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Defining Critical Factors in Multi-Country Studies of Assisted Reproductive Technologies (ART): Data from the US and UK Health Systems

ABSTRACT

As the worldwide use of assisted reproductive technologies (ART) continues to grow, there is a critical need to assess the safety of these treatment parameters, and the potential adverse health effects of their use in adults and their offspring. While key elements remain similar across nations, geographic variations both in treatments and populations make generalizability challenging. We describe and compare the demographic factors between the United States and the United Kingdom related to ART use and discuss implications for research. The United States and the United Kingdom share some common elements of ART practice and in how data are collected regarding long-term outcomes. However, the monitoring of ART in these two countries each bring strengths that complement each other's limitations.

INTRODUCTION

As the worldwide use of assisted reproductive technologies (ART) continues to grow, there is a critical need to assess the safety of these treatment parameters, and the potential adverse health effects of their use in adults and their offspring [1, 2]. The challenge for this type of research is that the practice of fertility treatment is constantly evolving, such that the long-term health outcomes evaluated today reflect therapies that have long since been updated. While critical, it can be challenging to assemble datasets that reflect contemporary IVF and ART therapies, but that also encompass enough prior years to have mature outcomes as the recipients (and offspring) have aged.

One of the lessons learned from the worldwide pandemic of 2019-20 has been the strength in collaboration between countries, which allows for increased participants for studies, faster enrollment, shared intellect and knowledge, and improved generalizability of cohorts given inherent variations in practice patterns and patient response to disease and therapy. By forming international partnerships, we can apply these lessons to studies of ART to construct linked datasets with larger sample sizes, greater statistical power, and with results that could potentially have wider applicability.

Historically, the Nordic countries have led the field in pooling their resources in the creation of the Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS) cohort [3]. This group was established in 2008 by members of the European IVF Monitoring group of the European Society of Human Reproduction and Embryology (ESHRE), and encompasses Denmark, Finland, Norway, and Sweden. These countries are unique in the widespread availability of ART to their citizens, and together they have about 12,000 annual births of ART-conceived children, accounting for 3-5% of their national births. The Nordic countries are comparable in their demography, culture, and health care systems, which makes pooling of their health data a strong and logical choice. The total population is about 5.5-5.8 million individuals each in Norway, Denmark, and Finland, and about 10 million in Sweden. Some 80-95% are native-born and of White race; the indigenous Sami people comprise about 0.1% of the populations of Finland, Norway and Sweden, with the remainder of the populations predominantly from other European countries and the Middle East. In publications from these pooled cohorts, the racial and ethnic composition of the combined study populations are not given, and often the distribution by country is also not provided, and their generalizability to other societies with very different ethnicities is unclear.

Using these strengths, the CoNARTaS group has published numerous important studies evaluating outcomes after ART, including perinatal outcomes of children born from frozen-thawed embryo transfer [4], the risk of stillbirth and infant deaths [5], cancer in children and young adults [6], trends in perinatal health [7], risk of hypertensive disorders in pregnancy [8], perinatal and maternal outcomes after vitrification of blastocysts [9], and imprinting disorders [10]. The foundation of the CoNARTaS group is the linkage of each country's national health registries, disease-specific registries, and other national databases. As Opdahl et al [3] indicate, although the national registries are of high quality and comparable, they are not identical in structure and content across the four countries. The data from the different registries are linked at an individual level using the national identity number assigned to all residents in each Nordic country at birth or immigration, which facilitates individual follow-up through their lifetime.

The Medical Birth Registries, National Patient Registries, and ART registries, respectively, date from 1967, 2008, and 1984 in Norway; 1973, 1987, and 1985 in Sweden; 1987, 1967, and 1990 in Finland; and 1973, 1977, and 1994 in Denmark. National Cancer Registries date from 1943 in Sweden, 1953 in Finland and Norway, and 1958 in Sweden. Available data on ART treatment in the CoNARTaS group ranges from no

details from Finland to about 50% of factors recorded from Norway to reporting all cycles in Denmark from 1994 and Sweden from 2007. Despite these limitations, the research findings from this consortium have advanced our understanding of IVF and the short-and long-term health outcomes.

