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Results of in vitro fertilization versus intrauterine insemination in patients with low anti-Müllerian hormone levels. A single-center retrospective study of 639 + 119 cycles

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ABSTRACT

Objectives. - The aim of this study was to evaluate the results of in vitro fertilization (IVF) and intrauterine insemination (IUI) in a population of infertile women with low AMH levels, in whom both techniques were possible.

Methods. - This was a retrospective analysis of 462 patients treated over 24 months in a single center comparing the live birth rates after 176 IUI and 639 IVF attempts in infertile couples. The women had AMH levels ≤ 1.2 ng/mL and at least one patent tube and their partner's sperm was of sufficient quality for IUI.

Results. – The live birth rate after IVF was not sufficiently higher than after IUI, or than after IVF attempts converted to IUI for low response (odds ratios in multivariate analysis with respect to IVF: 0.61, $p = 0.15$ for IUI and 0.73, $p = 0.6$ for conversions). The pregnancy rates after IVF (13.0%) and IUI (13.3%) were similar ($p = 0.4$), and were non-significantly higher than the pregnancy rate in the IUI conversion group (8.8%, $p = 0.9$). Nearly half (43.8%) of all IVF cycles did not lead to embryo transfer.

Conclusion. – In this group of women with AMH levels ≤ 1.2 ng/mL, IVF did not lead to a higher live birth rate than IUI, and more than 40% of all IVF attempts did not lead to embryo transfer, suggesting that diminished ovarian reserve is not an indication for IVF over IUI.

Keywords: Anti-Müllerian hormone; Infertility; Intrauterine insemination; In-vitro fertilisation; Live birth rate; Poor responder

Introduction

Societal changes have meant that women increasingly face the problem of diminished ovarian reserves by the time pregnancy is desired. This is one of the factors that explains the increase in infertility rates over recent decades and the increasing use of assisted reproduction technologies (ARTs). However, while low ovarian reserves mean low responses to ovarian stimulation (1), they do not necessarily mean low pregnancy rates, even less low natural conception rates (2,3). The main factor for decreasing pregnancy rates seems to be the increasing age of women attempting to get pregnant rather than their diminished ovarian reserves (4).

Ovarian reserve is typically measured either ultrasonographically, by performing an antral follicle count (AFC), or biochemically, by measuring anti-Müllerian hormone (AMH) levels. Neither test is perfect, but the advantages of AMH levels over AFCs are that they are not operator-dependent and can be measured at any time in the menstrual cycle (5).

In vitro fertilization (IVF) is the most commonly used procedure when ovarian reserves are reduced because live birth rates (LBRs) are higher with this technique than with intrauterine insemination (IUI) in the general population (6). It is not clear however whether this result also holds for patients with diminished ovarian reserves. The aim of this study was therefore to compare the LBRs with these two techniques in a retrospective cohort of patients with low AMH levels (≤ 1.2 ng/mL).

Material and methods

Study design

This was a single-center retrospective study of all IVF and IUI attempts made between January 2016 and December 2017 at the Hopital Mère Enfant (Lyon University Hospital), Bron, France, with no restrictions on age or body mass index (BMI). The inclusion criteria were an AMH concentration ≤ 1.2 ng/mL, at least one patent tube, and sperm quality sufficient for intrauterine insemination (IUI). Cycles with donated sperm were also included. The aim of these criteria was to include patients in whom both techniques were possible. Attempts for recipients of oocyte donations and for patients who had undergone ovarian transplant (as part of fertility preservation) were excluded. The study was approved by the local ethics committee (Comité d'éthique du CHU de Lyon N19-86). Patient data were collected and stored in compliance with local laws and regulations.

All patients had received an AMH assay, the majority in the study center, performed since 2015 by electrochemiluminescence (Elecsys®, Roche). The results in pmol/L were converted to ng/mL, the units we use in clinical practice (1 pmol/L = 0.14 ng/mL). Ovarian reserves were quantified in the study center by performing ultrasound AFCs (Voluson 730 pro, General Electric) between day 2 and day 5 of the cycle. Tube permeability had been checked previously, either by hysterosalpingography, or by laparoscopy and dye test. All data, collected prospectively, were accessed retrospectively via the specialized computer processing software MEDIFIRST.

