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Research Article

Obstetrical and Neonatal Outcome after Pre Implantation Genetic Diagnosis; Eight Year Experience at King Faisal Specialized Hospital & Research Center

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Abstract

Objectives: To determine if there is any observable effect of pre implantation genetic diagnosis (PGD) on obstetrical outcome and perinatal morbidity and mortality, birth defects, neonatal outcome in addition, finding the rate of misdiagnosis.

Setting: King Faisal Specialist Hospital and Research Center (Reproductive Medicine & Perinatology Sections) at Riyadh, Saudi Arabia.

Design: A retrospective chart review of PGD patients from Jan 2001- Dec 2009.

Materials and Methods: A total of 70 PGD pregnancies and 70 matching spontaneously conceived pregnancies were reviewed. The main outcome measures were rate of multiple pregnancies, gestational age (GA) at delivery, mode of delivery, sex, apgar score (A/S), birth weight, presence of birth defects, misdiagnosis and perinatal and neonatal mortalities.

Results: Data were collected from 79 children born after PGD and compared to 72 children born after spontaneous pregnancies. PGD group had significantly more multiple pregnancies. However, there was no statistically significant difference between other outcomes in terms of: birth weight, GA at delivery, sex distribution, perinatal mortality and presence of congenital malformations. The misdiagnosis rate was 1.4%.

Conclusion: PGD does not add risk factors to the health of babies born after the procedure. The perinatal death rate and rate of congenital malformations were not higher for PGD group in this study.

Keywords: pre-implantation genetic diagnosis (PGD); obstetrics, Neonatal; outcome; Perinatal

Introduction

Since the development of amniocentesis in the early 1970s, couples at risk for a genetic disease have been recommended to undergo prenatal diagnosis with the possibility of terminating an affected pregnancy and giving birth to only healthy children. More recently, preimplantation genetic diagnosis (PGD) has been proposed as an early form of prenatal diagnosis based on the analysis of a single cell: a blastomere biopsied from regularly cleaving day 3 embryos, or the polar bodies in the case of oocytes (Verlinsky et al., 1990).

PGD was first described in a clinical setting in a groundbreaking report published by Handy side et al., (1990). The first application for PGD was in patients who were carriers of an X-linked disease and had thus one chance in four of having an affected child. Sequences on the Y-chromosomes were amplified by PCR to discriminate male from female embryos, and only female embryos were transferred. Other indications for PGD were quickly introduced including; selected single gene disorders, the detection of aneuploidies, and structural chromosomal abnormalities. In addition, PGD cycles has also been performed for different indications like; repeated spontaneous abortions or ART failures, the selection of embryos according to their human leukocyte antigen type, search for genes that predispose for cancer or late onset diseases, and, social sexing (Simpson 2001, Sermon et al., 2004 & Basille et al., 2009).

Couples who are referred for PGD often have a complex reproductive history, including pregnancy terminations, birth of an affected child, or neonatal death. Structural chromosomal aberrations such as balanced translocations might also be associated with recurrent miscarriages and infertility (Feyereisen et al., 2007). All couples undergoing PGD are required to adhere to a strict family planning and effective contraceptive strategy, and undergo in vitro fertilization (IVF) treatment, even they are not infertile, to generate multiple embryos in vitro. This will start by controlled ovarian hyper stimulation, and then oocyte maturation is triggered by administering HCG, followed by oocyte retrieval under mild sedation.

The preferred method of fertilization is intracytoplasmic sperm injection (ICSI) which is the injection of a single spermatozoon into each oocyte to avoid any genetic contamination that might arise from excess spermatozoa. Embryo development is monitored daily until the diagnosis is made and the normal embryos are selected for transfer. Embryo transfers are usually performed on day's 4-6 post retrieval at morulae/blastocyst stages. The most common biopsy strategy is the removal of one or two blastomeres from 6-10 cell stage embryos (Coskun et al., 2010).

Since the procedures involve extra treatment of the patient and manipulations of the embryos, it could be suspected that PGD and related manipulations might affect the pregnancy and/or the offspring.

Review of earlier publications about this issue showed that there were no observable detrimental effects of PGD on children born after the procedure (Storm et al., 2000), PGD itself doesn't seem to cause an increased risk of any particular pregnancy complication (Storm et al., 2000). One recent study also showed that embryo biopsy doesn't add risk for the health of singleton children born after PGD (Liebaers et al., 2010).

