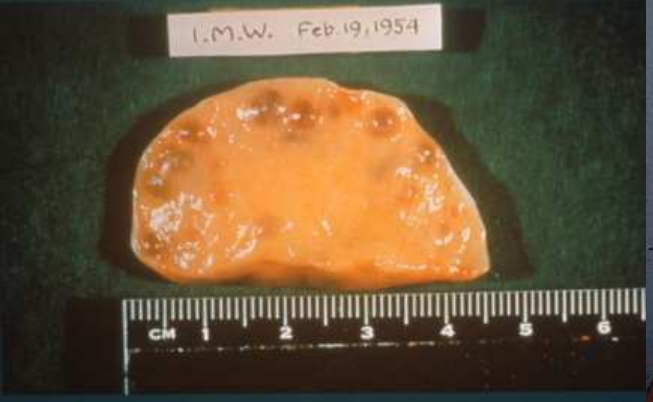
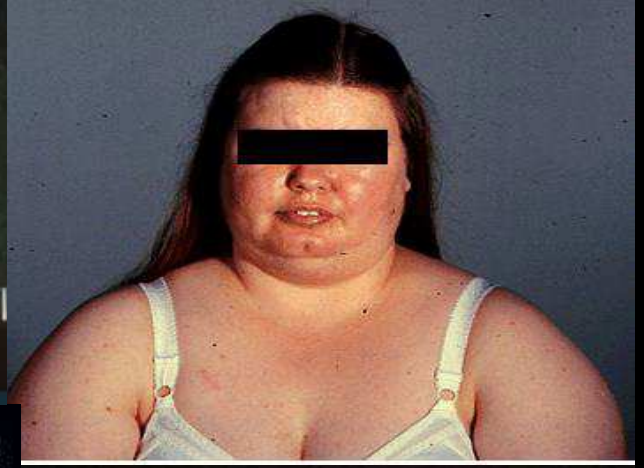
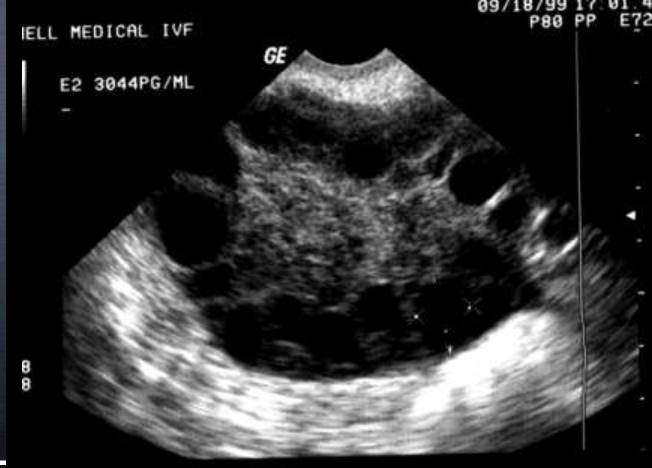
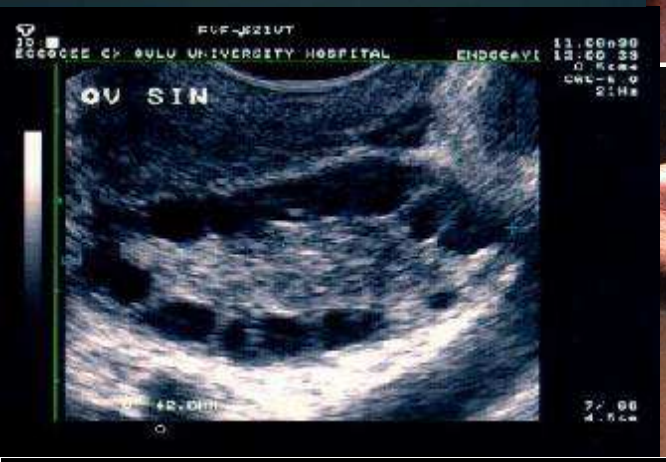
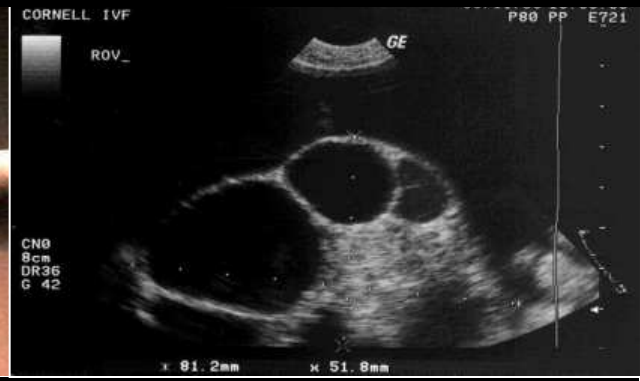






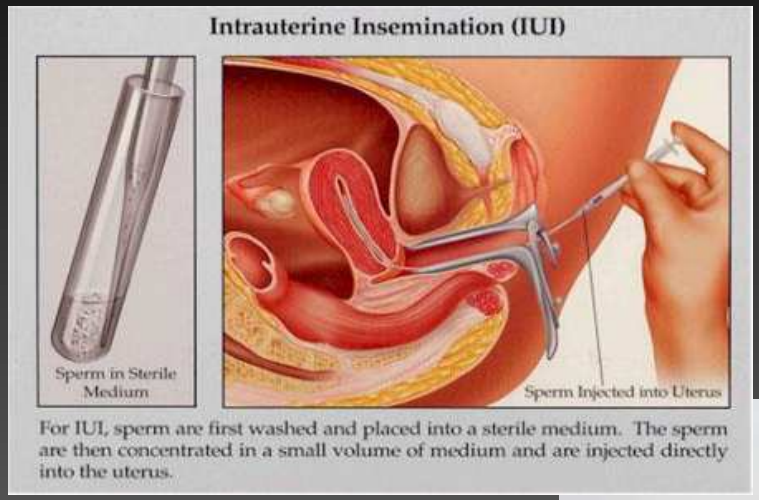


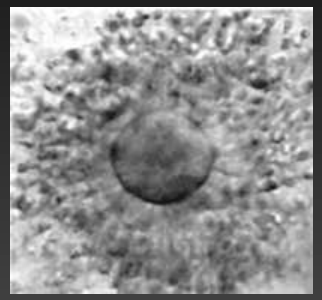


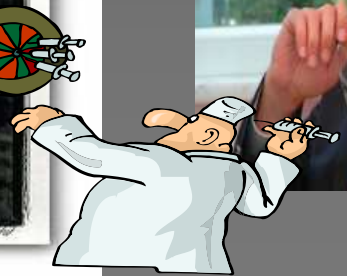
Ovaryen Hiperstimulasyon Sendromu (OHSS) Etyopatogenez ve Önleme Stratejileri

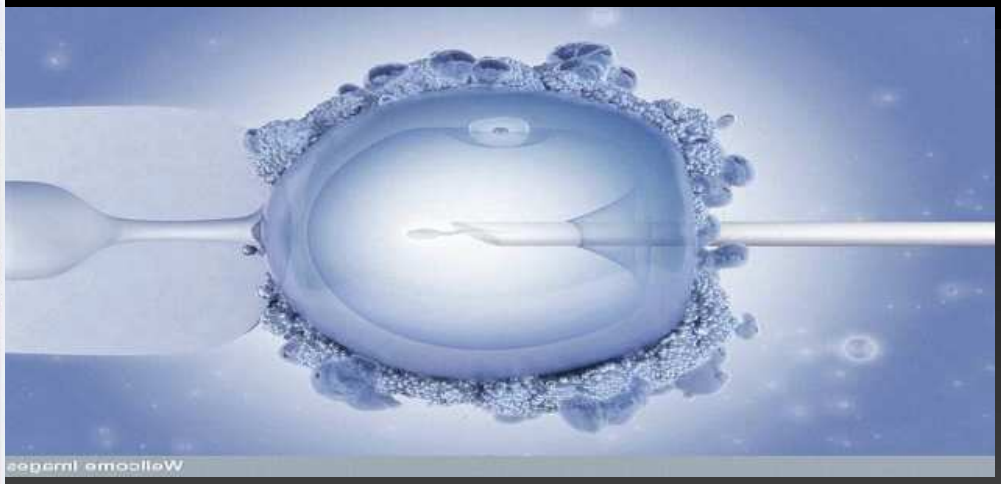
Prof.Dr. Timur Gürgan

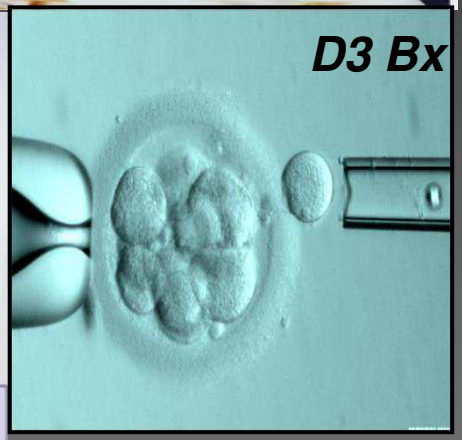
YÜT bir Tıp Sanatımıdır ?



