


A picture of medically assisted reproduction activities during the COVID-19 pandemic in Europe

The ESHRE COVID-19 Working Group, Nathalie Vermeulen ¹, Baris Ata ², Luca Gianaroli³, Kersti Lundin⁴, Edgar Mocanu⁵, Satu Rautakallio-Hokkanen⁶, Juha S. Tapanainen^{7,8}, and Anna Veiga ⁹*,*

¹ESHRE Central office, Grimbergen, Belgium ²Obstetrics and Gynecology Department, Koc University, Istanbul 34010, Turkey ³Società Italiana Studi di Medicina della Riproduzione, S.I.S.Me.R. Reproductive Medicine Institute, Bologna, Emilia-Romagna, Italy ⁴Reproductive Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden ⁵Department of Reproductive Medicine, Rotunda Hospital and Royal College of Surgeons in Ireland, Parnell Square, Dublin 1, Ireland ⁶Fertility Europe, Evere, Belgium ⁷University of Helsinki and Helsinki University Hospital, Department of Obstetrics and Gynaecology, Helsinki, Finland ⁸Oulu University Hospital and Medical Research Centre PEDEGO Research Unit, Department of Obstetrics and Gynaecology, Oulu, Finland ⁹Reproductive Medicine Service, Dexeus Mujer, Hospital Universitari Dexeus/Institut d'Investigació Biomèdica de Bellvitge, IDIBELL, Barcelona Stem Cell Bank, Regenerative Medicine Programme, Barcelona, Spain

*Correspondence address. Barcelona Stem Cell Bank, Regenerative Medicine Programme, Institut d'Investigació Biomèdica de Bellvitge, IDIBELL Hospital Duran i Reynals – 3^a planta, Gran Via de l'Hospitalet, 199-203, 08908 L'Hospitalet de Llobregat (Barcelona), Spain. E-mail: aveiga@idibell.cat;  <https://orcid.org/0000-0002-0943-9904>

Submitted on June 23, 2020; resubmitted on June 23, 2020; editorial decision on June 25, 2020

STUDY QUESTION: How did coronavirus disease 2019 (COVID-19) impact on medically assisted reproduction (MAR) services in Europe during the COVID-19 pandemic (March to May 2020)?

SUMMARY ANSWER: MAR services, and hence treatments for infertile couples, were stopped in most European countries for a mean of 7 weeks.

WHAT IS KNOWN ALREADY: With the outbreak of COVID-19 in Europe, non-urgent medical care was reduced by local authorities to preserve health resources and maintain social distancing. Furthermore, ESHRE and other societies recommended to postpone ART pregnancies as of 14 March 2020.

STUDY DESIGN, SIZE, DURATION: A structured questionnaire was distributed in April among the ESHRE Committee of National Representatives, followed by further information collection through email.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The information was collected through the questionnaire and afterwards summarised and aligned with data from the European Centre for Disease Control on the number of COVID-19 cases per country.

MAIN RESULTS AND THE ROLE OF CHANCE: By aligning the data for each country with respective epidemiological data, we show a large variation in the time and the phase in the epidemic in the curve when MAR/ART treatments were suspended and restarted. Similarly, the duration of interruption varied. Fertility preservation treatments and patient supportive care for patients remained available during the pandemic.

LARGE SCALE DATA: N/A

LIMITATIONS, REASONS FOR CAUTION: Data collection was prone to misinterpretation of the questions and replies, and required further follow-up to check the accuracy. Some representatives reported that they, themselves, were not always aware of the situation throughout the country or reported difficulties with providing single generalised replies, for instance when there were regional differences within their country.

WIDER IMPLICATIONS OF THE FINDINGS: The current article provides a basis for further research of the different strategies developed in response to the COVID-19 crisis. Such conclusions will be invaluable for health authorities and healthcare professionals with respect to future similar situations.

STUDY FUNDING/COMPETING INTEREST(S): There was no funding for the study, apart from technical support from ESHRE. The authors had no COI to disclose.

Key words: assisted reproduction / ESHRE / COVID-19 pandemic / SARS-CoV-2 / infertility / access to services / ART / severe acute respiratory syndrome coronavirus 2 / coronavirus disease 2019

WHAT DOES THIS MEAN FOR PATIENTS?

The coronavirus disease 2019 (COVID-19) pandemic had a large impact on infertile couples. Fertility clinics closed their doors or reduced their services either voluntarily or after a recommendation from national authorities. This article provides an overview of how and when COVID-19 impacted on access to fertility services within Europe, aiming to provide a basis for further research, for instance on the effects of stopping treatment on infertile couples. The data in this article combined with additional research will help fertility clinics and authorities to manage the care for infertile couples in a future global pandemic.

