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# Pregnancy with Oocyte Donation and In-vitro Fertilization in a Woman with Premature Ovarian Failure

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**A twenty eight year old nulliparous Bahraini lady, presented with four years history of primary infertility and thirteen years history of secondary amenorrhoea. A diagnosis of premature ovarian failure was made. She was advised to take hormonal replacement therapy in order to get monthly withdrawal bleeds and the dose was adjusted, so as to mimic as closely as possible the ovarian steroid profile in a normal ovulatory cycle. She had two trials of ovarian stimulation but no response was seen. Finally the couple decided to go through with an in-vitro fertilization (IVF) treatment using oocyte donation. Pregnancy resulted and proceeded well. Gestation was terminated at the 33rd week by caesarean section and two healthy infants were delivered.**

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Premature ovarian failure affects approximately 1% of all women at 40 years and 0.1% at 30 years and decreases with age[1]. Sexuality, fertility and menopause can occur in quick succession in women with premature ovarian failure[2]. Infertility is therefore another major problem. Spontaneous pregnancy may occur only with a normal karyotype but is unpredictable and rare[2]. The current treatment for this type of infertility is oocyte donation. This is the first case reported from Bahrain and is presented here to highlight its presentation, diagnosis, management and the obstetric outcome.

## THE CASE

A twenty eight year old Bahraini lady, presented to our outpatients clinic with four years history of primary infertility and thirteen years history of secondary amenorrhoea. She had attained the menarche at the age of 13 years. She had always had scanty and infrequent periods and she stopped having spontaneous menstruation 2 years after menarche. She remained persistently amenorrheic since then. She did not have any withdrawal bleeds either with progestogens alone or with its combination with oestrogens. Her sense of smell was normal and she was not taking any medication. There was no significant medical or family history.

Her husband was 41 years old and found to be fit and healthy. He had never fathered

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any children before. They live together and had no difficulty with coitus, which occurred 2-3 times weekly. His semen analysis was reported as normal.

On examination, she was in good physical and mental health. Her weight was 76 kg and height was 165 cm. She had normal secondary sexual characteristics and no clinical evidence of hypothyroidism or adrenal hypofunction. She had no hirsutism or voice change and no evidence of galactorrhea. There was no abnormality on abdominal examination. Her vulva, vagina and cervix were of normal appearance and bimanual pelvic examination showed a small, mobile, anteverted uterus with no palpable adnexal masses.

An ultrasound scan of the pelvis showed a normal sized uterus with no abnormal pelvic masses. However, the ovaries could not be demonstrated on several examinations. Her plasma prolactin was 154 mu/L, follicle stimulating hormone was 69.0 iu/L, luteinizing hormone was 74.6 iu/L and oestradiol was <30 pmol/L. These levels were similar to those measured one, two and six years earlier. Her thyroid and adrenal function tests were unremarkable. Buccal smear for sex chromatin revealed the presence of Barr bodies and chromosome analysis showed an apparently normal female karyotype (46 XX).

A diagnostic laparoscopy was performed which revealed an infantile uterus and streak ovaries with bilateral patent fallopian tubes. An ovarian biopsy from both ovaries was done and this confirmed the absence of any follicle.

A diagnosis of premature ovarian failure was made and the patient was put on Progyluton (Cyclo-Progynova) tablets but she failed to have any withdrawal bleeds. Therefore, it was changed to oestradiol valerate (Progynova) 1-2mg daily throughout a 28-day cycle, with maximum dosage on days 10-13, and progesterone pessaries (Cyclogest) on day 15-26, so as to mimic as closely as possible the ovarian steroid profile in a normal ovulatory cycle. She had two trials of ovarian stimulation but no response was seen.

The couple was anxious and adamant that they wanted to have children. Therefore, oocyte donation was discussed. At the beginning they were reluctant due to religious, social and legal implications but finally they decided to go through it in extreme secrecy.

They were referred to a tertiary center outside Bahrain for assisted reproduction techniques (oocyte donation and IVF). The patient was stimulated with Progynova tablets, Oestrogen patches and Cyclogest pessaries for six months in order to prepare the endometrium for implantation. A potential donor was advertised for through the egg donation programme and hence an anonymous donor was used.

Nine eggs were collected from the donor and seven were inseminated with the patient's husband's sperm and fertilized with conventional IVF. Of the seven embryos four have been frozen and three were replaced into the patient's uterus. The replaced embryos were all at the 4-cell stage and graded 4/4, 4/4 and 3/4. The embryo transfer was performed under ultrasound guidance and it was uncomplicated. Three weeks later the pregnancy test was fortunately positive and she was advised to

continue with Progynova tablets, Oestrogen patches and Cyclogest pessaries until 12 weeks of gestation.

She returned to Bahrain and attended the antenatal booking clinic at 7 weeks gestation. Ultrasound scan showed twin pregnancy and a repeat scan 4 weeks later confirmed the diagnosis. The patient continued to be seen fortnightly in the antenatal clinic. The fetal growth was monitored by serial scans which confirmed that both fetuses were growing well.

