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Factors associated with female infertility in Ukraine: results a multicenter study

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ABSTRACT

Aim: To determine the current prevalence of female infertility and characterize and identify risk factors associated with infertility in Ukraine.

Materials and Methods: Multicenter prospective cohort study was conducted from January 2021 to December 2023 in twelve medical centers from nine regions of Ukraine. Definitions of infertility were adapted from the World Health Organization. According to the data collected from questionnaire, participants were divided into infertile and fertile groups and analyzed associated factors.

Results: Among all the 7,618 participants in this study, the prevalence of female infertility was 24.3%. The prevalence of primary infertility was 5.9%, and the prevalence of secondary infertility was 18.4%. In logistic multivariate regression analyses, female infertility was associated with age of women (p<0.001), age of first sexual intercourse (p<0.001), history of gynecological surgery (p<0.001), marital status (p<0.001), age of marriage (p<0.001), decreased ovarian reserve (DOR) (p=0.006), family history of infertility (p<0.001), history of cervicitis (p=0.007), history of surgical abortion (p<0.001), history of endometritis (p=0.027), bacterial vaginosis (p=0.023), and aerobic vaginitis (< 0.001).

Conclusions: Our data suggest a high prevalence of female infertility in Ukraine. The prevalence of secondary infertility was higher than primary infertility. Age of women, age of first sexual intercourse, history of gynecological surgery, marital status, age of marriage, DOR, family history of infertility, history of cervicitis, history of surgical abortion, history of endometritis, bacterial vaginosis, and aerobic vaginitis were associated with infertility.

KEY WORDS: Epidemiology, Infertility, Reproduction, Prevalence, Risk factors, Ukraine

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INTRODUCTION

The infertility of the population worldwide is an important public health issue. Every human and couples have the right to decide the number, timing and spacing of their children. Infertility can negate the realization of these essential human rights. Addressing infertility is therefore an important part of realizing the right of individuals and couples to found a family [1].

The World Health Organization (WHO) has identified infertility as a global public health problem. Infertility affects millions of people – and has an impact on their families and communities. 2022 global infertility prevalence estimates are: Estimates suggest that approximately one in every six people of reproductive age worldwide experience infertility in their lifetime. This is regardless of where they live and what resources they have. Estimates of infertility prevalence are similar across countries with different income levels. Lifetime infertility prevalence was 17.8% for high-income countries and 16.5% for low- and middle-income countries. Period infertility prevalence was 12.6% for high-income countries and 12.6% for low- and middle-income countries. The available data indicate that estimated lifetime prevalence of infertility is highest in the WHO Western Pacific Region (23.2%) and lowest in the WHO Eastern Mediterranean Region (10.7%). The prevalence of infertility in WHO European Region were reported to 16.5% [2]. In Ukraine the prevalence of infertility was 25.4% [3].

Infertility may be caused by a number of different factors, in either the male or female reproductive systems. In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others [3-8]. The relative importance of these causes of female infertility may differ from country to country [9]. However, it is sometimes not possible to explain the causes of infertility. Understanding the magnitude of infertility is critical for developing appropriate interventions, for monitoring access to quality fertility care, and for mitigating risk factors for and consequences of infertility.

In Ukraine female infertility remains one of the mysteries in the reproductive health field, where the diagnostic evidence is still weak and the proposed treatments still work with unknown methods. However, several studies have proposed some possible causes and risk factors for female infertility [3, 5-8]. The high prevalence of infertility worldwide, especially in limited-resource countries like Ukraine, implies that the current assessment of the women reproductive system is far from perfect. Nevertheless, significant improvements in diagnostic tools and assisted reproductive technologies have led to the finding of many causes of infertility that in the past had only been suspected, but, up until now, some causes of female infertility are still unknown. Therefore, there is a need to search for more answers to the causes of female infertility to create better treatment options for patients. Currently, in Ukraine the risk factors of female infertility, have not been adequately studied.

