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**Conversion of in vitro fertilization cycles to intrauterine inseminations
in patients with a poor ovarian response: risk of multiple pregnancies.**

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Abstract

Purpose: To determine the risk of multiple pregnancies (MP) following conversion of in vitro fertilization (IVF) cycles to intrauterine insemination (IUI) when a poor ovarian response (POR) is diagnosed during controlled ovarian stimulation (COS).

Methods: We undertook a retrospective study in our teaching hospital from January 2012 to December 2017. We included all IVF cycles with POR that were converted to IUI (<5 follicles \geq 14 mm and peak estradiol level < 1000 pg/mL on trigger day).

Results: Overall, 205 IVF cycles that were converted to IUI in 128 patients were analyzed. Mean age was 34.1 ± 4.6 years, mean antral follicle count was 11 ± 5.3 and mean AMH was 1.8 ± 2.9 ng/L. The main causes of infertility were unexplained (41%) (84/205) and diminished ovarian reserve (35%) (72/205). Of all the cycles converted to IUI, 53 (26%) had one mature follicle on trigger day, 56 (27%) had 2, 56 (27%) had 3, and 40 (20%) had 4. The live birth rate (LBR) was 7.3% (15/205), and the miscarriage rate was 28.6% (6/21). There were 3 twin pregnancies, but no higher order pregnancies; the MP rate was 14.3% (3/21). There was no significant difference in the MP rate between patients with 1-2 mature follicles and patients with 3-4 mature follicles (18.2% vs 10%, $p=0.99$, respectively).

Conclusion: In IVF cycles converted to IUI for poor response, the risk of MP is acceptable (14%) with no higher order pregnancies, even with 3 or 4 follicles \geq 14 mm on trigger day.

Key words: multiple pregnancy, IVF, conversion to IUI, poor ovarian response.

Abbreviations:

AFC: antral follicle count

AMH: anti-Mullerian hormone

BMI: body mass index

COS: controlled ovarian stimulation

CPR: clinical pregnancy rate

GA: gestational age

ICSI: intracytoplasmic sperm injection

IU: International Units

IVF: intrauterine insemination

IVF: in vitro fertilization

LBR: live birth rates

MP: multiple pregnancies

MPR: multiple pregnancies rates

OATS: oligoasthenoteratospermia

PGD: Preimplantation Genetic Diagnosis

PGS: Preimplantation Genetic Screening

POR: Poor ovarian response

Introduction

Poor ovarian response (POR) to controlled ovarian stimulation (COS) is encountered in approximately 6% of in vitro fertilization (IVF) cycles [1,2]. In 2011, the European Society of Human Reproduction and Embryology (ESHRE) published the Bologna criteria in order to “standardize the definition of POR in a simple and reproducible manner [3]. At least two of the following three criteria are required to establish the definition of POR: (1) Advanced maternal age (>40 years) or any other risk factor for POR. (2) A previous POR (≤ 3 oocytes with a conventional stimulation protocol). (3) An abnormal ovarian reserve test (i.e. antral follicle count (AFC) less than 5–7 follicles or anti-Müllerian hormone (AMH) below 0.5–1.1 ng/ml). However, these criteria have been criticized for many reasons, and several revisions have been proposed. [4,5].

Patients diagnosed with a POR during a COS cycle can decide to continue the stimulation cycle all the way to the oocyte retrieval, and receive the embryo transfer if there are any available. [3,5]. Another option at the opposite spectrum is to cancel the cycle as soon as the POR is noted. However, it is a sensitive and difficult decision with important emotional and financial ramifications. The third and final option for these patients can be found half-way between the previous two: converting the IVF cycle to an intrauterine insemination (IUI), thus eliminating the risks of a failed oocyte retrieval/embryo transfer, while allowing the couple to still benefit from the ovarian stimulation.

In most cases of POR, less than 5 mature follicles are obtained following ovarian stimulation with high doses of exogenous gonadotropins, [1,2]. On the other hand, conversion of IVF to IUI can be offered to women with one to four mature follicles on ultrasound, with at least one patent tube and whose partner’s sperm parameters are

adequate [6,7]. Conversion to IUI takes into account other general factors as well, such as the woman's age, the etiology of infertility and the history of previous IVF or IUI attempts, as well as factors more specific to the cycle itself, such as the estradiol levels on trigger day [2,3,5,6,8-11].

Some studies suggest it remains advantageous to proceed with the planned IVF cycle, while others show comparable outcomes between IVF and conversion to IUI [2,3,5,6,8-11]. A French multicentric Randomized Controlled Trial is currently underway with the objective of assessing the best strategy for these patients [12].

