FPS (I)
Preserve- Create-Perpetuate

# Newsletter –

## Fertility Preservation Society of India

September 2014 (Volume 1)

Dear Friends,

Greetings.

The Fertility Preservation Society, the first of its kind in India, was formed a short while back with the aim of increasing awareness, furthering our knowledge and improving fertility preservation services for Oncological and Non-Oncological patients in India. This is a national body with an eminent group of clinicians, oncologist, hematologist, andrologist and reproductive biologist as founder members.

Cancer has always been a dreaded disease and survival not reproduction was the prime goal. Today cancer survival rates even in a developing country like ours, are nearing 80% in cases detected early. Improving quality of life for these patients should include the option of parenthood. On the non-oncology front we have auto-immune and genetic disorders that can compromise fertility, as also the delay in pregnancy sought by women for social and economic reasons.

Oncofertility and fertility preservation for medical and social reasons is a fast emerging field in Reproductive medicine. Today ART offers hope of parenthood to young cancer survivors and to women who because of a disease process or for social reasons lose their ability to conceive. It is an uphill task for us in India, as fertility preservation services are still in their infancy even around the world and we seek the help of the medical fraternity and society to help us achieve this goal. To echo some famous words ' Together We Can'.

I take great pride in announcing the launch of the society newsletter edited by our young and dynamic editors. I would also take this opportunity to thank the International Society of Fertility Preservation and The Japanese Fertility Preservation Society for their support and guidance.

Best wishes

Nalini Mahajan

President FPS(I)

Dear colleagues and friends,

Today is a great day for medicine and science in India: thanks to the strong will, great character, and scientific personality of Dr Nalini Mahajan a new society is being created. But it is not just a new society, it is a much needed one as it will dedicate its efforts to an area in which the advancement of science is allowing oncologic patients, whose fate was to live childless all their lives, to have their families with their own gametes and genetic background.
Congratulations to the President, all the Board Members, and to all of the speakers who travelled to Delhi to make this happen.

All the best,

Juan A Garcia-Velasco, MD
Coordinator of Fertility Preservation Program of IVI Group
Director IVI Madrid, Spain
Full Professor of Obstetrics and Gynecology

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# Fertility Preservation in Women

Dr. Padma Rekha Jirge MRCOG (UK), FICOG

Scientific Director, Sushrut Assisted Conception Clinic, Kolhapur

Advances in the fields of oncology and onco-surgery have improved the survival to >90% in young women and children affected with various malignancies. Surgical treatment for pelvic malignancies, radiotherapy and chemotherapy for pelvic and non-pelvic malignancies all can render a woman sterile. Improved survival in young women treated for cancer has brought to frontline the important issue of fertility preservation (FP) in such women.

The concept is daunting, involves co-ordination between specialists from different medical and allied specialties, ability to execute the preservation within a short span of time, sound counseling facilities and the need for regular updating of knowledge and techniques needed for this purpose. The area of ethical and legal issuesis an evolving situation rather than a set of well-defined criteria. Here is a brief review of the situations in which FP has been attempted successfully, and the modalities available.

**Early genital malignancies:**

Severe atypical endometrial hyperplasia and early focal endometrial carcinoma (Stage I Grade I)are two examples in which fertility preservation has been documented since early 1990s. Treatment with oral progestinsfor at least 12 weeks is known to reverse the abnormal changes. This is followed by active interventions for fertility including IVF–ET as demanded by the clinical situation. Subsequent definitive treatment including hysterectomy is mandatory. Case series have been reported with successful pregnancies in the above clinical scenario.

Radical trachelectomywith pelvic lymphadenectomy in women with Stage IA1 and IB1cervical cancer with conservation of uterus can be offered to women wishing to conserve fertility. Careful selection and follow up are mandatory in these women. Further, detailed assessment to rule out disease progression and definitive treatment are mandatory as well, following delivery.

Transposition of ovaries above pelvic brim during any surgical therapy for pelvic malignancies may minimise damage to ovarian function due to subsequent pelvic radiotherapy. This has been routinely practised in many units traditionally.

Unilateral borderline ovarian tumours have been successfully treated by oophorectomy and conservation of contralateral ovary and uterus, in young women desiring fertility. However, definitive surgical treatment is indicated following successful pregnancy.

