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RESEARCH ARTICLE

Preimplantation Genetic Diagnosis and Natural Conception: A Comparison of Live Birth Rates in Patients with Recurrent Pregnancy Loss Associated with Translocation

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Abstract

Background

Established causes of recurrent pregnancy loss (RPL) include antiphospholipid syndrome, uterine anomalies, parental chromosomal abnormalities, particularly translocations, and abnormal embryonic karyotypes. The number of centers performing preimplantation genetic diagnosis (PGD) for patients with translocations has steadily increased worldwide. The live birth rate with PGD was reported to be 27-54%. The live birth rate with natural conception was reported to be 37-63% on the first trial and 65-83% cumulatively. To date, however, there has been no cohort study comparing age and the number of previous miscarriages in matched patients undergoing or not undergoing PGD. Thus, we compared the live birth rate of patients with RPL associated with a translocation undergoing PGD with that of patients who chose natural conception.

Methods and Findings

After genetic counseling, 52 patients who desired natural conception and 37 patients who chose PGD were matched for age and number of previous miscarriages and these comprised the subjects of our study. PGD was performed by means of fluorescence in situ hybridization analysis. The live birth rates on the first PGD trial and the first natural pregnancy after ascertainment of the carrier status were 37.8% and 53.8%, respectively (odds ratio 0.52, 95% confidence interval 0.22-1.23). Cumulative live birth rates were 67.6% and 65.4%, respectively, in the groups undergoing and not undergoing PGD. The time required to become pregnancy was similar in both groups. PGD was found to reduce the miscarriage

Table 3. Characteristics of the 89 patients with a history of recurrent pregnancy loss who underwent PGD or conceived naturally.

	Patients with PGD	Patients who conceived naturally	P-value
No. of patients ←患者数	37	52	
Mean age (SD)	30.6 ± 3.0	30.9 ± 3.8	NS
Male: female	12: 23	23: 26	NS
Reciprocal: Robertsonian	33: 4	38: 14	NS
Complex translocation	0	4	
Translocation in both partner	0	1	
Mean (SD) No. of previous pregnancy losses	3.37 ± 1.26	3.10 ± 1.07	NS
2	10	16	
3	13	22	
4	7	10	
5	5	2	
6	1	1	
7	1	1	
No. of previous still births	0.08 ± 0.28	0.10 ± 0.30	NS
0	34	47	
1	3	5	
2	0	0	
No. of previous live births	0.14 ± 0.35	0.15 ± 0.36	NS
Primary	32 (86.5%)	44 (84.6%)	
Secondary	5 (13.5%)	8 (15.4%)	
Presence of infertility with IVF←体外受精を必要とする不妊症	6 (16.2%)	6 (11.5%)	NS

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abnormality [21]. In the present study, the mean age of patients who desired PGD was significantly higher. Thus, our comparison was carried out after the patients aged > = 35 years were excluded from the PGD group. This may be one of the limitations of the present study.

However, PGD did reduce the miscarriage rate significantly. The reported miscarriage rates in patients with PGD range from 0–10.2% [9–12], while those in patients undergoing natural conception are in the range of 37–62% [2, 13–16]. Since we selected and transferred embryos with normal or balanced FISH signals, we assumed that miscarriages after PGD were not caused by translocation-related chromosomes, but rather by aneuploidy. Thus, there are several technical limitations to PGD using FISH analysis for detecting two translocation-related chromosomes. To overcome this, it would be necessary to perform screening of the blastocyst trophectoderm for all 24 types of chromosomes by mean of array comparative genomic hybridization (CGH). However, preimplantation genetic screening (PGS) is not permitted for ethical reasons in Japan.

The live birth rate and miscarriage rate in patients with RPL associated with a translocation were 50.0% and 0% in Fiorentino's study in which CGH was used [22]. CGH might be superior to FISH in reducing the number of miscarriages, although a simple comparison might be difficult because of the differences in patient characteristics. CGH might have prevented the cases of fetal trisomy in the present study (Table 2), but it is unclear whether CGH would have improved the live birth rate.

