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Socioeconomic differences in access to and use of Medically Assisted Reproduction (MAR) in a context of increasing childlessness

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Abstract

The WHO estimates that around 186 million individuals live with infertility. Although the drivers of infertility are varied and complex, it is linked to the postponement of childbearing in Western countries, and unsafe abortions and deficits in maternal health in less affluent societies. The development of Medically Assisted Reproduction (MAR) has attracted increased attention of both researchers and the wider public. This report summarizes research on MAR and examines the main drivers behind its development, as well as the different contexts in which it takes place, and the main socioeconomic variables underlying variations in access and usage. We focus more specifically on Europe, where MAR is more extensively regulated, but also more widespread compared to other regions. The first section contextualises the emergence and increasing use of MAR from a sociodemographic perspective and describes the major fertility-related transformations and the socioeconomic correlates behind these trends. The second section engages with the phenomenon of infertility, providing evidence of its prevalence and underlying drivers from a biological and an environmental perspective. The third section provides an overview of MAR treatments offered and their regulation and use across countries, as well as the role of macro- and micro-level factors in explaining these variations. Lastly, the report discusses the implications and challenges posed by the development of MAR in contemporary societies.

Keywords: Infertility, Childlessness, Medically Assisted Reproduction, Social Inequalities, Health Inequalities

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Executive summary

Trends in childlessness and fertility postponement

1. Childlessness is neither a rare nor a recent phenomenon. In the early 20th Century, it was relatively prevalent in Western societies and in many European regions – at least 20% of women reached the end of their reproductive lifespan without children. The proportion of childless women has been increasing in European societies from the late 1960s and early 1970s, although developments have neither been simultaneous nor uniform across countries.
2. Factors underlying the secular increase in childlessness include women's increased autonomy and opportunity costs related to early marriage and childbearing, changes in norms regarding women's reproductive role, and increased availability and acceptance of contraception.
3. The line between decision and constraint, and thus between voluntary and involuntary childlessness, is often tenuous. The choices that individuals end up making throughout their life-courses can seldom be separated from structural, social, and biological constraints, as well as from their previous trajectories. Nevertheless, the percentage of individuals consciously rejecting parenthood appears to be generally low.
4. The postponement of childbearing until advanced ages is an increasingly generalized phenomenon in high-resource contexts. In many European countries and some East Asian societies, women have their first child, on average, in their early 30s, many enter motherhood at age 35 or above, and it is becoming increasingly common to have children over the age of 40. Fertility postponement has been more pronounced in low-fertility countries, where growing proportions of women are having their first child in their 40s and resorting to Medically Assisted Reproduction (MAR).
5. The structural context appears to have an important influence on discouraging fertility at earlier ages and encouraging it at later ages, and it also explains why compensation at later ages is more prevalent in some societies than in others. In countries where public policies favour work-family reconciliation, women end up with a greater final number of children despite postponement of the first birth.
6. Individuals with higher education tend to postpone childbearing the most. This is partly due to a delay in relevant life-course events such as the completion of education, which in turn often delays entry into employment and the formation of the first stable union.
7. There are growing educational and socioeconomic disparities, especially in societies with liberal welfare regimes or high levels of socioeconomic inequality. In these societies, reproductive polarization entails increasing differences regarding the timing of childbearing between socioeconomically less advantaged women and those in middle and upper socioeconomic strata, with the latter exhibiting a more pronounced tendency to postponement.
8. Highly educated women are more likely to recuperate postponed births and achieve their desired fertility at later ages.

Infertility: prevalence and drivers

9. The WHO estimates that about 48 million couples and 186 million individuals live with infertility, measured as the inability to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. The prevalence of infertility after one year of unprotected intercourse has been estimated to lie, on average, at around 9%. The most prevalent form of infertility across the world is secondary infertility (when at least one prior pregnancy/birth has been achieved without difficulty). While this phenomenon is linked to postponement in Western countries, in less affluent societies it is a result of unsafe abortions and deficits in maternal health.

10. The drivers of infertility are varied and complex to determine. Firstly, because both genetic, and more generally biological, factors but also environmental stressors are at work, and the effects of both types of determinants are expected to be interactive, not additive. Secondly, because there are several stages – from preconception to adult life – at which (in)fertility-related processes can occur. In addition, one infertility-promoting event can be consequential for events at other stages; insults are likely to have cumulative effects over the life-cycle.

11. Women's fertility starts to decline at 25-30 years of age. Besides the age-related loss of fertility caused by depletion of the oocyte reserve, oocyte quality also decreases with advancing reproductive age, while other factors resulting in reduced conception rates – premature recruitment of follicles, ovulatory disorders, reduced ovulatory frequency, impaired luteal phase – increase. Late pregnancies entail an increased risk of miscarriage, pregnancy complications, adverse maternal and perinatal health outcomes, and chromosomal abnormalities in the foetus. Many women are not aware of the consequences of postponement in terms of reduced fertility, while there is a relatively widely held belief that MAR will be able to compensate for the fertility decline resulting from postponement.

12. Paternal age has been found to be associated with declining sperm quality, an increased risk of failure to conceive, a higher probability of miscarriage and adverse perinatal outcomes, and risks of certain genetic mutations and chromosomal abnormalities. The combination of advanced maternal and paternal age entails particularly elevated risks.

13. Regarding environmental stressors, the most abundant and solid evidence on the decrease in reproductive capacities has been established for air pollution. The negative role of Persistent Organic Pollutants (POPs), notably certain polychlorinated biphenyls and organochlorine pesticides, some of the most common Endocrine Disrupting Chemicals (EDCs), such as bisphenol A (BPA), or high concentration of phthalates has also been shown. However, the lack of consideration of relevant confounding variables, low sample sizes, underreporting of methods, and the absence of evidence on another important outcome, namely live births, suggest that further research is needed.

14. Most of the existing evidence on the impact of environmental factors on (in)fertility is limited to exposures in adulthood. Identifying the impact of early exposure to these elements during other windows of susceptibility, such as the gestational period and puberty, is one of the main challenges at present.

MAR treatments and access

15. The term "Medically Assisted Reproduction" (MAR) covers a broad set of interventions to treat infertility, including treatments such as ovulation inducing drugs and assisted insemination, while "Assisted Reproductive Technology" (ART) is limited to interventions occurring outside of the patients' body. In practice, however, the two terms are sometimes used interchangeably in non-technical debates.

16. The birth of the first so-called "test tube baby", Louise Brown, in England in 1978 marks the beginning of the last forty years of continuous and successful use of ART in humans and the availability of an increasingly wider range of specific techniques.

17. At present, Europe is the only region in the world where most countries have MAR regulations, but these remain characterized by large variation in terms of available treatments and public funding. While MAR regulations in more than half of the countries covered by The European Atlas of Fertility are qualified as "excellent" or "very good", they still remain restrictive in many countries, especially in Central and Eastern Europe.

18. Norway was the first country to establish ART legislation in 1987, and was shortly followed by other Western and Northern European countries. Most European countries adopted legal changes between the mid-1990s and the 2010s, including countries in Southern Europe, as well

as many of the Member States entering the EU after 2004. In the most recent years ART legislation has been passed in Cyprus (2015), Poland (2015) and Malta (2018). However, there are still countries in which there is no specific ART legislation, such as Ireland and Romania.

19. Accessibility to the various MAR treatments varies across countries, but also for different population groups. Assisted insemination and IVF/ICSI with donor sperm are now considered standard treatments, while access to donor eggs and pre-implantation genetic testing are limited in a larger number of countries. In general, heterosexual couples have access to the widest array of treatments, followed by single women and female couples.

20. Some individuals seeking to become parents and unable to access MAR in their country of residence travel abroad for medical care, a phenomenon that has come to be known as "Cross-Border Reproductive Care" (CBRC). Four broad sets of factors underlie this phenomenon: resource constraints, legal and religious prohibitions, quality and safety concerns, and socio-cultural barriers.

21. Surrogacy is available in a limited number of countries in Europe and therefore involves individuals moving outside of the region. This form of CBRC has received the most attention due to the important ethical debates it raises, with many of the surrogate mothers coming from low-resource countries and/or groups, and controversies such as the abandonment of children with disabilities. Travel for selective technologies such as preimplantation genetic tests, but also sex selection remains understudied, but there is evidence on this phenomenon as well.

Statistics on MAR use

22. The clinical introduction of IVF in the 1980s raised many safety concerns (risk of congenital disorders, multiple and preterm births, maternal risks) and national ART surveillance systems were put in place to provide data on medical practices and pregnancy outcomes, in order to reassure society about the safety of treatments.

23. National ART surveillance systems differ in many dimensions: format of primary data provided by ART clinics (summary or cycle-level), registry requirements (compulsory vs. voluntary), and information collected (medical, characteristics of patients). While there are long-standing international efforts to coordinate these systems, providing comparable statistics still entails many challenges due to the differences in registries mentioned above, as well as to variations in completeness of reporting, detail of information, etc. The growing complexity of ART treatments raises additional issues and requires adapting surveillance systems.

24. Since the introduction of IVF in the 1980s, over 8 million children have been born in the world as a result of ART and around 500,000 ART deliveries take place every year. In 2017 (latest available year) around 2 million ART cycles were carried out worldwide. This represents a more than 14-fold increase from 1991 (first available year), when 140,000 cycles were reported. The majority of the cycles are carried out in high-income regions: around one half in Europe, followed by North America and Asia (Japan).

25. In Europe, countries with complete reporting of ART treatments have seen the proportion of live births following ART treatments increase from between 1% and 4% at the start of the 2000s to between 2.5% and 6% in the most recent years.

26. The number of ART cycles carried out in European countries varies. However, the highest numbers (14,000 or more cycles / million women aged 15-44 years) are observed in countries with less restrictive legislation for specific treatments and CBRC destinations within Europe: Denmark, Czech Republic, Belgium, Slovenia, Spain and Greece.

27. The majority of ART treatments are embryo transfers (ET) and can be done with fresh (IVF/ICSI) or frozen embryos (FER). The proportion of such treatments corresponding to IVF has been declining in all countries, while the use of ICSI increased in the start of the period and

stabilized since the mid-2000s. Frozen embryo transfers are becoming more widespread since the end of 2000s.

28. Egg donations (aspiration of eggs from a woman other than the one who will carry the pregnancy) are carried out in a limited number of countries (around 20 countries declare at least one cycle per year).

29. Intra-uterine insemination (IUI) treatments have existed for a longer time than ART. However, as their registration is incomplete – some countries do not provide any figures while in others these may be underestimated – it is harder to quantify them. Among countries having declared IUI treatments, the total number has been relatively stable. While in the mid-2000s several countries still had similar numbers of IUI and ART cycles every year, at present the ratio in most countries is less than 1 to 4.

Factors determining variation in the use of MAR

30. Cost- and affordability-related issues strongly influence access to MAR for different social groups, entailing considerable inequalities in countries where there is low public coverage. Even in Europe, where MAR is relatively widespread and there is a certain degree of public coverage, costs and affordability appear to be important determinants of both cross-country and individual-level differences in usage.

31. Whether individuals/couples have the economic means necessary to cover MAR related expenses appears to be far more important in explaining differences in MAR usage than legal and regulatory frameworks. Moreover, economic conditions not only influence whether individuals/couples access treatment, but also the types of treatment available to them and the characteristics of the treatment undergone (e.g., the number of embryos transferred).

32. At an aggregate level, the use of ART is more influenced by cultural values regarding its acceptability than by economic and sociodemographic variables such as country wealth, population-related characteristics, or the representation of different religious groups in society. A positive association has been found between higher normative age limits for childbearing – i.e., socially shared views on when individuals are too old to have children – and the availability of MAR in European countries (measured by number of MAR clinics). In countries where the belief that an embryo becomes a human being right after fertilization is less widespread, there is greater recourse to these technologies. Likewise, beliefs regarding whether individuals have a right to have children, or whether societies should provide funding for reproduction are important in this respect. So are views on whether it is ethical to discard healthy embryos or generate embryos with abnormalities. Beliefs also shape which techniques are more or less readily accepted.

33. Some differences across countries regarding MAR usage also bear an association to the degree to which fertility postponement is prevalent. In societies where postponement of first births is common, demand for these technologies is higher, mirroring the relation that exists at the individual-level behind fertility delay and recourse to MAR treatments.

Implications and challenges of MAR development

34. Further research on the impact of MAR on perinatal and infant health and children's cognitive and socioemotional development is needed. The higher probability of adverse obstetric and perinatal outcomes among medically assisted conceptions is in large part due to the fact that these are more often multiple pregnancies, although a smaller association is still observed in singleton pregnancies as well. Some of the increased risks are limited to specific treatments (for instance, certain risks are specific to IVF, while fresh and frozen embryo transfers have been linked to different types of adverse outcomes). Results regarding mental and neurodevelopmental health of individuals born after MAR are less consistent. Associations

between certain treatments and increased risk of some adverse health outcomes later in life (i.e., cardiovascular and metabolic conditions) have also been established. Further evidence is needed to disentangle and isolate the mechanisms involved – that is, the relative influence of treatments themselves, of medical or genetic factors associated with infertility/subfertility, and of environmental variables.

35. New research pathways around MAR should be sensitive to the ethical issues that have arisen so far and to those that will emerge in the future. Privately supplied ART has become a profitable business in a global fertility market. While many types of social and economic inequalities impinge on access to these technologies, concerns have also been raised regarding the risk of increasing commodification of reproduction and bodily tissues.

36. Other ethical dimensions are related to the use of screening instruments for the detection of potential disabilities, serious illnesses, or the transmission of inheritable conditions. This technology already exists and is applied in ART, which has elicited concerns about the possibility of discriminatory or eugenic practices, selection of embryos with characteristics considered most desirable, the use of preimplantation genetic diagnosis (PGD) for non-medical objectives (e.g., sex selection), and the selection of embryos on grounds of tissue matching with a previous child.

37. The great diversity of indicators and lack of data standardization makes it difficult to establish reliable country and region comparisons. Comparing between regions becomes particularly difficult given differences in affordability and accessibility of MAR. Variations in the typical characteristics of patients that might be consequential for fertility outcomes further complicate the task. Experts have emphasized the need to attain global consensus for unified procedures when reporting ART outcomes. Even though competences over policy matters are located at the national level, the Commission's recent proposal for a European Health Data Space (EHDS) could be an excellent tool to intensify efforts in this direction.

1. Introduction

This report aims to offer a comprehensive overview of the use of Medically Assisted Reproduction (MAR)[1] over the world, the main drivers behind its development in the last decades, as well as the different contexts in which it takes place, and the main socioeconomic variables underlying variations in access and usage. We focus more specifically on Europe, where MAR is more extensively regulated, but also more widespread compared to other world regions.

The first section contextualises the emergence and increasing use of MAR from a sociodemographic perspective. It pays attention to major fertility-related transformations having taken place in contemporary societies – namely the rise in childlessness at different stages over the past century; women's increasing reproductive autonomy; the trends towards increasing childbearing postponement observed in many regions; and its relation to infertility and the use of MAR –, while highlighting the socioeconomic correlates of these dynamics. The second section engages with the complex phenomenon of infertility, providing evidence of its prevalence and its main underlying drivers from both a biological and an environmental perspective.

The third section, in turn, deep dives into the many dimensions of MAR, dealing with its definition and conceptualization; the different treatments offered since its inception; and the specific regulations that delimit access in different societies, ultimately leading, in some instances, to increased supply and demand of "cross-border reproductive care" (CBRC). After mapping the most recent available evidence regarding the use of MAR across European countries, focus is placed on the importance of socioeconomic factors influencing access and usage of related technologies and treatments both across and within societies. The objective is to shed light on the role of macro- and micro-level socioeconomic and demographic differentials, in interaction with access regulations and public coverage, in facilitating or hindering a widespread use of MAR, while also paying attention to the importance of cultural values and normative standards.

2. A socio-demographic approach to childlessness

2.1. Trends in childlessness over the 20th Century -- in Europe and beyond

The concept of childlessness in socio-demography has been subject to a variety of definitions. Some authors restrict it to biological infecundity, while others have extended it to encompass broader social phenomena such as the lack of parental or nearly parental ties (e.g., those held to stepchildren or foster children) (Xu et al., 2022). Most generally, it refers to the fact of not having children at a given point in time or ending the reproductive period without children (see Kreyenfeld and Konietzka, 2017).

Despite wide variations in incidence throughout the world, childlessness is neither a rare nor a strictly recent phenomenon. In the early 20th Century, it was already relatively prevalent in Western societies and in many European regions, at least 20% of women remained childless. The phenomenon was linked to a relatively high age at marriage, as many young adults first left their home of origin to work as servants and maids, remaining unmarried and childless over long periods (Kreyenfeld and Konietzka, 2017); others entered institutionalized religious communities (Reher and Requena, 2019). The World War I generated a distortion in sex ratios, entailing that many young women were not able to find a husband (Beaujouan et al., 2017). Similarly, Australia and North America displayed high childlessness levels (between 25% and 30%) over the first decades of the century. Among the factors

[1] The term "Medically Assisted Reproduction" (MAR) is defined as: "Reproduction brought about through various interventions, procedures, surgeries and technologies to treat different forms of fertility impairment and infertility. These include ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures, uterine transplantation and intra-uterine, intracervical and intravaginal insemination with semen of husband/partner or donor." (Zegers-Hochschild et al., 2017).

underlying the phenomenon – as occurred in Europe – was the complicated social and economic context resulting from the Great Depression of 1929 (Kreyenfeld and Konietzka, 2017). In the US, childlessness in the early 1900s was especially prevalent among black women, who experienced particularly strong economic, social, and health disadvantages (Frejka, 2017). In several regions, childlessness rates remained high even in the 1940s, due to the gender imbalance in the marriage market stemming from World War II. Nevertheless, it subsequently experienced a sharp decline, as individuals in the 1950s and 1960s entered marriage significantly earlier than previous generations (Kreyenfeld and Konietzka, 2017).

