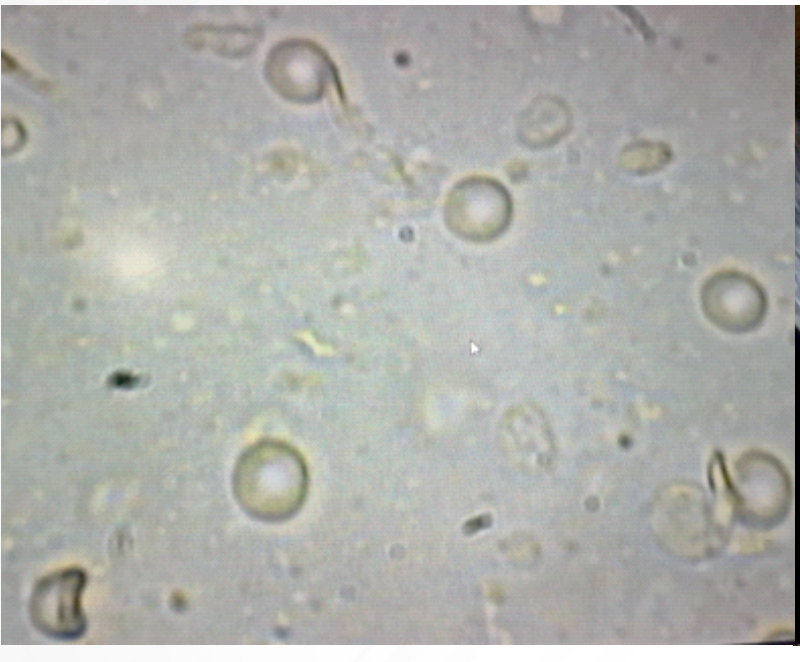
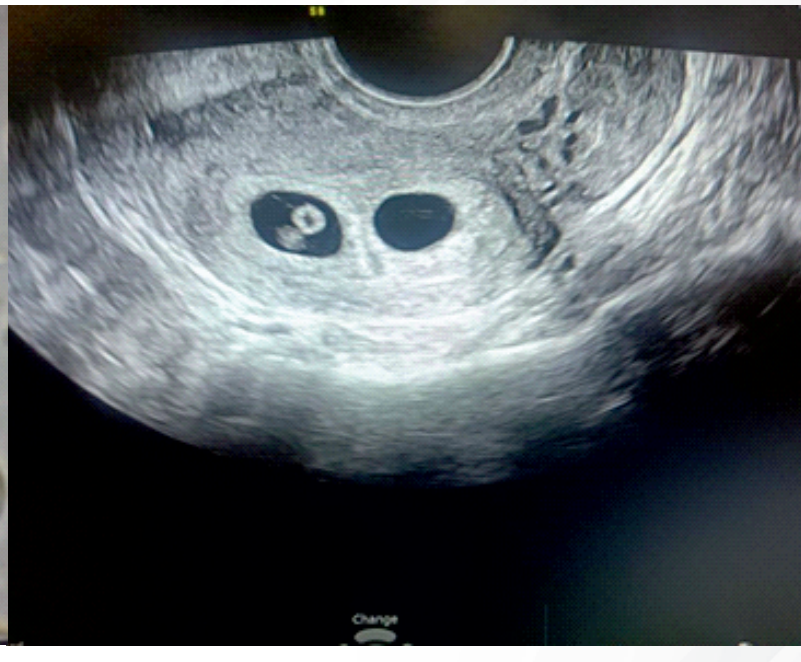
LIFE+VE

December 2025





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From the Editor's Desk.....

As the year 2025 draws to a close we are pleased to bring to you our last issue of Life +ve. As always we bring to you four interesting Case Reports from our own experiences in the field of Infertility.

The first case is that of a very advanced maternal age patient (vAMA) who presented to our Clinic at 49 years 6 months seeking assisted reproductive technology. She underwent donor egg IVF cycle, had single blastocyst transfer 45 days before her 50th birthday and conceived in her first IVF cycle. With a multidisciplinary approach and meticulous monitoring of her various comorbidities (Obesity, Type II DM on high dose Insulin, hypertension and very advanced age pregnancy) by Dr. Varini N & Dr. Utkarsha, she was successfully managed and delivered of a healthy live female baby at Milann Kumarapark.

Our second case by Dr. Meghana and Dr. Ankita, is that of testicular azoospermia (or primary hypogonadism) relating to an intrinsic defect in the testicles leading to impaired spermatogenesis and presenting as hyper gonadotrophic hypogonadism. The couple were counselled about the parameters and option of Micro TESE as the couple was keen on going ahead with self gametes only. Thanks to the use of Micro TESE(Testicular Sperm Extraction) which offers direct visualization of tubules which are more likely to contain sperms rather than blind needle pricks like in TESA, this couple were able to conceive and are now the proud carriers of a twin pregnancy.

Our next case describes the feasibility of fertility preservation in select patients with recurrent borderline ovarian tumour with microinvasion. With multidisciplinary planning, Letrozole-supplemented low-oestrogen stimulation and coordinated, vigilant oncologic surveillance, safe fertility preservation in selected patients with recurrent microinvasive SMBOT is possible with successful results.

Our last case is that of Conception following IUI after multiple failed IVF cycles. A multi disciplinary approach with proper immunological work up helped in achieving success in this case of Recurrent Implantation Failure.

We wish you a joyous holiday season filled with love, peace, and happiness and all good wishes for a Happy New Year!

