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Treatment

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Examination of Early Cleavage and its Importance in IVF Treatment

P. Fancsovits, F. Z. Takács, G. Z. Tóthné, Z. Papp, J. Urbancsek

Since the introduction of assisted reproduction, the number of multiple pregnancies has increased due to the high number of transferred embryos. There is an urgent need for IVF specialists to reduce the number of embryos transferred without the risk of decreasing pregnancy rates. Embryos are selected for transfer on the basis of their developmental stage and morphology. The number of blastomeres of the embryo indicates the speed of early embryo development which correlates to the viability of the embryo. Examination of early embryo development, especially the timing of the first cleavage, can be recommended as a tool for predicting embryo viability. Observation of timing of the first cleavage and its different stages helps us to identify fast- and slow-developing embryos. Early pronuclear breakdown and early cleavage of the zygote are indicators of fast embryo development and good embryo viability. Thereby, they can lead to high implantation and pregnancy rates. The aim of this paper is to provide an overview of the timing of early embryo development and to show its significance in IVF treatment. *J Reproduktsmed Endokrinol* 2006; 3 (6): 367–72.

Key words: in-vitro-fertilisation, pronuclear breakdown, early cleavage, embryo quality, cell cycle

In-vitro fertilisation and embryo-transfer (IVF-ET) have been routinely used procedures in treating infertility for more than 20 years. Their efficacy has considerably increased since the first treatments. As a result of the more effective ovarian stimulation protocols, patients may produce more and more oocytes. With the introduction of new micromanipulation techniques we can achieve fertilization in cases of serious andrological infertility. With the improved embryo culture techniques, embryos of higher quality can be produced. As a result of the improvement of assisted reproductive technology the pregnancy rate per stimulation cycle reaches almost 30 % worldwide [1]. This success rate, which is similar to the chance of pregnancy with a single intercourse around the time of ovulation (25–30 %), can be reached by transferring more than one embryo. It results in a considerable increase in the frequency of multiple gestations which is known to be linked to an increased risk of foetal and maternal morbidity and mortality. The only way of reducing the frequency of multiple pregnancies is to transfer less but higher-quality embryos. Determining the embryo viability and selecting the most viable embryos for transfer is a great challenge in clinically assisted reproduction.

Many embryo transfer (ET) strategies for transferring two, or even one embryo have been published without obvious reduction in pregnancy rates [2–4]. These studies pointed out the way to reduce the number of multiple pregnancies in assisted reproductive treatments.

In IVF-ET treatment, it is well known that transfer of faster-developing embryos with a higher number of blastomeres results in higher pregnancy and implantation rates than transfer of embryos which have a lower cell number [5]. Embryo viability can also be predicted on the basis of their morphological characteristics, like equal size and uniform shape of blastomeres or amount of anuclear fragmentation within the embryo [6–8]. Complex embryo grading systems have been developed on

the basis of these findings and are routinely used by most IVF units [9–13]. Embryo selection is usually based on the results of morphological assessment performed on the day of embryo transfer. However, data of morphological assessment performed at earlier stages of development can provide additional information which can be used in the selection process.

The morphological characteristics of oocytes (e. g. appearance of cytoplasm, morphological features of the first polar body, size of the perivitelline space) are closely correlated to the embryo viability [14–18]. Morphological assessment of zygotes can also give some help in embryo selection. Equal number and symmetrical alignment of nuclear precursor bodies in pronuclei (PN) indicate better viability and higher implantation rates [19, 20].

Time elapsed between fertilisation and first cleavage can be examined easily and objectively. On the basis of this feature embryo viability can also be predicted. In spite of the fact that timing of cleaving stage in embryo development have been known for many years, assessment of early cleavage and its importance in the embryo selection procedure have become the centre of interest only in the past few years.

In our review, we discuss the methods and results of the assessments of first cleavage during *in-vitro* fertilisation.

Fertilisation and First Cleavage

Fertilisation outside the human body can be achieved by conventional *in-vitro* fertilisation or intracytoplasmic sperm injection (ICSI). Our knowledge about the timing of the first cleavage cycle of the human zygote is based on both the conventional IVF [20, 21] and the ICSI treatments [22]. Oocytes are pre-incubated for 1–6 hours before fertilisation to reach the required maturation. During conventional IVF treatment, oocytes are co-incubated with the appropriate number of motile sperms for 16–18 hours. Normal fertilisation is indicated by presence of two pronuclei within the cytoplasm and the extrusion of the second polar body (PB) to the perivitelline space. During ICSI treatment, oocytes are first enzymatically treated to remove cumulus cells. After denudation, a single sperm is injected into the cytoplasm of the oocyte.