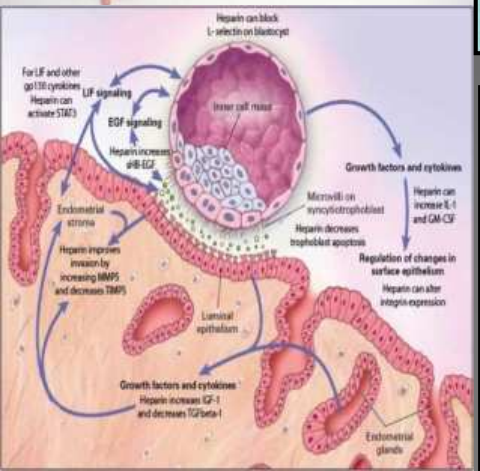


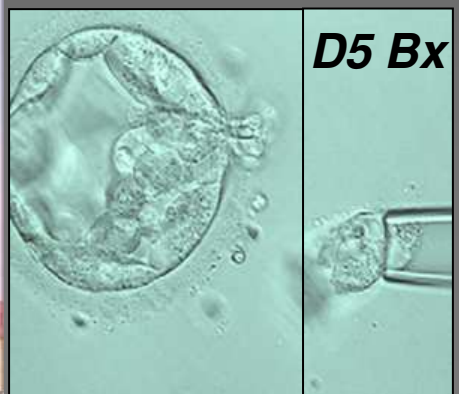


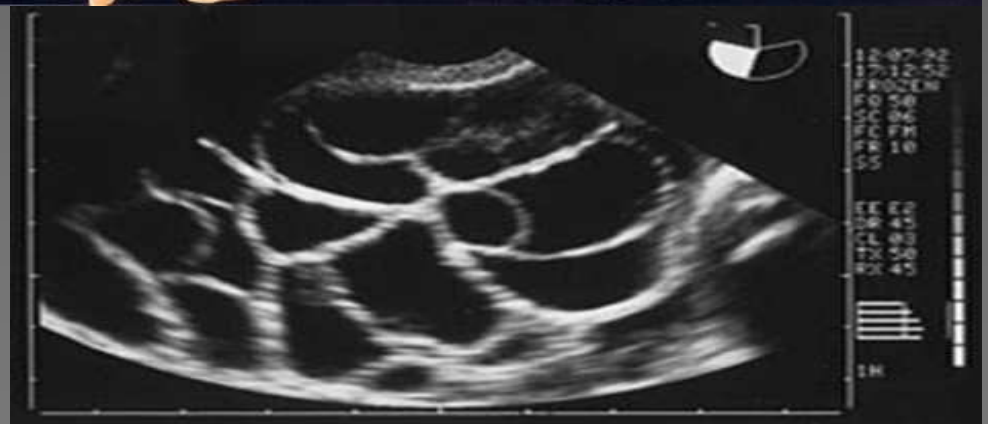



D3 Bx


RISKY BUSINESS?
Do infertility treatments damage babies' genes? Doctors used to think not. Now they are not so sure
By MICHAEL D. LEMONICK
BOTTOM LINE:


Heparin can block L-selectin on blastocyst
For LIF and other gp130 cytokines Heparin can activate STAT3
LIF signaling
EGF signaling
Heparin increases pHB-EGF
Inner cell mass
Growth factors and cytokines
Heparin can increase IL-1 and GM-CSF
Microvilli on syncytiotrophoblast
Heparin decreases trophoblast apoptosis
Regulation of changes in surface epithelium
Heparin can alter integrin expression
Endometrial stroma
Heparin improves invasion by increasing MMP9 and decreases TIMP3
Luminal epithelium
Growth factors and cytokines
Heparin increases IGF-1 and decreases TGFbeta-1
Endometrial glands

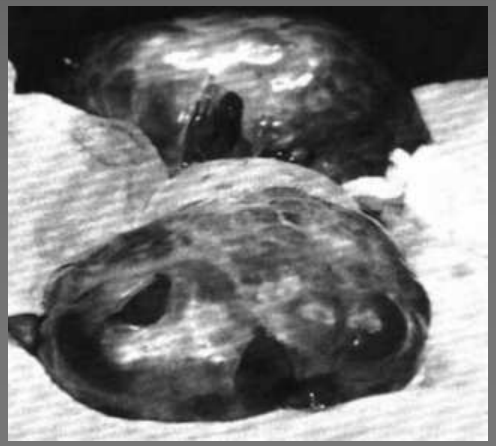

D5 Bx



Ovaryan Hiperstimulasyon Sendromu (OHSS)

- Ovaryan stimulasyonun en sık görülen ciddi komplikasyonu
- Şiddetli formu hayatı tehdit edebilir.
- Ovaryen stimülasyona yanıt veren kadınların birçoğunda bir miktar OHSS görülür.
- Her zaman tedaviye sekonder gelişim

ÖNLENEBİLİR !

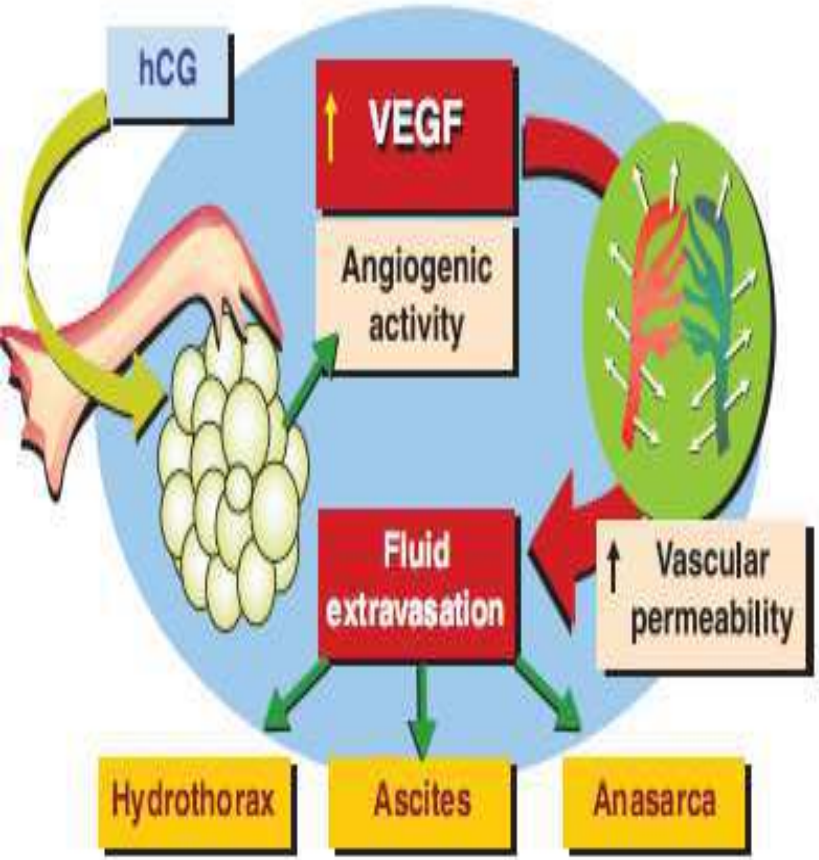


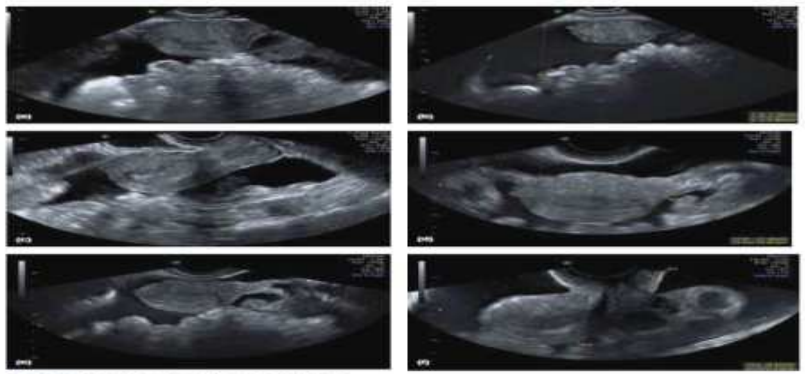
OHSS Görülme Sıklığı

Hafif –Orta OHSS	20-30%
Kliniğe uyumlu OHSS	10%
Şiddetli OHSS	0.5 - 4%

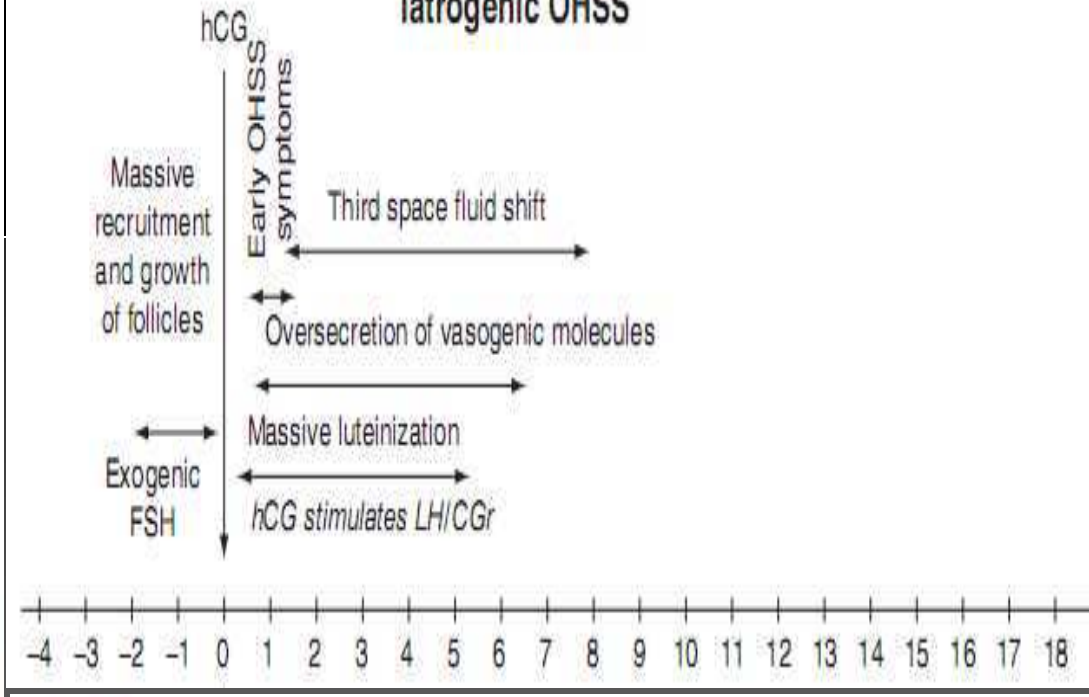
Raziel et al. (2002) Hum Reprod 17:107; Egbase et al. (2000) Hum Reprod !5:8; Whelan et al. (2000) Fertil Steril 73:883; Beerendonk et al. (1998) Ob Gyn Survey 53:439 Enskog et al. (1999) Fertil Steril 71:808; Navot et al. (1992) Fertil Steril; 58:24;Kolibianakis et al., (2006)HR Update

Pathophysiology:





Iatrogenic OHSS



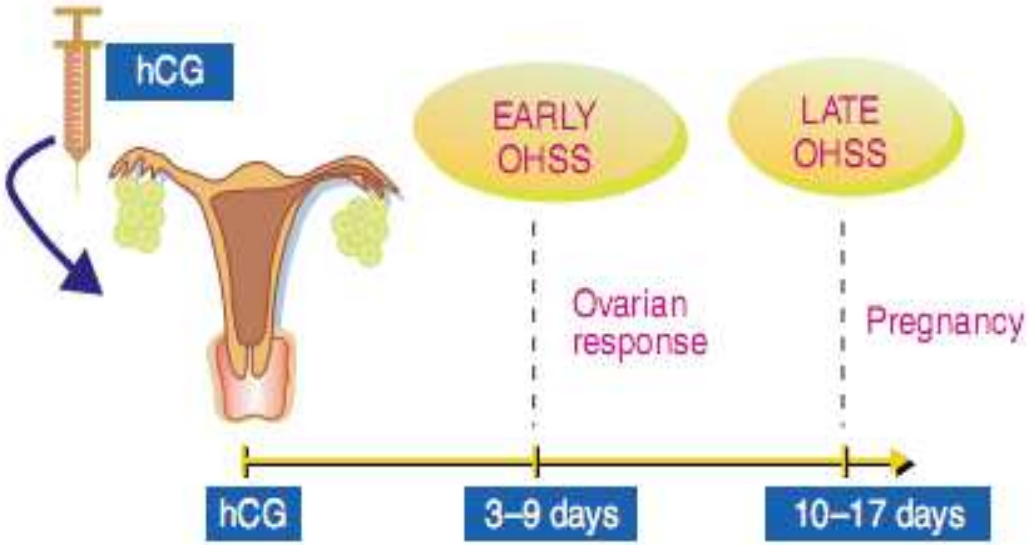


Figure 36.6. Classification of ovarian hyperstimulation syndrome: early and late.

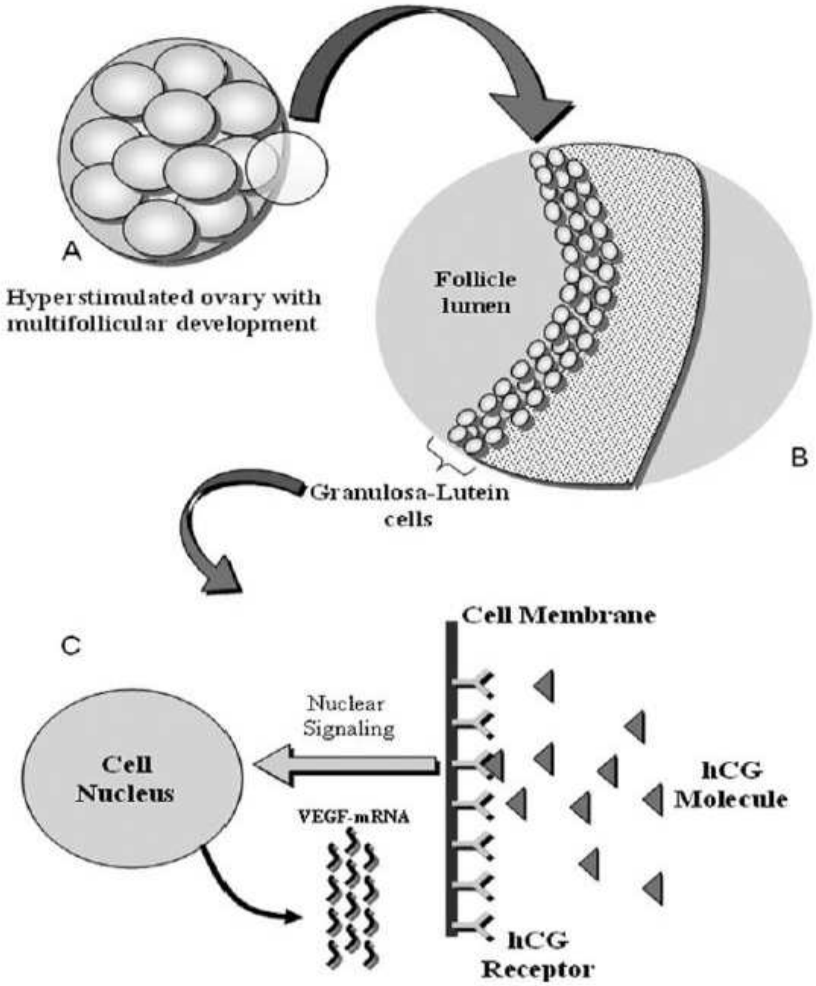


Figure 3: First steps in the pathophysiology of ovarian hyperstimulation syndrome.
A high number of granulosa-lutein cells are stimulated by hCG, which determines the increased production of VEGF-mRNA. VEGFR-2 mRNA production in granulosa-lutein and endothelial cells (see Fig. 4) is also increased by exposure to hCG.

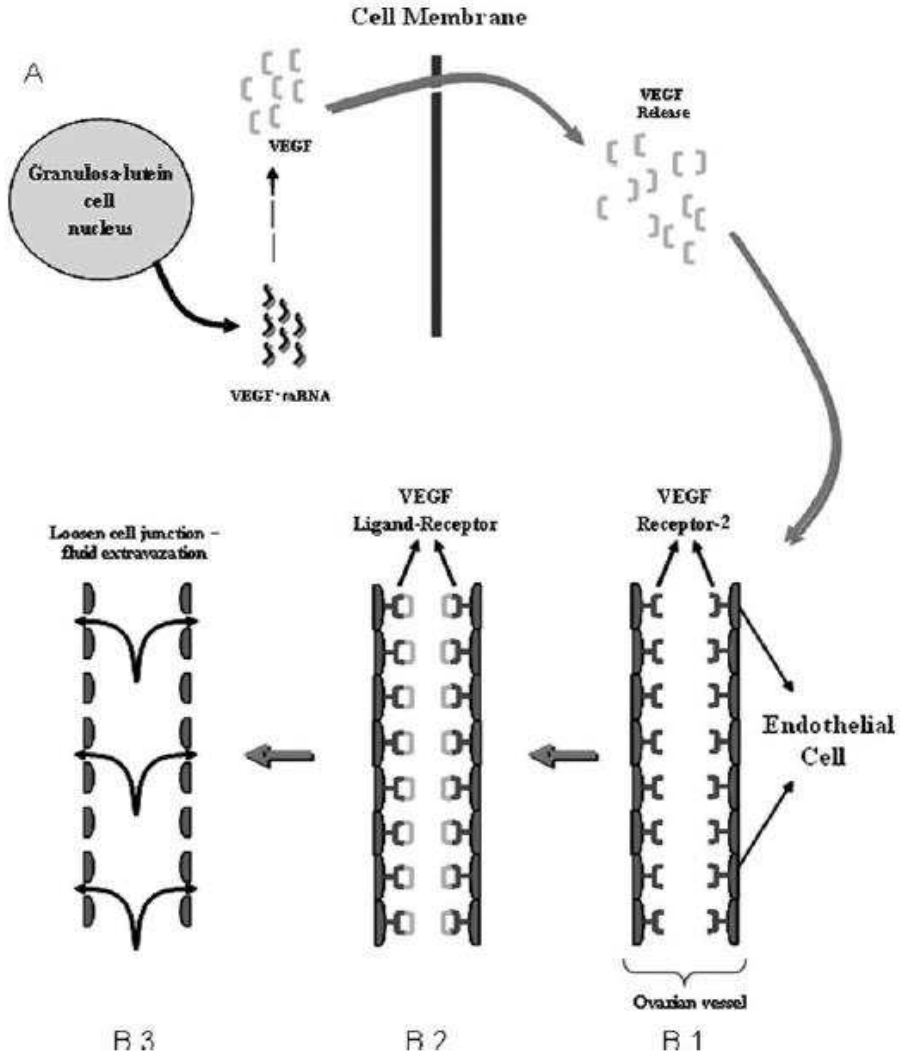
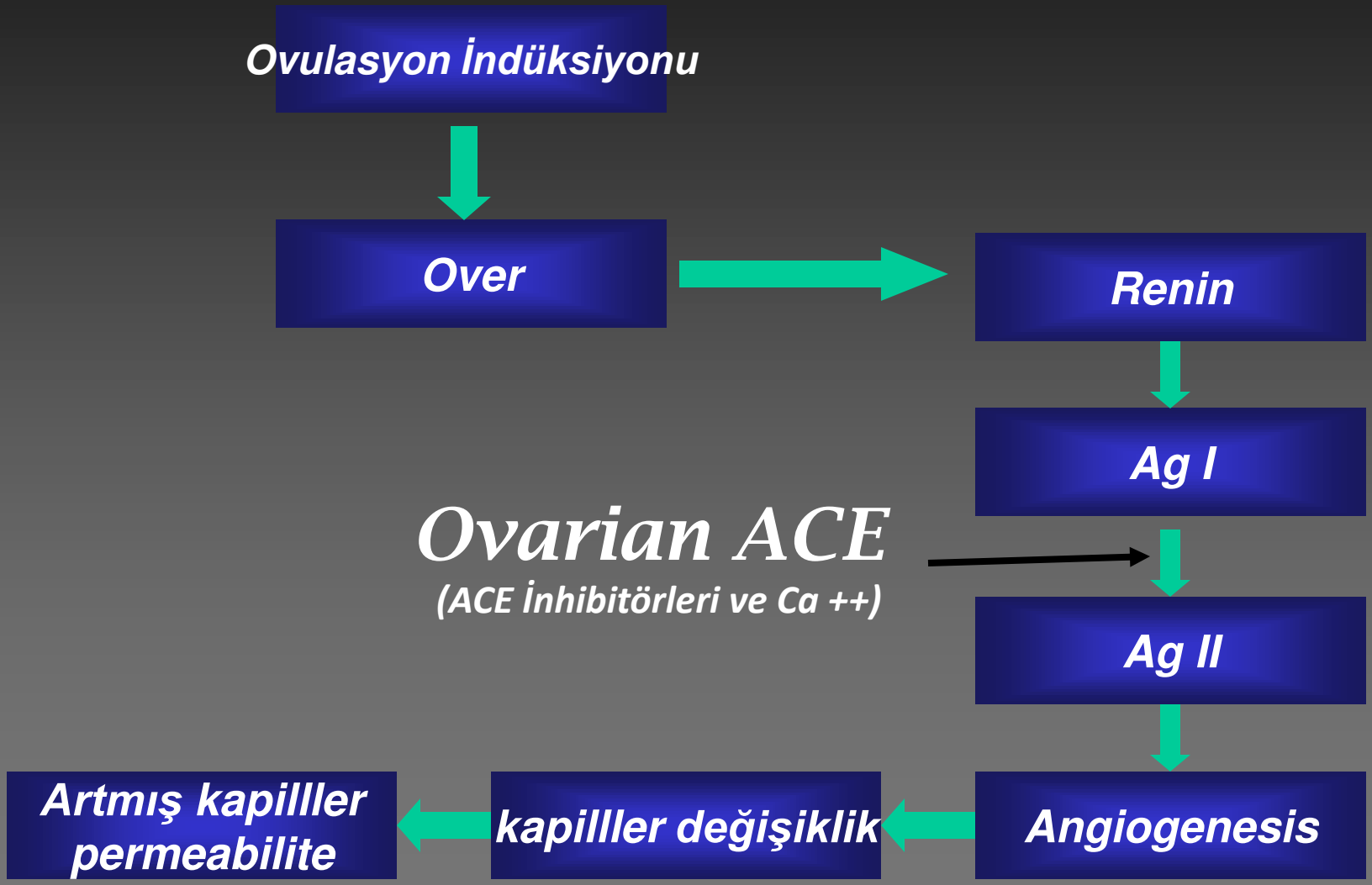


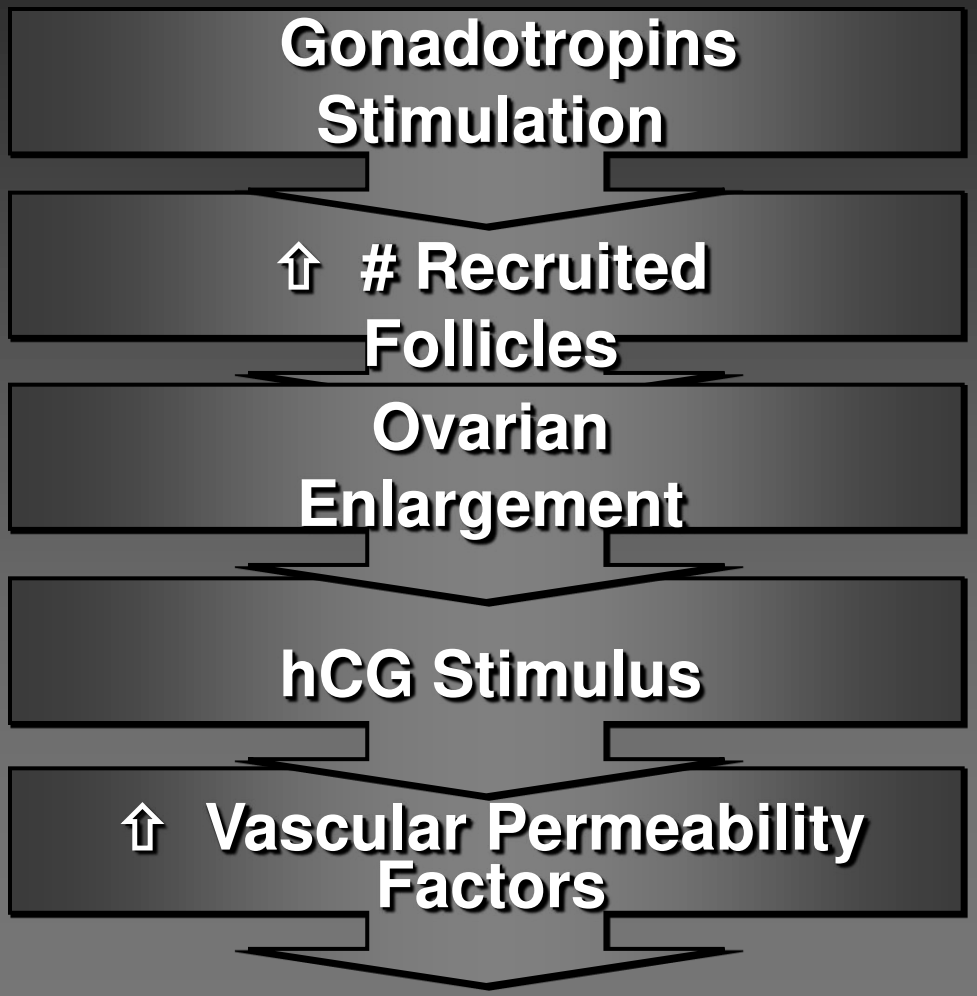
Figure 4: Ovarian hyperstimulation syndrome pathophysiology.
High amounts of VEGF are produced and released by granulosa-lutein cells (A) and bind to their receptors in the endothelial cells membrane (B.1, B.2). This determines downstream signaling that augments vascular permeability (B.3). This final effect seems to be related with changes in the actin fibres and in cellular shape, which in turn may be due to factors such as the rearrangement of endothelial junctional proteins like vascular endothelial cadherin (Bates *et al.*, 1999; Villasante *et al.*, 2007).

Pellicer et al., Hum Reprod

OHSS oluşmasında anjiotensin-renin sistemi



Ovaryen Hiperstimulation Sendromu



- Increased number of Follicles (> 20) resulting in inreased granulosa/luteal cell mass
- Exposure to hCG
- Increased vascular permeability resulting in extravasation of protein-rich fluid out of the intravascular space

Şiddetli Hayatı Tehdit eden OHSS*

Severe OHSS	Critical OHSS
Variably enlarged ovaries	Variably enlarged ovaries
Ascites ± Hydrothorax	Tense Ascites ± Hydrothorax
Hematocrit > 45%	Hematocrit > 55%
WBC > 15,000	WBC ≥ 25,000
Oliguria	Oligoanuria
Creatinine 1.0 – 1.5 mg/dL	Creatinine ≥ 1.6 mg/dL
Creatinine clearance ≥ 50 mL/mm	Creatinine clearance < 50 mL/mm
Liver dysfunction	Renal failure
Anasarca	Thromboembolic phenomena
	ARDS

*Navot et al. 1992

OHSS yi güvenilir yolla tahmin edip önleyebilirmiyiz ?

