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► **To cite this version:**

Lucie Rolland, Aurelie Amar-Hoffet, Vanessa Lubin, Lise Préaubert, Laura Miquel, et al.. Unexplained infertility: A French national survey of clinical practices. *Journal of Gynecology Obstetrics and Human Reproduction*, 2022, 51 (3), pp.102301. 10.1016/j.jogoh.2021.102301 . hal-03924595

HAL Id: hal-03924595

<https://hal.science/hal-03924595>

Submitted on 5 Jan 2023

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Unexplained infertility: A French national survey of clinical practices

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A B S T R A C T

Introduction: The aim of our study was to carry out a national survey of French practitioners to evaluate (i) their diagnostic criteria for making a diagnosis of unexplained infertility (UEI) and (ii) their management strategy when facing UEI.

Materials and Method: An online questionnaire comprising ten multiple-choice questions was sent by mail to French reproductive practitioners in 80 fertility centres.

Results: The response rate was 59.6% (195/327). Post coital testing was always or often prescribed by 14.8% of respondents ($n = 36$). Chlamydia trachomatis testing was never prescribed by 31.7% ($n = 59$) of them, 30.2% prescribed a pelvic MRI in cases of UEI and 18.4% ($n = 33$) always or often performed laparoscopy. For 87.6% ($n = 169$), advanced maternal age was always or often an indication for first-line IVF, with an average threshold of 37.4 years. For 68.6% ($n = 129$), diminished AMH was an indication for first-line IVF, with an average AMH threshold of 1.2 ng/ml. With respect to the management of UEI, we did not observe a consensus between the strategies of 2 to 6 intrauterine insemination cycles before IVF or IVF as the first-line treatment.

Conclusion: There is no consensus in France on what tests should or should not be carried out to conclude UEI, and there is also no consensus on the management of UEI. UEI is one of the top 10 priorities for future infertility research. The diagnostic criteria must be standardized to enable the comparison of studies on this topic as well as to improve the translation of research into clinical practice.

Keywords:

Unexplained infertility
Management
Diagnosis
Clinical practices

Introduction

Unexplained infertility (UEI) is a diagnosis made by “exclusion” for couples who have not conceived and for whom standard investigations have not detected any male or female disease of the reproductive system. According to literature data, UEI affects approximately 15–50% of couples consulting for infertility [1,2]. Based on the latest guidelines in the UK, Canada, USA and Cochrane [1–4], there is not a consensus in the literature regarding the methods for diagnosing UEI. For most authors, the definition of UEI is based only on the presence of normal ovulatory function, a normal semen analysis and at least one patent fallopian tube. Many factors are not taken into consideration for the definition of UEI, such as advanced maternal age (AMA), diminished ovarian reserve (DOR), body mass index, environmental exposure, tobacco, alcohol, or drug use, and sexual dysfunction. The management of couples consulting for UEI also varies from country to country. There is no consensus in France on what tests should or should not be carried out to conclude a diagnosis of UEI nor on the management of UEI. Indeed, there is a lack of clinical

evidence to affirm the best management strategy between expectant attitude, IUI, and IVF +/- ICSI. Recently, UEI has been identified as one of the top 10 priorities for future infertility research [5]. The diagnostic criteria must be standardized to enable a comparison of studies on this topic and to improve the translation of research into clinical practice.

The aim of our study was to carry out a national survey of French practitioners to evaluate (i) their diagnostic criteria for making a diagnosis of UEI and (ii) their management strategy for cases with a UEI diagnosis.

Materials and method

Population

We conducted a national survey via an online questionnaire among all practitioners certified in reproductive medicine who work in connection with assisted reproductive technology (ART) centres. For inclusion in the survey, practitioners must prescribe infertility tests in daily practice and perform at least intrauterine inseminations.

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Table 1

What tests do you prescribe before concluding - in case of normality - a diagnosis of unexplained infertility?

