Gli "Endocrine disrupters" : realta' o fantasia ?

S. Bernasconi

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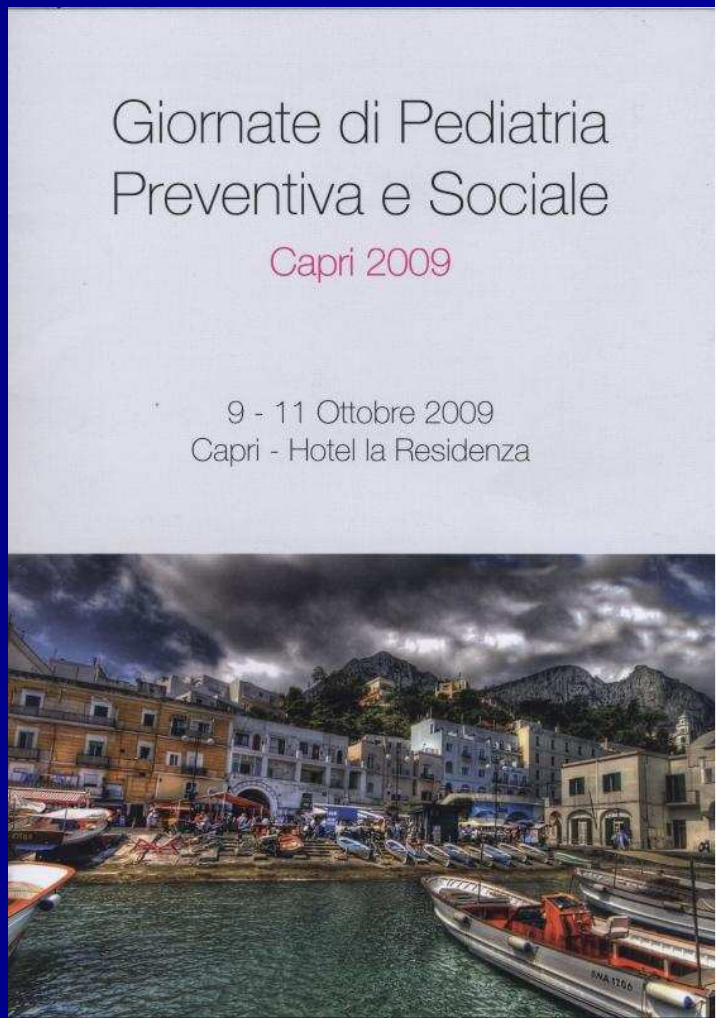

Gli “Endocrine disrupters” : realta’ o fantasia ?

- Definizione
- Interesse per i pediatri
- Esempio di possibile azione degli endocrine disrupters: la sindrome del testicolo disgenetico
- Una preoccupazione attuale : influenze sullo sviluppo puberale. Sicurezze e dubbi.

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Endocrine-Disrupting Chemicals

An Endocrine Society Scientific Statement

The Endocrine Society®

Key Points

- An endocrine-disrupting substance is a compound, either natural or synthetic, which through environmental or inappropriate developmental exposures alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment.

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Endocrine disrupting chemicals: a new and emerging public health problem?

C L Acerini, I A Hughes

Table 2 Endocrine disrupting chemicals: example of the known principal categories, their sources, and main contamination routes in humans

Category	Example	Source	Contamination route
Pesticides	2,4 Dichlorophen-oxyacetic acid	Herbicide	Foods: fruit/veg
	Hexachlorobenzene	Fungicides	Foods: fruit/veg, cereals
	Tributyltin		Water
	Benomyl/carbendazium		
	Vinclazolin		
	Malathion	Insecticides	Foods: fruit/veg
	Carbaryl		
	DDT (and metabolites DDE, DDD)		
	Aldrin		
Industrial chemicals	Bisphenol A	Plastics	Plastic items
		Polystyrene	Drinks
			Foods: packaging
	PCBs	Electrical: waste byproducts	Foods: fish/meat, dairy items
	Alkylphenols	Detergents	Household items
		Emulsifiers	Water
		Fertilisers	Foods: fish
	Phthalates esters	Plastics	Plastic items
			Drinks
			Foods: packaging
Natural plant compounds	Phytoestrogens, eg genistein, coumestrol	Soya Legumes/ beans	Food/diet

***Arch. Dis. Child.* 2006**

Environmental Factors and Puberty Timing: Expert Panel Research Needs

Germaine M. Buck Louis, PhD[a], L. Earl Gray, Jr, PhD[b], Michele Marcus, PhD, MPH[c], Sergio R. Ojeda, DVM[d], Ora H. Pescovitz, MD[e], Selma Feldman Witchel, MD[f], Wolfgang Sippell, MD, PhD[g], David H. Abbott, PhD[h], Ana Soto, MD[i], Rochelle W. Tyl, PhD[j], Jean-Pierre Bourguignon, MD, PhD[k], Niels E. Skakkebaek, MD, DMSc[l], Shanna H. Swan, PhD[m], Mari S. Golub, PhD[n], Martin Wabitsch, MD, PhD[o], Jorma Toppari, MD, PhD[p], Susan Y. Euling, PhD[q]

[a]Epidemiology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; [b]Endocrinology Branch, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina; [c]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia; [d]Division of Neuroscience, Oregon National Primate Research Center-Oregon Health and Sciences University, Beaverton, Oregon; [e]Department of Pediatrics and Cellular and Integrative Physiology, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana; [f]Division of Endocrinology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [g]Division of Endocrinology, Department of Pediatrics, University of Kiel, Kiel, Germany; [h]Department of Obstetrics/Gynecology and Wisconsin National Primate Research Center, University of Wisconsin, Madison, Wisconsin; [i]Department of Anatomy and Cell Biology, Tufts University School of Medicine, Boston, Massachusetts; [j]Center for Life Sciences and Toxicology, RTI International, Research Triangle Park, North Carolina; [k]CHU Sart-Tilman, University of Liege, Belgium; [l]University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark; [m]Department of Family & Community Medicine, University of Missouri, Columbia, Missouri; [n]Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California; [o]Department of Pediatric and Adolescent Medicine, University of Ulm, Ulm, Germany; [p]Departments of Physiology and Pediatrics, University of Turku, Turku, Finland; [q]National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC

Pediatrics 2008

American Academy of Pediatrics

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THE ENDOCRINE SOCIETY®

POSITION STATEMENT

ENDOCRINE-DISRUPTING CHEMICALS
JUNE 2009

Regulatory oversight of endocrine disrupting chemicals should be centralized such that regulations pass through a single office to ensure coordination among agencies. Coordination is required for comprehensive and consistent regulations among all relevant federal agencies setting guidelines for acceptable exposure, manufacturing, sale, and human use of EDCs.

Policy should be based on comprehensive data covering both low-level and high-level exposures. Furthermore, tests and screens used to determine EDC activity of chemicals should be balanced between those that examine simple mechanisms and others that instead measure integrated biological outcomes, thereby encompassing substances that have effects through several mechanisms, whether known or unknown.

ENDOCRINE-DISRUPTING CHEMICALS
JUNE 2009

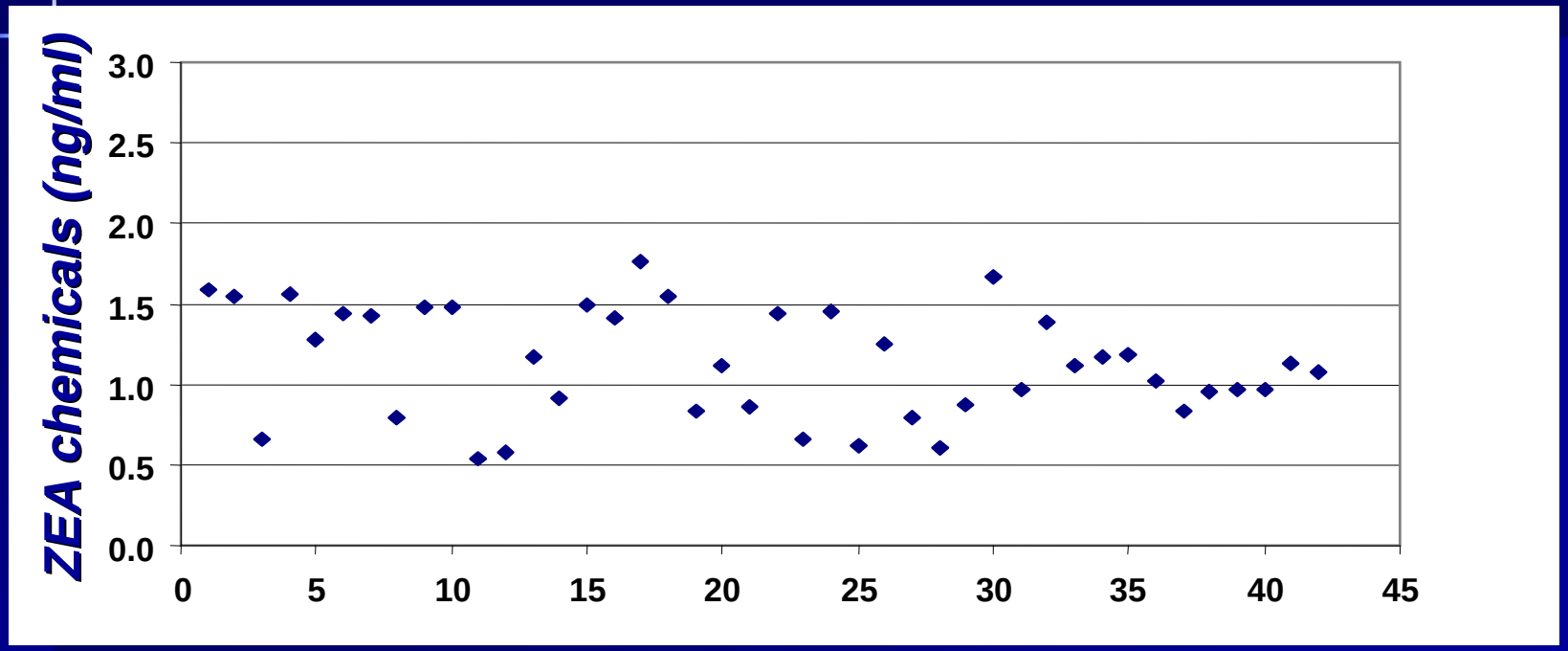
- Policy should be developed and revised under the direction of a collaborative group comprising endocrinologists, toxicologists, epidemiologists, and policymakers. The same group should identify knowledge gaps and recommend research directions to fill those gaps.

- Until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC policy.

- The federal government should develop a public awareness campaign to inform the public of the risks and potential risks related to the presence of EDCs in the environment and in the food supply.

- The federal government should support further research into EDCs, including the development of high-throughput assays that would allow the testing of many chemicals for EDC activity at a full range of concentrations

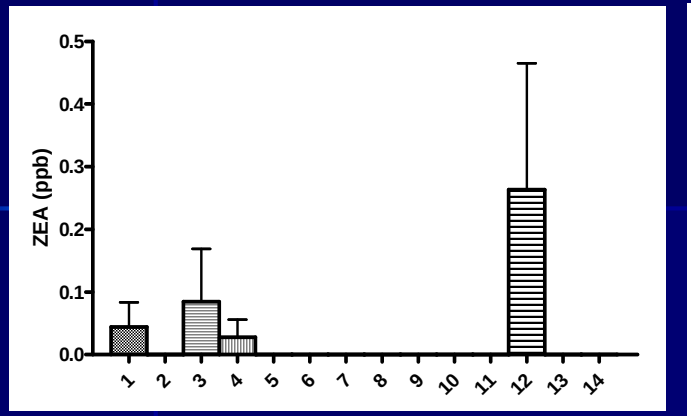
1st-month breast milk content of Mycoestrogens in 47 health primipara women