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In the conventional method, the fertilisation process takes place in a similar way to natural fertilisation. Performing ICSI, several steps of sperm-oocyte interaction do not take place [23]. Following sperm penetration, the oocyte metabolism intensifies, second meiotic division is completed, a second PB is extruded, which denotes the beginning of the G₁-phase of the first cell cycle (Fig. 1).

Most of the zygotes enter the G₁-phase 3 hours after sperm penetration. Formation of male and female pronuclei begins in this phase as well. The decondensed nucleus of a sperm forms the male pronucleus while the nucleus of the matured oocyte forms the female pronucleus. Male and female pronuclei usually have the same size and they form simultaneously. The earliest time when pronuclei can be seen by light microscopy is 7–8 hours after insemination [24]. Formation of pronuclei is usually finished 8–14 hours after insemination [22]. The male pronucleus evolves near the place of sperm penetration while the female pronucleus forms next to the first polar body [24]. The G₁-phase terminates 8–14 hours after fertilisation and is followed by the S-phase during which the chromosomes replicate. DNA synthesis in the pronuclei begins 8–14 hours post-insemination and terminates 14–24 hours after fertilisation. Apposition of pronuclei in the centre of the cytoplasm is directed by the cytoskeleton of the oocyte. Nucleoli appear and align into the equatorial plane of the two pronuclei. DNA synthesis cannot be observed any more during the 5–6-hour long G₂-phase. The M-phase of the first cell cycle begins with the disappearance of pronuclei (pronuclear breakdown, PNBD) and lasts until completion of the first cell division. The duration of the M-phase is relatively constant, 3–4 hours. During this phase, the membranes of the male and female pronuclei dissolve, chromosomes become free and incorporate in the central region of the cytoplasm (syngamia), which is followed by the first meiotic cell division of the zygote. Contrary to some mammalian species, fusion of pronuclei is not preceded by the incorporation of chromatin in the human zygote (for reviews see: [21, 22, 24–27]).

Pronuclear breakdown in some oocytes can be observed 17 hours after conventional IVF using light microscopy.

However, the majority of oocytes enter the M-phase 24–30 hours after fertilisation. Cleavage can be completed after 20–33 hours but in most oocytes this phase lasts until 27–30 hours post-insemination [27, 28].

It has been shown that there can be up to 12 hours difference between faster- and slower-developing embryos in view of the timing of the first cell cycle. The timing of zygote development can be influenced by the method of fertilisation or by *in-vitro* culture conditions. However, it is presumable that intrinsic factors of the oocytes are also responsible for the differences in the timing of the first cell cycle. The method of fertilisation influences the length of time elapsed between fertilisation and first cleavage. Sperm penetration through zona pellucida and oolemma to the cytoplasm takes a few hours during conventional IVF treatment. During ICSI treatment, however, several steps of sperm-oocyte interaction do not occur. Consequently, oocytes fertilised by ICSI undergo PNBD and the first cleavage division approximately 2–4 hours earlier than oocytes derived from conventional IVF [27].

Assessment of the First Cleavage

The dynamics of development in a cleaving-stage embryo can be determined by counting the number of blastomeres. It is well known that faster-developing embryos with higher numbers of blastomeres at the time of embryo transfer have a better viability and higher implantation potential. Thus, transfer of such embryos during IVF treatment results in a higher pregnancy and implantation rate [5]. Based on these findings, Shoukir and colleagues (1997) were the first to demonstrate that transfer of embryos which had already completed their first cleavage cycle within 25 hours after conventional *in-vitro* fertilisation, resulted in a higher pregnancy rate than transfer of embryos prior to their first cleavage. They designated an embryo as “early cleavage” (EC) if it had cleaved into the two-cell stage within 25 hours post-insemination while those that had not yet cleaved were designated “non-early cleavage” (NEC) [29]. On this basis, many IVF laboratories introduced the

assessment of early cleavage in the embryo selection procedure. Sakkas and colleagues (1998) reported that transfer of EC embryos results in a higher pregnancy rate in ICSI treatment as well [30]. Since then, several authors have reported higher pregnancy rates (Tab. 1) for the transfer of early-cleaving embryos [31–44]. These observations confirm the assumption that early cleavage of a fertilised oocyte is a predictor of better embryo viability, and may thus be used as a selection factor in both conventional IVF [29] and ICSI treatments [30].

