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EFFECTIVENESS OF PUSHPADHANVA RASA IN ANOVULATORY FACTOR OF VANDHYATVA.

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ABSTRACT

Introduction: Infertility is presently a leading and longstanding gynaecological issue affecting approximately 10-15% in Indian population, of which anovulation accounts for 40% of all its' causes. The incidences of complications of ovulation inducing drugs of modern medicine are found widely. On the contrary, safer, holistic, yet fast acting *rasaushadhi* (herbo-mineral drugs) formulations are mentioned in Ayurveda. The present study, thus aimed at evaluating the ovulation inducing effect of *Pushpadhanva rasa* by comparing with modern drug, Clomiphene citrate. **Methodology:** The study was conducted among 30 female subjects, diagnosed of anovulation with either primary or secondary infertility, fulfilling the inclusion criteria, randomly allocated into two equal groups. Group A received *Pushpadhanva rasa vati* (250 mg twice a day with milk, honey and sugar before food, from 1st day of menses till 20th day), while Group B was administered with Tab. Clomiphene citrate (50mg OD, from day 2 of menses, for 5 days) for three menstrual cycles. The observations and results were assessed by follicular study conducted from 9th day of menstrual cycle till 20th day for three consecutive cycles. **Results:** Ovulation was observed in 40% of subjects in Group A and 53.3% of subjects in Group B. **Discussion:** *Pushpadhanva rasa* has ingredients which pacify *vata, pitta* and *kapha dosha* thereby resulting in normal functioning of H-P-O axis, *beejotpatti* (oogenesis) and *beeejotsarga* (ovulation). **Conclusion:** Though *Pushpadhanva rasa* showed comparatively less percentage of improvement, it proves to be effective due to absence of side effects like ovarian hyper-stimulation, multiple pregnancies.

KEYWORDS: *Vandhyatva*, Anovulation, Infertility, *Pushpadhanva rasa.*

INTRODUCTION

The statement- '*Yadapatyanam moolam naryaha param nrinaam.*'[1] suggests the significance of female in achieving a progeny. Since times immemorial, possessing an offspring has been considered as a tool for assessing well-being, prestige and happiness of a couple in the society. Thus, reproducing a progeny is considered imperative, from a human, individual and social standpoint. Therefore, incapability to reproduce, termed as *Vandhyatva* in *Ayurveda*, is considered undesirable and as a matter of misfortune. In modern terminology, *Vandhyatva* can be correlated to infertility, which refers to inability to conceive even after regular unprotected intercourse for one year one more.

Anovulation is a condition wherein ovaries fail to release an ovum, accounting for about 40% of the causes of female infertility and often presents with oligomenorrhoea or amenorrhoea. Although the therapeutic armamentarium has developed significantly, in recent years, clomiphene citrate is considered as the most appropriate initial drug of choice in the largest majority of anovulatory infertility cases. *Ayurveda* has a precise literature on *nidana*, *samprapti* and *chikitsa* of *Vandhyatva*. Any disruption in *garbhadharana* is credited to the abnormalities or absence of either of the *garbhasambhava samagri*, namely *rutu*, *kshetra*, *ambu* and *beeja.*[2] *Tridosha dushti* with exclusive dushti of *apana vata* are responsible for *abeejotpatti* (lack of growth of follicles) and *Abeejotsarga (anovulation).*

The diversity of possible aetiological factors, wide ranging and grave impact of anovulation on hormonal symphony and consequently on fertility and psychology of infertile couple, calls for a meticulous concern and prompt management of anovulatory patients seeking fertility. Moreover, the present scenario necessitates a critical study and application of specific *rasaushadhis* like *Pushpadhanva rasa*, which are safer, cost-effective, holistic, yet fast acting formulations contradictory to the modern treatment protocols which account for growing incidences of complications of ovulation induction. The present study, thus aimed at evaluating the ovulation inducing effect of *Pushpadhanva Rasa* by comparing the same in the modern drug, Clomiphene citrate.

