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Age-specific anti-Mullerian hormone (AMH) levels poorly affects cumulative live birth rate after intra-uterine insemination

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ABSTRACT

Objective: To evaluate the impact of age-specific anti-Mullerian (AMH) levels on the cumulative live birth rate after 4 intra uterine inseminations (IUI).
Study Design: The retrospective study study involved 509 couples who underwent their first IUI between January 2011 and July 2017 in the Toulouse University Hospital. All IUI were performed after an ovarian stimulation combining recombinant FSH and GnRH antagonist. The main measure outcome was the cumulative live birth rate (LBR) defined as the number of deliveries with at least one live birth resulting from a maximum of 4 IUI attempts.
Results: When compared to normal or high levels, low age-specific AMH (<25th of the AMH in each age group) was associated to a non-significant lower live birth rate (31%, 38% and 42% respectively for low, normal and high age-specific groups; P = 0.170) and non-significant higher miscarriage rate (26%; 19% and 14% respectively for low, normal and high age-specific groups; P = 0.209). However, it must be pointed out that in low age-specific AMH the initial FSH doses used for stimulation were higher than in the other groups.
Conclusion: This study shows that the age-specific levels of AMH have only a slight effect on IUI outcome when adapting the stimulation protocols to their level.

Introduction

Intra-uterine inseminations (IUI) with fresh husband sperm is one of the first line treatments in case of subfertility. They can be used in mild male abnormality [1,2], ovulation disorders [3] and unexplained infertility (UI) [4].

Numerous factors have been reported to have a great influence on the success rate of IUI. The number of inseminated motile spermatozoa, as well as the number of mature follicles and the use of GnRH antagonist have been widely reported to be significantly linked to the chance to obtain a pregnancy after IUI [5–8]. Conflicting results have been reported concerning female age. Indeed, if some authors have shown that advanced age was associated with a lower pregnancy rate [3,8–10] or with an increased miscarriage rate [11], others found no correlation [12,13].

The influence of the ovarian reserve parameters has been studied by different authors with major discrepancies since some have found that high levels of ovarian reserve as measured by anti-Mullerian hormone (AMH) and/or antral follicle count (AFC) are good predictors of the pregnancy rate [11,14–18] while other have found that AMH was not a useful tool to predict IUI outcome [19,20]. These differences can be explained by the fact that ovarian reserve is closely correlated to age [21] making difficult to differentiate the respective part of age and of ovarian reserve on the ability of motherhood.

To try to answer this question, the present study aimed to evaluate the ability of the age-specific AMH levels [22,23] to predict the cumulative live birth rate after 4 IUI.

Materials and methods

Patients

Five hundred and nine couples who underwent their first IUI between January 2011 and July 2017 in the Toulouse University Hospital entered the study. The indications of IUI were: unexplained infertility (252; 49.5%), ovulation disorder (151; 29.7%), moderate oligo-asthenospermia allowing to inseminate at least 10^6 motile spermatozoa (59; 11.6%), stage 1 endometriosis

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(32; 6.3%), moderate oligo-asthenospermia associated to ovulation disorders or to stage 1 endometriosis (15; 2.9%). The means female age was 33.4 ± 4.2 and 385 (75.6%) women had a primary infertility.

All patients had an evaluation of tubal permeability using hysterosalpingography completed by laparoscopy in case of suspected abnormality before the beginning of IUI.

Couples were excluded when the female partner had no two patent tubes [24] or if less than 10^6 motile spermatozoa were obtained after semen preparation [25].

Semen preparation

Sperm were prepared according to WHO 2010 using discontinuous density gradient centrifugation (three layers: 60%, 80%, 90%) (Puresperm®, Nidacon, Mölndal, Sweeden). After preparation spermatozoa were incubated in 400 µl universal IVF medium (Origio, Versailles, France) at 37 °C in a 6% CO_2 atmosphere. The number of recovered spermatozoa and their progressive motility were assessed in the medium to allow the measurement of the number of recovered motile spermatozoa.

