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ABSTRACTS

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Costa do Sauípe, Bahia, Brazil, October 27–30, 2010

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Gil Guerra-Junior, Campinas, Brazil

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Invited Speakers

Prof. Dr. Alicia Belgorosky	Hospital de Pediatría Prof. Dr. J.P. Garrahan Buenos Aires, Argentina
Prof. Dr. Annette Grüters-Kieslich	Center for Women and Child Health Charité, Universitätsmedizin Berlin, Germany
Prof. Dr. Carlos Alberto Longui	Pediatric Endocrinology Unit Department of Pediatrics Faculty of Medical Sciences, Santa Casa de São Paulo São Paulo, Brazil
Prof. Dr. Irène Netchine	Laboratoire d'Explorations Fonctionnelles Endocriniennes Hôpital d'Enfants Armand Trousseau Faculté de Médecine Pierre et Marie Curie Paris, France
Prof. Dr. Rodolfo Alberto Rey	Pediatric Endocrinology Hospital de Niños Ricardo Gutiérrez Buenos Aires, Argentina
Prof. Dr. Stephanie Beth Seminara	Department of Medicine Reproductive Endocrinology Harvard Medical School Boston, USA
Prof. Dr. Maria Verónica Mericq Guilá	Institute of Maternal and Child Research Faculty of Medicine University of Chile Santiago, Chile
Prof. Dr. Wieland Kiess	Hospital for Children and Adolescence University of Leipzig Leipzig, Germany

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Program

October 27, Wednesday

03:00–6:00 pm	Registration & Satellite Symposia
07:00–8:00 pm	Opening Ceremony & Lecture: "Aromatase deficiency" **Alicia Belgorosky** (Argentina)
08:00–10:00 pm	Dinner

October 28, Thursday

08:00–09:00 am	Conference 1: "Genome-wide strategies and genetic factors associated with obesity and/or diabetes" **Wieland Kiess** (Germany)
09:00–10:00 am	Oral Presentation Section 1
10:00–10:30 am	Break
10:30–11:30 am	Conference 2: "Genes controlling human reproduction" **Stephanie Seminara** (USA)
11:30–01:00 pm	Oral Presentation Sections 2 & 3
01:00–03:00 pm	Lunch
03:00–04:30 pm	Posters Section 1
04:30–05:00 pm	Break
05:00–06:00 pm	Conference 3: "Genetic and epigenetic anomalies of IGF system leading to fetal growth disorders" **Irène Netchine** (France)
06:00–08:00 pm	SLEP Business Meeting
08:00–10:00 pm	Dinner

October 29, Friday

08:00–09:00 am	Conference 4: "Gene mutations, endocrine disruptors and primary hypothyroidism" **Annette Grüters** (Germany)
09:00–10:00 am	Oral Presentation Section 4
10:00–10:30 am	Break
10:30–11:30 am	Symposium 1: 1) "Current treatment of hypogonadism" **Stephanie Seminara** (USA) 2) "Intrauterine and perinatal influences in development of gonadal function" **Veronica Mericq** (Chile)
11:30–01:00 pm	Oral Presentation Sections 5 & 6
01:00–03:00 pm	Lunch
03:00–06:00 pm	Free afternoon
06:00–08:00 pm	SLEP Business Meeting
08:00–10:00 pm	Dinner

October 30, Saturday

08:00–09:00 am	Conference 5: "Update on the management of congenital hypothyroidism" **Annette Grüters** (Germany)
09:00–10:00 am	Oral Presentation Section 7
10:00–10:30 am	Break
10:30–11:30 am	Cesar Bergadá Lecture: "Fetal hypogonadism and sex differentiation disorders: what we learnt from anti-mullerian hormone" **Rodolfo Rey** (Argentina)
11:30–01:00 pm	Oral Presentation Sections 8 & 9
01:00–03:00 pm	Lunch
03:00–04:30 pm	Posters Section 2
04:30–05:00 pm	Break
05:00–06:00 pm	Symposium 2: 1) "Recent advances in genetic anomalies of GH deficiency: isolated and hypopituitarism" **Irène Netchine** (France) 2) "Clinical impact of the identification of glucocorticoid sensitivity" **Carlos Longui** (Brazil)
06:00–07:00 pm	Conference 6: "Metabolic syndrome in children and adolescents" **Wieland Kiess** (Germany)
07:00–08:00 pm	Closing Ceremony & Awards
08:00–10:00	Dinner

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Abstracts

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Oral Presentations

1

Glucocorticoid-remediable Aldosteronism (Familial Primary Hyperaldosteronism Type 1) in Children: Prevalence, Clinical and Biochemical Characteristics

R. Bancalari[1], *H. Garcia*[2], *M. Aglony*[3], *A. Martinez-Aguayo*[4], *C. Carvajal*[5], *C. Campino*[6], *V. Mericq*[7], *C. Fardella*[6]

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Familial hyperaldosteronism type I (FH-1) is caused by a chimeric gene (CG). **Aim:** To report the prevalence of FH-1 in hypertensive children and to describe their clinical and biochemical characteristics. **Patients and Methods:** We studied 120 untreated hypertensive children in which we determinated plasma potassium (K), Plasma Renin activity (PRA), serum aldosterone (SA) and the aldosterone to renin ratio (ARR). **Results:** We found 4/120 (3.3%) children with ARR>25. A CG was confirmed a in all of them. The same study was conducted in 20 first degree relatives, 8 of whom were affected, making a total of 12 patients. The PRA was suppressed (< 0.3 ng/mL/h) in 6/12 and hypokalemia (K <3.5 mEq/L) was present only in 3/12 patients. A high SA levels (>16 ng/dL) was present in 10/12 patients. The ARR >25 was observed in 11/12 affected subjects, the lower value corresponds to a young woman wich had pre-hypertension. **Conclusion:** The prevalence of FH-1 in pediatric hypertensive population was high when a ARR >25 was used as screening, we suggest that a lower ARR cut off should be determined in them.

2

Novel Mutations in the Growth Hormone Secretagogue Receptor Gene *(GHSR)* Associated with Constitutional Delay in Growth and Puberty (CDGP)

P.N. Pugliese-Pires[1], *J.P. Fortin*[2], *Y. Zhu*[2], *B.B. Mendonça*[3], *I.J.P. Arnhold*[4], *A. Kopin*[2], *A.A.L. Jorge*[5]

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Objective: To study the *GHSR* in children with idiopathic short stature (ISS). **Methods:** The coding region of *GHSR* was directly sequenced in 96 patients with ISS, 39 of them with CDGP. **Results:** Five different heterozygous mutations in *GHSR* were identified, all of them in patients with CDGP. None of them was found in 150 control individuals. One mutation is located in the 5'UTR (c.-6 G>C). The other 4 mutations predicted amino acid changes: p.Ser84Ile, p.Ala169Thr, p.Val182Ala and p.Ala358Thr. Functional studies of the missense mutations showed that p.Ser84Ile and p.Val182Ala mutants have a decrease in both basal activity and in ligand-induced signaling. The p.Ser84Ile also has a marked decrease in cell surface expression, whereas the p.Val182Ala has a tendency toward decreased expression. Both functionally-significant *GHSR* mutations were found in female CDGP patients (at 13 yr, prepubertal, height SDS of -2.4 and complete puberty development after this age). Analysis of first degree relative identified other individuals with mutation but without any specific phenotype. **Conclusion:** This is the first report of functionally-significant *GHSR* mutations in patients with CDPG. The fact that these mutations did not segregate with the phenotype in corresponding families is consistent with a dominant mode of inheritance with incomplete penetrance.

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3

Congenital Lipoid Adrenal Hyperplasia in a 46,XY Patient with Ambiguous Genitalia Harboring a Heterozygous *De Novo* Mutation in *StAR* Gene (Steroidogenic Acute Regulatory Protein)

G. Guercio[1], *M. Costanzo*[1], *M.S. Baquedano*[1], *E. Berensztein*[1], *M. Bailez*[2], *E. Vaiani*[1], *N. Saraco*[1], *R. Marino*[1], *M.A. Rivarola*[1], *A. Belgorosky*[1]

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Bialelic *StAR* gene mutations present with primary adrenal insufficiency (PAI) and female phenotype regardless of karyotype. Katsumata et al, reported a 46,XY patient with PAI and male genitalia carrying a heterozygous mutation IVS1 –2G>A in the *StAR* gene causing an aberrant splicing pattern with loss of exon 2 (mRNA –E2) (Or11-3 Endo09). We are reporting a 46,XY patient with ambiguous genitalia, PAI and severe impairment of adrenal and gonadal steroidogenesis. Molecular analysis revealed the heterozygous mutation IVS1 –2G>A in *StAR* and the pGly146Ala heterozygous polymorphism in *SF1* gene. Histopathological analysis of the gonads at 3 years of age was consistent with immature testes. Basal and post-hCG testosterone production of testicular cells in culture was normal. *StAR* mRNA expression in gonadal tissue revealed a 397pb band (mRNA -E2) and a weak wild-type 511pb band, and both were expressed equally in testicular cells in culture. These findings suggest that heterozygosis could affect testicular steroidogenesis in *utero*. We propose that local testicular factors might differentially regulate the splicing pattern determining the phenotypic differences between both patients described with this mutation. The presence of a potentially hypomorphic polymorphism in *SF1* gene may have contributed to the more severe clinical phenotype in our patient.

4

WNT/Beta–Catenin Pathway Dysregulation in Childhood Adrenocortical Tumors (ACT)

L.F. Leal[1], *L.M. Mermejo*[2], *C. Scrideli*[1], *L.G. Tone*[1], *C.E. Martinelli Jr*[1], *J.A. Yunes*[3], *A.L. Seidinger*[4], *M.J. Mastellaro*[5], *S.R. Brandalise*[6], *A.C. Moreira*[2], *M. Castro*[2], *S.R.R. Antonini*[7]

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Introduction: In Brazil the high incidence of Childhood ACT is associated with the R337H p53 mutation. Abnormalities of the Wnt pathway have been described in ACTs. *In vitro*, p53 regulates the Wnt pathway but this action has not been demonstrated *in vivo* in adrenal disease. **Objective:** To investigate abnormal expression of Wnt pathway genes in childhood ACT and its relationship with p53 mutation and outcome. **Methods:** 53 patients with ACT from two reference centers in Brazil were evaluated (12M/41F; age: 3.4±3.7 yrs). All but one patients present hormone excess. Tumor stage: I (n=28), II (n=8), III (n=8), IV (n=9). Expression of CTNNB1, Axin, DKK3, MYC, WISP2, and p53 was measured by RT-PCR and calculated by $2^{-\Delta\Delta Ct}$. Controls: 8 normal adrenals. **Results:** R337H p53 mutation was present in 87% of the patients. ACTs overexpressed CTNNB1 ($p=0.01$) and underexpressed DKK3 ($p<0.0001$), Axin ($p=0.05$) and MYC ($p=0.01$). ACTs III/IV presented lower expression of p53 than ACTs I/II and controls ($p=0.006$). Underexpression of p53 was observed in patients with R337H p53 mutation ($p=0.04$). There was a correlation of p53 and DKK3 ($p=0.004$), Axin ($p<0.0001$), MYC ($p=0.0003$) and WISP2 ($p=0.0017$). **Conclusion:** Wnt pathway is dysregulated in childhood ACTs and correlates with the R337H P53 mutation.

5

Novel Mutations (p.G6R and p.R511W) in *IGF1R* Gene in Children Born Small for Gestational Age (SGA) Without Catch-up Growth

D.C. Coutinho[1], *A.C. Leal*[1], *L.M. Ribeiro*[1], *B.B. Mendonca*[1], *I.J.P. Arnhold*[1], *A.A.L. Jorge*[1]

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Body: IGF-1 insensitivity caused by *IGF1R* mutations was identified as one of the causes of pre and post-natal growth impairment. **Objectives:** to study *IGF1R* of SGA children suspected to have IGF-1 insensitivity. **Patients and Methods:** 25 SGA children without catch-up growth were selected by the presence of IGF-1 SDS >0. The *IGF1R* cDNA was sequenced. Allelic variants were confirmed by direct sequencing of genomic DNA. Functional analyses of mutated IGF1R in fibroblasts were evaluated. **Results:** We identified 2 children (8%) carrying a nucleotide substitution in heterozygous state in *IGF1R*. The first variant was located in exon 1, leading to a substitution of glycine by arginine in codon 6 (p.G6R). The second variant was located in exon 7, leading to a substitution of arginine by tryptophan in codon 511 (p.R511W). Cell proliferation induced by IGF-1 was 50% lower in fibroblasts from affected patients in comparison to controls. Leucocytes and fibroblasts from the patient harboring p.G6R mutation presented 50% decrease in *IGF1R* expression (confirmed at protein level by Western blot). AKT phosphorylation was decreased in both mutated fibroblast lineages. **Conclusion:** Two novel mutations in *IGF1R* gene associated with pre and postnatal growth impairment are described.

