Effect of Phala Ghrita on Development of Ovarian Follicle Followed by Beejotsarga (Ovulation) in Patients of Infertility Due to Ovarian Factor in Comparison with Clomiphene Citrate

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Abstract---Background -Failure to ovulate is the major problem in approximately 30% - 40 % cases of female infertility. The Beeja is the core stone of the female reproductive process and absence of this factor Garbha cannot occur in spite of the proper Ritu, Kshetra and Ambu. Vagbhat stated the effect of Phalaghrita on Vandhyatva (infertility), so with an objective to study the effect of Phalaghruta in comparison with clomiphene citrate study will be carried out. Materials and methods-This Single blind(participant) randomized control clinical involves two groups with 30 subjects each. Group A (Study Group) will be treated with administration of Phala Ghritain the dose of 10 ml B.D. orally with Anupana of cow milk 100 ml. Group
(Control Group) will be treated with administration of Tab. Clomiphene citrate 50 mg O.D. orally for 5 days from day 3 to 7 of Menstrual cycle. Expected outcome - Primary outcome of study will be development of follicle and Beejotsarga (ovulation) and Secondary outcome will be conception. Conclusion- Effect of drug Phala Ghrita will be stated as per observed result.

**Keywords**--- beejostarga, clomiphene citrate, infertility, ovarian follicle, ovulation, phala ghrita.

**Introduction**

According to Indian culture marriages are a religious ritual necessary to each individual for completion of the life cycle to complete “Purushartha Chatushtaya”. Healthy progeny is the focal aim of marriages. Four vital factors are essential for formation of Garbha i.e.Ritu, Kshetra, Ambu, and Beeja. The union of Beeja of the both sides i.e. Shukra and Artava (ovum) with Atma inside the Kukshi is called Garbha. The Beeja is the fundamental part of the female reproductive process. Formation of Beeja takes place in ovary, so normalcy of ovary is important for Garbhahalan (Conception). Hence exploration of applied aspects of ovarian dysfunction is important along with Anatomical and Physiological aspects.

In Ayurvedic texts Beejotsarga (ovulation) process is elaborated. Vayu )Vata Dosha, Karma deeds (and Swabhava) nature (are accountable for folliculogenesis as well as ovulation) Ayurveda termed female infertility as Vandhyatva. Failure to achieve conception by a mature aged couple, having normal coitus during suitable period of menstrual cycle, on regular basis, for period of at least for one year is termed as infertility. Sushruta labelled Vandhyatva under Vandhyayonivyapada Harita cited six types of Vandhya with specific etiology for each with its prognosis Vagbhata mentioned different causes specially Abeejatva as a factor responsible for female infertility. Charaka in Sharir Sthana and Chikitsa Sthana has mentioned causes for Vandhayatva. Kashyap under chapter Revati Jataharni mentioned ‘Pushpaghni’ which can be co-related with anovulatory cause of infertility with obesity and hirsutism. In Madhava Nidana types of Vandhyatva has been described. Bhela has mentioned causes for Vandhyatva and classified it under Vata Vyadhis. Considering all the references, Revati Jataharini (Pushpaghni), Astaartava Dusti, Yonivyapada, Agnimandya, vitiation of Vata, Strotorodha, Avarana, Dhatuksaya are contributary aspects of Infertility due to Ovarian factors.

As per National Health Portal of India, 15% of reproductive-aged couples affected by infertility worldwide. World Health Organization estimated 3.9 to 16.8% of overall prevalence of primary infertility in India. The failure to ovulate is the major problem in approximately 30% - 40% cases of female infertility. This can be anovulation or severe oligo-ovulation. In the cases of oligo-ovulation even though the ovulation does occur, its irregular frequency decreases the chances of pregnancy. The ovarian dysfunction spectrum also includes development failure of an adequately functioning corpus luteum subsequent to ovulation. Hence females with issues of infertility needs an immediate attention; especially with ovarian
factor induced infertility. Effective treatment for infertility due to anovulation is found in modern medicine, but its side effects give worry in later stage. For induction of ovulation, hormonal based medicines are the drug of choice. Clomiphene citrate has risen as drug of choice in the induction of ovulation in the female. It is synthetic nonsteroidal triphenylethylene derivative. Alike other selective estrogen receptor modulators example, tamoxifen, it shows both estrogen agonist and antagonist properties, depending on the prevailing endogenous estrogen levels. Clomiphene citrate acts as estrogen agonist when extremely low endogenous estrogen levels otherwise, it acts as antiestrogen\textsuperscript{17}. It is seen very effective in many patients but still it causes various side effects like ovarian hyperstimulation, menstrual irregularity etc\textsuperscript{18}.