Treatment protocols

All patients had consulted in the department for infertility. The technique used was chosen by the attending clinician in agreement with the patient. Twelve different clinicians cared for patients in the centre over this period of time. Intrauterine insemination is typically

avored in clinical practice in cases of secondary infertility and young age, which are positive prognostic factors. Protocol types and gonadotropin doses were chosen according to the patients' age, BMI, AMH level, AFC, and history of response to ovarian stimulation if applicable.

Patients in the IUI group received ovarian stimulation starting on day 2 of the cycle, with recombinant FSH (Puregon®, MSD, France; Gonal-F® Merck-Serono, France).

Ovulation was triggered by administering human chorionic gonadotropin (HCG Ovitrelle® 250 mg, Merck-Serono, France) if the follicle size criteria were met (1 or 2 follicles > 17 mm). Insemination was carried out 36 h later, and was followed by vaginal micronized progesterone luteal phase support at 200 mg in the morning and 400 mg in the evening for 6 weeks.

Patients in the IVF or intracytoplasmic sperm injection (ICSI) group received either (i) long-term agonist treatment starting in the luteal phase of the previous cycle by daily administration of GnRH agonist (triptorelin, Decapeptyl® 0.1 mg, Ipsen Pharma, France; nafarelin, Synarel® twice daily, Pfizer, France) followed by ovarian stimulation with recombinant FSH, with or without LH (lutropin alfa, Luveris®, Merck-Serono, France) or (ii) antagonist treatment with a GnRH antagonist (ganirelix, Orgalutran®, MSD, France; cetrotorelix, Cetrotide® 0.25 mg, Merck-Serono, France) on day 6 of stimulation by recombinant FSH ± LH started in the follicular phase.

Beginning on day 7 or 8 of the cycle, ultrasound evaluations of the pelvis and serum E2 measurements were performed and repeated every 1–3 days depending on the stimulation protocol. The gonadotropin dose was adjusted accordingly. HCG was administered to trigger ovulation when the follicle size criteria were met (at least 3 follicles ≥ 17 mm). The oocytes were retrieved transvaginally 36 h after triggering, in the operation room, under sedation.

Conversion of IVF to IUI cycles were decided in multidisciplinary team meetings, if less than three growing follicles were obtained after ovarian stimulation. This threshold varied in some cases depending on the patient's age and the couple's medical history. Conversion was considered in the IVF group as a failure, and these cycles were analyzed separately.

Luteal support was provided by vaginal micronized progesterone, at a dose of two capsules of 200 mg morning and evening, started on the day of oocyte retrieval (OR), and continued until the first trimester ultrasound examination. Embryos were obtained by classic IVF or ICSI, as decided by the embryologist. If embryos were obtained, they were transferred on day 2, 3 or 5, by single or double transfer, as decided jointly by the embryologist and clinician. Excess embryos were frozen, and frozen–thawed embryo transfer (FET) was performed later in an artificial cycle using oral/vaginal micronized estradiol and vaginal progesterone.

Outcome measures

The primary outcome of the study was the live birth rate (LBR) per cycle. The secondary outcome was the early pregnancy rate. A live birth was defined as a healthy child delivered at > 25 weeks' gestation. Early pregnancy was defined as a positive blood pregnancy test (HCG > 100 UI/L) two weeks after embryo transfer or IUI. For patients in the IVF group, the LBR includes transfers of both fresh and frozen embryos from the same oocyte retrieval.

Statistical analysis

To avoid analyzing IVF attempts converted to IUI in both groups, they were counted as a failure in the IVF group and were also analyzed separately in a third group.

Continuous variables are reported as means and standard deviations and categorical variables as counts and percentages. Population characteristics by technique were compared

using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables. Factors associated with live births were analyzed using a logistic regression model, with a generalized estimating equation to account for the non-independence of multiples cycles for the same patient. Factor effects were quantified by odds ratios (ORs) and the associated 95% confidence intervals (CIs).

