The First Frozen Embryo Donation Pregnancy for Hypergonadotrophic Hypogonadism in Singapore – Hormonal Profile and Obstetric Outcome

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Summary

This is the first report in South East Asia of a singleton frozen embryo donation pregnancy for hypergonadotrophic hypogonadism. The hormonal profile was compared with that of a control group of normal uncomplicated singleton pregnancies in Singapore. The plasma ßhCG levels were lower compared to those of our normal uncomplicated singleton pregnancies at 2 to 3 weeks after the embryo transfer but became comparable at 4 to 5 weeks after embryo transfer. The successful vaginal delivery and the obstetric complications developed in this case are discussed.

Key Words: Frozen embryo, Embryo donation, Pregnancy, Hypergonadotrophic hypogonadism, Hormonal therapy

Introduction

With the success of the first frozen embryo donation pregnancy in 1987, frozen embryo donation has been an alternative to oocyte donation. It helps to minimise the problem arising from the shortage of donor oocytes as most IVF patients preferred to have the excess oocytes fertilised and resulting embryos frozen for their subsequent cycles. Besides, it eliminates the need of synchronisation between donor and recipient cycles. This case report illustrates a case of a oocyte recipient with hypergonadotrophic hypogonadism who had waited several years for oocyte donation, finally conceived and delivered after frozen embryo donation. It is the first case report in South East Asia.

Case Report

Mdm K N M is a 44-year-old Chinese housewife married to a 40-year-old Chinese businessman. She was amenorrhoeic for 3 years. Bilateral tubal blockage was diagnosed on laparoscopy by a private gynaecologist consultant.

Investigations in our hospital confirmed menopause. Plasma FSH was 41.7 iu/l and oestradiol was 29 pg/ml.

She was counselled and opted for embryo or oocyte donation programme. Cyclic steroid replacement therapy (CSRT) with oestradiol valerate tablets (Progynova, Schering AG, Germany) and progesterone vaginal pessaries (produced by Pharmacy Department, National University Hospital, Singapore) were administered as previously reported[1] (Ref). Endometrial biopsy taken on day 21 of the second CSRT cycle corresponded to day 19 to 20 of the endometrial cycle.

A donor aged 34 consented to donate her excess frozen embryos to other infertile couples. Three frozen embryos (4 cells to 8 cells stage, 3-day-old) were transferred transcervically on 24th August 1994, the

third day of progesterone vaginal pessary administration. Her plasma ßhCG became positive (6.3 miu/ml) on 1st Sept 1994. She was given daily progesterone by intramuscular injection 100mg and vaginal pessaries 400mg. The oral oestradiol valerate tablets were also increased to 10mg per day. The hormonal profile is shown in Table I.

Ultrasound examination confirmed a viable intrauterine singleton pregnancy on 21st September 1994. The measurements corresponded to 6 weeks of gestation.

The hormonal support has been slowly and finally withdrawn at 19 weeks of gestation. A scan for foetal abnormality done at 22 weeks of gestation showed no foetal abnormality and all the ultrasound parameters of foetal growth were within normal ranges. At 29 weeks of gestation, she developed moderate aproteinuric pregnancy-induced hypertension controlled with methyldopa 250mg thrice daily. She had a premature labour with mild abruption at 31 weeks of gestation. A baby boy weighing 1.2 kg was delivered vaginally with apgar scores of 6, 8 and 9 at 1, 5 and 10 minutes respectively. The mother was discharged well after 2 days. The baby was discharged well after 6 weeks.

Discussion

In addition to providing an alternative to oocyte donation, embryo donation programme also solves the problem of indefinitely freezing excess embryos derived from in-vitro fertilisation programmes. It is however not common because of its limited availability and fresh embryo donations are still more common than frozen embryo donations. The success of frozen embryo transfer is usually lower when compared to fresh embryo transfer ie. 20% against 39%.

In well established ART centres, the number of frozen embryos stored from excess embryos resulting from in vitro fertilisation is increasing. They are sometimes left in storage because the couple has already achieved their desired family size or they have lost interest in conception. This case illustrates an option for couples who are motivated to help other couples and provides a solution for increasing problems of storage of embryos, which are no longer wanted by the patients.

