Early pregnancy loss rates were different among singleton gestations conceived by ICSI using GnRH agonist and antagonist

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Abstract This study compared early pregnancy losses (termination of pregnancy before 12 weeks of gestation, EPL) among conceptions achieved by ICSI according to the type of GnRH analogue for ovarian stimulation. Only singleton gestations (2,184) and fresh embryo transfers were included. GnRH agonist was used in 848 gestations out of 2,184 and GnRH antagonist was used in the remaining 1,336 gestations. EPL was found to be significantly higher in GnRH antagonist gestations compared to GnRH agonist (27.2% vs 18.9%). This significant difference persisted when gestations were segregated according to maternal age, especially among women younger than 35 years old. Therefore our results suggest that gestations conceived by ovarian stimulation including GnRH antagonists may have higher propabilty of having EPL.

Keywords GnRH antagonist · GnRH agonist · Pregnancy · Miscarriage · ICSI

Short communication

The introduction of GnRH antagonist protocols to controlled ovarian stimulation for ART has been widely accepted for its practical advantages on the patient compliance compared to long GnRH agonist protocol [1]. Initial randomized clinical trial (RCT) declared that neither implantation nor pregnancy rates were significantly different than agonist protocol; however, subsequent meta analysis reported inferior pregnancy rates among patients

using GnRH antagonist [2–5]. Furthermore, some studies assessed ovarian compartment during stimulation with GnRH agonists and antagonists, as measured by expressions of hormones and paracrine growth factors, and none of them found significant differences in clinical outcome [6–8]. In order to determine whether this subtle clinical outcome difference between those GnRH analogues could be integral to endometrial microenvironment, some studies addressed endometrium as a confounding factor. Histologically no apparent differences were found enough to detect any deleterious effects of GnRH antagonists; others found significant ultrastructural differences such as different expressions of growth factors and chemokins from endometrial cells exposed to GnRH agonists and antagonists [9–12]. Bearing in mind that GnRH receptors exist on endometrium, it may be speculated that endometrial factor could be related to this clinical outcome difference between GnRH agonists and antagonists. A recent analysis by our group pointed out reduced pregnancy and implantation rates among women with good ovarain response during COH with GnRH antagonist compared to GnRH agonist; however, this difference disappeared among frozen-thawed embryo transfers out of those mentioned good responder patients [13]. Possibly an endometrial impact could be attributed to this result. In this regard, some investigators also used GnRH agonist following embryo transfer after the administration of GnRH antagonists in ovarian stimulation phase in order to increase pregnancy rates [14].

Early pregnancy loss (EPL) significantly reduces the initial success and efficiency of assisted reproductive therapy, thus increasing the physiological burden on patients. The underlying mechanisms leading to EPL have not been fully elucidated and include multiple etiological factors such as hormonal disturbances affecting endometrium. EPL rates reported in comparative studies of GnRH

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agonists versus antagonists were in part restricted mainly due to the small number of patients conceiving following the stimulation protocols. In other words, although the number of patients enrolled in those studies were enough to supply statistical power in terms of outcome, number of pregnancies were not statistically adequate to compare EPL. Moreover, a majority of studies compared pregnancy rates or live birth rates rather than EPL rates among specific infertility etiologies; i.e., poor or good ovarian responders [15].

Therefore we have retrospectively evaluated our records on whether the type of GnRH analogue has any impact on the rate of early pregnancy losses. The database of Bahceci Women Health Care Center were retrospectively sought for pregnancies conceived by ICSI between January 2003 and December 2006. Singleton gestations and in whom embryo transfers were performed on days 2–3 were included in the study. Ectopic gestations, vanished multiple gestations and pregnancy losses beyond 12 weeks of gestations were excluded.

For patients using GnRH antagonist (Cetrorelix) multiple dose antagonist protocol has been employed, whereas for patients using GnRH agonist (Leuprolide Acetate), long, short and microdose flare-up protocols were employed. The description of those above mentioned protocols can be found elsewhere. Embryo transfers were performed on days 2–3. Luteal phases were supported by progesterone in oil i.m. Clinical singleton gestation (CSG) was diagnosed when a transvaginal sonogram (TVS) performed 3–4 weeks after embryo transfer revealed a gestational sac along with a yolk sac. EPL was diagnosed when a singleton gestation failed to reach 12 weeks of gestation or when cardiac activity ceased or was undetected. EPL rate was calculated by dividing the number of EPL by the number of CSG.

