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Embriyo Transferinde Başarıyı Etkileyen Faktörler

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Üremeye yardımcı teknolojilerdeki sayısız gelişmeye rağmen implantasyon ve gebelik oranları hala göreceli olarak düşüktür. Buna neden olarak, endometrial reseptivite ve embriyo implantasyon kapasitesindeki düşüklük ve suboptimal embriyo transfer tekniği sayılabilir. Son zamanlardaki yayınlar, görünür basitliğine rağmen, embriyo transferi (ET) tekniğinin gebelik oranının en yüksek düzeye taşınmasında son derece önemli olduğunu göstermektedir. Bu yazıda, embriyo transfer işlemi ile ilgili olarak, başarıya etki edebilecek faktörler gözden geçirilecektir.

- ET'nin hangi evrede yapılması gerektiği konusu hala tartışımlı olup, bazı çalışmalarla transferin 2. günden 3. güne geciktirilmesi ile gebelik şansının artırıldığına dair iddialar vardır. Fakat bir Cochrane Review raporunda gebelik oranının 3. gün transferinde 2. güne göre daha yüksek (OR 1.26 %95 CI 1.06-1.51; 10 RKÇ) bulunmasına rağmen, ET'ni 2. günden 3. güne geciktirmenin devam eden gebelik ve canlı doğum oranlarını da aynı şekilde artırdığına dair henüz tatmin edici kanıt bulunmadığı bildirilmektedir (OR 1.05 %95 CI 0.83-1.32 ve OR 1.07 %95 CI 0.84-137; 3 RKÇ). Subgrup analizinde, klinik gebelik oranındaki söz konusu farkın ICSI alt grubundaki farktan kaynaklandığı saptanmıştır (4RKÇ). Bununla birlikte saptanan 3.Gün ET (ICSI) grubundaki daha yüksek gebelik kayıp oranı ise, klinik

gebelik oranları arasındaki farka rağmen 2. ve 3. gün ET gruplarının devam eden gebelik ve canlı doğum oranları açısından benzer bulunmasını açıklamaktadır¹.

- Aynı şekilde ET'ni blastokist evresine dek geciktirmenin de gebelik oranını artıracığı ve çoğul gebelik riskini azaltacağı düşündürülmüştür. Fakat yine bir Cochrane raporunda henüz blastokist transferinin, çift başına canlı doğum (OR 1.16, 95% CI 0.74 -1.44; 7 RKÇ) ve klinik gebelik (OR 1.05, 95% CI 0.88 -1.26; 15 RKÇ) oranlarını klivaj dönemi ET'ne göre artırdığına dair yeterli kanıt bulunmadığı gösterilmiştir. Üstelik, blastokist evresinde daha az embriyo transfer edilmesine rağmen çoğul gebelik riskinin de benzer (OR 0.85, 95% CI 0.63 - 1.13; 12 RKÇ) olduğu gösterilmiştir. Ayrıca yapılan ek değerlendirmede, blastokist ve klivaj evresi ET gruplarında benzer sayıda embriyoların transfer edildiği 6 RKÇ içinde de, gruplar çoğul gebelik oranları açısından benzer bulunmuştur. İki grup arasında fark olarak sadece, klivaj evresi ET'nde fazla embriyoların dondurularak saklanması olasılığının, blastokist evresi ET'nde ise transfer iptali olasılığının yüksek olması tespit edilmiştir².

- Üremeye Yardımcı teknolojilerin uygulamaya geçmesinden itibaren, tıbbi, sosyal ve ekonomik açıdan önemli kayıplara neden olan çoğul gebelik riskindeki artış gündemi meşgul etmektedir. Bu yüzden halen, IVF/ICSI programlarında transfer edilen embriyo sayısı 2 ya da 3 ile sınırlanmaktadır. Bu konuda Salha ve arkadaşlarının yaptığı bir retrospektif kohort çalışmada, 2 ya da 3 embriyonun transfer edildiği sikluslar karşılaştırılmıştır. Transfer edilen embriyolarından başka “iyi” embriyoları da olan 35 yaş altı kadınlarda, grupların gebelik ve total canlı doğum oranları benzer bulunmasına karşın, 3 embriyo transferi yapılan grupta ikiz ve üçüz gebelik riskinin artmış olduğu gözlenmiştir. Transfer fazlası “iyi” embriyosu bulunmayan 35 yaş altı kadınlarda ise, gebelik (%39.3 vs %28.8; p = 0.04) ve total canlı doğum (%32.7 vs %19.4; p = 0.02) oranları 3 embriyo transfer edilen grupta yüksek bulunurken, gruppardaki çoğul gebelik riski benzer bulunmuştur. 35 yaş üstü grupta ise, transfer fazlası

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- şarısızlığı bulunan kişilerde daha sonraki uygulamalarda otolog endometrial ko-kültür uygulamasının blastomer sayısını arttırmış, fragmentasyon oranını düşürdüğüne dair kanıtlar bulunmasına⁷¹ karşın klinik sonuçlar üzerine etkisi konusu henüz tartışılmalıdır^{72,73,74}.