VERY ADVANCED MATERNAL AGE (vAMA): NEW ERA OF PREGNANCY AT PERIMENOPAUSAL AGE

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CASE REPORT

Mrs XY , married for 10 years, presented to our Infertility clinic at 49 years and 6 months seeking assisted fertility treatment. At presentation, she had a BMI of 36.4kg/m^2(Grade 2 obesity). She was a known case of Type II Diabetes Mellitus for 10 years (since 2014) and was on insulin (Inj. Tresiba 0-0-28 units and Inj. Fiasp 22-22-22u) and oral hypoglycemic drugs. Her HbA1c was 8.8%. She was also a chronic hypertensive since September 2018 and was on Tab. Telmisartan 40mg. Her blood pressure was maintained within normal limits. She was managed with a multidisciplinary team. Investigations along with ECG and 2-D ECHO were done to know the baseline cardiovascular status, liver and renal functioning of the patient and were found to be within normal limits. Tab. Telmisartan was changed to pregnancy safe medicines, Tab Labetalol 100mg TID and Tab Nifedipine Retard 10 mg OD. Her blood sugars were brought to normal levels adjusting her Insulin and Metformin dosage. After optimizing her health parameters, she underwent donor egg IVF cycle. She had single blastocyst transfer 45 days before her 50th birthday and she conceived in her first IVF cycle.

Her uphill journey of pregnancy with multiple hurdles started then. The couple was counselled regarding the high risk pregnancy and the imperative need for compliance regarding medications along with regular antenatal visits was emphasized. Multidisciplinary approach was continued with regular consultations with physician, diabetologist, dietician and obstetrician. Diet chart was provided to allow adequate nutrition to growing fetus and at the same time care was taken to maintain her blood sugar levels within acceptable limits. She was given a target of 7-8 kgs weight gain throughout pregnancy. In view of her multiple risk factors (Obesity, Type II DM on high dose Insulin, hypertension and very advanced age pregnancy) she was started on LMWH (Inj. Enoxaparin 40 mg OD) and low dose Aspirin for thromboembolic prophylaxis. She had repeated episodes of per vaginal bleeding in her first trimester and Aspirin was stopped. LWMH was increased to 60mg daily.

She developed gestational hypothyroidism in first trimester and was started on Tab Thyronorm 12.5 mcg. NT Scan done at 12 weeks 6 days showed normal NT and presence of nasal bone. Double marker test was low risk for trisomy 21,13 and 18. She had regular iron and calcium supplementation. She received 2 doses of Tdap in second trimester. Early anomaly scan done at 18 weeks 4 days showed no obvious structural deformity followed by anomaly scan at 24 weeks 1 day which was normal as well. Fetal ECHO showed structurally normal fetal heart at 24 weeks gestation. In her second trimester, she had an emotional outburst due to family issues for which a psychiatrist was consulted. She was started on anti-depressants and relaxation techniques were taught. Her symptoms reduced and she was continued on low dose anti depressants in pregnancy. Growth scans done at 29 weeks and 33 weeks 6 days had good interval growth with normal fetal dopplers. Blood sugars and blood pressure was controlled well throughout pregnancy. ECG, 2D ECHO and cardiac evaluation were repeated at 32 weeks gestation and all parameters were within normal limits. She complained of decreased fetal movements at 37 weeks 2 days and NST was reactive. However, in view of persisting reduced movements, floating head and multiple risk factors, elective LSCS was done at 37 week 4 days. Her delivery was meticulously planned with multi- disciplinary approach involving anaesthetist, physician, obstetrician and paediatrician at Milann Hospital, Kumara Park. LMVH was stopped 24 hours prior to delivery. PT and INR were normal.

Hemoglobin was 11.4gm/dl. Spinal anesthesia was difficult because of obesity. Pfannenstiel incision was done. Lower uterine segment was opened by transverse incision and she delivered a live female baby with 10/10 Apgar score. Baby weight was 2.8kg. Intra-operatively, it was noticed placenta was anterior low lying placenta and uterine incision had gone through the lower edge of placenta. Also placenta was adherent and thick. Patient had blood loss about 1 litre (PPH) which was controlled with uterotonics and 1 unit PCV transfused. She had an uneventful recovery. LMVH was started after 12 hours of surgery and she received OD dosage for 7 days. She was started on Tab. Amlodipine 10mg OD for hypertension. Her blood sugars were managed with Tab. Metformin 500mg 1-1-1 and Anti-depressants were continued to prevent post-partum depression. She successfully breast fed her new-born and was discharged on third post-operative day.

DISCUSSION

In the past two decades, a new era of advanced maternal age has been witnessed with more and more women achieving their first pregnancy (Primigravida) at age of 45 years and beyond. This new trend can be explained by women choosing to pursue careers and achieve financial security, leading them to postpone childbearing.

Medical literature uses the term 'very advanced maternal age' (vAMA) to refer to women who are aged 45 years or more at the time of delivery.

With the decline in fertility, natural conception rate in women at 45yrs and more is less than 0.5%. The success rates in assisted conception at this age is also not promising with less than 1% live birth with self egg IVF cycle and 40-60% per embryo transfer in IVF with donor eggs. Many women would have attained menopause or be in their perimenopausal phase at this age.

ART at this age is associated with an increased risk of ovarian hyperstimulation syndrome, miscarriage, ectopic pregnancy, venous thromboembolism (VTE), genetic and chromosomal disorders and multiple pregnancies.

Women of vAMA have increased risk for miscarriage (53%), ectopic pregnancy (3 times more) and multiple pregnancy (79.3/1000) compared to younger women[1].

Pregnancies in women of vAMA have increased risks of pre-existing medical conditions, GDM, gestational hypertension, pre-eclampsia, hypothyroidism, abnormal placentation, ICU admission, caesarean delivery, postpartum haemorrhage (PPH), blood transfusion and prolonged admission to hospital[2].

