Is the type of gonadotropin-releasing hormone suppression protocol for ovarian hyperstimulation associated with ectopic pregnancy in fresh autologous cycles for in vitro fertilization?

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Objective: To evaluate the association between different ovarian hyperstimulation protocols and ectopic pregnancy (EP) in in vitro fertilization (IVF) cycles in fresh autologous embryo transfer cycles in the United States between 2008 and 2011 as reported to the Society of Assisted Reproductive Technology (SART).
Design: Historical cohort study.
Setting: Not applicable.
Patient(s): None.
Intervention(s): None.
Main Outcome Measure(s): All autologous cycles that resulted in a clinical pregnancy after a fresh, intrauterine embryo transfer and described characteristics of cycles according to protocol were included: luteal GnRH agonist, GnRH agonist flare, or GnRH antagonist. Multivariate logistic regression was conducted to investigate the association between type of protocol and EP.
Result(s): Among 136,605 clinical pregnancies, 2,645 (1.94%) were EP. Ectopic pregnancy was more frequent with GnRH antagonist (2.4%) cycles than with GnRH agonist flare (2.1%) or luteal GnRH agonist (1.6%) cycles. After adjusting for maternal and treatment characteristics, the GnRH antagonist and the GnRH agonist flare protocols were associated with increased odds of EP (adjusted odds ratio [aOR] 1.52; 95% confidence interval [CI], 1.39–1.65; and aOR 1.25; 95% CI, 1.09–1.44, respectively) compared with luteal GnRH agonist. Analysis of differences in the factors related to EP in luteal GnRH agonist versus GnRH antagonist protocols indicated that diminished ovarian reserve was associated with an increased risk of EP in luteal GnRH agonist but not in GnRH antagonist cycles.
Conclusion(s): The type of protocol used during ovarian hyperstimulation in fresh autologous cycles was associated with EP. This finding suggests a role for extrapituitary GnRH on the tubal and uterine environment during ovarian hyperstimulation treatment for IVF. (Fertil Steril® 2016;106:666–72. ©2016 by American Society for Reproductive Medicine.)
Key Words: Ectopic pregnancy, embryo transfer, IVF, fresh cycles, ovarian hyperstimulation protocol

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Although recent studies have shown that the overall proportion of ectopic pregnancy (EP) after in vitro fertilization (IVF) is similar to that of spontaneously conceived pregnancies, fresh autologous cycles are associated with the highest risk of an abnormally located implantation (1–3). Evidence for the association of the uterine environment in cycles with ovarian hyperstimulation and the increased risk of EP is based on comparing autologous versus donor and gestational carrier cycles, fresh versus frozen cycles, and multiple fresh and frozen cycles performed at different times in the same patient (1–6). Although the condition is infrequent, EP after IVF represents not only a life-threatening event but also a lost opportunity for couples who do not become pregnant as often as couples from the general population.

Despite a potential reduction in the risk of EP associated with elective frozen embryo transfer, the need for additional procedures and the cost associated with the storage of embryos and endometrial preparation cycle for the frozen embryo transfer could be a drawback for many infertile couples (7). Most importantly, pregnancies that result from frozen cycles are not free of risk, as they may be associated with increased risk of large for gestational age infants and placenta accreta (8, 9). Pregnancy outcomes after IVF are the result of multiple maternal and treatment-related factors, some of which are amenable to change. In debating the pros and cons of elective fresh or elective frozen embryo transfers, it is of the utmost importance to identify factors associated with increased risk of abnormal implantation in fresh cycles that may be amenable to such changes (7, 10).

We recently reported differences in the frequency of EP according to gonadotropin-releasing hormone (GnRH) protocol in a comparative study of fresh versus frozen embryo transfers. Specifically, we found reduced odds of EP associated with GnRH agonist cycles and elevated odds associated with GnRH antagonist, when used in autologous cycles. These associations were not observed in donor cycles. The strong interrelation between the GnRH protocol and the type of embryo transfer (fresh versus frozen) limited interpretation of the findings; yet these results suggested an effect of the ovarian hyperstimulation protocol on EP mediated by the uterine or fallopian tube environment, rather than one mediated by the oocyte or embryo.

Gonadotropin-releasing hormone is present in multiple extrapituitary reproductive tissues, including the endometrium and the fallopian tubes (11–13). It has been proposed that GnRH may have an important role in embryo development and normal implantation and placentation (11,14–17). The distinction between GnRH agonists and GnRH antagonists merits additional exploration as they differ in their mechanism of action: GnRH agonists induce a down-regulation of pituitary receptors after prolonged administration, whereas GnRH antagonists have a direct, competitive-based antagonist effect on GnRH receptors. The timing of administration of the treatments is also different: the GnRH agonist protocol can be started in the precedent luteal phase (luteal phase GnRH agonist protocol) or in the follicular phase (GnRH agonist flare protocol), whereas the typical GnRH-antagonist suppression protocol is established in the midfollicular phase.

Building on our previous study, our analysis investigated whether the type and timing of the GnRH-analog protocol used during ovarian hyperstimulation is associated with EP after IVF in autologous fresh cycles. Our analyses focused on autologous fresh cycles because, as opposed to frozen and donor cycles, they are associated with the highest risk of EP and are performed using either GnRH antagonist or GnRH agonist-based protocols.

MATERIALS AND METHODS

We used the Society for Assisted Reproductive Technologies (SART) database to identify pregnancies that resulted from fresh autologous transfers between the years 2008 and 2011 in the United States. This database includes maternal demographic and reproductive health information, and data on the characteristics and outcomes of IVF cycles from more than 90% of clinics in the United States. Information is reported in a standardized way by all SART participating clinics, and is verified and reported by SART annually. Specific datasets are made available for research purposes to SART members who have agreed to comply with SART guidelines. Institutional review board exemption for this study was granted from the Johns Hopkins Medicine Office of Human Subjects Research. We followed the recommendations from the STROBE guidelines (STrengthening the Reporting of OBservational studies in Epidemiology) for the analysis of the data for this study (18).

Study Population

There were 169,799 fresh autologous cycles that resulted in a pregnancy after the transfer of at least one embryo between 2008 and 2011. Figure 1 shows the process of selection of cycles to achieve the final study sample of 136,605 autologous cycles resulting in a clinical pregnancy, as reported by 127,507 patients. The first exclusions were 25,972 biochemical pregnancies and 127 pregnancies with unknown outcome, followed by 1,483 gestational carrier cycles. Because the analysis focused on differences between GnRH agonist and GnRH antagonist protocols in association with EP, we also excluded 4,839 cycles (3.4% of all fresh cycles that resulted in clinical pregnancies) for which no GnRH analog use was reported. We finally excluded 753 cycles because of double coding, as well as 20 cycles that were intrafallopian tube embryo transfers.

The definitions provided by SART for the reporting of pregnancy outcomes state that an intrauterine gestation should be reported in the presence of one or more gestational sacs in the uterus on ultrasound or the documentation of a birth, spontaneous abortion, or therapeutic abortion in cases of missing ultrasound data. An EP is reported when there is a gestational sac visualized by ultrasound that is outside the uterine cavity, and a heterotopic pregnancy is defined by the coexistence of a clinical intrauterine gestation and an EP. Although the definition of EP provided by SART appeared to be somewhat narrow, for the purposes of our analysis we assumed that providers would most likely have recorded an