

Polycystic Ovary Syndrome PCOS Adolescent Girls

Pathophysiology guided therapy
SPIOMET

Team



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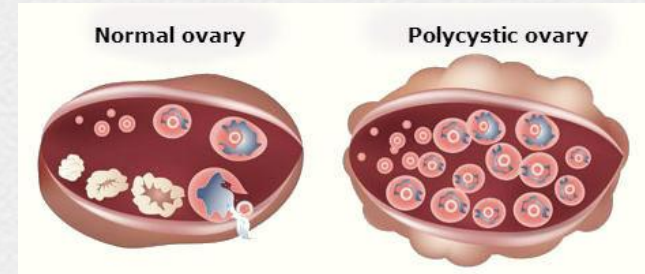
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Patient Need

Oligo-ovulatory androgen excess
Polycystic ovarian disease (NIH)



Adolescent diagnosis:

Commonly presented by hirsutism/oligo-menorrhoea


• Irregular menses

- At least 2 y beyond menarche
 - Oligomenorrhoea- sec. amenorrhoea – dysfunctional uterine bleeding
- Completed puberty & primary amenorrhoea






• Androgen excess

- **Clinical:** hirsutism
- **Biochemical:** high testosterone or Free Androgen Index

Patient Need

- **Prime cause of female subfertility**
- **Association:** *hypertension, cardiovascular, diabetes-T2, insulin resistance, mood disorder, endometrial cancer*
- **Prevalence: 2016:** *112.2 million (NIH) – 186.9 million (Rotterdam) 15-49 y. age cases*
-  expected 5,17% in 2016 – 2025
- No EMA/FDA approved therapy for PCOS in adolescent girls

Solution

- WO2017072243 (prior 2015-10-27):
- New & inventive:
 - “A pharmaceutical composition  or   
 - comprising *spironolactone*, *pioglitazone* and *metformin* 
 - for use in the prevention or treatment of *polycystic ovary syndrome*
 - in adolescent girls or women of childbearing age.”

 TW  AR  UY  KR  CA  AU  MX  IL
 EP  CN  BR  JP  US  EG  IR  SA

IP & FTO

Patient Need

Balance between
Prenatal Weight Gain &
Postnatal Weight Gain



Z-score



Birth Weight

Child/Adolescent BMI

Mismatch between
Less Prenatal Weight Gain &
More Postnatal Weight Gain



Z-score



Birth Weight

Child/Adolescent BMI

Patient Need

Pathophysiology

- Ovarian disorder
- Ectopic (hepato-visceral) fat storage & insulin resistance/hyperinsulinemia
- Neuroendocrine alterations: kisspeptin & GABA signaling, GnRH & gonadotropin secretion
- Genetic polymorphisms: *DENND1A*, *FSHB*, *LHCG-R*
- Epigenetics: methylation, miRNAs
- Altered sympathetic nerve activity
- **Multiple interconnected factors**



Horm Res Paediatr 2017

[Tena-Sempere, Witchel, Auchus, García-Rudaz, López-Bermejo & Ong]