From the late 1960s and early 1970s, European societies have witnessed a new upward trend regarding the proportion of women who reach the end of their reproductive lifespan without children. Nevertheless, developments have neither been simultaneous nor uniform across countries. Childlessness started increasing first in the Netherlands, some parts of the United Kingdom, Austria, West Germany, and Switzerland. The latter two came to surpass the 20% childlessness rate in the cohorts born in the late 1960s, although the phenomenon currently seems to be stabilizing or even declining somewhat (Sobotka, 2017). In the United Kingdom, likewise, cohort fertility rates for women born in the 1980s indicate that childlessness may no longer be increasing (Berrington, 2017). The trend towards growing childlessness rates started later in Southern Europe, where the rise has been rapid and very pronounced (Beaujouan et al., 2017).

In Spain, a country which has reached so-called lowest-low fertility levels – a total fertility rate at or below 1.3, as defined by Kohler et al. (2002) –, it has been estimated that around 25% of the women born in 1975 will remain childless (Esteve and Treviño, 2019). Similar figures – even slightly higher – have been calculated for Italy (Caltabiano et al., 2017). Portugal appears to be an exception in the region, with considerably lower childlessness rates (ca. 12% among women born in the late 1960s) (Sobotka, 2017). Eastern Europe, on its part, was characterized by early childbearing and low levels of childlessness (below 10%) until the post-communist transition. A relatively rapid increase in the prevalence of the phenomenon has taken place since, although childlessness rates are still below those found in Southern Europe (Sobotka, 2017).

In Belgium, France, and the Scandinavian countries, childlessness levels have remained relatively low and stable in comparison to other Western European societies (Kreyenfeld and Konietzka, 2017). Finland has long been an outlier within the Nordic context, with levels of permanent childlessness close to 20%. Nevertheless, a recent and strong fertility decline in Iceland and Norway appears to be accompanied – and partially driven – by an increase in childlessness as well (Hellstrand et al., 2021). Beyond Europe, the United States experienced a considerable rise in childlessness between the mid-1970s and the mid-2000s, when the proportion of women who ended their reproductive life without any children rose from 10% to 20%. Since then, the incidence of childlessness appears to be declining again, especially among white women, although the reasons for this trend are still unclear (Frejka, 2017).

The most economically developed East Asian societies currently show the highest levels of childlessness in the world, having witnessed an unusually rapid and significant increase in permanent childlessness rates over the past few decades. While starting from low levels (4%-12% among women born in the 1950s) Singapore, Hong Kong and Japan exhibit permanent childlessness rates close to 30% for the cohort born in the 1970s, while Taiwan and South Korea seem likely to follow suit (Sobotka, 2021). Latin America and the Caribbean region, on their part, appear to be departing since the early 2000s from their traditional pattern of early and universal childbearing (Rosero-Bixby et al., 2009), and permanent childlessness also seems to be on the rise in many countries. Argentina, Brazil, and Uruguay showed in 2010 the highest rates in Latin America (11.3%; 13.5% and 12%, respectively). Other Latin American countries also exhibit an upward trend, yet their childlessness levels still lie below 10% (Fanta Garrido and Sacco, 2018).

Low-income countries have generally been characterised by relatively high average fertility rates. Nevertheless, there is significant cross-national variability; not least regarding childlessness (Baudin et al., 2020), and the majority of childless and infertile couples actually live in such countries (Inhorn and Patrizio, 2015; Ombelet, 2011). In low-income countries, childlessness can have a very strong negative impact both on women's psychological well-being and social status, on account of a strong(er) normative pressure to reproduce (Dyer et al., 2002; Ombelet, 2011). Nevertheless, besides being the result of natural infertility/sterility, childlessness can also be driven, in many countries, by poverty, or by high opportunity costs of childrearing (Baudin et al., 2020). In the poorest countries and among women in the lowest socioeconomic strata, childlessness tends to be related to either biological infertility/sterility, to poverty, or to both; as lack of economic resources precludes individuals from accessing adequate healthcare – so that certain conditions do not receive adequate treatment and lead to infertility – or assisted reproduction techniques (Inhorn and Patrizio, 2015). In less disadvantaged societies, some individuals – especially those with a comparatively higher level of education and income – may start foregoing childbearing voluntarily due to high opportunity costs related to forgone income from work (Baudin et al., 2020; Verkroost and Monden, 2022).

There is still little knowledge on permanent childlessness in Africa, especially regarding countries south of Sahara. Still, while fertility in this part of the world is comparatively very high, there is a substantial proportion of individuals facing childlessness (Verkroost and Monden, 2022), particularly in areas with poor access to healthcare and to assisted reproductive techniques (ARTs) (Inhorn and Patrizio, 2015). As noted above with regard to low-income countries more generally, childlessness is viewed as an undesirable phenomenon in many African societies, due to the stigma that accompanies it – particularly in rural communities – and the negative social consequences it entails, especially for women (Boivin et al., 2020; Inhorn and Patrizio, 2015). Throughout these countries, children are regarded as "the" purpose and meaning of marriage, a source of power and family continuity, and an insurance for their parents as they age (Tabong and Adongo, 2013), as many families end up depending on their children to survive economically (Ombelet, 2011).

2.2. The thin line between voluntary and involuntary childlessness

The secular increase in childlessness observed in many societies, not least in some low-income countries, has multifactorial and context-dependent explanations. Among the arguments put forward to interpret this trend have been the noted opportunity costs related to foregone work, which in less affluent societies are particularly high for individuals with greater socioeconomic resources (Baudin et al., 2020; Verkroost and Monden, 2022). Another relevant factor is women's increased autonomy (Gillespie, 2000), itself often linked to an extension of the time spent in education and to improved labour market participation opportunities. The latter factors, on their part, raise the opportunity costs for women of early marriage and childbearing (Heath and Jayachandran, 2018), which also has an impact on the occurrence and timing of fertility and the probability of childlessness.

Other variables underlying the phenomenon are normative changes at the societal level: in the past, norms prescribed a focus (exclusive or majoritarian) on women's reproductive role (Russo, 1976). These norms have been gradually eroding in many parts of the world. Particularly – yet not solely – in Western societies, there is increased social acceptance of childlessness, not least among women (Koropeckyj-Cox and Pendell, 2007; Rijken and Merz, 2014; see also Skirbekk, 2022; Tsai et al., 2021). The increased availability and acceptance of contraception has also made it possible to choose, in many regions of the world, whether to have children altogether or not – as well as the timing of childbearing – to an extent that was unprecedented a few decades ago (Dykstra and Hagestad, 2007). In countries with widespread access to contraceptive methods, reproduction and its timing have thus to a significant degree become a matter of choice. As will be explained, women in high-income countries often postpone motherhood until they have finished their education, achieved a minimum degree of economic stability, found a suitable partner, or been able to reduce work-family reconciliation difficulties and related opportunity costs.

While the abovementioned factors would imply a choice to remain childless – either temporarily or permanently –, the line between decision and constraint, and thus between voluntary and involuntary childlessness, is often tenuous. For some childless individuals, childlessness is a lifestyle option resulting from a conscious rejection of parenthood (Gillespie, 2000). Nevertheless, the percentage of such cases appears to be generally low (see for instance Berrington, 2017). The pathways and mechanisms leading to permanent childlessness tend to be diverse and complex (Mynarska et al., 2015), as they result from the accumulation of decisions made over time under multiple constraints (Hagestad and Call, 2007). The choices that individuals end up making throughout their life-courses can seldom be separated from structural, social, and biological constraints, as well as from their previous trajectories (Gemmill, 2019). Some of the main factors associated with the decision not to have children – for example, the lack of a suitable or willing partner, economic or employment stability, unfavourable work-family balance conditions – are most often involuntary (Sobotka, 2010). Likewise, seemingly voluntary postponement due to such circumstances can eventually lead to undesired childlessness (Berrington, 2017), as conception, especially for women, becomes increasingly difficult with advanced age. There is empirical evidence showing that permanently childless women often had expected, in the past, to have a child at some point in their lives (Gemmill, 2019). It should also be borne in mind that preferences are often adaptive (Bruckner, 2009) – a voluntary decision to remain childless may in fact reflect implicit or explicit adaptation to involuntary structural constraints and to the options that are available and feasible. There is also research suggesting that, although women adapt their reproductive intentions and behaviours to the constraints experienced throughout their life-course, the rises in permanent childlessness observed in many societies do not necessarily reflect women's preferences as they come close to the end of their reproductive lifespan (Beaujouan, 2020).

2.3. Postponement of childbearing and its relation with fertility and childlessness

The postponement of childbearing to relatively advanced ages, from a reproductive point of view, is a global, increasingly generalized phenomenon in high resource contexts (Cooke et al., 2012). In several countries, women have their first child, on average, in their early 30s (Beaujouan, 2020), many enter motherhood at age 35 or above (Eijkemans et al., 2014), and it is becoming increasingly common to have children over the age of 40 (Beaujouan, 2020). The overall rise in the mean age at first birth, known as "the postponement transition", started in the 1970s in economically affluent societies. The first countries to experience the phenomenon were those in Northern and Western Europe, Canada, and the US, while the transition started in the late 1970s in East Asia, in the early 1980s in Southern Europe, and during the 1990s in Central and Eastern Europe (Frejka and Sobotka, 2008; Kohler et al., 2002; Mills et al., 2011). In some Latin American countries – Argentina, Chile, Uruguay –, indications of a similar transformation towards fertility postponement have also been observed since the 2000s (Nathan and Pardo, 2019).

As a result, societies have been witnessing increases in late childbearing. The phenomenon seems to be gaining momentum in several societies, with late first births standing for a growing proportion of first birth rates to an unprecedented degree. While most late births were higher-order births in the 1950s, they currently tend to correspond to first and second births. Since the 1990s, fertility postponement has experienced a particularly rapid increase in low-fertility countries, to the extent that growing proportions of women are having their first child in their 40s and – by means of Medically Assisted Reproduction (hereafter, MAR) –, even surpassing the natural fertility barrier. In contemporary societies, extremely late childbearing (beyond the usual biological limit for female reproduction) generally corresponds to first births. It seems, in contrast, that older mothers – understood as women in their 40s – would frequently forego altogether the transition to the second child (Beaujouan, 2020).

The global rise in maternal age at birth has been mainly attributed to a fertility decline among younger women. Among the main factors underlying this phenomenon are widespread access to effective contraception (Lesthaeghe, 2010); the extension of educational attainment (Neels et al., 2017; Ni Bhrolchain and Beaujouan, 2012); difficulties in entering the labour market or acquiring employment stability (Kreyenfeld et al., 2012; Sobotka, 2010); economic uncertainty (Balbo et al., 2013; Beaujouan, 2020); lack of access to affordable housing (Mills et al., 2011); the desire to invest in a professional career or living with a partner before entering parenthood; shifts in social norms and individual values (Lesthaeghe, 2010); changes in partnership trajectories (Kreyenfeld et al., 2012; Mazuy, 2006; Sobotka and Toulemon, 2008); the opportunity costs of motherhood (Balbo et al., 2013); and work-family reconciliation difficulties (Mills et al., 2011). At the same time, however, general improvements in health and pregnancy monitoring also facilitate successful later childbearing in comparison to the past (Kotelchuck, 2006; Prioux, 2005; Vallin and Meslé, 2004).

All in all, the delay of reproductive decisions is a product of changing economic conditions at the societal level and of the transformation of women's and men's life-courses and roles (Beaujouan, 2020; Mills et al., 2011). The structural context appears to have an important influence in terms of discouraging fertility at earlier ages and encouraging it at later ages, and it also explains why compensation at later ages is more prevalent in some societies than in others. For example, in Southern Europe (Italy, Spain), the decline of fertility at younger ages (below the age of 30) is not compensated by a rise in fertility at later ages, which entails a reduced final number of children. In contrast, in Northern and Western European countries (France, UK, the Netherlands, the Nordic countries), the reduction in fertility at younger ages is compensated by increased fertility at later ages, which results in the average number of children remaining relatively high or falling only moderately (Beaujouan and Toulemon, 2019).

Policies that reduce work-family trade-offs and the opportunity costs of motherhood have namely proven to counter fertility delays (Mills et al., 2011). In contrast, postponement of first births has become most prevalent in those countries with the most significant obstacles to relatively early childbearing, such as Japan, Southern European societies, or those in South-East Asia. Among the main factors involved are insufficient institutional support for work-family reconciliation (Gauthier, 2016) and, in the case of Southern Europe, harsh labour market conditions – especially for younger adults – and the adverse macroeconomic climate derived from the Great Recession and with lasting effects on labour market entry and stabilization prospects. The enduring preference for children in such societies even at ages when conception becomes biologically more difficult reflects strong structural barriers to fertility at earlier ages. Postponement started later in Eastern European countries, which have not yet shown late fertility levels like those observed in other regions. Nevertheless, they have also experienced a rapid rise in age at first birth related to economic insecurity and the interruption of the family-oriented policies available before the fall of the Berlin wall (Beaujouan, 2020). The reproductive polarization between early and late childbearing observed in Latin America – particularly in Chile and Uruguay –, in contrast, seems mainly related to individual socioeconomic characteristics. High rates of unplanned pregnancies among younger women with lower education are observed in parallel to a peak in first birth intensity in the early 30s for higher educated women (Lima et al., 2018).

The most evident consequence of the delayed transition to parenthood observed in many societies is the increase in childlessness among individuals aged below 35. This phenomenon has been most prominent among women with higher education. Most of them will end up having at least a child, since women with higher education frequently exhibit relatively high childbearing rates in their late 30s and up to their early 40s. Still, a non-negligible proportion experience permanent childlessness (Sobotka, 2010) – as noted, the figure is currently estimated at around one in four women in societies with very low fertility linked to postponement, such as Spain and Italy (Caltabiano et al., 2017).

The relation between postponement of childbearing and fertility, nevertheless, is multifaceted and context dependent. At the population level, in countries having made the transition from high to around replacement fertility, rapid increases in age at first birth (particularly women's) over the past decades have far from always been accompanied by declines in the total fertility rate (TFR). There are namely important variations regarding the extent to which declines in childbearing at younger ages are compensated by increases in births at later ages (Beaujouan and Toulemon, 2021). The postponement of parenthood does play an important role in the emergence of very low period fertility in many societies having reached below replacement levels. Countries such as Japan, South Korea, Spain, or Russia have seen their already low fertilities depressed to the lowest-low range as a result (Sobotka, 2017). In contrast, however, other European countries (e.g., Sweden, Denmark, Norway, France) have shown no evident association between postponement of first births and declines in total fertility. On the contrary, an inverse relation seems to be present, entailing that longer delays over time usually correlate with relatively smaller fertility declines. This has been attributed to contextual effects that absorb individual constraints and facilitate later childbearing. Very crucially, in countries where public policies favour work-family reconciliation, women end up with a greater final number of children despite postponement of the first birth, as they find it possible to have further births at a relatively fast pace at later ages (Beaujouan and Toulemon, 2019; Beaujouan and Toulemon, 2021). This scenario contrasts sharply with the one found in Southern Europe. In Spain, for instance, the transition from the first to the second child is often difficult due to structural constraints related to the nature of the labour market and to insufficient public support to families, work-family reconciliation, and co-responsibility in care (Castro Martín et al., 2018). This said, even in countries where individuals manage to compensate at higher ages for the births foregone at younger ages, such compensation is only partial (Beaujouan and Toulemon, 2019).

At the individual level, at any rate, the general finding is a strong negative relation between age at first birth and the total number of children women end up having (Beaujouan and Toulemon, 2021). Postponement is also associated with a higher probability of childlessness. Significant delays in fertility decisions ultimately entail an increase in the risk of a gap between desired and achieved family size, of involuntary childlessness, and of the need to resort to MAR (Schmidt et al., 2012; Beaujouan, 2020). In fact, the postponement of childbearing has been highlighted as one of the main factors associated with the increasing use of reproductive technologies (Kocourkova et al., 2014) and has been shown to have a measurable impact in the share of involuntarily infertile couples (Leridon and Slama, 2008). There is indeed consistent evidence that the risk of infertility rises with women's and men's age (Liu et al., 2011). Women's fertility starts to decline at around 25-30 years of age, while the median age at last birth lies at around 40-41 years in analysed populations experiencing natural fertility. The most prevalent form of infertility across the world is secondary infertility. In less affluent societies – those where it is most widespread –, it is a result of unsafe abortions and deficits in maternal health (Vander Borght and Wyns, 2018). In Western countries where postponement is common, nevertheless, it is more frequently linked to postponement.

Age-related fertility decline seems to follow a rather universal pattern (Vander Borght and Wyns, 2018). In natural fertility populations – that is, those where fertility is not regulated, limited, or controlled by any form of contraception (Day Baird, 2013) –, the age-related loss of fertility lies at 4.5% at age 25, at 12% at age 35, at about 50% at age 40 and almost 90% at age 45 (Eijkemans et al., 2014). In addition to the age-related loss of fertility caused by depletion of the oocyte reserve, oocyte quality also decreases with advancing reproductive age, while other factors resulting in reduced conception rates – premature recruitment of follicles, ovulatory disorders, reduced ovulatory frequency, impaired luteal phase – increase (Hart, 2016). Late pregnancies also entail an increased risk of miscarriage, pregnancy complications, adverse maternal and perinatal health outcomes, and chromosomal abnormalities (Sobotka, 2010; Frederiksen et al., 2018). Evidence shows that many women are not aware of the consequences of postponement in terms of reduced fertility (Schmidt, 2010; Cooke et al., 2012), while there is a relatively widely held belief that MAR will be able to compensate for the fertility decline resulting from postponement (Maheshwari, Shetty and Bhattacharya, 2008).