As previously mentioned, there are many elements that are taken into consideration when making the decision between IVF, IUI or cancellation. For instance, two factors usually lead physicians to favor IVF over IUI: (1) the lower overall success rates with IUI compared to IVF, (2) the risk of multiple pregnancies (MP) with IUI in cases with more than two mature follicles on ultrasound. While several studies addressed the former [6,8-11], there are no studies that have estimated the risks of MP in IVF cycles converted to IUI for POR. This is why we undertook this study with the primary objective of assessing the risks of MP following conversion to IUI in patients with POR to COS. Our secondary objectives were to evaluate the MP rates according to the number of mature follicles, to analyze the live birth rates (LBR) and miscarriage rates following conversion to IUI, and assess the outcomes according to the thresholds of age, antral follicle count (AFC) and serum anti-Mullerian hormone (AMH) levels, as defined by the Bologna criteria [3].

Methods

We undertook a retrospective study at the Angers university hospital in France, between January 2012 and December 2017.

The inclusion criteria were: (1) age ≥ 18 and < 43 years; (2) IVF cycles, with and without Intracytoplasmic sperm injection (ICSI), following COS using an agonist (long and short) or an antagonist protocol, urinary or recombinant gonadotropins, with only ≤ 4 mature follicles (≥ 14 mm) on trigger day. Each follicle was measured by taking the mean of two perpendicular diameters. We chose the threshold of ≥ 14 mm to define a mature follicle since it is the most commonly used in the literature [2,3,5,8-10], with studies showing that the probability of obtaining a mature oocyte is 93% in follicles ≥ 14 mm [13]. (3) Serum estradiol level < 1000 pg/mL on ovulation trigger day [10]; (4) Consent of the couple to convert the IVF cycle to an IUI.

We excluded from the study women: (1) with confirmed bilateral tubal occlusion; (2) whose partners have severe oligoasthenoteratospermia (OAT) (< 5 million motile spermatozoa in the ejaculate); (3) with a history of repeated IUI failure (≥ 4); (4) with suboptimal stimulation protocols (protocols with ≤ 150 IU of daily gonadotropins), as well as natural and modified natural cycle protocols.; (5) undergoing IVF for Preimplantation Genetic Diagnosis (PGD) or Preimplantation Genetic Screening (PGS); (6) under legal guardianship; (7) non-French speaking; (8) not beneficiaries of a social security scheme.

Our center's policy is to cancel the oocyte retrieval and convert the cycle to IUI in all patients fulfilling the aforementioned inclusion criteria and none of the exclusion criteria.

Ovulation was triggered with recombinant HCG (Ovitrelle®, 250 μ g), and IUI was

performed 24 to 36 hours later. The sperm, provided by the partner the day of the insemination, was treated with a two-layer density gradient. All inseminations were performed by the attending physicians, fellows and residents, using a soft catheter (Elliocath®). All women performed a serum pregnancy test 14 days after the insemination, and when positive, a transvaginal ultrasound was performed at seven weeks gestational age (GA). We defined a clinical pregnancy as positive fetal heart rate at the first ultrasound, and a miscarriage as loss of a recognized pregnancy <20 weeks GA. All pregnancies with ≥ 2 embryos visualized on ultrasound at 7 weeks GA were considered multiple pregnancies. Live birth was defined as delivery of a viable infant ≥ 25 weeks GA.

All information on pregnancy outcomes were collected by questionnaires sent to all women and their physicians, and by telephone queries for incomplete questionnaires. The questionnaire included questions about the progress of the pregnancy, the delivery date and route, the gender and weight of the baby, as well as the obstetric and neonatal complications if there were any.

Our main outcome measure was the multiple pregnancy (MP) rate. Secondary outcomes measures were: the LBR, overall and according to the thresholds defined by the Bologna criteria (Age (<40 or ≥ 40 years), AFC (<7 or ≥ 7) and serum AMH level (<1.1 ng/mL or ≥ 1.1 ng/mL)) [3]; the MP rate according to the number of mature follicles on trigger day. Statistical analysis was performed using SPSS Statistics 20.0.0 (Chicago, IL). We calculated mean values and standard deviations (SD) for continuous variables and percentages for categorical variables. We compared continuous variables with Student's t test and categorical variables with chi-square and Fisher's exact test. For the main

outcome, a multivariate logistic regression analysis was performed to adjust for age, a potential confounding factor.

Differences were considered statistically significant for p values <0.05.

The ethical review board of the Angers University Hospital approved the study (2018/58), which was performed in accordance with the Declaration of Helsinki and the guidelines of a Good Scientific Practice, as supported by the Head of the Institute. As this study comprises retrospectively collected and analyzed data, the ethical review board approved the waiver of written informed consent.