The mean age of women who conceived by ICSI using agonist protocol was 31.6 ± 4.6 years whereas the mean age of women with antagonist protocol was 33.6 ± 4.6 years ($p < 0.0001$). Among the 9,119 ET performed in ICSI cycles, 2,837 (31.1%) were conducted by GnRH agonist and 6,282 (68.8%) cycles with GnRH antagonist. Singleton gestations were achieved by 2,184 (23.9%) out of all performed ET cycles. The distribution of infertility etiologies were male

factor (39%), diminished ovarian reserve (11%), tubal/endometriosis (11%), chronic anovulation (8%), unexplained (21%) and coexisting factors (10%) among patients using GnRH antagonist, while male factor (43.8%), diminished ovarian reserve (5.2%), tubal/endometriosis (9%), chronic anovulation (7%), unexplained (23.9%) and coexisting factors (11.1%) were found among patients using GnH agonist. Number of EPL and rates were depicted in Table 1. Gestations in which GnRH antagonist was used had significantly higher EPL rate compared to GnRH agonist gestations. This difference persisted when gestations were further segregated into age groups, particularly in younger women of less than 35 years old. However, we have not found statistically significant difference among women over 35 years old, although there was a trend of increased EPL rate.

To the best of our knowledge, this study is the first in reporting and addressing EPL in a relatively large number of cases. Most previous studies evaluating EPL in ICSI pregnancies have not accounted for multiple gestations and defined EPL as total miscarriage of pregnancy. It is of importance that survival rates of singletons differ from those multiple gestations during the first trimester [16]. The true incidence of EPL rates in multiple pregnancies should not be more than 5% [17]. The inclusion of all gestations following ART regardless of plurality would erroneously decrease the EPL rate. We stress that this issue has not been taken into consideration in previous studies comparing GnRH agonist and antagonist. In this regard, a recent meta analysis comparing outcomes between antagonist and agonist cycles, including 13 randomized clinical trials with a range of 2–101 pregnant cases for each study, miscarriage rates were not found to be different (11.7% vs 11.5%) [18]. However, the studies in this meta analysis in the Cochrane review did not take into account the plurality of gestations and the definitions of miscarriage were not uniform [5–18].

The data presented here is the first to report differences in EPL rates according to the type of GnRH analogue used with a large series. It is interesting that EPL rates did not differ statistically among women over 35 years old. On the other hand, the sample size that achieved singleton

Table 1 Early pregnancy losses in a group of patients who underwent ovarian stimulation and ICSI with GnRH agonist and antagonist

	Agonist	Antagonist	P (OR, 95%CI)
Number of ET	2,837	6,282	
Number of gestations	848	1,336	
Number of early pregnancy losses (%)	161 (18.9)	364 (27.2)	0.0001 (0.6, 0.5–0.7)
Number of gestations of women < 35 years	605	794	
Number of early pregnancy losses (%)	95 (15.7)	191 (24.0)	0.0002 (0.5, 0.4–0.7)
Number of gestations of women over ≥ 35 years	243	542	
Number of early pregnancy losses (%)	66 (27.1)	173 (31.9)	0.2 (0.8, 0.5–1.1)

gestation among this relatively older group might have reduced the statistical power, as antagonist arm had still higher EPL rate compared to agonist arm. The results of this study will add to the ongoing debate between agonist and antagonist protocol. However, as mentioned above, multiple factors can be detrimental to the fate of an embryo implanted into the endometrium. Underlying infertility etiologies or ovarian responses as measured by Estradiol levels of the women involved in this analysis were not taken into account and possibly could raise concerns regarding the results. On the other hand, it was shown that the type of underlying infertility etiology, including male factor, did not have any impact on EPL rates following ICSI, and similarly, high Estradiol levels reached during ovarian stimulation were not found to be related to EPL rates [19–20]. It may be also questioned that poor ovarian responder patients in the antagonist arm may increase EPL; however, we have shown that poor ovarian response is not a risk factor for increased EPL [21].

Our study reports experience of a single center with GnRH antagonist. A relatively large series was evaluated compared to the relevant literature. Nevertheless, the data presented here should be meaningful after others reproduce the study findings in the near future.

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