EGP: expected gametes performance evaluated by blastocyst culture, a new standard to define “response” from a holistic viewpoint

Nicolas H. Zech · Pierre Vanderzwalmen · Astrid Stecher ·
Dietmar Spitzer · Barbara Wirleitner

Received: 24 April 2013 / Accepted: 17 May 2013 / Published online: 31 May 2013
© Springer Science+Business Media New York 2013

Expectation is the root of all heartache

William Shakespeare

Counseling couples regarding in vitro fertilization (IVF) therapy is a difficult task, particularly when estimating their chances to conceive. Take-home baby rates in a fresh cycle, cumulative pregnancy rates, and probability of surplus embryo cryopreservation are generally discussed. The basis to estimate what patients can expect is on one hand the patient's history, female hormone levels, and sperm parameters of the male partner. On the other hand important impacts can be anticipated from previous attempts. Based on the number of developing follicles and the number of retrieved oocytes, patients are grouped into different types of responders as follows: “normal responder” if the expected number of oocytes for a specific age group is reached, “low responder” or “high responder” if the number of oocytes is below or above this threshold, respectively. However, because this terminology only reflects ovarian reserves and response to hormonal stimulation, it is questionable whether it is tangible enough to provide the patient with meaningful predictions.

Capsule Introduction of EGP, combining ovarian response, gametes quality, fertilization, and embryo development to day 5, will redefine evaluation of IVF-success and quality control.

N. H. Zech (✉) · P. Vanderzwalmen · A. Stecher · B. Wirleitner
IVF Centers Prof. Zech—Bregenz, Römerstrasse 2,
6900 Bregenz, Austria
e-mail: n.zech@ivf.at

P. Vanderzwalmen
Centre Hospitalier Inter Régional Cavell (CHIREC),
Braine-l'alleud, Bruxelles, Belgium

D. Spitzer
IVF Centers Prof. Zech—Salzburg, Innsbrucker Bundesstr. 35,
5020 Salzburg, Austria

Furthermore, there are many other parameters that can be included for analysis, such as an increasing number of additional hormonal and immunological values, antral follicle count, detailed morphological analysis of the oocytes, 2PN scoring, sperm fine morphological conspicuities detected by motile sperm organelle morphology examination (MSOME), and DNA-integrity of the sperm nucleus. Morphokinetic analysis provides insights into fertilization patterns and developmental kinetics. In the future, techniques at the molecular level, such as proteomics, metabolomics, genomics or transcriptomics, will be introduced as routine aspects in development evaluations. After embryo transfer, additionally implantation rates and ongoing pregnancy rates can be added. In the end, we have a large pool of information that has to be combined to create a complete picture.

This situation leads us to the question, whether outcomes can be sufficiently predicted using these single parameters and taking into account ovarian response and endometrium receptivity to medication on one hand and sperm quality on the other hand in a rather non-linked manner. Isn't it time for a more holistic view by merging female and male factors in a new way? Our intent was to introduce a new component that already combines the majority of the above mentioned factors in order to facilitate counseling and better estimate expectations: ovarian response, oocyte and sperm quality, the fertilization process, and embryo developmental potential.

We identified blastocyst outcome as an easily applicable common denominator. With more than 15 years of experience in blastocyst culture, over 25.000 IVF cycles with blastocyst transfer, and experience in implementing new technologies, such as intracytoplasmic morphological selected sperm injection (IMSI) and aseptic vitrification, we think it is now time to change our way of thinking and counseling patients. During the first 5 days, embryos develop as a result of a harmonic interplay between maternal and

Table 1 Case descriptions

Case A: A 33-year-old female with a 42-year-old male partner, mild oligozoospermia, and secondary idiopathic sterility after biochemical pregnancy.

Cycle outcome: 7 oocytes obtained at pick-up; 6 mature oocytes; all 6 were fertilized (FR 100 %); 5 good quality blastocysts on day 5; transfer of 2 blastocysts (B1 5BA, B1 4AB) and birth of one boy; cryopreservation of 3 blastocysts.

Semen analysis: 2.6 ml; 11 Mio/ml; progressive motility: 57 %; IMSI report: 8 % Class I, 51 % Class II, and 41 % Class III sperm.

Case B: A 35-year-old female with a 38-year-old male partner, normozoospermia, and primary sterility by obstruction of the fallopian tubes.

Cycle outcome: 11 oocytes obtained at pick-up; 10 mature oocytes; all fertilized (FR 100 %); 1 blastocyst (fB1 c); transfer of 1 blastocyst; no pregnancy in this cycle.

Semen analysis: 3.5 ml; 18.4 Mio/ml; progressive motility: 55 %; IMSI report: 0 % Class I, 25 % Class II, and 75 % Class III sperm.

Case C: A 34-year-old female with a 37-year-old male partner, paraplegic, oligoasthenozoospermia, and primary sterility.

Cycle outcome: 16 oocytes obtained at pick-up; 13 mature oocytes; 12 fertilized (FR 92.3 %); 5 blastocysts (4 good quality and 1 very low quality); transfer of 1 blastocyst (B1 2AB) and birth of one healthy girl; cryopreservation of 3 blastocysts.

