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Study the effect of numbers of transferred embryos on pregnancy and abortion rates in day 3 and day 5 embryo transfer

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ABSTRACT

The goal of ART labs over the last ten years was to find embryos with the best chance of implantation. In order to improve selection and increase implantation rates, blastocyst stage transfers on day 5 become more frequent considering that morphology on day 3 embryos may not be a reliable indicator of pregnancy possibility. The current study aimed to assess the clinical outcomes of Day 3 ETs and Day 5 ETs and compare the effect of the number of transferred embryos in clinical pregnancy and early abortion rates performed on D3 and D5. A randomized controlled trial was performed with 200 women under 40 years with primary infertility undergoing ICSI. On day 3 and day 5 ET, participants were divided into two groups of 100 each. After ICSI and controlled ovarian hyperstimulation, ET was carried out under ultrasound monitoring. Clinical pregnancy rates and early abortion rates were among the outcome measures. The current results indicated that there were no significant differences among the two groups regarding sperm parameters, duration of infertility, oocyte retrieval. Day 5 transfers showed the highest clinical pregnancy (71.9%) followed by day 3 (46.9% and 50.0%). Abortion rates were highest on day 3 (50.0%) and lowest on day 5 (12.1%). It was concluded that Day 5 ET yielded the best pregnancy outcomes when compared with Day 3. Further prospective researches are essential to optimize ET numbers and enhance ART outcomes.

Keywords: Blastocyst, cleavage stage, clinical pregnancy, embryo transfer, Early Abortion rate.

INTRODUCTION

The evolution in assisted reproductive technology (ART) from early cleavage embryo transfer to blastocyst stage transfer has been made easier by developments in culture media (Glujovsky *et al*., 2022). Optimal embryo selection is made possible by delaying embryo transfer to later stages, which can greatly increase implantation rates and lower the frequency of multiple pregnancies (Gardner *et al*., 1998). The goal of ART labs is to choose the embryo that has the best chance of implantation in order to produce pregnancy. A high-quality embryo transferred often lowers the chance of multiple pregnancies, which involve dangers for the mother, fetus, and newborn (El-Toukhy *et al*., 2018). Depending on the stage of embryo development, embryo transfer can be carried either during the blastocyst stage (days 5–6) or at the cleavage stage (days 2-3) (Le Cruguel *et al*., 2013).

Transferring blastocysts on day five or six has been routine in many ART institutions over the past ten years, especially for patients who have a good prognosis (De Croo *et al*., 2020; Gardner and Balaban, 2016). The possibility of increased implantation rates is one benefit of blastocyst-stage transfer, which could have an impact on guidelines

controlling the quantity of embryos transplanted. The chance of multiple pregnancies can be decreased by transferring fewer embryos due to higher implantation rates (Kamath *et al*., 2020). The higher the implantation rate is, the lower the number of embryos is transferred. Additionally, a higher rate of clinical pregnancy and a lower rate of miscarriages are related to blastocyst transfer (Spangmose and Pinborg, 2020; Zilberberg *et al*., 2021).

Transferring cleavage-stage embryos into the uterus prior to fertilization may decrease the likelihood of a successful implantation and cause homeostatic stress (Gardner *et al*., 1996). This makes D3-ET less desirable in some circumstances as well as remains in alignment with studies showing greater implantation rates for blastocyst-stage transfers (Papanikolaou *et al*., 2006; Papanikolaou *et al*., 2005).

Therefore, the goal of this study was to assess the clinical outcomes of Day 3 ETs and Day 5 ETs. Also, to compare the effect of the number of transferred embryos in clinical pregnancy and early abortion rates performed on ETs on D3 and D5, through studying the implantation rates, clinical pregnancy rates, and early abortion rates.

MATERIALS AND METHODS

Ethics approval:

The written informed consent and the protocol was approved from the ethics committee at Research Ethics Committee, Faculty of medicine, Alexandria university, Egypt approved all experimental procedures (serial numbe:0108525). Participants submitted written, informed permission.

Confidentiality:

The privacy of each patient admitted for the study was preserved. No report or publication resulting from the project's data gathering will include the names of study participants. This study's procedures and techniques all adhere to the ARRIVE criteria.