1. Oatway C, Gunby J, Daya S. Day three versus day two embryo transfer following in vitro fertilization or intracytoplasmic sperm injection. Cochrane Database Syst Rev. 2004; 2:CD004378
 2. Blake D, Proctor M, Johnson N, Olive D. Cleavage stage versus blastocyst stage embryo transfer in assisted conception. Cochrane Database Syst Rev 2005 Oct 19;(4):CD002118
 3. Salha O, Dada T, Levett S, Allgar V, Sharma V. The influence of supernumerary embryos on the clinical outcome of IVF cycles. *J Assist Reprod Genet* 2000 ;17(6):335-43
 4. Setti PE, Cavagna M, Albani E, Morreale G, Novara PV, Cesana A, Parini V. Outcome of assisted reproductive technologies after different embryo transfer strategies. *Reprod Biomed Online* 2005; 11:64-70.
 5. Pandian Z, Bhattacharya S, Ozturk O, Serour GI, Templeton A. Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD003416.
 6. Pandian Z, Templeton A, Serour G, Bhattacharya S. Number of embryos for transfer after IVF and ICSI: a Cochrane review. *Hum Reprod* 2005; 20:2681-2687.
 7. Papanikolaou EG, Camus M, Kolibianakis EM, Van Landuyt L, Van Steirteghem A, Devroey P. In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos. *N Engl J Med.* 2006; 354:1139-1146.
 8. Bucket WM. A review and meta-analysis of prospective trials comparing different catheters used for embryo transfer. *Fertil Steril* 2006; 85:728-734.
 9. Abou-Setta AM, Al-Inany HG, Mansour RT, Serour GI, Aboulghar MA. Soft versus firm embryo transfer catheters for assisted reproduction: a systematic review and meta-analysis. *Hum Reprod* 2005; 20:3114-3121.
 10. Mansour R, Aboulghar M, Serour G. Dummy embryo transfer: a technique that minimizes the problems of embryo transfer and improves the pregnancy rate in human in vitro fertilization. *Fertil Steril.* 1990; 54:678-81.
 11. Henne MB, Milki AA. Uterine position at real embryo transfer compared with mock embryo transfer. *Hum Reprod* 2004; 19:570-572.
 12. Sallam HN, Agameya AF, Rahman AF, Ezzeldin F, Sallam AN. Ultrasound measurement of the utero-cervical angle before embryo transfer: a prospective controlled study. *Hum Reprod.* 2002; 17:1767-1772.
 13. Kovacs P, Matyas S, Boda K, Kaali SG. The effect of endometrial thickness on IVF/ICSI outcome. *Hum Reprod* 2003; 18:2337-2341.
 14. Garcia-Velasco JA, Isaza V, Caligara C, Pellicer A, Remohi J, Simon C. Factors that determine discordant outcome from shared oocytes. *Fertil Steril.* 2003; 80:54-60.
 15. Noyes N, Hampton BS, Berkeley A, Licciardi F, Griffio J, Krey L. Factors useful in predicting the success of oocyte donation: a 3-year retrospective analysis. *Fertil Steril* 2001; 76:92-97.
 16. Zenke U, Chetkowski RJ. Transfer and uterine factors are the major recipient-related determinants of success with donor eggs. *Fertil Steril.* 2004; 82:850-856.
 17. Ardaens Y, Gougeon A, Lefebvre C, Thomas P, Leroy M, Leroy JL, Dewailly D. Contribution of ovarian and uterine color Doppler in medically assisted reproduction techniques (ART). *Gynecol Obstet Fertil.* 2002; 30:663-672.
 18. Laasch C, Puschek E. Cumulative embryo score, not endometrial thickness, is best for pregnancy prediction in IVF. *J Assist Reprod Genet.* 2004; 21:47-50.
