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**Tambaram Sanatorium, Chennai - 47**

**Affiliated to**

**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,  
CHENNAI - 600 032**

**A STUDY ON**

**PENN MALADU**

**(DISSERTATION SUBJECT)**



*For the partial fulfillment of the  
requirements to the Degree of*

**DOCTOR OF MEDICINE (SIDDHA)**

**BRANCH I-MARUTHUVAM DEPARTMENT**

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# INTRODUCTION

“Foydpdp jpahopdp njd;g jk;kf;fs;

koiyr; nrhy; Nfshjth;“.

- jpUf;Fws;

The pipe is sweet, the bite is sweet,” say those who have not heard the prattle of their own children.

“ngWktw;Ws; ahkwpt jpy;iy awptwpe;j

kf;fl;Ng wy;y gpw”

- jpUf;Fws;

Among all the benefits that may be acquired, we know no greater benefit than the acquisition of intelligent children.

The basic biological function of a living organism is its capacity to reproduce. Among humans for every 80 married couples who produce children, there are 20 who are unable to have an offspring. Approximately one-half of all cases can be traced to either partner.

In the fast pace of modern life, dietary habits, increasing prevalence of obesity, stress, smoking, contraceptives have all contributed to the decline in fertility.

In many southeast Asian Countries, infertility is considered a curse and the inability to conceive is often a stigma attached to the female partner though she may not always be the cause of it.

Approximately 15% of couples attempting their first pregnancy meet with failure. Most authorities define these patients as primarily infertile if they have been unable to achieve a pregnancy after one year of unprotected intercourse. Conception normally is achieved within 12 months in 80 – 85% of couples who use no contraceptive measures and persons presenting after

this time should be therefore be regarded as possibly infertile and should be evaluated.

## **AIM AND OBJECTIVES**

1. To evaluate the therapeutic efficacy of Siddha Drugs, Maladu Neenga Thailam and Saaravalli Mathirai in Penn Maladu (female infertility) patients.
2. To increase the fertility rate among the female infertility patients.
3. To regularise the menstrual abnormalities
4. To evaluate the toxicity & pharmacological actions in experimental animals
5. To find out the adverse-effects of the drug in clinical trial, if any
6. To have a complete study of the disease, Penn Maladu (Female Infertility) under the headings of
  - a) Enn Vagai Thervugal
  - b) Udal Kattugal
  - c) Mukkutram etc.

## ngz; kyL

Foe;ijfisg; ngwhj jd;ikf;F 'kyL' vd;W ngah;.

kyil

1. Rj;j kyL
2. fjyp kyL
3. fhf kyL vd;W %tifahfg; gFj;Js;sdh;

### Rj;j kyL (**Primary Infertility**)

xU KiwahfpYk; fUj;jhpj;jNj fpilahj epiyikf;Fr; 'Rj;j kyL' vd;W ngah;.

### fjyp kyL (**Secondary Infertility**)

thio kuk; xU Kiw Fiy js;spaJk; kPz;Lk; Fiy js;shky; epd;WtpLk;. mJNghy; rpyh; xU kfit <d;W NkYk; fUj;jhpg;gNjapy;iy. ,jw;Ff; 'fjyp kyL' vd;W ngah;.

fhf kyL

fhfkhdJ ,uz;L ,dj;ijg; ngUf;fptpl;ljd; Nghpy; kPz;Lk; jd; ,dj;ijg; ngUf;Ftjpy;iy. mJNghy; kfspu; ,uz;NI kfit <d;W NkYk; fUj;jhpg;gNjapy;iy. ,jw;F 'fhf kyL' vd;W ngah;.

<jd;wpAk; fd;k kyL vd;W ehd;fhtjhf xd;iwAk; tFj;Js;sdh;.

fd;k kyL

#y; nfhs;;th;. Mdh; fUr;rpjT mbf;fb Vw;gl;L #y; fhy;ij  
ePbf;fnth;lhky; jLf;Fk; epiyf;F 'fd;k kyL' vd;W ngah;.

fhuzq;fs;

kfspUf;F g+g;G epfo;T elg;gjhy; fUj;jhpf;fg;gLths; vd;W epue;jukhf  
nrhy;tjw;fpy;iy.

(1) rpyUf;F fhkf;fpsh;r;rpapy;yhkNy g+g;G epfo;r;rp eilngWfpwJ.  
rpidg;igapy; ghprpid (Graffian Fallicle) Kjph;e;J rpid ntspg;gl;L  
tUtjpy;iy.

(2) rpy Ntisfsy; fUg;igr; rspr;rt;T rpidiag; gjpaitf;fj; jbg;GWtjpy;iy.

(3) kfsph;f;Ff; fUj;jhpg;gjpy; rpidg;gij kpfTk; gq;F nfhs;fpwJ.  
rpidg;igapd;W Rod;W ntspg;gl;l rpid (Ovum) FQ;rhe;jj;jhy;  
(Fimbriae) cwpQ;rg;gl;L> rpidg;ghijia milfpwJ. rpidg;ghijf; Foy;>  
rpidia fUg;ig miwia Nehf;fp ce;jr; nra;fpwJ. ce;jpf; nfhz;NI  
nry;Yk; rpid tpe;J mZf;fiser; re;jpj;Jf; fUf;nfhs;fpwJ. MfNt>  
rpidg;ghij rpw;rpy Neha;fsy; jhgpjkile;J> Foypy; jpR tsh;r;rp  
Vw;gl;L> rpidAk;> tpe;JTk; re;jpf;f tha;g;gpy;yh fhuzj;jhy; kfsph;  
fUj;jhpg;gjpy;iy.

- (4) rpy rkak; Gzh;r;rpapy; Vw;gl;l Nahdpf; frpT> fUg;ig Kff;frpT  
Mfpaitfs; tpe;J mZ caph; thoj;jf;fjhf ,y;yhtpl;lhy; fUg;ig .miwia  
miltjw;F Kd;Ng td;ikapoe;J kbe;J tpLfpd;wd.
- (5) kfspUf;F gpwg;GWg;Gfs; jhgpi Neha;fs; Vw;gl;bUe;jhYk;
- (6) kfsph; gpwg;GWg;Gfs; rhptu Rfu;zhPjpahf ,y;yhikahYk;
- (7) fUg;ig Raepiyapy; ,y;yhky; khWgl;l epiyapy; ,Ue;jhYk;>
- (8) fUg;igapy; foiyf; fl;bfs; ,Ue;jhYk; fUj;jhpf;f Kbahky; kyl;Lj;jd;ik  
cz;lhfK;.

## ngz; kyl;bd; Fzk;

jhNkjhd; khjhe;j UJ fhyj;jpy;  
jf;fhd uj;jkJ rpte;J fhZk;  
NtNkjhd; kQ;rs;epwq; fUikahFk;  
tpidahd ePyepwQ; rPo;Ngh yhFk;  
NghNkjhd; uj;jkJ TUz;il ahFk;  
nghy;yhj ky %j;jpu epwNk ahFk;  
ehNkjhd; nrhd;dgb rpfpr;rh rhuk;  
ehl;LNshh;f; fwpantrd;W etpd;wpl; lhNu.

- a+fpKdp

kfspu; kUj;Jtk;

nghUs;

khj khjk; epfo;TWfpd;w g+g;Gf; fhyq;fspy; Vw;gLk; g+g;Gf;frpT  
ed;F rpte;jpUj;jy;> kQ;rl;fUik epwkhfTk;> ePyepwr; rPo; NghyTk;  
rpw;rpW cUz;ilfshf ntspg;Nghe;jy;> NehAw;w fhyq;fspy; ,opAk; kyk;>  
rpWePh;fisnahj;jy; Nghd;w ,f;Fwp Fzq;fisg; ngw;wpUg;gjl;Fg; ngz; kyL  
vd;W ngah;.

### Meaning of the above:

- (i) Menstrual blood is bright red, yellowish black, and bluish red in colour.
- (ii) Menstrual blood is colloidal in consistency or like clots.
- (iii) Menstrual blood resembles motion and urine present in diseased condition.

## NOI VARUM VAZHICAL (AETIOLOGY)

### I. ACCORDING TO MANMURUGIYAM

fUg;ig jd;dpy; tspepiwe; jpLjy;  
fUf;Fopthapy; jirtsh;e; jilj;jy;  
GOg;gy Njhd;wfp; fUTz; bLjy;  
fUg;ig afj;Jg; ghrp gw;wy;  
mjpy;nrq; FUjp fl;b epw;wy;  
fUf;Fop kjh;j;jy; vDkpt;; thWk;  
fUg;ig Aw;wpL Nehnad nkhopg.

1. Amenorrhoea
2. Any benign or malignant growths in the uterus like leiomyoma
3. Infections of the genital tract like Pelvic Inflammatory Disease, genital tuberculosis
4. Peritubal adhesions and adhesions within the uterus
5. Blood stagnation within the uterus like adenomyosis
6. Due to obesity in conditions like Polycystic Ovarian Disease, hypothyroidism.

### II. ACCORDING TO PARARASASEKARAM

jpwpky lhFk;thW nrd;kehl; Nlhj; jhYk;  
cWjpUg; g+j;jehsh nuhsph;nja;t tpNuhjj; jhYk;  
nrwpAKj; Njhj;jhYQ; rpNyl;Lk kpFjpahYk;



kDTw kylh nkhd;W khjtdUr; nra;jhd;.

1. Congenital malformations of the genital tract or congenital sex chromosomal abnormalities.
2. Due to alterations in three humours.
3. Increased Kapha humour.

### III. ACCORDING TO ATHMARAKSHAMIRDHAM VAIDHIYA SAARA SANGIRAHAM

ghug;gh ngz;kylhq; fUg;gf; Nfhspd;  
gf;Ftj;jjr; nrhy;YfpNwd; gz;gha;f; NfS  
Mug;gh Mz;kyNI ahU ky;yhy;  
mg;gNd ngz;kyL ahU kpy;iy  
Neug;gh jtkpUe;Jk; nghUis aPe;Jk;  
Neuhf tpy;iyaJ #iy ahNy  
Ntug;gh NjtijNah Nlohq; fUg;gk;  
tphpj;J ed;wha; GfYfpNwd; tpUk;gpf;NfNs.

tsp epiwe; jpUg;gpd; GzUq; fhiyg;  
ngz;zp Dlk;G typjU nkd;g  
jir tsh;e; jpUg;gpd; neQ;R Fj;Jk;  
GOf;fs; epuk;gpd; KJF NehFk;  
ghrpg;gw;wpd; jiytyp Njhd;Wk;  
FUjpf;bd; nfz;il NehFk;

fUf;Fop kjh;g;gpd; Vg;ge; Njhd;Wk;

From the above verse, it is well known that the etiology of Maladu is same as mentioned in Manmurugium.

#### **IV. ACCORDING TO AGATHIYAR VAIDHYA KAVIYAM - 1500**

ghug;gh nfw;g fhyk; ghpTld; tha;T - Nja;T

Nrug;gh Te;jpNahL nrd;wpLq; fUj;jhd; khSk;

thug;ghGOj; jhZz;zpy; kynldr; nrhy;thug;gh

Mug;gh tpjldg; Nghf;fpyhz; gps;is nrwfp;Fe;jhNd.

- Increase in Vayu and Theyu elements.
- Infections of the genital organs.

#### **CLASSIFICATION OF PENN MALADU**

##### **I. According to YUGIMUNI CHIKITCHA SAARAM there are 3 types**

- (i) Sudhtha Maladu
- (ii) Kathali Maladu
- (iii) Kaka Maladu

##### **II. According to JEEVA RAKSHAMIRTHAM ANUBAVA DEVA RAGASIUM & SARABENTHIRAR KARPA PINI there are 4 types.**

- (i) Athi Maladu
- (ii) Kathali Maladu
- (iii) Kaka Maladu
- (iv) Karuppa Maladu

**III. According to MANMURUGIUM, there are 11 types**

- |                     |                      |
|---------------------|----------------------|
| (i) Vali Maladu     | (vii) Puzhu Maladu   |
| (ii) Anal Maladu    | (viii) Petra Maladu  |
| (iii) Iya Maladu    | (ix) Mutru Maladu    |
| (iv) Alagai Maladu  | (x) Noi Maladu       |
| (v) Varatchi Maladu | (xi) Seyarkai Maladu |
| (vi) Karupai Maladu |                      |

**IV. According to ATHMARAKSHAMIRTHAM VAIDHYA SAARA SANGIRAHAM.**

There are 7 types.

- (i) Vatha Maladu
- (ii) Pitha Maladu
- (iii) Alagai Maladu
- (iv) Petra Maladu
- (v) Varatchi Maladu
- (vi) Vayu Maladu
- (vii) Puzhi Mel Maladu

## CLINICAL FEATURES

### A. ACCORDING TO YUGIMUNI CHIKITCHA SAARAM

**Athi Maladu** - epue;ju kyl;bd; Fzk;

etpd;wplNt apLg;Gtapw; ngUj;Jf; fhZk;

eykhd NkdpaJ t+jpf; fhZk;

Ftpd;wplNt Kk;kg;G tapw;wpy; Njhd;Wk;

Fztjpahe; Njtjh ngz;zh dhYk;

etpd;wplNt rd;kj;jd; kyNI ahFk;

rjhfhyyq; fUg;gkJ jhpah njd;W

Gtpd;wplNt a+fpKdp rpfpr;rh rhuk;

Gfd;wpl;lhh; Nyhfj;J khe;jw; fhNk.

nghUs;: clypd; kw;w ghfq;fis tpl ,Lg;Gk;> tapWk; ngUj;jpUj;jy;> cly; mijj;Jf;

fhzy;> ce;jpapy; %d;W kbg;Gfs; fhZjy; Mfpa FwpFzq;fisf; nfhz;L vd;Wnk

fUj;jhpf;fhkypUf;Fk; jd;ikf;F epue;ju kyL vd;W ngah;.

### MEANING:

- ❖ Obesity
- ❖ Deposition of fat in the abdomen.

**Kathali Maladu** – fjyp kyl;bd; Fzk;

etpyNt fd;dpah;fs; fjyp Nghyhk;

ehl;INt thiokuj; jhW Nghy  
ftpyNt ike;jdhq; fUg;G nkhd;W  
fhjypah sPd;wgpD; fUg;g kpy;iy  
jtpyNt fUg;gFop kiwe;jJ Nkjhd;  
jq;fpNa KOFehs; jilAz; lhFk;  
GtpyNt a+fpKdp rpfpr;rh rhuk;  
g+jyj;jpy; khdpLw;Fg; g+l;b dhNu

nghUs;: Fiy <d;w thio kWKiw Fiy <dhj;jd;ik Nghy kq;ifah;fs; xU Foe;ijia  
<d;w gpD;dh; fUg;igf; Fop nrayw;W g+g;Gj; jil Vw;gl;L> Gzh;r;rpAw;w NghJk;  
kWKiw fUjhpf;fhj jd;ikf;Ff; fjyp kyL vd;W ngah;.

**Meaning:** After delivering a baby, woman attains menopause at or below the age of 40, (pre-mature menopause). This is called Kathali Maladu.

**Kaka Maladu** – fhf kyl;bd; Fzk;

MNkjhd; fhf;jpd; kyNI ahFk;  
mg;gNd fUg;igapy; Nrhhp nfl;L  
NghNkjhd; fUg;igAe; Je;J Nkjhd;  
Nghf;fhd fhAINd fjL Nghyhk;  
NtNkjh dpuz;L Ngh; ike;j Dz;lhk;  
NtWtif fUg;gJ kyNI ahFk;  
ehNkjhd; nrhd;dgb rpfpr;rh rhuk;  
ehl;LNshh;f; fwpantD;W etpd;wpl;NIhNk.

nghUs;: ,uz;L kfit <d;W fUg;igahdJ Nrhhp NfLw;w VJtpdhy; kWKiw  
fUj;jhpf;fhJ tpsq;Ffpd;w jd;ikf;Ff; fhf kyl vd;W ngah;.

## **B. ACCORDING TO JEEVARAKSHAMIRTHAM ANUBAVA DEVA RAGASIYAM, SARABENDRAR KARPAPINI**

The features of Athi, Kathali and Kaka Maladu are more or less same as described in Yugi Chikicha Saarum. And In addition,

### **Karpa Maladu**

Most of the women deliver a dead foetus.

## **C. According to MANMURUGIYAM**

### **1. Vali Maladu:**

‘tsp kylhapd; nre;ePh;’

In this type, the colour of the urine is red.

### **2. Anal Maladu**

‘mdy; ky lhapd; kQ;rs; fiuj;njdr;

rPWePh; hpwq;Fnkdr; nrg;Gth; Gyth;’

In this type of infertility, the urine becomes bright yellow in colour.

### **3. Iya Maladu**

‘lk;ky lhapd; rpWePh; kpfTk;

ntSj;J Njhd;W nkd;gh; Gyth;’

In this type, the urine becomes pale yellow in colour.