	Yes, always	Yes often	Yes rarely	No never	n
AMH	87.6% (n = 169)	8.3% (n = 16)	3.1% (n = 6)	1% (n = 2)	193
Hysterosalpingography	92.8% (n = 181)	5.1% (n = 10)	2.1% (n = 4)	0% (n = 0)	195
Spermogram	100% (n = 193)	0% (n = 0)	0% (n = 0)	0% (n = 0)	193
Total mobil sperm count	78.1% (n = 146)	18.7% (n = 35)	1.6% (n = 3)	1.6% (n = 3)	187
Ultrasound of antral follicles	95.9% (n = 187)	2.6% (n = 5)	1% (n = 2)	0.5% (n = 1)	195
Chlamydia trachomatis Serology	8% (n = 14)	6.8% (n = 12)	11.4% (n = 20)	73.9% (n = 130)	176
Post-coital testing	52.7% (n = 98)	15.6% (n = 29)	14.5% (n = 27)	17.2% (n = 32)	186
Pelvic MRI	3.9% (n = 7)	26.3% (n = 47)	53.6% (n = 96)	16.2% (n = 29)	179
Laparoscopy	1.1% (n = 2)	17.3% (n = 31)	49.7% (n = 89)	31.8% (n = 57)	179
Sperm DNA Fragmentation Test	2.2% (n = 4)	5% (n = 9)	27.9% (n = 50)	64.8% (n = 116)	179

Online survey

The questionnaire was designed using an online survey software tool, Survey Monkey® (San Mateo, California, USA). All French clinics licenced by national authorities to perform assisted reproductive technologies (ARTs) were contacted via the head of their department. A link to the survey was emailed with an explanatory cover letter. The survey began in December 2020, with an email reminder sent out a week later. The last of the completed surveys was received in June 2021. The questionnaire comprised ten short multiple-choice questions with a section for additional comments (Annex 1). The total time to complete the survey was between 8 and 10 min. Before being sent to participants, the questionnaire was tested and revised by five fertility consultants. The questionnaire focused on the definition, investigation and medical management of UEI. To obtain a response rate, we asked each department head to whom a questionnaire was sent the number of physicians to whom he transmitted the questionnaire. The data were analysed using Excel software® (Microsoft). Only descriptive statistics were calculated. Continuous variables were summarized using the following statistics: n (sample size), mean and percentage.

Ethical considerations

Ethical consent was not required for this survey as the findings were kept anonymous, and there was a link to opt out of the survey.

Results

Of the 104 ART centres identified, 80 centres were contacted by e-mail to obtain the email of the head of the department, and 24 centres were contacted by email or phone without response. Of the 80 centres that responded, 49 agreed to participate in the survey. The questionnaire was sent to 327 French practitioners, with a response rate of 59.6% (n = 195). Among the respondents, 18% (n = 35) were

male; 82% (n = 160) were female. Question 2 explored the medical specialization of physicians. 57.4% (n = 112) of practitioners were obstetrician-gynecologist, 33.3% (n = 65) were medical gynecologist, 8.2% (n = 16) were endocrinologist and 1% (n = 2) were biologist. A total of 27.7% (n = 54) of participants were working in a private ART center, 54.4% (n = 106) were working in a university teaching hospital, 8.2% (n = 16) were working in a non-university public hospital and 9.7% (n = 19) had a mixed public and private activity. The average time of practice was 12.6 years, with a median of 10 years (min: 0.5 years, max: 45 years). Responses to questions 5, 6, 7, 8, and 9 are summarized in Tables 1, 2, 3, 4, and 5, respectively. Responses to question 10 are summarized in Table 6.

Which tests must be performed before concluding UEI?

The tests that are most prescribed by the responding practitioners before the diagnosis of UEI are AMH (87.6%, n = 169), ultrasound of antral follicles (95.9%, n = 187), hysterosalpingography (92.8%, n = 181) and spermogram (100%, n = 195) with total mobile sperm count (78.1%, n = 146) (Table 1). Post coital testing is always or often prescribed by 14.8% (n = 26) of practitioners. Among respondents, 31.7% (n = 59) never prescribe chlamydia trachomatis testing, while hysterosalpingography is prescribed by 92.8% (n = 181). In our study, 30.2% (n = 59) of the practitioners prescribe an MRI in cases of UEI, and 18.4% (n = 33) of respondents always or often perform laparoscopy in cases of UEI.

Do environmental exposure factors rule out a UEI diagnosis?

In our study, 34.9% (n = 68) of respondents always or often exclude the diagnosis of UEI for women with a BMI > 30, and 57% (n = 110) discard the diagnosis of UEI for BMI > 35. A total of 43.1% (n = 74) of respondents always or often dismiss the diagnosis of UEI if women smoke more than 10 cigarettes per day (Table 2).

Table 2

Would any of the following data make you rule out the diagnosis of unexplained infertility?

