The ‘vanishing embryo’ phenomenon in an oocyte donation programme

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BACKGROUND: We studied the incidence of vanishing embryos (VE) in pregnancies achieved by oocyte donation and evaluated the obstetric and perinatal complications. METHOD: A retrospective study was carried out based on a chart review of 399 patients with multiple pregnancies from our oocyte donation programme. We defined vanishing phenomenon as the early resorption, in the first trimester, of one or more embryos in a multiple gestation, after confirming embryonic heart activity by transvaginal ultrasound. RESULTS: Vanishing embryo was observed in 75 patients (18.8%). In 60 patients (80%) this phenomenon occurred before the ninth gestational week. A higher incidence of VE was observed in patients who initially showed a higher number of gestational sacs (P < 0.03). Vaginal bleeding in the first trimester was significantly higher in patients with VE (P < 0.005). Miscarriage rate was similar in pregnancies with and without VE (P = NS). The incidence of pregnancy induced hypertension was decreased in the group with VE (P < 0.03). Preterm spontaneous rupture of membranes occurred more frequently in pregnancies with VE (P < 0.05). However, gestational age at delivery was similar in the group with VE and the controls. CONCLUSIONS: The high incidence of VE in pregnancies achieved by oocyte donation should be considered when counselling patients with high order multiple gestations.

Key words: oocyte donation/perinatal outcome/spontaneous embryo reduction/vanishing embryo

Introduction

Since assisted reproduction techniques were introduced in routine clinical practice, a rise in the incidence of multiple pregnancies has been observed (Bustillo and Zarutskie, 1998). This implies a higher rate of maternal as well as perinatal complications (Bernasko and Lynch, 1997). Among these complications is spontaneous fetal loss, whose incidence and aetiology remains unknown. In 1945, Stoeckel described a higher twin pregnancy rate than the observed twin delivery rate. Even though clinical evidence was not possible as ultrasound did not exist, the resorption of one of the fetuses (foetus papiraceous) was described (Stoeckel, 1945).

With the advent of transvaginal ultrasound and assisted reproduction techniques, we learned that ‘vanishing embryo’ (VE) is not an infrequent event. However, little is known about the pathophysiology of the process, an event that has been considered as a natural adaptation mechanism (Boklage, 1995). Other aetiological factors that may be involved are embryo aneuploidy (Tharapel et al., 1989; Rudnicki et al., 1991; Callen et al., 1991; Post and Nijhuis, 1992; Falik-Borenstein et al., 1994) or congenital abnormalities (Weissman et al., 1994). Due to the difficulties and limitations in its definition and diagnosis, the reported frequency of vanishing phenomenon has ranged from 3.7–100% (Dickey et al., 1990; Legro et al., 1995). The great diversity of the population studied and the limitations of the diagnostic techniques employed contribute to the confusion that exists around this particular event.

We defined vanishing phenomenon as the spontaneous loss of one or more embryos after identifying heart activity. Attempting to minimize interpretative error we identified a true intrauterine gestational sac using several sonographic characteristics. These included: a double contour, identification of a yolk sac within the gestational sac, and recognition of an embryonic heart after 6 weeks of gestation (Blumenfeld et al., 1992).

When a pregnancy achieved by oocyte donation becomes clinically evident and fetal heart activity is evidenced by ultrasound, early pregnancy loss has been estimated at around 20% (Cano et al., 1995). This rate of pregnancy loss is obtained from both singleton and multiple pregnancies. The multiple pregnancy rate in oocyte donation programmes ranges from 25–30% (Remohí et al., 1997). Interestingly, spontaneous pregnancy loss mainly occurs between 8 and 9 weeks of gestation (Sampson and de Crespiginy, 1992).

