Reproductive BioMedicine Online (2014) **28**, 475–484

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ARTICLE

The human first cell cycle: impact on implantation

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Dr Jesus Aguilar has been the Director of the IVF laboratory in IVI Vigo since 2011. He received his PhD in biology in 2008 from the Universidad de Jaén, Spain. Dr Aguilar has held embryologist positions in different clinics since 2003, and received the Basic Science Award for Oral Presentation at the 29th Congress of Spanish Fertility Association in 2012. The primary area of his research is embryology and analytical quality specifications. He has published several articles and book chapters.

Abstract The morphology of fertilization events has been related to successful implantation by subjective criteria (pronuclei score, pronuclei symmetry and position). This work first described these events by time-lapse technology and then compared the timings of fertilization events (second polar body extrusion, first and second pronuclei appearance, abuttal and fading) in implanted versus nonimplanted embryos in a 2-year cohort retrospective study. A total of 1448 transferred embryos from 842 patients undergoing intracytoplasmic sperm injection with oocyte donation were monitored, 212 embryos from treatments where the number of gestational sacs matched the number of transferred embryos and 687 embryos from treatments no biochemical pregnancy was achieved. The timings at which second polar body extrusion (3.3—10.6 h), pronuclear fading (22.2—25.9 h) and length of S-phase (5.7—13.8 h) occurred were linked successfully to embryo implantation. The other parameters were apparently not related, as determined by image acquisition and time-lapse analysis.
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KEYWORDS: cell cycle, early fertilization events, known implantation, pronuclei, S-phase, time-lapse

Introduction

Identification and selection of embryos with the highest implantation potential while avoiding multiple pregnancies (Beuchat et al., 2008) is a major objective of IVF laboratories worldwide. Elective single transfer has been suggested as the most successful method of accomplishing this (Cutting et al., 2008).

Over the last 30 years, most laboratories have routinely selected embryos on the basis of morphological characteristics, which have been continuously refined by studying the pronuclear stage and morphology, the symmetry,

http://dx.doi.org/10.1016/j.rbmo.2013.11.014
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fragmentation and multinucleation of the blastomeres and the ultimate morphology and in-vitro ability to progress to the blastocyst stage (Alikani et al., 2000; Baczkowski et al., 2004; Gardner et al., 2004; Neuber et al., 2003; Scott and Smith, 1998; Tesarik and Greco, 1999; Trounson et al., 1981).

Conventional embryo scoring depends on analysis of embryo morphology at predefined time points along the path of embryo development to obtain the most valuable information of embryo viability and implantation potential, but amongst these predetermined check points, there is a wealth of information that is not used. Time-lapse technology offers the possibility of observing the entire progression of embryo development, overcoming the limitations of the traditional periodical observations. In fact, morphokinetics has recently been proposed as an additional selection tool due to its strong relationship with other morphological parameters, and several studies support its link with in-vitro and in-vivo embryo viability (Chamayou et al., 2013; Ciray et al., 2006; Cruz et al., 2011, 2012; Hesters et al., 2008; Lemmen et al., 2008; Lundin et al., 2001; Meseguer et al., 2011a; Mio and Maeda, 2008; Pribenszky et al., 2010; Sakkas et al., 1998; Shoukir et al., 1997; Wong et al., 2010) and even with the ploidy of embryos more recently (Campbell et al., 2012, 2013; Chavez et al., 2012).

Fertilization includes the extrusion of the second polar body (PB), the appearance and fading of the pronuclei (PN) or the PN syngamy, events that frequently happen before or after the conventional first embryo observation performed at 16—22 h post insemination, frequently remaining unidentified when the assessment is performed at fixed time points. These events and their timings have previously been described by Payne et al. (1997). Following discrete zygote observation under light microscopy, fertilization was assessed, and pronuclear score also assisted embryo selection. The latter is a matter of controversy: some studies endorse the prognostic effect of pronuclear evaluation for embryo viability and chromosomal normalcy (Ebner et al., 2003; Garello et al., 1999; Gámiz et al., 2003; Montag and Van der Ven, 2001; Scott et al., 2000; Senn et al., 2006; Tesarik and Greco, 1999) while other studies have not been able to establish any correlation (Bar-Yoseph et al., 2011; James et al., 2006; Weitzman et al., 2010).