IUI procedures

Ovarian stimulation used a combination of recombinant FSH (Gonal F, Merck, Lyon, France or Puregon, MSD, Paris, France) and GnRH antagonist (Cetrotide 0.25 mg, Merck, Lyon, France or Orgalutran, MSD, Paris, France). The initial dose of FSH was chosen according the female age and the score described by Chalumeau et al. [26]. Ovulation was triggered with recombinant hCG (Ovitrelle, Merck, Lyon, France) when at least one follicle ≥ 18 mm was obtained. Insemination was performed 36 h after hCG injection. A luteal support of 400 mg per day of intra-vaginal progesterone was administrated during 15 days, starting on the day of insemination.

Clinical pregnancy was defined as the presence of a fetal heartbeat evaluated during the transvaginal ultrasonographic examination seven weeks after insemination. Live birth was defined as the delivery of at least one live born infant after a 22 weeks or more pregnancy [27].

Evaluation of the ovarian reserve

Evaluations were done in the year before the first IUI. The hormonal measurements (FSH, LH, AMH and E2) were performed between cycle days 2 and 5 in the biochemistry laboratory of the Toulouse University Hospital with the same kits and the antral follicle count (AFC) at the same time, through 2D transvaginal ultrasonography by several different physicians in the department of obstetrics of the Toulouse University Hospital. Every follicle within 2–9 mm mean diameter (after 2 measures on orthogonal plans) was count. Serum LH, FSH, and E2 levels were assayed by an automated electrochemiluminescent based-assay (Elecsys® e602 Roche Diagnostics, Meylan, France) The interassay coefficient of variation (CV) were respectively 3.4% (around 11 UI/L) for LH, 2.2% (around 17 UI/L) for FSH and 3.4% (around 95 pg/mL) for E2. AMH was measured by ELISA GENII Beckman essay (Beckman Coulter Inc, Brea, CA) with an interassay CV of 4.4% (around 3.8 ng/mL) and a 0.08 ng/mL low limit of detection.

Statistical analysis

Data were extracted from the Gynelog clinical database used in our department. This database is approved by the French National Commission for Information Technology and Civil Liberties (CNIL) to be used for clinical research. According to French law (2012−300), patients are aware that their data can be used for anonymous clinical studies unless they specifically state otherwise. This information is detailed in posters in the rooms of the centre, and patients can inform the centre through a letter if they do not want to participate in clinical studies.

The measured primary outcome was the cumulative live birth rate (CLBR) after a maximum of 4 attempts. Pregnancy loss was defined as the outcome of any pregnancy that does not result in at least one live birth [27].

Statistical analyses were performed using StatView software (Abacus Concepts Inc., Berkeley, CA). Data are means ± SD or median (range) according to the normality of the data. Percentages were compared by the χ^2 test. Means were compared using the Student's *t*-test and medians using the Mann-Whitney test according to the normality of data distribution.

Groups of age were defined by the 25th, 50th 75th percentiles. Groups of age-specific AMH were defined by the 25th and 75th percentiles of AHM inside each group of ageThe age-specific AMH was called "low" when it was lower than the 25th percentile, "normal" between the 25th and the 75th percentile and "high" when it was higher than the 75th percentile, to allow easy reading.

The demographic data of de different groups are described in Table1.

Results

Table 2 shows the results of IUI as a function of age-specific AMH. There was a trend, but not statistically significant, for a lower live birth rate in all low age-specific AMH groups. This was also true after considering age-specific AMH groups (low, normal and high)

Table 1
Demographic data of the different groups of age-specific AMH levels.

