ISRCTN11062950 https://doi.org/10.1186/ISRCTN11062950

Comparison of the effects of an oral contraceptive with those of a combined therapy with insulin sensitizers and anti-androgens in young girls with ovarian androgen excess and without pregnancy risk, on markers of cardiometabolic health

Submission date
16/09/2015

Recruitment status
No longer recruiting

Registration date
21/09/2015

Overall study status
Completed

Last Edited
04/10/2024

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Polycystic ovary syndrome (PCOS) is a medical condition that affects the function of a woman's ovaries. Women with PCOS may have cysts in the ovaries, irregular ovulation and high levels of androgens (male hormones). Symptoms include irregular periods (or no periods at all), difficulties getting pregnant, excessive hair (hirsutism), commonly on the face, chest, back and buttocks, gaining weight, hair thinning and acne. It is also associated with an increased risk of type 2 diabetes and other health problems later in life, such as cardiovascular disease. There is no approved therapy. Prime recommendation is to give an oral contraceptive (OC) which treats the symptoms, but may decrease the sensitivity to insulin, worsen markers of cardiovascular health, and therefore affect the long-term health. Here, we compare the long-term effects of an OC with those of a low-dose combination of medications that improve insulin sensitivity and decrease the affects of androgen to investigate whether besides the clinical symptoms, this combination is capable of improving the risks for future complications for young women with PCOS.

Who can participate?
Girls under 16 diagnosed with PCOS with decreased sensitivity to insulin, excess androgen levels and with no/irregular periods.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in group 1 are given Loette Diario (OC). Those in group 2 are given SPIOMET, that is, spironolactone, pioglitazone and

metformin; this combination aims to improve insulin sensitivity and reduce the effects of androgen. All participants are tested for insulinema (insulin in the blood) and their levels of visceral (abdominal) and hepatic (liver) fat.

What are the possible benefits and risks of participating?
This study compares the standard treatment with an alternative, pathophysiology-based therapy (with a low-dose combination of insulin sensitizers and anti-androgens). A preliminary study has been performed using the combinations to be used here and the results show a divergence in the outcomes, with the combination having more benefits on risk markers. The medications are safe and there is no evidence of side effects.

Where is the study run from?
Hospital Sant Joan de Déu, University of Barcelona (Spain)

When is the study starting and how long is it expected to run for?
December 2015 to December 2018

Who is funding the study?
Ministry of Science and Innovation, Institute of Health Carlos III (Spain)

Who is the main contact?
Prof Lourdes Ibañez
libanez@hsjdbcn.org

Contact information

Type(s)
Scientific

Contact name
Prof Lourdes Ibañez

ORCID ID
https://orcid.org/0000-0003-4595-7191

Contact details
Hospital Sant Joan de Déu
University of Barcelona
Esplugues
Spain
08950

Additional identifiers

Clinical Trials Information System (CTIS)
2015-005092-24

Protocol serial number
PI15/01078

Study information

Scientific Title
Ethinylestradiol-levonorgestrel versus spironolactone-pioglitazone-metformin (SPIOMET) for adolescent girls with hyperinsulinemic androgen excess: effects on hepatic and visceral fat and on insulin sensitivity

Acronym
OC vs SPIOMET

Study objectives
Oral contraceptives (OC) and SPIOMET will improve the measures of androgen excess comparably. SPIOMET treatment will be followed by more favorable changes of the primary outcomes (visceral and hepatic fat and insulinemia), and of secondary outcomes (lipids, CRP, carotic intima-media thickness [cIMT], high-molecular-weight adiponectin, miRNAs, leukocyte telomere length, microbiome, gene expression in subcutaneous adipose tissue).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Agencia Española del Medicamento y Productos Sanitarios, 22/01/2016

Study design
Interventional single-centre randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hyperinsulinemic androgen excess in adolescent girls

Interventions
In this single-centre, open-labelled, controlled trial, the randomization (1:1) will be web-based (http://www.SealedEnvelope.com), using random permuted blocks, with strata for age (<16.0 or ≥16.0 years) and BMI (<24.0 or ≥24.0 Kg/m2).

Girls will be randomly assigned to receive once daily, at dinner time, either Loette Diario (Pfizer, Madrid, Spain; 20 mcg ethinylestradiol plus 100 mg levonorgestrel for 21/28 days, and placebo for 7/28 days) or SPIOMET, a low-dose combination of separate generics: 50 mg spironolactone (one half of a 100 mg tablet of Aldactone from Pfizer, Madrid, Spain); 7.5 mg pioglitazone (one half of a 15 mg tablet of Actos from Takeda, Madrid, Spain); and 850 mg metformin (one full 850 mg tablet of Metformina from Sandoz, Barcelona, Spain).

The randomization will be performed by an investigator who will not be based in the recruiting hospital and who will be blinded to the patients' characteristics (except for age and BMI).