### **4. Alagai Maladu**

‘g+g;gpd; fhiy tapw;wpl kUq;fpy;

NehT Njhd;wy; rpWePh; fLj;Jk;  
ntSj;Jq; fWj;JQ; rpte;J kpwq;fy;  
vDkpit ayif kyl;Lf; FwpNa'

- There is pain in the lower abdomen during menstruation.
- Burning micturition
- The colour of the urine is pale yellow, red or black.

## 5. Varatchi Maladu

"cz;zpD Kly Kyu;e;J Nghjy;  
kpf nfhl;lhtp - Njhd;wy; gw;gy  
mr;rf; fdt}fs; Njhd;wy; vDkpit  
twl;rp kyl;bd; Fwpnad nkhopg"

- Weight loss
- Intractable yawning
- Experiences dreadful dreams often.

## 6. Karupai Maladu

'tapW nghUky; czt whik  
Vg;ge; Njhd;wy; fUf;Fop Rw;wp  
tspepd; wpLjy; vDkpit fUg;ig  
tspkyl;bd; Fwp ahnkd nkhopg'

## Signs and Symptoms

- Flatulence
- Loss of Appetite

- Belching
- Menstrual irregularities like oligomenorrhoea, hypomenorrhoea, amenorrhoea

## 7. Puzhu Maladu

‘kWg;G Njhd;wy; jpq;fs; tUKOf;  
 ,uz;nlhU jpq;f spilap YWjy;  
 clyk; ntSj;jy; Fwpjpd TWjy;  
 ,itGO kyl;Lf; Fwpnad nkhopg  
 fUg;ig apw;GO kpf;fpL khapd;  
 tapw;wb Fj;Jk; jpq;fl; g+g;Gj;  
 jirfOePh; Nghy; Njhd;Wk; Gzh;r;rpapy;  
 mopjU ePUw; whil fiwg;gLk;’

### Signs and Symptoms

- ❖ Dysfunctional uterine bleeding
- ❖ Pallor
- ❖ Pruritis vulva
- ❖ Intense pain in the lower abdomen
- ❖ The colour of the menstrual blood is like that of the water washed out from the meat
- ❖ Excessive vaginal discharge after coitus.

## 8. Petra Maladu

‘clyk; gUj;jy; ntk;gy; Nehjy;



fOePh; Nghyr; rpWeP hpwq;fy;  
iffh nyhpjy; vDkpit nay;yhk;  
ngw;w kyl;bd; Fwpnad nkhopg'

### **Signs and Symptoms**

- ❖ Obesity
- ❖ Burning Micturition
- ❖ Burning sensation in the extremities
- ❖ The colour of the urine is like the water washed out from the rice.

### **9. Mutru Maladu**

'kUe;jp Dk;gpw newpapD ePq;fh  
kyL Kw;W kynld nkhopg'

In this type, there is no improvement even on treatment.

### **10. Noi Maladu**

'Nehapd; tUtJ Neha;ky lhFk;  
tspKjw; gygpzp te;Jw khapDk;  
fUf;fha; fUf;fs; jhuh thapDk;  
ngz;ghy; Neha;ky nlhd;wpLk; nkd;g'

Chronic illnesses like endocrinal disorders (Hypothroidism), renal and cardiac diseases lead to Infertility in females.

### **11. Seyarkai Maladu**

'fUq;Nfh Sg;gpidf; fisj yhYk;

mWitapd; njhopYwr; nra;j yhYk;  
kUe;jpw; fUTwr; nra;j yhYk;  
vd;Wk; Gzuh jpUj;j yhYk;  
fUf;Nfh spy;tif Gzh;j yhYk;  
nraw;if kyL kUtpl apay;Ng'

- ❖ Surgical sterilization in the female or previous surgery in the abdomen leads to adhesions
- ❖ Taking contraceptives to avoid pregnancy
- ❖ Avoiding sexual intercourse
- ❖ Sexual intercourse during first trimester.

#### **D. ACCORDING TO ATHMARAKSHAMIRTHAM**

The clinical features described in Athmarakshamirtham are same as in Manmurugium.

#### **E. ACCORDING TO SARABENDRAR KARPA PINI**

##### **a) Karpa Sayu Puralal**

'Xjpa khkf tpy;yJ ePjpAie;jpL Ntd;wpUNt  
jhJFky; FypNy kyUz;IJ jhz;ilNa Guspy;  
ePjpa; tpOkh tKjy; Gfepd;wplkq; nfhUTk;  
NtjKkpg;gbNa AiuahbL nkd;nfhb ePawpNa'

The position of the uterus may be abnormal and it may be retroverted .

##### **Signs:**

'Nkypdp kq;ifah; khjtplhnad tpyfpa ehyehs;  
thypg thlth; \$ba Nghjpdpd; kq;if tpyhtJjhd;

NtypL Gz;nzdNt typAz;nldpd; nkd;gfkx kyUq;

Nfhy kpyhJGuz;IJ ntd;wwp \$wtdTljhNk'

From the above verse, it is known that women with Karpasayu Puralal experiences pain along the ribs during coitus on the fourth day of menstruation.

**b) Vayu Seruthal**

"ePawpkhlyh; jhdjpy; tha;ThpNdak ehkKje;

jhafkhfpa khlydw;wpjpd; rhunkyh nkhofpr;

rPnad ePnudNtaJNgha; tsh; Njfnky;yhk; typah

NahAk; tpjq;fspjhF kwpe;J nfhsnshz;nIhbapd;GwNt"

Since there is excessive vayu within the uterus, it reduces the virulence of the sperm and make it dead.

**Signs:**

cz;lhnk jpuz;BhpU ehspdpnyhz; fztd; Gzuj;

jz;lhh; Njfnkyhk; typnad;dpw; wq;fpa gfkyh;e;j

gz;lhh; thA ciwe;J ntd;wwp.....

In this type, the woman experiences pain all over the body during coitus on fourth day of menstruation.

**c) Thasai Seruthal**

,d;GW khkyh; jd;dpYNk jir Nafkjha; tsu

md;GWkg; nghONj tpOkhtKjQ; rsp NghYUfp

td;gbah JiwahJ fyq;fp tope;jpLNk ntspapy;

nkd;gj Ehypil fQ;rkjh Ky;nkd; Fod; nky;ypaNy

Benign or malignant growth in the uterus interrupts the passage of the semen.

### Signs

..... khjpil jhd; typfhZnkdpw;

fhj;jpu ty;FypNy jirnad;w wpfspub gpd;dKe;.....

There is pain in the groin or hip region during coitus.

#### d) Ushnathikam

nky;ypjo; g+tpdpy; ty;typAl;bz nkd; NkYz;lhfpy;

ey;ypjkha; tpOnkd;dKje; jz;dhba ntz;nzajhk;

nfh;yjp dpd;W kpFe;J ntJk;gpf; NfhKfkhk; topNa

nry;y Khpj;Jiw Ngha;tpL khkiwr; r+j;jpukpg;gbNa

Any inflammatory condition of the vagina, uterus or fallopian tubes destroy the sperm.

### Signs

Njd;nkhopiag; Gzh; NghjpdpNy Jil Nrh;e;J typf;Fnkdp;d;

khd;kyh; jhdjpYl;bz nkd;w khI;L ntd;Gq;

In this type, there is pain in both thighs during coitus.

#### e) Seethala Serkai

,g;gbg; g+tpd;w rPjsNk Awpdd; gkjhk; Ntisir;

nrg;gpa khtKjk; tpoepd;W njspe;J Kwpe;JINd

mg;Gntdg; gOjhfp eidae;jaNyhb aoep;JtpLk;

ikg;gbAq; Fow; nrg;gps nkd;;Kiy ty;yped; thZjNy

In kapha diseases like pyogenic infections and genital tuberculosis, it destroys the sperms.

**Signs:**

..... ePq;fpL khh;gjpNy  
fz;z typf;Fnkdpd; kyh;jhdjpw; fhz;gJ rPjsnkd;  
nwz;zp kUe;Jfs; nra;jpL nrg;GtNdh FoNye;jpioNa  
In this type, there is pain in the chest region during coitus.

**f) Puzhu Undathal**

thddp NahdpapNy kyh;kPjpdpd; khGOTq; FwpNyh  
Czpa khtKje; jidNanaLj; Jz;L fspj;Jkpf  
Mztkhf epiyj;J tsh;e;jpL khifapdh; kfitf;  
fhzpia nad;W fiue;jpL thhpJ fz;lwp fhhpifNa.  
nghUs;: Nahdp kw;Wk; ngz; ,dTWg;Gfspy; fpUkpfspd; jhf;fj;jhy;  
kfT mope;J tply;.

**Signs:**

..... khjiu kUtpa NghjpdpNa  
rpj;j kfpo;r;rp nfshkY Nkikay; jPh;f;fpiy nad;Wnrhypy;  
tpj;jf ty;FypNy GOntd;wwp  
In this type, there is no orgasm.

**g) Sanka Thosam**

fhhpifapd; Fwpkh kyh; Nkd;kpF fhw;nwDQ; rq;ifawpy;

tPhpaNk tpOk; NghjpNyaJ tPo;tjpd; Kd;ghfr;  
rhunkyhq; nfhLNgha; tpLNkapJ rj;jpaNk Aiuj;Njhk;  
thuzp nfhq;if ey;yhapij ePawp khkiw Ehz; KiwNa

**ngHUs;:** fhw;W vd;Dk; rq;if Njh\j;jhy; ngz; ,dTWg;Gfs;  
ghjpf;fg;gLtjhy; Vw;gLtJ.

### **Signs:**

ehafpNahL wthifapw; Fjpfhduk; gpOj;jpL nkd;whw;  
wPPaJw; rq;iffshkJ ntd;wwp Nrahp tpopkhNj

In this type, there is pain in calf muscles during coitus.

### **h) Avaya Ettra Thazhvugal**

Ehyphilahs; FwpahokjhFT Ehy; nfhO ed; Fwpjhd;  
rPyKId; rhpePs kpyhtpow;Nwa; tjpdhy Kjk;  
nghydNt AiwahkYId;gpw; gue;J fye;JtpLk;  
NtnyDik tpopahapJ fz;lwpNtjd; tpjpg;gbNa

Congenital elongation of the cervix, acute retroverted uterus, septate vagina, transverse vaginal septum are the anatomic defects that result in infertility.

### **i) Poorva Vinai**

kq;ifauhapD kltuhapD khtpidah tpo;jQ;  
rq;ifapy kyUe;jpajhYId; jq;fpa ntg;gkjhw;  
nghq;fpa khtKjQ; rykhfp kpFe;J nghope;J tpLk;  
,q;fpJ ePjpawpe;jpL Ntjkipir;j jpsq;nfhbNa

In this type, due to kanma vinai or excessive usage of medications, their sperm or ovum becomes inactive.

## **COMPLICATIONS:**

### **1. Malattu Vali**

kyl;L Neha;fs; kUtp kpFjydpd;  
fUg;igapy; typgy Njhd;wp Kjph;e;J  
tpyf;fpd; fhiy tFj;j kpUf;Fk;

On the days of menstruation, very severe dysmenorrhoea is present.

### **2. Malattu Janni**

tpyf;fpd; fhiyg; Gspj;jiy Az;zy;  
kpfT Kz;zy; cz;l jwhik  
kpfFsp Nuw;wy; Kjypa gpwTk;  
kyb jdf;Fk; fytg; gpzp jUk;.

On the days of menstruation, if rotten foods or excessive foods are taken or indigestion is present, it leads to Malattu Janni.

## **MODERN ASPECT**

### **INFERTILITY**

Infertility is defined as a failure to conceive within one or more years of regular unprotected coitus.

Primary infertility denotes those patients who have never conceived. Secondary infertility indicates previous pregnancy but failure to conceive subsequently.

80 percent of the couples achieve conception if they so desire, within one year of having regular intercourse with adequate frequency (4-5 times a week). Another 10 percent will achieve the objective by the end of second year. As such 10 percent remain infertile by the end of second year.



The relative prevalence of the etiologies of infertility is

Male factor	-	30 – 40%
Female Factor	-	40 – 50%
Both	-	10%

An association between the age of woman and reduced fecundability has been well documented. This decline begins in the early thirties and accelerates in the late thirties and early forties.

## **FEMALE INFERTILITY**

The female factor contribute to 40 – 50% of infertility.

The important causes of female infertility as given by FIGO manual (1990) are,

-	Tubal and peritoneal factors	-	25 – 35%
-	Ovulatory factor	-	15 – 25%
-	Endometriosis	-	1 – 10%

## **ETIOLOGY**

### **OVARIAN FACTORS**

The ovulatory dysfunctions encompass:

- ❖ Anovulation or oligo – ovulation
- ❖ Luteal phase defect (LPD)

- ❖ Luteinised unruptured follicle.

## **TUBAL FACTORS**

The impaired tubal function includes,

- ❖ Defective ovum pick up
- ❖ Impaired tubal motility
- ❖ Loss of cilia
- ❖ Partial to complete obstruction of the tubal lumen

The impaired function of above anyone is related to ,

- ❖ Tubal infection (or)
- ❖ Peritubal adhesions following pelvic surgery or infection or endometriosis.

## **PERITONEAL FACTORS:**

In addition to peritubal adhesions, even minimal endometriosis may produced infertility.

## **UTERINE FACTORS**

- ❖ Uterine Hypoplasia
- ❖ Inadequate secretry enclometrium
- ❖ Fibroid uterus
- ❖ Endometritis (tubercular in particular)
- ❖ Uterine synechiae
- ❖ Congenital malformation of uterus

## **CERVICAL FACTORS**

**Anatomic** : Anatomic defects preventing sperm ascent

- ❖ Congenital elongation of the cervix,
- ❖ Second degree uterine prolapse
- ❖ Acute retroverted uterus
- ❖ Pin hole os
- ❖ Cervical canal occluded by a polyp.

## **Physiologic**

The fault lies in the composition of the cervical mucus, so much that the spermatozoa fail to penetrate the mucus. The mucus may be,

- ❖ Scanty – following amputation ionisation or deep cauterisation of the cervix.
- ❖ Excessive, purulent – chronic cervicitis.
- ❖ Presence of Antisperm antibodies or sperm immobilizing antibodies.

## **VAGINAL FACTORS**

- ❖ Atresia Vagina (Partial or Complete)
- ❖ Transverse vaginal septum
- ❖ Septate vagina
- ❖ Narrow introitus.

## **IMMUNOLOGICAL FACTOR**

and

## **GENERAL FACTORS**

- ❖ Advanced age of the woman beyond 35 is related to infertility
- ❖ Use of lubricants during intercourse which may be spermicidal
- ❖ Anxiety and apprehension
- ❖ Infrequent intercourse, lack of knowledge of coital technique and timing of coitus to utilize the fertile period are very much common even amongst the literate couples.

## **ANOVULATORY INFERTILITY**

The ovarian activity is totally dependant on the gonadotrophins and the normal secretion of gonadotrophins depends on the pulsatile release of GnRH from hypothalamus.

As such, ovarian dysfunction is likely to be linked with disturbed hypothalamo pituitary ovarian axis either primary or secondary from thyroid or adrenal dysfunction.

Thus, the disturbance may result not only in anovulation but may also produce oligomenorrhoea or even amenorrhoea. Anovulatory cycles usually represent a lesser degree of disturbance with these normal pathways than does amenorrhoea.

As there is no ovulation, there is no corpus luteum formation. In the absence of progesterone, there is no secretory endometrium in the second half of the cycle.

### **POSSIBLE CAUSES OF ANOVULATION**

Any disturbance in hypothalamo – pituitary – ovarian action will result in anovulation.

### **DISTURBANCE AT THE LEVEL OF HYPOTHALAMUS**

1. Obesity or weight loss
2. Psychologic disturbances
3. Psychotropic drugs
4. Tranquilizers, oral pill

## **DISTURBANCE AT THE LEVEL OF PITUITARY**

### **Primary Causes**

1. Sheehan's syndrome
2. Tumour – Prolactinoma

### **Secondary Causes**

1. Hypo or Hyperthyroidism
2. Adrenal Hyperplasia

## **DISTURBANCES AT THE LEVEL OF OVARY**

1. Polycystic ovarian disease (PCOD)
2. Premature ovarian failure
3. Luteinised unruptured follicles
4. Endocrinopathy.

## **CHRONIC ANOVULATION**

At least 80% or more of gynecologic endocrine disorders result from chronic anovulation. Women with chronic anovulation fail to ovulate spontaneously but may ovulate with appropriate therapy. The ovaries of such women do not secrete estrogen in a normally cyclic pattern. It is clinically useful to differentiate those women who produce enough estrogen to have withdrawal bleeding after progestogen therapy from those who do not; the latter often have hypothalamic – pituitary dysfunction.