 19. Rashidi BH, Sadeghi M, Jafarabadi M, Tehrani Nejad ES. Relationships between pregnancy rates following in vitro fertilization or intracytoplasmic sperm injection and endometrial thickness and pattern. *Eur J Obstet Gynecol Reprod Biol* 2005; 120:179-184.
 20. Jarvela IY, Sladkevicius P, Kelly S, Ojha K, Campbell S, Nargund G. Evaluation of endometrial receptivity during in-vitro fertilization using three-dimensional power Doppler ultrasound. *Ultrasound Obstet Gynecol.* 2005; 26:765-769.
 21. Sharara FI, Lim J, McClamrock HD. Endometrial pattern on the day of oocyte retrieval is more predictive of implantation success than the pattern or thickness on the day of hCG administration. *J Assist Reprod Genet.* 1999; 16:523-528.
 22. Hearn-Stokes RM, Miller BT, Scott L, Creuss D, Chakraborty PK, Segars JH. Pregnancy rates after embryo transfer depend on the provider at embryo transfer. *Fertil Steril* 2000; 74:80-86.
 23. Barber D, Egan D, Ross C, Evans B, Barlow D. Nurses performing embryo transfer: successful outcome of in-vitro fertilization. *Hum Reprod* 1996; 11:105-108.
 24. Sinclair L, Morgan C, Lashen H, Afnan M, Sharif

- K. Nurses performing embryo transfer: the development and results of the Birmingham experience. *Hum Reprod* 1998; 13:699-702.
25. Bjuresten K, Hreinsson JG, Fridstrom M, Rosenlund B, Ek I, Hovatta O. Embryo transfer by midwife or gynecologist: a prospective randomized study. *Acta Obstet Gynecol Scand* 2003; 82:462-466.
26. Barber D, Barlow D, Balen A. Fertility nurses doing embryo transfers -- what is the impact of training? *Hum Fertil (Camb)*. 2000; 3:181-185.
27. Papageorgiou TC, Hearns-Stokes RM, Leondires MP, Miller BT, Chakraborty P, Cruess D, Segars J. Training of providers in embryo transfer: what is the minimum number of transfers required for proficiency? *Hum Reprod* 2001; 16:1415-1419.
28. Sallam HN. Embryo transfer: factors involved in optimizing the success. *Curr Opin Obstet Gynecol* 2005; 17:289-298.
29. Alvero R, Hearns-Stokes RM, Catherino WH, Leondires MP, Segars JH. The presence of blood in the transfer catheter negatively influences outcome at embryo transfer. *Hum Reprod* 2003; 18:1848-1852.
30. Tomas C, Tikkinen K, Tuomivaara L, Tapanainen JS, Martikainen H. The degree of difficulty of embryo transfer is an independent factor for predicting pregnancy. *Hum Reprod* 2002; 17:2632-2635.
31. Dorn C, Reinsberg J, Schlebusch H, Prietl G, van der Ven H, Krebs D. Serum oksitosin concentration during embryo transfer procedure. *Eur J Obstet Gynecol Reprod Biol* 1999; 87:77-80.
32. Lesny P, Killick SR, Robinson J, Raven G, Maguiness SD. Junctional zone contractions and embryo transfer: is it safe to use a tenaculum? *Hum Reprod*. 1999; 14:2367-2370.
33. Fanchin R, Righini C, Ayoubi JM, Olivennes F, de Ziegler D, Frydman R. [Uterine contractions at the time of embryo transfer: a hindrance to implantation?] *Contracept Fertil Sex*. 1998; 26:498-505.
34. Sallam HN, Agameya AF, Rahman AF, Ezzeldin F, Sallam AN. Impact of technical difficulties, choice of catheter, and the presence of blood on the success of embryo transfer--experience from a single provider. *J Assist Reprod Genet* 2003; 20:135-142.
35. Martinez F, Coroleu B, Parriego M, Carreras O, Belil I, Parera N, Hereter L, Buxaderas R, Barri PN. Ultrasound-guided embryo transfer: immediate withdrawal of the catheter versus a 30 second wait. *Hum Reprod* 2001; 16:871-874.
36. Matorras R, Mendoza R, Exposito A, Rodriguez-Escudero FJ. Influence of the time interval between embryo catheter loading and discharging on the success of IVF. *Hum Reprod* 2004; 19:2027-2030.
37. Lee HC, Seifer DB, Shelden RM. Impact of retained embryos on the outcome of assisted reproductive technologies. *Fertil Steril* 2004; 82:334-337.
