Prepubertal and Pubertal Predictors of Semen Quality in a Prospective Cohort Study of Russian Young Men: Focus on Endocrine Disrupting

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Oleg Sergeyev [a,b], Lidia Mínguez-Alarcón [c], Russ Hauser [c,d], Paige L. Williams [e], Jane S. Burns [c]
Susan A. Korrick [c,f], Yury Dikov [b], Luidmila Smigulina [b], Boris Revich [g], Mary M. Lee [h]

[a]Department of Genomics and Human Genetics, Vavilov Institute of General Genetics, Russian Academy of Science, Moscow, Russia; [b]Chapaevsk Medical Association, Chapaevsk, Samara Region, Russia; [c]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, USA; [d]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA; [e]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, USA; [f]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [g]Institute of Economic Forecasting, Russian Academy of Science, Moscow, Russia, [h]Departments of Pediatrics and Cell and Developmental Biology, University of Massachusetts Medical School, Worcester, Massachusetts, USA.

Background

We have a unique longitudinal study following a cohort of boys with prepubertal assessment of exposures to endocrine disrupting chemicals (EDCs) and annual term follow-up of growth and puberty to evaluate semen quality

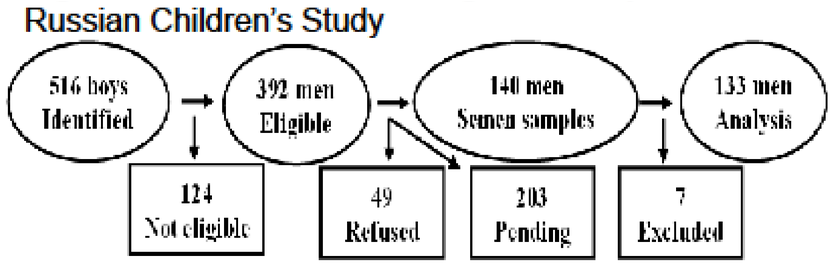
Objective

To describe semen quality and explore associations of prepubertal serum 2,3,7,8-tetrachlorodibenzodioxin (TCDD) levels and pubertal measures with semen parameters in a longitudinal cohort of Russian boys

Study Population

- 516 8-9-year-old boys were enrolled from 2003 to 2005 and underwent annual growth and sexual development assessments (Tanner staging and measurement of testicular volume) for ten years (total 4697 visits).
- At age 18 years, 392 subjects were eligible for semen sample collection.

Figure 1. Recruitment flow diagram for boys/men in Russian Children's Study



Footnote: Identified – using town records during 2003-2005; Not eligible – deceased, moved, location is unknown, refused to participate in follow-up; Pending – not responded yet, temporarily relocated, less than 18 years old, physically immature, postponed; Excluded – from analysis because no baseline serum EDCs measurements (n=4) and severe chronic disease (n=3)

Methods

- The study was approved by the Human Studies Institutional Review Boards of the Chapaevsk Medical Association (Chapaevsk, Russia); HSPH and BWH (Boston, MA, USA), and UMass Medical School (Worcester, MA, USA).

Semen Collection and Analysis:

- At age 18, the subjects were asked to provide two semen samples one week apart (October 2012 – February 2015).
- 133 men contributed 257 semen samples.
- Semen evaluation (SE) includes measurement of volume, sperm concentration and motility (a+b+c categories) by one technician (LS) according to the NAFA-ESHRE manual[1,2].

Organochlorine Exposure Assessment:

- Baseline serum samples were analyzed at the NCEH, CDC, Atlanta, USA for TCDD and 57 other organochlorine compounds (described in Burns et al [3]).

Pubertal Measures at Semen Evaluation:

- Testicular volume was measured using the Australian orchidometer (which extends the Prader orchidometer to 35 mL)

Statistical Analysis:

Prepubertal TCDD and Semen at 18 years

- Sperm concentration, total sperm count and total motile sperm count were log transformed
- Linear mixed models with random intercepts were used to examine the relation between quartiles of TCDD serum concentration with semen parameters
- Final models were adjusted for:
  - body mass index (BMI) (continuous)
  - season (autumn and winter vs. spring and summer)
  - abstinence time (<2days, 2-5 days, ≥5days)

Testicular Volume and Semen at 18 years

- Volume of left and right testicles was averaged
- Semen parameters were log10 transformed
- Linear univariate regression was used

Results

Descriptive Statistics of Cohort

Table 1. Baseline and exposure characteristics of young Russian adults

Baseline characteristics	*Median (IQR) or N (%)*
Age, years	18.3 (18.1, 18.7)
Body Mass Index, kg/m²	20.4 (18.8, 22.3)
Men with 2 semen samples	123 (93)
Abstinence time, hrs	70.5 (48.0, 144.0)
Serum organochlorine concentrations (pg/g lipid)	
TCDD	2.9 (1.8, 4.2)
PCDDs	157 (115, 200)
PCDFs	44.5 (29.4, 63.3)
Co-PCBs	188 (131, 273)
ΣPCBs	235 (152, 352)
Total TEQ	21.9 (16.8, 33.3)