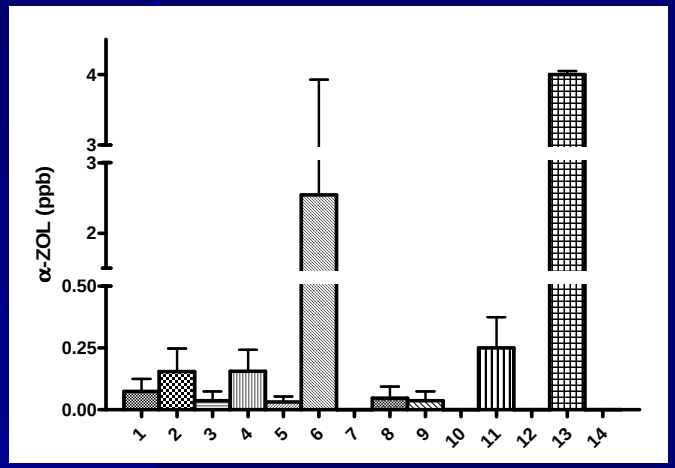


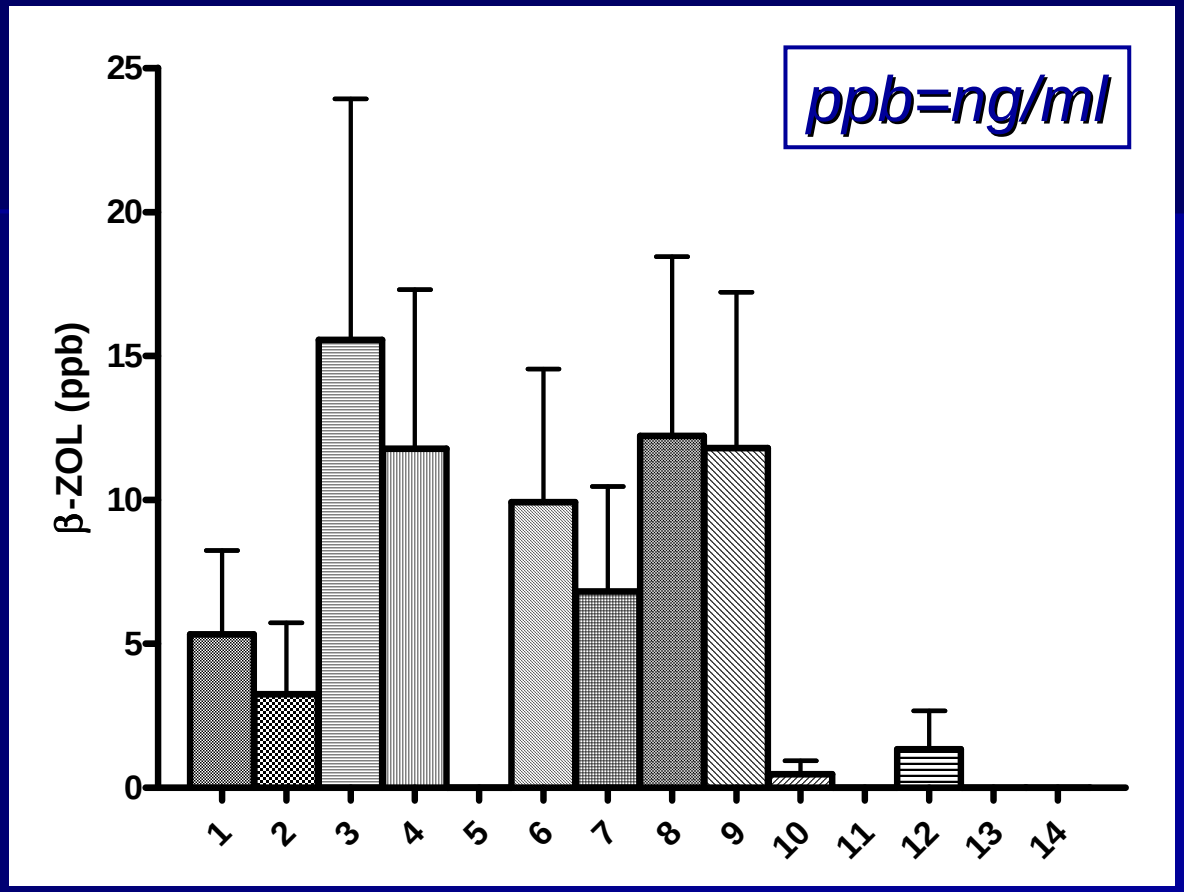
In 1st-month breast milk*, *mean ZEA content was ***1.1±0.4 ng/ml***, corresponding to a Neapolitan ***newborn TDI 1.4-1.6-told higher than 70-kg adult limit for ZEA toxicity (i.e. 0.2 µg/kg/day)***.

Massart et al. Miner Ped 2008; 60: 1277-78

Italian infant formula milks







28% of all infant formula milks (185 samples, 37 types) were contaminated by ***βZOL (6.76±14.17 ng/ml)***, while 5% and 20% by ***ZEA (0.02±0.11 ng/ml)*** and ***αZOL (0.35±1.58 ng/ml)***.

Massart et al. Horm Res 2008; 70:21

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testicular dysgenesis syndrome (TDS) :

- Criptorchidismo
- Ipospadia
- tumore testicolo
- infertilità

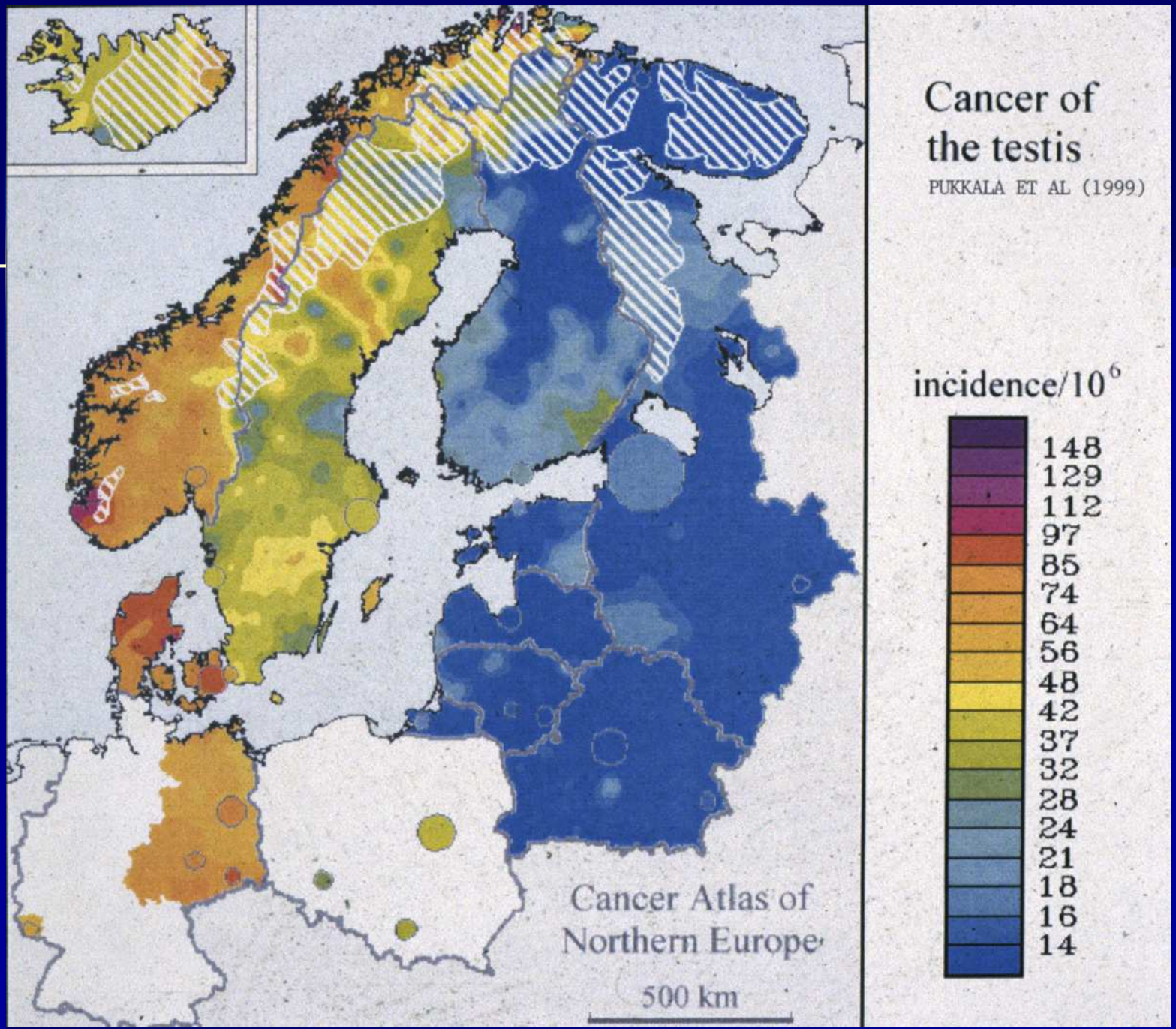
Geographic association between abnormalities in male reproductive health

Denmark

High incidence of testicular cancer

Finland

Low incidence of testicular cancer


Cancer of
the testis
PUKKALA ET AL (1999)
incidence/10^6
148
129
112
97
85
74
64
56
48
42
37
32
28
24
21
18
16
14
Cancer Atlas of
Northern Europe
500 km

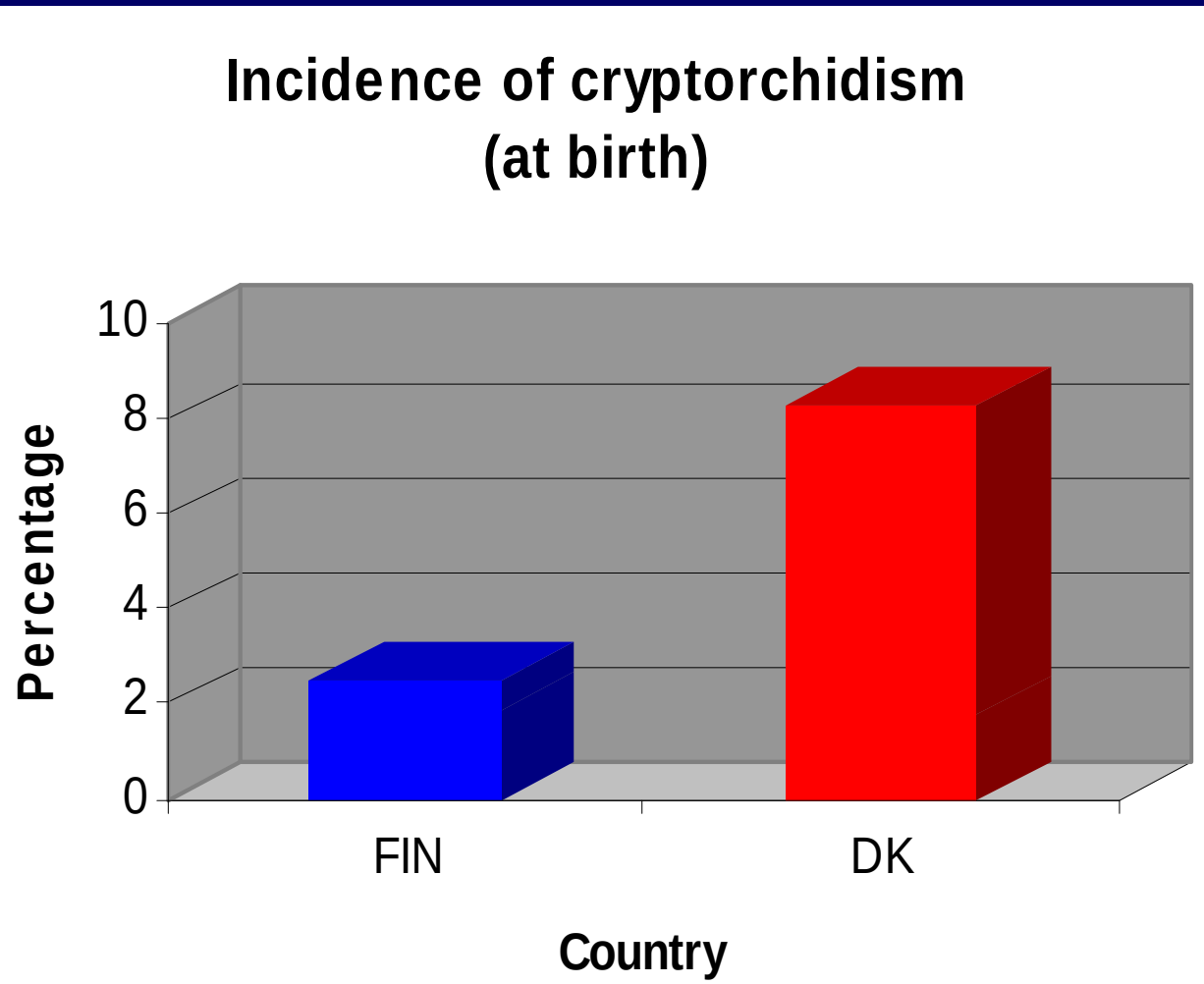
Geographic association between abnormalities in male reproductive health

Denmark

- High incidence of testicular cancer
- High incidence of cryptorchidism

Finland

- Low incidence of testicular cancer
- Low incidence of cryptorchidism


Incidence of cryptorchidism
(at birth)
Percentage
10
8
6
4
2
0
FIN
DK
Country

Geographic association between abnormalities in male reproductive health

Denmark

- High incidence of testicular cancer
- High incidence of cryptorchidism
- **High incidence of hypospadias**