The aim of this retrospective study was to evaluate if there is any effect of PGD on birth defects, perinatal morbidity and mortality, neonatal outcome and to find the rate of misdiagnosis.

Materials and Methods

1. Subjects and Setting:

This was a retrospective chart review of 94 pregnancies achieved after PGD from 2001-2009. All couples who had PGD for single gene disorders or chromosomal abnormalities at King Faisal Specialized Hospital & Research Center, who had clinical pregnancy, were included in the study. The patients got pregnant by IVF treatment followed by blastomere biopsy from 6-10 cells embryos.

2. Data Collection:

Data on pregnancy and perinatal outcome were collected. As for the comparison, spontaneous pregnancies were selected to match for maternal age, parity, year of birth, gestational age at delivery and fetal sex, from the Labour and Delivery unit registry in our hospital.

Main outcome measures: Multiple pregnancies, gestational age at delivery, mode of delivery, sex, apgar score (A/S), birth weight, presence of birth defects, misdiagnosis and perinatal and neonatal mortalities, were collected for both groups.

3. Definitions:

A birth defect in our study was defined as: Any anomaly, functional or structural, that presents in infancy or later in life and is caused by events preceding birth, whether inherited, or acquired.

Term delivery was defined as: A delivery after 37 completed weeks of gestation calculated from first day of last menstrual period for spontaneous conceptions and from the date of embryo transfer (+2 weeks) for the PGD pregnancies.

4. Statistical Analysis:

Obstetrical and neonatal outcomes of natural versus PGD pregnancies were compared. A Chi-squared test of significance of the difference between the groups was used. A P value of less than 0.05 is considered as significant.

5. Ethical Approval:

The management of each pregnancy was not modified by the study, so it was exempted from IRB approval. Department Approval was obtained prior to data collection process.

Results

In a total, 94 PGD pregnancies were available and reviewed. These resulted in 70 deliveries, 6 spontaneous miscarriages, 15 lost to follow up and 3 were still pregnant during data collection (Figure 1).

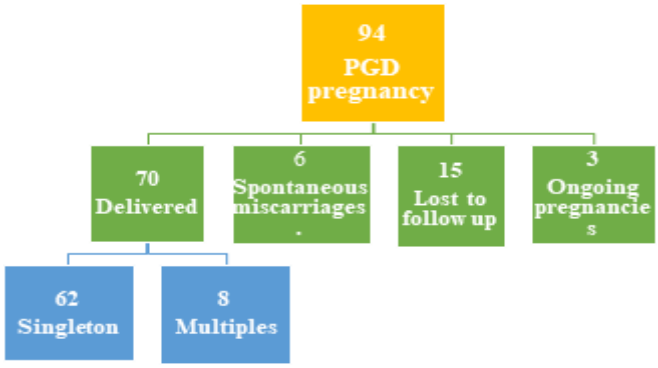

Figure.1

The indication for PGD in our study population varied from screening for aneuploidy (-3-), chromosomal rearrangements (-4-), to different single gene disorders, as shown in (Table 1).

Indication for PGD	Number of cases
Preimplantation genetic screening	3
Chromosomal rearrangement	4
Spinal muscular atrophy	10
Sanjad Sakati syndrome	7
Mucoploysacharoidosis	7
Sickle cell anemia	4
Ataxia telengectasia	1
X-linked hydrocephaly	1
Thalassemia	3
Cystic fibrosis	2
Carnitine acyl translocase deficiency	1
Severe combined immuno deficiency	2
Congenital adrenal hyperplasia	1
Non ketotic hyperglycinemia	2
Propionic academia	2
Methyl malonic academia	1
Wischot Aldrich	1
Hyperinsulinemia	1
Fragile X syndrome	1
Achondroplasia	1
Maple syrup urine disease	2
Phenyl ketonuria	2
Biotinidase deficiency	1
Familial intrahepatic cholestasis type 1	1
ATRX gene mutation	1
Bosley Saleh Orainy syndrome	1
VLCAD	1
Leucocyte adhesion defect type 1	1
Osteogenesis imperfect	1
Jaubert's syndrome	1
Arginino succinic aciduria	1
Non syndromic AR deafness	1
Total	**70**

Table 1: Indications for PGD in our population.

