occur. In the experimental procedure described in this article, the ooplasm is removed from the egg of a donor and transferred directly into the recipient's egg, together with a selected spermatozoon from the male partner.

The procedure was repeated with the goal of improving its efficiency and the viability of the embryo by testing the best method for transferring ooplasm into the recipient's egg (Cohen et al., 1998; Huang et al., 1999). While the procedure was highly controversial due to the uncertainties of epigenetic and genetic implications of ooplasm transfer (Brenner et al., 2000; Darbandi et al., 2017; Hawes et al., 2002), and has been prohibited in the USA by the Food and Drug Administration, it has marked an important scientific step in the production of a cellular ontology of age-related fertility decline. The relative success of the procedure confirmed that egg quality could be improved by injecting the ooplasm from the eggs of younger donors directly into the recipients' eggs, thereby drawing attention to the components of this cellular liquid which might impact on the age-related loss of quality of oocytes, especially mitochondria.

Mitochondria are essential components of the cells — cell organelles — found in high numbers in the cytoplasm. They are known to play an essential role in the production of cellular energy, in the control of cell death and in chromosome division during meiosis (Kujjo and Perez, 2012; Vaskivuo and Tapanainen, 2003). Their role in general ageing has been recognized since the 1970s in the work of the gerontologist Harman (Harman, 1992, 1981, 1972), but their role in human reproduction has been foregrounded by ooplasmic transfers. As mitochondria are located in all cells of the body, not only in gametes, the visibilization of their active role reconceptualizes the 'biological clock' in terms of general ageing, happening at the cellular level. This reconceptualization of reproductive ageing is representative of a more global shift in 21st century reproductive and ageing biopolitics where stem cells and mitochondrial replacement therapies open up new prospects for optimizing both ageing and fertility processes; a shift that van der Wiel calls 'cytoplasmic politics' (van der Wiel, 2020). The division of the egg cell between its nucleus and cytoplasm via the use of ART involving the manipulation of mitochondria entails a redistribution of biological agency. However, more than the cytoplasm (Wiel, 2020), I and Herbrand have argued elsewhere that mitochondria acquire central value and become bio-objects invested for their potential to 'boost' life processes in reproductive cells (Bühler and Herbrand, 2020). In this way, their technologization turns them into biological technologies used to optimize life processes at the cellular level and generating 'mito-enhanced eggs' [i.e. an egg whose quality has been 'revitalized' by the addition of younger and healthier mitochondria, then used to optimize fertility and health, countering ageing processes (Bühler and Herbrand, 2020)].

Jonathan Tilly's work is interesting to examine in this respect, resulting as it does from the encounter between the science of reproduction and ageing and the examination of cell death processes in oocytes (Morita and Tilly, 1999; Tilly, 1996, 2003). Trying to understand the precise biological processes involved in the ageing of oocytes, his research group has identified oogonial stem cells and regenerative processes taking place in ovaries, shaking in this way the fundamental notions on which reproductive biomedicine is based (Johnson et al., 2004; Telfer et al., 2005; Tilly et al., 2009). Contesting what they consider the 'dogma' of reproductive biomedicine, also called the 'fixed-pool model', which states that the production of oocytes stops after birth and established by Zuckerman in the 1950s, Tilly et al. defend the idea that oocytes are still produced after birth in a way very similar to the production of sperm. In contrast with stem cell research and technologies where regenerative potential comes from discarded embryos or donor eggs, raising ethical and political issues (Thompson, 2013; Wiel, 2020), these findings situate its origin within women themselves, circumventing in this way both the need for external donors and the legal restrictions on genetic manipulation of embryos.

However, in a way very similar to the logics at work in stem cell research, where the 'biological clock' 'symbolizes the agency that may be extended over the passage of bodily time via the egg' (Wiel, 2020: 208) and its cytoplasmic 'fountain of youth', these findings shed light on the blurring of reproduction and ageing. In a review article published in *Nature* in 2001, the reproductive biologist Jonathan Tilly suggests turning to ovaries themselves as 'a powerful model that permits in vivo testing of the conclusions from studies that use in vitro organ or cell-culture systems' (Tilly, 2001: 838), thus enabling an understanding of the mechanisms of cell death:

> Assuming that other steps in the oocyte death programme are similarly conserved, there is the prospect

> that promising new therapies could be used to prolong the natural lifespan of ovaries. As such, perhaps strategies that are developed to combat premature menopause will also be useful 'anti-ageing' agents in women, to alleviate the postmenopausal health problems that are attributed to ovarian senescence (Pru and Tilly, 2001: 846).