	Yes, always	Yes often	Yes rarely	No never	Total
AMH < 1 ng/ml (7.1 pmol/l)	49.5% (n = 95)	25% (n = 48)	10.9% (n = 21)	14.6% (n = 26)	192
AMH < 2 ng/ml (14.3 pmol/l)	3.2% (n = 6)	21.1% (n = 38)	26% (n = 48)	49.7% (n = 92)	185
Age of women 36–38 years	1.6% (n = 3)	17% (n = 32)	29.8% (n = 56)	51.6% (n = 97)	188
Age of women 38–40 years	13.5% (n = 26)	38.3% (n = 74)	21.2% (n = 41)	26.9% (n = 52)	193
Age of women 40–42 years	41.5% (n = 81)	31.3% (n = 61)	9.2% (n = 18)	18% (n = 35)	195
BMI > 25 kg/m2	1% (n = 2)	9.8% (n = 19)	19.7% (n = 38)	69.4% (n = 134)	193
BMI > 30 kg/m2	7.7% (n = 15)	27.2% (n = 53)	26.7% (n = 52)	38.5% (n = 75)	195
MBI > 35 kg/m2	20.2% (n = 39)	36.8% (n = 71)	21.8% (n = 42)	21.2% (n = 41)	193
Woman smoking > 10 cig / j	12.3% (n = 24)	30.8% (n = 60)	24.6% (n = 48)	32.3% (n = 63)	195
Woman smoking 5 à 10 cig/j	5.7% (n = 11)	17.1% (n = 33)	26.4% (n = 51)	50.8% (n = 98)	193
Woman smoking < 5 cig/j	2.6% (n = 5)	9.4% (n = 18)	17.7% (n = 34)	70.3% (n = 135)	192
Moderate spermogram abnormalities with normal mobil sperm count	13% (n = 25)	25.9% (n = 50)	34.2% (n = 66)	26.9% (n = 52)	193
Paternal toxic exposure and normal spermogram	4.2% (n = 8)	19.3% (n = 37)	36.5% (n = 70)	40.1% (n = 77)	192

Table 3

Depending on the woman's age, what period of regular sexual intercourse must transpire before actively managing unexplained infertility?.

Age (years)	Time of regular sexual intercourse					Total
	6 months	More than 1 year	More than 2 years	More than 3 years	Immediately upon diagnosis	
18–29	3.6% (n = 7)	78% (n = 152)	16.4% (n = 32)	0% (n = 0)	2.1% (n = 4)	195
30–35	8.7% (n = 17)	79% (n = 154)	9.2% (n = 18)	0% (n = 0)	3.1% (n = 6)	195
36–39	57.4% (n = 112)	32.3% (n = 63)	1.5% (n = 3)	0% (n = 0)	8.7% (n = 17)	195
>40	66.3% (n = 128)	11.9% (n = 23)	0.52% (n = 1)	0% (n = 0)	21.2% (n = 41)	193

Table 4

A couple with a 28-year-old woman has been referred for primary infertility for one year. The initial infertility assessment did not find any abnormalities (regular sexual intercourse, antral follicle count, hormonal assessment, hysterosalpingography, spermogram). What is your first-line medical practice?.

	Yes always	Yes often	Yes rarely	No never	Total
Expectation and targeted sexual intercourse	10.2% (n = 19)	18.82% (n = 35)	29.57% (n = 55)	41.4% (n = 77)	186
Ovarian stimulation	7% (n = 13)	23.8% (n = 44)	20% (n = 37)	49.2% (n = 91)	185
Intrauterine insemination	20.7% (n = 39)	43.1% (n = 81)	17.6% (n = 33)	18.6% (n = 35)	188
In vitro fertilization	2.7% (n = 5)	6.5% (n = 12)	21.5% (n = 40)	69.4% (n = 129)	186
Invitro fertilizaton/ intracytoplasmic sperm injection	0.5% (n = 1)	1.6% (n = 3)	4.9% (n = 9)	92.9% (n = 171)	184

Table 5

A couple with a 39-year-old patient was referred for the first time for primary infertility for one year. The initial infertility assessment did not find any abnormalities (regular sexual intercourse, antral follicle count, hormonal assessment, hysterosalpingography, spermogram). What is your first-line medical practice?.