As far as is known, the present study provides the largest-ever description of the dynamics of the first cell cycle in human zygotes using time-lapse imaging. Moreover, the main fertilization events are related with the in-vivo developmental ability, by evaluating all transferred embryos with known implantation data and correlating the morphokinetic parameters of the fertilization events with implantation rate and ongoing pregnancy using a time-lapse system.

Materials and methods

The research was conducted at the Instituto Valenciano de Infertilidad (IVI) in Valencia and Vigo. All procedures and protocols were approved by the institutional review board in 2008, which regulates and approves clinical use of IVF procedures for research at IVI (ref. no. 0711-C-034-MM, approved 28 October 2008). The project complies with the Spanish law governing assisted reproductive technologies (14/2006).

The study was based on 1448 transferred embryos developed from normally fertilized oocytes supplied by 842 patients undergoing intracytoplasmic sperm injection (ICSI) cycles from the oocyte donation IVF programme between July 2009 and January 2012: 435 patients from IVI Vigo and 407 from IVI Valencia. Embryos were studied by time-lapse analysis, where the exact timing of the fertilization events cited below were evaluated in hours post insemination by ICSI.

Embryo implantation was confirmed by ultrasound scanning for gestational sacs with fetal heart beat after 7 weeks of pregnancy. Only embryos from treatments where the number of gestational sacs matched the number of transferred embryos (full implantation; $n = 212$) and embryos from treatments where no biochemical pregnancy was achieved (no implantation; $n = 687$) were included in the study; these embryos were defined as KID (known implantation data; Alikani et al., 1999). Treatments with partial implantation ($n = 549$ embryos) were excluded because it was not possible to determine which of the two transferred embryos implanted. It is still possible that certain embryos may split into two, in which case about 2% of the matches may be erroneous as reported (Knopman et al., 2010). This potential error must be taken into account in the KID analysis as a small bias.

Ovarian stimulation in oocyte donors

All donors were selected from the IVI oocyte donation programme. The donor selection criteria were as set out in Garrido et al. (2002) and in compliance with Spanish law (14/2006).

The mean age of the recipient was 38.4 years (range 24—50). All donors had normal menstrual cycles lasting between 26 to 34 days, body mass index 18—28 kg/m^2, no endocrine treatment (including gonadotrophins and oral contraception) for the 3 months preceding the study, normal uterus and ovaries at transvaginal ultrasound (no evidence of polycystic ovary syndrome) and an antral follicle count >20 on the first day of gonadotrophin administration after down-regulation with gonadotrophin-releasing hormone (GnRH) agonist (Meseguer et al., 2011b). Prior to the ovarian stimulation, the pituitary was down-regulated using GnRH agonist protocols (Melo et al., 2010).

Ovarian stimulation was carried out as previously described (Meseguer et al., 2008). Human chorionic gonadotrophin (HCG, Ovitrelle; Serono Laboratories, Madrid, Spain) was administered subcutaneously when at least eight leading follicles reached a mean diameter of $\geq$18 mm. Transvaginal oocyte retrieval was scheduled 36 h later. Protocol for endometrial preparation of recipients was performed according to Meseguer et al. (2008, 2011b).

Oocyte recovery, ICSI and embryo culture

Follicles were aspirated 36 h after HCG administration and oocytes were washed in Global w/HEPES (LifeGlobal, Canada) and cultured in Global for fertilization (LifeGlobal) at 37.0°C under a 6.0% CO_2 and 20.0% O_2 atmosphere for 3 h

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