Patients:

Patients with primary infertility and females under 40 years of age were allowed to participate in the study. On the day of oocyte retrieval, the number of fertilized oocytes, the number of mature oocytes, the day of transfer, and the number of transferred embryos were all randomly assigned. Over ten recovered oocytes were used in the study. There were two groups of patients; group (A): 100 patients underwent treatment with IVF and embryo transfer on day three, group (B): 100 patients received the same procedure on day 5.

Ovarian Stimulation Protocol

Each participant undergoing the GnRH agonist long protocol received a 14-day dose of triptorelin to induce pituitary down-regulation during the luteal peak time. After that, a basic assessment was performed by using an ultrasound and a hormone level blood test. On the day of the ultrasound examination, recombinant FSH (Gonal-F, Merck Serono) was used to start the medication. Patients under the age of 35 got two ampoules (150 IU) of (Gonal-F) per day, while those over the age of 35 received three ampoules (225 IU) of (Gonal-F) per day. For the first five days of stimulation, the dosage was determined. Following five days of treatment, a transvaginal ultrasonography B examination was conducted to track follicle development. The dosage of rFSH was then appropriately adjusted based on the size and the number of growing follicles.

ICSI and embryo culture:

When at least two follicles reached a mean diameter of 18 mm, final oocyte maturation was induced with 10,000 IU of human chorionic gonadotropin (HCG). Transvaginal ovum retrieval was performed 34 to 36 hours post-HCG administration after the preparation of semen using swim-up or gradient procedures. ICSI was used to inseminate matured metaphase II oocytes that had been processed chemically and mechanically to prepare them for injection. Embryos cultured in drops of global media

dishes covered by Nid oil. The presence of two pronuclei was used to measure fertilization (17–19) hours after insemination. Cleavage media was removed on day three, and blastocyst medium was added. According to the ESHRE Istanbul Consensus Conference, the development of the embryos was described on days three and five.

Embryo scoring criteria:

Prior to the embryo transfer, embryo grading was carried out using a 200× magnification Olympus microscope. The following three factors were used to determine the cleavage embryos' score. Fragmentation, symmetry, and blastomere number. The evaluation of the blastocyst involves assessing the quality of the inner cell mass (ICM), the trophectoderm (TE), and the stage of expansion. The blastocoel's volume and the properties of the ICM and TE cells are evaluated using the popular Gardner grading method (Gardner *et al*., 2000).

Embryo Transfer strategy and Luteal Phase Support:

Embryo transfer (ET) was conducted using transabdominal ultrasound guidance Embryo deposition typically occurs 1.5 to 2 centimeters below the uterine fundus. Embryos are selected for day 3 ET and day 5 ET according to morphology of embryos and patients' age. Each patient received a maximum of three embryo transfers. Luteal phase support involved the use of Crinone gel and dydrogesterone tablets, continuing until days 13–14 post-ET. Support was maintained until weeks 10–12 of pregnancy.

Outcome Measurement:

Pregnancy outcomes were defined according to the CSRM consensus on key indicators for quality control in ART clinical operatio**ns** (CSRM, 2018).

Clinical pregnancy rate: defined as the presence of gestational sac(s) by ultrasonography and high serum β-HCG 14 days after ET.

Early abortion rate: The percentage of the number of clinical pregnancy cycles to the number of spontaneous abortion cycles during the first 12 weeks of pregnancy, then multiplied by 100%.

Statistical analysis of the data:

The statistical analysis of the data was performed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp, released 2011). Categorical data were summarized as numbers and percentages. To compare between the two studied groups, the Chi-square test was used. However, when more than 20% of the cells had an expected count less than 5, the Monte Carlo correction was applied. For continuous data, normality was assessed using the Kolmogorov-Smirnov. Quantitative data were presented as range, mean, standard deviation, median and interquartile range (IQR). For normally distributed quantitative variables Student t-test was used to compare two groups, while for non-normally distributed quantitative variables the Mann Whitney test was used. The significance level for all statistical tests was set at 5%.

