Medically Assisted Reproduction in Natural Cycle: Outcome Evaluation of a Reproductive Medicine Department

Procriação Medicamente Assistida em Ciclo Natural: Avaliação dos Resultados de um Departamento de Medicina da Reprodução

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Acta Med Port 2019 Jan;32(1):25-29 ▪ https://doi.org/10.20344/amp.10195

ABSTRACT

Introduction: Medically assisted reproduction in natural cycle has been investigated, especially in women with poor response to conventional ovarian stimulation, with endometrial receptivity improvement, lower cost and possibility of successive cycles. The disadvantages are: lower profitability per treatment cycle and higher cancellation rate. The aim of this study was to determine the rate of clinical pregnancy in infertile women subjected to medically assisted reproduction in natural cycle.

Material and Methods: Retrospective study of 149 medically assisted reproduction without ovarian stimulation of 50 infertile women, between January/2011 and October/2014.

Results: The mean age of women undergoing medically assisted reproduction in natural cycle was 36.1 years. Approximately half (46.0%) of the cycles were performed in poor responders. On the day of ovulation trigger, the mean diameter of the follicle was 17.5 mm. Twenty-three cycles (15.4%) were canceled prior to ovulation trigger. In 8 cycles (5.3%), ovulation occurred between ovulation trigger and oocyte retrieval. In the majority of cycles (n = 118; 79.2%) oocyte retrieval was executed, a medically assisted reproduction technique was performed in 71 (47.6%), mostly intracytoplasmic injection. The overall fertilization rate was 77.5%. In 40 cycles (26.8%) there was embryo transfer. The implantation rate and the clinical pregnancy rate by embryo transfer was 35.0% and 25.0%, respectively. Most pregnancies occurred in poor responders, according to Bologna criteria.

Discussion: Although the pregnancy rate per cycle started was 6.7%, the rate of clinical pregnancy per embryo transfer is quite satisfactory, being a group of women with unfavorable responses in previous treatments. The relatively high rates of cycle cancellation are mitigated by the greater simplicity and lower cost of these cycles.

Conclusion: The results obtained in this study demonstrate that Medically Assisted Reproduction in natural cycle may be an alternative treatment for ovarian stimulation in patients with poor prognosis, whose only alternative would be oocyte donation.

Keywords: Menstrual Cycle; Pregnancy; Reproductive Techniques, Assisted

RESUMO

Introdução: As técnicas de procriação medicamente assistida em ciclo natural têm sido investigadas, sobretudo em mulheres com má resposta à estimulação ovárica convencional, observando-se melhor recetividade endometrial, custo inferior e possibilidade de realização de ciclos sucessivos. Como desvantagens salientam-se: menor eficácia por ciclo de tratamento e maior taxa de cancelamento. O objetivo definido para este trabalho foi determinar a taxa de gravidez evolutiva em mulheres inférteis, submetidas a procriação medicamente assistida em ciclo natural.

Material e Métodos: Estudo retrospetivo de 149 ciclos de procriação medicamente assistida sem estimulação ovárica de 50 mulheres inférteis, entre janeiro de 2011 e outubro de 2014.

Resultados: As mulheres submetidas a procriação medicamente assistida em ciclo natural tinham, em média, 36,1 anos. Aproximadamente metade (46,0%) dos ciclos realizaram-se em más respondedoras. No dia do desencadeamento da ovulação o diâmetro médio do folículo foi 17,5 mm. Cancelaram-se 23 ciclos (15,4%) previamente ao desencadeamento. Em 8 ciclos (5,3%) ocorreu ovulação entre o desencadeamento e a punção folicular. Na maioria dos ciclos (n = 118; 79,2%) efetuou-se punção folicular, realizando-se técnica de procriação medicamente assistida em 71 (47,6%), maioritariamente injeção intracitoplasmática. A taxa de fecundação global foi 63,8%. Em 40 ciclos (26,8%) houve transferência embrionária. A taxa de implantação e de gravidez evolutiva por transferência embrionária foram de 35,0% e 25,0%, respetivamente. A maioria das gestações ocorreu em más respondedoras, conforme critérios de Bolonha.

