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Effect of Ayurvedic Treatment Protocol on Diminishing Ovarian Reserve

Research Article

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Abstract

Diminishing ovarian reserve (DOR) is a condition in which the ovary loses reproductive potential, compromising fertility. Nowadays 10-30% of female infertility is due to DOR and considered as "expected poor responder" for In vitro fertilisation (IVF). Correlation of DOR can be done with *Dathukshaya vandya* (depletion or inadequate formation of *dhatus*) explained in *Harithasamhita*. The objective of the study was to evaluate the effect of Ayurvedic treatment protocol on Diminishing ovarian reserve. The study protocol includes- *ashtachurna* for *deepana* (appetiser), *pachana* (digestives) and *kolakulathadi churna* for *udwarthana* (powder massage). *Sukumaragrutha* used for *snehapana* (oral administration of medicated ghee), *utharabasthi* (intrauterine administration) *and rasayana* (rejuvenation therapy). *Danwantarathaila abhyanga* (oleation) and *ooshmasweda* (sudation) done for 3 days. *Sukumaraeranda* was used for *virechana* (therapeutic purgation) and also *Yogabasthi* (medicated enema). The study design was pre and post interventional study with a sample size of 15 selected as per inclusion and exclusion criteria, conducted at hospital for women and children, Government Ayurveda College, Thiruvananthapuram. Assessment was based on Bologna criteria for DOR. The statistical techniques employed are Wilcoxon's signed rank test and Paired t test. Results showed statistically significant effect on improving Antral follicle count (AFC) (p- 0.01), Estradiol (p- 0.005), conception (p- 0.014), on regulating amount of bleeding (p- 0.003), menstrual interval correction (p-0.001) and dyspareunia (p-0.005). But insignificant effect on improving Anti Mullerian Hormone (AMH) (p- 0.469) and regularising LH/FSH ratio (p-0.104) was found.

Key Words: *Dhatukshaya vandhya, AMH, AFC, LH, FSH, Estradiol, Yogavasthi, Snehapana.*

Introduction

Diminishing ovarian reserve (DOR) refers to the reduction of oocyte quantity, quality and reproductive potential (1). As per European Society of Human Reproduction and Embryology (ESHRE) & Bolognas criteria for DOR at least any of the two of the following should be present i.e. Age<38 years, abnormal ovarian reserve test, and poor response to previous stimulated cycle(2). Nowadays 10-30% of female infertility is due to DOR (3). As per Institute for social and Economic Change (ISEC) survey 14% of Indian women attains menopause between the ages of 29-34 years (4) Aetiologies are heterogeneous, associated with X chromosome abnormalities causing ovarian dysgenesis (5). Other factors include autoimmune (auto-reactive lymphocytosis, organ specific autoantibodies), iatrogenic (chemotherapy, ovarian drilling and uterine artery embolization), oxidative stress (ROS-induced DNA damage causes granulosa cell apoptosis, follicular atresia, chromosomal abnormalities) and endocrine disrupting chemicals (e.g. Polycyclic aromatic hydrocarbons, tobacco (6). Exact mechanism for development of DOR is obscure. It can be due to preliminary decrease/ defective maturation/ recruitment of primordial follicles and accelerated atresia of follicles. Clinical features include vasomotor symptoms such as hot flushes, osteoporotic changes, vaginal dryness, dyspareunia, sleep disturbances and mood swings etc. The long term consequences are infertility, premature ovarian failure, osteoporosis, cardiovascular, neurologic diseases and risk of premature death (7).

Table 1: Assessment factors (8)

Assessment factors	Levels (DOR)
Basal Antimullerian Hormone (AMH)	Below 1.5 ng/dl
Basal Follicle stimulating hormone (FSH)	10 - 15 IU/ L
Basal Estradiol	60 - 80 pg/ ml
Basal Inhibin B	Less than 400 pg/ ml
Ultra sonography	• Antral follicular count (AFC< 10 both ovaries) • Ovarian volume, Ovarian artery blood flow

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Dynamic test	• Clomiphene citrate challenge test (CCT), Exogenous FSH ovarian response (EFTORT), Gonadotropin agonist stimulation test (GAST)

In conventional medicine system the treatment options are limited. DOR is considered as "expected poor responder" for In vitro fertilisation (9). Adjuvant therapy with LH, DHEA and growth hormones shows some benefit in oocyte yield but long term treatment may leads to conditions like breast CA, ovarian CA and fibroid uterus etc (10).