RESULTS

When comparing between the 2 groups (Day 3 and Day 5 ET) there was no significant difference observed with regard to sperm count, abnormality, and motility. Also, there was no significant difference between groups when comparing duration of infertility, number of retrieved oocytes. As regard to age of participants, there were no significant differences between groups as shown in Table (1),

The number of transferred embryos showed highly significant difference with P value (0.031). The highest number was detected among Day 3 transfer group, followed by Day 5. On the other hand, Day 5 transfer group showed the highest implantation rate (IR), followed by Day 3 transfer groups. As shown in table (2). The clinical pregnancy rate was significantly higher among Day 5 transfer group (70%)

then Day 3 transfer group (53.0%) with (P<0.013). Day 3 showed the highest abortion rate (49.1%) followed by Day 5 (22.9%) with P value <0.002 (Table 2).

In the comparison of number of transferred embryos, it was highest on Day 3 (n =266), while in day 5 the number of transferred embryos was 248. The proportion of triple embryo transfers (E3) was significantly higher on Day 3 compared to Day 5. This followed by E(2) then E (1) as shown in Table (3)

Table (4) presents the distribution of the number of transferred embryos among pregnancy cases on different embryo transfer days. In the Day 3 transfer group, 53 cases (53%) resulted in pregnancy. The highest pregnancy rate was observed with 3 embryos transferred (79.2%), followed by 2 embryos (17.0%) and single embryo transfers (3.8%). There was no statically significant difference between the two groups according to the number of transferred in pregnant cases (p=0.095).

For Day 5 transfer group, 70% of cases resulted in pregnancy, with the highest rate among those receiving 3 embryos (61.4%), followed by 2 embryos (28.6%) and single embryo transfers (10.0%). There was no statistically significant difference in the number of transferred embryos among pregnant cases across the two groups (p = 0.095). Table (5) shows that Day 3 has the highest abortion rate when compared to Day 5, whatever the number of transferred embryos (p = 0.833).

Table (1): Comparison between Day3 and Day5 according to different parameters.

	Day 3 (n = 100)	**Day 5 (n = 100)**	**Test of Sig.**	**p**
Age (years)				
Min. – Max.	29.0 – 39.0	28.0 – 39.0	t= 1.751	0.081
Mean ± SD.	34.84 ± 3.07	34.16 ± 3.14		
Median (IQR)	35.0 (32.0 – 37.50)	33.50 (31.0 – 37.50)		
Sperm Count				
Min. – Max.	1.0 – 250.0	3.0 – 200.0	U= 4452.50	0.181
Mean ± SD.	61.82 ± 64.54	47.47 ± 51.47		
Median (IQR)	42.50 (10.0 – 85.0)	30.0 (10.0 – 67.50)		
SP abnormality				
Min. – Max.	85.0 – 99.0	90.0 – 100	U= 4828.50	0.671
Mean ± SD.	94.60 ± 4.14	94.85 ± 3.90		
Median (IQR)	95.50 (93.50 – 97.0)	96.0 (93.0 – 97.0)		
Motility				
Min. – Max.	1.0 – 94.0	1.0 – 95.0	U =4987.50	0.976
Mean ± SD.	43.78 ± 32.04	43.12 ± 29.29		
Median (IQR)	40.0 (12.50 – 72.50)	40.0 (15.0 – 70.0)		
Duration of infertility (years)				
Min. – Max.	1.0 – 19.0	1.0 – 17.0	U= 4742.50	0.528
Mean ± SD.	7.12 ± 4.37	7.27 ± 3.87		
Median (IQR)	7.0 (3.0 – 9.50)	7.0 (4.0 – 10.0)		
Number of retrieved oocytes				
Min. – Max.	11.0 – 30.0	12.0 – 40.0	U= 4679.0	0.431
Mean ± SD.	16.47 ± 4.89	16.96 ± 5.18		
Median (IQR)	15.50 (12.0 – 20.0)	15.50 (13.0 – 18.0)		
Number of M2				
Min. – Max.	7.0 – 25.0	4.0 – 30.0	U= 4579.50	0.302
Mean ± SD.	11.97 ± 4.15	12.57 ± 4.53		
Median (IQR)	11.50 (8.0 – 14.0)	12.0 (10.0 – 15.0)		

IQR: Inter quartile range SD: Standard deviation U: Mann Whitney test
t: Student t-test p: p value for comparing between the studied groups

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Table (2): Comparison between the different days according to the number of transferred embryos.

