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The Demographic Consequences of Assisted Reproductive Technologies*

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Abstract

The use of assisted reproductive technology (ART) is widespread, with an estimated five million ART-conceived children born now worldwide. Despite this marked increase in the use of ART, little is known about the demographic consequences. We explore several dimensions of demographic consequences of ART. The proportion of ART-conceived babies varies greatly across countries, and our analyses suggest that ART costs, policies and regulations, and national norms and values are core determinants of these differences. Based on a review of the literature, we conclude that ART has a negligible impact on national fertility rates, thereby suggesting that it is not an effective policy instrument to counter low fertility. Furthermore, we show that the recent increase in twin births in Europe can be attributed to ART usage. A case study of Italy reveals that ART mothers were more likely to deliver prematurely, even when controlling for maternal age.

Keywords: Assisted reproductive technologies, twin births, late childbearing, ART success, ART at late ages

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Table 1: Country abbreviations used in this document

Country abbreviation	Country
BE	Belgium
BG	Bulgaria
CZ	Czech Republic
DK	Denmark
DE	Germany
EE	Estonia
IE	Ireland
GR	Greece
ES	Spain
FR	France
HR	Croatia
IT	Italy
CY	Cyprus
LV	Latvia
LT	Lithuania
LU	Luxembourg
HU	Hungary
MT	Malta
NL	Netherlands
AT	Austria
PL	Poland
PT	Portugal
RO	Romania
SI	Slovenia
SK	Slovakia
FI	Finland
SE	Sweden
UK	United Kingdom
IS	Iceland
NO	Norway
CH	Switzerland
ME	Montenegro
MK	Macedonia
RS	Serbia
TR	Turkey
GE	Georgia
MD	Moldova
KZ	Kazakhstan
RU	Russia
UA	Ukraine
US	United States

1 Introduction

The use of assisted reproductive technology (ART) treatments has substantially increased since the birth of the first child conceived via in vitro fertilization (IVF) in 1978 (Step toe and Edwards, 1978). Since this initial treatment, an estimated five million ART children have been born worldwide, with this trend continuing to accelerate over time. The number of ART births reached one million in 2003 and by 2007 it climbed to 2.5 million, followed by a doubling of that figure by the end of 2013. The number of ART cycles and transfers worldwide likewise continues to grow (Adamson *et al.*, 2013).

Despite this marked increase in the use of ART, little is known about the demographic consequences of these treatments. In this report we broadly define demographic consequences as the proportion of ART births and ‘net impact’ of ART on national fertility levels, the effectiveness of ART usage at later ages, the impact of ART on multiple births and differences in pregnancies and deliveries of ART conceptions versus non-ART births. A comprehensive review of the ART literature demonstrated that previous research has primarily focused on the economic and policy-related consequences of ART (Mills *et al.*, 2013), often ignoring demographic questions.

This report asks and answers key questions that are highly relevant to policy makers, ART providers, and patients. Our central research questions ask: Could ART treatments operate as an effective policy instrument to counter low fertility? Why are there considerable cross-national differences in the proportion of ART births across nations? How has ART usage in older mothers above 40 years increased over time and how effective is ART at these advanced ages? Is it delayed childbearing or ART policies that related to the dramatic growth in twinning and multiple births across time? How do ART users and pregnancies and deliveries differ from their non-ART counterparts? Which types of treatments are more likely to result in a successful birth?

The motivation to study the demographic consequences of ART is spurred by key fertility changes across most European societies, namely the postponement of births to advanced ages and fertility levels below replacement rates. Since the late 1980’s, many European countries reached very low fertility levels, referred to as ‘lowest-low’ fertility or the ‘postponement transition’ (Kohler *et al.*, 2002; Mills *et al.*, 2011). This has recently been countered with a reversal of the fertility decline in the early 2000’s in most countries, albeit with considerable heterogeneity (Balbo *et al.*, 2013). These initial changes resulted in many nations searching for policy solutions to counter low fertility, and searching for ways to extend particularly women’s reproductive period, with ART often the focus of this debate.

As ART became widespread, a debate emerged about its potential influence on fertility rates and, subsequently, whether its wider provision should be

considered as a part of policies that can eventually boost fertility rates in low-fertility countries and, even more radically—serve to alter broader population trends, slow down the pace of population aging and prevent the population from declining (Connolly *et al.*, 2010; Grant *et al.*, 2006; Hoorens *et al.*, 2007; Ziebe and Devroey, 2008). One report went as far as to argue that policies stimulating ART use might be considered as a part of population policy mix to “increase fertility in Europe” (Grant *et al.*, 2006). The most radical view was expressed by Thaele and Uszkoreit (2007), who suggested that ART could be a “‘tool’ in combating negative population growth in countries with declining birth rates.” Others, however, have expressed more skepticism towards this perspective (Lassen *et al.*, 2012; Leridon, 2004; Leridon and Slama, 2008; te Velde *et al.*, 2008).

The aim of this report is to document the broader demographic consequences related to the increased usage of ART and is divided into four central research aims. First, we answer the question of whether ART could be a useful policy response to counter low fertility. We achieve this by examining the proportion of ART births across countries, potential reasons for large cross-national differences and consider the ‘net impact’ of ART on national fertility rates. Recent research has shown that ART utilization varies greatly between countries (Chambers *et al.*, 2014; Kocourkova *et al.*, 2014). We will explore the ensuing differences in ART birth rates across countries and explore potential hypotheses and correlates related to ART birth rates to foster an understanding the differences emerging between countries.

Second, we examine ART usage at later ages, how this varies across countries, and most importantly, examine how effective ART treatments are at advanced ages. The postponement of childbearing has been a striking factor across many European countries (Mills *et al.*, 2011), but it remains unclear as to whether there has been an increase of users of very advanced ages above 40, how this varies by country and type of treatment and how effective treatments are at older ages. In this section we likewise explore individuals’ self-reported conceptions of their own levels of infertility, an aspect that is often ignored in the literature. The recent debate about the benefits and downsides of so-called social freezing and move of companies such as Google and Facebook to pay for the cryopreservation of oocytes for later IVF for non-medical reasons (Tran, 2014) reflects the desire of many women (and their employers) to use ART as a means to reconcile employment and childbearing. The substantial effects of the introduction of oral contraception of women’s careers—what Goldin and Katz (2002) termed ‘the power of the pill’—might have created similar expectations for ART, and it is questionable whether ART can fulfill those expectations with respect to women’s career and childbearing reconciliation. In order to shed light onto this issue, we compare ART usage rates among different age groups across

European countries, distinguishing between different types of ART treatments. Furthermore, we look at the success rates of ART treatments over age groups and across countries to gauge how effective ART is for different groups.

Thirdly, we look at the explicit demographic consequence of ART treatments, namely linking the growth in multiple births to ART treatments. While multiple births are an important health risk both for children and their mothers, the development of the multiple birth rate also highlights the importance of ART regulation (Felberbaum, 2007). In this section we ask whether twinning rates have grown over time across Europe and how this might be related to delayed childbearing and ART policy. Here we link our findings to our previous report which examined the regulatory and economic aspects of ART (Mills *et al.*, 2014a).

As we note in our analyses until now, we are often left with aggregated macro-level data on ART rates and usage, resulting in an inability to link it to individual characteristics or outcomes. The fourth and final part of this report overcomes these problems by using micro-level individual data from Italy in order to ask key questions that macro-data evade. Here we are able to examine the individual characteristics of ART mothers and whether there is variation by the type of ART and probability to have a successful birth.

2 The proportion of ART births and net impact of ART on fertility rates

2.1 Proportion of ART births versus ‘net impact’ on fertility rates

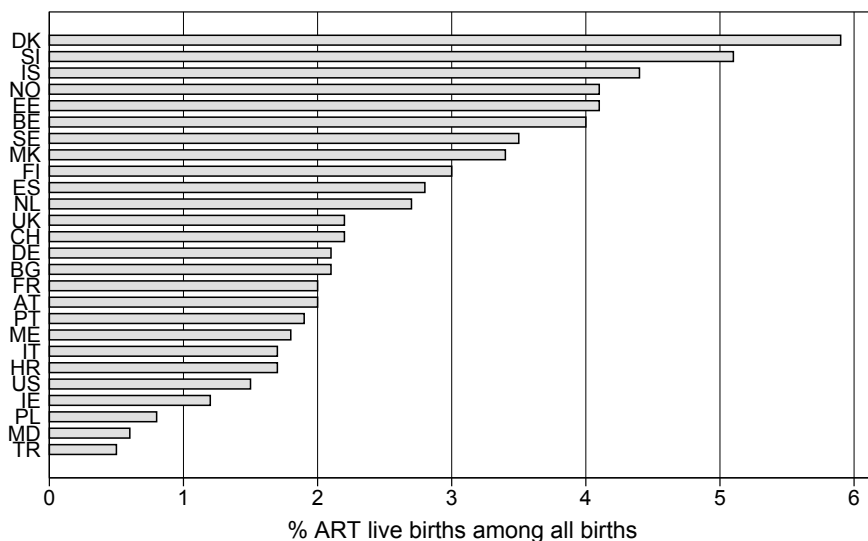
This report is based on data that stem from two different sources. Firstly, we present data on ART regulation across a large number of countries. Secondly, we make use of selected measures from large-scale survey data to present the social context in which ART regulation is taking place. The data set assembled for this report is publicly available, including a technical manual that describes all measures, which will allow readers to conduct further analyses.

This section first examines the ART contribution to the total number of births, followed in the last section by an examination of the contribution of the ‘net impact’ of ART on national fertility rates. The ‘net impact’ represents the difference between the observed number of births and a hypothetical one achieved in the absence of ART treatments, which is a more accurate means to examine whether ART has a strong impact on fertility and demographic trends. We explain the factors of why the net impact might be smaller than the simple proportion of ART live births shortly.

Important shortcomings of the data that we examine in this section also need to be acknowledged, as some countries do not register all ART cycles properly and some pregnancies might be lost from observation making it impossible to determine their outcome (Kupka *et al.*, 2014). Furthermore, some women travel abroad to undergo ART treatments (Shenfield *et al.*, 2010), which is responsible for additional misclassifications of births. Reasons for seeking cross-border care are manifold, ranging from attempts to access treatments that are prohibited in the country of origin (e.g. German couples desiring IVF of donated eggs, Bergmann (2011), or lesbian couples and single women going from France to Belgium to receive IVF, van Hoof *et al.*, 2015), access difficulties (e.g. UK couples going abroad to avoid long waiting lists, Culley *et al.*, 2011), to better expected quality and previous failed treatments in the country of residence (Shenfield *et al.*, 2010). Shenfield *et al.* (2010) report that a conservative estimate of cross-border reproductive care (i.e. crossing country borders in order to undergo ART) in 2008/2009 would be one of 11,000–14,000 patients and 24,000–30,000 treatment cycles in Europe. When confronted with the number of ART cycles (2008: 532,000; 2009: 537,000) and aspirations (2008: 340,000; 2009: 383,000) counted in Europe at that time (Ferraretti *et al.*, 2012, 2013), this is a small, yet substantial share of patients and cycles.

2.2 Cross-national differences in proportion of ART births to all births

Figure 1 reports recent data for those European countries considered to have the most complete data registration of ART treatments, in addition to the United States for comparative purposes. The Figure reveals substantial variation between countries. In Denmark and Slovenia, the share of ART children among all births has surpassed five per cent. In Iceland, Norway, Estonia, and Belgium, the share is four per cent or slightly above. Countries where ART births are least prevalent are Turkey, Moldova, Poland, Ireland and the United States, with a share of less than 1.5 per cent. We now turn to possible substantive reasons for this variation by country.



Note: Data refer to 2010 or latest available (no earlier than 2007)

Figure 1: Cross-national differences in ART birth rates

Sources: De Mouzon *et al.* (2012); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014); Sunderam *et al.* (2013)

2.3 Understanding cross-national differences in national ART levels

How can these differences in the proportion of the ART births between the countries be understood? There are five central hypotheses that can be explored in order to understand and interpret these differences, namely whether they are related to: postponement, the demand for children (using a proxy of the overall fertility rate), country affluence (and thus lower treatment provision) and the

related aspect of affordability and finally, ART policy measures. In this section, we correlate aggregate ART success levels with macro-level indicators to explore associations. We recognize the shortcomings of this approach and inability to make causal statements, but considering the lack of micro- and longitudinal data of a cross-national comparative nature, we are still able to indicate plausible relationships and outline future areas of research.

2.3.1 Fertility postponement

The first simple hypothesis is that late childbearing in the form of a late average age at first birth would result in higher national levels of ART. Figure 2 plots the mean age at mother's first birth by the percentage of ART infants, showing that there is no meaningful correlation. For countries with a mean age at first birth between 28 and 29 years, the percentage of ART infants ranges from about one per cent (Ireland) to about six per cent (Denmark). This corroborates the finding by Kocourkova *et al.* (2014), who showed that ART use in European countries was not correlated with Lesthaeghe and Neidert's (2006) fertility postponement index. One reason for this lack of an association might be related to the low effectiveness of ART when attempting late childbearing, which we explore in detail in the next section. In other words, since our measure is of successful live births, we may be missing unsuccessful ART treatments that did not result in a live birth, particularly of older women.

