ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Old habits die hard: retrospective analysis of outcomes with use of corticosteroids and antibiotics before embryo transfer

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Objective: To evaluate clinical pregnancy rates in embryo transfer (ET) cycles with and without peri-implantation corticosteroid and oral antibiotic administration.
Design: Retrospective cohort study.
Setting: University-affiliated in vitro fertilization (IVF) clinic.
Patient(s): Eight hundred and seventy-six ETs with or without the routine use of methylprednisolone and doxycycline.
Intervention(s): Embryo transfer procedures.
Main Outcome Measure(s): Clinical pregnancy rates (CPR).
Result(s): The CPR with the routine use of methylprednisolone and doxycycline was 56.1% compared with 61.5% after discontinuation of these medications. Ongoing pregnancy rates were 49.5% with medications versus 53.2% without medications. Of the cleavage-stage embryos, 79% underwent assisted hatching; among these, the CPR was 28.7% when treated with corticosteroids and antibiotics compared with 47.4% without medications.
Conclusion(s): No statistically significant difference in overall IVF outcomes was noted after the discontinuation of routine peri-implantation corticosteroids and antibiotics. The use of these medications varies across the country and may be a result of habit rather than evidence-based medicine. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Corticosteroids, doxycycline, embryo transfer, IVF, peri-implantation prophylaxis

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The zona pellucida (ZP), thought to protect the cleavage-stage embryo, prevents direct contact between the embryo and immune cells, spermatozoa, other embryos, and the epithelial lining of the reproductive tract early after conception (1). After hatching has occurred, the trophoblast cells of the blastocyst can dock and implant within the endometrial stroma. Micromanipulation of the ZP often occurs throughout the process of in vitro fertilization (IVF), particularly when performing intracytoplasmic sperm injection (ICSI), embryo biopsy, or assisted hatching (AH), when mechanical, chemical, or laser methods are used to thin or breach the ZP before transfer (1). This disruption of the ZP may compromise the embryo.

As a result, a number of studies have been performed administering glucocorticoids and/or antibiotics to protect the embryo. The hypotheses were that steroids functioned to suppress the maternal immune response and the antibiotics decreased the possibility that vaginal microbes could be carried into the uterine cavity by the transfer catheter.

Many of these studies were performed when a day-3 embryo transfer (ET) at the cleavage stage was the standard protocol. However, day-5 transfers of a blastocyst are now preferred due to improved pregnancy rates. By the blastocyst stage, the ZP has greatly thinned, and there are signs that hatching is imminent. These signs are often considered favorable for implantation after transfer (2). Given the high blastocyst-transfer pregnancy rates, it

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is unclear whether there is a need to protect an embryo—with or without a compromised ZP—with antibiotics and steroids. Our study investigated whether prophylaxis with methylprednisolone and doxycycline affected IVF outcomes; we hypothesize that there is no difference in treatment groups with and without these medications.

MATERIALS AND METHODS

Fresh and frozen ETs performed at a university-affiliated IVF center during the period of 2014–2015 were identified based on whether they received oral doses of methylprednisolone (16 mg daily) and doxycycline (100 mg twice daily) for 4 days commencing on the day of oocyte retrieval, or for 4 days immediately preceding ET in the case of a frozen ET. It was our standard practice to provide both an oral antibiotic and corticosteroid to all women undergoing ET before July 2015; at that time, this practice was discontinued. Therefore, cycles from 2015 completed without the use of oral antibiotics or steroids are compared with a historical cohort from 2014, and use of these medications was confirmed for all 2014 cycles. Of note, some practices with the onset of blastocyst-stage transfer extended the use of these medications from 4 days to 6 days to reach the day of transfer, but our practice did not.

All ages, all stimulation protocols, and all endometrial preparation protocols were included. The cycle outcomes evaluated included clinical pregnancy rates (gestational sac seen on ultrasound), ongoing pregnancy rates (pregnancy reaching 12 weeks of gestation), and miscarriage rates (pregnancy loss per clinical pregnancy, before 20 weeks). The decision to perform blastocyst-stage transfer rather than cleavage-stage transfer was based on the presence of at least three good-quality embryos on day 3. Institutional review board approval was obtained for this retrospective cohort study, and the data were collected from a single electronic medical record.