Results

Overall, 205 IVF cycles that were converted to IUI in 128 patients with POR to COS were included.

Patients' characteristics are listed in Table 1. The mean age was 34.1 ± 4.6 years and the mean body mass index (BMI) was 23.3 ± 3.7 Kg/m². The mean duration of infertility was 2.9 ± 2.4 years, and 79% of cycles (162/205) were cases of primary infertility. Diminished ovarian reserve (DOR) was defined as AMH levels below < 2 ng/ml, or antral follicles count < 10 . The main causes of infertility were unexplained (41%) (84/205) and DOR (35%) (72/205). Mean AMH was 1.8 ± 2.9 ng/mL, mean FSH was 9.4 ± 3.8 IU/L and mean AFC was 11 ± 5.3 . Prior to inclusion in this study, patients had already had a mean of 2 ± 0.9 IUI cycles. We used an antagonist protocol in 67% of cycles (137/205) and a long agonist protocol in 33% (68/205). The mean daily dose of gonadotropins was 321.1 ± 89.5 International Units (IU). On the day of ovulation triggering, the mean number of follicles ≥ 14 mm was 2.5 ± 1.3 , and the mean level of serum estradiol was 465.9 ± 247.1 pg/mL. Of all the cycles converted to IUI, 53 (26%) had one mature follicle on trigger day, 56 (27%) had 2, 56 (27%) had 3, and 40 (20%) had 4. The mean post-wash total motile sperm count on insemination day was 8.05 ± 2.3 million.

Following conversion to IUI, the clinical pregnancy rate (CPR) was 10.2% (21/205), the LBR was 7.3% (15/205), and the miscarriage rate was 28.6% (6/21). There were 3 twin pregnancies, but no higher order pregnancies; the MP rate was therefore 14.3% (3/21) (Table 2). One twin pregnancy occurred in a cycle with 1 mature follicle on trigger day and a peak estradiol level of 583 pg/ml, one in a cycle with 2 mature follicles and an

estradiol level of 456 pg/mL, and one in a cycle with 4 mature follicles and a serum estradiol level of 461 pg/mL. All twin pregnancies were bichorial-biamniotic.

The obstetrical outcomes of the twin pregnancies were as follows: one ended in a normal delivery at 38 weeks gestational age; one was complicated by preterm premature rupture of membranes at 32 weeks GA, with delivery of both twins occurring 3 days later with good neonatal outcomes; and one was complicated by the intra uterine demise of one of the twins at 18 weeks GA; the other was delivered at 38 weeks GA without any complications.

We then divided patients into 2 groups based on the number of mature follicles on trigger day: the “1-2 follicles” and the “3-4” follicles groups. Out of the 205 insemination cycles, 109 (53%) had 1-2 mature follicles on trigger day, and 96 (47%) had 3-4 follicles. (Table 3). There were no significant differences in the patients’ characteristics (age, BMI, type, cause and duration of infertility, and ovarian reserve) between these two groups. Moreover, there were no statistically significant differences in the CPR (10.1% vs 10.4%, $p=0.94$), the miscarriage rate (27.3% vs 30%, $p=0.99$), the MPR (18.2% vs 10%, $p=0.99$), and the LBR (7.3% vs 7.3%, $p=0.99$) between the “1-2” and “3-4” follicles groups, respectively.

After logistic regression controlling for the age, there were no significant differences in the LBR and the miscarriage rate between the “1-2 follicles” group and the “3-4 follicles” group (OR=0.92; 95%CI 0.34-2.57 and OR=1.03; 95%CI 0.3-3.7, respectively).

Table 4 shows LBR according to the thresholds of age, AFC and AMH as defined by the Bologna criteria. LBR was 9.4% (14/176), in women <40 years, compared to 3.4% (1/29) in women ≥ 40 years ($p=0.39$). There were no live births in women with an AFC<7

compared to 8.3% (15/180) in women with an AFC >7 (p=0.14). Finally, LBR was also comparable between women with a serum AMH level < 1.1 ng/mL compared to AMH \geq 1.1 ng/mL (9.8% vs 5.7%, p=0.27).

Discussion

Our study has shown a multiple pregnancy rate of 14.3% following conversion to IUI of IVF cycles in patients with POR to COS, and no higher order pregnancies. Moreover, we did not find any difference in the multiple pregnancy rate according to the number of mature follicles on trigger day (18.2% in patients with 1-2 mature follicles versus 10% with 3-4 follicles, $p = 0.99$). To the best of our knowledge, our study is the first to report on multiple pregnancy rates and compare these rates according to the number of mature follicles in IVF cycles converted to IUI in patients with POR to COS.

