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Original Article

A real-world study of ART in France (REOLA) comparing a biosimilar rFSH against the originator according to rFSH starting dose

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ABSTRACT

Background: Since the first launch of a biosimilar recombinant follicle stimulating hormone (rFSH), Bemfola®, in Europe in 2014, it has been possible to study in routine clinical care throughout France the effectiveness of a biosimilar rFSH including according to different rFSH starting doses.
Methods: REOLA was a non-interventional, retrospective, real world study using anonymized data from 17 Assisted Reproductive Technology (ART) centres' data management systems across France including 2,319 ART ovarian stimulation cycles with Bemfola® and 4,287 ART ovarian stimulation cycles with Gonal-f®. For both products, four populations were studied according to starting dose of rFSH: < 150 IU, 150 - 224 IU, 225 - 299 IU and ≥ 300 IU. The primary endpoint was the cumulative live birth rate (cLBR) per commenced ART ovarian stimulation cycle including all subsequent fresh and frozen-thawed embryo transfers starting during a follow up period of at least 1 year following oocyte retrieval.
Results: A direct relationship of increasing rFSH starting dose with increasing age, increasing basal FSH, decreasing AMH and increasing body mass index was noted. No clinically relevant differences were seen in all outcomes reported, including the cLBR, between Bemfola® and Gonal-f®, but for both drugs, an association was seen with increasing rFSH starting dose and decreasing cLBR.
Conclusions: The REOLA study demonstrates that the cLBR with Bemfola® is very similar to Gonal-f® across all patient subpopulations. The cLBR is inversely related to the rFSH starting dose irrespective of the drug used, and the REOLA study provides reassurance of the clinical effectiveness of a biosimilar rFSH used in a real world setting.

Background

For 2015 France reported to the European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) 68,258 cycles of IVF/ICSI including oocyte donors; following which, when including frozen embryo replacement cycles, 19,181 infants were born, equivalent to 2.4% of all births in France [1]. Gonadotrophin therapy is a significant proportion of Assisted Reproductive Technology (ART) costs, which in France are generously reimbursed by the state [2], thus the introduction of rFSH

Abbreviations: AMH, Anti-Mullerian Hormone; ART, Assisted Reproductive Technology; CEREES, Committee for Expertise in Research, Studies and Evaluations in the field of Health; CI, Confidence interval; cLBR, Cumulative live birth rate; ET, Embryo transfer; FH, Foetal heart; FSH, Follicle stimulating hormone; INDS, National Institute for Health Data; CNIL, Commission National Data Protection Authority; EIM, European IVF-monitoring Consortium; Ph.Eur, European Pharmacopoeia; EDQM, European Directorate for the Quality of Medicines and Healthcare; MESA, Microscopic Epididymal Sperm Aspiration; OS, Ovarian stimulation; PESA, Percutaneous Epididymal Sperm Aspiration; rFSH, Recombinant follicle stimulating hormone; TESA, Testicular Sperm Aspiration; TESE, Testicular Sperm Extraction; US, Ultrasound

[1] A full list of the REOLA Study Group can be found at the end of the article, in Appendix 1.

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(recombinant follicle stimulating hormone) biosimilars such as Bemfola®, the first rFSH alpha biosimilar launched in Europe in 2014, [3] could have a positive impact on public health care funding [4].

The approval of Bemfola® by the European Medicines Agency was primarily based on extensive physicochemical and biological comparisons to the originator Gonal-f®, further supported by clinical studies [5, 6], leading to the conclusion that there were no clinically relevant differences between Bemfola® and Gonal-f® [3]. Beyond the strictly controlled studies demonstrating the efficacy of Bemfola® [5, 6], the effectiveness of Bemfola® with respect to clinical pregnancy rates following embryo transfer has also been demonstrated in four populations of differing ovarian responsiveness in a real world study of 1,222 women treated in Spain [7].

A preliminary report of the REOLA study was presented at the 2020 annual meeting of ESHRE of very similar cumulative live birth rates with Bemfola® compared to other rFSH alpha options; cumulative live birth rates per stimulated cycle of 20.0% (95% CI: 18.4%-21.5%) with Bemfola® (n=2,478) and 20.8% (95% CI: 19.7%-21.9%) with other follitropin alfas (n=4,970) [8]. However, this data was criticised in that the "other follitropin alfas" population included both Gonal f® and Ovaleap® (Theramex, UK) and there were slight imbalances in the populations compared with respect to the starting dose of rFSH used. To correct these issues the present paper presents only data from Bemfola® and Gonal-f® treatment and this data is presented according to rFSH starting dose to ensure homogeneity in the populations being compared. Real world studies provide the opportunity to assess the effectiveness of new drugs in different populations [9]. Although the patient's age is generally the top prognostic factor for ART outcome, numerous other factors are relevant, although incorporation of many further factors to define prognostic groups presents significant challenges [10]. With regard to the assessment of the effectiveness of Bemfola® the starting dose for ovarian stimulation chosen by doctors defines relevant real-world populations, as the chosen rFSH starting dose is ultimately an overall assessment by the treating doctor of anticipated ovarian responsiveness, which is not the sole but a critical factor influencing prognosis [7]. Thus, this paper analyses the effectiveness of Bemfola® with respect to cumulative live birth rates per stimulated cycle according to the rFSH starting dose in comparison to the originator Gonal-f®.

Methods

Study design

The REOLA study was a non-interventional, retrospective, observational study conducted in 17 French ART centres, which had used Bemfola® for at least 100 IVF/ICSI cycles.

In accordance with French legislation on non-interventional studies anonymized data from women, who received the REOLA information sheet at least one month prior to the data collection and did not express formal opposition to the use of their data, were extracted from the data management system of the ART centres. Each clinic used one of three different ART database software packages, Medifirst (https://www.medifirst.fr/, n=11), InfoFIV (http://www.infofiv.org/, n=5) and BabySentry (http://www.babysentry.com/, n=1). Data were collected from cycles of women who underwent ovarian stimulation (OS) between January 1st, 2016 and February 28th, 2017 and also including a follow-up to livebirth of all pregnancies following embryo transfer within 12 months of oocyte retrieval. The following treatments were excluded from the analyses: 1) OS with follitropin alfa in association with another gonadotropin; 2) cycles with sperm obtained by Microscopic Epididymal Sperm Aspiration (MESA), Testicular Sperm Extraction (TESE), Testicular Sperm Aspiration (TESA), Percutaneous Epididymal Sperm Aspiration (PESA); 3) cycles with oocytes from donors; 4) cycles with genetic preimplantation diagnosis; 5) cycles with female fertility preservation. Further this paper presents only cases treated with Bemfola® (Gedeon Richter Plc, Budapest, Hungary) or Gonal-f® (Merck KGaA, Darmstadt, Germany). For both Bemfola® and Gonal-f® four populations were studied according to starting dose of rFSH: < 150 IU, 150 - 224 IU, 225 - 299 IU and ≥ 300 IU.

