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Key Words: Early pregnancy loss, mifepristone, in vitro fertilization, embryo transfer

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Capsule: Retrospective case series describing a single institution's experience using mifepristone-misoprostol to manage early pregnancy loss (EPL) following in vitro fertilization with embryo transfer (IVF-ET).

ABSTRACT

Objective: Evidence strongly supports the use of mifepristone-misoprostol combination treatment for early pregnancy loss (EPL) among pregnancies conceived without assisted reproductive technologies (ART). No literature exists, however, regarding the efficacy of this treatment in the medical management of EPL among pregnancies following in vitro fertilization and embryo transfer (IVF-ET). These patients differ as some utilize exogenous hormonal supplementation to provide pregnancy support. Thus, the management for EPL may differ between unassisted conceptions and those following ET. Mifepristone, a progesterone receptor antagonist, may demonstrate an altered treatment effect when used with misoprostol to manage EPL in ART-conceived pregnancies.

Objective: To describe our institution's experience using mifepristone-misoprostol to manage early pregnancy loss (EPL) following in vitro fertilization with embryo transfer (IVF-ET).

Design: Retrospective Case Series

Setting: Single academic institution from 2020–2022.

Patients(s): Nine patients with ultrasound confirmed EPL following IVF-ET.

Intervention(s): All 9 patients underwent in vitro fertilization followed by fresh or frozen embryo transfer. All 9 received 200 mg of mifepristone 24 hours prior to 800 mcg of misoprostol.

Main Outcome Measurement(s): Incomplete abortion, need for surgical management, number of days to negative serum hCG.

Results: Of the 9 subjects included, 1 had a programmed FET cycle, 6 had modified natural FET cycles, and 2 underwent fresh ET. Eight subjects had successful expulsion of tissue with 1 dose of treatment, and 1 required uterine aspiration. No subjects required additional dosing of misoprostol. The mean number of days elapsed from mifepristone treatment to tissue expulsion

was 4.89 ± 11.30 days, and mean days to negative-range serum hCG was 36.89 ± 18.59 days. At initial ultrasound, all pregnancies had 1 gestational sac seen; 5/9 had a yolk sac; only 3 had fetal cardiac activity. The mean gestational age at time of EPL diagnosis was 55.22 ± 8.77 days, with the majority (8/9) having completed 7 weeks gestation.

Conclusions: Mifepristone-misoprostol combination treatment appears to be a reasonable option for those with EPL following IVF-ET. Future, larger studies comparing combination treatment to misoprostol only among various ET protocols are needed.

INTRODUCTION

Early pregnancy loss (EPL) occurs in approximately 15% of in vitro fertilization (IVF) conceived pregnancies and represents both an emotionally and physically difficult experience for patients and a medically complex challenge for providers(1). Many patients have diagnostic findings of EPL on ultrasound prior to onset of symptoms, and although expectant management is safe among hemodynamically stable patients, only 25-30% of asymptomatic missed abortions following unassisted conception will go on to have complete expulsion by 7 days(2). The majority of women choose to undergo medical or surgical management to expedite expulsion of the pregnancy(3). Although surgical management of EPL in IVF patients is identical to that of pregnancies conceived without assisted reproductive technologies (ART), best practices in specific dose regimens of medical management for these patients has not been established. IVF pregnancies are physiologically distinct from unassisted pregnancies, as many require exogenous hormonal supplementation with estrogen and progestin. Thus, the management needed to stop growth and support of the pregnancy and encourage expulsion may be different between unassisted conceptions and assisted conceptions complicated by EPL.

Misoprostol, a prostaglandin analogue, has long been the standard of care for expedited medical management of EPL(4). Mifepristone is a synthetic steroid that, at low doses, competitively binds to the progesterone receptor and acts as an antagonist, both blocking progesterone from binding and downregulating the progesterone receptor's transcription activity. Recent evidence has supported the use of mifepristone pretreatment in addition to misoprostol in the management of EPL(5). As such, the American College of Obstetricians and Gynecologists (ACOG) now recommends pretreatment with mifepristone for EPL, when available. Because mifepristone-misoprostol treatment is also the medication regimen used in medically-induced

abortion(6), the U.S. Food and Drug Administration restricts access to mifepristone(7). Only physicians and pharmacies registered with the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) may prescribe mifepristone(8). While there is no longer a requirement for in-person dispensing, these restrictions currently limit providers' ability to conveniently and expeditiously manage EPL with mifepristone-misoprostol treatment.

Given the improvement in efficacy for medical management of unassisted conceptions with EPL, we sought to describe the outcomes of medical management with mifepristone and misoprostol of EPL among pregnancies conceived following embryo transfer after IVF.

MATERIALS AND METHODS

This is a retrospective case series of patients with early pregnancy loss treated with mifepristone-misoprostol following embryo transfer after IVF from January 2020 – May 2022 at a single tertiary academic medical center. This study examined patient characteristics and treatment efficacy. The institutional review board at the institution approved this study. The selected time period was chosen as this was when practice protocol changed to allow prescribing of mifepristone for pregnancy losses. All patients undergoing IVF/ET during this time period were screened for study inclusion.

Data Collection, Inclusion Criteria and Outcomes

We screened all patients at our institution who received mifepristone for EPL from January 2020 – May 2022, and identified for inclusion those who conceived via IVF-ET. We excluded subjects who had spontaneous expulsion of tissue prior to treatment, and subjects experiencing a loss beyond 20 weeks gestation. Demographic, cycle, and outcome information

was collected via review of the electronic health record (EHR). The outcomes of interest were incomplete abortion, need for surgical management, number of days to negative serum hCG.

Embryo Transfer Protocol

Embryos were made using previously outlined protocols and laboratory procedures(9). Among programmed ET cycles, subjects were pretreated with oral contraceptives followed by endometrial preparation with either oral estradiol or leuprolide with estradiol. Intramuscular progesterone 50 – 100 mg daily was added after endometrial thickness was found to be adequate with trilaminar appearance. After 6 days of progesterone exposure, embryo transfer was performed under direct ultrasound guidance. Estradiol and intramuscular progesterone were to be continued through the 12th week of pregnancy.

Modified natural ET cycles involved monitoring for ovulation with at-home ovulation predictor kits followed by in-office ultrasound-monitoring to confirm presence of dominant follicle(s) with assessment of serum LH. If endometrial lining was of adequate thickness with trilaminar appearance, patients were instructed to trigger with hCG, followed by administration of luteal phase supplementation with vaginal progesterone 200 mg either twice or three times daily beginning 2 – 4 days after trigger. ET at the blastocyst stage was performed under direct ultrasound guidance 7 days following hCG trigger. Vaginal progesterone was to be continued through 12 weeks gestation.

Early Pregnancy Loss Diagnosis and Mifepristone-Misoprostol Treatment

Early pregnancy loss was diagnosed in accordance with transvaginal ultrasound guidelines from The American College of Obstetricians and Gynecologists and Society of Radiologists in Ultrasound for diagnosis of pregnancy failure (3).

Statistical Analysis

We present baseline demographic information and clinical characteristics of the patients in this series. Descriptive statistics were used to report baseline characteristics, IVF-ET cycle information, and treatment outcomes. Study outcomes included proportion of subjects with incomplete abortion, number of days to tissue expulsion, and number of days to negative-range serum hCG following mifepristone-misoprostol.

RESULTS

Of the 41 patients who were identified to have early pregnancy loss treated with mifepristone-misoprostol in the study timeframe, 9 conceived via IVF-ET. Patient baseline demographic, and clinical characteristics are presented in Table 1.

All subjects transferred embryos derived from autologous oocytes, 2 via fresh ET and 7 frozen ET, of which 5 were tested via PGT-A and designated as euploid. The majority of patients (6/9) underwent a modified natural cycle protocol for their embryo transfer, all of whom had vaginal progesterone supplementation for luteal support in the setting of a modified natural cycle protocol. The remaining three patients had support with intramuscular progesterone in oil. Additional IVF-ET clinical characteristics are presented in Table 2.

At initial obstetric ultrasound, all cases demonstrated a single gestational sac, while 5 (55.6%) demonstrated a yolk sac; fetal heart activity was seen in 3 (33.3%). All pregnancies were singletons. The mean gestational age at time of diagnosis of pregnancy loss was 55.22

days. The number of days from initial mifepristone treatment to negative-range hCG ranged from 3 – 60 days, with an average of 36.89 ± 18.59. Eight of the 9 patients had a complete abortion without additional treatment needed. One had an incomplete abortion and showed retained products of conception with vascular flow 50 days after initial dose of Mifepristone. This was managed with uterine aspiration. She was a 38 year old with a history of recurrent pregnancy loss who conceived following a modified natural cycle ET protocol with transfer of a single day 6 euploid blastocyst graded 3BB-. Initial obstetric ultrasound at 6 weeks and 3 days demonstrated a gestational sac, yolk sac, and crown-rump length of 5.8mm with fetal heart rate of 69 bpm and normal adnexa. Repeat ultrasound at 7 weeks revealed faint cardiac activity, and follow-up ultrasound at 8 weeks confirmed EPL. She was instructed to discontinue hormonal support and received mifepristone-misoprostol two days later. A follow-up ultrasound performed for slowly decreasing hCG values revealed a thickened/heterogenous endometrial focus with vascular flow suggesting retained products of conception. After being counseled on options of repeat misoprostol versus surgical management, she opted for uterine aspiration which confirmed retained products on pathology. No subject received a second dose of misoprostol. Additional EPL diagnosis and treatment outcomes are presented in Table 3.