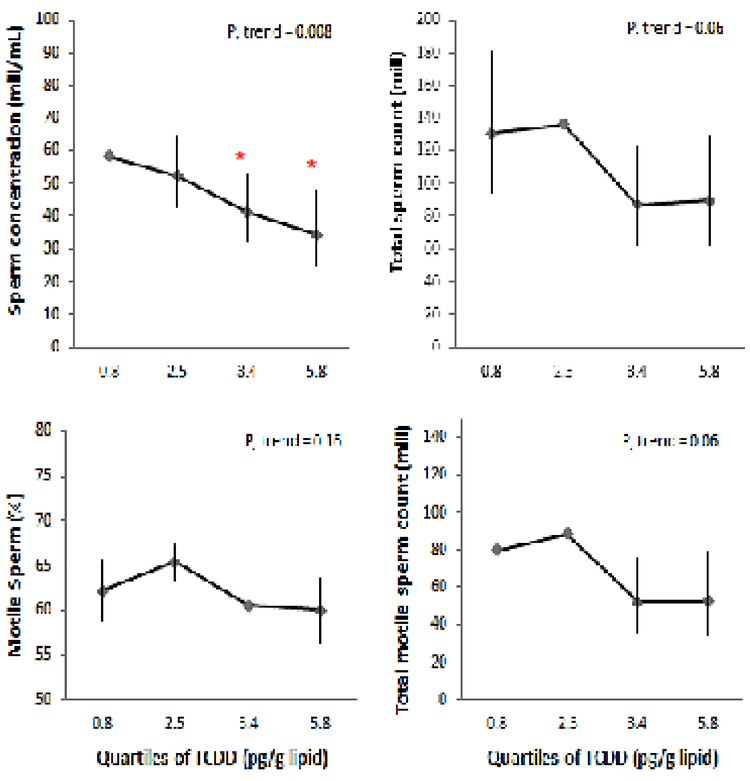
Semen Parameters

Table 2. Distribution of semen parameters among 133 young Russian adults, 257 samples

Semen parameters	*Median (IQR)*	*WHO 2010 cutoffs*	*n (%) < WHO 2010*
Semen volume, mL	2.4 (1.8, 3.5)	1.5	46 (18%)
Sperm concentration, mill/mL	51.3 (26.6, 78.8)	15	23 (9%)
Total sperm count, mill	127 (61.0, 222)	39	38 (15%)
Sperm motility, %	64.0 (57.0, 68.0)	40	10 (4%)
Total motile sperm count, mill	80.5 (35.8, 141)	-	-

Prepubertal TCDD and Semen

Figure 2. Associations between prepubertal TCDD concentration and semen parameters among 133 young Russian adults



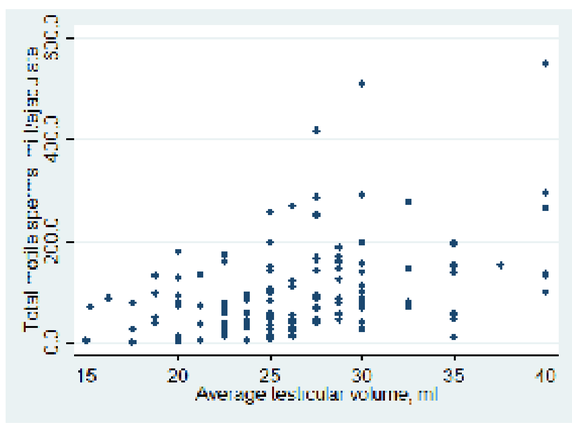
*** p<0.05 compared to Q1**

Testicular Volume and Semen

Table 3. Average testicular volume (ml) as predictor of log semen parameters among young Russian adults

Parameters	*Estimate*	*95% CI*	*P-value*
Semen volume, ml	0.020	(0.002 - 0.038)	0.029
Motility, %	0.009	(0.002 - 0.015)	0.008
Sperm count, mill/ml	0.064	(0.038 - 0.091)	<0.001
Total sperm, mill	0.084	(0.054 - 0.114)	<0.001
Total motile sperm, mill	0.092	(0.059 - 0.125)	<0.001

Figure 3. Association between average testicular volume and total motile sperm among young Russian adults



- For every 1 ml increase in average TV, we observed a mean increase of 9.6% in total motile sperm count per ejaculate, p<0.001

Conclusion

In a prospective cohort of 18 year old Russian men:

- *higher* prepubertal serum TCDD levels are associated with *lower* semen parameters: sperm concentration, total sperm count, and total motile sperm count
- *higher* testicular volume is associated with *higher* semen parameters

In Summary

- This is one of the first prospectively designed studies to follow a large cohort of boys annually from prepuberty until young adulthood, including collection of semen samples at 18 years
- Consistent with the Seveso study, our results suggest that the prepubertal period is a sensitive window of exposure to dioxin for adult sperm quality[4]
- Collection of semen samples is ongoing with anticipated participation of 250 young men
- We are studying EDCs effects on sperm epigenetic programming among this Russian male cohort.

Grant Support US NIH Grants R-01 ES014370; P30ES000002; Russian Science Foundation Grant 14-45-00065

Acknowledgments We thank the Chapaevsk Local Government, staff of Chapaevsk Medical Association and Chapaevsk Central Hospital. We are grateful to the boys/young adults in Chapaevsk for their participation

References:

[1] KVIST, U. & BJORNDAHL, L. 2002. Manual on Basic Semen Analysis. ESHRE Monographs, Oxford: Oxford University Press.

[2] BJÖRNDAHL, L. et al. 2010. A Practical Guide to Basic Laboratory Andrology, Cambridge, UK: Cambridge University Press.

[3] BURNS, J. S. et al. 2009. Predictors of serum dioxins and PCBs among peripubertal Russian boys. *Environ Health Perspect,* 117, 1593-1599.

[4] MOCARELLI, P. et al. 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect, 116, 70-7.

Further Information: olegsergeyev1@yandex.ru; rhauser@hshp.harvard.edu

ESPE 2015 987--P3

Gonads

Oleg Sergeyev

DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology