Treatment and preservation at the extremes of reproductive age: a case report outlining the ethical dilemmas

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Abstract

Purpose The purpose of the study was to report a livebirth from a cryopreserved embryo created from autologous oocytes collected at 47 years and 9 months that outlines the ethical difficulties of decision-making at the extreme of reproductive age.

Methods The method used was IVF and embryo cryopreservation within an assisted conception unit prior to adjuvant cancer treatment in a nulliparous patient diagnosed with breast carcinoma (47 years and 9 months at oocyte collection).

Results A 47-year-old nulliparous woman was diagnosed with breast malignancy during work-up for fertility treatment. Ovarian stimulation yielded one embryo from four oocytes that was cryopreserved to allow completion of adjuvant treatment. Subsequent embryo transfer cycle led to a live birth of a healthy baby girl at term, weighing 3.37 kg.

Conclusion This paper demonstrates the oldest reported age of autologous oocyte collection to have achieved a livebirth. In women where most would consider treatment futile, we highlight the difficulties in decision-making in this group of patients.

Keywords Advanced maternal age · Autologous oocytes · Fertility preservation · Frozen transfer

Capsule The decision to treat at the upper extremes of reproductive age can be ethically difficult but success possible even deemed potentially futile.

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Introduction

The decision to provide or withhold fertility treatment to those at the extremes of reproductive age involves a complex interplay of emotional, psychological, ethical and on occasion financial factors. This can be further complicated where factors beyond the supposed “futility” of treatment also exist such as the effect of an oncological diagnosis and the desire for fertility preservation.

Within the context of fertility services, the ethics committee of the American Society for Reproductive Medicine (ASRM) suggest that treatment is “futile” where the desired physiological goal is live birth and there is no or virtually no reasonable likelihood that this goal will be achieved through the proposed treatment [1]. Quantitatively, “futility” was defined as a <1 % chance of achieving a livebirth. However, any decision to deny treatment to those at extremes of reproductive age, especially those with seemingly good markers of ovarian reserve, is complicated by a lack of a defined age cut-off above which autologous oocytes from premenopausal women will be completely futile [1].

The continuous attrition of oocytes within the human female ovary begins in utero. From approximately 6–7 million oocytes at 20 weeks gestation, by birth 1–2 million remain and 400–500,000 are present at puberty [2]. Thereafter, through the years of reproductive function, a small proportion will be destined for ovulation whilst the majority undergoes apoptosis. Alongside this quantitative decline, there is an age-related increase in oocyte aneuploidy as a likely consequence of segregation errors during meiosis [3] and a postulated deterioration in the dominant oocyte selection process that leads follicles to mature that earlier in the reproductive lifespan would have undergone atresia [4].

As a consequence, even allowing for altered sexual behaviour with age, it is clear that fecundity decreases with

increasing female age [5]. Within the context of assisted reproduction, a similar negative effect of age on pregnancy outcome is demonstrated. The percentage of cycles started in the USA that result in livebirths decreases from 41.5 % at <35 to 31.9 % at 35–37, 22.1 % at 38–40, 12.4 % at 41–42, 5.0 % at 43–44 and 1.0 % at age 44 [6]. This is mirrored in the UK, where all cycles and outcomes performed are reported, as a licensed condition of continued practice, to the Human Fertilisation and Embryology Authority (HFEA [7]. At the extremes of age, where cycle numbers become low, accurate data on outcome is limited with studies of women over 45 undergoing IVF demonstrating no live births [8, 9].

Recent studies have stimulated the debate as to the potential benefit of frozen embryo transfer as a viable alternative to fresh embryo transfer [10]. Although a negative effect of ovarian stimulation on optimal endometrial preparation as a mechanism for improved pregnancy outcome [11] and a benefit on perinatal outcome [12] with frozen embryos has been reported, this, as of yet, does not translate to clinical practice. Both UK and US datasets continue to demonstrate an impaired livebirth rate in frozen transfers compared to fresh where data can be compared by age at egg collection [6, 7].

We present a report that demonstrates a livebirth from a single frozen embryo created from autologous oocytes collected at 47 years and 9 months of age in a woman undergoing treatment for a breast carcinoma. The combination of advanced or extreme reproductive age, the need for embryo freezing for fertility preservation purposes and the subsequent need for frozen transfer outline the potential “futile” nature of her treatment and therefore highlights the difficult decision-making process in such a group of women.

Methods

A case report of an individual patient within an assisted reproduction clinic is presented. As a case report, this did not require Institutional Review Board approval, but was reported with the patient’s informed consent.

Results

A 45-year-old woman initially presented in January 2010 with a 1-year history of subfertility, having had a previous first trimester miscarriage at 5 weeks gestation in September 2009. She had regular cycles with no significant gynaecological symptoms or history (previous laparoscopy with normal tubal patency and no pelvic pathology identified). Of note, in her past history was a diagnosis of chronic urticaria and idiopathic anaphylaxis.

Her partner had three children from a previous relationship with no past history of note. Neither partner smoked, and their

alcohol intake was between 10 and 15 units (UK unit equivalent to 8 g of alcohol) per week.

Initial investigation demonstrated normal pelvic anatomy on transvaginal scan with an antral follicle count of 8 and normal sperm parameters. An endocrine profile demonstrated an FSH of 11.8 iu/l, LH 8.7 iu/l, estradiol of 60 pmol/l and anti-Müllerian hormone (AMH) of 4.20 pmol/l (0.59 ng/ml). Although these markers were suggestive of an ovarian reserve better than average for age [13], she was counselled on the age-related decline in oocyte quality and strongly advised to proceed with oocyte donation but remained keen on initial conception attempts with her own oocytes.

She conceived with a first cycle of ovulation induction with clomiphene citrate but suffered a further first trimester miscarriage, managed surgically, at 7 weeks gestation. Thereafter, further cycles of follicular tracking (to January 2011), one of which with gonadotrophin stimulation, with timed intercourse proved unsuccessful.

She represented in February 2012 to discuss an attempt at IVF, as oocyte donation remained an option they did not wish to pursue. She was strongly counselled of “negligible” chances of success, an AMH repeated and any potential trial of stimulation delayed to April due to work-related travel commitments. The AMH result demonstrated a drop to 0.73 pmol/l (0.10 pg/ml) and as a consequence she was again counselled of the likelihood of “the fertility drugs having little or no effect over and above what your body is achieving”.

Whilst considering her options, routine mammography (recommended in all undergoing fertility treatment over 45 within our unit as national screening programme begin at 50) demonstrated an abnormality in the left breast subsequently diagnosed as malignant. She underwent breast-conserving surgery (wide local excision) and sentinel node biopsy in April 2012. Histology demonstrated complete excision of a small Grade II infiltrating ductal carcinoma within a bed of low/intermediate grade ductal carcinoma in situ with a total volume of 45 mm. The sentinel node was clear of disease, and the immunophenotype was oestrogen and progesterone receptor positive, HER-2 negative and had a very low Ki-67 score of 5 %. In view of the many positive prognostic indicators, chemotherapy was not required but adjuvant endocrine therapy and local radiotherapy was recommended which was to commence in June 2012.

In view of the upcoming endocrine therapy and need to delay any pregnancy (however conceived), a single cycle of ovarian stimulation and embryo freezing was planned after multidisciplinary discussion between the reproductive endocrinology and oncology teams. Using an antagonist protocol and 300 iu recombinant FSH (rFSH, Gonal-F®, Serono Europe, UK) for stimulation, 4 oocytes were collected (at maternal age 47 years and 9 months) after 16 days of stimulation and one achieved normal fertilisation using IVF. One of the four fertilised abnormally (three pronuclei), and the other two found

to be in metaphase-I on stripping. The one embryo was cryopreserved on Day 1 post-oocyte collection at the pronuclear stage. The option of genetic testing and later freezing was also addressed but in view of the risk of mosaicism and damage from biopsy, this was not carried out.

Following cessation of tamoxifen in mid 2013, and after unequivocal support from the oncology team, a natural cycle frozen embryo cycle was scheduled in April 2014. Follicle tracking demonstrated normal unifollicular growth and endometrial thickening to 10.6 mm. Ovulation was triggered, and vaginal progesterone (Cyclogest®, 400 mg bd; Shire Pharmaceuticals) commenced 3 days later. As per unit protocol, unprotected intercourse was abstained from as from the beginning of the treatment cycle. Her single embryo was thawed on the day of progesterone commencement and cultured overnight. An uncomplicated embryo transfer under abdominal ultrasound guidance of a 4-cell Grade II (Graded I–V: Grade I as top quality) embryo was performed using an 18-cm Wallace Sure View Embryo Transfer catheter.

A positive pregnancy test was demonstrated 12 days following embryo transfer. Following an uneventful obstetric course, a baby girl was delivered by Caesarean section at 39 weeks gestation weighing 3.374 kg.

Discussion

This paper demonstrates the oldest reported age of autologous oocyte collection to have achieved a livebirth at 47 years and 9 months. Furthermore, this livebirth was from a single cryopreserved embryo following a cycle of ovarian stimulation performed for fertility preservation purposes.

