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Characteristics of preeclampsia in donor cell gestations

Attina Ervaala [a], Hannele Laivuori [b,c,d], Mika Gissler [e,f], Juha Kere [g,h], Katja Kivinen [c], Anneli Pouta [i], Eero Kajantie [j,k,l,m], Seppo Heinonen [a], Satu Wedenoja [a,g,*]

[a] Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, 00290 Helsinki, Finland
[b] Department of Obstetrics and Gynecology, Tampere University Hospital and Tampere University, Faculty of Medicine and Health Technology, 33520 Tampere, Finland
[c] Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, 00290 Helsinki, Finland
[d] Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, 00290 Helsinki, Finland
[e] Information Services Department, Finnish Institute for Health and Welfare, Helsinki, Finland
[f] Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[g] Stem Cells and Metabolism Research Program, University of Helsinki, and Folkhälsan Research Center, 00290 Helsinki, Finland
[h] Department of Biosciences and Nutrition, Karolinska Institutet, 14183 Huddinge, Sweden
[i] Information Services Department, Finnish Institute for Health and Welfare, 00300 Helsinki, Finland
[j] PEDEGO Research Unit, MRC Oulu, Oulu University Hospital and University of Oulu, 90570 Oulu, Finland
[k] Public Health Promotion Unit, Finnish Institute for Health and Welfare, 00300 Helsinki and 90220 Oulu, Finland
[l] Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, 7491 Trondheim, Norway
[m] Children's Hospital, Helsinki University Hospital and University of Helsinki, 00290 Helsinki, Finland

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ABSTRACT

Pregnancies conceived through donor oocytes or sperm show increased risk for preeclampsia. We studied this issue in a preeclampsia case-control cohort (n = 2778), and found overrepresentation of donor cell gestations among women with preeclampsia (14/1627, 0.86%; OR 1.81; 95% CI: 1.07–3.08; P = 0.025) compared to the population data. Moreover, we observed excess of male births from donor cell pregnancies (male-to-female ratio 2.5 vs. 0.97; OR 2.57; 95% CI 1.02–6.36; P = 0.043). Maternal age (36.7 vs. 30.2; P < 0.0001) and preterm deliveries (64% vs. 38%; P = 0.046) distinguished donor cell gestations from other pregnancies with preeclampsia. These results support foreign fetal antigens as modulators of preeclampsia.

1. Introduction

Preeclampsia is a severe hypertensive complication of human pregnancy, affecting 2–8% of pregnancies worldwide [1]. While only delivery of the placenta provides a cure for preeclampsia, none of the theories of placental etiology have withstood time [2]. Remarkably, mechanisms that normally protect the fetus from maternal immune responses, such as HLA-G expression specific to fetal trophoblasts or expansion of regulatory T cells, are dysregulated in preeclampsia [3–5]. In animals, maternal innate immunity drives not only fetal rejection but also angiogenic imbalance [6], which is the hallmark of human preeclampsia [7].

The role of maternal immune reactivity against foreign fetal antigens is further supported by the high risk for preeclampsia in gestations conceived through donor oocytes. The earliest findings of preeclampsia rates of up to 38% in donor oocyte gestations [8], and later reports showing rates of 20–25% [9–10], have been confirmed in meta-analyses with the odds ratios of 2–3, compared with other methods of assisted reproduction, and 4 compared with natural conception [11–13]. In contrast, the risk of preeclampsia in gestations with donor sperm, with half of the fetal genes foreign to the mother, show preeclampsia rates of 8 to 11% [14–15] and the odds-ratio of 1.63 in a meta-analysis [16]. We sought to assess characteristics of preeclampsia in donor cell gestations using a large nation-wide case-control cohort of preeclampsia.

Methods

We studied 2778 women with a singleton pregnancy from the Finnish Genetics of Preeclampsia Consortium (FINNPEC) cohort. Preeclampsia was defined as hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic ≥ 90 mmHg) and proteinuria (urinary protein ≥ 0·3 g/24 h or 0·3 g/L or two ≥1+ readings on a dipstick) after 20 weeks of gestation [17]. Written informed consent was received from all participants and methods were approved by the institutional ethics

* Corresponding author at: Folkhälsan Research Center, Haartmaninkatu 8, 00290 Helsinki, Finland.
E-mail address: satu.wedenoja@helsinki.fi (S. Wedenoja).

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Table 1
Characteristics of women with donor cell pregnancies in the preeclampsia case-control series.

