PCSK9 and Lp(a) levels of children born after Assisted Reproduction Technologies

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Introduction and objectives : Since the introduction of Assisted Reproduction Technologies (ART), including classic In Vitro Fertilization (IVF) and Intacytoplasmic Sperm Injection (ICSI), in clinical practice, several studies have addressed concerns regarding the long-term health of the offspring, revealing indications of an adverse cardiometabolic outcome. Proprotein convertase subtilisin/kexin type 9 (PCSK9) circulating level is significantly associated with an increased risk of cardiovascular events and may be used as a reliable biomarker. In this study, we aimed at investigating the PCSK9 levels and lipidemic profile of children born ART compared with naturally conceived (NC) controls.

Methods: In this cross-sectional, case-control study, 73 sex- and age-matched children (mean age 98 ± 35 months) of ART (ICSI: n=33, classic IVF: n=40) and 73 NC children were assessed. Blood was drawn for assessment of lipid biomarkers, including PCSK9 and Lp(a) levels, as well as glycemic and inflammatory biomarkers. For the purpose of this analysis, subjects were classified according to their age in 3 groups (group 1: <8 years, group 2: 8-10 years and group 3: ≥10 years).

Table 1. Characteristics of the study population

Variable	Control (n=73)	IVF–ICSI (n=73)	p-value
Age (months)	98±35	97±35	0.867
Boys, n (%)	26 (36)	28 (38)	0.732
Birth data			
Gestational age, (weeks n=64/60)	38.0±2.1	36.0±2.8	<0.001
Preterm birth, n (%)	14 (19)	29 (40)	0.006
Birth weight, (gr, n=70/61)	3013.7±609.8	2417.7±672.2	<0.001
SGA/LGA, n (%)	16 (22)	25 (34)	0.097
Birth length, (cm, n=68/47)	49.8±3.4	47.7±3.7	0.003
Primiparous, n (%)	28 (38)	50 (69)	<0.001
Singleton birth, n (%)	60 (82)	43 (59)	0.002
Parental characteristics			
Maternal dyslipidemia, n (%)	7 (10)	8 (11)	0.785
Maternal age at birth, (years, n=73/58)	31.7±5.0	36.4±5.3	<0.001
Paternal dyslipidemia, n (%)	12 (16)	12 (16)	1.000
Paternal age at birth, (years, n=72/55)	35.5±5.1	39.1±5.8	<0.001
Children's characteristics			
Systolic blood pressure (mmHg, n=70/65)	105.0 (100.0-110.0)	100.0 (90.0-110.0)	0.064
Diastolic blood pressure (mmHg, n=70/65)	60.0 (50.0-60.0)	60.0 (50.0-70.0)	0.067
Height (cm)	130.5±19.3	131.0±18.7	0.892
BMI, kg/m^2 (n=73/71)	17.7 (15.7-21.0)	17.6 (15.4-21.0)	0.923
Waist-to-hip ratio (n=71/72)	0.93±0.08	0.91±0.09	0.163
Prepubertal stage (Tanner I), n (%)	13 (18)	14 (19)	0.831

Results and Conclusions:

❑ No significant differences were observed regarding lipid parameters between ART and NC children (Table 2)

❑ Univariate model of the overall population:

- ***PCSK9 levels*** were related to total cholesterol (r=0.186, P=0.025) LDL (r=0.180, P=0.029) and systolic blood pressure (SBP) (ρ=0.199, P=0.021)
- ***Lp(a) levels*** were related to age (r=0.269, P=0.001), apoB (r=0.214, P=0.01), birth weight (r=−0.183, P=0.037), height (r=0.263, P=0.001), waist to hip ratio (r=−0.350, P<0.001), HOMA-IR (r=0.319, P<0.001), insulin (r=0.316, P<0.001), and high-sensitivity C-reactive protein (ρ=0.241, P=0.018).