Women aged 48 years or more are more likely to be overweight or obese than younger women. Pregnant women who are obese are at greater risk of pre-eclampsia, GDM and caesarean birth than women with a normal body mass index (BMI). There is also a higher risk of foetal neural tube defects associated with obesity

Table 1 : A summary of maternal complications, risks and recommendations in women of very advanced maternal age (vAMA)[3]

Maternal Complication	Risk	Recommendation
Pre-existing Medical Complication	44% (of women aged 48 years or older)	Early referral to a high-risk antenatal clinic or maternal medicine clinic
Gestational Diabetes Mellitus	12.6–21.0% 35.1% (in twin pregnancies conceived by assisted reproductive technology)	Offer screening at 16–18 weeks of gestation in addition to screening at 26–28 weeks of gestation Women of vAMA are nine times more likely to require insulin
Hypertensive Disease	6–32%	Pre-pregnancy counselling should be offered to all women with pre-existing hypertension, including a review of antihypertensive medications, an up-to-date echocardiogram, renal function tests and renal imaging Advise low-dose aspirin 150 mg from 12 weeks of gestation until delivery Regular blood pressure monitoring in the third trimester
Previous Uterine Surgery	26% (of women aged 48 years or older)	Early referral to a high-risk antenatal clinic
Placenta Praevia	Three times more likely to have placenta praevia than younger women	Foetal anomaly ultrasound scan between 18 and 21 weeks of gestation Those involved in scanning should be aware of the increased risk of placenta praevia in women of vAMA
PPH	25% Women of vAMA are almost four times more likely to need blood products than younger women	Plans and precautions to minimise the risk of PPH should be discussed. Investigate and treat anaemia Discuss the role of prophylactic uterotonics in the management of the third stage of labour
Antenatal Hospital Admission	30%	Thromboprophylaxis is recommended for women of vAMA with additional risk factors Admission alone increases venous thromboembolism risk 12-fold
Admission to Intensive Care Unit	33.5 times more likely to be admitted than younger women	Consider offering care in a place with appropriate intensive care support for both mother and neonate(s) High-risk women of vAMA to be seen in a high-risk anaesthetic clinic at 30–32 weeks of gestation On-call consultant anaesthetist should be made aware when a woman of vAMA is admitted to the unit

Review of studies have shown that maternal mortality rate (MMR) of 7.7 times for vAMA compared to women aged <25 years and 3.8 times higher compared to women aged 35 years. This relatively high rate can be explained by comorbidities and other coexisting diseases. Amniotic fluid embolism and obstetric shock are eight-fold and three-fold higher at vAMA compared to 25–29 years old women.

Children born to women of vAMA have increased perinatal morbidity. Women aged 45 years and above are twice as likely to deliver spontaneously before 37 weeks of gestation and 4.5 times more likely to deliver prematurely because of iatrogenic intervention. Women of vAMA are twice as likely to have a SGA baby and have a 32% chance of having a baby with a birthweight of less than 2500 gms. The high rate of babies born with a weight below 2500 gms was shown to be associated with prematurity rather than FGR. One in six babies born to women of vAMA need admission to NICU.

Many studies report adverse perinatal outcomes in women of vAMA, the absolute rate of stillbirth and perinatal death is between 1.00 and 1.87% compared with 0.55% in younger women. Perinatal mortality rates are 2.0–3.8 times higher in babies born to women of vAMA.

Both advanced maternal and paternal age are risk factors for autism in offspring. Possible biological mechanisms include de novo aberration and mutations, or epigenetic alterations associated with aging.

CONCLUSION

vAMA is the new trend of pregnancies. With ART, many women are conceiving in perimenopausal age. These women have background risk of medical co-morbidities along with increased risk of complications due to ART. They have high incidence of maternal and fetal mortality and morbidity. Meticulous planning, vigilant supervision and multi-disciplinary approach are key factors for optimal outcomes.

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UNLOCKING FATHERHOOD: THE MEDICAL AND SURGICAL PATHWAY TO PREGNANCY WITH NON OBSTRUCTIVE AZOOSPERMIA

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INTRODUCTION

Infertility affects 1 in 6 couples, and male factor infertility has been implicated as a cause in about 50% of cases and is the main cause of infertility in 30% of the cases[1]. Azoospermia is defined as the absence of spermatozoa in the ejaculate and is considered the most extreme form of male factor infertility. Azoospermia is classified as Non-Obstructive Azoospermia (NOA) or obstructive azoospermia (OA). NOA occurs when there is an impairment of spermatogenesis, whilst OA is caused by occlusion of the testicular and genital ductular system. NOA has been estimated to affect 1 in 100 men[2]. Historically, these men were considered sterile but, with the advent of testicular sperm extraction and assisted reproductive technology (ART), advanced reproductive science has made it possible for these men to be able to biologically father their own children.

CASE REPORT

Mrs M, aged 33 years married to Mr S, aged 34 years for 5 years and the couple was attempting conception for the past 4 years. She was a case of primary infertility with diagnosis of PCOS. She had irregular menstrual cycles and an AMH value of 6.68ng/ml with anovulation for which she had received multiple cycles of ovulation induction outside but failed to conceive upon which her husband's investigations were done and he was found to have azoospermia. A diagnosis of non-obstructive azoospermia was made based on semen analysis and high FSH levels (>25 miu/ml in more than 2 tests). They were given the option of donor sperm insemination which was not acceptable to the couple and had stopped seeing doctors for almost 2 years with loss of hope of achieving parenthood..

The couple then visited Milann Fertility in May 2025 seeking treatment for primary infertility.

Semen analysis of Mr S at Milann Fertility also showed azoospermia with hormone levels being FSH - 27.8mIU/ml, LH -5.05 mIU/ml, total testosterone -270ng/ml, and was diagnosed as a case of non obstructive azoospermia with hypergonadotrophic hypogonadism. On examination, Mr S had bilateral small testes. Karyotyping showed normal male karyotype of 46XY. Y -chromosome microdeletion was not detected. The couple were counselled about the parameters and option of Micro TESE given as the couple was keen on going ahead with self gametes only. To improve the chances of obtaining sperms, Mr.S was put on Injections HMG and HCG for 6 weeks. The treatment plan included controlled ovarian stimulation for the wife followed by oocyte retrieval and Micro TESE procedure for the husband on the same day.

