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Obstetric and neonatal outcomes of pregnancies conceived after preimplantation genetic diagnosis: cohort study and meta-analysis

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KEY MESSAGE

Neonatal and obstetrical outcomes of preimplantation genetic diagnosis (PGD) and intracytoplasmic sperm injection pregnancies are comparable for both singletons and twins. The results of this cohort study and meta-analysis provide sufficient support on the safety of PGD. This is clinically significant as these invasive procedures raise concerns about pregnancy outcome.

A B S T R A C T

Preimplantation genetic diagnosis (PGD) may pose risks to pregnancy outcome owing to the invasiveness of the biopsy procedure. This study compares outcome of singleton and twin clinical pregnancies conceived after fresh embryo transfers of PGD ($n = 89$) and matched intracytoplasmic sperm injection (ICSI) pregnancies ($n = 166$). The study was carried out in a single university affiliated centre. Because of the paucity of available data, a literature-based meta-analysis of studies comparing neonatal outcome of PGD and ICSI pregnancies was also conducted. In the retrospective cohort study, obstetric and neonatal outcome were available in 67 PGD and 118 ICSI pregnancies. Perinatal outcomes were comparable between PGD and ICSI pregnancies. Meta-analysis revealed similar outcomes, except for higher rate of low birth weight (<2500 g) neonates in ICSI twin pregnancies (RR 0.86, 95% CI 0.74 to 1.0). Mean birth weight, gestational age at birth, pre-term deliveries (<37 weeks) and malformations were all comparable. In this cohort study and subsequent meta-analysis, no association was found between PGD conceived pregnancies and risks of adverse neonatal or obstetrical outcomes compared with ICSI pregnancies. Hence, blastomere biopsy for PGD does not seem to increase the risk for adverse perinatal outcome compared with ICSI pregnancies.

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Introduction

Preimplantation genetic diagnosis (PGD), first reported in the early 1990s (Handyside et al., 1990), allows genetic analysis of in-vitro created embryos to enable transfer of embryos unaffected by an existing parental genetic aberration. It offers a viable reproductive option for patients who may have concerns about the ethical, moral, emotional and medical aspects of a possible pregnancy termination after prenatal testing. It mostly involves fertilization by intracytoplasmic sperm injection (ICSI) (Basille et al., 2009), whereas the retrieval of embryonic DNA for genetic analysis is conducted by direct biopsy of blastomeres from cleavage-stage embryos or by extracting trophectoderm cells after blastulation. Indications for carrying out PGD include inheritable monogenic diseases, chromosomal structural abnormalities, human leukocyte antigen matching with siblings, sex selection for medical reasons and screening against cancer predisposition genes in affected families (Daina et al., 2013).

The incidence of obstetrical and neonatal complications among assisted reproduction technique pregnancies is reported to be higher compared with spontaneously conceived pregnancies (Davies et al., 2012; Jackson et al., 2004). Although part of this inferior outcome may be related to the higher number of multiples and the underlying infertility of couples who use assisted reproduction techniques, recent data suggest that the use of assisted reproduction techniques *per se* is an independent risk factor for adverse perinatal outcome (Pinborg et al., 2013). The introduction of ICSI in 1992 (Palermo et al., 1992) intensified neonatal follow-up of pregnancies conceived through IVF–ICSI owing to the invasive nature of the procedure. By adding an additional invasive procedure by removing cells from either the embryo or the trophectoderm, concern about potentially adverse pregnancy outcomes is natural and warranted.

To date, a limited number of studies have assessed neonatal outcome of PGD pregnancies (Bay et al., 2016; Desmyttere et al., 2012; Eldar-Geva et al., 2014; Liebaers et al., 2010; Strom et al., 2000). Moreover, the obstetrical complications and postpartum outcomes of PGD pregnancies has scarcely been reported to date. Nevertheless, these outcome data are important to both healthcare providers and patients, who pursue complex assisted reproduction technique treatments albeit not being necessarily infertile.

This study compares obstetrical and neonatal outcomes after PGD to that of matched ICSI pregnancies, both singleton and twins. In addition, because of the relative paucity of published data and lack of direct comparisons, the second aim of this study involved a literature-based meta-analysis of studies that have compared neonatal outcome of PGD pregnancies with ICSI pregnancies, incorporating the data obtained from our study population. The comparison to ICSI pregnancies was carried out to isolate the obstetrical and neonatal effects of the biopsy itself, if they exist.

Materials and methods

Cohort study

The study population included all clinical pregnancies achieved after PGD fresh blastocyst transfers between 2002 and 2010 in Tel Aviv Sourasky Medical Center, a university-affiliated medical centre. Biochemical pregnancies (defined as positive beta-HCG test 14 days after embryo transfer but without sonographically proven gestational sac) were not included. Each clinical pregnancy in the PGD group was matched in a 1:2 ratio with two clinical pregnancies from fresh ICSI blastocyst transfer without PGD, which were used as the control group. Pregnancies in the control group were conceived during the same time period as the PGD pregnancies and were randomly selected by computer software (Microsoft Excel) after matching for maternal age and pre-gestational body mass index.

Ovarian stimulation, IVF–ICSI, laser zona pellucida breaching, cleavage stage blastomere biopsy and embryos cultures were carried out as previously described elsewhere (Brezina et al., 2012; Verlinsky et al., 1992). All biopsies were carried out on fresh cleavage-stage embryos (day 3) and all embryo transfers were carried out at the blastocyst stage (day 5).

Preimplantation genetic diagnosis was carried out for high-risk genetic indications where parents were carriers of either a monogenic disease or chromosomal abnormalities, i.e. translocations. Clinical pregnancy was defined as intrauterine gestational sac seen by transvaginal ultrasound at 6–7 weeks of pregnancy. Clinical pregnancy outcome was categorized as miscarriage (spontaneous termination of the pregnancy up to 20 weeks gestation), stillbirth (intrauterine fetal death after 20 weeks gestation) or live birth. The primary perinatal outcomes included were as follows: preterm delivery, delivery before complete 37 gestational weeks; early preterm delivery, delivery before complete 34 gestational weeks; intrauterine growth restriction, birth weight below the 10th percentile for gestational age using population-based growth curves and corrected for singletons and twins; low birth weight (LBW), birth weight <2500 g) and very low birth weight, birth weight <1500 g.

Data collection

All relevant data were collected from the computerized database of our hospital. The database includes electronic patient charts, which contain all relevant details on assisted reproduction technique treatments, prenatal care, delivery course and data on neonates. In cases where data were missing or when patients were delivered at other hospitals, data were retrieved by phone call interviews with patients. Data collected included the following: parental demographic details (age, smoking status, pre-gestational and pre-delivery body mass index, PGD indication), pregnancy outcomes (number of gestational sacs and positive fetal heart rate, prenatal evaluations, obstetrical complications during pregnancy), neonatal data (gestational age at delivery, mode of delivery, neonates birth weight, gender) and postpartum outcome (days of postpartum admission, postpartum haemorrhage, placenta-related complications, need for blood transfusion, post-partum fever, rate of emergency department re-evaluation within 45 days postpartum). Placental related complications included postpartum haemorrhage, placental abruption, manual lysis of placenta, uterine revision, and postpartum curettage.

Meta-analysis

Literature search

The meta-analysis included all studies published from 1 January 1980 to 31 October 2016. The bibliographical *PubMed*, *OVID/Medline* and *Cochrane Library* databases were searched for studies with combinations of the terms: 'PGD' or 'preimplantation diagnosis' or 'preimplantation genetic diagnosis' AND 'outcome' or 'neonatal' or 'perinatal' or 'obstetrical'. There were no study design limitations and

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