Measurements

The primary endpoint was the cumulative live birth rate (cLBR) per started ART ovarian stimulation cycle including all subsequent fresh and frozen-thawed embryo transfers during a follow up period of at least 1 year following oocyte retrieval. A live birth was defined as a delivery of at least 24 weeks gestation with a heartbeat. Demographic data and secondary endpoints were limited to variables collected consistently across the three databases by the different centres and these included number of days of rFSH stimulation, total dose of rFSH administered, number of oocytes retrieved, number of MII oocytes, and number of fertilized oocytes.

Statistical analysis

Since the purpose of this study was descriptive, no formal sample size calculations were conducted, instead the sample size was based on ensuring adequate numbers to describe the effectiveness of Bemfola® in routine use. As doctors had treated patients as they felt appropriate it would be anticipated that there would be considerable heterogeneity within populations, which might be subject to both overt and covert biases. Thus, to avoid misleading the reader with comparative analyses, particularly if logistic regression is applied potentially introducing distortions, comprehensive data is provided descriptively with continuous data expressed as mean ± standard deviation or, if non-normally distributed, by median [interquartile ranges]. Nevertheless, to appreciate the similarity of the Bemfola® and Gonal-f® subpopulations the primary endpoint (cLBR) is presented with the 95% Confidence Intervals (CI), which are relatively narrow given the large sample size. Statistical analyses were performed using SAS® Version 9.4, and SAS/STAT 14.1 software under Windows (SAS Institute, North Carolina USA).

Results

The REOLA study results presented included 2,049 women treated for 2,319 ART OS cycles with Bemfola® and 3,731 women treated for 4,287 ART OS cycles with Gonal-f®. Note patients may have had more than 1 cycle of ART OS and multiple frozen embryo cycles.

Similar baseline characteristics were seen for the populations receiving Bemfola® and those receiving Gonal-f® but differed according to the starting dose of rFSH (see Table 1). There were direct relationships of increasing age, increasing basal FSH, decreasing AMH and increasing body mass index (BMI) with increasing rFSH starting dose. Primary infertility and ovulatory dysfunction were commoner with the lowest rFSH starting doses, whereas the duration of infertility was longest and the diagnosis of endometriosis were commoner with the highest rFSH starting doses.

Pituitary desensitization was used in almost all ART cycles, although short agonist protocols were commoner in patients on higher rFSH starting doses and antagonist protocols were commoner with lower rFSH starting doses (see Table 2). Irrespective of rFSH starting dose the median duration of rFSH stimulation was 10 days for both Bemfola and Gonal-f, except for Gonal-f <150 IU, which had a median value of 11 days of FSH stimulation. Moreover, irrespective of rFSH starting dose the interquartile range of the duration of rFSH stimulation fell within 9 to 12 days for both products. The median values of total rFSH administered were the same for Bemfola and Gonal-f and increased with the rFSH starting doses.

Irrespective of rFSH starting dose no appreciable difference was seen in number of oocytes retrieved between Bemfola® and Gonal-f®, but for both products there was a trend of decreasing number of oocytes retrieved with increasing rFSH starting dose (see Table 3). Similar trends were seen for the numbers of metaphase II oocytes and numbers of embryos. For both products the proportion of embryos transferred at the blastocyst stage declined and the number of embryos per embryo transfer increased with increasing rFSH starting dose.

Irrespective of rFSH starting dose no significant difference was seen in cLBR between Bemfola® and Gonal-f®, but for both products there was a trend of decreasing cLBR with increasing rFSH starting dose (see Fig. 1).

Discussion

The REOLA study presents results of the initial use of a biosimilar rFSH, Bemfola®, against the originator Gonal-f® in 17 ART centres across France while studying the variation of the rFSH starting dose, which is an important and controversial topic. The REOLA study confirms the similar efficacy of Bemfola® vs the originator Gonal-f® supporting prior studies [6, 7] but on a much larger number of cases and in real life. The analyses according to starting rFSH dose provides homogeneity of the comparative populations and interesting data on the relationship between FSH dose, conditions of use of these doses and results.

There is a clear relationship between higher total dose of rFSH and lower chance of livebirth [11]. Further there is a significant inverse relationship between the starting daily dose of gonadotrophins and pregnancy rates, whereas there is no significant difference in pregnancy rates between women who were stimulated for <9 days, 10 −11 days or >12 days. [12]. As the REOLA study demonstrates, the total dose of rFSH is driven principally by the daily rFSH dose as the duration of rFSH stimulation remains relatively constant, thus confirming the starting dose of rFSH defines populations of interest to study the clinical effectiveness of Bemfola®. It is more likely that the relationship between higher total dose of rFSH and lower chance of cLBR is due to the patients' prognoses rather than an adverse effect of higher doses of rFSH. A study of oocyte donors found no adverse effect from higher rFSH doses during stimulation; aneuploidy rates not showing any relationship with either total FSH dose or number of oocytes [13]. Although the latter study does not confirm for an individual patient that obtaining more oocytes will increase her chance of pregnancy, it suggests that higher doses of FSH do not have an adverse effect on oocytes. Further the REOLA study suggests a relationship in ART between higher prescribed rFSH doses and lower patient fertility evidenced by patient age and biomarkers of ovarian response.

With increasing embryo cryopreservation effectiveness and the trend to "freeze all" cycles the clinical pregnancy rate per fresh embryo transfer is becoming less relevant as a measure of clinical effectiveness, as good responding patients likely to achieve a pregnancy may not have the opportunity for pregnancy in the fresh ART cycles [14]. Although the retrieval of up to 12 to 18 oocytes is associated with the maximal fresh LBR, when including cryopreserved embryo cycles there is a continuing positive association between the number of oocytes retrieved and cLBR [15]. Note for biosimilar rFSH development the European Medicines Agency (EMA) recommends the "number of oocytes retrieved" as the primary endpoint to demonstrate comparability of clinical efficacy against the reference product, as pregnancy rates are influenced by multiple factors unrelated to ovarian stimulation [16]. The clinical development program of Bemfola® confirmed an equivalent number of oocytes retrieved between Bemfola® and Gonal-f® [6] and the REOLA study now provides evidence of clinical effectiveness with respective to similar cLBRs in actual clinical practice across a range of patient populations.

The goal of setting the rFSH starting dose is to achieve an adequate response to ovarian stimulation while minimising the risk of ovarian hyperstimulation syndrome and numerous factors are relevant including age, BMI, weight, polycystic ovarian syndrome, smoking history, severe endometriosis, prior ovarian response, prior pelvic surgery, AFC, ovarian volume, ovarian stromal blood flow, serum AMH, serum FSH, serum LH, serum oestradiol, serum inhibin B, serum testosterone and various dynamic tests of ovarian reserve [17–19]. Although various predictive algorithms are available to help the determination of the rFSH starting dose [17–19], in clinical practice patients are very heterogeneous. In addition, the interaction between prognostic factors is complex, hence no simple consistent way has been widely adopted to set the rFSH alpha starting dose for all patients, which has ultimately relied on the professional judgement of the treating doctor. During the recent development of rFSH delta (Rekovelle®, Ferring Pharmaceuticals) due to differences in pharmacokinetic and pharmacodynamic properties of rFSH delta compared to rFSH alpha [20] it was necessary to introduce a new dosing algorithm for OS with rFSH delta, which was proposed from a phase 2 study based on achieving a desired number of oocytes according to a patient's body weight and serum AMH [21]. However, in the confirmatory phase 3 trial of this dosing algorithm 33.2% of investigators would have preferred to alter the dose of rFSH delta during OS from that determined by the algorithm, illustrating the challenge of selecting the "ideal" starting rFSH dose [22].

