Chromosomal anomaly spectrum in early pregnancy loss in relation to presence or absence of an embryonic pole

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Objective: To compare the cytogenetic findings in a series of missed miscarriages evaluated by chorionic villus sampling, in relation to embryonic pole presence (embryonic or anembryonic).
Design: Prospective cross-sectional study.
Setting: Tertiary referral hospital.
Patient(s): Women presenting with a missed miscarriage.
Intervention(s): Transcervical chorionic villus sampling and cytogenetic studies in the chorionic villi with use of the semidirect method.
Main Outcome Measures(s): Embryonic pole presence or absence assessed by transvaginal ultrasound examination. Type of chromosomal anomalies found in both subgroups.
Result(s): Although the chromosomal abnormality rate was similar for miscarriages with absent or present embryo (61% vs. 68% respectively), frequencies for viable autosomal trisomies (2.3% vs. 19%) and monosomy X (0% vs. 9.2%) were significantly lower when no embryonic pole was seen.
Conclusion(s): Viable autosomal trisomies and monosomies X appear not to be a common cause of miscarriage with an early fetal demise (anembryonic miscarriage). (Fertil Steril® 2010;94:2564–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: Miscarriage, missed abortion, karyotype, chromosomal abnormalities, anembryonic pregnancy, chorionic villi sampling

It is well established that approximately 10% to 15% of clinically recognized pregnancies result in miscarriage, 80% of which are in the first 12 weeks of the pregnancy (1). Accurate reporting of the cytogenetic characteristics of a missed miscarriage to the pregnant woman with an early pregnancy loss is useful to provide her genetic counseling and prenatal care in future pregnancies. For this reason, etiologic considerations of early pregnancy loss involve ascertaining whenever possible the cause of fetal death.

Chromosomal anomalies are found in half of early pregnancy losses and are less common thereafter. Autosomal trisomy is the most frequent chromosomal anomaly associated with first-trimester miscarriage, typically because of maternal nondisjunction. Other common chromosomal abnormalities are monosomy X, triploidy, tetraploidy, and translocations.

Classically "anembryonic" missed miscarriages were defined by an absent embryo, but it now is clear that, when the embryo is not seen, this is due to a very early demise. In a previous study, similar chromosomal abnormality rates were found in missed miscarriages with or without an embryonic pole on ultrasound examination (68% vs. 58%) (2). The aim of this study was to determine the chromosomal abnormalities found in very early pregnancy losses and compare the abnormality types among miscarriages with and without embryonic tissue (the fetal pole) on ultrasound examination.

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MATERIALS AND METHODS

From January 2002 to January 2009, chorionic villi sampling (CVS) was offered in our Prenatal Diagnosis Unit in recurrent miscarriages and to women already scheduled for CVS because of an increased risk for chromosomal anomalies who presented with an early pregnancy loss (high-risk population). From January 2007, all women with a missed miscarriage diagnosed in our center also were offered a CVS before evacuation of products of conception (general population), to obtain a fetal karyotype, because cytogenetic analysis after evacuation has typically a lower success rate (3). All women consented to CVS before evacuation.

Miscarriage in the high-risk population was diagnosed at the time of the scan performed before any scheduled CVS (high risk for aneuploidy) or in the early gestation clinic (recurrent miscarriage). In the general population, miscarriage was detected at the routine 12-week scan or after consultation due to clinical symptoms. At transvaginal ultrasound examination, the gestational sac and the crown-rump length were measured if a fetus was observed

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and chorionic location was determined. When no embryo was seen in a gestational sac with a mean diameter of >16 mm or no cardiac activity was observed in an embryo with a crown-rump length >5 mm (4), transvaginal ultrasound examination was repeated 1 week afterwards. Early pregnancy losses were classified in two subgroups, based on whether or not an embryo could be seen. Following the Royal College of Obstetricians and Gynaecologists recommendations, the term used in the subgroup with no embryo was "early fetal demise" instead of "anembryonic pregnancy" (5).

