BÖLÜM 49

# Tekrarlayan İmplantasyon Başarısızlığı ve Yönetimi

Ümit ÇABUŞ[1]

## GİRİŞ

İmplantasyon, üreme fizyolojsinin en önemli basamaklarından biridir ve zonadan ayrılmış blastokistin endometriyal dokuya appozisyonu, adezyonu ve invazyonu olarak tanımlanır (1). Başarılı bir implantasyon embriyoya, endometriuma ve embriyo ile endometrium arasındaki aktif etkileşime bağlıdır.

Tekrarlayan implantasyon başarısızlığı (TİB) birkaç embriyonun transferinden sonra implantasyon oluşmaması ile karakterize klinik bir durumdur. In vitro fertilizasyon (IVF) ve embriyo transferi yapılan çiftlerin yaklaşık % 10'unda görülür. TİB ile ilgili literatürün artmasına rağmen, tanı ve tedavisi için hala yaygın olarak kabul görmüş bir tanım veya standart protokol yoktur. Ancak bütün tanımlamalar değerlendirildiğinde TİB, 40 yaşın altındaki bir kadında en az üç taze veya dondurulmuş döngüde en az dört kaliteli embriyonun transferinden sonra klinik bir gebeliğin sağlanamaması olarak tanımlanabilir (2). En olası etiyolojileri belirlemek önemlidir. Birincil nedene yönelik bireyselleştirilmiş tedavi implantasyon oranını artırmak için etkili bir yöntem gibi görünmektedir.

## A. ETİYOLOJİ

TİB maternal faktörler, paternal faktörler ve embriyo faktörü olmak üzere birkaç farklı etiyolojik nedeni olan karmaşık klinik bir durumdur. Etiyolojisinde tek bir neden olmayabilir ki genellikle birlikte çalışan birçok faktör TİB'e yol açar. Bunlar;

### 1. İmmunoloji

Uterin ve periferal kanda veya dokuda bulunan doğal katil hücreler (NK), T hücreleri, desidual dendritik hücreler (DCs), makrofajlar ve çeşitli sitokinler (TNF-α, INF-γ, IL-17, IL-6, IL-1β, IL-4) gibi immünolojik faktörlerin TİB ile arasında ilişki olduğunu gösteren birçok çalışma bulunmaktadır. Ancak yapılan değerlendirmelerde yeterli kanıt olmadığı belirtilmektedir.

Uterin NK hücreleri (uNk) erken gebelikte tüm endometriyal lökositlerin % 70'inden fazlasını oluşturur (3,4). Desidual stromadaki NK hücreleri sitokinler salgılar ve maternal-fetal bağışıklığa aracılık eden reseptörleri eksprese eder. uNK hücreleri, fetal ekstravillous trofoblast (EVT) hücrelerine doğrudan sitolitik değildir (5). Yarı allojenik fetüs için gerekli olan uNK hücrele-

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ve randomize kontrollü olarak yapılan inSIGHT çalışmasında ilk IVF tedavi döngüsünden önce rutin histeroskopi yapılmasının canlı doğum oranını artırıp artırmadığı değerlendirilmiş ve transvajinal ultrasonografi ile uterin kavitesi normal olarak değerlendirilen infertil kadınlarda canlı doğum oranlarını iyileştirmediği görülmüştür (132). Benzer şekilde tekrarlayan implantasyon başarısızlığı olan kadınlarda yapılan TROPHY çalışmasında da IVF öncesi rutin histeroskopi yapılmasının canlı doğum oranını iyileştirmediği görülmüştür (133).

### 7. Erkek faktörü

Spermdeki ciddi anormallikler düşük döllenme, implantasyon ve gebelik oranları ile ilişkilidir (134). İntrasitoplazmik morfolojik olarak seçilmiş sperm enjeksiyonu (IMSI), optimal sperm elde etmek için enjeksiyondan önce spermi 6000 × büyütme altında inceleyen invaziv olmayan bir yöntemdir. Shalom-Paz ve ark. ICSI öncesi IMSI prosedürünün, tekrarlayan IVF-ICSI yetmezliği olan hastalarda implantasyon ve klinik oranlar için faydalı olduğunu bildirmiştir (135). Ancak, diğer çalışmalar benzer sonuç çıkarmamıştır (136). Bu nedenle, sperm morfolojisini değerlendirmek için spesifik bir mikroskobik kriter yoktur ve IMSI'nın IVF-ET sonuçları üzerindeki etkisini değerlendirmek için daha fazla çalışmaya ihtiyaç vardır.

### 8. Anöploidiler için preimplantasyon genetik test (PGT-A)

PGT-A, IVF-ET'deki embriyoların kromozomlarını analiz edebilen ve sonraki transfer için euploid embriyoları seçebilen bir teknolojidir. Greco ve ark. yaptığı çalışmada karşılaştırmalı genomik hibridizasyon ile seçilen tekli euploid embriyolar TİB'li hastalara transfer edildiğinde TİB'li olmayan gruptaki hastalara benzer implantasyon oranları izlenmiştir (137). Aksine başka bir retrospektif kohort çalışmasında, TİB'li ve tekrarlayan düşük öyküsü olan hastalarda PGT-A kullanmanın yararı gösterilmiş ve implantasyon oranlarında önemli bir artış izlenmiştir (138). Yine benzer bir çalışmada euploid embriyo transferi yapılan TİB'li hastaların kümülatif implantasyon oranı % 95.2 bulunmuş. Buna bağlı olarak çoğu TİB'in kromozom anöploidisine bağlı olduğu ve euploid embriyoların transfer edilmesiyle iyileştirilebileceği öne sürülmüştür (139). Bu nedenle PGT-A, TİB'li hastalar için önemli bir tedavi seçeneği gibi görünmektedir (140). Ayrıca, her hastanın durumu dikkatli bir değerlendirme yapıldıktan sonra PGT-A uygulanmalıdır. Ancak mozaisizm etkisi mulaka göz önünde bulundurulmalıdır.

## SONUÇ

TİB birçok hastayı etkileyen karmaşık ve büyüyen bir sorun olmaya devam etmektedir. TİB'in nedenlerini belirlemek, hastaları bilgilendirmek ve kişiselleştirilmiş tedavi sağlamak implantasyon oranını artırabilir. Ancak her tedavinin potansiyelini değerlendirmek ve her hasta için standart bir protokol oluşturmak için tedavi seçenekleri hakkında daha fazla araştırmaya ve zamana ihtiyaç vardır.

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