Finland

- Low incidence of testicular cancer
- Low incidence of cryptorchidism
- **Low incidence of hypospadias**

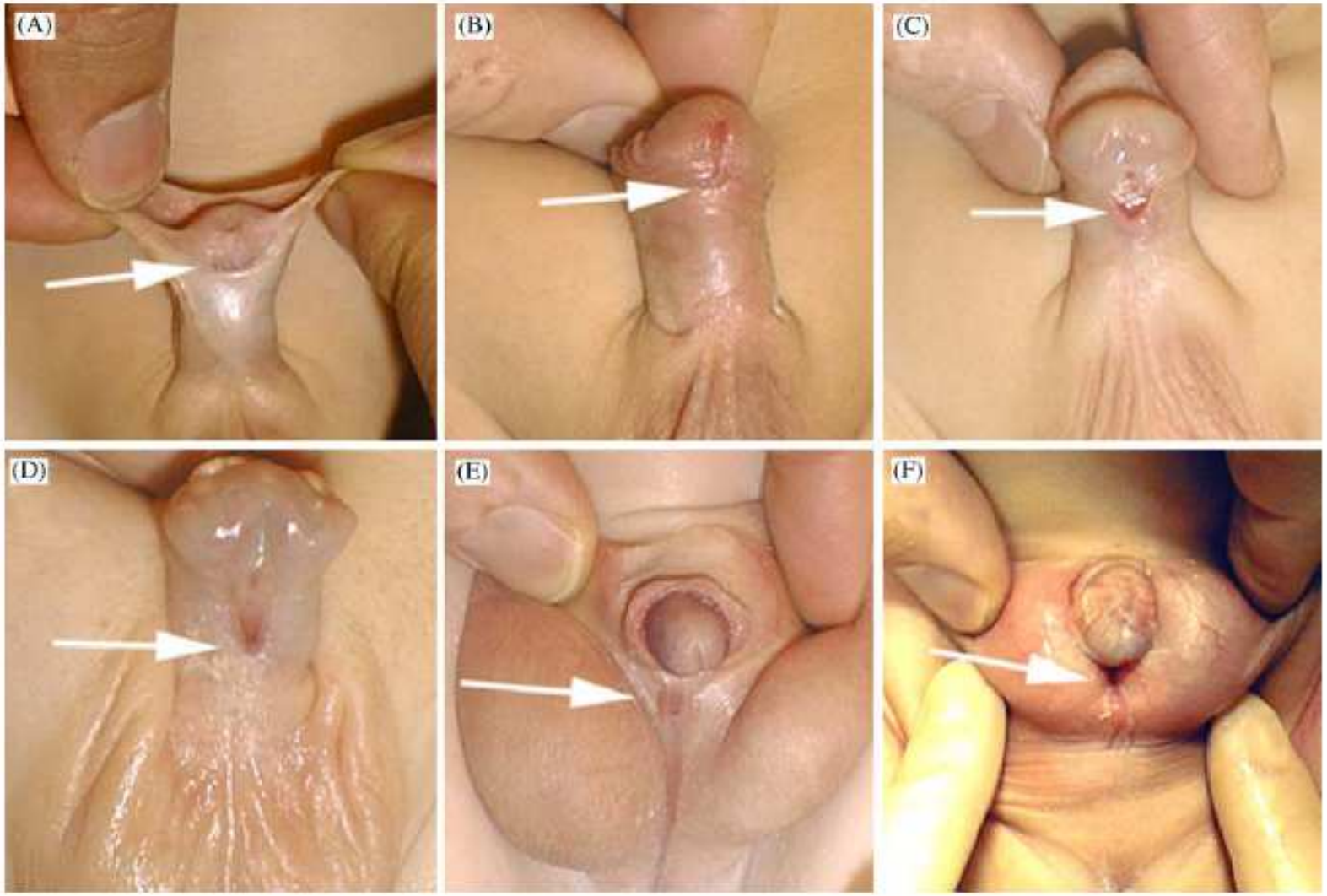
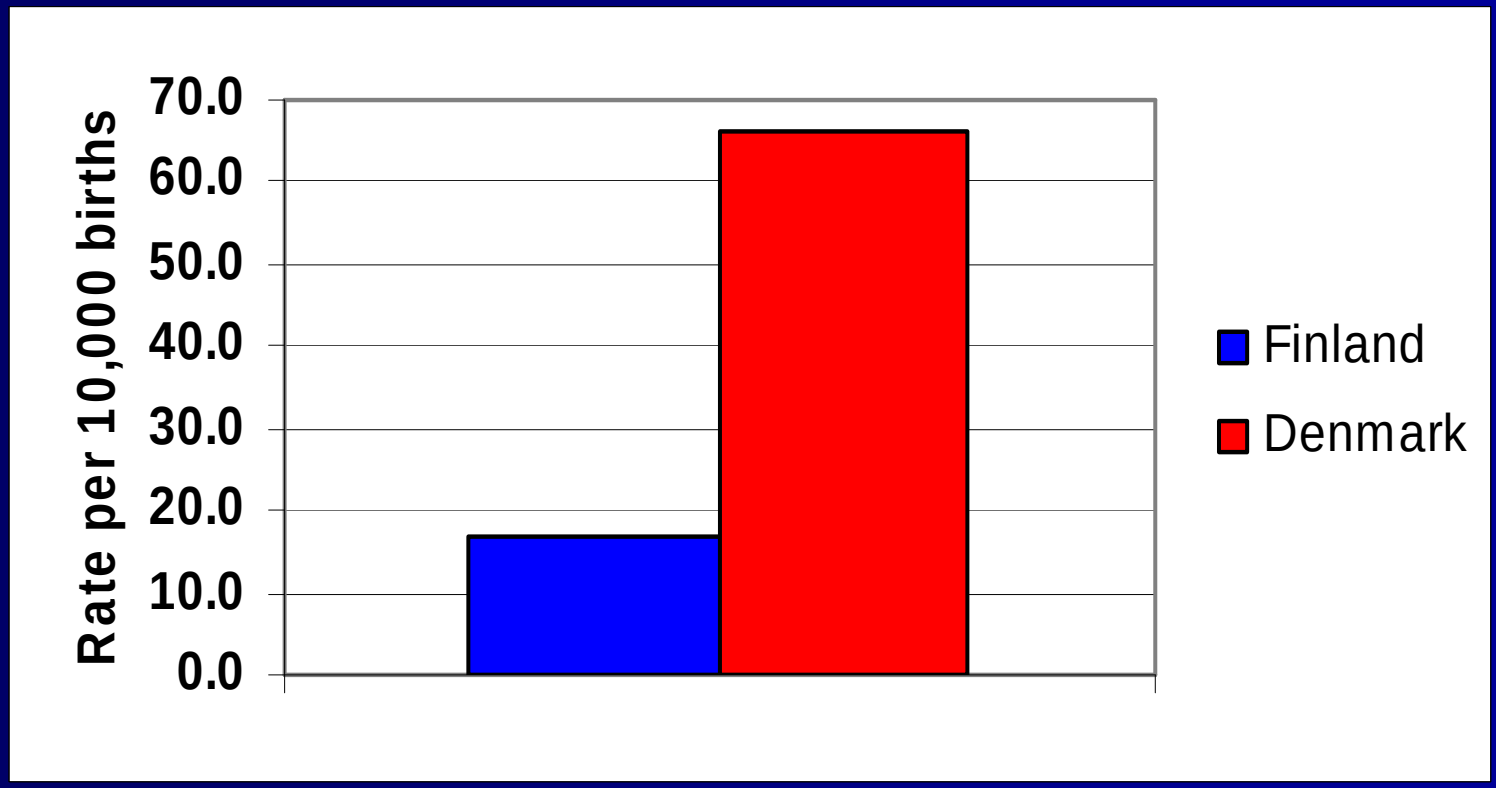


Fig. 1. Variations of hypospadias from mild to severe. (A) Anterior, where the urethral meatus is on the dorsal surface of the glans penis. (B) Coronal, where the meatus is in the balanopenile furrow. (C) Distal, on the distal third of the penile shaft. (D) Peno-scrotal, at the base of the shaft in front of the scrotum. (E) Scrotal, on the scrotum or between the genital swellings. (F) Perineal where the meatus is below the scrotum or genital swellings. Note that the more severe forms of hypospadias are associated with penile curvature.

Birth rate of hypospadias 1997-2000



Geographic association between abnormalities in male reproductive health

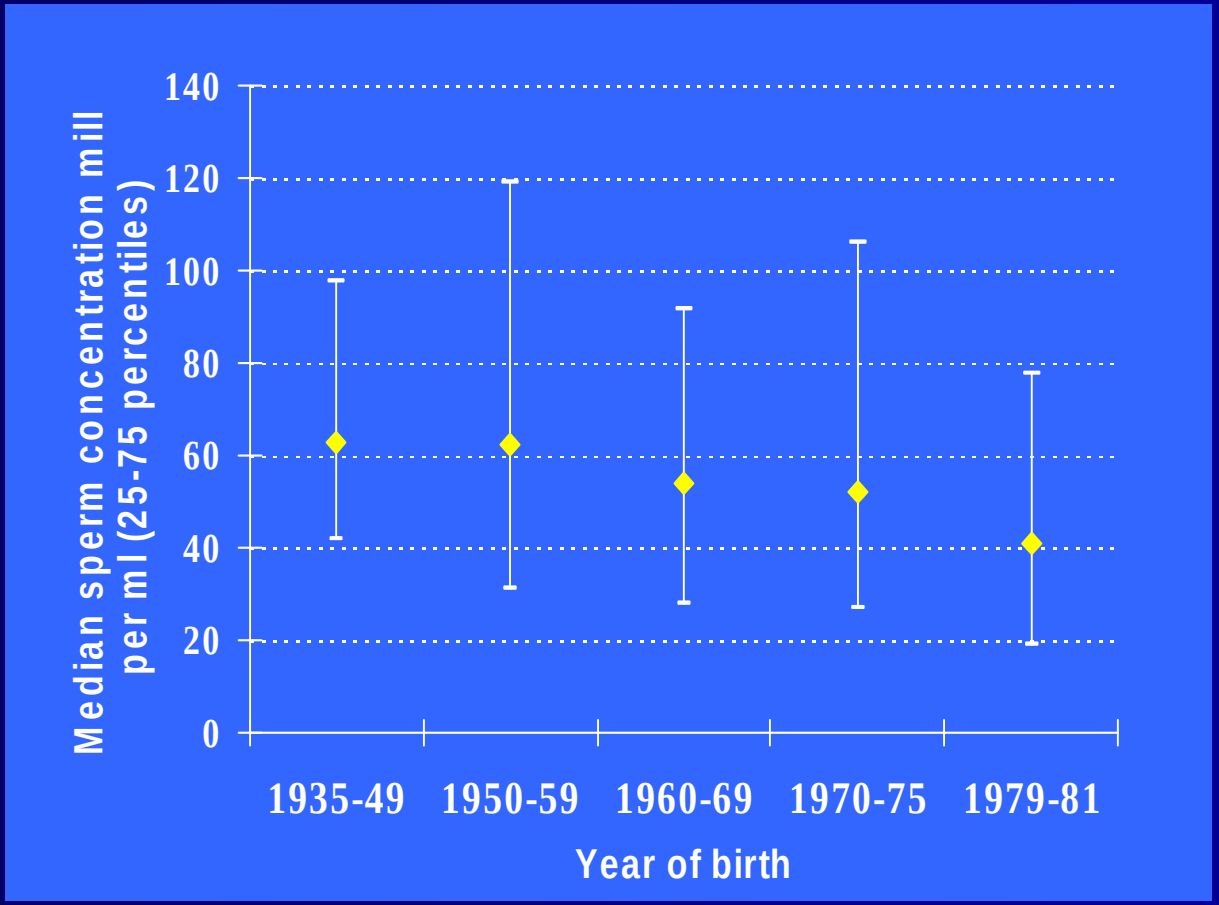
Denmark

- High incidence of testicular cancer
- High incidence of cryptorchidism
- High incidence of hypospadias
- Low sperm counts

Finland

- Low incidence of testicular cancer
- Low incidence of cryptorchidism
- Low incidence of hypospadias
- Normal sperm counts

Median sperm concentration and 25-75 percentiles according to year of birth from 10 Danish studies of men born between 1935-75 (reconstructed from Bonde) and 708 men from the general Danish population born from 1979-81.



Skakkebaek N.E.

