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### Original article

# Does unplanned agonist-stop protocol rescue the intracytoplasmic sperm injection cycle?: a randomized controlled study



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#### ABSTRACT

**Objective:** The aim of this study was to evaluate the effect of stopping the agonist with the first follow up visit when the initial response was poor in cases undergoing intracytoplasmic sperm injection, comparing this to the conventional continuation of the agonist.

**Methodology:** A prospective single blinded study was conducted on 50 infertile cases who were planned to have intracytoplasmic sperm injection by long protocol in infertility unit of El-Shatby Maternity University Hospital in the period between May 2011 and January 2013 and these patients had poor response on day 6 of stimulation (serum estradiol (E2) less than 100 pg/ml and 5 or less follicles developed). They were randomly allocated by closed envelope method into two groups, (I) 30 patients to whom we stopped the agonist and continued stimulation and (II) 20 patients to whom we continued the agonist together with stimulation.

**Results:** Group II had statistically higher days of stimulation than group I ( $p=0.009$ ). The number of metaphase II oocytes did not show statistical significant difference between the two groups ( $p=0.418$ ). The mean of number embryos replaced were statistically higher in group II than group I ( $p=0.025$ ). Pregnancy rate showed no statistical significant differences between the two studied groups ( $p=0.466$ ).

**Conclusions:** There was no difference between stopping the agonist or continuing it when the initial response was poor on first follow up visit in cases undergoing intracytoplasmic sperm injection.

**Recommendations:** Alternative measures should be looked for, to improve results of intracytoplasmic sperm injection when initial response is poor.

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## Protocolo de interrupção não planejada de agonista: essa medida resgata o ciclo de injeção intracitoplasmática de espermatozoide? Estudo randomizado e controlado

### R E S U M O

#### Palavras-chave:

Agonista do GnRH

IICE

Indução da ovulação

Reserva ovariana

**Objetivo:** O objetivo desse estudo foi avaliar o efeito da interrupção do agonista por ocasião da primeira consulta de seguimento, quando a resposta foi insatisfatória em casos tratados com injeção intracitoplasmática de espermatozoide (IICE), e comparar essa medida com a continuação convencional do agonista.

**Metodologia:** Um estudo prospectivo monocego foi realizado em 50 casos de infertilidade, com planejamento de IICE por protocolo longo na Unidade de Infertilidade da Maternidade do Hospital Universitário El Shatby no período entre maio de 2011 e janeiro de 2013; essas pacientes tiveram resposta insatisfatória no Dia 6 da estimulação (estradiol sérico [E2] < 100 pg/ml e desenvolvimento de 5 ou menos folículos). As pacientes foram randomicamente designadas pelo método do envelope fechado para a formação de dois grupos: Grupo I, 30 pacientes que tiveram interrompida a medicação com o agonista e continuaram com a estimulação, e Grupo II, 20 pacientes que continuaram com o agonista juntamente com a estimulação.

**Resultados:** O Grupo II apresentou um número estatisticamente maior de dias de estimulação versus Grupo I ( $p = 0,009$ ). O número de ovócitos em metáfase II não exibiu diferença estatisticamente significativa entre os dois grupos ( $p = 0,418$ ). O número médio de embriões recuperados foi estatisticamente maior no Grupo II versus Grupo I ( $p = 0,025$ ). O percentual de gestações não revelou diferenças estatisticamente significativas entre os dois grupos estudados ( $p = 0,466$ ).

**Conclusões:** Em casos tratados com IICE, não foi observada diferença entre a interrupção do agonista ou sua continuação, quando a resposta inicial foi insatisfatória na primeira consulta de seguimento.

**Recomendações:** É preciso se pensar em medidas alternativas para melhorar os resultados da IICE, nos casos em que a resposta inicial não for satisfatória.

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## Introduction

Low ovarian response to stimulation protocol in intracytoplasmic sperm injection (ICSI) is frustrating to physicians and patients especially when the initial evaluation seems to be fair. Regarding this emerging problem, different measures usually taken trying to rescue the cycle and avoid cancellation. It was estimated that about 9–18% of cycles result in this low response with small number of follicles and low estradiol level.<sup>1</sup>

The term “poor responder” has been used to determine women who require large doses of stimulation medications and who make less than an optimal number of eggs. The definition of low responders differs from center to other, but the most used one is that less than four dominant follicles on day of human chorionic gonadotropin (hCG) administration.<sup>2</sup>

The occurrence of low response to ovarian stimulation is usually suspected in old age, although it could occur at any age. Ovarian reserve is the main factor affecting response to stimulation, it could be assessed by many parameters as basal follicle stimulating hormone (FSH), antral follicle count (AFC) and anti-mullarian hormone (AMH). These parameters could be normal, yet poor response happen. A lot of explanations trying to answer the question of: why low ovarian reserve in young patients.<sup>3</sup>

The optimal protocol to deal with poor responders is controversial, the same as the definition. There are many trials, including the use of higher doses of gonadotropins, different doses of gonadotropin releasing hormone (GnRH) agonists, adding estrogen or growth hormone, using combined oral contraceptive pills or the use of natural cycle.<sup>1,2</sup>

The long GnRH agonist protocol is the most widely used and is the preferred for women planned to have ICSI. In poor responders, release of this suppressive effect of GnRH may change the response of the ovary by opening the ovarian receptors. The concept of: *GnRH agonist stop protocols developed depending on this theory*.<sup>4,5</sup>

These protocols are characterized by the use of somewhat low doses of GnRH agonists from the mid-luteal phase of the cycle till the time of menses or soon later, this usually occurs in combination with high doses of gonadotropins. Although GnRH agonist is stopped, it was found that the occurrence of unprogrammed luteinizing hormone (LH) surge is still low.<sup>4,5</sup>

## Materials and methods

The aim of the study was to compare the results of ICSI in cases of poor response on day 6 stimulation of long protocol between patients who stopped the agonist and those who continued it.

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