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Original Research Article

Practice of ovarian stimulation among poor responders in a country with limited resources: case of the Paul and Chantal Biya human reproduction center, Yaoundé, Cameroon

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ABSTRACT

Background: Approximately 2 to 30% of women who undergo ovarian stimulation have a poor response. The management is not clearly defined, constituting a challenge for clinicians and biologist.

Methods: This was a longitudinal descriptive study with prospective data collection that took place at Paul and Chantal Biya Gynecological Endoscopic surgery and Human Reproductive Teaching Center, during a period of 1 year and 6 months, from June 2020 to November 2021. Our objective was to describe the practice of ovarian stimulation of patients judged to be poor responders in CHRACERH. We highlighted the numbers, percentages, averages and their standard deviations. Statistical analyzes were carried out using SPSS v15.0 software.

Results: Out of 159 cycles included, we identified 55 patients considered possible poor responders, i.e. a prevalence of 34.6%; the average age was 36.36±6.2 years with extremes ranging from 33 to 44 years, mainly overweight in 81.8% of cases. The average AMH level was 0.9±0.4 ng/ml, the average CFA 6.15±3.7. 87.3% of patients were on their first stimulation attempt, the long-delay agonist protocol and the short agonist protocol were used in 58.2% and 41.8% respectively. The maximum daily dose in patients was 300 IU with an average total dose of gonadotropin used of 3371.8±874 IU. At the end of the ovarian stimulation, the average number of follicles collected and mature oocytes were respectively 5.6±3.6 and 4±2.9 with an average maturity rate of 70.7±31% as well as an average fertilization rate in ICSI of 45.2±32%. The pregnancy rate was 12% among poor responders.

Conclusions: Poor responders constitute a large proportion of patients stimulated at CHRACERH; their still low pregnancy rates prompt an improvement in care.

Keywords: CHRACERH/Yaoundé, IVF/ICSI, Ovarian stimulation, Poor responders

INTRODUCTION

According to literature data, 2 to 30% of women who undergo ovarian stimulation have a poor response.¹ However, despite advances in ART techniques, there is no universally accepted definition of poor responders to ovarian stimulation and management is not clearly stated, therefore constituting a challenge for clinicians and

biologists.^{2,3} The creation of the first public ART center in Cameroon, the “hospital center for research and application in endoscopic surgery and human reproduction” (CHRACERH) in Cameroon in 2016 aroused great hope among the populations. However, the economic cost in the absence of health insurance makes a personalized therapeutic offer imperative, the latter depending on the clinical and paraclinical characteristics

of the patients, thus maximizing the chances of pregnancy. These characteristics having genetic and environmental variabilities, we set out to describe the epidemiological, clinical and therapeutic profile of poor responders in CHRACERH, Cameroon.

METHODS

This was a longitudinal descriptive study with prospective data collection, taking place at CHRACERH (Yaoundé-Cameroon), during a period of 1 year and 6 months, from June 2020 to November 2021.

We selected poor responders to stimulation among patients admitted for ovarian stimulation at CHRACERH during our study period.

Thus, all patients presenting at least 2 of the 3 POSEIDON criteria and who agreed to participate in our study were included in our study.^{3,4} We then carried out non-exhaustive consecutive sampling. The clinico-biological data were collected and anonymized using a technical sheet previously designed and tested.

Statistical analysis

Statistical analysis were carried out by SPSS v15.0.

Description of the stimulation protocol

In our center at this time, poor responders were placed either on a long-delayed agonist protocol in the luteal phase or on a short “micro-flare” agonist protocol. The gonadotropins used were either hMG or a recombinant FSH at 300 IU directly in poor responders, the doses having to be revised downwards depending on the evolution. Sono-biological monitoring until at least 2 follicles of 19 mm were obtained. The trigger was based on an intramuscular injection of 10,000 IU of human chorionic gonadotropin (HCG), followed by an oocyte retrieval 36 hours later. The luteal phase was supported by daily intake of micronized progesterone 600 mg/day vaginally from the day of oocyte retrieval until the pregnancy test (12 days later). The embryo transfer was most often carried out on day 2 or day 3 after the puncture under ultrasound control. Pregnancy was initially diagnosed by a positive plasma HCG level on day 12 after embryo transfer.