Ayurveda supported variety of herbo mineral medication, which may provide good results on these issues without any adverse effects. While thinking about applied aspect of Rachana Sharir in the context of female reproductive system, ovarian defects come in the priority area. Phala Ghrita is very popular classical formulation indicated in problems related to conception and infertility due to various causes. It is used for various Yonivapats, infertility, Graharoga also having Medhya, Balya, Dehavardhan, properties. It is one of the most commonly prescribed classical Ayurvedic formulation for reproductive problems. Sharangadhara, Vagbhata, Yogratanakar and Bhavprakasha mentioned Phalagrittha in treatment of Vandhyattva. According to Vagbhata, Phalasarpi Phalaghrita (which comprises Kalka of Manjishta, Kushtha, Tagara, Amalaki, Haritaki, Vibhitaki, Vacha, Haridra, Daruharidra, Madhuka, Deepyaka, Katuohini, Payasya, Hingu, Musali, Vajigandha and Shatavari, each taken in equal quantity). The ghee was prepared by adding ghee, milk and sugarto the Kalka as per Snehapakamethod\textsuperscript{19}. Various research works were done to evaluate the efficacy of Phala Ghrita administered in the cases of infertility\textsuperscript{20}. Phala Ghrita was found effective on infertility especially infertility due to cervical\textsuperscript{21} and uterine factors\textsuperscript{22} through oral and intra uterine route. Whereas no studies were carried out to find out its role in development of follicle and Beejotsarga (ovulation) in the cases with un-ovulatory cycles. Thus, considerable knowledge gap exists regarding the mode of action of Phala Ghrita, especially its role on structural development of follicle and functional development of female reproductive system in terms of Beejotsarga (ovulation) in anovulatory/Oligo ovulatory cycle. Hence present study is proposed to evaluate the development of follicle followed by Beejotsarga (ovulation) through treatment of Phala Ghrita in comparison with Clomiphene Citrate in patients of infertility due to ovarian factor induced.

### Table 1

Properties of ingredients of Phala Ghrita

<table>
<thead>
<tr>
<th>Sr</th>
<th>Drug</th>
<th>Part used</th>
<th>Rasa</th>
<th>Guna</th>
<th>Virya</th>
<th>Vipaka</th>
<th>Dosha-ghnata</th>
<th>Karma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Manjistha (Rubia Cordifolia)</td>
<td>bark</td>
<td>Tikta</td>
<td>Guru</td>
<td>Ushna</td>
<td>Katu</td>
<td>KaphaPitta</td>
<td>JwaraVarnyakara, VishnayaYonivikar, Kushta</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kashay</td>
<td>Ruksha</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Madhura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Kushtha (Saussurealappa)</td>
<td>root</td>
<td>Tikta</td>
<td>Laghu</td>
<td>Ushna</td>
<td>Katu</td>
<td>VataKapha</td>
<td>Analomana, Vrushya, Artavajanana, Garbhashayottejaka</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Katu, Madhura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aim and objectives

Aim: Evaluation of developmental changes in ovarian follicle followed by Beejotsarga (ovulation) through treatment of Phala Ghrita in comparison with Clomiphene citrate in the patients of infertility due to ovarian factor.

Primary Objectives

- To assess developmental changes in ovarian follicle followed by Beejotsarga (ovulation) through treatment of Phala Ghrita.
• To assess developmental changes in ovarian follicle followed by Beejotsarga (ovulation) through treatment of clomiphene citrate.
• To compare the efficacy of Phala Ghrita and Clomiphene citrate on developmental changes in ovarian follicle followed by Beejotsarga (ovulation).

Secondary Objectives

• To access the effectivity of both drugs on secondary outcome i.e. conception
• To evaluate the effect on of both drugs menstrual abnormalities if any
• To analyze effects of both drugs in the context of different Deha Prakruti

Material and Methods

Study Design - This study will be single blind(participant) randomized control clinical trial in which sample will be collected with computer generated Simple Random method. Study involves two groups with 30 patients in each group. Group A (Study Group) will be treated with Phala Ghrita orally and Group B (Control Group) will be treated with Tab. Clomiphene citrate.