AIM

The aim this study to determine the current prevalence of female infertility and characterize and identify risk factors associated with infertility in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTING AND POPULATION

We performed a multicentre, prospective cohort study. The study was carried out during the period from January 2021 to December 2023. Twelve medical centers (Maternity Hospital, Reproductive Clinic, and Fertility Center) from nine regions (Lviv, Vinnytsia, Cherkasy, Zhytomyr, Kyiv, Kharkiv, Kherson, Dnipropetrovsk, and Odessa) of Ukraine were all used to collect study samples. Those centers were purposefully selected because they are the largest centers providing assisted conception and modern antenatal care in Ukraine. In this study cities located respectively in the west and east, and north and south, as well as the in central region of Ukraine were used as objects of comparison, since they often resemble opposing views on social and demographic processes. The current study targeted 7,618 Ukrainian women between the ages of 19 and 50. The case group included 1,850 women with infertility. The women were chosen using a systematic random sampling technique from patients who had tried but were unable to conceive for at least a year (maintain regular unprotected vaginal sexual intercourse with their partner at least twice a week for a year) [10]. The control group consisted of 5,768 fertile, nonpregnant women who had at least one healthy 2-year-old child (end of lactation). In this study to exclusion criteria for participants were as follows: never had sexual intercourse; received continuous medical treatment that could affect fertility. In addition to that, women were also excluded if they were under the effect of anti-inflammatory medicines or if they were under the effect of hormonal contraception within the last 6 mo. Any women who refused to sign the informed consent form or withdrew during the study were excluded.

DEFINITION

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved [2]. Infertility among women was classified as primary and secondary. In our study primary infertility is defined as a woman who has never been diagnosed with a clinical pregnancy and meets the criteria of being classified as being infertile, while secondary infertility is defined as a woman unable to establish a clinical pregnancy who has previously been diagnosed with a clinical pregnancy [11]. Body Mass Index (BMI) is defined as an estimation of human body fat based on height and weight. BMI is expressed in kg/m², resulting from dividing body mass in kilograms by height in meters. Thin' means that BMI is less than 18.5 kg/m². 'Normal' means 18.5 kg/m²≤ BMI < 24 kg/m². 'Overweight' means 24 kg/m² ≤ BMI < 28 kg/m². 'Obesity' means that BMI is more than 28 kg/ m² [3]. The waist-to-hip ratio (WHR) was defined as an estimation of fat stored around the waist and hips. The waist-hip ratio was calculated by dividing the waist measurement by the hip measurement.

DATA COLLECTION

Our study includes interviews and questionnaires of women, also analyses medical records infertile women's. To assess female infertility risk factors, a structured pre-tested questionnaire containing information on socio-demographic variables, anthropometrics, clinical diagnosis of infertility, behavioral factors, physical activity assessment, dietary diversity, and consumption of different food groups by study participants was used. The questionnaire was prepared by reviewing several relevant published articles [3-8, 12-15] and adopting standardized data collection tools. After passing all quality check-ups, the questionnaire was filled out with the help of 9 research assistants who are experts in reproductive health (one in each previously mentioned healthcare facility). In this study the completeness of the data was checked each day at the end of data collection. Incomplete data was traced back and edited accordingly. The follow-up of study participants was done by tracking information (address, phone number of the participant as well as of relatives and close friends) and making periodic contact to minimize loss of follow-up, and the overall follow-up and data collection processes were coordinated and supervised by the research assistants' and principal investigators.

ETHICS

This study was carried out after obtaining the approval from the Ethics Committee of Shupyk National Healthcare University of Ukraine. Informed consent was obtained from all the study participants, and all necessary information regarding the study (objectives, requirements of the participants, and duration of the study) was given to the prospective study participants on an information sheet to ensure an informed decision to participate in the study.

STATISTICAL ANALYSIS

Data collected from this study were sorted and recorded in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) for analysis. To characterize the study population, descriptive statistics, frequencies, and percentages for categorical data and summary statistics (mean standard deviation (SD) with a 95% confidence interval (CI) for continuous data normally distributed and median and interquartile range for continuous data not normally distributed) were used. In addition, tables were used for data presentation. The association between the categorical variables in the study population was checked using the chi-square test at the statistically significant level of P = 0.05. A binary logistic regression analysis (bi-variable and multivariable) was carried out to identify the independent predictors of unexplained infertility. All independent variables with a P value of less than 0.05 in the bivariable logistic regression model were considered candidate variables for the multivariable model. Finally, the relationship was presented using a crude odds ratio and an adjusted odds ratio (AOR) with their corresponding 95% confidence intervals, and a P value of 0.05 or less was considered to be statistically significant.