Men's fertility is also affected by age. Paternal age above 40 has been found to be associated with declining sperm quality, an increased risk of failure to conceive, and a higher probability of miscarriage and adverse perinatal outcomes, while the combination of advanced maternal and paternal age entails particularly elevated risks (Nybo Andersen and Kjaer Urhoj, 2017; McPherson et al., 2018). Among the reproductive risks associated with advanced paternal age – especially after age 40, when they increase significantly – are also certain genetic mutations and chromosomal abnormalities (De la Rochebrochard and Thonneau, 2002; Brandt et al., 2018). In particular, the association with an increased risk of autism spectrum disorders (ASD) seems well-established (Sandin et al., 2015).

Even though both advanced maternal and paternal age are important for reproductive and perinatal outcomes, the fertility-related constraints associated with postponement are obviously most significant for women, given their limited physiological time for reproduction. The probability that a conception results in a live birth – for both first and higher order conception events – decreases significantly from age 35. It is also from this age that the demand for MAR has become particularly high over the past decades (Beaujouan, 2020). Health risks for the mother and the offspring also increase from age 35 (Schimmel et al., 2015). Social norms, furthermore, reinforce differences between women and men regarding how they are affected by postponement – from a normative point of view, there are more rigid upper age limits for motherhood than for fatherhood (Billari et al., 2011).

2.4. The heterogeneous impact of the postponement transition

The above notwithstanding, the impact of postponement on fertility is heterogeneous both across societies and across socioeconomic groups. Studies based on microsimulation have suggested that the delay of childbearing would lead to more involuntary childlessness and smaller families in certain countries, but not necessarily in others, where individuals manage to have the number of children envisaged at an older age. Among the reasons for such differences are structural factors such as the macroeconomic climate affecting individuals' financial and labor market prospects, cultural variables, and, as previously noted, the existence or the lack of family-friendly policies (te Velde et al., 2012) affecting work-family balance.

At the individual level, dispersion in age at first birth in high- and medium-income countries having undergone or started the postponement transition has also been identified. There appears to be growing educational and socioeconomic disparities in this respect, leading to reproductive polarization, especially in societies with liberal welfare regimes or high levels of socioeconomic inequality (e.g., the US, the UK, Latin American countries). In these societies, reproductive polarization entails growing differences regarding the timing of childbearing between socioeconomically less advantaged women and those in middle and upper socioeconomic strata, with the latter exhibiting a more pronounced tendency to postponement than the former. A certain heterogeneity regarding postponement patterns has also been observed in some Central and Eastern European societies as they ventured into the transition (Nathan and Pardo, 2019), and in Southern European countries with familistic welfare regimes – that is, those relying mainly on the family for provision of care and welfare for children and other dependants (León and Miggliavacca, 2013) – and high barriers to work-family reconciliation. In Southern Europe, nonetheless, trends towards postponement of births have been comparatively very pronounced and have involved to some extent women in all educational strata. In contrast, in universalistic countries such as Norway or France, with generous work-family reconciliation measures, increases in median age at birth have been more moderate and less polarization has been observed between lower and higher educational strata (Rendall et al., 2010).

In general terms, individuals with higher education tend to be those who postpone childbearing the most (Rendall et al. 2010). This is partly due to a delay in relevant life-course events – notably, the completion of education, which in turn could delay entry into employment and the formation of the first stable union (Ravanera and Rajulton, 2006). Highly educated women are also likely to experience greater opportunity costs, trade-offs and competition between motherhood and other life goals. Research has namely shown that, after finishing their education, women with university studies wait longer before having a child than women in other educational strata (Sobotka, 2010). There is also evidence that they would be generally less likely to make the transition to the first birth than women with low- and medium level education, although the educational gradient of primo-fertility varies considerably across contexts (Wood et al., 2014). Recent research, moreover, suggests that the overall negative educational gradient of fertility previously observed could be changing – drawing on European data, it has been found that highly educated women appear, overall, more likely to end up becoming mothers at some point in their lives, even if it tends to happen comparatively later. In addition, among women who postpone, those with a higher level of education are more likely to make the transition to motherhood. The phenomenon is particularly evident in the Nordic countries. In Southern and Western European societies, it is women with middle-level education who show lowest intensity of first births at the end of their reproductive stage (d'Albis et al., 2017).

Highly educated women are also more likely to recuperate postponed births and achieve their desired fertility at later ages (Sobotka, 2004; Kravdal and Rindfuss, 2008; Balbo et al., 2013). In fact, it has been proposed that the increase in late and very late fertility may have been most significant in contexts where union forms are diverse, and women are – in relative terms – highly educated (Beaujoan, 2020). There is also evidence from the UK indicating that older mothers have most often relatively high socioeconomic status and that the gap in terms of advantage with respect to younger mothers has been widening (Goisis et al., 2018). There seems thus to be a positive educational gradient not only regarding postponement, but also the extent to which fertility is recuperated once it has been delayed. It should be borne in mind, nonetheless, that patterns are context-dependent and the relation between education, postponement and fertility is complex (Balbo et al., 2013), as well as affected by structural variables. This results in cross-country differences in educational gradients in fertility (Wood et al., 2014). For example, even among high income countries, there remain several societies – such as South Korea and Spain, characterized by very low fertility, a high degree of postponement, but also difficult work-family reconciliation conditions – that still exhibit a negative educational gradient in fertility (see Shin, 2019; Requena, 2022). These findings could be explained by the greater sensitivity of highly educated women to contextual variables, which would also account for certain cross-country differences in progression to second and higher-order births (Wood et al., 2014).

2.5. Who remains childless in contemporary societies?

Besides educational gradients in fertility, postponement, and its consequences, it is pertinent to examine differences in childlessness across educational – and, more generally, socioeconomic – strata. Even though women with higher education having postponed childbirth appear more likely to recuperate delayed fertility once they make the transition to motherhood, higher educated women also have shown, in different contexts, higher childlessness rates (Wood et al., 2014; Burkimsher and Zeman, 2017; Köppen et al., 2017). While these findings might seem contradictory or at the very least puzzling at first sight, they are likely to be explained by selective entry into parenthood. Highly educated women who make the transition to the first birth and then proceed to higher-order births could be particularly selected in terms of relatively strong family orientation (see Wood et al., 2014), as compared to lower educated women who postpone and to higher educated women who eventually remain childless.

Nevertheless, context proves, once more, a relevant mediating factor of the significance of education. For example, in the relatively traditional German context, where the male-breadwinner model was long encouraged and the costs of motherhood for working mothers are considerable, highly educated women are overrepresented within those who have non-coresidential relationships and remain childless (Raab and Struffolino, 2019). Likewise, in Italy, highly educated women have a relatively lower probability of union entry and thus of family-building (Präg et al., 2017). In contrast, such is not the case in Finland, characterized by a more gender egalitarian society, where men and women with a low level of education show the greatest probabilities of childlessness (Jalovaara and Fasang, 2017; Rotkirch and Miettinen, 2017), possibly because they conform a very selective group, not as "successful" in the marriage market, in a context where tertiary education is widespread, not least among women (Präg et al., 2017). In some countries – e.g., France – higher education is associated with a higher probability of childlessness for women, but not for men (Köppen et al., 2017). In others, such as Switzerland, there are small differences by education for men, and those with a lower level of education are more likely to remain childless (Burkimsher and Zeman, 2017).

Beyond education, childlessness in Europe has been found to be strongly related to partnership trajectories. The lack of a partner – especially among men –, unstable union histories, late entry into partnerships, and a history of long-term non-coresidential relationships have been found to bear significant associations to the phenomenon in a variety of countries (see Seiz, 2013; Berrington, 2017; Jalovaara and Fasang, 2017; Kreyenfeld and Konietzka, 2017; Köppen et al., 2017; Rotkirch and Miettinen, 2017; Chudnovskaya, 2019; Raab and Struffolino, 2019).

Attention has also been drawn to the importance of the intersection between educational, employment, and union trajectories, given that the pathways leading to childlessness are often the result of a complex accumulation of decisions and events rather than attributable to a single factor (Präg et al., 2017). Interestingly, it has been found that individuals who remain childless are in many relevant respects similar to those who postpone childbearing. All in all, the lack of a stable partner seems the main factor underlying both phenomena, although the noted positive educational gradient is present as well in many societies among women. This said, some European countries – the Nordic ones, and, in particular, Finland – appear to be experiencing a reversal in the educational gradient of childlessness among younger individuals (Präg et al., 2017). In the United States, childlessness rates among women with tertiary-level education also seem to be declining and converging with those of women with secondary-level education, which could be indicative of a similar pattern. Among the explanations proposed are the increasing heterogeneity characterizing women with higher education, their holding a more attractive position in the marriage market in a context of diffusion of the dual-earner model and rising costs of life; and reduced work-family reconciliation tensions for this group due to increased availability of telework and flexible schedules (Rybínska, 2020). A similar development has been recently observed in Australia, where the educational gap in childlessness has narrowed, and the tendency to rising childlessness among women with university-level education has reversed (Lazzari, 2021). Against these experiences, it seems a plausible scenario that increasing postponement across educational strata increasingly could come to blur differences among them, while the greater ability of highly educated women to compensate for postponed births – to some extent, possibly due to a greater access to MAR – might, in some societies, continue to work in the direction of a shift in the educational gradient.

MAR is frequently expected to alleviate infertility for those individuals who face the possibility of childlessness but who do wish to have children (Präg et al, 2017). For instance, it has been argued that IVF could compensate to a large degree for the increasing risk of permanent involuntary childlessness by postponement if all eligible couples could complete three IVF cycles (te Velde et al., 2012). Nevertheless, it has been estimated that, for multiple reasons that will be dealt for further below, a large proportion of couples experiencing infertility do not seek medical attention or do not eventually receive treatment (Boivin et al., 2007). Although the exact contribution of MAR to fertility is difficult to assess (Passet-Wittig and Martin Bujard, 2021), it is known that the degree to which treatments are successful varies across societies and depending on women's age (Präg et al., 2017), while parental socioeconomic resources affect the probability of conceiving through MAR (Goisis et al., 2020). Accordingly, the compensatory effect of MAR on infertility – at the micro level – and low fertility – at the aggregate level – can hardly be regarded as sufficient, even though it is an increasingly used resource throughout the world as a result of postponement-derived, age-related childlessness and infertility (Präg et al., 2017).

3. Infertility and infecundity from a biological and social perspective

Changes in reproductive ideals and behaviour (desire of smaller families, later childbearing) are one of the major drivers of fertility decline observed in many regions of the world today. Economic and socio-demographic factors (economic precariousness, absence of a partner) account for a large part of the gap between desired and completed fertility (involuntary childlessness). However, the role of biological factors in these trends, and more specifically, whether human fecundity, i.e. the biological capacity of humans to reproduce, is changing (Smarr et al., 2017), and if so, for what reasons, is also under debate (Skakkebæk et al., 2022).

3.1. Concepts and definitions

The World Health Organization (WHO) defines infertility as "a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse" (WHO Key Facts, 2022). Estimates from the WHO suggest that between 48 million couples and 186 million individuals live with infertility globally. The prevalence of infertility after one year of unprotected intercourse has been estimated to lie on average, at around 9% (Passet-Wittig and Greil, 2021; Boivin et al., 2007). In some parts of the world, nevertheless, significantly higher rates have been found, especially in economically disadvantaged areas (Mascarenhas et al., 2012). However, the quantification of the prevalence might be biased in some instances and the comparability across countries might be endangered by issues in microdata collection, for instance incomplete information in contraceptive use, couple status, intercourse frequency, etc. These problems are likely to lead to an under-diagnosis (and under-reporting) of infertility in certain contexts.

Infertility can be primary or secondary. Primary infertility takes place when a pregnancy has not been achieved after at least one year of regular, unprotected intercourse, while secondary infertility occurs when at least one prior pregnancy/birth has been achieved without difficulty. Although of course related to the concept of infertility, sterility usually refers to the inability to procreate, while difficulties to conceive are much more common than sterility (Rochon, 1986) and so not everyone diagnosed with infertility is sterile.

3.1.1. Measurement of infertility

Measuring human fecundity poses important methodological and data challenges (Inserm and Agence de la Biomédecine, 2012; Smarr et al., 2017). Contrary to fertility, which can be measured at the population level using estimates of live births and sometimes stillbirths, directly measuring fecundity at this level is often impossible and proxy measures are used. For couples, the number of calendar months or menstrual cycles required to become pregnant (time-to pregnancy, TTP) is often used as a proxy of fecundity. However, having the couple (and not the individual) as the unit of observation makes it more complex to interpret the results as the outcome (infertility) depends on the combined characteristics of – and interaction between – both partners and may well change with another partner.

Semen quality, clinical measures of testicular volumes and hormonal profiles are commonly used proxies of male fecundity. Although relatively easy to collect, especially sperm, the fact that they vary for the same individual requires repeated observations at different moments, which is not always done. Hormonal profiles, menstruation and ovulation, and biomarkers of follicular reserve (anti-Müllerian hormone) are used as proxies of female fecundity, but they are harder to collect than male samples and may be affected by hormonal contraception.

Another approach consists in studying alterations in the human reproductive system (specific symptoms or illnesses) that may potentially affect fecundity, such as certain types of cancer or genital malformations. There is consistent evidence of temporal changes for male fertility (increase of genital malformations, such as cryptorchidism, hypospadias, anogenital distance[2]; testicular and prostate cancer; decrease in sperm quality). Evidence regarding female fertility is scarcer, but some studies also show an increase in breast and ovarian cancers, as well as changes in menstrual/ovulation cycle

[2] Cryptorchidism: undescendened testis (UDT). Hypospadias: opening of the urethra is not located at the tip of the penis.

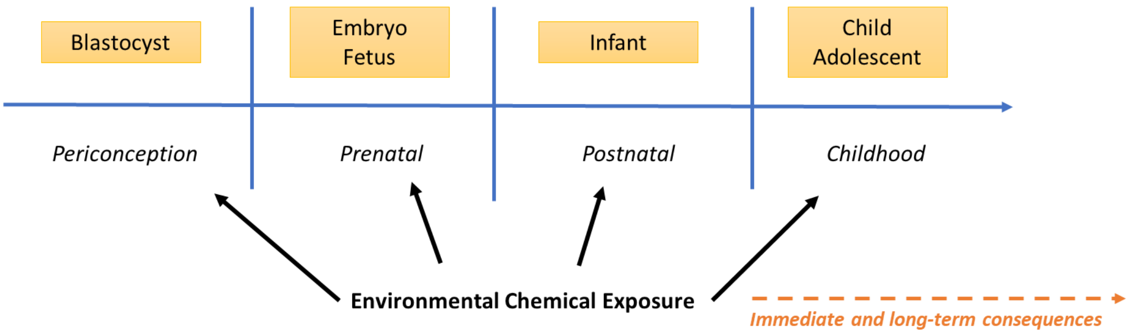
and the onset of puberty and menopause. Although existing data sources – registries of fertility/infertility treatments, live births, reproductive cancers and genitourinary malformations, nationally representative surveys of reproductive health – provide partial evidence on the above indicators, critical data gaps remain making it for the moment impossible to accurately answer the question of whether human fecundity is changing (Smarr et al., 2017).

3.2. Concepts and definitions

Broadly speaking, four types of issues constitute the main drivers of infertility in the male reproductive system, namely issues in the ejection of semen, low levels of sperm or absence of sperm, issues related to the morphology of sperm, and problems with the movement (motility) of the sperm. In the female reproductive system, infertility may be originated by a variety of one or more conditions pertaining to the endocrine system, the ovaries, the uterus, the fallopian tubes, etc. (WHO Key Facts, 2022).

The drivers of infertility are varied and complex to determine for several reasons, as Figure 1 below illustrates. Firstly, because both genetic, and more generally biological, factors but also environmental stressors are at work, and the influence of both types are expected to be interactive, not additive, in line with findings in the epigenetics field. Secondly, because there are several stages – from preconception to adult life – at which (in)fertility-related processes can occur. In addition, one infertility-promoting event can be consequential for events at other stages; insults are likely to have cumulative effects over the life-cycle.

Figure 1: Stages at which infertility-related processes occur



Source: Adapted from the figure "Child Development and Windows of Susceptibility", Sutton et al. 2014.

This glimpse into the complex generative process of infertility allows anticipating that potential treatments or interventions to tackle it are necessarily far from simple. In the next two sections, we briefly summarize the main findings from the literatures addressing biological and environmental factors, respectively, underlying infertility.

3.2.1. Biological mechanisms

In contrast with gametogenesis among women, men's allow them to produce germ cells, and in consequence to reproduce, throughout most of their lives. Nonetheless, both fertility and semen quality do seem to decline partly as men age (Damario, 2014), even though the correlation between semen characteristics and fertility is not complete. In addition, a notable decline in sperm concentration in European men has been shown over the last decades (Sengupta et al., 2017). Sperm morphology, concentration and motility are the main indicators involved in semen analysis. Other tests aiming at identifying male infertility deal with endocrine evaluation or analyses of sperm DNA integrity. In a substantial proportion of cases in which male infertility is diagnosed, a specific cause is not identified. However, according to some experts (Aston, 2014) many of these idiopathic cases of male infertility are likely to have a genetic basis, often unidentified. Advances in genome-wide association studies (GWAS) allow better understanding genetic underlying causes, although there is ample room for research using these tools (Lin and Matzuk, 2014). In a systematic review of monogenic causes of male infertility, 104 genes that were linked to some extent to 120 infertility phenotypes were detected, and a substantial increase in the number of "high-probability human infertility genes" was identified relative to prior recent reviews (Houston et al., 2021).