Outcomes: Primary – Development of follicle and Beejotsarga (Ovulation), Secondary – Conception

Source of Data

Subjects will be collected from approved centers by D.M.I.M.S. (D.U.), Wardha. Mahatma Gandhi Ayurved College, Hospital and Research Centre, Salod (H). Sample size was calculated by software n Master 2.0 by which total 60 subjects will be enrolled considering 10% drop out rate and distributed evenly into two groups by random sampling. The groups will be as follows.

• Group A - study group with 30 patients – Phala Ghrita treatment
• Group B - control group with 30 patients – Clomiphene citrate treatment

Intervention and Grouping

• Group A (Study Group):
  Treated with Phala Ghrita
  Route - Oral
  Dose - 10 ml B.D.
  Anupana – Cow milk 100 ml
• Group B (Control Group):
  Treated with Tab Clomiphene citrate
  Route - Oral
  Dose – 50 mg O.D. for 5 days from day 3 to 7 of Menstrual cycle
  Anupana – Plane Water

Inclusion criteria

• Females having active married life and unable to conceive from 1 year.
- Patients with primary or secondary Infertility due to ovarian factors
- Irregular or scanty menses due to anovulatory cycle
- Unruptured ovarian follicle

Exclusion criteria

- Females less than 18 years and non-fertile age group patients
- Infertility other than ovarian causes e.g. cervical, uterine causes.
- Congenital anomalies in female genital tract
- Known Tubercular endometritis, Malignant and cytotoxic patients
- Non-Cooperative patients

Figure 1. Plan of work
Table 2
Details of method and experimental design

<table>
<thead>
<tr>
<th>Heading</th>
<th>Group A (Study Group)</th>
<th>Group B (Control Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Intervention</td>
<td>Phala Ghrita</td>
<td>Tablet Clomiphene citrate</td>
</tr>
<tr>
<td>Dose</td>
<td>10 ml B. D.\textsuperscript{23}</td>
<td>50 mg O. D. for 5 days\textsuperscript{24,25}</td>
</tr>
<tr>
<td>Anupan</td>
<td>100 ml Cow Milk</td>
<td>Water</td>
</tr>
<tr>
<td>Duration of Intervention</td>
<td>60 days</td>
<td>5 days/cycle- started from day 3 – 7 of menstrual cycle up to 2 cycles.</td>
</tr>
<tr>
<td>Follow up</td>
<td>Cycle- 1 TVS from day 10\textsuperscript{*}</td>
<td>Cycle- 1 TVS from day 10\textsuperscript{*}</td>
</tr>
<tr>
<td></td>
<td>Cycle- 2 TVS from day 10\textsuperscript{*}</td>
<td>Cycle- 2 TVS from day 10\textsuperscript{*}</td>
</tr>
<tr>
<td></td>
<td>Cycle- 3 TVS from day 10\textsuperscript{*}</td>
<td>Cycle- 3 TVS from day 10\textsuperscript{*}</td>
</tr>
<tr>
<td></td>
<td>Post Test Sampling</td>
<td>Post Test Sampling</td>
</tr>
<tr>
<td>Total trial duration</td>
<td>90 days</td>
<td>90 days</td>
</tr>
</tbody>
</table>

\textsuperscript{*} - as per Transe Vaginal Sonography Protocol

**Preparation of trail drug**

- All the raw ingredients will be collected and authentication will be done at Department of Dravyaguna, M.G. A. C. Salod, Wardha
- Phala Ghrita will be prepared according to textual reference of Ashtanga Sangraha Uttara 38/110-111 in the Pharmacy of M. G. A. C. Salod, Wardha. Prepared Ghrita will be package in PET jars with quantity of 300 gm.
- Prepared product will be standardized at Central Laboratory of M. G. A. C., Salod, Wardha.

**Control drug**

Tablet clomiphene citrate – 50 mg of reputed brand will be dispensed to patients under guidance of department of Gynecology.

**Detailed plan of treatment**

- Already diagnosed/patients coming to O.P.D. with the complaints of anovulation/ infertility due to Ovarian factors / referred from other centers as per selection criteria will be selected for screening after written consent.
- Screening- Trans vaginal Sonography (T.V.S.) will be done from day 10\textsuperscript{th} of menstrual cycle up to at least 20th day of cycle to diagnose status of ovulation.
- After confirmation of diagnosis grouping of patients will be done as per computerized randomization and treatment will be started.
- Patient will be called for T.V.S. from 10\textsuperscript{th} day of Menstrual cycle as per TVS protocol by sonologist.
- Oral administration of drugs will be given up to maximum 60 days or conception.
• Group A (Study Group) will be treated with ‘Phala Ghrita’ in the dose of 10 ml B.D. with 100 ml lukewarm cow milk preferably empty stomach
• Group B (Control Group) will be treated with tablet Clomiphene citrate in the dose of 50 mg O.D. at morning for 5 days from day 3 to 7 of menstrual cycle
• T.V.S. will be carried out for Consecutive 2 cycles during trials and 1 cycle after completion of trial or conception.