### **CHRONIC ANOVULATION WITH ESTROGEN PRESENT**

This disorder is most commonly caused by polycystic ovarian syndrome. Chronic anovulation with estrogen present may also occur with tumors of the ovary. These include granulosa – theca cell tumors, Brenner tumors, cystic teratomas, mucous cystadenomas, and Krukenberg tumors. Such tumors can either secrete excess estrogen themselves or produce androgens that are aromatized in extraglandular sites. Chronic anovulation and the clinical features of PCOS result. Occasionally, areas of the ovary not involved with tumors show the characteristic histologic changes of PCOS. Other causes of chronic anovulation with estrogen present include adrenal production of excess androgen, (usually adult-onset adrenal hyperplasia due to partial 21-hydroxylase deficiency) and hypothyroidism.

### **CHRONIC ANOVULATION WITH ESTROGEN ABSENT**

Women with chronic anovulation who have low or absent estrogen production and do not experience withdrawal bleeding after progestogen treatment usually have hypogonadotropic hypogonadism due to disease of either the pituitary or the central nervous system.

Isolated hypogonadotropic hypogonadism associated with defects of smell (olfactory bulb defects) is known as the Kallmann syndrome, which is due to a single gene defect in the X-linked KAL gene. Affected women are sexually infantile and have a defect in the synthesis and/or release of GnRH. Hypothalamic lesions that impair GnRH production and cause hypogonadotropic hypogonadism include craniopharyngioma, germinoma (pinealoma), glioma, Hand-Schuller-Christian disease, teratoma, endodermal-sinus tumors, tuberculosis, sarcoidosis, and metastatic tumors that cause suppression or destruction of the hypothalamus. Central nervous system trauma and irradiation can also cause hypothalamic amenorrhea and deficiencies in secretion of growth hormone, adrenocorticotropic hormone (ACTH), vasopressin, and thyroid hormone. Rare, autosomal recessive defects in the GnRH receptor have also been described.

More commonly, gonadotropin deficiency leading to chronic anovulation is believed to arise from functional disorders of the hypothalamus or higher centers. A history of a stressful event in a young woman is frequent. Gonadotropin and estrogen levels are in the low to low-normal range as compared with normal women in the early follicular phase of the cycle. In addition, rigorous exercise, such as jogging or ballet, and diets that result in excessive weight loss may lead to chronic anovulation, particularly in girls with a history of prior menstrual irregularity. The amenorrhea in these women does not appear to be a result of weight loss alone but a combination of a decrease in body fat and chronic stress. An extreme form of weight loss with chronic anovulation occurs in anorexia nervosa. In anorexia nervosa amenorrhea can precede, follow, or coincide with weight loss.



In addition, chronic debilitating disease such as end-stage kidney disease, malignancy, inflammatory bowel disease, and malabsorption can lead to hypogonadotropic hypogonadism via hypothalamic mechanism.

Treatment of chronic anovulation due to hypothalamic disorders includes ameliorating the stressful situation, decreasing exercise, and correcting weight loss, as appropriate. These women are susceptible to the development of osteoporosis; estrogen replacement therapy is recommended to induce and maintain normal secondary sexual characteristics and prevent bone loss in those who do not desire pregnancy, and gonadotropin or gonadorelin therapy is indicated when pregnancy is desired. When appropriate, therapy is directed at the primary disease of the hypothalamus.

Disorders of the pituitary can lead to the estrogen-deficient form of chronic anovulation by at least two mechanisms – direct interference with gonadotropin secretion by lesions that either obliterate or interfere with the gonadotrope cells (chromophobe adenomas, Sheehan's syndrome) or inhibition of gonadotropin secretion in association with excess prolactin (prolactinoma). Pituitary tumors may secrete no hormone, one hormone, or more than one hormone. Prolactin levels are elevated in 50 to 70% of patients with pituitary tumors, either because of prolactin secretion by the tumor itself (in the case of prolactinomas) or because the tumor mass interferes with the normal hypothalamic inhibition of prolactin secretion.

Prolactin excess associated with low levels of LH and FSH constitutes a specific subtype of hypogonadotropic hypogonadism. One-tenth or more of amenorrheic women have increased levels of prolactin, and more than half of women with both galactorrhea and amenorrhea have elevated prolactin levels. The amenorrhea is most often associated with decreased or absent

estrogen production, but prolactin-secreting tumors on occasion are associated with normal ovulatory menses or chronic anovulation with estrogen present. In the latter half of pregnancy, prolactin-secreting pituitary tumors may expand, leading to headache, compression of the optic chiasm, bitemporal hemianopia, and blindness. Therefore, before inducing ovulation for the purposes of achieving pregnancy, it is mandatory to exclude the presence of a pituitary tumor.

Large pituitary tumors such as null cell adenomas—whether or not hyper-prolactinemia is present—are likely to be associated with deficiency of hormones in addition to gonadotropins.

Craniopharyngiomas, which are thought to arise from remnants of Rathke's pouch, occur most frequently in the second decade of life and often extend into the suprasellar region. Many of these tumors calcify and can be diagnosed by conventional skull film or CT. Patients often present with sexual infantilism, delayed puberty, and amenorrhea due to gonadotropin deficiency; secretion of TSH, ACTH, growth hormone, and vasopression may also be impaired.

Panhypopituitarism can be caused by mutations in transcription factors (Pit-1; Prop-1) involved in pituitary gland development, result from surgical or radiation treatment of pituitary adenomas, or develop after postpartum hemorrhage (Sheehan's syndrome).

## **THE OVARIAN CYCLE**

Within the ovary, the menstrual cycle can be divided into three phases:

- ❖ The follicular phase
- ❖ Ovulation
- ❖ The luteal phase

### **FOLLICULAR PHASE**

The development of the oocyte is the key event in the follicular phase of the menstrual cycle. The ovary contains thousands of primordial follicles that are in a continuous state of development from birth, through periods of anovulation, such as pregnancy, to the menopause. These initial stages of follicular development are independent of hormonal stimulation. In the absence of the correct hormonal stimulus however, follicular development fails at the preantral stage, with ensuing follicular atresia. Development beyond the preantral stage is stimulated by the pituitary hormones, (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) which can be considered as key regulators of oocyte development.

At the start of the menstrual cycle, FSH levels begin to rise as the pituitary is released from the negative feedback effects of progesterone, oestrogen and inhibin. Rising FSH levels rescue a cohort of follicles from atresia, and initiate steroidogenesis.

### **Steroidogenesis**

The basis of hormonal activity in preantral to pre-ovulatory follicles is described as the 'two cell, two gonadotrophin' hypothesis. Steroidogenesis is compartmentalized in the two cell types within the follicle: the theca and

granulosa cells. The two cell, two gonadotrophin hypothesis states that these cells are responsive to the gonadotrophins, LH and FSH respectively.

Within the theca cells, LH stimulates the production of androgens from cholesterol. Within granulosa cells, FSH stimulates the conversion of thecally derived androgens to oestrogens (aromatization). In addition to its effects on aromatization, FSH is also responsible for proliferation of granulosa cells. Although other mediators are now known to be important in follicular development, this hypothesis is still the cornerstone to understanding events in the ovarian follicle. The respective roles of FSH and LH in follicular development are evidenced by studies on women undergoing ovulation induction in whom endogenous gonadotrophin production has been suppressed. If pure FSH alone is used for ovulation induction, an ovulatory follicle can be produced but oestrogen production is markedly reduced. Both FSH and LH are required to generate a normal cycle with adequate amounts of oestrogen.

Androgen production within the follicle may also regulate development of the preantral follicle. Low levels of androgens enhance aromatization and therefore increase oestrogen production. In contrast, high androgen levels inhibit aromatization and produce follicular atresia. A delicate balance of FSH and LH is required for early follicular development. The ideal situation for the initial stages of follicular development is low LH levels and high FSH levels, as seen in the early menstrual cycle. If LH levels are too high, theca cells produce large amounts of androgens causing follicular atresia.

## **Selection of the Dominant Follicle**

The developing follicle grows and produces steroid hormones under the influence of the gonadotrophins LH and FSH. These gonadotrophins rescue a cohort of preantral follicles from atresia. However, normally only one of these follicles is destined to grow to a pre-ovulatory follicle and be released at ovulation the dominant follicle.

The selection of the dominant follicle is the result of complex signalling between the ovary and the pituitary. In simplistic terms, the dominant follicle is the largest and most developed follicle in the ovary at the mid-follicular phase. Such a follicle has the most efficient aromatase activity and the highest concentration of FSH – induced LH receptors. The dominant follicle therefore produces the greatest amount of oestradiol and inhibin. Inhibin further amplifies LH-induced androgen synthesis, which is used as a substrate for oestradiol synthesis. These features mean that the largest follicle therefore requires the lowest levels of FSH (and LH) for continued development. At the time of follicle selection, FSH levels are declining in response to the negative feedback effects of oestrogen. The dominant follicle is therefore the only follicle that is capable of continued development in the face of falling FSH levels.

Ovarian-pituitary interaction is crucial to the selection of the dominant follicle, and the forced atresia of the remaining follicles. When this interaction is bypassed, as in ovulation induction with the administration of exogenous gonadotrophins, many follicles continue to develop and are released at ovulation with an ensuing multiple gestation rate of around 30 per cent. During in vitro fertilization (IVF) the production of many ovulatory follicles is desired since the oocytes are harvested, and fertilized in vitro, and the

number of embryos replaced can be carefully controlled. However, if such multiple follicular development occurred unchecked in the normal cycle, it would lead to the production of multiple gestations of high-order numbers, with their associated problems.

### **Inhibin and Activin**

Although folliculogenesis, ovulation and the production of progesterone from the corpus luteum can be explained largely in terms of the interaction between pituitary gonadotrophins and sex steroids, it is becoming clear that other autocrine or paracrine mediators also play a role. One of the most important of these is inhibin.

Inhibin was originally described as a testicular product that inhibited pituitary FSH production, hence its name. However, inhibin is also produced by a variety of other cell types, including granulosa cells within the ovary. Granulosa cell inhibin production is stimulated by FSH but in women, as in men, inhibin attenuates FSH production. Within the ovary, inhibin enhances LH – induced androgen synthesis. The production of inhibin is a further mechanism by which FSH levels are reduced below a threshold at which only the dominant follicle can respond, ensuring atresia of the remaining follicles.

Activin is a peptide that is structurally related to inhibin. It is produced both by the granulosa cells of antral follicles, and also by the pituitary gland. The action of activin is almost directly opposite to that of inhibin in that it augments pituitary FSH secretion, and increases FSH binding to granulosa cells. Granulosa cell activin production therefore appears to amplify the effects of FSH within the ovarian follicle.

## **Insulin-like Growth Factors**

Insulin-like growth factors (IGF-I and IGF-II) act as paracrine regulators. Circulating levels do not change during the menstrual cycle, but follicular fluid levels increase towards ovulation, with the highest level found in the dominant follicle. The actions of IGF-I and – II are modified by their binding proteins; insulin-like growth factor binding proteins (IGFBPs).

In the follicular phase, IGF-I is produced by theca cells under the action of LH. IGF-I receptors are present on both theca and granulosa cells. Within the theca IGF-I augments LH induced steroidogenesis. In granulosa cells, IGF-I augments the stimulatory effects of FSH on mitosis, aromatase activity and inhibin production. In the preovulatory follicle, IGF-I enhances LH-induced progesterone production from granulosa cells. Following ovulation, IGF-II is produced from luteinized granulosa cells, and acts in an autocrine manner to augment LH-induced proliferation of granulosa cells.

## **OVULATION**

Late in the follicular phase, FSH induces LH receptors on granulosa cells. Oestrogen is an obligatory co-factor in this effect. As the dominant follicle develops further, follicular oestrogen production increases. The production of oestrogen is eventually sufficient that the threshold required for oestrogen to exert a positive feedback effect on pituitary LH secretion is achieved. Once this occurs, LH levels increase, at first quite slowly (day 8 to day 12 of the menstrual cycle) and then more rapidly (day 12 onwards.) During this time, LH induces luteinization of granulosa cells in the dominant follicle, so that progesterone is produced. Progesterone further amplifies the positive feedback effect of oestrogen on pituitary LH secretion, leading to a

surge of LH, Ovulation occurs 36 hours after the onset of the LH surge. The LH surge is one of the best methods by which the time of ovulation can be determined, and is the event detected by most over-the-counter 'ovulation predictor' kits.

The periovulatory FSH surge is probably induced by the positive feedback effects of progesterone. In addition to the rise in LH, FSH and oestrogen that occur around ovulations, a rise in serum androgen levels also occurs. These androgens are derived from the stimulatory effect of LH on theca cells, particularly those of the non-dominant follicle. This rise in androgens may have an important physiological effect in the stimulation of libido, ensuring that sexual activity is likely to occur at the time of ovulation when the woman is at her most fertile.

Prior to the release of the oocyte at the time of ovulation, the LH surge stimulates the resumption of meiosis, a process which is completed after the sperm enters the egg. In order for the ovary to release the oocyte at ovulation, breakdown of the follicular wall is required. This event is coordinated by LH, TSH and progesterone which stimulate the activity of proteolytic enzymes such as plasminogen activators (which produce plasmin, which stimulates collagenase activity) and prostaglandins. Prostaglandins not only stimulate the activity of proteolytic enzymes, but also promote an inflammatory-type response within the follicle wall, and by stimulation of smooth muscle activity may help extrusion of the oocyte.

The crucial importance of prostaglandins and other eicosanoids in the process of ovulation is demonstrated by studies showing that inhibition of prostaglandin production may result in failure of release of the oocyte from the ovary, despite apparently normal steroidogenesis (the luteinized unruptured



follicle syndrome, LUF). Although LUF appears to be an uncommon cause of infertility, women wishing to become pregnant should be advised to avoid taking prostaglandin synthetase inhibitors such as aspirin and ibuprofen which may inhibit oocyte release.

## **LUTEAL PHASE**

The luteal phase is characterized by the production of progesterone from the corpus luteum within the ovary. The corpus luteum is derived both from the granulosa cells that remain after ovulation, and from some of the theca cells which differentiate to become theca lutein cells. The granulosa cells of the corpus luteum have a vacuolated appearance associated with the accumulation of a yellow pigment, lutein from where the corpus luteum derives its name. Extensive vascularization within the corpus luteum ensures that the granulosa cells have a rich blood supply providing the precursors for steroidogenesis.

The production of progesterone from the corpus luteum is dependent on continued pituitary LH secretion. However, serum levels of progesterone are such that LH and FSH production is relatively suppressed. This effect is amplified by moderate levels of oestradiol and inhibin that are also produced by the corpus luteum. The low levels of gonadotrophins mean that the initiation of new follicular growth is inhibited for the duration of the luteal phase.

## **Luteolysis**

The duration of the luteal phase is fairly constant, being around 14 days in most women. In the absence of pregnancy and the production of human chorionic gonadotrophin (hCG) from the implanting embryo, the

corpus luteum regresses at the end of the luteal phase, a process known as luteolysis. The control of luteolysis in women remains obscure. As the corpus luteum dies, oestrogen, progesterone and inhibin levels decline. The pituitary is released from the negative feedback effects of these hormones and gonadotrophins, particularly FSH, start to rise. A cohort of follicles which happen to be at the preantral phase are rescued from atresia and a further menstrual cycle is initiated.

## **SUMMARY OF OVARIAN EVENTS**

### **FOLLICULAR PHASE**

- ❖ LH stimulates theca cells to produce androgens.
- ❖ FSH stimulates granulosa cells to produce oestrogens.
- ❖ The most advanced follicle at mid-follicular phase becomes the dominant follicle.
- ❖ Rising oestrogen and inhibin produced by the dominant follicle inhibit pituitary FSH production.
- ❖ Declining FSH levels cause atresia of all but the dominant follicle.

### **OVULATION**

- ❖ FSH induces LH receptors.
- ❖ LH surge.
- ❖ Proteolytic enzymes within the follicle cause follicular wall breakdown and release of the oocyte.

## **THE LUTEAL PHASE**

- ❖ The corpus luteum is formed from granulosa and theca cells retained after ovulation.
- ❖ Progesterone produced by the corpus luteum is the dominant hormone of the luteal phase.
- ❖ In the absence of pregnancy, luteolysis occurs 14 days after ovulation.

## **PITUITARY GLAND**

The process of follicular development, ovulation and the maintenance of the corpus luteum has been described in terms of ovarian physiology. In reality however, the ovary, pituitary and hypothalamus act in concert (the hypothalamo-pituitary-ovarian axis) to ensure the growth and development of (ideally) one ovarian follicle, and to maintain hormonal support of the endometrium to allow implantation.

The pituitary hormones LH and FSH are, as we have seen, key regulators of folliculogenesis. The output of LH and FSH from the pituitary gland is stimulated by pulses of gonadotrophin-releasing hormone (GnRH) produced by the hypothalamus and transported to the pituitary in the portal circulation. The response of the pituitary is not constant but is modulated by ovarian hormones, particularly oestrogen and progesterone. Thus low levels of oestrogen have an inhibitory effect on LH (negative feedback) whereas high levels of oestrogen actually stimulate pituitary LH production (positive feedback). In the late follicular phase, serum levels of oestrogen are sufficiently high so that a positive feedback effect is triggered thus generating the periovulatory LH surge. In contrast, the combine contraceptive pill

produces serum levels of oestrogen in the negative feedback range, so that measured levels of gonadotrophins are low.