Our unique solution

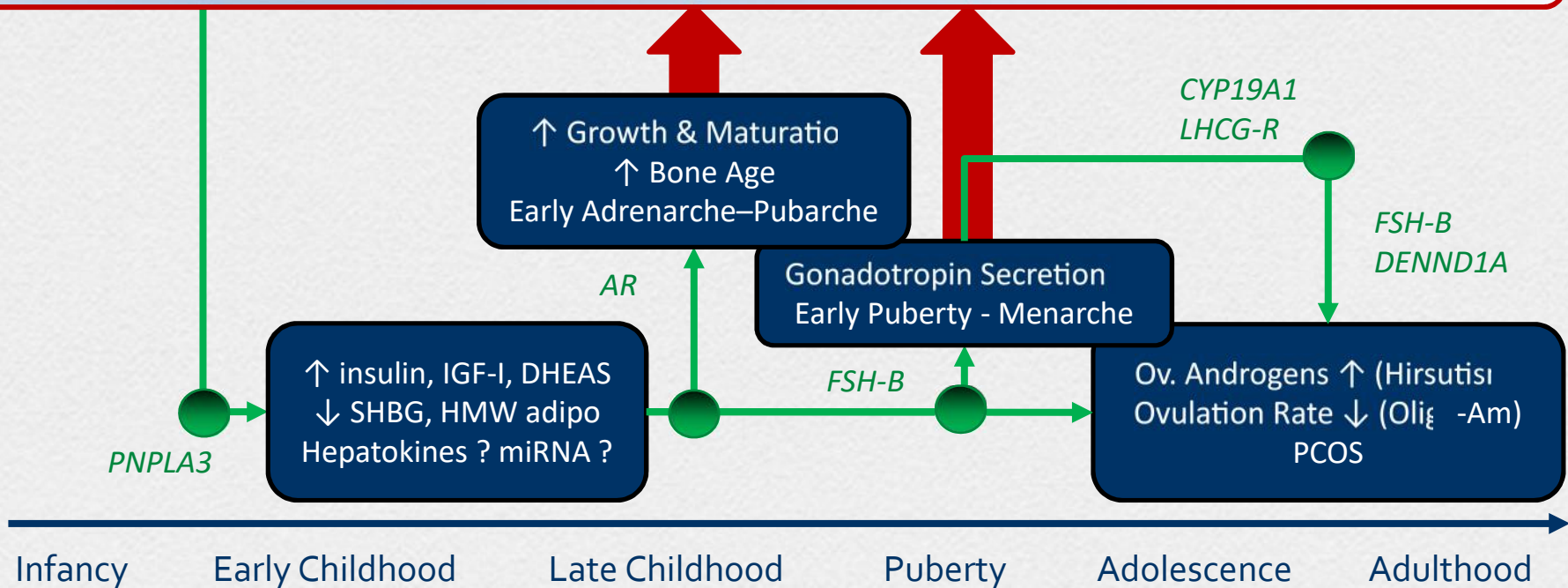
In monotherapy, each SPIOMET component is known to reduce hepatic fat.

Garg, Curr Opin Endocrinol Diabetes Obes 2012
Sivalingam, Hum Reprod Update 2015
Díaz, Pediatric Diabetes 2015
Cusi, Ann Int Med 2016

Healthy lifestyle
(diet, exercise)

Spirolactone
 Pioglitazone
 Metformin
 (SPIOMET)

Hepato-Visceral Fat Excess
(Central Obesity)



Technology at start

Oral Contraceptive (OC) *versus* SPIOMET

- Randomized, open-label, single-center study
- **OC vs SPIOMET** treatment for 12 mo, follow-up for 12 mo
 - OC: ethinylestradiol + levonorgestrel (21/28 d)
 - **SPIOMET**: low-dose combination of separate generics
 - ✓ Spironolactone 50 mg/d
 - ✓ Pioglitazone 7.5 mg/d
 - ✓ Metformin 850 mg/d

Technology at start

Study Population & Assessments

- 34 girls, ~16 yr, birthweight Z-score -0.5, BMI Z-score +0.7
- PCOS by the latest update criteria (\approx NIH criteria)
- Exclusion criterion: sexual activity
- Key endpoints:
 - ✓ Androgens (LC-MS/MS), insulin, lipids
 - ✓ Liver fat (MRI) & body composition (DXA)
 - ✓ Post-treatment ovulation rates (salivary progesterone)

Our unique solution

Different Post-Treatment Results

	OC	SPIOMET
Androgen Excess*		More normal
Insulin (oGTT)		More normal
CRP, HMW Adiponectin		More normal
Visceral Fat (MRI)		More normal
Hepatic Fat (MRI)		More normal

* by circulating testosterone & hirsutism score (Ferriman & Gallwey)