The variables compared between groups in univariate analysis were the patients' age, AMH level, BMI, smoking status, infertility duration (in months), infertility type (primary/secondary), gonadotropin doses (in international units, IU). All the variables considered in univariate analysis were included in a multivariate model, except for those with too many missing data (BMI, smoking status and infertility duration). The total gonadotropin dose was removed from the multivariate model because it was strongly correlated with the technique variable. Results were considered statistically significant at $p < 0.05$. All analyses were performed using the software R, version 3.6.1 (R Core Team, Vienna, Austria, 2019) and the geepack library (7).

Results

Eight hundred and fifteen cycles for 462 patients met the inclusion criteria, of which 639 were IVF/ICSI attempts and 119 were IUI attempts. In the IVF group, ICSI was performed in 391 (94.4%) of the 414 cycles in which oocytes were retrieved, while IVF was used in the remaining 23 cycles (5.6%). Fifty-seven (8.9%) of the IVF attempts were converted to IUI because of insufficient ovarian response.

The main demographic and clinical characteristics of the two groups are compared in Table 1. Patients in the IUI group were significantly younger than those in the IVF group, but the difference in mean age was just 1.2 years. On average, patients in the IUI group had

significantly higher AMH levels (difference in means, 0.07 ng/mL), longer durations of infertility, and a higher proportion of secondary infertility (Table 1).

Table 1

Clinical and demographic characteristics of the IUI and IVF groups

	IUI	IVF/ICSI	IVF conversion to IUI	p value
Cycles	119	639	57	
Age (years)	34.9 (4.0)	36.1 (3.8)	36.7 (4.1)	0.001
BMI	25.1 (5.8)	24.2 (5.0)	23.3 (4.5)	0.2
AMH (ng/mL)	0.74 (0.38)	0.67 (0.32)	0.42 (0.27)	<0.001
Duration of infertility (months)	69 (34)	62 (35)	60 (36)	0.01
Primary infertility, n (%)	71 (59.7)	470 (73.6)	41 (71.9)	0.01

Values are reported as mean (standard deviation) or frequency (percentage)

ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in-vitro fertilization

There were 71 live births in total (Table 2), 59 from IVF (9.2% of all IVF attempts), 9 from IUI (7.6% all IUI attempts), and 3 from IVF attempts converted to IUI (5.3% of all conversions). Among the 55 IVF attempts (8.6%) that resulted in frozen embryos, 9 resulted in live births (16.3% of all FETs). The pregnancy rates in the IVF and IUI groups were similar (13.0 vs 13.3%, respectively), and higher than the rate in the IVF conversion group (8.8%). The miscarriage rates were higher in the IUI and IVF conversion groups (respectively 31.2 and 40.0%) than in the IVF group (20.5%).

Two hundred and eighty (43.8%) of the IVF attempts did not lead to embryo transfer, in 130 cases because of non-response (20.3% of all IVF attempts), in 57 cases because of conversion to IUI (8.9%), in 38 cases because no oocyte was retrieved (5.9%), and in 55 cases

(8.6%) because no embryo developed. In the IUI group, 15.3% of all attempts (27/119) were cancelled for a variety of reasons.

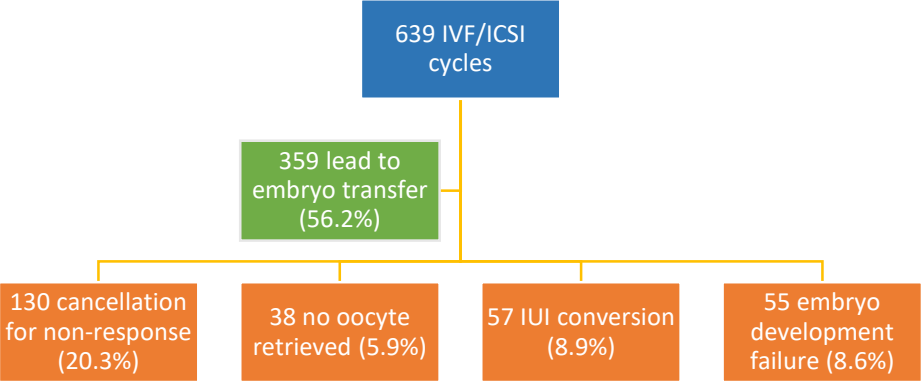


Figure 1. IVF/ICSI cycles outcomes

Table 3

Statistical analysis of the association between selected variables and the live birth rate per cycle