The multiple pregnancy rate following IUI with the partner's sperm for all other indications combined is 10% in Europe and 11% in France [14], which seems to be comparable to the 14% twin pregnancy rate found in our study in POR. It is worth noting that patients could have up to four follicles before IUI in our study, whereas patients with more than three mature follicles might be canceled in other indications (mild male factor or anovulatory infertility).

We found more than 10 studies reporting on the outcomes of conversion to IUI in POR [1,2,10,11,15-20], but only two of them analyzed the twin pregnancy rates [10,11]. The first is a retrospective review by Norian et al. [10] of 269 cycles, where IVF were converted to IUI if there were <5 follicles ≥ 14 mm, and a serum estradiol level <1000 IU/L. The CPR was 5.2% (14/269), the twin pregnancy rate was 21% (3/14), and the mean number of mature follicles on trigger day was 2.3 ± 1.1 [10]. However, there were no information on the number of mature follicles on trigger day in the 3 cycles that ended in twin pregnancies [10]. The second study is a retrospective analysis of 47 conversions to IUI in POR which found a CPR of 14.9% (7/47) and a twin pregnancy rate of 15%

(1/7) [11]. However, the study did not report the number of mature follicles available on trigger day in the twin pregnancy cases, but only the overall mean number (2.73 ± 1) [11].

We did not find any study in the literature reporting on twin pregnancy rates in the presence of 3-4 mature follicles on trigger day in IVF cycles converted to IUI for poor ovarian response. In fact, very few studies have addressed the issue even in normal responders. A recent large retrospective study from China reported LBR by type of ovarian stimulation (natural cycle, letrozole, clomiphene citrate, or gonadotropins) in 14519 IUI cycles for various indications (mild male factor, unexplained) [21]. In the 2579 IUI cycles with gonadotropins, the LBR was 9.5%, and the rate of twin pregnancies was 11.3%, 16.9%, 13.2% and 19.4% in cycles with 1, 2, 3 or ≥ 4 mature follicles, respectively. Moreover, there was only one triplet pregnancy reported, in the ≥ 4 follicles subgroup [21]. Another retrospective study included 1038 IUI cycles for various indications in order to find the predictive factors for twin pregnancies [22]. The twin pregnancy rate was 38% (5/13) when there were more than two follicles >16 mm on trigger or peak LH day [22]. The rate seems high compared to the 10% reported in our study with 3-4 follicles ≥ 14 mm. This can be explained by the different populations (poor responders compared to normal responders) and indications, but also by the fact that Merviel et al. [22] used a higher threshold (16 mm versus 14 mm) to define a mature follicle, thus increasing the chances of having mature oocytes after trigger.

On the other hand, the relatively low twin pregnancy rate in women with 3-4 mature follicles in our study could be explained by the low oocyte quality in women with DOR (35% of the study population) and POR (100% of study population). Indeed, several

studies have reported decreased embryo morphology grades, increased pregnancy losses, and increased aneuploid miscarriages and viable aneuploid pregnancies (trisomy 13,18 and 21) in young patients with DOR and POR [23-28].

The overall LBR following conversion to IUI in our study was 7.3%, which is comparable to rates reported by other studies using the same criteria for conversion to IUI in POR (≤ 4 follicles ≥ 14 mm with serum estradiol level ≤ 1000 pg/ml on trigger day): 4.1% in the study by Norian et al. [10] and 7.4% in the study by Shohieb et al. [20].

Furthermore, we analyzed the LBR according to the thresholds used in the Bologna criteria to define POR [3], and noted the following: (1) the LBR was lowered by three in patients ≥ 40 years (3.4% versus 9.4% in women < 40 years, NS (the numbers were too low to reach statistical significance)); (2) there were no live births in women with an AFC < 7 ; (3) the LBR was acceptable (9.8%) in women with an AMH < 1.1 ng/mL. These results confirm that maternal age and AFC are significant predictive factors of pregnancy and live birth in IUI cycles [29], while AMH is not an independent predictive factor [30].

The main limitation of our study is the retrospective, single-center design. Moreover, despite including a considerable number of cycles, the number of live births was not high enough to allow us to compare outcomes between different subgroups and draw more significant conclusions, mostly because of the poor overall prognosis of patients with POR. However, to the best of our knowledge, our series is the first in the literature specifically designed to assess multiple pregnancy rates in IVF cycles converted to IUI for POR. Moreover, we compared for the first time the multiple pregnancy rates according to the number of mature follicles on trigger day, and provided data on live

births. However, there are still considerable data missing on the outcome of conversion of IVF to IUI in POR that retrospective and single center studies cannot provide.