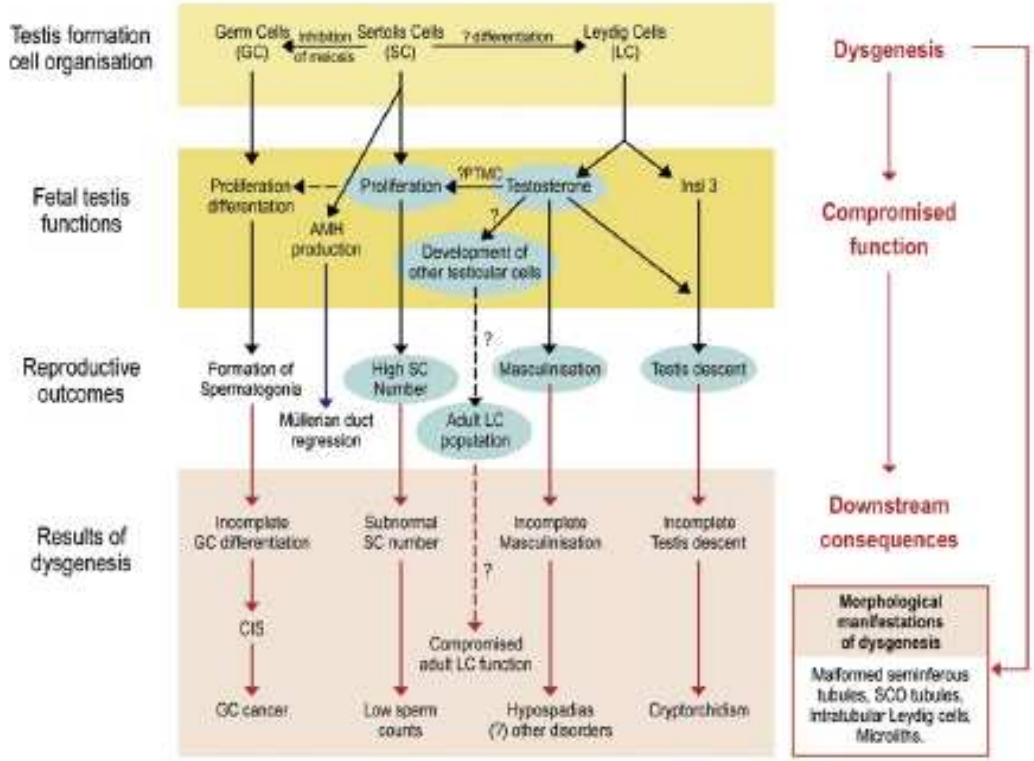
- Time trends and geographical variations strongly suggest environmental influence.
- Epidemiological data suggests that the fetal/neonatal reproductive system may be the most vulnerable organism to environmental influences.
- Testicular cancer shares common risk factors and geographic prevalence trends with other disorders of male reproductive health, and may be the most severe symptom of a common entity: The testicular dysgenesis syndrome (TDS).
- Although some trends in male reproductive health problems can be explained from endocrine disruption, genetic and life style factors should also be kept in mind.

Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects

Richard M. Sharpe, Ph.D.,[a] *and Niels E. Skakkebaek, M.D.*[b]

FIGURE 1

Schematic diagram to illustrate how dysgenesis of the early fetal testis is thought to lead to abnormalities of somatic cell function, resulting in hormonal changes and the downstream disorders that comprise testicular dysgenesis syndrome (TDS). The central role of testosterone is highlighted by the blue boxes. Dashed lines show pathways that are hypothesized but unproven. PTMC = peritubular myoid cell; Insl3 = insulin-like factor 3; AMH = antimüllerian hormone; CIS = carcinoma in situ; SCO = Sertoli cell only.



Sharpe. Testicular dysgenesis syndrome. Fertil Steril 2008.

Fertility and Sterility 2008

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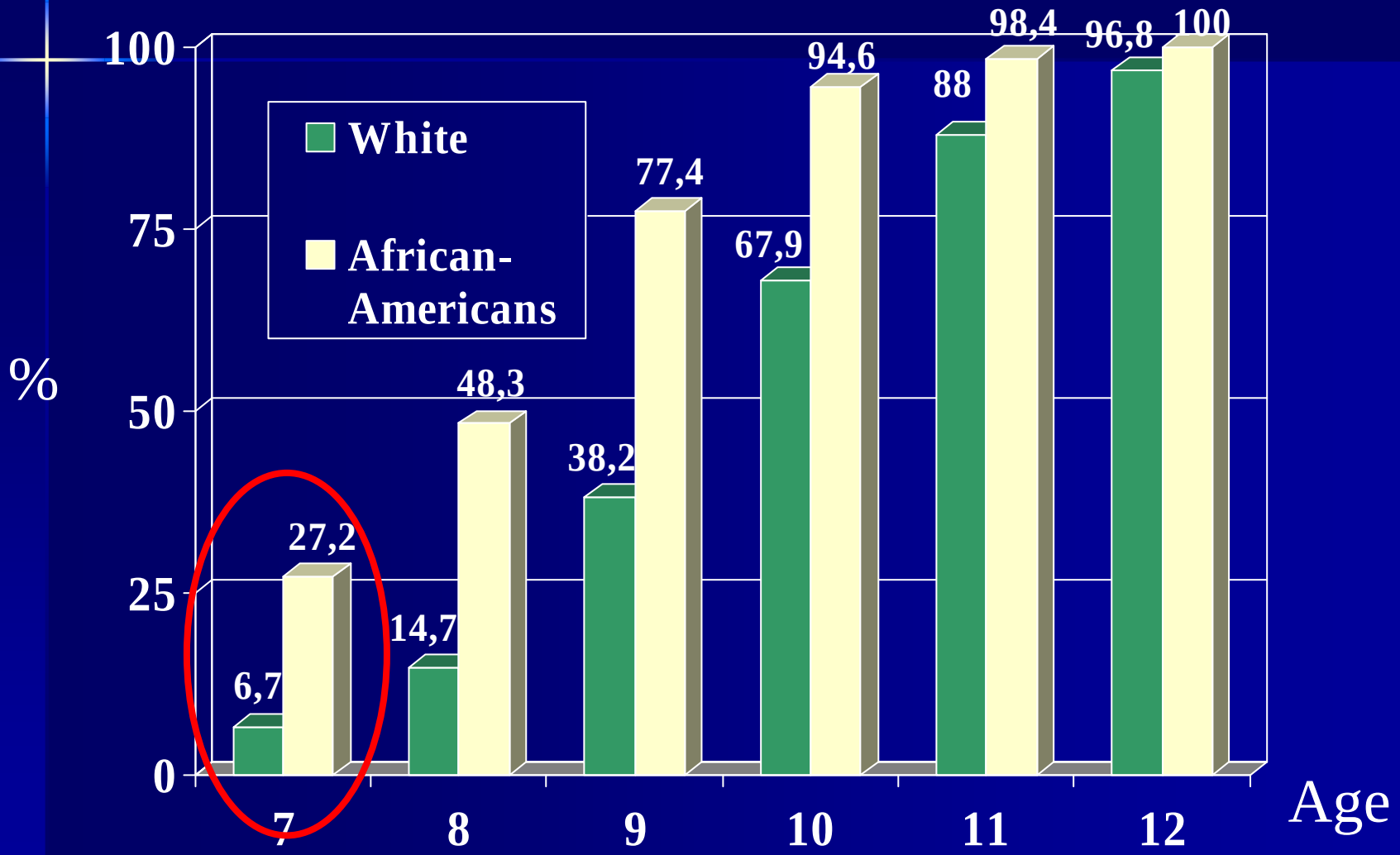
- Alterazioni Puberali

  - anticipo puberale soprattutto femminile

Secular trend

Prevalence of breast and/or pubic hair development at Tanner stage 2 or greater (17,077 girls)



Herman – Giddens ME et al., Pediatrics,1997

Prevalence and Incidence of Precocious Pubertal Development in Denmark: An Epidemiologic Study Based on National Registries

Grete Teilmann, MD*; Carsten B. Pedersen, MSc‡; Tina Kold Jensen, MD, PhD*;
Niels E. Skakkebæk, MD, DMSc*; and Anders Juul, MD, DMSc, PhD*

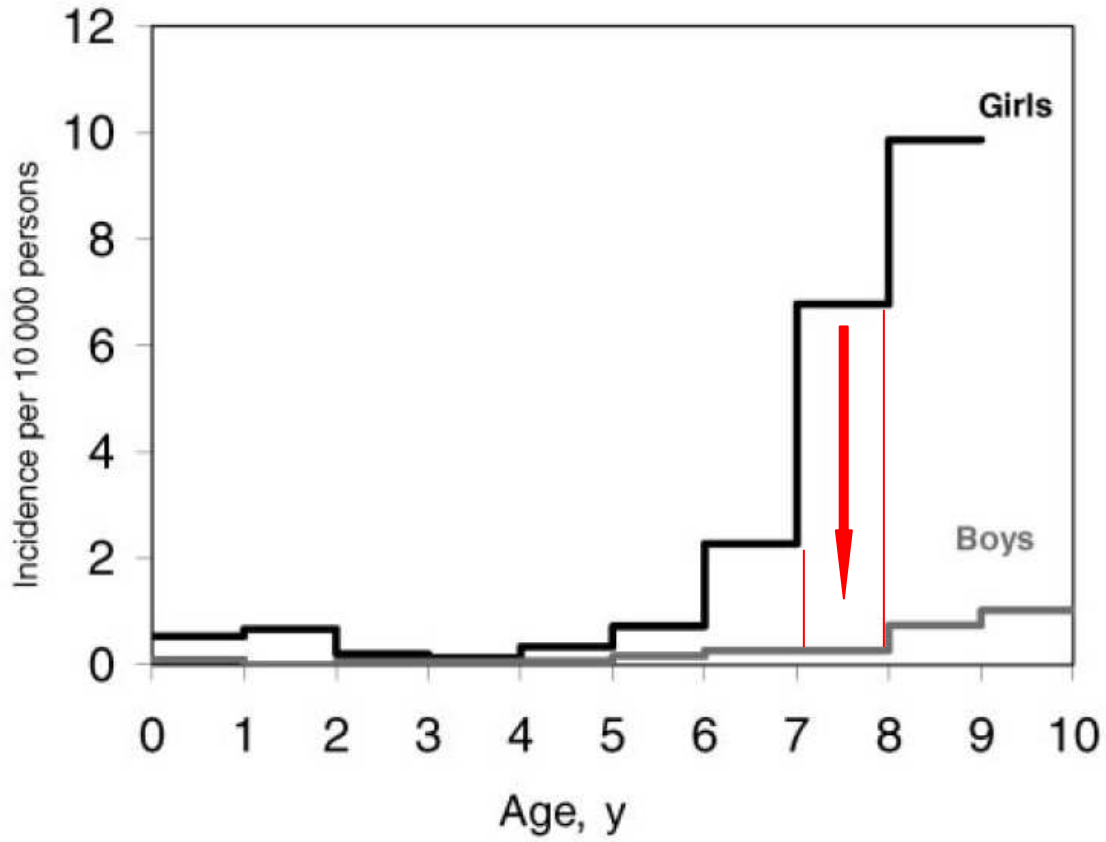
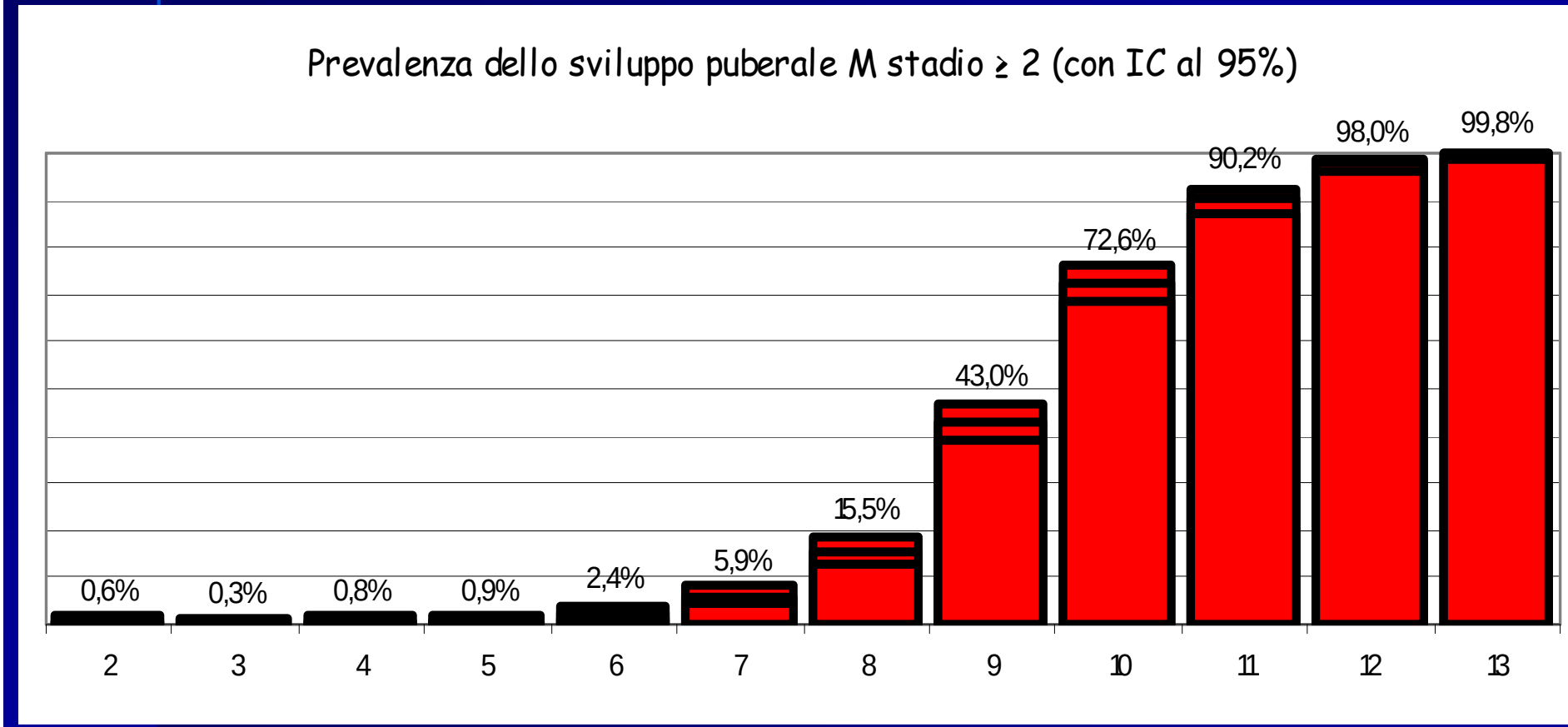