Vanishing embryos may be observed in 21% of dichorionic
twins and in up to 50% of monochorionic twins (Benson et al., 1993). In triplet pregnancies, VE of one of the embryos may be observed in 90% of the cases during the first 7 gestational weeks (Manzur et al., 1995). Spotting is the most frequent clinical sign, being observed in 15–25% of the cases (Falco et al., 1996). This spotting is associated with early pregnancy loss in 7.8–76.5% (Yoshida, 1995). When the placenta is studied, the vanished embryo is described as a placental cyst (Nerlich, 1992), degenerated chorionic villi (Rudnicki et al., 1991), fibrin deposition (Yoshida, 1995), nodules or macerated embryos (Blumenfeld et al., 1992).

Several variables have been investigated in order to avoid selective embryo reduction in high order multiple gestations. Serum levels of HCG (Kelly et al., 1991), crown–rump length (Kol et al., 1993), or bradycardia in early pregnancy (Falco et al., 1996) as well as first trimester vaginal bleeding have been evaluated, but none of them seemed to be predictive of VE.

As oocyte donation offers an excellent model to monitor multiple pregnancies from the beginning, the aim of our study was to establish the incidence of VE in a population of infertile patients undergoing this particular assisted reproduction technique, and to describe the perinatal complications that may occur.

Materials and methods

Patients

A total of 581 pregnancies from our oocyte donation programme were retrospectively studied from January 1997 to December 1999. A total of 1189 donation cycles were carried out and the number of oocytes donated and embryos transferred were 7.4 ± 1.9 and 3.2 ± 1.5 respectively. The age of recipient patients was 37.5 ± 5.6 years. Multiple pregnancies with evidence of VE were allocated to group I (study group). Recipients with either singleton pregnancies or multiple pregnancies without VE were included in group II (control group) (Figure 1). The obstetric outcome of singleton and twin pregnancies after VE was compared with that of initial singleton and twin pregnancies respectively. VE was diagnosed when at least one embryo vanished after previous identification of embryonic heart activity. Cases with blighted ova, biochemical pregnancy, miscarriage, induced selective reductions and ongoing triplets were excluded from this analysis. We defined ‘miscarriage’ as the loss of fetal heartbeat in a clinical pregnancy.

There were no differences between the established groups of recipients regarding age, cause of infertility, or distribution of donor oocytes (Table I). The protocol of ovarian stimulation, steroid replacement, oocyte retrieval and gamete handling in the IVF laboratory has been described elsewhere (Pellicer et al., 1989).

Methods

The protocol of steroid replacement for recipients has also been described previously (Remohi et al., 1995). Briefly, patients with ovarian function were desensitized with i.m. administration of depot leuprolerin acetate (Ginecrin® depot; Abbott S.A., Madrid, Spain) beginning in the secretory phase of the previous cycle. HRT started on day 1 of the cycle with the administration of 2 mg/day of estradiol valerate (Progynova®, Schering Spain, Madrid, Spain) from days 1–8; 4 mg/day from days 9–11; and 6 mg/day from day 12 onwards. After 13 days of estradiol valerate administration, recipients were ready to receive oocytes and they waited until a donation became available. At the day of recovery of donated oocytes, 800 mg/day of micronized vaginal progesterone (Progeffik®; Laboratories Effik S.A., Madrid, Spain) were administered. Embryo transfer was performed 48 h after oocyte recovery using the transcervical approach. The regimen of 6 mg/day of estradiol valerate and 800 mg/day of progesterone was maintained for 15 days, after which serum HCG analysis was performed. When pregnancy was achieved (serum β-HCG ≥5 mIU/ml, Axsym®; Abbott), gestational sac and embryo assessment were performed weekly by transvaginal ultrasound test (Siemens Sonoline SI 410). The first sonogram was performed 7 days after a positive pregnancy test (fifth gestational week). Estradiol valerate and progesterone were maintained at the same dosage until day 80 of pregnancy (Guanes et al., 1996).

Statistical analysis

Continuous data were expressed as mean ± SD. Categorical values were expressed as n (%). Student’s t-test, χ², and Fisher’s exact test were used where appropriate. A value of P < 0.05 was considered as significant. Statistical calculations were performed using Sigmastat® for Windows, version 2.0 (Jandel Scientific Corporation, San Rafael, CA, USA).