Semen analysis: 1 ml; 2.5 Mio/ml; progressive motility: 5 %; IMSI report: 0 % Class I, 11 % Class II, and 89 % Class III sperm.

early as well as late paternal factors. One crucial step is onset of the embryonic genome between day two to day three. New techniques and sophisticated applied methods for optimizing the number of developing embryos to the blastocyst stage, such as oocyte activation, IMSI, application of different culture media, microfluidics, and innovative, well adapted incubators, are all reflected in these parameters. The “product” of this interplay is the blastocyst, which dissolves the entanglement of individual maternal and paternal parameters.

Implementation of blastocyst culture has led to new insights in assisted reproductive technology (ART). We know today that although we can achieve relatively constant fertilization rates (FR), and cleavage rates until day 3 of over 95 % using the above-mentioned techniques, on day 5 we often see unexpected results. Although some patients may be considered “poor responders” because they produce a low number of oocytes, we can still obtain a decent number of good blastocysts and vice versa. This knowledge leads us to conclude that the terminology used to predict individual chances of conception should be revised. In the future, we suggest that this will be done based on blastocyst development rather than the expected number of oocytes. Embryo

culture to the blastocyst stage provides a more holistic insight by combining ovarian response, oocyte quality and potential, early and late paternal influences, and the experience of clinicians and staff at the IVF laboratory. This parameter brings together complex single values into expressive data for improved prognosis.

Cycle outcome should be expressed as the number of (good quality) blastocysts obtained. According to this number, patients are classified by “expected gametes performance” (EGP). When grouping patients, empirical values are employed according to the stimulation protocol and age of the patients. Applying our clinical experience, we would consider patients between the age of 30–35 years as EGP when producing 4 to 5 blastocysts per fresh cycle, whereas 1 to 3 blastocysts should be expected in a patient age 39–42 years independent of the number of oocytes retrieved. Patients with a greater number of blastocysts are “above EGP”, whereas those with a lower number are “below EGP”. The experienced data are based on our optimized blastocyst culture protocol and patients with normal BMI and Caucasian background.

In this report, we describe three cases to illustrate application of the EGP classification. All of the women evaluated

Fig. 1 Classification of cases A, B, and C into prognosis groups based on number of oocytes (poor responder: 1–8 oocytes, normal responder: 9–12 oocytes, or high responder: >12 oocytes), fertilization rate FR

(%) classified as normal between 80 % and 100 %, or blastocyst outcome on day 5 (below EGP: 1–3 blastocysts, EGP: 4–5 blastocysts, or above EGP: >5 blastocysts)

were ages 30–35, stimulated with the long protocol, had FSH and TSH levels within the normal range, and underwent ICSI/IMSI (Table 1). In terms of responder groups, there was one low responder (case A), one normal responder (case B), and one high responder (case C; Fig. 1). A FR of more than 80 % was obtained for all patients. But when we evaluate outcome on day 5, the low responder (case A) was in the EGP group due to very good blastocyst development. In addition to a child from the fresh transfer, we cryopreserved 3 surplus blastocysts for this couple. The normal responder (case B) slipped to a “below EGP” as only one blastocyst was obtained, likely due to sperm parameters. Further, the high responder (case C) in terms of oocyte yield, only had 5 blastocysts and was ranked as “EGP”. Three blastocysts were vitrified for subsequent cryo-cycles. IVF clinics frequently calculate not only in terms of pregnancy rate per cycle, but rather in terms of cumulative pregnancy rates. By implementing blastocyst development as EGP, a more reliable prognosis for subsequent cryo-cycles can be made due to known blastocyst quality. In general, counseling becomes more sophisticated. These examples show that EGP provides significantly more valuable information compared to responder classes.

We are sure that EGP is useful for all patients, especially including those with diminished ovarian reserve, very low responders, or patients with a history of previous implantation failure(s). There is no reason not to go to the blastocyst stage and perform transfer on day 2 or 3. With blastocyst culture to day 5 we transfer the embryo into an optimally prepared uterine environment. It mimics best the physiological situation, *in vivo* the embryo travels down the fallopian tube until it reaches the uterus on day 5 or 6. Reduced occurrence of uterine contractions is measured on day 5 as

compared to day 3, and a lower rate of ectopic pregnancies is observed.

In ART, the primary goal is to achieve a viable and ongoing pregnancy as rapidly and safely for the patient as possible. The current question should be ‘How many live births are obtained from one stimulation cycle’ rather than ‘How many IVF cycles are necessary for a patient to give birth to one baby’. The vision is a “normal” response in terms of hyperstimulation after follicular superovulation, preventing women from experiencing symptoms of severe hyperstimulation syndrome, with a target take-home baby rate of 100 %. With EGP, we will no longer work toward producing as many oocytes as possible, but instead toward obtaining enough blastocysts to produce at least one baby.

To properly establish EGP benchmarks for distinct stimulation protocols and age groups, we propose consensus meetings where best practice EGP benchmarks are discussed and defined. This should be done based on the experiences of a large number of IVF centers. A task force on EGP with regular meetings should maintain current benchmarks and implement new techniques or medications. EGP standards would be valuable for counseling patients. In addition EGP is a precise and meaningful parameter in IVF laboratory performance that can easily be implemented in quality control.

In our opinion, EGP standards represent an essential step in ART. The ultimate vision is to link EGP with implantation potential, which is a combination of endometrium receptivity and embryo potential. Additional factors, such as environmental pollution, ethnicity, and the number and history of previous IVF attempts, should be integrated, just to mention a few. Establishing criteria and benchmarks for EGP will provide tremendously more insight into the chances of conception for individual couples.