Variable	Control (n=73)	IVF–ICSI (n=73)	p-value
Lipid biomarkers			
Total cholesterol, (mg/dL)	169.0±25.7	168.3±24.0	0.871
LDL, (mg/dL)	100.5±21.0	100.3±20.9	0.962
HDL, (mg/dL)	56.7±11.5	56.7±11.0	0.988
Triglycerides, (mg/dL)	52.0 (39.0-71.5)	50.0 (41.0-62.5)	0.754
ApoA1, (mg/dL)	154.0±19.2	150.2±21.7	0.259
ApoB, (mg/dL, n=73/72)	72.6±15.9	74.8±15.1	0.411
Lp(a), (mg/dL)	6.5 (3.5-17.3)	9.2 (2.6-24.8)	0.277
PCSK9 (ng/ml)	184.4 (133.8-235.5)	189.2 (148.7-226.8)	0.515
Glycemic biomarkers			
Glucose, (mg/dL)	83.0 (77.5-88.0)	84.0 (77.5-88.0)	0.854
Insulin (mU/L, n=72/71)	5.14 (4.32-8.55)	6.20 (4.10-12.50)	0.392
HOMA (n=72/71)	1.096 (0.856-1.839)	1.274 (0.816-2.473)	0.454
Inflammatory biomarkers			
sCRP, (mg/L, n=32/64)	0.39 (0.15-0.71)	0.52 (0.21-1.40)	0.086
hsIL-6 (pg/mL, n=43/68)	1.09 (0.60-1.93)	1.25 (0.72-1.99)	0.443

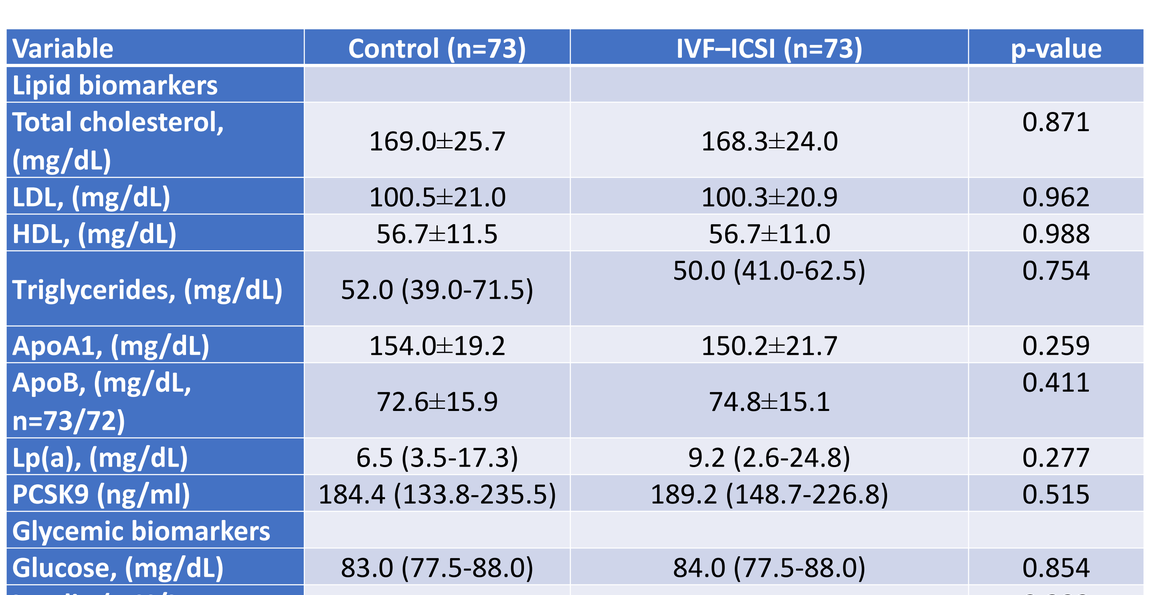
❑ **NC vs ART** (Two-way between groups ANCOVA)

- After adjusting for gender and LDL, a significant interaction was found between age groups and conception method regarding **PSCK9 levels** (p for interaction<0.001), **indicating that ART children increase their PCSK9 levels with age in contrary to NC children where levels of PCSK9 decrease with age** (Figure 1).

❑ **ICSI vs IVF** (Two-way between groups ANCOVA)

- After adjusting for age, gender and apoB, **ART children conceived with IVF showed significantly higher levels of Lp(a) compared to ART children conceived with ICSI** (6.5mg/dl vs. 12.0 mg/dl, p=0.022)

Figure 1.



✓ PCSK9 levels increase with age in ART, but not in NC, children, forecasting a gradual deterioration of their lipidemic profile that could progressively further lead to increased cardiovascular risk in the future.

✓ The method of ART may be of importance

✓ Important role of novel lipid factors as early indices of latent cardiometabolic derangements according to the conception method.

References:

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