	Yes always	Yes often	Yes rarely	No never	Total
Expectation and targeted sexual intercourse	1.6% (n = 3)	3.3% (n = 6)	12% (n = 22)	83.1% (n = 152)	152
Ovarian stimulation	2.2% (n = 4)	8.8% (n = 16)	18.7% (n = 34)	70.3% (n = 128)	128
Intrauterine insemination	5.4% (n = 10)	27.2% (n = 50)	30.4% (n = 56)	37% (n = 184)	68
In vitro fertilization	30.4% (n = 58)	48.2% (n = 92)	8.4% (n = 16)	13.1% (n = 191)	25
Invitro fertilizaton/ intracytoplasmic sperm injection	5.5% (n = 10)	16.6% (n = 30)	16% (n = 29)	61.9% (n = 112)	112

Table 6

In your opinion, what are the indications of in vitro fertilization for couples with unexplained infertility?.

	Yes always	Yes often	Yes rarely	No never
After failure of one or more intrauterine insemination	69.1% (n = 134)	26.3% (n = 51)	2.6% (n = 5)	2.1% (n = 4)
In first intention from a certain maternal age	42.5% (n = 82)	45.1% (n = 87)	7.3% (n = 14)	5.2% (n = 10)
In first intention from a certain level of AMH	22.3% (n = 42)	46.3% (n = 87)	17% (n = 32)	14.4% (n = 27)
In first intention from a certain duration of infertility (if regular sexual intercourse)	30.2% (n = 58)	43.8% (n = 84)	13% (n = 25)	13% (n = 25)
In first intention if total mobile sperm is insufficient	65.1% (n = 125)	25% (n = 48)	4.7% (n = 9)	5.2% (n = 10)
In first intention in all cases because unexplained infertility is an indication of in vitro fertilization	5.9% (n = 11)	18.1% (n = 34)	30.9% (n = 58)	45.2% (n = 85)

Should the management of UEI depend on maternal age?

Among respondents, 51.8% (n = 100) always or often exclude the diagnosis of UEI when the woman is over 38 years old (Table 2). At the age of 28 and after one year of UEI, 63.8% (n = 120) of respondents always or often perform IUI (Table 4). When the woman is 39 years old, IVF is always or often prescribed as the first-line treatment by 78.5% (n = 150) of the respondents (Table 5).

For 87.6% (n = 169) of the practitioners, AMA is always or often an indication of first-line IVF, with an average threshold of 37.4 years (median: 38 years, min: 30 years, max: 41 years) (Table 6).

Should the management of UEI depend on AMH?

For respondents, the management strategy also depends on AMH: 74.5% (n = 143) always or often dismiss a UEI diagnosis if AMH < 1 ng/ml (7.1 pmol/L) (Table 2). For 68.6% (n = 129), a diminished or low AMH is an indication for a first-line IVF, with an average AMH threshold of 1.2 ng/ml (8.6 pmol/L) (median: 1 ng/ml (7.1 pmol/L), min: 0.5 ng/ml (3.6 pmol/L), max: 2 ng/ml (14.3 pmol/L)) (Table 6).

UEI: expectant management, IUI or IVF first?

Out of 195 respondents to question 7 concerning the time of regular intercourse, 78% (n = 152) wait for at least one year of regular

intercourse before initiating ART management when women are between 18 and 20 years of age. In contrast, 57.4% (n = 112) do not wait for more than 6 months for women between 36 and 39 years of age; this rate rose to 66.3% (n = 128) for patients over 40 (Table 3).

For 74% (n = 142) of the practitioners, a long time to conceive is always or often an indication for IVF as a first intention, with an average delay of 2.75 years (median: 3 years, min: 1 year, max: 6 years) (Table 6).

Concerning the number of IUIs performed before IVF, 96% (n = 185) of the practitioners responded that the failure of one or more IUIs is an indication for IVF as a second step, and the average number of attempts is 3.65 IUIs (median: 4 IUIs, min: 2 IUIs, max: 6 IUIs) (Table 10). UEI is an indication for first-line IVF for 5.8% (n = 11) of the physicians questioned (Table 6).

Discussion

Need of consensus to define UEI diagnosis

UEI is a diagnosis of exclusion that depends on the investigations undertaken. For WHO, infertility is defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. The diagnostic testing required to meet the definition of UEI that is most commonly described in the literature is based only on the presence of normal ovulatory function, a normal semen

analysis and at least one patent Fallopian tube [1–4,6]. For the American Fertility Society (AFS), UEI could be a diagnosis even in cases of mild endometriosis (AFS criteria I) or early-stage endometriosis [2,4].