6

Expression Levels of the Supressors of Cytokine Signaling Type SOCS 1, 2 and 3 in Children with Idiopathic Short Stature

P. Ocaranza[1], *F. Morales*[2], *R. Román*[1], *R. García*[1], *T. Salazar*[1], *F. Cassorla*[1]

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Background: SOCS proteins are involved in the intracellular signaling for growth hormone (GH). It is unknown whether some patients with idiopathic short stature (ISS) have a reduction in GH sensitivity due to differences in the expression of the *SOCS1*, *2* and *3* genes. **Objective:** To quantify the intracellular expression of the *SOCS 1, 2* y *3* genes in children with ISS and in control children. **Methods:** We studied 21 prepubertal children between the ages of 5–10 years. Ten of these patients had short stature and possible evidence of partial GH insensitivity based upon a stimulated GH level >20ng/mL and a serum IGF-I level <1SDS for age. They were compared to eleven children with normal stature. RNA was extracted from fibroblast cultures obtained from skin biopsies, and gene expression was quantified by RT-PCR. **Results:** RT-PCR assays revealed an increased basal expression of the *SOCS* genes in ISS children compared to the controls, which increased further after stimulation with GH, particularly for *SOCS2* (*0.77±0.08 vs 0.50±0.06, *p<0.05) and *SOCS3* (*0.59±0.08 vs 0.38±0.05, *p<0.05). **Conclusion:** Some children with ISS show evidence of increased *SOCS* expression, which may inhibit the GH signaling pathway and contribute to a reduced tissue sensitivity to GH. (FONDECYT 1095118).

7

A Novel *GPR54* Mutation in a Patient with Gonadotropin-dependent Precocious Puberty (GDPP)

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Background: GDPP etiology is unknown in most cases. The molecular basis was elucidated in single patients harboring mutation in the GPR54 and Kiss1 genes. Aims: To analyzed the *GPR54* gene in patients with GDPP. **Methods:** A prospective and retrospective study evaluated the GPR54 gene in 105 patients with GDPP (101F: 5.7±2.2yrs and 4M: 8±1yrs; 12% familial). **Results and Conclusion:** The novel heterozygous mutation (c.109C>T; p.P37S) was found in one girl with sporadic GDPP. This mutation was absent in controls (100 alleles) or in the other GDDP patients (184 alleles). Affected patient presented with thelarche since birth (B3). Until 7 years she presented slow pubertal progression, no accelerated growth and skeletal maturation and estradiol, pelvic ultrasound and LH (Basal: <3.9–12.2, NR<15; Stimulated: 32–56.6 ng/mL; NR <65-RIA) were within pre-pubertal range. At 7 yrs developed accelerated growth (8.2 cm/yr) skeletal maturation (BA: 10yrs), being treated with GNRHa until 12.1 yrs. Menarche occurred at 12.2 yrs and final height was normal (Z= 0.69). The affected residue (GPR54 P37) is well conserved among different species and lies in the extracellular portion of the N-terminal domain. *In silico* analysis demonstrated that this mutation is likely to be damaging. Ongoing functional studies will elucidate genotype-phenotype correlation.

8

Gene and Protein Expression of the Acid Labile Subunit (ALS) in Term Placentas from Small (SGA), Appropriate (AGA) and Large (GEG) for Gestational Age Newborns (NB)

I. Germán[1], *F. Arganfoña*[1], *P. Medina*[1], *C.A. González*[1], *S. San Martín*[2], *E. Kakarieka*[1], *M.C. Johnson*[1], *F. Cassorla*[1]

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Background: IGF-I increases in circulation its half-life by forming a ternary complex with IGFBP-3 and ALS.. **Objective:** To study whether the human placenta expresses the mRNA and protein for ALS; and to investigate possible differences in placentas from SGA, AGA and LGA NB. **Methods:**We studied 42 SGA,47 AGA and 20 LGA full term placentas. We determined mRNA expression by RT-PCR and protein contents using specific immunoassays in both the basal(BP) and chorionic(CP) plates of the placentas. Statistics:ANOVA and Spearman´s correlation test. **Results:** Mean±SEM

		SGA(42)	AGA(47)	LGA(20)
Birth Weight(SDS)		–2.11±0.10*	0.11±0.11	2.54±0.33**
ALS/rRNA18S	CP	0.15±0.01*	0.12±0.01	0.09±0.02
	BP	0.14±0.02*	0.11±0.01	0.09±0.01
ALS ng/g placenta	CP	31.7±3.3*	22.1±4.2	23.1±3.7
	BP	27.7±3.7	24.0±4.1	22.5±3.4

*p<0.05 SGA vs AGA; **p< 0.05 LGA vs AGA

The ALS gene and protein expression were confirmed by sequencing and by Western blot/immunohistochemistry respectively. Conclusion:We describe for the first time that the mRNA and protein for ALS are present in human placenta. The increased mRNA expression and protein content for ALS observed in SGA placentas suggests a possible role for this protein in fetal growth. (Fondecyt 1061082)

9

Differences in Early Infancy Patterns of Growth and Metabolic Profile in Very Low Birth Weight (VLBW) Preterms (PT) Born Either Appropriate (AGA) or Small (SGA) for Gestational Age (GA)

V. Peña[1], K. Rossel[1], M.I. Hernandez[3], M. Garcia[2], T. Salazar[2], A. Avila[4], G. Cavada[5], I. Germán[6], V. Mericq[6]

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Being born preterm is associated with later cardiovascular risk. Early infancy weight gain is a key factor. We aimed to evaluate whether early patterns of infancy anthropometry and metabolic hormonal profile differs in preterms born SGA or AGA. We recruited 75 VLBW preterms ,44 AGA, 27 males. Mean BW –1.36±1.06 SDS, 29 weeks GA, and birth length –0.8±0.8 SDS. Complete anthropometry and blood sampling for Insulin, IGF-I, IGF-II and leptin determination performed at 72 hrs,15,28,60 days and 0, 1,3 and 6 months corrected age (CA=40 weeks GA). Differences in patterns of length SDS ($p<0.02$), tricipital and bicipital skin folds ($p<0.001$) are observed in SGA vs AGA PT.A 56% of SGA and 11% AGA had length <–2SDS by 3 months CA ($p<0.001$). In all infants Insulin levels by age 60 days correlated positively with head circumferences ($p<0.005$). Weight SDS correlated positively with Insulin at 15, 28 days and IGF-I 60 days, length SDS with insulin 60 days weight/length SDS with IGF-I 72hr. In spite of being shorter and lighter, IGF-I and leptin levels are higher by 6 months in SGA infants. Differences in patterns of growth and hormonal profile are present in SGA vs AGA which are evidenced after CA_0.

10

Intracellular Trafficking Effects of Insulin-like Growth Factor Acid Labile Subunit Gene (IGFALS) Mutations Identified in Idiopathic Short Stature (ISS) Children

M.C. Guida[1], R. Nitschke[2], H.M. Domené[1], L. Karabatas[1], P. Scaglia[1], A. Martinez[1], A. Keselman[1], I. Bergada[1], H. Cassinelli[1], S.V. Bengolea[3], J.J. Heinrich[1], V. Pipman[4], M.G. Ropelato[1], M.G. Ballerini[1], R.A. Rey[1], H.G. Jasper[1]

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Heterozygous IGFALS gene mutations are present in 11.2% of ISS children. Three of these mutations (P287L, A330D and R548W) were selected to determine their *in vitro* effects on intracellular ALS trafficking. ALS, IGFBP-3 and IGF-I serum levels were <–2 SDS in the patients carrying the P287L or R548W mutations but normal in the patient with A330D. The effects of the mutations on intracellular trafficking were studied by generating expression vectors of ALS, wild type (WT) or mutated, tagged to a fluorescent protein (pECFP-N1-ALS). CHO cells were cotransfected with pECFP-N1-ALS WT or mutated and a fluorescent trans-Golgi marker vector, TGN38.YFP. We found a significant increase in localization of P287L and R548W ALS mutants, but not of A330D, in trans-Golgi as compared to ALS-WT (Pearson's colocalization coefficient between ALS and TGN38, mean±SE: WT 0.32±0.03; P287L 0.46±0.03; A330D 0.27±0.02; R548W 0.48±0.03; ANOVA $p<0.0008$, Tukey: P287L vs WT $p<0.05$; A330D vs WT $p>0.05$; R548W vs WT $p<0.05$). Our findings indicate that P287L and R548W ALS mutants affect the intracellular trafficking of ALS and could be involved in the short stature phenotype of both patients since they are associated to low serum levels of ALS, IGFBP3 and IGF-I.

11

Growth Hormone (GH) Pharmacogenetics: Positive Influence of GH Receptor (GHR) Exon 3 Deleted Allele (d3) on First-year Growth Velocity and Final Height in Patients with Turner Syndrome (TS) Treated with Recombinant Human GH (rhGH)

A.F. Braz[1], E.F. Costalonga[1], A.C. Malaquias[1], B.B. Mendonça[1], I.J.P. Arnhold[1], A.A.L. Jorge[2]

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Objective: To assess the influence of GHR-exon 3 genotype on the variability of growth response in TS patients treated with rhGH. Subjects and **Methods:** GHR-exon 3 was genotyped by multiplex PCR in TS patients treated with rhGH (mean dose of 50 µg/kg.d.). The main outcome measures were first year growth velocity (GV) (only prepubertal patients, n=61) and adult height (n=31, median 5.4 years of treatment). **Results:** TS patients carrying at least one *GHR*d3 allele had a significantly higher GV in the first year of treatment (d3/* 8.2 ± 1.3 vs fl/fl 6.9 ± 1.7 cm/y, $p = 0.001$) and reached a taller adult height SDS (d3/* –1.3 ± 0.5 vs fl/fl –2.5 ± 0.9, $p < 0.001$) when compared with patients homozygous for *GHR*fl alleles. The influence of GHR-exon3 genotype was independent of other clinical variables, as demonstrated by multiple linear regression analyses (independent variables with $p < 0.05$, for GV: age and GHR-exon 3 explained 47% of the variability; and for final height SDS: GHR-exon 3 and basal height SDS explained 57%). **Conclusion:** The presence of GHRd3 allele has a positive influence on first-year growth response and final height in TS patients treated with rhGH.

12

Assessment of Testicular Sertoli Cell Function in Chemotherapy – Treated Prepubertal and Pubertal Male Survivors of Childhood Cancer

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Background: Male germ cells are highly sensitive to chemotherapy, whereas quiescent Leydig cells seem to be less affected in prepubertal boys. Sertoli cells have rarely been studied. **Objective:** To assess pituitary-testicular function, with emphasis on Sertoli cell function, in boys and adolescents with extragonadal tumors having received chemotherapy exclusively. **Methods:** A retrospective analysis including 51 patients treated <10yr and 38 treated between 10–18 yr. FSH and AMH levels were the primary endpoints. LH and testosterone were also assessed. **Results:** In 35/51 patients treated <10yr, evaluation before puberty (9.7±2.3 yr; 3.0±2.6 yr post-chemotherapy) showed normal AMH in all, with mild elevation of FSH in 31.4% and LH in 14.3%. In 30/51 cases treated <10 yr, evaluation at pubertal age (15.0±2.2 yr; 8.8±3.5 yr post-chemotherapy) showed low AMH in 3.8%, low testosterone in 13.3% and mildly elevated FSH and LH in 13.3%. In 38 patients treated during puberty, analysis 5.0±4.5 yr post-chemotherapy showed normal AMH in all, low testosterone and moderately elevated LH in 5.2%, and elevated FSH in 28.9%. **Conclusions:** Like Leydig cells, Sertoli cells have low sensitivity to chemotherapy in prepubertal and pubertal males. Pubertal elevation of FSH in a subset of patients might be due to germ cell loss.

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Turner Syndrome and Y Chromosome: There are Gonadal Tumors Only Diagnosed by Immunohistochemistry

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The frequency of gonadal tumors is higher among patients with dysgenetic gonads and in the presence of a Y chromosome. The aim of this work was to investigate the frequency of these tumors among patients with Turner syndrome (TS) and a Y in their chromosome constitution. Among 260 patients with TS, six were mosaics with an entire Y chromosome and ten had Y molecular sequences detected by PCR with specific probes (*SRY, TSPY* and *DYZ3*) and confirmed by FISH. In all 16 cases the patients were subject to bilateral gonadectomy (8.7 to 18.2 years), anatomopathological study with hematoxylin-eosin (HE) and immunohistochemical analysis with anti-OCT4 antibody. No gonadal neoplasia was detected in the 32 gonads evaluated by HE; however, four gonads (12%) from three patients (19%) had positive OCT4 staining in more than 80% of nuclei, suggesting the existence of germ cell tumors (gonadoblastoma or carcinoma *in situ*). We conclude that the diagnosis of gonadal tumors in young TS patients with a Y chromosome requires a specific anatomopathological study, such as immunohistochemistry, and that prophylactic gonadectomy is indeed indicated in these cases. (Support by Fapesp and CNPq).

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Evaluation of Vitamin D (VitD) Adequacy in a Brazilian Pediatric Group of Diabetes Mellitus Patients (DM1)

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Introduction: Low levels of VitD may be associated with increased risk of fractures in patients with type 1 diabetes mellitus in adulthood. **Objective:** To evaluate the adequacy of VitD in children and adolescents with DM1. **Methods:** Deficiency, insufficiency and sufficiency of VitD were characterized respectively by the concentrations of 25OHVitD <10,10–30, and > 30ng/mL. PTH, urine calcium and HbA1c were also evaluated in 117 patients with DM1 and compared with age, metabolic control and duration of disease by nonparametric t test and gender by c^2 test. **Results:** Insufficiency in VitD was found in 75% of patients. No VitD deficiency was diagnosed. Patients with VitD insufficient levels had higher mean age (11.9 years ± 6.0 vs 9.9 ± 7.6, $p < 0.05$), longer disease duration (7.5 years ± 7.0 vs 5 , 4 ± 5.8, $p < 0.05$) and higher levels of HbA1c (9.8 ± 4.34% vs 8.7 ± 4.3%, $p < 0.05$) when compared with patients with sufficient levels of 25OHVitD. No significant differences were found in the other variables. **Conclusion:** In this population we found 75% of VitD insufficiency, which was associated with older age, worse metabolic control and longer duration of disease.