The mechanism of action of the positive feedback effect of oestrogen involves an increase in GnRH receptor concentrations and an increase in GnRH production, whilst the mechanism of the negative feedback effect of oestrogen is uncertain.

In contrast to the effects of oestrogen, low levels of progesterone have a positive feedback effect on pituitary LH and FSH secretion. Such levels are generated immediately prior to ovulation, and contribute to the FSH surge. High levels of progesterone such as those seen in the luteal phase inhibit pituitary gonadotrophin production. Negative feedback effects of progesterone are generated both via decreased GnRH production, and via decreased sensitivity to GnRH at the pituitary level. Positive feedback effects of progesterone operate at the pituitary level only and involve increased sensitivity to GnRH. Importantly, progesterone can only have these effects if there has been prior priming by oestrogen.

As we have seen, oestrogen and progesterone are not the only hormones to have an effect on pituitary gonadotrophin secretion. The peptide hormones inhibin and activin have opposing effects on gonadotrophin production: inhibin attenuates pituitary FSH secretion whereas activin stimulates it.

### **Prolactin**

Prolactin is secreted from the alpha cells and is a polypeptide.

Its role in the maintenance of corpus luteum in human is not well documented, but the fact remains that there is high incidence of anovulation in women with elevated plasma prolactin level.

### **Thyrotrophic Hormone (TSH)**

TSH (thyroid stimulating hormone) is produced by the beta cells. It acts on the thyroid gland and regulate the production of thyroxine. It has got  $\alpha$  and  $\beta$  subunits like those of FSH and LH, with functions of  $\beta$  subunits being different. Abnormal TSH secretion is associated with menstrual and ovulatory dysfunction.

## **THE HYPOTHALAMUS**

The hypothalamus, via the pulsatile secretion of GnRH, stimulates pituitary LH and FSH secretion. Production of GnRH not only has a permissive effect on gonadotrophin production, but alterations in amplitude and frequency of GnRH pulsation throughout the cycle are also responsible for some fine tuning of gonadotrophin production.

The importance of GnRH secretion is seen in disorders such as anorexia nervosa, and the amenorrhoea associated with excessive exercise. In these disorders, GnRH production is suppressed leading to anovulation and amenorrhoea. Ovulation can be restored in these women by the administration of GnRH in a pulsatile manner (although this should be approached carefully since pregnancy is relatively contraindicated in women whose body weight is significantly below average).

It is important to remember that GnRH is produced in a pulsatile manner to exert its physiological effect. Drugs that are GnRH agonists (e.g. buserelin and goserilin) are widely used in gynaecology for the treatment of

endometriosis and other disorders. Although these drugs act as GnRH agonists, they cause a decrease in pituitary LH and FSH secretion. The reason for this is that these agonists are long acting and the continued exposure of the pituitary to moderately high levels of GnRH causes down regulation and desensitization of the pituitary. LH and FSH production is therefore markedly decreased. Ovarian steroidogenesis is suppressed so that serum oestrogen and progesterone fall to postmenopausal levels. Most women become amenorrhoeic whilst taking GnRH agonists. A potential disadvantage of the currently available GnRH agonists is that such down-regulation and desensitization of the pituitary takes up to three weeks to exert its effects. The initial effect of GnRH administration is to stimulate pituitary LH and FSH production, leading to increased ovarian steroidogenesis. When a patient commences GnRH therapy, this temporary increase in ovarian steroidogenesis leads to a vaginal bleed within the first month of administration and it is important to warn the patient of this.

# **HYPERPROLACTINEMIA**

## **PROLACTIN**

### **Functions**

The primary function of prolactin is to enhance breast development in pregnancy and to induce lactation after delivery. In addition, by binding to specific receptors in the gonads, lymphoid cells and liver it affects fertility, immunity and liver functions.

## **HYPERPROLACTINEMIA**

A condition characterised by elevated serum prolactin levels, is the most common endocrine disorder of the hypothalamo – pituitary axis. It could result from a variety of conditions both physiological and pathological. The prevalence varies from less than 1% of the general population, to almost 17 percent in women with reproductive disorders.

### **ETIOLOGY OF HYPERPROLACTINEMIA**

Physiological  
REM Sleep  
Pregnancy  
Nipple Stimulation  
Stress  
Coitus

Pathological  
Tumors – Prolactinoma  
Hypothalamic (pituitary lesions)  
Idiopathic  
Polycystic ovarian disease  
Hypothyroidism  
Chest wall injury  
Renal Failure  
Liver Failure  
Drugs – dopamine analogs  
Phenothiazines  
Estrogen  
Opiates  
Cimetidine  
Methyldopa  
Reserpine.

## **EFFECT ON FEMALE REPRODUCTIVE FUNCTION**

Prolactin has a significant effect on the female reproductive function by acting on the hypothalamo-pituitary ovarian axis. In addition, it has a direct action on the ovaries, which is supposed to be responsible for the menstrual irregularities associated with hyperprolactinemia ; probably regulating ovarian steroidogenesis by its actions on the aromatase enzyme. It is interesting to note that the action of prolactin on the ovaries varies in the different phases of the menstrual cycle.

In the follicular phase, elevated prolactin level can disrupt normal follicular development, cause atresia of the dominant follicle and inhibit ovulation. On the other hand, the role of prolactin in the luteal phase is not very clear, as it is supposed to both stimulate (by inducing LH receptor formation) and inhibit corpus luteal functions (by inhibiting corpus luteal steroidogenesis). Animal experiment have found that elevated prolactin level can induce the development of adenomyosis – a condition characterized by the implantation or extension of the endometrial glands into the myometrium, apart from ovulatory dysfunction that could cause the infertility associated with hyperprolactinemia.

### **Effect of Hyperprolactinemia on female reproductive function**

1. Disrupts normal follicular development.
2. Atresia of the dominant follicle.
3. Inhibits aromatase enzyme.
4. Inhibits progesterone synthesis by the corpus luteum.
5. Premature destruction of the corpus luteum.
6. Induces uterine adenomyosis.



## **DIAGNOSIS**

As prolactin is a dynamic hormone that responds readily to a variety of stimuli, caution must be exercised during diagnosis.

Women typically present with a history of amenorrhea, oligomenorrhea or infertility. Occasionally galactorrhea may be the only presenting symptoms. Both sexes may present with visual field defects and headaches if associated with a pituitary tumour.

### **Common Presenting symptoms in prolactin related disorders.**

1. Amenorrhoea
2. Oligomenorrhoea
3. Galactorrhoea
4. Unexplained Infertility
5. Headache
6. Visual field defects
7. Symptoms of hypothyroidism
8. Drug intake
9. Decreased libido

### **Adjuvant investigation in a case of hyperprolactinemia**

1. Serum TSH
2. BUN - Blood Urea Nitrogen
3. Serum Creatinine
4. Liver function tests
5. Visual field testing
6. CT - Brain
7. MRI - Brain

## **THYROID DISORDERS IN INFERTILITY**

Thyroid disorders both hypo and hyperthyroidism are known to have a profound effect on pregnancy and reproduction.

### **HYPERTHYROIDISM**

The effect of severe hyperthyroidism on the fertility potential of an individual is well documented, but the effects of the mild and moderate forms of this disorders are not very clear.

#### **ETIOLOGY OF HYPERTHYROIDISM**

1. Grave's disease.
2. Solitary toxic nodule.
3. Toxic multinodular goitre.
4. Acute thyroiditis- viral
  - a. Autoimmune
  - b. Post-radiotherapy
5. Thyrotoxicosis.
6. Exogenous iodine administration.
7. Metastatic differentiated thyroid carcinoma.
8. TSH secreting tumours.
9. HCG secreting tumours.
10. Hyperfunctioning ovarian teratomas.

## **CLINICAL FEATURES**

### **Symptoms**

- Hyperactivity,
- irritability, dysphoria
- Heat intolerance and sweating
- Palpitations
- Fatigue and weakness
- Weight loss with increased appetite
- Diarrhoea
- Polyuria
- Oligomenorrhoea, loss of libido.

### **Signs**

Tachycardia: atrial fibrillation in the elderly

- Tremor
- Goiter
- Warm, Moist skin
- Muscle weakness, proximal myopathy
- Lid retraction or lag
- Gynaecomastia.

## **HYPERTHYROIDISM AND FEMALE FERTILITY**

Elevated thyroxine concentrations lead to increased levels of the sex hormones binding globulin. This, in turn, accounts for the raised concentrations of Estradiol and testosterone in the blood. Apart from this, the follicular phase baseline serum FSH and LH concentrations are also increased with an attenuated mid-cycle LH surge. Consequently oligovulatory or anovulatory cycles with a wide range of menstrual disorders (ranging from amenorrhoea to menometrorrhagia) may be seen.

### **DIAGNOSIS**

The diagnosis of hyperthyroidism is based upon clinical findings and serological assays.

Assessment of the clinical manifestations would give a reasonable indication to the presence of the disorders, which could then be confirmed by serum hormonal assay.

The best screening tool, however, is the serum TSH assay. This is based on the fact that as the level of the serum T3 and T4 rise, the concentration of TSH will fall exponentially giving an accurate estimation of the severity of the condition.

Once the diagnosis is established further tests to identify a possible cause may be carried out- ultrasound, radioactive iodine uptake, anti thyroid antibody titers etc.

Serum TSH

Serum T4

Serum T3

Radioactive Iodine uptake

Ultrasound

Antithyroid antibodies.

## **HYPOTHYROIDISM**

Hypothyroidism is characterized by a spectrum of clinical manifestations that are directly or indirectly related to the deficiency of the thyroid hormones.

Moderate and severe degrees of hypothyroidism have a detrimental effect on the reproductive potential of both men and women, but the same cannot be said of the mild and sub-clinical forms.

Primary hypothyroidism is due to thyroid gland failure, while secondary hypothyroidism occurs due to disorders of the hypothalamo - pituitary axis, which results in the inadequate production of bio-active TSH.

## **ETIOLOGICAL FACTORS OF HYPOTHYROIDISM**

### **Primary**

1. Congenital - Agenesis
  - Ectopic thyroid remnants.
2. Defect in synthesis -
  - Iodine deficiency
  - Dyshormogenesis
  - Antithyroid drugs
3. Autoimmune
  - Hashimoto's thyroiditis.

4. Atrophic.
5. Infective.
6. Post - surgery.
7. Post - radiotherapy.
8. Peripheral resistance to thyroid hormones.

### **Secondary**

1. Hypopituitarism.
2. Isolated TSH deficiency.

## **CLINICAL FEATURES**

### **Symptoms**

- Tiredness, weakness
- Dry skin
- Feeling cold
- Hair loss
- Difficulty concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (later oligomenorrhoea or amenorrhoea)
- Paresthesia
- Impaired hearing

## **Signs**

- Dry coarse skin; cool peripheral extremities
- Puffy face, hands and feet (myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral oedema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

## **HYPOTHYROIDISM AND FEMALE FERTILITY**

The effect of hypothyroidism on the reproductive potential has been well documented in women probably due to the fact this disorder is more often seen in females.

Menstrual irregularities, spontaneous first trimester miscarriages, premature deliveries, unexplained stillbirths and infertility are some of the manifestations.

Almost 70 percent of infertility in hypothyroid females is due to anovulation.

Hypothyroidism is also common in women with unexplained infertility, and not often seen in women with tubal factor.

Menstrual irregularities are seen in approximately 23 to 25 percent. Oligomenorrhoea is probably the most common clinical manifestation.

Menorrhagia, sometimes seen in these women is due to a combination of anovulation, poor uterine muscle tone and platelet dysfunction.

## DIAGNOSIS

Confirmation of the diagnosis is by serological assay, which would demonstrate a deficiency of the thyroid hormones.

### Thyroid function Test

Test	Use	Misleading
Total T <sub>4</sub>	Hypothyroidism	Pregnancy
Free T <sub>4</sub>	Thyrotoxicosis Hypothalmo - pituitary disease	Estrogen therapy NSAID therapy
Total T <sub>3</sub>	Thyrotoxicosis screening	
TSH	Neonatal hypothyroidism Thyrotoxicosis Hypothalamo pituitary disease	

Once the diagnosis is established, the presence of autoimmune disorders must be looked for. Assay of antimicrosomal antibodies and antithyroglobulin antibodies are useful indicators of the risk of progression.

Screening for hypothyroidism is best done using a sensitive TSH assay. However, this may not be very accurate in conditions that do not produce enough bioactive TSH as seen in recent onset hypothyroidism and in hypothalamo-pituitary disorders. In these cases it would be better to assay free T<sub>4</sub> along with the TSH.



## **POLYCYSTIC OVARIAN SYNDROME (PCOS)**

In 1935, Irving F. Stein and Michael L. Leventhal first described a symptom complex associated with infertility. They described 7 patients, 4 of whom were obese, with amenorrhoea, hirsutism and enlarged polycystic ovaries. Based on their observation that several amenorrhoeic patients menstruated after ovarian biopsy, they subjected the 7 patients to bilateral wedge resection, wherein, they removed half to three-fourth of each ovary. They observed that all 7 women resumed regular menses and 2 of them even conceived.

The National Institute of Health Conference (1990) gave a working definition whereby it is enough if a patient has chronic ovulatory dysfunction and any evidence of hyperandrogenism excluding other causes such as adult onset congenital adrenal hyperplasia (CAH) Cushing's syndrome, androgen secreting neoplasms.

The incidence varies between 0.5-4 per cent, more common amongst infertile women. It is prevalent in young reproductive period.

### **PATHOLOGY**

Typically, the ovaries are enlarged two to five times the normal size. Stroma is increased. The capsule is thickened and pearly white in colour. On bisection, multiple follicular cysts measuring about 8-10mm in diameter are crowded around the cortex.

Histologically, there is thickening of tunica albuginea. The cysts are follicles at varying stages of maturation and atresia. There is theca cell

hypertrophy (stromal hyperthecosis). Patient may present with features of diabetes mellitus (insulin resistance).

## **CLINICAL FEATURES**

The patient complains of increasing obesity, menstrual abnormalities in the form of oligomenorrhoea, amenorrhoea or DUB (Dysfunctional uterine bleeding) and infertility.

Amenorrhoea was the presenting complaint for all the patients in the series reported by Stein and Leventhal, however, Gold Heizer in his classic review of 187 reports described 1079 cases, he identified amenorrhoea in an average of 47% of patients only, while 16% had regular menses. Conway and co-workers found 20-25% of patients with ultrasound findings of polycystic ovarian syndrome, to have regular period. Grossly abnormal menstrual cycles usually signal ovulatory dysfunction. There may be hirsutism. Virilism is rare. The patient may not always be obese.

Acanthosis nigricans is characterized by specific skin changes due to insulin resistance. The skin is thickened and pigmented. Commonly affected sites are nape of the neck, inner thighs, and axilla.

HAIR-AN syndrome in patients with PCOS is characterized by hyperandrogenism, insulin resistance and acanthosis nigricans.

Internal examination reveals bilateral enlarged cystic ovaries which however, may not be revealed due to obesity.

## **INVESTIGATIONS**

### **Sonography**

Transvaginal sonography is specially useful in obese patient. Ovaries are enlarged in volume. Increased number of peripherally arranged cysts are seen.

### **Serum values**

- LH level is elevated and / or the ratio LH: FSH is  $> 3:1$ .
- Reversible oestradiol: oestrone ratio – The oestrone level is markedly elevated.
- SHBG level is reduced.
- Androstenedione is elevated.
- Serum testosterone and DHEA –S may be marginally elevated.
- Raised serum insulin level (insulin resistance) / or the ratio of fasting glucose : fasting insulin is  $<4.5$

### **Laparoscopy**

Bilateral polycystic ovaries are characteristic of PCOS.

## **PATHOPHYSIOLOGY**

Exact pathophysiology of PCOS is not clearly understood. It may be discussed under the following heads .

- (a) Hypothalamic – Pituitary compartment abnormality.
- (b) Androgen excess
- (c) Anovulation.

- (d) Obesity and insulin resistance.
- (e) Long-term consequences

### **HYPOTHALAMIC – PITUITARY COMPARTMENT IN PCOS**

- Increased pulse frequency of GnRH leads to increased pulse frequency of L.H. (Leptin, a peptide, secreted by fat cells and by the ovarian follicle, in presence of hyperinsulinaemia may be responsible for this).
- GnRH is preferential to LH rather than FSH.
- Increased pulse frequency and amplitude of LH results in tonically elevated level of LH.
- FSH level is not increased. This is mainly due to the negative feedback effect of chronically elevated oestrogen and the follicular inhibin.
- Increased free oestradiol due to reduced sex hormone binding globulin (SHBG) bears positive feedback relationship to LH.
- The LH: FSH ratio is increased.

