Idiopathic recurrent miscarriage is caused mostly by aneuploid embryos

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the RPL couple be compared with other couples undergoing PGS, with or without infertility, or only those with a history of RPL (21)? To overcome this issue, Garrisi et al. (17) and Munné et al. (18) compared pregnancy loss with the expected rate based on Brigham et al. (23) and found that PGS using FISH significantly reduced miscarriage rates, from 36% expected rate to 13% (14). Patients that were offered PGS but rejected it had a 44% miscarriage rate, which is also another way to compare RPL patients using PGS with an appropriate control. This beneficial effect of PGS for RPL was observed in both fertile and infertile RPL patients undergoing IVF (17). However, these studies used FISH, evaluated a limited number of chromosomes and used day 3 embryo biopsy, which very recent evidence suggests it can negatively affect the implantation potential of the biopsied embryo, whereas blastocyst biopsy does not seem to be detrimental (24).

Recent evidence demonstrates that there is an increase in accuracy using array comparative genomic hybridization (aCGH), where all 24 chromosomes can be evaluated, ruling out aneuploidies that would not otherwise be identified (24–27). In addition, the use of blastocyst biopsy, in which more than one cell is biopsied, could further reduce misdiagnosis, both by analyzing more cells and because there seems to be less mosacism in blastocysts than in cleavage-stage embryos, and when mosacism is present, it seems to be similarly allocated to both the inner cell mass and the trophectoderm (25, 26). Blastocyst culture is becoming more common, and combined with full chromosome analysis it is producing high pregnancy rates after PGS (27–30).

Although the previous PGS technology of FISH already demonstrated a significant reduction in miscarriages in patients with RPL, current advances in technology, such as blastocyst biopsy and aCGH may allow for further reduction in miscarriage risk while simultaneously increasing pregnancy rates, eventually moving toward single-embryo transfer. The objective of the present study was to determine any beneficial effects of PGS by aCGH for RPL patients compared with the expected loss rate in RPL patients and a control infertile population.

MATERIALS AND METHODS

Patient Population

Patients with normal karyotypes, without uterine anomalies or endocrine disorders, and with a history of two or more previous unexplained (idiopathic RPL) miscarriages that occurred after %20 weeks of gestation were included in the study. All translocation carriers were excluded. Patients included 287 cycles of both fertile and infertile couples. Couples were undergoing assisted reproductive technologies (ART) at multiple fertility centers (mainly NYU Fertility Center, New York, NY; ART Reproductive Center, Beverly Hills, CA; Fertility Centers of Illinois, Highland Park, IL; Lifequest Centre for Reproductive Medicine, Toronto, ON; and Main Line Fertility and Reproductive Medicine, Bryn Mawr, PA). PGS was done using day 3 biopsy (n = 193) or day 5 biopsy (n = 94), followed by analysis with aCGH at Reprogenetics, Livingston, NJ. All day 3 biopsied embryos were transferred on day 5.

In addition, the observed spontaneous abortion rate after PGS in each subject was compared with the expected rate on the basis of the individual's history, according to: 1) the predictive parameters (age, number of prior losses) from the study by Brigham et al. (23), which has been used in similar previous RPL studies (17, 18); and 2) with the expected rate of miscarriage in a control infertile population as reported in the United States to the Society of Assisted Reproduction Technology (SART) according to maternal age and clinical center (excluding five patients from Lifequest Centre for Reproductive Medicine, Toronto, ON).

Variables in the study groups were compared by c^2 analyses and Fisher exact

Aneuploidy Results

Of those 2,282 embryos, 35.2% (n = 803) were euploid, 60.8% (n = 1,388) were aneuploid, and 4.0% (n = 91) were not analyzable (Table 1). On average, 8.0 ± 4.7 (range 1–35) embryos were biopsied and 2.8 ± 2.9 (range 0–21) were found to be normal. A significantly larger portion of euploid embryos were found on day 5 biopsy compared with day 3 biopsy (47.0% vs. 31.2%; $P<.0001$; risk ratio 1.51, 95% confidence interval 1.35–1.68; Table 1). Of note, there were 52 cycles (18.1%) where there were no available euploid embryos for transfer. Thirty-four of those cycles were after day 3 biopsy. The chance of not having aneuploid embryo increased with age from 5% (4/80) in women <35 years old to 23% (48/207)in those R 35 years old ($P<.001$).

Transfer and Pregnancy Outcomes

Of those 287 biopsy cycles, there were 181 transfer cycles (one patient had two transfers from one biopsy cohort), 52 cycles

and revealed again the same “euploid” diagnosis as the PGS one, suggesting mosacism as the cause of the misdiagnosis.

An expected loss rate was calculated based on Brigham et al.'s expected rates in those with recurrent pregnancy loss (17, 18, 23) (according to maternal age and number of prior losses) and then again according to the SAR

treatment. A randomized control trial in recurrent miscarriage patients has not been performed, and some might consider it to be unethical given the existing data, though not randomized, suggesting lower miscarriage rates with PGS in this population. Without an appropriate control group, there is no way to directly compare the rate of aneuploidy.

In addition, we are greatly limited by the loss to follow-up leading to selection bias. However, those with transfer data were similar in baseline characteristics to the larger sample and those lost to follow-up were younger, so their inclusion might have improved our results. These results can be extrapolated to a large population of RPL patients, because they came from centers from all over the country. However, this also leads to a great variability in treatment protocols and laboratory methods, which may affect outcomes and reproduction. Our overall SABR was small, which makes comparisons about methods and age difficult to perform.

This study does confirm that idiopathic RPL is mostly caused by chromosomal abnormalities, with only a residual 6.9% miscarriage rate. These losses demonstrate that a pregnancy loss can be a result of a factor beyond euploidy, mosaicism, or a genetic abnormality below the resolution of this technology. These new PGS technologies, aCGH and blastocyst biopsy, may allow us to finally provide RPL patients with not only an explanation but a cure.

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