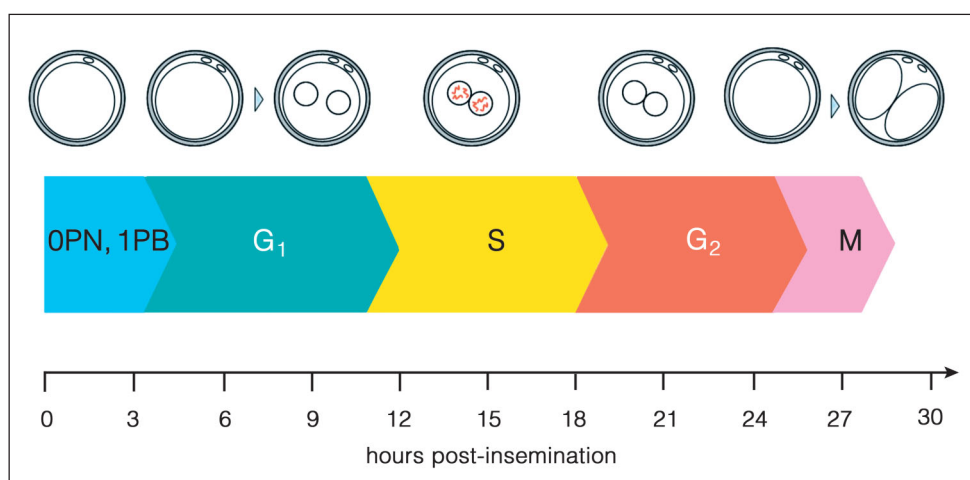


Figure 1. Timing of the first cell cycle of a human zygote. The upper figure line indicates the biological occurrence in oocytes from fertilization to first cleavage. Following sperm penetration, the second meiotic division is completed. After first polar body extrusion, the G₁-phase of the first cell cycle begins, in which male and female pronuclei appear. The G₁-phase is followed by the S-phase in which the chromosomes replicate. It is followed by the G₂-phase in which DNA synthesis cannot be observed any more. The M-phase of the first cell cycle begins with the disappearance of pronuclei and lasts until completion of the first cell division. OPN = no pronucleus; 1PB = one polar body; G₁, S, G₂, M: phases of cell cycle [Author permission granted by P. Fancovits]

It has also been shown that early-cleaved embryos have a faster development and better embryo quality than those with late cleavage. These embryos have a higher number of blastomeres and better morphology [34, 38, 39], and a higher proportion develops to the blastocyst stage [35, 40].

Most of the early cleavage studies compared the outcome of those IVF-ET cycles where at least one EC embryo was transferred to those cycles where only NEC embryos were transferred [29–31, 35]. In most EC cycles, early- and late-cleaved embryos were transferred simultaneously and we cannot ascertain which embryos were implanted and which were not. Thus, it is not easy to draw conclusions about the implantation potential of embryos transferred in these heterogeneous transfers. To solve this problem, some research groups compared the outcomes of homogeneous embryo transfers, where only early-cleaving or only late-cleaving embryos were transferred [33, 36–38]. These studies clearly demonstrated that transferring EC embryos results in a higher pregnancy (Tab. 1) and implantation rate (Tab. 2). Salumets and colleagues (2003) published a remarkable study [34] where they reported the results of 178 elective single-embryo transfer cycles. This study offered a good opportunity to analyse the effect of early cleavage on embryo viability and implantation potential. The number of good-quality embryos was higher, embryo development faster and clinical pregnancy rates almost doubled (50 % vs. 26.4 %; $p = 0.001$) (Tab. 1).

In the majority of studies, early cleavage status was not taken into consideration when embryos were selected for transfer. Thus, examinations where early cleavage was included in the embryo selection procedure are especially remarkable. These studies suggested that the embryo selection process should be determined by the result of early cleavage assessment [29–32]. So far, Sakkas and colleagues (2001) have been the only group to perform a controlled randomised study to demonstrate the importance of early cleavage assessment. After randomisation, embryos were selected for transfer on the basis of their early cleavage status in one IVF treatment group, while in the other treatment group embryo selection was based on the number of blastomeres and on embryo morphology assessed prior to transfer. Embryo selection based on EC status resulted in a significantly higher clinical pregnancy rate than selection based on the conventional morphological examination (clinical pregnancy rate: 47.7 % vs. 31.2 %; $p < 0.05$) [33]. The M-phase of the first cell cycle of human embryos began with the breakdown of the pronuclear membrane and was completed by the first cleavage. This is the only phase of the cell cycle which has a rela-