Introduction

After the local outbreak of coronavirus disease 2019 (COVID-19) in Wuhan (China) in December 2019, it did not take long before the virus reached Europe and then the rest of the world. The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Europe were reported in France on the 24th of January 2020 and in Germany on the 28th of January 2020 (Fig. 1). On the 30th of January 2020, the World Health Organization (WHO) declared this first outbreak of novel coronavirus a 'public health emergency of international concern' (World Health Organization, 2020a). By the end of February, the Italian authorities reported clusters of cases in Lombardy and additional cases in two other regions, Piedmont and Veneto. Public health measures were installed shortly thereafter. On the 11th of March 2020, the Director-General of the WHO declared COVID-19 a global pandemic (World Health Organization, 2020b). As of 25th of March 2020, cases have been reported in all European Union/European Economic Area countries (European Centre for Disease Prevention and Control, 2020), with Montenegro as the last European country to report SARS-CoV-2 positive patients.

In response to the outbreak of the virus in Europe, ESHRE launched, on the 27th of February 2020, a first statement advising a precautionary approach and recommending avoiding ART pregnancies in patients who meet the diagnostic criteria for COVID-19. In mid-March, ESHRE recommended expanding this advice to all patients even if they did not meet the COVID-19 diagnostic criteria. A more elaborated statement was published in early April 2020, advising not to start new ART for the following reasons: to avoid complications from ART and ART-pregnancy; to avoid potential SARS-CoV-2-related complications during pregnancy; to mitigate the unknown risk of vertical transmission in SARS-CoV-2 positive patients; to support the necessary re-allocation of healthcare resources; and to observe the current recommendations of social distancing. This statement also included an exception for urgent fertility preservation treatments, stating that cryopreservation of gametes, embryos and germinal tissue should still be considered, being an emergency procedure for patients that otherwise could potentially

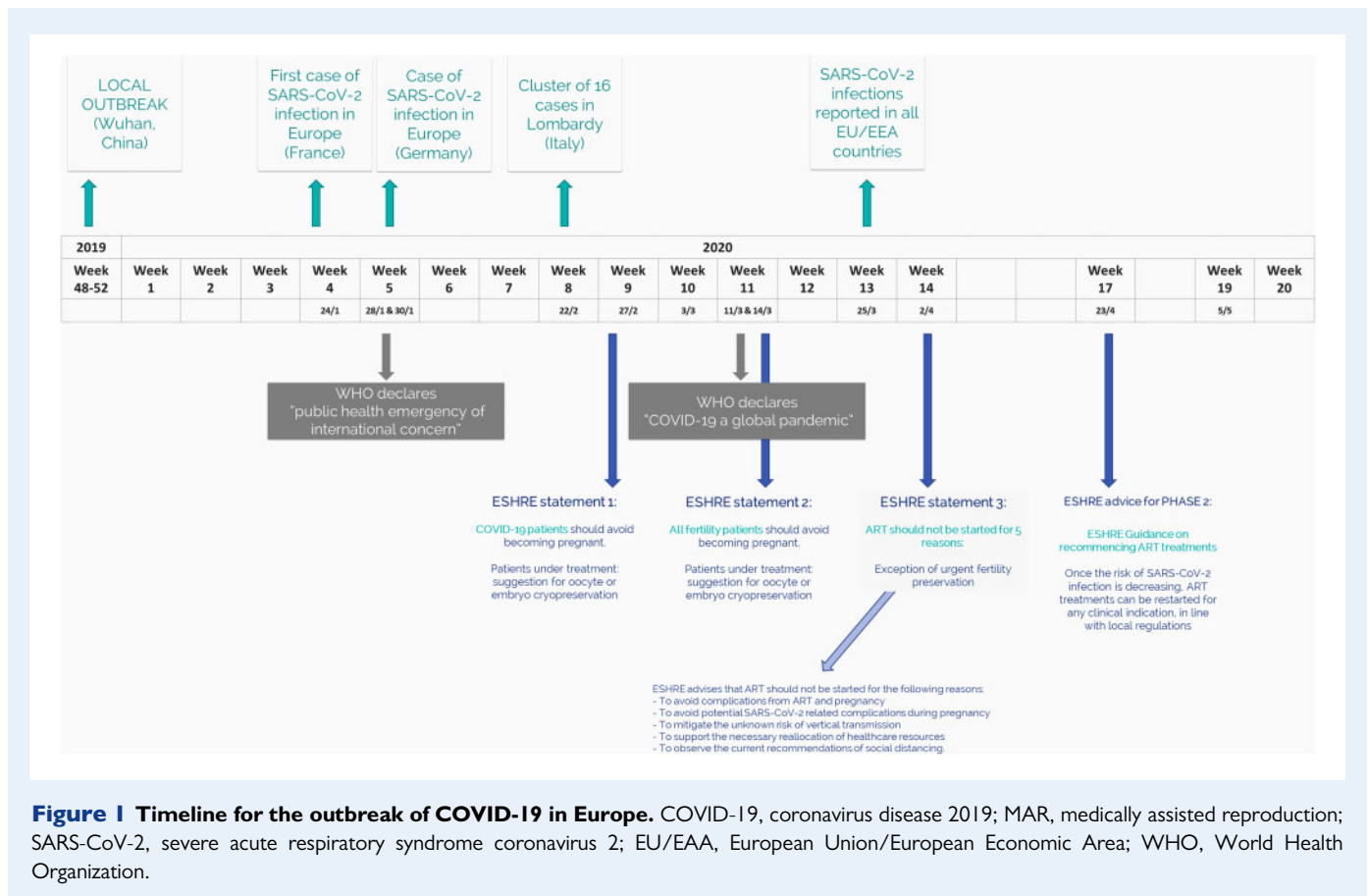
become sterile. In addition, ESHRE took the initiative to measure the impact of COVID-19 pandemic on the practice of medically assisted reproduction (MAR)/ART across Europe by using a purposely devised questionnaire.

Materials and methods

An eight-question survey (Supplementary Data) was distributed among the members of the ESHRE Committee of National Representatives (CNR) on the 7th of April 2020. The national representatives were asked about the status of ART activity in their respective countries at that time. They were also asked to detail the treatments being performed, and the ones temporarily stopped. After the initial survey, the CNR was approached to give a regular update on the activity status in their country. If treatments restarted, they were asked for more details on restrictions or precautions. Data were analysed and presented in a table and visual format, published on the ESHRE site at the time of creation and in a time progressive manner (www.eshre.eu/covidwg). Discrepant or unclear data were clarified with the CNR through email, and the same country representatives were asked to confirm that the overview of information on their country (Supplementary Table S1) was correct.

To investigate any factors that could be linked to both the date of stopping treatments, the date of the restart of treatments and the duration of activity cessation, we included national data on daily reported COVID-19 cases and deaths, available from the European Centre for Disease Control (<https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide>). The dates of stop and restart of MAR/ART treatments were added to the curves and alignment with different phases in the curves was assessed.

Furthermore, we investigated the possible correlation between the duration of the MAR/ART treatment cessation and the reported COVID-19 cases per 100 000 population: the latter was calculated from the national data from the European Centre for Disease Control.



Results

Information was collected from 41 out of 51 European countries, and all results below are based on data from the 41 European countries unless otherwise specified.

Timeline of MAR/ART treatments stop/restart

Collected data from the survey on MAR/ART activity allowed the construction of a timeline. An overview of discontinuation and restart of MAR/ART activities in Europe at 2-week intervals between the 1st of March and the 29th of May 2020 is represented in Fig. 2. Italy was the first country where MAR/ART activity was halted, as of the 1st of March 2020. By the 15th of March, nine countries had stopped all ART activity, and in four additional countries, some centres had stopped their activity. By the 1st of April, all countries for which data are available reported a halt (complete or partial) of MAR/ART activity. For some countries (Norway, Sweden), the representatives reported only a minimal impact of the COVID-19 pandemic on MAR/ART activity, limited to public centres that reduced activities mainly due to the re-allocation of health resources or staff.

The first countries to restart activities were the Czech Republic, Denmark, Germany, Luxemburg and Norway, during the week of the 20th of April 2020. Most of the remaining countries awaited the beginning of May to restart MAR/ART activity. These data focused on MAR/ART treatments being performed, excluding fertility preservation

treatments (see below) and online or telephone patient consultations, before reopening. In most countries, online and telephone patient support were available during the period when MAR/ART centres were closed.

In 57.5% (n = 23) of 40 countries for which the information was available, stopping ART activities was recommended by local or national authorities and in 27.5% (n = 11) of countries stopping was enforced by the local authorities. Six representatives reported that clinics stopped their activities voluntarily in their country and some indicated that this was based on international recommendations such as the ESHRE statement (Fig. 3).

Public versus private ART centres

In most European countries, ART is performed in private and public centres. Representatives were asked to indicate whether there was a difference in MAR/ART activity with regards to the status of public or private services in the period of treatment suspension. Analysis excluded countries in which there are either only private or only public ART centres (n = 5) or for which the information was not available (n = 7). Of the remaining 29 countries, 18 (62.1%) reported that there was no difference between public or private centres, 11 (37.9%) reported that there was less impact on the private centres, stating that either fewer private centres were closed or that activity in the private centres was not interrupted. None of the country representatives reported more activity in the public centres compared to the private centres. Although the question

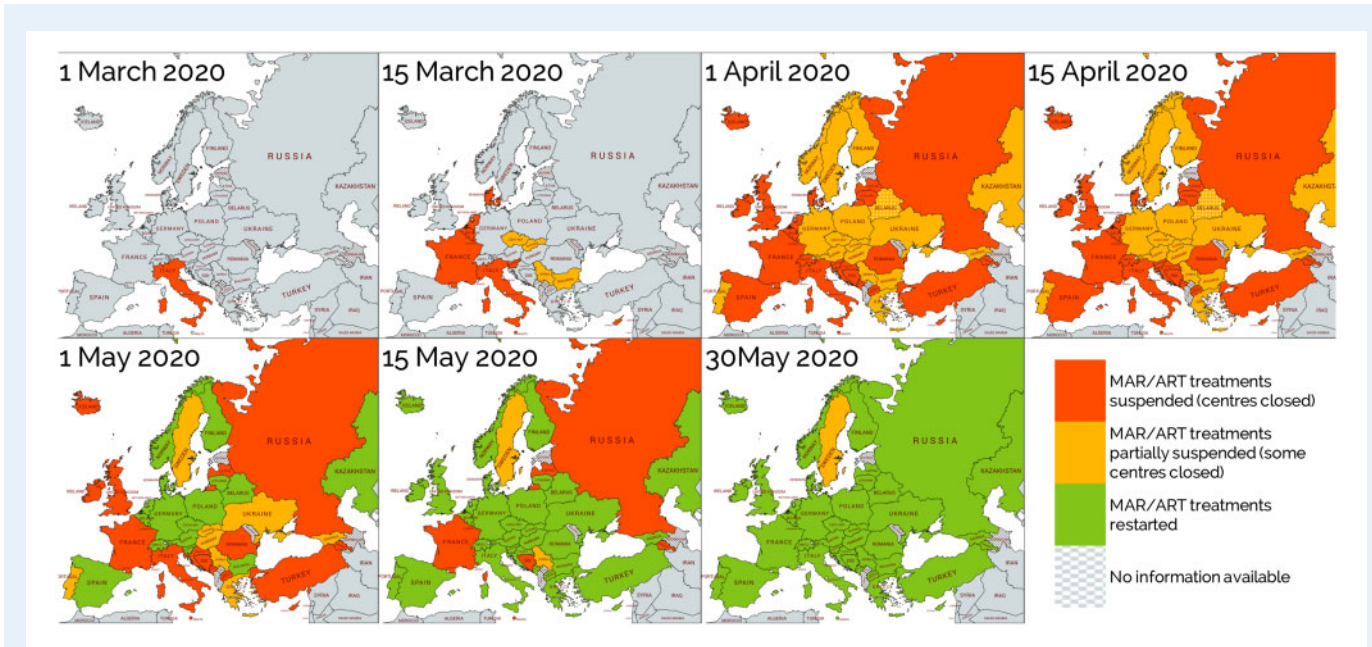


Figure 2 Overview of cessation and restart of MAR/ART activities in Europe between 1st of March and 30th of May 2020.