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS

In during study period (2021-2023), we sampled 7,618 women who were 19–50 years old in nine hospitals of eight regions, Ukraine. Of all participants infertile was 1,850 and the fertile was 5,768. The mean \pm SD age was 31.8 \pm 0.3 years for the fertile group and 33.7 \pm 0.4 years for the control (infertile) group. The difference in mean age between these two groups was statistically significant (p<0.001). Socio-demographic characteristics of study participants, and history and clinical characteristics of study participants are presented in Table 1 and Table 2, respectively.

As shown in Table 1 and Table 2, the difference in the region, residence, age, age of marriage, marital status, history of gynecological surgery, previous miscarriage or abortion, family history of infertility, ovarian dysfunction (Decreased Ovarian Reserve), history of cervicitis, aerobic vaginitis, bacterial vaginosis, and history of endometritis between the two groups were statistically significant (p<0.05).

PREVALENCE OF INFERTILITY

The prevalence of female infertility in this study cohort was 24.3% [95% confidence interval (Cl) 23.8-24.8]. The prevalence of primary infertility and secondary infertility was about 5.9% (95% Cl 5.6-6.2) and 18.4% (95% Cl 18.0-18.8), respectively. Among the infertile women, the difference between primary and secondary infertility was statistically significant (p < 0.05) by factors associated with female infertility. Comparison of characteristics of primary and secondary infertile in study participants are presented in Table 3.

FACTORS ASSOCIATED WITH FEMALE INFERTILITY

To identify the infertility predictor factors among Ukrainian women, a logistic multivariate regression

Table 1	Characterization of selected anthropometry and socio-demographic variables of st	tudy partic	ipa	nts
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	Infertile cases (n=1,850)		Control (fertile)		-
Characteristic			(n=5,		p value
	n	%	n	%	
Region	(10	22.0	1.240	21.5	0.012
North	610	33.0	1,240	21.5	0.013
South	433	23.4	1,443	25.0	
East	454	24.5	1,608	27.9	
West	353	19.1	1,477	25.6	
Residence					
Rural	396	21.4	1,234	11.1	0.005
Urban	1,454	78.6	616	88.9	
Age (years)					
19-21	20	1.1	58	5.7	<0.001
22–26	217	11.7	675	27.4	
27–31	738	39.9	2,302	32.4	
32–36	531	28.7	1,655	16.5	
37–41	237	12.8	738	12.3	
46–50	107	5.9	340	5.7	
Education status					
Primary	242	13.0	750	17.6	0.396
Secondary	275	15.8	911	13.3	
Junior college degree	418	22.5	1,298	20.2	
Bachelor's degree and above	915	48.7	2,809	48.9	
Occupation					
Unemployed	296	16.0	921	12.8	0.541
Governmental	285	15.4	889	13.7	
Housewife	590	31.9	1,840	39.2	
Clerk	50	2.7	156	4.2	
Private business	256	13.8	796	13.7	
Agricultural and related worker	69	3.7	214	2.3	
Student	10	0.5	29	0.7	
Other	294	16.0	923	13.5	
Marital status					
Married	1,833	99.1	5,716	89.5	0.006
Divorced	17	0.9	52	6.8	
Widow	0	0	0	3.7	
BMI (kg/m²)					
Underweight	158	8.5	493	6.8	0.486
Normal weight	1,082	58.5	3,377	64.6	
Overweight	472	25.5	1,470	21.7	
Obesity	138	7.4	428	6.9	
WHR					
Less than 0.75	407	22.0	1,271	28.0	0.08
075-0.84	467	25.2	1,454	18.4	
0.85-0.90	396	21.4	1,234	21.6	
Greater than 90	580	31.4	1,809	31.6	
Smoking					
No	20	1.1	81	1,4	0.592
No, secondhand smoke	383	20.7	1,390	24,1	
Yes	1,447	78.2	4,297	74,5	
Drinking					
No	148	8.0	162	12,8	0.072
Yes	1,702	92.0	5,606	97,2	