Screening parameters

• Trans Vaginal Sonography (B.T. & A.T.) for the ovulation study.
  (Trans vaginal Sonography will be done from day 10th of menstrual cycle up to at least 20th day of cycle to diagnose status of ovulation. T.V.S. will be carried out Consecutive 2 cycles during trials and 1 cycle after completion of trials.)
• Hormonal assay – FSH, LH, TSH, PRL

Subjective parameters

Table 3
Frequency of menses

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular (Cycle of 21 to 35 Days)</td>
<td>0</td>
</tr>
<tr>
<td>Irregular (Cycle of &lt;21 to &gt;35 Days)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4
Bleeding quantity

<table>
<thead>
<tr>
<th>Amount of bleeding</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotting</td>
<td>0</td>
</tr>
<tr>
<td>scanty</td>
<td>1</td>
</tr>
<tr>
<td>moderate</td>
<td>2</td>
</tr>
<tr>
<td>excessive</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 5
Duration of Bleeding

<table>
<thead>
<tr>
<th>Type</th>
<th>Days</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpartava</td>
<td>1 or &lt;1 day</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2 days</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>4 – 7 days</td>
<td>0</td>
</tr>
<tr>
<td>Atyartava</td>
<td>8 days</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>9 days</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10 or &gt; 10 days</td>
<td>3</td>
</tr>
</tbody>
</table>
Menstrual pain will be assessed by VAS scale

**Objective parameters**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Follicle size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 - 12 mm</td>
</tr>
<tr>
<td>1</td>
<td>12- 18 mm</td>
</tr>
<tr>
<td>2</td>
<td>19 - 23 mm</td>
</tr>
<tr>
<td>3</td>
<td>Ovulated</td>
</tr>
</tbody>
</table>

**Table 7**

<table>
<thead>
<tr>
<th>Grade</th>
<th>thickness of endometrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;5 mm</td>
</tr>
<tr>
<td>1</td>
<td>5-7 mm</td>
</tr>
<tr>
<td>2</td>
<td>7-9 mm</td>
</tr>
<tr>
<td>3</td>
<td>&gt;9 mm</td>
</tr>
</tbody>
</table>

**Assessment of total effect of the therapy**

<table>
<thead>
<tr>
<th>Effect of Therapy</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1 Complete Remission | If ovulation occurs it will be considered as complete remission OR patient get conceived.  
Improvement in size of follicle up to fully mature size i.e.up to 19-23 mm size will be considered as markedly improved. |
| 2 Markedly Improved | Improvement in the size of follicle i.e.12-18 mm will be considered as Moderately improved. |
| 3 Moderately Improved | No improvement in the size of follicle i.e. les than 12 mm will be considered as Not improved. |
| 4 Not Improved | Secondary outcome: Conception |

**Analysis plan (Statistical test)**

- Interim analysis will be done.
- I.T.T.
- Statistical assessment will be done through paired t test and unpaired test
Outcome

- Primary - Development of follicle and Beejotsarga (Ovulation)
- Secondary - Conception

Discussion

This study may contribute as effective treatment in the cases of ovarian failure as easy and safe therapy. This study can create wide scope to promote Ayurveda in flourishing infertility clinic sector. If the effectiveness of trial drug is proved as a management of ovarian failure, then it will prove great hope for childless couples suffering due to this problem. This will set a standard treatment for induction of ovulation. If trial drug is proved effective, it can be used as alternative treatment in management of infertility due to abnormal development of ovum and ovulation. This study may contribute as alternate treatment for induction of ovulation. This study may also useful for females having risk factors of ovulation related infertility. Further researches of present drug can be carried out for various other causes of infertility.

Conclusion

This study can be used as alternative treatment in management of infertility due to abnormal development of ovum and ovulation. This study will contribute as alternate treatment for induction of ovulation. This study will also useful for females having risk factors of ovulation related infertility as a preventive measure.

Type of Article – Study Protocol
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Ph.D. Registration Letter no. – DMIMS(DU)/PhD Regn/2020/538 Dated 10.10.2020
Conflict of Interest – None

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