Variable	Outcome ^a	Univariate analysis		Multivariate analysis	
		OR ^b (95% CI)	p value	OR ^b (95% CI)	p value
ART					
IVF	59 (9.2%)	ref	–	–	–
IUI	9 (7.6%)	0.8 (0.41–1.56)	0.5	0.61 (0.31–1.19)	0.15
IVF conversion	3 (5.3%)	0.55 (0.16–1.82)	0.3	0.73 (0.21–2.46)	0.6
Age	34.1 (4.2)	0.61 (0.49–0.75)	< 0.001	0.59 (0.47–0.74)	< 0.001
AMH	0.75 (0.32)	1.31 (1.02–1.69)	0.03	1.32 (1.03–1.69)	0.03
Infertility type					
Primary	52 (8.9%)	ref	–	–	–
Secondary	19 (8.2%)	0.9 (0.52–1.58)	0.7	1.06 (0.59–1.88)	0.8
Body mass index	24.04 (5.46)	0.94 (0.7–1.27)	0.7	–	–
Smoking status					
No	29 (7.6%)	ref	–	–	–
Yes	15 (9.7%)	1.31 (0.67–2.53)	0.4	–	–
Duration of infertility	59.2 (30.8)	0.86 (0.66–1.13)	0.3	–	–
Gonadotropin dose	3351 (1616)	0.84 (0.67–1.05)	0.13	–	–

^aThe outcomes presented are the mean (SD) for continuous variables, and the number (%) of successful attempts for categorical variables

^bOdds ratios are presented as the per-SD increase for continuous variables and relative to the reference category for categorical variables

AMH, anti-Müllerian hormone; ART, assisted reproductive technology; CI, confidence interval; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in-vitro fertilization; OR, odds ratio; SD, standard deviation

In univariate analysis, older age and higher AMH levels were respectively associated with significant decreases and increases in the LBR (Table 3). Adjusted on age, AMH level and infertility type, IVF was associated with a slightly higher LBR than IUI was (OR for IUI compared with IVF, 0.61; 95% CI, 0.31–1.19; $p = 0.15$), age was negatively associated with

the LBR (OR, 0.59 per 4 year increase; 95% CI, 0.47–0.74; $p < 0.001$) and the AMH level was positively associated with the LBR (1.32 per 0.3 ng/mL increase; 95% CI: 1.03–1.69; $p = 0.03$).

Including an age–ART interaction term in the multivariate model showed that there was a greater negative association between age and the LBR for IUI attempts than for IVF attempts (Fig 2a; interaction p -value, 0.08). Accounting for the interaction between the ART and AMH level variables in the regression model showed that while there was no association between the AMH level and the LBR in IUI cycles, there was a positive association for IVF cycles (Fig. 2b, interaction p -value, 0.05).

