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Dydrogesterone or micronized progesterone related birth defects in children

Submission date
21/11/2018

Recruitment status
No longer recruiting

Registration date
11/01/2019

Overall study status
Completed

Last Edited
29/07/2019

Condition category
Pregnancy and Childbirth

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Progesterone is an essential hormone for creating a suitable endometrial (womb) environment for embryo implantation, pregnancy maintenance and delivery at term. Presently, progesterone is used as the first-line drug for luteal phase support (LPS) in IVF treatment. On the other hand, dydrogesterone, an orally active progestogen, is well-tolerated and has a higher patient satisfaction rate than micronized vaginal progesterone. However, a few clinicians have expressed concern about the associated risk of birth defects in newborn infants born to women treated with oral dydrogesterone during early pregnancy. Therefore, it is important to ensure that there is no increased indication of birth defects in children owing to maternal use of dydrogesterone during pregnancy. This motivates us to compare congenital birth defects in children born to women receiving dydrogesterone or micronized progesterone following ovulation induction (OI), intrauterine insemination (IUI) or IVF. A third group of women conceiving spontaneously during investigation are also included for comparison purposes. The aim of this study is to assess and compare the incidence of birth defects among children of infertile couples who conceived either spontaneously during investigation, or with micronized progesterone or dydrogesterone for luteal phase support.

Who can participate?
Women aged 21-45 with infertility

What does the study involve?
Participants unable to conceive spontaneously are randomly allocated to be treated with either oral micronized progesterone or oral dydrogesterone. Following successful conception, all women are followed up regularly. Fetal viability scan and detailed anatomy scans are performed at 6-7 weeks and 20-22 weeks of gestation, respectively. Fetal echocardiography is performed at around 22 weeks of gestational age to exclude congenital cardiac defects. The women are routinely examined by the obstetrician and the babies are thoroughly examined by a pediatrician during their postnatal visit. Electronic records are maintained for all women until their postnatal checkup. Demographic characteristics, pregnancy rate, miscarriage rate, congenital anomalies and fetal outcome are recorded. Information related to growth, learning abilities, and psychological functioning are recorded by a trained child psychologist and trained nurses. The functional abnormalities in children are closely monitored. These follow-up reports are collected

using various methods such as analysis of birth records, regular health check-up of children by the pediatricians and pediatric-psychologist during annual baby get-together, and parents' feedback.

What are the possible benefits and risks of participating?
This study is the first of its kind where congenital abnormalities in children born to women receiving oral dydryogesterone following IVF are investigated. The result will shed some light on a new treatment method for infertile women. There is no risk for patients.

Where is the study run from?
Institute of Reproductive Medicine (India)

When is the study starting and how long is it expected to run for?
January 2002 to June 2017

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
1. Prof. Baidyanath Chakravarty
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2. Prof. Koel Chaudhury
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
IRM/IEC/BNC-IHP-50

Study information

Scientific Title
Congenital anomalies in children following maternal use of dydrogesterone or micronized progesterone as luteal support in infertile women: A retrospective, observational study

Study objectives
Oral dydrogesterone may be a promising drug for luteal phase support in infertility treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Institute of Reproductive Medicine Ethics Committee, 07/01/2002, ref: IRM/IEC/BNC-IHP-50

Study design
Retrospective observational study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Infertility, luteal phase support

Interventions
A total number of 6537 women reporting for infertility treatment were screened for the present study. A total of 239 women with adenomyosis, congenital uterine anomalies and uterine synechiae, baseline FSH >12 IU, donor oocyte recipients and gestational surrogates were excluded from the study. Out of the remaining 6298 women, 2003 conceived spontaneously during investigation (Group A), while the remaining infertile women (n=4295) were randomly allocated for ovulation induction (OI), intrauterine insemination (IUI) or in vitro fertilization (IVF) treatment. Randomized allocation was such that 2103 women received oral micronized progesterone (Group B) as luteal phase support (LPS) and 2192 women received oral dydrogesterone (Group C) as LPS, while Group A did not require the necessary support (control group).

Patients in group B and group C undergoing OI/IUI received clomiphene citrate (50 mg) twice daily from days 3-7 of their menstrual cycle. Intramuscular 75 IU gonatropin was administered to patients undergoing OI on day 3, and was administered to patients undergoing IUI on day 3 and day 8. OI cases were advised of timed intercourse during the fertile window for conception. From day 10 onwards, IUI patients were monitored for ovarian follicular development and their endometrial thickness was monitored by transvaginal ultrasound. Ovulation was triggered with 5000 IU urinary hCG subcutaneously as a single dose when the leading follicle was ≥18 mm and endometrial thickness was ≥7 mm. Insemination was performed with ≥5 × 106/ml motile spermatozoa 36 hours post hCG injection following confirmation of ovulation.