In view of her PCOS status, IVF cycle with Antagonist Protocol was started for Mrs M. Since she was a hyperresponder, antagonist trigger was given with a plan to defer fresh embryo transfer in order to avoid OHSS(Ovarian Hyperstimulation Syndrome). All other measures to avoid OHSS like cabergoline on day of trigger, aromatase inhibitors and calcium gluconate post oocyte retrieval were taken to mitigate the risk of OHSS. At oocyte retrieval 24 oocytes were retrieved of which 20 were mature. Mr S underwent MICRO TESE procedure on the same day and sperms were retrieved (Fig 1). After careful check, sperms were selected and ICSI done on the 20 mature oocytes, out of which 14 fertilized. This procedure gave us 10 blastocysts which were kept frozen.

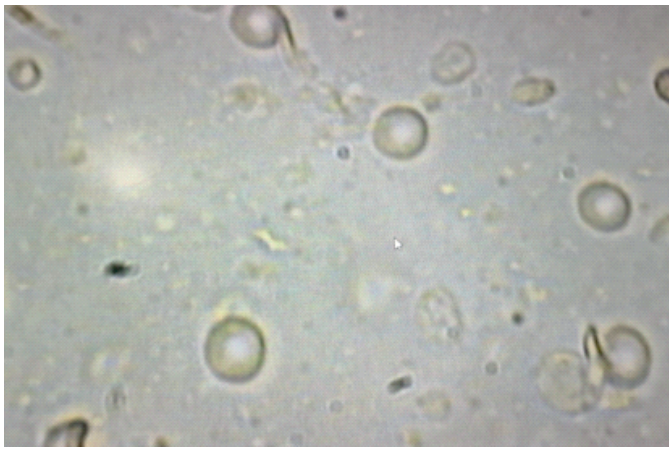

Fig 1: Image showing sperms following Micro-TESE under microscope (40x magnification)

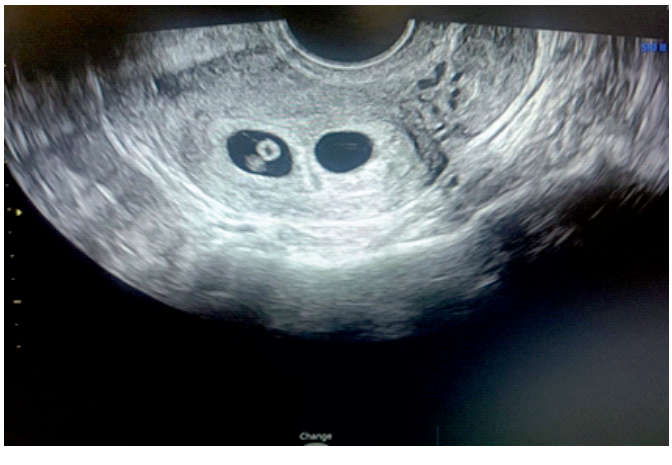

Fig 2: Ultrasound image showing DCDA twin pregnancy

2 months later, endometrial preparation was done with hormone replacement therapy and Frozen Embryo transfer (FET) of 2 Blastocysts was done.

Serum beta -HCG measured 975mIU/ml fifteen days post transfer confirming pregnancy. In USG dichorionic diamniotic twin gestational sacs of 5 weeks were noted(Fig 2).

Currently , Mrs M is at 5 weeks 6 days gestation with DCDA twins.

DISCUSSION

Testicular azoospermia (or primary hypogonadism) relates to an intrinsic defect in the testicles leading to impaired spermatogenesis presenting as Hypergonadotrophic hypogonadism.

There have been several retrospective case reports [3,4] and case series [5,6] and a limited number of case control studies supporting the use of hormone stimulation (Medical management) in men with primary testicular NOA. Gonadotrophin therapy, using HCG and FSH has been shown to promote spermatogonial proliferation and DNA synthesis in these patients which was used as pretreatment in this patient.

Historically, testicular sperm aspiration (TESA) and extraction (TESE) involved random biopsies of testicular tissue. Micro TESE(Testicular Sperm Extraction) uses optical magnification with the help of a microscope to target specific seminiferous tubules that are more likely to contain spermatozoa.

The advantage of the use of optical magnification is that it offers direct visualization of tubules which are more likely to contain sperms rather than blind needle pricks like in TESA and also lesser risk of inadvertent vascular damage and potential hypogonadism. Consequently, microdissection testicular sperm extraction (mTESE) has been adopted as the optimal technique of surgical sperm retrieval.

CONCLUSION

So, in the era of in vitro fertilization with intracytoplasmic sperm injection, medical management followed by surgical sperm extraction techniques (like Micro TESE) can afford men with non obstructive azoospermia(NOA) biologic paternity.

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BALANCING CANCER RISK AND MOTHERHOOD: PREGNANCY AFTER SEROMUCINOUS BORDERLINE OVARIAN TUMOUR

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INTRODUCTION

Seromucinous borderline ovarian tumors (SMBOTs) with microinvasion are rare and present management challenges in reproductive-age women desiring fertility, particularly when disease is recurrent. We describe a 32-year-old woman with recurrent microinvasive SMBOT who sought fertility preservation prior to definitive surgery. After multidisciplinary evaluation, she underwent right adnexectomy and left ovarian cystectomy, with pathology confirming microinvasive SMBOT and no extraovarian spread. Controlled ovarian stimulation using a progestin-primed ovarian stimulation (PPOS) protocol with letrozole minimized oestrogen exposure, resulted in eight retrieved oocytes and four blastocysts. Following an initial failed frozen embryo transfer, a second stimulation cycle produced two additional blastocysts. Hysteroscopy identified chronic endometritis, which was treated before a natural-cycle frozen transfer of a single 4AA blastocyst, resulting in an ongoing singleton intrauterine pregnancy. This case demonstrates that thoughtfully planned, low-oestrogen stimulation and coordinated oncologic surveillance may allow safe fertility preservation in selected patients with recurrent microinvasive SMBOT.