In the US, our group has also applied this collaborative model to combine ART data from several states to answer questions about the potential effects of ART treatment on mothers and children. In general, data sources in the US are good with 448 of 498 clinics (90%) of all clinics reporting IVF cycles in the 2017 (the last year complete data was available). An expansion of these collaborations has led us to consider other, non-Nordic cross-country alliances, including expanding the current multi-state study in the United States [NIH grant R01 HD084377] to include the United Kingdom (UK) to study ART and associated health outcomes to achieve a broader and more diverse population of men, women, and children. Table 1 shows a comparison of the number of IVF births and all births in 2010 in the four Nordic countries in the CoNARTaS consortium, the US, UK, and the four-States in the current NIH study. In the US, nonreporting occurs rarely with

Integrated comparisons and analyses of combined US and UK data will allow improved understanding of the associations between infertility and health. Specifically, the possible etiologic links between infertility and health and the interplay with socioeconomic and environmental factors can be better explored. While variables specific to ART cycles are captured and reported in a standard manner around the world, other aspects of the parents and their offspring must be individually considered. The United States and the United Kingdom share some common elements in how data are collected, but also complement each other. That is, in areas where one country's data has some shortcomings, the other country has strengths. Using large, combined datasets that collect a variety of lifestyle factors allows for the most robust assessment of long-term health outcomes after ART, permitting the evaluation of important covariates. The quality and availability of demographic information in both the US and UK are summarized below (Table 2).

SOCIOECONOMIC STATUS

Social determinants of health (SDOH) are defined by the World Health Organization as the conditions in which individuals are born, grow, live, work, and age, and the wider set of forces and systems shaping the conditions of daily life [11]. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems. Socioeconomic status has been defined as education, income, occupation, and neighborhood factors, as well as a combination of these four factors. Neighborhood factors have included a composite score of census data on mean neighborhood income, employment rate, and proportion of residents with no high school diploma [12, 13].

In the United States, the 2003 revision of the birth certificate contains several factors that can be used to characterize socioeconomic status. These factors include zip code of residence, mother's and father's education attainment (also present on the 1989 revision), receipt of WIC (food stamps for pregnant women), and principal source of insurance (private insurance, Medicaid, self-pay, or other).

In the United Kingdom, individual level demographic data can come from the following main sources: the Human Fertilisation and Embryology Authority [14], which has a statutory requirement to record of all assisted conception cycles in the UK, the Clinical Practice Research Datalink [15], which records patient data from a network of doctors' practices across the UK, and data from NHS-digital, the information & technology partner to the National Health Service (NHS) in England. NHS-digital provide a variety of

demographic (and outcome) data via linkage to national datasets including, Hospital Episode Statistics (HES), records of all admissions, accident and emergency attendances and outpatient appointments at NHS hospitals in England, NHS registration data via the Personal Demographics Service and civil death registrations [16]. Similar data are collected by Information Services Division, National Services Scotland. In addition, over 93% of children in the UK attend state schools [17]. Educational data for school age children who attend state schools can be obtained from the National Pupil Database (NPD) [18].

Individual level socioeconomic data such as income, occupation and educational attainment for adults is not available from these sources. However, neighborhood level measures of socioeconomic status can be used as proxies for individual level data in medical research when such data is not available [19, 20]. The UK collects information for the Index of Multiple Deprivation which can be used for this purpose [21]. The use of such regional proxies introduces some bias as compared to using individual level data [22], although this bias can be mitigated to some extent by using aggregate measures from the smallest units of area available [23].

NEIGHBORHOOD FACTORS

United States

Neighborhood factors can affect an individual's and family's safety, access to food, health care access and behaviors, education, social connections, and level of stress [24]. In addition, neighborhood factors may affect an individual's exposure to environmental threats, including air pollution, noise pollution, water quality, and environmental toxins. County-level, census-level, and census block-level data have been used to characterize geographic areas in the US and their relationship to health status [25-29]. As small areas comprising relatively economically homogeneous populations, census tracts contain approximately 1,800-4,000 residents; census block groups are subdivisions of census tracts and include about 1,000 residents. Several factors can be used to characterize the neighborhood of the individual and their family. In a study of sources of socioeconomic inequality in children's reading and mathematics achievement using data from the Los Angeles Family and Neighborhood Survey, mother's reading scores and average neighborhood levels of income accounted for the largest proportion of inequality in children's achievement [30]. Using the 2010 US census tracts, home address zip codes can be used to categorize neighborhoods by economic status (median family income), residential stability (percentage of households that did not move between 2005-2010, owner-occupied households, dwellings in multiple-unit structures, and nonfamily households) [31]. A deprivation index (a composite index of percentage of males in management and professional occupations; percentage of residents living in crowded housing; percentages of households in poverty, female-headed households with dependents, households on public assistance, and households earning <\$30,000 per year; percent with < high school education; and percent unemployed) has also been used in prior studies [32, 33]. Parental addresses from the birth certificate or outpatient/inpatient hospital discharge records can be geocoded to identify residential census tracts, and then linked to census data [34]. Summary scores based on the socioeconomic environment of a neighborhood regarding income, education, and occupation have been used in studies of coronary disease risk and mortality [35-37]. Neighborhood poverty has been defined in prior studies as the percentage of families below the poverty level and the percentage of youths not in school and not high school graduates according to the census tract neighborhood in which they lived [38].