When considering the relevance of the rFSH staring dose to ART treatment outcome, it is important to question if the daily rFSH dose should be adjusted during stimulation. Although it is tempting to

Table 1
Baseline characteristics of women according to the starting dose of Bemfola® or Gonal F®.

	Bemfola® (n=2319)				Gonal F® (n=4287)			
N	< 150 IU 197	150 - 224 IU 698	225 - 299 IU 527	≥ 300 IU 897	< 150 IU 834	150 - 224 IU 1518	225 - 299 IU 730	≥ 300 IU 1205
Age (years)	30.6 ± 4.4	32.4 ± 4.3	34.0 ± 4.3	36.0 ± 4.3	31.4 ± 4.2	32.8 ± 4.3	34.8 ± 4.2	36.4 ± 4.2
Dysovulation	37.6%	24.3%	20.5%	21.8%	41.8%	25.9%	28.2%	32.3%
Primary infertility	74.9%	74.7%	76.7%	64.5%	81.9%	71.9%	70.6%	63.0%
Duration of infertility (months)	41 [30-63]	42 [30-64]	44 [32-72]	48 [30-73]	45 [31-69]	47 [32-73]	49 [32-76]	52 [35-78]
Body Mass Index (kg/m^2)	23.0 ± 3.81	23.8 ± 4.7	24.2 ± 5.0	24.4 ± 4.8	22.5 ± 3.8	23.9 ± 4.7	24.3 ± 4.7	24.8 ± 5.2
Obesity*	6.0%	11.5%	15.7%	13.8%	6.3%	13.0%	14.3%	16.2%
Smoker	24.1%	23.4%	23.1%	18.6%	18.4%	19.2%	20.1%	16.6%
Basal FSH concentration (IU/L)	6.01 ± 1.56	6.43 ± 1.92	7.05 ± 2.16	7.42 ± 2.50	6.14 ± 1.68	6.52 ± 1.91	7.05 ± 2.08	7.84 ± 2.58
Basal AMH concentration (ng/mL)	6.86 ± 4.28	4.44 ± 3.59	2.96 ± 2.12	1.72 ± 2.03	7.95 ± 6.43	4.54 ± 4.46	3.00 ± 2.94	1.85 ± 2.46
Male **Infertility**	17.7%	32.3%	27.1%	18.1%	27.6%	34.9%	30.2%	21.1%
Female **Infertility**	50.4%	40.1%	42.9%	50.4%	35.9%	33.7%	37.5%	45.7%
Both **Infertility**	21.2%	16.0%	16.7%	21.9%	28.6%	19.0%	20.0%	22.4%
Idiopathic **Infertility**	10.6%	11.6%	13.4%	9.6%	7.8%	12.4%	12.4%	10.8%
Endometriosis	7.1%	12.4%	13.1%	19.0%	5.8%	7.4%	6.8%	12.6%

Table 2
Details of ovarian stimulation cycles according to the starting dose of Bemfola® or Gonal F®.

	Bemfola® (n=2319)				Gonal F® (n=4287)			
	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU
N	197	698	527	897	834	1518	730	1205
Pituitary desensitization								
Short agonist	0%	1.2%	6.6%	17.9%	0.6%	4.7%	9.9%	22.7%
Long agonist	17.0%	31.3%	31.8%	23.9%	30.9%	37.0%	36.7%	23.8%
Antagonist	83.0%	66.3%	60.0%	58.1%	66.8%	58.0%	52.4%	52.9%
Days of rFSH stimulation								
Median	10	10	10	10	11	10	10	10
Interquartile range	9-11	9-11	9-12	9-12	9-12	9-11	9-12	9-12
Total rFSH dose IU								
Median	1100	1500	2250	3300	1008	1500	2250	3300
Interquartile range	825 -1313	1350 - 1800	2025 -2700	2700 -4200	700 - 1275	1200 - 1900	1800 - 2625	2700 - 4400

Data are displayed as: number, % cycles or medians and interquartile ranges based on the number of patients with non-missing data.

adjust the rFSH dose during stimulation when the ovarian response does not meet expectations, ovarian biology makes such change futile within the timescale of an ART cycle. After adjusting the daily dose of rFSH in view of FSH pharmacokinetics there is a delay of 3 to 4 days for the circulating FSH levels to increase to a new stable level [23] and it takes a further 4 days to achieve pharmacodynamic responses of the ovary with respect to follicular growth and increased oestradiol levels [24]. Moreover, the REOLA study demonstrates that the daily dose of rFSH has little impact on the duration of rFSH stimulation.

Although the starting rFSH stimulation dose varies significantly, it has been suggested this variation may in fact have little impact on the ultimate outcome of an ART cycle [25]. For anticipated poor responder patients, the OPTIMIST study did not find any increase in livebirth rates in those patients receiving an increased FSH daily dose of 225 IU or 445 IU compared to a standard daily dose of 150 IU FSH daily [26]. Also, for anticipated hyper responder patients the OPTIMIST study comparing a reduced dose of 100 IU daily versus a standard dose 150 IU FSH daily did not find any difference in cumulative live birth rate nor occurrence of severe OHSS, although the occurrence of any grade of OHSS was lower with reduced FSH dose [27]. Further in cases considered at particular risk of OHSS avoiding an injection of HCG and instead using GnRH agonist trigger with cryopreservation of all embryos for delayed transfer may largely eliminate the risk of OHSS [14]. REOLA shows that varying the rFSH starting dose according to the anticipated ovarian response does not normalise the number of oocytes obtained suggesting an inevitability of outcome such that the precise rFSH starting dose may not be critical. However, if there had been no dose adjustment according to anticipated ovarian response in the ART cycles reported by the REOLA study, the differences in number of oocytes obtained might have been even greater. Taken into account the views of international experts in ART regarding the FSH starting dose, ESHRE proposes to optimally use a GnRH antagonist protocol from 150 IU FSH daily for anticipated high responders up to a maximum of 300 IU FSH daily for anticipated low responders based on serum AMH or AFC determination by ultrasound, advising against changing the FSH dose during stimulation [28]. The REOLA study would further support the ESHRE guidance as duration of rFSH stimulation does not appear to relate to daily rFSH dose, thus changing dose during stimulation is unlikely to be helpful.

No formal cost efficiency analysis was performed, as this would require further details that were not available; for instance, in addition to the total amount of rFSH administered it would be important to consider the rFSH dose wasted. However, within each REOLA study subpopulation comparing Gonal-f® and Bemfola® the total rFSH administered and cumulative cLBR are similar. Further a real-world study of 4,078 IVF cycles in five UK clinics modelled the actual usage of Gonal-f® including wastage against potential usage of Bemfola® suggesting a 5.7% greater rFSH wastage in Gonal-f® pens than Bemfola® pens, even if patients administered two Gonal-f® injections

Table 3
Outcomes of oocytes retrievals according to the starting dose of Bemfola® or Gonal F®.