Women's fertility is conditioned by the limited amount of germ cells that they have, the declining number of oocytes over the lifespan, and the accelerated speed of follicular loss after age 37-38 (Damario, 2014); declining fertility with age has been long ago proved for populations in which no contraception is used (Tietze, 1957). The reduced sexual activity at later ages does not fully explain fertility fall with age, and success rates of ART are also lower as women age (CECOS Fédération et al., 1982). Identifying the influence of age on the appearance of infertility-inducing conditions is, in addition, cumbersome. Usual etiologies of female infertility include an abnormal ovulatory function, a diminished ovarian reserve, problems in the uterine cavity and in the fallopian tubes, or endometriosis. Conditions such as pelvic inflammatory disease led by sexually transmitted diseases, sometimes untreated or inadequately treated (Hillis and Wasserheit, 1996) also condition fertility. In the study of female infertility, genetic studies have addressed factors affecting the length of the reproductive lifespan. Genetic factors regulating the timing of puberty and menarche, on the one hand, and age at menopause, on the other, have been identified (see Gajbhiye et al., 2018 for a review). Successful reproduction, as measured by age at first birth (a far from ideal indicator if we consider changes in voluntary childlessness and postponement explained above) has been found to be associated with 10 independent genomic loci in women, men or both (Day et al., 2016). Similarly, a genetic association has been established with ovarian reserve and primary ovarian insufficiency (Laisk-Podar et al., 2016). With postponement (attempts) of childbearing over the generations, the importance of factors limiting the number of oocytes available might be becoming more evident (Hart 2016). Studies on the gene-based role of polycystic ovary syndrome and endometriosis – two common causes of female infertility – are also frequent (f.i. Mykhalchenko, K. et al., 2017; Sapkota, Y. et al., 2017). Besides discovering the role played by individual genes on aspects leading to female infertility, GWAS data and analysis is expected to bring about relevant progress in our understanding of this very complex phenomenon.

The role of certain lifestyles on fertility has also been subject to scientific scrutiny. Among those, smoking is probably the factor most clearly associated with fertility problems at all stages (Damario, 2014 for a review), from gamete production to implantation, to birth outcomes, including an increased risk of spontaneous abortion, a lower birthweight, higher risk of prematurity. Smokers tend to show a general higher infertility (relative to non-smokers) both in women who naturally conceive and in those who undergo an IVF treatment, and an earlier transition to menopause. The influence of other substances such as caffeine or alcohol is less well established so far. Similarly, even though a normal weight is associated with a higher fertility, pursuing dietary changes does not seem to affect fertility in women within the normal weight range. An excessive amount of exercise can lead to a reduction in the frequency of ovulation, endometrial issues, amenorrhea, and subfertility (Hart, 2016). The effects of high metal concentrations and other substances in the environment will be addressed in the next section.

3.2.2. Environmental influences

The increasing evidence in alterations of the human reproductive system, among both male and female, have raised the question of whether some of these changes are "man-made", due to the growing presence of toxins and chemicals in the environment (Buck Louis et al., 2008; Inserm, 2011; Rodprasert et al., 2019). The identification of reproductive health issues among populations affected by environmental disasters constituted some of the first evidence pointing in this direction. Some of the major first events of this type include the Love Canal neighbourhood, near Niagara Falls, which was affected by decades of hazardous waste, and that first received public attention in 1978 (Austin et al., 2011), or the methyl isocyanate gas leak after an explosion near the Union Carbide plant in Bhopal, India, gas in 1984 (Dhara and Dhara, 2002). In 1971 a pioneer study among young women having been exposed in utero to distilbene (a treatment to prevent miscarriage) and having a higher risk of cancers (clear cell adenocarcinoma of the vagina and cervix), followed by other studies[3], showed the intergenerational effects of these toxic exposures. Shortly after, the book "Our Stolen Future" explored, for the first time, how chemicals interfered with hormone action – endocrine disruption– (Colborn et al., 1996). In the following decades (2000s-2010s) there was increasing evidence linking environmental factors and adverse reproductive health outcomes (Crain et al., 2008; Hauser and Sokol, 2008; Inserm, 2011; Segal and Giudice, 2019; Skakkebæk et al., 2022; Sutton et al., 2014). This hype in scientific research on the topic was accompanied by rising awareness among professional associations and practitioners on the necessity to take these risks into account when designing health intervention policies (ACOG, 2013; Di Renzo et al., 2015). Although these advances have led to some policy changes, such as the stricter regulation of EDCs in the EU[4], all studies conclude that more research is needed to understand the precise role of environmental factors on human fertility – critical exposure windows, exposure to multiple elements, specific mechanisms.

Studies describing trends in human reproductive function (genital malformations, testicular, prostate, breast and ovarian cancers, production of male and female gametes, timing of puberty and menopause) often do not allow identifying the effect of specific environmental factors. However, the accumulation of evidence in such a short period of time clearly suggests the role of the environment in these changes. Based on evidence for male populations, Skakkebæk et al. developed the paradigm of a common testicular dysgenesis syndrome (TDS), which is more frequent among recent cohorts of individuals due to adverse environmental influences (Skakkebæk et al., 2001):

> *"Growing evidence from clinical observations of individual patients and from larger epidemiological studies indicates a synchronized increase in the incidence of male reproductive problems, such as testicular cancer, genital abnormalities, reduced semen quality and subfertility. Temporal and geographical associations, as well as frequent combination of more than one problem in one individual, strongly suggests the existence of a pathogenetic link. The association of male reproductive problems is probably not coincidental but reflects the existence of a common underlying cause resulting in a maldeveloped testis. We named the resulting phenotype the testicular dysgenesis syndrome (TDS). Experimental biological investigations and epidemiological studies leave little doubt that the TDS can be a result of disruption of embryonal programming and gonadal development during foetal life. As the rise in the incidence of the various symptoms of TDS occurred rapidly over few generations, the aetiological impact of adverse environmental factors such as hormone disrupters, probably acting upon a susceptible genetic background, must be considered." (Skakkebæk et al., 2001).*

This paradigm was later used to examine health across the woman's lifespan and the role of environmental factors, and the evidence was grouped under the term of ovarian dysgenesis syndrome (Buck Louis et al., 2011a). However, its definition is more loosely encompassed as there is much less evidence on the mechanisms through which environmental factors can impair female reproduction (van Duursen et al., 2020).

Measuring fecundity, the biological capacity to conceive, and a fortiori the role of environmental factors at the population level is not possible and requires specific and often complex study designs,

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[3] For more information on the DES Cohorts Follow-up Study: https://dceg.cancer.gov/research/what-we-study/des-study

[4] The first "Community Strategy for Endocrine Disruptors - a range of substances suspected of interfering with the hormone systems of humans and wildlife" (COM(1999) 706) was developed in 1999 (https://ec.europa.eu/environment/chemicals/endocrine/). A new strategy on EDCs is being developed by the EU. In the framework of this work, eight research projects aiming to propose new testing and screening methods to identify EDCs are financed (https://eurion-cluster.eu/).

with simultaneous collection on information on partners' background (socio-demographic, medical), reproductive histories, as well as biological samples and measures of contaminants. An example of such a study is the prospective LIFE cohort, which recruited 501 couples planning pregnancies who were then followed up while trying to conceive and throughout pregnancy (Buck Louis et al., 2011b). However, as noted by the authors, given the absence of appropriate sampling frameworks only a small percentage of couples contacted were found eligible and reportedly planning pregnancy at any point in time, resulting in small sample sizes. Studies among patients of fertility clinics allows to bypass this issue as these are couples actively seeking to conceive. An example, of a such a prospective cohort is the Environment and Reproductive Health (EARTH) study, which recruited 799 women and 487 men since 2004 among patients of a large academic fertility centre (Messerlian et al., 2018). However, these studies also have potential issues, as the results observed among infertile/sub fertile couples may not always be extrapolated to the entire population. In this context, many of the existing studies on reproduction and environmental factors focus on later endpoints (Gómez-Roig et al., 2021; Nieuwenhuijsen et al., 2013; Slama and Cordier, 2013): spontaneous abortion (pregnancy loss before ~20-22 weeks); stillbirths (pregnancy loss ~20-22 weeks); course of pregnancy (pregnancy-induced hypertension, foetal growth), as well as pregnancy outcomes (preterm births, low birthweight, congenital anomalies, sex-ratio).

The most abundant and solid evidence on the decrease in reproductive capacities in exposed populations is established for air pollution (Carré et al., 2017). For example, pregnant women exposed to peaks of air pollution were at a higher risk of spontaneous abortion (Enkhmaa et al., 2014; Ha et al., 2018; Leiser et al., 2019). A recent systematic review found evidence that Persistent Organic Pollutants (POPs), notably some polychlorinated biphenyls and organochlorine pesticides, may impair embryo quality and pregnancy rates among IVF patients (Lefebvre et al., 2021). However, it also pointed out risk of biases in the studies analysed, such as the lack of consideration of relevant confounding variables, low sample size or underreporting of methods, but also absence of evidence on another important outcome: live births.

Among the most common Endocrine Disrupting Chemicals (EDCs), bisphenol A (BPA) has been shown to affect oocyte quality, implantation, embryo development, and placentation among IVF patients as well as result in lower semen quality among men (Segal and Giudice, 2019). Women undergoing IVF with a higher concentration of phthalates had lower numbers of oocytes retrieved, lower pregnancy rates, and higher risk of early pregnancy loss before 20 weeks of gestation (Messerlian et al., 2018), while for men they were associated with abnormal semen parameters, specifically decreased motility, and increased time to pregnancy (Segal and Giudice, 2019). The presence of certain metals (lead, mercury, cadmium) is also associated with adverse reproductive outcomes.

Most of the existing evidence on the impact of environmental factors on fertility is limited to exposures in adulthood, i.e., in the relatively short term. However, one of the challenges when trying to determine the possible impact of the environment is identifying early exposure to these elements, including before adulthood. As mentioned above, several windows of susceptibility have been identified, specifically the gestational period and puberty, with different effects for male and female. The chromosomal sex of the embryo is established at fertilization (existence of chromosome Y), but additional signs of sex differentiation occur later over the pregnancy. During the gestational period in humans, the embryo is susceptible to the influence of chemicals.

Male genitalia are formed during this period and studies have found that male children of mothers with higher levels of bisphenol A (BPA) or Persistent Organic Pollutants (POPs), were more likely to have cryptorchidism – undescended testis – at birth. Women are born with a given stock of oocytes which diminishes with age; decreases in quality are also observed as women age. Recent studies suggest that premature ovarian insufficiency (POI) could be due to environmental factors. While there are no studies addressing the effects of EDCs on the initial stock (quantity / quality), this is an obvious direction for future research (van Duursen et al., 2020).

The reproductive systems of new-borns continue to develop in the first months after birth (a period some researchers refer to as "mini-puberty") and there is evidence that exposure to certain chemicals during this period may affect them (Lucaccioni et al., 2021). The timing of exposure is important: while maternal exposure to combined EDCs was associated with a higher risk of testicular cancer in male offspring, estimates related to postnatal adult male EDC exposures were inconsistent (Bräuner et al., 2021). Puberty is marked by the development of secondary sexual characteristics, accelerated growth, behavioural changes, and eventual attainment of reproductive capacity. Although there are global trends towards an earlier onset of puberty, the specific role of EDCs in this evolution is not clear as some studies show that exposure to EDCs are associated with an earlier timing, but other studies report that it is associated with a later timing (van Duursen et al., 2020).

Although exposure during these key life stages – gestational period and puberty – are likely to affect long-term reproductive health, including the capacity to conceive and carry out a pregnancy, existing data sources rarely include information on this early exposure and thus make it difficult or impossible to study their long-term effects. Currently, there is only knowledge on the long-term impact of a small number of environmental factors, such as tobacco use, exposure to distilbene or to some persistent organic pollutants (Inserm, 2011). Distilbene (DES) was a hormonal treatment prescribed to women at risk of miscarriage from the mid-1940s until the early 1970s in many western countries. In the first generation of patients exposed to DES (mothers) a modestly increased risk of breast cancer was observed.[5] The second generation (daughters) experienced more often adverse reproductive health outcomes (greater risk of infertility, spontaneous abortion, preterm delivery…). Results from a new study launched in the 2000s on the third generation (granddaughters) are also suggestive of reproductive health issues (greater likelihood of amenorrhea, menstrual irregularity). However, given their young age and the fact that many of them had not yet finished their reproductive lives, it was important to continue follow-up as the risk of other adverse health outcomes increases with age.

However, for many other elements it is difficult to establish a causal link due to the complexity of the mechanisms at play. For example, in males, in-utero exposure to EDCs leads to cryptorchidism, which is associated with lower sperm quality in adults and may lead to lower fertility. Among females, prenatal exposure to EDCs may lead to higher risk of endometriosis, which in turn affects women's ability to conceive and carry out pregnancy. As a result, for many types of chemical exposures the only existing scientific evidence available comes from animal experiments. However, as the sensitivity of the reproductive function to environmental factors may be different from that of humans, the automatic transposition of these findings raises questions.

4. Medically Assisted Reproduction (MAR) to tackle infertility

This section provides an overview of the main medical interventions and treatments available to deal with fertility issues and infertility, how they are regulated under the national normative frameworks, and what are the access requirements to these treatments. Statistics on their use and outcomes are also provided. While the primary focus in this section is on EU27 countries, evidence from other countries in Europe and from other regions in the world is provided when relevant.

4.1. Concepts and definitions

The International Glossary on Infertility and Fertility Care (Zegers-Hochschild et al., 2017) defines Medically Assisted Reproduction (MAR) as:

> Reproduction brought about through various interventions, procedures, surgeries, and technologies to treat different forms of fertility impairment and infertility. These include

[5] Key findings from the DES Cohorts Follow-up Study can be found here: https://dceg.cancer.gov/research/what-we-study/des-study

> ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures, uterine transplantation, and intra-uterine, intracervical and intravaginal insemination with semen of husband/partner or donor.

According to the same source, Assisted Reproductive Technology (ART) comprises:

> All interventions that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction. This includes, but is not limited to, IVF and embryo transfer ET, intracytoplasmic sperm injection ICSI, embryo biopsy, preimplantation genetic testing PGT, assisted hatching, gamete intrafallopian transfer GIFT, zygote intrafallopian transfer, gamete and embryo cryopreservation, semen, oocyte and embryo donation, and gestational carrier cycles.

In other words, MAR covers a broad set of interventions to treat infertility, including treatments such as ovulation inducing drugs and assisted insemination, while ART is limited to interventions occurring outside of the patients' body. In practice however, the two terms are sometimes used interchangeably, and discussions of ART may include assisted insemination. In addition, although surrogacy is not an ART treatment per se, it is dependent upon these technologies and is often used by infertile couples, as well as by same-sex couples and single persons, to become parents.

4.2. Brief history and overview of treatments

Infertility has been known since ancient times and attempts to treat it, for example through artificial insemination, have been documented prior to the advent of modern medicine (Ombelet and Van Robays, 2015). However, most of the modern MAR treatments were developed starting from the end of the 19th and throughout the 20th centuries.

The history of artificial (or assisted) insemination (AI) goes back to the 19th century. The first practical methods were established for animals (dogs, rabbits, poultry, and later cattle), and would later be used for humans as well starting from the 1940s (Ombelet and Van Robays, 2015). Homologous artificial insemination is carried out with the sperm of the husband or male partner (AIH) and can be used in some cases of physiological and psychological dysfunctions, as well as for unexplained and mild male-factor subfertility. Artificial insemination with donor semen (AID), which developed with the introduction and availability of donor sperm, allows addressing other medical issues (azoospermia, very low sperm count, inherited genetic diseases linked to the Y-chromosome) and makes available the treatment to single women and female couples. More recently, AI treatments "benefitted" from ART-related discoveries – preparation of sperm ("washing" and concentration) before placing in the uterus – leading to higher success rates. Depending on the reasons for infertility, intra-uterine insemination (IUI) can be coordinated with the normal cycle or in combination with hormonal stimulation to facilitate ovulation. One of the advantages of AI is that it is a relatively easy procedure (no pain, no anaesthetics required) and less costly compared to other ART treatments. Because of these advantages, it is sometimes offered as a first-line treatment of infertility, a situation which raises debates in the medical community (Wyns et al., 2019).

At present, embryo transfers are the most frequent type of ART treatments. As in the case of assisted insemination, these techniques were first developed among animals. The first known case of embryo transplantation happened in the 1890s, when Walter Heape successfully completed this procedure in rabbits. The first actual live births in mammals (again, rabbits) via in vitro fertilization (IVF) did not occur until 1959, when a white rabbit delivered using eggs and sperm from black rabbits. Research with women's eggs and men's sperm developed throughout the 20th century, with the following most relevant milestones. In 1948, the first massive retrieval of women's oocytes was achieved; in 1961, the first retrieval of oocytes by laparoscopy was achieved; in 1965 the first attempts to fertilize human oocytes in vitro were made, in 1973 the first IVF pregnancy was reported, although it resulted in an early miscarriage (less than one week).

The birth of the first so-called "test tube baby", Louise Brown, in England in 1978 marks the beginning of the last forty years of continuous and successful use of ART in humans and the availability of an increasingly wider range of specific techniques. In the years after the birth of Louise Brown, several other IVF babies were born in Australia, the United States, and several European countries. Further refinements in the various procedures and adjustments to specific conditions (Kamel, 2013) were successfully researched and introduced in clinical practice over time. The British physiologist Robert Edwards, co-developer of the first IVF programme, received the Nobel Prize in Physiology or Medicine in 2010. This recognition offered broad visibility to the wealth of achievements developed in the previous decades by teams from various disciplines and in several regions of the world. It also stimulated further innovations to deal with increasingly more specific and less common infertility- and subfertility-leading issues in both women and men, and to increase efficiency in the treatments – rising rates of pregnancies and live births, lowering the number of cycles required, minimising the risks of multiple births, etc.

In the remainder of this section, some conceptual definition and basic explanation of specific procedures is provided.

In Vitro Fertilisation (IVF) consists of the combination of an egg and sperm outside the woman's body: eggs are placed in dish with washed and highly motile sperm and one or more of the resulting fertilized eggs – embryos – are then transferred into the woman's uterus. When there are more severe male infertility problems and the sperm does not succeed in breaking the cytoplasm of the egg, it can be injected with a needle in order for fertilization to take place. This treatment is called Intracytoplasmic Sperm Injection (ICSI). The first successful ICSI pregnancy took place in 1991, followed by a delivery the following year. Both IVF and ICSI usually require previous ovarian stimulation, using ad hoc oral and/or injected medications, to ensure that multiple eggs, instead of the usual single egg after natural processes, are produced.