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Human Prepubertal Testis (HPPT) in Organotypic Culture: New Tool for Basical and Clinical Research

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Organotypic cultures are good systems for study development of somatic cells and gonocytes in fetal testis. No reports are available for normal or dysgenetic HPPT. **Aim:** to develop a micro-method to study Sertoli cells (SC), Leydig cells (LC) and germ cells (GC) development from HPPT biopsies, in order to study normal and dysgenetic testis in histo-architecture preserved conditions.Three PP (2mo, 2mo and 2.5y) and one Pu (13y) testes were studied. Testicular tissue, dissected into $3mm^3$ fragments, was cultured for 5 days. Acute hCG stimulation was carried out at day 5. Conditioned media (CM) was collected and stored. Immunoexpression of cell markers was used to identify cell types: P450scc for LC, AMH for SC and c-kit for GC. Testosterone secretion was detected in CM, increasing with culture day in PP testis and decreasing in Pu testis. Testosterone increased under hCG in 3 PP cultures. Estradiol secretion was also detected in 1 PP and in the Pu culture. AMH was detected only in PP cultures. A preserved histo-architecture was observed. **Conclusion:** organ culture proved to be an efficient tool for studying the early development of HPPT functions. Indeed, this system was able to maintain satisfactory development of the SC, LC and GC.

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Functional Analysis of 3-bp Deletion in SRY Promoter Region Associated with 46,XY Complete Gonadal Dysgenesis

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The expression of *SRY* gene (Sex-Determining Region on the Y-chromosome) is responsible for testicular determination. *SRY* mutations are found in cases of gonadal development anomalies, leading generally to XY sex-reversal phenotypes. We had previously identified the 3-bp deletion by sequencing the *SRY* promoter region of a patient with 46,XY karyotype, completely female external genitalia, normal Müllerian ducts and streak gonads. The mutation is located in one of the two Sp1 transcription factor binding-sites. In order to investigate the effects of the mutation upon Sp1 protein interaction with *SRY* promoter region, a binding analysis was conducted. The interaction of the Sp1 transcription factor with normal and mutant binding sites was analyzed using Electrophoretic Mobility Shift Assays (EMSA). Tests with increasing concentrations of the transcription factor in the reaction were performed. Those analyses revealed that the three base pair deletion abolish the Sp1 binding to the mutant site, while the binding to the adjacent normal site is maintained indicating that two Sp1 molecules bind this region independently. Therefore, *in vitro* analysis confirms that two Sp1 binding-sites are probably necessary to promote correctly SRY gene transcription. Consequently, the results indicate that in this case the 3-bp deletion might be responsible for the phenotype.

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A Novel Mutation in CBX2 Gene in a Brazilian Patient with 46,XY Disorders of Sex Development (DSD) Due to Gonadal Dysgenesis

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Introduction: CBX2 mouse homologue, *M33,* was found to play role in the gonadal development. One mutation in CBX2 has been described in a 46,XY patient with ovaries and female phenotype. **Objective:** To analyze *CBX2* gene in patients with 46,XY and 46,XX Disorders of Gonadal Development (DGD). **Patients/Methods:** We evaluated 60 patients. Forty 46,XY DGD patients from 36 families, eighteen 46,XX DGD patients from 13 families and a family with one sibling with 46,XX DGD and other with 46,XY DGD. Mutations in *SRY*, *SF1* and *FSHR* gene were excluded as well as autoimmunity. The entire coding region and the splicing sites flanking regions of *CBX2* was amplified and sequenced. **Results:** We identified 12 allelic variants in our patients: 7 known polymorphisms and five new ones. Moreover, the novel homozygous mutation, C132R, was found in a 46,XY DGD patient with partial gonadal dysgenesis and was absent in 206 normal control alleles. **Conclusion:** This is the first study of the *CBX2* in a large cohort of patients with DGD. We identified one new *CBX2* homozygous mutation in a patient with 46,XY DSD due to partial gonadal dysgenesis. Additional analysis will be performed in order to determine its deleterious effect on the CBX2 protein.

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Central Precocious Puberty Caused by Chronic Renal Insufficiency

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28mo male with chronic renal insufficiency secondary to posterior urethral valve developed central precocious puberty (CPP). Uncomplicated term pregnancy. Oligohydramnios noticed at delivery.

Birth weight: 3675 g , length: 50 cm. Renal insufficiency was diagnosed soon after. At 13 mo pubic hair was noticed. Androgen panel was normal. At 27 mo penis started to enlarge and he was referred to a Pediatric Endocrinologist. Weight: 12.1 kg (–0.77 SDS). Height: 85.2 cm (–1.04 SDS). PH Tanner II, genitals Tanner II, penis 5.2 cm and testicles 4ml. Bone age: 3y. Testosterone: 151ng/dl, LH 3.5mUI/mL and FSH 4.4mUI/mL (electrochemiluminescence). After 100 mcg of GnRH peak LH 37.1mUI/mL and FSH 7.4mUI/mL. Brain MRI was normal.

Diagnosed with CPP and GnRHa was initiated. 1 month later received a kidney transplant. 1 year after the transplant BA was 5.5y and GnRHa was discontinued. Serum levels of LH, FSH and testosterone remain at pre-pubertal levels for another 1 year without bone age advancement. There are two previously published cases of children with CRI and CPP. In one CPP was "cured" after kidney transplant, similar to this case. We speculate that accumulation of metabolites could induce puberty and that after the transplant the clearance increased, diminishing the stimuli.

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Cytochrome P450 Oxidoreductase Deficiency in a Brazilian Patient: Clinical and Molecular Features and Follow-Up

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P450 oxidoreductase (POR) is the electron donor protein for all microsomal P450 enzymes, including CYP17, CYP21A2 and CYP19. Only 50 patients with POR mutations have been reported. An 8 month-old patient raised as a boy was referred due to non-palpable gonads. Maternal virilization was observed in the 3rd trimester of gestation. External genitalia: Prader V (1.3cm-length phallus). Karyotype: 46,XX. The Table shows hormonal levels during follow-up.

	8 months	18 months	4 years	7 years
FSH (IU/L)	43.3	18.4	1.3	1.8
LH (IU/L)	0.5	0.5	0.1	0.1
ACTH (pg/mL)	10.3	20.7	20.9	10.3
Cortisol (μg/dL)	8.7	7.3	7.0	9.6
17OH-progesterone (ng/mL)	11.6	2.5	3.8	3.3
DHEA (ng/mL)	0.6	1.2	1.4	1.1
Androstenedione (ng/mL)	0.8	0.2	0.3	0.3

Bone survey showed synostosis of carpal bones compatible with Antley-Bixler syndrome. There were two novel mutations in *POR* gene: c.659C>T (nonsense) and c.1215T>A (missense). At 11 months the gender was changed to female. She is now 7 years old and shows normal growth and development, absence of adrenal crisis though she is not under medication. The diagnosis of POR deficiency requires a comprehensive assessment of pregnancy course, physical examination, bone evaluation, adrenal and gonadal function, and molecular analysis.

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Quality of Life in a Large Cohort of Patients with 46,XX and 46,XY Disorders of Sex Development (DSD)

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Background: Disorders of sex development (DSD) refer to a group of congenital conditions in which atypical development of sex occurs. Few studies have focused the quality of life (QoL) of affected individuals. Our aim is to evaluate the QoL using the WHOQOL-BREF questionary in 46,XX and 46,XY DSD patients followed until adulthood in a single center. **Patients and Methods:** 112 adult DSD patients answer the 26 questions related to general Qol and health and to its four domains: physical, psychological, social and environment. **Results:** General quality of life and at physical, psychological and social domains were better in the patients (n=28) with final male social sex than in patients (n = 84) with the female social sex ($p<0.05$). There was a significant difference between the female social sex group regarding general health ($p = 0.05$) indicating that female 46,XX patients (n = 38) are more satisfied with their health than 46,XY female patients (n=46). **Conclusion:** DSD patients with male social sex have a better quality of life than patients with female social sex probably reflecting the impact of infertility in the female social sex group.

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Measurement Uncertainty (U) of Serum GH Applied to the Cut Off Value in Pharmacological Tests (PhT) of GH Secretion

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U is the interval of possible values among which the true value is placed with a high degree of probability. Auxological criteria, as well as serum GH response to PhT (sGHrPhT), are used for the diagnosis of GH deficiency (D) using a 6.1 ng/ml cutoff, as previously reported. **Objectives:** To determine the implication of the uncertainty zone(UZ) of cut off sGHrPhT, generated from the U of immunoassay used, and If basal serum IGF1 determination improves diagnostic decision. **Clinical Material:** 656 PhT from 338 patients with auxological parameters compatible with GHD. We analyzed the maximum peak (Maxp) reached in one of two PhT. **Materials and Methods:** Internal and external quality control. GH and IGF1 were assayed by Chemiluminescence, IMMULITE. U by Analytical Methods Committee. **Results:** U for GH in our analytical platform is 10.19%. Applation of U to the cut off limit of 6.1 ng/ml, generated a UZ, between 5.4 and 6.7 ng/ml in 8% of patients.

Maxp (ng/ml)	response <5,4	UZ (below cutoff)	UZ (above cutoff)	response >6,7
IGF-1SDS, mean±SD	–1,63 ±1,68	–0,38 ±0,82*	–0,53 ±1,37*	–0,58 ± 1,12

*no significant difference

Conclusions: the cutoff limit diagnosis should include the evaluation of a UZ for each analytical platform. The serum IGF1 does not improve diagnostic decisions in this zone

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Growth Hormone Treatment in Children with Idiopathic Short Stature: Correlation of Growth Response with Peripheral Thyroid Hormone Action

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Objective: GH treatment increases height in Idiopathic Short Stature (ISS), however growth rate differs among patients. Thyroid hormones (TH) are also essential for growth acting through TH receptors (TR) α and β. We reported that GH reduced peripheral TH action in Turner Syndrome. We aimed at assessing the effect of GH treatment in ISS on peripheral TH action and the correlation between thyroid status and growth response. **Methods:** 18 normal and 25 ISS were evaluated before and after 12 months of life time (normal) or 12 months of GH therapy (ISS). Blood was collected to assess serum markers of peripheral TH action and peripheral blood mononuclear cells for TR mRNA determination by QRT-PCR. Growth parameters were also determined. **Results:** Although GH treatment did not modify TR mRNA and serum markers of TH action in ISS as a whole group, the individual growth response to GH correlated positively with the change in TRα mRNA level and negatively with TRβ mRNA, TSH and SHBG. The change in each TR mRNA correlated negatively with their basal levels. **Conclusions:** GH therapy induced individual TR changes that correlated with growth velocity. Basal TR mRNA could predetermine the change in TR expression and therefore GH response.

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Intake and Energy Metabolism Characteristics in a Sample of Overweight and Obese Chilean Adolescents

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Background: The sustained increase of shildhood obesity is a consequence of the failure of preventive and therapeutic strategies. Interventions aimed to obtain a negative energy balance have been based mainly on dietary restriction, without increasing energy expenditure. In this study our objective was to describe the characteristics of intake and energy metabolism in a sample of overweight and obese adolescents. **Methods:** In a sample of 113 overweight and obese Chilean adolescents (13–16 year old, 67 females) we studied anthropometry, body composition (deuterium isotope dilution water), rest metabolic expenditure (indirect calorimetry) and 24 hours diet and physical activity recalls. **Results:** In 24.8% of the sample the intake was excessive (> 110% of FAO/WHO 2005 recommendations); the average adequacy was 94.5%. On the other hand, 83.2% of subjects had unsatisfactory energy expenditure (< 90% of recommendations) with an average of 78.9%. The median physical activity index was 1.29, qualifying the subjects as sedentary. **Conclusion:** In our sample of overweight and obese adolescents there was an important sedentary and low energy expenditure that would explain a sustained caloric retention. Preventive and therapeutic interventions should encourage the increase in energy expenditure.

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The Relationship Between Aerobic Capacity, Physical Activity Level and Glycemic Control of Teenagers with Diabetes Mellitus Type 1: A Cross-sectional Study

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The purpose of this study was to evaluate the relationship between Aerobic Capacity ($VO2_{peak}$), Physical Activity Level (PAL) and Glycemic Control (A1C) of teenagers with Diabetes Mellitus Type 1. The sample was composed of 61 subjects, 34 male subjects (18.88±2.13 years) and 27 female subjects (17.16±2.27 years). The $VO2_{peak}$ was measured by direct analysis of oxygen uptake, the PAL was estimated by the International Physical Activity Questionnaire (IPAQ) and the A1C values were taken by the Turbidimetric Immunoassay method. The $VO2_{peak}$ of the boys and girls were respectively 46.23±7.93 and 31.8±6.98 mL/Kg/min. The A1C values of the boys and girls were respectively 9.35±2.08 and 11.39±3.13 %. The PAL of the boys was significantly higher (p=0.0208) than the girls. There was an association between $VO2_{peak}$ and PAL for the boys (p=0.0077) and for the girls (p=0.0008). There was a negative association (ρ=–0.6544) between $VO2_{peak}$ and A1C only for the girls (p=0.0002). There was no association between PAL and A1C. We concluded that girls showed a lower level of physical activity and aerobic capacity added to a worse glycemic control when compared with boys. The PAL was correlated with $VO2_{peak}$, which alone was correlated with the A1C only for the girls.