Discussão: Apesar de a taxa de gravidez por ciclo iniciado ser de 6,7%, a taxa de gravidez evolutiva por transferência embrionária é bastante satisfatória, sendo mulheres com respostas desfavoráveis em tratamentos prévios. As taxas relativamente elevadas de cancelamento do ciclo são atenuadas pela simplicidade e menor custo destes ciclos.

Conclusão: Os resultados obtidos neste trabalho demonstram que as técnicas de procriação medicamente assistida em ciclo natural podem ser uma alternativa de tratamento à estimulação ovárica em doentes com mau prognóstico, cuja alternativa seria o recurso à doação de ovócitos.

Palavras-chave: Ciclo Menstrual; Gravidez; Técnicas de Reprodução Assistida

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Recebido: 06 de janeiro de 2018 - Aceite: 26 de setembro de 2018 | Copyright © Ordem dos Médicos 2019

INTRODUCTION

The retrieval of multiple oocytes and multiple follicular growth leading to higher profitability and success rate are affected by controlled ovarian stimulation, a relevant component of medically assisted reproduction (MAR).[1] Ovarian stimulation protocols combining agonists or antagonists of gonadotropin-releasing hormone (GnRH) with follicle-stimulating hormone (FSH) are most frequently used[2,3] even though involving some complications[4] including the ovarian hyperstimulation syndrome[5] and high levels of stress,[1,2,7-9] apart from being an expensive treatment.[6] In addition, some doubts remain regarding long-term risks, namely the risk of developing ovarian cancer.[1,2,10] A potential negative effect of supra-physiological levels of steroids on endometrial receptivity has also been described, as well as on embryo quality and on an increasing incidence of obstetric complications.[11-13]

Monitoring of a spontaneous cycle, going without the standard ovarian stimulation, aimed at egg retrieval immediately upon luteinising hormone (LH) surge are involved in MAR in a natural ovulatory cycle.[2,5,14] This is a less expensive procedure, less physically demanding and can be carried out in consecutive cycles.[15-17] Apart from these advantages, it is not associated with the risk of ovarian hyperstimulation syndrome, with an apparently higher endometrial receptivity.[5,18-21] However, high cycle cancellation rates have been found, mostly due to the presence of ovulation prior to egg retrieval[20] leading to lower pregnancy rates.[9] The fact that only one embryo is usually obtained corresponds to another disadvantage associated with MAR in a natural cycle, corresponding to a lower pregnancy rate per cycle.[2] No major advances have emerged regarding an increasing efficacy of MAR in poor responder patients. According to the Bologna criteria (European Society of Human Reproduction and Embryology - ESHRE),[22] the presence of at least two out of the following three characteristics will be enough to consider a patient as poor responder: advanced maternal age (aged 40 or older) or another risk factor for poor ovarian response, poor ovarian response (retrieval of three or less oocytes with standard stimulation protocols) and / or abnormal ovarian reserve testing (antral follicle count <5-7 or anti-Mullerian hormone level < 0.5 – 1.1 ng/mL). A classification of low prognosis patients in MAR into four subgroups has recently been proposed by the POSEIDON stratification (Humaidan *et al.*)[23] based on ovarian quantitative and qualitative parameters, including patients with poor ovarian response in addition to those with sub-optimal response.

No therapeutic alternative has emerged over the past few years for this group of patients with lower success rates in MAR when compared to other patient subgroups.[24] MAR in a natural cycle is a relevant alternative in this subgroup of patients.[6,25]

This study was aimed at assessing the pregnancy rate in infertile patients submitted to MAR in a natural cycle.

MATERIAL AND METHODS

This was a retrospective study of 149 natural cycles in 50 infertile patients attending the Human Reproduction Department (*Serviço de Reprodução Humana*) at the *Centro Hospitalar e Universitário de Coimbra* from Jan 2011 to Oct 2014. Patients included in the study had previously undergone unsuccessful MAR treatment corresponding to poor responder patients, classified according to the Bologna criteria, in addition to poor outcome patients having undergone at least one MAR cycle with standard ovarian stimulation and systematically obtaining poor oocyte quality or transfer cancellation due to poor embryo quality. All patients having undergone MAR in a natural cycle throughout this period of time were included in the study.

