CLINICAL ASSISTED REPRODUCTION

What Is a Preclinical Pregnancy Loss?¹

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Purpose: To evaluate the contribution of embryo quality to preclinical loss rates after in vitro fertilization (IVF)/embryo transfer (ET) pregnancy, multiple gestation, and clinical loss rates were compared to preclinical pregnancy loss rates over a 3-year period.

Methods: The pregnancy outcomes after 1675 fresh ETs from 1994 to 1997 were studied. While establishment of a clinical pregnancy confirms uterine receptivity, multiple gestation rates reflect embryo quality. Because the majority of clinical losses are chromosomally abnormal, clinical loss rates serve as another indicator of embryo quality.

Results: The overall preclinical pregnancy loss rate was 5% (78/1675) of ETs and 17% (78/472) of pregnancies. During the 3-year period the pregnancy rates per ET increased from 19 to 36% ($P < 0.0001$), multiple gestation rates increased from 21 to 48% ($P < 0.008$), clinical loss rates decreased from 20 to 6% ($P < 0.0001$), and preclinical pregnancy loss rates remained unchanged from 13 to 19% ($P = 0.1$).

Conclusions: Preclinical pregnancy loss more likely reflects abnormalities in uterine receptivity rather than embryo quality. If recurrent preclinical pregnancy loss occurs after IVF/ET, evaluation for abnormalities of uterine receptivity should be performed.

KEY WORDS: preclinical pregnancy loss; uterine receptivity; embryo quality; multiple gestation rates.

INTRODUCTION

Preclinical pregnancy loss refers to reproductive loss that occurs between the time of implantation and onset of menses (1). Preclinical pregnancy loss has been

reported to occur in approximately 20% of cycles (range, 8 to 57%) in couples attempting to conceive (2–7). Subfertile women have increased preclinical pregnancy loss rates compared to fertile women (8). Women with a history of subfertility had a preclinical pregnancy loss rate of 70%, compared to 21% for women without fertility problems (relative risk, 2.6; 95% confidence intervals, 1.8 to 3.8) (8). The frequency of preclinical loss after in vitro fertilization (IVF) and embryo transfer (ET) has been reported to be as high as 30 to 50% (7,9,10).

Pregnancy loss can be the result of abnormal concepti or decreased uterine receptivity (7). The majority of clinical pregnancy losses are chromosomally abnormal (11,12). Thus, clinical pregnancy loss rates could serve as an indicator of embryo quality. Because no tissue is available for chromosomal analysis after preclinical pregnancy losses to determine embryo quality, other indicators are needed. While establishment of a clinical pregnancy would confirm uterine receptivity, multiple gestation rates would reflect embryo quality. Therefore, pregnancy, multiple gestation, and clinical pregnancy loss rates were compared to preclinical pregnancy loss rates after ET to evaluate the relative contribution of embryo quality to preclinical pregnancy loss rates.

MATERIALS AND METHODS

Consecutive pregnancies resulting from transfer of fresh embryos after IVF between January 1, 1994, and January 1, 1997, were followed for outcome. The frequencies of preclinical and clinical pregnancy losses were determined. A preclinical pregnancy loss was defined as one or more serum human chorionic gonad-

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otropin (hCG) concentration >5 mIU (conversion factor to SI unit A, 1.00) beginning 14 days after ET, without a gestational sac seen on ultrasonographic examination (7). A clinical pregnancy loss was defined as a spontaneous or missed abortion occurring during the first trimester after visualization of a gestational sac by transvaginal ultrasonography using a 7.5-mHZ probe (7).

Ovarian stimulation, oocyte recovery, and embryo culture procedures have been published previously (13). Briefly, multiple follicular development was induced using the gonadotropin releasing hormone analogue (GnRHa), leuprolide acetate (LA; Lupron; TAP Pharmaceuticals, Chicago, IL), plus gonadotropin [follicle stimulating hormone (FSH) or (hMG); Metrodin, Fertinex, or Pergonal; Serono, Inc., Randolph, MA]. Follicular development was monitored by serial hormone and ultrasonographic measurements. Follicles were aspirated under transvaginal ultrasonographic guidance 34 to 36 hr after injection of (hCG), 10,000 U intramuscularly (Profasi; Serono, Inc.). Frozen and thawed ETs and donor oocyte ETs are not included in this study.