RESULTS

Clinical and biological characteristics of poor responders

The average age of poor responders was 36.36 ± 6.2 years with extremes ranging from 33 to 44 years. Only 18.2% had normal BMI the rest were at least overweight. The mean AMH level was 0.9 ± 0.4 ng/ml, and the mean CFA was 0.9 ± 0.4 .

Therapeutic characteristics of poor responders

The majority of patients, 48/55 (87.7%), were on their first attempts, the most used stimulation protocol was the long agonist protocol 32/55 (58.2%). All patients on the agonist protocol received pre-treatment with COCs for 12-21 days. The mean total gonadotropin dose was 3371.8 ± 874 IU.

Table 1: Clinical and biological characteristics of poor responders.

	Frequency	Percentage
Age (years)		
<35	17	30.9
35 and more	38	69.1
Mean±SD (Min-Max) 36.36±6.2 (33-44)		
BMI (kg/m²)		
18.5-25	10	18.2
25-30	18	32.7
30-35	5	9.1
35-40	1	1.8
Mean±SD (Min-Max) 27.04±4.254 (19-37)		
AMH (ng/ml)		
<1.2	44	80.0
≥1.2	11	20.0
Mean±SD (Min-Max) 0.9±0.4 (0.12-2.31)		
CFA		
Less than 5	23	41.8
5 and more	32	58.2
Mean±SD (Min-Max) 6.15±3.7 (0-17)		

Table 2: Therapeutic characteristics of poor responders.

	Frequency	Percentage
Attempt range n=55		
1	48	87.3
2	5	9.1
3	2	3.6
Type of protocol n=55		
Short agonist	23	41.8
Long-delayed agonist	32	58.2
Prior treatment with COCs n=23		
Yes	23	100
No	00	00
Type of gonadotropin n=55		
FSHr (Gonal F*)	05	9
HMG (Menopur*)	50	91
Total dose of gonadotropins	Mean±SD	Min-max
	3371.8±874 UI	1500-5400

Outcome of ovarian stimulation

The average number of follicles collected was 5.6 ± 3.6 with extremes of 0 and 22 follicles. 2/55 (3.6%) had had blank punctures, but the majority of patients, i.e. 34/55

(61.8%), had sub-optimal responses (4-9) follicles, and only 18/55 (32.7%) actually had poor response.

When we looked at mature oocytes among the 53 patients who obtained at least one follicle during the puncture, almost all of the patients according to the POSEIDON criteria had either a poor response 24/53 (45.3%) or a sub-optimal response 28/53 (52.8%).

Table 3: Outcome of ovarian stimulation.

Variables	Frequency	%
Punctured follicles (N=55)	mean±SD (Min Max): 5.6±3.6 (0-22)	
0	2	3,6
1-3	16	29,1
4-9	34	61,8
>9	3	5,5
Number of matured oocytes (N=53)	Mean±SD (Min-Max): 4±2.9 (0-20)	
0	3	5.7
1-3	21	39.6
4-9	28	52.8
>9	1	1.9
Percentage of maturity (N=53)	Mean±SD 70.7±31.4%	
<25	3	5.7
25-50	9	17
50-75	13	24.5
75 and more	28	52.8
Fertilization rate (N=50)	Mean ±SD 45.2±31.8%	
<25	13	26
25-50	9	18
50-75	21	42
75 and more	7	14

Table 4: Outcome of medically assisted procreation, MAP.

