Konu 15

Kontrollü Over Hiperstimülasyonu Protokolleri

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A-Giriş

1978 yılında "doğal in vitro fertilizasyon (IVF) siklusu" ile elde edilen ilk canlı doğumun ardından, nasıl olur da kontrollü şekilde daha fazla yumurta elde edilerek (Kontrollü over hiperstimülasyonu (KOH)) daha fazla embriyo transfer edilir ve bu şekilde gebelik şansı arttırılabilir sorusuna cevap aranmaya başlandı. Ovulasyon indüksiyonu, intrauterin inseminasyon, IVF ve intrastoplazmik sperm enjeksiyonu (ICSI) gibi yöntemler geliştirilerek uygulanıma sunuldu. 1990'lı yıllarda popüler olan daha az riskli "doğal siklus IVF" protokollerinin, siklus başına tek embriyo elde edilmesi ve yaklaşık %20 oranında yetersiz embriyo gelişimi nedeniyle 2000'li yıllarda popülaritesi azaldı. Yine doğal siklus IVF'e kabul edilen olguların ancak %50'si embriyo transfer aşamasına ulaşabilmekteydi. Zaman içerisinde geliştirilen gonadotropin preparatlarının rutin kullanıma girmesiyle yeni tedavi stratejileri geliştirilmeye başlandı. Hastaların over rezervlerine ve stimülasyona alınacak cevapların farklılığına göre birtakım protokoller geliştirilmeye çalışıldı. Hastaya göre dizayn edilen KOH protokollerinde en yüksek gebelik oranları ile birlikte en az istenmeyen yan etkiler hedeflendi. Bu bölümde KOH protokolleri detaylı şekilde incelenerek tartışılmaya çalışılmıştır.

B-Gonadotropinler

İnfertilite tedavisinde gonadotropin preparatlarının kullanılması 20. yüzyılın ilk yarısından itibaren bilinmektedir (1). İlk olarak gebe kısrak serumundan, domuz ve insan hipofiz ekstrelerinden elde edilen preparatlar ovarian stimülasyon için kullanılmıştı. 1927 yılında Ascheim ve Zondek ön hipofizdeki gonadotropik faktör ile aynı etkiyi gösteren bir maddeyi gebe kadınların idrarından izole ettiler (2). Bu maddeyi "gonadotropin" ya da "prolan" olarak isimlendirdiler.

1930 yılında Zondek gonadotropinlerin aynı zamanda postmenopozal kadınların idrarlarında da mevcut olduğunu gösterdi (3). Yine aynı yıl Cole ve Hart, gonadotropinleri gebe kısrakların serumundan (PMSG) izole ettiler ve PMSG'nin hayvanlarda potent gonadotropik etkili olduğunu gösterdiler (4). 1948 yılında Stewart, Sano ve Montgomery'nin çalışmalarıyla gebe kadınların idrarlarındaki gonadotropinlerin sadece hipofiz kaynaklı olmadıkları, bunun yanısıra plasental koryonik villuslardan orijin aldıkları gösterilmiştir (5). Bu çalışmanın ardından plasenta kökenli olanlar "koryonik gonadotropin" olarak tanımlanmıştır. Uzun yıllar yapılan çalışmaların ardından koryonik gonadotropinlerin sadece matür folikül varlığında ovulasyonu indükleyebildiği ve matür folikül gelişimi için hipofiz kaynaklı bir faktöre ihtiyaç olduğu savunulmuştur. Bu aşamada LH ve FSH içeren postmenopozal idrar kaynaklı insan menopozal gonadotropin (hMG) ekstreleri elde edilmiştir. 1961 yılında ise sekonder amenore tanısı olan bir hastada hMG ile ilk canlı gebelik elde edilmiştir.

Spesifik monoklonal antikorların kullanıldığı yeni teknolojilerin gelişimi ile üriner FSH ve yüksek oranda saflaştırılmış FSH preparatları, ve ardındanda rekombinant teknolojinin kullanılması ile rekombinant FSH üretilebilmiştir.

Üriner hMG

İnsan menopozal gonadotropini in vivo bioaktivite gösteren eşit miktarda FSH (75 IU) ve LH (75 IU) içerir. hMG içerisindeki FSH ve LH aktivitesi %5'lik kısmı oluştururken geri kalan %95'lik kısım farklı idrar protein-

foliküller toplandığında oosit elde edilemediyse hCG seviyesine bakılır. hCG >100 IU/ml ise hasta hCG'sini yapmıştır ancak hCG'nin doku etkisi veya biyoyararlanımı farklı olabilir. hCG düzeyi yeterli olgularda 6 saat daha beklenerek tekrar OPU işlemi yapılması matür oosit eldesi ve gebelik imkanı tanıyabilir.

J-Gelecek İle İlişkili Öngörüler

Gelecek hastaya özgü tedavi protokollerinin tasarlanmasını ve tek enjeksiyon ile kontrollü over hiperstimülasyonu sağlayan rFSH preparatlarını içermektedir. Her hastanın overinin gonadotropinlere verdiği cevap farklıdır. KOH sonrası oluşan östrojen ve progesteron gibi hormon seviyelerinin, uygulanan hCG'nin implantasyona etkisi tam çözümlenememiştir. Bu çözümlemeler endometriyumun gen ekspresyonunun farklı KOH protokollerinde nasıl olduğunun bulunması ile gerçekleşecektir. Farklı KOH protokollerinin embriyo üzerindeki etkisi embriyo kültür ortamlarının protein ve metabolik aktivitesinin incelenmesi ile açıklığa kavuşturulabilir. En nihayetinde farklı genetik yapıdaki insanların farklı stimülasyon ihtiyaçları da genofarmakoterapinin gelişmesi ile belirlenecektir.

TEŞEKKÜR

Bu yazının hazırlanmasında deneyim ve bilgisini bizimle paylaştığı için Acıbadem Üniversitesinden Doç. Dr. Cem Demirel'e teşekkür ederiz.

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