	Day 3 (n = 100)	Day 5 (n = 100)	Test of sig.	p
Number of transferred embryos	**266**	**248**		
Min. – Max.	1.0 – 3.0	1.0 – 3.0		
Mean ± SD.	2.66 ± 0.61	2.48 ± 0.67	U= 4262.00*	0.031*
Median (IQR)	3.0 (2.0 – 3.0)	3.0 (2.0 – 3.0)		
Implantation rate (%)				
Min. – Max.	33.33 – 100.0	33.33 – 100.0		
Mean ± SD.	58.17 ± 25.68	71.50 ± 23.84	U= 3489.00*	<0.001*
Median (IQR)	50.0(33.33–66.67)	66.67(50.0–100.0)		
Pregnancy rate	**53 (53.0%)**	**70 (70.0%)**	□□□ □□□□□*	0.013*
Abortion rate	**26 (49.1%)**	**16 (22.9%)**	□□□9.207*	0.002*

IQR: Inter quartile range SD: Standard deviation U: Mann Whitney test

χ^2: Chi square test p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

Table (3): Comparison between the Day 3 and Day 5 according to the number of transferred embryos,

	Day 3 (n = 100)	Day 5 (n = 100)	□□	p
Number of transferred embryos	**266**	**248**		
E (1)	7 (7%)	10 (10%)		
E (2)	20 (20%)	32 (32%)	5.016	0.081
E (3)	73 (73%)	58 (58%)		

χ^2: Chi square test p: p value for comparing between the studied groups

Table (4): Comparison between the different days according to the number of transferred embryos in pregnant cases.

Number of transferred embryos	No of pregnant cases		χ^2	p
	Day 3 (n = 53)	Day 5 (n = 70)		
	No. (%)	No. (%)		
Pregnancy				
E (1)	2 (3.8%)	7 (10.0%)		
E (2)	9 (17.0%)	20 (28.6%)	4.702	0.095
E (3)	42 (79.2%)	43 (61.4%)		

χ^2: Chi square test p: p value for comparing between the studied groups

Table (5): Comparison between the different days according to the number of transferred embryos in abortion cases,

Number of transferred embryos	Number of Abortion		χ^2	p
	Day 3 (n = 26)	Day 5 (n = 16)		
	No. (%)	No. (%)		
Abortion cases				
E (1)	6 (23.1%)	3 (18.8%)		
E (2)	9 (34.6%)	5 (31.2%)	0.250	0.833
E (3)	11 (42.3%)	8 (50.0%)		

χ^2: Chi square test p: p value for comparing between the studied groups

DISCUSSION

Since the inception, morphological assessment of gametes and embryos has been an essential part of IVF procedures (Edwards *et al*., 1981). During in vitro culture, cleavage rate and morphological characteristics are the main indicators of embryonic maturity. Evaluation of a cleavage stage embryo in IVF cycles usually involves determining the multinucleation, fragmentation rate, blastomere abnormalities and blastomere number (Nasiri and Eftekhari-Yazdi, 2015).

Although blastocyst-stage embryo transfer is becoming increasingly common, there is still disagreements about whether it is better than cleavage-stage transfer with regard to live birth rates. Although some studies indicated that live birth rates may increase, cumulative pregnancy rates—which include both fresh and frozen cycles—tend to favor transfers at the cleavage stage (Glujovsky *et al*., 2022). However, there are a number of benefits to the blastocyst stage transfer, such as a higher number of live births per cycle and a lower chance of multiple gestations due to the transfer of fewer embryos (Glujovsky *et al*., 2016).

Furthermore, improvements in embryo culture media prolonged the embryo culture period, which has increased implantation rates and allowed for a better selection of embryos with greater developmental potential (Jones *et al*., 1998; Menezo *et al*., 1992).

Research has indicated that blastocyst-stage transfers, as opposed to D3-ET, result in better implantation rates and live birth outcomes. (Wang *et al*., 2017; Martins *et al*., 2016). Furthermore, prolonged culture improves implantation capacity by enabling the differentiation of embryos with regular cell division compared to those with slowed or arrested development (Gardner *et al*., 1998; Patton *et al*., 1999).