### **ANDROGEN EXCESS**

Abnormal regulation of the androgen forming enzyme (P450 C17) is thought to be the main cause for excess production of androgens from the ovaries and adrenals. The principal sources of androgens are (A) Ovary (B) Adrenal (C) Systemic metabolic alteration.

**A. Ovary** produces excess androgens due to:

- (i) Stimulation of theca cells by high LH
- (ii) P450 C17 enzyme hyperfunction
- (iii) Defective aromatisation of androgens to oestrogen
- (iv) Stimulation of theca cells by IGF-1 (insulin growth factor-1).

**B. Adrenals** are stimulated to produce excess androgens by:

- (i) Stress
- (ii) P450 C17 enzyme hyperfunction
- (iii) Associated high prolactin level (20%).

**C. Systemic metabolic alteration**

**(i) Hyperinsulinaemia causes :**

- (a) Stimulation of theca cells to produce more androgens.
- (b) Insulin results in more free IGF-1. By autocrine action, IGF-1 stimulates theca cells to produce more androgens.
- (c) Insulin inhibits hepatic synthesis of SHBG, resulting in more free level of androgens.

Features Suggestive of insulin resistance are: BMI  $>27 \text{ kg} / \text{M}^2$ , Acanthosis nigricans and waist to hip ratio  $> 0.85$ .

**(ii) Hyperprolactinaemia**

In about 20 per cent cases, there may be mild elevation of prolactin level due to increased pulsitivity of GnRH or due to dopamine deficiency or to both. The prolactin further stimulates adrenal androgen production.

## **ANOVULATION**

Because of low FSH level, follicular growth is arrested at different phases of maturation (5-10 mm diameter). The net effect is diminished oestradiol and increased inhibin production. Due to elevated LH, there is hypertrophy of theca cells and more androgens are produced either from theca cells or stroma.

There is defective FSH induced aromatisation of androgens to oestrogens.

Follicular microenvironment is therefore more androgenic rather than oestrogenic.

Unless there is oestrogenic follicular micro-environment, follicular growth, maturation and ovulation cannot occur. There is huge number of atretic follicles that contribute to increased ovarian stroma (hyperthecosis). LH level is tonically elevated without any surge. LH surge is essential for ovulation to occur.

## **OBESITY AND INSULIN RESISTANCE**

Obesity has been classically regarded as an important feature but its presence is extremely visible being found in 35-60% of polycystic ovarian syndrome. It has no diagnostic value but the greater the body mass index, the higher the testosterone levels and hirsutism. They have a characteristic distribution of body fat known as android obesity. The fat is metabolically active and less sensitive to insulin. It is associated with hyperinsulinemia, impaired glucose tolerance, decrease in SHBG and increase in the level of testosterone. A waist hip ratio greater than 0.85 indicates android fat.

distribution. Hyperinsulinemia and hyperandrogenism however, are not confined to obese polycystic ovarian syndrome. However, insulin levels are higher, luteinizing hormone, SHBG and IGFBP-1 levels are lower in obese, compared to non-obese individuals. Obesity, defined as BMI greater than 27 is found in 30-35% of women with polycystic ovarian syndrome. Hirsutism is found in 70-73% of obese polycystic ovarian syndrome compared to 56-58% of normal weight polycystic ovarian syndrome and infertility is 40% more in polycystic ovarian syndrome with BMI greater than 30. Also menstrual cycles are more irregular.

### **LONG TERM CONSEQUENCES IN A PATIENT SUFFERING FROM PCOS INCLUDES**

The excess androgens (mainly androstenedione) either from the ovaries or adrenals are peripherally aromatised to oestrone (E<sub>1</sub>). There is concomitant diminished SHBG. Cumulative excess unbound E<sub>2</sub> and oestrone results in a tonic hyperoestrogenic state. There is endometrial hyperplasia.

- ❖ Risk of developing diabetes mellitus due to insulin resistance..
- ❖ Risk of developing endometrial carcinoma due to persistently elevated level of oestrogens. Oestrogen effects are not opposed by progesterone because of chronic anovulatory state.
- ❖ Risk of hypertension and cardiovascular disease due to abnormal lipid profile.

## DIAGNOSIS OF OVULATION

The various methods used in practice to detect ovulation are grouped as follows:

Diagnosis of ovulation
<b>Indirect</b> Menstrual history Evaluation of peripheral or endorgan changes <ul style="list-style-type: none"><li>• BBT (Basal Body Temperature)</li><li>• Cervical mucus study</li><li>• Vaginal cytology</li><li>• Hormone estimation<ul style="list-style-type: none"><li>- Serum progesterone</li><li>- Serum LH</li><li>- Serum oestradiol</li></ul></li><li>• Endometrial biopsy</li></ul> Sonography
<b>Direct</b> Laparoscopy
<b>Conclusive</b> Pregnancy

### INDIRECT

The indirect or presumptive evidences of ovulation are commonly used in clinical practice. These are inferred from:

- Menstrual history.
- Evaluation of peripheral or end-organ changes due to oestrogen and progesterone.



- Direct assays of gonadotrophins or steroid hormones preceding, coinciding or succeeding the ovulatory process.

## **MENSTRUAL HISTORY**

The following features in relation to menstruation are strong evidences of ovulation.

- Regular normal menstrual loss between the age of 20-35.
- Midmenstrual bleeding (spotting) or pain or excessive mucoid vaginal discharge (Mittelschmerz syndrome)
- Features suggestive of premenstrual syndrome or primary dysmenorrhoea.

## **EVALUATION OF PERIPHERAL OR ENDORGAN CHANGES**

### **Basal body temperature (BBT)**

**Observation** – There is “biphasic pattern” of temperature variation in ovulatory cycle. If pregnancy occurs, the rise of temperature sustains along with absence of the period. In anovulatory cycle, there is no rise of temperature throughout the cycle.

**Principle** – The rise of temperature is secondary to progesterone output. The primary reason for the rise is the increase in the production and secretion of norpinephrine which is thermogenic neural hormone.

**Procedures** – The patient is instructed to take her oral temperature daily on waking in the morning before rising out of the bed. The temperature is recorded on a special chart. Days when intercourse takes place should also be noted on the chart for better evaluation of coital frequency.

**Interpretation** – The body temperature maintaining throughout the first half of the cycle is raised to 0.5 to 1<sup>0</sup>F (0.2-0.5<sup>0</sup>C) following ovulation. The rise sustains throughout the second half of the cycle and falls about 2 days prior to the next period - called “biphasic pattern”. There may be a drop in the temperature to about 0.5<sup>0</sup>F before the rise and almost coincides with either LH surge or ovulation. The demonstrable rise actually occurs about 2 days after the LH peak and with a peripheral level of progesterone to greater than 4 ng / ml.

**Clinical Importance** – Maintenance of BBT charge during investigation is of help in determining ovulation and timing of post coital test, endometrial biopsy, cervical mucus or vaginal cytology study for ovulation. It also helps the couple to determine the most fertile period, if the cycle is irregular.

#### **Limitations of BBT**

- BBT indicates ovulation retrospectively.
- It cannot predict ovulation precisely with time.
- Rarely ovulation has been observed though BBT is monophasic.

It should not be continued for more than 3-4 months for investigation purpose. However, it has to be maintained for longer periods during management of ovulation induction.

#### **Cervical mucus study**

Alteration of the physico-chemical properties of the cervical mucus occurs due to the effect of oestrogen and progesterone.

Disappearance of fern pattern beyond 22<sup>nd</sup> day of the cycle which was present in the midcycle is suggestive of ovulation. Persistence of fern pattern even beyond 22<sup>nd</sup> day suggests anovulation. Progesterone causes dissolution of the sodium chloride crystals. Following ovulation, there is loss of stretchability (spinbarkeit) which was present in the midcycle.

### **Vaginal cytology**

Maturation index shifts to the left from the midcycle to the mid second half of cycle due to the effect of progesterone. However, a single smear on day 25 or 26 of the cycle reveals features of progesterone effect, if ovulation occurs.

### **Hormone estimation**

**Serum progesterone** – Estimation of serum progesterone is done on day 8 and 21 of a cycle. An increase in value from less than 1 ng / ml to greater than 6 ng / ml suggests ovulation.

**Serum LH** – Daily estimation of serum LH at midcycle can detect the LH surge. Ovulation occurs about 34-36 hours after beginning of the LH surge. It coincides about 10-12 hours after the LH peak.

**Serum oestradiol** - attains the peak rise approximately 24 hours prior to LH surge and about 24-36 hours prior to LH surge and about 24-36 hours prior to ovulations.

The serum LH and oestradiol estimation is used for in vitro fertilization.

## **Endometrial biopsy**

Endometrial tissues to detect ovulation (endometrial sampling) can easily be obtained as an out-patient procedure using instruments such as Sharman curette or Pipelle endometrial sampler. Dilatation and curettage is however reserved in cases where bulk endometrial study is required as in endometrial tuberculosis.

Biopsy is to be done on 21-23<sup>rd</sup> day of the cycle. Barrier contraceptive should be prescribed during the cycle to prevent accidental conception. However, if the cycle is irregular, it is done within 24 hours of the period.

Findings - Evidences of secretory activity of the endometrial glands in the second half of the cycle give not only the diagnosis of ovulation but can predict the functional integrity of the corpus luteum.

Subnuclear vacuolation is the earliest evidence appearing 36-48 hours following ovulation.

Cause - The secretory changes are due to the action of progesterone on the oestrogen primed endometrium.

## **SONOGRAPHY**

Serial sonography during midcycle can precisely measure the Graafian follicle just prior to ovulation (18-20 mm). It is particularly helpful for confirmation of ovulation following ovulation induction, artificial insemination and invitro fertilization. The features of recent ovulation are collapsed follicle and fluid in the pouch of Douglas.

## **DIRECT**

### **Laparoscopy**

Laparoscopic visualization of recent corpus luteum or detection of the ovum from the aspirated peritoneal fluid from the pouch of Douglas is the only direct evidence of ovulation.

## **CONCLUSIVE**

Pregnancy is the surest evidence of ovulation.

# **MATERIALS AND METHODS**

## **POPULATION AND SAMPLE**

The population consists of Penn Maladu (Polycystic ovarian disease, Hypothyroidism) patients satisfying the inclusion and exclusion criteria mentioned below.

The sample consists of Penn Maladu patients attending the OPD of Ayothidoss Pandithar Hospital of National Institute of Siddha, Chennai - 47.

## **SAMPLE SIZE**

The trial size will be 20 patients

## **INCLUSION CRITERIA**

- a. Age 20 to 40 years
- b. Normal report of semen analysis of male partner
- c. Willing to produce sonography before the start of the trial
- d. Willing to give blood specimen for investigation when required

## **EXCLUSION CRITERIA**

1. Congenital Defects
2. Endometriosis
3. Tuberculosis
4. Sexually transmitted disease
5. Genital Malignancy
6. Tubal factors

## **WITHDRAWAL CRITERIA**

1. Development of severe adverse drug reactions
2. Occurrence of any other serious illness

## **TRIAL DRUG, DOSAGE, DURATION**

1. Maladu Neenga Thailam : 3g o.d. at morning for the first 3 days of a menstrual cycle.
2. Saaravalli Mathirai : 2g b.d. from 4<sup>th</sup> day of menstrual cycle to 30<sup>th</sup> day  
Trial treatment period is 90 days or 3 cycles.

## **TESTS AND ASSESSMENTS**

### **(a) CLINICAL ASSESSMENT**

Oligomenorrhoea, Amenorrhoea, Regular Periods, Hypomenorrhoea, Pain during menstruation.

### **(b) INVESTIGATIONS**

1. Blood Test  
TC, DC, ESR, Hb, Blood Sugar, Serum Creatinine, Serum Cholesterol, Serum Progesterone, FSH, LH, T3, T4, TSH.
2. Sonography
3. Urine Analysis  
Albumin, Sugar, Deposits, HCG.

**(c) TEST IN SIDDHA ASPECTS**

❖ Envagai Theruvugal

Naadi, Sparism, Naa, Niram, Mozhi, Vizhi, Malam, Moothiram

❖ Neerkuri

Nirma, Edai, Manam, Nurai, Enjal

❖ Neikuri

**CONDUCT**

Penn Maladu patients satisfying the inclusion and exclusion criteria will be admitted to this trial. Informed consent will be obtained from the patients.

They will be instructed to come for next visit after 7 days and asked to bring back the unconsumed drug during their next visit and return the same.

**FORM**

**(A) Form – I :** Selection Proforma - It is used before admission to the Trial

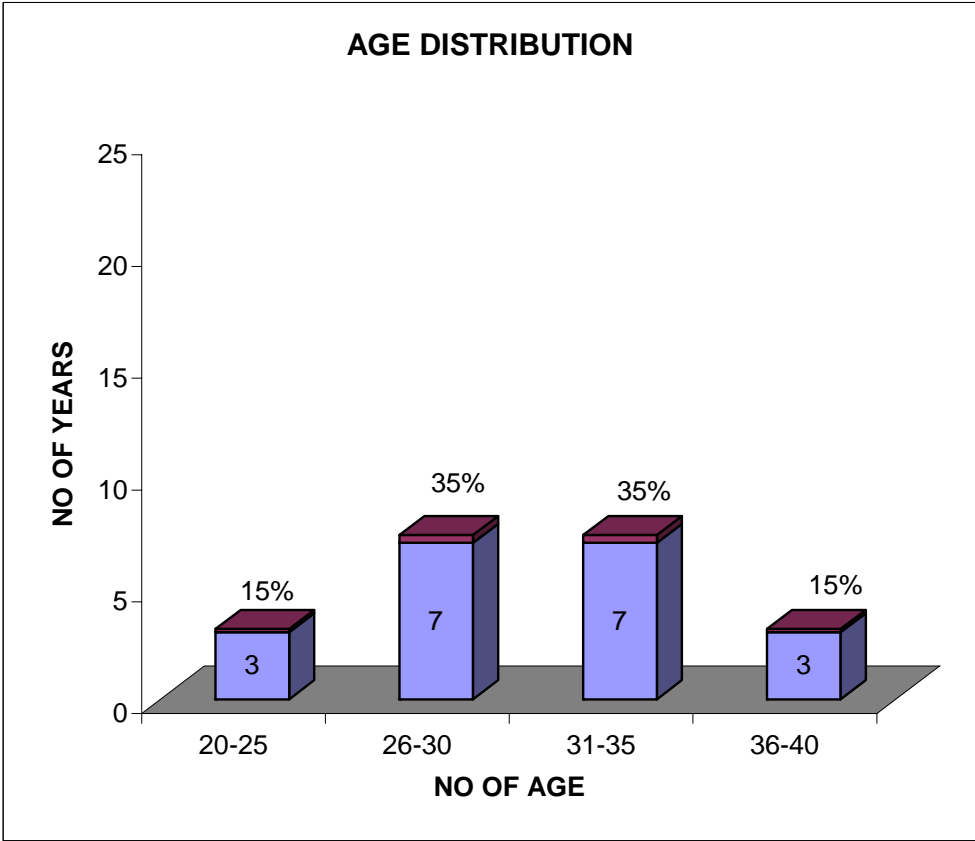
**(B) Form-II :** Assessment Proforma – It is used during clinic visits once in 7 days.