38. Tur-Kaspa I, Yuval Y, Bider D, Levron J, Shulman A, Dor J. Difficult or repeated sequential embryo transfers do not adversely affect in-vitro fertilization pregnancy rates or outcome. *Hum Reprod* 1998; 13:2452-2455.
39. Nabi A, Awonuga A, Birch H, Barlow S, Stewart B. Multiple attempts at embryo transfer: does this affect in-vitro fertilization treatment outcome? *Hum Reprod* 1997; 12:1188-1190.
40. Visser DS, Fourie FL, Kruger HF. Multiple attempts at embryo transfer: effect on pregnancy outcome in an in vitro fertilization and embryo transfer program. *J Assist Reprod Genet*. 1993; 10:37-43.
41. Loutradis D, Drakakis P, Dallianidis K, Blesta SR, Milingos S, Doumplis N, Sofikitis N, Asteriou-Dionyssiou A, Michalas L, Michalas S. A double embryo transfer on days 2 and 4 or 5 improves pregnancy outcome in patients with good embryos but repeated failures in IVF or ICSI. *Clin Exp Obstet Gynecol* 2004; 31:63-66.
42. Sallam HN, Sadek SS. Ultrasound-guided embryo transfer: a meta-analysis of randomized controlled trials. *Fertil Steril* 2003; 80:1042-1046.
43. Buckett WM. A meta-analysis of ultrasound-guided versus clinical touch embryo transfer. *Fertil Steril* 2003; 80:1037-1041.
44. Drakeley AJ, Lunt R, Aust T, Williamson P, Gazvani R, Sklavounos J, Kingsland C. A randomized trial of 2250 women having ultrasound guided embryo transfer. *Hum Reprod* 2006; 21:Supp 1:i82.
45. Pope CS, Cook EK, Arny M, Novak A, Grow DR. Influence of embryo transfer depth on in vitro fertilization and embryo transfer outcomes. *Fertil Steril*. 2004; 81:51-58.
46. Oliveira JB, Martins AM, Baruffi RL, Mauri AL, Petersen CG, Felipe V, Contart P, Pontes A, Franco Junior JG. Increased implantation and pregnancy rates obtained by placing the tip of the transfer catheter in the central area of the endometrial cavity. *Reprod Biomed Online* 2004; 9:435-441.
47. Schats R, Lambers MJ, Dogan E, Lens JW, Hompes PGA. Air bubble position is related to pregnancy rate. *Hum Reprod* 2006; 21(Supp 1):i82.
48. Nazari A, Askari HA, Check JH, O'Shaughnessy A. Embryo transfer technique as a cause of ectopic pregnancy in in vitro fertilization. *Fertil Steril*. 1993; 60:919-921.
49. Mansour R. Minimizing embryo expulsion after embryo transfer: a randomized controlled study. *Hum Reprod* 2005; 20:170-174.
50. Sharif K, Afnan M, Lashen H, Elgendi M, Morgan C, Sinclair L. Is bed rest following embryo transfer necessary? *Fertil Steril* 1998; 69:478-481.
51. Botta G, Grudzinskas G. Is a prolonged bed rest following embryo transfer useful? *Hum Reprod* 1997; 12:2489-2492.
52. Amarin ZO, Obeidat BR. Bed rest versus free mo-

- bilisation following embryo transfer: a prospective randomised study. *BJOG* 2004; 111:1273-1276.
53. Tremellen KP, Valbuena D, Landeras J, Ballesteros A, Martinez J, Mendoza S, Norman RJ, Robertson SA, Simon C. The effect of intercourse on pregnancy rates during assisted human reproduction. *Hum Reprod* 2000; 15:2653-2658.
 54. Moon HS, Park SH, Lee JO, Kim KS, Joo BS. Treatment with piroxicam before embryo transfer increases the pregnancy rate after in vitro fertilization and embryo transfer. *Fertil Steril* 2004; 82:816-820.
 55. Salim R, Ben-Shlomo I, Colodner R, Keness Y, Shalev E. Bacterial colonization of the uterine cervix and success rate in assisted reproduction: results of a prospective survey. *Hum Reprod* 2002; 17:337-340.
 56. Egbase PE, Udo EE, Al-Sharhan M, Grudzinskas JG. Prophylactic antibiotics and endocervical microbial inoculation of the endometrium at embryo transfer. *Lancet*. 1999 Aug 21;354(9179):651-652.