**Non-Gynaecological malignancies:**

Radiotherapy and chemotherapy used in the management of many non-pelvic malignancies may be gondadotoxic and survivors of such malignancies may experience premature ovarian failure (POF). A comprehensive list of conditions in which FP is an option is given in the third article of this newsletter. Advances in the field of ART and the process of vitrification have brought the hope of conserving fertility until a future date to many young children and women.

Table 1: Chemotherapeutic agents and probability of POF

| High risk | Moderate risk | Low risk |
|---|---|---|
| Cyclophosphamide | Cisplatinum | Vincristine |
| Ifosfamide | Adriamycin | Vinblastine |
| Chlorambucil | Actinomycin | Methotrexate |
| Melphalan | | Bleomycin |
| Busulfan | | Dactinomycin |
| Nitrogen mustard | | Mercaptopurines |
| Procarbazine | | |
| Nitrosureas | | |

**Modalities of FP:**

Different modalities of FP available include cryopreservation(CP) of embryos, CP of oocytes, in vitro maturation (IVM) of immature oocytes, and ovarian tissue cryopreservation (OTC). Academic bodies such as ASCO, ASRM, RCOG now advise that FP should be an integral part of pre-treatment discussion in young women affected by malignancies. Important factors,which determine the modality of FP are age, ovarian reserve and the duration of time available for fertility preservation.

**Prepubertal children:**

As ovaries at this stage contain only immature eggs, the only option is the OTC, which is still considered as experimental procedure. The likelihood of development of POF following chemotherapy and the general health of the child to withstand a laparoscopic or open surgery should be considered prior to OTC. Children with lymphomas prior to bone marrow transplantation may withstand the procedure well. However, risk of haemorrhage and infection in many children with leaukaemia demands highest diligence while offering FP to such children.

**Young women:**

Breast cancer is the most common malignancy seen in young women of reproductive age group and fertility following chemotherapy induced ovarian reserve depletion is an important concern. Controlled ovarian stimulation (COS) and ovum pickup (OPU) followed by embryo cryopreservation in those in a stable relationship or CP of oocytes in those who are single have been now accepted modalities of FP. COS is associated with supraphysiological increase in oestradiol levels which may be undesirable in breast cancer. Inclusion of Letrozole in COS has been effective in preventing this undesirable effect. Depending on the time interval between surgery and initiation of chemotherapy, 1-2 cycles of COH and oocyte retrieval have been performed without any reported increase in recurrence rates. Use of antagonists and random start protocols cut short the duration of IVF and use of GnRHa in place of HCG for ovulation trigger minimizes the risk of severe OHSS in these women. It is generally considered that 2 years of disease free period is warranted prior to any fertility treatment. Women with BRCA mutations may consider multiple IVF attempts and embryo or oocyte CP prior to bilateral oophorectomy performed to minimise the risk of ovarian cancer in them.

IVM may be an alternative when sufficient time is not available for COS or in women with oestrogen sensitive tumors where COS may not be preferred. Increasingly,OTC is considered as a practical option available to many young women when there is lack of time prior to chemotherapy. 30 successful pregnancies have been reported so far in young women who have undergone subsequent ovarian cortex re-implantation. However, no data is available regarding re-implantation and pregnancies in those who have undergone OTC in prepubertal age.

The choice of FP modality in women with haemopoetic and other malignancies when there is a high likelihood of post treatment POF is along similar lines to that for breast carcinoma. However, general health of the individual, haematological parameters, risk of haemorrhage and infection should be considered in these women and a strong co-ordination between the oncology, haematology and ART team is mandatory if FP is to be offered to them.

**Other Considerations:**

Women with non-malignant conditions such as SLE and other autimmune diseases requiring cytotoxic drugs; conditions such as thalassaemia major, sickle cell anaemia which may benefit from bone marrow transplant, and Turner's mosaics with residual ovarian function, Fragile X syndrome and women with endometriomas requiring multiple surgeries with a high risk of subsequent POF may all be suitable candidates for FP.

Concerns exist regarding the presence of residual leukemic cells in ovarian tissue and hence reactivation of the disease condition following re-implantation of the cryopreserved ovarian tissue in survivors of haemopoetic malignancies. Methods are under evaluation to identify presence of leukemic activity in the ovaries prior to OTC and also before re-implantation of the ovarian tissue.

