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SHORT COMMUNICATION



Population implications of cessation of IVF during the COVID-19 pandemic

**BIOGRAPHY**

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KEY MESSAGE

The radical transformation of healthcare in response to SARS-CoV-2 and the COVID-19 pandemic has included temporary cessation of fertility treatment provision by many IVF centres around the world. We show the potential population impact of short-term laboratory closures on cumulative live-births from IVF within the US, highlighting the urgent need to recommence age-sensitive fertility treatments in a safe manner.

ABSTRACT

Research question: Discontinuation of IVF cycles has been part of the radical transformation of healthcare provision to enable reallocation of staff and resources to deal with the COVID-19 pandemic. This study sought to estimate the impact of cessation of treatment on individual prognosis and US population live birth rates.

Design: Data from 271,438 ovarian stimulation UK IVF cycles was used to model the effect of age as a continuous, yet non-linear, function on cumulative live birth rate. This model was recalibrated to cumulative live birth rates reported for the 135,673 stimulation cycles undertaken in the USA in 2016, with live birth follow-up to October 2018. The effect of a 1-month, 3-month and 6-month shutdown in IVF treatment was calculated as the effect of the equivalent increase in a woman's age, stratified by age group.

Results: The average reduction in cumulative live birth rate would be 0.3% (95% confidence interval [CI] 0.3–0.3), 0.8% (95% CI 0.8–0.8) and 1.6% (95% CI 1.6–1.6) for 1-month, 3-month and 6-month shutdowns. This corresponds to a reduction of 369 (95% CI 360–378), 1098 (95% CI 1071–1123) and 2166 (95% CI 2116–2216) live births in the cohort, respectively. The greatest contribution to this reduction was from older mothers.

Conclusions: The study demonstrated that the discontinuation of fertility treatment for even 1 month in the USA could result in 369 fewer women having a live birth, due to the increase in patients' age during the shutdown. As a result of reductions in cumulative live birth rate, more cycles may be required to overcome infertility at individual and population levels.

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KEYWORDS

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INTRODUCTION

Discontinuation of the 2.5 million IVF cycles performed annually (Fauser, 2019) has been part of the radical transformation of healthcare provision to enable reallocation of staff and resources to deal with the COVID-19 pandemic. As of 14 March 2020, the European Society for Human Reproduction and Embryology (ESHRE), the American Society for Reproductive Medicine (ASRM) and other international professional bodies all recommended that assisted reproduction treatments should no longer be commenced, with national authorities aligning to ensure rapid cessation of treatment and prevent overburdening healthcare systems.

The success rates of infertility treatment are, however, acutely time sensitive, with progressive monotonic declines with advancing maternal age from age 34 years (Smith *et al.*, 2015). With most cycles starting in women older than 34 years (e.g. in the USA approximately 61% are aged over 35 years, and mean age at ovarian stimulation is 35.5 years in the UK and 38.0 in Japan [Ishihara, *et al.*, 2020]), it is likely that a temporary shutdown of IVF treatment could cause a reduction in the number of IVF live births. Even as clinical services are recommenced, they are likely to be at differential rates depending on local resources and policies, with the potential for variable delays in treatment. The purpose of this short communication is to estimate the extent of such a reduction in individual prognosis and population live birth rates.

MATERIAL AND METHODS

Data from the Human Fertilisation and Embryology Authority (HFEA) on IVF treatment in the UK were used to model the effect of age on cumulative live birth rate. The HFEA dataset recorded age in years, without groups, which allowed the effect of age to be modelled as a continuous, yet non-linear, function (Smith, *et al.*, 2015; Smith, *et al.*, 2019). This model was then recalibrated to the most recent cumulative live birth rates reported for the USA by the Centers for Disease Control and Prevention (CDC) as detailed in the latest Assisted Reproductive Technology Fertility Clinic Success Rates Report (CDC, 2019).

The development model incorporated 158,197 women undergoing 271,438 ovarian stimulation cycles for IVF in the UK between 1 January 2003 and 31 December 2010, with follow-up of all embryo transfers until 30 June 2012. The recalibration model incorporated the 135,673 stimulation cycles undertaken by the 448 clinics in the USA that commenced between 1 January 2016 and December 2016, with inclusion of all embryo transfers that occurred within 12 months, and live birth follow-up to October 2018 (CDC, 2019). The cumulative live birth rate was defined as the probability of a live birth from an ovarian stimulation encompassing all subsequent fresh and frozen embryo transfers from that stimulation. In the USA this was time limited to an embryo transfer occurring within 12 months. In the UK live birth was defined as birth of one or more infants born alive after 24 weeks' gestation and surviving more than 1 month, while in the USA live birth was defined as birth one or more infants with any sign of life (CDC, 2019). Full details of the model and assumptions are given in the Supplementary Material. The effect of a 1-month, 3-month and 6-month shutdown in IVF treatment was calculated as the effect of the equivalent increase in a woman's age, stratified by age group.

