Placenta 36 (2015) 921–925

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

First trimester placental markers in oocyte donation pregnancies

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ARTICLE INFO

Article history:
Received 6 February 2015
Received in revised form
15 June 2015
Accepted 19 June 2015

Keywords:
Oocyte donation pregnancies (OD IVF/ICSI)
Pregnancies with autologous oocytes (autologous IVF/ICSI)
PAPP-A
Free β-hCG
Placental markers

ABSTRACT

Introduction: This study investigates the hypothesis that placenta works differently in oocyte donation (OD) compared to spontaneous pregnancies. To verify this hypothesis we examine the first trimester maternal serum levels of free β-hCG and pregnancy-associated plasma protein-A (PAPP-A). Then we evaluated for potential differences of Down syndrome screening between OD pregnancies, in vitro fertilization/intracytoplasmic sperm injection pregnancies with autologous oocytes (IVF/ICSI) and spontaneous pregnancies.

Methods: We analyze 13624 spontaneously conceived pregnancies (Controls), 171 oocyte donation pregnancies (OD IVF/ICSI) and 76 IVF pregnancies with autologous oocytes (Autologous IVF/ICSI). Furthermore, we collect a cohort of 802 spontaneously conceived age-matched pregnancies, in order to evaluate how older uteri contribute to explain the changes in markers concentrations (Age-matched controls We compare the multiples of the median (MoM) of free β-hCG and PAPP-A and nuchal translucency.

Results: Free β-hCG levels are significantly higher both in OD IVF/ICSI pregnancies (1.44 ± 1.06 MoM) and Autologous IVF/ICSI (1.48 ± 1.02 MoM) compared to Controls (1.15 ± 0.84 MoM; $p < 0.05$) and Age-matched Controls (1.18 ± 0.98 MoM; $p < 0.05$). PAPP-A levels do not significantly differ among the four groups. Significantly lower nuchal translucency is detected in Controls (1.41 ± 0.36 mm) compared to OD IVF/ICSI (1.46 ± 0.44 mm; $p < 0.05$), in Autologous IVF/ICSI (1.51 ± 0.34 mm; $p < 0.05$) and Age-matched Controls (1.44 ± 0.42 mm; $p < 0.05$).

Discussion: Oocyte donation pregnancies (OD IVF/ICSI) are significantly related to altered maternal serum placenta marker levels. These alterations might be due to the IVF technique.

1. Introduction

Since the first successful pregnancy from donated oocytes in 1984, the number of cycles from oocyte donation continually increased in Europe and United States, becoming nowadays a common treatment option for infertility, especially to overcome advanced age problems [1–3].

Few studies investigate the placenta in the oocyte donation (OD) pregnancy and none considers the hypothesis that placenta may work differently in OD pregnancy compared to spontaneous pregnancies, especially in the first trimester. Considering that first trimester maternal–fetal assessment has become a pivotal part of antenatal care, also pregnant women from donated oocytes routinely undergo first trimester screening [4]. Among these procedures, screening for Down syndrome (DS) is performed by combining background risk of maternal age to measurement of nuchal translucency (NT) and examining two feto-placental markers in maternal serum, i.e. free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A).

Data on first trimester serum markers of aneuploidies are well established in literature on spontaneous pregnancy. Less we know about pregnancies conceived after in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), which have been

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http://dx.doi.org/10.1016/j.placenta.2015.06.009
0143-4004/

associated with different results, either related to infertility itself or to IVF/ICSI procedures [5]. These findings require specific precautions both in singleton and twin pregnancies [6].

Among IVF/ICSI pregnancies, oocyte donation (OD) pregnancies present specific issues. In oocyte donation pregnancies, the discrepancy between the donated oocyte, fully allogeneic to the recipient, and the elderly uterine compartment of the mother, affected by hormonal preparation to achieve implantation, could potentially have an impact on markers and modify the performance of the algorithm used for the antenatal screening.

The first purpose of this study is to investigate the hypothesis that placenta could work in a different way in oocyte donation (OD) compared to spontaneous pregnancies. In order to test this hypothesis, we undertake a comparison between serum maternal analytes concentration in singleton pregnancies conceived using oocyte donation, IVF with autologous oocyte and naturally conceived ones. The second purpose is to examine if possible differences could affect the Down syndrome screening performance. To explore this second point we also compared NT values in all groups.

2. Materials and methods

2.1. Patients and method of screening

We performed a prospective cohort study to analyze data of singleton pregnant women who underwent their first trimester screening for aneuploidies between January 2000 and June 2013 carried out in a single reference, quality controlled and accredited laboratory.