Ovarian reserve strongly influences the ovarian response to any fertility treatment. Hence, assessment of ovarian reserve markers such as AMH in children and women prior to FP and gonadotoxic therapy is very important. Changes in AMH values post-therapy is often used to assess the residual ovarian function.

Improvement in AMH levels have been documented following ovarian tissue re-implantation. Also, in women with benign conditions where FP is contemplated or recommended, assessment of existing ovarian reserve helps such young women to have a realistic understanding of any benefits of FP.

GnRHa have long been used prior to chemotherapy to suppress the ovarian function and thus to prevent damage to gametes, with variable success. However, this is still considered experimental.

Genetic counseling is strongly recommended when considering FP in women with breast cancer with BRCA1 & 2 mutations to discuss the potential risks of transmission to their offspring and the possibility of pre-implantation genetic diagnosis of BRCA mutations in the embryo before embryo transfer. It is also necessary in those who are affected with malignancies or diseases of inheritable nature.

**Social Indication for FP:**

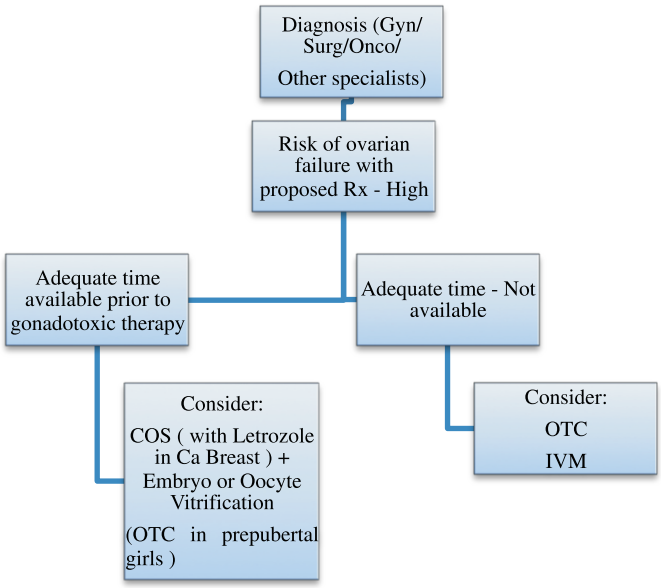
Women are increasingly delaying childbirth for voluntary or involuntary reasons and FP may offer an opportunity to achieve pregnancy with one's own eggs even in their forties. There is a small but steadily increasing demand for multiple IVF and CP of oocytes or embryos for future use by women wishing to delay pregnancy. Even though it is considered as a social indication at present, preservation of fertility in the face of declining ovarian reserve may become recognized as an additional medical indication for FP in future. However, caution should be exercised while offering FP for social indications as CP of gametes, embryos or OTC may not necessarily translate into a pregnancy when desired.

**Requirements for a successful FP Program:**

There needs to be good co-ordination between medical and surgical oncologists, reproductive endocrinologists and surgeons, at times other specialists, geneticist and counselor. A smooth and rapid access to various specialists is very essential. A dedicated ART team with the infrastructure and trained staff to provide the services of COH, OPU, oocyte/embryo cryopreservation, IVM and OTC throughout the year plays a vital and central role in the success of such a program.

It is to be understood that it is a progressively evolving field and regular upgradation of knowledge and expertise is very essential. Counseling of and obtaining consent for FP from very young people fighting for survival poses ethical, emotional and legal challenges and the entire team needs to be geared up to this multidimensional task.

Figure I: A guideline for fertility preservation in cancer affected young women and children.

