Cord blood insulin-like peptide 3 is reduced in idiopathic cryptorchidism and inversely related to free bisphenol A:

a marker and/or an actor of fetal exposure to endocrine disruptors?

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OBJECTIVES

- Most cases of congenital cryptorchidism remain idiopathic, but epidemiological and experimental studies suggest the role of hormonal, genetic and environmental factors
- Fetal exposure to several Environmental Endocrine Disruptors (EEDs), has been suspected to be involved in the occurrence of idiopathic cryptorchidism.
- INSL3 is a major actor of testicular descent which gene is negatively regulated by etsradiol and positively by testosterone
- Could INSL3 be regulated by fetal exposure to endocrine disruptors with estrogenic or anti-androgenic effects ?

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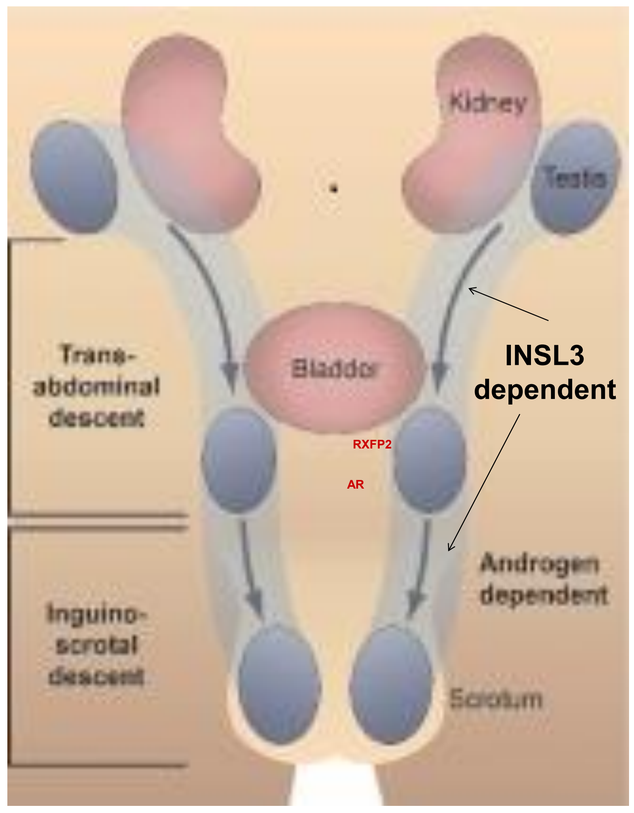


METHODS

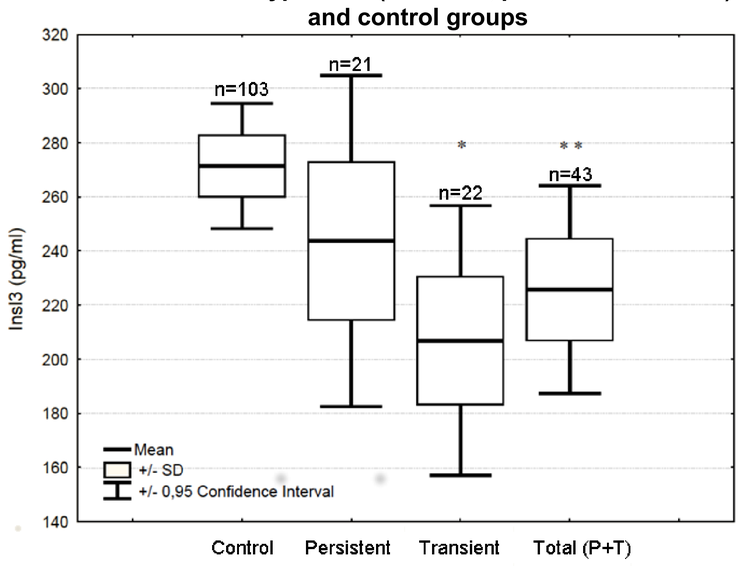
Correlations between cb INSL3 or testosterone and cb free bioactive bisphenol A (BPA) and maternal milk polychlorinated biphenyls (PCB153), dichlorodiphenyldichloroethylene (DDE), and monobutylphtalate (mBP) were assessed in newborn boys issued from a case-control study. All boys born after 34 weeks of gestation were systematically screened at birth for cryptorchidism over a 3 year period (2002-2005), diagnosis of cryptorchidism confirmed before discharge by a senior pediatrician.