DISCUSSION

We report a descriptive study detailing clinical outcomes of patients following IVF-ET conceived EPL treated with combination mifepristone-misoprostol. This case series explores a population in which current literature is lacking on outcomes of treatment efficacy. While the current standard of care for medical management of early pregnancy loss includes combination treatment with both mifepristone and misoprostol, less is known on this regimen for pregnancies

conceived following IVF-ET. A large randomized control trial in 2018 showed that the addition of pretreatment with the 19-nor-steroid mifepristone resulted in higher likelihood of successful management of first-trimester pregnancy loss than treatment with misoprostol alone. It demonstrated a complete expulsion rate of 83.8% with mifepristone pre-treatment compared to 67.1% for misoprostol alone. Uterine aspiration was also performed less frequently with mifepristone pre-treatment—only 8.8% requiring surgical intervention versus 23.5% in the misoprostol-only group(5). These findings were further supported in large randomized control trials that followed (10)(11).

IVF-ET conceived pregnancies utilize exogenous hormone supplementation, particularly progesterone, for pregnancy support(12). Given that many IVF-ET patients are instructed to discontinue exogenous hormone supplementation at time of diagnosis of EPL, the impact of pretreatment with mifepristone—and thus the impact of the associated progesterone receptor modulation—remains unclear. Mifepristone acts as a progesterone receptor antagonist in the setting of elevated progesterone levels, while acting as a partial agonist in the setting of low progesterone(12). As such, it is not immediately clear that mifepristone is necessary and/or innocuous in all clinical scenarios. This study provides insight into patient outcomes following combination treatment for EPL following embryo transfer cycle conceptions.

While the majority of patients in our series conceived following a modified natural cycle in which a dominant follicle either spontaneously ovulated or was triggered using an exogenous hCG injection, they all received luteal progesterone supplementation for continued pregnancy support. The expulsion rate of 88.9% in our small cohort is comparable to the rate of 83.8% reported in the large randomized control trial from 2018(5). Here we demonstrate a mean of 4.89 days to tissue expulsion and 36.89 days to a negative-range serum hCG following initial

treatment with mifepristone. Existing studies lack reporting of serial hCG values after mifepristone-misoprostol treatment as a primary outcomes, however, following hCG to undetectable is common practice in fertility clinics. One study demonstrated that 77% of patients who received mifepristone-misoprostol combined treatment achieved a negative urine pregnancy test 21± 2 days after initiation of treatment regimen(11). In our study, patients had a slightly longer course, with a mean of 36.89 ± 18.59 days to an undetectable hCG. While these studies cannot be directly compared, the results from our series are reassuring. One of our subjects underwent uterine aspiration, and none received a second dose of misoprostol. Although no associations can be drawn given the role of patient and physician preference in surgical versus medical management for incomplete abortion, this percentage (11%) is slightly higher but perhaps comparable to that of 8.8% found in previous literature(5) and should therefore be an outcome of interest in future, larger studies powered to detect a meaningful difference between treatment groups.

While the majority of subjects conceived following modified natural FET cycles, one patient conceived following a programmed ET cycle, while two conceived after fresh ET cycles. These three subjects each demonstrated 1 day to tissue expulsion following medical treatment for EPL. Following discontinuation of luteal support and administration of mifepristone-misoprostol, the number of days to negative-range serum hCG was only 3 for the single programmed cycle conception, while all others ranged from 22 – 60 days. Overall, our results do suggest that mifepristone-misoprostol combination treatment may be a reasonable option for those with EPL following pregnancies conceived by IVF-ET.

This is the first case series to our knowledge that assesses treatment outcomes for management of EPL following conception with IVF-ET. We acknowledge limitations inherent to

all retrospective case series that limit our ability to draw conclusions and generalizability. Pretreatment with mifepristone was incorporated relatively recent into our clinical management of EPL following IVF-ET, resulting in small sample size overall. As a consequence of the case series study design, the results are purely descriptive in nature, and do not address the question of whether or not the addition of mifepristone is necessary or helpful in this patient population. We propose larger cohort studies comparing combination treatment to misoprostol alone to further investigate this hypothesis. We note that the majority of our study cohort conceived following a modified natural cycle, which by definition, have corpus lutea that produce endogenous progesterone. Thus these conceptions are overall more similar to unassisted conceptions when compared to programmed ET cycles. Interestingly the one patient who underwent uterine aspiration conceived following a modified natural cycle protocol.