2.3.2 Changes in the demand for children: total fertility rate

Another hypothesis is that the national levels of ART usage might be related to the overall growth in the increased demand for children, in which the total fertility rate (TFR) can be used as a proxy. Figure 3 demonstrates that we are in fact able to show that there is an association with ART usage (and subsequently ART birth rates) in countries that also have a high TFR. This supports a recent finding by Kocourkova *et al.* (2014) who suggest that increases in ART utilization increased in tandem with the fertility rates in many European countries. It is vital to note, however, that the results by these authors and our macro-level associations are unable to specify any causal direction of the effect. While studies have suggested that the effect of ART births on fertility rates are not negligible (Hoorens *et al.*, 2007; Sobotka *et al.*, 2008), both trends could also be driven by an increasing demand for children in many countries in the last years.

2.3.3 Country affluence

In addition to arguments related to postponement and total fertility rates, an additional hypothesis is that varying national degrees of ART usage might be

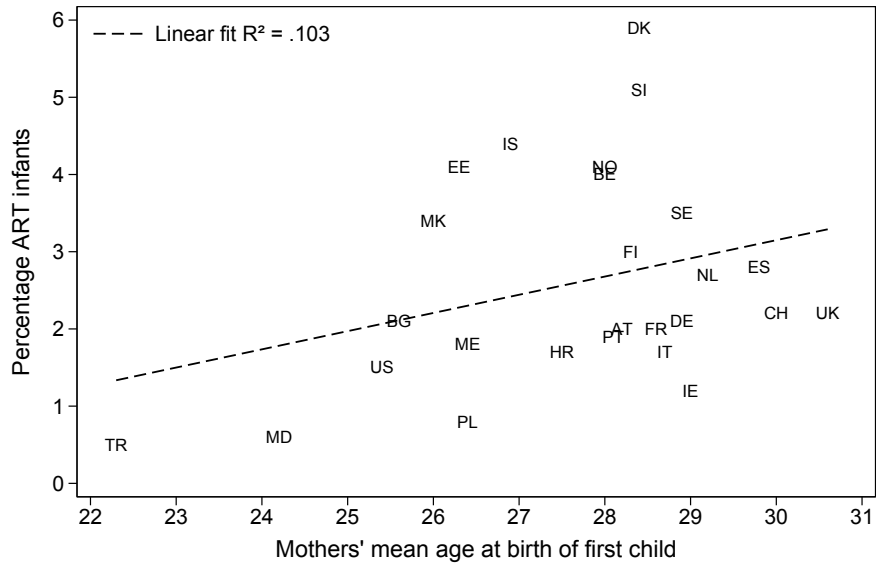


Figure 2: Correlation of mother's age at first birth and ART birth rates

Sources: De Mouzon *et al.* (2012), Eurostat (2014b, demo_find), Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014).

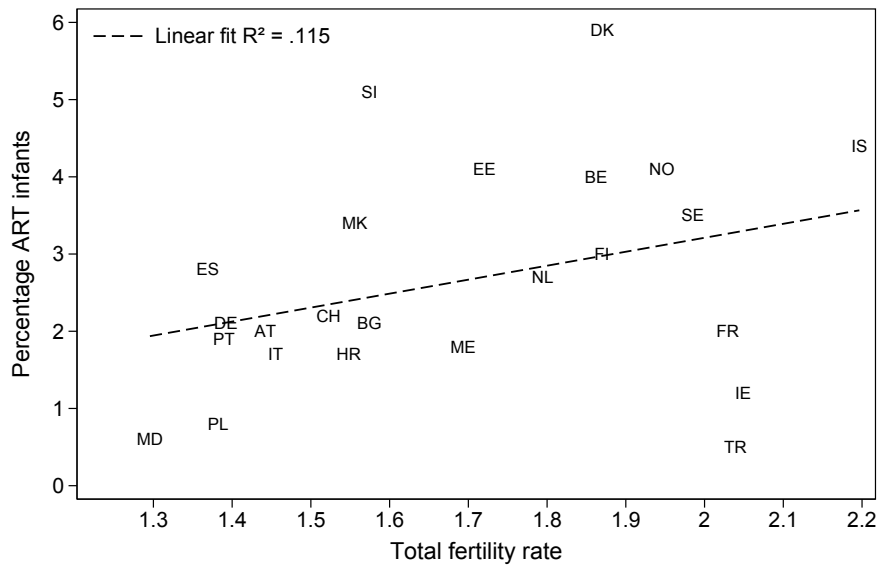


Figure 3: Correlation total fertility rate and ART birth rates

Sources: De Mouzon *et al.* (2012), Eurostat (2014b, demo_frate), Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014).

explained by the level of country affluence. Here the explanatory mechanism is that the lowest-income countries of Europe may have a lower provision of ART treatments for economic reasons.

Figure 4 plots the percentage of ART infants by the GDP per capita and demonstrates that the cross-country differences in ART rates cannot be explained by country affluence. High-income countries such as Norway, Switzerland, the US and Denmark vary greatly in the share of ART births, ranging from one to two per cent in the US and Switzerland to four to nearly six per cent in Norway and Denmark. Among low-income countries, the variation is also substantial: from less than one per cent in Turkey to more than three per cent in Macedonia. This indicates that the wealth of countries is clearly not the driving force behind ART birth rates. This result is in line with the recent finding by [Chambers *et al.* \(2014\)](#), who show that country affluence is unrelated to ART utilization.

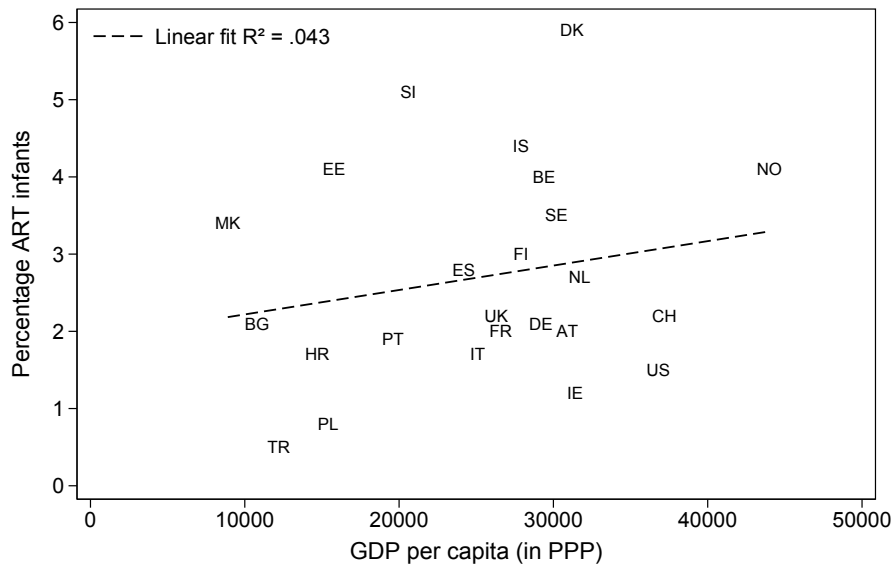


Figure 4: Correlation GDP per capita and ART birth rates

Sources: [De Mouzon *et al.* \(2012\)](#), [Eurostat \(2014a, nama_gdp_c\)](#), [Ferraretti *et al.* \(2012, 2013\)](#); [Kupka *et al.* \(2014\)](#).

2.3.4 Affordability of treatments

It might be, however, that GDP and national levels of affluence are simply too crude of an indicator to capture the economic factors that impact national levels of ART usage. A more direct measure is the affordability of ART treatments, which is defined as the net cost of a fresh ART cycle as a percentage of aver-

age annual disposable income (Chambers *et al.*, 2014). We therefore propose an additional hypothesis, which is that the more affordable a treatment is for individuals in a particular country; the more likely they are to utilize these treatments. In other words, we argue that a major driving force of ART birth rates is related to the affordability of ART treatments (Chambers *et al.*, 2013, 2009; Dunn *et al.*, 2014; Mladovsky and Sorenson, 2010). Figure 5 plots the national levels of affordability against the ART birth rates and forcefully underlines the importance of affordability of ART treatments for ART utilization. The negative relationship between costs and ART birth rates clearly holds, even when excluding the US—where costs for ART treatments can be particularly high—from the analysis. ART utilization does not appear to be impacted by the overall level of affluence in a country, but rather it is the costs for individuals and couples which drive utilization and birth rates.

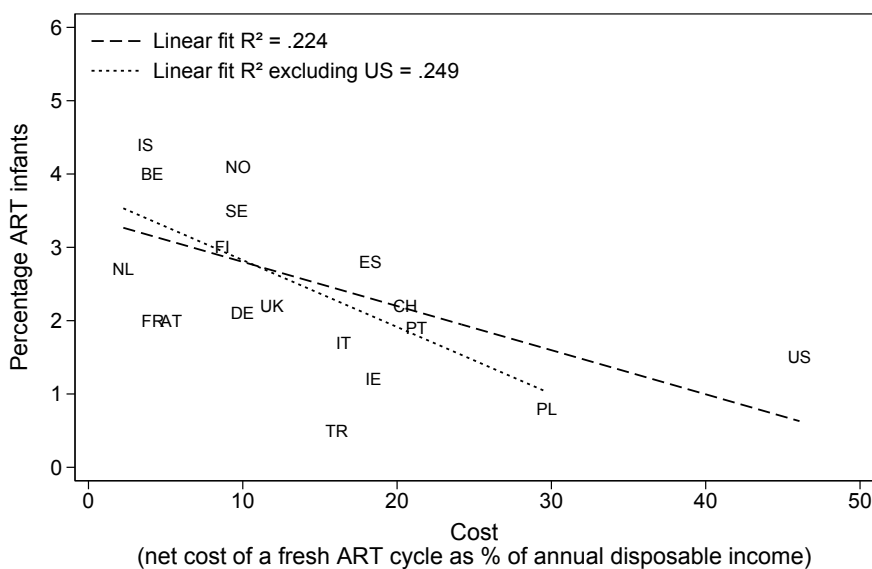


Figure 5: Correlation ART costs and ART birth rates

Sources: Chambers *et al.* (2014); De Mouzon *et al.* (2012); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014).

Mills *et al.* (2014b) likewise noted considerable variation across countries regarding whether ART was covered or not covered by national, private or both types of insurance, which is inherently related to affordability and ability to engage in a treatment. For many European countries, ART was either partially or completely covered as part of the national health plan of a country. Other countries, however, such as Poland and the U.S. had coverage by private insurance with others having even no coverage (Ireland, Latvia, Lithuania, and

Romania).

2.3.5 ART policies and cultural values

We also anticipate that national ART policies, which are often intertwined with cultural values, underlie the disparities in ART usage across countries. The previous report from this Work Package explored this aspect in detail and demonstrated how national ART policies and cultural values impacted ART usage (Mills *et al.*, 2014a). The report noted a striking lack of coherence and even contradiction regarding ART policies, within countries and over time. Although there has been a general move to more formalized legislation and statutory laws, considerable variation still exists. As we will touch upon shortly in relation to the rise of multiple births, one striking policy change has been the move to more stringent regulations regarding the transfer of embryos over time, which started in the early to mid-2000s, first in the Scandinavian countries. As explored in more detail in the previous deliverable in this Working Package (Mills *et al.*, 2014a), ART usage and specific policies such as the number of embryos that are transferred is highly correlated to national religious, cultural and political values regarding whether a fertilized embryo is a human being.

Figure 6 reveals that there is also a correlation between attitudes about the moral status of human embryos and the share of ART births in a country. The moral status of human embryos was assessed with the agreement to the statement “Immediately after fertilization the human embryo can already be considered to be a human being” (Eurobarometer 73.1 (2010), European Commission, 2012). Agreement was measured on a four-point scale with the options “Totally agree,” “Tend to agree,” “Tend to disagree,” and “Totally disagree.” For the analysis below, we calculated the average percentages of respondents tending to disagree and totally disagreeing to the statement that embryos are human beings right after fertilization.

Indeed, in countries where a lower moral status is attached to embryos, ART birth rates are higher. Given the fact that ART techniques require the handling of embryos and often ethically charged actions such as elective single embryo transfer (Thurin *et al.*, 2004), this association is not surprising. What is remarkable is the strength of the association; it is comparable to the size of the association of ART births and affordability of ART treatments (Figure 5).

Figure 7 however reveals that the correlation between views on the moral status of an embryo in a country are not as clear-cut as they appear in Figure 6. When embedded in a specific example, the correlation is considerable weaker. Here, agreement to the statement “We have a duty to allow research that might lead to important new treatments, even when it involves the creation or use of human embryos” (Eurobarometer 73.1 (2010), European Commission, 2012) was assessed. Again, response options were “Totally agree,” “Tend to agree,”

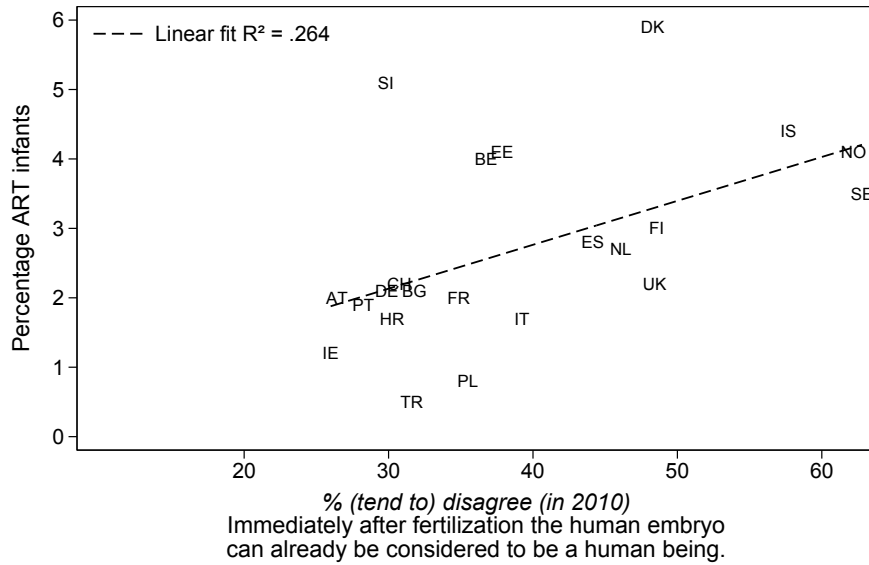


Figure 6: Correlation moral status of an embryo and ART births

Sources: De Mouzon *et al.* (2012); European Commission (2012); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014).