PARTICIPANTS, MATERIALS, SETTINGS, METHODS

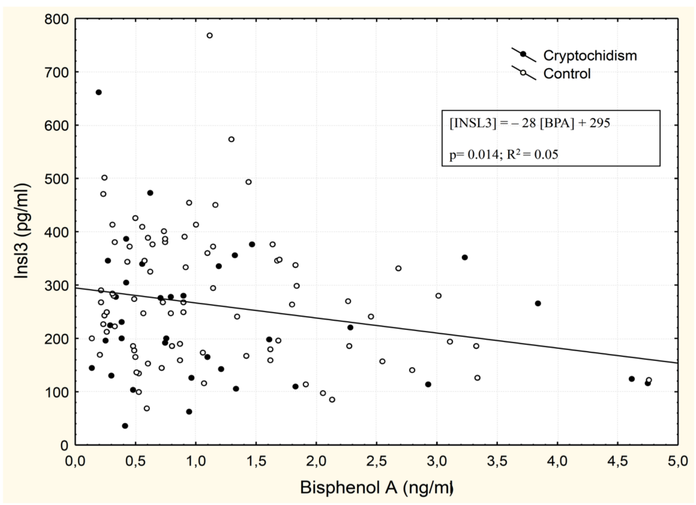
•52 cryptorchid (26 transient, 26 persistent) and 128 control boys, were studied here. They were born at the Maternity ward of the University Hospital of Nice or the nearby Grasse General Hospital. INSL3 was assayed in CB by a modified validated EIA. Testosterone was measured in CB after diethyl-ether extraction by means of ultra-pressure liquid chromatography-tandem mass spectrometry. Free cbBPA was measured after an extraction step, with a radioimmunoiassay (RIA) validated after comparison of values obtained by high-pressure liquid chromatography-mass spectrometry. The xenobiotic analysis in milk was performed after fat extraction by gas chromatography-mass .

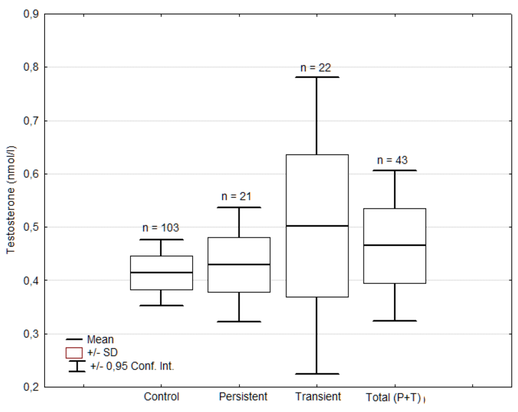
RESULTS

Cb INSL3 in cryporchid (transient, persistent and total) and control groups



Cb INSL3 in relation to cb free bisphenol A in the whole population





Cb testosterone in cryporchid (transient, persistent and total) and control groups

Correlation between hormones and xenobiotics.

	INSL-3		Testosterone	
	P	r^2	*P*	r^2
PCB153	0.26	0.018	0.67	0.003
mBP	0.45	0.022	0.68	0.007
DDE	0.64	0.003	0.98	0.000
BPA	**0.01**	0.05	0.19	0.01

BPA was measured in cord blood (ng/ml) and the other environmental endocrine disruptors in maternal milk.
P-value corresponds to the significance level for the linear regression test.
Bold font underlines the significant parameters.

Cord blood hormone and xenobiotic levels in cryptorchid and control boys.

	Cryptorchid *N* = 52 mean ± SEM	Controls *N* = 128 mean ± SEM	*P*
Hormones			
Insl3 pg/ml	225.7 ± 19.3	271.4 ± 18.4	**0.03**
Testosterone ng/ml	2.92 ± 0.25	2.73 ± 0.19	NS
Xenobiotics			
BPA ng/ml	1.26 ± 0.17	1.14 ± 0.13	0.1
PCB153 ng/g	88.3 ± 11.16	65.5 ± 23.2	NS
DDE ng/g	213.6 ± 54.2	139.9 ± 28.1	NS
mBP ng/g	33.2 ± 9	11.3 ± 3.7	0.09

P-value corresponds to the significance level for the logistic regression test.
BPA was measured in cord blood (ng/ml) and the others in maternal milk.
Concentrations of mBP in milk is given in ng/g of milk and the others in ng/g of fat in milk.
Insl3, Insulin-like peptide 3; BPA, bisphenol A; PCB153, polychlorinated biphenyl 153; DDE, dichlorodiphenyldichloroethylene; mBP, monobutyl phthalate.
Bold font underlines the significant parameters.

•Cord blood (cb) INSL3 but not cb testosterone was decreased in unilateral idiopathic cryptorchidism (p=0.03) especially in transient forms (p=0.02) and in the subgroup of non-palpable testis compared to the subgroup of palpable testes (supra-scrotal, inguinal or high scrotal) according to Scorer classification (p=0.01).

•cb free BPA in cryptorchid boys was not significantly increased (p=0.1). However, in the whole study population (cryptorchid and control), cb free BPA correlated negatively with INSL3 (p=0.01; R2=0.05) but not with testosterone.

•Monobutylphtalate was higher in cryptorchid group without reaching significativity (p=0.09

CONCLUSIONS

cbINSL3, a major actor of testicular descent, is decreased in idiopathic UDT and inversely related, in the whole population of newborn males, to bioactive cbBPA concentrations.

This negative correlation provides indirect evidence for an impact of endocrine disruptors on INSL3 Leydig production during fetal development. It strongly suggests that INSL3 is a possible target of fetal exposure to EEDs.

However, the deleterious impact of EEDs on fetal testicular descent, via the disturbance of INSL3 pathway, has yet to be demonstrated.

The challenge is to design prospective studies correlating INSL3 with the most appropriate EEDs or their metabolites, in the most appropriate fluids of the maternal-fetal unit, during the specific windows of development.

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