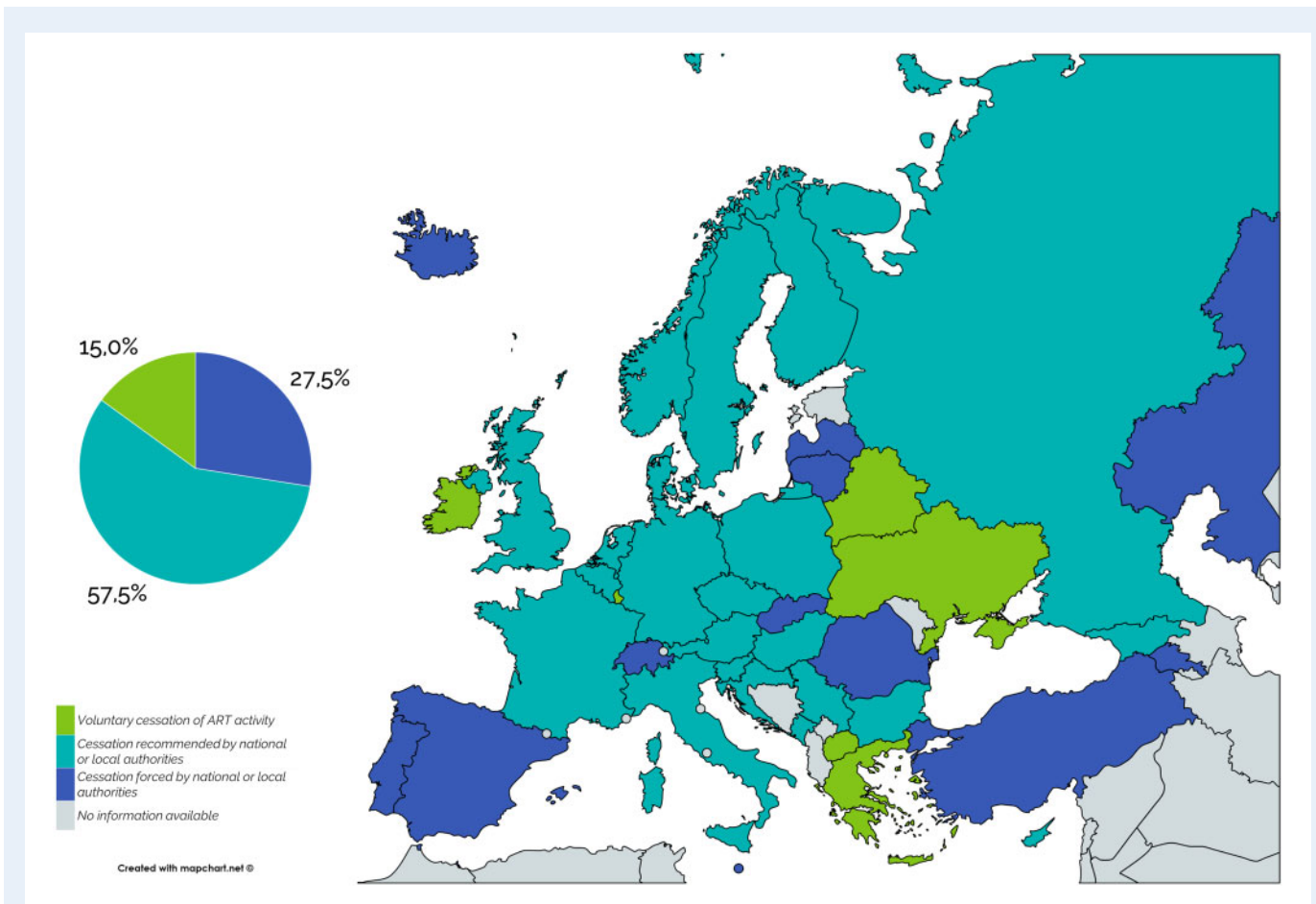


Figure 3 Overview of whether suspension of MAR/ART treatments was voluntary, recommended or enforced by national or local authorities.

was not asked specifically, some countries (Slovakia, Montenegro) reported a discrepancy in restarting activities, with activity restarting earlier in private centres.

Urgent fertility preservation treatments

Although not included in the initial survey, several CNR commented that interventions for urgent fertility preservation were not interrupted. After further questioning, representatives of 38 countries were able to provide information on the availability of medical fertility preservation treatments. In 32 countries (84.2%), treatments for urgent fertility preservation were performed throughout the entire period and in six countries (15.7%), ART centres were closed for all patients, including fertility preservation patients.

Factors related to the date of stop and restart of activities

To elucidate if the decision to restart ART therapy was based on the reported number of newly diagnosed COVID-19 cases in a country, we superimposed the date of ART 'stop' and ART 'restart' on the timeline of the number of daily diagnosed COVID-19 cases, as published by the European Centre for Disease Control (<https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide>). It should be noted that the number of daily COVID-19 cases is dependent on the country reporting and testing availability and methods, which varied over the duration of the pandemic.

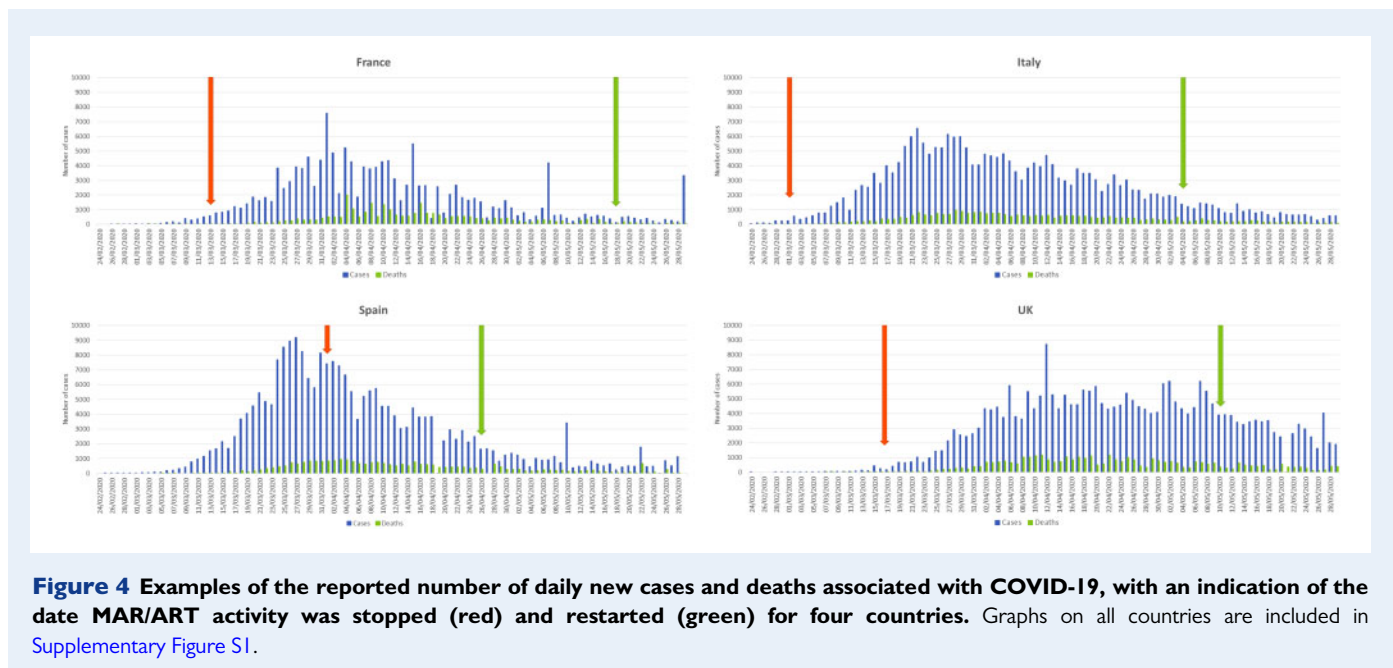
On the respective charts, the date ART activity was stopped (partial or complete) and the date of restart is indicated (Fig. 4 and Supplementary Fig. S1).

