The Cycle disturbances, OLigomenorrhea and Amenorrhea (COLA) Study

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This research proposal has multiple aims for research in women with WHO I, II or III status, including extended care and general health assessment, diagnosis/etiology, assessment of best approach/treatment, cardiovascular risk assessment, and...

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37641

Source
ToetsingOnline

Brief title
COLA

Condition

- Other condition
- Endocrine disorders of gonadal function
- Menstrual cycle and uterine bleeding disorders

Synonym
amenorrhea, cycle disturbances, oligomenorrhea

Health condition

infertiliteit

Research involving
Human

Sponsors and support

Primary sponsor: Voortplantingsgeneeskunde
Source(s) of monetary or material Support: Ministerie van OC&W,De Cola studie wordt gefinancierd uit de eerste geldstroom van de divisie Vrouw & Baby. Daarnaast deels uit de Grant WKZ Fonds voor Child Health. Daarnaast is er addtionele funding voor genetica research vanuit het Erasmus MC voor GWAS PCOS en vanuit het NGI (Netherlands Genomics Initiative) en Global menopause SNP consortium voor GWAS POI.

Intervention

Keyword: Amenorrhea, Cycle disturbances, Oligomenorrhea

Outcome measures

Primary outcome

1. To improve accuracy and reproducibility of diagnostic criteria for

oligomenorrhea and amenorrhea (WHO classes I, II, and III)

2. To better understand etiologic factors involved in cycle disturbances

(including metabolic disturbances and ethnic variation)

3. To better assess the extent of other female health implications in women

with cycle disturbances (including bone density, quality of life, and

cardiovascular risk)

4. To identify genetic factors associated with oligomenorrhea or amenorrhea

(using both conventional and newly developed molecular technologies)

5. To enable long-term follow-up regarding pregnancy, children*s health by

providing baseline (cross-sectional) data

6. To enable long-term follow-up regarding the woman/mother by providing

baseline (cross-sectional) data

Secondary outcome

1. Identification of periconceptional health status in PCOS (CoPPer study;

protocol 07-331, year 2007)

a. Prediction of pregnancy in women with PCOS

b. Prediction of pregnancy risks in women with PCOS

c. PM: Pregnancy outcome: health of children born in women with PCOS (protocol in preparation)

2. Cardiovascular risk profile inventarisation

a. Cross-sectional in all women with WHO I, II or III (current protocol)

b. Follow-up in women with POI or PCOS (protocol in preparation)

3. Evaluation of quality of life in all women with WHO I, II, or III (current protocol)

a. Lifestyle (current protocol) and life style intervention (protocol in preparation)

b. Inventarisation of emotional distress

c. Sexual well-being

4. Family studies in women with POI or PCOS (also in previous protocols 04-263 (year 2004) and 05-047 (year 2005))

a. Genome wide linkage analysis; ethnic variation

5. Genetic studies in women with POI or PCOS (also in previous protocols 04-263 (year 2004) and 05-047 (year 2005))

a. Candidate gene studies

b. Single nucleotide polymorphism (SNP) analysis through genome wide sssociation studies (GWAS)

c. Copy number variance (CNV) analysis through GWAS.

d. Whole genome sequencing

Study description

Background summary

Women of reproductive age consult the gynaecologist often for cycle disturbances, such as oligomenorrhea or amenorrhea. Most frequently (approximately 80%), women with cycle disturbances present with chronic anovulation along with normal gonadotropin serum concentrations and normal estradiol serum concentrations. Normogonadotropic normo-estrogenic anovulation is classified as World Health Organization (WHO) class II {Rowe PJ, 1993 171 /id}. Polycystic ovary syndrome (PCOS) is a specific subgroup of WHO class II. PCOS is diagnosed if at least two of the following criteria are present: (i) oligo-/anovulation, (ii) clinical and/ or biochemical hyperandrogenism, or (iii) polycystic ovaries on ultrasonography {Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004 1272 /id}. The prevalence of PCOS is 91% of all women with WHO II status {Broekmans, 2006 1276 /id}.