Anapathyatha/ Vandhyaha is one among *vaataja yonivyapath* and mentioned as symptom, sign and complication of diseases. It means failure to achieve a child rather than pregnancy as *garbha strava* (repeated abortions) and *mrutvatsa* (repeated still births) are also included in types (11). Improper dietetics and mode of life, abnormalities in the *sukra* (spermatozoa) and *asrug* (oocyte), diseases of reproductive tract, *akalayoga* (sexual intercourse during non-ovulatory phase) and *balakshaya* (reduction of reproductive potential) all are included in the causative factors (12). As per Ayurveda, DOR can be most appropriately correlated with *Dathukshaya vandya*, explained in Haritha samhita (13). It is due to depletion or inadequate formaton of *dhatus* which leads to reduction in fertility potential and ultimately anapathyatha. Vandhya chikithsa in Ayurveda comprises a multifactorial approach *rasayana chikitsa* followed by *shodhana* is found to have promising results in management of DOR.

Objective

To evaluate the effect of Ayurvedic treatment protocol on Diminishing Ovarian Reserve.

Methodology

Single group**,** pre and post interventional study with sample size of 15 was conducted in the OPD and IPD of Govt. Ayurveda college Hospital for women and children, Thiruvananthapuram. Inclusion criteria: Females in the age group 20-35 years, diagnosed as per Bologna criteria.

Exclusion criteria: Peri- menopausal women, systemic illness excluding diabetes mellitus and thyroid dysfunction, history of chemotherapy, ovarian drilling and auto immune disease.

Sampling technique: Consecutive selection of subjects satisfying inclusion and exclusion criteria

Primary outcome variables: Basal values of AMH, LH/FSH ratio, AFC, and Estradiol.

Secondary variables: Conception, Amount of menstrual bleeding, Menstrual interval dyspareunia

The statistical techniques: Descriptive statistics, Wilcoxon's signed rank test and Paired t test.

Table 2: Description of study protocol

Day	Treatment Protocol	Medicine
1st-5th	*Deepana- Pachana* (digestives & appetisers)	*Ashtachurna* (14) Dose- 15 gm BD orally
1st-5th	*Udwarthanam* (Powder massage)	*Kolakulathadi churna* (15)
6th-12th	*Snehapanam* (Internal administration of medicated ghee)	*Sukumara grutham* (16). Progressively increasing dose 25 ml to 175 ml
13th-15th	*Abhyanga and ooshma sweda*. (Oleation & sudaton for 30 minutes)	*Dhanwantharam thailam* (17). Dose- Quantity sufficient.
16th	*Mruduvirechanam*. (Therapeutic purgation)	*Sukumara erandam*. Dose- 20 ml on empty stomach
17th	Rest	
	YOGA BASTHI (Therapeutic enema)	
18th	*Sneha basthi*. (Enema with medicated oil)	*Dhanwanthara thailam*. Dose – 60 ml
19th	*Sneha basthi*	*Dhanwantharam thailam*, -60ml
20th	*Kashaya basthi*. (Medicated decoction enema)	*Sapthasaram kashayam* (18), -480 ml *dhanwantharam thailam*- 120 ml, *sathapushpa kalkam* 30 gm, *Saindavam*10gm *and madhu* 120 ml.
21st	*Sneha basthi*	*Dhanwantharam thailam*. 60 ml
22nd	*Kashaya basthi*	*Sapthasaram kashayam 480 ml*, *Dhanwantharam thailam* 120 ml.
		Sathapushpa kalkam 30 gm, *Saindavam* 10gm, *Madhu* -120 ml

23rd	*Sneha basthi*	*Dhanwantharam thailam*. -60 ml
24th	*Kashaya basthi*	*Sapthasara kashayam*-480 ml *Dhanwantharam thailam*- 120 ml
		Sathapushpa kalkam, - 30 gm *Saindavam*10 gm *and Madhu*-120ml
25th	*Sneha basthi*	*Dhanwantharam thailam*.60 ml
26th-28th	*Uthara basthi*. (Intrauterine instillation of medication)	*Sukumaram grutham*- 30 ml
60days	*Rasayana* (Rejuvenation therapy)	*Sukumara grutham*

The study was commenced after the 4th day of menstrual cycle and *sodhana* suspended during bleeding phase.