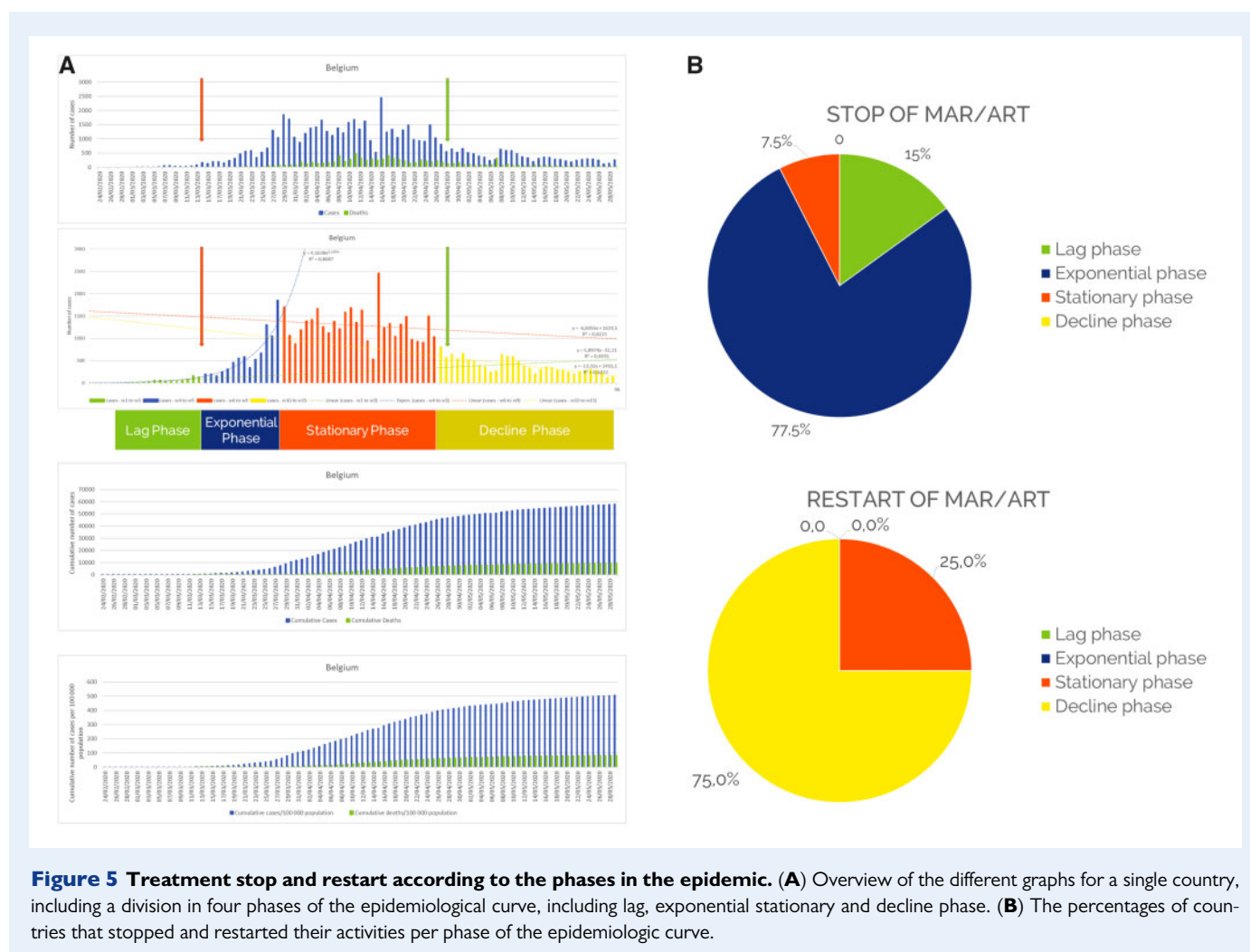
From the graphs, it can be concluded that there is a large variation in the time when MAR/ART treatments were suspended and when they were restarted. Similarly, a large variation was found in the