	Bemfola®				Gonal F®			
	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU	< 150 IU	150 - 224 IU	225 - 299 IU	≥ 300 IU
Oocyte retrieval (n)	191	673	508	812	801	1484	709	1148
Number of oocytes retrieved	14.1 ± 7.4	12.9 ± 7.2	10.1 ± 5.8	6.6 ± 5.1	13.0 ± 7.1	12.1 ± 6.3	10.3 ± 6.0	7.4 ± 5.0
Number of metaphase II oocytes	9.8 ± 6.7	9.9 ± 6.1	7.8 ± 4.7	4.9 ± 4.0	9.9 ± 6.0	9.3 ± 5.4	8.0 ± 5.0	5.6 ± 4.1
Fertilisation rate*								
IVF	66.6%	64.0%	68.0%	64.0%	62.7 %	69.6 %	69.6 %	70.1 %
ICSI	72.4 %	66.7 %	67.2 %	65.0 %	70.2 %	67.8 %	70.2 %	65.1 %
Number of embryos	7.9 ± 5.2	7.2 ± 5.1	5.7 ± 4.0	3.3 ± 3.1	7.0 ± 5.1	6.7 ± 4.8	5.6 ± 4.0	3.8 ± 3.3
Stage of ET								
Cleavage stage	62.1%	73.3%	82.0%	89.8%	60.1%	73.0%	76.8%	90.0%
Blastocyst	37.9%	26.7%	18.0%	10.2%	39.9%	27.0%	23.2%	10.0%
Number of embryos per ET								
Mean	1.37	1.34	1.47	1.49	1.41	1.47	1.57	1.61
1	63.3%	66.5%	55.3%	54.3%	59.9%	54.0%	45.5%	43.3%
2	36.7%	32.7%	42.6%	42.3%	39.0%	44.7%	51.8%	52.2%
3	0.0%	0.8%	2.2%	3.2%	1.1%	1.3%	2.7%	4.4%
4	0.0%	0.0%	0.0%	0.2%	0.0%	0.0%	0.0%	0.1%

Data are displayed as: n (%) or by their mean ± standard deviation based on the number of patients with non-missing data.
ET: embryo transfer
* Fertilization rate % was calculated as the number of oocytes with 2 pronuclei (PN) on day 1 divided by the number of injected or inseminated oocytes

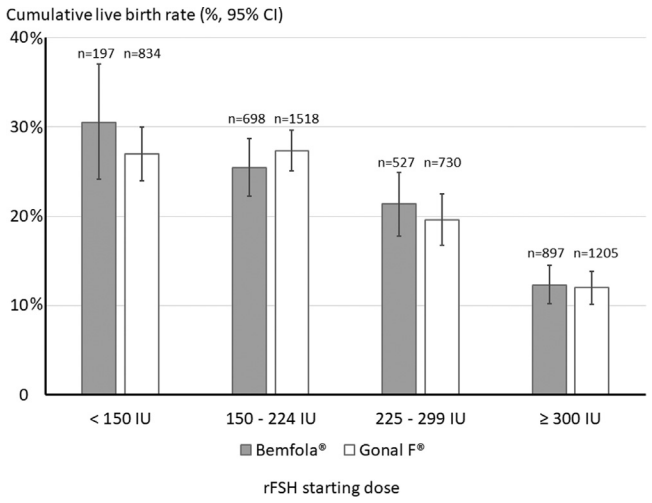

Fig. 1. Cumulative live birth rate (%, 95% CI) following fresh and all cryopreserved embryo transfer cycles starting within at least 1 year post oocyte retrieval per commenced ART ovarian stimulation cycle according to the starting dose (IU rFSH) of Bemfola® or Gonal F®.

on days when the residual rFSH in the Gonal-f® pen was inadequate for that day's prescribed dose to reduce wastage [4]. The routine practice in France, where rFSH costs are fully reimbursed, if the residual rFSH in the Gonal-f® pen should be inadequate to administer that days FSH dose would be usually to give only one injection and discard the pen with the inadequate Gonal-f dose to reduce the risk of dosing errors.

Beyond potential reduced rFSH wastage a single use, multidose rFSH pen product was considered to have several advantages over multiple use rFSH pens in a comparative study of different types of FSH delivery [29]. In particular, the simplicity of a single use pen that does not require a treatment diary to keep a record of the residual rFSH to determine whether it is adequate for the next injection or whether two injections may be required was seen as important factor to reduce the risk of dosing errors. Further an easier-to-use FSH administration option was seen as preferable to shorten the time required for training thereby reducing the number of persons simultaneously present in the IVF centre, which is a recommendation to reduce the risk of Covid-19 transmission [30].

There are limitations with the REOLA dataset reflecting real world clinical practice where patients may have multiple cycles of ART with different treatment protocols, different ART laboratories and even moving between clinics. Further not all relevant data to ART outcome may be captured by different clinics' databases consistently [31], for instance embryological data was not collected consistently hence has been omitted from this paper. Consequently, the REOLA study data is presented transparently using appropriate descriptive statistics with a sufficiently large sample size to provide helpful information to guide clinical practice when considered with other relevant publications [3, 5, 6]. Although logistic regression could have been applied to this real-world data attempting to correct for imbalances between groups to make comparative analyses, the lack of randomisation between groups risks significant imbalances arising between groups that may not even be recognised leading to misleading comparisons. The impact of such potential imbalances between groups may be increased by the many challenges of applying logistic regression to ART real world data including multicollinearity of variables (e.g. age, oocyte number and AMH are highly correlated yet also have non-redundant contribution to outcomes), non-linear relationship between variable and outcome (eg age and pregnancy rate), the need to use both continuous and categorical variables (e.g. age, AMH and BMI are continuous; whereas diagnosis and treatments are discrete), and the impacts of outliers and missing data [10, 32]. At the time of completion of the REOLA study there were still cryopreserved embryos that could allow patients to have further treatment, hence the ultimate cumulative livebirth rate per stimulated cycle might increase slightly, and some patients might eventually even have more than one livebirth per stimulation cycle. However, French ART regulations require all cryopreserved embryos to be transferred prior to further fresh ART attempt and there was a follow up period of one year following the oocyte retrieval to transfer cryopreserved embryos, hence the number of further livebirths outside the study period would be expected to be low and not make a significant difference to the results.

Although for demonstration of a fertility drug's effectiveness the cLBR is a relevant measure, it is important to note that in view of multiple confounding factors, an even more important and sensitive comparison of the similarity of a biosimilar to an originator product is provided by extensive, meticulous laboratory comparisons [3]. Taken this into account, it is interesting to note that for any follitropin that a gold standard for comparisons of the active drug substance (the follitropin for peptide mapping and glycan analysis chemical reference substance) according to the European Pharmacopoeia (Ph.Eur) of the European Directorate for the Quality of Medicines and Healthcare (EDQM) since 2018 has been the Bemfola® drug substance [33, 34].

Conclusions

The REOLA study demonstrates that the CLBR with Bemfola® is very similar to Gonal-f® across all patient subpopulations. Complementary to the Bemfola® clinical development program [3, 5, 6] and other real-world studies [4, 7] the REOLA study provides further support for the clinical effectiveness of Bemfola® across different populations of patients undergoing ART from patients receiving a low rFSH starting dose to those patients receiving a high rFSH starting dose. The cLBR is inversely related to the daily dose of rFSH administered, which has little influence on the duration of rFSH stimulation, and this inverse relationship appears to result from worse prognoses of the patients who are given higher rFSH doses. The results of the REOLA study support the simplified approach to OS for ART suggested by ESHRE guidance that is based on sound scientific evidence and international expert opinion [28].