Cycle disturbances may also be associated with elevated gonadotropins and hypoestrogenism, suggesting that the primary defect resides within the ovary, which is classified as WHO class III {Rowe PJ, 1993 171 /id}. The typical form of WHO class III is menopause. Menopause is defined as the permanent cessation of menstrual cycles due to ovarian follicle pool depletion. On average, menopause occurs at the age of 51 years, along with a WHO III status {Treloar, 1981 232 /id}. However, in 10% to 15% of women menopause occurs before the age of 45 (early menopause, EMP) {Luoto, 1994 139 /id} and in 1% to 2% it occurs before the age of 40 (primary ovarian insufficiency, POI) {Coulam, 1986 7 /id}. Ovarian follicle pool depletion or dysfunction may even occur before menarche, as is the case in most Turner (45,X0) patients. This phenomenon is referred to as primary hypergonadotropic hypoestrogenic amenorrhea, or primary gonadal failure {Reynaud, 2004 1274 /id}. The final groups of women with WHO III status involve women with incipient (IOF) or transitional ovarian failure (TOF). In these women, elevated basal FSH serum concentrations are identified, along with regular (IOF) or irregular cycles (TOF) before the age of 40 yrs.

Finally, women presenting with cycle abnormalities show a hypogonadotropic hypoestrogenic, i.e. WHO I, status {Rowe PJ, 1993 171 /id}. Functional hypogonadotropic amenorrhea, also known as a hypothalamic amenorrhea, is mostly reversible and may be triggered by stressors such as excessive exercise, nutritional deficits (incl. anorexia nervosa) or psychological factors {Perkins, 2001 1297 /id}.

Study objective

This research proposal has multiple aims for research in women with WHO I, II or III status, including extended care and general health assessment,

diagnosis/etiology, assessment of best approach/treatment, cardiovascular risk assessment, and complication prediction (regarding pregnancies, children, and future health). These include the aims of the original protocols for cycle disturbances (METC protocols 04-263 and 05-047).

Up until now we have collected data, serum and DNA samples according to the METC protocols 04-263 and 05-047:
- WHO II status: 998 women, of whom 804 women with PCOS (81%)
- WHO III status: 1317 women, of whom 477 women with POI (36%), 392 women with IOF (30%), 227 women with TOF (17%), 105 women with early menopause (8%), 68 women with poor response (5%), and 48 women with hypergonadotropic primary amenorrhea (4%) (Multicenter collaboration).

The collection of these data and samples has already led to the publication of a series of papers by our group regarding the phenotype and genotype of PCOS . Since the writing of the previous research protocols, however, it has become clear that much larger cohorts of well-phenotyped patients are needed to perform genetic studies focusing on small genetic variations (e.g. using genome-wide association studies and possibly *next generation sequencing* studies in the near future), and findings of such studies need to be replicated. Moreover, there is a need for continued cardiovascular follow-up and the follow-up of children born in women with PCOS. This can only be performed adequately when a thorough initial screening is performed.

Despite the association of premature cessation of ovarian function and short term health problems such as decreased fertility and climacteric symptoms in women with POI, there is a lack of both baseline and prospective follow up data for CVD, osteoporosis, cognition, emotional well-being, and sexual health. Moreover, the mechanism for CVD in women with POI is undiscovered. Finally, there is a lack of prospective follow-up data and hard clinical endpoints to substantiate the current advice or hormone substitution therapy in women with POI. We will especially focus on cardiovascular health to investigate a possible relationship with the occurrence of early reproductive ageing.
While the association between PCOS and CVD seems relatively better understood, CVD risk and events have not been studied in a Dutch population. From recent studies persued by our group, it has become clear that Dutch women with PCOS may have an altered profile compared to other (mostly North-American) study populations. Furthermore, long term follow-up of these women beyond the cessation of fertility is indicated, because unfavorable hormonal, metabolic and inflammatory alterations may persist after menopause in PCOS. This will be studied in a separate protocol that is now under construction.

Study design

Design
This proposed study part, focusing on the first, second and third primary objectives, is designed as a prospective cohort study for evaluating phenotype

and genotype characteristics of women with WHO I, II, or III status. The COLA study protocol is in line with previous protocols 04-263 and 05-047.