Ovulation inducing drugs can be used independently to treat female infertility issues (anovulation), in combination with other treatments (IUI, IVF/ICSI) or in order to produce eggs for donation or freezing – either as eggs or fertilized eggs [embryos] – (ASRM, 2016). These drugs are used for two main situations: 1) to cause ovulation in a woman who does not ovulate regularly, and 2) to cause multiple eggs to develop and be released at one time (superovulation). Superovulation implies very close monitoring, daily injections that can be painful, and it is generally physically and emotionally strenuous. If and when the follicles are prepared, drugs help in the maturation and increase the ability of eggs to be fertilized.

Fertility preservation involves the storage of cells and tissues at low temperatures for future use (cryopreservation or cryoconservation). While conventional freezing by slow cooling methods could result in the damage of cells and tissues, vitrification, a process developed in the 1980s and involving ultra-rapid cooling, allows to reduce this risk. Semen, oocytes, embryos, or ovarian tissue can be preserved. While initially fertility preservation was mainly done for medical reasons (for example, before cancer treatment), a greater number of women doing this in anticipation of age-related fertility decline (Varlas et al., 2021). Superovulation in the context of IUI or IVF/ICSI leads to the creation of multiple embryos, and some may be cryopreserved and transferred to the woman in the future. This technique is named Frozen Embryo Replacement (FER).

Compared to other ART, preimplantation genetic testing (PGT) does not primarily treat classic infertility issues, but it allows couples with a serious hereditary condition to detect in vitro whether the embryo carries these conditions. The first genetic testing techniques were developed in the 1980s and new developments allow screening for an expanded array of genetic disorders (Boulet et al., 2019). For PGT a classic IVF is carried out, then a small sample of cells is biopsied from each embryo which are then sent out for PGT. At present there are three main types of tests:

- PGT for aneuploidies (PGT-A): this test seeks to identify embryos with abnormal chromosome numbers (aneuploid), – previously known as PGS (Preimplantation Genetic Screening;

- PGT for monogenic/single gene defects (PGT-M): this test allows identifying whether the embryo carries a specific genetic disorder, – previously known as Preimplantation Genetic Diagnosis, PGD;
- PGT for chromosomal structural rearrangements (PGT-SR).

4.3. Regulation and access to MAR

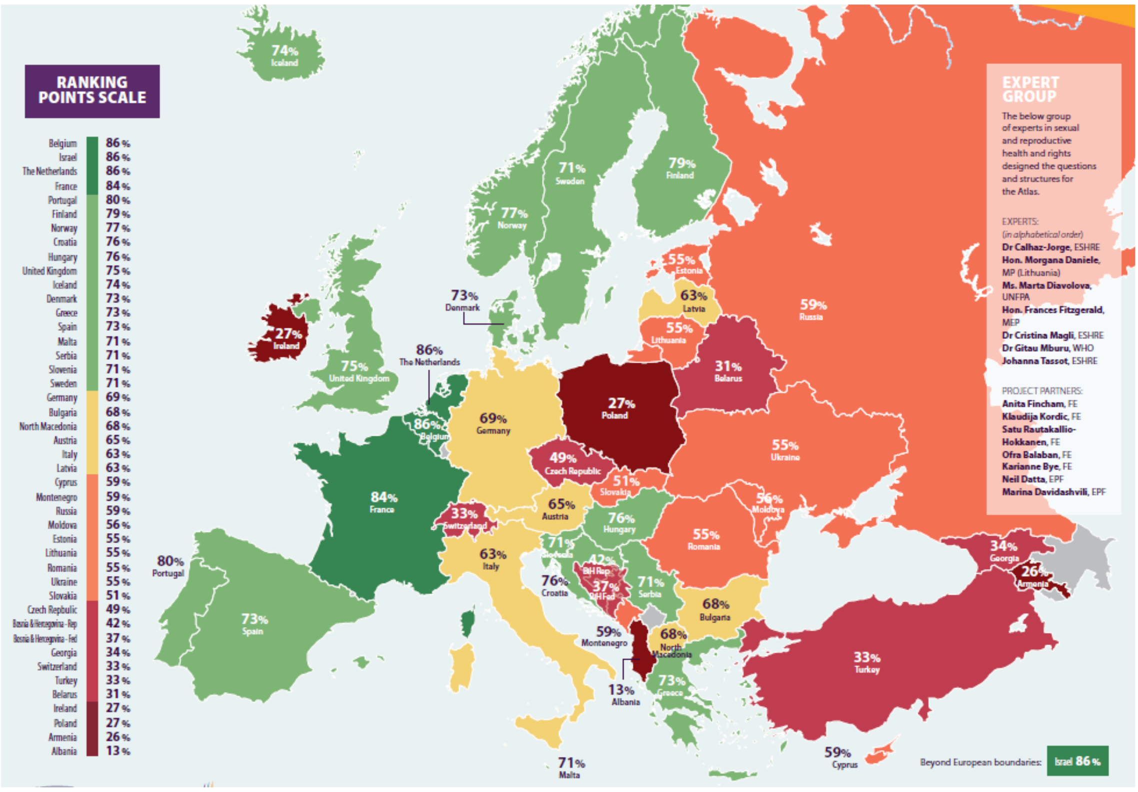
The analysis of MAR regulations across countries is a complex task as they cover multiple areas, but also take a variety of forms: legislation, professional guidelines and insurance coverage (Präg and Mills, 2017a). At present, Europe is the only region in the world where most countries have MAR regulations, but the latter cover several dimensions and are characterized by large variation, making cross-national comparisons complex. Building on the comparison of ART policies in Western Europe, Engeli and Rothmayr Allison (2016) identify three dimensions: (1) the autonomy granted to the medical community to practice ARTs; (2) the constraints imposed upon access to treatment; and (3) the availability of healthcare coverage for fertility-related treatment – and conclude that:

> "These three dimensions of the ART issue do not necessarily follow a linear regulatory pattern and they can be combined in multiple ways. Indeed, several regulatory regimes in Western Europe grant broad autonomy to physicians while strictly limiting patient access to heterosexual couples and those who can afford the financial cost of such treatments. From a gender perspective, such policies cannot be considered as being in any way permissive, because they impose heteronormative standards on access to treatments and reinforce existing sexual orientations and socio-economic discrimination."

In this context, the European Atlas of Fertility Treatment Policies aims to compare ART legislation across multiple dimensions: existence of ART legislation, available treatments, existence of public funding and patients' perspective.[6] It attributes a score between 0 and 100 to each country, with an optimal country (scoring 100), having, among others, specific ART law, wide variety of treatments available to the majority of the population (not only heterosexual couples, but also single women and homosexual couples), and reimbursement of multiple fertility treatments. The map in Figure 2 shows the diversity of the current policy situation in Europe (as of December 2021). Although, more than a half of the countries are qualified as "excellent" or "very good", mainly located in Western, Northern and Southern Europe, the figure also shows that MAR regulations remain more restrictive in many countries today, especially in Central and Eastern Europe.

[6] The European Atlas of Fertility Treatment Policies is carried out by Fertility Europe (FE) in conjunction with the European Parliamentary Forum for Sexual and Reproductive rights. For more information: https://fertilityeurope.eu/european-atlas-of-fertility-treatment-policies/

Figure 2: European Atlas of Fertility Treatment Policies, 2021



Source: Fertility Europe (FE) and European Parliamentary Forum for Sexual and Reproductive rights.

In the remaining sections, we focus our attention on several key aspects of these regulations. Firstly, we discuss the existence and timing of ART legislation. Secondly, we review which types of treatments are allowed by the legislation and who has access to them. Lastly, we briefly explain how this situation is linked to the phenomenon of cross-border reproductive care (CBRC).

Given the multiplicity of existing regulations and their frequent changes, we refer readers to reports of international organizations that regularly compile the most updated information. The International Federation of Fertility Societies (IFFS) publishes a triennial survey assessing practices of ART at the global level since 1998; the most recent report refers to the situation in 2021 (IFFS, 2022).[7] The European Society of Human Reproduction and Embryology (ESHRE) published a first report on the situation in EU Member States (MS) in 2009 (ESHRE, 2010); the most recent report published in 2020 refers to the situation in 2018 and covers a larger number of countries (Calhaz-Jorge et al., 2020). In addition, the ESHRE website provides an interactive map that reflects the situation of ART in Europe at end of 2020.[8] A synthetic presentation of these reports can be found in academic publications (Passet-Wittig and Bujard, 2021; Präg and Mills, 2017a), but also publications for a larger audience.[9] More detailed analyses of national regulations focusing on Europe can be found in the following publications: Griessler et al., 2022; Lie and Lykke, 2016; Nordic Council of Ministers, 2006.

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[7] https://www.iffsreproduction.org/our-journal/iffs-surveillance/

[8] ESHRE interactive map of the accessibility of ART and IUI treatments: https://cm.eshre.eu/cmCountryMap/home/index/2020

[9] Article on ART access in Europe: https://civio.es/medicamentalia/2021/11/02/ART-EU-access/

4.3.1. ART specific legislation

Having ART specific legislation is important as it offers a stable legal framework, allows a better overview of professional practices and patient care and follow-up, and provides greater visibility to the issue of infertility. Although at present almost all European countries have already introduced this legislation, up until recently fertility treatments were mostly regulated by professional guidelines (“soft” regulation) or a generic health law (ESHRE, 2010).

Table 1 illustrates the timing of the introduction of ART specific policies in European countries defined as the first norm aimed at providing a legal framework for the application of MAR for professionals. These norms were identified based on the overviews of legal frameworks in ART policies (Busardò et al., 2014; Nordic Council of Ministers, 2006), complemented by literature reviews for countries not covered or addressing more recent changes. Two limitations should be noted. Firstly, while in some countries the identification of this norm is straightforward (for example, the Norwegian Act on Artificial Fertilization 68/1987), in others the norm is formulated in a more general manner (Law on Bioethics in France, Law on Embryo Protection in Germany, etc.). Secondly, the year refers to the passing of the legal norm, but its implementation could take place later in time, or it could never be actually applied. In addition, some countries have recalled these laws and there may be periods with no legislation before a new law can be passed (this is the case in Bulgaria at present in which the ART law had been recalled in 2020).

Norway was the first country to establish ART legislation in 1987, shortly followed by other Western and Northern European countries. The largest share of countries adopted legal changes between the mid-1990s and the 2010s, including countries in Southern Europe, as well as many of the Member States (MS) entering the EU after 2004. In the most recent years ART legislation has been passed in Cyprus (2015), Poland (2015) and Malta (2018). However, there are still countries in which there is no specific ART legislation: Ireland and Romania. In the first case, fertility treatments are practiced in the country since 1987 and, although the Irish Commission on Assisted Human Reproduction (CAHR) formulated a first proposal for a law in 2000, there has been a delay in the legislation due to a lack of sufficient consensus (Allison, 2016; McDermott et al., 2022). In the Romanian case the issue of ART is very present in public debates, but although there were several attempts to create a comprehensive legal framework policy (law proposal in 2011), policy makers have been reluctant to introduce these changes (Bretonnière, 2014; Brodeală, 2016).

Table 1: Timeline of the introduction of ART-specific policies in Europe.

Country	Legal norm	Year
	Before 1990	
Norway	Norwegian Act on Artificial Fertilization (68/1987)	1987
Sweden	Act on In Vitro Fertilization (1988:711)	1988
	1990s	
Germany	Embryo Protection Act [Embryonenschutzgesetz (ESchG)] 13. December 1990	1990
United Kingdom	Human Fertilization and Embryology Act 1990	1990
Austria	Reproductive Medicine Law (FMedG)	1992
France	1° Law on Bioethics	1994
Iceland	Act on Artificial Fertilization (55/1996)	1996
Denmark	Law 460 of June 1997 on artificial fertilization in connection with medical treatment, diagnosis, and research	1997

Estonia	Law "Assisted fertilization and Protection of the Embryo" (RT I 1997, 51, 824)	1997
Hungary		1997
Belgium	Law of 15 February 1999: regulation of IVF centres	1999
	2000s	
Lithuania	Law on Ethics of Biomedical Research in 2000	2000
Slovenia	Law on Biomedically Assisted Fertilisation number 70/2000	2000
Greece	Law 3089/2002. Law number 3305/2005	2002
Latvia	Sexual and Reproductive Health Act of 2002	2002
The Netherlands	Embryos Law of 2002	2002
Bulgaria	Health Act of August 2004. Order 28 on Assisted Reproduction Activities 2007	2004
Italy	Law 40/2004: Regulations on access to ART and on ART activity, embryos' rights, institution of a national ART registry.	2004
Slovakia	Act No. 576/2004 Coll. on Health Care	2004
Czech Republic	Law 227/2006 on research on human embryonic stem cells and related activities	2006
Finland	Act on Assisted Fertility Treatments (1237/2006)	2006
Portugal	Law 32/2006	2006
Spain	Law 14/2006. Royal Decree 1301/2006	2006
Croatia	Law on medical reproduction	2009
	2010s	
Cyprus	Medically Assisted Reproduction Law 69(I)/2015	2015
Poland	Act on Infertility Treatment 25 June 2015	2015
Malta	Embryo protection Act, Chap. 524 of the Maltese Law of 2018	2018
Ireland	n/a	
Romania	n/a	
Luxembourg	Exists but could not identify norm / date	
Switzerland	Exists but could not identify norm / date	

Source: Busardò & al (2014). Nordic Council of Ministers (2006). Karajičić (2013). Köppen et al. (2021). Griessler et Hager (2016). Janicka et al. (2021). https://cmar.org.cy/en/law_eng/.

These legal changes in the region must be understood within a broader international context. Firstly, the International Conference on Population and Development (ICPD) in Cairo in 1994 established, for the first time, an international consensus in support of reproductive rights, of which health care allowing the "prevention and appropriate treatment of infertility" was mentioned. Secondly, the EU

Directive 2004/23/EC[10] setting out standards for the safe use of human tissues and cells, included an obligation for Member States to regulate the use of assisted reproduction technologies. Some countries already had MAR-specific legislation and may have revised it; in other countries MAR was covered by a general health law and a specific legislation was passed for the first time following the Directive, including many new Member States (ESHRE 2010). In addition, in 2008 the European Parliament passed a resolution[11], which among other points, called on MS to recognize infertility as a public health issue and ensure the right to undergo infertility treatments.

It is important to recall that prior to these legal changes (or in their absence), other regulations may have existed, mainly professional guidelines ("soft" regulations). However, providing an overview of this soft type of regulations is more complex as they are often not centralized, not immediately available to external users, etc. In addition, in some contexts, the implementation of an ART legislation could lead to a reduction in the type of treatments offered, as well as access to specific groups. For example, in Finland, the last Nordic state to implement ART legislation in 2006, "Finnish infertility doctors have been able to experiment with a wide range of treatments offering the most permissive regime of assisted reproduction in the Nordic region [...] Although the absence of legislation is a source of concern for many, it has enabled Finnish infertility doctors to excel in clinical practice" (Nordic Council of Ministers, 2006). In Denmark, single women and lesbian couples were offered treatment at private infertility clinics before the introduction of the Act on Artificial Fertilization in 1997. This act limited fertility treatments to only heterosexual couples, and these groups only obtained the right to access to treatments again in 2006 when the law was revised (Nordic Council of Ministers, 2006).

4.3.2. Available treatments and access

Accessibility to MAR treatments depends on their type, but also varies for different groups of the population. Assisted insemination and IVF/ICSI with donor sperm were considered standard treatments and heterosexual couples in all countries had access in all countries (30 in total, situation as of the end of 2018) (Table 2). IVF/ICSI with donor eggs were not possible in three countries – Germany, Norway[12] and Switzerland – as egg donation was not allowed. Additional four countries – Croatia, France[13], Slovenia and Sweden – did not allow combining donated eggs and donated sperm in the same treatment. Lastly, the donation of embryos was not allowed in ten countries: Austria, Bulgaria, Denmark, Iceland, Italy, Norway, Romania, Slovenia, Sweden, Switzerland.

Single women did not have access to AID and IVF/ICSI in around one third of countries. Most countries applied this restriction to all the above treatments: Austria, Czech Republic, France[14], Italy, Lithuania, Norway[15], Poland, Slovakia, Slovenia, Switzerland. However, some countries applied it to specific treatments: Bulgaria and Latvia prohibited AID, but allowed IVF/ICSI; in Croatia, Germany, and Sweden AID only IVF/ICSI w/egg donation was not available to single women.

Access to these treatments for female couples was restricted in a greater number of cases. Most of the countries mentioned above imposed restrictions for this group as well, with the addition of Croatia,

[10] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

[11] European Parliament resolution of 21 February 2008 on the demographic future of Europe (https://www.europarl.europa.eu/doceo/document/TA-6-2008-0066_EN.html).

[12] From 1 January 2021, egg donation in Norway is allowed (https://www.helsenorge.no/en/refusjon-og-stotteordninger/involuntary-childlessness-and-assisted-reproduction/).

[13] The combination of donor eggs and donor sperm is allowed in France since 2021 (https://www.procreation-medicale.fr/ce-que-dit-la-loi/).

[14] From 2021 assisted conception for single women and female couples in France is allowed.

[15] From 1 July 2020, assisted conception for single women living alone was allowed (https://www.helsenorge.no/en/refusjon-og-stotteordninger/involuntary-childlessness-and-assisted-reproduction/).

Cyprus, Greece and Hungary which also did not allow access to any type of treatment. The only exception to this pattern – greater access for female couples than single women – was observed in Austria where they had access to all three types of treatments. Male couples had access to IVF/ICSI with eggs donation in the following countries: Belgium, Malta, Romania, The Netherlands, the United Kingdom.