Results

From 581 oocyte donation pregnancies followed up in our institution, we found 399 multiple pregnancies (68.7%). VE was observed in 75 cases (18.8%) (Figure 1). The incidence
of VE increased with the higher number of gestational sacs initially seen (Table II) \((P < 0.03)\). Sixty patients \(80\%) \) experienced VE before completing the eighth gestational week, and only 15 \(20\%) \) between the ninth and the eleventh week. Mean gestational age at which VE was observed was \(7.1 \pm 1.7\) gestational weeks, and there were no differences between twins, triplets and quadruplets. The incidence of VE was not influenced by the age of the women, number of embryos transferred or any other baseline characteristic of the women, except for the donor serum estradiol on day 15 (Table I).

First trimester bleeding was more common among pregnancies with VE than in the control group \(P < 0.005\). However, there were no significant differences in the miscarriage rate between both groups \(P = NS\) (Table III).

In the same period of time we analysed the incidence of VE in IVF and ICSI and saw that the incidence of VE in oocyte donation was higher than in IVF \((75/399; 18.8\%) \) versus \(82/1058; 7.6\%) \) or ICSI \((75/399; 18.8\%) \) versus \(124/1469; 8.4\%) \) pregnancies \(P < 0.001\). Although the media of embryos transferred were similar in the all of them, pregnancy and multiple pregnancies rates were significantly lower in IVF and ICSI.

The perinatal outcome of pregnancies that experienced VE was also compared with that of pregnancies without the vanishing phenomenon (Table IV). The pregnancies with VE were singletons or twins pregnancies since the end of the first trimester. The incidence of pregnancy induced hypertension was lower in pregnancies with VE than in the controls \(P < 0.03\). In contrast, preterm spontaneous rupture of membranes was higher in the group with VE \(P < 0.05\). Term spontaneous rupture of membranes was also increased in twin pregnancies with VE \(P < 0.001\). Gestational age at delivery, mode of delivery and birthweight was similar in the group with VE and the controls \(P = NS\).

### Table I. Baseline characteristics in groups I (evidence of vanishing embryo) and II (lack of vanishing embryo)

<table>
<thead>
<tr>
<th></th>
<th>Group I ((n = 75))</th>
<th>Group II ((n = 397))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of recipient</td>
<td>37.9 ± 6.1</td>
<td>38.1 ± 5.4</td>
</tr>
<tr>
<td>Age of donor</td>
<td>27.6 ± 4.4</td>
<td>26.6 ± 4.1</td>
</tr>
<tr>
<td>No. of oocytes donated</td>
<td>8.4 ± 1.9</td>
<td>8.6 ± 3.2</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>4.3 ± 0.8</td>
<td>4.1 ± 1.2</td>
</tr>
<tr>
<td>Donor serum estradiol (pg/ml) ((on day 15 of HRT))</td>
<td>226.5 ± 114.3</td>
<td>324.8 ± 101.3(^a)</td>
</tr>
<tr>
<td>Recipient endometrial thickness ((mm)(on day 15 of HRT))</td>
<td>10.7 ± 1.7</td>
<td>11.5 ± 2.1</td>
</tr>
<tr>
<td>Days of estradiol (days of HRT until embryo transfer)</td>
<td>38.1 ± 7.0</td>
<td>37.5 ± 8.5</td>
</tr>
</tbody>
</table>

\(^aP < 0.005\)

POF = premature ovarian failure; ART = assisted reproduction techniques. Values in parentheses are percentages.