J Adolesc Health 2017

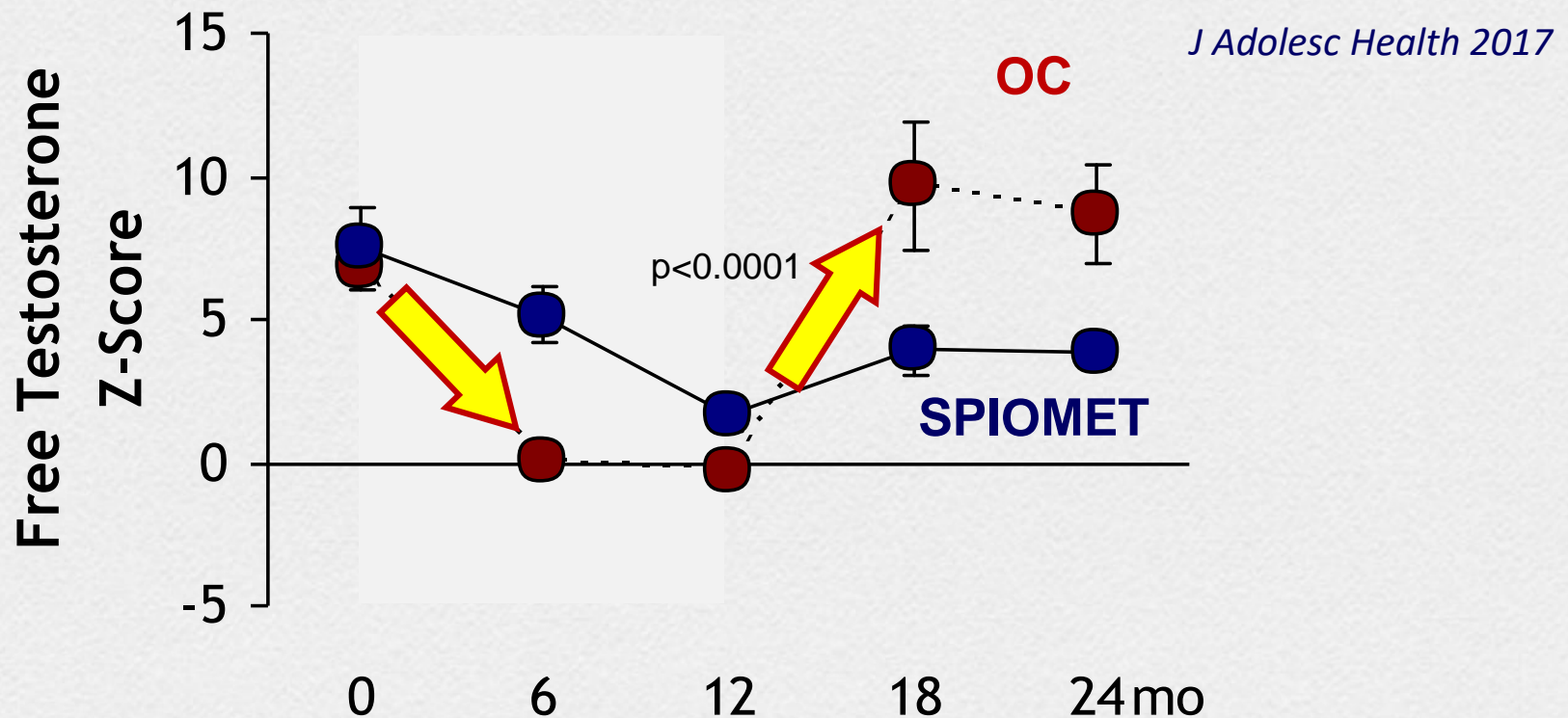
Body Mass Index / Lean mass (DXA) / subcutaneous Fat (MRI) : No changes