Singh developed and validated a factor-based area deprivation index (ADI) for the United States that uses 17 poverty, education, housing, and employment indicators drawn from US census data to create a measure of socioeconomic context for a particular census-based region [39]. This measure has been used

in studies evaluating relationships between area deprivation and all-cause mortality, cardiovascular, cancer, and childhood mortality rates, readmission rates, and prevalence of cervical cancer and multimorbidity (two or more chronic disease conditions) [39-47].

United Kingdom

The Index of Multiple Deprivation, part of the Indices of Deprivation, combines information from seven domains to produce an overall relative measure of deprivation [48]. These seven measures include: income deprivation; employment deprivation; education, skills and training deprivation; health deprivation and disability; crime; barriers to housing and services; and living environment deprivation. Each country within the United Kingdom produces their own Index of Multiple Deprivation using similar methodologies. The Index of Deprivation ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area). Deprivation deciles are generated to accompany these ranks, calculated by ranking the 32,844 small areas and dividing them into 10 equal groups. The small areas (also called Lower-layer Super Output Areas, or neighborhoods) are designed to be of a similar population size, averaging about 1,500 residents in each area. The Index of Multiple Deprivation has been used to characterize the socioeconomic conditions of a neighborhood, including studies of cardiovascular disease risk [49], life expectancy [50], childhood and adolescent obesity [51, 52], and premature mortality attributable to socioeconomic inequality [53]. The Index of Multiple Deprivation has been shown in various studies to be associated with higher prevalence of smoking, obesity, elevated levels of hemoglobin A_{1c} [49], premature mortality among individuals with type 1 diabetes [54], and lower likelihood of conception after in vitro fertilization [55].

Many studies have shown that individuals living in the most deprived areas have higher rates of physical and mental multimorbidity (the presence of two or more chronic conditions) than those living in the least deprived areas, and that these morbidities developed 10-15 years earlier [47, 56-62].

Characterizing Individual-level, family-level, and neighborhood-level SES

Among people from all areas, the risk of multimorbidity has been shown to be increased by 50% among persons in the lowest versus highest quintile of area deprivation [47]. This association strengthened after adjustment for individual level of education, suggesting that neighborhood context may influence health above and beyond that of individual measures of socioeconomic status. In addition, this study showed interactions between the area deprivation index (ADI, an area-level of socioeconomic status) and age, between ADI and sex, and between ADI and individual level of education, with stronger associations in younger individuals and in women.

EDUCATION

United States

The 2003 revision of the US birth certificate includes eight categories of parental education (separately for mother and for father): 8th grade or less; 9th to 12th grade, no diploma; high school graduate or GED (General Educational Development); some college credit but no degree; associate degree (e.g., AA, AS); bachelor's degree (e.g., BA, AB, BS); master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA); doctorate (e.g., PhD, EdD) or professional degree (e.g., MD, DDS, DVM, LLB, JD). In our group's prior analyses investigating the impacts of infertility on maternal and offspring health, we collapsed these eight categories into three categories: high school graduate or less; some college; and bachelor's degree or

higher [63-66]. Importantly, lower educational attainment has been shown to be associated with a greater than 50% increased risk of multimorbidity [67].

United Kingdom

The educational background of patients is not recorded in HFEA, CPRD or HES data. For school age children attending state schools, data on educational attainment is available from the National Pupil Database, including attainment in reading, writing, math, and science at ages 7, 11 and 16 [68].