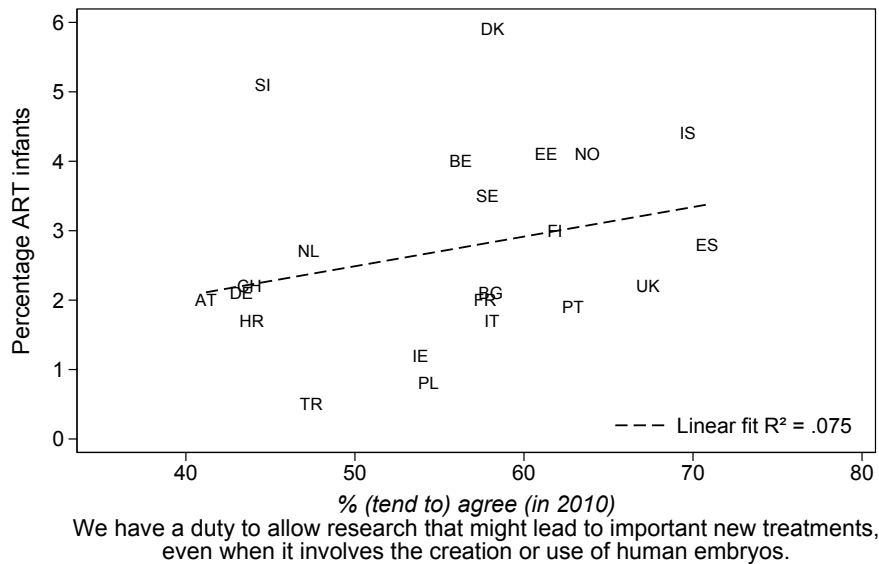


Figure 7: Correlation attitudes to research on embryos and ART births

Sources: De Mouzon *et al.* (2012); European Commission (2012); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014).

“Tend to disagree,” and “Totally disagree.” For the analysis, we calculated the average percentages of respondents tending to agree and totally agreeing to the statement that we have a duty to allow research that creates or uses human embryos for the sake of medical progress. While the overall trend in the scatterplot is positive, the fit of the regression line is far from perfect. A reason for the difference between the findings in Figure 6 and Figure 7 might be that people’s opinions on the moral status of human embryos are more complex or more diffuse than the survey items at hand can capture. Also, the item in Figure 7 brings in very different assumptions than the one in Figure 6, in that it is open for the respondents’ interpretation what a “duty” or “important new treatments” constitute, also using and creating human embryos have different moral implications that are being conflated in the item in Figure 7.

In sum, we were able to show here and in other work (Mills *et al.*, 2014a; Präg and Mills, 2017b,a; Präg *et al.*, 2017; Präg and Mills, 2017c) that both ART usage as well as ART birth rates are correlated with ART costs, ART regulation, as well as norms and values across countries, in complex ways that need further elucidation.

2.4 ART birth rates over time

Figure 8 presents the development of ART birth rates from 1997 to 2010 in selected countries. While we have seen great heterogeneity in the level of ART births between countries (Figure 1), the trend over time is unequivocal. In all countries we observe an upward trend in the past decade. The only exception is Germany, where a change in reimbursement regulations in 2004 caused a drop in ART uptake.¹ Until 2004, the German public health insurance system paid a hundred per cent of up to four treatment cycles; since then, only 50 per cent of the costs of up to three cycles are covered (Fauser and Devroey, 2011, p. 206). The drop in ART births again underlines the importance of affordability of ART. But since the drop in 2004, the trend has been upward. Between countries, there are differences in the strength of the upward trend. The slope in some countries such as France, the UK, and the US is rather flat. For instance, in the UK and in France, the share of ART births roughly doubled over a period of 14 years. In other countries, the slope is even steeper, such as in Belgium, where the rate increased from 1.5 per cent in 2001 to four per cent in 2010.

2.5 Contribution of ART to the net birth rates

Focusing on the ‘net impact’ rather than the simple proportion of ART live births is essential to avoid making exaggerated claims about the policy rel-

¹It is likely that the drop in 2004 was inflated in the sense that couples who were anticipating the change in regulations underwent treatment in 2003 which they would have only had later if there had not been a policy change.

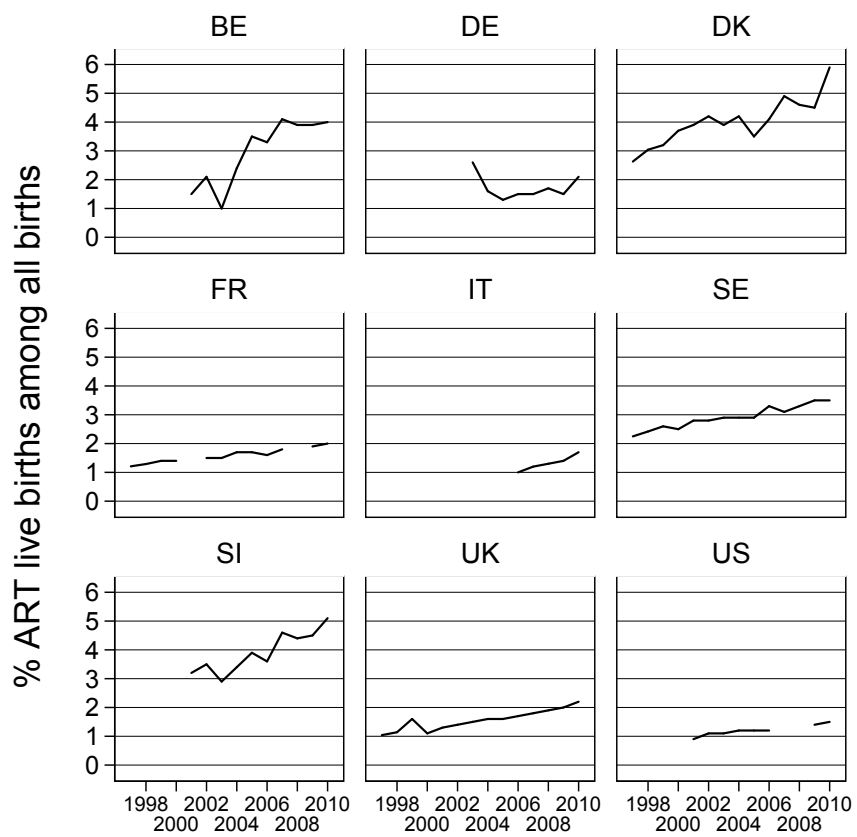


Figure 8: Development of ART birth rates, selected countries

Sources: De Mouzon *et al.* (2010, 2012); ESHRE (2001a,b, 2002, 2004, 2005, 2006, 2007, 2008); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014); Nyboe Andersen *et al.* (2009); Sunderam *et al.* (2009, 2012, 2013); Wright *et al.* (2004, 2005, 2006, 2007, 2008).

evance of ART treatments as a solution for low-fertility societies. The ‘net impact’ is defined as the difference between the observed number of births and a hypothetical one achieved in the absence of ART treatments.

Two factors make this ‘net impact’ smaller than the simple proportion of ART live births. First, some couples undergoing ART would eventually achieve spontaneous conception. Brandes *et al.* (2011) were for instance able to show that of 437 subfertile couples seeking ART in a fertility clinic, 56 per cent conceived before treatment, although those couples had on average experienced two years of unexplained subfertility before that. Troude *et al.* (2012) and Steures *et al.* (2006) report similar findings. A review of figures from previous studies (Cahill *et al.*, 2005; Eijkemans *et al.*, 2008; Osmanagaoglu *et al.*, 2002; Pinborg *et al.*, 2009) suggests that there is quite a range of estimates in the literature when it comes to naturally conceived pregnancies among couples undergoing ART treatment and that it is safe to say that well above ten per cent and possibly close to twenty per cent would eventually become pregnant without the treatment (Mills *et al.*, 2013).

Second, ART partly leads to unintended or unplanned ‘extra’ births due to very high rates of multiple deliveries. Thus, a portion of ART births would be eliminated if unintended twin and triplet births had not inflated the number of observed ART infants. This development is already under way with a spread of single embryo transfers and the tendency of ART to result in more multiple births is not constant over time and between countries (see also section 4). In some countries the trend in ART moves away from multiple embryo transfer to elective single embryo transfer (Maheshwari *et al.*, 2011), however in many parts of the world, including the US and Asia, multiple birth rates after ART are still at 20–30 per cent (Templeton, 2010). While it seems straightforward to calculate the contribution of multiple births due to ART (also see the section on multiple births below), research has shown that not all multiple births after ART are undesired (McLernon *et al.*, 2010). Some parents want to have more than one child, and having twins can be seen as a money-saving strategy when faced with high costs for ART treatments. Furthermore, some women would go back to ART to have another child through additional ART treatments (Mills *et al.*, 2013).

So far, only few studies tried estimating the contribution of ART to fertility rates (Mills *et al.*, 2013). Hoorens *et al.* (2007) took a simple approach that did not account for the chance of spontaneous natural conception nor multiple births and estimated that ART contributed to the period total fertility rate in the United Kingdom .02 (from 1.62 without ART to 1.64 with ART) and .07 in Denmark (from 1.65 without ART to 1.72 with ART). Sobotka *et al.* (2008) examined cohort fertility rates of Danish women. For women born in 1970, they reached results similar to those of Hoorens *et al.* (2007) for the total fertility

rate. The estimated net effect however, was considerably lower, ranging from .04 to .06, conditional on the assumptions made regarding multiple births and spontaneous conception. For the Netherlands, [Habbema *et al.* \(2009\)](#) arrived at a higher estimate for the increase in period total fertility rate of .08 (from 1.79 to 1.86), however this increased would be cut by more than half if multiple births were eliminated. For French women born in 1968, [Leridon and Slama \(2008\)](#) estimated a .04 increase in the total fertility rate if all couples resorted to ART within one to four years and a .02 increase if only half of the couples did this. In sum, these studies reveal that any views that ART might have a substantial and large effect on fertility rates are exaggerated.

3 ART usage and effectiveness at later ages

Fertility postponement is one of the main drivers of low fertility in European societies. The average age at first birth has increased by about one year per decade since the 1970's in most OECD countries (Mills *et al.*, 2011). Maternal age is, however, the most important predictor of achieving pregnancy and successful delivery (Dunson *et al.*, 2004). While research has shown that there is a remarkable variability in female reproductive aging (te Velde and Pearson, 2002), female fertility traditionally ends with menopause. As te Velde *et al.* (1998) illustrated, the number of follicles starts to decrease with age, with sharper decreases starting at the age of 31, menopause at the average age of 45, and fertility generally ending for most women in their early 40's. Eijkemans *et al.* (2014) report that the age at last birth is around 40–41 years across a range of natural fertility populations.

The WHO defines infertility as the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year. On the one hand, this definition poses problems with respect to measurement; on the other hand, research has shown that couples who seek infertility treatment regularly conceive under conditions of expectant management (Brandes *et al.*, 2011; Steures *et al.*, 2006; Troude *et al.*, 2012). Due to these considerable measurement problems, it is difficult to obtain individual-level data regarding the timing of the onset of infertility. For this reason, we first turn to recent and rare data that show individuals' self-reported ideas about their own infertility.

3.1 Self-reported infertility by age groups and across countries

A recent albeit less precise approach to gauge infertility—taken by the Generations and Gender Survey (GGS, Vikat *et al.*, 2007)—is to collect self-reports of infertility directly from respondents in a survey. In the first wave of the GGS, respondents were asked ‘Some people are not physically able to have children. As far as you know, is it physically possible for you, yourself, to have a/another baby?’ Figure 9 plots the percentage of (non-pregnant) women reporting that it is ‘definitely not’ or ‘probably not’ possible to get pregnant over age groups and countries. While all countries show a clear upward trend in (suspected) infertility over age groups, there is quite a variation in the slopes reported by women. Whether these differences are rooted in different cultural beliefs about fertility or reflect biological differences due to factors such as genetic dispositions (e.g. for early menopause, endometriosis) is not possible to determine using the GGS data.