Borderline ovarian tumours (BOTs) account for 10–20% of epithelial ovarian neoplasms and typically affect women in the reproductive age group[1]. Among BOT subtypes, seromucinous borderline ovarian tumours (SMBOTs) are rare, accounting for <5% of cases[2]. They have a 1–3% risk of malignant transformation to seromucinous or low-grade serous carcinoma[3]. Management becomes complex in cases with bilaterality, microinvasion, or recurrence, where oncologic safety must be balanced against reproductive goals. We report a young woman with recurrent microinvasive SMBOT who achieved a successful pregnancy following fertility-preserving surgery and IVF using a tailored low-oestrogen stimulation strategy.

CASE REPORT

A 32-year-old woman, married for three years and attempting conception for one year, presented for onco fertility consultation following recurrence of a borderline ovarian tumour.

Initial Presentation and First Surgery:
At age 30, she was diagnosed with an 11.2 × 7.6 × 8 cm right ovarian complex cyst and a 2.2 × 1.2 cm left endometriotic cyst. Laparoscopic right ovarian cystectomy revealed seromucinous borderline ovarian tumour with microinvasion; peritoneal fluid cytology showed atypical cells. She was under periodic ultrasound follow-up.

Recurrence and Second Surgery:
Fifteen months later, MRI demonstrated a left ovarian complex cyst measuring 9.5 × 10.8 × 15.2 cm. Left cystectomy was performed, and histopathology revealed microinvasive borderline seromucinous tumour with abnormal p53 expression (90%).

Within just a span of three months she had a recurrence on the same side. She was referred to our unit for fertility preservation prior to a definitive surgery. She was found to have a 11.3 x 7.4 x 7.4 cm left ovarian complex cyst with two residual follicles (Figure 1). Right ovary was not visualized. AMH was found to be 0.6ng/ml.

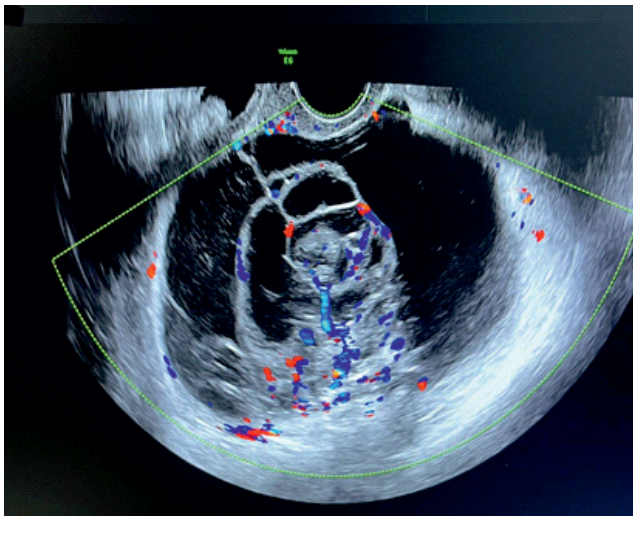

Fig1: Left Ovarian heteroechoic Cystic solid mass with Septations and Vascularity

Multidisciplinary Discussion and Surgical Plan:

A tumour board including reproductive medicine, gynaecologic oncology, and oncopathology specialists reviewed the case. Given recurrence and microinvasion, staging surgery (bilateral salpingo-oophorectomy with uterine preservation and omentectomy) was advised. However, the couple were keen to use autologous oocytes despite poor ovarian reserve. A two-step plan was agreed upon:

1. Left cystectomy to enable follicular access and disease control.

2. Controlled ovarian stimulation and oocyte retrieval for fertility preservation prior to eventual completion staging surgery.

The patient underwent right adnexectomy, left cystectomy, infracolic omentectomy, and peritoneal biopsies. Histopathology confirmed borderline seromucinous tumour with microinvasion; all peritoneal and omental biopsies and endometrial curetting was negative for malignancy.

Controlled Ovarian Stimulation and Embryo Development:

Post-surgery, she presented on cycle day 2 with six antral follicles in the left ovary (Figure 2). Controlled ovarian stimulation was initiated using a progestin-primed ovarian stimulation (PPOS) protocol (rFSH 225IU/d + HMG 75 IU/day + Medroxyprogesterone acetate 10 mg/day), with letrozole 5 mg/day throughout stimulation to limit oestradiol elevation.

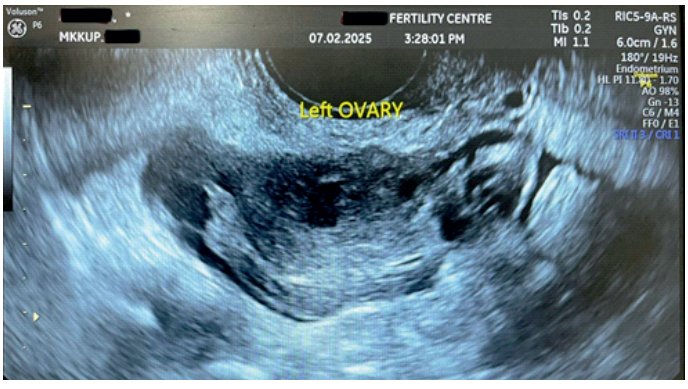

Fig 2: Post left Ovarian Cystectomy showing residual Ovarian Tissue with 6 Antral Follicles

After 11 days of stimulation, agonist trigger was given and eight oocytes were retrieved. Five M2-5F-5C-4 blastocysts obtained (2-4AA,1-4BB,1-4BC)

First Frozen Embryo Transfer (FET):
A mild stimulation FET cycle using tamoxifen was undertaken with one 4AA blastocyst with optimal endometrial thickness and blood flow but did not yield pregnancy.