number of COVID-19 cases/deaths at the date of stopping MAR/ART treatments, with a mean number of cumulative COVID-19 cases of 3568.82 (ranging from 3 to 111 680 cases) and a mean cumulative number of COVID-19 deaths of 222.03 (ranging from 0 to 8189). Calculating the cumulative cases per 100 000 population did not reduce the variation, with a mean of 16.39 cases per 100 000 (ranging from 0.01 to 239.02) and 0.50 deaths (ranging from 0 to 17.53) per 100 000 population at the date treatments were stopped.

On average, ART activity was paused for 48.76 days, ranging from 23 to 92 days, based on data from 37 countries for which the exact date of stop and start of activity was available. The possible correlation between the duration of ART activity discontinuation and the impact of the COVID-19 pandemic on the respective country was analysed: the latter quantified by the number of reported COVID-19 cases/deaths per 100 000 inhabitants. No correlation between the duration of ART activity discontinuation and the impact of the COVID-19 pandemic on the respective country was detected (Supplementary Fig. S2)

On the graphs of the different countries, we could divide the curves into four phases of the epidemic, starting with a linear phase ('lag phase'), a phase of an exponential increase in the daily reported COVID-19 cases ('exponential phase'), a plateau ('stationary phase') and a phase of decrease in the reported cases ('decline phase') (Fig. 5A). For every country, the stage of the curve was estimated for the day that stop and restart of activity occurred. In most of the countries (77.5%, 31/40), the MAR/ART activity was stopped during the exponential phase, mostly at the beginning of the phase. Some countries ($n=6$, 15.0%) had already stopped ART at the lag phase, while others ($n=3$, 7.5%) postponed any action until the epidemiologic curve reached the stationary phase. Similarly, for restarting activity, most countries ($n=30$; 75.0%) restarted during the early decline phase, although in 10 (25.0%) countries activity was already restarted in the stationary phase before the decline phase started (Fig. 5B).





Discussion

The current article presents a longitudinal overview of the impact of the COVID-19 pandemic on the provision of ART activities in Europe.

In most European countries, MAR/ART activities were stopped in March, most often after a recommendation from the local authorities or national scientific society. As of the second half of April, treatments resumed gradually in different countries.

In addition to representing the data from different countries, we investigated possible factors related to the date of stopping and restarting activity. We could not find any specific threshold in the epidemiologic curve related to the stop or restart of treatment, nor did we detect a correlation between the number of reported cases per 100 000 population and the duration the treatments were halted. From the data and the graphs per country, we could derive that in most countries MAR/ART activity was stopped when the epidemiologic curve hit the exponential phase (i.e. when the daily increase of COVID-19 patients was exponential), and activities were restarted when the daily number of new COVID-19 patients declined (decline phase).

We have no detailed information as to the reasoning behind the stopping and restarting of MAR/ART activity. ESHRE stated (2nd of

April 2020) that treatments should be suspended for the reasons already mentioned in the introduction of this article. With regards to restarting, it can be assumed that activity restarted when the impact of COVID-19 on healthcare resources was reduced. Also, at that time, the chance of infection and hence potential SARS-CoV-2-related complications during pregnancy was reduced. In this reasoning, it can be assumed that the unknown risk of vertical transmission was not a major factor in decision-making. Another hypothesis is that treatment halt and resumption is influenced by international guidance, and by actions in neighbouring countries. These factors could indeed explain that apart from Italy, ART activities were stopped as of 14 March, shortly after the WHO declared 'COVID-19 a global pandemic' and after ESHRE and other international scientific societies recommended to postpone pregnancies through ART. Similarly, activity restarted mainly in Week 17 and 18, shortly after ESHRE published its guidance for recommencing ART treatments. This guidance provided information on how to reorganise MAR/ART activities to ensure social distancing requirements are met (The ESHRE COVID-19 Working Group, 2020).

The current report has some limitations with regards to the data, which were collected on a voluntary basis by the members of the ESHRE CNR. There was room for interpretation in the questions and

discrepancy in the initial replies to the survey, which was circumvented by asking for further details and a confirmation that the information summarised in the table (Supplementary Table S1) reflected the situation in the country. Still, some representatives reported that they themselves were not always aware of the situation throughout the country. Another limitation was the collection of data at a national level, while for some larger countries, the recommendations, and actions were performed at a regional level. As the impact of the COVID-19 pandemic differed between regions of the same country, the impact on ART varied similarly. At least for some countries, such as Italy, France, Russia and Germany, there were regional variations. The information in this article did not allow the inclusion of such details for each country, but the dates for stop and restart of activity in these countries may represent an oversimplification.