Ovariyan Hiperstimulasyon Sendromu (OHSS)

Riskli olguların tespiti

- İlk muayenede (LOD ?)
- HCG gününde
- ET öncesinde

OHSS

Tanıma

History and physical

1. OHSS in a previous cycle
2. Polycystic syndrome
3. Young patient
4. Low body mass index
5. Hyperinsulinism
6. Allergies

During ovarian stimulation

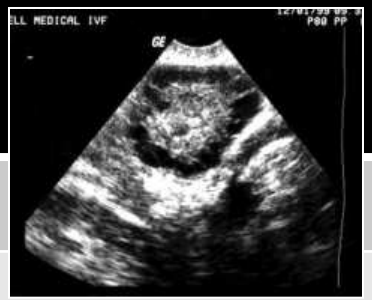
1. High serum estradiol, rapid slope of E_2, and absolute value
2. Ultrasonography
   a. Baseline PCO pattern
   b. PCO pattern of response to GnRH before gonadotropins
   c. Large number of follicles, >20, in each ovary
3. Doppler: low intraovarian vascular resistance

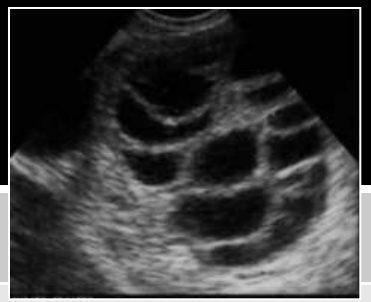
Outcome of ART cycles

1. Conception cycles
2. Multiple pregnancy

Primer risk faktörleri

İlk Muayenede





- Genç yaş age (35 yaş altı)
- Düşük BMI
- OHSS hikayesi
- PCOS / PCO /MFO
- Yüksek antral follikül sayısı
- Doppler kan akımları, Over volümü
- Yüksek AMH düzeyi, Bazal FSH, İnhibin B düzeyi
- Genetik yatkınlık / FSH reseptör polimorfizimi

USG

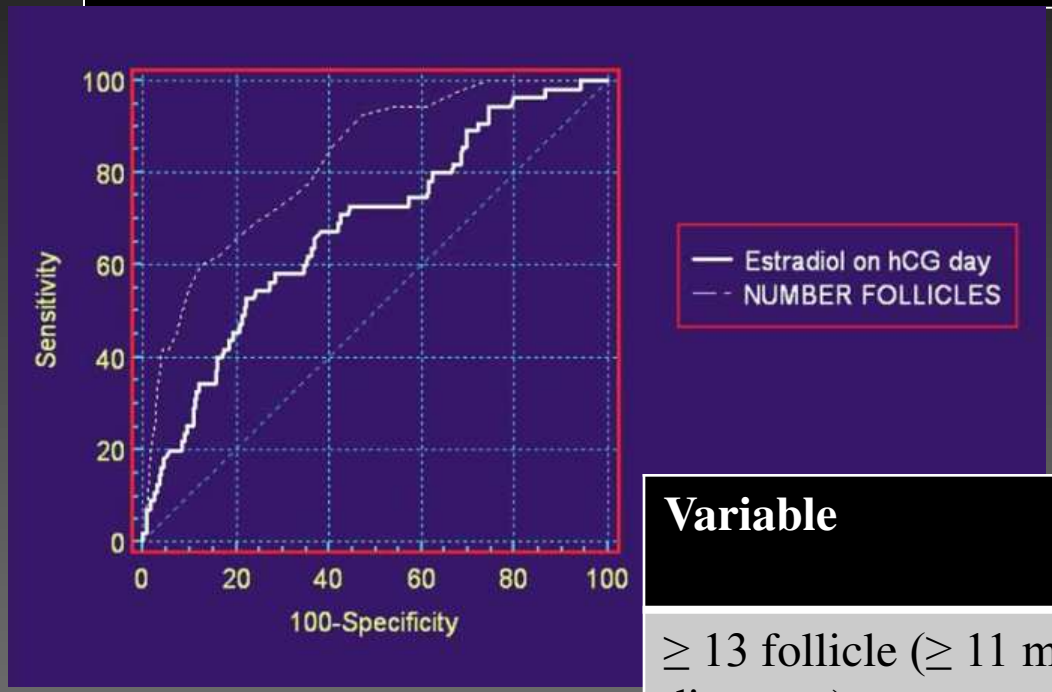
Limitli FSH stimulasyonu

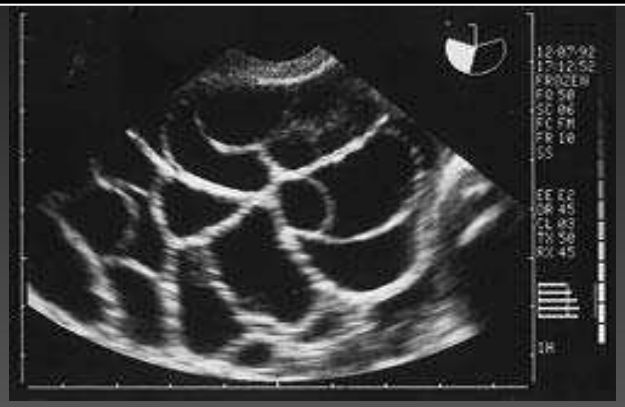
Table 2 Risk factors/predictive factors for OHSS (adapted from Humaidan et al [10])

Risk factor	Threshold of risk
Primary risk factors (patient related)	
- High basal AMH	- >3.36 ng/mL independently predicts OHSS [12]
- Young age	- <33 years predicts OHSS [12]
- Previous OHSS	- Moderate and severe cases, particularly those with hospitalization
- PCO like ovaries	- >24 antral follicles in both ovaries combined
Secondary risk factors (ovarian response-related)	
On day of hCG trigger	
- High number of medium/ large follicles	- ≥13 follicles ≥11 mm in diameter [14] - >11 follicles ≥10 mm in diameter [12]
- High or rapidly rising E2 levels and high number of follicles	- E2 5,000 ng/L and/or ≥18 follicles predictive of severe OHSS [14]
- Number of oocytes retrieved	- >11 predicts OHSS [12]
- VEGF levels	- Not applicable
- Elevated inhibin-B levels	- Elevated levels on day 5 of gonadotropin stimulation, at oocyte retrieval and 3 days before
- hCG administration for LPS	- Not applicable
- Pregnancy (increase in endogenous hCG)	- Not applicable

Sekonder risk faktörleri

E2 +follikül sayısı





Variable	Sensitivity (%)	Specificity (%)
≥ 13 follicle (≥ 11 mm diamater)	85.5	69
E2 ≥ 2560 ng /L	53	77
≥ 18 follicles and /or E2 ≥ 5000 ng /L	83	84

Papanikolaou EG et al, F&S, 2006, 85: 112 – 20.

OHSS: Önleme için Stratejiler

Oosit Toplaması Öncesi

- Hastanın riskinin belirlenmesi
- Hafif stimulasyon (granulosa hücre/follikül havuzunun azaltılması)
- hCG geri çekilmesi (siklus iptali)
- Coasting (hCG uygulama öncesi gonadotropinlerin durdurulması)
- hCG dozunun azaltılması
- Ovulasyonun rLH yada GnRHa ile tetiklenmesi

OHSS yi Önlemek için Stratejiler

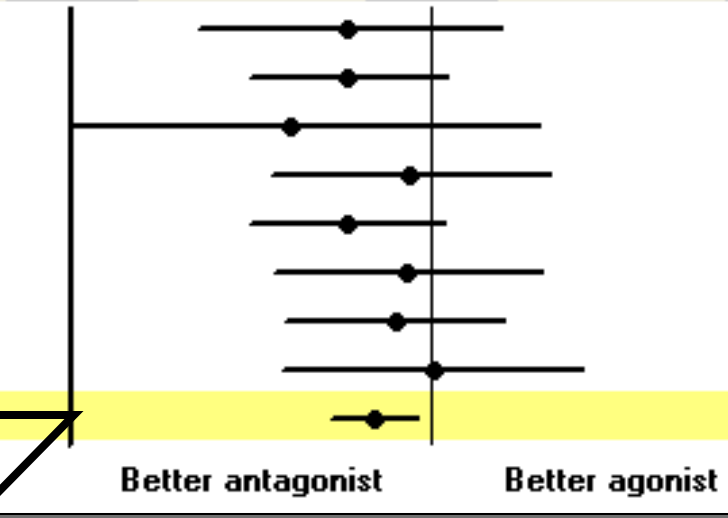
Stimulasyon protokolerinin bireyselleştirilmesi

- En düşük gonadotropin dozu
- OCP/Leuprolide ikili süpresyon
- OCP/GnRH antagonist/Gonadotropinler
- OCP/Low gonadotropins/GnRH agonist as ovulatory trigger
- CC/Low dose gonadotropins/GnRH antagonist
- Hafif stimulasyon ile gonadotropinlerigeç başlamak(5.GÜN)
- FSH stimulasyonu yalnız hCG ile sona erdirmek
- IVM /hafif gonadotropin stimulasyon ile birlikte veya uyarısız

OHSS yi Önlemek için Stratejiler

GnRH Antagonistleri

Citation	Year	Antagonists	Agonists	Effect	PValue
Olivennes	2000	2 / 126	2 / 43	0,34	0,25
European	2000	4 / 486	6 / 244	0,33	0,07
Albano	2000	0 / 198	1 / 95	0,16	0,20
North American	2001	3 / 208	2 / 105	0,76	0,76
Middle East	2001	4 / 236	6 / 119	0,34	0,07
Lee	2005	3 / 41	2 / 20	0,73	0,72
Bahceci	2005	3 / 73	5 / 75	0,62	0,49
Badrawi	2005	2 / 50	2 / 50	1,00	1,00
Combined (8)		21 / 1418	28 / 751	0,47	0,01