tively constant length. Thus, the pronuclear breakdown precedes the first mitotic division by 3–4 hours [27, 41]. From this stationary difference in the timing between PNBD and first cleavage we can conclude that zygotes with an earlier pronuclear breakdown will also pass the first cleavage earlier. On the basis of this finding, Neuber and colleagues (2003) distinguished different groups of zygotes: one with two clearly visible pronuclei (2PN), one whose pronuclei had already disappeared (PNBD) and one with embryos having passed their first cleavage (EC) at the time of early embryo development assessment [35]. They reported that embryos in both the PNBD and EC groups developed faster and a higher proportion reached the blastocyst stage during *in-vitro* culture, compared to embryos in the 2PN group. Wharf et al (2004), similarly to the previous study, classified the zygotes into 2PN, PNBD and EC groups [36]. They found that transferring embryos which had passed the pronuclear breakdown or cleavage early resulted in a higher implantation rate than transferring embryos which had intact pronuclei at the time of assessment of early embryo development (implantation rates: 2PN: 10.3 %; PNBD: 22.4 %; EC: 32.1 %; $p < 0.05$). In one of our recent studies (2005), we analysed the correlation between early embryo development and outcome of IVF treatments [41]. Our results clearly demonstrated that embryos showing pronuclear breakdown early (22–25 hours post-insemination) devel-

Table 1. Clinical pregnancy rates during IVF-ET treatment according to the early cleavage (review)

Clinical pregnancy rates (%)				p	Time of assessment (hours ¹)	Source
Early cleavage		Non-early cleavage				
9/27	(33.3)	17/119	(14.7)	0.045	25	Shoukir et al., 1997 [29]
14/54	(25.9)	2/34	(5.9)	0.04	27	Sakkas et al., 1998 [30]
23/42	(55)	8/32	(25)	0.02	25–27–29	Bos-Mikich et al., 2001 [31]
45/100	(45)	31/130	(23.8)	< 0.01	25–28	Sakkas et al., 2001 [33]
10/32	(31.3)	4/38	(10.5)	< 0.05	24.5–25.5	Fenwick et al., 2002 [40]
38/98	(38.8)	41/160	(25.6)	0.026	24–26	Tsai et al., 2002 [42]
36/72	(50)	28/106	(26.4)	0.001	25–27	Salumets et al., 2003 [34]
41/95	(43.2)	20/58	(17.2)	< 0.001	25–27	Wharf et al., 2004 ² [36]
36/97	(37.1)	7/68	(10.3)	< 0.001	23–28	Van Montfoort et al., 2004 [37]
26/63	(41.3)	16/80	(20)	0.0092	25–27	Windt et al. 2004 [39]
28/58	(48.3)	38/139	(27.3)	0.0045	22–25	Fancsoviets et al., 2005 ³ [41]

¹Time elapsed between fertilisation and early cleavage assessment; ²zygotes with disappeared pronuclei were excluded from the study; ³assessment of early pronuclear breakdown (PNBD)

Table 2. Implantation rates during IVF-ET treatment according to the early cleavage (review)

Implantation rates (%)				p	Time of assessment (hours ¹)	Source
Early cleavage		Non-early cleavage				
27/72	(23.6)	24/322	(7.5)	0.0001	25	Shoukir et al., 1997 [29]
21/150	(14)	3/93	(3.2)	0.01	27	Sakkas et al., 1998 [30]
28/152	(18)	9/115	(8)	0.024	25–27–29	Bos-Mikich et al., 2001 [31]
58/219	(25.5)	43/290	(14.8)	< 0.01	25–28	Sakkas et al., 2001 [33]
165/589	(28.0)	200/1057	(19.5)	< 0.0001	25–27	Lundin et al., 2001 [38]
15/70	(21.5)	5/83	(6.0)	< 0.005	24.5–25.5	Fenwick et al., 2002 [40]
62/333	(18.6)	62/534	(11.6)	0.004	24–26	Tsai et al., 2002 [42]
40/183	(21.9)	53/371	(14.3)	0.03	23–28	Neuber et al., 2003 [35]
60/187	(32.1)	12/117	(10.3)	< 0.001	25–27	Wharf et al., 2004 ² [36]
41/155	(26.5)	61/404	(15.1)	0.0019	22–25	Fancsoviets et al., 2005 ³ [41]

