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

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**Research Question**

Discontinuation of in vitro fertilisation (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. We sought to estimate the impact of cessation of treatment on individual prognosis and United States 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. We recalibrated this model to cumulative live-birth rates reported for the 135,6733 stimulation cycles undertaken in the USA in 2016, with live-birth follow-up to October 2018. We calculated the effect of a one-month, three-month and six-month shutdown in IVF treatment 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% CI: 0.3, 0.3], 0.8% [0.8, 0.8] and 1.6% [1.6, 1.6] for a one-month, three-month and six-month shutdown, respectively. This corresponds to a reduction of 369 [95% CI; 360, 378), 1,098 [1071, 1123] and 2,166 [2,116, 2,216] live-births in the cohort, respectively. The greatest contribution to this reduction was from older mothers.

**Conclusions**

We demonstrate 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 an individual and population level.

## Introduction

Discontinuation of the 2.5 million in vitro fertilisation (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 prevention of 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 (e.g. in the US ~61% >35years and mean age at ovarian stimulation 35.5 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.

## Methods

We used data from the Human Fertilisation and Embryology Authority (HFEA) on IVF treatment in the UK to model the effect of age on cumulative live-birth rate. The HFEA dataset recorded age in years, without groups, which allowed us to model the effect of age as a continuous, yet non-linear, function (Smith, et al., 2019, Smith, et al., 2015). 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 January 1, 2003 and December 31, 2010, with follow-up of all embryo transfers until June 30, 2012. The recalibration model incorporated the 135,673 stimulation cycles undertaken by the 448 clinics in the USA that were commenced between January 1, 2016 and December 31, 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 US 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 surviving more than one month, while in the US 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 supplementary material. We calculated the effect of a one-month, three-month and six-month shutdown in IVF treatment as the effect of the equivalent increase in a woman's age, stratified by age group.

**Results**

Our model showed 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 duration 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% CI: 0.3, 0.3], 0.8% [0.8, 0.8] and 1.6% [1.6, 1.6] for a one-month, three-month and six-month shutdown, respectively.

This corresponds to a reduction of 369 [95% CI; 360, 378], 1,098 [1071, 1123] and 2,166 [2,116, 2,216] live-births in the cohort, respectively. Older mothers would contribute disproportionately to this reduction, with a one month delay resulting in 2.9% [95% CI; 2.8, 2.9] fewer live-births from 41-42 year olds as compared to 0.35% [95% CI; 0.3, 0.4] fewer births from women ≤35 years old.

**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. We demonstrate 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 on 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 our 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-birth 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 US will have been attenuated. Additional limitations of the modelling are discussed in the Supplemental Information.

Recommencement of infertility services needs to occur soon, as accommodating social distancing working patterns and other SARS-CoV-2 transmission risk mitigation measures are likely to impact further on capacity facilitating further delays. Whether the rapid rises in US unemployment and / or 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 CDC, and equivalent data custodians in other countries (e.g. HFEA in the UK) reporting or making data available on cumulative live-births, and we acknowledge that this may be less or greater than modelled here. Further national or local SARS-CoV-2 epidemics, or even another pandemic, are possible, and that would mean our results were 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 ASRM and ESHRE, is likely to have an unrecognised persistent emotional and economic impact for many patients and staff. Particularly as the re-initiation and regaining of patient confidence in healthcare services may take substantially longer than the simple reversal of a professional bodies edict. Irrespective of the drivers, more cycles may be required to overcome infertility at an individual and population level.

**Consent to publish**

All authors consent to publication.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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**Competing interests**

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. SMN has participated in Advisory Boards and received consultancy / speakers fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, MSD, Roche Diagnostics and The Fertility Partnership. DAL has received grant funding for other studies, not related to this one, from government, charity and industry funders, including Roche Diagnostics and Medtronic.

**Author contributions**

AS, PG, KT, JA, DAL and SMN designed the study and AS analysed the data, with AS, PG producing the figures. SMN, DAL and AS drafted the initial manuscript. All authors contributed to data interpretation, critical revision, and final approval of the submitted manuscript.

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**Table 1**

Estimated changes in cumulative live-birth rates and number of live-births associated with shutdown of IVF treatment, by age of patient, in sample of 135,673 IVF cycles representing one year of treatment provision.

| Age group (years) | < 35 | 35-37 | 38-40 | 41-42 | >42 |
|---|---|---|---|---|---|
| Number of cycles per year* | 52,428 | 28,996 | 28,287 | 14,358 | 11,604 |
| **Without shutdown** | | | | | |
| Estimated cumulative live-birth rate (95% CI) | 46.3% (45.7,47.0) | 40.6% (39.9,41.2) | 27.7% (27.2,28.2) | 14.6% (14.2,15.1) | 5.8% (5.3,6.3) |
| Estimated number of live-births per year (95% CI) | 24,284 (23,941, 24,651) | 11,766 (11,579, 11,956) | 7,841 (7,693, 7,991) | 2,099 (2,032, 2,168) | 672 (617, 732) |
| **1-month shutdown** | | | | | |
| Estimated cumulative live-birth rate (95% CI) | -0.2% (-0.1,-0.2) | -0.4% (-0.4,-0.4) | -0.3% (-0.3,-0.3) | -0.4% (-0.4,-0.4) | -0.2% (-0.2,-0.2) |
| Estimated number of live births per year (95% CI) | -85 (-73,-95) | -112 (-106,-118) | -91 (-86,-95) | -60 (-57,-64) | -21 (-20,-23) |
| **3-month shutdown** | | | | | |
| Estimated cumulative live-birth rate (95% CI) | -0.5% (-0.4,-0.5) | -1.2% (-1.1,-1.2) | -1.0% (-0.9,-1.0) | -1.2% (-1.2,-1.3) | -0.5% (-0.5,-0.6) |
| Estimated number of live births per year (95% CI) | -254 (-219,-286) | -335 (-318,-352) | -270 (-256,-283) | -177 (-167,-187) | -62 (-59,-65) |
| **6-month shutdown** | | | | | |
| Estimated cumulative live-birth rate | -1.0% (-0.8,-1.1) | -2.3% (-2.2,-2.4) | -1.9% (-1.8,-2.0) | -2.4% (-2.2,-2.5) | -1.0% (-1.0,-1.1) |
| Estimated number of live births per year | -507 (-437,-571) | -666 (-633,-699) | -533 (-507,-560) | -341 (-323,-360) | -119 (-112,-125) |

* Based on 2017 figures from CDC report