Nevertheless, there are risks associated with blastocyst-stage transplants. In vitro, almost half of human embryos do not develop to the blastocyst stage (McCollin *et al*., 2020). Due to embryo loss during in vitro development, prolonged culture may result in fewer embryos available for transfer. Patients with less eggs are at risk for some embryos surviving in the extended culture, although they may survive if they are moved on day three. Day 3 transfer may therefore be the best option for patients with restricted embryo availability in order to optimize embryo usage and lower the chance of cycle cancellation. (Levi-Setti *et al*., 2018).

The present results showed that Day 5 transfers showed the highest pregnancy (71.9%). Also, the implantation rate was highest for Day 5 transfers followed by Day 3 transfers, while the abortion rate was highest for Day 3 transfers (50.0%), followed by Day 5 transfers.

The revision of the literature about comparisons between clinical outcomes of different embryo transfer days detected high level of variations between different studies, in addition to our study results. According to Niakan *et al*. (2012) high-quality Day 2 and Day 3 cleavage-stage embryos are susceptible to developmental arrest because of an inactive embryonic genome. On the other hand, a prospective research by Montag *et al*. (2006) assessed the rates of implantation and pregnancy according to the day of transfer. According to their findings, transfers performed on day three had a considerably greater pregnancy rate than those performed on day five, and day three implantation rates were noticeably higher than day five. Nevertheless, their research showed that their rates of implantation and pregnancy were lower than those of earlier studies.

In contrast to our study, some studies haven't found any variations in IVF success rates between Day 3 and Day 5 embryo transfers (Bungum *et al*., 2003; Coskun *et*

al., 2000; Hatırnaz and Pektaş, 2017). Even with the use of the most advanced sequential culture media, day 5 embryo transfer (ET) at the blastocyst stage nevertheless presents certain risks, such as developmental arrest and decreased embryo quality in vitro (Phillips *et al*., 2003; Smeltzer *et al*., 2020). Additionally, blastocyst transfer is linked to a higher rate of clinical pregnancy and a lower rate of miscarriages (Spangmose and Pinborg, 2020; Zilberberg *et al*., 2021).

Most studies have found that high-quality cleavage-stage embryos of D2 and D3 could be threat of unexplained and fertilization developmental arrest as a result of an inactive embryonic genome (Niakan *et al*., 2012).

In the current study, comparing the number of embryos per transfer across Day 3 and Day 5 revealed no significant differences in pregnancy rate (p=0.081) between the two groups. Also, transferring three embryos was more common among the two groups, with higher pregnancy cases observed in transfers of three embryos, followed by two-embryo transfers, compared to single embryo transfers. However, there was no statistically significant difference between the two groups.

Pregnant cases in this study revealed that, the number of embryos transferred was significantly higher for E2 and E3 on Day 3 and Day 5($p < 0.095$). Also, the present study showed that, the abortion rate was highest for Day 3 transfers (50.0%), followed by Day 5 transfers (p=0.833).

Careful embryo selection is necessary for in vitro fertilization to be successful in order to produce a healthy singleton baby. Although this increased the danger of multiple gestations, transplanting several embryos has historically enhanced conception rates. Because it lowers triplet pregnancies and lowers risks including premature birth and hypertension, single embryo transfer (SET) has gained popularity, particularly in areas where ASRM is advised. Because older women have a lower implantation potential, the ASRM advises transferring two blastocysts in women 37 years of age or younger and increasing embryos in older women to lower the possibility of triplet pregnancies (Practice Committee of the American Society for Reproductive Medicine, 2017; Zhu *et al*., 2016). Conversely, Xin *et al*. (2012) showed that, despite the ovarian response, women under 35 had greater clinical pregnancy rates with D3-ET.

Interestingly, (Alfaraj *et al*., 2017) showed that the day 3 and day 5 embryo transfer groups did not significantly differ in terms of clinical pregnancy or implantation rates. Although the day 5 transfer group experienced a greater trend in miscarriage rates than the day 3 group, this difference was not statistically significant. Additionally, there was little variation in the two groups' biochemical pregnancy rates. This inconsistent proof points to the need for more thorough investigation on the results of pregnancies after various transfer dates.