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**A Glimpse into our Academia – The First Step**

The First CME at Medanta, Gurgaon – 7th May 2014

# Preservation of Fertility in Male Cancer Patients

Dr Devika GunasheelaMRCOG, FIRM( Fellow in reproductive medicine )

Director, Gunasheela Surgical and Maternity Hospital & Gunasheela IVF Centre, Bangalore

It is estimated that one out of every two men will be diagnosed with cancer in his lifetime, of which 4% are under the age of 35. Traditionally, the role of cancer treatment has focused on disease cure. However, with advances in treatment efficacy and safety there are a growing number of young adults who are long-term survivors of cancer. Patients under 15 years of age undergoing cancer treatment are projected to have a 75% five-year cancer survival rate. Patients between the ages of 15-44 yrs with a diagnosis of cancer are now projected to have a survival rate of 66%. In Europe, most commonly occurring cancers among young people aged 15 – 24 yrs include Hodgkin's Lymphoma, Testicular cancer & Malignant Melanoma *(Cancer Research UK, 2009).* Five-year survival rates of over 90% for these malignancies are reported in young people in Europe.

### Impact of Cancer on Male Reproductive Health

Cancer as a disease process can have many deleterious effects on male reproduction, even before any therapy has been initiated. These effects include disruption of the hypothalamic-pituitary-gonadal (H-P-G) axis, direct immunological or cytotoxic injury to the germinal epithelium within the testis, systemic processes such as fever & malnutrition, & psychological issues such as anxiety & depression.

### Effects of Cancer Treatment

### Radiotherapy

The testis is one of the most radiosensitive organs in the body, & the most immature cell types are the most sensitive to injury. Despite improvement in radiotherapy detrimental & irreversible effects on the testis, particularly the germinal epithelium do occur. Radiation therapy causes germ cell loss in a dose-dependent fashion. Recovery of spermatogenesis depends on radiation dose, and use of adjuvant chemotherapy. The return of spermatogenesis is impaired in men with low pretreatment total motile sperm counts and those over 25 years of age. Sperm concentrations usually reach nadir by 4–6 months after the conclusion of radiation therapy. Return to pretreatment levels is typically seen within 10–24 months.

### Effects of Radiation Therapy

| Dose of Radiation | Effect |
|---|---|
| 0.1 Gy | Spermatogonia |
| 2-3 Gy | Significant Spermatocyte Damage |
| 4-6 Gy | May cause permanent damage – Depletion of both stem cells and differentiating spermatogonia. |

There is compelling evidence of short-term DNA damage to sperm following cancer treatment, but same has not been proven in long-term survivors.

### Risk levels for infertility by various chemotherapeutic agents:

| Risk level | Agents |
|---|---|
| High | Alkylating agents: chlorambucil, chlormethine, cyclophosphamide, ifosfamide, &procarbazide |
| Medium | Cisplatin, carboplatin, doxorubicin |
| Low | Vincristine, methotrexate, dactinomycin, bleomycin, mercaptopurine, vinca alkaloids (vinblastine), fluorouracil |
| Risk exists – Unknown level | Nitrosources& antimetabolites: cytosine arabinoside |
| Unknown risk | Taxanes, oxaliplatin, monoclonal antibodies (trastuzumab, bevacizumab,cetuximab), tyrosine kinase inhibitors (eriotinib, imatinib) |

**Effects of Surgery**

Men suffering from testicular cancer typically sustain a significant loss of overall testicular mass when undergoing orchiectomy, and subsequent retroperitoneal lymphadenectomy, potentially resulting in anejaculation or retrograde ejaculation. Men with bladder or prostate cancer who require extirpative surgery will suffer disruption of the genital ductal system as the prostate gland and seminal vesicles are routinely removed.

**Fertility Preservation for Patients With Cancer:**

ASCO Guideline Update – 2013
Adult Males - Quality of Evidence supporting current opinion for fertility preservation in males:

The new evidence continues to support the conclusion that sperm cryopreservation is an effective method of fertility preservation in males treated for cancer. In contrast, gonadoprotection through hormonal manipulation is ineffective. Testicular tissue or spermatogonial cryopreservation & transplantation or testis xenografting are still experimental. However, such approaches may be the only methods of fertility preservation potentially available to prepubertal boys.

Sperm should not be banked while a patient is receiving chemotherapy. Contraceptive intercourse is advised during chemotherapy treatment. Fertility should not be considered until at least 6 months after chemotherapy finishes.