According to the natural cycle protocol in use at the department, an ultrasound was performed on day 2-3 and on day 9-10 of the cycle, in addition to LH and estradiol levels in case of the development of a dominant follicle (follicle ≥ 10 mm); all patients were ideally given 5,000 IU i.m. of hCG, except with LH level > 20 IU/L; egg retrieval was performed without sedoanalgesia 24-36 hours upon the administration of hCG and/or with spontaneous LH surge, defined by a LH level ≥ 20 mIU/mL). A luteal phase supplementation with intravaginal progesterone was started from the day of egg retrieval (200 mg, 3 x /day). Embryo grading into three levels was carried out, according to morphological criteria (number, size and blastomere regularity, degree of fragmentation, multinucleation and cytoplasmic appearance) and grade 1 and 2 embryos were considered as having good quality.

The following parameters were considered: mean age, rate of poor respondent patients, number of cycles, average follicle diameter at the time of ovulation triggering, number of cancelled cycles prior to triggering, number of cycles submitted to egg retrieval (ET), number of eggs retrieved, number of cycles in which a MAR treatment has been carried out, total fertility rate, number of cycles with embryo transfer, grade and type of transferred embryos, implantation rate, ongoing pregnancy rate – defined as the presence of intrauterine pregnancy with an embryo with heart beat at 7-8 weeks and pregnancy number in poor respondent patients. The classification of a patient as poor respondent was made according to the Bologna criteria.[4]

Data were obtained from the review of patient's clinical record and were processed with the Statistical Package for the Social Sciences (SPSS®, version 21) software and analysed with the use of descriptive statistics.

RESULTS

A mean age of 36.7 years was found in our group of patients having undergone MAR in a natural cycle (SD = 2.6). A total of 30 patients (60%) were considered as poor responders in 69 cycles (46.3%). The remaining 20 patients (40.0%) were considered as poor outcome patients in 80 cycles (53.7%).

Two or more treatment cycles were performed in most patients (59.7%) and a 2.96 mean number of cycles per patient has been found (SD = 2.3).

A 17.5 mm mean follicular diameter has been found at the day of ovulation induction (SD = 2.1). Cycle cancellations have occurred due to (i) absence of follicular dominance found in ultrasound monitoring performed at day 9-10 of the cycle (n = 4), (ii) presence of functional ovarian cyst (n = 2) (diameter >22 mm) or (iii) spontaneous ovulation prior to ultrasound monitoring (performed in a day to be defined according to the size of the follicle at day 9-10) (n = 17). Ovulation was obtained in eight cycles (5.4%) following the administration of hCG and before egg retrieval. No complications were found in any patient regarding egg retrieval and the procedure was well tolerated, even though no pain scores were ever used in pain assessment. MAR treatment was used in 71 cycles (47.6%), including in vitro fertilisation (IVF) in 17 (23.9%) and intracytoplasmic sperm injection (ICSI) in 54 cycles (76.1%). A 69.0% fertility rate has been found, with embryo transfer in 26.8% (n = 40) and a 35.0% and 9.4% implantation rate per embryo transferred and per started cycle were obtained (n = 14), respectively. An ongoing pregnancy rate per started cycle of 6.7% (n = 10) has been found, with a pregnancy rate per ET and per patient of 25.0% and 20.0%, respectively. A pregnancy was achieved by 13.3% (n = 4) of poor responder patients, with a lower ongoing pregnancy rate (10.0%; n = 3). Results are shown in Table 1 while transferred embryo quality is shown in Table 2.

DISCUSSION

No major advances in terms of increased efficacy of medically-assisted reproduction in poor responder patients have been found. MAR in a natural cycle seems an adequate alternative to ovarian stimulation, due to the fact of being more user-friendly, less expensive and free from the complications associated with ovarian stimulation.[15,16,28,29] The fact that no sedoanalgesia is required in egg retrieval is an additional advantage.[30] It is also known that, in order to improve its efficacy, MAR in a natural cycle can be performed in consecutive cycles, involving no risk for patients.[2,17,29] As no more than one embryo is usually obtained with these treatment protocols, a strong decline in multiple pregnancy rate has been found,[9] which is still a major issue associated with MAR with ovarian stimulation. However, MAR in a natural cycle is associated with high cancellation rates due to premature LH surge, with the subsequent loss of the single follicle usually in development within each cycle.[20] On the other hand, it has been suggested that oocytes of a worse quality may be recruited under high doses of gonadotropins that are used in cycles with ovarian stimulation that would not have been selected in a natural cycle, which is a particularly important issue in poor responder patients. Therefore, better oocyte quality seems to exist in natural cycle, which is due to the natural selection of a dominant follicle.[31] Some authors have described modified natural cycles using GnRH antagonist as an alternative to natural cycles in poor responder patients, as these are associated with a lower incidence of premature LH surge and subsequent lower cycle cancellation rate.[24,32] The use of oral progesterone from day 3 of the cycle in poor responder patients have been suggested in recent studies in order to avoid spontaneous LH surge and premature ovulation, not affecting oocyte quality.[32] A reduction in the incidence of LH surge and subsequent reduction in cycle cancellation rate are the main benefits of progestin-primed ovarian stimulation. This means however the use of low doses of exogenous gonadotropins by the end of the follicular phase, as well as blastocyst vitrification and deferred transfer, with an increased cost per cycle and no significant outcome improvement in terms of ongoing pregnancy and live birth rate.[32]