Surrogacy was legal in seven countries: Belgium, Cyprus, Czech Republic, Greece, Romania, The Netherlands, UK. Only two countries also allowed access to single women, female and male couples (Belgium, The Netherlands) and Greece only allowed it for single women.

PGT for monogenic/single gene defects (PGT-M) and chromosomal structural rearrangements (PGT-SR) were allowed in all countries, with the exception of Malta. However, this situation is recent as their authorization in German-speaking countries only dates back several years: Germany (2011), Austria (2015), Switzerland (2015). However, there remain important differences in the regulation of these tests (Ginoza and Isasi, 2020) and the specific medical conditions which are taken into account. PGT-A tests are more controversial and were not offered in Denmark, France, Germany, Hungary, Lithuania, Malta, Norway, Slovenia, Sweden, and The Netherlands.

Table 2: Access to specific types of treatments across countries, end of 2018

Countries	Heterosexual couples								Single women								Female couples								Male couples						
		IVF/ICSI				PGT				IVF/ICSI				PGT				IVF/ICSI				PGT			IVF/ICSI				PGT		
	AID	w/ donor sperm	w/ donor eggs	w/ donor sperm + eggs	w/ donor embryos	PGT – M/SR	PGT-A	Surrogacy	AID	w/ donor sperm	w/ donor eggs	w/ donor sperm + eggs	w/ donor embryos	PGT – M/SR	PGT-A	Surrogacy	AID	w/ donor sperm	w/ donor eggs	w/ donor sperm + eggs	w/ donor embryos	PGT – M/SR	PGT-A	Surrogacy	w/ donor sperm	w/ donor eggs	w/ donor sperm + eggs	w/ donor embryos	PGT – M/SR	PGT-A	Surrogacy
Austria	x	x	x	x		x	x										x	x	x	x		x	x								
Belgium	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Bulgaria	x	x	x	x		x	x			x	x	x		x	x		x	x	x	x		x	x								
Croatia	x	x	x		x	x	x		x	x			x	x	x																
Cyprus	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x																
Czech Republic	x	x	x	x	x	x	x	x																							
Denmark	x	x	x	x		x			x	x	x	x		x			x	x	x	x		x									
Estonia	x	x	x	x	x	x	x			x	x	x	x	x	x		x	x	x	x	x	x	x								
Finland	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x	x								
France	x	x	x		x	x																									
Germany	x	x			x	x			x	x							x	x													
Greece	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x															
Hungary	x	x	x	x	x	x			x	x	x	x																			
Iceland	x	x	x	x		x	x		x	x	x	x		x	x		x	x	x	x		x	x								
Ireland	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x	x								

Italy	x	x	x	x		x	x																								
Latvia	x	x	x	x	x	x	x			x	x	x						x	x	x	x	x	x								
Lithuania	x	x	x	x	x	x																									
Malta	x	x	x	x	x				x	x	x	x	x				x	x	x	x	x				x	x	x	x			
Norway	x	x				x											x	x													
Poland	x	x	x	x	x	x	x																								
Portugal	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x	x								
Romania	x	x	x	x		x	x	x	x	x	x	x		x	x		x	x	x	x		x	x		x	x	x		x	x	
Slovakia	x	x	x	x	x	x	x																								
Slovenia	x	x	x			x																									
Spain	x	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x	x								
Sweden	x	x	x			x			x	x				x			x	x				x									
Switzerland	x	x				x	x																								
The Netherlands	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x	x		x	x	x	x	x	x		x
UK	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x				x	x	x	x			

Note: AID: Assisted insemination with donor sperm. IVF: In vitro fertilization. ICSI: Intracytoplasmic Sperm Injection. PGT: preimplantation genetic testing. PGT-A: PGT for aneuploidies. PGT-M: PGT for monogenic/single gene defects. PGT-SR: PGT for chromosomal structural rearrangements.
Source: Calhaz-Jorge et al. (2020).

Regarding the preservation of fertility potential, most countries in Europe allowed the preservation of sperm, eggs, embryos, and gonadal tissue for medical reasons or did not have a specific legislation (prohibiting it) and performed these treatments (Calhaz-Jorge et al., 2020). The only exceptions were Germany, Italy and Portugal which did not allow preservation of embryos. However, preservation of fertility for non-medical reasons was prohibited in a greater number of countries: Austria, France[16], Hungary, Lithuania, Malta, Norway, Slovenia.

4.3.3. Cross-border reproductive care (CBRC)

The marked differences in regulations and access to MAR has led individuals seeking to become parents to look for medical attention in other countries. Although the issue of cross-border reproductive care (CBRC) has gained wide attention since the 2000s (see Whittaker et al., 2019 for a recent literature review), it is by no means a recent phenomenon as it is contemporary to the invention of modern ART. For example, in the 1980s the UK had the most advanced clinics and methods, so couples with resources from neighbouring countries, such as Norway, went there (Sundby, 2010). Although the phenomenon remains difficult to estimate, evidence points to an increase since the 2000s fuelled by a rise in the demand for and unequal access to MAR (Inhorn and Patrizio, 2015). The terms to describe the phenomenon have also evolved moving away from the initial term of “reproductive tourism” to “reproductive exile” (Matorras, 2005; Pennings, 2005), and the more umbrella term of “cross-border reproductive care” (CBRC).

Scholars point to four broad sets of factors behind CBRC: resource constraints, legal and religious prohibitions, quality and safety concerns, and socio-cultural barriers (Inhorn and Patrizio, 2015; Whittaker et al., 2019). Legal barriers to MAR legislations are most evident for groups mentioned above – single women and homosexual couples – who are most likely to travel abroad. In Europe heterosexual couples have legal access to most standard treatments; however, their reimbursement may be inexistent or limited (important out of pocket expenses, small number of trials covered by the public system). In addition, insufficient public financing may result in other obstacles, such as long waiting lists. As a result, some couples may decide to travel to another country right from the start or after they have extinguished their treatment rounds at their country of residence.

Travel for selective technologies such as preimplantation genetic tests, but also sex selection remains understudied, but there is evidence on this phenomenon as well. For example, in the United States there is no regulation regarding preimplantation genetic tests, which has made it a destination for European couples as in most countries these tests are not allowed or strictly regulated (testing is only possible for specific diseases and not for the entire array of medical conditions).

Surrogacy is available in a limited number of countries in Europe and therefore involves individuals moving outside of the region. This form of CBRC has received the most attention due to the important ethical debates it raises, with many of surrogate mothers coming from low-resource countries and/or groups, but also controversies, such as parents abandoning their children with disabilities. This situation has led different destination countries to restrict this practice. India was the most important destination in the 2000s but banned surrogacy for foreigners by 2014 following several controversies. After this moment, several countries in the region appeared as new hubs – Thailand, Nepal, Laos –, but those also progressively restricted this practice.

4.4. Statistics on MAR use

4.4.1. Establishment of ART surveillance

The clinical introduction of IVF in the 1980s raised many safety concerns (risk of congenital disorders, multiple and preterm births, maternal risks) and national ART surveillance systems were put in place to provide data on medical practices and pregnancy outcomes in order to reassure society about their safety (Kissin et al., 2019). Shortly after, the first regional reports were published: North America,

[16] From 2021 fertility preservation for non-medical reasons in France is allowed.

South America…. The European IVF Monitoring (EIM) Consortium was set up by the European Society of Human Reproduction and Embryology (ESHRE) in 1999.

National ART surveillance systems differ in many dimensions: format of primary data provided by ART clinics (summary or cycle-level), registry requirements (compulsory vs. voluntary), information collected (medical, characteristics of patients). International efforts to coordinate these systems include the development of common instruments: for example, in 2006 the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) developed the first glossary on ART terminology; a revised and expanded version was developed with the World Health Organization and was published in 2017 (Zegers-Hochschild et al., 2017).

Despite these efforts, providing comparable international statistics in this area still entails many challenges due to differences in registries, completeness of reporting, detail of information, etc. (Fauser, 2019). In addition, the growing complexity of ART treatments (multiple treatments, time elapsed between different steps) raises additional issues and requires developing systems allowing to follow up. Similar issues also exist with clinical studies in this area (Wilkinson et al., 2016): a systematic review of Randomized Controlled Trials (RCTs) on IVF trials published in English in 2013 and 2014 identified 361 different numerators and 87 denominators used in these studies. It is also important to mention that while ART treatments are relatively well registered (Fauser, 2019), data on non-ART treatments, for example assisted insemination, are collected in a smaller number of countries.

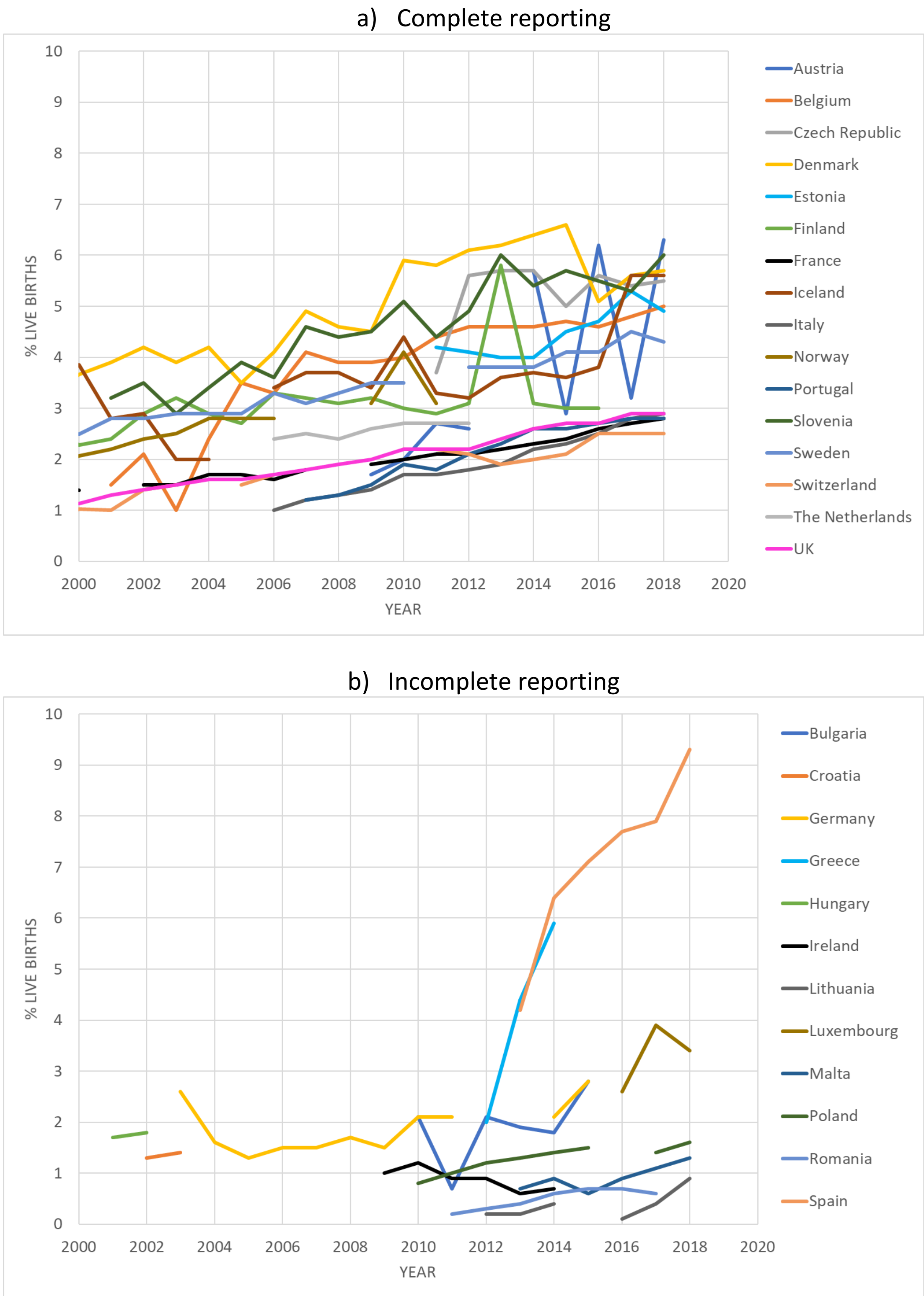
In the rest of this section, we primarily use the annual reports published by the EIM Consortium to analyse trends in the use of MAR technologies in Europe in recent decades. The number of countries providing information on MAR has increased over the last decades, going from 18 countries in 1998 to 39 in 2018. In this section we limit our analyses to EU Member States, as well as the UK and EFTA countries. In addition, it is important to consider that reporting methods vary by countries (compulsory / voluntary, all / some clinics report to the EIM),[17] which may affect comparability in terms of levels and/or trends. In general, the reporting situation for countries has become more complete, due to legislation changes (for example, requirement for clinics to provide statistics to a national authority). However, in some cases countries ceased may have ceased to provide data altogether or for specific indicators for a limited or an indefinite period of time due to other circumstances (for example, change in structure and content of data sources). This has led us to separate countries into two groups for some analyses: countries with complete reporting throughout most of the period under study (complete reporting); countries with incomplete reporting or complete reporting for a shorter period of time (incomplete reporting).

4.4.2. ART infants

Since the introduction of IVF in the 1980s, over 8 million children have been born in the world (Adamson et al., 2013) and around 500,000 ART deliveries take place every year (Fauser, 2019). In Europe the proportion of live births following ART treatments has been increasing in the last decades (Figure 3).

[17] The detailed description of reporting methods for each country can be found in the annual report for each year (Latest year: Supplementary Table SIII Reporting methods in all countries reporting to the EIM in 2018).

Figure 3: ART infants per national births (%), 2000-2018



<u>Source</u>: European IVF Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE).

Whereas at the start of the 2000s their proportion in countries with complete reporting ranged between 1% and 4%, in the most recent years it has grown to between 2.5% and 6% (Figure 4a). [18] The highest proportions are observed in the Nordic countries, as well as Central European countries. However, while some countries show relatively stable levels (Finland) or limited increase (Sweden), for others a significant increase is observed (Denmark, Iceland, Czech Republic). Western European countries, such as France, the UK, Switzerland, have lower levels at the start of the period (less than 2%) and the increase in the proportion of ART births is more limited (2.5-3% in the latest year). This is also the pattern observed in some Southern European countries (Italy, Portugal) which only have data for a shorter period.

The proportion of ART births in countries with incomplete reporting (Figure 4b), many of which are more recent EU Member States, are generally lower than in the first group and do not surpass 2%. However, Southern European countries present a notable exception, with Spain exhibiting the highest level in the region (9.3% in 2018), followed by Greece (5,8%). However, a methodological clarification is required regarding the results for specific contexts. In countries receiving an important number of cross-border reproductive care patients, such as Spain and the Czech Republic (see following sub-sections on specific ART treatments), this indicator over-estimates the importance of ART births as statistics include births to women residing abroad and who have returned to their country of residence to give birth (and who are therefore not captured in the denominator). A recent study on the Czech Republic using data from the Institute of Health Information and Statistics and allowing to distinguish births to resident mothers from those to “reproductive tourists”, estimated the proportion of live births following MAR to be 3.9% in 2018 (compared to 5.5% in the above mentioned estimates) (Šťastná et al., 2022). To sum up, data limitations (incomplete reporting, lack of information on patient characteristics) make it difficult to provide accurate estimates and these should be taken with caution.

4.4.3. ART treatments

In 2017 (latest available year) around 2 million ART cycles were carried out worldwide, with the majority of the cycles being carried out in high-income regions: around one half in Europe, followed by North America and Asia (Japan) (ICMART).[19] This represents a more than 14-fold increase from 1991 (first available year) when 140,000 cycles were reported. Although this increase reflects the greater access to and use of ART treatments in the world, it is also due to the continuing improvement of data collection practices in this area, including the continued increase in the number of reporting countries and fertility clinics. Almost half of these cycles are carried out in Europe (47,9% in 2017), while access to these remains more limited in other world regions. For example, only 1,7% of cycles were registered in Africa.

In Europe the access to ART treatments has increased over time, but there remain important variations in the region as is illustrated by the number of ART cycles carried out for every one million females of reproductive age (15-44 years) (Figure 5). The trends observed earlier – a higher number of cycles in the Nordic countries at the start of the period, intermediate levels and limited increase in Western European countries, and lowest levels in Central and Eastern European countries – is equally observed here. However, several countries present a significantly high number of cycles (14,000+ / million women): Denmark, Czech Republic, Belgium, Slovenia, Spain and Greece. As we show later one, this situation is linked in many cases to a less restrictive legislation for certain treatments, which promotes the arrival of infertile couples and single women from other countries.