# OBSERVATION AND RESULTS

Table - 1  
Age Distribution

Age	Cases	
	No	Percentage (%)
20 – 25	3	15%
26 – 30	7	35%
31 – 36	7	35%
36 – 40	3	15%
Total	20	100%



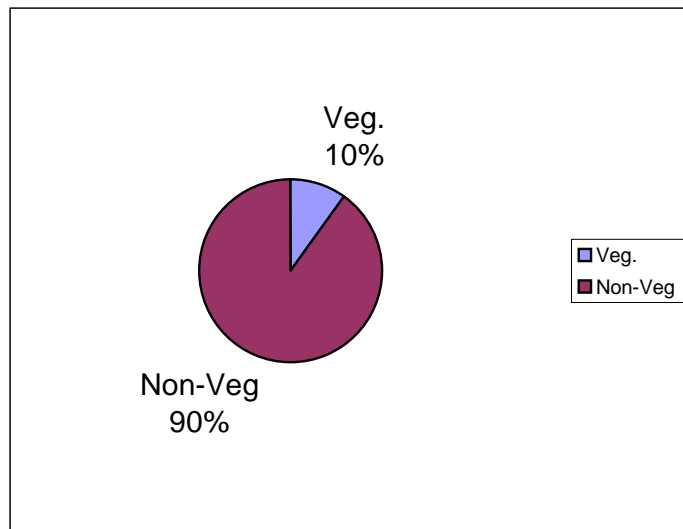
**Table - 2**  
**Occupation History**

Working in Night Shifts	Cases	
	No	Percentage (%)
Yes	1	5%
No	19	95%
Total	20	100%

**Table - 3**  
**Food Habits**

Food Habits	Cases	
	No	Percentage (%)
Veg	2	10%
Non-Veg	18	90%
Total	20	100%

**Food Habits**



**Table - 4**  
**Years of Infertility**

Duration (Yrs)	Cases	
	No	Percentage (%)
0 - 3	6	30%
3 - 6	9	45%
6 - 9	2	10%
10 +	3	15%
Total	20	100%

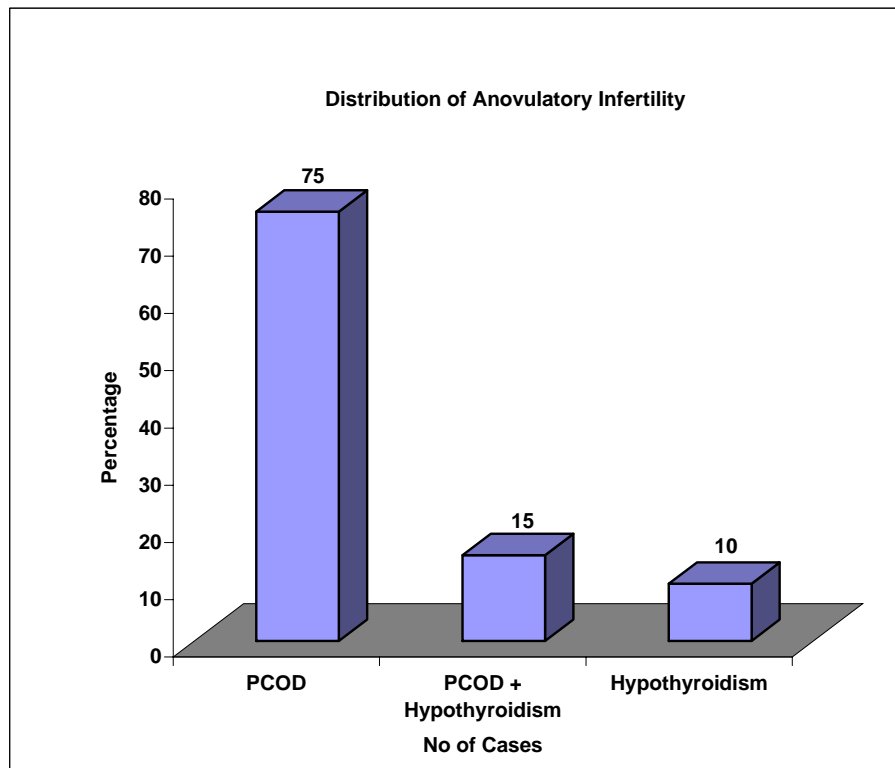
**Table - 5**  
**Thinai**

Duration (Yrs)	Cases	
	No	Percentage (%)
Kurunji	1	5%
Mullai	0	0%
Marutham	0	0%
Neithal	19	95%
Palai	0	0%
Total	20	100%

**Table - 6**

**Distribution of Anovulatory Infertility**

<b>Anovulation</b>	<b>No of Cases</b>	<b>Percentage (%)</b>
PCOD	15	75%
PCOD + Hypothyroidism	3	15%
Hypothyroidism	2	10%
<b>Total</b>	<b>20</b>	<b>100%</b>



**Table - 7**  
**Distribution of Menstrual Pattern**

Menstrual Pattern	PCOD		PCOD + Hypothyroidism		Hypothyroidism	
	No of Cases	Percentage (%)	No of Cases	Percentage (%)	No of Cases	Percentage (%)
Oligomenorrhoea	9	45%	1	5%	0	0%
Amenorrhoea	3	15%	2	10%	0	0%
Regular Periods	3	15%	0	0%	2	10%
Hypomenorrhoea	6	30%	1	5%	2	10%

**Table - 8**  
**Udal Thathukkal**

Udal Thathukkal	No. of Cases	Percentage (%)
Saarum	20	100%
Senneer	7	35%
Oon	1	5%
Kozhuppu	2	10%
Enbu	0	0%
Moolai	0	0%
Suronitham	20	100%

**Table - 9**

**Neerkuri**

<b>Neerkuri</b>	<b>No of Cases</b>	<b>Percentage (%)</b>
Pale Yellow	10	50%
Yellow	5	25%
Dark Yellow	2	10%
Straw	1	5%
Total	20	100%

**Table - 10**

**Neikuri**

<b>Neikuri</b>	<b>No of Cases</b>	<b>Percentage (%)</b>
Slowly Spread	15	75%
Fastly Spread	2	10%
Muthu	3	15%
Total	20	100%

**Table - 11**  
**Envagai Thervu**

<b>Envagai Thervu</b>	<b>No of Cases</b>	<b>Percentage (%)</b>
Naa Dryness	2	10%
Niram Vatham Pitham Kapham	9 6 5	45% 30% 25%
Mozhi	0	0%
Vizhi	0	0%
Malam	5	25%
Moothiram	0	0%
Sparisam Veppam Thatpam	2 18	10% 90%
Naadi Vatha Pitham Pithavatham Vathakapham	10 8 2	50% 40% 10%

**Table - 12**  
**Result**

<b>Anovulatory Infertility</b>	<b>PCOD ± Hypothyroidism</b>	<b>Hypothyroidism</b>
Ovulation / Fertility	13	2
Failure	5	-

# DISCUSSION

## **Age Distribution**

Out of 20 patients, most of were between 25 – 35 yrs of age. Due to late marriages now-a-days, the distribution of age among infertility patients is increased to 25-35 yrs.

Though ovulation is same in all age groups, the decline in fertility begins in the early thirties and accelerates in late thirties and early forties.

## **Occupational History**

Out of 20 patients, one is working in night shifts. Due to alteration in the circadian rhythm and stress, the menstrual pattern is also affected. This may be the one of the cause for infertility.

## **Food Habits**

Out of 20 patients, 18 were non-vegetarians. In the fast pace of modern life, dietary habits lead to obesity and a decline in fertility rate.

## **Years of Infertility**

Out of 20 patients, 15 patients were below six years of duration. They have good improvement.

## **Thinai**

Most of the patients came from Neithal Thinai. Commonly Vali is deranged in its state in this thinai. Abana Vayu is affected in female infertility patients.



## **Clinical Features**

Patients enrolled had varying menstrual patterns from regular periods through oligomenorrhoea to amenorrhoea.

### **Oligomenorrhoea**

Out of 20 patients, 10 patients has Oligomenorrhoea in whom menstrual bleeding occurring more than 35 days apart and which remains constant at that frequency. All the patients were improved and had regular periods.

### **Amenorrhoea**

Out of 20 patients, 5 patients had Amenorrhoea. All the 5 patients menstruate after the treatment. But ovulation / fertility is not achieved.

### **Regular Periods**

Out of 20 patients, 5 patients had regular periods, but biochemical markers of infertility are positive. Of them, 3 becomes pregnant and 2 has ovulation.

### **Hypomenorrhoea**

Out of 20 patients, 9 patients had hypomenorrhoea. All are relieved from the symptoms after treatment.

### **Vali**

Amenorrhoea, Oligomenorrhoea, Hypomenorrhoea are due to deranged Abana Vayu. 15 patients affected by Abana Vayu.

## **Azhal**

Sathaga Pitham (life energy) was affected in most of the infertility patients.

## **Udal Thathukkal**

Suronitham affected in all patients. Saarum affected in 20 patients. Senneer affected in 7 patients. Derangement of Suronitham, saarum, senneer or any one of this lead to development of infertility. Sometimes oon & kozhuppu may be affected.

## **Envagai Thervu**

Niram-9 patients came with Vatha niram, 6 patients came with pitha niram and five with kapha niram.

Sparisam- Sparisam was veppam in 2 patients , thatpam in 18 patients.

Malam was affected in 5 patients due to hypothyroidism .

Nadi – Vatha pitham & pithavatham was the commonest nadi in majority of cases.

## **Neerkuri**

The colour of the urine was pale yellow in 10 patients, yellow in 5 patients, dark yellow in 2 patients. The yellow colouration is due to pithathontham.

## **Neikuri**

Most of the patients it was slowly spread (i.e.) curable condition.

## **Result**

Out of 20 Anovulatory patients 15 ovulate and 8 of them even conceived. Failure of ovulation is in 5 patients.

## SUMMARY

The aim of the study is to evaluate the efficacy of the Siddha drugs 'Maladu Neenga Thailam and Saaravalli Mathirai' for the treatment of Penn Maladu. The drugs are prepared as per the literature. 20 patients are selected for the trial, based on inclusion and exclusion criteria.

Before treatment, consent is obtained from the patients. With the help of routine blood and urine examination biochemical parameters, clinical markers and ultrasound, diagnosis is made. At least two markers should be positive.

They are given trial drugs for 7 days and is instructed to come for next clinical visit after 7 days. Also they are asked to bring back the unconsumed drug during their next visit and return the same. The assessment form is noted in every clinical visit.

At the end of treatment the clinical symptoms are reduced in majority of patients and ovulation occurred in 75% patients. Of them 40% patients even conceived. There is failure of ovulation in 25% patients. After treatment no adverse-effect is noted.

## **CONCLUSION**

Clinical trial revealed that the trial drugs "Maladu Neenga Thailam and Saaravalli Mathirai" produce ovulation in 75% of cases and failure of ovulation in 25% of cases.

There is no adverse effects observed during the course of treatment. It is concluded that these Drugs are effective in the treatment of Penn Maladu.

Because of the encouraging results clinically, the study may be undertaken with the same drugs for a prolonged period of time in more number of cases and it may throw new lights for the treatment of Penn Maladu.

# ANNEXURE-I

## PREPARATION OF TRIAL MEDICINE

### TRIAL DRUG 1

#### MALADU NEENGA THAILAM

##### Ingredients

Raw drugs	-	Each 250 gm
1. Seeds of Kumatti	-	Citrullus colocynths
2. Seeds of Nervalam	-	Croton tiglium
3. Garlic	-	Allium Sativum
4. Seeds of Aamanakku	-	Ricinus communis

##### Method of Preparation

All the above raw drugs are put into kuzhithaila Karuvi and burnt with 50 dried cow dung cakes. Then the oil obtained from the raw drugs is collected.

**Dose** : 3 grams as single dose on morning in empty stomach. It produces purgation.

**Duration** : On the first 3 days of menstruation.

**Literature evidence** : Agasthiyar Kanagamani 100 Page No.34.

Fkl;b tpj

**Botanical name** : **Citrullus Colocynthis**

Rit - ifg;G> jd;ik - ntg;gk;> gphpT - fhh;g;G

Fzk;

fpilnaq;Nf Nrhk;gnyq;Nf NfLwr;nra; thjf;

filnaq;Nf ahw;Wf; fypq;f - kiljpwf;fpd;

mz;il ailr;rnyq;Nf ahapioahh; #jfj;jpd;

cz;il Ailr;rnyq;Nf NahJ. (Nj.F)

### **Chemical Constituents**

Colocynthin, Colocynthein, Colocynthetin

Neh;thsk;

**Botanical name - Croton tiglium. Linn**

Rit - ntFl;IYld; \$ba ifg;G> jd;ik-ntg;gk;> gphpT-fhh;g;G.

Fzk;

Xjp Yjtj; JWkyk;gd; Ndha; tpyFk;

Ngjp kUe;jpw; nghpjhFk; - thjkWq;

\$h;this nahj;jtpopf; nfhk;gidNa! gz;bjh; nrhy;

Neh;thsf; nfhl;ljid eP. (m.F)

### **Chemical Constituents**

Tiglinic acid, Crotonic or quartenylic acid, Crotonoleic acid

nts;Ss;sp

**Botanical Name** : **Allium Sativum, Linn**

Rit - fhh;g;G> jd;ik-ntg;gk;> gphpT-fhh;g;G.

Fzk;

rd;dpnahU thje; jiyNehT jhs;typ  
kd;dptU ePh;f;Nfhit td;rPjk; - md;dNk!  
cs;Ss;sp fz;gha; cis%y NuhfKk; Nghk;  
nts;Ss;sp jd;dhy; ntUz;L. (m.F)

### **Chemical Constituents**

Volatile essential oil contains allyl, propyl, disulphide and other organic sulphides or sulphur compounds.

Mkzf;F tpjj

**Botanical Name** : **Ricinus inermis**

Rit - ifg;G> jd;ik-ntg;gk;> gphpT-fhh;g;G

Fzk;

thjj; njhlf;if tunthl;lh kw;gbf;Ff;  
fhjj;Jf;; fg;ghw; fbANk - #jj;ijg;  
Nguz;lg; ge;jpf;Fk; Ngjpf;F Neha;f;fhl;il  
Nauz;l nkd;gjpdNa. (Nj.ntz;gh)

### **Chemical Constituents**

Ricinoleate of glycerol, and tri-ricinolein



## TRIAL DRUG - 2

### SAARAVALLI MATHIRAI

#### Ingredients

#### Raw Drugs

Omum – Carum Coptium	-	120gms
Chithramoola verpattai – Plumbago zeylanica	-	110gms
Kadukkai Thol – Terminalia chebula	-	100gms
Kostum – Costus Speciosus	-	90gms
Thippili – Piper longum	-	80gms
Milagu - Piper nigrum	-	70gms
Chukku – Zingiber officinale	-	60gms
Sevvrium – Root of Piper nigrum	-	50gms
Kothamalli – Coriandrum Sativum	-	40gms
Vaividangam – Embelia ribes	-	30gms
Seeragam – Cuminum cyminum	-	20gms
Perungayam – Ferula asafoetida	-	10gms
Palm Jaggery	-	1560gms

### **Method of Preparation**

All the above raw drugs are purified and powdered well. Then the powder is grind with palm jaggery and is made into balls weighing 2 gms each.

### **Dose**

2 grams twice a day.

### **Indications**

Regulates the menstruation and induces ovulation.

### **Literature evidence**

Nam Naatu Vaidhiyam - Kannapar

Page No.268

Xkk;

**Botanical Name : Carum Copticum**

Rit - fhh;g;G jd;ik - ntg;gk;> gphpT - fhh;g;G.

Fzk;

rPjRuq; fhrQ; nrhpahke; jk;nghUky;

Ngjpapiur; ry;fLg;G Nguhkk; - XjpUky;

gy;nyhLgy; %yk; gfkpitNeh nad;nrANKh?

nrhy;nyhLNghk; xknkdr; nrhy;. (m.F)

### **Chemical Constituents**

Essential oil, Thymol

rpj;jpu%y Nth;gl;il

**Botanical Name : Plumbago Zeylanica**

Rit-fhh;g;G> tpWtpWg;G> jd;ik-ntg;gk;> gphpT-fhh;g;G

Fzk;

fl;btpu zq;fpue;jp fhy;fs; miuahg;Gf;

fl;br;# nytPf;fq; fho;%yk; - Kl;buj;jf;

fl;L eP Nuw;wq; fdj;j ngUtapWk;

ml;Lq; nfhbNtyp ahk;.

### **Chemical Constituents**

Plumbagin.

fLf;fha;j; Njhy;

**Botanical Name : Terminalia Chebula**

Rit - Kf;fpa Rit-Jth;g;G> mj;Jld; rpwpJ ,dpg;G> Gspg;G> fhh;g;G ifg;G

ngw;wpUf;Fk;. jd;ik-ntg;gk;> gphpT-,dpg;G

Fzk;

jhil fOj;jf;fp jhY Fwpaptplg;

gPil rpypgjKw; NgjpKlk; - Milnal;lhj;

Jhykpb Gz;thj Nrhzpfh khiyapuz;

lhykpb Nghk;thpf;fh ahy;.

### **Chemical Constituents**

Tannin, Gallic acid, Chebulinic acid.

Nfh\;lk;

**Botanical Name : Costus Speciosus**

Rit - ifg;G> tpWtpWg;G> jd;ik-ntg;gk;> gphpT-fhh;g;G

Fzk;

ehl;bYW ntl;il eLf;fk; vDNeha;fs;

Nfhl;lnkdr; nrhd;dhy; FiyAq;fhz; - \$l;bw;

RuNjhle; njhz;ilNeha; Njhyhj gpj;jk;

guNjrk; NghNk gwe;J.

mhprpj; jpg;gpyp

**Botanical Name : Piper longum**

Rit - ,dpg;G> jd;ik-ntg;gk;> gphpT-,dpg;G.

Fzk;

jpg;gpypapd; ez;LyQ; rpNyj;kj;ijg; Nghf;fptpLk;

cg;gprj;ij Nkfj;ij xl;Lq;fhz; - jg;ghky;

thj Rue;jzpf;Fk; khfgNuh fe;njhiyf;Fk;

jhJit tsh;g;gpf;FQ; rhw;W.