In Tilly's work, knowledge produced in the ART clinic becomes a model for understanding the ageing processes taking place at the cellular level at the same time as clinical applications for infertile and ageing women become a horizon for capitalizing on his basic research findings. Going back to the procedure of ooplasmic transfer, he suggests that 'apoptosis [programmed cell death] — and mitochondria — might also be at the heart of the age-related decline in fertility in women' (Tilly, 2001: 843). Recognizing that it is not clear which components of the ooplasm play a role in reproductive ageing, he makes the hypothesis that donor mitochondria 'boost' recipients' eggs in ooplasmic transfers, and that their dysfunctions are thus 'at least one cause of the decline in oocyte quality with age' (Tilly, 2001: 844). The ontological choreography of ooplasmic transfer illustrates thus how turning attention to the cellular and molecular processes at stake in reproductive ageing has led to increased traffic between reproductive and anti-ageing science, technologies and medicine, and mitochondria have become a key site where they meet and a more plastic understanding of reproductive ageing is produced. The rejuvenating effects of mitochondria highlighted in the choreography of reproductive ageing when ooplasmic transfer is involved help transform age-related fertility decline into a matter of cellular ageing which can be regenerated and optimized, but also capitalized on, as the next section will show.

Targeting the inside or the outside of the body?

Scientific research on the role of mitochondria in reproductive ageing has grown since the 2000s (Baumann, 2016; Bentov et al., 2011; Bentov and Casper, 2013; Brenner et al., 2000; Chappel and Chappel, 2013; Dorland et al., 1998; Keefe et al., 2015; Kirkwood, 1998; Pacella-Ince et al., 2014). Moreover, the importance of mitochondria in reproductive ageing has led to the development of experimental techniques — MitoTechnologies (Bühler and Herbrand, 2020) — aiming at boosting old eggs and improving their health by adding mitochondria to the fertilized egg, the 'mito-enhanced egg' (Bühler and Herbrand, 2020). Such an example is the Augment (Autologous Germline Mitochondrial Energy Transfer) technique (Woods and Tilly, 2012, 2015), which used the controversial oogonial stem cells identified by Tilly and his team. The flagship product of the company 'Ovascience', which was created by Tilly and colleagues, capitalizing on the potential for immature egg cells to rejuvenate 'old eggs' or boost 'egg health', the technique has been tested experimentally (Fakih, 2015) and is highly controversial (Gosden and Johnson, 2016). While the lack of clinical success of the procedure has led to the reselling of the company, it nevertheless contributes to a reproductive bioeconomy in which mitochondria play a central role (Bühler and Herbrand, 2020).

Cytoplasmic choreography produces an understanding of fertility decline as a cellular ageing process which can be boosted using the mitochondria of immature egg cells through a highly technologized procedure. However, the focus on mitochondria has also led to other types of less technical interventions being revalorized. As an example of this, I suggest turning to a special issue of *Fertility and Sterility* published in 2013. This issue presents five review articles which examine several aspects of the effects of ageing on fertility, including male infertility. They illustrate the tendency to reintroduce environmental factors into the ontological choreography of a more plastic understanding of reproductive ageing. For example, the article by two Canada-based reproductive biologists, Bentov and Casper (2013), tries to understand how the energetic metabolism of the cell is affected by ageing, leading to possible higher rates of chromosomal abnormalities, and discusses possible means of intervening in the processes of oocyte ageing itself. Instead of proposing intervention with more biotechnologies manipulating cellular metabolism and functioning, they suggest supplementing the diet of older women with mitochondrial nutrients, based on the assumption that this should improve the functionality and thus cellular metabolism of mitochondria, with a positive impact on fertility. The nutrients they propose are 'naturally occurring chemicals' such as CoQ10, an enzyme which plays a role in the energetic metabolism of the cell, and r-alpha lipoid acid, an antioxidant known for its protective effects against oxidative stress, one of the key mechanisms of ageing. These molecules can be found in the general market of anti-ageing and health products and dietary supplements.

A similar tendency can be observed in the second review article published by an Italian team based in Naples (Tatone and Amicarelli, 2013). Drawing on the free radical theory of ageing proposed by the famous gerontologist Harman (Harman, 1992), they review the mechanisms leading to age-related molecular 'damage' in the human ovary and the cell's ability to repair them. Interested in the elements capable of stopping or slowing down the accumulation of biochemical 'damages' in the cell, they end up by mentioning several molecules, but also dietary agents, medicinal plants (e.g. green tea, known for its antioxidant benefits) and physical exercise, as means of slowing down reproductive ageing processes. The focus on environmental elements, which allow women to act on the biological clock at a personal level and complementary to ART, is repeated in the conclusion of the editorial of the issue, written by the California-based reproductive clinician Meldrum, and entitled 'Aging gonads, glands, and gametes: immutable or partially reversible changes?' (Meldrum, 2013):

> The potential for improving the fertility and IVF success of our older couples is exciting. We will be able to partially turn back the clock for many of those patients, but the real value of the present review may be to emphasize that better life choices must be made throughout the period when a woman's oocytes are lying in waiting, and

at the very latest as soon as she and her partner begin their effort to conceive (Meldrum, 2013: 3).