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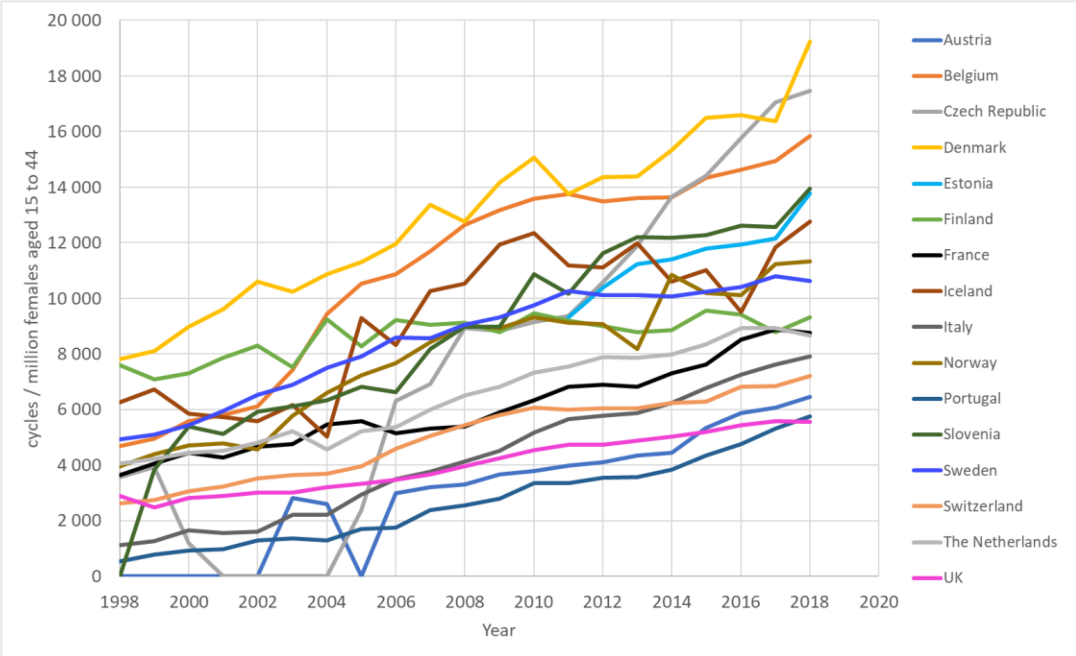
[18] The proportion of live births following ART treatments is estimated by comparing their number to the total number of live births registered in the country. In some countries, both the numerator and the denominator may come from the same data source (population register), while in others they may originate from different sources (medical reports, vital statistics), which may result in some inconsistencies.

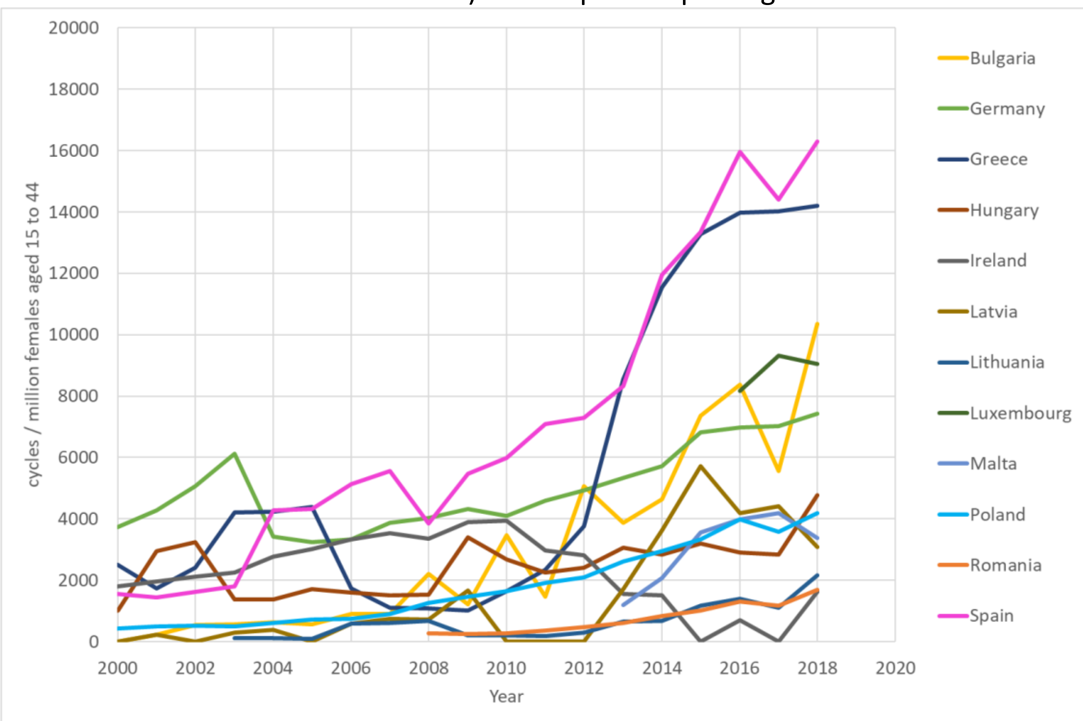
[19] https://www.icmartivf.org/reports-publications/

Figure 4: ART Cycles/million females aged 15 to 44, 2000-2018

a) Complete reporting



b) Incomplete reporting

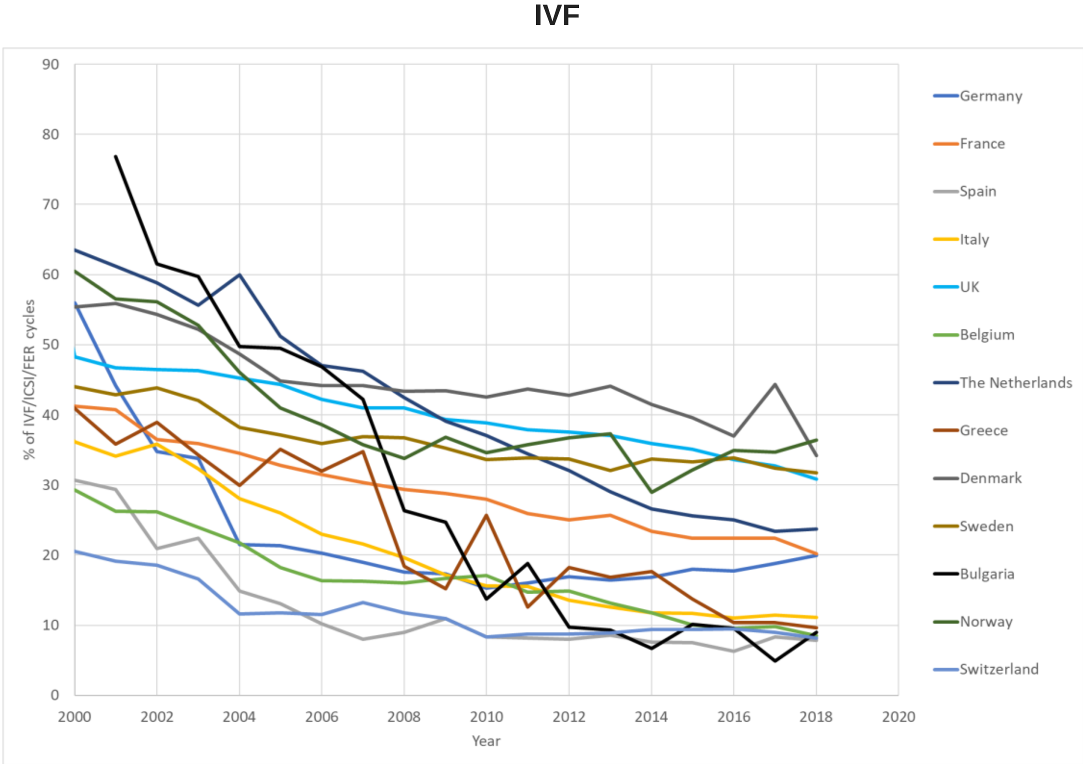


Source: European IVF Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Population on 1 January by age group and sex [DEMO_PJANGROUP].

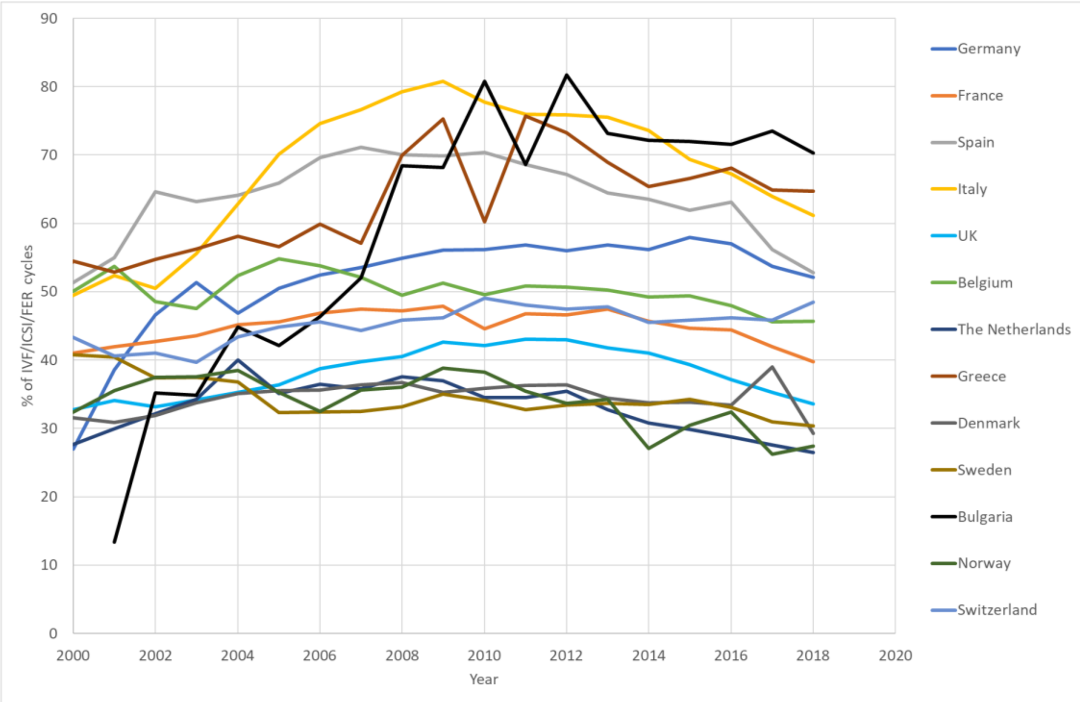
4.4.4. Embryo transfers

The majority of ART treatments carried out are embryo transfers (ET) and they can be done with fresh (IVF/ICSI) or frozen embryos (FER). Parallel to the increase in the number of cycles, the types of treatments have also changed. Figure 6 shows the distribution of these treatments type – IVF, ICSI, FER – in the countries which carry out the most treatments. Although national differences remain, we can notice that the proportion of IVF has been declining in all countries, while that of ICSI increased in the start of the period and stabilized since the mid-2000s. Frozen embryo transfers are becoming more widespread since the end of 2000s.

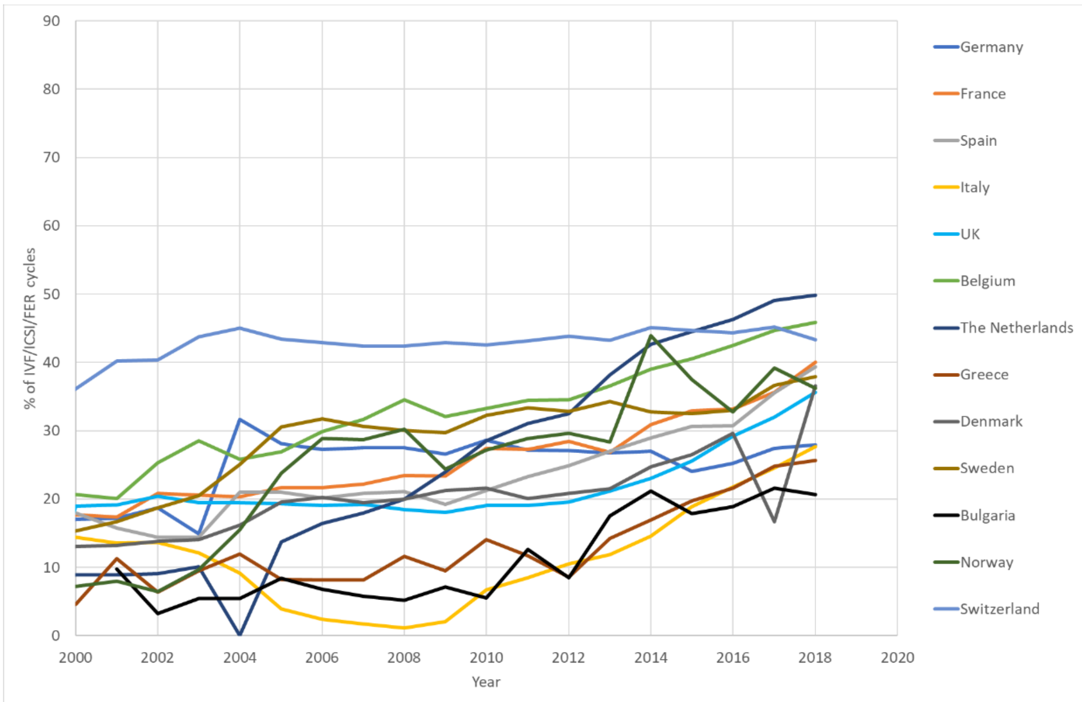
Figure 5: Distribution of main ART treatments (IVF, ICSI, FER), selected countries, 2000-2018



ICSI



FER



Source: European IVF Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE).

4.4.5. Egg donation

Egg donations (aspiration of eggs from a woman other than the one who will carry the pregnancy) are carried out in a limited number of countries (around 20 countries declare at least one cycle per year). To recall, some countries do not allow ED (Germany, Norway, Switzerland), while others lack legal enforcement and/or do not collect relevant statistics (The Netherlands) (Calhaz-Jorge et al., 2020). Since the start of the 2000s more than half of the cycles take place in just one country – Spain –, while the Czech Republic and Greece came in 2nd and 3rd positions. In these countries the number of ED is substantially higher than in other countries, when we take into account the size of the female population of reproductive age (2500 or more ED / million women aged 15 to 44).[20]

The high number of EG in Spain has been noted in the literature and is attributed to a combination of factors: altruistic culture; anonymity of oocyte providers; absence of a national donor registry, as well as the existence of a €1,000 monetary compensation (Degli Esposti and Pavonen, 2019). Although the ED is framed as an altruistic act, the authors note that in a complex economic situation (high unemployment rates, low wages), especially for young adults, the monetary compensation can be particularly attractive. This has made Spain an important destination for ARTs with third-party oocyte (Shenfield et al., 2010).

Table 3: Egg donations, selected countries, 2000-2018

	Number of cycles					Cycles / million females aged 15-44				
	2000	**2005**	**2010**	**2015**	**2018**	**2000**	**2005**	**2010**	**2015**	**2018**
Spain	1 577	5 875	12 928	34 176	37 618	170	609	1 316	3 808	4 361
Greece	244	249	446	5 182	4 875	104	108	198	2 534	2 523
Czech Republic	64	125	2 365	4 961	5 007	29	58	1 082	2 376	2 486
Iceland	23	29	117	108	101	369	462	1 753	1 612	1 435
Denmark	158	67	225	360	1 120	147	63	212	340	1 045
Bulgaria		24	76	612	1 140		15	52	457	901
Estonia				180	212				718	879
Portugal		37	282	797	1 496		17	131	400	785
Belgium	500	531	1 412	802	1 603	236	254	673	379	760
Finland	290	426	763	831	714	283	429	776	851	730
Total	5 993	10 190	22 189	56 297	66 993					

Source: European IVF Monitoring Consortium (EIM), for the European Society of Human Reproduction and Embryology (ESHRE). Population on 1 January by age group and sex [DEMO_PJANGROUP].

4.4.6. IUI

IUI treatments have existed for a longer time than ART. However, as their registration is incomplete – some countries do not provide any figures (Czech Republic or the Netherlands) while in others these may be underestimated – it is harder to quantify them. Among countries having declared IUI treatments to the EIM, the total number has been relatively stable, especially when compared to the evolution of ART: 159,000 IUI cycles registered in 2008 and 181,000 in 2018 (+14%), while the number of ART nearly doubled in the same period (435,000 and 796,000 respectively).

[20] As age limits for egg donors in most countries are between 18 and 35 years old (Calhaz-Jorge et al., 2020), the ratio is higher.

While in the mid-2000s several countries still had similar numbers of IUI and ART cycles every year – Denmark, Poland, Bulgaria, France, Italy – at present the ratio in most countries is less than 1 to 4. Denmark, where this is still the case, remains a rare exception, while Belgium also has a high number of IUI. The majority of IUI are carried out with husband sperm (3/4) and IUI with donor sperm (IUI-D) were especially low (<10%) in countries such as France and Italy. Inversely, inseminations with donor sperm accounted for 40% or more in countries with the largest numbers of IUI (Denmark, Belgium), as well as the UK, and remained relatively frequent in Spain.

4.5. Factors explaining variations in the use of MAR

It is difficult to obtain a clear picture of variations at the macro and micro level in the use of MAR, since studies on its prevalence and medical attention-seeking are hardly comparable across temporal and spatial contexts. There are also concerns regarding the reliability of data and the different criteria used to measure whether a person has resorted to MAR (Passet-Wittig and Greil, 2021). This notwithstanding, the considerable variation in usage identified above raises the question of its underlying factors. Those highlighted by previous research as most important determinants of variations in MAR access and use are described in what follows.

4.5.1. Economic costs of MAR

It has long been observed that cost- and affordability-related issues strongly influence access to MAR for different social groups, entailing considerable inequalities in countries where there is low public coverage (McCarthy-Keith et al., 2010). Affordability is also an evident hindrance to MAR use in low-income countries, although other limitations – such as scarce sociocultural and political support – are present as well, as will be described. In low-income countries, only a very small proportion of infertile women/couples can benefit from MAR, due to – inter alia – their high costs (Ombelet and Campo, 2007).

Even in Europe, where MAR is relatively widespread and there is a certain degree of public coverage, costs and affordability appear to be important determinants of both cross-country and individual-level differences in usage. At the aggregate level, nonetheless, the degree of economic development does not account for the large cross-country differences observed in MAR usage. Although MAR usage is somewhat more prevalent in richer countries, the relation is complex and some poorer countries in Europe, for instance, report high levels of use. Research points at the importance of affordability at the micro-level instead (Präg and Mills, 2017a). Using data on 30 high and upper middle-income countries, Chambers et al. (2014) find that affordability, operationalized as the net cost of an ART cycle as a share of the average disposable income in the country, shows a strong and robust association with greater MAR use, even after controlling for factors such as the country's GDP per capita or the number of MAR clinics available in the country. On average, a 10-percentage-point decrease in affordability was associated with a decline in usage by 32%. Accordingly, countries where MAR treatments are largely covered by insurance or are publicly subsidized exhibit higher levels of usage. This said, socioeconomic barriers to the use of MAR use have been detected in countries with relatively generous public funding as well (Goisis et al. 2020; Lazzari et al., 2022).