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17 OH Progesterone (17OHP) Extraction on Filter Paper: A New Tool in Newborn Screening (NS) for Congenital Adrenal Hyperplasia (CAH)

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The implementation of the NS Program of HSC in Argentina, with a commercial kit of Cuban origin (17OHP UMELISA-SUMA TecnoSUMA), led us to evaluate strategies for reducing the current recall rate. **Objective:** To evaluate a modified methodology aimed to reduce the recall rate, in dried blood samples (DBS) collected on filter paper, for the measurement of 17OHP. **Materials and Methods:** 49 DBS and serum from 37 Normal (Group A) and 12 CAH infants with (Group B) with postnatal diagnosis, obtained after 48 hours of life. DBS samples were evaluated by the commercial TECNOSUMA enzyme immunoassay, directly and after extraction with ether. Sera (directly and after extraction) were measured for 17OHP by RIA-DSL. **Results:**

DBS	17OHP Direct (nM)	17OHP After Extraction (nM))	17OHP Serum (ng/ml) Direct/ After Extraction
Group A (normal) Median (range)	103 (15–229)	18,9 (6–85)	18.9(2.2–48.8)/ 2.1(0.1–7.3)
Group B (CAH) Median (range)	263 (229–271)	229 (148–263)	>20/>20

The results of direct and post-extraction samples were compared: Group A: p<0.0001, Group B: p:ns. (Wilcoxon test). **Conclusion:** The extraction technique significantly decrease the rate of false positives, and would discriminate patients with high suspicion of CAH, and shorten the time for definitive diagnostic confirmation.

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Pubertal Growth and Adult Height in Patients with Classical Congenital Adrenal Hyperplasia

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In patients (p) with CAH and heterogeneous long-term follow up, Adult Height (AH) outcome and reduced total pubertal (Pu) growth has been reported. Thirty CAH p, 20 females (F): salt wasting (SWF),n=15 and simple virilizing (SVF),n=5, and 10 males (M) (SWM, n=5 and SVM,n=5 were retrospectively analyzed . Mean (+/- SD) values, of chronological age (CA), bone age (BA) and Height H(SDS) at Pu onset (PuO) and Total(T),Pu growth and AH were similar in FSW and FSVp (SWF: 9.41+/–1.84y; 10.9+/–1.48y; 0.56+/–1.39SDS; 19.6+/–9.7cm; –1.01+/–1.38SDS and 154.4+/- 8.5cm and SVF: 7.62+/–2.33y; 9.26+/–1.49y; 0.72+/-.1.09SDS; 20.8+/–11.8cm; –1.2+/–0.96 SDS and 153+/–5.9cm, respectively). During Pu similar accumulative Hydrocortisone doses in SWF and SVFp were found (15.3 +/–2.5 and18.2 +/–3.9 mg/m2 body surface respectively) In SWMp CA (10.28+/–1.96y) was significantly higher, p< 0.01, and H(0.71+/–1.24SDS) was significantly lower,p<0.02 than SVMp at PuO (7.84+/–2.6y and 2.95+/–1.27SDS),respectively) In SWM:TPu growth (24.0+/–8.4) and AH(165+/–0.68) were significantly higher p:0.02 and p:0.04 than in SVM (11.25+/–6.56 cm and 160 +/- 4.7cm).

During Pu similar accumulative Hydrocortisone doses were also found. Conclusions AH in p with classical CAH might falls short of genetic potential secondary, among other factors, to lower tPu growth, delayed in the onset of hormonal substitutive therapy and early or precious puberty

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Expression of a New 3′ End Variant of Human P450 Aromatase (ARO) Transcript (Intron 9, IN9) in the Term Human Placente (Pl)

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In human placenta, Aro is expressed exclusively in syncytiotrophoblast. Alternative splicing of the coding region of Aro was previously described in other species but not in humans. Alternative splicing events could be involved in the control of Aro expression. The aim of our study was to evaluate the expression of the IN9 variant in Pl. Total RNA was isolated from 17 Pl tissues from 6 males (m) and 11 females (f) newborn deliveries. Aro mRNA variant expression was analyzed by Real-time RT-PCR. Aro protein was analyzed by Western blot. We found expression of the IN9 variant in Pl. IN9 mRNA related to total Aro mRNA (CYP19) or active Aro mRNA (Arom) in m was significantly higher than in f (IN9/CYP19: 7.74±5.04 and IN9/Arom: 10.82±7.33 AU, mean±SD, n=6) (IN9/CYP19: 1.77±1.53 and IN9/Arom: 2.10±2.36 AU, mean±SD, n=11), p=0.006. We are describing for the first time a new Aro mRNA variant in Pl that has a gender-specific expression. As the IN9 variant is a truncated Aro mRNA translating a non active protein, we propose that the expression of this variant would be involved in the regulation of Aro activity in human term placenta.

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Ovotesticular Disorder of Sex Development with Unusual Karyotype: Case Report

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Ovotesticular disorder of sex development (OT-DDS) (true hermaphroditism) is an anatomopathological diagnosis based on the findings of testicular and ovarian tissues (seminiferous tubules and follicles or *corpora albicans*) in the same subject, in the same gonad (ovotestis) or in separate gonads. OT-DDS is a rare cause of sex ambiguity (2–10%). A 46,XX karyotype is found in 60% of cases, 46,XY in 10–20% and mosaics and chimeras in 10–20%. We report the case of a 2-month-old child with male sex assignment referred to us to investigate sex ambiguity. He was the second child of healthy unrelated parents; pregnancy and labor were uneventful. On physical examination, he had a 2.3cm-phallus, perineal hypospadia (Prader grade III), the right gonad was in the scrotal fold and the left was found in the inguinal channel. Karyotype was 46,XX/47,XXY/48,XXYY (30 metaphases). Anatomopathological examination of gonads revealed right testis and left ovotestis. The male sex assignment was maintained; the child underwent left gonadectomy, removal of müllerian structures and urethroplasty. A thorough revision of literature revealed a single case of OT-DDS with the same chromosome constitution (Sano *et al.*, 1993). In all cases of sex chromosome mosaicism gonadal biopsy is necessary to establish the diagnosis.

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Analysis of the *LIN28B* Gene in Patients with Gonadotropin-Dependent Precocious Puberty (GDPP)

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Introduction: Etiopathogenesis of GDPP is unknown in most patients. LIN28B gene regulates microRNAs processing and temporal development in *C. elegans*. Wide genome association studies correlated age of menarche and menopause with SNPs in the *LIN28B* gene. **Objective:** Investigate the presence of LIN28B mutations in GDPP patients. **Patients and Methods:** 102 GDPP patients were evaluated (12% familial). Female patients (n=97) started puberty at 5.9±2 years (0.1–7.9) and male (n=5) at 8±1 years (7–8.9). GDPP was confirmed by advanced bone age, basal or stimulated LH and normal SNC MRI. Subjects with normal development (n=101) were analyzed as controls. The entire coding region (4 exons) and proximal promoter region of the *LIN28B* gene were automated sequenced. **Results and Conclusion:** No mutations in the LIN28B gene coding and boundary regions were found, suggesting that mutations in this gene are not common in GDPP. However, a novel variant (heterozygous c.-11C>T) was identified in the 5' untranslated region of this gene in 2 patients with GDPP and in 1 healthy control, suggesting it being a rare SNP. As the regulatory region of the *LIN28B* has not yet been characterized, the involvement of this rare variant in the expression of this gene cannot be ruled out.

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Influence of Hyperandrogenism on Cardiometabolic Risk Factors in Mexican Adolescents

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Background: Hyperandrogenism has been proposed as an independent risk factor for cardiometabolic abnormalities. **Aim:** To compare how several cardiometabolic risk factor components behave in Mexican adolescents with different hyperandrogenic states. **Methods:** We analyzed girls with hyperandrogenism. We classified them as hyperandrogenic (HA, n=9) if history of precocious pubarche or hirsutism hyperandrogenism and no evidence of Polycystic Ovarian Syndrome (PCOS), patients with PCOS (n=13) and patients with congenital adrenal hyperplasia (CAH n=10). Anthropometric and laboratory data (fasting insulin, OGTT, lipid profile, androgens, SHBG, LH, FSH and 17 OHP4) were analyzed. Muscle biopsies were performed in patients and healthy controls and glucose uptake analyzed. **Results:** Factor 1 included Testosterone, androstenodione, DHEA-S and 17OHP4. Factor 2 included 17OHP4 and LH/FSH; and F3 was cortisol and SHBG. We made ANOVA and performed orthogonal contrast for diagnosis. PCOS were older (15.7+–2 vs 12.7+–2.5 $p<0.03$).HDL-C was significantly different (35+–6 vs 42.3+–10 vs 56+–19, for CAH, HA and PCOS respectively, $p<0.03$). LH/FSH ratio and 17OHP4 were linearly combined (Factor 2) and showed opposite direction: as the factor score increased, the LH/FSH ratio increased (SOP > HA > CSH, $p>0.05$). No differences but trends were found for other metabolic variables. Glucose uptake was variably blunted in all hyperandrogenic groups compared to controls ($p<0.05$). **Conclusions:** Hyperandrogenism was associated to cardiometabolic abnormalities that were diagnosis independent.

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IGF-I ICMA and RIA Assays: Methodological Aspects and Its Implications in the Diagnosis of Disorders of the GH-IGF-I Axis in Short-Statured (SS) Children

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The diagnosis of GH-IGF-I axis disorders is partially dependent on accurate measurements of IGF-I. **Objectives:** To evaluate: 1-Analytical performance (ISO-15189) of ICMA-IGF-I, 2-The prevalence of low IGF-I levels in SS by ICMA compared to an in-house extractive RIA. IGF-I concentration was measured in 193 normal children, 17 GHD and 76 idiopathic-SS, 5.0–17.5yr by ICMA (IMMULITE2000, Siemens) and RIA. Log-transformed IGF-I results were compared using Passing-Bablok analysis. IGF-I<–2.0SDS were considered low for both methods. **Results:** ICMA analytical performance was acceptable: linearity ($r=0.986$), total CVs(<5.4%), bias (<8.7%), total error (19.4%) and sigma(>3.0). ICMA results were positively biased compared to RIA ($y=1.567x–41$, $r=0.92$) and showed higher divergences at puberty. In normal children, ICMA-IGF-I increased with age and puberty without sexual dimorphism. Low IGF-I values were observed in 12 versus 10/17GHD and in 25 versus 11/76 ISS by RIA and ICMA respectively, being the between-method agreement 83%(GHD) and 44%(ISS). Patients with discordant ICMA- and RIA-IGF-I results (n=16, 2/12GHD and 14/25 ISS), showed higher IGFBP3-SDS($p=0.005$) and ALS-SDS($p=0.007$) than those with low IGF-I results by both assays. In conclusion, some interference of IGFs binding proteins may not be completely nullified in ICMA and could explain its lower diagnostic accuracy at low IGF-I levels in short-statured children.

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Pure Gonadal Dysgenesis in Clinical Practice: the 46,XY Karyotype Accounts for More Than One Third of Cases

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Pure gonadal dysgenesis (PGD) is characterized by internal and external female genitalia and streak gonads, with hypergonadotropic hypogonadism that manifests in adolescence with delayed puberty and primary amenorrhea, and a normal karyotype (46,XX or 46,XY). XY PGD is usually studied in the context of disorders of testicular differentiation and XX in the context of premature ovarian failure, but in clinical practice both have the same phenotype and treatment, which consists of hormone replacement and assisted fertilization. In XY PGD prophylactic gonadectomy is also needed due to the high risk of neoplasia; however, the proportion of cases with this chromosomal constitution is unknown. This work was carried out to analyze the proportion of XX and XY karyotypes among PGD patients and the frequency of *SRY* mutations and gonadal tumors in XY cases. We analyzed data from 32 patients with PGD diagnosed in our service since 1989, 30 of them without a previous karyotype. More than 1/3 (11/30) were 46,XY, indicating that the karyotype is essential to evaluate women with dysgenetic gonads; 7/9 had *SRY* gene mutations, a frequency higher than found on the literature, and 4/9 had a tumor, emphasizing the need for gonadectomy. (Support by PIBIC-CNPq)

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Long Term Glucocorticoid Exposition Does Not Play the Major Role in the Development of Obesity and Metabolic Syndrome in Classical Form of 21-Hydroxylase Deficiency

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Treatment of 21-hydroxylase deficiency (21OHD) is based on glucocorticoid (GC) replacement; however, it contributes for obesity and/or metabolic syndrome (MS) development and their incidence in 21OHD is unknown. The little data available used mixed cohorts and different GC regimes. **Objective:** to evaluate obesity/MS incidence in 21OHD-patients on homogeneous GC therapy. **Patients and Methods:** 42 patients at a mean age of 11.4 ± 3.9 yrs received cortisone acetate (CA) (18–20 mg/m²/day) followed by dexamethasone (DEX) 0.25 mg/day after final height achievement. GC doses aimed to obtain normal androgen levels. Cumulative GC doses were expressed in cortisol equivalents. SW-patients received 50 µg/day fludrocortisone. Analysis of MS parameters (NCEP-ATPIII criteria), obesity/MS familial history and cumulative GC doses were evaluated by Chi-square and *t*-test. **Results:** Obesity and MS were observed in 26.2% and 12% of patients, respectively, lower than in our population. Obese patients had lower HDLc levels and higher HOMA-IR. Obesity and/or MS were not associated with clinical forms, treatment duration and cumulative GC doses. Additionally, obesity/MS familial history was identified in 60% of obese patients. **Conclusions:** in 21OHD-patients, CA treatment based on the normal androgen level achievement, familial predisposition plays a major role in obesity/MS development rather than the cumulative GC doses.