Second IVF Cycle (Pooling):
A second cycle of embryo pooling was planned in view of high risk of recurrence of disease with the aim of having supernumerary embryos. The patient was started on PPOS stimulation with letrozole 5 mg daily. Four oocytes were retrieved, and two blastocysts were formed (4AB,3BB).

Endometrial Evaluation:
Hysteroscopy was done which revealed focal hyperaemia; MUM1 immunostaining was positive, suggestive of chronic endometritis. She received an extended course of broad-spectrum antibiotics followed by probiotics.

Second FET and Pregnancy Outcome:
A natural cycle FET was chosen to minimize hormonal exposure. A 19 mm follicle with 9.5 mm trilaminar endometrium with good doppler parameters were noted on day 15. Single 4AA blastocyst was transferred on day 20 (Figure 3). Serum β-hCG on day 14 post-transfer was 3089 mIU/ml. A transvaginal ultrasound at 7 weeks confirmed a single live intrauterine pregnancy. Pregnancy is ongoing with regular oncologic surveillance (Figure 4).

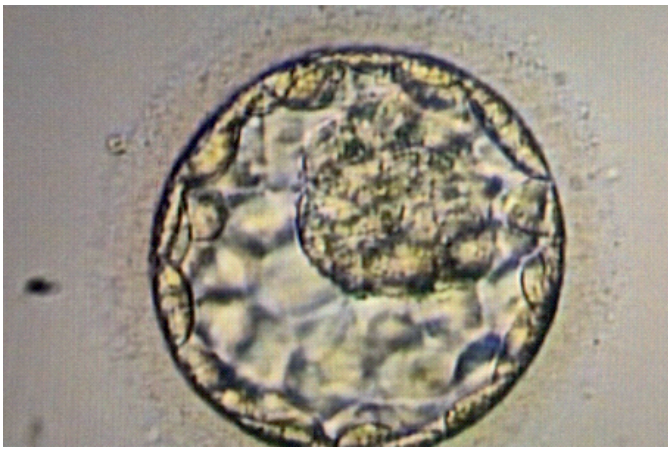

Fig 3: One 4AA Grade Blastocyst that was transferred

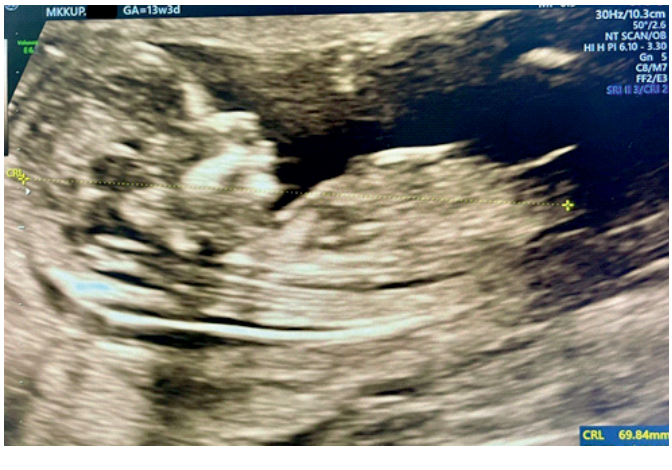

Fig 4: Ongoing Pregnancy of 13 weeks Gestation

DISCUSSION

This case describes the feasibility of fertility preservation in select patients with recurrent borderline ovarian tumour with microinvasion, provided there is multidisciplinary planning and meticulous oncologic monitoring.

Oncologic Consideration:
Seromucinous BOTs are a distinct subtype combining serous and endocervical-type mucinous epithelium, representing <5% of all BOTs[2]. They are frequently associated with endometriosis (40–60%)[4] and show ER/PR positivity in most cases, indicating possible hormonal responsiveness. They present in early stage and have 10-year survival rates of >90% and 1–3% risk of malignant transformation. However, late recurrence can occur up to 10 years post-treatment[5]. Recurrence risks rise with incomplete staging, bilaterality, and microinvasion[6]. Definitive management involves total hysterectomy with bilateral salpingo-oophorectomy and staging, which is curative in >95% of patients[7]. In young women desiring fertility, conservative management may be offered if there is complete cytoreduction and histologic confirmation of non-invasion.

Fertility Preservation with Poor Reserve:
While natural fertility in women after conservative surgery can be favourable, recurrence risk and time constraints often justify assisted reproduction. Ovarian stimulation in BOT patients poses concern due to oestrogen sensitivity. However, studies show no significant increase in recurrence with ART when stimulation is carefully controlled[8]. In our case, letrozole-supplemented PPOS minimized oestradiol peaks (<1000 pg/mL), theoretically reducing hormonal stimulation of residual disease. Dosing has to be individualized to maximize retrieval as achieving adequate oocyte yield is challenging with low AMH.

Chronic Endometritis and Implantation:
The incidental finding of MUM1-positive chronic endometritis after failed embryo transfer highlights the importance of endometrial evaluation. Treatment with antibiotics and probiotics and the subsequent natural cycle FET resulted in successful implantation, emphasizing that fertility optimization extends beyond ovarian management.

Ethical and Emotional Considerations:
Patient autonomy and informed choice were central. The couple's desire for genetic parenthood required sensitive counselling about recurrence risk and fertility prognosis.

Outcome and Prognosis:
This case illustrates that fertility preservation is achievable even in recurrent, microinvasive BOTs when guided by stringent histologic verification, low-oestrogen stimulation, and vigilant surveillance. She remains under oncologic follow-up.

CONCLUSION

Fertility preservation in recurrent BOTs with microinvasion requires individualized, multidisciplinary planning. Letrozole-supplemented ovarian stimulation and vigilant oncologic follow-up can yield favourable reproductive outcomes without compromising safety. This case illustrates that even in complex oncologic scenarios, autologous conception is possible through coordinated oncofertility care.