RESULTS

The model showed that the decline in cumulative live birth rate is observable from 33 years of age, for women using their own oocytes (Supplemental Figure 1). **TABLE 1** shows the estimated effect of shutdowns of various durations on the cumulative live birth rate, and the estimated reduction in number of IVF live births in the US CDC cohort, stratified by age. The average reduction in cumulative live birth rate would be 0.3% (95% confidence interval [CI] 0.3–0.3), 0.8% (95% CI 0.8–0.8) and 1.6% (95% CI 1.6–1.6) for a 1-month, 3-month and 6-month shutdown, respectively. This corresponds to a reduction of 369 (95% CI 360–378), 1098 (95% CI 1071–1123) and 2166 (95% CI 2116–2216) live births in these cohorts. Older mothers would contribute disproportionately to this reduction, with a 1-month delay resulting in 2.9% (95% CI 2.8–2.9) fewer live births from 41- to 42-year-olds compared with 0.35% (95% CI 0.3–0.4) fewer births from women aged 35 years or less.

DISCUSSION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease 2019 (COVID-19) pandemic has been responsible for the transformation of infertility service provision. This study demonstrates that the discontinuation of fertility treatment for even 1 month in the USA could result in 369 fewer women having a live birth, due to the increase in patients' age during the shutdown. There was evidence of divergence in the overall contribution to live births with increasing maternal age, with older women greatest affected by delays in treatment.

Due to the pre-existing legal regulations and new HFEA guidance introduced in 2015, the equivalent UK data for cumulative live births could not be obtained. We sought to recalibrate this model for the most recent population dataset reporting cumulative live birth outcomes with an extended follow-up to allow for frozen embryos to be included in the analysis (CDC, 2019). By using cumulative live births from a single ovarian stimulation cycle, thereby allowing for the transfer of fresh or frozen embryos, and by accounting for multiple births as a single event, differences in clinical practice between the UK and USA will have been attenuated. Additional limitations of the modelling are discussed in the Supplementary Material.

Recommencement of infertility services needs to occur soon, as accommodating social distancing working patterns and other SARS-CoV-2 transmission risk mitigation measures is likely to impact further on capacity, facilitating further delays. Whether the rapid rises in US unemployment and/or a fear of engaging with the healthcare sector or concerns regarding pregnancy and perinatal outcomes despite reassuring data (ACOG, 2020) will further contribute to a reduction in clinical activity on reopening is unclear. Accurate quantification of the overall impact will not be available for several years due to the timelines of the CDC, and equivalent data custodians in other countries (e.g. HFEA in the UK) reporting or making data available on cumulative live births; it is acknowledged that this may be less or greater than modelled here. Further national or local SARS-CoV-2 epidemics, or even another pandemic, are possible,

TABLE 1 ESTIMATED CHANGES IN CUMULATIVE LIVE BIRTH RATES AND NUMBER OF LIVE BIRTHS ASSOCIATED WITH SHUTDOWN OF IVF TREATMENT, BY AGE OF PATIENT

Age group (years)	<35	35–37	38–40	41–42	>42
Number of cycles per year ^a	52,428	28,996	28,287	14,358	11,604
Without shutdown					
Estimated cumulative live birth rate (%)	46.3	40.6	27.7	14.6	5.8
95% CI (%)	45.7 to 47.0	39.9 to 41.2	27.2 to 28.2	14.2 to 15.1	5.3 to 6.3
Estimated number of live births per year (95% CI)	24,284	11,766	7,841	2,099	672
95% CI (%)	23,941 to 24,651	11,579 to 11,956	7,693 to 7,991	2,032 to 2,168	617 to 732
1-month shutdown					
Estimated cumulative live birth rate (%)	-0.2	-0.4	-0.3	-0.4	-0.2
95% CI (%)	-0.1 to -0.2	-0.4 to -0.4	-0.3 to -0.3	-0.4 to -0.4	-0.2 to -0.2
Estimated number of live births per year	-85	-112	-91	-60	-21
95% CI (%)	-73 to -95	-106 to -118	-86 to -95	-57 to -64	-20 to -23
3-month shutdown					
Estimated cumulative live birth rate (%)	-0.5	-1.2	-1.0	-1.2	-0.5
95% CI (%)	-0.4 to -0.5	-1.1 to -1.2	-0.9 to -1.0	-0.9 to -1.0	-0.5 to -0.6
Estimated number of live births per year	-254	-335	-270	-177	-62
95% CI (%)	-219 to -286	-318 to -352	-256 to -283	-167 to -187	-59 to -65
6-month shutdown					
Estimated cumulative live birth rate (%)	-1.0	-2.3	-1.9	-2.4	-1.0
95% CI (%)	-0.8 to -1.1	-2.2 to -2.4	-1.8 to -2.0	-2.2 to -2.5	-1.0 to -1.1
Estimated number of live births per year	-507	-666	-533	-341	-119
95% CI (%)	-437 to -571	-633 to -699	-507 to -560	-323 to -360	-323 to -360

^a In a sample of 135,673 IVF cycles representing 1 year of treatment provision based on 2017 figures from the Centers for Disease Control and Prevention report (*Centers for Disease Control and Prevention, 2019*).

CI, confidence interval.

and that would mean these results are an underestimate and the long-term consequences considerable.

The personal and societal toll of the cessation of infertility treatments, despite being recommended for only a short period of time by both the ASRM and ESHRE, is likely to have an unrecognized persistent emotional and economic impact for many patients and staff. This is particularly so as the reinitiation of, and regaining of patient confidence in, healthcare services may take substantially longer than the simple reversal of a professional body's edict. Irrespective of the drivers, more cycles may be required to overcome infertility at an individual and population level.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.rbmo.2020.07.002](https://doi.org/10.1016/j.rbmo.2020.07.002).

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