Result

Analysis showed among the study population 80% were *vata-paithika prakruthi* (body constitution) and 20 % *vata-kapha prakruthi*. Regarding psychological statuses 46.67 % anxious and 26.67% were depressed. Majority of patient had relevant family history of premature menopause (33.33%). In the population (80%) were passive smokers. Primary infertility was reason for encounter among all the subjects. All the subjects had history of negative results for stimulation strategy. Detailed clinical picture are shown in the diagram 1, 2.

Diagram: 1 Data regarding treatment history

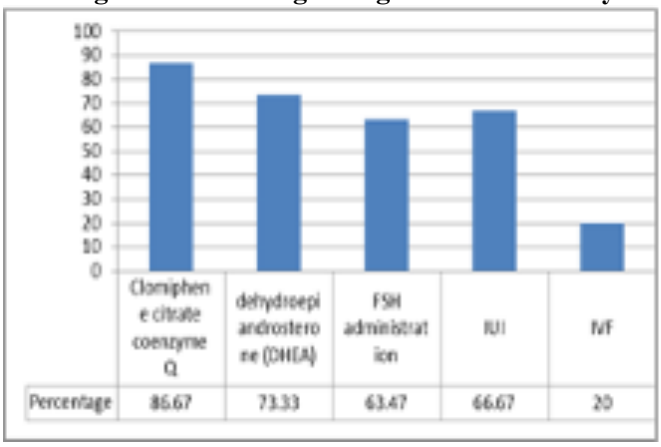


Diagram: 2 Data regarding clinical picture

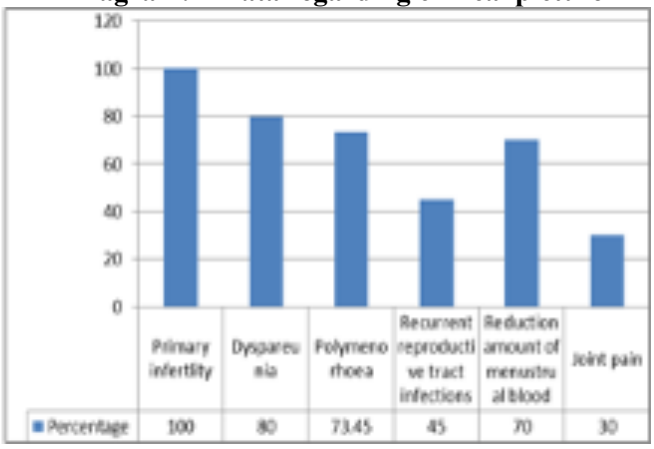


Table 3: Data related to effectiveness of treatment on AMH &AFC

No	AMH BT (pmol/L)	AMH AT (pmol/L)	AFC BT	AFC AT(3 months)	AFC AF (6 months)
1	3.99	4	5	8	6
2	8.72	8.1	5	10	9
3	3.57	4.29	2	10	Conceived
4	11.74	7.46	6	12	7
5	10.26	20.2	6	8	Conceived
6	15	34.28	5	7	6
7	7.46	Conceived	2	Conceived	Conceived
8	1.36	Conceived	4	Conceived	Conceived
9	8.31	6.9	2	14	10
10	7.31	4.3	6	16	8
11	2.71	3.5	3	15	12
12	12.27	12.95	4	4	4
13	12.74	9.006	6	11	12
14	12.12	11.9	3	11	10
15	5.53	4.2	5	8	6

Two patients conceived during treatment and 4 patients conceived after treatment. A patient who was suggested IVF with donor oocyte (AMH level 1.36 pmol i.e. very low fertility rate) conceived after treatment. Data on pre-test and post-test were collected for parameters for rest of the subjects (n=13). Data was assessed with paired t-test and Wilcoxon's signed rank test.

