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ARTICLE

Is it acceptable to destroy or include human embryos before day 5 in research programmes?

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Abstract Day-3 poor-quality embryos (PQE) from IVF–embryo transfer cycles are usually destroyed or are included in research programmes. Knowing that these embryos have the ability to evolve to the blastocyst stage and yield embryonic stem cell lines, this study postulated that they could also give rise to live births. This is a prospective study including 186 IVF–embryo transfer candidates who had obtained at least one supernumerary PQE on day 3. PQE were kept for extended culture and high-quality blastocysts were frozen. A total of 620 PQE were eligible for the study, 217 (35.0%) reached the blastocyst stage and 73 (33.6%) were frozen. Blastulation rates were 7-fold higher (OR 7.29, 95% CI 5.01–10.61) in embryos compacted on day 4. Of the frozen blastocysts, 40 were thawed during 33 thawed blastocyst transfer cycles, which led to 10 clinical pregnancies. These pregnancies resulted in five miscarriages and five healthy live births at full term. PQE may achieve their development to the blastocyst stage, be frozen–thawed and harbour reasonable implantation potential. These results, thereby, raise an ethical issue regarding the fate reserved to PQE.

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KEYWORDS: PQE, embryo wastage, blastulation, implantation, live-birth rate, ethical practice

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Introduction

Since the first human embryonic stem cell lines reported by Thomson et al. (1998), numerous cell lines have been derived from human blastocysts. The self-renewing potential of these cell lines provides an unlimited source for regenerative medicine (Hwang et al., 2013; Lan et al., 2013; Trounson, 2001). Currently, three sources of embryos are used for stem cell establishment: (i) residual human poor-quality embryos (PQE) obtained from IVF programmes (Reubinoff et al., 2000) and unsuitable for fresh embryo transfer and cryopreservation because of decreased morphological criteria (Chen et al., 2005; Lerou et al., 2008; Taei et al., 2013; Yang et al., 2013; Zhang et al., 2006); (ii) frozen embryos unwanted for reproductive purposes (Cowan et al., 2004; Galan et al., 2013; Li et al., 2010; Niakan and Eggan, 2013); and (iii) genetically affected embryos provided by preimplantation genetic diagnosis programmes (Aran et al., 2012; Ben-Yosef et al., 2008; Frydman et al., 2009; Mateizel et al., 2006; Pickering et al., 2003). Many authors have proposed the use of PQE as a potential source for increasing the number of embryos available for research and have reported the derivation of human embryonic stem cell lines with variable efficiency (Chen et al., 2005; Fan et al., 2010; Lerou et al., 2008; Liu et al., 2009, 2011; Lysdahl et al., 2006; O'Leary et al., 2011, 2012; Qian et al., 2007; Shetty and Inamdar, 2012; Taei et al., 2013; Yang et al., 2013; Zhang et al., 2006).

PQE represent 'spare' embryos discarded from IVF—embryo transfer cycles because of their supposed impaired developmental and implantation potential. The definition of PQE is based on morphological appearance (Alikani et al., 1999; Giorgetti et al., 1995; Hardarson et al., 2001; Ziebe et al., 1997). However, the criteria for the definition of PQE may be subject to discrepancies (Paternot et al., 2011). A consensus has been recently established (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011) to prevent subjective appreciation of embryo morphology. Indeed, day-3 embryos harbouring >25% fragmentation and/or evidence of multinucleation and/or no stage-specific cell size for the majority of cells are considered as PQE. Although this consensus indicates which embryos may be scored as poor quality, no recommendation is given concerning their fate and it is likely that they are frequently destroyed or included in a research programme. Academic and legal documents make no mention of the important decision-making process that results in an embryo being labelled as 'spare'.

In many countries, couples having undergone IVF—embryo transfer may consent to destroy surplus day-3 PQE or donate them to research. In this case, it cannot be known how these embryos may have evolved. This study postulates that PQE may have the ability to evolve to the blastocyst stage and give rise to live births. This study analyses the development potential and outcome of 620 PQE kept for extended culture in terms of live births and discusses in which cases an embryo can be discarded, either for destruction or for research protocols.

Materials and methods

Study group

This prospective study included 186 couples enrolled in IVF—embryo transfer cycles from May 2010 to December 2011 in the academic centre of Clamart, France. This investigation received the approval of the internal Institutional Review Board (Form EN43V1, approved the 16th March 2010). Females were 21—42 years of age and underwent ovarian stimulation and egg retrieval for IVF—embryo transfer with or without intracytoplasmic sperm injection (ICSI). Informed consent summarizing the IVF, ICSI, extended culture and embryo freezing procedures as well as the possible inclusion of their PQE in a research programme was obtained from all couples.

The inclusion criteria were couples who signed informed consent and had obtained at least one supernumerary PQE according to Istanbul consensus recommendations (severe fragmentation, >25%) and/or cell size not stage specific and/or evidence of multinucleation). Patients were only included once during the study period. Exclusion criteria were: (i) no surplus PQE; or (ii) surplus PQE with <5 cells on day-3.

Ovarian stimulation

Women underwent ovarian stimulation as previously described (Genro et al., 2011) and gonadotrophin doses were adjusted according to the usual criteria of follicular maturation. Administration of human chorionic gonadotrophin (HCG; 10,000 IU i.m.; gonadotrophine chorionique 'Endo'; Organon Pharmaceuticals, Saint-Denis, France) was performed when follicles recruited exceeded 17 mm in diameter and oestradiol concentrations per mature follicle were higher than 300 pg/ml. Oocytes were retrieved 36 h after HCG administration by transvaginal ultrasound-guided aspiration.

Fertilization and embryo culture

Cumulus—oocyte complexes were washed and preserved in 3 ml IVF medium (Origio, Lyon, France) until sperm preparation. According to usual sperm parameters, conventional IVF or ICSI was performed when necessary. Fertilization was determined by confirmation of the 2 pronuclei (2PN) and polar bodies 17—19 h after microinjection insemination on an inverted microscope TE 300 (Nikon, Champigny sur Marne, France). Zygotes with normal fertilization were then individually cultured in droplets (40 μl) of ISM1 culture medium (Origio) covered by mineral oil at 37°C under 5% CO_2 until the second day of embryo development.

At the cleavage stage, embryos were scored on the basis of number and stage-specific cell size, fragmentation rate, multinucleated blastomeres and development kinetics between days 2 and 3 according to the consensus on embryo assessment (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Embryos with severe fragmentation (>25%), and/or cell size non-stage-specific and/or evidence of multinucleation were

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