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Ethinyloestradiol-Levonorgestrel versus Low-Dose Spironolactone-Pioglitazone-Metformin for Adolescent Girls with Polycystic Ovary Syndrome: On-Treatment and Post-Treatment Observations.

Submission date
29/07/2012

Recruitment status
No longer recruiting

Registration date
08/08/2012

Overall study status
Completed

Last Edited
31/03/2021

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims:
Hyperandrogenism is a medical condition where the body produces too much of the male sex hormone androgen and insulin levels are elevated. Hyperandrogenism is one of the primary components symptoms of polycystic ovary syndrome (PCOS). It can cause a variety of symptoms, such as irregular or complete absence of periods, problems with getting pregnant, excessive hair growth (hirsutism), , thinning hair and acne. It may be also linked to other health conditions such as infertility, type 2 diabetes and high cholesterol. The aim of this study is to compare the effects of a low-dose combination of two insulin sensitizers (drugs developed to address insulin resistance) and an antiandrogen (a drug that blocks the function of androgen) with those of an oral contraceptive in girls with signs and symptoms of androgen excess or hyperandrogenism, such as hirsutism and menstrual disturbances. The researchers want to know which is the best treatment not only to ameliorate the clinical symptoms but also to reduce future risks for infertility, type 2 diabetes and cardiovascular disease, because these girls, as adults, may have more predisposition to suffer from these disorders.

Who can participate?
Adolescent girls with hyperandrogenism who are not at risk of pregnancy.

What does the study involve?
The girls are randomly allocated to one of two groups. Those in group 1 are given the insulin sensitizers plus antiandrogen treatment for 12 months. Those in group 2 are given an oral contraceptive for 12 months. At the start and at the end of the treatment , and then again 12 months after the treatment has been stopped, an oral glucose test is performed for all participants. Blood samples for androgens, lipids (fats) and insulin are also taken at the start of the treatment, 6 and 12 months into the treatment and then, finally, after 6 and 12 months after the treatment. All girls also have a DXA scan and a magnetic resonance of the abdomen to see

whether there have been any changes in body composition, abdominal fat and lipids within the liver at the start of the study and then four further times, 6 months apart. An abdominal ultrasound and a carotid ultrasound are also performed. Between three months and six months after treatment, and then again between nine months and 12 months after treatment, ovulation is also tested, by measuring salivary progesterone every week for 12 consecutive weeks.

What are the possible benefits and risks of participating?
The researchers foresee no specific risks with any of the two treatments. This is an important study because it will clarify which is the best treatment option to give to adolescents with androgen excess, which is the most common endocrine disorder in adolescents and young women.

Where is the study run from?
University of Barcelona (Spain)

When is study starting and how long is it expected to run for?
October 2012 to April 2014

Who is funding the study?
National Health Service of Spain

Who is the main contact?
Professor Lourdes Ibáñez

Contact information

Type(s)
Scientific

Contact name
Prof Lourdes Ibañez

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Additional identifiers

EudraCT/CTIS number
2012-004100-35

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

ECO-120729

Study information

Scientific Title
Ethinyloestradiol-Levonorgestrel versus Low-Dose Spironolactone-Pioglitazone-Metformin (SPIOMET) for Adolescent Girls with Polycystic Ovary Syndrome: On-Treatment and Post-Treatment Observations.

Study objectives
As of 21/07/2016:
Treatment with low-dose spironolactone- + pioglitazone- + metformin will be accompanied by more reduction of central fat and hyperinsulinaemia, and will be followed by a higher ovulation rate than treatment with an oral oestro-progestagen contraceptive in adolescent girls with polycystic ovary syndrome.

Initial
Treatment with Spironolactone + Pioglitazone + Metformin will be more effective on ovulation rates, endocrine-metabolic parameters and body composition and in the normalization of cardiovascular risk markers than that with an oral contraceptive containing ethinylestradiol and levonorgestrel in girls with hyperinsulinemic androgen excess and without pregnancy risk.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Ethical Committee of Clinical Research at Hospital Sant Joan de Déu, 16/10/2012, ref: AC-23-12
2. Spanish Agency for Medicines and Health Products (Agencia Española del Medicamento y Productos Sanitarios) (AEMPS), 17/12/2012, ref: EUDRACT: 2012-004100-35

Study design
As of 21/07/2016:
Randomized, open-label study with an on-treatment phase of 12 months followed by a post-treatment phase of 12 months.