Fig 2. Gender-specific incidence of PP among Danish girls and boys who were born between 1983 and 2001.

Pediatrics 2005

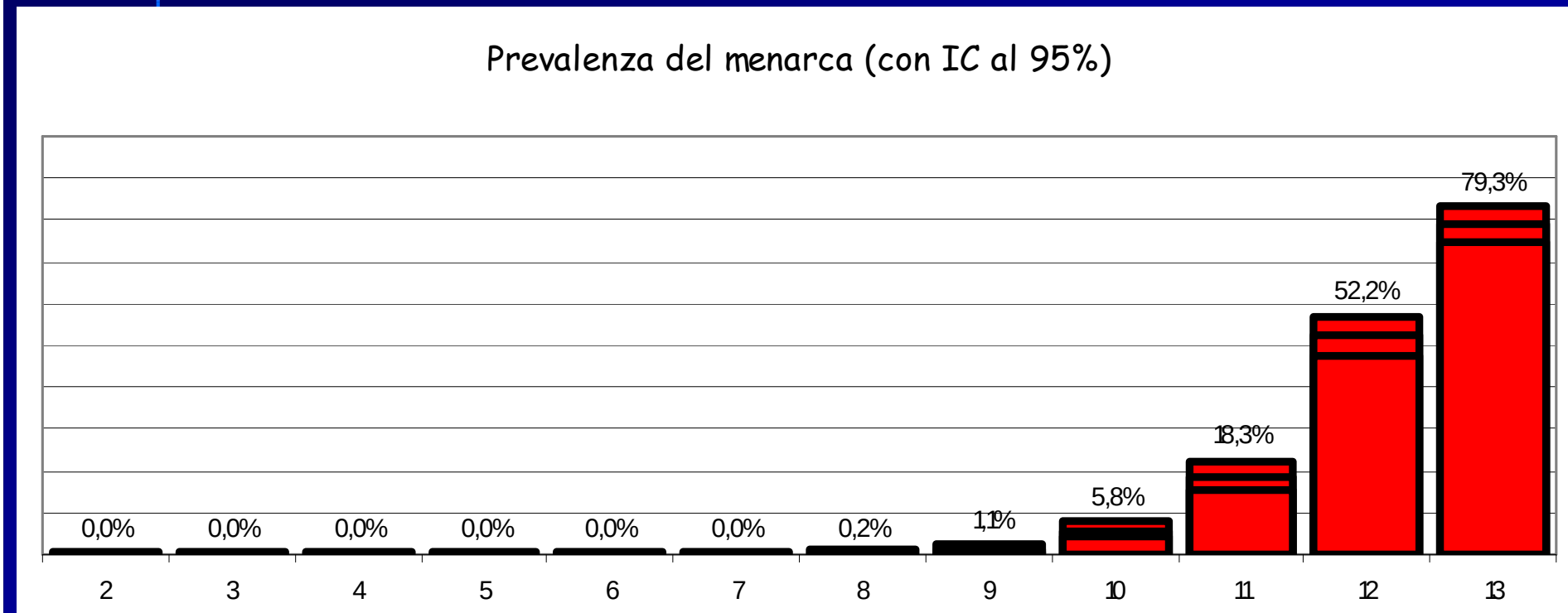
Telarca > 2

- 2 DS	media	+ 2 DS
7.09 aa	9.73 aa	12.36 aa



Menarca

	3° c.le	media	97° c.le
Figlie	10.24 aa	12.47 aa	14.71 aa
Madri	10 aa	12.45 aa	15 aa



ELSEVIER

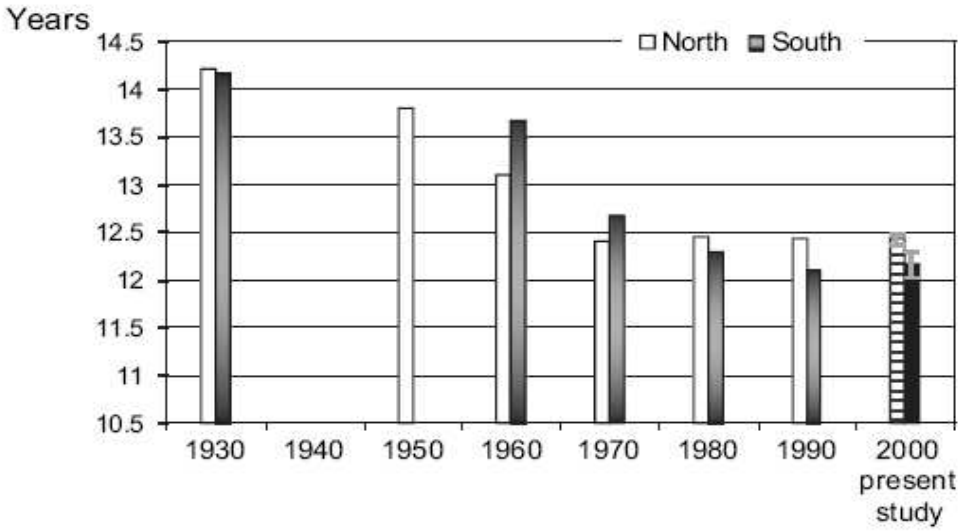
Journal of Adolescent Health ■ (2009) 1–7

JOURNAL OF ADOLESCENT HEALTH

Original article

Update on Age at Menarche in Italy: Toward the Leveling Off of the Secular Trend

Franco Rigon, M.D.[a], Luigi Bianchin, M.D.[b], Sergio Bernasconi, M.D.[c], Gianni Bona, M.D.[d], Mauro Bozzola, M.D.[e], Fabio Buzi, M.D.[f], Alessandro Cicognani, M.D.[g], Carlo De Sanctis, M.D.[h], Vincenzo De Sanctis, M.D.[i], Giorgio Radetti, M.D.[j], Luciano Tatò, M.D.[k], Giorgio Tonini, M.D.[l], and Egle Perissinotto, Sc.D.[m,*]



* Data for previous studies are from Rigon et al. [36].

Figure 2. Secular trend for age at menarche in northern and southern Italy*. Grey vertical lines represent 95% CI for the results of the present survey. Data for previous studies are from Rigon and Bianchin [31].

Recent data on pubertal milestones in United States children: the secular trend toward earlier development

Marcia E. Herman-Giddens

international journal of andrology 2006

Table 7 Earlier puberty: theories and speculations

- Genetic differences among racial/ethnic groups
- Overweight and obesity, decreased physical activity
- Pre- and postnatal exposure to endocrine disrupter chemicals
- Infant soy-based formulas
- Girls born small for gestational age
- Stress, absent fathers, unrelated males in the household
- Effects of different types of diet
- Exogenous hormones
- Hypersexualization of culture

Environmental Factors and Puberty Timing: Expert Panel Research Needs

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[a]Epidemiology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; [b]Endocrinology Branch, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina; [c]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia; [d]Division of Neuroscience, Oregon National Primate Research Center-Oregon Health and Sciences University, Beaverton, Oregon; [e]Department of Pediatrics and Cellular and Integrative Physiology, Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana; [f]Division of Endocrinology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania; [g]Division of Endocrinology, Department of Pediatrics, University of Kiel, Kiel, Germany; [h]Department of Obstetrics/Gynecology and Wisconsin National Primate Research Center, University of Wisconsin, Madison, Wisconsin; [i]Department of Anatomy and Cell Biology, Tufts University School of Medicine, Boston, Massachusetts; [j]Center for Life Sciences and Toxicology, RTI International, Research Triangle Park, North Carolina; [k]CHU Sart-Tilman, University of Liege, Belgium; [l]University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark; [m]Department of Family & Community Medicine, University of Missouri, Columbia, Missouri; [n]Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California; [o]Department of Pediatric and Adolescent Medicine, University of Ulm, Ulm, Germany; [p]Departments of Physiology and Pediatrics, University of Turku, Turku, Finland; [q]National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC

Pediatrics 2008;121;S192-S207

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- Hypersexualization of culture

Weight Status in Young Girls and the Onset of Puberty

Joyce M. Lee, MD, MPH[a,b], Danielle Appugliese, MPH[c], Niko Kaciroti, PhD[d], Robert F. Corwyn, PhD[e], Robert H. Bradley, PhD[e], Julie C. Lumeng, MD[d,f]

Pediatrics 2007

TABLE 1 Descriptives and Bivariate Comparisons for the Sample According to Puberty Status at Grade 4

Variable	Total ($n = 354$)	Earlier Puberty (Tanner Stage ≥2; $n = 168$)	Later Puberty (Tanner Stage <2; $n = 186$)	*P*
Age, mean (SD), y	9.6 (0.1)	9.6 (0.1)	9.6 (0.1)	.36
Race, *n* (%)				.002
White	291 (82.2)	127 (75.6)	164 (88.2)	—
Nonwhite	63 (17.8)	41 (24.4)	22 (11.8)	—
Maternal education, mean (SD), y	14.6 (2.3)	14.3 (2.2)	14.8 (2.5)	.03
ITN ratio, mean (SD)	3.7 (3.1)	3.5 (3.2)	3.9 (3.2)	.21
Age of maternal menarche, mean (SD), y	12.7 (1.5)	12.5 (1.4)	12.9 (1.5)	.01
Weight status, *n* (%)				
Normal weight (BMI <85th percentile)	257 (72.6)	102 (60.7)	155 (83.3)	<.0001
At risk for overweight (85th ≤ BMI < 95th percentile)	52 (16.8)	30 (22.7)	22 (12.4)	.02
Overweight (BMI ≥ 95th percentile)	45 (12.7)	36 (21.4)	9 (4.8)	<.0001

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international journal of andrology 2006

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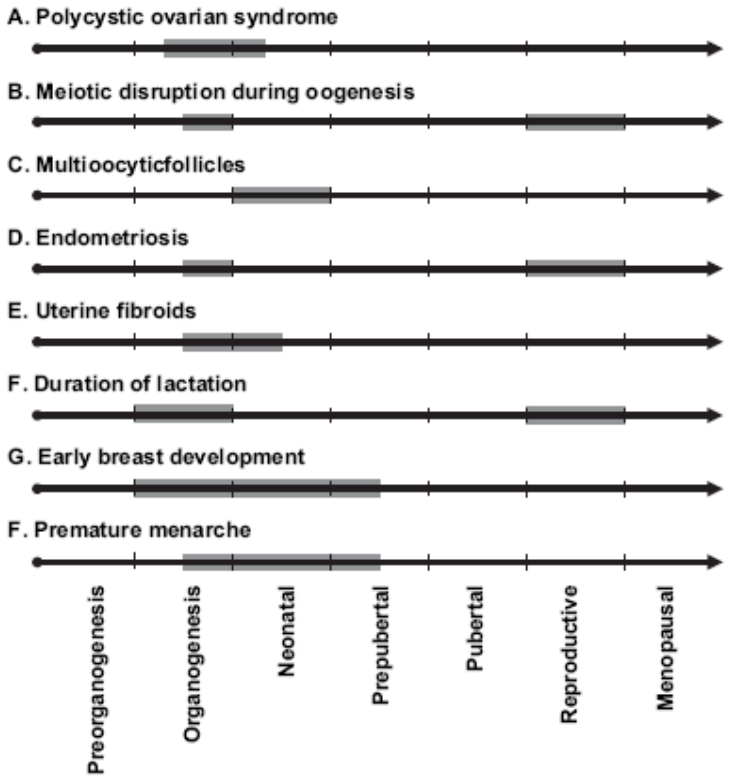
Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing

D. A Crain

FIGURE 3

Well-defined developmental periods of sensitivity when EDC exposure greatly increases the risk for reproductive disorders.