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Measurements of PTH by Chemiluminescence Immunoassay Intra or Postoperative Predict Hypocalcemia Postthyroidectomy in Children

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Objective: To evaluate the effectiveness of intra and postoperative PTH determination to predict postoperative hypocalcemia in thyroidectomized patients. **Methods:** 20 patients undergoing total thyroidectomy were prospectively and longitudinally studied. PTH (ICMA, CVs <5.4%, functional sensitivity=8pg/mL) was measured pre, intra and post surgery (baseline, 5 and 60 minutes after glandular extraction). Signs or symptoms of hypocalcemia and total calcium (TCa) or ionized calcium (iCa) were monitored regularly for 48 hours postoperative. Hypocalcemia was defined as TCa <8 mg/dL and/or iCa <0.8 nmol/L. ROC curves were used to identify the PTH level that provided the best prediction of postoperative hypocalcemia according to their sensitivity (S), specificity (Sp) diagnostic efficiency (DEf) and positive predicted value (PPV). **Results:**10/20 patients developed hypocalcemia, 40% in the first 6 hours, 40% at 24 hours and 20% at 48 hours post surgery. In 3/10 it was symptomatic. Intraoperative PTH<14 pg/mL predicted hypocalcemia with S: 80%, Sp:100%, DEf: 90%(95%CI, 72–100) and PPV:100%, while postoperative PTH<14 pg/mL showed S: 80%, Sp:90%, DEf: 82%(95%CI, 63–100) and PPV:80%. Relative Risk of developing hypocalcemia after thyroidectomy was 9 when PTH intra/postoperative <14 pg/mL. **Conclusion:** Intra and postoperative PTH accurately predicts postoperative hypocalcemia, identifying those thyroidectomized patients at risk and allowing immediate prophylactic treatment.

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Mean Age at Diagnosis of Type 1 Diabetes Mellitus Throughout the Last Thirty Years in Brasilia–DF, Brazil

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Introduction/Objective: Several epidemiological studies have shown a continuous reduction in the age of type 1 diabetes mellitus (*T1DM)* manifestation throughout the last decades. The aim of this study was to recognize and compare the mean ages at diagnosis (*mADx*) of *T1DM* throughout the last thirty years in Brasília-DF. **Methods:** Retrospective muticenter study of the records of 500 patients with *T1DM* followed at Hospitals and Medical Units in Brasilia. **Results:** Currently, the mean age of the patients (50.6% females) is 15.4±8.2 years (1.1–53.8 years). The whole group *mADx* was 8.7±5.9 years (0.33–40 years); no statistical difference between sexes (p=0.386). After grouping the patients in decades in which *T1DM* was diagnosed, *mADx* and the proportions of patients who became diabetic younger than 5 years of age and between 5–10 years, were, respectively: decade of 1981–1990 (n=22)- 9.7±8.7 years, 50.0%, 18.2%; 1991–2000 (n=104)- 7.7±5.8 years, 41.3%, 29.8%; 2001–2010 (n=374)- 8.9±5.7 years, 27.8%, 34.2%. No statistical differences were found in *mADx*, not even after grouping patients by sex. **Conclusions:** Throughout the last 3 decades *mADx* of *T1DM* among patients in Brasilia presented no statistically significant change, independently of sex, and the proportion of children under 5 years of age becoming diabetic has been decreasing.

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Down Syndrome and Disorders of Sex Development – Only Coincidence or More?

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Introduction: Down syndrome (DS) is a common condition and its association with DSD is quite rare. We report 5 DS patients with DSD. Patient 1 – 22 days old, undefined sex. 2.5cm phallus, non-palpable gonads, and perineal urethra. Testosterone (T)=332ng/dL (at 1 mo), uterus on ultrasound, 47,XY +21 Karyotype. A gonadoblastoma on the left gonad and a streak on the right. Dx - DSD Mixed Gonadal Dysgenesis. Patient 2 – 7.1 year old, male. 3cm phallus, non-palpable gonads, proximal hypospadia. No response of T under hCG. 46,XY+t(21q 21q) karyotype. Dx – DSD dysgenetic. Patient 3 – 1.1 year old, male. 47,XX + 21 karyotype. T=250.5ng/dL under hCG, no müllerian remnants, SRY +. Histology – bilateral testes . Dx- DSD testicular. Patient 4 – 5.1 year old, male. 1cm phallus, palpable gonads, topic urethra. No T response to hCG. 47,XY qh +21 Karyotype. Dx- DSD dysgenetic. Patient 5 – 1.7 year old, male, 2,5cm phallus, palpable left gonad, topic urethra. T= 125 ng/dL under hCG. Karyotype: 47,XY+21. Biopsy: pré-pubertal testis with intraluminal calcifications. Dx: DSD dysgenetic. **Conclusion:** Although uncommon, DS patients may present DSD and it is important not to miss these cases, since it will change the future approach with regard of rearing sex.

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Secretory Profile of 6 Sulfatoxymelatonin (6-SM) in Normal and Obese Pubertal Males and in Growth Hormone Deficient Children With and Without GH Replacement Therapy

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The relationship between melatonin and endocrine-metabolic alterations such as obesity, is contradictory. In addition, melatonin variations in GHD remain unclear. We studied 32 children: non-treated GHD, n:5 CA:11–14 (GHDnt), treated GHD, n:7 CA:10.5–15.7 (GHDtx), normal weight controls, n:10 CA:10–15.7 (C), and obese, n:10 CA:10–14.9 (Ob). Urinary 6-SM was measured (radioimmunoassay, Stockgrand Ltd, Guildford, UK) in diurnal (8AM to 6PM) and nocturnal (6PM to 8AM) samples.

Results (Mean ± SEM):

	GHDnt	GHDtx	C	Ob
6-SM nocturnal (ug/ per time interval)	0.37 (±0.14)	1.42 (±0.57)	1.88 (±0.57)	8.36 (±1.57)*
Delta (nocturnal–diurnal)	0.16 (±0.26)**	6.13 (±2.56)***	5.52 (±2.75)	9.09 (±2.41)

*p<0.05 vs. GHDnt, GHtx and C (Kruskall-Wallis,Dunn test)
**p<0.05 vs. GHDtx, C and Ob (Kruskall-Wallis,Dunn test)
***p<0.05 vs. GHDnt (Mann Whitney)

Conclusion: Obesity demonstrated to modify 6-SM to a larger extent. The nocturnal-diurnal amplitude showed higher values in GHDtx than in GHDnt, which would indirectly indicate an absence of pulsatility in the latter. This difference in amplitude between GHDnt and GHDtx and the similarity between the latter and controls appear to support the idea that GH therapy would contribute to normalize melatonin secretion.

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Two Novel Mutations of the TSH-β Subunit Gene Underlying Congenital Central Hypothyroidism (CCH) Undetectable in Neonatal TSH Screening

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Patients with TSH-β subunit defects and CCH are missed by TSH-based neonatal screening. **Aim:** To report the molecular consequences of two novel mutations in the TSH-β subunit gene found in two patients (P) with CCH and anemia. P1 had a homozygous G to A nucleotide change at the 5′ donor splice site of exon/intron2 resulting in a silent change at codon 34 of the mature protein. Splicing assays showed the mutant minigene resulted in complete exon2 skipping. The putative product from a new out-of-frame ATG in exon3 is expected to yield a nonsense 25-aminoacid peptide. P2 is compound heterozygous for the reported C105Vfs114X mutation and for a novel mutation in exon3, substituting G for A at cDNA position 323, resulting in a C88Y change. This cysteine residue is conserved among all dimeric glycoprotein hormone β-subunits. PolyPhen and SIFT analysis predicted C88Y to be a damaging substitution, confirming that it would affect subunit conformation. **Conclusions:** Novel splice-junction, c162G>A, and missense, C88Y, TSH-β mutations caused CCH not detected by TSH-based neonatal screening. The molecular diagnosis of TSH deficiency is mandatory for diagnosis, prognosis, and genetic counseling. Diagnosis of CCH should be considered in the face of severe infant anemia of uncertain etiology.

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Cardiovascular Risk Factors in Overweight Children with Family History (FH) for Non Transmissible Chronic Diseases

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Background: In Chile, the metabolic syndrome (MetS) affects 25% of children with overweight and fasting hyperglycemia (FH) was the least prevalent (4%) cardiovascular risk factor (CVRF). **Objective:** To study the prevalence of MetS and CVRF in overweight children with a family background of non transmissible chronic diseases (NTCD) and analyze its association with the number of relatives with NTCD. Material and Methods. In 185 children aged 7 to 14 years (87 males) with BMI ≥ 85 and a FH of chronic diseases, we assessed the magnitude of the overweight through BMI z (CDC / NCHS), waist perimeter, blood pressure and baseline levels of HDL cholesterol, triglycerides, glucose and insulin. The MetS and the CVRF were diagnosed using the Cook phenotype and the insulin resistance (IR) through the HOMA-IR (≥ 2.1 and ≥ 3.3 in prepuberal and puberal children respectively). Chi^2 was used to look associations, ANOVA and Bonferroni to compare means. **Results:** The frequency of FH of DM2, hypertension and dyslipidemia were 80.5%, 87.0%, and 70.8% respectively. The 11.9% of children were slightly overweight (BMI z between 1.0 and 2.0) and only 19.5% were severely obese (BMI z ≥ 4.0); 41.4% children showed IR and 48.0% had the MetS. Abdominal obesity and hypertriglyceridemia were the most prevalent CVRF (90.8% and 54.6% respectively), while fasting hyperglycemia affected 31.4% of the sample. There was no association between the number of relatives with NTCD and the cardiovascular risk profile. **Conclusion:** In overweight children with FH of chronic diseases, the prevalence of MetS, dyslipidemia and fasting hyperglycemia are significantly higher, than those observed in the general population of obese children. The importance of FH in the targeting of children with higher biological risk is discussed.

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Transient Neonatal Diabetes Mellitus and Later Onset Hyperinsulinism Due to Uniparental Disomy of Chromosome 6q

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Neonatal diabetes mellitus is defined as severe hyperglycemia requiring insulin, beginning during the first six months of life and lasting at least one month. We report a 1 yr old boy, born at term with a BW: 2100 grs. (SGA), length: 42.5 cm, and dimorphic features (dolicochephaly, macroglosia, triangular facies). At 48 hours of life during IV glucose infusion he shows a glycemia 381mg/dl, normalized reducing the glucose load. After the sixth day of life due to persistent hyperglycemia inspite of no glucose infusion, no weight gain (without ketoacidosis) insulin infusion is started. Insulin requirements reaches doses up to 0.68U/Kg/day and near the second month of life he maintains more stable blood glucose levels with reduced insulin requirements which finally is suspended. Later he presents hypoglycemia and a fasting test shows hyperinsulinism, starting diaxoside which is requested for 2 weeks. Currently he is being fed with 3 milk bottles plus 2 meals, has fasting periods of 8 hrs. Weight at 75th, height 25th percentile, and has stable blood glucose without treatment. The molecular study showed uniparental disomy (UPD) (Peninsula Med School, UK) which extends across the full length of chromosome 6. The mechanism of this biphasic behavior of insulin secretion is under current study.

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Evaluation of the Use of Detemir X NPH Insulin on Glycemic Control and Change in BMI in Brazilian Children with Type 1 Diabetes

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Aim: To compare long-acting analogue insulin detemir with NPH associated with rapid acting insulin in multiple daily injections with respect to glycemic control and BMI changes after 1 year of treatment. **Methods and Subjects:** Files of 30 children type 1diabetes,12 males, ages 4.3 – 17.2 years (mean 10.3±3.2) that switched to detemir between 2007–2009 were reviewed for glycated hemoglobin (HbA1c), BMI and adverse effects. Data were compared between 12 months NPH injections that preceded detemir and one year after. Indications for transition were uncontrolled hypoglycemia (n=7), lability (n=17), antiinsulin antibodies (n=9) and lipodystrophy (n=2). **Results:** Duration of diabetes before transition was 4.7± 2.2 years. Mean HbA1c was 8.2±1.5 vs 8.6±1.6 and mean BMI z score 0.7±0.7 vs 0.4±0.7 were not different one year before and after detemir, but 17/30 patients reduced their BMI z score and 3 became obese. After transition there was one episode of severe hypoglycemia and one of diabetic ketoacidosis. No one returned previous scheme. **Conclusion:** Use of detemir analogue in children did not show significant effects on glycemic control and BMI. Although our population was not obese, some children were able to decrease BMI. There was indirect perception of improvement of patients based on indications for transition.