Authors' contributions

All authors contributed to the design of the study, execution of the study and/or drafting of the publication and all authors confirm the validity of the results.

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Ethics approval and consent to participate

The non-interventional study protocol received a positive opinion of the Committee for Expertise in Research, Studies and Evaluations in the field of Health (CEREES), on 26 September 2017, a positive opinion on the public interest nature of the study by the National Institute for Health Data (INDS) on 17 October 2017, as well as the authorization of the Commission National Data Protection Authority (CNIL) on 23 March 2018. Further, a non-opposition form was sent to all patients informing them that their data would be used for a research purpose unless they declined for such use. Data were collected retrospectively in 2018 and therefore the study did not influence drug prescription nor medical practice.

Competing interests

EA is an employee of Gedeon Richter, and JJ is a scientific advisor to Gedeon Richter. SH received funding for scientific projects from Gedeon Richter, Merck and Ferring. MG received fees from Merck Serono, Ferring, MSD, Besins, GE, Samsung and Gedeon Richter. PB received fees as consultant and/or speaker for Merck, Genevrier, Ferring, Teva, MSD and Gedeon Richter. CA received consulting fees from Gedeon Richter. The other co-authors declare that they have no competing interests.

The data analysis was performed by the Contract Research Organisation, Monitoring Force, under the direction of the Medical Affairs department of Gedeon Richter France and the final manuscript was drafted by the Medical Affairs department in collaboration with the authors; in both cases there was no involvement of Gedeon Richter marketing or commercial teams.

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Original Article

The impact of the COVID-19 pandemic on ectopic pregnancy presentation and treatment: A retrospective cohort study

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ABSTRACT

Objective: We examined ectopic pregnancy (EP) incidence, presentation and management, before and during the COVID-19 pandemic, and following initiation of vaccination against COVID-19.
Study design: In a single-center retrospective cohort study, we compared incidence, presentation and management of EP, between 98 women who presented during the pandemic (March 1 2020 to August 31, 2021), and 94 women diagnosed earlier (March 1 2018 to August 31, 2019). Sub-periods before and after introduction of the vaccination were compared.
Results: Age and parity were similar between the periods. For the pandemic compared to the earlier period, the median gestational age at EP presentation was higher (6.24 ± 1.25 vs. 5.59 ± 1.24, $P<0.001$), and the proportions were higher of symptomatic women (42.9% vs. 27.7%, $p = 0.035$) and urgent laparoscopies (42.9% vs. 24.5%, $p = 0.038$). In a multivariable linear model, women who presented during the pandemic were more likely to undergo an urgent laparoscopy [OR 2.30, 95%CI (1.20–4.41)], $P = 0.012$. In urgent surgeries performed during the pandemic compared to the earlier period, the proportion of women with a hemoglobin drop >2 gr/dL was greater (60% vs. 30%, $p = 0.024$). Statistically significant differences were not found in sonographic or laboratory findings, in rupture or massive hemoperitoneum rates, or in the need for blood transfusion in urgent laparoscopy. Outcomes were similar before and after introduction of vaccinations.
Conclusion: During the pandemic, and even after the introduction of vaccination, women with EP were more likely to undergo urgent surgery, and blood loss was greater. This is likely due to delayed diagnosis.

Introduction

Ectopic pregnancy (EP) occurs in 1–2% of all pregnancies [1]. Since the implementation of earlier use testing of beta human chorionic gonadotropin (beta-HCG) and transvaginal ultrasound (TVS) in first-trimester pregnancy, about 85% of women with EP are diagnosed early, before the onset of symptoms [2]. Consequently, maternal mortality and morbidity have decreased significantly. Moreover, several clear benefits have been demonstrated for early diagnosis of EP, which enable conservative follow-up or medical treatment with methotrexate (MTX), without surgical intervention [3,4]. EP may be managed by watchful waiting, by MTX in hemodynamically stable patients, or by surgical intervention. Up to 50% of EP can be managed expectantly, without medical or surgical intervention [5,6]. The success rate of MTX treatment is estimated at 87–93% [6]. Nowadays, surgery remains the approach only for failed MTX treatment, EP with embryonic cardiac motion on ultrasound, recurrent EP in the same tube, contraindication for medical or expectant management, or suspected EP rupture and hemodynamic instability. Delayed diagnosis of EP can result in a life-threatening medical condition resulting from intra-abdominal bleeding and hypovolemic shock [7].

In late 2019, the first patients with COVID-19 were reported in China, and the World Health Organization declared a pandemic on March 11, 2020. On February 21, 2020, Israel reported the first cases of COVID-19, and restrictions began. Shortly afterward, the first lockdown was announced on March 23, 2020.

Since March 2020 and throughout the pandemic, several lockdowns and significant restrictions have been implemented, together with social distancing. Although restrictions regarding seeking pregnancy and emergent-related medical care have not been dictated, some individuals have distanced themselves to the extent of avoiding medical care due to the fear of contracting COVID-19.

The pandemic has affected the presentation and the incidences of several gynecological and non-gynecological medical conditions. We reported an increase in molar pregnancy incidence during the

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pandemic, which was probably due to late diagnosis [8]. Others reported more urgent surgical intervention in EP during the first lockdown in Israel [9]. In addition, fewer urgent medical conditions such as appendicitis, stroke, and heart attacks were reported in emergency rooms in this period [10–13].

No studies examined the presentation and treatment of EP during the COVID-19, a long period of 18 months in addition to the examination of these parameters before and after introduction of the vaccination. The aim of this study was to examine EP incidence, presentation, and management during the COVID pandemic compared to previous years, and to examine a possible collateral effect of introduction of the vaccination in the presentation and the management of EP.

Materials and methods

This study was approved by the Institutional Review Board (Helsinki Committee) of Galilee Medical Center and the Israeli Ministry of Health before data collection (authorization number 0138–21-NHR, August 2021).

The study population consisted of women diagnosed with EP in the Obstetrics and Gynecologic Department at the Galilee Medical Center, Israel, between March 2020 and August 2021 (during the COVID-19 pandemic) and women diagnosed in a parallel period before the pandemic, between March 2018 and August 2019. We compared between the periods, incidences of EP per number of deliveries at our institution, and the volume of urgent surgeries. In addition, we aimed to identify possible changes in presentation and treatment trends following the introduction of vaccination in January 2021. To this end, we divided the pandemic (COVID-19) period into two sub-periods, from March 2020 to December 2020, and from January 2021 to August 2021.

During the study period, EP was diagnosed, and managed according to current practice, based on the American College of Obstetricians and Gynecologists Practice Bulletin [14]. This included a combination of serial beta-HCG measurements and the absence of evidence of an intrauterine gestational sac, with or without sonographic suspicion of extrauterine pregnancy. When EP was suspected and the TVS was inconclusive, the diagnosis was confirmed during laparoscopic surgery and pathology assessment. The location of extra tubal EP was confirmed during laparoscopy. The pregnancy week at presentation was calculated by the date of the last menstrual period.