We collected 13624 spontaneously conceived pregnancies (Controls), 171 oocyte donation pregnancies (OD IVF/ICSI), and 76 autologous IVF/ICSI pregnancies (Autologous IVF/ICSI). In order to evaluate how older uteri contributed to explain the change in markers' concentrations, we then selected a cohort of 802 spontaneously conceived pregnancies with maternal age matched to OD recipients' age (Age-matched Controls). To this aim we excluded, in the spontaneous group, all patients younger than the youngest OD recipient. The age range was 38–46 years and the mean age 39.7 (±1.53) years. All participants granted a written informed consent.

First trimester combined screening for Down syndrome was performed at $11–13^{+6}$ weeks of pregnancy. The screening was performed according to the recommendation of the Fetal Medicine Foundation for nuchal translucency measurement, and gestational age was calculated from the crown-rump length (CRL) both in spontaneous and in assisted reproductive technique (ART) pregnancies. The measurement of the concentration of free β-hCG and PAPP-A by immunofluorescence was carried out in a single, quality controlled, accredited reference laboratory (Bi-tech Ltd, Milan, Italy) which employed the following fully automatic random access immunoassays analyzer systems: the COBAS 6000 e601 system of Roche Germany Holding GmbH and the KRYPTOR system of Brahms GmbH. As concentrations of free β-hCG and PAPP-A are influenced by the machine, reagents used, gestational age, maternal weight, ethnicity, gravidity and smoking statuses, the measured marker levels are expressed as multiples of the gestation-specific normal median value (multiples of the median - MoM) after adjusting for these characteristics. No corrections for the mode of conception were applied by the laboratory. We used the software program PRISCA for the routine calculation of Trisomy 21 (T 21) and Trisomy 18 (T 18) during the first trimester. We used the donor age to calculate the age related risk of Down syndrome. When risk was equal or greater than 1 in 350 for T 21 (the cut off was customized in the lab to obtain a 5% overall screen positive rate) or 1 in 150 for T 18, the pregnant women were routinely offered invasive diagnosis by chorionic villus sampling or amniocentesis for fetal karyotyping.

We compared free β-hCG and PAPP-A MoM values among Controls, Age-matched Controls, OD IVF/ICSI and Autologous IVF/ICSI. Furthermore, to study the effect of oocyte donation on the first trimester screening test, we also compared the NT values normalized to crown-rump length among the four groups. Information about NT measurments and patients carachetristics were collected from patients records in the same laboratory where serum markers measurments were obtained.

To compare serum maternal analytes concentration between the groups we excluded multiple gestations, structural fetal malformations and chromosomal abnormalities.

In OD pregnancies, all women were advised to take estradiol valerate 2 mg, 3 tablets daily, and 400/600 mg of micronized progesterone vaginally/daily during preparation of transfer and until the end of the first trimester. No patients in the oocyte donation group underwent a simultaneous ovarian stimulation. All the embryos transferred were fresh. Information about days of embryo culture, culture medium and number of embryo transferred were not available. IVF/ICSI patients underwent hormonal stimulation to obtain controlled ovarian stimulation using recombinant gonadotropins preparations. Protocols of controlled ovarian stimulation were decided individually according to each patient's clinical characteristics.

2.2. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science version 17.0 (SPSS Inc., Chicago, IL, USA). Usual descriptive statistics were computed considering 4 main groups (spontaneously conceived pregnancies (Controls), N = 13624; oocyte donation pregnancies (OD IVF/ICSI), N = 171; autologous IVF/ICSI pregnancies (Autologous IVF/ICSI), N = 76; spontaneously conceived age-matched pregnancies (Age-matched Controls), N = 802).

The significance of the differences between groups' means was tested using one-way analysis of variance (ANOVA) and Student's t test for post-hoc comparisons, following the Fisher's Least Square Difference Method. The Kruskal–Wallis one-way non parametric ANOVA on medians was also applied to confirm the results, taking into account the skewedness of the distributions of the variables implied.

Means, standard deviations, medians and other quartiles, when appropriate, were used for description.

The p values were reported, and a p less than 0.05 (two tails) was considered for the statistical significance.

Finally, 95% confidence intervals were also computed.

Ethics approval number N.48 2013.

3. Results

3.1. Study population

Table 1 presents the baseline characteristics of the study population. As expected, mean maternal age varied among groups (Controls: 30.4 ± 3.6 years; OD IVF/ICSI - oocyte recipients: 41.9 ± 4.2 years; OD IVF/ICSI - oocyte donors: 25.9 ± 3.7 years; Autologous IVF/ICSI: 36.0 ± 4.8 years; Age-matched Controls: 39.7 ± 1.5 years).

Women in the OD IVF/ICSI group were more likely to be primigravida than Controls.

The totality of patients was of southern European Caucasian ancestry.

3.2. Biochemical markers

Comparisons of free β-hCG and PAPP-A maternal serum levels