AIMS AND OBJECTIVES

Aim: Aim of the present study was to elicit the effectiveness of *Pushpadhanva rasa* in *Vandhyatva* with special reference to anovulation.

OBJECTIVES

Objectives of the study were to study the effect of *Pushpadhanva rasa* in ovulation induction and also to compare the efficacy of *Pushpdhanva rasa* and Clomiphene citrate on ovulation induction.

MATERIALS AND METHODS

Clinical source

Either women with primary or secondary infertility fulfilling the inclusion and exclusion criteria were registered for the study from out-patients department of Prasuti Tantra Evum Stri Roga of Parul Ayurveda Hospital and Parul Sevashram Hospital (Urban Health Training Centre), Raopura.

Drug source: *Pushpadhanva rasa* - The *bhasmas* required for the drug preparation were procured from Bharadwaj Pharmaceutical works, Indore. Few drugs required as *Bhavana dravyas* were obtained from authentic suppliers while others were procured by collecting from the natural source. All the ingredients and *bhavana dravyas* were used after identifying and assuring the quality of each drug from the Department of Rasashastra and Bhaishajaya Kalpana as well as Department of Dravyaguna, PIA, Parul University. The preparation of *Pushpadhanva rasa* was done in the GMP certified Pharmaceutical unit of Parul Institute of Ayurveda, according to the classical reference of *Yoga tarangini* (Rasatarangini, Parishishta, pg.no.766).Clomiphene was purchased and dispensed from UHTC, Raopura.

Drug Manufacturing

The ingredients, *rasasindoora, naga bhasma, vanga bhasma, loha bhasma* and *abhraka bhasma* were taken 100 gm each in a *Khalva yantra* and were mixed uniformly. *First bhavana* of *dhattura (Dhatura stramonium) patra swarasa* was given for 10 hrs. *Bhanga (Cannabis sativa) patrashodhana* was done by *dolayantra swedana* with *baboola twak kwatha* for 2 hrs. The *shodhitapatra* (purified leaves) were dried in sunlight. *Kwatha* was prepared out of the dried *shodhita patra* and second *bhavana* with *Bhanga patrakwatha* was given for 12 hrs. Third *bhavana* was given with *Yashtimadhu (Glycyrrhiza glabra) moola kwatha* for 11 hrs. *Shalmali (Salmalia malabarica) twak kwatha* was made and fourth *bhavana* was given with it for 10 hrs. *Nagavalli (Piper betle) swarasa* was extracted and fifth *bhavana* was given for 13 hrs. At the end of last *bhavana*, the *dravya* was rolled into *Vatis* weighing 250 mg each. The brick red colored *Vatis* were dried in shade and were stored in a

clean, air-tight container. The *Vatis* were then packed into packets of 40 tablets each and were made ready for administration.

Pharmacognostic study was conducted over the finished drug, *Pushpadhanva Rasa* at the Quality control laboratory of Parul Institute of Ayurveda. (Table no.1, 2 and 3).

Inclusion criteria

1. Female patients with Primary and Secondary infertility aged between 20-35 years.
2. Diagnosed cases of anovulation irrespective of menstrual pattern.
3. Inclusion was done after the follicular study to confirm anovulation
4. Patient willing to sign informed written consent form.

Exclusion criteria

1. Patients with previous history of ovulation induction.
2. Patients with other systemic illness like DM, HTN etc.
3. Evidence of pelvic pathologies like PCOD, CA cervix, cervical polyp, Tubercular endometritis.

Diagnostic criteria

1. Infertile female patients due to Anovulation
2. Patients with or without menstrual irregularities

Study Design: Prior to the commencement of study, ethical clearance was obtained from the institutional ethical committee of Parul Institute of Ayurveda, Limda, Vadodara. Vide ref: PU/PIA/IECHR/2017/22, date: 10.04.17.

