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Original Article

Protocol shift from agonist to antagonist or vice versa after an unsuccessful intracytoplasmic sperm injection cycle on the same patient does not improve outcome

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ABSTRACT

Objective: While there's a growing data on the comparison of GnRH agonist and GnRH antagonist protocols, no clear study exists on the effects of both protocols on the same patient. The aim of the present study was to compare the success rates of protocol shift and proceeding with the same protocol after an unsuccessful intracytoplasmic sperm injection (ICSI) cycle.

Materials and Methods: Three hundred and forty-five normal responder patients who had a previously failed ICSI cycle between January 2011 and December 2015 were reviewed. The study (n = 73) and control (n = 93) groups in the first cohort were composed of patients whose protocol were shifted to antagonist and who proceeded with agonist. The study (n = 33) and control (n = 146) groups in the second cohort were composed of patients whose protocol were shifted to agonist and who proceeded with antagonist.

Results: Total dose of gonadotropins, maximum estradiol levels, and number of oocytes collected were significantly higher in agonist protocol than in antagonist protocol ($P = 0.021$, $P = 0.013$, and $P = 0.003$, respectively). Cycle cancellation rates were significantly lower in agonist protocol than antagonist protocol ($P = 0.005$). The pregnancy rates in patients who shifted to antagonist and proceeded with agonist were 57.8% and 50.8%, respectively ($P = 0.399$). The pregnancy rates in patients who shifted to agonist and proceeded with antagonist were 33.3% and 47.9%, respectively ($P = 0.202$).

Conclusion: Protocol shift following a failed ICSI cycle with either agonist or antagonist protocol does not affect outcome.

Introduction

Premature luteinizing hormone (LH) surge has been one of the main challenges during assisted reproductive technology (ART) cycles. Eventually, pituitary down-regulation has come into use to overcome this issue. Gonadotropin releasing hormone (GnRH) agonists have long been used for pituitary down-regulation since 1980s. After initial short period of gonadotropin hypersecretion, so called flare-up effect, the GnRH agonists suppress the secretion of endogenous pituitary gonadotropins by desensitizing the pituitary receptors [1]. However, at the end of 1990s GnRH antagonists have been utilized to prevent premature LH surge. GnRH antagonists directly bind to pituitary receptors and block the receptor activity in a dose dependent competitive manner [2]. GnRH antagonists induce an immediate and rapid suppression of gonadotropin release without flare-up effect [1–4].

Since the introduction of GnRH antagonists into the market, many studies have compared agonist and antagonist protocols to find the best. In the last decade GnRH antagonists have begun to be widely used among most infertility centers. The advantages of GnRH antagonists are shorter treatment period, less gonadotropin requirement, less follicular cyst formation, and reduced risk of ovarian hyperstimulation syndrome (OHSS) [5–7]. Antagonist cycles result in similar live birth rates with agonist cycles [7]. While the incidence of cycle cancellation due to OHSS risk is lower, GnRH antagonist cycles are associated with higher cycle cancellation risk due to poor ovarian response [7]. The number of oocytes retrieved is significantly lower in antagonist cycles [8]. It has been suggested that more follicles and oocytes in GnRH agonist cycles allow a better selection of high quality embryos to be transferred [1].

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While both protocols have similar outcome but their own advantages and disadvantages, the choice of protocol selection depends on the clinician's preference and is individualized for every patient. Although GnRH agonist and antagonist protocols have been found comparable in large meta-analyses, the benefit of protocol shift on the same patient following a failed ART cycle is still to be questioned. Each woman has her own multifunctional pituitary and extrapituitary receptors for GnRH. The divergence of signaling pathways that are activated by GnRH receptors can result in multiple actions. Similarly, those receptors may have different responses to agonists or antagonists in different patients. While agonist and antagonist protocols have been well compared in large cohorts, we do not know if they may show different efficacies in the same patient. Hence, the aim of the present study was to assess the success rates of protocol shift and proceeding with the same protocol after an unsuccessful intracytoplasmic sperm injection (ICSI) cycle.

Materials and methods

In this retrospective cohort study data of infertile and normal responder patients who had a previously failed ICSI cycle at a university-based infertility clinic between January 2011 and December 2015 were reviewed. The study was approved by the Institutional Review Board of Ankara University School of Medicine. All patients were evaluated in the subsequent cycle following an unsuccessful ICSI cycle (Fig. 1). An unsuccessful cycle was defined when the result was no clinical pregnancy. The first cohort in the analysis composed of patients who failed to conceive in a GnRH agonist down-regulation cycle. The study and control groups in that cohort were composed of patients whose protocol were shifted to GnRH antagonist down-regulation in the subsequent cycle and who proceeded with GnRH agonist down-regulation, respectively. The second cohort in the analysis composed of patients who failed to conceive in a GnRH antagonist down-regulation cycle. The study and control groups in that cohort were composed of patients whose protocol were shifted to GnRH agonist down-regulation in the subsequent cycle and who proceeded with GnRH antagonist down-regulation, respectively.