Figure 10 shows the remarkable differences between countries for a particularly relevant group, the 35–39 year-olds. Whereas among French, Polish,

Hungarian, Bulgarian, and Norwegian women the self-reported infertility rate ranges around five per cent, in countries such as Austria, Romania, Belgium, the Czech Republic it ranges around ten per cent, and in Russia and Georgia it has clearly surpassed ten per cent. The lower panel of Figure 10 shows the same rates as reported by 35–39 year-old men, however both absolute rates as well as cross-national variability are lower than for women. In most countries the rate of male self-reported infertility ranges well below or around five per cent. Only in Germany and Norway the rate is higher than five per cent.

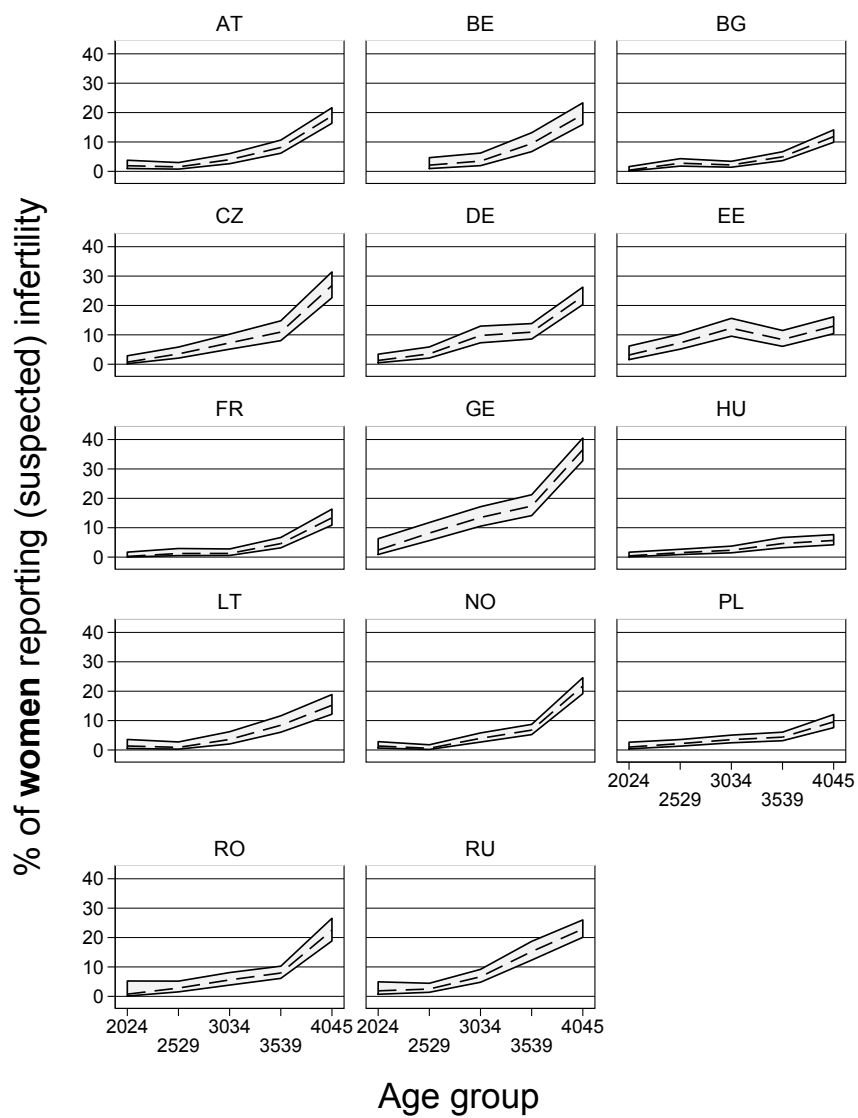
Infertility, particularly as it is perceived by individuals, is an important driver of the demand for ART treatments. While the data show that women in generally perceive infertility to increase with age, which is in line with the medical literature (e.g. *te Velde et al., 1998*), there is substantial variation between countries with respect to the pace of the perceived fertility decline. In how far these differences reflect biological conditions, differences in the desire to have children (e.g. women who are voluntarily childless will not be aware of the fact that they are unable to conceive naturally), norms regarding older parents, and differences in cultural reporting standards have to be left to future research. Nonetheless, these differences should be kept in mind when interpreting cross-country differences in ART demand and utilization.

3.2 Increase of women over 40 years receiving treatment over time

Given the trend towards late childbearing, it is likewise interesting to explore whether this fertility postponement has translated into increasingly older women (i.e. over the age of 40) seeking ART treatments. Figure 11 reveals a growing trend in the development of ART aspirations by women aged forty and older over time and across different European countries.² Unfortunately, data do not allow us for a more detailed breakdown by higher ages. Most countries reveal indeed an upward slope in the demand by older women for ART treatments, most remarkably Iceland, Italy, and Denmark. In some countries, such as Sweden and the UK, the increase is slower, whereas in other countries, such as Hungary and France, the ART demand among older women remains largely stable over time. This can reflect differences in access regulations to ART across countries (*Mills et al., 2014b*).

Also, Figure 11 shows that there are stark differences in the level of ART use among older women. Whereas in Poland or Portugal the share of women 40 and older using ART treatment is less than one out of a thousand, in countries such as Norway, Switzerland, Denmark, and Italy, the shares are several times of that.

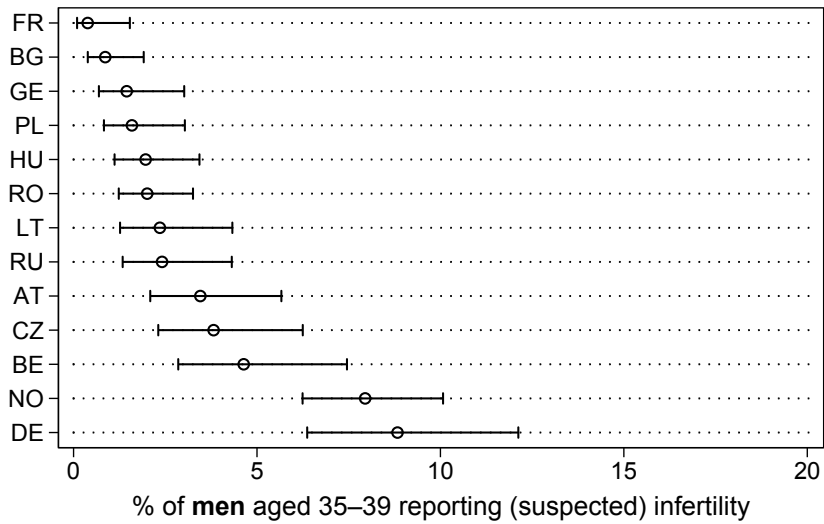
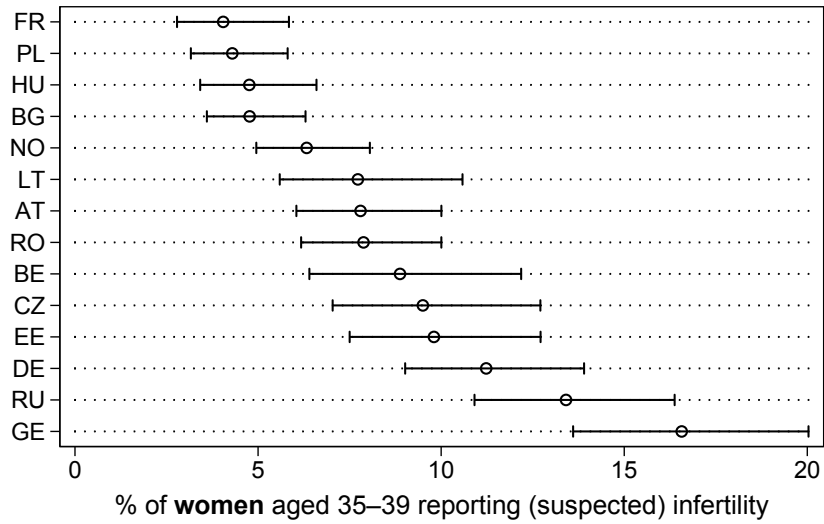
²Aspirations are initiated ART cycles in which one or more follicles are punctured and aspirated irrespective of whether or not oocytes are retrieved (*Zegers-Hochschild et al., 2006*).



Note: Gray areas denote 95 % confidence intervals

Figure 9: Self-reported infertility among old women by age group and country, 2005–2011

Source: Generations and Gender Survey (Vikat *et al.*, 2007), own calculations.



Note: Error bars denote 95 % confidence intervals

Figure 10: Self-reported infertility among 35–39 year olds by sex and country, 2005–2011

Source: Generations and Gender Survey (Vikat *et al.*, 2007), own calculations.

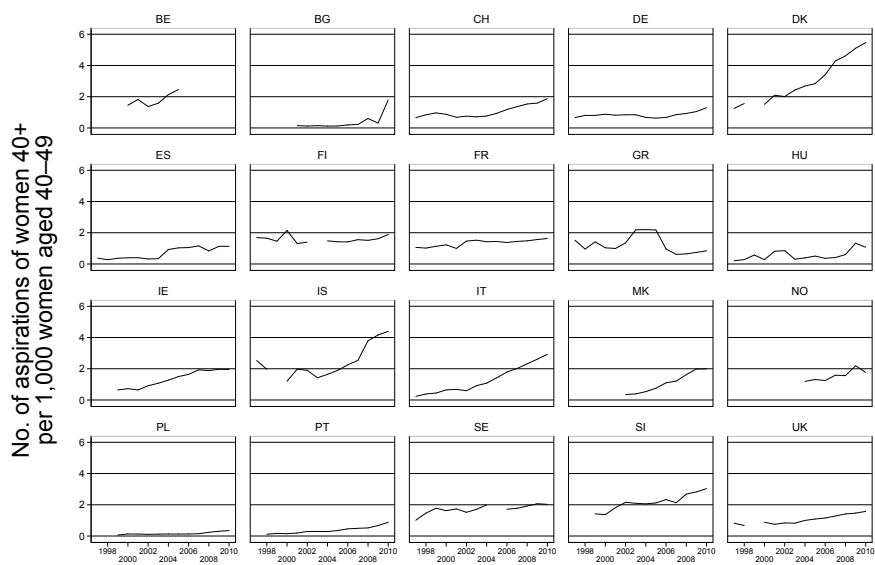


Figure 11: Increase in ART use (ICSI and IVF) among women age 40+, selected countries, 1997–2010

Sources: De Mouzon *et al.* (2010, 2012); ESHRE (2001a,b, 2002, 2004, 2005, 2006, 2007, 2008); Eurostat (2014b, demo_pjan); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014); Nyboe Andersen *et al.* (2009).

3.3 ART usage by age, country and type of treatment

The data used for Figure 11 do not allow us to distinguish between which type of ART treatment women utilize. The most recent ESHRE data (Kupka *et al.*, 2014), however, allow us to distinguish this. Figure 12, Figure 13, Figure 14, and Figure 15 present data on ART patients broken down by age, country, and type of treatment. We can only distinguish between rather broad age categories, namely women age 34 and below, 35 to 39 years of age, and 40 years and above. Figure 12 reveals substantial variation across countries with respect to in vitro fertilization (IVF) across countries. In Greece, Italy, Switzerland, Ireland, Denmark, Lithuania, Iceland, Germany, and Spain, the share of patients age 40 and older is 20 per cent or greater, in other countries, such as Montenegro, Poland, Kazakhstan, or the Czech Republic, it is less than ten per cent. Across the countries under study, the average share of IVF patients 40 years and older is 16.7 per cent, for those between 35 and 39 it is 37.6 per cent, and 45.6 per cent of IVF treatments are administered to women aged 34 and younger.

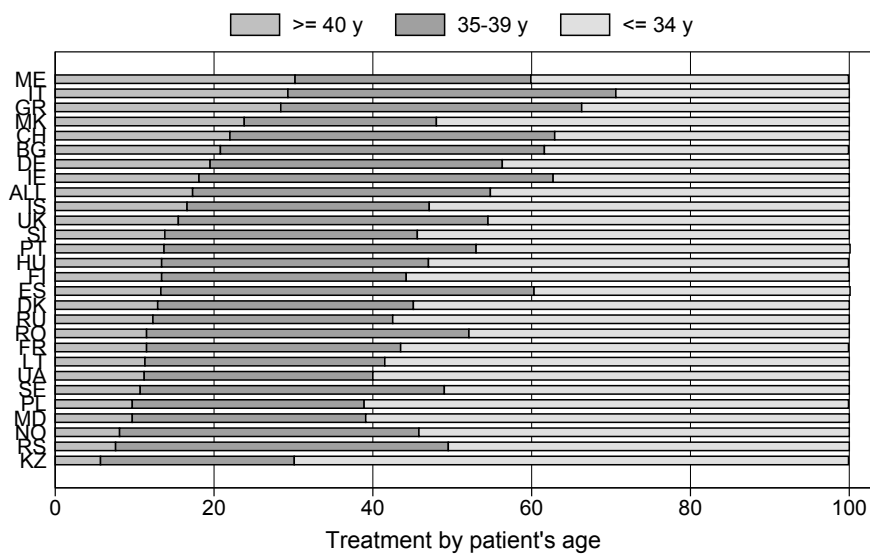


Figure 12: IVF patients by age and by country, 2010

Source: Kupka *et al.* (2014).

