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Predictors of spontaneous reduction in multiple pregnancies conceived following assisted reproductive technology

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ABSTRACT

Objective: To identify patient and cycle parameters that relate to spontaneous reduction in multiple pregnancies following in vitro fertilization (IVF) and embryo transfer (ET).
Study design: A retrospective cohort study was conducted in an academic infertility center. All IVF cycles between January 2007 and June 2008 were evaluated and 69 infertile women were diagnosed with multiple gestation following IVF. Multiple pregnancy was diagnosed by transvaginal sonography at 6–7 weeks gestation following embryo transfer (ET). Repeat ultrasonography undertaken in late first trimester assessed ongoing multiple pregnancy versus occurrence of spontaneous reduction. Patient and IVF cycle parameters were compared between patients experiencing spontaneous reduction ($n = 26$, cases) compared to those where the multiple pregnancy proceeded uneventfully ($n = 43$, controls).
Results: Spontaneous reduction (SR) was observed in almost 38% of the studied multiple gestations ($n = 69$). Women experiencing SR were significantly older ($p = .047$), of a leaner body mass ($p = .049$), and exhibited significantly higher serum estradiol (E_2) levels in the early follicular phase ($p = .016$) compared to the controls. Endometrial thickness (EMT) on the day of hCG administration related inversely ($p = .017$), whereas the number of embryos transferred (ET) related positively with the likelihood of SR ($p = .027$). On multivariate analyses, EMT and the number of ET were identified as independent predictors of SR following IVF–ET; EMT of less than 10 mm was associated with a fourfold increased likelihood of SR (OR 4.18; 95% CI 1.02–17.01) whereas each additional embryo transferred doubled the risk of SR in multiple pregnancies resulting from IVF (OR 2.39; CI 1.02–5.58).
Conclusions: In multiple pregnancies conceived following IVF, occurrence of SR is relatively common. Increasing number of ET and EMT measuring <10 mm are identified as independent predictors of likelihood of SR. While advancing age, body mass and baseline E_2 levels were associated with likelihood of SR, these associations disappeared on adjusted analyses. The observed relationship between EMT and SR is novel: the underlying mechanisms are unclear and merit further investigation.

1. Introduction

Since their inception and introduction into clinical practice, assisted reproductive technologies (ART) have revolutionized the management of infertility. The fervor of ART related successes however is dampened by the burden of ART multiple pregnancies and consequences thereof [1,2]. While the risk of preterm delivery is recognized to relate to the numerical burden of multiples, a propensity for early pregnancy losses in the setting of multiple implantations is also appreciated [3]. Moreover, subclinical pregnancy losses can also be higher than expected in ART cycles. The arrest of development and subsequent resorption of an embryo may occur at any point in early gestational life, and with the advent of ultrasonography it has been observed that embryo loss is not an infrequent event [3].

Spontaneous reduction (SR) in a clinically established intrauterine multiple pregnancy refers to the failure of one or more of the identified early gestations to continue to develop, in the setting of at least one ongoing pregnancy [4]. The phenomenon of "vanishing twin" or "vanishing embryo" is an example of SR whereby in a previously sonographically documented twin gestation, subsequent evaluation confirms a singleton ongoing pregnancy [4–8]. Although in earlier studies, this term was used to describe first trimester pregnancies in which two gestational sacs were observed, but ultimately only one fetus delivered [5,6], in

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recent studies it is used to describe the loss of a live embryo at some point beyond initial confirmation of viability [4,7,8].

The incidence of SR after ART cycles is variably reported to be around 30%, ranging from 5% to 52.6% [9–11]. Occurrence of SR is suggested to associate with increased risks of cerebral palsy, preterm birth and very low birth weight infants [8]. While the relative frequency of this occurrence must be kept in perspective in couples considering the option of selective reduction, factors contributing to the risk of this occurrence are relatively poorly understood. The present study was undertaken in an attempt to identify patient and cycle parameters that may relate to likelihood for SR in multiple pregnancies conceived following ART.

2. Materials and methods

All ART cycles undertaken at the Yale Fertility Center (YFC) between January 2007 and June 2008 that resulted in a multiple pregnancy were reviewed. Patients were identified from review of Society for Assisted Reproductive Technology (SART) data and from review of patient records. Patients who, following documentation of pregnancy by serum testing, were monitored at facilities outside YFC, and for whom details of implantation rate and multiplicity of gestation were thus unavailable, were excluded, as were those who experienced spontaneous miscarriage or chose to undergo selective embryo reduction in the setting of ongoing multiple pregnancy. Approval from the Human Investigation Committee at Yale University was obtained: given the retrospective study design and use of de-identified data, the study was deemed as exempt from consent requirement. Early follicular phase (cycle days 1–3) serum levels of FSH reflected ovarian reserve status [12]. Patient management was as per routine clinical practice. Briefly, ovarian downregulation was achieved by use of GnRH agonist (Lupron®, Abbott Labs., IL, USA) in a long luteal protocol for all patients. Standard formulations of gonadotrophins (Follistim®, Organon Inc., NJ, USA) were used for COH (controlled ovarian hyperstimulation): ovarian response was monitored by serial assessments of serum estradiol (E_2) and by serial transvaginal sonography (TVS) assessments. Oocyte maturation was triggered with 10,000 IU of human chorionic gonadotrophin (hCG) (Pregnyl®, Organon Inc., NJ, USA), when a minimal of three dominant follicles attained a size of 17 mm or more. TVS-guided oocyte retrieval was performed approximately 34 h after the hCG injection. Trans-cervical ultrasound-guided embryo transfer (ET) was performed between days 3 and 6 post-insemination. Intramuscular progesterone was used for luteal support. First trimester sonography at approximately 6–7 weeks' gestation (based on date of ET + 2 weeks) identified 69 clinical multiple pregnancies: the number of ultrasonically visible gestational sacs ranged between 2 and 4. Patients underwent repeat TVS in the late 1st trimester for the assessment of ongoing pregnancy. The rate of SR was calculated for each patient as the number of ongoing multiple gestations divided by the initial number of intrauterine gestations × 100. Patient and cycle parameters were compared between those patients experiencing SR of one or more implanted gestations (cases, $n = 26$) with those in whom multiple pregnancy proceeded uneventfully (controls, $n = 43$).