Pregnancy rate with MAR in a natural cycle in patients having unsuccessfully undergone standard MAR treatments has been assessed in this study. An ongoing pregnancy rate per started cycle, per egg retrieval and per patient of 6.7%, 25.0% and 20.0% have been found, respectively, in line with literature.[2,27] This was a group of poor responder patients to previous treatments, in whom oocyte donation would be the only alternative. ICSI was the most frequently used technique in this study, in line with literature in which ICSI is associated with higher fertility rates with minimal ovarian stimulation protocols associated with low number of oocytes.[26]

Table 1 - Outcome with MAR in a natural cycle

	n	%
Cancellation	31	20.8
previous to triggering	23	15.4
following the administration of hCG	8	5.4
Egg retrieval	118	79.2
Egg retrieval		
1 oocyte	69	58.5
2 oocytes	11	10.2
Overall fertility	54	69.0
Fertility per technique		
IFV	11/17	64.7
ICSI	40/54	74.1
Embryo transfer	40	26.8
Implantation (n = 14)	%	
Per started cycle	9.4	
Per egg retrieval	35.0	
Ongoing pregnancy (n = 10)	%	
Per started cycle	6.7	
Per egg retrieval	25.0	
Per patient	20.0	

Table 2 - Embryo transfer quality

Embryo quality	*n*	%
G1	23	57.5
G2	14	35.0
G3	3	7.5

Improved embryo quality has been found in this group of patients when compared to what has been obtained in previous treatments (as described, these were patients in whom transfer had been cancelled due to poor oocyte quality and / or no transfer had been planned due to poor embryo quality). Oocyte quality (namely as regards aneuploidy rate) does not seem to be affected by standard stimulation. However, only a group of oocyte donors (young and non-infertile patients) has been analysed by the most relevant studies[33] or cryopreserved embryos were compared with embryos obtained within a modified natural cycle in a group of infertile patients,[34] not reflecting the reality of our group of patients.

An increased risk of low birthweight associated with MAR with ovarian stimulation has been found in studies aimed at assessing perinatal outcome.[35-37] Improved perinatal outcome has been found by Mak *et al.* in patients under MAR in a natural cycle, when compared to those having undergone standard ovarian stimulation, raising the hypothesis that more physiological levels of estradiol and progesterone during the follicular phase and at the moment of implantation can have an important role.[37] In addition, supernumerary oocytes recruited with ovarian stimulation may show worst quality when compared to a single follicle / oocyte selected within a natural cycle, as suggested by the authors.[37] Therefore, the assessment of these results will certainly be relevant in further studies.

Some limitations of this study have been found, mainly regarding its retrospective nature. In addition, the fact that a heterogeneous group of patients has been selected, with similar unsuccessful outcome with standard MAR treatments even though regarding different aetiologies is worth mentioning as a limitation. Further prospective studies are required in order to control some biases and to compare the cumulative results of these cycles with the different ovarian stimulation protocols, aimed at reaching a definition of the most adequate protocol for specific populations from the different ovarian stimulation protocols currently in use.

CONCLUSION

MAR in a natural cycle may be a reasonable alternative in poor outcome patients, with previous unsuccessful outcomes with standard ovarian stimulation, namely in poor responder patients. The results of this study have shown that a chance of pregnancy can exist even in this group of patients, in whom oocyte donation would be the only alternative.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SUPPORT

The authors declare that there was no financial support in writing this manuscript.

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