¹Time elapsed between fertilisation and early cleavage assessment; ²zygotes with disappeared pronuclei were excluded from this analysis; ³assessment of early pronuclear breakdown (PNBD)

oped faster and had a better embryo quality than embryos which passed the pronuclear breakdown later. Transferring only early-PNBD embryos resulted in a significantly higher pregnancy rate (47.4 % vs. 33.3 %; $p = 0.004$), clinical pregnancy rate (41.6 % vs. 28.0 %; $p = 0.005$) and implantation rate (19.5 % vs. 14.9 %; $p = 0.002$) than in those IVF cycles where only late-developing embryos were transferred. On the basis of our results, we concluded that assessment of early pronuclear breakdown, similarly to early cleavage assessment, can be a good predictor of better embryo development. Thus, the assessment of early pronuclear breakdown should be included in the scoring system to select the most viable embryos for transfer.

In most of the studies, the observations of early embryo development were performed in different periods, 25–27 hours after fertilisation in most cases (Tab. 1). Most authors agreed that this period is the most suitable for performing the assessment. However, Bos-Mikich and colleagues (2001) noticed that transferring embryos which cleaved 27–29 hours post-insemination resulted in a higher clinical pregnancy rate than those which cleaved later [31]. Only a small proportion of zygotes cleave before 25 hours post-insemination, while most of the embryos exhibit a 2-cell stage 28–29 hours after fertilisation. Assessing early embryo development in these periods, we can select too few or too many embryos for transfer. Thus, assessment of early cleavage in these early or late periods is not recommended [31, 41]. The authors of the above-mentioned studies performed the assessment of early pronuclear breakdown or early cleavage in the same period. However, there is a 3–4-hour difference between these two events of the cell cycle, which suggests assessing the early pronuclear breakdown and early cleavage at different times. Our own results show that

less than 20 % of zygotes show PNBD before 22 hours post-insemination while in more than 70 % of the zygotes the pronuclei had disappeared 25 hours after insemination. This means that an early PNBD assessment performed prior to 22 hours post-insemination results in too few embryos selectable for transfer, while an assessment performed later than 25 hours post-insemination results in too many embryos. These observations suggest that early pronuclear breakdown should be assessed between 22 and 25 hours after *in-vitro* fertilisation or microinjection [41].

Discussion

The simplest way to avoid multiple pregnancies is to transfer fewer embryos during *in-vitro* fertilisation. However, it can result in a decrease of the treatment's effectiveness. To avoid this reduction in pregnancy rate, we have to select those embryos for transfer which have the highest viability and implantation potential. In most IVF laboratories, embryos are selected on the basis of their morphology assessed on the day of embryo transfer. However, it is well known that data on oocyte and zygote morphology and assessment of early embryo development can also be used as an additional tool in embryo selection procedure. Timing of the first cleavage can be easily observed by light microscopy. Thus, it becomes the centre of interest in the development of more effective embryo selection protocols in human IVF treatment. However, the mechanism of early cleavage is not yet completely understood. The molecular and genetic conditions of gametes or the zygote are thought to have an effect on the duration of the first cell cycle. It is known that the cleavage cycles up to the 4–8-cell stage are controlled by the maternal genome [45]. Thus,

the genes and proteins inherited from oocytes can be responsible for the faster or slower development of the early embryo. The relationship between early cleavage and genetic constitution of the oocyte or embryo has also been confirmed by Anderson and colleagues [46]. Paternal factors can also play an important role in the dynamics of early embryonic development [47]. These findings indicate that early cleavage is a biological indicator of fertilisation with fitting gametes which requires less time for the cell cycle [44]. Therefore, a better embryo morphology and higher implantation rate can be observed when transferring embryos developed from these faster-cleaving zygotes.