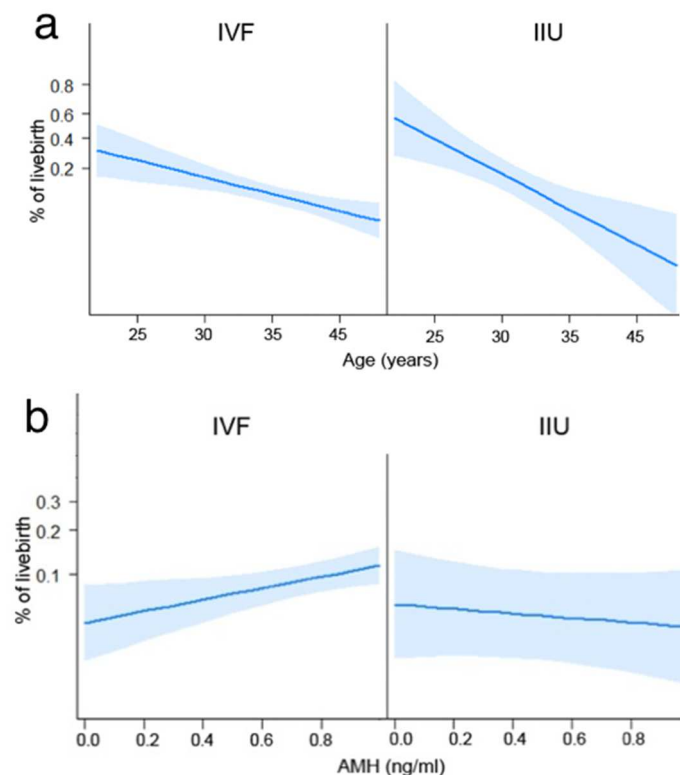


Fig. 2. Interaction plots of the live birth rate per cycle by assisted reproductive technology as a function of (a) patient age and (b) anti-Müllerian hormone level. IUI, intrauterine insemination; IVF, in-vitro fertilization.

Discussion

In this study of patients with AMH levels ≤ 1.2 ng/mL and treatable by IVF or IUI, the LBR per cycle was not significantly higher with IVF than it was with IUI. The question this study attempts to answer is which of these two techniques should be chosen when both are possible, i.e. for patients with one or more permeable tube, compatible sperm parameters, and low AMH levels (diminished ovarian reserve)? Very few studies have focused on this question. Dosso et al. (8) found no significant difference (14.2% vs 18.4%, $p = 0.159$) in the pregnancy rates after IUI and IVF in patients with AMH levels < 1.68 ng/mL treatable by either technique. Quinquin et al. (9) compared the results of IVF versus conversion to IUI in cases of poor follicular recruitment after stimulation in Bologna-criteria poor responders, and found that the LBR was significantly higher after IVF than after conversions to IUI when two follicles were present (11.6% vs 1.6%), but similar when just one follicle was recruited. The results of the CONFIRM study (10), a multicenter prospective randomized trial, will be interesting in this context.

The literature on the association between AMH levels and insemination outcomes is conflicting. Two studies have found that patients who achieved clinical pregnancy after IUI had significantly higher AMH levels. Li et al. (11) proposed a threshold of 1.8 ng/mL (cumulative birth rate after four IUIs, 49.6% above vs 27.3% below), while Moro et al. (12) found that patients with AMH levels above 2.3 ng/mL were more likely to become pregnant than those with AMH levels below this threshold. On the contrary, Moreau et al.'s (13) analysis in terms of age-specific AMH, using the 25th and 75th percentile of each age group, found no significant association with the LBR after four IUIs. Lamazou et al. (14) found no significant difference in pregnancy rates after IUI between patients with AMH levels < 1 ng/mL and those with AMH levels between 1.01 and 4.5 ng/mL (15.5% vs 15.2%). Likewise,

Gonzalez-Foruria et al. (15) found that the AMH level was not predictive of pregnancy in women undergoing IUI with donor sperm (area under the ROC curve, 0.53).

The association between AMH levels and IVF success has been more widely studied. Two meta-analyses focusing on pregnancy rates (16) and LBRs (17) have both found that AMH levels are excellent predictors of ovarian response and are associated with pregnancy rates and LBRs but with poor predictive accuracy.

Two interesting findings of the present study are first, that advanced age appears to have a greater negative effect on the LBR for IUIs than for IVFs, suggesting that IUI should not be offered to older patients. And second, that while IUI results were not associated with AMH levels, the latter were positively associated with IVF outcomes. This suggests that young patients with very low AMH levels should be offered IUI rather than IVF.

The IUI group in this study consisted of patients that on average were significantly younger, had higher AMH rates, and were more likely to have secondary infertility than those in the IVF group. This suggests that clinicians knew that these are good prognostic factors for IUI. Paradoxically, the duration of infertility was significantly longer in the IUI group, despite this factor being an indication for IVF in clinical practice.