Initial
Open prospective randomized study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Polycystic ovary syndrome

Interventions
Two treatment subgroups:
Ethinylestradiol (20 ug) + levonorgestrel (100 mg), once daily at dinner time
Spironolactone (50 mg/d) + pioglitazone (7.5 mg/d) + metformin (850 mg/d), once daily, at dinner time.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
1. Spironolactone 2. Pioglitazon 3. Metformin 4. Ethinylestradiol-levonorgestrel (added 18/03 /2016)

Primary outcome measure
As of 21/07/2016:
1. Post-treatment ovulation rate: (judged by a combination of menstrual history and weekly salivary progesterone concentrations for 12 consecutive weeks, in the second and the fourth quarters of the first post-treatment year (months 15-18 and 21-24 of the study).

As of 15/03/2016:
1. Ovulation rate: (weekly salivary progesterone for 12 consecutive weeks, ELISA): post-treatment; second and fourth quarters of the post-treatment year (months 15-18 and 21-24)

Initial
1. Fasting insulin
2. Visceral fat
3. Hepatic fat
4. Carotid intima-media thickness

Secondary outcome measures
As of 15/03/2016:
1. Fasting insulinemia (immunochemiluminescence): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment
2. Visceral fat (MRI): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment
3. Hepatic fat (MRI): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment
4. Carotid intima-media thickness (ultrasound): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment
5. Hirsutism (Ferriman & Gallwey score): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment

6. Testosterone and androstenedione (LC-MS/MS): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment (changed from 6. Androgens (immunochemiluminescence): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment on 21/07/2016))
7. Lipids (absorption spectrometry): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment
8. C-reactive protein (Architect c8000) : at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment
9. HMW adiponectin (ELISA): at baseline, 6 months and 12 months on treatment and 6 and 12 months off treatment

Added 27/02/2019:
10. Serum miRNAs assessed by RNA-seq at baseline, and at 12 months and 24 months of follow-up

Initial:
1. Ferriman & Gallwey score
2. Androgens
3. Lipids
4. C-reactive protein
5. High molecular weight
6. Adiponectin
7. Insulin resistance index in adipocytes
8. Ovulation
9. Breast density (DXA)

Overall study start date
05/12/2012

Completion date
20/06/2016

Eligibility

Key inclusion criteria
As of 21/07/2016:
1. Clinical androgen excess (hirsutism) and/or biochemical hyperandrogenismwith or without biochemical androgen excess
2. Chronological age between 14.0-17.9 years at study start
3. Gynecological age (= time post-menarche) >2.0 years at study start
4. Absence of sexual activity (intercourse)

Initial:
1.Clinical and biochemical hyperandrogenism
2. Hyperinsulinemia (fasting and/or after an oGTT)
3. Age >14 and >18 year
4. Menarche at least 2 years before
5. BMI <97th percentile and >10th percentile

Participant type(s)
Patient

Age group
Child

Lower age limit
14 Years

Upper age limit
17 Years

Sex
Female

Target number of participants
n=40

Total final enrolment
42

Key exclusion criteria
As of 21/07/2016:
1. Evidence for adrenal hyperplasia, Cushing syndrome, hypothyroidism
2. Evidence for lLiver or kidney dysfunction, diabetes, glucose intolerance
3. Treatment with oral contraceptives, antiandrogens, or insulin sensitizers in past 6 months

Initial:
1. Pregnancy or pregnancy risk
2. Late onset congenital adrenal hyperplasia, Cushing's syndrome, uncompensated hypothyroidism
3. Liver or renal dysfunction, diabetes, glucose intolerance
4. Treatment with oral contraceptives, antiandrogens, or insulin sensitizers over the previous 6 months
5. Severe bacterial infections

Date of first enrolment
23/12/2012

Date of final enrolment
01/07/2014

Locations

Countries of recruitment
Spain

Study participating centre

Hospital Sant Joan de Déu
Esplugues de Llobregat
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Sponsor information

Organisation
Hospital Sant Joan de Deu

Sponsor details
University of Barcelona
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08950

Sponsor type
Hospital/treatment centre

Website
http://www.hsjdbcn.org/

ROR
https://ror.org/001jx2139

Funder(s)

Funder type
Government

Funder Name
National Health Service (Spain) ref: PFIS 0069

Results and Publications

Publication and dissemination plan
Publication of on-treatment and post-treatment findings by mid-2017.

Intention to publish date
01/07/2017

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available for the time being because this action is pending of the publication of the institutional policy of open access in the coming months, that will allow researchers to institutionally systematize open data management.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/10/2017	29/01/2019	Yes	No
Results article		29/03/2021	31/03/2021	Yes	No