Table 2. History and clinical characteristics of study participants in Ukraine, 2021-2023

Characteristic	Infertile (n=1,		Control (n=5,		p valu
	n	%	n	%	-
Irregular menstruation					
No	1,201	64.9	4,027	69.8	0.204
Yes	649	35.1	1,741	30.2	
Dysmenorrhea					
No	1,013	54.8	3,301	57.2	0.563
Yes	837	45.2	2,466	42.8	
Age of marriage (yrs.)					
≤24	768	41.5	3,031	52.5	0.042
25–29	964	52.1	2,549	44.2	
≥30	118	6.4	193	3.3	
Age of first sexual intercourse (yrs.)					
<20	177	9.6	776	13.5	0.197
20–25	1,209	65.4	3,821	66.2	
>25	463	25.0	1,173	20.3	
History of gynecological surgery					
No	1,467	79.3	5,373	93.2	< 0.00
Yes	383	20.7	394	6.8	
Previous miscarriage or abortion	505	20.7	554	0.0	
No	1,745	94.3	5,007	86.8	0.021
Yes	106	5.7	764	13.2	0.021
Family history of infertility	100	5.7	704	15.2	
No	1,330	71.9	5,402	93.7	0.001
Yes			366		0.001
Decreased ovarian reserve	520	28.1	500	6.3	
	1 (1 4	07.2	F (04	07.2	(0.00)
No	1,614	87.2	5,604	97.2	<0.00
Yes	236	12.8	164	2.8	
History of colpitis	1.260	72.0			
No	1,368	73.9	4,039	70.0	0.304
Yes	482	26.1	1,733	30.0	
History of cervicitis					
No	1,761	95.2	5,647	97.9	0.048
Yes	88	4.8	88	2.1	
History of uterine fibroids					
No	1,761	95.2	1,761	97.7	0.071
Yes	88	4.8	134	2.3	
History of medical abortion					
No	1,584	85.6	4,688	81.3	0.172
Yes	266	14.4	1,076	18.7	
History of surgical abortion	0				
No	1,475	79.7	5,388	93.4	< 0.00
Yes	375	20.3	381	6.6	
History of spontaneous abortion					
No	1,614	87.2	5,263	91.2	0.116
Yes	236	12.8	505	8.8	
History of endometritis					
No	1,451	78.4	5,379	93.3	< 0.001
Yes	399	21.6	385	6.7	
Bacterial vaginosis		-			
No	1,611	87.1	5,601	97.1	< 0.00
Yes	239	12.9	167	2.9	
Aerobic vaginitis		/			
No	1,744	94.2	5,004	86.5	0.032
	1,744	2 4. Z	767	00.5	0.032

Table 3. Logistic multivariate regression analyses of the factors associated with female infertility in the study participants, Ukraine, 2021-2023

p-value Unadjusted OR (95% Cl)		p-value	Adjusted OR (95% CI)
<0.001		<0.001	
	Ref		Ref
0.276	2.297(0.515–10.249)	0.587	1.523 (0.334–6.942
0.011	6.618(1.549–28.274)	0.031	5.038 (1.163–21.830)
0.003	9.379 (2.165–40.622)	0.011	6.862 (1.557–30.248)
0.025	5.577 (1.244–25.007)	0.109	3.49 (0.758–16.070)
0.035	5.500 (1.131–26.756)	0.174	3.096 (0.607–15.798)
< 0.001		0.003	
	Ref		Ref
0.867	1.098 (0.371–3.248)	0.648	1.302 (0.42–4.035)
0.018	3.752 (1.257–11.201)	0.017	4.696 (1.326–16.635)
	Ref		Ref
< 0.001	3.611 (2.235–5.832)	< 0.001	3.063 (1.819–5.159)
0.006		0.003	
	Ref		Ref
0.003	0.563 (0.386–0.822)	0.002	0.517 (0.342–0.781)
0.017		0.008	0.494 (0.294–0.830)
< 0.001		0.006	
	Ref		Ref
0.024	2.102 (1.103-4.005)	0.373	1.434 (0.649–3.168)
< 0.001		0.002	6.258 (1.962–19.956)
	Ref		Ref
0.006		0.005	3.987 (1.52–10.456)
	Ref		Ref
< 0.001		< 0.001	2.695 (1.548-4.695)
	Ref		Ref
0.007		< 0.001	0.289 (0.152–0.547)
	Ref		Ref
< 0.001		0.002	3.145 (1.532–6.455)
	Ref		Ref
0 027		0.002	3.145 (1.532–6.455)
5.027	0.007 (0.120 0.750)	0.002	515 (1.552 0. . 55)
	Rof	· · · · · · · · · · · · · · · · · · ·	Ref
0 0 2 3		0.043	0.650 (0.428–0.987)
0.020	0.037 (0.720-0.230	CTU.U	0.030 (0.720-0.907)
	Ref		Ref
	<0.001 0.276 0.011 0.003 0.025 0.035 < 0.001 0.867 0.018 	(95% CI) <0.001	p-value (95% CI) p-value <0.001