2.1. Statistics

Data distribution for continuous variables was assessed. Associations of SR with patient characteristics (i.e. age, BMI, baseline FSH, infertility etiology, ethnicity) and ART cycle parameters (i.e. duration of COH, total dose of gonadotrophins, serum E_2 levels and endometrial thickness (EMT) in mm on day of hCG, number of eggs retrieved, post fertilization day of ET and number of ET) were evaluated using Student's *t* test (for normally distributed data) or the Mann–Whitney *U* (for skewed data) test as appropriate. Multivariable logistic regression models were created to determine independent predictors of SR in multiple pregnancies following ART. Given the limited dataset size, propensity score, a well described methodology for analyses of small datasets with limited outcomes, was utilized for multivariable analyses. Briefly, propensity score is a single calculated value that represents the individual covariates of interest (age, BMI, baseline E_2, EMT and number of ET), and is used as an adjustment variable within the logistic regression models determining an association between SR and independent variable of interest [13]. Sensitivity analyses further assessed the relationship between EMT and likelihood of SR by restricting analyses to cycles resulting in twin implantation. The likelihood of association between SR and various evaluated parameters is reported as odds ratios (OR) ± 95% confidence interval (CI). Goodness of model fit was assessed by Hosmer–Lemeshow Test [14]. STATA Intercooled 10.0 (StataCorp, College Station, TX) was utilized for the analyses and a two tailed *p*-value of $<.05$ was considered significant.

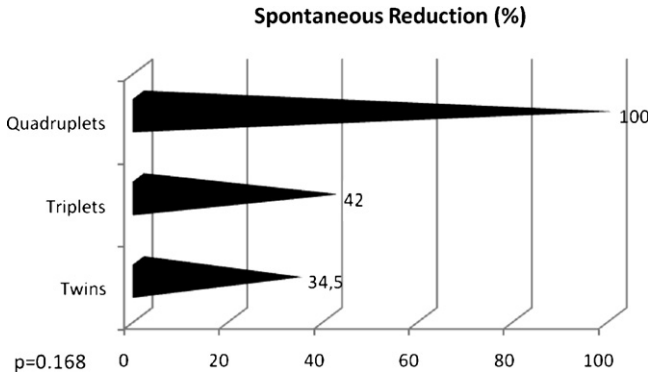

Fig. 1. Risk of spontaneous reduction increases with increasing multiplicity of gestation in pregnancies following ART.

3. Results

Data from 69 multiple pregnancies achieved following in vitro fertilization and ET are reported. Twin implantation represented the commonest numerical variant (55/69, 80%) followed by triplets (12/69, 17%) and quadruplets (2/69, 3%). The overall SR rate in multiple pregnancies achieved following ART was almost 38% (26/69). The likelihood of SR was observed to increase with the number of implantations (Fig. 1), albeit insignificantly.

Table 1 presents patient characteristics by the specified outcome of interest (i.e. SR versus ongoing multiple pregnancies).

Table 1
Patient characteristics in cases of multiple pregnancies undergoing spontaneous reduction versus unaffected ongoing multiple pregnancies following ART.

	Cases (SR[a]) $n = 26$	Controls $n = 43$	*p*
Mean age (years)	34.7 ± 4.4	32.5 ± 4.3	.047
Mean parity (*n*)	0.5 ± 0.8	0.4 ± 0.7	.389
Baseline FSH (mIU/mL)	5.7 ± 1.9	7.1 ± 7.4	.606
Baseline E_2 (pg/ml)	49.1 ± 17.7	39.2 ± 19.1	.016
Mean BMI[b] (kg/m^2)	23.8 ± 8.0	27.2 ± 6.1	.049
Previous abortion (%)	38.5	34.9	.764
Indications for in vitro fertilization			
Endometriosis (%)	3.8	7	.590
Anovulation (%)	23.1	23.3	.986
Tubal/uterine factor (%)	19.2	16.3	.754
Male factor (%)	38.5	34.9	.764
Unexplained infertility (%)	15.4	20.9	.568

[a] SR, spontaneous reduction.
[b] BMI, body mass index.