All patients with male, tubal, and unexplained infertility were assessed for eligibility. The inclusion criteria were female age 18–40 years, baseline FSH level 3–15 IU/l, baseline LH level >3 IU/l, a previously failed ICSI cycle. The exclusion criteria were secondary infertility, body mass index (BMI) >30 kg/m^2, poor or hyperresponse to COS in the preceding cycle, presence of any untreated thyroid dysfunction/hyperprolactinemia, and/or presence of uterine abnormality. For eligible participants, all data regarding COS and clinical outcomes were extracted from the database.

Ovarian stimulation was carried out with recombinant FSH (Gonal-F, Merck-Serono, Istanbul, Turkey) beginning from the second day of the menstrual cycle with a starting dose of 150–225 IU/day. Dose adjustment was performed individually according to ovarian response evaluated by transvaginal ultrasonography and/or serum estradiol measurements. When GnRH agonists were used for pituitary down-regulation, leuprolide acetate 1 mg s.c. (Lucrin; Abbott, Istanbul, Turkey) was commenced on 21st day of preceding menstrual cycle and the dose was reduced to half at the beginning of menstrual bleeding and continued at the same dose until hCG injection. When antagonists were used for pituitary down-regulation, the GnRH antagonist (Cetrotide, Merck-Serono, Istanbul, Turkey) was introduced (0.25 mg/day) on the sixth day (fixed antagonist protocol) and continued throughout ovarian stimulation. When at least three follicles were ≥18 mm, final oocyte triggering was performed by 10.000 IU hCG (Pregnyl; Schering-Plough, Istanbul, Turkey). Transvaginal ultrasonography guided oocyte pick-up (OPU) was performed 35–36 h after final oocyte triggering. Embryo transfer was performed on the 3rd day of OPU. A maximum of two embryos were transferred under ultrasound guidance due to national embryo transfer regulations. Vaginal micronized progesterone 90 mg/day (Crinone 8% gel; Merck-Serono, Istanbul, Turkey) was administered to all patients for luteal phase support (LPS) starting on OPU day until the pregnancy test, and women with a positive result continued progesterone supplementation until 10 weeks of gestation.

Pregnancy was defined by positive serum β-hCG levels 2 weeks after ET. Clinical pregnancy was defined as the presence of heartbeat at 6–7th gestational weeks. The implantation rate was calculated separately for each woman as gestational sacs/transferred embryos × 100. The primary outcome measures were clinical pregnancy rate.

Statistical methods

Data analyses were performed by using SPSS Version 21.0 (IBM Corporation, Armonk, NYC, USA). Samples were tested with Shapiro–Wilk to determine normality of distributions. According to

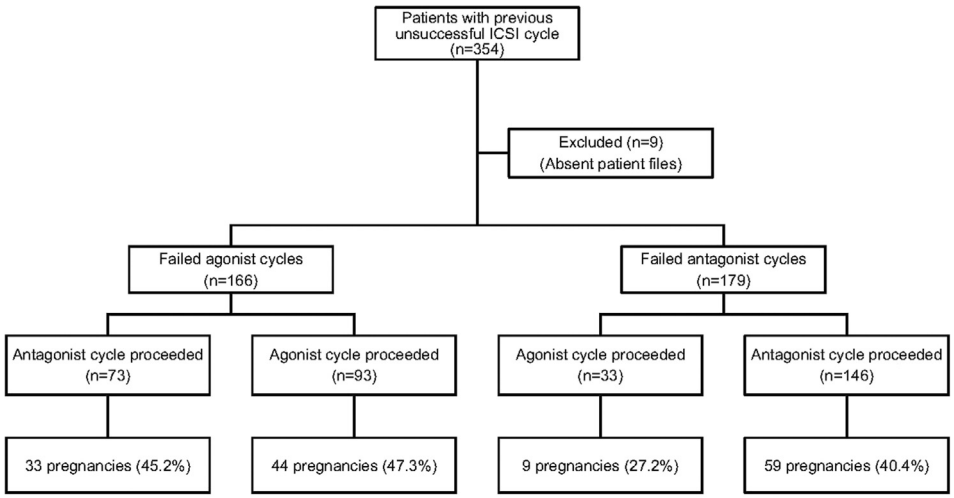

Fig. 1. Flow chart of the study.