Our unique solution

OC vs **SPIOMET**

Longitudinal Changes in Free Testosterone Z-Scores

On-Treatment (0-12 mo) and Post-Treatment (12-24 mo)

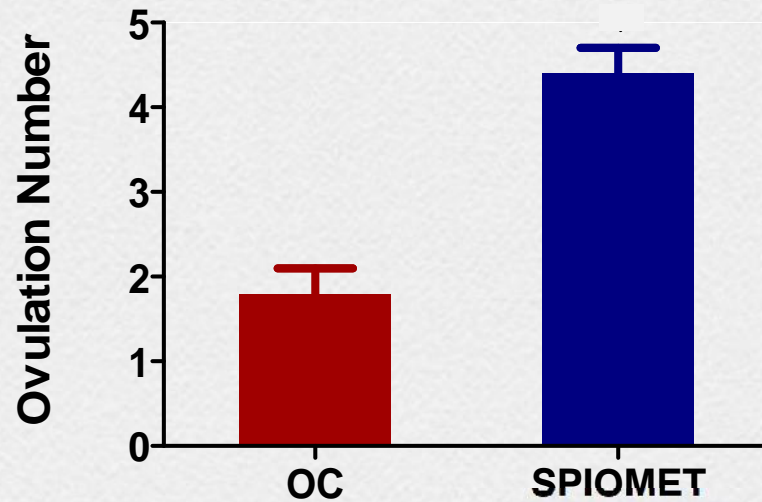


Our unique solution

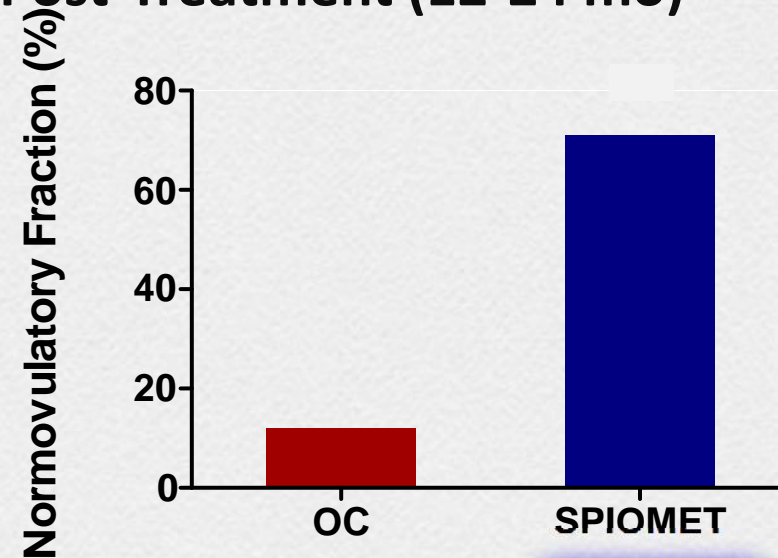
OC vs SPIOMET

Post-Treatment Ovulation Rate

On-Treatment (0-12 mo) and Post-Treatment (12-24 mo)



x 2.5
P<0.001



x 6
P<0.001

More post-treatment ovulations

- after more on-treatment loss of liver fat
- after less post-treatment testo rebound

Technology Roadmap -Value chain -GoToMarket strategy -Milestones -Model

- New organized trial - epigenetic markers and miRNAs
- Resources need depending on (starting) indication
- The final protocol yet to be submitted to EMA & FDA.
 - Multicenter Phase 2-3 study in Europe & USA (about 240 patients (1 y))
 - FDA granted an orphan drug designation the treatment of adolescent pediatric PCOS by metformin
 - Orphan Drug status exclusively for girls aged 12-18

Value proposition SPIOMET

- PCOS treatment
 - Targeting the pediatric and adolescent patient population (unmet need).
 - An age appropriate formulation.
 - Normalizing post treatment ovulation rates.
 - Preventing part of later oligoanovulatory subfertility.

Partnership in this opportunity

Thank You!

