

Association between duration of controlled ovarian stimulation and live birth rate in women undergoing In Vitro Fertilization: a SART CORS analysis

Statistical Analysis Plan

Covariates

Information on baseline demographic, hormonal assessment, and treatment characteristics (Table 1) was collected from SARTCORS database. Baseline demographic characteristics included age, BMI, smoking status, race, infertility diagnosis, and previous reproductive history. Treatment characteristics included total FSH dose, type of treatment protocol, type of insemination, the stage and number of embryos transferred. The FSH dose in international unit (IU) was the gonadotrophins used prior to the oocyte retrieval. Embryo stage at transfer was classified based on the difference in days between oocyte retrieval and embryo transfer as cleavage stage (days 2 to 4), or a blastocyst stage (days 5 to 7). IVF treatment protocols examined included a long agonist, agonist-flare, and an antagonist protocol. Based on the type of oocyte insemination in the embryology laboratory, each treatment cycle was classified as IVF (standard insemination), intracytoplasmic sperm injection (ICSI) or combined (included treatment cycles with both IVF and ICSI inseminations).

Association of LBR with d-COS in an Agonist protocol

The analysis of reproductive outcomes based on duration of ovarian stimulation in an agonist treatment protocol are shown in Supplementary Table 4. The LBR was 49.4% (7,302/14,788). There was a decrease in the *live birth rate* with d-COS beyond 10 days and statistically significant for a woman who had ≥ 14 days of COS (AOR (95% CI, p-value was 0.8 (0.69-0.93), $p < 0.01$). There was a trend of increase in *biochemical pregnancy* and *miscarriage rate* in woman with prolonged d-COS. With d-COS beyond 10 days, the *implantation rate* (IR) and *clinical pregnancy rate* (CPR) showed a decreasing trend, becoming significantly lower in women with ≥ 14 days of COS. The RR (95% CI, p-value) for implantation rate in this group, compared to referent was 0.89 (0.81-0.98), $p = 0.02$. The adjusted OR (95% CI) of CPR for a woman in the same group was 0.78 (0.67-0.90), $p < 0.01$. The association of other reproductive outcomes with increasing d-COS remained variable, with no significance.

With d-COS less than 10 days, the RR (95% CI) for *implantation rate* in a woman who had ≤ 8 days, compared to referent was 0.68 (0.49-0.94), $p = 0.02$. Compared to referent, the crude OR (95% CI) of *clinical pregnancy rate and live birth rate* in a woman who had ≤ 8 days was 0.63 (0.44-0.89), $p = 0.01$ and 0.66 (0.47-0.93), $p = 0.02$. When adjusted for multiple covariates, these associations were no longer statistically significant. The association of other reproductive outcomes with decreasing d-COS remained variable, with no significance.

Association of LBR with d-COS in an Agonist Flare Protocol

The analysis of reproductive outcomes based on duration of ovarian stimulation in an agonist treatment protocol are shown in Supplementary Table 4. The LBR was 32.0% (1,216/3,805). With d-COS beyond 10 days, there was a trend of decrease in the *live birth rate*, *implantation rate* and clinical pregnancy rate and a trend of *increase in biochemical pregnancy rate and miscarriage rate*. However, none of the associations in this treatment protocol were statistically significant.

With less than 10 days d-COS, there was a trend of increase in clinical pregnancy and live birth rates and a trend of reduction in miscarriage rate, although not statistically significant. There was no significant association of biochemical pregnancy rate and implantation rate with decreasing d-COS.

Association with Antagonist Protocol

The analysis of reproductive outcomes based on duration of ovarian stimulation in an agonist treatment protocol are shown in Supplementary Table 6. The live birth rate was 43.4% (16,525/38,073). There was a statistically significant decrease in the *live birth rate* with d-COS beyond 10 days. The adjusted OR (95% CI) of LBR for a woman who had 11, 12, 13 and ≥ 14 days of COS, compared to referent was 0.90 (0.83-0.97), 0.90 (0.83-0.98), 0.79 (0.72-0.86) and 0.71 (0.65-0.77) respectively. There was a trend of increase in *biochemical pregnancy rate* and *miscarriage rates* in woman with prolonged d-COS. With d-COS beyond 10 days, the *implantation rate* (IR) and *clinical pregnancy rate* (CPR) also showed a linear decreasing trend, as with other reproductive outcomes. The RR (95% CI) for implantation rate in a woman who had 11, 12, 13 and ≥ 14 days of COS, compared to referent was 0.95 (0.91-0.99), 0.91(0.87-0.95), 0.81(0.76-0.85), and 0.75 (0.71-0.80) respectively. The adjusted OR (95% CI) of CPR for a woman who had 11, 12, 13 and ≥ 14 days of COS, compared to referent was 0.9 (0.84-0.97), 0.88 (0.82-0.96), 0.75 (0.69-0.82) and 0.66 (0.61-0.73) respectively. The significant negative association for the reproductive outcomes with d-COS beyond 10 days for both crude and adjusted OR followed the same pattern when embryos were analysed separately at the cleavage and blastocyst stage. The threshold of d-COS for significantly poorer outcome for this protocol seems to be 11 days or longer.

With less than 10 days d-COS, the crude RR (95% CI) for *implantation rate* in a woman who had ≤ 8 days, compared to referent was 0.82 (0.69-0.97), $p=0.02$. Compared to referent, the crude OR (95% CI) of *clinical pregnancy rate and live birth rate* in a woman who had ≤ 8 days was 0.75 (0.61-0.91), $p<0.01$ and 0.81 (0.66-0.99), $p=0.04$ respectively. When adjusted for multiple covariates, these associations were not statistically significant. The association of other reproductive outcomes with less than 10 days d-COS remained variable, with no significance.