	Frequency N (50)	%
Pregnancy/transfer		
Yes	6	12
No	44	84
Evolution		
Spontaneous AB	4	8
Delivery	1	2

Although 28/53 (52.8%) of poor responders had a maturity percentage above 75%, almost half had percentages below. Among the patients whose oocytes had been fertilized, only 7/50 (14%) had ICSI fertilization rates greater than 75%.

Outcome of medically assisted procreation (MAP)

The pregnancy rate per transfer was 12%, resulting in 2% live births.

DISCUSSION

At CHRACERH only long-delayed and short agonist protocols are used in poor responders. This could be justified by the availability of the products and their costs. In literature the superiority of one stimulation protocol compared to another has not yet been clearly demonstrated, however at present the antagonist protocol is the most used due to its ease of use and number days of stimulation which is reduced.⁵⁻⁸ An experimental study on the use of the antagonist protocol is underway in the department.

All patients on a short agonist protocol had benefited from pretreatment with COCs, contrary to the ESHRE recommendations in 2019 which do not suggest their use because it would reduce the response to ovarian stimulation.⁸ Some studies have demonstrated that pretreatment with estradiol in the luteal phase would improve the number of follicles collected, and therefore the pregnancy rate in poor responders.⁹⁻¹¹ But all these studies focused on the antagonist protocol which until now was reserved for potential hyper responders due to the cost of the products and the unavailability of the latter in our context. It would therefore be interesting for us to conduct a study on the use of estradiol as pretreatment.

In our practice hMG (MENOPUR*), as to FSHr (GONAL F*), is used as second line in long protocols. However, although there is no superiority in the use of urinary HMG compared to recombinant FSH, in the case of a long protocol there is strong pituitary desensitization preventing the production of endogenous LH necessary for follicular maturation, the place of rFSH in the long-delay protocol is yet to be demonstrated.¹² Based on the data in the literature, it would not seem wise to use rFSH in poor responders after long-term desensitization to GnRH agonists.¹²

Furthermore, FSHr-LHr is not used in our service due to the unavailability of the drug on one hand and its cost on another.

The maximum dose of gonadotropin did not exceed 300IU in our protocols, which is in accordance with the 2019 ESHRE recommendations, unlike the American recommendations which go up to 650 IU.

However, alternative attitudes and adjuvant treatments such as double oocyte stimulation or cumulative oocyte collection are not yet adopted in our practice to increase the number of oocytes and thus increase the chances of transferring euploid embryos.^{9,13} Adjuvant treatments such as growth hormone, androgens which in certain RCTs have raised hope in terms of follicles collected and even pregnancy rates are not yet implemented in our context.¹⁴⁻¹⁹

After ovarian stimulation, the average number of follicles collected and mature oocytes were 5.6± 3.6 and 4± 2.9,

respectively. Our results are comparable to those of Dermirol et al in 2009 who found an average number of mature oocytes of 4.3 ± 2.1 . Merviel in 2015 reported an average number of mature oocytes above our results, i.e. 6 ± 4 mature oocytes.^{6,7}

After embryo transfer the pregnancy rate was 12%, which is consistent with literature data which reports a pregnancy rate in poor responders ranging from 8-29%.⁸ This wide interval would result in the heterogeneity of poor responders in the literature. Same as Ebrahemi reported a rate of 14.6% or even Schimberni et al a rate of 29.3%. As described above, some RCTs have demonstrated the beneficial effects of certain therapies such as androgens, myo-inositol, pre-treatment based on estradiol, etc. which it would be interesting to implement in our socio-economic context or IVF is not managed and the expected result often seems imperative for the couple.

CONCLUSION

The poor responders in CHRACERH had an average age of 36.36 ± 6.2 years, mostly overweight. The long-delay agonist protocol and the short agonist protocol were the only ones used, mainly with hMG (MENOPUR). Few therapeutic interventions specific to this group of patients have been implemented to date in our practice, and the results in IVF/ICSI constitute a real challenge.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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