A vaginal speculum was inserted, and the cervix swabbed with povidone solution. A round-tip curved steel forceps (1.9 mm in diameter and 25 cm in length), first introduced by Rodeck (De Elles Instruments, Coulsdon, Surrey, United Kingdom), was inserted under continuous ultrasound guidance (6). Samples were evaluated for adequacy by the clinician performing the procedure, transported in RPMI culture medium, and subsequently inspected under the dissecting microscope to release from maternal deciduas and blood clots. The processing for cytogenetic analysis was done by a semidirect method after 20 to 24 hours incubation to obtain G-banded metaphase chromosome preparation (G-banding was obtained with use of the Wright technique). Karyotype was performed with use of Cytovision (Applied Imaging, Sunderland, Tyne and Wear, United Kingdom) software. The number of cells examined varied between 2 and 38 (mean number: 10.75) (7). Autosomal trisomies involving the 21, 18, and 13 chromosomes were considered as viable trisomies, whereas other autosomal trisomies were considered nonviable. Dilatation and curettage was performed to evacuate the uterus 1 week after miscarriage was diagnosed, if spontaneous abortion did not occur before. Cytogenetic results were compared between the groups defined by the presence or absence of an embryo, and 95% confidence intervals were calculated to compare means and proportions. A P value $<.05$ was considered statistically significant in Student's t-test for means and Pearson's χ^2 for proportions. Institutional Review Board approval was obtained for the study.

RESULTS

From January 2002 to January 2009, 258 CVSs were performed to diagnose the cause of early pregnancy loss in our unit. The mean maternal age was 35.2 years (range 22–45 years), and the mean menstrual gestational age was 10.5 weeks (range 5–14 weeks), significant differences between "anembryonic" and "embryonic" groups being found for the latter (Table 1). In 103 miscarriages, an increased risk for chromosomal anomalies was noted based on advanced maternal age or a positive first-trimester combined screening. There were 70 recurrent miscarriages (at least two previous miscarriages), without differences between groups, and, in 85 cases, no risk factors were identified.

In 220 (85%) procedures, chorionic villi were obtained, whereas in 38 only maternal tissue was retrieved. A cytogenetic result was available in 185 (84%) samples, and a chromosomal anomaly was found in 122 (66%) of them: 28 viable autosomal trisomies (including trisomies 21, 18, and 13), 42 nonviable autosomal trisomies, 14 monosomies, 15 triploidies, 8 structural anomalies, 11 double anomalies, and 4 mosaicisms. The specific anomalies are highlighted in Table 2.

When comparing the two groups defined by embryo absence or presence at transvaginal ultrasound examination, no differences were found in either the proportion in which chorionic villi were retrieved (82% vs. 87%) (P=.33), cytogenetic success rate (81% vs. 85%) (P=.50), or chromosomal anomaly rate (61% vs. 68%) (P=.39) (Table 1). In miscarriages with early fetal demise (absent embryo) the rates of viable autosomal trisomies (2.3% [95% confidence interval 2.2%–6.8%] vs. 19% [95% confidence interval 12.6%–25.5%]) and monosomies (0% [95% confidence interval 0%–0%] vs. 9.9% [95% confidence interval 5.0%–14.8%]) were significantly lower than they were in missed abortions with a fetal pole on ultrasound examination. In the early loss group, a single trisomy 13 was the only viable trisomy or monosomy in the group (Table 3).

DISCUSSION

In this study, the chromosomal anomaly spectrum found in missed miscarriages without an embryo seen on ultrasound examination

TABLE 1

Comparison of demographic data and sampling characteristics between missed miscarriages with an absent or present embryo using 95% confidence intervals for means and proportions.

	Absent embryo (95% CI)	Present embryo (95% CI)	*P* value	All missed miscarriages (95% CI)
Maternal age (y)	36.2 (35.1–37.3)	34.9 (34.1–35.7)	.06	35.2 (34.5–35.9)
Menstrual gestational age (wk)	9.3 (8.8–9.9)	11 (10.6–11.36)	<.001	10.5 (10.2–10.9)
Percent recurrent miscarriages	29.2 (18.2–40.3)	26.7 (20.4–33.0)	.69	27.3 (21.9–32.8)
Recurrent miscarriages, no.	19/65	51/191		70/256
Percent chorionic villi obtained	81.5 (72.1–91.0)	86.5 (81.7–91.3)	.33	85.3 (80.9–89.6)
No. chorionic villi obtained	53/65	167/193		220/258
Cytogenetic success rate, %	81.1 (70.6–91.7)	85.0 (79.6–90.4)	.50	84.1 (79.3–88.9)
Cytogenetic success, no.	43/53	142/167		185/220
Chromosomal abnormality rate, %	60.5 (45.9–75.1)	67.6 (59.9–75.3)	.39	65.9 (59.1–72.8)
Chromosomal abnormality, no.	26/43	96/142		122/185

Note: CI = confidence interval.

Muñoz. Chromosomal anomalies in miscarriages. Fertil Steril 2010.