Crain. Endocrine-disrupting compounds and female reproduction. Fertil Steril 2008.

Fertility and Sterility 2008

Best Practice & Research Clinical Endocrinology and Metabolism
Vol. 16, No. 1, pp. 105–121, 2002
doi:10.1053/beem.2002.0184, available online at http://www.idealibrary.com on IDEAL

BEST PRACTICE & RESEARCH

9

Putative effects of endocrine disrupters on pubertal development in the human

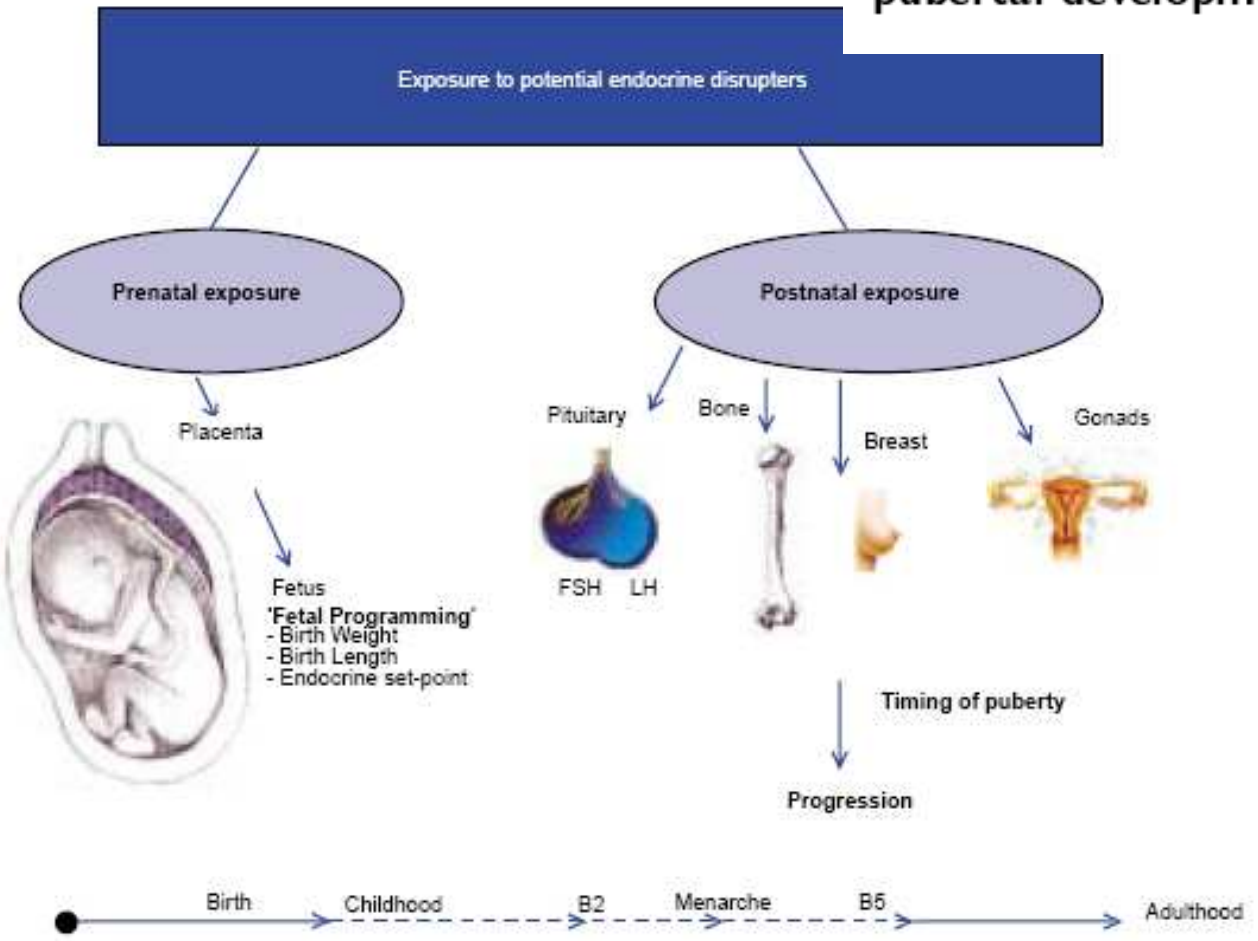


Figure 1. Exposure to endocrine disrupters can permanently influence the fetal programming of the endocrine system, influencing the size of the baby and, thereby, altering the endocrine set-points that putatively regulate puberty. Postnatal exposure may influence pubertal development directly at several targets: centrally in the hypothalamus and pituitary, and peripherally in bone, breast and gonads.

Teilmann et al

Gli “Endocrine disrupters” : realta’ o fantasia ?

1) evidenze sperimentali e tossicologiche

2) Evidenze epidemiologiche

a) pochi studi

Endocrine disrupters and human puberty

E. Den Hond and G. Schoeters

Table 1 Overview of epidemiological studies investigating the relation between potential endocrine disrupting agents and onset of puberty in girls

Reference	Study area	Pollutant	Exposure	Subjects	Findings associated with higher exposure
Blanck *et al.*, 2000	Michigan (exposure through food chain)	PBBs PCBs	Prenatal + lactational	327 girls	High PBBs are associated with earlier menarche and earlier pubic hair stage PBBs had no effect on breast stage PCBs hand no effect on menarche or pubertal stages
Gladen *et al.*, 2000	North Carolina cohort	DDE PCBs	Prenatal + lactational	316 girls	No effect on age at menarche No effect on pubertal stages
Colon *et al.*, 2000	Case–control study of thelarche patients in Puerto Rico	Pesticides Phthalates	Pubertal	41 patients and 35 controls	Phthalate esters were significantly elevated in thelarche patients
Krstevska-Konstantinova *et al.*, 2001	Precocious puberty patients in Belgium	DDE	Pubertal	26 immigrant and 15 Belgian girls	Serum DDE was significantly elevated in immigrant children with precocious puberty
Den Hond *et al.*, 2002	One rural and two urban villages in Belgium	PCBs Dioxin (Calux®)	Pubertal	120 girls	High serum dioxin was associated with retarded breast development Dioxin did not effect menarche or pubic hair stage PCBs had no effect on menarche or pubertal stages
Selevan *et al.*, 2003	U.S. (NHANES III)	Lead (Pb)	Pubertal	2186 girls (aged 8–18 years)	Delayed menarche, retarded breast and pubic hair stage
Wu *et al.*, 2003	U.S. (NHANES III)	Lead (Pb)	Pubertal	1235 girls (aged 10–16 years)	Delayed menarche, retarded pubic hair stage No change in breast stage
Warner *et al.*, 2004	Seveso, girls exposed at age 0–17 years	Dioxin (TCDD)	Postnatal but prepubertal	282 girls	No effect on age at menarche
Vasiliu *et al.*, 2004	Michigan angler cohort	DDE PCBs	Prenatal	151 girls	DDE was associated with earlier menarche No effect of PCBs on age at menarche

PBBs, polybrominated biphenyls; PCBs, polychlorinated biphenyls; DDE, dichlorodiphenyldichloroethylene (=metabolite of DDT); NHANES, National Health and Nutrition Examination Survey; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

International journal of andrology 2006

Gli “Endocrine disrupters” : realta’ o fantasia ?

1) evidenze sperimentali e tossicologiche

2) Evidenze epidemiologiche

a) pochi studi

B) risultati in linea con le aspettative con qualche eccezione

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Advance Access publication May 6, 2004

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In utero exposure to organochlorines and age at menarche

O.Vasiliu[1], J.Muttineni[1] and W.Karmaus[1,2]

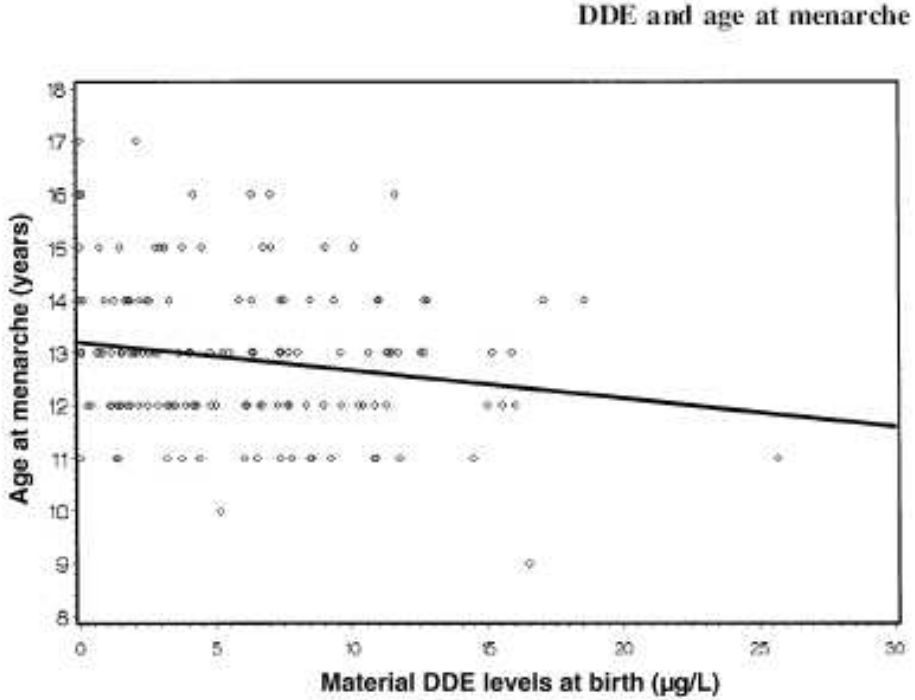


Figure 2. Plot of age at menarche over the extrapolated maternal DDE concentration at birth (n = 151). The linear regression line is the estimate of age at menarche (13.185 – 0.0525 × extrapolated maternal DDE concentration, non-adjusted regression). See Table III for the adjusted regression coefficient.

The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration

ANNE-SIMONE PARENT, GRETE TEILMANN, ANDERS JUUL, NIELS E. SKAKKEBAEK, JORMA TOPPARI, AND JEAN-PIERRE BOURGUIGNON

Endocrine Reviews 2003

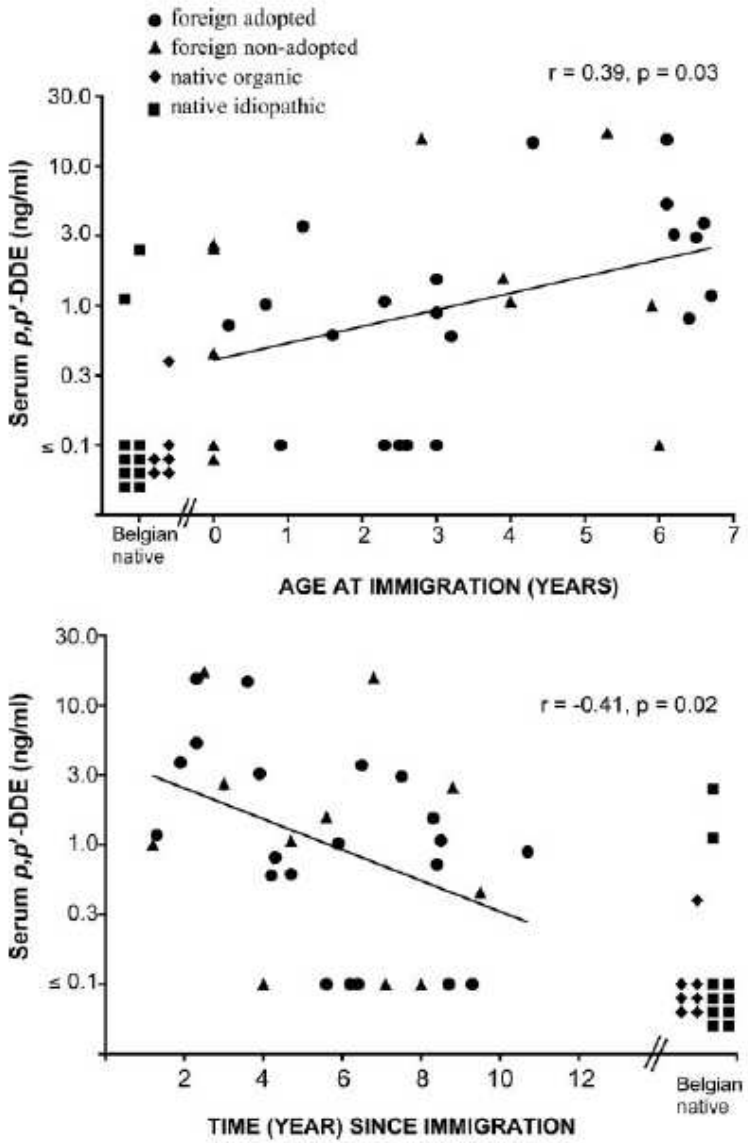


FIG. 7. Serum levels of p,p'-DDE, a derivative of the organochlorine pesticide DDT in different patients with sexual precocity. The Belgian native patients have central precocious puberty of organic or idiopathic origin. The foreign migrating patients with sexual precocity are adopted or nonadopted. The data of foreign patients are represented in relation to age at immigration and time since immigration.

