

# Empty Follicle Syndrome

## BOŞ FOLİKÜL SENDROMU

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### Abstract

Empty follicle syndrome is defined as the failure to retrieve oocytes for in-vitro fertilization(IVF) from a patient deemed to have responded normally to controlled ovarian hyperstimulation. The etiology is not completely clarified yet. We aimed to describe empty follicle syndrome and to identify possible underlying mechanisms for accurate diagnosis and management .Most of the studies in the literature support that empty follicle syndrome (EFS) may be in part avoided by taking simple preventive measures. However in minority of cases EFS can not be prevented. Further research is necessary to enlighten the possible etiologies .

**Key Words:** Empty follicle syndrome, controlled ovarian hyperstimulation, in-vitro fertilization

### Özet

Boş folikül sendromu, ovulasyon indüksiyonuna normal cevap alınmasına karşın in vitro fertilizasyon için oosit elde edilememesi olarak tanımlanır. Etiyolojisi henüz tama olarak açıklanamamıştır. Bu derlemede boş folikül sendromunu tanımlamaya, doğru teşhis ve yaklaşım için altta yatan olası mekanizmaları belirtmeye çalıştık. Literatürdeki çalışmaların büyük bir çoğunluğu, boş folikül sendromundan basit önlemlerle kısmen kaçınılabileceğini desteklemektedir. Fakat halen vakaların küçük bir kısmında, boş folikül sendromunun basit tedbirlerle önlenemediği bildirilmektedir. Olası etiyolojilerin aydınlığa kavuşması için daha fazla araştırmaya ihtiyaç vardır.

**Anahtar Kelimeler:** Boş folikül sendromu, kontrollü over hiperstimülasyonu, in-vitro fertilizasyon

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Empty follicle syndrome(EFS) is defined as the failure to retrieve oocytes for IVF, in the presence of normal serum E2 levels and follicular development after controlled ovarian hyperstimulation induction, despite repeated aspiration and flushing performed transvaginally by ultrasound guided puncture, 35 hours after human chorionic gonadotropin (hCG) injection.

EFS was first reported in 1986 by Coulam.<sup>1</sup> Since then, many researchers have investigated its etiology, prediction, diagnosis and management.<sup>2-7</sup> The problem occurs in 0,5-2% of IVF cycles.<sup>2,4</sup>

Initial reports suggested that it may be a manifestation of intrinsic ovarian dysfunction.<sup>8</sup> Later it was concluded that EFS was a drug related phenomenon, caused by improper administration of hCG resulting in very low serum hCG levels.<sup>7</sup>

Empty follicle syndrome is both a devastating and annoying disorder, the patients and the physician having invested time, effort and money to reach oocyte recovery.<sup>2-8</sup>

In this review , we aimed to describe EFS and identify possible underlying mechanisms for accurate diagnosis and management.

### Possible Underlying Mechanisms of EFS

Currently there is no universally accepted explanation of the underlying mechanism of EFS. A number of possible mechanisms have been proposed.

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Altered folliculogenesis is likely to be involved in the etiology of EFS. Early oocyte atresia or a strong attachment of the oocyte cumulus complex were previously suggested to have role in the etiology.<sup>8,9</sup> Follicular growth and rupture lead to oocyte cumulus complex (OCC) detachment from the granulosa cells and connective tissue of the follicle.

In most of the cases, follicular fluid, obtained from the follicles contained degenerated granulosa cells. Ben Schlomo et al<sup>4</sup> reported poor follicular growth in 31% of patients with EFS. Pellicer et al suggested in some cases, EFS may represent an advanced stage of ovarian ageing characterized by residual responsiveness of granulosa cells while oocytes can not develop adequately.<sup>10</sup> This may indicate that the oocyte surrounded by the cumulus oophorus underwent an early process of atresia, apoptosis and degeneration.<sup>11</sup> Identification of cumulus oophorus confirms that a cystic structure is indeed containing an oocyte containing follicle. The release of OCC requires perfectly coordinated LH surge (or hCG as a substitute) so that meiosis may resume and subsequently ovulation may occur.<sup>3</sup>

Administration of hCG plays a crucial role in intrafollicular events such as softening of the connective tissue elements of the follicle, which facilitates the detachment of the OCC complex from the follicle wall. The time between hCG administration and oocyte retrieval is important. Inappropriate timing of hCG administration or lack of hCG administration may also result in EFS.<sup>3,7</sup>

A low bioavailability of the administered hCG or an insufficient end-organ response to biologically active hCG may also be the cause of the syndrome. Zegers-Hochschild et al detected absence of immunoreactive hCG in follicular fluid of the six EFS cases.<sup>2</sup>

Ndukwe et al proposed that serum measurement of  $\beta$ -hCG levels, 36 hours after intramuscular hCG, may predict empty follicle syndrome. The  $\beta$ -HCG levels were all  $<10$  mIU/ml in EFS patients, whereas in cycles in which oocytes were retrieved, serum levels ranged from 106 to 291 mIU/ml.<sup>6</sup>

Ndukwe et al also concluded that EFS was a drug related problem.<sup>6</sup> The possibility of an intrinsic

defect in the in vivo biological activity of some batches of the commercially available hCG is proposed.<sup>6,12</sup> Salvage of the cycle was achieved after giving a second ovulatory dose of hCG from a different batch and repeating the oocyte retrieval for 24-36 hours later.<sup>2,6,12</sup> Pellicer and Ubaldi et al also achieved pregnancy in 2 patients with previous EFS after the administration of a second ovulatory dose of hCG.<sup>10,13</sup>

Recently, EFS was reported in two sisters highlighting the possibility of genetic factors that could be responsible for some cases of EFS or even unexplained infertility.<sup>14</sup> Recurrence of EFS has also been reported by various authors which may also predict the possible genetic etiology.<sup>1-3,15-17</sup> Patients with recurrent cycles of EFS cycle should be counselled regarding the possibility of recurrence of such an event in future cycles.

Implantation may also be impaired in patients with sporadically occurring EFS, as pregnancy rates achieved in this group were below normally expected. These patients are more likely to have advanced age, poor response, cancelled cycles and diminished pregnancy rate.<sup>16</sup>

## Conclusion

EFS is a devastating condition which can not be, only explained by low bioavailability of HCG alone. Unfortunately only measurement of serum  $\beta$ -hCG on the day of oocyte recovery is not always sufficient for diagnosis, except the cases when serum  $\beta$ -hCG concentration is very low.

In our experience we had 3 EFS patients among 306 IVF patients during the last 3 years. Two of the three patients were sisters. They did not have any accompanying problem. They had recurrent EFS in two consecutive IVF cycles, despite repeated hCG administration. The elder sister conceived following oocyte donation after being referred to a foreign center where this procedure was legal.

We may conclude that empty follicle syndrome (EFS) may be in part avoided by taking simple preventive measures. However, as it can not be prevented totally, further research is necessary to enlighten the possible etiologies.

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