Diagram no.3: Data related to AFC

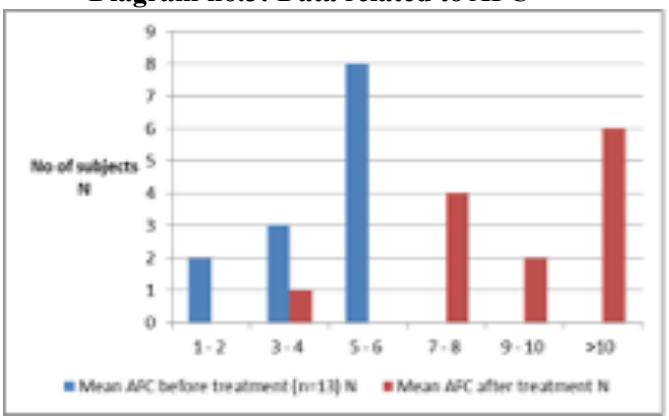
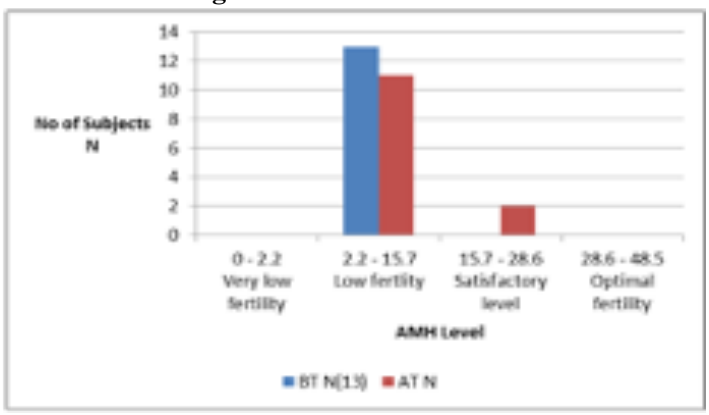