The study was conducted as an open labelled, single-blind, randomised comparative clinical study. Out of 30 patients, 15 were allocated by lottery method under Trial group and were administered with *Pushpadhanva rasa vati* while 15 patients were administered with Tab. Clomiphene Citrate in Control Group. Lottery method was adopted for randomisation. The nature of the study was explained to every patient in details and a written consent was obtained at the beginning of the study. The patient's identity and other personal data of the patient was kept confidential.

Case recording: A detailed case history taking and assessment of patients was done before and after treatment as per assessment criteria and the data was recorded in special case record form (CRF).

Study duration: The study was carried out from 1st day of menstrual cycle till ovulation (14-20th day) for 3 menstrual cycles.

Investigations: Transvaginal Sonography (Follicular study) - Transvaginal sonography was done from 9th day of the cycle till 20th day or during predicted ovulatory phase in case of irregular menses for 3 menstrual cycles.

Posology

Group A: Patients of this group were given *Pushpadhanva rasa* 250 mg 1 *vati* twice a day in *apana kala* (before food) with *godugdha* (cow's milk), *Madhu* (honey), *and Sharkara* (sugar), from 1st day of menses for 20 days for three consecutive menstrual cycles.

Group B: Patients of this group were given Tab. Clomiphene citrate 50 mg 1 OD after food with water for 5 days starting from day 2 of spontaneous or progesterone induced menses.

ASSESSMENT of RESULTS

Assessment of results was done on the basis of subjective and objective parameters with a gradation pattern. Regularity of menses, duration of menses, quantity of menses and interval of menses were considered as subjective parameters. The objective parameters assessed were follicular growth, rupture of follicle (ovulation) and endometrial thickness. Overall effect of the treatment was assessed according to the improvement in the follicular growth and ovulation.

Statistical Analysis

The observations were subjected to statistical analysis using Paired t-test and Wilcoxon Signed Rank Test and the results were interpreted.

OBSERVATIONS AND RESULTS

A total of 34 patients were registered, 17 in Group A and Group B each**,** out of which 15 patients in each group continued the treatment whereas 2 patients from both the groups discontinued the treatment. 56.6% subjects were from the age group of 26- 30 years of age. 80% of the subjects were Hindus. Maximum number of patients i.e. 56.6% patients were

graduates and 56.6 % patients were housewives. 36.6% subjects belonged to middle class. It was evident from the data that 73.3% patients had irregular menstrual cycles and 26.6 % patients had regular menstrual cycles. 46.6 % patients had the duration of menses of 2 days while 43.3% of the patients had menstrual duration of 3-5 days and 10% had a duration of menses of 1 day. 50% of the patients had the quantity of menses of 2 pad/day while remaining 50% had 3-4 pads/ day of quantity of menses. Maximum number of patients (40%) had menstruation at an interval of 36-40 days. Observations regarding chief complaints reflected that 66.6% patients had primary infertility. 50% of patients had married life between 6 to 10 years. 63.3% patients reported of consumption of *katu rasapradhana ahara.* Majority (70%) of the subjects had the habit of *vishamashana.* 53.3% patients consumed tea as supplementary diet. 73.3% patients had sexual intercourse (*vyavaya)* 3- 4 times/week. 76.6% (maximum percentage) of patients had *asamadhankaraka malapravritti*.. 36.6% patients had *pitta-kapha prakriti*.. *Krura koshtha* was observed in 53.3% patients. Maximum (46.6%) patients had *mandagni,* 43.3% patients had *vishamagni*. *Chinta* was observed in 50% of the patients. *Rasavaha srotasa dushti* was observed in maximum percentage (96.6%).

RESULTS

In Group A, the results obtained were statistically significant where, 50.7% improvement was noted in the regularity of menses, 78.3% in duration of menses, 66.6% in interval of menses. 39.2% improvement was found in follicular growth while 40% results were found in rupture of follicles (ovulation). Results were not significant in quantity of menses and endometrial thickness. Group B also provided significant results in both subjective and objective parameters. 95% improvement was found in regularity of menses. Duration of menses showed 54.7% improvement. The results in quantity of menses were significant with 88.3% improvement. It revealed 62.9% improvement in terms of interval of menses. There was 54.2% improvement in growth of follicles in Group B while 53% results were found in rupture of follicle (ovulation).