Before making a diagnosis of UEI, most French reproductive physicians who participated in this survey perform an evaluation of the ovarian reserve (by AMH and ultrasound of antral follicles), the tubal permeability and the sperm. More than 30% of physicians never prescribe chlamydia trachomatis testing, while hysterosalpingography is prescribed by more than 92% of practitioners. The major sequelae of *C. trachomatis* infection in women are tubal factor infertility and tubal ectopic pregnancy. A Chlamydia antibody test (CAT) could be interesting if anamnesis provides indications for tubal pathology, such as (recurrent) previous infections or lower abdominal surgery [7]. The NICE guidelines recommend screening for Chlamydia trachomatis before undergoing uterine instrumentation. Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out [3]. There is a lack of valid evidence on the attributable risk of post-infective tubal factor infertility after genital chlamydial infection [8,9].

14.8% of French practitioners still prescribe post coital testing of cervical mucus. However, the routine use of post coital testing of cervical mucus in the investigation of fertility problems is no longer recommended in many guidelines because of the low predictive value for the pregnancy rate [3,10].

What pelvic exploration is required before reaching a UEI diagnosis?

In the UK, the Royal College of Gynaecology and Obstetrics recommends that women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) are screened for tubal occlusion using hysterosalpingography (HSG) because it is a reliable test for ruling out tubal occlusion, is less invasive and makes more efficient use of resources than laparoscopy [3]. There are still insufficient data for recommending hysteroscopy instead of hysterosalpingography [11,12].

In our study, 18.4% of practitioners always or often perform laparoscopy to rule out subclinical endometriosis. In the absence of evidence for tubal or other pelvic pathologies (history of complicated appendicitis, pelvic surgery, pelvic inflammatory disease, clinical evidence of endometriosis, seropositivity for chlamydia and/or the presence of hydrosalpinx), laparoscopy is not systematically warranted before making a UEI diagnosis [1,3,10]. In our study, 30.2% of the practitioners questioned prescribe an MRI in cases of UEI. Data are still insufficient to assess the value of MRI and laparoscopy in diagnosing UEI [13].

Age-specific management of UEI

Age-related infertility is one of the top 10 research priorities for females and UEIs [5]. Female age is a strong predictor of both natural and treatment-related live birth rates, with rates decreasing at age 35 years in ART [14]; for spontaneous pregnancies these rates begin to decrease at age 30 [15].

For 87.6% of the practitioners, maternal age is an indication of IVF as a first-line treatment, and this age is, on average, 37.4 years. However, IVF has not been shown to be the treatment for age-related infertility [16]. In several studies, neither IUI nor IVF showed superiority in cases of age-related reduction of ovarian reserve [17–19]. Some authors currently recommend a shorter period of expectant management for women who are 36 years or older [3]. UEI for more than 3 years would be a poor prognostic feature for future chance of pregnancy [20].

Should AMH guide the management strategy for UEI?

We observed that 75% of practitioners consider an AMH rate <1 ng/ml to exclude the diagnosis of UEI. For 68.6% of participants, a

reduction in AMH is an indication for first-line IVF, with an average AMH level of 1.2 ng/ml (8.6 pmol/L) in the UEI. Although AMH is considered the best marker of the ovarian reserve, the existing literature does not support the use of AMH as a marker of reproductive potential in the general population [21,22]. Several studies have reported a positive association of AMH levels with pregnancy rates after IVF treatment [23]. Nevertheless, other studies reported a weak or non-significant association between AMH levels and a natural or medically assisted pregnancy outcome [24,25]. Thus, if only AMH is decreased in the situation of apparent UEI, there is no evidence that AMH levels should guide management towards IVF or IUI.

Considering environmental exposures before concluding UEI

Studies defining the criteria to diagnose UEI generally do not consider the deleterious effects of environmental factors such as obesity and smoking.

In our study, 35.5% of respondents always or often exclude the diagnosis of UEI in women with a BMI > 30 kg/m², and 58.6% discard the diagnosis of UEI for BMI > 35 kg/m².

For a BMI above 29 kg/m², every one point increase in BMI results in a 4% decrease in the chance of pregnancy (HR: 0.96; 95% CI: 0.91 to 0.99) [26]. Severe obesity (> 35 kg/m²) reduces the chances of a live birth by a factor of 2 compared to women with BMI < 25. [3,10]. Similarly, for couples undergoing IVF, a decreased live birth rate following IVF was observed in obese (BMI ≥ 30 kg/m²) women compared with normal weight (BMI 18.5–24.9 kg/m²) women [27].