Table 4. Comparison of characteristics of primary and secondary infertile in Ukrainian women, 2021-2023

Characteristics	Primary infertility (n=450)		infer	Secondary infertility (n=1,400)	
	n	%	n	%	-
Age (years)					
19-21	18	4.0	0	0.0	<0.001
22–26	144	32.0	62	4.4	
27–31	189	42.0	548	39.1	
32–36	81	18.0	457	32.6	
37–41	18	4.0	222	15.9	
46–50	0	0.0	112	8.0	
Age of marriage (years)					
≤24	135	30.0	640	45.7	0.012
25–29	252	56.0	710	50.7	
≥30	63	14.0	51	3.6	
Age of first sexual intercourse (years)					
<20	36	8.0	141	10.1	<0.001
20–25	207	46.0	1,015	72.5	
>25	207	46.0	243	17.4	
History of gynecological surgery					
No	357	79.3	1,305	93.2	<0.001
Yes	93	20.7	95	6.8	
Previous miscarriage or abortion					
No	424	94.3	1,215	86.8	0.021
Yes	26	5.7	185	13.2	
Family history of infertility					
No	323	71.9	1,312	93.7	0.001
Yes	127	28.1	88	6.3	
Decreased ovarian reserve					
No	392	87.2	1,361	97.2	<0.001
Yes	58	12.8	39	2.8	
History of cervicitis					
No	423	94.0	263	18.8	0.028
Yes	27	6.0	1,137	81.2	
History of surgical abortion					
No	358	79.7	1,307	93.4	<0.001
Yes	92	20.3	93	6.6	
History of endometritis					
No	353	78.4	1,306	93.3	<0.001
Yes	97	21.6	94	6.7	
Bacterial vaginosis					
No	392	87.1	1,360	97.1	<0.001
Yes	58	12.9	40	2.9	
Aerobic vaginitis			_		
No	424	94.2	1,211	86.5	0.032
Yes	27	5.8	189	13.5	

analyses was used. Table 3 showed the odds ratio (OR) and 95% confidence interval (CI) for the factors associated with infertility in logistic multivariate regression analyses. The results found that the female infertility was associated with age of participants (p<0.001), age of first sexual intercourse (p<0.001), history of gynecological surgery (p<0.001), marital status (p<0.001), age of marriage (p<0.001), decreased ovarian reserve (DOR) (p=0.006), family history of infertility (p<0.001), history of cervicitis (p=0.007), history of surgical abortion (p<0.001), history of endometritis (p=0.027), bacterial vaginosis (p=0.023), and aerobic vaginitis (< 0.001) as shown in logistic regression analysis (Table 3).

Furter, our results found that there were differences among factors associated with female infertility, primary infertility and secondary infertility. Comparison of characteristics of factors associated with primary and secondary infertile in Ukrainian women showed in Table 4.

DISCUSSION

Reports about the prevalence of infertility are rare currently in Ukraine. This study is the first to investigate prevalence and characteristics of risk factors for infertility among 19–50 year old women in Ukraine. This study expands upon the previous reports focused to the prevalence and factors associated with female infertility in Ukraine [3].