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CONCEPTION FOLLOWING IUI AFTER MULTIPLE FAILED IVF CYCLES: ROLE OF IMMUNOLOGY WORK-UP IN RECURRENT IMPLANTATION FAILURE

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INTRODUCTION

Recurrent implantation failure (RIF) is a clinical phenomenon where no clinical pregnancy occurs despite multiple embryo transfers. Its true prevalence is unknown due to inconsistency in the definition of RIF. According to a study by Pirtea et al., the true incidence of RIF is between 1% and 5%[1]. A study by Gill P et al, suggested the estimated prevalence would be <1%.[2]

Definition of RIF by ESHRE[3]

	Maternal age	Implantation rate/ pregnancy rate[1]	Cumulative likelihood of implantation for each embryo transfer (embryos of unknown euploidy)						RIF THRESHOLD of >60%
			FIRST ET (n=1)	SECOND ET (n=2)	THIRD ET (n-3)	FOURTH ET (n=4)	FIFTH ET (n=5)	SIXTH ET (n=6)	
Embryos of unknown euploidy	<34	31,5	31,5	53,1	67,9	78,0	84,9	89,7	Intervene after 3 ETs
	35-39	25,9	25,9	45,1	59,3	69,9	77,7	83,4	Intervene after 4 ETs
	≥40	15	15,0	27,8	38,6	47,8	55,6	62,3	Intervene after 6 ETs
Euploid embryos	<35	68,4	68,4	90,0	96,8	99,0	99,7	99,9	Intervene after 1 ETs
	35-40	64,1	64.1	87,1	95,4	98,3	99,4	99,8	Intervene after 1 ETs
	>40	58,0	58,0	82,4	92,6	96,9	98,7	99,5	Intervene after 2 ETs

Definition of RIF by ASRM[4]

Estimation model for the number of unscreened good-quality embryos needed to be equivalent to 3 successive euploid embryo transfers & achieve a 95% chance of sustained implantation on the basis of the observed aneuploidy rate (20).

Age (y)	Observed aneuploidy rate	No. of untested blastocysts to achieve a 95% chance of sustained implantation
<35	20%	4
35-37	30%	5
38-40	50%	7
41-42	70%	13
≥43	85%	27

Recurrent implantation failure. Fertil Steril 2023.

RIF is a complex clinical condition with several different etiologies, including maternal factors, paternal factors and embryo factors. Though a good quality embryo is the foundation for successful implantation, the state of the endometrium to accept the embryo also plays a crucial role.

ETIOLOGY

1. Embryonic Factors: Embryos with abnormal chromosomes are recognized as important factors that cause implantation failure or pregnancy loss. The probability of chromosomal aneuploidy in embryos also increases with age. Poor embryo quality and suboptimal eggs or sperm can lead to less viable embryos.

2. Male factors: Sperm DNA damage is related to poor embryo development and reproductive failure.[5]

3. Maternal factors:

   3a) Endometrial Receptivity: An endometrial biopsy obtained from patients with RIF on the seventh day of progesterone administration revealed 313 genes that were differentially expressed between patients with RIF and the control group[5]. This is assumed to be due to the displacement of the window of implantation (WOI), which affects more than 25% of patients with RIF.

   3b) Infections: Chronic endometritis is often asymptomatic, leading to inconsistencies in prevalence. The reported prevalence in patients with RIF ranges from 7.7% to 66%, with a prevalence of 2.8% in patients with general infertility. The uterine immune status in chronic endometritis is altered.[5]

   3c) Lifestyle: Smoking- Significantly reduces implantation success.

   3d) Medical Conditions like Obesity/Weight Issues, Stress are also associated with RIF.

3e) Immunological Factors: Successful implantation is a process of maternal-fetal immune tolerance involving various molecules. Trophoblast invasion can activate the maternal immune response to fetal antigens. Local immune cells at the implantation site in the endometrium, which are activated by the embryos, mediate maternal-fetal immune tolerance and promote placental development. In this stage, immune cells, including innate lymphocytes, T cells, decidual dendritic cells, and macrophages, are activated, and they are also associated with adverse pregnancy outcomes such as RIF.[5]

NK cells in the uterus (uNk cells) account for over 70% of all endometrial leukocytes they mediate maternal-fetal immunity. The function of uNK cells depends on the balance between inhibitory and activating receptors. Each pregnancy involves different maternal/fetal genetic combinations that deliver activating or inhibitory signals to uNK cells. uNK cells are the main source of angiogenic growth factors such as placental growth factor, vascular endothelial growth factor (VEGF)-A, and angiopoietin, which may direct angiogenesis during embryo implantation.

T cells play an important role in immunity during pregnancy. In patients with RIF, the Th1/Th2 ratio increases in the peripheral blood with an increasing Th1 immune response. An abnormal Th17 increase in the peripheral blood and decidua is associated with recurrent miscarriages. Treg cells are known to mediate pregnancy tolerance and can potently suppress Th1/Th17-mediated immunity. Exhausted Treg cells may lead to adverse pregnancy outcomes.

The maternal immune system treats the fetus as a foreign agent. Excessive immune activation results in implantation failure. Tacrolimus, an immunosuppressant, has been demonstrated to suppress immunological rejection by inhibiting cytotoxic T cell generation, alloantigen-induced lymphocyte proliferation, and the production of IL-2 and IFN-Y. It has been used as a plausible treatment for patients with RIF who have an elevated Th1/Th2 ratio and appears to improve pregnancy outcomes.

There are various immune therapies with controversial evidence available like intravenous immunoglobulin therapy, Thymosin-alpha, Intrauterine infusion of PRP, subcutaneously administered G-CSF, endometrial scratch and endometrial receptivity assay. Tailoring treatment to the individual, based on comprehensive investigations can significantly enhance success and prevent irrational use of drugs.