In order to increase the chances of a successful pregnancy, more embryos are usually transferred on day three due to the weak predictive value of early cleavage stage embryo morphology. But performing this increases the chance of getting pregnant more than once. (Hershlag *et al*., 1990; Nada *et al*., 2015).

On the other hand, Chang *et al*. (2010) investigated the pregnancy outcomes in women with advanced maternal age after transferring embryos on Days 3 and 5. After day 5 ET, they showed increased clinical pregnancy in women of advanced maternal age. According to their data, the quantity of oocytes retrieved seems to have an impact on the physician's choice to transfer on day three or day five (Chang *et al*., 2010).

Conclusion:

The conflicting data across various studies on the optimal timing for embryo transfers in IVF cycles highlight the complexity of this decision. The current study, along with others, demonstrates that while Day 5 transfers often yield higher pregnancy, however, Day 3 transfers can still be beneficial in certain clinical scenarios, particularly when fewer embryos are available or in cases where earlier transfer may align better with individual patient circumstances. For women of any age, a single, high-quality blastocyst transfer is advised. When high-quality cleavage embryos are available, the age of the woman should determine whether to transfer a single, double, or triple embryo with an embryo of good or average quality. For women over 40, a double or triple embryo transfer using the best quality of embryos is advised.

Recommendations:

Further extensive, prospective studies are necessary to conclusively determine the relative benefits and drawbacks of Day 3 and Day 5 embryo transfers, including larger sample sizes and various patient demographics and clinical settings.

Clinicians should adopt an individualized approach, considering factors such as age and embryo quality, to optimize outcomes by tailoring the transfer day to each patient's specific circumstances. Enhanced training and education for clinicians and embryologists on the potential benefits and risks of Day 3 and Day 5 transfers to improve decision-making and patient outcomes.

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Study the effect of numbers of transferred embryos on pregnancy and abortion rates in day3 and day 5 embryo transfer

دراسة تأثير أعداد الأجنة المنقولة على معدلات الحمل والإجهاض في اليوم الثالث واليوم الخامس من نقل الأجنة

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المستخلص

كان هدف مختبرات ART على مدى السنوات العشر الماضية هو العثور على الأجنة التي تتمتع بأفضل فرصة للزرع. من أجل تحسين الاختيار وزيادة معدلات الزرع، تصبح عمليات نقل مرحلة الكيسة الأريمية في اليوم الخامس أكثر تواتراً مع الأخذ في الاعتبار أن شكل الأجنة في اليوم الثالث قد لا يكون مؤشراً موثوقاً لاحتمال الحمل. تهدف الدراسة الحالية إلى تقييم النتائج السريرية لفحوصات اليوم الثالث واليوم الخامس ومقارنة تأثير عدد الأجنة المنقولة في الحمل السريري ومعدلات الإجهاض المبكر التي يتم إجراؤها على نقل الاجنة فى الوم الثالث وليوم الخامس.

تم إجراء تجربة عشوائية محكومة على 200 امرأة تحت سن 40 عامًا تعاني من العقم الأولي وتخضع للحقن المجهري في اليوم الثالث واليوم الخامس. تم تقسيم المشاركين إلى مجموعتين تضم كل منهما 100 شخص. بعد الحقن المجهري وفرط تحفيز المبيض الخاضع للرقابة، تم إجراء نقل الاجنة ET تحت مراقبة الموجات فوق الصوتية. وكانت معدلات الحمل السريري ومعدلات الإجهاض المبكر من بين مقاييس النتائج. أشارت النتائج إلى عدم وجود فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بمؤشرات الحيوانات المنوية، ومدة العقم، واسترجاع البويضات. أظهرت عمليات النقل في اليوم الخامس أعلى حمل سريري (71.9%) يليه اليوم الثالث (46.9% و50.0%). وكانت معدلات الإجهاض أعلى في اليوم 3 (50.0٪) وأدنى فى اليوم الخامس (12.1٪). وخلصت الدراسة إلى أن اليوم الخامس من ET حقق أفضل نتائج الحمل بالمقارنة مع اليوم الثالث. ومن الضروري إجراء المزيد من الأبحاث المستقبلية لتحسين أرقام ET وتعزيز نتائج العلاج المضاد للفيروسات القهقرية.