Despite the above limitations, the presented impact of a global pandemic upon ART activity provides valuable information. First of all, the cessation of ART activities was of a relatively short duration, about 7 weeks, and it seems that activity was restarted as soon as a decline in the curve of daily new confirmed cases was established. This could also be related to the fact that infertility is a WHO recognised disease and that ART treatment should be considered of major importance. Furthermore, the significant impact that a cessation of treatments could have on the psychosocial health of infertile couples was a factor to be considered. This impact is highlighted in a statement from the American Society for Reproductive Medicine, ESHRE and the International Federation of Fertility Societies (Assisted Reproduction and COVID-19, 2020). A second observation was the significant variation between European countries, both on the impact of the COVID-19 crisis and the actions with regards to MAR/ART treatments. The latter is seen in the variation in the duration of time when activity was stopped and the phase and number of COVID-19 cases at the dates of stopping and restarting activity. Finally, documented data such as those presented in this article will provide a basis for further research regarding different strategies developed by countries in response to the COVID-19 crisis, and such conclusions will be valuable for health authorities and healthcare professionals in case of a future global pandemic.

This manuscript can act as a blueprint for performing data collection and assessment of services in the circumstances of a major global event that has an immediate impact upon daily life and the provision of medical assistance to all in need.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Authors' roles

N.V. prepared the report. All authors participated in design of the questionnaire and critical discussion and approved the final version.

Acknowledgements

The authors would like to thank the members of the ESHRE Committee of National Representatives (2017–2020), selected EIM

country representatives and local ART professionals for their help in collecting the data: Eduard Hambartsoumian (Armenia), Kazem Nouri (Austria), Thomas Ebner (Austria), Christine Wyns (Belgium), Greta Verheyen (Belgium), Elena Petrovskaya (Belarus), Sasha Vujnic (Bosnia and Herzegovina), Sanja Sibincic (Bosnia and Herzegovina), Gueorgui Nikolov (Bulgaria), Petya Andreeva (Bulgaria), Dinka Baldani (Croatia), Patrik Stanic (Croatia), Sozos Fasouliotis (Cyprus), Christiana Antoniadou (Cyprus), Anna Agathangelou (Cyprus), Alice Malenovská (Czech Republic), Karel Rezabek (Czech Republic), Ursula Bentin-Ley (Denmark), Marie Louise Grøndahl (Denmark), Anja Pinborg (Denmark), Laure Morin-Papunen (Finland), Sirpa Mäkinen (Finland), Pierre Boyer (France), Catherine Rongieres (France), Jacques de Mouzon (France), Daniela Nogueira (France), Tamar Barbakadze (Georgia), Lika Chkonia (Georgia), Markus Kupka (Germany), Verena Nordhoff (Germany), Thomas Strowitzki (Germany), Basil Tartzis (Greece), Peter Kovacs (Hungary), Mátyás Szabolcs (Hungary), Hilmar Björgvinsson (Iceland), Mary Wingfield (Ireland), Joyce Leyden (Ireland), Gianluca Gennarelli (Italy), Lucia De Santis (Italy), V.N.Lokshin (Kazakhstan), Valerija Magomedova (Latvia), Raminta Baušytė (Lithuania), Ieva Masliukaitė (Lithuania), Caroline Schilling (Luxemburg), Thierry Forges (Luxemburg), Zoran Petanovski (Macedonia), Valentina Sotirovska (Macedonia), Jean Calleja Agius (Malta), Tatjana Motrenko Simic (Montenegro), Jesper M.J. Smeenk (The Netherlands), SM Chuva de Sousa Lopes (The Netherlands), Annemiek Nap (The Netherlands), Liv Bente Romundstad (Norway), Anna Janicka (Poland), Robert Spaczynski (Poland), Ana Luisa Sousa Ramos (Portugal), Isabel Doria Reis (Portugal), Corina Manolea (Romania), Monica Dascalescu (Romania), Ioana Rugescu (Romania), Tatyana Kodyleva (Russia), Sergei Nikitin (Russia), Elena Zakharova (Russia), Lela Šurlan (Serbia), Martin Stimpfel (Slovenia), Milan Reljič (Slovenia), Ladislav Maršik (Slovakia), Joaquin Llácer (Spain), Francisco Domínguez Hernández (Spain), Carmina Vidal (Spain), Kjell Wånggren (Sweden), Isabelle Streuli (Switzerland), Oliver Sterthaus (Switzerland), Hakan Yarali (Turkey), Lale Karakoc Sokmensuer (Turkey), Mykola Gryshchenko (Ukraine), Julia Gontar (Ukraine), Virginia Bolton (UK), Maya Chetty (UK), and Raj Mathur (UK). The authors also acknowledge Veerle Goossens for valuable comments and the ESHRE executive Committee for supporting the working group.

Funding

There was no funding for the current article, apart from technical support from ESHRE.

Conflict of interest

The authors had no conflicts of interest to disclose.

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