Diagram no.4: Data related to AMH



BT – Before treatment, AT – After treatment, AF – After follow up

Diagram no.5: Data related to LH/FSH

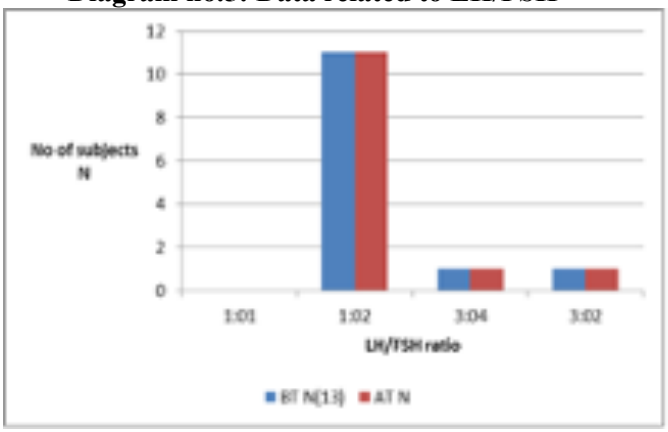


Diagram no.6: Data related to Esrtadiol

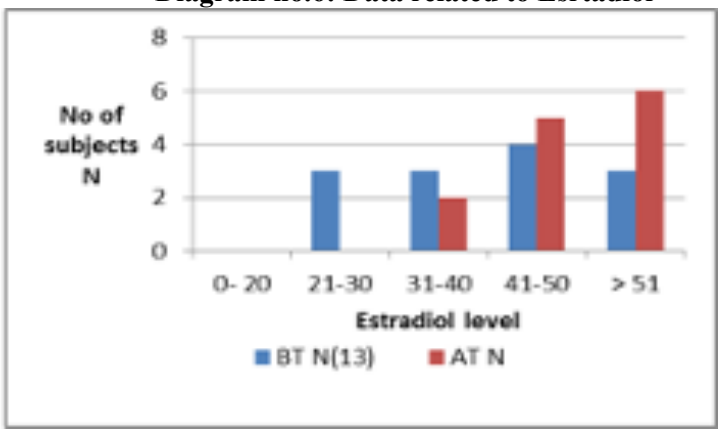


Diagram no.7: Data related to Conception

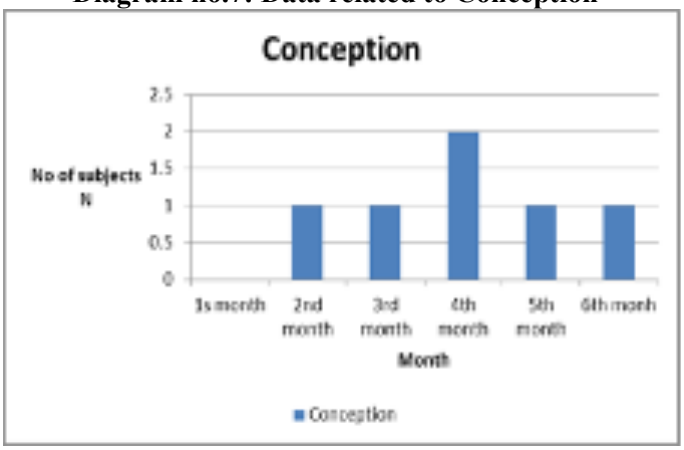


Diagram no.8: Data related to bleeding

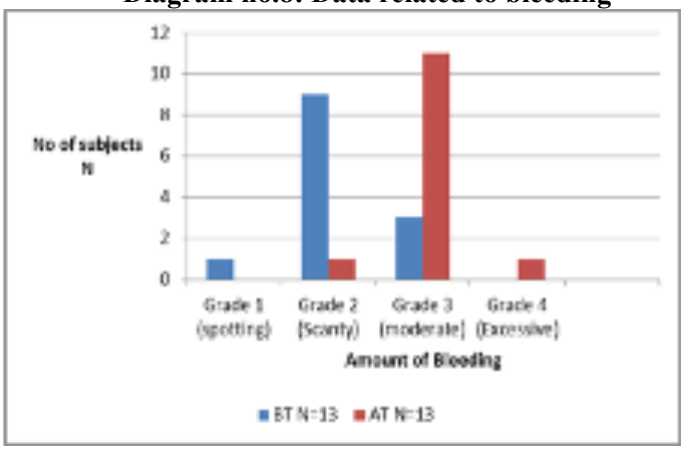


Diagram no.9: Data related to menstrual interval

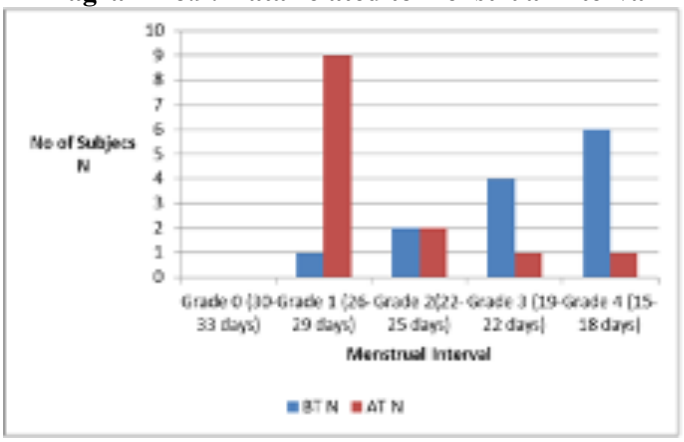


Diagram no.10: Data related to Dyspareunia

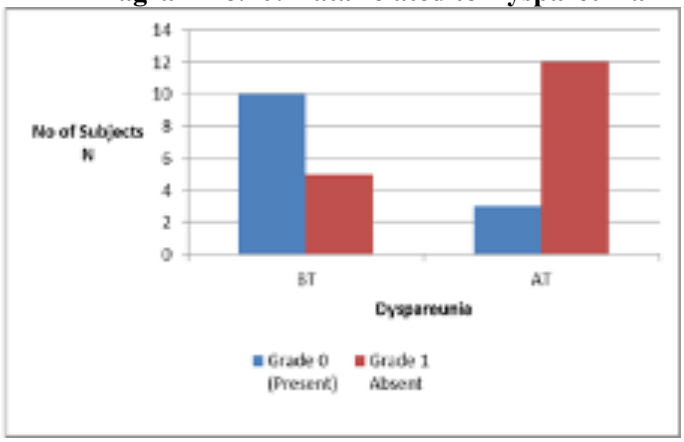


Table 4: Paired t-test results

Variable	Test	Z	P
Conception	AF-BT	-2.249	0.0414
Amount of bleeding	AT-BT	-3	0.003
Menustral interval	AT-BT	-3.225	0.001
Dyspareunia	AT-BT	-2.828	0.005

Table 5: Wilcoxon's signed rank test results

Variable	Test	Z	P
Conception	AF-BT	-2.249	0.0414
Amount of bleeding	AT-BT	-3	0.003
Menustral Interval	AT-BT	-3.225	0.001
Dyspareunia	AT-BT	-2.828	0.005

Results showed statistically significant values obtained on conception (p-0.014, six patients conceived among 15 subjects), regulating amount of bleeding (p-0.003), menstrual interval correction (p-0.001), minimising dyspareunia (p-0.005), and improving AFC (p-value <0.01). After treatment no considerable change in ratio LH/FSH ratio (p-value 0.104) was found. Before treatment all the patients had normal level of mean ovarian volume (>15 cc) Majority were under the group7-9 cc and after treatment no difference was observed. As the paired t test showed a p-value 0.005, it can be concluded that there is statistically significant increase of S. Estradiol before treatment and after treatment. After treatment considerable increase in value AMH was not found. As the paired t test showed a p-value 0.469 (i.e., p >0.05), it can be concluded that there is statistically insignificant difference between AMH before treatment and after treatment (details are given in table 4,5).

Discussion

From the broad references described in the classics the condition like *arthava kshaya* (19) due to *apakwa rasadhathu* formation as a consequence of *vishamagni* (20) can be considered as reduction in reproductive potential due to oxidative stress. Symptoms like *daaha, santhaapa* (hot flushes) *rajo athipravruthi* (shortening of menstrual cycle) are