### Table II. Vanishing embryo (VE) in relation to the number of gestational sacs initially observed

<table>
<thead>
<tr>
<th></th>
<th>Twins</th>
<th>Triplets</th>
<th>Quadruplets</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial multiple pregnancies</td>
<td>284</td>
<td>102</td>
<td>13</td>
<td>399</td>
</tr>
<tr>
<td>One vanished embryo</td>
<td>45 (15.8)</td>
<td>17 (16.6)</td>
<td>0 (0)</td>
<td>62 (15.5)</td>
</tr>
<tr>
<td>Two vanished embryos</td>
<td>0 (0)</td>
<td>8 (7.8)</td>
<td>5 (38.4)</td>
<td>13 (3.2)</td>
</tr>
<tr>
<td>Total VE (%)</td>
<td>45 (15.8)(^a)</td>
<td>25 (24.5)(^a)</td>
<td>5 (38.4)(^a)</td>
<td>75 (18.8)</td>
</tr>
</tbody>
</table>

\(^aP < 0.03\).

Values in parentheses are percentages.
### Table III. Early pregnancy losses in oocyte donation pregnancies with and without vanishing embryo (VE)

<table>
<thead>
<tr>
<th></th>
<th>Singletons</th>
<th></th>
<th>Twins</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VE (n = 53)</td>
<td>Control (n = 182)</td>
<td>VE (n = 22)</td>
<td>Control (n = 215)</td>
</tr>
<tr>
<td>First trimester bleeding</td>
<td>28 (52.8)(^b)</td>
<td>29 (15.9)(^b)</td>
<td>14 (63.6)(^a)</td>
<td>34 (15.8)(^a)</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>3 (5.6)</td>
<td>19 (10.4)</td>
<td>2 (9.0)</td>
<td>55 (25.5)</td>
</tr>
<tr>
<td>Early miscarriages (&lt;12 weeks)</td>
<td>2 (3.7)</td>
<td>18 (9.8)</td>
<td>2 (9.0)</td>
<td>45 (20.9)</td>
</tr>
<tr>
<td>Late miscarriages (13–24 weeks)</td>
<td>1 (1.8)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td>10 (4.6)</td>
</tr>
</tbody>
</table>

\(^a\)P < 0.005
\(^b\)P < 0.005
Values in parentheses are percentages

### Table IV. Perinatal outcome in oocyte donation pregnancies with and without vanishing embryo (VE)

<table>
<thead>
<tr>
<th></th>
<th>Singletons</th>
<th></th>
<th>Twins</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VE (n = 50)</td>
<td>Control (n = 163)</td>
<td>VE (n = 20)</td>
<td>Control (n = 160)</td>
</tr>
<tr>
<td>Fetal growth retardation</td>
<td>2 (4.0)</td>
<td>17 (10.4)</td>
<td>4 (20.0)</td>
<td>26 (16.2)</td>
</tr>
<tr>
<td>Pregnancy induced hypertension</td>
<td>3 (6.0)(^a)</td>
<td>29 (17.7)(^a)</td>
<td>1 (5.0)(^b)</td>
<td>41 (25.6)(^b)</td>
</tr>
<tr>
<td>Preterm spontaneous rupture of membranes</td>
<td>12 (24)(^c)</td>
<td>9 (5.5)(^c)</td>
<td>4 (20.0)(^d)</td>
<td>9 (5.6)(^d)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>2 (4.0)</td>
<td>0 (0)</td>
<td>1 (5.0)</td>
<td>12 (7.5)</td>
</tr>
<tr>
<td>Term spontaneous rupture of membranes</td>
<td>4 (8.0)</td>
<td>12 (7.3)</td>
<td>5 (25.0)(^e)</td>
<td>4 (2.5)(^e)</td>
</tr>
<tr>
<td>Birth weight (g) (first twin)</td>
<td>3016 ± 620</td>
<td>3071 ± 641</td>
<td>2503 ± 408</td>
<td>2353 ± 563</td>
</tr>
<tr>
<td>Birth weight (g) (second twin)</td>
<td>3016 ± 620</td>
<td>3071 ± 641</td>
<td>2367 ± 448</td>
<td>2265 ± 570</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>37.0 ± 2.6</td>
<td>35.5 ± 4.1</td>
<td>36.5 ± 1.7</td>
<td>34.8 ± 4.4</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>32 (64.0)</td>
<td>100 (61.3)</td>
<td>15 (75.0)</td>
<td>119 (74.3)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1 (2.0)(^f)</td>
<td>2 (1.2)(^f)</td>
<td>1 (5.0)(^b)</td>
<td>3 (1.8)(^i)</td>
</tr>
<tr>
<td>Admission to NICU &gt; 5 days</td>
<td>2 (4.0)</td>
<td>8 (5.0)</td>
<td>5 (25.0)</td>
<td>61 (38.1)</td>
</tr>
</tbody>
</table>