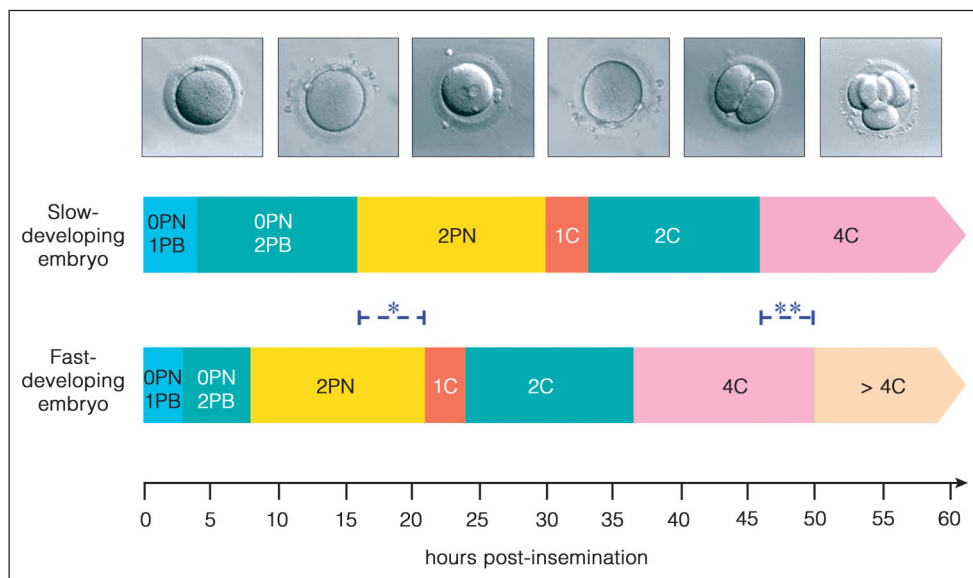


Figure 2. Comparison of the development of slow- and fast-cleaving embryos from fertilisation to the 4-cell stage. Pronuclear breakdown and first cleavage occur earlier in faster-developing embryos than in those with slow development. The time-span between the development of faster- and slower-developing embryos can be up to 8–12 hours. It can easily occur that faster- and slower-developing embryos have the same number of blastomeres at the time of morphological assessment performed before embryo transfer.

OPN = no pronucleus; 2PN = two pronuclei; 1PB = one polar body; 2PB = two polar bodies; 1C, 2C, 4C = 1-, 2- and 4-cell stage of the embryo; *Too early assessment of pronuclear breakdown does not help to distinguish early- and late-developing embryos. **Morphological assessment in the indicated period does not allow differentiation of early- and late-developing embryos. Assessment of early pronuclear breakdown or early cleavage can help to determine viability in case of embryos with similar morphological characteristics. [Author permission granted by P. Fancovits]

First cleavage is considered early when completed 25–27 hours after fertilisation. Early cleavage results in faster embryo development, better embryo morphology and a higher rate of blastocyst development. Transferring these embryos in IVF treatments results in a higher pregnancy and implantation rate. Besides several retrospective studies, a prospective randomised study also verifies that assessment of early cleavage can be used as a selection factor in the embryo selection process. Pronuclear breakdown precedes first cleavage by 3–4 hours and this interval between the two events of the cell cycle is relatively constant among different zygotes. Observation of pronuclear breakdown can also help us predict further embryo development and select the most viable embryos for transfer.

Early disappearance of pronuclei and early cleavage of zygotes are positive signs of dynamic development and better viability of embryos. Transferring these early-developing embryos also pre-indicates the favourable outcome of IVF treatments. Both pronuclear breakdown and first cleavage can be assessed using a normal inverted light microscope, which is one of the primary pieces of equipment in all IVF laboratories. These observations are not time-consuming and do not impair the viability of the embryos.

The optimal period for assessment of early pronuclear breakdown is 22–25 hours after fertilisation, while early cleavage can be best observed 25–27 hours post-insemination [31, 41].

By observing zygotes and cleaving embryos in different periods we can get an exact view of the dynamics of embryo development. Pronuclear breakdown and first cleavage occur earlier in faster-developing embryos than in those with slow development [33, 41]. The time-span between the development of faster- and slower-developing embryos can be up to 8–12 hours. However, it can easily occur that faster- and slower-developing embryos have exactly the same number of blastomeres at the time of morphological assessment performed before embryo transfer (Fig. 2). Furthermore, it is also possible that faster- and slower-developing embryos have similar morphological characteristics before embryo transfer. Observation of early pronuclear breakdown or early cleavage offers a valuable support in distinguishing between embryos – showing similar morphological characteristics – according to their viability.

Based on a thorough review of the literature, we can conclude that morphological assessment performed at different times during IVF treatment is able to show the dynamics of embryo development. At the same time, we have the possibility to observe some morphological characteristics of the developing embryo which are known to be efficient markers of embryo viability. Complex embryo selection strategies can be developed on the basis of this knowledge which can improve the efficacy of IVF treatment. Assessment of early embryo development will certainly be involved in these improved complex embryo selection systems.

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