**What can be done with frozen samples?**

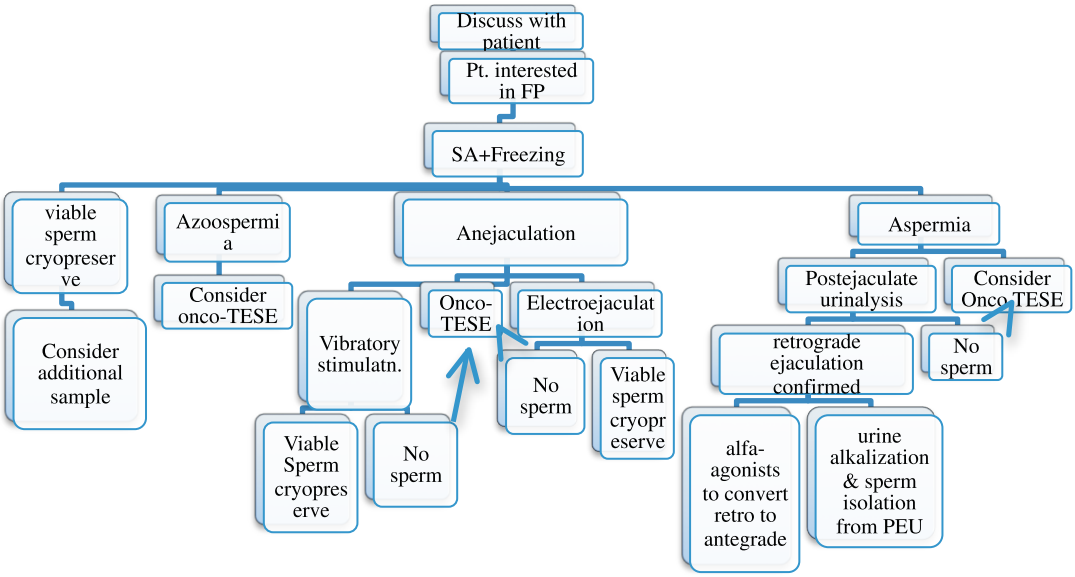
- Artificial Insemination - Requires at least 10 million motile sperm per insemination (about
- 20 million per sample). Almost always requires multiple samples.
- IVF – Best for limited number of samples, good success rates & expensive
- Intracytoplasmic sperm insemination (ICSI) - Required for low sperm numbers, good success rates even with low numbers, & slightly more expensive than IVF.

**Consent to Freeze Sperm should include:**

Inherent risks of freezing and thawing sperm, damage to sperm or reduced capacity to fertilize, cost, depositor's responsibility to remain in contact with our facility & Sperm can be utilized by patient or authorized designee.

**Conclusion:**

This is an area, which is open to extensive research & opens new vistas in the realm of fertility preservation. The western world has come this far after decades of dedicated research. The path is paved with innumerable difficulties, **BUT** we have made a start & it is our duty to spread awareness amongst the doctors as well as our young patients afflicted with cancer that we can help them to become biological parents and remember surviving cancer is not the end of a gruesome story – it is the beginning.




**Fertility preservation Algorithm for Male Cancer Patients**

# Fertility Preservation: Who needs it?

Dr Shivani Singh,
MD,DNB,FNB(Reprod Med),MNAMS
Director, SRIJAN Fertility,Janak Puri, Delhi.

Fertility preservation is the very essence of science of reproductive medicine. From time immemorial, man always runs behind youth and fertility. Off late, lot of progress has been made in this field and this brings us to the question: WHO NEEDS FERTILITY PRESERVATION?

INDICATIONS:

Indications to preserve fertility can broadly be divided into:

1. Medical indications:
   i. Oncological causes
   ii. Non-oncological causes
2. Social indications.

Causes of diminished fertility due to **oncological causes** can be due to tumour per se (eg due to testicular carcinoma) , because of cancer surgery ( eg bilateral oophorectomy in case of endometrial carcinoma or ovarian carcinoma) or it can be attributed to cancer chemotherapy or radiotherapy.