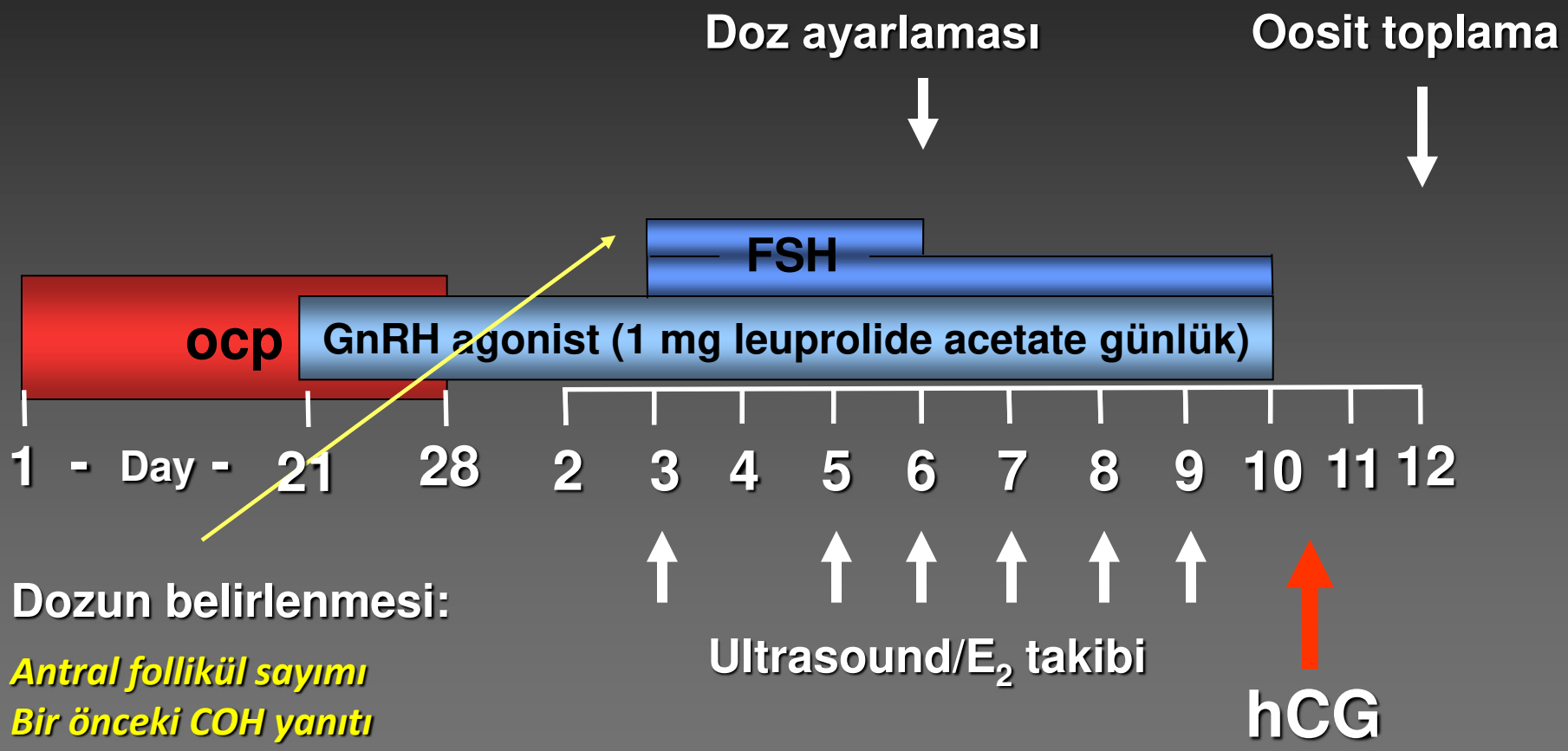


1.49% 3.46%

RR = 0.47, 95% CI 0.27–0.82, P = 0.01

Kolibianakis et al., Hum Reprod Update 2006

İkili Supresyon Protokolü



Dozun belirlenmesi:

Antral follikül sayımı
Bir önceki COH yanıtı
BMI
Day 3 FSH/LH/E_2
AMH
Yaş

FSH 75 Units

ÖZET

GnRha Downregulasyonu öncesinde OCP kullanılması

- Gonadotropinlere over cevabını azaltır
- Siklus ipalini azaltır
- Olgun ve fertilize olmuş oosit sayısını arttırır
- PCOS ve yüksek cevaplı hastalarda gebelik şansını arttırır
- OHSS riskini azaltır

Azaltılmış hCG dozu

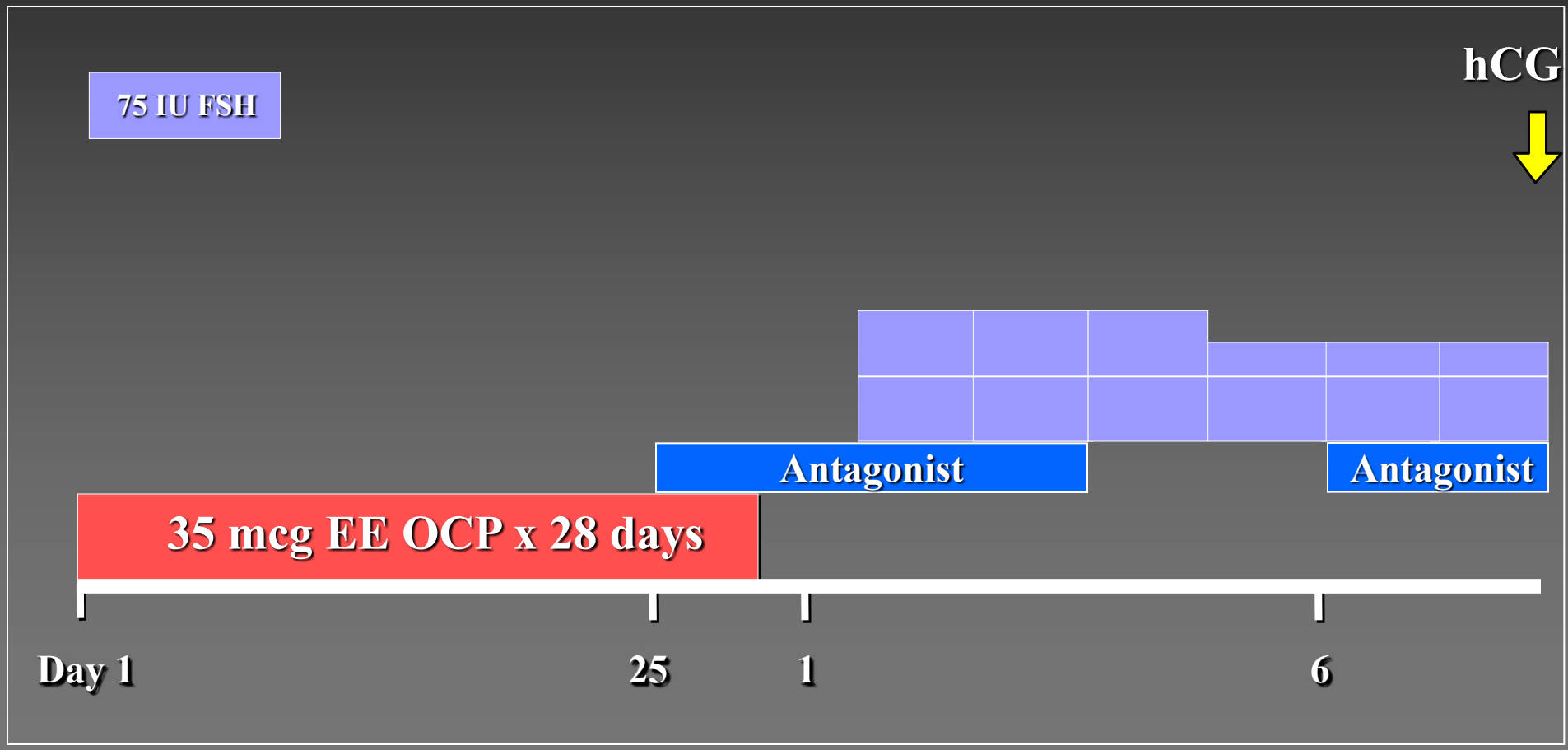
- *RCT, n= 80 PCOS*
- *GnRH-antagonist protokol*

	10,000 IU (n = 28)	5,000 IU (n = 26)	2,500 IU (n = 26)
E_2 (pg/mL)*	2076 (1793)	2391 (1990)	2147 (2399)
Fertilization rate	52.8%	65.4%	55.6%
Ong. Preg./transfer (%)	7 (26.9)	8 (30.8)	8 (34.8)
OHSS III (%)°	1 (3.5)	1 (3.8)	0

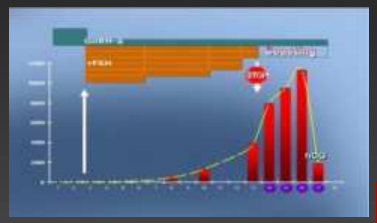
** Median*

Kolibianakis et al.,(2007) Fertil Steril 88:1382-1388

OCP/Antagonist/ Gonadotropins/ Antagonist Protocol



OHSS : Tanınması ve Önlenmesi



2. hCG gününde :