The pregnancy progressed uneventfully and she was normotensive until the beginning of 32 weeks gestation, when she developed pregnancy-induced hypertension. Urinalysis was normal. Pitting oedema of her ankles was elicited. She was therefore admitted to hospital and started on Aldomet tablets. Haematological investigations were normal including her platelet count and coagulation profile. Liver and renal function tests were also normal.

She remained in hospital until 33 weeks gestation, when she had premature uterine contractions with spontaneous rupture of membranes. The first fetus presented by breech and an emergency lower segment caesarean section was therefore decided and performed.

The first infant was a female weighing 1.880 kg with Apgar scores of 9 and 10 at 1 and 5 minutes. The second infant was a male weighing 1.980 kg with Apgar score of 9 and 10 at 1 and 5 minutes. Both infants were transferred to special care baby unit in view of prematurity. The puerperium was uneventful. She was normotensive and her Aldomet tablets were stopped. She went home along with both infants on the 11$^{th}$ postnatal day.

## DISCUSSION

The criteria for diagnosis of premature ovarian failure are more than four months of amenorrhoea, with two serum follicle stimulating hormone values >40 iu/L taken four months apart in women less than 40 years of age[2]. The absence of ovarian follicles on the biopsy confirms the diagnosis, but it is not usually necessary because it will not affect the future management[3]. The aetiology of the vast majority of these cases is difficult to define. In a recent review of 323 women with premature ovarian failure the causes were[4]: Idiopathic 59%, Turner's syndrome 23%, Iatrogenic 10%, familial premature ovarian failure 4%, galactosaemia 2% and 46XY gonadal dysgenesis 2%.

One of the main clinical concerns of premature ovarian failure is the effect of hypo-estrogenism on young women, resulting in an earlier risk of cardiovascular disease and osteoporosis[2-3]. Therefore, hormone replacement therapy should be offered as soon as the diagnosis is made[3]. This patient had been diagnosed and treated rather late and her previous hormonal treatment had obviously been inadequate. Therefore, the larger dose of oestrogens in combination with progestogen was the treatment of choice in this case to overcome her hypo-oestrogenised condition.

In women with normal karyotype, spontaneous pregnancy and recovery of ovarian function with ovulation is unpredictable and may occur in less than 10% of cases[2]. Oocyte donation has now become a widely used and successful method of treating

infertility[5-13], especially in women with premature ovarian failure or those who are carriers of a genetic disorder. The major difficulties associated with an oocyte and embryo donation programme are the availability of donated oocytes and embryos together with the need for synchronization of ovarian cycles in donor and recipient[9].

Just as sperm donation is the only remedy for couples where the man is azoospermic, oocyte donation is the only way of producing a pregnancy for couples where oocytes are not available[9]. This was indeed the case in this patient whose ovarian biopsies confirmed the absence of any follicle and also failed to respond to two trails of ovarian stimulation. However, this method is not accepted in our country due to religious, social and legal implications but if the couple decided to go through with this, it has always been shrouded in secrecy.

Pregnancies resulting from oocyte donation are unique since they are immunologically foreign to the recipient. Majority of the studies concerning obstetric outcome have suggested that ovum donation pregnancies should be considered obstetrically high risk[14-15], especially those with ovarian failure because of the increased incidence of small-for-gestational age infants in these pregnancies[15]. They are also at higher risk of miscarriage, pregnancy-induced hypertension, pre-eclamptic toxaemia and postpartum haemorrhage, which can be very severe. These complications are not associated with the age of the recipient and younger women receiving oocyte donation should also be considered as high risk patients as well as those who are of older age[15].

Pados et al[14] found that pregnancy-induced hypertension and threatened miscarriage occurred in one-third of women in their series of the first trimester. A maternal death due to subarachnoid haemorrhage associated with pregnancy-induced hypertension was reported in 1991[16]. Antinori et al. in 1993[17] reported one case of severe hypertension in 21 term pregnancies in menopausal women.

There is a tendency for obstetricians to perform caesarean sections in women who have undergone assisted conception, especially with ovum donation, but in the majority these were for obstetric reasons: 18% were associated with pregnancy-induced hypertension and 17% were because of malpresentaion[15]. This was indeed the case in our patient who developed pregnancy-induced hypertension at 32 weeks gestation with breech presentation of the first fetus. Moreover, she developed premature uterine contractions with spontaneous rupture of membranes, which is an indication for an emergency caesarean section.

Considering all these complications that may occur in oocyte donation pregnancies, all these pregnant women should be cared for by a consultant obstetrician. They should be appropriately counselled about these complications and they can expect an excellent outcome, provided they have good medical care and cared for in centres that can supervise high risk pregnancies[15].

## CONCLUSION

**Women suffering a premature ovarian failure should be offered a balanced hormone replacement therapy as soon as a diagnosis is made in order to overcome their hypo-oestrogenised state and prevent its consequences.**

**Although oocyte donation has now become a well established method of treating infertility especially in women with premature ovarian failure, it is not accepted in our country due to religious, social and legal implications. However, the women who become pregnant following oocyte donation should be considered obstetrically as high risk and managed accordingly.**

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