**Social indications:**
Social indications of fertility preservation include freezing of the gametes or embryos or gonadal tissues in individuals or couples who want to delay child bearing due to social circumstances. This arena of fertility preservation is in a grey zone and has received a lot of bouquets as well as brick bats. In the absence of any solid evidence, currently it is at the discretion of individual clinics whether they want to offer fertility preservation to such individuals/couples. According to Hirshfeld-Cytron and Grobman (Fertil Steril 2012) , Neither oocyte cryopreservation nor ovarian tissue cryopreservation, appear to be cost-effective under current circumstances for otherwise healthy women planning delayed childbearing.

| Malignant | Non-malignant |
|---|---|
| **Extrapelvic diseases**<br>• Bone cancer (osteosarcoma—Ewing's sarcoma)<br>• Breast cancer<br>• Melanoma<br>• Neuroblastoma<br>• Bowel malignancy | **Uni/bilateral oophorectomy**<br>• Benign ovarian tumours<br>• Severe and recurrent endometriosis<br>• BRCA-1 or BRCA-2 mutation carriers |
| **Pelvic diseases: Gynaecological cancers**<br>• Early cervical carcinoma<br>• Early vaginal carcinoma<br>• Early vulvar carcinoma<br>• Selected cases of ovarian carcinoma (stage IA)<br>• Ovarian borderline tumours | **Risk of premature menopause**<br>• Turner's syndrome<br>• Family history<br>• Benign diseases requiring chemotherapy: autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease and Wegener's disease |
| **Pelvic diseases: Non-gynaecological cancers**<br>• Pelvic sarcoma<br>• Rhabdomyosarcoma<br>• Sacral tumours<br>• Rectosigmoid tumours | **Bone marrow transplantation**<br>• Benign haematological diseases: sickle cell anaemia, thalassaemia major and aplastic anaemia<br>• Autoimmune diseases unresponsive to immunosuppressive therapy |
| **Systemic diseases**<br>• Hodgkin's disease<br>• Non-Hodgkin's lymphoma<br>• Leukaemia<br>• Medulloblastoma | |

**Non oncological causes** include severe and recurrent endometriosis, benign ovarian tumours, BRCA 1 or BRCA 2 mutation carriers, auto-immune disorders like SLE, Rheumatoid arthritis, Behcets disease, requiring chemotherapy, women with high risk of premature ovarian failure as seen in Turners syndrome, Fragile x syndrome etc, women with very strong family history of premature ovarian failure, Benign haematological diseases: sickle cell anaemia, thalassaemia major and aplastic anaemia, Non-Hodgkin's lymphoma requiring bome marrow transplantation.

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**Some interesting facts about Fertility Preservation**

- Number of publications on FP in the first eight months of this year is a whopping 291 compared to mere 8 in 1970 - reflects the amount of ever increasing work & research in this area of medical science.
- Approximately 20 conferences have been or will be held in 2014 across the world with the central theme of fertility preservation in children and young adults.
- Even though ovarian tissue cryopreservation is considered as experimental, live births have been reported following orthotopic re-implantation of ovarian tissue.
- Heterotopic ovarian tissue re-implantaion requires ovarian stimulation, follicle aspiration and IVF ET to achieve pregnancy, whereas spontaneous conceptions can happen with orthotopic re-implantation.
- Unlike OTC & re-implantation, cryopreservation of spermatogonial stem cells (SSC) in prepubertal boys has largely remained a research tool & its clinical relevance in fertility preservation is yet to be proven in humans.

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## The Journey Continues…..

There have been two meetings of the executive committee to plan the path of FPS(I) meticulously and here is a peek into the results……


CME at India Habitat Centre, New Delhi, 12th July 2014.

**The first Annual conference of the Fertility Preservation Society of India (6-7 Sep 2014)** – 'Fertility Preservation – Current Concepts', in addition to being a great academic event, incorporates a hands-on training workshop on Ovarian Tissue Cryopreservation on 8 Sep 2014. World renowned experts in this field are here to equip our embryologists with the skill of OTC.

**It is indeed of note that the very first annual conference of a young academic body such as FPS(I) is endorsed by prestigious international organisations such as International Society of Fertility Preservation (ISFP) and Japan society for Fertility Preservation (JSFP).**

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## From the Editorial team …….

Welcome to all!

The first edition of the newsletter of FSPI has been created with the thought of providing an overview of the science of fertility preservation and its current status. This edition is meant to serve as a ready guideline to clinicians and specialists to deal with this challenging science. The future editions will bring more diverse issues concerned with fertility preservation to your doorstep.

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Warm regards,

Padma Rekha Jirge  Devika Gunasheela  Shivani Singh