\(^a\)P < 0.03; \(^b\)P < 0.05; \(^c\)P < 0.005; \(^d\)P < 0.05; \(^e\)P < 0.001.
\(^f\)A case of preterm spontaneous rupture of membranes (30th gestational week).
\(^g\)A case of preterm spontaneous rupture of membranes (29th gestational week) and a case of fetal cardiopathology.
\(^h\)A case of preterm spontaneous rupture of membranes (28th gestational week).
\(^i\)Intrauterine fetal death of one fetus: in a twin to twin transfusion syndrome, in a preterm rupture of membranes (29th gestational week) and in a polymalformative syndrome.

NICU = neonatal intensive care unit.

Only pregnancies progressing beyond 24 weeks have been included in this analysis.

Values in parentheses are percentages.

Vanishing embryo in oocyte donation

Oocyte donation offers an excellent model of controlling multiple pregnancies from the early stages of pregnancy. Oocytes are obtained from fertile women under 35 years of age, and then transferred after fertilization to a receptive endometrium previously primed with estrogen and progesterone. This HRT is maintained during the first trimester of pregnancy. However, among oocyte donation pregnancies, a higher rate of miscarriage is observed in older women (Cano et al., 1995). Thus, uterine ageing is also a factor influencing reproductive performance, a fact that we should consider when multiple implantation is observed in the early stages of pregnancy. However, we did not find any relationship between donor or recipient age and incidence of VE (Table I). Interestingly, a lower miscarriage rate was found in oocyte donation pregnancies with VE compared with those without VE (particularly among twin pregnancies), but the differences did not reach statistical significance (Table III).

Although it is difficult to think that the difference in estradiol level on day 15 is the cause of VE, we are now investigating...
other factors that could be involved in miscarriage cases in oocyte donation (days on waiting list, a GnRH effect, endometrial thickness).

In our study the most common complications among pregnancies with VE were first trimester bleeding and spontaneous rupture of membranes. Remnants of intrauterine fetal tissues may diminish the placental bed surface in direct contact with the uterus, reducing the transport of nutrients from the mother to the fetus and develop a subclinical inflammatory condition, starting the preterm labour syndrome (Vadillo-Ortega et al., 1990; Hulboy et al., 1997) or a preterm rupture of membranes.

As a previous pregnancy (even if it is an early miscarriage) is known to protect against pre-eclampsia, we could speculate that a VE might exert a similar effect. This hypothesis might explain the lower incidence of pregnancy induced hypertension found in the group with VE (Table IV).

In order to avoid medical complications of high order multiple pregnancies, and emulating the natural process of embryo selection, multifetal pregnancy reduction is a valid alternative (Yaron et al., 1998). However, multifetal pregnancy reduction is a psychologically traumatic intervention (Bergh et al., 1999), and it is not free of complications (Torok et al., 1998; Coffler et al., 1999; Mansour et al., 1999). In our series, the outcome of oocyte donation pregnancies with spontaneous or induced embryo reduction was similar (unpublished data).

All this information may be useful in counselling patients on the prognosis and outcome of pregnancies achieved by oocyte donation. It may be a very valuable tool in assisting with decision making about multifetal pregnancy reduction before the ninth week of gestation. Additionally, it may add interesting information to the continuous debate on the number of embryos to be transferred.

References


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