Maternal complications in oocyte donation pregnancies include multiple gestation, pregnancy induced hypertension, intrauterine growth retardation, placenta praevia, preterm labour and higher Caesarean section

Table I
Plasma β hCG levels (miu/ml) of the patient, in comparison to those from group of normal uncomplicated singleton pregnancies in Singapore

Gestation	Patient	Normal Singleton (Median; 0.25 – 2 M) (Number)
4 5	6.4 262	> 17,168; 429–34,336 (n = 21)
6 7	7618 15,043	> 38,259; 957–7,6590 (n = 40)
8 9	60,100 81,800	> 177,098; 4,427–354,196 (n = 31)
10 11	68,900 54,200	> 186,242; 4,656–372,484 (n = 19)
12 13	60,100 63,100	> 128,005; 3,200–256,010 (n = 8)

rate[2]. Pre-eclampsia of 17 to 33% and Caesarean section rate of 64% to 82% are quoted[2]. However, there was no differentiation made between fresh oocytes or frozen embryo pregnancy. In this case, in addition to the pre-eclampsia, the mild abruption may be an additional causative factor for the preterm labour.

It has been shown that relaxin is deficient in premature ovarian failure patients pregnant while on the oocyte donation programme. This may suggest the origin of the relaxin in pregnancy is mainly secreted from the ovarian tissue (possibly corpus luteum) even though other sites like decidua, placenta, myometrium have been postulated. Contrary to the conventional belief, its presence may not be important for successful vaginal delivery as illustrated in this case and others[3]. In its absence or deficiency, oestrogens and prostaglandins may induce cervical ripening, while prostaglandins, progesterone and oxytocin (or even catecholamines) may be involved in induction of uterine contractions. The exact physiological role played by relaxin remains unclear. With more experience, it is likely that the high Caesarean section rate can be reduced. The recent theory of relaxin stimulating the production of nitric oxide, leading to dilatation of microvessels and depression of platelet aggregation might be one of the theories to explain the higher pre-eclampsia rate in oocyte donation pregnancy in the absence of a corpus luteum.

The serum ßhCG, oestradiol and progesterone levels of this patient were shown in Table I. In our department, the serum ßhCG levels between 4 and 12 weeks of gestation in normal, uncomplicated, singleton pregnancies were collected (Table I). It appears that the serum ßhCG levels in this frozen embryo pregnancy initially was lower than the medians in the normal conception. The discrepancy was obvious between 2 and 3 weeks after the embryo transfer (or 4 to 5 weeks of gestation). The levels were below 3000 miu/ml (compared to median 17,268 miu/ml in the normal samples). The discrepancy diminished at 4 to 5 weeks post embryo transfer (6 to 7 weeks of gestation). Similar observations in frozen embryo and fresh oocyte donation pregnancies has been reported. More observations are needed before a final conclusion can be drawn as to whether all frozen embryos produce ßhCG at a slower pace initially and whether the frozen embryo needs some momentum to regain its speed of development as in the normal uncomplicated singleton pregnancy. It is tempting to postulate that the initial number of cells surviving the freezing and thawing is less and therefore needs time to divide to adequate number of cells.

Finally, compared to our previous report of fresh oocyte donation pregnancy, the gestation at which the exogenous oestradiol and progesterone were withdrawn is similar to this frozen embryo donation pregnancy. It was said that the luteo-placental shift occurs around 60 days of gestation. However in a clinical situation, the decision to tail off the replacement is usually guided by the increase of plasma hormonal levels with the same amount of exogenous hormonal replacement. In the past, it was suggested daily plasma hormonal assays were done for 2 weeks after the withdrawal of exogenous hormones. However in our experience, twice weekly monitoring of the hormonal levels is adequate. Provided the plasma progesterone levels are maintained over 40 ng/ml, it is our experience that, there is no miscarriage from the withdrawal of hormonal support in all our oocyte or embryo donation pregnancies in hypergonadotrophic hypogonadism patients.

References

1. Chan C, Bongso A, Goh V, Devendra S, Ratnam SS. The first oocyte donation pregnancy home-bred and illustrate simplified oocyte donation programme. No more embryo freezing, synchronisation or disruption of social life. Sing Med J 1992;33 : 401-3.

2. Pados G, Gamus M, Van-Steirteghem A, Bonduelle M, Devroey P. The evolution and outcome of pregnancies from oocyte donation. Hum Reprod 1994;9 : 538-42.

3. Eddie LW, Cameron IT, Leeton JF, Healy DL, Renou P. Ovarian relaxin is not essential for dilatation of cervix. Lancet 1990;336 : 243.