Age	≤ 30			30 – 33			33 – 37			≥ 37		
AMH (ng/ml)	≤ 1.6	1.6 – 4.6	≥ 4,6	≤ 1.2	1.2 to 3.8	≥ 3.8	≤ 1.1	1.1 – 3.8	≥ 3.8	≤ 1.0	1.0 – 2.6	≥ 2.6
n	34	67	43	33	58	32	33	63	32	35	59	29
Origin of infertilty (%)												
Ovulatory	17 (50)	16 (28)	14 (33)	16 (48)	12 (21)	13 (41)	18 (55)	8 (13)	8 (25)	10 (29)	9 (15)	10 (34)
Endometriosis	0	3 (5)	9 (21)	3 (9)	6 (10)	1 (3)	2 (6)	4 (6)	1 (3)	1 (3)	2 (3)	0
Male	3 (9)	8 (14)	4 (9)	3 (9)	3 (5)	1 (3)	3 (9)	12 (19)	3 (9)	5 (14)	12 (20)	2 (7)
Male and female	0	2 (3)	2 (5)	0	3 (5)	2 (6)	0	0	4 (13)	0	2 (3)	0
Unexplained	14 (41)	29 (50)	14 (33)	11 (33)	34 (59)	15 (47)	10 (30)	39 (62)	16 (62)	19 (54)	34 (58)	17 (58)
Primary infertility (%)	30 (88)	50 (86)	33 (77)	29 (88)	50 (86)	19 (59)	25 (76)	(44 (70)	24 (75)	26 (74)	34 (57)	21 (72)
Basal FSH (mIU/ml)	7.9 ± 3.0	7.2 ± 1.5	6.5 ± 1.5	8.3 ± 2.2	7.1 ± 1.8	6.8 ± 1.7	7.9 ± 1.6	7.5 ± 2.2	6.7 ± 1.5	8.0 ± 2.1	7.1 ± 2.1	6.6 ± 1.1
Basal LH (mIU/ml)	4.8 ± 1.6	5.2 ± 2.0	6.7 ± 3.0	5.3 ± 1.9	6.2 ± 4.7	6.6 ± 2.9	4.6 ± 1.5	5.5 ± 2.1	6.9 ± 2.9	4.8 ± 2.0	5.2 ± 2.0	6.6 ± 4.5
Antral follicle count	15 ± 6	25 ± 9	33 ± 13	13 ± 6	19 ± 8	32 ± 14	11 ± 5	21 ± 8	34 ± 13	11 ± 4	17 ± 6	29 ± 15

Groups of age were defined as the 25th, 50th and 75th percentile.
Groups of AMH were defined as the 25th and the 75th percentile in each group of age.

Table 2
Results of IUI as a function of age and age-specific AMH levels.

Age	≤ 30			30 – 33			33 – 37			≥ 37		
AMH (ng/ml)	≤ 1.6	1.6 – 4.6	≥ 4.6	≤ 1.2	1.2 – 3.8	≥ 3.8	≤ 1.1	1.1 – 3.8	≥ 3.8	≤ 1.0	1.0 – 2.6	≥ 2.6
n	34	58	43	33	58	32	33	63	32	35	59	29
N IUI	2.5 ± 1.3	2.4 ± 1.3	2.4 ± 1.2	2.9 ± 1.3	2.3 ± 1.3	2.6 ± 1.2	2.8 ± 1.2	2.5 ± 1.2	2.7 ± 1.3	2.6 ± 1.2	2.9 ± 1.2	2.5 ± 1.2
Initial FSH dose	73 ± 29	58 ± 13	62 ± 24	76 ± 17	71 ± 14	60 ± 15	86 ± 22	72 ± 15	64 ± 14	97 ± 24	82 ± 16	75 ± 23
N follicles ≥ 15 mm	1.5 ± 0.6	1.3 ± 0.4	1.3 ± 0.5	1.7 ± 0.8	1.5 ± 0.5	1.2 ± 0.5	1.6 ± 0.7	1.5 ± 0.6	1.3 ± 0.5	1.8 ± 0.7	1.6 ± 0.8	1.6 ± 0.7
N inseminated motile spermatozoa (10^6)	24.3 ± 28.0	19.4 ± 28.5	22.0 ± 30.6	22.9 ± 28.2	28.2 ± 25.7	18.6 ± 15.9	23.3 ± 25.4	21.1 ± 28.6	18.2 ± 19.0	19.4 ± 23.5	26.0 ± 32.2	23.2 ± 29.3
Cumulative live birth after 4 IUI (%)	12 (35)	25 (43)	19 (44)	11 (33)	26 (45)	14 (44)	9 (27)	26 (41)	12 (38)	10 (29)	14 (24)	12 (41)
Cumulative pregnancy losses after 4IUI (%)	5/17 (29)	4/29 (14)	7/23 (30)	2/13 (15)	3/29 (10)	2/16 (12)	3/12 (25)	8/34 (24)	5/17 (29)	6/16 (37)	10/24 (42)	3/15 (20)
Ratio of the number of newborns to the cumulative number of follicles ≥ 15 mm (%)	13/129 (10)	28/192 (15)	19/137 (14)	12/165 (7)	27/192 (14)	18/100 (18)	11/160 (7)	30/242 (12)	14/121 (12)	10/161 (6)	15/293 (5)	15/124 (12)

Groups of age were defined as the 25th, 50th and 75th percentile.
Groups of AMH were defined as the 25th and the 75th percentile in each group of age.

whatever the age (Table 3), the CLBR rate was not significantly different but showed a trend for a decrease in the low group. It must be pointed out that patients in the low AMH group had significantly higher initial FSH administrated doses and more mature follicles. Therefore, we have calculated the ratio of the number of newborns to the cumulative number of mature follicles. This ratio appeared significantly different among the groups of age-specific AMH: it appeared that, to obtain a newborn, twice more mature follicles were needed in the low than in the high AMH group (Table 3). There was a non-significant trend for a higher miscarriage rate per pregnancy in the low AMH group.