The analysis of results in between the Groups A and Group B did not show any significance in all parameters. (Table No. 4).

Overall effect of therapy: In group A, there was complete remission i.e. ovulation in 6 patients (40%) while in Group B there was 53.3% (8 patients) ovulation. Marked improvement was reported in 20% (3 patients) with follicular size >20mm in Group A, whereas it was 40% (6 patients) in Group B. Moderate improvement (follicular size of 12-20

mm) was found in 66.6% (10 patients) patients of Group A and 53.3% (8 patients) patients of Group B. The results were found to be unchanged in 13.3% patients of Group A and 6.7% in Group B. (Graph No.1).

DISCUSSION

'Beeja' (*Shukra* and *Artava*) as prime factor in conception, is explained precisely by *Acharya Sushruta*, under *garbhasambhava samagri*, which are the crucial elements for *garbhotpatti*. At majority of instances, ovum/stree *beeja* is included in the pathology of *vandhyatva*, which is suggestive of the topmost importance of *beeja* in *garbhotpatti*. This is similar to the ovulatory factor in modern science. The growth and rupture of follicle is a result of a synchronised normal functioning of *Tridosha (3 humours- vata, pitta and kapha).* Inversely, abnormalities in any of *tridoshas* leads to malfunctioning of the process thereby culminating into various ovarian dysfunctions. Vitiated *kapha* leads to a*gnimandya* i.e. the action of conversion of androgen to estrogen is hampered, thus leading to failure of further growth and maturation of follicles. Also vitiated *kapha* causes obstruction of *vata* and thus there is improper differentiation and structural changes in the follicle making the follicle unfit for maturation and ovulation. *Pitta dushti* may cause either scanty or excessive conversion of androgen to estrogen. Estrogen having similar qualities as that of *kapha*, its excessive production causes *avarodha* of *vata* causing trapping of the matured ovum known as luteinised unruptured follicle. Vitiation of *vata* plays a vital role in anovulation by hampering the *vyuhana, nishkramana, sanghata-vighatakara karmas*[3] responsible for transportation, differentiation of follicles and rupture of the follicle.

In Group A *(Pushpadhanva rasa)*, the *panchavataniyamana* (regulation of all five types of *vata) karma* of *Rasasindoora*[4], results in normal functioning of all types of *Vata. Due to prakruta karma of vyana vayu* the *artavavahana karma (hormones)* is regulated, which reflects on proper steroidogenesis. *Vata-kaphashamaka* property of the drug also helps in clearing the *srotorodha.* Most of the *dravyas* being *tikta, kashaya* render *shoshana* and *vishyandana* of *dushta pitta, kleda, kapha* and *rakta*. Thus, *vikruta pitta* and *kapha* are eliminated from circulating *rasa-rakta* and the *avarodha* created by *kapha* is relieved by *shoshana karma of tikta, kashaya dravyas.* Due to *prakrut karma* of *vyana, apana* and *samana vayu* and release of the *srotorodha, artava* in the form of hormones and menstrual blood is formed in a proper way. Along with *vataniyamana*; *pitta* and *kaphanashaka karmas* of the *dravya* bring about a check over *atipravritti* as well as *alpapravritti*, thus correcting the

artava pravartana kala. The *deepana, pachana, tridoshahara* properties of the *dravya* also contribute in correction of *artava pravritti* by correcting *rasa dhatu utpatti*. *Abhraka bhasma, Rasasindoora* and *Vanga bhasma* have specific *karma* on *manas*[5,6,7] hence relieve the stress factor which hinders the normal *artavotpatti*. Therefore, entire process of *artavotpatti* in terms of regularity, duration and interval is corrected by the virtue of these properties. However, *Pushpadhanva rasa* did not show significant result in quantity of menses. For increase in the quantity of menses, the drug might be given for a longer duration along with *rasa vardhaka ahara.*

In Group B (Clomiphene citrate), the results were due to increased action of gonadotrophins (FSH, LH), which led to regulation of ovarian and endometrial cycles. The proper action of estrogen and progesterone results in normalisation in proliferative and secretory changes in the endometrium leading to a proper duration of menstrual flow. Results were found to be significant in quantity of menses due to correction in the secretory phase brought about by synchronous action of gonadotrophins and steroid hormones. Improvement was found in interval of menses due to hormonal regulation. The anti-estrogenic effect causes reduction in the length of proliferative phase, thus bringing about regulation in further hormonal functions of LH, estrogen and progesterone.