	Donor cell pregnancies (n = 21)	*Ovum donation (n = 13)*	*Sperm donation (n = 8)*	Other pregnancies (n = 2757)	*P* value
Age (y)	35.6 (±6.1)	*35.0 (±7.0)*	*36.5 (±4.6)*	30.0 (±5.4)	**<0.0001**
Nulliparous	15 (71%)	*9 (69%)*	*6 (75%)*	1836 (67%)	0.640
Gravidity	1.9 (±0.9)	*1.8 (±1.1)*	*1.9 (±0.6)*	2.1 (±1.7)	0.770
Parity	0.4 (±0.8)	*0.5 (±1.0)*	*0.3 (±0.5)*	0.6 (±1.2)	0.601
Preeclampsia	14 (67%)	*9 (69%)*	*5 (63%)*	1613 (59%)	0.450
Gestational hypertension	2 (10%)	*1 (8%)*	*1 (13%)*	168 (6.1%)	0.371
Preterm birth	9 (43%)	*5 (38%)*	*4 (50%)*	704 (26%)	0.070
SGA	4 (19%)	*1 (8%)*	*3 (38%)*	442 (16%)	0.763
Offspring sex ratio (Male/Female)	2.5 (15 M/6F)	*2.3 (9 M/4F)*	*3.0 (6 M/2F)*	0.97 (1359 M/1398F)	**0.043**

SGA, small for gestational age. Data are reported as mean ± SD or n (%). P values are shown for Donor cell pregnancies vs. Other pregnancies.

Table 2
Characteristics of women with preeclampsia in association with donor cells, autologous IVF, and non-donor pregnancies.

	Donor cell gestations (n = 14)	*Ovum donation (n = 9)*	*Sperm donation (n = 5)*	Autologous IVF (n = 30)	P value (donor vs. autologous)	Pregnancies without donor treatments (n = 1613)	P value (donor vs. without donor treatments)
Age (y)	36.7 (±6.2)	*36.9 (±7.0)*	*36.4 (±5.1)*	33.6 (±4.2)	0.054	30.2 (±5.5)	**<0.0001**
Gravidity	2.0 (±1.0)	*2.0 (±1.2)*	*2.0 (±0.7)*	2.1 (±1.6)	0.823	1.9 (±1.6)	0.264
Parity	0.5 (±0.9)	*0.7 (±1.1)*	*0.2 (±0.4)*	0.3 (±0.6)	0.783	0.5 (±1.1)	0.807
Nulliparous	10 (71%)	*6 (67%)*	*4 (80%)*	22 (73%)	0.999	1196 (74%)	0.765
Chronic hypertension	2 (14%)	*1 (11%)*	*1 (20%)*	7 (23%)	0.695	283 (18%)	0.410
Diagnosis of preeclampsia (gestation week)	34.0 (±2.9)	*35.1 (±2.3)*	*32.1 (±3.0)*	36.0 (±3.2)	**0.048**	35.2 (±4.0)	0.086
Early onset of preeclampsia (<34 weeks)	6 (43%)	*3 (33%)*	*3 (60%)*	8 (27%)	0.283	477 (30%)	0.279
Highest systolic blood pressure (mm Hg)	168 (±17)	*160 (±13)*	*182 (±16)*	165 (±16)	0.614	167 (±19)	0.807
Highest diastolic blood pressure (mm Hg)	111 (±6.6)	*108 (±4.9)*	*115 (±7.4)*	109 (±8.4)	0.543	110 (±9.4)	0.645
HELLP	2 (14%)	*2 (22%)*	*0*	1 (3.3%)	0.234	124 (7.7%)	0.296
Gestational age at birth (week)	35.8 (±2.5)	*36.3 (±2.6)*	*34.9 (±2.5)*	37.3 (±3.1)	0.062	36.7 (±3.6)	0.095
Preterm birth (<37 weeks)	9 (64%)	*5 (56%)*	*4 (80%)*	8 (27%)	**0.017**	616 (38%)	**0.046**
SGA	3 (21%)	*1 (11%)*	*2 (40%)*	2 (7%)	0.307	353 (22%)	0.571
Offspring sex ratio (M/F)	2.5 (10 M/4F)	*2.0 (6 M/3F)*	*4.0 (4 M/1F)*	0.4 (9 M/21F)	**0.020**	0.9 (766 M/847F)	0.105
Birthweight (grams)	2566 (±783)	*2749 (±726)*	*2236 (±852)*	2806 (±789)	0.352	2670 (±904)	0.634
Relative birthweight, (z score)	−1.0 (±1.3)	*−0.6 (±1.2)*	*−1.5 (±1.3)*	−0.9 (±1.0)	0.767	−1.0 (±1.3)	0.607

HELLP, hemolysis, elevated liver enzymes and low platelets. SGA, small for gestational age. Data are reported as mean ± SD or n (%).