 57. Peikrishvili R, Evrard B, Pouly JL, Janny L. [Prophylactic antibiotic therapy (amoxicillin + clavulanic acid) before embryo transfer for IVF is useless. Results of a randomized study]. *J Gynecol Obstet Biol Reprod (Paris)*. 2004; 33:713-719.
 58. Waldenstrom U, Hellberg D, Nilsson S. Low-dose aspirin in a short regimen as standard treatment in in vitro fertilization: a randomized, prospective study. *Fertil Steril*. 2004; 81:1560-1564.
 59. Rubinstein M, Marazzi A, Polak de Fried E. Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: a prospective, randomized, double-blind placebo-controlled assay. *Fertil Steril* 1999; 71:825-829.
 60. Pakkila M, Rasanen J, Heinonen S, Tinkanen H, Tuomivaara L, Makikallio K, Hippelainen M, Tapanainen JS, Martikainen H. Low-dose aspirin does not improve ovarian responsiveness or pregnancy rate in IVF and ICSI patients: a randomized, placebo-controlled double-blind study. *Hum Reprod* 2005; 20:2211-2214.
 61. Hurst BS, Bhojwani JT, Marshburn PB, Papadakis MA, Loeb TA, Matthews ML. Low-dose aspirin does not improve ovarian stimulation, endometrial response, or pregnancy rates for in vitro fertilization. *J Exp Clin Assist Reprod*. 2005; 2:8.
 62. Lok IH, Yip SK, Cheung LP, Yin Leung PH, Haines CJ. Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial. *Fertil Steril*. 2004; 81:556-561.
 63. Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. *Fertil Steril* 2002; 78:1073-1076.
 64. Polak de Fried E, Blanco L, Lancuba S, Asch RH. Improvement of clinical pregnancy rate and implantation rate of in-vitro fertilization-embryo transfer patients by using methylprednisolone. *Hum Reprod*. 1993; 8:393-395.
 65. Lee KA, Koo JJ, Yoon TK, Do BR, Ko JJ, Cha KY. Immunosuppression by corticosteroid has no effect on the pregnancy rate in routine in-vitro fertilization/embryo transfer patients. *Hum Reprod*. 1994; 9:1832-1835.
 66. Moffitt D, Queenan JT Jr, Veeck LL, Schoolcraft W, Miller CE, Muasher SJ. Low-dose glucocorticoids after in vitro fertilization and embryo transfer have no significant effect on pregnancy rate. *Fertil Steril*. 1995; 63:571-577.
 67. Mottla GL, Smotrich DB, Gindoff PR, Stillman RJ. Increasing clinical pregnancy rates after IVF/ET. Can immunosuppression help? *J Reprod Med*. 1996; 41:889-891.
 68. Fridstrom M, Carlstrom K, Sjoblom P, Hillensjo T. Effect of prednisolone on serum and follicular fluid androgen concentrations in women with polycystic ovary syndrome undergoing in-vitro fertilization. *Hum Reprod*. 1999; 14:1440-1444.
 69. Ubaldi F, Rienzi L, Ferrero S, Anniballo R, Iacobelli M, Cobellis L, Greco E. Low dose prednisolone administration in routine ICSI patients does not improve pregnancy and implantation rates. *Hum Reprod*. 2002; 17:1544-1547.
 70. Seif MM, Edi-Osagie EC, Farquhar C, Hooper L, Blake D, McGinlay P. Assisted hatching on assisted conception (IVF & ICSI). *Cochrane Database Syst Rev*. 2006 Jan 25;(1):CD001894.
 71. Spandorfer SD, Barmat L, Navarro J, Burmeister L, Veeck L, Clarke R, Liu HC, Rosenwaks Z. Autologous endometrial coculture in patients with a previous history of poor quality embryos. *J Assist Reprod Genet*. 2002; 19:309-312.
 72. Barmat LI, Liu HC, Spandorfer SD, Kowalik A, Mele C, Xu K, Veeck L, Damario M, Rosenwaks Z. Autologous endometrial co-culture in patients with repeated failures of implantation after in vitro fertilization-embryo transfer. *J Assist Reprod Genet*. 1999; 16:121-127.
 73. Rubio C, Simon C, Mercader A, Garcia-Velasco J, Remohi J, Pellicer A. Clinical experience employing co-culture of human embryos with autologous human endometrial epithelial cells. *Hum Reprod*. 2000 Dec;15 Suppl 6:31-38.
 74. Seta M. Embryo transfer after autologous endometrial coculture improves pregnancy rates. *Hum Cell*. 2001 Jun;14(2):135-140.