In Group A, 39.2% improvement was seen in follicular growth while 40% improvement was found in the rupture of follicle. The division and proliferation of follicles is brought about by *vata* and *kapha. Prinana karma* of *kapha* is regulated thus aiding in proper nourishment of the growing follicle. *Pitta* is responsible for transformation and maturation of the follicle. The hormone receptors on the granulosa cells and the theca cells necessary for utilising FSH and LH; and the aromatisation and luteinisation necessary for estrogen and progesterone production respectively, all come under the *pachana karma* of *pitta. Tridoshahara* property hence brought about the normalcy in functioning of *tridoshas* leading to growth of the follicle. Moreover, the *agneya guna* of *artava*[8] was restored effectively due to removal of *srotorodha* and due to *tridosha shamana* which helped in reducing the *avarana* of *vikruta vata* and *kapha*. The pulsatile pattern of GnRH is maintained by Up-regulation. This function can be attributed to *prana vata. Panchaavata niyamana* property of *Rasasindoora and vatashamaka* property of other drugs showed effect on regulation of H-P-O Axis. The *pushpaketaka* and *bahuapatyaprada karmas*[9] of *Abhraka* substantiate the growth and rupture of follicle. *Loha bhasma* with its *vatasthana dourbalyanashak*[10] property showed

effect on proper growth and maturation of follicle. *Agnimandya* and *vata dushti* was also corrected by the *bhavana dravya, Yashtimadhu*. *Dhatura, Bhanga, Nagavalli* had stimulant effect on neuroendocrinal system. *Bhanga* has a unique property of *garbhashaya* and *basti sankochana*[11], which can be related with the contractile function of prostaglandins on smooth muscles of ovaries, aiding in the act of ovulation.

Group B showed 54.2% improvement in follicular growth while 53% in rupture of follicle. The significant results in CC are due to estrogen-binding effect of Clomiphene and thus creating an oestrogen deficient environment leading to increased GnRH pulsations and thereby increasing the levels of gonadotrophins which enhance growth and rupture of follicle. The *prakrut karmas* of *vata*, of *vyuhana, sanghatkara, vibhajana, rasa-rakta samvahana* and *utsarjana karma* are all restored resulting in proper *beejotpatti* and *beejotsarga. Naga bhasma* and *Abhraka bhasmas* with their *madhura, snigdha*[12,13] properties bring about *dhatu poshana* and *bala vardhana. Naga, Vanga, Abhraka* have unique property of acting directly on *prajanana sansthana* and *andakosha* (ovaries). Therefore, have a specific effect on growth, maturation and rupture of follicles on account of their *prabhava.* Most of the *bhavana dravyas* have *tikta, and katu rasa* which will help in *kapha shamana.* Also due to *ushna veerya, vata shamana* and *pitta niyamana* properties imbibed into the *yoga, prakrut pitta karma* of *pachana* and *parinamana* as well as *vata karma* of *utsarjana* are regulated. *Madhura rasa* of *Shalmali* contributes in bringing about *prinana, brimhana*, required for the growth of *beeja.*

The observations pertaining to endometrial thickness did not show significant results as maximum patients had endometrial thickness within normal range. This shows that, in case of *srotorodhaja samprapti, prakupita kapha* obstructs the *adhogati* of *apana* needed for expulsion of menstrual blood. Thus, clinically thickness is seen but menstrual abnormalities like scanty menses is manifested.