Urgent laparoscopy was performed when ruptured EP was suspected by hemodynamic instability, acute abdomen, sonographic evidence of large free fluid in the cul-de-sac, or acute anemia diagnosed by hemoglobin < 9 gr/dL [15]. The surgical modality was chosen according to the EP location: salpingectomy for tubal pregnancy [18], wedge resection for ovarian pregnancy [16], lesion excision for abdominal pregnancy [17], and cornual excision for interstitial pregnancy [18].

In women for whom urgent surgery was not indicated, three treatment modalities were possible: expectant management, MTX, and planned laparoscopy.

Expectant management (observation) was selected for early EP, asymptomatic and hemodynamically stable patients, with spontaneous beta-HCG decline [15].

MTX was selected for hemodynamically stable patients, with beta-HCG level < 5000 (IU/L), gestational sac <4 cm and the absence of embryonic cardiac motion detected on TVS [14].

Planned laparoscopy was selected for those who declined treatment by MTX and those with contraindications to MTX.

We searched the hospital's database using the International Classification of Diseases, Ninth Revision (ICD-9) Codes 633, 633.90, and 633.9. After validating the data, we included those confirmed as EP. We included all women assessed for EP and excluded cervical and scar pregnancies due to the different guidelines for treatment modality [19,20].

We also accessed demographic characteristics, presenting symptoms (asymptomatic, abdominal pain, vaginal bleeding or both), indications of surgical management, ultrasonographic reports and laboratory data. The ultrasonographic reports included mass size, embryonic cardiac motion, and the presence of free fluid in the cul-de-sac. The laboratory data included hemoglobin (g/dL), beta-HCG at presentation, and treatment modality. Additional variables were intraoperative findings, estimated blood loss (mL), the administration of blood products, postoperative care, and the duration of hospitalization.

EP complications were defined as ruptured EP confirmed in laparoscopy, massive bleeding as either (hemoperitoneum >1000 ml), a hemoglobin decline greater than 2 gr/dl (admission-discharge) or the need for blood transfusion.

The primary outcome was the proportion of women with EP requiring urgent surgical intervention. Secondary outcomes were gestational age at presentation, symptoms at presentation (vaginal bleeding, abdominal pain, asymptomatic), the need for blood product transfusions, estimated blood loss, ectopic embryonic cardiac motion identified by TVS, and beta-HCG level at admission. Massive blood loss was defined as *a* >2 gr/dl decline in hemoglobin level from admission until discharge. Hemoperitoneum was defined as at least 1000 ml of blood as assessed by the surgeon.

Statistical analysis

We described the categorical data using frequencies and percentages. Continuous variables with normal distributions were presented as means ± standard deviations. Median values and ranges were used for variables that did not meet the normal distribution assumption.

For the inferential analysis, we compared categorical variables between the groups using the Chi-square test, or alternatively Fisher's exact test (when expectancy <5).

We compared continuous variables between the groups using the independent *t*-test or Wilcoxon rank-sum test according to the variable distributions. Accordingly, if a normal distribution was found, the independent *t*-test was presented; a histogram determined the distribution shape.

A multivariable linear model was adapted to examine the correlation between the pandemic period and urgent laparoscopy in EP. The dependent variable was urgent laparoscopy. Women's age, gravidity, and the pandemic period were included as independent variables.

P <0.05 was considered to be significant. SPSS Version 27.0 statistic software was used for the statistical analysis.

Results

We identified 102 women with an EP during March 2020 - August 2021 (the pandemic period) and 100 women during the same months of 2018–2019 (the earlier period). These included four cervical or scar pregnancies in the pandemic period, and six in the earlier period. After excluding these, the pandemic period comprised 98 women with confirmed EP, and the earlier period included 94. The ectopic to delivery rate was similar between the pandemic and earlier period (1.37% and 1.18%, respectively, $p = 0.344$) (Fig. 1).

The baseline characteristics of all the patients are presented in Table 1. The median gestational age of the EP at presentation was significantly higher in the pandemic than the earlier period (6.24 ± 1.25 vs. 5.59 ± 1.24, P<0.001). No difference was found in age, gravidity, parity, EP history, and EP location between the two periods.

The clinical, laboratory and sonographic presentation are presented in Table 2. In the pandemic compared to the earlier period, a larger proportion of women presented with abdominal pain (42.9% vs. 27.7%, $P = 0.035$), and a smaller proportion was asymptomatic

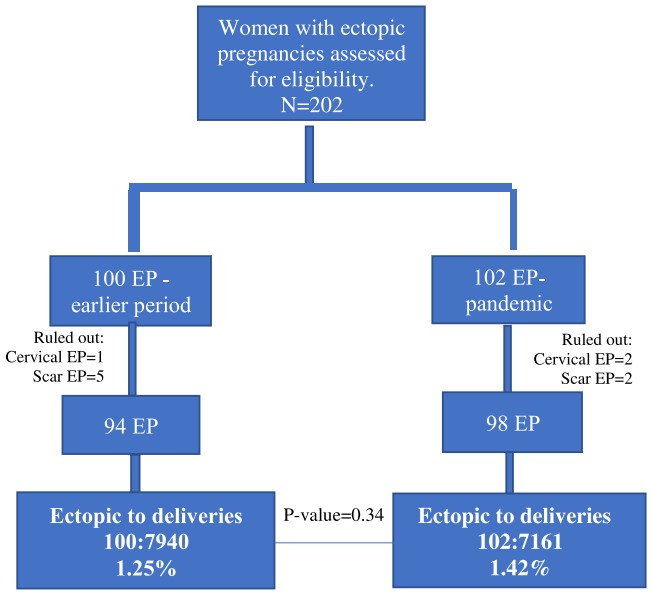

Fig. 1. Ectopic pregnancy to delivery rates in the COVID-19 pandemic and in an earlier period.

The p value that compares ectopic pregnancy to delivery rates between the two periods was calculated by the Chi-square exact test.

Table 1
Baseline characteristics of women with ectopic pregnancy in the pandemic period (March 2020 to August 2021) and an earlier period (March 2018 to August 2019).

	Pandemic period	Earlier period	P- value
Age (mean ± SD)	31.31±5.53	31.79±5.82	0.565[c]
Gravidity (median, range)	3.0 (1–8)	2.5 (1–7)	0.241[b]
Parity (median, range)	1 (0–6)	1 (0–6)	0.434[b]
Previous EP (%)	8.2% (8)	4.3% (4)	0.373[c]
Presenting week (mean ± SD)	6.24±1.25	5.59±1.24	*P*<0.001[c]
Location:			
Fallopian tube	88 (89.8%)	84 (89.4%)	0.288[d]
Ovarian	1 (1%)	0 (0%)	
Abdominal	3 (3.1%)	0 (0%)	
Interstitial	2 (2%)	2 (2.1%)	
Rudimentary horn	0 (0%)	2 (2.1%)	
Ectopic of unknown location	4 (4.1%)	6 (6.4%)	

EP- ectopic pregnancy, SD- standard deviation.
[b] Wilcoxon rank-sum test
[c] independent samples *t*-test.
[d] Fisher's test.