70 PGD pregnancies were matched to 70 naturally conceived pregnancies for: maternal age, parity, GA at delivery, year of birth & reproductive history (Table 2). There was no significant differences between these two groups.

Natural group	PGD group	Characteristics
33 years	32 years	Mean age
20-43 years	22-42 years	Age range
3	3	Mean parity
13 918%)	11 (16%)	History pf RPL

Table 2: Maternal characteristics.

Of the 70 PGD pregnancies that ended by delivery, 8 (12%) were multiple pregnancies (7 twins and 1 triplet) , and 62 (88%) were singletons, whereas the 70 spontaneous pregnancies resulted in significantly less multiples (3%, two twins) (Table 3).

Items	PGD group	Natural group	Z value	P value
Multiple pregnancy	12%	3.0%	1.968	0.0488
Delivery at < 37 weeks	17%	20%	-0.434	>0.05
Delivery by C/S	40%	37%	0.347	>0.05
Male sex	43%	50%	-0.856	>0.05
Birth defects	5.0%	4.1%	0.261	>0.05
Perinatal death	6.3%	1.4%	1.552	>0.05
NICU admissions	25%	14%	1.757	>0.05
B.wt < 2000 grams	3.0%	6.0%	-0.235	>0.05
Old maternal age (> 40 years)	7.0%	6.0%	0.344	>0.05
Parity < or > 5	20%	23%	-0.563	>0.05
History of RPL	16%	18%	-0.448	>0.05

Table 3: Comparison between PGD vs Natural pregnancy groups using Chi-square test.

The PGD pregnancies resulted in delivery of 79 babies, three were stillborn, of which, two were monochorionic twins in a set of triplet pregnancy, and the third was an anencephalic baby in a set of dichorionic twins, resulting in 76 born alive, two died as neonates, one of them secondary to prematurity and the other was a sudden death with no clear cause identified, leaving 74 babies alive, so overall perinatal mortality rate was calculated to be 6.3% and 3.2% for singletons.

On the other hand, the spontaneous pregnancy group ended in delivery of 72 babies, one died in the neonatal period secondary to prematurity, which was the outcome of a singleton pregnancy, giving an overall perinatal mortality rate of 1.4% (Table 3)

Major congenital malformations (Table 4) were seen in 4 children of the PGD group (two congenital heart disease, one anencephaly and one with multiple congenital anomalies including left lung hypoplasia, absent left pulmonary artery , polydactyly and dysmorphism).

Natural group (3 cases)	PGD group (4 cases)
Cervical Teratoma (Singleton)	Ventricular Septal Defect (Singleton)
Congenital Heart Disease (Singleton)	Ventricular Septal Defect (Singleton)
Ectopic Kidney (Singleton)	Anencephaly (Twins)
	Multiple Congenital Malformations (Twins)

Table 4: Types of congenital malformations seen in both groups.

Two of these birth defects were diagnosed in one of the two fetuses of two twin pregnancies and the other two were seen in singletons, giving a rate of (5%) in total and 2/62 (3.2%) in the sub group of singletons of PGD pregnancies. Of those babies, one died neonatally and three are still alive. In comparison, major malformations were seen in three of the 72 babies naturally conceived, (one cervical teratoma, one congenital heart disease and one right ectopic kidney), all of them were in the singleton group and the three are still alive. This gives an overall rate of (-4.1 %-), but if calculated for singletons alone would be 3/68 (4.4%). (Table 3)

The mean gestational age at delivery in the PGD pregnancies was 37.5 weeks for singletons and 34 weeks for multiples. Prematurity was observed in 12 deliveries (17%), 7 singletons and 5 multiples. So the percentage of singletons delivered preterm was (11%). Median birth weight was 3031 grams for singleton and 2067 grams for multiples. Spontaneous pregnancies had similar outcome of the PGD group, the mean gestational age at delivery was 38 weeks for singletons and 31 weeks for multiples.

Prematurity was observed in 14 (20%) of all deliveries, 12 of them were among singletons and 2 were among multiples. By this preterm delivery among singletons in this group was (18%). Median birth weight was 2919 grams for singletons and 1512 grams for multiples (Table 5).