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We assessed patient records for pregnancies conceived through donor oocyte (n = 13) or sperm (n = 8), and compared their clinical findings with other pregnancies. Of the pregnancies with donor sperm, 2 had been conceived through in vitro fertilization (IVF), while the method for assisted reproduction was unavailable for 6. We also studied characteristics of donor cell gestations resulting in preeclampsia (n = 14; 10 IVF and 4 without detailed data on the assisted reproduction), and compared them with other preeclamptic pregnancies, and with preeclamptic pregnancies after IVF without donor treatments (n = 30).

To get population level data on the prevalence of donor cell gestations, we used registry data recorded by the Finnish Institute for Health and Welfare. We studied the number of pregnancies (n = 241,968), which started during the collection of the FINNPEC cohort in 2008–2011, and live births after IVF with donor oocyte/sperm treatments (n = 1152).

Statistical analyses were performed using the GraphPad Prism software, version 8.4.3 (GraphPad Software, San Diego, CA). Normality tests were performed by the Kolmogorov-Smirnov test. For categorical variables, Chi-Square test or Fisher exact test (cell count < 5) was used. Continuing variables were analyzed by the Mann-Whitney *U* test or Student's *t* test. *P* values < 0.05 were considered statistically significant.

2. Results

We found overrepresentation of donor cell gestations (21/2778 births; 0.76%) in the whole case-control cohort compared to the number of donor pregnancies resulting in birth (1152/241,968 births; 0.48%) in the population (OR 1.59, 95% CI: 1.03–2.46; P = 0.034). Specifically, the rate of donor cell gestations was increased among women with preeclampsia (14/1626 births; 0.86%; OR 1.81; 95% CI: 1.07–3.08; P = 0.025), but not in control women (7/1152 births; 0.61%; P = 0.52).

Altogether 14 (67%) of the total 21 pregnancies conceived through donor cells were complicated by preeclampsia. The women who conceived through donor cells were older compared to other women in the cohort (mean 35.6 vs 30.0 years; P < 0.0001). Moreover, the offspring sex-ratio was increased (male-to-female ratio of 2.5) in donor cell pregnancies when compared to the sex ratio of 0.97 in the remaining cohort (OR 2.57; 95% CI 1.02–6.36; P = 0.043) (Table 1).

When only preeclamptic pregnancies were evaluated, women who conceived through donor cells were older (mean 36.7 vs 30.2 years; P < 0.0001) and had more preterm deliveries (64% vs. 38%; OR 2.91, 1.03 – 7.80; P = 0.046) compared to other women with preeclampsia (Table 2). In comparison with preeclamptic pregnancies after IVF without donor treatments, donor cell pregnancies were associated with earlier

diagnoses of preeclampsia (mean 34.0 in donor vs 36.0 weeks of gestation in non-donor gestations; P = 0.048), increased rate of preterm deliveries (64% vs 27%; OR 4.57; 95% CI 1.23 – 17.01; P 0.017), and higher male-to-female ratio of offspring (sex ratio 2.5 vs. 0.4; OR 5.83; 1.49–19.6; P = 0.020) (Table 2). When the data were stratified by pregnancies with donor oocyte (n = 9) and sperm (n = 5), the characteristics of preeclampsia were highly similar between the groups, with the only difference being the higher maximal systolic blood pressure in donor sperm vs. oocyte gestations (mean 182 ± 16 vs. 160 ± 13 mm Hg; P = 0.017; Table 2).

3. Discussion

Our results support the increased risk of preeclampsia in donor cell gestations. Consistent with earlier studies, we found advanced maternal age [10] and increased rate of preterm deliveries [13] in donor cell gestations, particularly in the context of preeclampsia. While the risk of preterm birth might also be related to assisted reproductive technology [18], donor cell gestations showed more preterm deliveries, and earlier onset of preeclampsia, compared to IVF pregnancies without donor treatments.

Our study implicates an association between male fetal sex and preeclampsia in donor cell gestations. Biased male-to-female ratio of children after donor treatments have been proposed in small series [19], but failed to confirm in larger studies [14,20]. Our findings support that more pronounced maternal immune responses in donor cell gestations [21] and foreign fetal antigens, such as the male H-Y antigen [22], might contribute to the pathogenesis of preeclampsia. In contrast, the observed female bias after autologous IVF might be related to loss of male conceptions before the pregnancies with preeclampsia [4,23–25].

Although the number of subjects with donor treatments was low and did not allow stratification of analyses by donor cell types, the characteristics of preeclampsia were highly similar after ovum and sperm donor cell treatments. However, the risk of preeclampsia is much higher after donor oocyte [8–10] compared with donor sperm treatments [14–15], and various mechanisms are likely to modulate the risk and characteristics of preeclampsia. These results support the higher rate of preeclampsia in donor cell gestations in this small cohort, and shed light on the role of fetal sex and foreign antigens in preeclampsia. Collectively, these results support immunological dysregulation of placentation and gestation in donor cell pregnancies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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