### **Chemical Constituents**

Resin, Volatile oil, Starch, Fatty oil, inorganic matter and an alkaloid, piperine.

kpsF

**Botanical Name : Piper nigrum**

Rit - ifg;G> fhh;g;G> jd;ik-ntg;gk;> gphpT-fhh;g;G

Fzk;

NfhZfpd;w gf;ftyp Fa;aTNuh fk;thj

Nrhzpjq;f oj;jpw;Fs; Njhd;WNeHa; - fhzhpa

fhJNeHa; khjh;Fd;kq; fhkhiy ke;jnkD;wPh;

vJNeHa; fhapUf;fpy; <q;F.

### **Chemical Constituents**

Piperine or Pipirine, Piperidine, Chavicin.

Rf;F

**Botanical Name : Zingiber officinale**

Rit - fhh;g;G> jd;ik-ntg;gk;> gphpT-fhh;g;G.

Fzk;

#iyke;jk; neq;nrhpg;G NjhlNkg; gk;koiy

%yk; ,iug;gpUky; %f;FePh; - thyfg

Njhlkjp rhue; njhlh;thj Fd;kePh;j;

Njhlk;M kk;Nghf;FQ; Rf;F

### **Chemical Constituents**

Camphene, Phellandrene, Zingiberine, Cincol, borneol, gingerol and an aleo-resin, gingerin.

nrt;tpak; **(Black Pepper Root)**

**Botanical Name : Piper nigrum**

Fzk;

#iy mUrprd;dp njhy;ypUky; <isgpj;jk;  
Nkiyf; Fuw;fk;ky; ntq;fsNeha; - %yRuk;  
ft;tpaq;fj; NjW fdjh tutpIKQ;  
nrt;tpaq; nfhs;stpLe; Njh;.

### **Chemical Constituents**

A volatile alkaloid Piperine, piperidine, Chavicin.

nfhj;jky;yp

**Botanical Name : Coriandrum Sativum**

Rit - fhh;g;G> jd;ik-rPjntg;gk;> gphpT-fhh;g;G.

Fzk;

nfhj;jky;yp ntg;gk; Fsph;fha;r;ry; gpj;jke;jQ;  
rh;j;jptpf;fy; jhfnkhL jhJel;lk; - fj;jpnaOk;  
thj tpfhh;klh; td;fh;j;j gptpuzk;  
g+jyj;jpy; yhjfw;Wk; Nghw;W.

## Chemical Constituents

Coriandrol, d-pinene, 1-pinene, geraniol and baborneol.

tha;tps;fk;

**Botanical Name : Embelia ribes**

Rit - ifg;G> jd;ik-ntg;gk;> gphpT-fhh;g;G.

Fzk;

ghz;LFI;lk; Fd;kk; gUe;Jhy Neha;thje;

jPz;L jphptlQ; rpue;Jz;lk; - g+z;lkb

Neha;tps;ff; fhl;lhj Ez;fpUkp ahrdg;Gz;

tha;tps;;fq; fhl;l tpUkhh;.

## Chemical Constituents

Embelic acid, tannin, christembine alkaloid, Vidangin, Embelin.

rPufk;

**Botanical Name : Cuminum Cyminum**

Rit - fhh;g;G> ,dpg;G> jd;ik-jl;gk;> gphpT-,dpg;G.

Fzk;

thAnthL ehrpNeha; td;gpj;jQ; NruhJ

fhak; nefpohJ fz;FspUe; - Jhakyh;f;

fhusfg; ngz;kapNy! iffz;l jpj;jidAQ;

rPufj;ij ePjpdKe; jpd;.

### **Chemical Constituents**

Cuminol, Cymene, Carvone.

ngUq;fhak;

**Botanical Name : Ferula asafoetida**

Rit - ifg;G> fufug;G> jd;ik-ntg;gk;> gphpT-fhh;g;G

Fzk;

je;jNt je;j %yj;njOk;gpzp

rUtfhsk; tpUr;rpfq;fPlk;kh

ke;jk;thjk; cjuth;j;jk; my;fpy;Neha;

khh;gzq; fl;l Fd;kk; kNfhjuk;

ce;Jnfh;g;gj;jpd; tpj;jpuQ;#iy;#h;

cjpug;g+r;rp rpNyj;Jkj;JWk;typ

te;jnka;fLg; Nghbit Kw;WNk

khAehWew; fhaq;fpilf;fpNd;.

### **Chemical Constituents**

Organic Sulphur compound, Ferulic acid ester of asaresino-tannol, essential oil of garlic-allyl, persulphide and two turpenes.



## ANNEXURE - II

### Qualitative analysis of Acidic/Basic radicals and phytochemical constituents in test drugs

Procedure	Observation	inference
<b>Test for Calcium</b> : 2 ml of extract is taken in a clean test tube. To this add 2 ml of 4% ammonium oxide solution.	No white precipitate is formed	Absence of calcium
<b>Test for Sulphate</b> : 2 ml of the extract is added to 5 % barium chloride solution.	No white precipitate is formed	Absence of Sulphate
<b>Test for Chloride</b> : The extract is treated with Silver nitrate solution	No white precipitate is formed	Absence of Chloride
<b>Test for carbonate</b> : The substance is treated with Conc. HCl.	No effervescence is formed	Absence of carbonate
<b>Test for Starch</b> : The extract is added with weak iodine solution	Blue colour is formed	Presence of starch
<b>Test for Iron (Ferric)</b> : The extract is treated with glacial acetic acid and potassium ferrocyanide	No blue colour is formed	Absence of Ferric iron
<b>Test for Iron (Ferrous)</b> : The extract is treated with Conc. HNO <sub>3</sub> and ammonium thiocyanate	No Blood red colour is formed	Absence of Ferrous iron
<b>Test for phosphate</b> : The extract is treated with ammonium molybdate and conc. HNO <sub>3</sub>	Yellow precipitate is formed	Presence of phosphate
<b>Test for Tannic acid</b> : The extract is treated with Ferric chloride	Blue black precipitate is formed	Presence of Tannic acid
<b>Test for Unsaturation</b> : 1 ml of Potassium permanganate solution is added to the extract.	Does not get decolourised	Absence of unsaturated compound
<b>Test for saponins</b> : Dilute extract+ 1ml of distilled water shake well.	Froth formation	Presence of saponins

<p><b>Test for sugars :</b>  <b>Benedict method ;</b> 5ml of Benedict solution heated gently then add 8 drops of diluted extract then heated in a boiling water bath.</p> <p><b>Molisch test;</b> Dilute extract+2 drops of Molisch+3ml conc.H<sub>2</sub>SO<sub>4</sub>.</p>	<p>No colour change</p> <p>No Reddish violet zones appeared</p>	<p>Indicates the Absence of sugar</p> <p>Absence of carbohydrate</p>
<p><b>Test for steroids :</b> Liberman Burchard test ; Dilute extract +2 ml acetic anhydride+conc.H<sub>2</sub>SO<sub>4</sub> .</p>	<p>No Formation of red colour</p>	<p>Absence of steroids</p>
<p><b>Test for amino acids:</b> Dilute extract +2ml of Ninhydrin's soln .</p>	<p>Formation of violet colour</p>	<p>Presence of amino acids</p>
<p><b>Test for proteins:</b> Biuret method ; 1ml of dilute extract+1ml of 5%CuSO<sub>4</sub>+ 1%NaOH.</p>	<p>Formation of Violet colour</p>	<p>Presence of proteins</p>
<p><b>Test for Flavanoids :</b> Dilute extract+ mg bits+2drops of conc.HCl and gently heated.</p>	<p>No formation of pink colour</p>	<p>Absence of Flavanoids</p>
<p><b>Test for phenol;</b> Dilute extract+2drops of FeCl<sub>3</sub> soln.</p>	<p>Deep green colour is formed</p>	<p>Presence of phenols</p>
<p><b>Test for Tannins ;</b> dilute extract +2ml of 10%lead acetate add.</p>	<p>White precipitate formed</p>	<p>Presence of tannins</p>
<p><b>Test for alkaloids;</b>  Mayer's method;1ml of dilute extract + 1ml reagent.</p> <p>Dragendroff's method; 1ml of dilute extract+ 1ml of reagent.</p>	<p>Appearance of cream colour precipitate</p> <p>Appearance of orange colour precipitate</p>	<p>Presence of alkaloids</p> <p>Presence of alkaloids</p>

**Table 1****Preliminary acid, basic radicals and phytochemical screening**

<b>S.No.</b>	<b>Constituents</b>	<b>MNT</b>	<b>SVM</b>
1.	Calcium	+	+
2.	Iron (Ferric)	-	-
3.	Iron (Ferrous)	+	+
4.	Sulphate	+	+
5.	Chloride	+	+
6.	Carbonate	+	-
7.	Starch	Trace	-
8.	Phosphate	+	+
9.	Tannic acid	+	+
10.	Unsaturated	-	+
11.	Sugar	+	+
12.	Alkaloids	+	+
13.	Steroids	Trace	+
14.	Protein	+	+
15.	Tannins	+	+
16.	Phenols	-	+
17.	Flavanoids	-	-
18.	Saponins	-	-
19.	Amino acid	+	+
20.	Glycosides	+	+

**Table 2**

**Effect of Siddha Formulations (MNT + SVM ) on Haematological parameters after 15 days repeated oral dosing (500 mg/kg)**

Groups	Hb (gm/100ml)	RBC (millions/cu.mm)
Control	12.49±0.4113	5.20±1.047
Test (500mg/kg. p.o.,)	13.37±0.5164 <sup>*</sup>	5.737± 2.033 <sup>*</sup>

N=6; Values are expressed as mean ± S.D followed by Students Paired 'T' Test  
<sup>\*</sup>P<0.004 as compared with that of control.

**Table 3**

**Effect of Siddha formulation (MNT + SVM ) on Biochemical markers of liver and kidney after 15 days repeated oral dosing (500 mg/kg/po) in rats**

Groups	ALP (K.A.Units)	AST (IU/L) SGOT	ALT (IU/L) SGPT	Urea (mg/100ml)	BUN (mg/ 100ml)
Control	4.973±0.3929	52.89±1.906	15.43±2.93	13.38±2.12	7.35± 0.84
Test (500mg/kg. p.o.,)	12.850±0.2074 <sup>***</sup>	163.3±5.164 <sup>***</sup>	76.75±0.88 <sup>***</sup>	18.93±0.79 <sup>ns</sup>	8.12 ± 0.37 <sup>ns</sup>

N=6; Values are expressed as mean ± S.D followed by Students Paired 'T' Test  
<sup>\*\*\*</sup>P<0.001 as compared with that of control.  
 ns – non significant when compared to control groups

**Table 4**

**Anti oxidant activity of (MNT + SVM ) after 15 days  
repeated oral dosing (500 mg/kg)**

<b>Groups</b>	<b>LPO (n moles)</b>	<b>GSH (n moles)</b>
Control	0.59 ± 1.67	13.56 ± 0.632
SVM (500mg/kg. p.o.,)	0.29 ± 2.31***	47.56 ± 0.339***

N=6; Values are expressed as mean ± S.D followed by Student T- Test.

\*\*\*P<0.001 as compared with control.

**Table 5**

**Effect of (MNT + SVM ) treatment in stress induced disturbance  
in estrous cycle in female rats**

<b>Groups</b>	<b>Oestrous cycle in days</b>				
	<b>Dio estrous 0 day</b>	<b>Proestrous 1<sup>st</sup> day</b>	<b>Frank estrous 2<sup>nd</sup> day</b>	<b>Frank estrous 3<sup>rd</sup> day</b>	<b>Meta estrous 4<sup>th</sup> day</b>
Control group before stress	5/6	6/6	5/6	6/6	6/6
Test group before stress (500mg/kg. p.o.,)	6/6	5/6	4/6	6/6	6/6
Control group after stress	6/6	0/6	0/6	0/6	0/6
† Drug treated group after stress (500mg/kg. p.o.,)	4/6	6/6	6/6	6/6	5/6

Data show the number of animals (n=6) in each group showed different stages of oestrous cycle observed by vaginal cytology, starting from diestrous to metaestrous at 9 am on the days of examination.

† The drug treatment was given for 3 days prior to the induction of stress.

## **ANNEXURE - III**

**Preclinical pharmacological & Toxicological  
studies of Maladu Neenga Thylam (MNT) and  
Saravalli Mathirai (SVM) on Estrous cycle in  
experimental animals**

# Index

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- 1.3 Drugs and Chemicals
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## **2.0 Results**

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- 2.3 Repeated oral toxicity study for 21 days
- 2.4 Antioxidant activity

## **3.0 Discussion**

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## **1.0 MATERIALS AND METHODS**

### **1.1 Test Drugs**

The following Therapeutic Siddha Medicines used in the study were processed by the methods prescribed in standard text books of siddha medicines.

1. Maladu Neenga Thailam (MNT)

MNT was prepared by the method described in Agathiyar Kanagamani -100 P.No.34.

2. Saaravalli Mathirai (SVM)

SVM was prepared by the method described in Nam Naatu Vaidhiyam P.No : 268)

### **1.2 Preparation of drug for dosing**

All drugs used for the study was suspended each time with 1% (w/v) solution of sodium carboxy methyl cellulose before administration.

### **1.3 Drugs and chemicals**

Fine chemicals used in these experiments were obtained from Sigma Chemicals company, U.S.A. Other analytical grade chemicals were obtained from S.d. Fine Chemicals Ltd., Mumbai.

### **1.4 Experimental animals**

Colony inbred animals strains of wistar rats of either sex weighing 200 - 250 g and swiss albino mice of either sex (18-25 g) were used for the pharmacological and toxicological studies. The animals were kept under standard conditions 12:12 (day/night cycles) at 22<sup>0</sup>C room temperature, in polypropylene cages. The animals were fed on standard pelleted diet



(Hindustan Lever Pvt Ltd., Bangalore) and tap water *ad libitum*. The animals were housed for one week in polypropylene cages prior to the experiments to acclimatize to laboratory conditions. The experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC).

### **1.5 Acute oral toxicity study**

Acute oral toxicity was conducted as per the OECD guidelines (Organization of Economic Cooperation and Development) 423 (Acute Toxic Class Method). The acute toxic class method is a stepwise procedure with 3 animals of a single sex per step. Depending on the mortality and /or moribund status of the animals, on the average 2-4 steps may be necessary to allow judgment on the acute toxicity of the test substance. This procedure results in the use of a minimal number of animals while allowing for acceptable data based scientific conclusion.

The method uses defined doses (5, 50, 300, 2000 mg/kg body weight) and the results allow a substance to be ranked and classified according to the Globally Harmonized System (GHS) for the classification of chemicals which cause acute toxicity

Wistar albino rats of either sex weighing 200-250 g were fasted overnight, but allowed water *ad libitum*. Since the formulation is relatively non toxic in clinical practice the highest dose of 2000 mg/kg/p.o (as per OECD guidelines "Unclassified") was used in the acute toxicity study.

The animals were observed closely for behavioural toxicity, if any by using FOB (Functional observation battery).

## **1.6 Repeated oral toxicity study**

Repeated oral toxicity studies can be used to get additional information regarding the toxicity profile of a chemical. Repeated oral toxicity studies are defined as those studies where the chemical is administered to the animal for a period covering approximately 10% of the expected life of the animal. Usually, the dose levels are lower than for acute studies and allow chemicals to accumulate in the body before lethality occurs, if the chemical possess this ability.

### **Experimental procedure**

The following experimental procedure was followed to evaluate the repeated oral toxicity study of

1. Maladu Neenga Thylam (MNT) and Saravalli Mathirai (SVM).

Group I : Control animals received 1% Sodium carboxy methyl cellulose (CMC), 2 ml/kg/p.o. for 21 days

Group II : Drugs suspended in CMC was given at the dose Level of 500 mg/kg/p.o. for 21 days

Body weight, food intake and water intake was recorded at two intervals with simultaneous observation for toxic manifestation and mortality, if any. At the end of 21 days treatment all the animals were sacrificed by over dosage of ether anaesthesia. Blood was collected and used for haematological studies. Section of liver, kidney, and heart were dissected out and kept in 10% formalin for histopathological studies.

## **1.7 Biochemical studies**

### **Aspartate aminotransferase (AST)**

Aspartate aminotransferase was estimated using commercial AST kit (Span Diagnostics) by the method of Reitman and Frankel (1957).

### **Alanine aminotransferase (ALT)**

Alanine aminotransferase was estimated using commercial AST kit (Span Diagnostics) by the method of Reitman and Frankel (1957).

### **Alkaline phosphatase (ALP)**

Alkaline phosphatase was assayed using commercial ALP kit (Span Diagnostics) by the method of King (1934).

### **Urea**

Urea was assayed using the commercial kit (Span Diagnostics) by the method of Coulambe *et al.*, (1965).

## **1.8 Haematological studies**

### **Erythrocyte count**

Erythrocyte count was estimated by Hemocytometer method of Ghai (1995).

### **Total Leukocyte Count (WBC)**

Total Leukocyte Count was estimated by Hemocytometer method of John (1972).