RACE AND ETHNICITY

United States

The 2003 revision of the US birth certificate includes 15 categories for parental race (separately for mother and father): white, black or African American, American Indian or Alaska Native, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander, and Other; and an additional checkbox for Hispanic origin (yes/no) and four categories of Hispanic origin (Mexican, Mexican American, Chicano; Puerto Rican; Cuban; and other Spanish/Hispanic/Latino). In the 2010 US census, there were 308.7 million residents, 16.3% were of Hispanic ethnicity [69]. Of the 97.6% individuals reporting being of one race in the 2010 census, 72.4% were White, 12.6% were Black or African American, 4.8% were Asian, 6.2% were other races, 0.9% were American Indian or Alaskan Native, and 0.2% were Native Hawaiian and Other Pacific Islander. In most of our prior infertility analyses, we have categorized race as White, Black or African American, Asian, and Other (or mixed), and categorized Hispanic ethnicity as yes/no [63-65, 70-72]. We identified significant diversity in our studies, with the number of non-white participants ranging from 8.6 to 34.5% of the study populations, and Hispanic participants ranging from 1.0 to 26.5% of the study populations.

United Kingdom

The self-reported ethnic group of patients is recorded in HES data in 9 categories (1995/96 to 2000/01) and in 16 categories (2000/01 onwards) [73]. Patient's self-reported ethnic group is also recorded by the HFEA [74]. In the UK, live birth rates following IVF have been shown to differ by ethnic group [75]. These groups included white-British, white-Irish, white-Gypsy or Irish traveler, white-European, black-African, black-Caribbean, black-British, South Asian Bangladeshi, middle eastern, South Asian Pakistani, South Asian Indian, Other Asian, Chinese, Mediterranean European, and mixed race. According to the 2011 census, the UK includes 56.1 million inhabitants, 86.0% of whom are White. Among the specific ethnic groups, individuals from the White British ethnic group comprise the largest percentage of the population (80.5%), followed by Other White (4.4%) and Indian (2.5%). Asian ethnic groups comprise the second largest percentage of the population (7.5%), followed by Black ethnic groups (3.3%), mixed and multiple ethnic groups (2.2%), and other ethnic groups (1.0%) [76].

NATIVITY

Information on parental nativity (born in the US versus born outside the US) is available on both the 1989 and 2003 revisions of the US birth certificate. Nativity has been shown to be an important factor in perinatal research [77, 78], with US-born Black women having more adverse outcomes than their foreign-born counterparts. In the UK, HFEA data records patient's place of birth [73].

OCCUPATION

Data on an individual's usual occupation and type of business/industry is available on the US Standard Certificate of Death (both the 1989 and 2003 revisions). In the UK, a patient's occupation is not recorded in HFEA, CPRD or HES data.

INCOME

Two items on the 2003 revision of the US birth certificate can be used to indicate lower income status: the mother's receipt of WIC during the pregnancy, and Medicaid (government assistance) as the principal source of payment for the delivery. The income eligibility guidelines for the WIC program is 185% of the Federal Poverty Level, adjusted for household size; for 2019-20, the annual income levels are \$23,107, \$31,284, \$39,461, and \$47,638 for households of 1-4 persons, respectively. In the UK, the patient's income group is not recorded in HFEA, CPRD or HES data.

HEALTH INSURANCE

In the US health insurance coverage includes private insurance (employment-based, direct-purchase, and TRICARE) or public insurance (Medicare, Medicaid, and CHAMPVA or VA). The single largest source of health coverage in the US is Medicaid, a joint federal and state program that together with the Children's Health Insurance Program (CHIP) provides health coverage to over 72.5 million US citizens. Federal law requires States to provide Medicaid to certain groups of individuals, including low-income families, qualified pregnant women and children, and individuals receiving Supplemental Security Income (SSI). In addition, States may offer coverage to individuals receiving home and community-based services and children in foster care who are not otherwise eligible. The Affordable Care Act of 2010 created the opportunity for States to expand Medicaid to cover nearly all low-income Americans under age 65, with eligibility for children and adults extended to at least 133% of the Federal Poverty Level (FPL). For 2019-20, the Federal Poverty Level is \$12,490, \$16,910, \$21,330, \$25,750 annual income for households of 1-4 persons, respectively. Estimates of percent of individuals without health insurance in the four US study States include <5% in Massachusetts, 5.0-6.9% in New York, 9.0-11.9% in North Carolina, and ≥12.0% in Texas [79]. In the UK, when a patient is admitted to an NHS hospital as a private patient this is recorded in HES data [74]. In 2015, an estimated 10.5% of the UK population had private voluntary health insurance [80].