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The Pluripotential Cell Marker, OCT 3/4, Is Only Expressed in Some Sub-types of Human Dysgenetic Testes (HDT), and in Prepubertal Androgen Insensitivity Syndrome (CAIS)

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OCT-3/4 is detected in CIS germ cells (GC). OCT 3/4, C-KIT (SCFreceptor) and MAGE-A4 (mature spermatogonia marker) immunoexpression in HDT and in CAIS gonads during prepuberty (PP) and puberty (PU) was analyzed: 1 PU and 2 PP 46,XY HDT patients (p) with *SF-1* gene mutation (Gr1); 1 46,XY PPp without mutations (Gr2); 2 46,XX ovotesticular dysgenesis (Gr3); 2 mixed gonadal dysgenesis (Gr4); 2 CAIS PPp (Gr5) and tissues from PP and PU (n=23) control testes (CGr) were analyzed. Strong OCT 3/4 signal (range 18–67%) in all gonads from Grs 2, 3, 4 and 5 but not Gr1 or CGr was found. C-kit was absent in most pGrs while it was present in CGr. MAGE A4, was only present in CGr, in Gr2 and in one patient from Gr4. No AR or ERa expression was detected in any sample. In contrast to a high expression of ERb and ARO in CGs, no positive signal was found in pGrs. Genomic SF1 gene mutations might protect from CIS. The expression of OCT 3/4 in PP CAIS GC suggests that there is a risk in postponing gonadectomy to PU age. Local GC estrogens might be involved in preservation of GC pool in human testis.

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Peripheral Precocious Puberty (PPP) in Two Girls Treated with Mitotane for Adrenocortical Carcinoma (ACC)

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Objective: to describe two patients who developed PPP on the course of mitotane. Case 1: 7.7 y old girl, with stage IV ACC and virilization at age 4.9, was operated on and put on adjuvant treatment with mitotane, cysplatin, etoposide and doxorubicin. Six months later, started telarche and had menarche at age 6.7 (Tanner, B4). Laboratory work-up ruled out central precocious puberty (peak LH on GnRH 2.3 mIU/mL); estradiol < 10 pg/mL; uterus volume (26 cc); bone age: 10 y (G&P). Case 2: 8.9 y old girl with stage IV ACC and virilization at age 6.0 y. At age 7 radical adrenalectomy, followed by adjuvant treatment with mitotane, cysplatin, etoposide and doxorubicin. At age 7.8 y started telarche and had menarche at age 8.0 y (Tanner B 3). Laboratory work-up showed: FSH 0.05 and LH: <0.07 (mIU/mL); pelvic ultrasound: uterus with 15.9 cc and presence of a cystic image on right ovary (5.0X4.4 cm); bone age (G&P): 8 y. Comments: PPP has not been reported in girls treated with mitotane. Possibly, mitotane and/or its metabolites could act as endocrine disruptor and induce PPP as mitotane has weak estrogen receptor agonistic action and could have direct effect on steroidogenic enzymes.

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DSD Testicular (XX male) with 45, X Mosaicism – The Only Case in the Literature

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Introduction: DSD Testicular is an entity where individuals have karyotype 46, XX with male genitalia and development of testes. The incidence is 1:20000 live births and among the cases 10–20% have genital ambiguity. We will describe a case of DSD testicular followed in endocrinology unit of Instituto da Criança -HC-FMUSP without genital ambiguity, with Turner´s syndrome mosaicism. Case report: ALM, 10 months of life, created as male, referred for investigation of abnormalities of sexual differentiation. Physical exam: almond eyes, round face, low set ears, weight = 7325g (z = –2.74) length = 68 cm (z = –2.16); phallus 3 cm , topical urethra, palpable gonads. Testosterone after hCG stimulation = 422 ng / dl, karyotype 46, XX / 45, X with SRY +, Ultrassound: prostate and seminal vesicles were normal, without Müllerian remnants. Biopsy: left and right gonads: pre-pubertal testicular parenchyma. **Conclusion:** DSD Testicular is an uncommon diagnosis among the DSD and so far we know, there is no description concerning the association of DDS testicular with Turner mosaicism.

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Smell Abnormalities and Pubertal Development in Hypogonadotropic Hypogonadism (HH) Patients

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HH is a congenital disorder of GnRH involving alterations in sexual maturation, has an incomplete penetrance with variable phenotypes. Our aim was to evaluate the pubertal development of patients with HH and the correlation with familial characteristics and smell abnormalities. **Methods:** 41 women (WH) and 27 men (MH) under treatment for HH. A complete interview and a smell test were performed. **Results:** Family history of delayed puberty was present in 65,9% of WH and 62,9% of MH. Fathers or brothers "late bloomers" were more frequent in MH (40,7% vs. 14,6%,p<0,015). Mothers or sisters with late menarche were more frequent in WH (51,2% vs. 23,1%,p<0,022). Menarche in WH with spontaneous menarche was earlier than in those of the induced group (14,3±1,9yrs vs. 18,9±4,4yrs,p<0,0001). Spontaneous gonadarche occurred in 6/27 MH at 15,0±2,7yrs, with 13 patients with prepubertal testis at the evaluation (~19.9yr). Anosmia was present in 56,5% of MH and 15,2% of WH (p<0,03), and in those patients, had a tendency towards an absence of puberty in MH and a late induced menarche in WH. **Conclusions:** A history of delayed puberty in the parents may induce an early suspicion of HH. The smell abnormalities appear to correlate with a more severe HH.

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Increased IGFBP-3 Secretion by Fibroblast Cultures of Children with Idiopathic Short Stature (ISS)

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Background: The IGF binding proteins play a key role in IGF action, by modulating the interaction of these growth factors with target tissues. **Objective:** To quantify the concentration of IGFBP-3 in culture medium of fibroblasts obtained from children with ISS and from control children. **Methods:** We studied 30 prepubertal children between 5–10 years of age. Thirteen patients had short stature, and possible evidence of partial GH insensitivity, based upon a stimulated GH level > 20ng/mL and a serum IGF-I level <1SDS for age. They were compared to children with normal stature (n=17). Protein concentrations of IGFBP-3 were measured in the fibroblast culture medium by ELISA, both basally and 48h after stimulation with GH (200ng/mL). **Results:** Both basal (51.6±14.3* vs 6.3±1.5, *p<0.001) and stimulated (106.4±29.5* vs 18.2 ±4.4; *p<0.001) IGFBP-3 protein concentrations were significantly increased in ISS children compared to controls. **Conclusion:** These results suggest that some children with ISS and possible GH insensitivity show evidence of increased IGFBP-3 protein concentrations in fibroblast culture medium. We postulate that the increased tisular concentrations of IGFBP-3 may hamper the interaction of IGF-I with target tissues in some children with ISS. (FONDECYT 1095118)

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Growth Hormone (GH) Peak After Common Pharmacological Stimulation Tests in Children

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Introduction: There's great variability about the times of blood samples for measurement stimulated GH. **Objective:** to determine the GH peak and the important times for measurement GH after three pharmacological stimuli. **Methods:** We studied 168 children(122 male), mean age 9,9 yrs(2–16), subjected to 3 different GH stimuli: clonidine (72), insulin (48), glucagon (48). We analyzed the following times after stimulus: 15, 30, 45, 60, 90, 120 min for clonidine and insulin; 30, 60, 90, 120, 150, 180 min for glucagon. GH >5,0 ng/mL (Siemens/Immulite-Chemiluminescent assay) was considered as

normal response. **Results:** 57(79%) patients had GH peak at 60 or 90 min after clonidine. Three patients had GH peak before stimulus (0 min). GH peak occurred at other times on 11(15%) patients, but they had GH>5, 0 ng/mL at 60 or 90 min. After insulin, GH peak was most observed (73%) at times 45, 60, 90 min. Two patients had peak at 120 min, both didn't reach 5,0 ng/mL at anytime. After glucagon, GH peak occurred at 90 min or after in all patients; only one had a different diagnosis when 90 min was excluded from analysis. **Conclusions:** GH measured at 60 and 90 min after clonidine was enough for GHD diagnosis. After insulin, GH measured at 120 min wasn't necessary. After glucagon, it was important to measurement GH only at 120,150 and 180 min.

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Bariatric Surgery in Obese Adolescents

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Objective: Describe our experience with twenty obese adolescents submitted to Bariatric Surgery. **Material and Methods:** All patients were submitted to 'Gastric Bipartition' technique between July 2003 and April 2010. Anthropometric and biochemical measures were analyzed initially, after six months and annually for three years of follow-up. **Results:** Initial mean BMI was 48 Kg/m^2 and percentage of weight loss was 33% (47,4Kg) in six months and 37% (48,4Kg) after one year. Initial co-morbidities were distributed as: 45% systemic hypertension; 80% insulin resistance; 55% dyslipidemia; 35% steatohepatosis; and 29% left ventricular hypertrophy. Only one patient developed significant surgical complication – peritonitis without suture dehiscence – and mortality was zero. There was no dumping, malabsorption or reflux and one patient had polyneuropathy, which subsided . During follow-up, 8 patients had cholecystopathy and 4 of them underwent uncomplicated laparoscopic cholecystectomy. Six months after surgery there was evidence of improvement in blood pressure and remission of insulin resistance and dyslipidemia in all but one patient, who took one year to achieve those goals. Every patient presented higher quality of life score. **Conclusions:** Extremely obese adolescents experienced evident and sustained weight loss and significant improvements of all co-morbidities after bariatric surgery with acceptable risk.

Posters

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Impact of Maternal Thyroid Disorders and/ Or the Consequences of Its Treatment on Newborns of the Newborn Screening Program of the State of Minas Gerais – Brazil (PETN-MG)

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Introduction: The normal maternal and fetal thyroid functioning is essential to ensure the child's adequate neuropsychomotor development. **Objective:** To evaluate the thyroid function in children born to mothers with thyroid abnormalities. **Methods:** Thirty five children with abnormal screening test for congenital hypothyroidism (CH) carried out in PETN-MG between 1993 and 2009 and one with normal neonatal TSH born to mothers with autoimmune thyroid disease or who were inadvertently submitted to radioiodine therapy, were studied. **Results:** Out of 33 children with positive anti-thyroid antibodies (ATPO and/or TRAB). 72.7% presented CH (median TSH: 234.8µUI/mL, FreeT4: 0.39ng/dL), 21.2% transient hyperthyrotropinemia (median TSH:13,1µUI/mL, FreeT4: 1,17ng/dL) and two (6.1%) neonatal Graves disease, one of whom had a transient central hypothyroidism. Of the three children exposed to ^{131}I, two had permanent CH due to thyroid destruction (TSH:>100 and 657,9µUI/mL; FreeT4: 0,33 and 0,10ng/dL respectively) and one, who was exposed to ^{131}I in the seventh week of pregnancy had no changes in thyroid function (TSH: 1,18 µUI/mL; T4 livre: 1,25ng/dL). **Conclusion:** Maternal thyroid disorders during pregnancy should be properly diagnosed and treated. The investigation of their effects on the offspring is essential to establish the diagnosis and deal adequately with patients who presented thyroid dysfunction.

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Spontaneous Ovarian Hyperstimulation Syndrome Due to Extraovarian Pathologies

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To describe 3 adolescents with bilateral multicystic ovarian masses. 1-A 13 years old girl with abdominal distention and secondary amenorrhea. Referred for an oophorectomy. Ultrasound (US) showed enlarged multicystic ovaries (15x9 and 15x15cm). Biochemical assays: negative

serum βsubunit chorionic gonadotrophin(βHCG), Estradiol 8643pg/ml, LH<0.05IU/l, FSH:25.7IU/l, prolactin 66ng/ml. MRI revealed pituitary adenoma. Transsphenoidal surgery confirmed FSH secreting adenoma. Spontaneous ovarian hyperstimulation syndrome (SOHS) remitted after tumor resection. 2-A 13 year old girl admitted after complete mola hydatiform evacuation suffering from progressive abdominal girth. βHCG: 171000IU/l. US: bilateral multicystic enlarged ovaries (18x10 and 18x10cm). Miometrial infiltration. Estradiol 3800pg/ml, LH< 0.1UI/l, FSH<0.1UI/l and βHCG 31000UI/l. Lung metastases. SOHS due to trophoblastic gestational neoplasia.Treated with chemotherapy. 3-A 15 year old girl admitted after surgical acute abdomen due to multicystic bilateral ovarian masses. Giant cysts relapsed after resection. She had clinical signs of hypothyroidism and galactorrhea. TSH>100μU/ml, T4<1.0μg/dl, LH<0.05UI/l, FSH:8.1UI/l. SOHS remitted after treatment with thyroid hormone. Follicular recruitment occurs through stimulation of FSH receptor either by hypersecretion of FSH itself or by promiscuous activation of βHCG or TSH. Massive luteinization of enlarged stimulated ovaries leads to the development of SOHS. Giant multicystic ovaries must alert about SOHS that improves after treatment of its etiological cause.