High prevalence of female infertility remains one of the mysteries in the reproductive health field, where the diagnostic evidence is still weak and the proposed treatments still work with unknown methods. Infertility rates vary from country to country, and change all the times. According to the literature, infertility rates were highest in Africa and Central/Eastern Europe. Additionally, according to a variety of sources, rates of male infertility in North America, Australia, and Central and Eastern Europe varied from 45-6%, 9%, and 8-12%, respectively [16]. In the United States, the infertility prevalence rate of women in 2002 was 15.5% [17], in Canada ranged from 11.5% to 15.7% in 2009 [18], in Britain, during 2010–2012 was 12.5% [19], and 24.6% in 2019 in China 24,6% [20]. While in Turkey, the infertility rate decreased from 12.0% to 8.6% in 1993-2003 [21].

Ukraine is European country with large population. The infertility rates will be different in different regions of Ukraine. We performed a multicentre, prospective cohort study. In this study, nine family planning and reproductive health centers from different regions of Ukraine were all used to collect study samples. A self-reported questionnaire was used, which was been found to be a useful measure for quantifying fertility problems experienced in the community. In this study also investigated the clinical histories of the study participants. We designed a series of questions to determine infertility and specifically to minimize recall bias. The crude prevalence of infertility in this study cohort was 24.3%, which was close to the infertility rate of 25.4% among women attempting to become pregnant during 2019-2021 in Ukraine [3] and 24.6% among women in 2019 in China [20].

The occurrence of female infertility is related to various factors. In our study, multivariable logistic regression analyses showed that age of participants, age of first sexual intercourse, history of gynecological surgery, marital status, age of marriage, DOR, family history of infertility, history of cervicitis, history of surgical abortion, history of endometritis, bacterial vaginosis, and aerobic vaginitis were associated with infertility. In addition, our results showed that there are differences between factors associated with female infertility, primary infertility, and secondary infertility. It is universally acknowledged that fertility declines as age grows, and research reported that fertility starts declining approximately at age 32 years and rapidly declines after age 37 years. In this study, age has correlation with infertility obviously. One possible reason why the prevalence of infertility did not increase with age was that the desire of pregnancy decreased and the rate of protected sexual intercourse was high in women aged 40-49 years, so some potential infertile women aged 40-49 years were ignored according to our decision process. It could be explained that young infertile women were more likely to develop primary infertility than secondary infertility possibly. Further, age of marriage and age of first sexual intercourse might have a more important effect than age on primary infertility.

In our study the diagnosis of DOR was based on information from questionnaires filled out by participants of this study. Though recall bias did exist, DOR was still one of risk factors of infertility, primary infertility and secondary infertility according to our results. DOR means that response of child-bearing women to ovarian stimulation or fecundity is reduced when compared with women of same age [22].

History of gynecological surgery was another associated factor for female infertility, especially for secondary infertility. One research reported that surgery might reduce ovarian reserve [23]. Another research reported that myomectomy, as well as the coexistence of post-operation pelvic infection reduced the chance of conception among women [5, 8].

Our study found a significant association between the family history of infertility and unexplained infertility. Similar results to the findings of this study describing the association between family history of infertility and female infertility were reported in Netherlands [24]. This may indicate that there may be some genetic factors for unexplained female infertility, but due to the complexity of the reproduction process in females, this possible gene(s) is still unknown. Nevertheless, many studies found that most infertility causes and conditions, such as poor egg quality or low egg reserves and blocked or damaged fallopian tubes, can't be inherited and can happen to anyone, regardless of family history [25, 26].

CONCLUSIONS

Our data suggest a high prevalence of female infertility in Ukraine. The prevalence of secondary infertility was higher than primary infertility. Age of women, age of first sexual intercourse, history of gynecological surgery, marital status, age of marriage, DOR, family history of infertility, history of cervicitis, history of surgical abortion, history of endometritis, bacterial vaginosis, and aerobic vaginitis were associated with infertility. Understanding the magnitude of infertility is critical for developing appropriate interventions, for monitoring access to quality female fertility care, and for mitigating risk factors for and consequences of female infertility.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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