The question of which group IVF cycles converted to IUI should be considered in is debatable. We chose to consider them as IVF failures, because the ovarian response did not meet the oocyte retrieval criteria. We chose to analyze these cycles as a separate group rather than include them in the IUI group because the conversion patients were older and had lower AMH levels, and because the initial decision was to perform IVF. Births that resulted from these converted cycles were not counted in the IVF group. Had we performed an intention-to-treat analysis, only three additional births would have been added to the IVF group and would not have significantly altered the results of the comparative analyses. In any case, the results

of this comparison between IVF and IUI should be interpreted cautiously because the study was a retrospective analysis rather than a randomized trial.

It is important to note the 130 cycles cancelled in the IVF group and not converted to IUI. The reasons for non-conversion were diverse: mono-follicular recruitment in a patient > 35 years of age, clinician's willingness not to convert, patient's refusal to convert, etc. We do not have the exact distribution of these reasons for non-conversion. We can consider that it is a loss of chance in these patients who had even a low chance of pregnancy. Another limitation of this study is the uncertainty of the AMH assays. Peigné et al. (18) note that while automated assays have been used since 2014, results differ from 4 to 14% between measurement kits. The AMH concentrations used in this study mostly came from the study center's laboratory, where automated assays (Cobas Elecsys®, Roche) have been used since 2015. However, the inclusion of patients based on AMH concentrations measured using different assays may have biased the results.

The most appropriate AMH cut-off to use is also a matter of debate. The threshold level used in this study was set in accordance with the Poseidon criteria (19), which is the most recently proposed classification of poor responders in IVF. However, as pointed out by Leijdekkers et al. (20), the cut-off in this classification is based on pre-existing assays, and these authors propose an adjusted threshold of 0.96 ng/ml for Elecsys assays. We did not apply this adjustment because it would have reduced our sample size and therefore the power of our analyzes. While we used the AMH level as the main inclusion criterion, classifications of poor responders (such as the Poseidon classification) offer a more complete definition of patient subgroups with different prognoses.

Note that the predominance of ICSI in the IVF-ICSI group (94.4% of the 414 attempts) reflects the treatment center's strategy to broaden the indications of ICSI compared

with IVF rather than ICSI having been chosen based on sperm characteristics (since the included cases were compatible with IUI).

The slightly (non-significantly) higher LBR in the IVF group must be weighed against the risks associated with IVF (hyperestrogenism, anesthetic-related and those associated with transvaginal oocyte retrieval). From a medico-economic point of view furthermore, IUI is preferable to IVF if the LBRs with the two techniques are similar. Indeed, the overall cost of an IUI cycle is about half that of IVF (1000–1500 vs 3000–4100 euros) (21). Do the few percent of additional live births justify the risks and costs of IVF compared to IUI? Unlike IUI furthermore, IVF cycles cannot be strung together, which may delay the time to pregnancy.

Finally, it should not be forgotten, and couples should be reminded, that spontaneous pregnancy remains possible, even with low AMH levels. In a study of women aged 30 to 44 years with no history of infertility, Steiner et al. (22) found that the cumulative probability of conception after 6 and 12 months was respectively 65% and 84% in those with AMH levels < 0.7 ng/mL. In one of the only studies of AMH levels and spontaneous pregnancy rates in patients with unexplained infertility, Casadei et al. (23) found, albeit for a small sample size, that patients with AMH levels < 0.75 ng/mL had a spontaneous pregnancy rate at six months of 18.5%. In this population, it would be interesting to compare the rate of spontaneous pregnancies in a control group with the outcomes of patients treated by IUI and IVF.

To conclude, in this study of women with AMH levels ≤ 1.2 ng/mL, the LBR after IVF was not significantly higher than after IUI and more than 40% of IVF attempts did not lead to embryo transfer. These results suggest that the choice between IVF and IUI should be guided by the patient's age rather than her ovarian reserves.

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