Among women undergoing intracytoplasmic sperm injection (ICSI) (Nyboe Andersen *et al.*, 2008), the average across countries is similar (Figure 13, 17.3 per cent), but the distribution is slightly different. Here, Montenegro, which has the youngest IVF patients, has among the oldest ICSI patients. Other countries where the share of ICSI patients that are 40 and older are above 20 per cent

are again Italy, Greece, and Switzerland, but also Macedonia and Bulgaria. The countries with the smallest share of ICSI patients aged 40 and older can be found in Kazakhstan, Serbia, Norway, Moldova, and Poland, where shares are all below ten per cent. Similar to IVF treatments, across all countries the share of ICSI cycles among women 34 years or younger is 45.2 per cent, among those between 35 and 39 it is 37.5 per cent, and, as mentioned above, among women age 40 and older it is 17.3 per cent.

Figure 14 presents data on frozen embryo replacement (FER), a technique used in repeated ART treatments (Stoop *et al.*, 2014). It is common during IVF/ICSI treatments to fertilize more than the oocytes required at the time. Good quality embryos are then cryopreserved for later use, for instance when the current ART attempt does not result in a successful delivery. Whereas in Lithuania and Montenegro, FER is not practiced among women 40 and older, in Switzerland twenty per cent of patients undergo FER. Ireland, the Czech Republic, and Greece are also countries where FER is not uncommon among patients forty years or older.

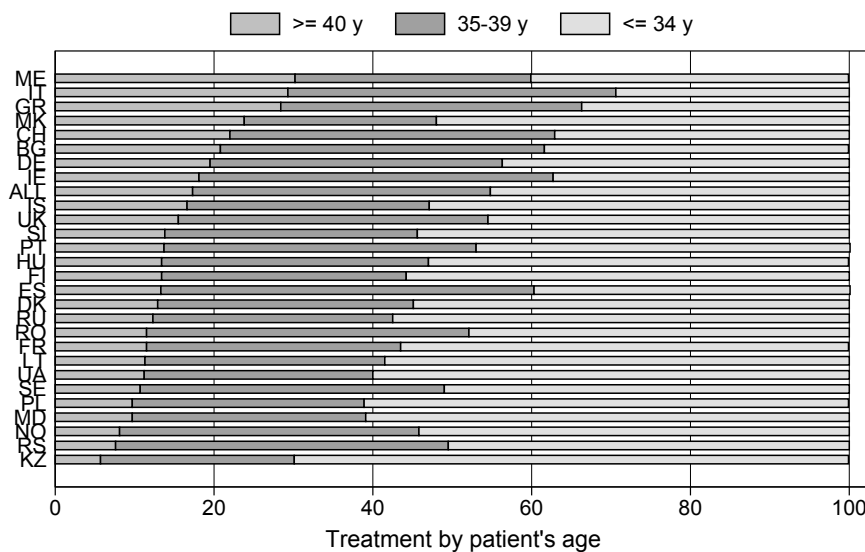


Figure 13: ICSI patients by age and by country, 2010

Source: Kupka *et al.* (2014).

For egg donation (ED), the age distribution among patients is markedly different. Egg donation is a technique that allows women who are unable to produce their own oocytes to achieve pregnancy (Grossman *et al.*, 2012; Keenan *et al.*, 2012; Paulson *et al.*, 2002). Reasons for this can be premature ovarian insufficiency (which often occurs spontaneously or related to cancer treatment)

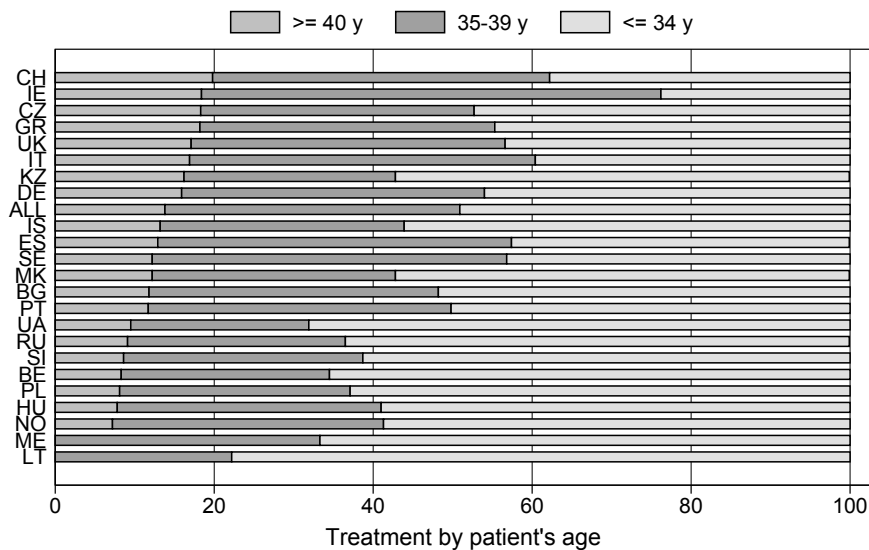


Figure 14: FER (frozen embryo replacement) patients by age and by country, 2010

Source: Kupka *et al.* (2014).

or because of a depleted ovarian reserve (and is related to female aging). Women are transferred an oocyte of a donor and thus give birth to a child which does not carry any of their own biological material. In some countries, such as Germany, egg donation is outlawed. Figure 15 shows that women receiving ED are in most countries indeed past the age of 40.

3.4 ART effectiveness at later ages

We now ask how ART use at higher ages translates into pregnancies and deliveries. Research has suggested that maternal age is a major predictor of an ART pregnancy (Lintsen *et al.*, 2007). Figure 16, Figure 17, and Figure 18 reveal two indicators of ART success by treatment type, age groups, and across selected countries for which data is available. For women age 34 or younger, pregnancy rates after IVF (Figure 16) are around thirty per cent in all countries, sometimes (in Slovenia) as high as forty per cent. The delivery rate is usually a few percentage points lower due to miscarriages and spontaneous abortions, but sometimes (Spain and Germany), those differences are marked. When comparing the pregnancy and delivery rates of women aged 34 or younger to those of women between the ages of 35–39 years of age, a clear decline can be seen. In virtually all countries (Sweden is an exception), the slope is even more negative for women aged forty or older. After IVF, the pregnancy rate among women

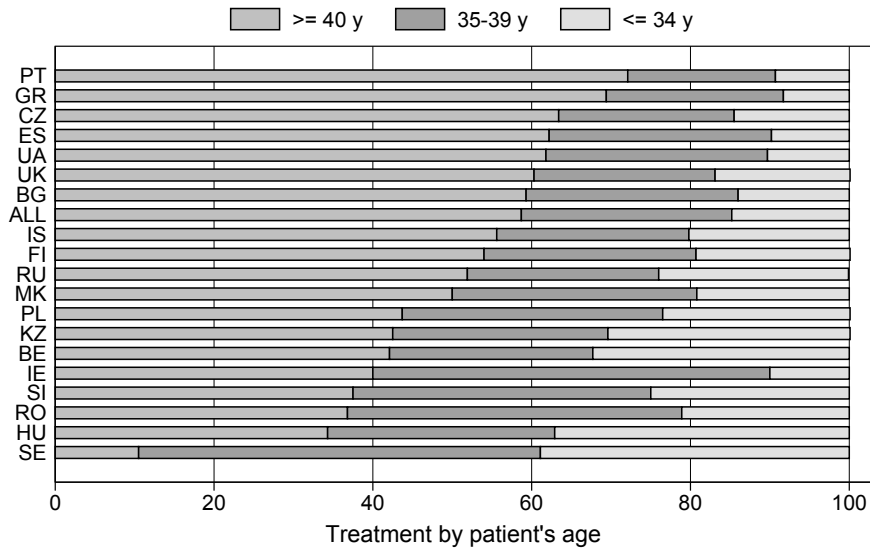


Figure 15: ED (egg donation) patients by age and by country, 2010

Source: Kupka *et al.* (2014).

40+ is only around ten per cent, which is in line with research from the US (Malizia *et al.*, 2009).

For ICSI success (Figure 17), the picture is virtually identical. In all countries, the success rates for women age 40 and older decline markedly. For FER, shown in Figure 18, the age differences in ART success are less marked, however, the overall level of success is substantially lower. Pregnancy rates are often around twenty per cent even for women 34 or younger.

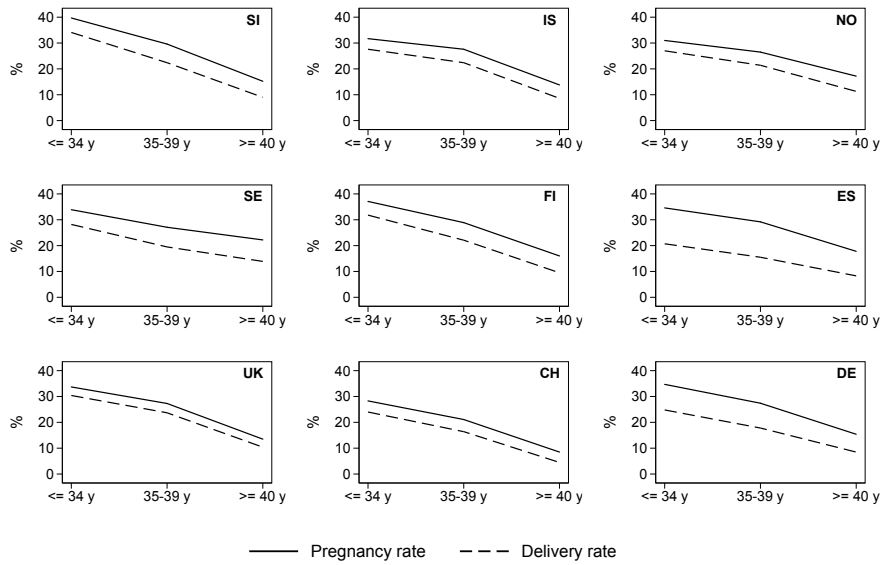


Figure 16: Higher maternal age goes along with decreasing success of IVF treatment, 2010, selected countries

Source: Kupka *et al.* (2014).

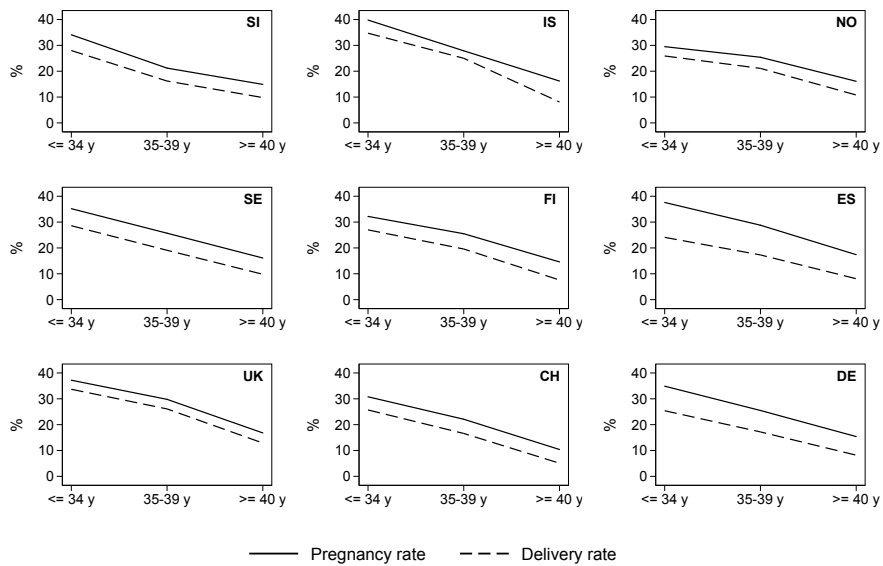


Figure 17: Higher maternal age goes along with decreasing success of ICSI treatment, 2010, selected countries

Source: Kupka *et al.* (2014).

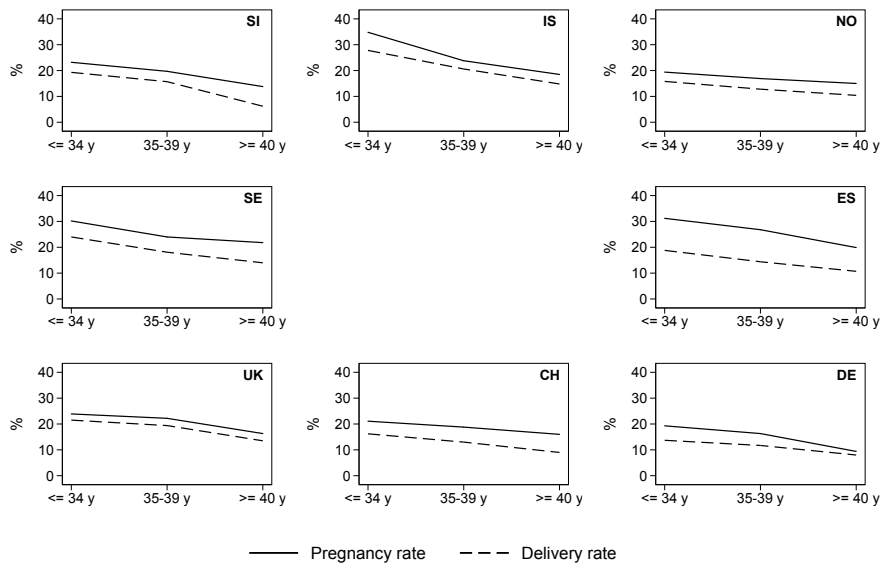


Figure 18: Higher maternal age goes along with decreasing success of FER (frozen embryo replacement), 2010, selected countries

Source: Kupka *et al.* (2014). Note: Data for Finland missing.