All patients undergoing IVF received subcutaneous injection of 1 mg (40 IU) daily of a GnRH agonist (leuprolide acetate) starting from the mid-luteal phase of the previous cycle which continued for a period of 14 days, or until the onset of the next menstruation (whichever was earlier). The dose of leuprolide acetate was reduced to 0.2 mg (8 IU) from 1 mg when the patient was down-regulated. Recombinant FSH was administered 150–300 IU with adjustment of the dose wherever necessary. Ovarian follicular development was monitored from day 6 of stimulation using transvaginal ultrasonography. Human chorionic gonadotropin injection was administered intramuscularly when the average diameter of the leading follicle (s) reached ≥18 mm. This occurred approximately between days 9 and 13 of stimulation. Serum peak E2 was assessed on the day of hCG administration. Oocytes were retrieved transvaginally under ultrasound guidance 34–36 hours post hCG injection. Subsequently, conventional IVF was performed when the semen sample of the male partner was normal. Intracytoplasmic sperm injection (ICSI) was the treatment option in case of azoospermia or severe oligoasthenozoospermia. An average of three embryos was transferred between 40 and 44 hours post insemination at the 4–8 cell stage.
LPS was initiated on day 16 and continued for 10 days, from the day after insemination and from day of embryo transfer of OI, IUI and IVF respectively.

Group B received oral micronized progesterone 200 mg three times daily and Group C received oral dydrogesterone 10 mg three times daily. While Group B and C received LPS up to 12 weeks of gestation, Group A did not require this support. Serum β-hCG level was estimated 13 days after OI/IUI/ET to confirm pregnancy. If the test was positive, LPS was continued up to 12 weeks of pregnancy.

Following successful conception, all participants were followed up regularly. Fetal viability scan and detailed anatomy scans were performed at 6-7 weeks and 20-22 weeks of gestation,

respectively. Fetal echocardiography was performed at around 22 weeks of gestational age to exclude congenital cardiac defects. The women were routinely examined by the obstetrician and the babies thoroughly examined by a pediatrician during their postnatal visit. Electronic records till their postnatal checkup were maintained for all women. Demographic characteristics, pregnancy rate, miscarriage rate, congenital anomalies and fetal outcome were recorded. Information related to growth, learning abilities, psychological function were recorded by a trained child psychologist and trained nurses. The functional abnormalities in children were closely monitored.

Intervention Type
Supplement

Primary outcome measure
1. Congenital anomalies detected during pregnancy or following birth
2. Functional abnormality

Secondary outcome measures
1. Pregnancy rate
2. Miscarriage rate
3. Intrauterine fetal outcome (including gestational age)
4. Intrauterine growth restriction (IUGR)
5. Intrauterine fetal death (IUFD)
6. Neonatal characteristics including number of live births, body weight, APGAR score, neonatal intensive care unit (NICU) admission, respiratory distress syndrome (RDS), neonatal jaundice, hypoglycaemia and hypocalcaemia.

Overall study start date
08/01/2002

Completion date
30/06/2017

Eligibility

Key inclusion criteria
1. Female
2. Aged 21-45 years
3. Primary and secondary infertility (e.g. ovulatory and hormonal disorders, fallopian tube obstruction, endometriosis and having partners with male factor infertility)

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants

6298

Key exclusion criteria
1. Adenomyosis
2. Congenital uterine anomalies
3. Uterine synechiae
4. Baseline FSH >12 IU
5. Donor oocyte recipients
6. Gestational surrogates

Date of first enrolment
08/01/2002

Date of final enrolment
30/06/2017

Locations

Countries of recruitment
India

Study participating centre
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

Website

http://www.irm-bnc.org/contactus.php

ROR
https://ror.org/03jgxy838

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
A manuscript will be published in a peer reviewed scientific journal. Additional documents such as study protocol and statistical analysis plan are available upon request from the principal investigator, Dr. B.N. Chakravarty.

Intention to publish date
31/08/2019

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Baidyanath Chakravarty (irmbnc@gmail.com).
Type of data: Demographic data and baseline characteristics of women, fetal and neonatal outcome of women and congenital, functional and chromosomal anomalies in infants born to women with spontaneous conception during infertility investigation and those receiving luteal progesterone following OI/IUI/IVF.
Time duration for data: Data will be available after publication
Criteria for access data: any scientist or doctor

IPD sharing plan summary
Available on request