Identification of Phthalate Esters in the Serum of Young Puerto Rican Girls with Premature Breast Development

Ivelisse Colón,[1] Doris Caro,[1] Carlos J. Bourdony,[2,3] and Osvaldo Rosario[1]

***Environ Health Perspect* 2000**

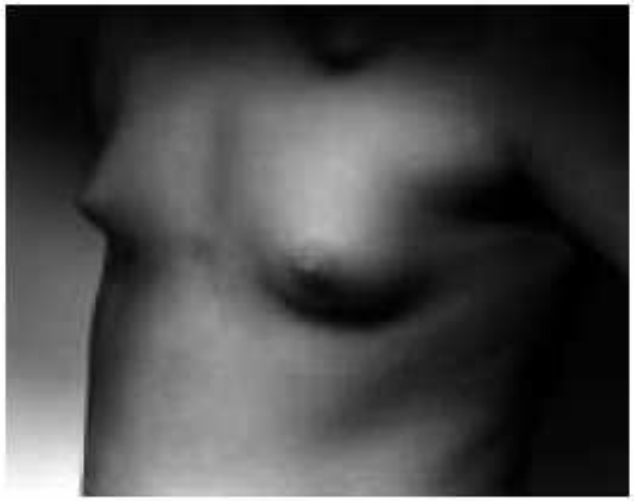


Figure 1. Twenty-three-month-old Puerto Rican girl with premature breast development (thelarche).

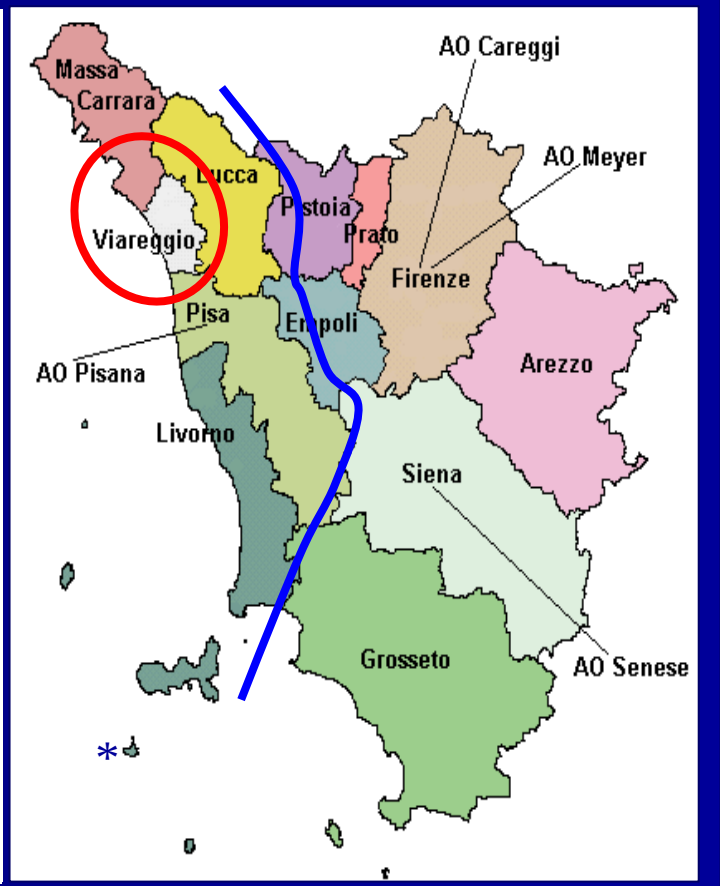
Phthalate esters were consistently detected at significant concentration levels (ranging from tens of parts per billion to units of parts per million) in 28 of 41 (68%) serum samples obtained from the thelarche patients.

High incidence of precocious puberty in a bounded area of northwest Tuscany

CPP prevalence in the five major health service areas (Livorno, Lucca, Massa, Pisa and Viareggio cities) of northwest Tuscany

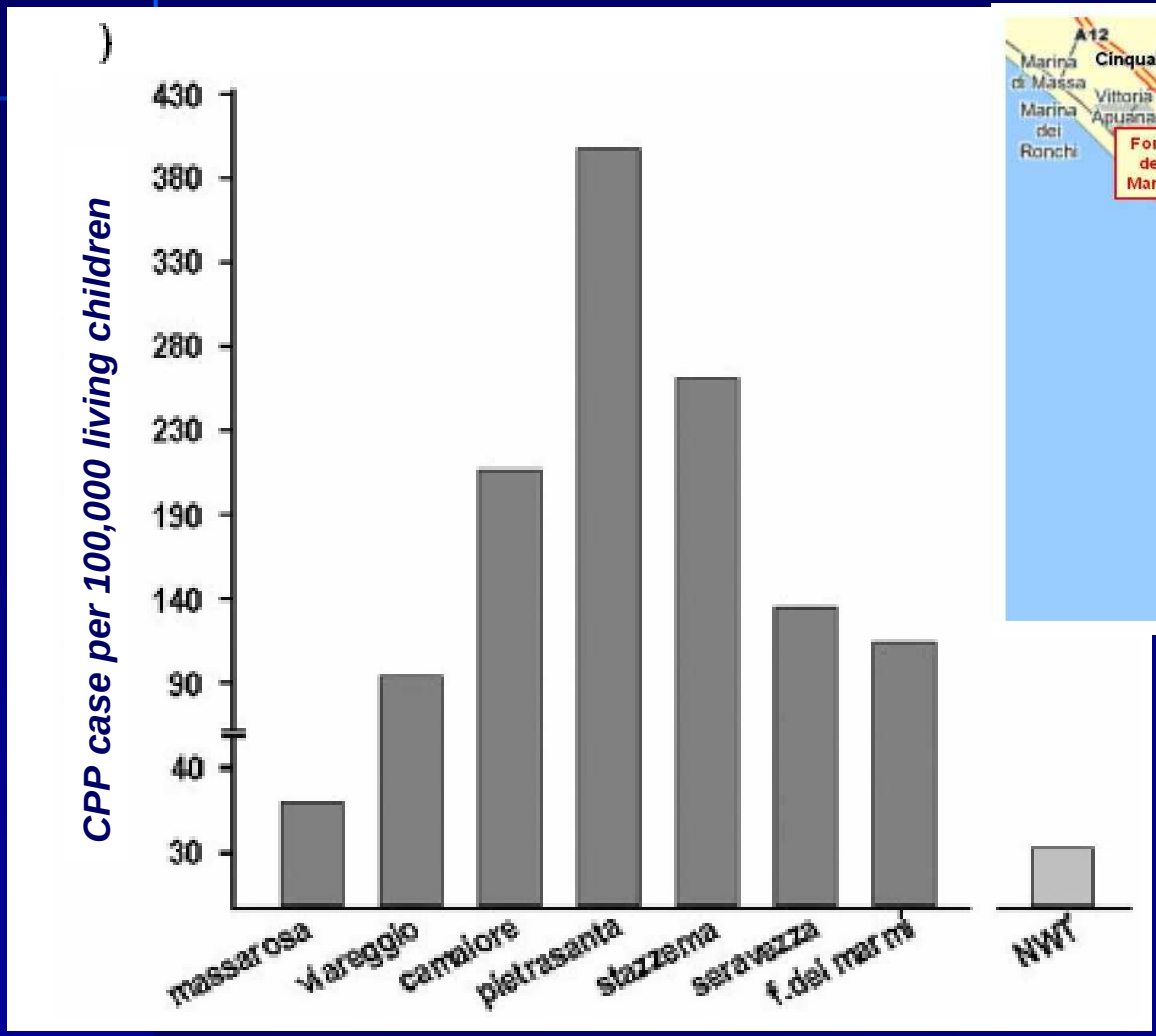
City area	Total number of 0-14 yr-old children	CPP cases	♀/♂ ratio	CPPs *per* 100000 children
Livorno	37332	7	12:1	18.7
Lucca	24630	5	10:1	20.3
Pisa	36420	9	7:2	24.7
Massa	22370	13	12:1	58.1*
Viareggio	19219	31	26:5	161.3*

*significant difference, $P<0.05$



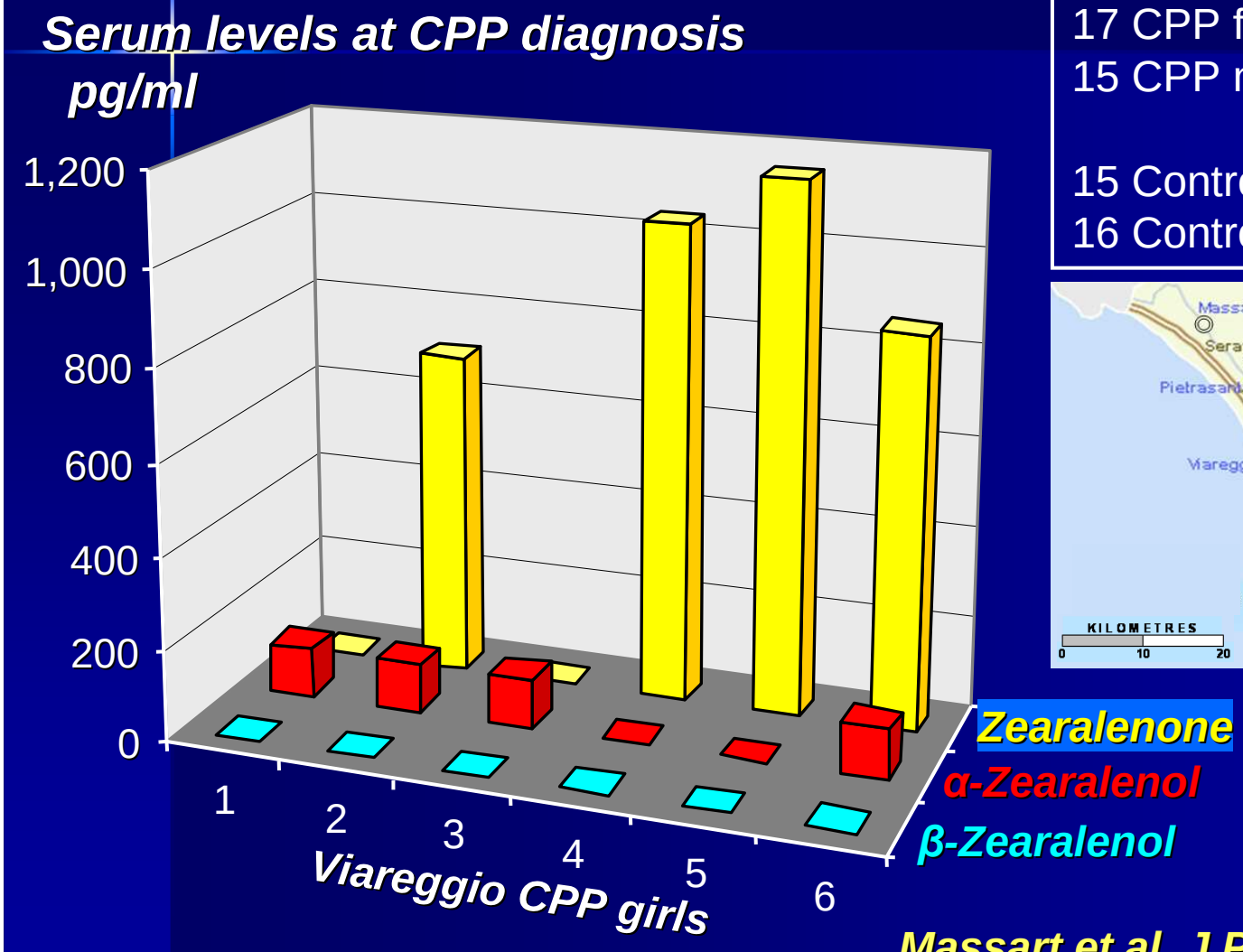
Massart et al. Gynecol Endocr 2005; 20:92

CPP prevalence in 80-km^2 area next to Viareggio is 25-times higher than others



Massart et al. Gynecol Endocr 2005; 20:92

Mycoestrogens are only HPLC-detected in 6 CPP girls from Viareggio area



17 CPP from Viareggio area
15 CPP not from Viareggio
vs.
15 Controls from Viareggio
16 Controls not from Viareggio

Massart et al. J Pediatr 2008; 152:690-5

Endocrine disrupters and human puberty

E. Den Hond and G. Schoeters

International journal of andrology 2006

Epidemiological research on the effects of endocrine disrupters on sexual maturation is hampered by numerous pitfalls.