4 ART and multiple births

One possible demographic consequence of ART is an increase in the number of multiple births. In the following analysis, we restrict our examination to twins, as the data on triples and higher-order multiple births is relatively sparse. Both more traditional hormonal treatments and multiple embryo transfers increase the likelihood of a twin birth, however, other factors affect twinning rates as well.

The specific relevance of multiple births for societies lies in the adverse outcomes associated with them. Multiple births are a major health risk both for mothers and children. Having twins is generally associated with more complications during pregnancy, such as ectopic pregnancies, spontaneous miscarriage, pre-eclampsia, placenta praevia, gestational diabetes, fetal growth restriction, pre-eclampsia, and pre-term birth (Talaulikar and Arulkumaran, 2013). There is a greater rate of caesarean sections for twin pregnancies. In addition, the risk of postpartum depression increases (Choi *et al.*, 2009) as well as the risk of parental divorce (Jena *et al.*, 2011). In general, the economic costs associated with multiple pregnancies appear to be higher than singleton births (Chambers *et al.*, 2014).

4.1 Dramatic changes in twinning rates across Europe

It is well documented that the twinning rate has increased dramatically since the early 1970's in nearly all countries for which reliable data from vital statistics is available (Hoekstra *et al.*, 2008; Pison and D'Addato, 2006). The increase is so strong that several European countries are now experiencing rates of twinning that previously were only observed in Western and Central Sub-Saharan Africa, which has the highest naturally occurring twin rates (Bulmer, 1970; Smits and Monden, 2011). In Denmark, for instance, the twinning rate has more than doubled between 1975 and 2001, from 9.6 to 21.2 twin deliveries per 1,000 deliveries. Also Estonia and Greece have twinning rates of more than 20. For England and Wales, the rate increased from 9.9 to 16.1, in Germany from 9.2 to 17.2, and in France from 9.3 to 17.4. These last two trends are comparable to the development in the United States, where the twin rate increased from 9.5 to 16.9. Figure 19 gives an overview of the trends in twinning for a selection of countries over the last century up to the most recent year for which data is available.

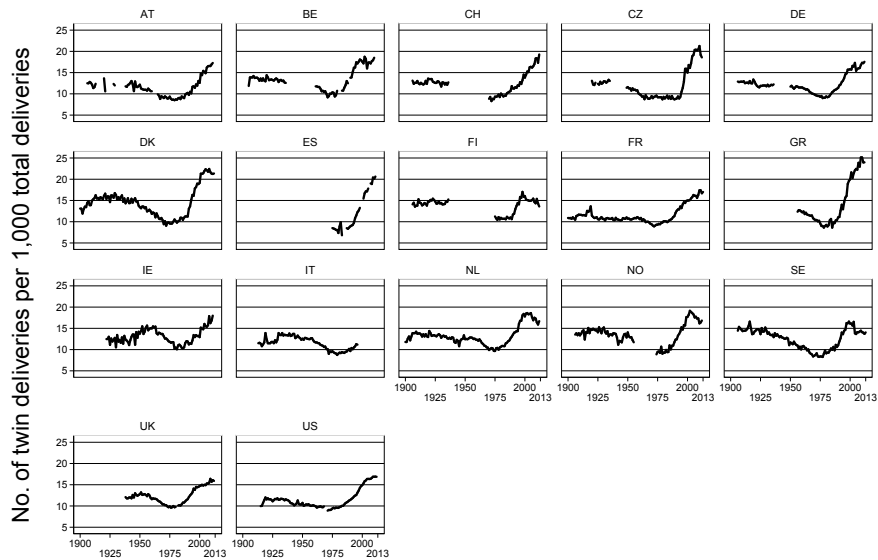


Figure 19: Evolution of twinning rates in a selection of countries, 1900–2013

Source: Pison *et al.* (2015). Note: UK refers to England and Wales only.

4.2 Is delayed childbearing the driving factor behind twinning rates?

Apart from ART, there are other factors that may also be driving the increase in twinning. The most important factors affecting twin birth are maternal age, number of children, and region or country (Hoekstra *et al.*, 2008, partially reflecting genetic differences,). A twin birth is more likely at higher maternal ages and higher parities. While the average age at childbearing has changed dramatically over the past thirty years (Mills *et al.*, 2011), the number of children among women who already have children has not changed as much. Also, there is no reason to assume that the genetic propensity for twinning has changed in this time period. Thus, part of the increase in twinning may be a result of the shift to later births that we can observe throughout Europe and North America. ART and delayed childbirth are likely to be the two most important drivers of the increase twinning rates.

As an illustration, Figure 20 shows how maternal age was related to the chances of a twin birth before ART was available, namely in 1965–1969. Clearly, the frequency of spontaneously conceived twin deliveries varies with maternal age. The pattern is very similar across the four countries presented in the Figure. The twin rate increases with maternal age and is highest when a woman gives birth between the ages of 35 and 39.

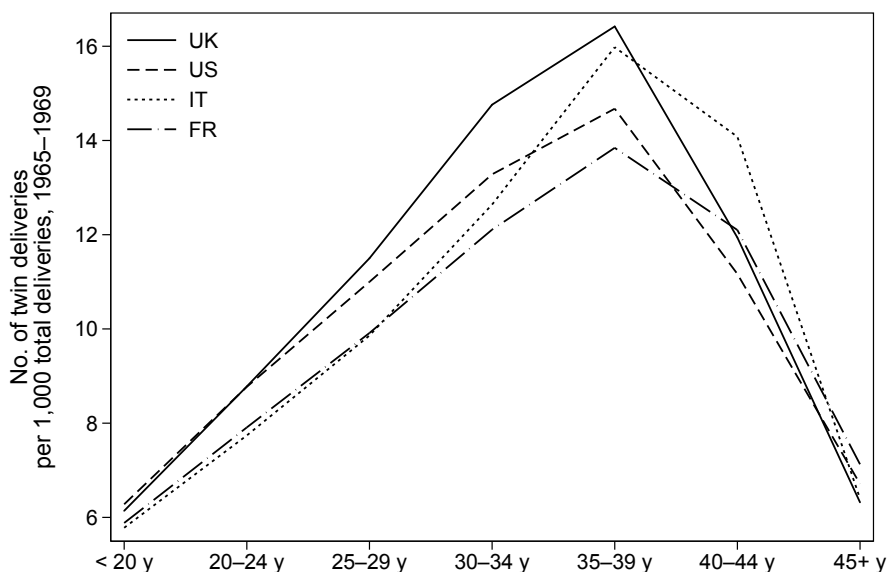


Figure 20: Twinning rates by age group before the invention of ART in a selection of countries

Source: Pison *et al.* (2015). Note: UK refers to England and Wales only.

Therefore, we may expect changes in the overall twinning rate when childbearing is delayed. Figure 21 illustrates the relationship for France. The Figure shows the strong association between mean age at childbearing and the twinning rate; both lines move virtually in lockstep.

4.3 Distinguishing between the effects of ART and delayed childbearing

The question now is how much of the increase in twinning can be attributed to delayed childbearing and how much to ART. Only if we had individual-level data on twin status, maternal age, and ART, we would be able to determine exactly which factor, ART or delayed childbearing, contributed how much to the increase in twinning. Given only aggregate data on twin rates and information on the distribution of maternal age, however, we can at least estimate how much each factor has contributed to the change in twin rates. We have to assume that the relationship between maternal age and the likelihood of a twin birth—as shown in Figure 20—has not changed over time and is similar across countries.

Taking France as an example, we can calculate the relative contributions of ART and childbearing. The observed twinning rate for France was 9.4 in 1970

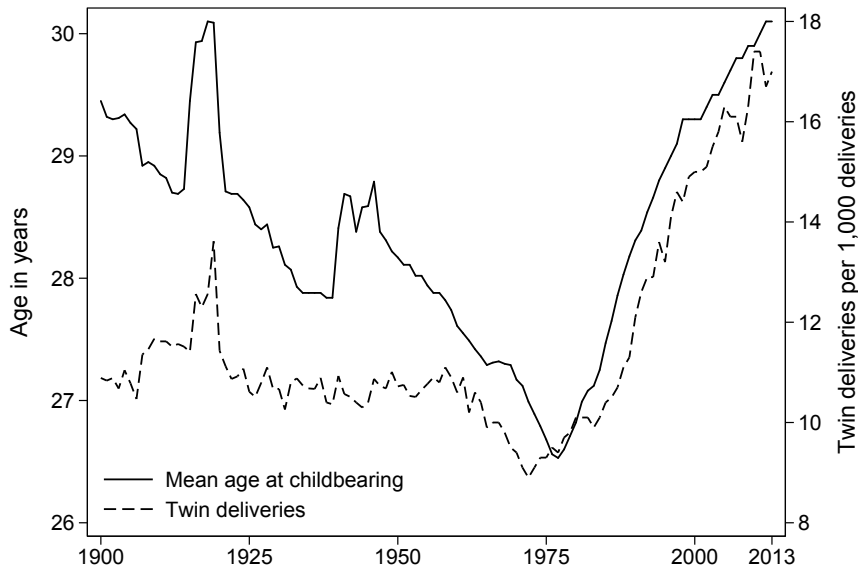


Figure 21: Twinning rates and average age at childbearing in France, 1900–2013

Source: Pison *et al.* (2004).

and 16.3 in 2005. This means it has multiplied by a factor of 1.73 over 35 years. To assess the contribution of delayed childbearing, we calculate what the increase in twin rates, assuming only the age distribution at birth has changed. The distribution of age at birth is taken from the Human Fertility Database (HFD, 2014). Using the age-specific twin rates from Figure 20 (averaged over the four countries) and applying them to the actual distribution of age at birth, we find that the increase in twinning would have been far less: from 9.4 to 10.9, a multiplication by 1.16. If we assume that delayed childbearing and other factors are independent and combine their effects, we can conclude that other factor—mostly ART—have been responsible for an increase of the twin rate by a factor of 1.50 ($1.16 \times 1.50 = 1.73$). In other words, the French twin rate increased by about 16 per cent due to delayed childbearing and by about 50 per cent due to all other factors, most likely predominantly the use of ART.

We can apply the same logic to countries for which we have an actual twin rates in the period 1970–2005 and for which we know the changes in the distribution of age at birth. Figure 22 shows the results of such an analysis for twelve countries. The countries are ordered by the absolute increase in the twin rate that is associated with factors other than delayed childbearing. For the Czech Republic, for instance, we estimate that factors other than delayed childbearing are responsible for an increase in the twin rate (between 1970 and 2005) of 64 per cent (or 1.64). Delayed childbearing is associated with an increase of

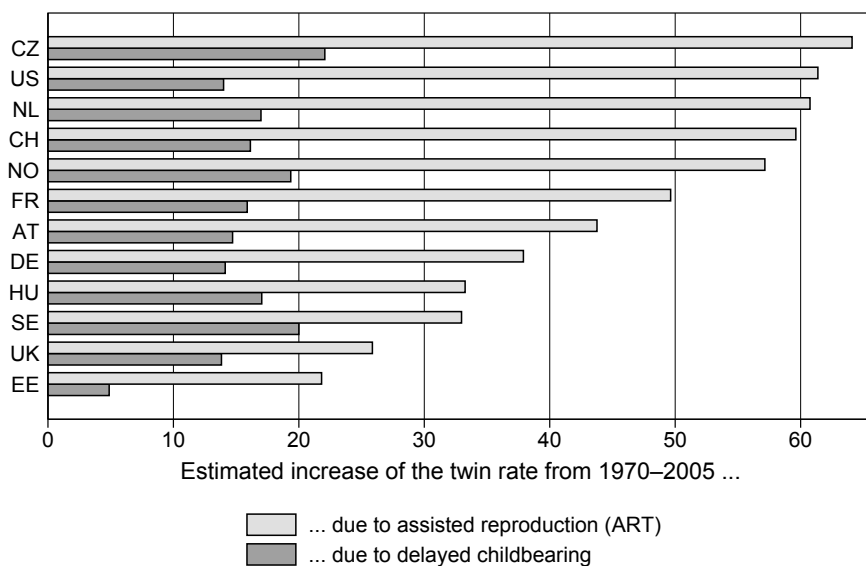


Figure 22: Estimated increase of the twinning rate due to delayed childbearing and to other factors (mainly ART) in selected countries, 1970–2005

Source: Pison *et al.* (2015). Notes: UK refers to England and Wales only. US from 1971–2005.

22 per cent (or 1.22). Of these twelve countries, the Czech Republic has the strongest increase in twinning: 100 per cent (or $1.22 \times 1.64 = 2.00$). The twin rate doubled from 9.6 to 19.2. Estonia had the smallest increase, merely 28 per cent. Only a small part of this overall increase by a factor of 1.28 can be attributed to delayed childbearing (1.05). Most of the change is driven by other factors (1.22), which we assume are mostly ART-related.

Figure 19 showed that some countries had a much stronger increase in twin rates than others. Despite these big differences there is a remarkably strong pattern in Figure 22: The increase due to late childbearing (the dark bar) is always substantially smaller than the increase due to other factors (the light bar). In all countries, the share of change in the total change due to delayed childbearing is less than 50 per cent. In Sweden its share is highest at 45 per cent, in Estonia it is lowest at 21 per cent. Across these countries, roughly only one-third of the increase in twinning can be attributed to delayed childbearing. The other two-thirds are most likely attributable to ART.

4.4 Multiple births and multiple-embryo transfer policies

Multiple-embryo transfer as well as ovarian stimulation were common practices in the early years of ART (Dickey, 2007), however, with the mounting success rates of ART treatments, the risks of multiple births are now a more prominent

factor in the discussion of ART treatments (Chambers *et al.*, 2013; Dunn *et al.*, 2014). Several methods to reduce multiple pregnancies are now gaining popularity, such as single embryo transfer (SET) and increasing the time in culture for the embryos to reach the blastocyst stage for transfer (Baruffi *et al.*, 2009; Gerris, 2009; Karlström and Bergh, 2007; Wang *et al.*, 2010).

Figure 23 shows the development of the number of embryos transferred across countries over time. It reveals a considerable degree of heterogeneity in the development and level of single-embryo transfers. While there seems to be a general trend towards single-embryo transfers, this is not without exception. Countries with strong upwards slopes are Finland, Denmark, Sweden (where the medical profession moved to SET without any intervention by other regulating bodies), and Belgium (who has reinforced single-embryo policies by tying them to reimbursement) (Jones *et al.*, 2007). In Germany, where elective single embryo transfer is outlawed, a trend from three-embryo to two-embryo transfers is visible. Germany and Spain are also two countries where governments abolished transferring more than three embryos (Cook *et al.*, 2011), which is reflected in the Figure. In other countries, the slope is flatter and also the overall level is much lower. Moving from aggregated country-level data, we now turn to an individual case study of Italy where we are able to explore more nuanced findings at the individual level.

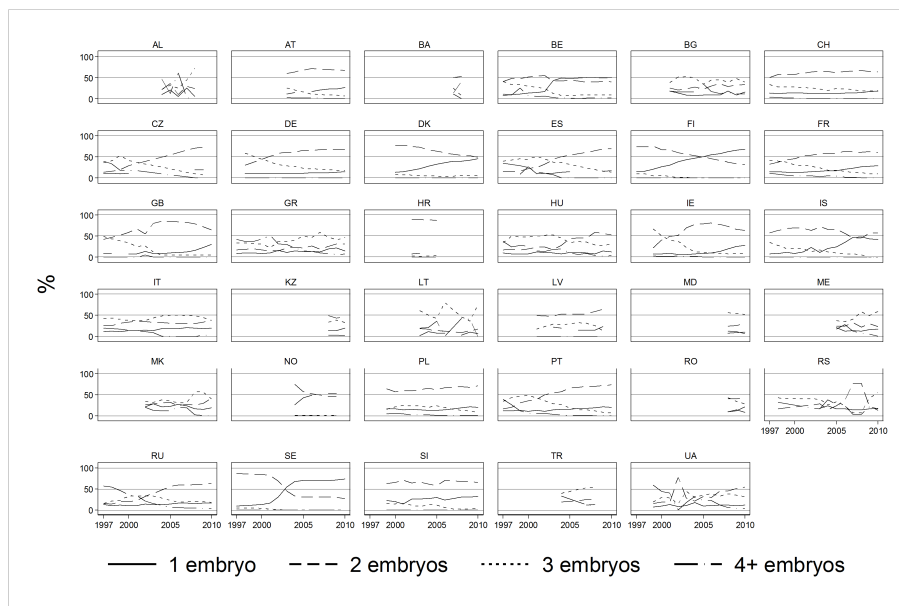


Figure 23: Development of single embryo transfers across countries

Source: De Mouzon *et al.* (2010, 2012); ESHRE (2001a,b, 2002, 2004, 2005, 2006, 2007, 2008); Ferraretti *et al.* (2012, 2013); Kupka *et al.* (2014); Nyboe Andersen *et al.* (2009).

5 ART and pregnancy outcomes: The case of Italy

5.1 Background and aim of case study

In Italy as in other countries, the postponement of childbearing caused a rise in late fertility, in childlessness levels, and use of assisted reproductive technology. Despite a restrictive legislation in Italy, ART has created new opportunities for many Italian couples who were previously considered unable to have children at later ages. In 2010, 1.7 per cent of all live births in Italy were the result of ART treatments (Figure 1). While this is still comparably low in international terms, the share of ART births among all live births in Italy nearly doubled from 2006 to 2010 (Figure 8). Also, it is essential to note that the share of Italians seeking fertility treatment abroad is high due to restrictive legislation (Mills *et al.*, 2014b; Robertson, 2004; Turone, 2004, 2005, 2009; Zanini, 2011), making this figure likely an underestimation of its true value. The Osservatorio per il Turismo Procreativo (Observatory for Procreative Tourism)—managed by the Italian Association CECOS (Center for Study and Preservation of Eggs and Sperm)—estimates that around 4,000 Italian couples undertook cross-border reproductive care in 2011.

While one pathway by which ART can lead to detrimental outcomes for children is multiple births, studies have also shown that ART singleton births can be at a disadvantage to their naturally conceived counterparts. Numerous studies already point in the direction of usually small, yet considerable risks for ART children (Hart and Norman, 2013a,b; Helmerhorst *et al.*, 2004; Pinborg *et al.*, 2013; Sazonova *et al.*, 2011; Scherrer *et al.*, 2012; Talaulikar and Arulkumaran, 2013; Williams and Sutcliffe, 2009) and this field of research is generally seen as very important (Grace and Sinclair, 2009; Kissin *et al.*, 2014). The lack of proper individual-level data to study outcomes of ART conception is one of the main reasons that impede demographic studies in this field. In our case study on Italy, we contribute to closing this knowledge gap, drawing on a combination of administrative data sources in order to answer to two research questions.

First, we distinguish between important characteristics (e.g. age, education, citizenship) distinguishing mothers who underwent ART treatment from those who have not used ART. Secondly, we investigate whether ART treatment (distinguishing between different types of ART) is associated with the probability to have a live birth versus an adverse outcome (miscarriage or stillbirth).

5.2 Data and methods

For our analyses, we draw on two different data sets: The Birth Assistance Certificate (CEDAP) register and the Register of Miscarriages (AS), both collected

in 2009, respectively by the Ministry of Health and the Italian Statistical Office ISTAT. CEDAP is a register running since 2002 containing about 550,000 annual deliveries, drawing on hospital information. It contains information on parents' socio-demographic background (age, residence, citizenship, marital status, education, labor market status), mother's reproductive history (parity, live births, stillbirths, previous induced abortions, previous miscarriages), pregnancy characteristics (medical examinations, ultrasound examinations, gestational age etc.), assisted reproductive technology (by type), delivery (place of birth, mode of delivery, date of birth, plurality etc.), neonatal characteristics (sex, external genitals, birth weight, length, vital status, neonatal presentation, etc.), fetal mortality, and the presence of malformations.

AS comprises information on miscarriages occurred in both private and public hospital since 1979. Miscarriages that occurred at home are not included in AS. Furthermore, AS contains women's socio-demographic information (age, residence, citizenship, marital status, education, labor market status), reproductive history (live births, stillbirths, previous induced abortions, previous miscarriages), on miscarriage (gestational age, kind of operation, analgesic therapy, length of stay in hospital, and complications. Since 2000, information on ART treatments is also included.

In order to distinguish the differential characteristics distinguishing mothers who gave birth after ART treatment from those who have not used ART, a logit model is estimated, using the CEDAP data set. Furthermore, using another logit estimation we show whether ART treatments (according to the kind of treatment) increase the likelihood of having a stillbirth or miscarriage instead of a live birth.

Unfortunately, the data come with some restrictions. CEDAP contains no information at all on the Molise region. In the Lazio region, information on ART is missing. Large shares of missing data for covariates in the regions Marche, Campania, Basilicata, Calabria, and Sicilia make it impossible to use data from these regions as well. The regions Piemonte, Lombardia, Trentino-Alto Adige, Emilia-Romagna, and Toscana are the only regions having good quality data for both data sources.

5.3 Results

5.3.1 Who uses ART? Individual characteristics of mothers

The descriptive results underpin the data shown for many countries earlier in this report, demonstrating that in Italy, women who seek ART treatment and have a birth are on average older (average age is 35.7 years) than those who conceived naturally (31.8 years). Most of them are experiencing a first birth (81 per cent versus 51 per cent). In Figure 24, we compare the age pattern of

first births by type of conception. Not surprisingly, those who conceived due to ART treatment are clearly older. The modal age for the first birth is 31 years for a natural conception and 36 years for births conceived after ART treatments, and in the latter case the percentages of births remain high until around age 40.

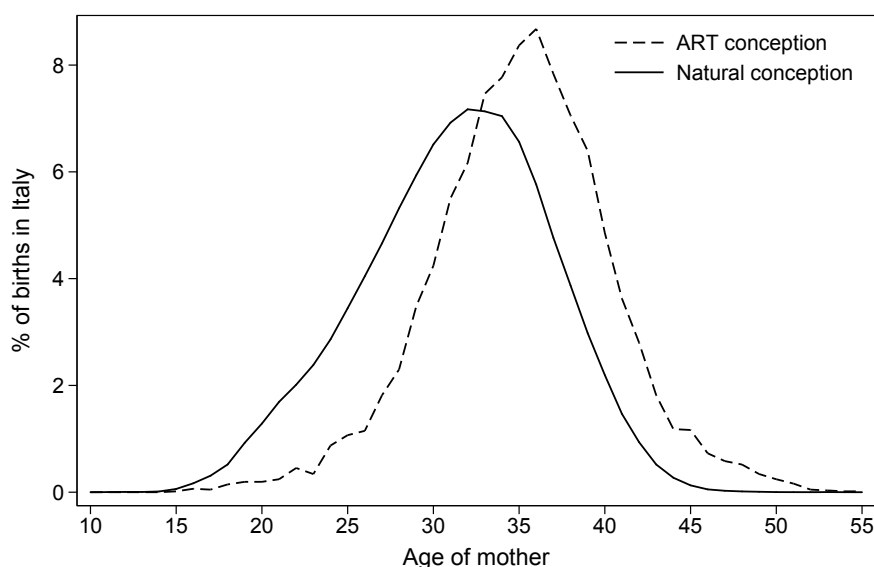


Figure 24: Type of conception by mother's age in Italy

Source: CEDAP (2009), own calculations.

Among fathers, a smaller age difference is observed: 38.6 years for those whose partners underwent ART versus 35.4 years for those who conceived their child naturally. With regard to socio-demographic characteristics mothers who used ART are more often married, more educated and less often foreign citizens (8 per cent versus 18.7 per cent). They had more frequently experienced one or more spontaneous miscarriages before delivery (but those differences disappear once we control for age).

In a logit model, we verify whether these results hold also net of other factors. Results presented in Figure 25 show that compared to those giving birth in their twenties, mothers having a child in their thirties are more than four times more likely to have used ART, while the odds ratio increases up to 14 if they give birth in their forties. They are also more likely to be at first birth, net of other factors. Italian mothers are 69 per cent more likely to use successful ART treatment than foreigners. They are also substantially more likely to be married. Surprisingly, the effect of employment status is small in magnitude (working mothers are 22 per cent more likely to have used ART), as well differences in educational attainment. Having experienced previous miscarriages increase the probability

to have used ART to conceive by 14 per cent, net of other factors such as age.

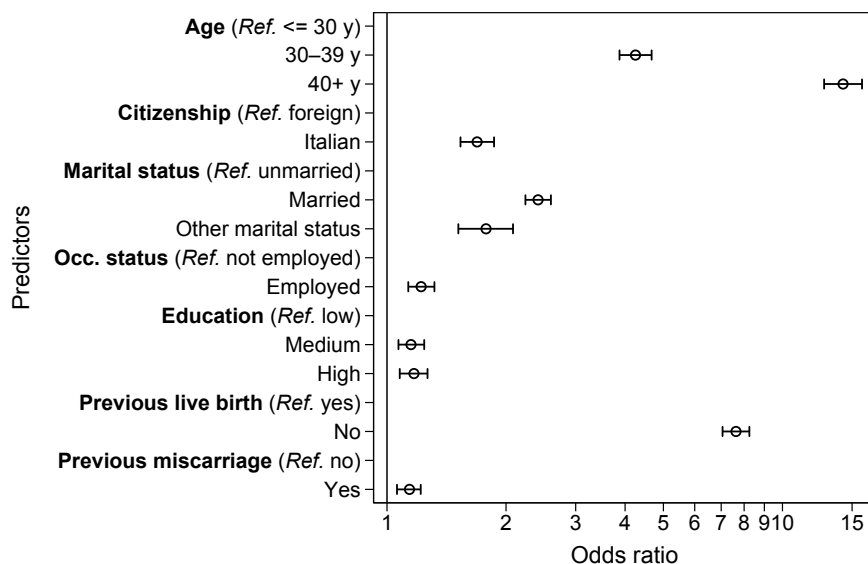


Figure 25: Predictors of giving birth after ART (as opposed to natural conception), logit model. Odds ratios and 95 per cent confidence intervals.

Source: CEDAP (2009), own calculations.

5.3.2 How do ART pregnancies and deliveries differ from non-ART ones?

We contrast the risk of having a premature delivery or a cesarean section for those mothers who have conceived via ART with those who conceived naturally in Table 2. Controlling for women’s characteristics and also for type and number of medical check-ups during the pregnancies, we estimated that mothers who conceived by ART (versus those who conceive without ART) have 54 per cent higher odds to give birth between the 32nd and the 38th week of gestation and a 59 per cent higher probability to have either a planned or urgent cesarean delivery.