seen in early stages of DOR. When untreated and *apathya sevana* (unwholesome habits*)* is continued leads to *vaata vrudhi*, *pitha-kapha kashaya* causing *rasadi dhathu kshaya* i.e. *roopaavastha* (disease manifestation). *Vandhyathwa* (infertility) due to *beeja* dhushi as seen in *shanda*, *vartha* (21) etc. can be correlated with premature ovarian failure in X –linked chromosomal abnormities. In ovarian surgery *arthavavaha srotho vighatha* (22) can be seen leading to *arthava nasha* (destruction of follicular reserve), *vandhyathwa*m and *maithuna asahishnutha* (dyspareunia) gradually leads to *uthorathara dhathukshaya* (impaired formation of further dhatus) where *upadrava lakshanaas* (complications) like a*kala jara* and *bala kshaya* (e.g. symptoms of early aging.).

As per Ayurveda *vandhyathwa* is managed with *sodhanachikithsa* (body purification) and *utharavasthi* so as to get a healthy progeny devoid of *beeja dhushti* (abnormalities of germ cells). Ashta churna is used for *deepana* is *kaphavatahara* in action. As per Ashtanga hrudaya *dwividha upakramaneeya adhyaya, rookshana* should be done prior to *snehana chikithsa*. (23) Thus for *rookshana udwarthana* is carried out along with *deepana pachana*. Kolakulathadi churna is *vatakaphahara* in nature. It removes the *samaavastha* and detaches the vitiated *dhosha*s adhered to *srothas*. *Snehana* (*abhyanthara* and *bahyasneha)* done after *deepana- pachana*. *Saptha dhathu*s are formed from the essence of *sneha* thus proper *snehana* does *jaataragni vrudhi (*enhances digestive power), *koshta visudhi* (Purifies channels), formation of *prathyagra dhathu* (enhances quality of *dhatus*), *bala* (immunity) and *varna* (complexion) also increases life span. Sukumara ghritha is used for *snehapana*, as per indication it is *pushtidham* (improves vitality) also enhances *kanthi lavanya* (complexion), *yonishoolahara* (reduces painful conditions of reproductive tract) and also for men who are debilitated with excess sexual intercourse *(Nrinaam sthreevrinttha barthrunam alakshmi kali nashanam).* For *abhyanga dhanwantharam thailam* which is *tridhoshahara* is selected. According to indication it can be used in diseases of *vata* and diseases of female reproductive tract *(sarvavata vikarajith, kshata ksheeneshu poojitham yoniroga kshayapaham).*