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
1. Loette Diario (Pfizer, Madrid, Spain; 20 mcg ethinylestradiol plus 100 mg levonorgestrel) 2. Spironolactone (100 mg tablets of Aldactone, Pfizer, Madrid, Spain) 3. Pioglitazone (15 mg tablet of Actos, Takeda, Madrid, Spain) 4. Metformin (850 mg tablet of Metformina, Sandoz, Barcelona, Spain)

Primary outcome(s)
Current primary outcome measures as of 14/09/2018:
1. Insulinemia assessed by immunochemiluminescence every 6 months while on treatment and 6 months after end of treatment
2. Visceral and hepatic fat assessed by MRI every 6 months while on treatment and 6 months after end of treatment
Post-treatment endpoints:
3. Ovulation rates assessed by ELISA of weekly salivary progesterone during the second and fourth quarter of the follow-up year

Previous primary outcome measures as of 07/03/2016:
On-treatment endpoints:
1. Insulinemia: on treatment every 6 months; 6 months off treatment. Method: immunoquimioluminescence
2. Visceral & hepatic fat: MRI. on treatment every 6 months; 6 months off treatment
Post-treatment endpoints:
3. Ovulation rates

Previous primary outcome measures:
1. Insulinemia: on treatment every 6 months; 6 months off treatment. Method: immunoquimioluminescence
2. Visceral & hepatic fat: MRI. on treatment every 6 months; 6 months off treatment

Key secondary outcome(s))
Current secondary outcome measures as of 17/09/2018:
On-treatment endpoints:
1. Measures of androgen excess: hirsutism (Ferriman & Gallwey score); acne (Leeds score); testosterone (immunochemiluminescence), and AMH (ELISA) at baseline and after 12 months on treatment.
2. Measurements of cardio-metabolic risk: C-reactive protein (Architect c8000; Abbott); HMW adiponectin (ELISA), carotid intima-media thickness (ultrasound); insulinemia (Immunochemiluminiscence); visceral and hepatic fat (MRI); HMW adiponectin (ELISA), S100A4 (ELISA), at baseline and after 12 months of treatment.

Post-treatment endpoints:
3. Measures of androgen excess: hirsutism (Ferriman & Gallwey score); acne (Leeds score); testosterone (immunochemiluminescence) and AMH (ELISA) after 6 and 12 months off treatment.
4. Measurements of cardio-metabolic risk: C-reactive protein (Architect c8000; Abbott); HMW

adiponectin (ELISA), carotid intima-media thickness (ultrasound); insulinemia (Immunochemiluminiscence); visceral and hepatic fat (MRI); HMW adiponectin (ELISA), S100A4 (ELISA), at 6 and 12 months off treatment.

Previous secondary outcome measures as of 13/09/2018:
On-treatment endpoints:
1. Measures of androgen excess: hirsutism (Ferriman & Gallwey score); acne (Leeds score); testosterone (immunochemiluminescence)
2. C-reactive protein (Architect c8000; Abbott); HMW adiponectin (ELISA), carotid intima-media thickness (ultrasound)
Post-treatment endpoints:
3. Insulinemia
4. Visceral & hepatic fat
5. Measures of androgen excess
6. C-reactive protein, HMW adiponectin, carotid intima-media thickness
7. Serum S100A4 on treatment
8. Anti-Mullerian hormone (AMH) at baseline and after 12 months on treatment

Previous secondary outcome measures as of 07/03/2016:
On-treatment endpoints:
1. Measures of androgen excess: hirsutism (Ferriman & Gallwey score); acne (Leeds score); testosterone (immunochemiluminescence)
2. C-reactive protein (Architect c8000; Abbott); HMW adiponectin (ELISA), carotid intima-media thickness (ultrasound)
Post-treatment endpoints:
3. Insulinemia
4. Visceral & hepatic fat
5. Measures of androgen excess
6. C-reactive protein, HMW adiponectin, carotid intima-media thickness

Previous secondary outcome measures:
1. Measures of androgen excess: hirsutism (Ferriman & Gallwey score); acne (Leeds score); testosterone (immunochemiluminescence)
2. C-reactive protein (Architect c8000; Abbott); HMW adiponectin (ELISA), carotid intima-media thickness (ultrasound)

Completion date
20/09/2019

Eligibility

Key inclusion criteria
1. Hyperinsulinemia, defined as fasting insulinemia >15 IU/mL and/or a peak insulinemia >150 IU /mL and/or mean insulinemia >84 IU/mL on a 2-hour oral glucose tolerance test (oGTT)
2. Presence of both clinical and endocrine androgen excess, as defined by hirsutism score >8 (Ferriman-Gallwey scale), amenorrhea (no menses for more than 3 months) or oligomenorrhea (menstrual intervals >45 days), and high circulating concentrations of testosterone in the follicular phase (cycle day 3-7) or after 2 months of amenorrhea

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Sex
Female

Total final enrolment
41

Key exclusion criteria
1. Pregnancy risk (throughout the study)
2. Anemia or bleeding disorder
3. Evidence of thyroid, liver or kidney dysfunction; abnormal electrolytes
4. Hyperprolactinemia
5. 21-hydroxylase deficiency (17-hydroxyprogesterone levels ≥ 200 ng/dL in the follicular phase or after two months of amenorrhea)
6. Glucose intolerance or diabetes mellitus
7. Use of medication affecting gonadal or adrenal function, or carbohydrate or lipid metabolism

Date of first enrolment
10/12/2015

Date of final enrolment
10/12/2016

Locations

Countries of recruitment
Spain

Study participating centre
Hospital Sant Joan de Déu, University of Barcelona
Passeig de Sant Joan de Déu, 2
Esplugues
Spain
08950

Sponsor information

Organisation
Hospital Sant Joan de Deu, University of Barcelona

ROR
https://ror.org/001jx2139

Funder(s)

Funder type
Not defined

Funder Name
Ministry of Science and Innovation, Institute of Health Carlos III (Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III) (Spain)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the study contact Prof Lourdes Ibañez, libanez@hsjdbcn.org.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	14/03/2020	07/10/2020	Yes	No
Results article		29/03/2021	31/03/2021	Yes	No
Results article	Primary results	14/07/2017	12/08/2022	Yes	No
Results article		16/05/2024	04/10/2024	Yes	No
Protocol file	version 2.0	31/08/2018	16/08/2022	No	No