While in popular narratives, the biological clock is often presented as an ineluctable and irreversible decline about which nothing can be done, except for turning to ART treatments such as egg freezing or egg donation, and which, like a ticking bomb, urges women to have a child before it is too late, here the process of reproductive ageing emerges as something that can be intervened upon by women themselves by consuming the right products and adopting a healthy lifestyle — not dissimilar from recommendations about slowing down ageing in general (Cardona, 2008; Vincent et al., 2008). Instead of the dormant, inactive, decaying properties associated with oocytes in the medical literature, and analysed by the anthropologist Martin as rooted in gender stereotyped representations of the masculine and the feminine (Martin, 1991), here eggs are portrayed as sensitive to the environment, and as more active and thus in need of more energy than other cells of the body.

Conclusion

A concern for age-related fertility decline has been present since the early days of IVF and has framed the development of this medical sector. In a European and American context of demographic anxiety about ageing populations and fertility decline, reproductive biomedicine has become a space promising to bring medical and technical solutions to the problem of the so-called 'biological clock'. Egg freezing and egg donation, for instance, are technologies which allow fertility to be extended. However, this article has shed light on an often overlooked aspect of ART: its role in the production of scientific knowledge about fertility decline and in the making of 'old' and 'healthy' eggs. Focusing on technologies of egg donation and cytoplasmic transfer, it has shown how clinical reproductive medicine, concerned for clinical efficiency, has attempted to better understand the various ways in which age affects fertility and reproductive potential. It especially highlights the pivotal role of egg donation in locating age in the eggs, drawing attention to egg quality which is at the core of the second set of technologies explored. Drawing the attention to the role of mitochondria, which are found in all bodily cells and are key to cellular metabolism, cytoplasmic transfer contributes to an understanding of age-related fertility decline as a matter of ageing taking place at the cellular level. While ART contributes to a biologization of age in relation to reproduction, the two ontological choreographies of egg donation and cytoplasmic/mitochondrial transfer also produce two contrasting realities of the biology of fertility decline: one which is fixed, cannot be remade functional and about which technologies lack agency; and one which is more plastic and sensitive to the environment of a given woman, and is open to both high- and low-tech interventions targeting the ageing process of the reproductive cell itself and aiming to make it functional again.

Focusing on this second ontological choreography, especially the work of the American reproductive biologist Tilly, illustrates how: (i) reproduction becomes a model to understand ageing at the cellular level, with clinical reproductive medicine evidences of cytoplasmic transfer feeding the basic science of cell and developmental biology; (ii) the logics of anti-ageing medicine, which transform chronic diseases into age-related diseases, and are based on the idea that intervening at the fundamental level of ageing will help improve health, enter the domain of reproductive science; and (iii) the prospect of clinical interventions in reproductive medicine, for fertility purposes, but also for alleviating menopause-associated symptoms provides an horizon for developmental and cell biology which is marked by an increase of capitalization logics in a flourishing reproductive bioeconomy (Cooper and Waldby, 2014). In this context, MitoTechnologies, such as Augment, and the new hybrid to which they give rise, the mito-enhanced egg, become emblematic of the cytoplasmic politics identified by Van der Wiel (2020).

If egg donation allows researchers to separate and control factors in order to locate age in the eggs, ooplasmic transfer plays an important role in the understanding of reproductive ageing in terms of general cellular ageing, which, surprisingly, brings back the environment and lifestyle, previously omitted. In this context, the biological clock becomes an ageing problem, the biological mechanisms of which — when understood properly — can be intervened upon, either technologically by mitochondrial transfer expected to 'boost' or 'regenerate' unhealthy ageing eggs, or individually by consuming the right products and adopting an anti-ageing lifestyle. In this way, the boundary between the reproductive and non-reproductive parts of women's lives becomes blurred. While it seems far removed from real practice, and illusory or even naïve to think that just by consuming antioxidants and anti-ageing products, or by turning to controversial regenerative technologies, women could extend fertility and prevent age-related fertility decline, another reality of the biological clock emerges from this. This plastic version of fertility decline is less ineluctable and more sensitive to the internal and external factors to which women are exposed. In this way, a door is opened to another type of imaginary where the inside — immature ovarian stem cells — and the outside of the body — lifestyle and consumption — are granted more weight, and reproductive ageing itself can be targeted either technologically or by women themselves. Embedded in an empowering narrative, these low-tech interventions seem to extend the anticipatory logics at stake in reproduction, and increase the burden of women's responsibility, while the promissory 'egg boosting' high technologies have so far proved to be less efficient in extending fertility than the older technology of egg donation and its fixed understanding of 'old eggs'.

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