## Haemoglobin

Haemoglobin was estimated by method of Ghai (1995).

### 1.9 Swimming induced stress in irregularities of estrous cycle in rats

Female rats (125-150 g) were randomized into groups of six animals each. Vaginal smear was taken at 9 am daily to evaluate the status of estrous cycle. Those animals showed the regular estrous cycle were selected for the study. The animals were divided into following groups and they received the respective regimen of treatment.

Group I - Control

( n = 6)

Group II - Test drug (KT + SVL, 500 mg/kg/p.o)

( n = 6)

The animals in Group I and II were given swimming stress for 30 mts in a vertical tub containing water upto 15 mm high maintained at room temperature. The vaginal smears of the stressed animals were examined for the stages of estrous cycle. The animals showed the diestrous stage after the swimming test were given the test drug at the dose of 500 mg/kg/p.o for 3 days and animals in the control group received vehicle only for same period. At the end of 3<sup>rd</sup> day after the drug/vehicle treatment the vaginal smears of all the animals were tested for the different stages of estrous cycle for the 4 consecutive days. The same experiment is continued for 4 cycles after the induction of swimming stress as explained above

### **1.10 In Vivo Antioxidant study**

Samples of serum collected from rats treated with test drugs were assayed for GSH (Moron *et al* , 1979) and LPO (Yagi, 1976) and the results were compared with control group.

## **2.0 Results**

### **2.1 Preliminary basic, acidic radicals and phytochemical studies**

The qualitative chemical analysis and acidic, basic radicals assay of the drugs showed the presence of phytoconstituents and minerals as depicted in (Table 1).

### **2.2 Acute oral toxicity study**

MNT and SVM at the dose of 2000mg/kg/po did not exhibit any mortality in rats. As per OECD 423 guidelines the dose is said to be “Unclassified” under the toxicity scale. Hence further study with higher doses was not executed.

### **2.3 Repeated oral toxicity for 21 days**

Test drug MNT and SVM at the dose of 500 mg/kg/po when administered orally for 21 days in rats did not show toxicity in renal functions. However the drug exhibited significant reduction in RBC count and elevation of marker enzyme levels of liver (Table 2 and 3).

### **2.4 Antioxidant activity**

At the end of 21 days repeated oral toxicity study when the plasma of drug treated animals was examined for GSH activity, the level of GSH activity was increased significantly ( $p>0.001$ ) in test groups (Table 4).

## Results and Discussion

Normal menstrual cycle in women is often disturbed by physical and mental stress. These changes in menstrual cycle may be attributed to psychological stress compounded by endocrine disturbances. Menstrual irregularities in women in reproductive age may also be attributed to the work environment, circadian changes precipitated by working in night shifts and odd hours of the day, life style etc.

Irregular menstruation is regularized by siddha medicinal practitioners using herbo mineral preparations. Even these drugs are also used to treat clinical conditions like polycystic ovary. Though an model similar to human menstrual cycle cannot be developed in animals, stress induced changes in estrous cycle of rat can be used as a model to screen drugs which correct menstrual irregularities. The estrous cycle in rats will be completed in  $\frac{3}{4}$  days and this will ease the cost and time of study for 5-6 cycles. The diestrous, proestrous, frank estrous and meta estrous can be identified by examining the vaginal cytology of rats.

The swimming stress is an ideal model, can be taken for evaluating drugs acting on the regularization of estrous cycle in rats.

In the present study all stressed rats uniformly showed diestrous phase of estrous cycle. The pretreatment with test drugs for 3 days before induction of swimming stress, helped to proceed the estrous cycle normally from diestrous to estrous, whereas the groups received no treatment were still on diestrous phase continuously for 3 cycles as evidenced by the vaginal cytology.

The exact mechanism of test drug that showed the reversal of irregularity on the estrous cycle of the rats after swimming test is not fully understood. The reversal of irregularity and maintenance of estrous cycle by drug treatment for another 3 consecutive cycles over untreated animals clearly establishes the positive correlation of results between clinical and experimental studies. Rat shows polyestrous, hence the results obtained from the rat study could be extrapolated to human study, is debatable. The hormonal profile of normal and stressed rats, before and after treatment and their reversal, if any, may give some more authentic data about the efficacy of drug in the treatment of menstrual irregularities in human beings.

The another important question to be answered on the efficacy of the drug treatment to prevent the irregularity of estrous cycle in 3-4 cycles is sustainable or not for a longer period or the drug treatment should be continued after a washout period of 3-4 cycles to maintain the regular cycle on a sustained basis.

## 4.0 REFERENCES

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## ANNEXURE - IV

### AN OPEN PILOT CLINICAL TRAIL OF SIDDHA DRUGS *MALADAU NEENGA THAILAM* WITH *SAARAVALLI MATHIRAI* FOR THE TREATMENT OF *PENN MALADU* (INFERTILITY)

#### CONSENT FORM

#### CERTIFICATE BY INVESTIGATOR

I certify that I have disclosed all details about the study in the terms readily understood by the patient.

Date

Signature

Name

#### CONSENT BY PATIENT

I have been informed to my satisfaction, by the attending physician, the purpose of the clinical trial, and the nature of drug treatment and follow-up including the laboratory investigations to be performed to monitor and safeguard my body functions.

I am aware of my right to opt out of the trial at any time during the course of the trial without having to give the reasons for doing so.

I, exercising my free power of choice, hereby give my consent to be included as a subject in the clinical trial of Siddha drugs *Maladu Neenga Thailam* with *Saaravalli Mathirai* for the treatment of *Penn Maladu*.

Date

Signature

Name

Date

Signature of Witness

Name

Relationship

# NATIONAL INSTITUTE OF SIDDHA, CHENNAI-47

## AN OPEN PILOT CLINICAL TRIAL OF SIDDHA DRUGS *MALADU NEENGA THAILAM WITH SAARAVALLI MATHIRAI* FOR THE TREATMENT OF *PENN MALADU* (FEMALE INFERTILITY)

### FORM-I SELECTION PROFORMA

1. O.P.No: \_\_\_\_\_ 2. Date : \_\_\_\_\_
3. S.No. \_\_\_\_\_
4. Name: \_\_\_\_\_ Age (years): \_\_\_\_\_
5. Occupation \_\_\_\_\_
6. Husband's Name \_\_\_\_\_ Age (years): \_\_\_\_\_
7. Address:  
\_\_\_\_\_  
\_\_\_\_\_
8. Complaints and duration: \_\_\_\_\_  
\_\_\_\_\_

#### MEDICAL HISTORY

	Yes	No
9. Tuberculosis	<input type="checkbox"/>	<input type="checkbox"/>
10. Sexually Transmitted Disease	<input type="checkbox"/>	<input type="checkbox"/>
11. Pelvic Inflammatory Disease	<input type="checkbox"/>	<input type="checkbox"/>
12. Diabetes Mellitus	<input type="checkbox"/>	<input type="checkbox"/>
13. Chronic Illnesses	<input type="checkbox"/>	<input type="checkbox"/>
14. Thyroid disorder	<input type="checkbox"/>	<input type="checkbox"/>
15. HISTORY OF NIPPLE DISCHARGE	<input type="checkbox"/>	<input type="checkbox"/>
16. HISTORY OF VISUAL FIELD DEFECTS / HEADACHE	<input type="checkbox"/>	<input type="checkbox"/>

**SURGICAL HISTORY**

17. Previous abdominal / pelvic surgery

Yes  No

**MENSTRUAL HISTORY**

18. Age of menarche

Yes  No   
\_\_\_\_\_ years

19. Secondary amenorrhoea

Yes  No

20. Cycle length

\_\_\_\_\_ days

21. Duration of flow

\_\_\_\_\_ days

22. Quantity – No. of pads used

23. Last Menstrual Period

\_\_\_\_\_

24. Dysmenorrhoea

Yes  No

25. Leucorrhoea

Yes  No

**MARITAL HISTORY**

26. Duration of Marriage

\_\_\_\_\_ Years

27. Consanguinous

Yes  No

**SEXUAL HISTORY**

28. Coital frequency

per week

29. History of Dyspareunia

Yes  No

30. History of Apareunia

Yes  No

31. Loss of libido

Yes  No

**OBSTETRIC HISTORY**

32. No. of live children if any

\_\_\_\_\_

33. No. of Spontaneous abortions if any

\_\_\_\_\_

34. No. of induced abortions if any

\_\_\_\_\_

**OCCUPATIONAL HISTORY**

35. Working in night shifts

Yes  No

**PERSONAL HABITS**

36. Diet habits Veg  Non Veg
37. Bowel habits  
Constipation Yes  No
38. **FAMILY HISTORY** Yes  No
39. History of Previous Investigations if any:  
\_\_\_\_\_

**GENERAL EXAMINATION**

40. Physical built Obese  Normal   
BMI
41. Body Weight (kg):
42. Height (cm)
43. Temperature (°F):
44. Pulse rate / minute:
45. Heart rate / minute:
46. Respiratory rate / minute:
47. Blood pressure (mmHg): \_\_\_\_\_  
Yes No
48. Pallor:
49. Jaundice:
50. Cyanosis:
51. Lymphadenopathy:
52. Pedal oedema:
53. Clubbing:
54. Jugular vein pulsation:
55. Congenital Abnormalities
56. Goitre
57. Hirsutism

58. Tracheal deviation
59. Development of axillary and pubic hair
60. Breasts Normal  under development

**EXAMINATION OF VITAL ORGANS**

- |            | <b>Normal</b>            | <b>affected</b>          |
|------------|--------------------------|--------------------------|
| 61. Heart  | <input type="checkbox"/> | <input type="checkbox"/> |
| 62. Lung   | <input type="checkbox"/> | <input type="checkbox"/> |
| 63. Liver  | <input type="checkbox"/> | <input type="checkbox"/> |
| 64. Spleen | <input type="checkbox"/> | <input type="checkbox"/> |

**SYSTEMIC EXAMINATION**

65. Per speculum Examination
66. Bimanual Pelvic examination
- Palpation of the uterus
- Palpation of the uterine appendages
- The pouch of Douglas

- |           | <b>Normal</b>            | <b>affected</b>          |
|-----------|--------------------------|--------------------------|
| 67. Heart | <input type="checkbox"/> | <input type="checkbox"/> |

**SIDDHA SYSTEM OF EXAMINATIONS**

**68. THINAI**

1. Kurunji     2. Mullai     3. Marutham
4. Neithal     5. Palai

**69. GUNAM**

1. Sathuva gunam     2. Rajo gunam
3. Thamo gunam

**IYMPORIKAL**

- |         | 1. Normal                | 2. Affected                    |
|---------|--------------------------|--------------------------------|
| 70. Mei | <input type="checkbox"/> | <input type="checkbox"/> _____ |

- |            |                          |                          |       |
|------------|--------------------------|--------------------------|-------|
| 71. Vaai   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 72. Kan    | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 73. Mookku | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 74. Sevi   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

**KANMENTHIRIUM**

- |              |                          |                          |       |
|--------------|--------------------------|--------------------------|-------|
| 75. Kai      | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 76. Kaal     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 77. Vaai     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 78. Eruvai   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 79. Karuvaai | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

**UYIR THATHUKKAL**

**VALI**

1. Normal      2. Affected

- |                 |                          |                          |       |
|-----------------|--------------------------|--------------------------|-------|
| 80. Pranan      | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 81. Abanan      | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 82. Samanan     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 83. Udhanan     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 84. Viyanan     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 85. Nagan       | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 86. Koorman     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 87. Kirukaran   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 88. Devathathan | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 89. Tananjeyan  | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

**AZHAL**

1. Normal      2. Affected

- |                   |                          |                          |       |
|-------------------|--------------------------|--------------------------|-------|
| 90. Anala pittham | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
|-------------------|--------------------------|--------------------------|-------|

- |                      |                          |                          |       |
|----------------------|--------------------------|--------------------------|-------|
| 91. Prasaka pittham  | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 92. Ranjaka pittham  | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 93. Aalosaka pittham | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 94. Saathaka pittham | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

**IYAM**

- |                 | 1. Normal                | 2. Affected              |       |
|-----------------|--------------------------|--------------------------|-------|
| 95. Avalambagam | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 96. Kilethagam  | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 97. Pothagam    | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 98. Tharpagam   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 99. Santhigam   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

**UDAL THATHUKKAL**

- |                 | 1. Normal                | 2. Affected              |       |
|-----------------|--------------------------|--------------------------|-------|
| 100. Saaram     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 101. Chenneer   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 102. Oon        | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 103. Kozhuppu   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 104. Enbu       | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 105. Moolai     | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 106. Suronitham | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

**ENVAGAI THERVUKAL**

- |            | 1. Normal                | 2. Affected              |       |
|------------|--------------------------|--------------------------|-------|
| 107. Naa   | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 108. Niram | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 109. Mozhi | <input type="checkbox"/> | <input type="checkbox"/> | _____ |
| 110. Vizhi | <input type="checkbox"/> | <input type="checkbox"/> | _____ |

111. **Sparisam:** 1.Mithaveppam  2.Miguveppam   
 3. Thatpam

**Malam** 1. Normal 2. Affected

112. Niram    
 113. Nurai    
 114. Karumai    
 115. Kalappu    
 116. Thanmai

**Moothiram**

**Neerkuri**

117. Niram   \_\_\_\_\_  
 118. Eadai   \_\_\_\_\_  
 119. Manam   \_\_\_\_\_  
 120. Nurai   \_\_\_\_\_  
 121. Enjal   \_\_\_\_\_

122. **Neikuri:** 1.Vatham  2. Pittham  3. Kapham

123. **Naadi:** 1.Vatham  2.Pittham  3.khabam   
 4. Vathapittham  5. Vathakhabam  6. Pitthavatham   
 7. Pitthakhabam  8. Khabavatham  9. Khabapittham

**INVESTIGATIONS**

**BLOOD**

124. TC (cells /cumm):

125. DC (%): P  L  E  B   
 M

126. Hb (gm %):  .

ESR (mm/hr): 117. 1/2hr  118.1hr





If yes

144. S. No:

145. O.P No.

146. Drug issued (g):

Station

Date:

Signature of the doctor

# NATIONAL INSTITUTE OF SIDDHA, CHENNAI-47

## AN OPEN PILOT CLINICAL TRIAL OF SIDDHA DRUGS *MALADU NEENGA THAILAM WITH SAARAVALLI MATHIRAI* FOR THE TREATMENT OF *PENN MALADU* (FEMALE INFERTILITY)

### FORM-II ASSESSMENT PROFORMA

1. O.P.No \_\_\_\_\_ 2. S.No: \_\_\_\_\_

3. Name: \_\_\_\_\_ 4. Age \_\_\_\_\_

5. Date of the Assessment 

--	--	--	--	--	--

6. Day of Assessment 

--	--

### CLINICAL ASSESSMENT

	1. Yes	2.No
7. Oligomenorrhoea	<input type="checkbox"/>	<input type="checkbox"/>
9. Amenorrhoea	<input type="checkbox"/>	<input type="checkbox"/>
10. Regular Periods	<input type="checkbox"/>	<input type="checkbox"/>
11. Hypomenorrhoea	<input type="checkbox"/>	<input type="checkbox"/>
12. Pain during menstruation	<input type="checkbox"/>	<input type="checkbox"/>
13. Date of Menstruation	<input type="checkbox"/>	<input type="checkbox"/>
14. Naddi	<input type="checkbox"/>	<input type="checkbox"/>

### INVESTIGATIONS: (after treatment)

15. Mid luteal phase progesterone estimation

16. Ultrasound – Follicular study

17. Urine for gravidex

18. DRUGS ISSUED      1. No. of tablets       2. Volume of Thylam

19. DRUGS RETURNED      1. No. of tablets       2. Volume of Thylam

Date

Station

Signature of the doctor

**RESULT**      Ovulation / Fertility       Failure

Date:

Station:

Signature of the Doctor

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- Dr.K.S.Murugesu Mudaliar
2. Magalir Maruthuvam  
- Dr.P.M.Venugopal
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- C.Kannusamypillai
4. Noi Nadal Noi Mudhal Nadal Thirattu - Part-1  
- Dr.M.Shanmugavelu
5. Athmarakshamirtham- Vaidhya Saara Sangiraham.
6. Jeevarakshamirtham
7. Manmurugium
8. Pararasa Sekarm
9. Sarabenthirar Karpapini
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**SEEDS OF NERVALAM**



**SEEDS OF KUMATTI**



**SEEDS OF AAMANAKKU**



**VELLAI POONDU**



**CHITRAMOOLA VERPATTAI**



**OMUM**



**KADUKKAI THOL**



**KOSHTUM**





**THIPPILI**



**MILAGU**



**CHUKKU**



**SEVVIUM**



**KOTHAMALLI**



**VAIVIDANGAM**



**SEERAGAM**



**PERUNGAYAM**



**MALADU NEENGA THAILAM**



**SAARAVALLI MATHIRAI**