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ARTICLE

Altered first-trimester screening markers after IVF/ICSI: no relationship with small-for-gestational-age and number of embryos transferred

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Abstract First-trimester serum markers in 110 in-vitro fertilization (IVF) and 331 intracytoplasmatic sperm injection (ICSI) pregnancies were compared with 1431 pregnancies with spontaneous conception. Alterations of serum markers were evaluated with respect to small-for-gestational-age (SGA) growth and number of embryos transferred. For pregnancy-associated plasma protein A (PAPP-A), significantly lower concentrations were observed in IVF and ICSI pregnancies compared with controls (0.86 and 0.9 versus 1.06; $P < 0.001$). Free β-human chorionic gonadotrophin (βHCG) values were significantly higher in the IVF/ICSI groups than in controls (1.1 and 1.1 versus 0.94; $P < 0.005$). IVF and ICSI pregnancies showed higher rates of SGA (10.0% and 8.2%) compared with natural conception (4.6%), but differences in PAPP-A concentrations remained significant ($P < 0.005$) after the exclusion of SGA pregnancies. No relationship between serum values and the transfer of one, two or three embryos was observed. Centre-specific corrections may be needed to adjust screening parameters for assisted reproductive technology.

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KEYWORDS: β-human chorionic gonadotrophin (βHCG), first-trimester screening, ICSI, IVF, pregnancy-associated plasma protein A (PAPP-A), small-for-gestational-age

Introduction

Women with pregnancies achieved by assisted reproduction treatment are older than average and are therefore at higher risk for Down syndrome and other aneuploidies (Anckaert et al., 2008; Gjerris et al., 2009a). However, after overcoming the obstacles to conception with assisted reproduction treatment, avoidance of invasive cytogenetic testing is preferred by the majority of women (Geipel et al., 1999, 2004; Meschede et al., 1998; Schover et al.,

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1998). An effective screening test with a low false-positive rate should be applied to those patients. Combined first-trimester screening, utilizing maternal age, nuchal translucency (NT) measurement and maternal biochemistry [free beta-human chorionic gonadotrophin (free βHCG) and pregnancy-associated plasma protein A (PAPP-A)], has been shown to detect about 85–90% of cases with trisomy 21 and other major aneuploidies at a screen positive rate of 5–6% (Krantz et al., 2000; Spencer and Nicolaides, 2003; Spencer et al., 1999, 2003). In most studies, nuchal translucency measurement does not seem to be affected by the method of conception, but analysis of the serum markers free βHCG and PAPP-A has demonstrated some variations compared with spontaneous conception (Anckaert et al., 2008; Ghisoni et al., 2003; Gjerris et al., 2009a; Liao et al., 2001; Maymon and Shulman, 2002; Niemimaa et al., 2001; Orlandi et al., 2002). In IVF pregnancies, the currently largest explored group, an increase in free βHCG and/or decrease in PAPP-A values have been reported in some studies (Liao et al., 2001; Niemimaa et al., 2001; Orlandi et al., 2002; Maymon and Shulman, 2002, 2004; Ghisoni et al., 2003). For intracytoplasmatic sperm injection (ICSI) pregnancies, only a limited number of cases have been studied (Anckaert et al., 2008; Bellver et al., 2005; Ghisoni et al., 2003; Gjerris et al., 2009a; Liao et al., 2001; Orlandi et al., 2002).

Assisted-conception singleton pregnancies also demonstrate increased rates of perinatal complications, such as small-for-gestational-age (SGA) infants, preterm delivery, as well as maternal complications, such as pre-eclampsia, gestational diabetes and placental abruption (Helmerhorst et al., 2004; Reddy et al., 2007). In some studies, a relationship between unexplained elevations and reductions in maternal serum markers and obstetric complications has been reported (Ong et al., 2000; Phil et al., 2008). Therefore, altered first-trimester serum concentrations in assisted-conception pregnancies could be an indicator of abnormal throphoblast invasion.

The aim of the present study was to examine whether the concentrations of first-trimester maternal biochemical marker were affected by conception after assisted reproduction treatment, including a large group of ICSI pregnancies. The second issue was to evaluate the effect of the number of embryos transferred on maternal serum concentrations in IVF and ICSI pregnancies. Furthermore, the PAPP-A concentrations were analysed with respect to the occurrence of growth restriction (SGA).

Materials and methods

The study is a retrospective analysis of singleton pregnancies conceived either spontaneously or by assisted reproduction treatment, who received combined first-trimester Down syndrome screening from January 1998 to October 2007 in a tertiary-level referral unit. All patients referred in this time period were routinely offered combined screening. Appropriate patients with evaluation between 11 + 0 and 13 + 6 weeks of gestation were identified from the study's perinatal database. Of these, 97% were Caucasians and 5% were smokers. Exclusion criteria were pregnancies with structural fetal malformations or aneuploidy, pregnancies resulting in miscarriage and stillbirth, singleton pregnancies following embryo reduction or spontaneous reduction of earlier multiple implantation and those without available follow up (90 after spontaneous conception, 26 after ICSI, two after IVF). Gestational age in IVF and ICSI pregnancies was calculated from the day of oocyte aspiration and was not corrected according to crown–rump length (CRL) measurement.

In total, 110 in-vitro fertilization pregnancies, 331 intracytoplasmic sperm injection (ICSI) pregnancies and 1431 spontaneous singleton pregnancies were studied. No frozen embryo transfer cycles were included. The information on the number of embryos transferred as well as earlier multiple gestational sacs were requested from the reproductive medicine units (>80% of patients had the treatment at the Department of Endocrinology and Reproductive Medicine, University Hospital Bonn).

First-trimester ultrasound examination included fetal anatomical evaluation, confirmation of gestational age by CRL and measurement of nuchal translucency according to the Fetal Medicine Foundation protocol by three certified examiners (AG, CB and UG). Maternal blood samples were collected at the time of ultrasound examination. Values of free βHCG and PAPP-A were determined by a certified in-house laboratory using a Krypter analyser (Brahms Diagnostics, Berlin, Germany). Laboratory methods were regularly monitored by internal and external quality control programmes. The maternal serum free βHCG and PAPP-A values were expressed as multiples of the median (MoM) after correction for maternal weight and if required after adjustment for gestational age (according to CRL measurement) in spontaneous conceptions. All data were entered into the fetal database at the time of assessment in order to calculate a patient-specific risk for trisomy 21.

Outcome data are routinely obtained from the delivery unit, patients themselves or their referring doctors. Outcome variables included gestational age at delivery, preterm birth <37 weeks, birthweight, mode of delivery and the question of any fetal abnormalities. Infants were classified as small-for-gestational-age (SGA; <10th centile) and appropriate for gestational age (AGA; 10–95th centile) according to conventional population-based German birthweight sample (Voigt et al., 1996).

Statistical analyses

Statistical analysis was performed with BMDP New System (Los Angeles, USA). To achieve normal distribution, screening marker MoM values were log transformed. Significance of differences between the groups was determined by the non-parametric Mann–Whitney *U*-test. Differences in serum values and fetal NT with regard to the number of embryos transferred were evaluated with the Kruskal–Wallis test. Significance was assumed at *P*-value of <0.05.

Results

The characteristics of the studied groups are displayed in **Table 1**. Median maternal age was not different in assisted conceptions and controls. As expected, the percentage of nulliparous women was significantly higher ($P < 0.02$) in

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