RESULTS

From January 1, 1994 to January 1, 1997, 1675 transfers of fresh embryos occurred. The number of ETs increased each year (Table I). As the number of ETs increased each year, the pregnancy rate increased from 19 to 36% per ET ($P < 0.0001$).

Table II presents the outcomes of 472 pregnancies. The overall preclinical pregnancy loss rate over the period studied was 5% (78/1675) of ETs and 17% (78/1472) of pregnancies. As the pregnancy rates increased from 19 to 36% per ETs the multiple gestation rates increased from 21 to 48% ($P = 0.0008$) and the clinical pregnancy loss rates decreased from 20 to 6%. During

the same period the preclinical pregnancy loss rate did not change significantly ($P = 0.1$).

DISCUSSION

Preclinical pregnancy loss occurred in 17% of pregnancies resulting from IVF/ET in the present study. This value compares with a frequency of 22% preclinical pregnancy loss in the fertile population (5) and 11 to 28% in other populations after IVF/ET (7,9,14,15). The preclinical pregnancy loss rate did not change during a period when pregnancy rates and multiple gestation rates increased and clinical pregnancy loss rates decreased. Because multiple gestation rates increase with increased quality of embryos transferred after IVF/ET and clinical pregnancy loss rates decrease with decreased chromosomal abnormalities among concepti (increased embryo quality), preclinical pregnancy loss does not appear to be largely the result of decreased embryo quality.

That preclinical pregnancy loss is not the result of decreased embryo quality is supported by results of previous studies describing the relationship between preclinical pregnancy loss rate and age of oocyte donor (7). Although linear regression analysis revealed a significant increase in clinical pregnancy loss with increasing maternal age ($r = 0.971$, $r^2 = 0.95$, $P = 0.005$), no association was found between preclinical pregnancy loss and age of oocyte donor ($r = 0.80$, $r^2 = 0.65$, $P = 0.65$). Because an increase in chromosomal abnormalities has been observed in embryos from older women (16) and because a large proportion of chromosomally abnormal concepti either does not implant (17) or results in early pregnancy wastage (11), a lack of increase in preclinical pregnancy loss with advancing maternal age supports the concept that preclinical pregnancy loss is not largely due to embryo quality.

Preclinical pregnancy loss after IVF/ET could result from abnormalities within the conceptus or uterus. Because data do not support evidence for increased abnormalities within the conceptus, preclinical loss could be the consequence of uterine abnormalities resulting from decreased uterine receptivity (7). Decreased uterine receptivity has been associated with cycles stimulated with gonadotropins compared to unstimulated cycles (18). A significantly higher preclinical (but not clinical) pregnancy loss rate has been reported after ET in stimulated compared with unstimulated cycles (7, 18). Evidence is accumulating to suggest that the processes involved in lowering receptivity involve immunologic as well as endocrinologic mecha-

Table I. Pregnancy Rates per ET from January 1, 1994, to January 1, 1997

Year	ETs (No.)	Pregnancies [No.(%)]
1994	375	70 (19)
1995	571	132 (23)
1996	747	270 (36)
Total	1675	472 (28)
<i>P</i> value		<0.0001

Table II. Outcomes of 472 Pregnancies Resulting from IVF/ET

Year	Pregnancies (No.)	Multiple gestations [No. (%)]	Pregnancy loss	
			Clinical No. (%)	Preclinical No. (%)
1994	70	15 (21)	14 (20)	9 (13)
1995	132	44 (33)	21 (16)	18 (14)
1996	270	130 (48)	16 (6)	51 (19)
<i>P</i> value	<0.0001	0.0008	<0.0001	0.1

nisms (18–21). A significantly higher rate of preclinical loss among women with circulating autoimmune antibodies who underwent IVF/ET has been reported previously (22). Thus, preclinical pregnancy loss more likely reflects abnormalities in uterine receptivity rather than embryo quality.

Preclinical pregnancy loss occurs in only 5% of IVF cycles and hence is not a frequent cause of IVF failure or unexplained infertility (23). However, if recurrent preclinical pregnancy loss occurs after IVF/ET, evaluation for abnormalities of uterine receptivity should include anatomic (24), endocrinologic (18–21), and immunologic (23,25–29) factors.

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