Natural group	PGD group	Characteristics
36 (50%)	34 (43%)	Male sex
36 (50%)	45 (57%)	Female sex
10 (14%)	20 (25%)	NICU admissions
0 (0%)	3 (4%)	A/S ≤ 3 at 5 min
2919 grams	3031 grams	Mean B.wt for singletons
1512 grams	2067 grams	Mean B.wt for multiples

Table 5: Newborns characteristics.

There was a tendency to have more NICU admissions in the PGD group (25%) compared to the naturally conceived babies (14%), (Tables 6).

P value	Z value	Natural group	PGD group	Item
		3%	88%	Percentage
>0.05	0.584	1.40%	3.20%	Perinatal Mortality
>0.05	-0.455	4.40%	3.20%	Birth Defects
>0.05	-1.234	18%	11%	Delivery < 37 weeks
>0.05	0.543-	34%	30%	Delivery by C/S
>0.05	1.794	12%	26%	NICU admissions

Table 6: Comparison between singletons of both groups.

As for the mode of delivery (Table 3), 28 (40%) of our PGD pregnancies were delivered by C/S, compared to 26 (37%) of the naturally conceived pregnancie. Among singletons, the rate was (30% vs 34% in PGD group and spontaneous group respectively).

The sex distribution of the children born after PGD was 34 (43%) males and 45 (57%) females, while in the other group 36 (50%) of the born babies were males and 36 (50%) were females (Table 5).

From the PGD group, 11 (16%) chose to undergo PND and the pregnancies were found to be free from the disease for which PGD was performed. Chorionic villous sampling was carried out in eight patients and the other three had amniocentesis. One misdiagnosis was seen in a case of Joubert's syndrome giving a misdiagnosis rate of (1.4%), no PND was performed for this case.

Discussion

This retrospective study of babies born after PGD, was done to assess the possible risks of PGD associated procedures on pregnancy outcomes by compare it to pregnancy outcomes after natural conception in a similar group.

The data obtained in this study confirmed the earlier findings showing that PGD doesn't increase the risk of major malformations nor does it add any extra risks to the health of the born babies (Storm et al., 2000).

When we compared the outcomes of our PGD babies, with the data collected on babies born after spontaneous pregnancies, we found very comparable results for GA at delivery and birth weight as reported by (Storm et al., 2000) publications and in the 8th ESHRE PGD consortium report (Goossens et al., 2008).

A finding to be mentioned in our study is that the PGD group has significantly more multiple pregnancies compared to the spontaneous pregnancy group. This finding is easily explained by the fact that all PGD pregnancies are originating from IVF, which puts them at higher risk of having multiples (Ryan et al., 2004).

In our study, there was no statistically significant difference in the incidence of perinatal mortality, risk of congenital malformations or C/S rate between the PGD group and the natural conception group. Similar results were reported by different researchers (Storm et al 2000, Goossens et al., 2008)

The sex ratio of 57% females to 43% males in the PGD group compared to 50% females and 50% males in the spontaneous pregnancy group in our study is in favor of girls in the PGD babies maybe because of PGD for some X-linked diseases, again this didn't show statistical significance. Similarly, this was reported by (Liebaers et al 2010).

The higher rate of NICU admissions observed in our study n the PGD group (26% vs 12%), could be attributed to more concern towards those babies from the attending staff. This issue was not clearly addressed in other studies.

The misdiagnosis rate in our study was 1/70 or 1.4% which is comparable to rates mentioned in some other reports, (Mateo et al 2008) who reported an accuracy of 98%, and is slightly higher than what is reported in other's work (0.6%,Verlinsky et al 2005, Liebears et al 2010). This supports that PGD is not as accurate as prenatal diagnosis via chorionic villous sampling, amniocentesis or cordocentesis. Thus prenatal diagnosis is recommended to all patients after PGD. In our study, only 11 patients (16%), underwent prenatal diagnosis after PGD.

Conclusion

The conclusion of our study is that, embryo biopsy is unlikely to be adding any risk to the health of babies born after PGD when compared to that of babies born after natural conception. Further data on the health of these children at later ages seems necessary, including even larger numbers of children. Strategies for single embryo transfer should be considered to reduce the multiples and their associated complications in PGD pregnancies.

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