(35.7% vs. 57.4%, *P* = 0.004). Statistically significant differences were not found between the groups in vaginal bleeding, or in hemoglobin or beta-HCG level at presentation. Sonographic details such as EP size and embryonic cardiac motion were similar in the two groups. However, in the pandemic compared to the earlier period, a higher proportion of women underwent urgent laparoscopy (42.9% vs. 24.5%, *P* = 0.038), and a lower proportion underwent planned laparoscopy (5.1% vs. 14.9%, *P* = 0.029). Similar proportions of women in the two periods were treated by expectant management and MTX (Fig. 2).

The multivariable linear model showed that during the pandemic period, women with EP were more likely to undergo urgent laparoscopy than women before the pandemic; the OR (95% confidence interval) was 2.30 (1.20–4.41), *P* = 0.012. Correlations of the remaining variables (age and parity) with the need for urgent laparoscopy were not statistically significant.

Table 3 presents a sub-analysis of the 42 women in the pandemic period and the 23 in the earlier period who underwent urgent surgery for treatment of EP. Statistically significant differences were not found between the two periods in surgical findings such as EP rupture rate and massive intra-abdominal bleeding above 1000 ml; and in laboratory findings such as postoperative hemoglobin level and anemia rate (defined as hemoglobin <9 gr\dL). A hemoglobin drop of more than 2 gr/dL was twice as common in the pandemic than the earlier period (60% vs. 30%, *P* = 0.009). A smaller proportion of women in the pandemic period, received blood product transfusion, though the difference was not statistically significant. The median post-surgery hospitalization length was longer in the earlier than the later period (1.54 (range: 1–5) vs. 2 (range: 1–5), *p* = 0.036). No complications were reported in any of the urgent surgeries.

In a sub-analysis of the pandemic period, statistically significant differences were not found between the pre- and post-vaccination sub-periods, in any of the parameters examined (Table 4). These included features of EP presentation such as presenting week, symptoms (asymptomatic, abdominal pain or vaginal bleeding), and hemoglobin and beta-HCG levels at admission; sonographic details such as EP size (cm); or embryonic cardiac motion. The rate of urgent laparoscopy was equal, 46%, in the pre- and post-vaccination periods, Surgical findings in urgent laparoscopy, including intra-abdominal bleeding, ruptured EP, and massive hemoperitoneum >1000 ml, were also similar.

Discussion

In this study, we showed that women who presented with EP during the COVID-19 pandemic period were more likely to undergo urgent laparoscopy than women in an earlier period. Additionally, we showed that during the pandemic compared to the same months in a previous year, women with EP presented later (6.24±1.25 vs. 5.59±1.24, *P*<0.001), and the proportion with blood loss >2 gr/L was higher. Moreover, for the respective periods, a greater proportion of women with EP presented with abdominal pain, and a smaller proportion were asymptomatic at

Table 2
The presentation of ectopic pregnancy in the pandemic (March 2020 to August 2021) and in an earlier period (March 2018 to August 2019).

	Pandemic period	Earlier period	P- value
Abdominal pain as a presenting symptom (%)	42 (42.9%)	26 (27.7%)	0.035[a]
Vaginal bleeding as a presenting symptom(%)	23 (23.5%)	23 (24.5%)	1[a]
Asymptomatic (sonographic presentation or inappropriate beta-HCG rise) (%)	35 (35.7%)	54 (57.4%)	0.004[a]
Hemoglobin at presentation (g\dL) (mean ± SD)	12.13±1.24	12.27±1.38	0.439 [c]
Beta-HCG at presentation (IU/L)(median, range)	1421.5 (14–70,628)	903.5 (27–45,797)	0.591[b]
Peak beta-HCG value (IU/L) (median, range)	1502.5 (51–81,490)	1236.5 (27–45,797)	0.594 [b]
EP size at presentation (cm) (median, range)	2 (0.8–6.4)	1.95 (0.69–6)	0.614 [b]
Embryonic cardiac motion in EP at presentation (%)	14 (14.3%)	7 (7.4%)	0.166[a]

EP- ectopic pregnancy, SD- standard deviation.
[a] Chi-square Exact test.
[b] Wilcoxon rank-sum test.
[c] independent samples *t*-test.

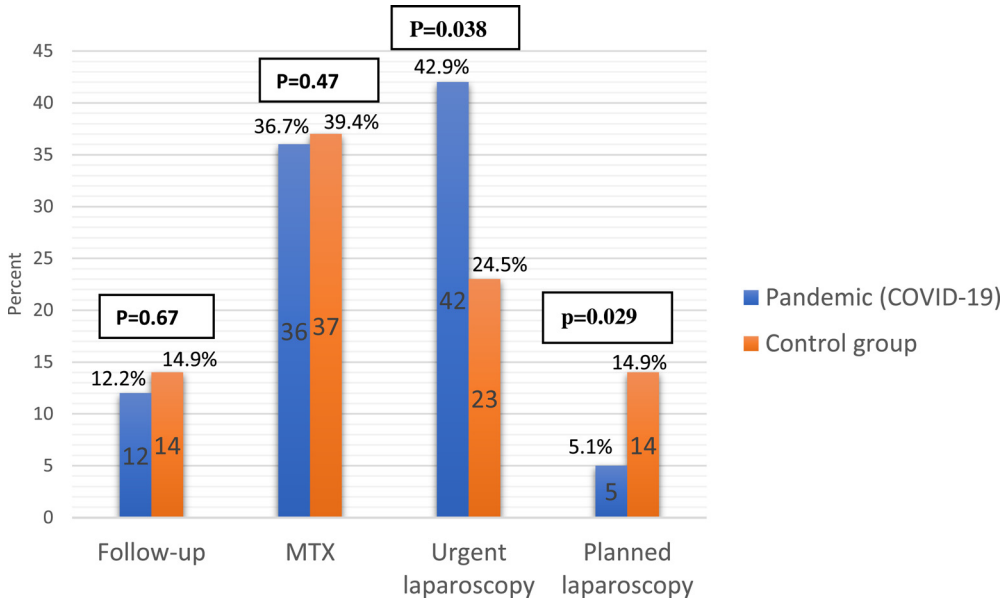

Fig. 2. Treatment modalities for ectopic pregnancies in the pandemic and earlier periods.
MTX- methotrexate
The p values comparing treatment modalities between the periods were calculated by the Chi-square exact test.

the diagnosis of EP. However, similarities were found between the periods in the rate of EP, the proportion of women with EP who required blood products, the proportion with an embryonic cardiac motion on TVS, and the ratio between surgical, MTX, and expectant management. Moreover, we found no differences in EP presentation and treatment trends before and after introduction of vaccination against COVID-19.

The impact of this pandemic on several medical conditions has been described, mainly in the fields of emergent surgery [13,21-23] and cardiology [12]. A multicenter analysis demonstrated a significant reduction in the volume of ST-elevation myocardial infarction-related catheterization due to the late presentation of patients in the emergency room during the COVID-19 outbreak [12]. Other study reported increased perforated and gangrenous appendicitis due to delayed care [13].