Discussion

Even if low age-specific AMH tend to be associated with a lower live birth rate and with a higher risk of miscarriage, its predictive value remained poor. The impact of AMH levels on the chances of success in ART highly varies among the studies.

The ability of AMH to predict the ovarian response to stimulation has been widely reported and numerous studies have shown good correlations between AMH and the ovarian stimulation index [26] or the number of collected oocytes in IVF [28] and thus has a good ability to diagnose high and poor responders [29,30]. In IUI, Freiesleben et al., using the same FSH dose (75UI) for all patients, have shown that the number of recruited mature follicles (18 mm) was dependent on the AMH levels [19]. We found opposite data but this can be explained by the fact that we have adapted FSH dose to age-specific AMH in order to compensate the defect in ovarian responsiveness of patients with low AMH, as attested by the significantly higher follicles≥ 15 mm obtained when age-specific AMH is low.

Concerning the relations between AMH and pregnancy rate in IUI, several authors have reported a significantly higher AMH in patients who achieved a clinical pregnancy [15,17,18]. In the same way, Moro et al. found a threshold of 2.3 ng/ml allowing to discriminate women according their chances of success [16] and Li et al. found a similar threshold at 1.8 ng/ml [14]. However, other authors found a modest [14] even a non-significant [20] correlation between the AHM level and the chances of ongoing pregnancy. Similar discrepancies have been reported in IVF with a significant impact on the results for some authors [31–35] and no predictive value for others [18,36–38].

These discrepancies could be due to the fact that these studies were focused on the sole AMH level. While AMH and age are closely linked, wide variations exist inside a year of age [39], thus the use of age-specific AMH allows to better discriminate the effect of age and of diminished ovarian reserve [40].

In our study, there were a non-significantly higher miscarriage rate when age-specific AMH was low. Low AMH has been shown to be linked, independently of age, to increased pregnancy loss as well in naturally conceived pregnancies [41] as after IVF [42], probably due to a higher embryonic aneuploidy [43,44] These data suggest that the diminution of the ovarian reserve; notably when unexplained, may not only be a quantitative problem but also a qualitative one. Our observation of a significant decrease of the efficiency of the stimulation, which we have estimated through the ratio of the number of newborns to the cumulative number of follicles ≥ 15 mm, with the age-specific AMH levels, is in line with this hypothesis. For example, the mechanisms by which some molecules, such as environmental pollutants, can alter the pool of follicles, can also impair oocyte quality [45].

The main limitation of this study is the relatively low number of subjects in each group of age and AMH, which decrease the statistical power of the analyses.

In conclusion, these data show that correct live birth rates can be obtained by IUI in case of low age-specific AMH if higher doses

Table 3
Results of IUI when regrouping age specific AMH into low, normal and high groups.

	Age specific AMH			
	Low	Normal	High	Statistical comparison
n	135	238	136	
Initial FSH administrated dose (UI)	83 ± 25	71 ± 17	65 ± 21	P < 0.0001
Number of follicles ≥ 15 mm	1.7 ± 0.7	1.5 ± 0.6	1.3 ± 0.5	P < 0.01
Cumulative live births after 4 IUI (%)	45 (31)	91 (38)	57 (42)	P = 0.344
Ratio of the number of newborns to the cumulative number of mature follicles	0.075 (46/615)	0.109 (100/919)	0.137 (66/482)	P = 0.0035
Miscarriages (%)	12/57 (26)	22/113 (19)	9/66 (14)	P = 0.209

of FSH are used. Indeed, our results have shown that, to obtain a newborn, patients with low AMH required 1.5 more follicles than those with normal AMH and twice more than those with high AMH.

Conflict of interest

The authors have no conflicts of interest to declare.

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