Several randomized controlled trials (RCT) have demonstrated that PGS with comprehensive chromosome screening or FISH can increase the live birth rates in groups with a good prognosis [23–25]. The inclusion criteria in those studies consisted of younger women, lower serum FSH levels, a higher number of retrieved oocytes, no more than one failed IVF, and no more than one miscarriage. PGS might be a good method for selecting the best of many

Table 4. Subsequent live birth rate in patients who underwent PGD or conceived naturally. ↓患者数

	患者数→ 37 patients aged < = 34 years who underwent PGD	52 patients who conceived naturally	OR (95% CI) *	p-value
Live birth rate on the first trial	37.8% (14/37)	53.8% (28/52)	0.52 (0.22–1.23)	0.10
Cumulative live birth rate	67.6% (25/37)	65.4% (34/52)	1.10 (0.45–2.70)	0.83
Infertility ←不妊症	18.9% (7)	3.8% (2)	**1.19 (1.00–1.40)**	**0.03**
Total (range) and mean number of further miscarriages until a live birth	9 (0–1) and 0.24 ± 0.40	30 (0–3) and 0.58 ± 0.78	-	**0.02**
Biochemical pregnancy*	1	1		
Ectopic pregnancy*	2	1		
Mean number of oocyte retrievals	2.46 (2.30)	-		
Mean number of embryo transfers	2.16 (1.85)	-		
Mean (SD) months from genetic counseling until successful pregnancy	12.4 (13.95)	11.4 (10.9)	NS	
Congenital anomaly	1**	1		
Twin pregnancy/live birth	29.0% (9/31) at 25w (1), 36w (4), 37w (3), 38w (1)	5.1% (2/39) at 36w (2)	**7.57 (1.50–38.26)**	**0.009**
Cost/ patient	$7,956 U.S.***	-		

*Biochemical and ectopic pregnancies were included.

**A fetus with 21 trisomy was terminated at 18 weeks' gestation.

***The cost is speculated to be lower. The cost ranged from $8,000–10,000 U.S. per trial in other hospitals in Japan. A technical charge was not included in the cost because this study was conducted for clinical research.

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embryos in patients with a good prognosis and allow for delivery one or two months earlier than with natural conception. PGS might have no benefit in patients with a poor prognosis who cannot give birth by natural conception.

Scott et al. proved that the live birth rate with trophectoderm biopsy was superior to that with cleavage stage biopsy though their sample size was relatively small [26]. Use of a cleavage stage biopsy might be one of the reasons why the pregnancy rate decreased in an RCT comparing PGS+IVF and IVF alone [27]. On the other hand, the improvement in the live birth rate of patients with an advanced maternal age was shown by PGS with the use of both a day 3 biopsy and FISH [24].

Further RCTs incorporating new technologies should be implemented as soon as possible. For over 15 years, PGD/PGS using older technology has been performed worldwide without ever establishing that PGD improved the live birth rate. Several researchers including us speculated that PGD could not improve the live birth rate though it might initially reduce the miscarriage rate [28]. The present study is important because this is the first comparison of the live birth rate in patients with RPL associated with a translocation. It was worth nothing that none of the previous studies employed controls [9–12, 22].

Three reports have indicated that IVF-PGD causes multiple pregnancies. Lim et al. reported one case of a preterm twin delivery at 26 weeks of gestation because of an incompetent internal os as well as 2 cases of twin deliveries at term [9]. Feyereisen et al. reported 5 cases of twin pregnancies and one case of triplet pregnancies [11]. Fiorentino et al. reported 2 twin pregnancies that had completed at least 20 weeks of gestation [22]. Thus, because PGD is associated with a higher risk of multiple pregnancies, the risk of preterm delivery is also higher. Single embryo transfer should therefore be selected.