In gynecology, we described a higher rate of molar pregnancy in the pandemic due to delays in diagnosis [8]. The present report corroborates reports of a higher rate of symptomatic presentation of EP and more surgical interventions for EP [9,24]. A possible explanation for this trend is delays in seeking timely medical care due to the pandemic and to fears of exposure to the virus.

This study's novelty is that women with EP during the pandemic were more likely to undergo urgent laparoscopy and to present at advanced gestational age at the first medical encounter. Notably, the median gestational age at presentation was only three days greater during the pandemic period. Nonetheless, this delay in presentation likely explains the higher rates of symptomatic patients and urgent surgery, and the greater blood loss in the pandemic compared to the earlier period. This is because even a slight delay in presentation can affect morbidity and management of EP.

We presume that the diagnostic delay did not result from government prohibitions, as the staffing of pregnancy clinics did not change during the pandemic. We suspect that the delay in presentation is related to the reluctance to seek medical care due to fear of exposure to COVID-19. Surprisingly, the concern continued in the post-vaccination period. This is evident from the lack of differences in presentation, and rates of urgent surgery, and morbidity between the pre-and post-vaccination periods. Further, no differences were observed in the presentation week, symptoms, or beta-HCG levels between women who underwent urgent surgery in the pandemic and the earlier period.

A higher proportion of women in the pandemic compared to the earlier period had post-surgical anemia, this finding supports the appropriateness of more frequent decisions to perform urgent surgery for EP treatment during the pandemic, and suggests that these decisions did not stem from collateral effects of the pandemic. The likelihood of conservative or medical treatment of EP decreases with increased gestational week and symptoms.

Table 3
Characteristics of women who underwent urgent laparoscopy for ectopic pregnancy (EP) in the pandemic (March 2020 to August 2021) and in an earlier period (March 2018 to August 2019).

	Pandemic period *N* = 42	Earlier period *N* = 23	P- value
Ruptured EP in urgent surgery (%)	20 (48%)	15 (65%)	0.173[a]
Presence of intrabdominal bleeding in urgent surgery (%)	30 (71%)	20 (87%)	0.155[a]
Intrabdominal bleeding>1000 ml (%)	4 (10%)	6 (26%)	0.076[b]
Intrabdominal bleeding in urgent surgery (ml). (median, range)	200 (30–2800)	400 (0–3000)	0.268[b]
Hemoglobin: Hb after urgent surgery (median, range)	10.5 (6.8–13.2)	10.85 (6–12.8)	0.568[b]
Anemia at discharge (Hb<9 gr\dL) (%)	9 (21%)	4 (17%)	0.697[a]
Delta Hb>2 gr/dL urgent surgery (%)	25 (60%)	7 (30%)	**0.024**[a]
Blood products transfusion (%)	3 (7%)	6 (26%)	**0.086**[a]
Post- surgery Hospitalization (days)(median, range)	1.54 (1–5)	2 (1–5)	**0.036**[b]

EP- ectopic pregnancy, HB- hemoglobin.
[a] Chi-square Exact test.
[b] Wilcoxon Rank-Sum test.

Table 4
Presentation and outcomes of ectopic pregnancy in the pre- and post- vaccination periods of the pandemic.

	Pre-vaccination *N* = 48	Post-vaccination *N* = 49	P- value
Presenting week (mean ± SD)	6.46±1.14	6.03±1.23	0.081[c]
Presenting symptom:			
Abdominal pain (%)	24 (50)	18 (36)	0.221[a]
Vaginal bleeding (%)	12 (25)	11 (22)	0.819[a] 0.211[a]
Asymptomatic (%)	14 (29)	21 (42)	
Laboratory at presentation:			
Hemoglobin (g\dL) (mean ± SD)	11.98±1.29	12.27±1.2	0.265[c] 0.833[b]
Beta-HCG (IU/L) (median, range)	1421.5 (14–47,785)	1398 (51–70,628)	
Sonographic:			
EP size (cm) (median,range)	2 (0.8–6.4)	2 (0.9–5)	0.709[b]
Embryonic cardiac motion (%)	8 (17)	6 (12)	0.573[a]
Urgent laparoscopy:			
Urgent laparoscopy (%)	22 (46)	23 (46)	1[a]
Ruptured EP (%)	9 (41)	11 (48)	0.767[a]
Intrabdominal bleeding>1000 ml (%)	1 (5)	3 (13)	0.316[b]
Intrabdominal bleeding in urgent surgery (ml) (median, range)	200 (50–1000)	400 (30–2800)	0.675[b]

EP- ectopic pregnancy, SD- standard deviation.
[a] Chi-square Exact test.
[b] Wilcoxon Rank-Sum test
[c] Independent samples t-test.

To the best of our knowledge, this study comprises one of the largest samples and the greatest time spans of the pandemic, of explorations of the collateral effect of this period on the presentation, severity and treatment of EP. An indirect negative effect of the pandemic throughout the entire period was demonstrated regardless of the lockdowns and the vaccine introduction. Notably, the earlier period comprised the same months as the pandemic period, during two previous consecutive years. This avoided changes in the rate of EP due to seasonal or holiday effects.

Certain limitations of our study should be acknowledged, foremost is its retrospective design. Moreover, since our medical center is a regional referral center, the patient population may not represent the entire population. This raises the possibility of referral bias. In addition, the reported rate is an approximation of EP incidence. Nonetheless, the ideal incidence of EP should be calculated as the proportion of pregnancies and not only deliveries.

We report a higher risk of urgent surgery for women with EP in the pandemic than an earlier period. This trend can be explained by the delay in presentation and diagnosis of EP during the Covid-19 pandemic period, even following the introduction of vaccination.

Our data suggest that the delay in diagnosis was caused by women's worry of exposure to the disease at the time of the medical follow-up and not a pandemic collateral effect on the doctor's decision. This concern did not change during the pandemic, subsequent to initiation of vaccination. Accordingly, obstetricians and gynecologists should encourage women to seek early medical evaluation in pregnancy, even during a pandemic, a war or other challenging situations. Evidence shows that social media has become an important vehicle for rapid information dissemination, particularly during the COVID-19 pandemic [25]. We suggest that during a pandemic, this platform can be used to increase public knowledge of EP and early pregnancy complications. Adopting a proactive approach to diagnosing EP early in pregnancy may facilitate anticipating women with symptomatic EP who present later than usual, with a high risk of urgent surgical intervention.

Authors' contributions

Ala-Aiob- Planning, conduct, data analysis, design, manuscript writing and revision.

Raneen Abu shqara - Planning, conduct, data analysis, design and manuscript writing and revision.

Susana Mustafa Mikhail - Planning, conduct, data analysis and manuscript revision.

Avishalom Sharon- Planning, conduct, manuscript revision

Marwan Odeh- Planning, conduct, manuscript revision.

Lior Lowenstein- Planning, conduct, data analysis, design and manuscript revision.

All the authors interpreted the data, reviewed drafts and approved the final draft of the manuscript.

Details of ethics approval

This study was approved by the Institutional Review Board (Helsinki Committee) of Galilee Medical Center and the Israeli Ministry of Health before data collection (authorization number 0138–21-NHR, August 2021).

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Declaration of Competing Interest

The authors have no conflicts of interest related to this work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jogoh.2022.102508.

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