Sodhana (vamana, virechana) done after *purvakarma* expels the vitiated *dhosha*s from *koshta*. As per kasyapa *virechana* is the main treatment for improving *beeja karmukatha* (increased fertility potential of germ cells) (24). It pacifies the vitiated *kapha* and *vatadosha* and removes vitiated excessive *Pitta* and thus does *raktashodhana* (blood purification). In the present study *mrudhu virechana* with sukumara eranda (dose 20 ml) was opted as it is a *dhatuksheena avastha* (debilitated condition). As it was *mudu shodhana* one day *samsarjana karma* (regimen after *sodhana*) was done. *Vasthi karma* is indicated in *alparaja* and *anarthava* (conditions associated with male and female infertility) especially *yapanna vasthi* is indicated in infertility.(25) Here *madhuthailika vasthi* is chosen is having *bhrimhana* in nature and the drugs are *dhanwnatharam thailam* as *snehadravya*, *sapthasaram kashayam* which is *kapha vatahara* in nature and indicated in diseases of yoni (reproductive organs). *Utharavasti* should be administered after *sodhana*. It facilitates direct drug administration into uterus and accelerates formation of *avyapanna garbhava samagri* (factors essential conception). As per Charaka substance which maintains health by producing the best quality of *rasa*, *rakta dhatu* etc *dhatu*s are called as *rasa*yana. It is *vayasthapana*, *ayushkara, medhakara and urjaskara* (delays aging process, improves memory power and vitality). (26) Thus the medicines included in treatment protocol will enhance production of *avyapanna garbha sambhava samagri* and hence the preservation of fertility status can be restored.

Role of *vata* in the manifestation of disease was substantiated by prakruthi assessment i.e *vata-paithika, vata-kapha prakruthi* of subjects. Strong association of passive smoking was found. Tobacco is an endocrine disrupting chemicals (EDCs) causing alteration of ovarian function. EDCs can be correlated with *dhushivisha* (substances in small doses are asymptomatic but cumulative effect are hazardous). When accumulated over *rasadi dhathu*s causes *pradhoshaja rogas* (diseases due vitiation of dhathu) like *vandyathwa* (27). Primary infertility, shortening of menstrual cycle, scanty menstruation, hot flushes and dyspareunia are seen in all cases. The study was significant at 1% level on conception (46.15%), normalizing menstrual interval, increasing amount of bleeding, AFC, and dyspareunia though it was not effective in increasing in AMH, and regularising FSH/ LH ratio. All the subjects had treatment history unresponsive to stimulation strategy. Conception was occurred in a patient suggested IVF with donor oocyte having AMH level 0.01 (very low fertility rate), AFC= 0 (value BT) got conceived and also in patients who had AMH level below satisfactory level. This indicates AMH is not a determining factor and there are other unknown factors which favors fertility potential of oocyte. Increasing basal values of antral follicles, esteradiol indicates appropriate oogenesis. Adopted protocol improves the quality of ovum thus restoration of fertility potential, along with reduction in the magnitude of associated complaints. Cost effectiveness, enhanced safety and efficacy will benefit for the society and will project Ayurveda into the main stream treatment.

Conclusion

Study shows significant effect on markers of ovarian reserve such as antral follicle count and estradiol and also in the clinical parameters such as conception, regulating menstrual bleeding pattern, interval and dyspareunia. But significant effect on Anti Mullerian Hormone and regularising LH/FSH ratio was not found. For precise data researches on larger samples have to be conducted. Pregnancy is the conclusive evidence for restoration fertility potential. Even though conspicuous change in the markers of ovarian reserve was established it's evident that the study is effective in managing diminishing ovarian reserve.

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