There is a need for future, larger studies comparing combination treatment to misoprostol only among pregnancies conceived following ET, as well as studies assessing mifepristone-misoprostol treatment outcomes among various cohorts of pregnant subjects who conceived following different ET protocols, such as programmed cycles in which there is no corpus luteum. Cost-effectiveness analyses of the addition of mifepristone for EPL following IVF-ET are needed as well.

CONCLUSIONS

Mifepristone-misoprostol combination treatment may be a reasonable option for EPL among pregnancies conceived following IVF-ET, especially those that utilized a modified natural cycle. Larger, future studies comparing different ET protocols as well as those comparing

combination mifepristone-misoprostol therapy to misoprostol-only treatment are critical to informing clinicians on best practices for treatment of early pregnancy loss in this population.

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TABLES

Table 1: Baseline Characteristics of Subjects Treated with Mifepristone-Misoprostol following Embryo Transfer

	N=9
Age, years	36.89 ± 2.47
BMI, kg/m^2	25.1 ± 4.77
Tobacco use history	1 (11.1)
Race/ethnicity	
- White	7 (77.8)
- Black or African American	0 (0)
- American Indian or Alaska Native	0 (0)
- Asian	1 (11.1)
- Native Hawaiian or Other Pacific Islander	0 (0)
- Other	1 (11.1)
Parity	
- 0	7 (77.8)
- 1	0 (0)
- 2	2 (22.2)
Primary Fertility Diagnosis	
- Diminished ovarian reserve	2 (22.2)
- Male factor	4 (44.4)
- Uterine factor	3 (33.3)
Anti-mullerian hormone, ng/mL	2.55 ± 1.77
Cycle day 2/3 Estradiol, pg/mL	54.56 ± 20.50
Cycle day 2/3 FSH[a], IU/mL	7.32 ± 1.84
Antral Follicle Count	15.1 ± 5.99

Continuous data expressed as mean ± standard deviation; Categorical data expressed as N (%);
[a]FSH: follicle stimulating hormone

Table 2: IVF and Embryo Transfer Characteristics of Subjects Treated with Mifepristone-Misoprostol following Embryo Transfer

	N=9
Number of embryos transferred: - 1 - 2	 6 (66.7) 3 (33.3)
Stage of embryo at transfer: - Day 3 cleavage - Day 5 blastocyst - Day 6 blastocyst	 1 (11.1) 6 (66.7) 2 (22.2)
Mean number of follicles >14mm	1.17 ± 0.41*
Ovulatory support type - Ovulation predictor kit positive + hCG[a] - hCG alone - None (programmed or fresh)	 2 (22.2) 4 (44.4) 3 (33.3)
Cycle day of LH[b] surge/trigger	12.50 ± 3.21
ET protocol (N=9) - Fresh - Modified natural - Programmed cycle	 2 (22.2) 6 (66.7) 1 (11.1)
PGT-A[c] utilized (N=9)	5 (55.6)
Progesterone type (N=9) - Vaginal progesterone - IM[d] progesterone	 6 (66.7) 3 (33.3)

Continuous data expressed as mean ± standard deviation; Categorical data expressed as N (%); [a]hCG: human chorionic gonadotropin; [b]LH: lutenizing hormone; [c]PGT-A: preimplantation genetic testing for aneuploidy; [d]IM: intramuscular

*N=6

310 Table 3: Early Pregnancy Loss Characteristics and Treatment Outcomes of Subjects Treated with
311 Mifepristone-Misoprostol following Embryo Transfer

	N=9
Initial serum hCG[a], mIU/mL	203.48 ± 150.12
Second serum hCG, mIU/mL	564.56 ± 410.46
Rise in hCG between initial and second levels, %	192.89 ± 157.33
Initial serum progesterone, ng/mL	38.69 ± 15.15
Type of early pregnancy loss - Anembryonic pregnancy - Embryonic/fetal demise	 4 (44.4) 5 (55.6)
Fetal cardiac activity at initial ultrasound	3 (33.3)
Gestational age at diagnosis of loss - < 10 weeks - 10 weeks or greater	 8 (88.9) 1 (11.1)
Gestational age at diagnosis of loss, days	55.22 ± 8.77
Complete expulsion after single treatment	8 (88.9)
Days to tissue expulsion	4.89 ± 11.30
Uterine aspiration performed	1 (11.1)
Days from mifepristone treatment to negative-range hCG	36.89 ± 18.59

312 Continuous data expressed as mean ± standard deviation; Categorical data expressed as N (%);
313 [a]hCG: human chorionic gonadotropin
314