CASE REPORT

A 33-year-old woman, married for 7years, presented with a long-standing history of primary infertility, previously evaluated and diagnosed with Polycystic Ovarian Disease (PCOD). Husband was 35 years old with normozoospermia and DFI of 25%. The couple had undergone two cycles of in vitro fertilisation (IVF), 3 frozen embryo transfers, each with euploid blastocysts, 5 euploid blastocyst transfers in total, yet none resulted in a sustained pregnancy.

Despite multiple attempts at conception with good quality embryos, she had experienced recurrent implantation failure (RIF). Recognizing the complexity of her case, a multidisciplinary team approach was used, including experts from the field of reproductive medicine, reproductive immunology, embryologist, andrologist, nutritionist and geneticist to conduct a thorough evaluation for RIF. Patient underwent diagnostic hysteroscopy where the uterus appeared normal, peripheral NK cell profile done, endometrial biopsy report suggested positive for uNK cell.

Immune profile like APLA, ANA, Anti -TPO were negative and the couple karyotyping normal. The endometrial immune profile suggested a mixed profile.

After detailed investigations, potential subtle factors possibly immunological and endometrial receptivity related were considered contributors to her repeated failures. Based on the team's recommendations, a revised and individualised treatment plan was designed. Patient was started on oral HCQs 400mg per day and oral prednisolone 20mg per day.

After 6 months of the patient being treated for immune factors, an IUI cycle was planned. Stimulated with Tamoxifen and gonadotrophins. Patient was continued on oral HCQs, oral prednisolone and vitamin E 1g/day. On Day 15, TVS was done, endometrial thickness was 13.9mm-Triple line, LO- 3 dominant follicles + (19.5mm, 19mm,17mm) Inj Fertigyn 10000IU IM given. On the day of ovulation trigger, Tacrolimus, an immunomodulatory agent was introduced.

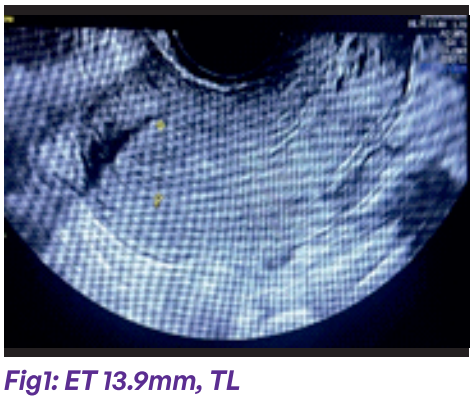

Fig1: ET 13.9mm, TL

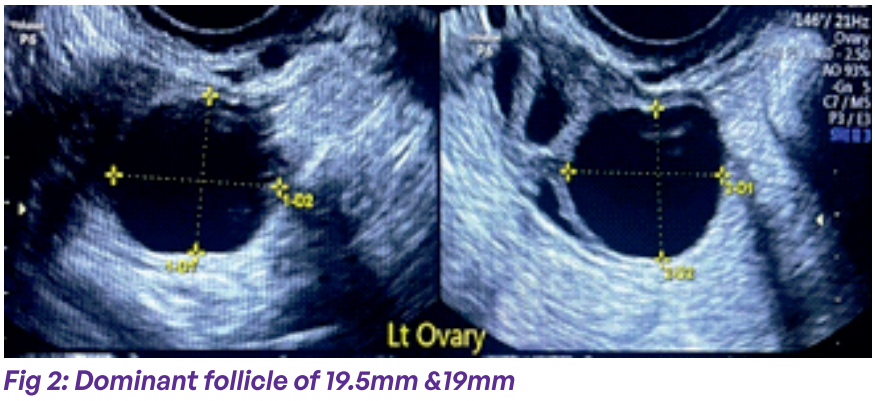

Fig 2: Dominant follicle of 19.5mm &19mm

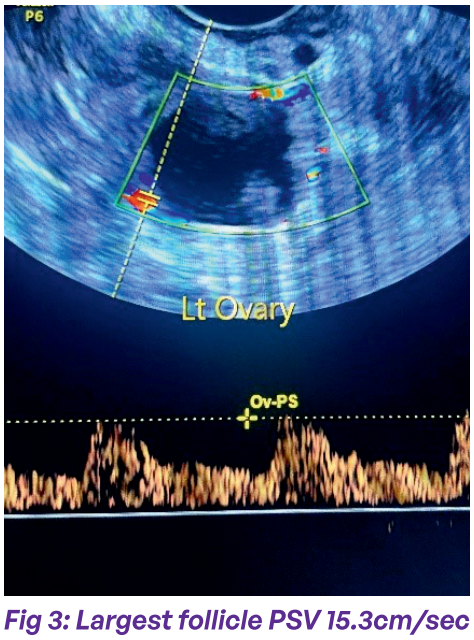

Fig 3: Largest follicle PSV 15.3cm/sec

Luteal phase support with micronized vaginal progesterone 1200mg/dl per day was given.

Unlike her previous high-tech ART attempts, this cycle- a simple, well-timed IUI with immunomodulation drugs proved to be transformative. Within two weeks, her serum β-hCG was positive marking the long-awaited success. Immediately after confirmation of the pregnancy, patient was transfused with intralipid injections 2 doses- 3 weeks apart, and G-CSF given subcutaneously weekly for 4 weeks, Tacrolimus was tapered monthly with monitoring of renal function tests and serum Tacrolimus levels, stopped by 10th week of pregnancy. Today, she carries a healthy foetus at 5th month of pregnancy with pride.

CONCLUSION

After the weight of repeated failed IVFs, all it took was a quest into science and correction of the underlying cause by a multidisciplinary team. The immunological work-up helped identify the cause behind failed the IVFs. Thus we can we see that persistence, a multi disciplinary approach and science can together effectively address complex challenges and lead to positive results. While IUI with immunosuppression may not be effective for all patients, it presents a straightforward and potentially viable approach for managing recurrent implantation failure, offering renewed hope for individuals navigating this challenging fertility landscape.

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