Table 2: Odds of premature birth and c-section by type of conception

	Premature birth	Cesarean section
ART (<i>Ref.</i> natural conception)	1.54 (1.37–1.74)	1.59 (1.48–1.70)

Source: CEDAP (2009), own calculations. *Notes:* 95 per cent confidence intervals in parentheses. Controlling for women’s characteristics, such as age, educational level, marital status, occupational status, and check-ups during pregnancy (e.g. number of ecographies, visits, prenatal diagnosis)

5.3.3 Variation in ART treatments and probability to have a successful live birth

The combination of data sources (CEDAP and AS)—although possible only for selected regions (see previous data description)—, allows us to verify whether the risk of having a live birth versus an adverse outcome (either a miscarriage or a stillbirth) differs between those who used ART and those who did not (Figure 26). The probability of having a live birth seems to be unaffected by the use of ART, with the exception of IVF, which seems even to give a 30 per cent higher chance to have a live birth than natural conception, other things being equal. This remarkable finding shows even though we are controlling for age, citizenship, marital status, labor market status, education, previous live births, and previous miscarriages.

5.4 Case study conclusions

This section provided analyses of a unique combination of administrative microdata sources to study the ART use in Italy. In particular, the data allows us to compare the profiles of mothers, the outcomes of pregnancies and deliveries of mothers having used ART to conceive. There are no previous studies in Italy based on micro data on this issue.

If the rise in late fertility fuelled the rapid diffusion of various types of Assisted Reproductive Technologies (ART), the use of ART treatment contributed to the accentuated fertility postponement among the Italians. Not surprisingly, the over 40s and childless women are the most likely to use ART. Net of other factors, ART usage is not clearly over-represented among more educated and employed mothers, which can be interpreted as a sign of a spread of equal usage over social classes.

Conception by ART is linked to (perceived) higher risk pregnancies and deliveries, and as a consequence they turn to be are clearly more medicalised. Those who conceived via ART have a higher risk of severely premature births and cesarean deliveries, but in most cases this is explained by a higher risk of multiple births. The probability of having a live birth versus either a miscarriage

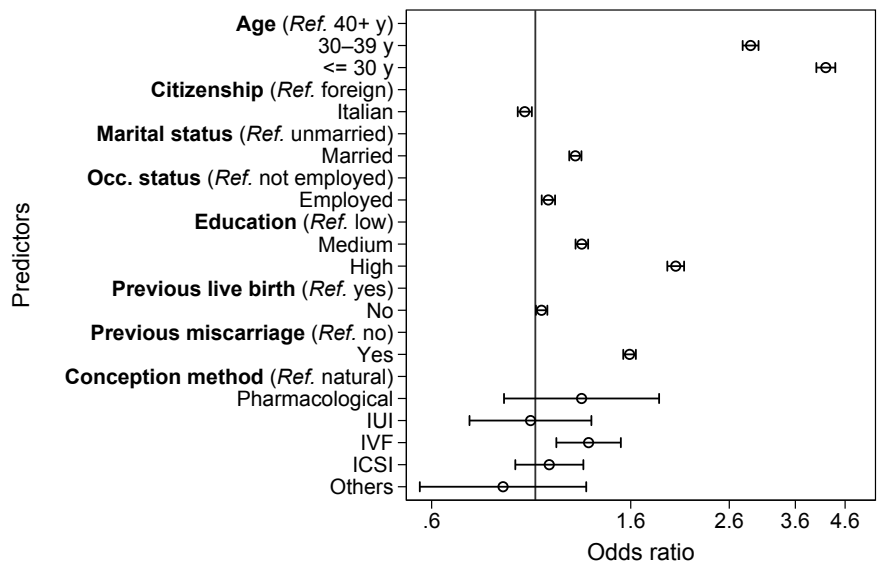


Figure 26: Predictors of giving live birth (as opposed to stillbirth and miscarriage), logit model. Odds ratios and 95 per cent confidence intervals.

Source: CEDAP (2009), own calculations.

or a still birth is not affected significantly by the method used among the ART. A younger age and a reproductive history not characterised by miscarriages are factors of reproductive success also among the ART users.

The recourse to ART by using the FIVET method seems to increase the probability to have a live birth compared to a birth by natural conception, while there is not a statistically significant association between the other ART methods and natural conception in the chance to have a successful outcome.

In conclusion, we can state that ART represents an important opportunity for Italian women who have difficulties in getting pregnant, but they also present some risks. These results are also useful to discuss the opportunity to subsidize ART treatments as a demographic or health policy, in order to know the possible efficacy of the treatments in term of successful outcomes.

6 Conclusions

6.1 Summary of main results

6.1.1 ART is not an effective policy measure to counter low fertility, but usage has grown over time and varies across nations largely due to differences in affordability and normative values

In this report, our aim was to document the demographic consequences of ART, which was achieved by focusing on four central research aims. Our first aim was to answer the highly pertinent policy question: Is ART a useful policy mechanism to counter low levels of fertility? To tackle this question, we went beyond research that only examined the proportion of ART births as total national births across countries to look at research that included the more accurate measure of the ‘net impact’ of ART on national fertility rates. We concluded that when we examine the more accurate measure of ‘net impact’ of ART on national fertility rates, ART has a negligible impact on national fertility rates, thereby suggesting that ART treatments would not be an effective policy instrument to counter low fertility.

By virtue to answering this question, we also explored the large cross-national differences across Europe in the proportion of ART births and potential reasons for these variations. We found a large variation from around 1.5 per cent in countries such as Turkey, Moldova, Poland and Ireland to above 4 per cent (Iceland, Norway, Iceland, and Belgium) and even almost six per cent in Denmark. We then attempted to understand why these differences existed by posing and exploring five central hypotheses. First, we found no support for our ‘postponement hypothesis’ that later age at first births in countries was linked to the growth in ART. It may be that poor effectiveness at later ages and the high number of unsuccessful births at advanced ages, however, masked this link. Second, we found support for our expectation that the increased demand in children—using the proxy of the TFR—was linked to high ART usage.

A third expectation found no clear evidence, with country affluence was not a driving force behind ART usage. We concluded that this was likely too crude of a measure with considerable ‘noise’ and was therefore impotent in uncovering any association. We therefore turned to a fourth hypothesis, which measured the affordability of treatments. Here we found that this more nuanced measure was indeed a strong predictor driving ART utilization. Fifth, we explored the power of cultural values particularly in relation to values regarding whether a human embryo is considered human directly after fertilization. In countries with a lower moral and ethical stance attached to embryos, there was a strong association with higher ART births rates.

We also examined how ART birth rates changed over time from 1997 to 2010. Although there is considerable variation in ART birth rate levels between

countries, we found a clear pattern of upward growth over time across all countries. This was with the exception of Germany, where a large policy change in reimbursement rates in 2004 resulted in a drop in ART.

6.1.2 Perceived infertility differs widely across nations and there is increased usage over age 40, where it is least effective

A second aim of this report was to examine ART usage at later ages and how this varies across countries and effectiveness particularly at later ages. It is difficult to obtain accurate estimates on the onset of infertility and detailed disaggregated data at older ages. For this reason, we first examined an alternative measure of self-reported infertility.

We illustrated that there are large national differences in self-perceived infertility, particularly between the ages of 35 to 39 and within this group between different countries. For women, there were particularly high rates of perceived own infertility at around ten per cent in nations such as Austria, Belgium, Romania and the Czech Republic, compared to much lower levels of five per cent in many countries. In most countries, the men in the same age group reported generally low levels below five per cent.

We also found a strong increase of ART users at advanced ages above 40, with sharp variations by country and the type of treatment. The majority of ART treatments (around 45 per cent) still take place at age 34 years and under, followed by those between 35 to 39 (around 38 per cent), with around 17 per cent aged 40 and above. There was a strong growth in the ART usage by women over 40 between 1998 and 2000, particularly in Iceland, Denmark, and Italy. We then broke down these differences between age group, country, and type of treatment. In general, there was a similar age pattern as stated above for those seeking IVF, ICSI, and FER treatment. Egg donation showed a markedly different pattern of the majority of women above 40 years of age, which is not surprising since the need for egg replacement is related to the depletion of fertility at later ages. Here, around seventy per cent of those receiving donated eggs were above 40 years of age.

Since there was a surge in older women receiving these treatments, we found that the effectiveness of these treatments were very low at older ages. We found that higher maternal age is paired with a decreased success rate of IVF treatments for those aged 40 and over of around ten per cent (delivery) and twenty per cent (pregnancy), compared to those who were 34 years and under at thirty per cent (delivery) and 35 per cent (pregnancy), respectively. A similar drop is shown for ICSI and FER, with FER having the lowest success rates, even women 34 and younger.

6.1.3 Dramatic increase in twinning rates largely attributed to ART and not birth postponement

The third aspect of this study demonstrated the explicit demographic consequences of ART in relation to a growth in multiple births, particularly twins, in relation to ART treatments. We showed that there has been a dramatic increase in twinning rates since the 1970's, with rates more than doubling in many countries from the mid-1970's to the early 2000's. Since there have also been strong increases in maternal age at birth, which is linked to twinning, we explored whether it was birth postponement or ART that contributed to the growth of the twinning rate. We demonstrated that the majority of the changes in the twinning rate—or around two-thirds—can be attributed to ART, compared to only around one-third related to the advanced age at childbearing. We then linked this to multi-embryo transfer policies, which have shown considerable heterogeneity in the move towards single embryo transfer (SET). Yet we note that a general shift in a lower number of embryo transfers over time in many nations can be related to an (expected) drop in the twinning rates.

6.1.4 ART pregnancies and deliveries can be more problematic

The fourth goal of our report was to go beyond aggregated macro-level data and use micro-level individual data to answer key questions that evade aggregated figures. Using Italy as a case study, we examined the characteristics of ART mothers and examined the variation by the type of ART and probability to have a successful birth outcome. We found that, echoing our aggregated results, ART users were older (on average 35.7 years) than those who conceived naturally, but more interestingly the new information gained from this individual level analysis was that it was more often for first births, married, higher educated, native Italians that had previously experienced a miscarriage.

ART pregnancies and deliveries also differed significantly from those from natural conception. ART mothers were more likely to deliver prematurely and have a higher probability of a caesarean section. However, an interesting result was that the probability of having a live birth did not differ between those with and without ART treatments. In fact, those who underwent an IVF treatment had a thirty per cent higher chance for a live birth than those who conceived naturally, also controlling for multiple factors (e.g., age, education, miscarriage history).

6.2 Policy recommendations and future research directions

ART is often heralded as a potential policy solution for low fertility. We examined research that predicted the net impact of ART live births, which is

the difference between the observed number of births and a hypothetical one achieved in the absence of ART treatments. The net impact is a smaller, but also more realistic measure of the impact of ART since it takes into account that couples who undergo ART treatment might spontaneously conceive and the unplanned extra multiple births. Under realistic conditions, the net contribution of ART on the overall birth rate ranges from 0.04 (Habbema *et al.*, 2009; Leridon and Slama, 2008) to 0.06 (Sobotka and Testa, 2008), suggesting that view that ART might have a substantial impact on fertility rates are exaggerated. We can therefore conclude that ART has a negligible impact on national fertility rates, thereby suggesting that ART treatments would not be an effective policy instrument to counter low fertility.

The strongest associations driving cross-national differences in ART success were affordability of treatment and ethical values regarding when an embryo is a human, influencing the number of embryo replacements. Future policy directives that would like to increase access to ART or understand why or why not certain policies may work should not only prioritize affordability and economic aspects, but consider the oft-forgotten normative and cultural values surrounding human embryos.

Although the number of women 40 and older aspiring ART treatment has grown over time, a striking finding of this study is that success rates for this group are markedly lower. With the chance of around ten per cent for a successful birth in some treatments such as IVF, the question remains as to whether women and couples at these advanced ages are aware of the very low chances (Maheshwari *et al.*, 2008; Wyndham *et al.*, 2012). Future policy directives should focus on ensuring that this growing group of ART users and postponers above the age of 40 are aware of the limited success rates of ART at advanced ages. Kocourkova *et al.* (2014) suggest that ART can be a greater driving factor in fertility rates if it is used earlier in women's life rather than later. While this is of course true, one of the most important reasons for the growing demand for ART is the postponement of childbearing, which is a larger policy question.

In this report we also demonstrated that ART treatments have had explicit demographic consequences in the form of a dramatic growth in the twinning rate. The growth of multiple births highlights the importance of ART regulations related to multiple embryo placement due to the important health risks for both children and their mothers.

A central shortcoming of this study was that we often lacked detailed individual-level data in our analyses. Certain aspects have also evaded measurement until now, such as infertility, which is difficult to assess when defined as having problems to conceive naturally for at least one year. These questions are rarely asked in surveys. We therefore turned to data on self-reported infertility, which also appeared to vary widely by countries, suggesting that norms and non-biological

factors may also play a strong role.

In our examination of ART treatments and success rates at older ages, we were also left with an examination of only broad age groups of younger than 34 years, 35–39 years, and 40 years and older. Particularly for the group above 40, it would be important to know at just what age thresholds women have more problems achieving a healthy pregnancy.

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