All in all, it has been shown that accessibility of MAR – in terms of rights of access – and the availability of different techniques seem less important for MAR usage than whether individuals/couples have the economic means necessary to cover such treatments. It must also be borne in mind that costs also hinder individuals in countries with restrictive regulations to travel to other countries to access treatment (Präg and Mills, 2017a). Costs also affects the profile of the patients who use these treatments, both from a sociodemographic and a reproductive point of view. Data from the US has shown that improving ART affordability by decreasing costs increases use by some minorities or groups with lower socioeconomic status, although not all (McCarthy-Keith et al., 2010). It has also been found that lower MAR costs attract more individuals at both ends of the distribution in terms of prognosis; that is, those who could expect better vs. poorer outcomes (Chambers et al., 2014).

In many contexts, moreover, costs do not only influence whether individuals/couples access treatment, but also the types of treatment available to them (Connolly et al., 2010) and the characteristics of the treatment eventually undergone (Chambers et al., 2014). For instance, in the United States, although certain standards for compensation to oocyte donors exist, couples/individuals are sometimes willing to pay extremely high amounts to obtain gametes from a donor with what are considered "exceptional qualities" (Lindheim et al., 2014). Likewise, in other settings, decreases in affordability were found to be associated with lower proportions of fresh single embryo transfers and with a greater share of fresh cycles where several embryos were transferred. Thus, affordability also appears to affect, at least in some jurisdictions, the characteristics and safety of ART processes (Chambers et al., 2014).

4.5.2. Norms and beliefs

The widespread adoption of MAR throughout the world has been sometimes regarded as surprising, given the many normative, social, and cultural issues that emerge in relation to these technologies – for instance, those having to do with cross-border reproductive care, the motivations of gamete donors, oncofertility preservation, fertility insurance, posthumous reproduction, or gamete retrieval, inter alia (Lindheim et al., 2014).

Different types of norms appear to influence the use of MAR in societies in various ways. Social norms about reproduction and its timing are one example. A substantial, positive association has been found between higher normative age limits for childbearing – i.e., socially shared views on when individuals are too old to have children – and the availability of MAR in European countries. The higher these normative age limits, the greater the availability of MAR clinics (Billari et al., 2011).

Beliefs about the moral status of fertilized eggs – that is, on whether a human embryo can be regarded as a human being immediately after fertilization – are also associated with the prevalence of MAR utilization. In general, in countries where the belief that an embryo becomes a human being right after fertilization is less widespread, there is greater recourse to these technologies (Präg and Mills, 2017b). Likewise, beliefs regarding whether individuals have a right to have children, or whether societies should provide funding for reproduction are also important in this respect. So are views on whether it is ethical to discard healthy embryos or create embryos with abnormalities. Beliefs also shape which techniques are more or less readily accepted. Oocyte donation, for instance, has gained increasing social acceptance, wherefore the demand throughout the world keeps growing (Lindheim et al., 2014).

Many of the considerations regarding the right to reproduction, the use of third-party gametes, or the status of embryos are shaped by religious norms and beliefs. Accordingly, these also influence the extent to which MAR in general and some specific techniques are resorted to, as well as the family contexts in which they are used. Jewish law is generally favourable to IVF and embryo transfer – although some rabbis hold stricter positions and most Orthodox Jews reject third party involvement. Islamic law supports attempts to cure infertility and accepts IVF, yet, in general, only within the context of marriage and using the husband's and wife's own gametes. Shi'a Islam, nonetheless, accepts sperm and oocyte donation. The Catholic Church has positioned itself against insemination, IVF, cryopreservation of embryos, research on embryos, and use of donor gametes. It considers that assisted reproduction techniques break the bond between procreation and sexual intercourse within marriage and are contrary to the child's right to be the fruit of the conjugal act. Eastern Orthodox Christianity, on its part, is supportive of medical and surgical infertility treatment, yet rejects gamete donation, and sometimes other assisted reproduction techniques. Protestantism partly accepts ART. Assisted reproduction – even including gamete and embryo donation – is also acceptable for Hinduism, which places great importance on reproduction. Buddhism, in turn, accepts any form of procreation which does not entail any harm to others, although it encourages avoidance of sperm and oocyte donation. Chinese culture, under the influence of Confucianism, accepts any form of assisted reproduction that does not involve third parties. When it comes to fertility preservation prior to oncologic treatment, some religions – Roman Catholicism, Islam, Orthodox Judaism – do not support gamete collection and/or storage from unmarried individuals (Lindheim et al., 2014; Sallam and Sallam, 2016).

In summary, social and cultural norms appear to be of considerable importance for both usage and availability of MAR treatment. In fact, it has been found that the use of assisted reproduction techniques in Europe – where they are relatively widespread – is more influenced by cultural determinants than by economic and sociodemographic variables such as country wealth, population-related characteristics, or the representation of different religious groups in society. The strongest predictor of the extent to which MAR is resorted to are actually normative, cultural values regarding its acceptability (Präg and Mills, 2017b). There is also evidence suggesting that cross-country differences as regards eligibility criteria for publicly funded treatments are not solely and strictly based on medical considerations, but also on interpretations impregnated by social norms on the acceptability of different family forms and pathways to family-building (Passet-Wittig and Bujard, 2021).

4.5.3. Demographic variables influencing demand

It has been observed that some differences across countries regarding MAR usage also bear an association to the degree to which fertility postponement is prevalent. In societies where postponement of first births is common, demand for these technologies is higher (Kocourkova et al., 2014), mirroring the relation that exists at the individual-level behind fertility delay and recourse to MAR treatments (Leridon and Slama, 2008). Still, the association is no longer as evident when other variables – i.e., value-related ones – are controlled for (Präg and Mills, 2017b). Fertility postponement is also linked to the increasing use of some treatments, such as those involving oocyte donation (Passet-Wittig and Bujard, 2021).

5. Concluding comments

Gaining knowledge on the characteristics and usage of MAR in contemporary societies, as well as on the factors that condition its usage and accessibility, is necessary given the increasingly important contribution of related technologies to fertility. A fast-growing proportion of births worldwide are a product of MAR, which calls for a better understanding of the phenomenon and its implications in several domains. The dissociation of reproduction and pregnancy (Bahnsen and Spiewak, 2008 in Trappe, 2017) entails the emergence of an increasing complexity of family formation and reproductive processes, sometimes leading to the involvement – even genetic – of three individuals, or to a differentiation between biological, genetic, and social parents. In the future, the use of automation and Artificial Intelligence (AI) in some of these medical procedures, which might reduce costs and facilitate certain processes, could come to further increase the demand for MAR.

As noted, the growing preponderance of MAR usage in fertility dynamics must be seen in the light of increasingly generalized childbearing postponement. MAR treatments have an evident role – despite their so far limited compensatory effect (Präg et al., 2017) – when it comes to addressing infertility and the risk of permanent childlessness. They could potentially contribute to counterbalancing, at least partially, the negative effect of delayed childbearing on total fertility rates (Sobotka et al., 2008), despite potential undesirable side effects such as leading individuals to believe that their fecundity is extended (Correll, 2010 in Trappe, 2017). In the low-fertility context characterizing many societies, especially those where fertility delay is associated to structural barriers, MAR also helps narrowing the gap between desired and achieved fertility. If the accessibility and affordability of MAR were to increase, furthermore, it may come to play a more preponderant role in mitigating trends towards decreasing fertility rates in some countries.

Socioeconomic gaps related to accessibility and affordability, indeed, have proven to underlie some of the current differentials in access and actual use of MAR. Usage is very unequally distributed across world regions, with low-income countries having very restricted access to MAR. At the individual level, individuals with higher resources are more likely to use MAR treatments altogether, given the generalized importance of affordability for usage. Furthermore, the fact that women with higher education manage to recuperate more easily delayed births suggests a potentially compensatory role of MAR – at least partially – within this group. So do recent findings on high-resource couples' greater success in ART treatments based on empirical research on Finland (Klemetti et al., 2007; Räisänen et al., 2013), the United States (Wilcox and Mosher, 1993; Stephen and Chandra, 2000), Norway (Goisis et al., 2020) and a comparison of five European countries (Goisis et al. 2022), even though further research on a variety of indicators of parental resources, countries, periods, etc. is needed. Understanding whether there are systematic resource-related socioeconomic gradients in MAR use and success, and whether gaps persist even in contexts where access is more universal and less costly, is crucial, as this would entail that it is not necessarily those most in need of treatments who eventually benefit from them. Furthermore, an association of social advantage with greater probability of MAR use or success in treatments could constitute an additional, still largely unexplored mechanism of intergenerational transmission of inequalities, especially if in addition selection of embryos or gametes with given characteristics came to play.

Another related, important field for further research is the impact of MAR on perinatal and infant health and children's cognitive and socioemotional development. There is evidence pointing to a significant association between assisted conception and a higher probability of adverse obstetric and perinatal outcomes in singleton pregnancies (Berntsen et al., 2019; Helmerhorst, 2004). Some of the increased risks are specific to IVF (Halliday, 2007; Sullivan-Pyke et al., 2017); others have been linked to the type of embryo transfer – fresh embryo transfer bears an association with a higher probability of small for gestational age (SGA) infants, low birthweight (LBW), and pre-term birth (PTB), whereas frozen embryo transfer has been linked to large for gestational age infants and pre-eclampsia. An association has also been found between ICSI and certain birth defects, as well as between oocyte donation and a higher risk of SGA babies and pre-eclampsia. Results regarding mental health and neurodevelopmental health are less consistent (Berntsen et al., 2019; Punamäki et al., 2016), although there could be an association between ART and cerebral palsy (Berntsen et al., 2019). A potential increase in the risk of depression in adults conceived through IVF has also been suggested (Hart and Norman, 2013). Additionally, there are studies showing associations between IVF and increased risk of certain adverse health outcomes later in life – in particular, some cardiovascular and metabolic conditions – (Hart and Norman, 2013).

Further evidence is nonetheless needed to disentangle and isolate the mechanisms involved – that is, the relative influence of treatments themselves, of medical factors associated with infertility/subfertility, and environmental variables. Additional work will also be necessary to appropriately account for factors that could potentially play a confounding or mediating role (e.g., prematurity, multiple gestations/births, neonatal hospitalization, etc.); paying particular attention to the identification of the most appropriate groups for comparison (Berntsen et al., 2019). Interestingly, differences in terms of perinatal and obstetric risks between twin pregnancies conceived through MAR and those resulting from natural conception appear to be relatively small (Bensdorp et al., 2016; Chen et al., 2019).

Attention should also be paid to longer-term health outcomes, as perinatal and infant health can have an enduring impact on children's cognitive and socioemotional development, as well as on physical and mental health later in life. It will be crucial to understand whether children conceived through MAR show any differences in development with respect to naturally conceived children, and whether any potentially worsened outcomes could be compensated by greater parental resources. Outcomes derived from complex family structures – i.e., when genetic, biological, and social parenthood do not coincide – also merits comprehensive exploration, given that technologies giving rise to non-standard family-building are still relatively new and increasingly widespread. Existing evidence on long-term outcomes for children conceived through surrogacy, egg, sperm, or embryo donation reveals, in general, good functioning and psychological adjustment, as well as positive parent-child relationships (Golombok, 2013; Imrie and Golombok, 2018). Nevertheless, there also is research identifying disadvantages in terms of cognitive skills for children in households with absent fathers (Radl et al., 2017). Further research should therefore pay heed to a wide range of potential long-term outcomes associated with non-standard family forms and their interaction with socioeconomic variables.

Finally, new research pathways around MAR should also be sensitive to the different ethical issues that may arise. Privately supplied ART has become a profitable business in a global fertility market, while many types of social and economic inequalities impinge on access to these technologies. Concerns have been raised regarding the risk of increasing commodification of reproduction and bodily tissues (Schurr, 2018). There is also an incipient egg freezing market, as clinics increasingly present this option – initially developed for medical fertility preservation purposes – as an innovative technology that allows women to have control over reproductive aging and greater autonomy over their fertility timing (Gürtin and Tiemann, 2021). Some companies have also started to offer financial support for elective egg freezing to female employees (see f.i. Johnston et al., 2021). Ethical concerns have been raised regarding misleading messages and a poor balance between information on benefits and risks, respectively (Bayefsky, 2020). It has also been pointed out that employer-sponsored egg freezing (ESEF) could potentially reinforce perceived conflicts between career and family (Johnston et al., 2021). Some authors hold nonetheless a positive view and regard social egg freezing as a fertility insurance, even if partial. There are also debates regarding the time span during which frozen oocytes should be preserved and related ethical implications (see Lockwood and Fauser, 2018).

Other ethical dimensions are related to the use of screening instruments for the detection of potential disabilities, serious illnesses, or the transmission of inheritable conditions. This technology already exists and is applied in ART, which has elicited concerns about the possibility of discriminatory or eugenic practices (de Wert et al., 2021), selection of embryos with characteristics considered most desirable (Ziebe and Devroey, 2008), the use of preimplantation genetic diagnosis (PGD) for non-medical objectives (e.g., sex selection) (Robertson, 2003), and the selection of embryos on grounds of tissue matching with a previous child (Robertson, 2004). Likewise, frequent debates have also arisen on the limits of professional and parental responsibility, risk-benefit consideration, and equity issues regarding access to the different screening technologies (de Wert et al., 2021). Developments including the creation of artificial gametes, artificial wombs and results of parthenogenesis even in mammals (mice) are also already in place (Wei et al., 2022). This rapid acceleration of technical capacities calls for a thorough and broad societal discussion, not restricted to the biomedical sphere, on how to legislate on such advancements.

6. Limitations and challenges

Among the main challenges associated with gaining knowledge on MAR and its socioeconomic ramifications is the fact that it is a quickly evolving phenomenon. Available data get dated very fast – for instance, the most recent report from the International Committee for Monitoring Assisted Reproductive Technology (ICMART) is from 2017. Another relevant limitation is the lack of systematic data collection in many countries and of potential underreporting in others. Data on low-income countries is very scarce, even though MAR use is likely to be limited in these societies due to early fertility, economic costs, and cultural barriers. There is also insufficient data coverage regarding countries in which surrogacy takes place. The situation is different in Europe, where MAR use is widespread and the European Society for Human Reproduction and Embryology (ESHRE) has been monitoring Assisted Reproduction since 1997. Nevertheless, even in European societies there is room for improvement regarding data collection. While there exist ART registries for several regions in the world, there is considerable variation in the range of outcomes reported and how these are measured (Wilkinson et al., 2016). This diversity of indicators and lack of data standardization makes it difficult to establish reliable country and region comparisons. Comparing between regions, moreover, becomes particularly difficult given differences in affordability and accessibility of MAR. Variations in the typical characteristics of patients that might be consequential for fertility outcomes further complicate the tasks. Accordingly, experts have emphasized the need to attain global consensus for unified procedures when reporting ART outcomes, and which places the most relevant outcomes for the patients and their offspring in focus (Fauser, 2019). Even though competences over policy matters are located at the national level, the Commission´s recent proposal for a European Health Data Space (EHDS) could be an excellent tool to intensify efforts in this direction.

7. Glossary

Assisted Reproductive Technology (ART):

All interventions that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction. This includes, but is not limited to, IVF and embryo transfer ET, intracytoplasmic sperm injection ICSI, embryo biopsy, preimplantation genetic testing PGT, assisted hatching, gamete intrafallopian transfer GIFT, zygote intrafallopian transfer, gamete and embryo cryopreservation, semen, oocyte and embryo donation, and gestational carrier cycles.

CBRC:

Cross-Border Reproductive Care.

Childlessness:

The fact of not having children at a given point in time or ending the reproductive period without children.

EDCs:

Endocrine Disruptor Chemicals.

Fertility preservation:

The storage of cells and tissues at low temperatures for future use (cryopreservation or cryoconservation). Semen, oocytes, embryos, or ovarian tissue can be preserved.

Total fertility rate:

The number of children that would be born to a woman if she were to live to the end of her childbearing years and bear children in accordance with age-specific fertility rates of the specified year.

Frozen Embryo Replacement (FER):

Also known as Frozen Embryo Transfer. The actual transfer is identical to the one performed in a fresh IVF or ICSI cycle, except that the embryos will first be thawed in the lab at the appropriate time ahead of the procedure.

Human fecundity:

The biological capacity of humans to reproduce. Time-to pregnancy, TTP, is often used as a proxy of fecundity.

Infertility:

A disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.

Intracytoplasmic Sperm Injection (ICSI):

When the sperm does not succeed in breaking the cytoplasm of the egg, it is injected with a needle in order for fertilization to take place.

Intra-uterine Insemination (IUI):

Procedure that puts sperm directly inside the woman’s uterus around ovulation time.

In Vitro Fertilisation (IVF):

The combination of an egg and sperm outside the woman’s body.

Lowest-low fertility level:

A total fertility rate at or below 1.3.

Medically Assisted Reproduction (MAR):

Reproduction brought about through various interventions, procedures, surgeries, and technologies to treat different forms of fertility impairment and infertility. These include ovulation induction, ovarian stimulation, ovulation triggering, all ART procedures, uterine transplantation, and intra-uterine, intracervical, and intravaginal insemination with semen of husband/partner or donor.

Postponement of childbearing transition:

The overall rise in the mean age at first birth.

Preimplantation Genetic Testing (PGT):

A screening test that can be performed on embryos created via in vitro fertilization (IVF) to genetically analyse the embryos prior to transfer.

Primary infertility:

A situation where a pregnancy has not been achieved after at least one year of regular, unprotected intercourse.

Replacement fertility:

The total fertility rate at which women give birth to enough babies to sustain population levels, assuming that mortality rates remain constant and net migration is zero.

Secondary infertility:

A situation of infertility where at least one prior pregnancy/birth has been achieved without difficulty.

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