A power analysis was performed for binary outcome equivalence with an equivalence limit d = 10%. With an α of 5% and 80% power, assuming 55% clinical pregnancy rates in both groups and accepting a difference of <10% to be clinically equivalent, we determined that we would need 429 ET cycles in each group to be sufficiently powered to show equivalence. The subgroup analyses were performed by transfer stage and fresh/cryopreserved-thawed transfers, but the power is insufficient to show statistically significant differences.

Data were analyzed using SPSS (release 24.0; SPSS, Inc.), and the results are presented as mean ± standard deviation unless otherwise stated. Independent *t* test or Pearson's chi-square test were used for continuous or categorical variables, respectively; in the case of non-normally distributed data, a Mann-Whitney *U* test was performed. A binomial logistic regression was performed for clinical pregnancy with covariates including use of steroids/antibiotics, age at time of retrieval, use of ICSI, fresh versus frozen ET, and the stage of the embryo at time of transfer. $P<.05$ was considered statistically significant.

RESULTS

We analyzed 442 ETs with the routine use of methylprednisolone and doxycycline and 434 ETs after the discontinuation of routine steroid and antibiotic use. Of the medicated transfers, 73.5% were at the blastocyst stage compared with 88.5% of cycles without medications before transfer; the remaining transfers were cleavage-stage embryos. In the medicated group, 1.72 ± 0.8 embryos were transferred compared with 1.49 ± 0.6 without medications. Other characteristics of each group are found in Table 1; statistically significant differences are identified for some independent variables.

Table 2 reports the reproductive outcomes overall and broken down by blastocyst-stage versus cleavage-stage ET. The clinical pregnancy rate with the routine use of methylprednisolone and doxycycline before ET was 56.1% compared with 61.5% after discontinuation of these medications (unadjusted odds ratio [OR] 1.25; 95% confidence interval [CI] 0.96–1.64; $P=.10$). A binomial regression was performed with clinical pregnancy rate as the dependent variable, looking for correlation with age at oocyte retrieval, ICSI (versus conventional insemination), fresh versus frozen ET, number of embryos transferred, and stage of transfer (day 3 versus blastocyst). The results showed that age (OR 0.92; 95% CI, 0.90–0.96), number of embryos transferred (OR 1.28; 95% CI, 1.03–1.6), and stage of ET (OR 0.46; 95% CI, 0.31–0.67) were correlated with clinical pregnancy ($P<.05$) whereas ICSI and fresh versus frozen ET were not. An adjusted OR (1.09; 95% CI, 0.82–1.45; $P=.56$) was found, and there were no differences with or without the use of medications after correcting for these confounders.

The implantation rate for the medicated group was 45.4% compared with 54.3% for the unmedicated group ($P=.06$). Additionally, there were equivalent rates of ongoing pregnancy, clinical miscarriage, and live birth.

Table 2 includes data from multiple cycles for 19.8% of couples who had two or three cycles meeting inclusion criteria; when analyzing first cycles only, the clinical

TABLE 1

Characteristics of cycles treated and not treated with periimplantation corticosteroids and oral antibiotics.

Characteristic	Medicated	Unmedicated	*P* value
Total cycles	n = 442	n = 434	
Age at ET, y	35.18 (±4.51)	34.56 (±4.02)	.048
Age at oocyte retrieval, y	34.76 (±4.52)	34.12 (±4.03)	.041
Peak E_2, pg/mL	1,672 (±939)	1,388 (±962)	<.05
PGS, n (%)	4 (0.9)	4 (0.9)	1.00
ICSI, n (%)[a]	282 (63.8)	240 (55.3)	.01
Assisted hatching performed, n (% of cleavage-stage ET)	96 (82.1)	39 (78.0)	.53
Transfer type			
Fresh ET, n (%)	314 (71.0)	267 (61.5)	.003
Frozen ET, n (%)	128 (29.0)	167 (38.5)	
Transfer stage			
Blastocyst, n (%)	325 (73.5)	384 (88.5)	<.05
Cleavage, n (%)	117 (26.5)	50 (11.5)	
No. transferred, n	1.7 (±0.81)	1.5 (±0.60)	<.05

Note: E_2 = estradiol; ET = embryo transfer; ICSI = intracytoplasmic sperm injection; PGS = preimplantation genetic screening.

[a] Sixty-two cycles used both conventional insemination and ICSI at time of fertilization. As the method could not be traced back to each individual transferred embryo, these cycles were analyzed in the ICSI category.

Kaye. Steroids/antibiotics not indicated for ET. Fertil Steril 2017.