- *Coasting*
- *hCG dozu azaltılması*
- *Agonist trigger*
- *Dopamin agonist*
- *Ca gluconate infusion*

- Serum Estradiol düzeyi
- Follikül sayısı

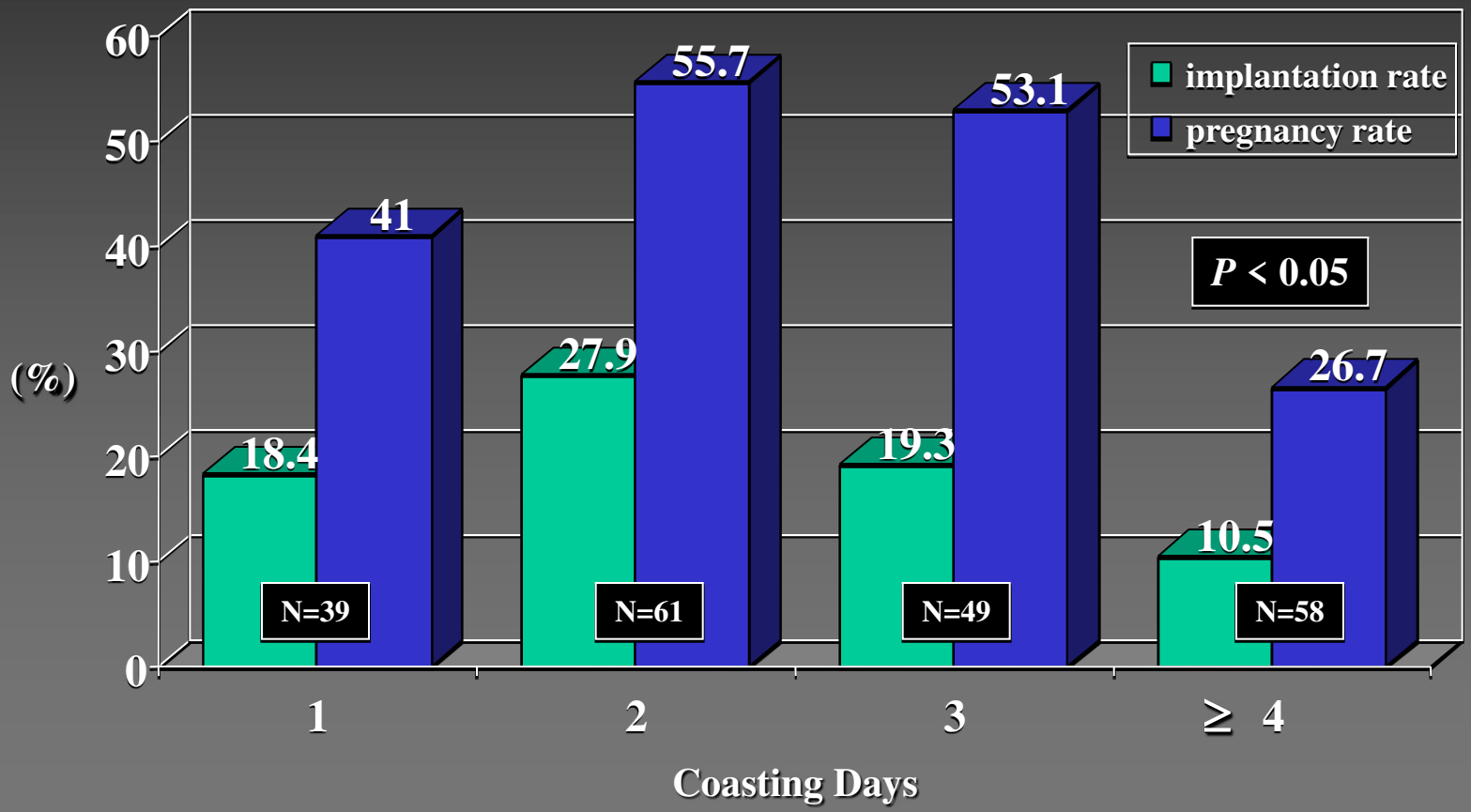
3. Embryo Transferi öncesi :

- *tek blastcyst transferi*
- *"embryo Freezing "*

Coasting

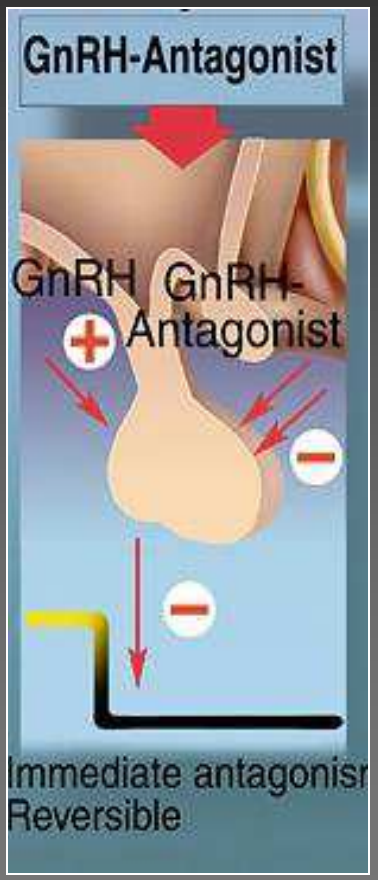
- Hipofiz down regülasyonu için GnRH-a uygulaması devam ederken gonadotropinlerin durdurulması ve serum E2 konsantrasyonunun güvenli seviyeye gerileyene kadar hCG nin verilmemesi.

Coasting gün sayısı ile İmplantasyon & Gebelik Oranları



Ulug et al., Hum Reprod 17(2):310-313, 2002

Ovariyen Stimulasyon



GnRH agonist
Ovulatosyon için uyarı

Çekilme kanaması

Antagonist

FSH/LH

Day 1 2 3 4 5 6 7 8 9 10 11 12

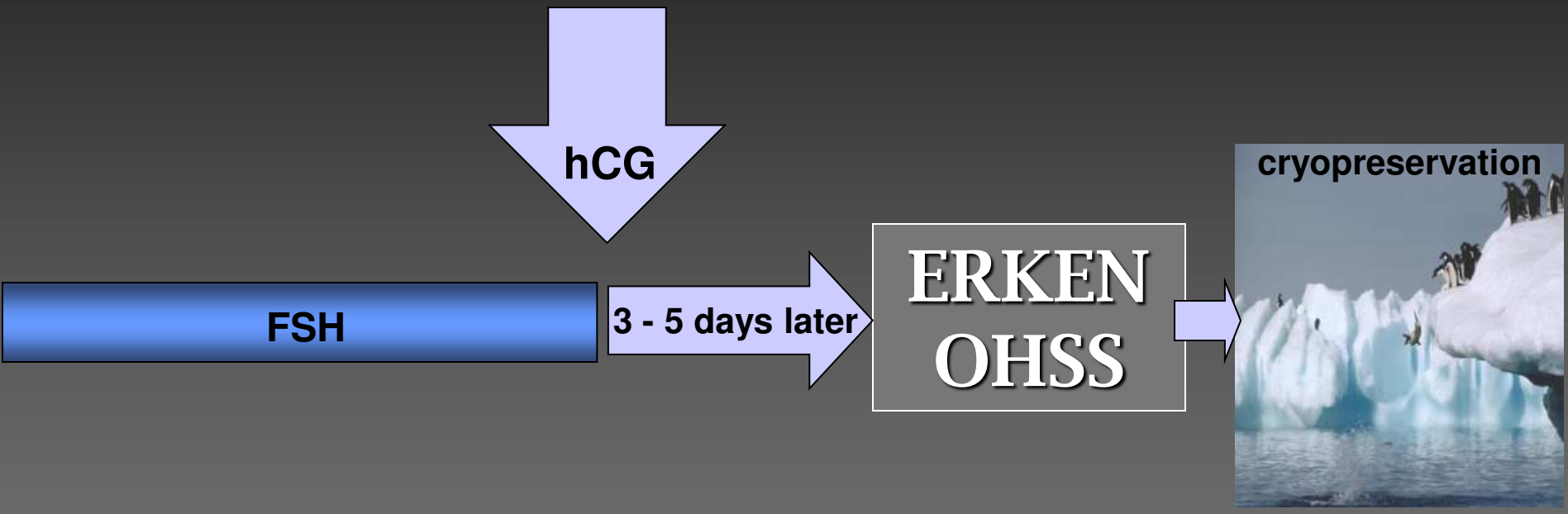
Oosit toplamansı

FSH 75 Units

OHSS: Önlemek için Stratejiler

- Toplanan bütün embryoları dondurup saklama
- 5.güne kadar transferi geciktirmek
  - Yalnız iyi klinik ilerleme olduğunda transfer etme
- Olgun olmayan oositlerin invitro olgunlaştırılması
  - Hiç yada hafif stimule overlerde (PCOD)
- Luteal fazda GnRH antagonist uygulaması
- Profilaktik I.V. albumin yada hydroxyethylstarch
- Methylprednisolone uygulaması
- Metformin uygulaması
- Kabergolin uygulaması
- Kalsiyum glukonat infüzyonu

Blastokist /Beşinci Gün Transfer



Yalnız iyi klinik ilerleme olduğunda transfer !