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R337H p53 Mutation and the Expression of microRNAs in Adrenocortical Tumor

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There are few data on microRNAs (miR) in the molecular pathogenesis of adrenocortical tumor (ACT). We studied 26 ACT (8M/18F; 28.5±37months; 13 tumors at stage I, 2/II, 6/III and 5/IV; 16 Cushing's syndrome (CS)/virilization, 9 virilization and 1 CS) and 6 normal adrenals. Relative quantification of miR expression was calculated by real time PCR, using the $2^{-\Delta\Delta}$Ct method. R337H p53 mutation was observed in 22/26 ACTs. No different expression of miR-16, miR-16.1, miR-143 and miR-145 and hyperexpression of let-7a (5.4 fold; p =0.006) and miR-449 (5.5 fold; p=0.03) were found in ACTs. Higher miR-449 expression was associated with R337H mutation (3.8 fold; p=0.01) and with ACTs stage III/IV (5.9 fold; p=0.02). let-7a and miR-145 were hyperexpressed (1.6 fold; p=0.03 and 2.1 fold; p=0.02, respectively) in ACTs producing CS/virilization. There was no association of miR expression and age or tumor size. Patients who died presented ACT with lower expression of miR-16.1 (5.7 fold; p=0.02).The underexpression of the tumor suppressive miR-16.1 in ACT with poor prognosis indicates its putative role in ACT pathogenesis. miR-449 hyperexpression in ACT with R337H p53 mutation confirm the hypothesis that transcription-independent modulation of miR biogenesis is intrinsically embedded in a tumor suppressive program governed by p53.

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Ovarian Function in Adolescents with McCune-Albright Syndrome

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Objective: To evaluate ovarian function in adolescents with McCune-Albright syndrome (MAS) and a history of peripheral precocious puberty. **Methods:** We studied 8 adolescents with MAS and 15 healthy adolescents matched by age, Tanner stage and BMI. We determined basal gonadotropins, sex steroids, sex hormone binding globulin (SHBG), antimullerian hormone (AMH), glucose and insulin. In addition, a Leuprolide acetate test (500 ug sc) was performed to measure LH and FSH (at 0 and 3 hours) and 17B-estradiol, testosterone and 17-OH-progesterone (at 0 and 24 hours). Salivary progesterone levels were used to assess ovulation (>0.06 ng/ml) during the 13th, 18th, 23rd and 28th days of each menstrual cycle for three to five cycles, and one pelvic ultrasound was performed during the follicular phase. **Results:** After Leuprolide acetate stimulation, the increment in gonadotropin levels was significantly greater in MAS patients. We observed ovulatory cycles in the 52,6% of control girls compared to 35,7% of MAS patients (p<0.05). We identified 3 adolescents with MAS with characteristics of Polycystic Ovary Syndrome. **Conclusion:** The adolescents with MAS have a lower ovulatory rate compared to control girls, and that some of these patients show evidence of hyperandrogenism, suggesting that their ovarian function may be impaired during adolescence.

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Novel 9-bp Deletion in CYP21A2 Gene Identified in Two Siblings with 21-Hydroxylase Deficiency

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Mutations in *CYP21A2* gene cause steroid 21-hydroxylase deficiency, an inherited disorder of adrenal steroidogenesis. Impaired

enzymatic activity leads to the accumulation of metabolic intermediates, progesterone and 17-hydroxyprogesterone. We describe two siblings in a family of non-consanguineous parents with 21-hydroxylase deficiency. A girl born with ambiguous genitalia, complete labioscrotal fusion and non-palpable gonads presented the following serum levels: ACTH 1234 pg/mL (VR < 46), 17OHP 2400 ng/dl (VR 17–204), Na^+ 129 mEq/L and K^+ 4.8 mEq/L. She had never presented dehydration crisis. Upon molecular investigation a novel 9-bp deletion (del2291_2299AAGGCGCCC) was identified in exon 9 of *CYP21A2* gene. This *in frame* deletion eliminates three amino acids (Q389, G390 and A391) from the protein. The mutation was inherited from the mother and it is in compound heterozygosis with gene deletion/conversion inherited from the father. Her young brother was prenatally diagnosed as having the same genotype. Treatment with hydrocortisone has initiated 3 days after he was born; and, introduction of fludrocortisone with saline supplement started with 7 days. *In silico* analysis based in PDB ID:1DT6 structure used as model demonstrated that this novel mutation causes severe structural damages to the deletion neighborhood and also within important regions for enzymatic activity.

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VHL Disease in Infancy and Adolescence : Clinical Presentation and Long-term Follow-up

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von Hippel Lindau disease(VHL) is an inherited syndrome caused by mutations of the VHL gene. It predisposes to the development of hemangioblastomas, renal or pancreatic cysts or tumors, endolymphatic sac tumors or pheochromocytomas. We aimed to evaluate the presentation and outcome of VHL in patients under 20 years of age. We studied 23 patients (16 males) belonging to 15 families with VHL disease confirmed by molecular biology. Mean age at presentation:12 years (range 4–20). The initial manifestation of VHL was pheochromocytoma in 20/23 patients (11/20 bilateral). The remaining patients presented endolymphatic sac tumor (1) and CNS angioma (2). Median disease-free interval 8 years (2–42). 11/22 had no recurrence (follow up 6–42 years, median 14). One patient died after six years (cerebral hemorrhage). 11/22 later developed other tumors (between 2 to 31 years, median 16). 4/11 presented CNS or retina hemangiomas, 4/11 pheochromocytoma, 3/11 hemangioblastoma, kidney or pancreas tumors or cysts simultaneously. Members of the same family presented diferent tumors. We emphasize the need for the search for VHL disease in children mainly with pheochromocytoma, as well as whole life surveillance, since comorbid pathology can show up after a long disease-free period.

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Growth and Metabolic Outcomes in Short Children Born Small for Gestational Age Treated with Recombinant Growth Hormone

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Introduction/Objective: Children born small for gestational age (*SGA*) without adequate catch-up growth may benefit from recombinant growth hormone (*rGH*) therapy. This study evaluated growth and metabolic [IGF1:IGFBP3 molar ratio (*IGF1:BP3-mr*), glucose, insulin, lipids and transaminases] outcomes after 1, 2 and 3 years of *rGH* therapy in short *SGA* children. **Methods:** Retrospective analysis of records from 14 short children born *SGA* receiving *rGH*. **Results:** Fourteen (8 females) short children born *SGA* presenting z-score of height (*zH*) –2.13±0.63, initiated *rGH* at mean age of 8.8±3.2 years. After 1 (n=14), 2 (n=13) and 3 years (n=9), it was observed, respectively, significant increases in *zH* (–1.53±0.79, p=0.001; –1.00±0.60, p=0.001; –0.97±0.41, p=0.008) and in IGF1:BP3-mr (0.37±0.13, p=0.011; 0.38±0.11, p=0.046; 0.48±0.16, p=0.021). No differences were observed comparing initial and subsequent levels of glucose, lipids and transaminases, but there were statistically significant increases in insulin in the second (p=0.012) and third years (p=0.038). No correlations were found between sex, birthlenght or birthweight with metabolic profiles before nor after *rGH*. **Conclusions:** The *rGH*-mediated improvement in *zH* this group presented was achieved inside a safe *IGF1:BP3-mr* range (<0.5). Despite isolated increases in insulin, *rGH* therapy was not associated with undesirable nor harmful metabolic alterations.

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Limited Weight Loss or Simply No Weight Gain Following Lifestyle-only Intervention Tends to Redistribute Body Fat, to Decrease Lipid Levels and to Improve Parameters of Insulin Sensitivity in Obese Children

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Objectives: To investigate whether lifestyle-only intervention in obese children who either maintain their weight or lose modest weight

Table 1. Metabolic parameters between young SGA and AGA adolescents grouped by sex. (for Abstract 57)

	Male		Female	
	SGA (n=11)	AGA (n=146)	SGA (n=31)	AGA (n=177)
Age (years)	14.42 ± 2.25	14.92 ± 4.01	13.60 ± 1.89	13.56 ± 2.09
Weight (kg)	54.46± 13.27	54.36 ± 15.71	47.83± 10.51	50.83 ± 12.19*
Height (m)	1.63 ± 0.12	1.62 ± 0.14	1.54 ± 0.08	1.55 ± 0.08
BMI	20.11 ± 3.12	20.26 ± 3.62	20.11 ± 3.12	20.26± 3.60*
Waist (cm)	70.62 ± 8.42	70.21 ± 9.71	65.56± 7.44	66.91 ± 8.90
Blood glucose (mg/dl)	85.82± 30.16	83.56 ± 30.95	91.83± 15.25	85.23 ± 28.86*
Insulin (iU/L)	4.51 ± 4.96	5.20 ± 4.58	6.81 ± 6.12	6.43 ± 5.00
HOMA-IR	0.64 ± 1.13	0.99 ± 1.09	1.08 ± 1.39	0.81 ± 1.09

* p< 0.05

redistributes parameters of body composition and reverses metabolic abnormalities. Study design: We evaluated 126 obese children before and after 8 months of lifestyle intervention. Patients either maintained or lost weight (group A) or gained weight (group B). **Results:** Group A patients presented with a significant decrease in Z-score BMI, waist circumference and in fat area (p<0.0001), following intervention, while physical activity increased (p<0.001). Diastolic blood pressure (p<0.03), total cholesterol (p<0.07), LDL cholesterol (p<0.01), triglycerides (p<0.01), triglyceride/HDL ratio (p<0.05), postprandial glucose (p<0.07), basal and postprandial insulin (p<0.004 and p<0.0001) and HOMA (p<0.01) decreased significantly, while QUICKI increased (p<0.01). Conversely, group B patients increased their BMI and waist circumference (p<0.0001 and p<0.02), systolic blood pressure (p<0.05), triglycerides (p<0.05) and postprandial glucose (p<0.05) between visits, while markers of insulin resistance remained stable. C-reactive protein tended to decrease in group A and did not change in group B. **Conclusions:** Obese children who are able to either maintain their weight or lose a small amount of weight following modest lifestyle-only intervention tend to redistribute their body fat, decrease lipid levels and to improve parameters of insulin sensitivity.

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Metabolic Parameters Among Adolescents Born Small (SGA) and Appropriate (AGA) for Gestational Age

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Introduction: Children born SGA are at risk for metabolic diseases. **Aim:** To compare metabolic parameters between young people born SGA (term, <2500 grams) and born AGA. **Methods:** 365 adolescents (57% girls), 12% born SGA, on puberty. **Results:** Table shows the results for boys and girls. **Conclusion:** Weight, BMI and blood glucose levels were higher in girls born SGA compared with girls born AGA. No difference was found among boys.

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Management Indicators of a Newborn Screening Program (NSP) of Congenital Adrenal Hyperplasia (CAH): Its Impact on Program and Methodology Evaluation

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The inespecificity of 17-OH-Progesterone (17OHP)kits, generates high recall rates (RR) in NSP for CAH, especially in preterm and/or sick babies. A Cuban kit in Argentina (17OHP UMELISA-SUMA) added additional considerations. **Objective:**To compare RR by Gestational Age (GA) using SUMA&DELFIA methodologies. Analyze recalled cases that required medical intervention(RMI). **Materials and Methods:** 307 recalled cases from 32953 dried blood samples(DBS). SUMA RR was compared with DELFIA by GA. In 53 RMI (GA:24–41wk; PN:2291±941g) we evaluated: 17OHP(*n=38), method and time of resolution(TR) (*n=24), clinical condition, GA and birth weight (BW)(*n=40).*:Available information. **Results:**

Global RR (TSH+Phe+Gal + 17OHP+IRT+Biot)	17OHP SUMA RR	17OHP SUMA + DELFIA RR	17OHP DELFIA RR
4.85% (n=32953) Chi2 (A vs.C):p<0.001	5.6% (n=22091)	1.1% (n=22091)	1.2% (n=17175)

In 53 RMI/307 recalled cases 37/53 (69.8%) were preterm and 21/53 (39.6%) newborns in NICU.

BW	17OHP DBS (µmol/l) (Mean±DS)	TR (days:Mean±DS)
<2500g	185.1 (±140)	31.4±22.5
≥2500g	132.1 (±145.4)	35.7±17
<2500vs ≥2500g	Test t-p:ns	Test t–p:ns

33/53 RMI (62.3%) were resolved by: a)Follow-up with DBS:26/33 (78.8%), b)Serum check (direct+extracted 17OHP): 7/33(21.2 %). Inconclusive (or in follow-up): 14/53(26.4%) and 6 died (other causes). **Conclusion:** DELFIA methodology showed lower RR than UMELISA-SUMA, avoiding unnecessary medical interventions. RMI were higher in preterm infants. 17OHP&TR in RMI divided by BW were no different. Mostly, it was possible to resolve diagnosis by follow-up with DELFIA in DBS.

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Usefulness of Neuroimaging in Central Precocious Puberty (CPP)

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There is controversy about the usefulness of cranial resonance image (MRI) in girls with CPP older than 7 years. To determine the incidence of intracranial lesions by MRI in girls with CPP at different age of presentation, we reviewed hospital records from one hundred and six girls were evaluated by MRI. Age at diagnosis and the history of neurological disorders (HND) were recorded. From 106 patients studied by MRI, 80 had normal image and 26 were pathological. Patients were divided into 3 groups according to age at diagnosis. GI: < 5 years old (n=15), 9 normal image, 6 were pathological (16% HND). GII: between 5 and 6.9 (n=21), 17 normal image, 4 pathological (100% HND). GIII: between 7 and 9 years (n=70), 54 normal image, 16 pathological (31.2% HND). Eight patients in group III had intrapituitary hypodense imaging resembling microadenomas; during follow-up, 4 of these patients, spontaneously normalized MRI. **Conclusion:** Twenty two % of all girls in GIII had MRI showing neurogenic lesions, and 68.8% of them did not have history of neurological disorders. If abnormalities detected by MRI in patients older than 7 are discovered incidentally or they are truly related to aetiology of CPP need further investigations.