We have therefore launched a prospective multicenter randomized trial to compare the rate of multiple pregnancies between IVF and conversion to IUI in POR, and analyze the chances of multiple pregnancies according to the number of mature follicles on trigger day [12]. The results will be available in 2021.

Conclusion

Our study shows that the overall multiple pregnancy rate in IVF cycles converted to IUI for POR is 14.3%, without any higher order pregnancy. Even in patients with 3 or 4 mature follicles on trigger day, the multiple pregnancy rate was 10% and was comparable to the rates of women with 1 or 2 follicles. These results confirm that IUI is a viable alternative for patients with POR, offering acceptable live birth rates without significantly increasing the risk of multiple pregnancies. Therefore, we believe that conversion to IUI can be offered to patients with a poor response to COS when there are less than 5 mature follicles on trigger day with a serum estradiol level lower than 1000 pg/ml.

Author contributions SA: project development/data collection and data analysis. CV: data collection and data analysis. PMP: project development/data collection and data analysis. RC: data collection and data analysis. GL: data analysis and manuscript editing. PD: data analysis and manuscript editing. HEH: data analysis and manuscript writing/editing. PEB: project development/data collection/data analysis and manuscript writing/editing.

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Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: The ethical review board of the Angers University Hospital approved the study (2018/58). All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: as this study comprises retrospectively collected and analyzed data, the ethical review board approved the waiver of written informed consent.

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Table 1. Baseline characteristics of patients and stimulation cycles.

		IUI conversion (n = 205)
Age (years)		34.1 ± 4.6
Body Mass Index (kg/m ²)		23.3 ± 3.7
Primary infertility		79% (162/205)
Duration of infertility (years)		2.9 ± 2.4
Causes of infertility	Unexplained	41% (84/205)
	Diminished ovarian reserve*	35% (72/205)
	Endometriosis	15% (30/205)
	Ovulation disorder	9% (19/205)
Number of prior IUI attempts		2 ± 0.9
Antral Follicle Count		11 ± 5.3
AMH (ng/mL)		1.8 ± 2.9
Day 3 FSH (IU/L)		9.4 ± 3.8
Day 3 Estradiol (pg/mL)		48.6 ± 31
Stimulation protocol	GnRH antagonist	67% (137/205)
	GnRH agonist	33% (68/205)
Mean daily dose of exogenous gonadotropins (IU)		321.1 ± 89.5
Peak E2 (pg/mL)		465.9 ± 247.1
Mean number of mature follicles (≥ 14 mm) on trigger day		2.5 ± 1.3
Total number of mature follicles (≥ 14 mm) on trigger day	1	26% (53/205)
	2	27% (56/205)
	3	27% (56/205)
	4	20% (40/205)
Post-wash Total Motile Sperm Count (million)		8.05 ± 2.3

Data are expressed as percentage (n/total) or mean +/- standard deviation.

* Diminished ovarian reserve was defined as AMH levels below < 2 ng/ml, or antral follicles count < 10.

Table 2. Cycle outcomes after conversion to IUI

	IUI conversion (n = 205)
Clinical pregnancy rate	10.2% (6.6-15.4; 21/205)
Miscarriage rate	28,6% (12.2-53.3; 6/21)
Twin pregnancy rate	14.3% (3.8-37.4; 3/21)
Higher order pregnancy rate	0% (0/21)
Live birth rate	7.3% (4.3-12.0; 15/205)

Data are expressed as percentage (Confidence interval 95%; n/total)

Table 3. Cycle outcomes according to the number of mature follicles.

	1-2 follicles (n = 109 cycles)	3-4 follicles (n = 96 cycles)	p
Clinical pregnancy rate	10.1% (11/109)	10.4% (10/96)	0.94 ^a
Miscarriage rate	27.3% (3/11)	30% (3/10)	0.99 ^b
Multiple pregnancy rate	18.2% (2/11)	10% (1/10)	0.99 ^b
Live birth rate	7.3% (8/109)	7.3% (7/96)	0.99 ^a

Data are expressed as percentage (n/total) ^aChi-Square test ^bFischer's exact test

Table 4. Live birth rates according to the Bologna criteria.

		LBR	p
Age (years)	< 40	9.4% (14/176)	0.39
	≥ 40	3.4% (1/29)	
AFC	< 7	0% (0/25)	0.14
	≥ 7	10% (15/180)	
AMH (ng/mL)	< 1.1	9.8% (8/82)	0.27
	≥ 1.1	5.7% (7/123)	

Data are expressed as percentage (n/total)