A total of 44.3% of respondents dismiss the diagnosis of UEI if women smoke more than 10 cigarettes per day. Tobacco is harmful to natural fertility with the consequence of prolonging the time for conception and reducing the chances of a live birth. This deleterious effect appears to be dose dependent [28]. The environmental impact on fertility is not yet clearly defined, even if its implication is strongly suspected and increasingly studied [29]. In apparent UEI, screening for exposure to reprotoxic agents should be carefully performed.

What ART strategy for managing UEI?

For couples with UEI, Wang et al. concluded that there was insufficient evidence of differences in terms of live birth rates between expectant management and IVF/intracytoplasmic sperm injection (ICSI), ovarian stimulation (OS) with IUI or OS with sexual intercourse [4]. The management of infertile couples should depend on the synthesis of multiple factors, including prognostic factors (age, duration of infertility, ovarian reserve), cost and side effects of treatments.

Clomiphene citrate or gonadotropins alone with timed intercourse should not be offered to couples with UEI. [2–4]. The North American guidelines state that the best initial therapy for couples unsuccessful in achieving a pregnancy is 3 or 4 cycles of OS/IUI followed by IVF [1,2]. For them, there is good evidence that immediate IVF in women ≥ 38 years of age may be associated with a higher pregnancy rate and shorter time to pregnancy compared to a strategy consisting of OS with IUI treatments prior to IVF [2,7]. The NICE guidelines recommend first-line IVF after 2 years of regular sexual intercourse without pregnancy and to provide care without delay if maternal age is > 36 [3]. The Cochrane analysis concluded that there was no superiority in live birth rates between expectation, OS and IUI and IVF +/- ICSI. For couples with bad prognostic factors as determined according to the Hunault 2010 criteria (including age, duration of infertility, number of mobile spermatozoa and primary or secondary infertility) [15], management by IUI or IVF is probably of value [4]. However, in a cohort study of UEI with women aged ≤ 40, we previously reported that no clinical characteristics could identify favourable or unfavourable prognostic factors before starting ART [30]. There is no reported difference in clinical pregnancy and live birth rates

when comparing IVF with conventional fertilization to IVF with ICSI in the setting of UEI [1,2,4].

Limits

In our study, more than 50% of respondents work in a university teaching hospital, which is not representative of current practice and may lead to a bias.

In addition, infertility management depends on access to care. For many centres access to IVF is more complex and requires a longer waiting period than the IUI. IUI cycles are often performed before validation of IVF management.

Conclusion

Our study showed heterogeneity in the diagnostic criteria and management of UEI in a sample of French reproductive physicians. Moreover, some clinical practices have no clear scientific basis, such as the orientation of management according to AMH level. There is a lack of clinical studies evaluating the value of additional tests such as MRI and laparoscopy in the diagnostic strategy. Moreover, there is still insufficient evidence to advise IVF or IUI rather than expectant management, and every practitioner often has an empirical strategy for UEI. Different countries have different recommendations for UEI. Thus, UEI would benefit from a diagnostic consensus so that all studies on management strategies could be comparable.

Funding source

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None

Acknowledgement

The authors would like to thank all colleagues from participating ART centres. CH Aix-en-Provence, Créteil, Quatres-villes (Saint-Cloud), Saint-Denis, Saint-Nazaire, CHU de Amiens, Angers, Besançon, Bordeaux, Brest, Clermont-Ferrand, Grenoble, Lilles, Limoges, Lyon, Marseille, Montpellier, Nancy, Nantes, Nice, Nîmes, Paris (APHP Site Antoine Bécère, Site Bichat, Site Tenon, Site Jean Verdier), Pointe-à-Pitre, Rennes, Rouen, Saint-Etienne, Strasbourg, Toulouse, Tours, Clinique Belharra (Bayonne), Clinique Bouchard-IMR (Marseille), Clinique Jules Verne (Nantes), Clinique La croix du Sud (Toulouse), Clinique Mutualiste de la Sagesse (Rennes), Clinique Natécia (Lyon), Clinique Procrealis (La Roche sur Yon), center Sainte Colette (Marseille), Clinique Saint-Georges (Nice), Clinique Saint-Michel (Toulon), Clinique Saint-Pierre (Perpignan), Clinique Saint-Roch (Montpellier), Clinique Val D'Ouest (Ecully), Institut Mutualiste Montsouris (Paris), Polyclinique Courlancy (Reims), Polyclinique Jean Villar (Bruges), Polyclinique Urbain V (Avignon).

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