ANALYTICAL STUDY OF *PUSHPADHANVA RASA*

Table No.1: Organoleptic study.

Sr.No.	Parameter	Observations
1	Color	Brick red
2	Odor	Odorless
3	Taste	Tasteless
4	Consistency	Solid pill form

Table No.2: Quantitative analysis.

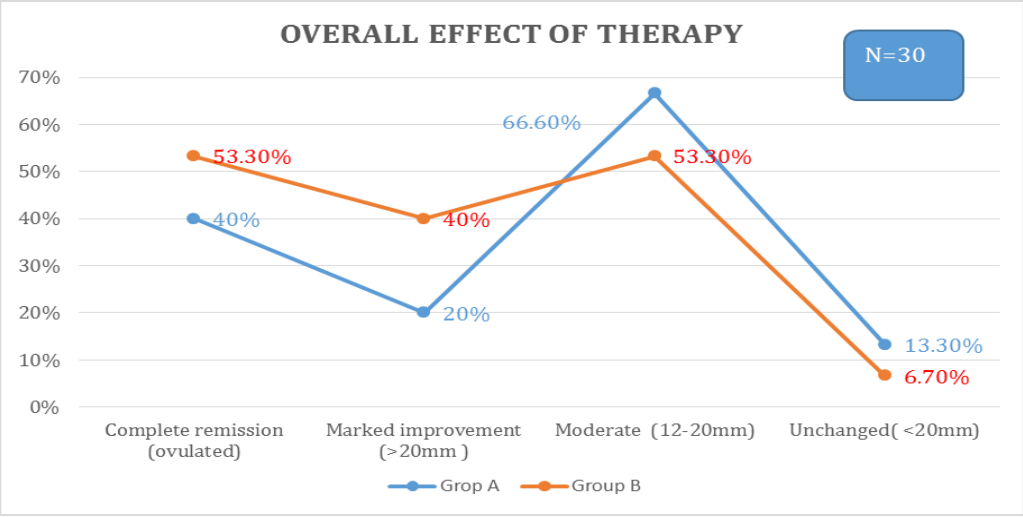
Sr.No.	Parameter	Observations
1	Weight variation	Average weight-236 mg
	Hardness test	5.34 kg/cm^2
2	Loss on drying	1% w/w
3	Ash value	74%
4	Alcohol soluble extract	10.07%
5	Water soluble extract	19.20 %
6	Acidic insoluble ash	69%
7	Disintegration time	49 minutes
8	Ph	8 (5% aqueous solution)
9	Friability test	1.5%

Table No.3: Qualitative Analysis.

Sr.No.	Parameter	Observation
1.	Alkaloid	Methanol-Absent HCl- Absent
2.	Tanins	Present (White precipitate found)
3.	Flavanoids	Present (Pink precipitate found)
4.	Saponin test	Negative

Table No.4: Analysis of results between the groups.

Parameter	Mean. Diff		T value	'P' value
	Group A	Group B		
Regularity of menses	0.33	0.40	0.36	>0.05
Duration of menses	0.47	0.40	0.31	>0.05
Quantity of menses	0.27	0.53	1.31	>0.05
Interval of menses	0.80	0.80	0.00	>0.05
Follicular growth	0.60	0.87	1.42	>0.05
Rupture of follicle	0.40	0.53	0.71	>0.05
Endometrial thickness	0.20	0.13	0.47	>0.05



Graph No. 1: Overall effect of treatment.

CONCLUSION

Ovulatory effect of *Pushpadhanva rasa* was found in 40% (6) of patients while that of Clomiphene citrate was 53.3%. Though *Pushpadhanva rasa* showed comparatively less percentage of improvement, its merits weigh more than that of CC in terms of absence of side effects like multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), cardiac diseases etc. It showed moderate (12-20mm sized follicle) and marked (ovulation) results in anovulatory factor of infertility *(abeejotsargajanya vandhyatva).* Thus, it can be concluded that *Pushpadhanva rasa* can be effectively administered in cases of anovulatory infertility.

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