One major problem is the **mixture of different agents** with potential oestrogenic, anti-oestrogenic and anti-androgenic activities in the environment.

Another important problem is the limited knowledge about the time **lag between exposure and effect**. For most effects, the critical window of exposure has not yet been identified, so that it is not always clear whether to look at in utero, lactational, pubertal or life-long exposure.

Additionally, epidemiological research in general may be influenced by **many factors** such as selection of the study area, sample size, adjustment for confounders, choice of the endpoints, etc.

Endocrine disrupters and human puberty

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One of the reasons for the negative results on PCBs, is that often total PCB concentrations in serum are measured, while various PCB congeners may have different, sometimes antagonistic, effects.

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1) evidenze sperimentali e tossicologiche

2) Evidenze epidemiologiche

a) pochi studi

B) risultati in linea con le aspettative con qualche eccezione

c) meccanismi

Endocrine disrupting chemicals: a new and emerging public health problem?

C L Acerini, I A Hughes

Arch. Dis. Child.
2006;91;633-641

Table 1 Endocrine disrupting chemicals (EDCs)

1. Definition: "any exogenous substance or material that alters the function(s) of the endocrine system and consequently causes adverse health effects in a intact organism, its progeny or its (sub)population"[2]

2. EDCs include certain synthetic man-made chemicals, but also many naturally occurring plant compounds (table 2)

3. EDCs may act as hormone system agonists or antagonists (or both)

4. EDCs interfere with hormone action by a variety of mechanisms:
   a. Hormone receptor binding
   b. Hormone production and synthesis
   c. Hormone transport
   d. Hormone metabolism and excretion

5. EDCs come from a large variety of sources and include:
   a. Pesticides, herbicides, and pharmaceutical agents
   b. Cosmetics, sunscreens, and plastic formulations

6. Many chemicals have yet to be tested for any EDC activity

Sexual Maturation in Relation to Polychlorinated Aromatic Hydrocarbons: Sharpe and Skakkebaek's Hypothesis Revisited

Elly Den Hond,[1] Harry A. Roels,[2] Karel Hoppenbrouwers,[3] Tim Nawrot,[1] Lutgarde Thijs,[1] Corinne Vandermeulen,[3] Gerhard Winneke,[4] Dirk Vanderschueren,[5] and Jan A. Staessen[1]

Environ Health Perspect 2002

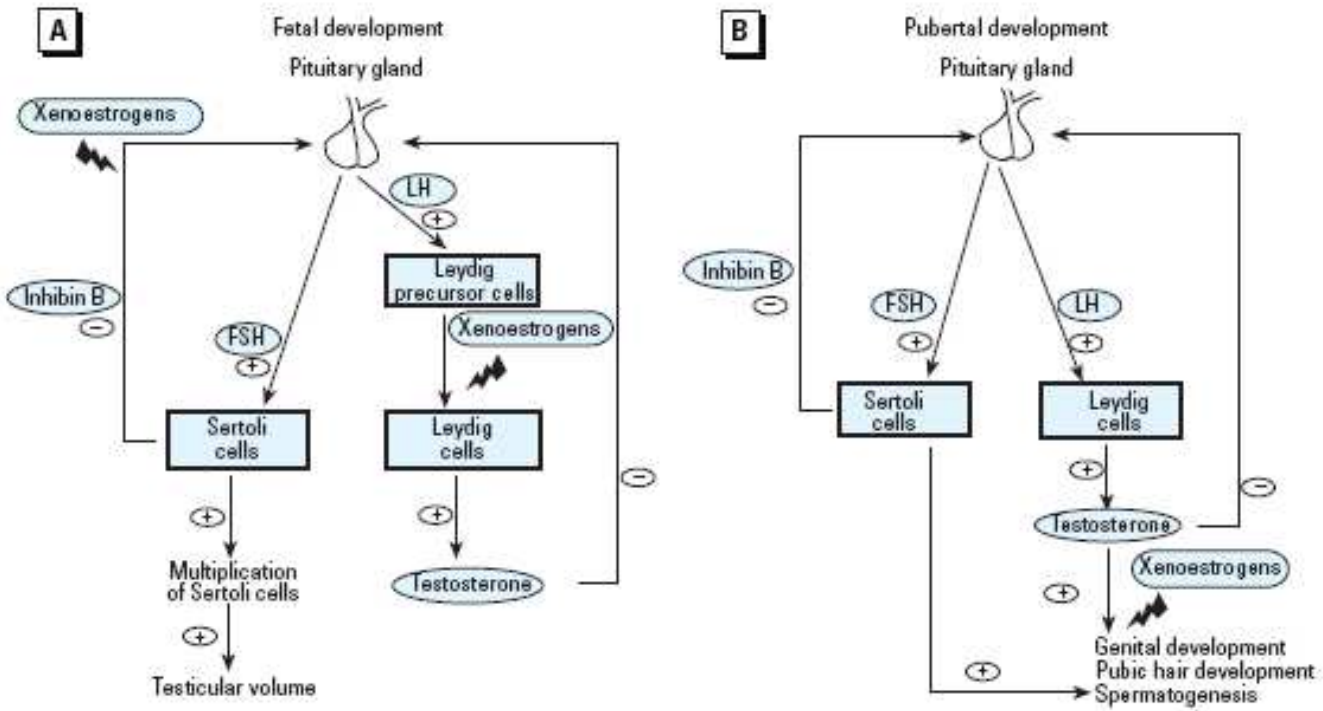

Figure 3. Mechanisms by which xenoestrogens may interfere with the sexual development in boys during fetal and neonatal development (*A*) and during puberty (*B*).

Female sexual maturation and reproduction after prepubertal exposure to estrogens and endocrine disrupting chemicals: A review of rodent and human data

G. Rasier[a], J. Toppari[b], A.-S. Parent[a], J.-P. Bourguignon[a,*]

Molecular and Cellular Endocrinology 2006

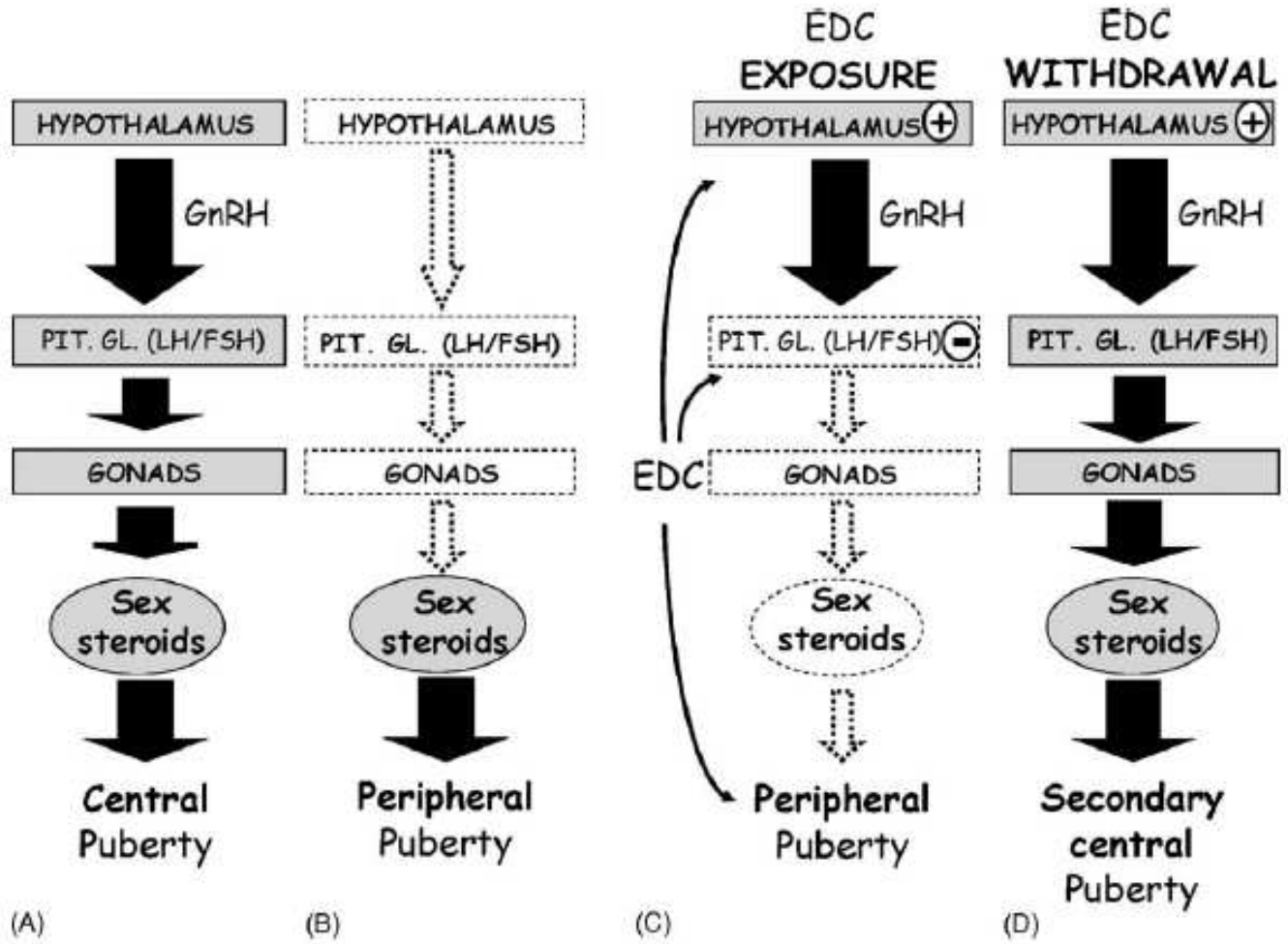

Fig. 2. Schematic illustration of the hypothalamic–pituitary–gonadal (HPG) axis function in different conditions: stimulation in physiological or precocious central puberty (A), inhibition in peripheral puberty due to steroids of extra-gonadal origin (B), hypothalamic stimulation and PG inhibition in the presence of an estrogenic EDC (C) and HPG stimulation after withdrawal from the EDC (D).

Gli “Endocrine disrupters” : realta’ o fantasia ?

- **- They can interact at <u>any step</u> of the <u>signalling pathway</u> = receptor binding, activation, nuclear transfert, transcriptional co-factor modulation, chromatin modification, gene expression**
- **- Environmental chemicals may play a role in <u>programming</u> or <u>imprinting genes</u> involved in cell differentiation and proliferation with a risk of unknown <u>long-term</u> consequences.**

Gli “Endocrine disrupters” : realta’ o fantasia ?

- Conclusioni :

Endocrine-Disrupting Chemicals

An Endocrine Society Scientific Statement

The Endocrine Society

- The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis.
- The Precautionary Principle is key to enhancing endocrine and reproductive health, and should be used to inform decisions about exposure to, and risk from, potential endocrine disruptors.
- Scientific societies such as The Endocrine Society should partner with other organizations with the scientific and medical expertise to evaluate effects of endocrine disrupting chemicals in humans.

Gli “Endocrine disrupters” : realta’ o fantasia ?

- **International agencies (U.N, WHO, EPA, E.C.) should be deeply concerned by the emerging trends**
- **Despite no direct proof that pesticides and other environmental chemicals cause developmental abnormalities, the existing data suggest we need to take the threat of environmental chemical very seriously**
- **Pediatric endocrinologists should intensify research efforts (regional, epidemiological studies, case-control studies ….)**

(C. Sultan 2006)

Gli “Endocrine disrupters” : realta’ o fantasia ?

Last thoughts :

To wait until that one has enough
evidence
to justify action,
can be at times,
the sign of great
foolishness

J. Rostand

Grazie per l'attenzione

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