ACCESS TO INFERTILITY TREATMENT AND NATIONAL GUIDELINES

United States

As of 2020, 18 States have mandated insurance coverage for infertility treatment, including Arkansas, California, Colorado, Connecticut, Delaware, Hawaii, Illinois, Louisiana, Maryland, Massachusetts, Montana, New Hampshire, New Jersey, New York, Ohio, Rhode Island, Texas, and West Virginia. The American Society of Reproductive Medicine/Society for Assisted Reproduction issue guidelines on number of embryos to transfer by maternal age, reproductive history, and treatment factors, but there are no other restrictions regarding parental age, BMI, or other factors.

United Kingdom

IVF treatment is offered by the UK National Health Service (NHS) if certain criteria are met, although as health care is devolved, the separate nations of the UK (England, Wales, Scotland and Northern Ireland) can provide different access. If an individual or couple does not meet these criteria, they can pay for private IVF treatment. The National Institute for Health and Care Excellence (NICE) fertility guidelines are those primarily used in the England and Wales [81]. While NICE guidelines currently recommend that all citizens diagnosed with infertility should be offered at least 3 cycles of IVF, the level of funding (and therefore access criteria) is set nationally in Scotland, Wales and Northern Ireland, but in England is currently determined by 208 local Clinical Commissioning Groups (CCGs) leading to considerable local variation in access to NHS funding: the so called 'postcode lottery'. Only a minority of CCGs (12% currently) allow women aged up to and including age 39 the recommended 3 cycles of IVF, and a growing number provide no funding. In addition, some CCGs impose further local criteria, such as BMI, smoking status, or whether or not either partner currently has any previous children from other relationship. The source of funding is recorded by the HFEA for each treatment cycle in the UK, but since 2009, patients have been able to 'opt out' of having their identifiable data used in research. It is not clear whether those who opt out are more or less likely to be in receipt of NHS funding.

COMPARABILITY OF IVF TREATMENTS BETWEEN the UK and US

There are many similarities in the practice of ART between the United States and the United Kingdom. In both countries, like in most of the world, ART includes ovarian stimulation, oocyte retrieval, fertilization by either conventional IVF or intracytoplasmic sperm injection (ICSI), culture of embryos and embryo transfer, with GIFT and ZIFT rarely practiced in the past two decades. Frozen embryo transfer has historically been used for only surplus embryos which were not transferred during the fresh cycle. However, more recently, IVF treatment has increasingly involved freezing all embryos, and frozen embryo transfers have become a more important contribution to the number of babies born by IVF.

In the United States, ovarian stimulation often aims for 15-20 oocytes, if this number of eggs can be retrieved in light of a woman's ovarian reserve: in the UK, 15 is also regarded as an optimal number, based on analysis of success rates [82]. ICSI is commonly used for mild to severe male factor infertility in both countries, but also widely used without a 'male factor' indication in the US (approximately 69% in the US), but much less so in the UK, with current data showing a small decline in its usage to approximately 30% of all IVF cycles [83, 84]. In the last several years, embryo biopsy with pre-implantation genetic testing is being increasingly utilized in the US, with much more limited usage in the UK. The number of embryos transferred has fallen significantly in the United States over the past decade [82], from an average of 4 at all ages in 1995 to under 2 embryos in women less than 35 years of age in 2017. There has also been a dramatic increase in the percentage of single embryo transfers performed, from effectively 0 in 2002 to 30% of all embryo transfers in women less than age 35 in 2014 and 34.7 in 2015 [83, 85]. In UK, an active promotion of single elective embryo transfer (One at a Time) by the regulator, the HFEA, to reduce the multiple pregnancy rate has led to the rate being reduced from 24% in 2008 to 8% at a national level [84], below the target set some years ago of 10% which was achieved in 2017. Given the evolution of the practice of IVF and the efficiency of data collection, analysis of more recent data may prove better suited to certain clinical studies of IVF.

SUMMARY AND CONCLUSIONS

The United States and the United Kingdom share some common elements of ART practice and in how data are collected regarding long-term outcomes. Missing data elements will vary based on data source, which will create methodologic challenges inherent in large administrative databases. However, the

monitoring of ART in these two countries each bring strengths that complement each other's limitations. Integrated comparisons and analyses of combined US and UK data will allow improved understanding of the associations between infertility and health in patients and their children on a large, racially and ethnically diverse population scale.

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