The quality of reporting of ART outcomes worldwide remains variable as a consequence of the lack of consistency amongst regulatory bodies. Even within the USA, the Society of Assisted Reproductive Technology (SART) that maintains standards and report data has over 90 % but not all clinics as members. Within the UK, the accurate data provision to the HFEA is a regulatory requirement of continued clinic practice. As such, the patient data we have presented is verifiable and, to our knowledge, this is the oldest age at autologous oocyte collection to achieve a livebirth reported in the literature. One study of a series of 288 women aged 45 or over to use autologous oocytes demonstrated only livebirth success in women no older than 45 and who produced at least five oocytes [9]. The oldest age at livebirth previously reported was 46 years [14], but from a fresh cycle where 7 oocytes collected and four embryos transferred.

The ASRM suggest that fertility treatment is “futile” where the desired physiological goal is live birth and there is no or virtually no reasonable likelihood that this goal will be achieved through the proposed treatment [1] and quantitatively define “futility” as a <1 % chance of achieving a live birth.

The decision to proceed with treatment within this context is complicated by differing perceptions between clinician and patient of risk and potential benefit. A patient may perceive the <1 % chance of success along with the feeling of closure given by having tried all reproductive options is enough to proceed with treatment. Within the framework of ethical decision-making in medicine, this highlights the patient’s right to autonomy having had all risks and potential benefits and likelihood of success explained and these decisions respected. In contrast, a clinician will have a duty to balance the potential complications of treatment against this negligible success rate. The bedrock of medical ethics, nonmaleficence, requires healthcare providers to avoid causing harm to their patients. Within the field of reproductive medicine, this is especially pertinent where the doctrine of “double effect”, where a beneficial treatment intended for good unintentionally causes harm, particularly applies.

As well as the risks of ovarian stimulation and oocyte collection, studies are consistent as to the increase in perinatal (pre-eclampsia, maternal hypertension, preterm labour, perinatal mortality) and maternal risks (operative delivery and maternal morbidity and mortality) with advanced maternal age at delivery (50 years and 3 months in this case [15–18]). Specifically assessing the more extremes of maternal age, Laopaiboon et al. [15] demonstrated adjusted odds ratios of 3.7 for a severe maternal adverse outcome (defined as a maternal death or a maternal near-miss up to 7 days after giving birth) and 1.6, 1.9 and 2.1 for a low Apgar score at delivery, perinatal mortality and stillbirth in women 45 or over at delivery. Schimmel et al. [16] demonstrated a significant increase in maternal hypertension (7.3 vs. 4.7 %), maternal diabetes (11.7 vs. 1.2 %), emergency operative delivery (0.9 vs. 0.3 %) and preterm delivery (5.2 vs. 4.0 %) in those between 43 and 47 compared to those 24–27. Data from the EUROCAT registries of congenital anomaly demonstrate that although overall congenital anomalies increase with age, there is no significant increase in non-chromosomal anomalies [19]. This confirms that oocyte age and therefore chromosomal aneuploidy rather than maternal age at delivery is the main driver behind such an increased anomaly risk.

Within the NHS, respect for the last of the four principles of medical ethics, justice, leads to treatment being withheld at the extremes of maternal age where outcomes are deemed too low to warrant the use of scarce resources. However, within the private sector, justice is less well served where the need of individual clinics to maintain their success rates often outweighs patient autonomy.

The ASRM ethics committee concludes that clinicians may ethically offer treatment “they deem futile if, in their professional judgement, they believe the couple or individual will receive some psychological benefit from proceeding” (ASRM, 2012).

In the context of this clinical case, the patient had been appropriately counselled of the “futility” of treatment (namely success rate of <1 % and no clinic or national success at this age or markers of ovarian reserve). Despite this, with oocyte donation not an option that they were open to, the use of autologous oocytes remained a desired option. The unexpected diagnosis of a breast malignancy and the subsequent delay required prior to conception whilst undergoing adjuvant therapy affirmed the decision to treat. In essence, ovarian stimulation and embryo cryopreservation (even at almost 48) conferred this “psychological benefit” by maximising potential future fertility chances and perhaps offering the only chance of future success (however slim). Furthermore, from the patient’s perspective, the presence of a cryopreserved embryo offered considerable hope and comfort and acted as a vital coping-mechanism during her period of adjuvant cancer treatment and convalescence.

In conclusion, we have presented a case reporting the oldest autologous oocyte to produce a livebirth complicated by the need for embryo freezing of the single fertilised embryo in an oncology patient. Although this success should not actively encourage the routine treatment of women of advanced reproductive age, it demonstrates potential success when treatment may be deemed, and will remain deemed, futile and outlines the difficulties faced for both clinical and patient in deciding whether to offer or proceed with treatment with autologous oocytes.

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