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Contiguous Gene Syndrome Caused by an Interstitial Deletion in the Short Arm of X-chromosome Diagnosed by MLPA

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Background: Contiguous gene syndrome (CGS) is characterized by the association of different phenotypes due to abnormalities of 2 or more adjacent genes. When the Xp22.3 region is affected, it can result in short stature, mental retardation, icthyosis and hypogonadotropic hypogonadism. Case report: A 16-year-old male, small for gestational age, with bilateral cryptorchidism, presented with neurodevelopment retardation and short stature noted since first years of life. He was treated from 7 to 10 years old with hGH with no growth gain. He was referred to our hospital at the age of 16 due to short stature [–6.5 SDS height (127.8 cm)], no pubertal development, bimanual synkinesis, icthyosis, reduced sense of smell and mental retardation. Hormonal evaluation showed a prepubertal gonadotropin pattern, without other pituitary hormone deficiencies. Karyotype was 46,XY and genetic analysis by MLPA technique (SALSA MLPA KIT P018-D1 SHOX, MCR Holand, Netherlands) revealed a 8.4–9.4 Mb interstitial deletion in Xp22.3 region (from genes PPP2R3B to KAL1) including the short stature homeobox (SHOX) and steroid sulfatase (STS) genes. **Conclusion:** CGS caused by deletion in the Xp22.3 region should be considered in patients with hyposmic hypogonadotropic hypogonadism, icthyosis, short stature and mental retardation. The MLPA technique was useful to confirm CGS diagnosis.

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Adiposity Indexes Among Brazilian Survivors of Acute Lymphocytic Leukemia: Beyond Mass Index

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Purpose: To analyse the effect of sex and cranial radiotherapy (RT) on adiposity indexes in survivors of childhood acute lymphocytic leukemia (ALL). **Methods:** Fifty six survivors, divided into irradiated (n=25/56; 44.6%), and nonirradiated (n=31/56; 55.4%), transversally evaluated according to body mass index (BMI), circumferences, fat composition, and distribution. **Results:** Age at evaluation was 18.6 ± 2.5 yr, 8.5 ± 3.5 yr after therapy withdrawal, 42.8% males. Neither sex nor RT influenced BMI SD. Twenty-one out of 56 (37.5%) subjects showed an increase in waist-to-height ratio, with a trend toward elevation in irradiated group (p=0.06). Female sex and RT exposure showed an increase in total body fat. Two out of 56 (3.6%) patients were considered obese (BMI SD), while 20/56 (35.7%) according to total body fat, predominantly in irradiated group (p=0.02). Irradiation also showed a positive effect on abdominal fat (p<0.01). Additionally, there was a positive correlation between adiposity indexes. **Conclusions:** Adolescent and young adult survivors of ALL showed increased body fat and altered distribution, every

index related to cranial RT. Fat compartment modifications possibly indicate a disease of adipose tissue, role of cranial RT, even though other determinants (such as ethnics and genetics) should be further studied.

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Hypoglycemia in Pediatric Population: Our Experience

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Introduction: Hypoglycemia represents an emergency in pediatric population due to the risk of seizures and neurological damage. It is not a frequent referral in pediatric endocrinology. **Objective:** Evaluate the epidemiology (age at presentation, at referral, time at diagnosis, symptoms) within the different diagnosis found in children with symptomatic hypoglycemia referred at the Endocrinology Unit of Elizalde Hospital. **Methods:** Retrospective, observational study. Referred Patients´ Clinical record were reviewed from 1995 to 2010. Hypoglycemia was defined as glucose less than 40 mg% (less than 30 mg% in neonates). **Results:** 48 patients were studied (23 females, 25 males) with a mean age at referral: 1,55 years. Seizures was the most frequent symptom at presentation (32%). Regarding the etiologies, recurrent ketotic hypoglycemia was present in 25 % of the patients, hyperinsulinism in 21% and panhypopituitarism in 12,5%, with a mean age at presentation: 1,89 years; 0,4 years and 0,8 years respectively. **Conclusions:** Hypoglycemia is an important entity as it implies serious risks. In our population we found the diagnosis in 95,8% of the patients. The age at presentation is an important issue while evaluating the different etiologies. The complete workout allows the different diagnosis, avoiding future recurrences.

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Are All Metabolic Syndrome (MS) Components Associated with the Same Cardiovascular Risk, as Measured by hsCRP?

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Background: Levels of c reactive protein (hsCRP) increases as more components of MS are present. In adults it is able to predict cardiovascular risk independently. The association of hsCRP with the different MS components in children has not been established. **Objectives:** To determine levels of hsCRP in children with and without MS and to determine the association of hsCRP with each component of MS. **Methods:** 344 children of 11.24 ±2.73 years old (47.25% female) were recruited. In them weight, height, waist circumference, blood pressure, fat mass were measured and z-BMI was calculated. Plasma glucose, lipids profile and hsCRP were quantified. HsCRP values were determined for each of the factors of MS, in children with and without MS. **Results:** The overall prevalence of MS was 12,46%. Those with MS presented higher levels of hsCRP (mean: 2.98 ±3.22 mg/L) vs. patients who did not have MS (mean: 1.61 ±2.73 mg/L) (p=0,003). For each component of MS, hsCRP was significantly higher in children who presented MS. **Conclusions:** The components of MS that were most significantly associated with a high value of hsCRP were hypertension, waist circumference and triglycerides. (Funded by Chilean FONDECYT number: 1100356)

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Cardiovascular Risk in Adolescents: Association with Biological Factors

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Background: Early cardiovascular risk factors (CVRF) presence is associated with an increased of type 2 diabetes and coronary heart disease risk, being overweight, insulin resistance (IR) and sarcopenia the major determinants. **Methods:** In 166 adolescents of 17 years (79 males) from a longitudinal study, we evaluated zBMI (WHO) and body composition (DEXA). CVRF were diagnosed according to Cook criteria, HOMA-IR was used for IR. Chi2 for associations, ANOVA and Bonferroni tests were performed. **Results:** 9% of adolescents had three or more CVRF, with higher prevalence ($p<0.05$) in males (13.9%) than females (4.6%). There were no gender differences in zBMI, waist circumference (WC) and HOMA-IR. Males showed increased triglycerides, blood pressure and glucose as compare to females; HDL-cholesterol was higher in women. Higher number of CVRF reflected increased zBMI, WC, body fat and HOMA-IR and decreased muscle mass. There was a direct and significant association ($p<0.01$) between 5 and 10 year-old zBMI with the current number of CVRF . **Conclusion:** In adolescents, the number of CVRF was associated with sex, abdominal obesity, body composition, insulin resistance as well as with current zBMI and 5 and 10 year-old zBMI.

Table 1 (result expressed in mean ± SD) (for Abstract 66)

	Whole group (n: 52)	≤ 6 years old at diagnosis (n:16)	> 6 años years old at diagnosis (n: 36)
Age at diagnosis (year)	9.11 (± 4.60)	3.44 (± 1.28)	11.6 (± 2.99)
Z score height (SD)	–0.82 (± 1.46)	–0.40(± 0.79)	- 1.01 (± 1.66)
Z score weight (DS)	–0.73 (± 1.36)	–0.33 (± 1.03)	- 0.90 (± 1.47)
BMI	18.11 (± 4.14)	18.10 (± 0.9)	17.30 (± 3.74)
BMD Lumbar Spine (SD)	–1.1 (± 1.5)	– 0.45(± 0.45) *	- 1.38 (±1.09) *
BMD Lumbar Spine (g/cm2)	0.642 (± 0.18)	0.48 (± 0.45)	0.687 (± 0.187)
25 (OH) D (ng/ml)	25.58 (± 13.48)	31.66 (± 15.66) **	23.37 (±12.13) **

*p < 0.019 LS: L2 – L4 Lumbar Spine; ** p < 0.04

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The c.278delG Novel Deletion in 5α-redutase Type 2 Deficiency in Brazilian Patient with 46,XY Karyotype and Genital Ambiguity

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The steroid 5α-redutase type 2 is the main enzyme in male urogenital tract and plays a critical role on 46,XY embryo virilization. It is produced by 5-alpha steroid reductase type 2 gene (*SRD5A2*). Mutations in *SRD5A2* gene are responsible for the autossomal recessive 5-alpha reductase deficiency, which results in male pseudohermaphrodism caused by decreased levels of dihydrotestosterone. Affected individuals may present either ambiguous genitalia or normal female phenotype. The aim of this investigation was to screen for nucleotide alterations within the five exons of *SRD5A2* gene including exon-intron junctions in a patient with clinical and hormonal characteristics suggestive of *SRD5A2* deficiency. Molecular analysis included the amplification of the five *SRD5A2* exons followed by direct sequencing. A novel c.278delG deletion was found in exon 1. This guanine is the last nucleotide of exon 1 within the donor-splicing region and its deletion may affect the production of normal mRNA. Alternatively, it may cause a frameshift creating a stop signal at codon 130. The patient is heterozygous for the mutation and no other sequence variation has been identified. Genital ambiguity in this case is probably a result of *SRD5A2* reduced production and consequently a dose effect might have led to the phenotype.

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Metabolic Bone Disorders in Children and Adolescents with Celiac Disease: Diagnosis Age Influence

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Celiac Disease (CD) is a frequent cause of malabsortion in childhood and affects calcium and vitamin D absorption. **Aim:** Analyze the vitamin D levels and bone mineral density (BMD) at diagnosis in patients affected with Celiac Disease, and the influence of the age of diagnosis in the clinical presentation. **Patients and Methods:** 52 patients (Female: 26) were evaluated. Results (Table 1). The percentage with Vitamin D < 20ng/ml was 32, 7 % at the moment of diagnosis and 26 % of the patient had BMD LS below 2 SD. In the whole group we found positive correlation between: BMD Z score and Vitamin D levels (p: < 0.001, r: 0.544) and BMD Z Score and Chronological age at the moment of diagnosis (p: < 0, 02 r: 0, 35). **Conclusions:** We found an important percentage of vitamin D deficiency and insufficiency and low bone mass at the moment of diagnosis in the whole group. The age at the diagnosis influenced clinical and biochemical manifestations. Our results suggest that the early diagnosis is essential for the bone health of patients affected with CD.

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Consumptive Hypothyroidism Due to Massive Hepatic Hemangiomas

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Consumptive hypothyroidism due to hepatic hemangiomas is a rare event in early childhood. It is produced by an increased type 3 iodothyronine deiodinase activity, with elevated rT3 levels, and an increased degradation of biological active thyroid hormones, T4 and T3. Clinical case: we present a female patient, 45 days old, with normal newborn screening, who presented with progressive jaundice and

abdominal distension. Physical examination revealed an euthyroid girl, without goiter, with cutaneous hemangiomas and hepatomegaly. Laboratory profile showed abnormal liver enzyme tests. Computed tomography revealed hepatic hemangiomas. Thyroid profile: TSH 194 uUI/ml (3.5±2.6), T4L 0.6 ng/dl (0.9–1.9), T4 6.5 ug/dl (4.9–14.7), T3 0.5 ng/ml (1.12–2.34), with negative thyroid antibodies. She had a normal thyroid ultrasound, positive Beclard and maternal thyroid function was normal. L-thyroxine replacement was iniciated. Her hypothyroidism improved concomitantly with the involution of hemangiomas, with a TSH level that decreased gradually. Her growth and neurological development have been normal. **Conclusions:** Detection of hypothyroidism in early infants is crucial in preventing intellectual impairment and growth retardation. This reinforces the need to screen for hypothyroidism in the presence of hepatic hemangiomas.

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Multiple Endocrine Neoplasia Type 2B (MEN2B): Relevance of Early Diagnosis

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Multiple endocrine neoplasia Type 2B (MEN 2B),an autosomal dominant syndrome is characterized by peculiar phenotype, aggressive medular thyroid carcinoma (MTC) and pheochromocytoma. Progress in the field of molecular biology and phenotype recognition have enabled early diagnoses substantially improving patients survival. The prolonged life-span of these patients has opened concerns about long-term morbidity, reproductive capacity and future of offspring´s. The aim of this study was to present clinical, biochemical and genetic studies in a group of MEN 2B patients. Seventeen individuals, male 9 females 8 (aged 6–42y), belonging to 14 families were studied. All of them presented the characteristic phenotype and the classical M918T mutation. Twins carriers 7-years old were detected. MTC was present in all index cases and also in the two twins in whom profilactic thyroidectomy was performed. All patients show increased calcitonin levels before thyroidectomy. After surgery calcitonin levels remained high in all of index cases. In two carriers became undetectable after surgery. Six patients died from MTC (range 17–42y).Bilateral pheochromocytoma was present in 5/15 patients. We conclude that genetic screening and early diagnosis is highly recommended to improve the outcome of the disease in affected patients.

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