Duration of the study
This study was originally initiated in 2004. We expect to need at least five more years to complete inclusion. Moreover, research towards the identification of genes and variants associated with complex genetic traits is still developing. One can imagine that ongoing research projects and newer techniques will enable us to continue our work for some decades.

Setting of the study
This study will be performed at the department of Reproductive Medicine and Gynaecology, division Woman & Baby, University Medical Center Utrecht (UMCU). In addition, collaboration will be established with the following centers for the inclusion of women with cycle disturbances (similar to protocol 04-263): Erasmus Medical Center (Rotterdam) and Vrije Universiteit Medical Center (Amsterdam). Furthermore, collaboration will be established with the following centers for the inclusion of women with WHO III status (similar to protocol 05-047): Erasmus Medical Center (Rotterdam), Medical Center Alkmaar, University Medical Center Groningen, Leiden University Medical Center, Medisch Spectrum Twente (Enschede), Isala Clinics (Zwolle), University Medical Center St. Radboud (Nijmegen), Amphia Hospital (Breda), Deventer Hospital, Catharina Ziekenhuis (Eindhoven), Amsterdam Medical Center, Maastricht University Medical Center.

If collaboration can be affirmed the necessary documents will be added in an addendum.

Study burden and risks

With this observational study we intend to identify phenotypic and genetic factors related to the phenotype and the pathophysiology of cycle disturbances. Moreover, we aim at developing predictive models for ovarian ageing, cycle abnormalities and the probability to conceive in the future. Results will not be analyzed and interpreted individually. As such, the participants will not benefit from the results of this study. However, women with cycle disturbances could benefit from this study as it aims to decipher the yet unknown etiology behind these disturbances. Knowing the etiology of the cycle disturbance may help identify whether the children of these women are at risk for developing identical phenotypes.
The burden associated with participating in this study will be mostly originate from the collection of two extra blood vials when blood is drawn during routine medical care. Venapuncture is generally accepted to be minimally invasive. Therefore the risks and burdens for the participating patients of this study are negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

WHO I
Hypogonadotropic hypoestrogenic status (previously: *hypothalamic amenorrhea*)
1. Low to normal serum FSH concentrations
2. Low serum estradiol concentrations;WHO II
1. Amenorrhea or oligomenorrhea (mean cycle >35 days during the last 6 months)
2. Normal serum FSH concentrations (<12 IU/L)
3. Absence of other causes for the cycle disturbance, including: normal prolactin concentrations (<1.0 IU/L), normal TSH concentrations (0.2 * 4.2 mU/L), abnormalities on ultrasonography.;Within women with WHO II status, PCOS is diagnosed when at least 2 of the following

criteria are met:
1. Oligo-/anovulation
2. Clinical and/ or biochemical hyperandrogenism
3. Polycystic ovaries on ultrasonography;WHO III
1. POI: defined as secondary amenorrhea before the age of 40 years and basal FSH > 40 IU/L.
2. IOF: defined as normo-ovulatory cycles with raised basal FSH > 12 IU/L before the age of 40 years.
3. TOF: defined as irregular cycles with raised basal FSH > 12 IU/L before the age of 40 years.
4. Poor ovarian response: defined as less than 4 oocytes retrieved or cancellation in case of absent follicle growth after ovarian hyperstimulation with 300 IU gonadotropins.
5. Early menopause: menopause occurring between age 40 and 45 years.
6. Hypergonadotropic primary amenorrhea: primary amenorrhoea with raised basal FSH > 12 IU/L.;When a familial component can be identified from the family history (i.e. * 3 affected relatives), the 1st and/or 2nd degree relatives will be approached for participation in the genetic screening. (for procedure; see question F1)

Exclusion criteria

- Age: younger than 12 yrs.
- Regularly cycling women, with the exception of women with elevated basal FSH concentrations (IOF cases).
- Hypergonadotropic primary amenorrhea caused by early development disorders causing absence of ovaries and Swyer syndrome (XY).

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4000

Type:	Anticipated

Ethics review

Not approved

Date:	27-09-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL40437.041.12