OHSS Önleme Stratejileri

Hydroxyethylstarch

A high-polymeric glucose compound

- **"a safe, biologicical substitute for human albumin" with comparable physical properties**
- **1000 ml 6% HAES at time of retrieval**
- **500 ml 6% HAES two days later**

Graf et al., Hum. Reprod. 1997; 12:2599-2602

Strategies for Preventing OHSS

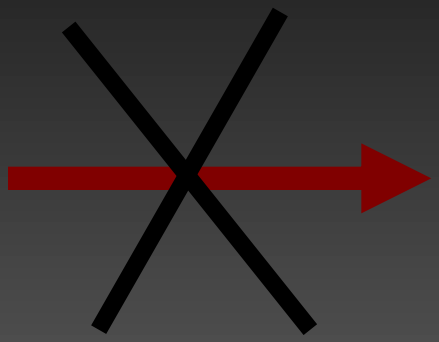
Efficacy

- **A meta-analysis concluded that prophylactic albumin at the time of oocyte retrieval may reduce the risk of severe OHSS***
- **Other studies concluded that albumin did not prevent severe OHSS, especially in cycles associated with pregnancy****

•Aboulghar et al. (2000) The Cochrane Library, issue 3; Isik et al.(1996) Europ J Obstet Gynecol Reprod Biol 70:170; Shalev et al. (1995) Hum Reprod 10:1373; Shoham et al. (1994) Fertil Steril 62:137;Al-Inany, Acta Obs Gyn Scand (2001) 80:878-882

*** Chen et al. (1995) Fertil Steril 68(2):287; Ndukwe et al. (1997) Fertil Steril 68(5):851; Ng et al. (1995) Hum Reprod 10:807; Orvieto et al. (1995) Fertil Steril 64(4):860; Mukherjee et al. (1995) Fertil Steril 64:641; Ben-Chetrit et al.(2001) Hum Reprod 16:1880 Bellver, et al (2003) Hum. Reprod. 18:2283-2288; D'Angelo et al. Cochrane Database Syst Rev (2007) 3: CD002806*

İkinci bir şans için IVM



10,000 IU HCG

Immatür oosit toplama + *İptal yerine IVM*

Lider follikül= 12-14 mm

47 % KLİNİK GEBELİK

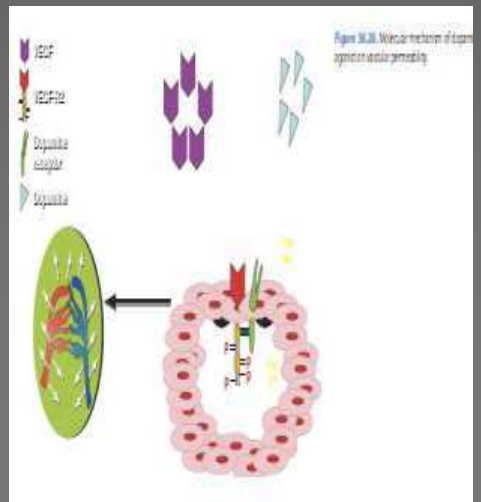
OHSS yok

Lim et al. Fertil Steril 2002

Tedavideki yeni fikirler: Kabergolin

Geçmiş:

VEGF → VEGF R2 → Damarsal sıvı kaçışı



Kabergolin
Dopamine Reseptör agonisti

Alvarez et al, JCEM 2007

Intravenous calcium infusion as a novel preventive therapy of ovarian hyperstimulation syndrome for patients with polycystic ovarian syndrome

Timur Gurgan, M.D.,[a,d] *Aygul Demirol, M.D.,*[a] *Suleyman Guven, M.D.,*[b] *Moncef Benkhalifa, M.D.,*[c] *Bagdagul Girgin,*[a] *and Tin Chiu Li, M.D.*[e]

Intravenous Calcium Infusion Protocol

All patients were preoperatively evaluated by cardiologist for possible toxic effect of IV calcium infusion. Intravenous calcium was administered as described by Yakovenko et al. (9). Intravenous 10% calcium gluconate, 10 mL in 200 mL of physiologic saline on the day of ovum pickup, day 1, day 2, and day 3 after ovum pickup were administered in study group. Intravenous infusion was performed within 30 minutes. In the control group, no preventive measures were taken for OHSS.

TABLE 2

Comparison of embryologic characteristics and cycle outcome in calcium gluconate–administered group (group I) and control group (group II).

Parameter	Group I (n = 84)	Group II (n = 371)	Absolute difference or risk estimate with 95% confidence interval	*P* value
Mean no. of oocytes retrieved	13.21 ± 6.98	13.24 ± 5.66	−0.03 (−1.924, 1.856)	.971
Mean no. of metaphase II oocytes retrieved	11.15 ± 6.61	10.32 ± 4.89	0.82 (−0.885, 2.535)	.342
Fertilization rate (%)	88.18 ± 19.98	88.14 ± 17.09	0.04% (5.415%, 5.501%)	.988
Mean no. of available embryos				
Grade 1	4.63 ± 3.38	2.26 ± 2.87	2.37 (1.664, 3.075)	<.001
Grade 2	4.17 ± 3.01	1.72 ± 2.30	2.44 (1.863, 3.026)	<.001
Grade 3	0.11 ± 0.38	0.11 ± 0.52	0.00 (−0.123, 1.116)	.956
Mean no. of embryos transferred				
Grade 1	1.91 ± 0.51	1.74 ± 0.76	0.17 (−0.18, 0.352)	.077
Grade 2	1.70 ± 0.77	1.39 ± 0.59	0.31 (0.078, 0.542)	.009
Implantation rate (%)	12.02 ± 25.5	11.08 ± 25.6	0.42% (−6.5%, 5.6%)	.892
Clinical pregnancy rate (%)	34 (40.53)	107 (28.82)	1.678 (1.028, 2.739)	.049
Pregnancy outcome (%)				
Biochemical pregnancy	1 (2.9)	6 (5.6)	—	—
Missed abortion (<20 wk)	1 (2.9)	9 (8.4)	—	—
Full-term pregnancy (≥37 wk)	31 (91.2)	90 (84.1)	—	—
Preterm delivery (20–37 wk)	2 (5.8)	8 (7.5)	—	—
Singleton pregnancy	30 (88.2)	101 (94.4)	—	—
Twin pregnancy	4 (11.8)	6 (5.6)	—	—
OHSS (%)				.001
Mild	3 (3.6)	28 (7.5)	—	
Moderate	—	12 (3.2)	—	
Severe	—	20 (5.4)	—	

Note: Values are mean ± SD or number of patients (percentage).

Gurgan. Intravenous calcium and OHSS. Fertil Steril 2011.

Management

1. Moderate OHSS → conservative treatment and follow-up

2. Severe OHSS:

Admission for monitoring

1. Strict fluid chart
2. Plasma and urine osmolarity
3. Urea and electrolytes
4. Clotting parameters
5. Liver function tests
6. Pregnancy test
7. Pelvic sonography
8. Invasive hemodynamic monitoring

Medical treatment

1. Correction of circulatory and electrolyte imbalance
   - correction of electrolyte imbalance
   - plasma expanders
2. Anticoagulants: clinical or laboratory evidence of thromboembolism
3. Prostaglandin synthetase inhibitors could be hazardous to renal perfusion
4. Antihistamines: not effective
5. Danazol: not effective
6. Diuretics: deplete intravascular volume
7. Dopamine: in oliguric patients

Surgical treatment

Laparotomy
1. Experienced surgeon
2. Only if hemorrhage
   - torsion
   - rupture
   - ectopic
3. Only hemostatic

Laparoscopy
Unwinding of twisted ovarian cyst

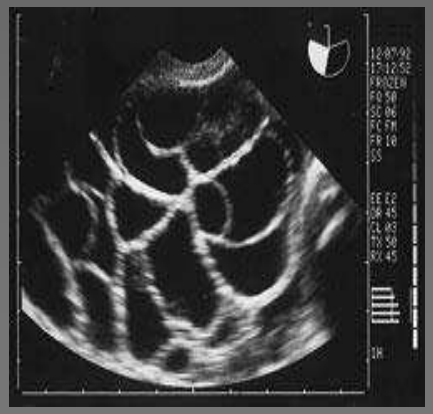
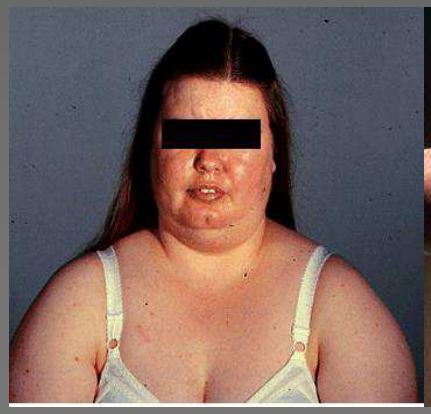
Aspiration of ascitic fluid
1. Abdominal paracentesis
2. Transvaginal aspiration

Advantages:
1. Improves symptoms
2. Improves renal function and urine output
3. Shortens venous return and cardiac output
4. Improves venous return and cardiac output

Precautions:
1. Sonographic guidance
2. Replacement of plasma protein
3. Repeat aspiration may be required

OHSS

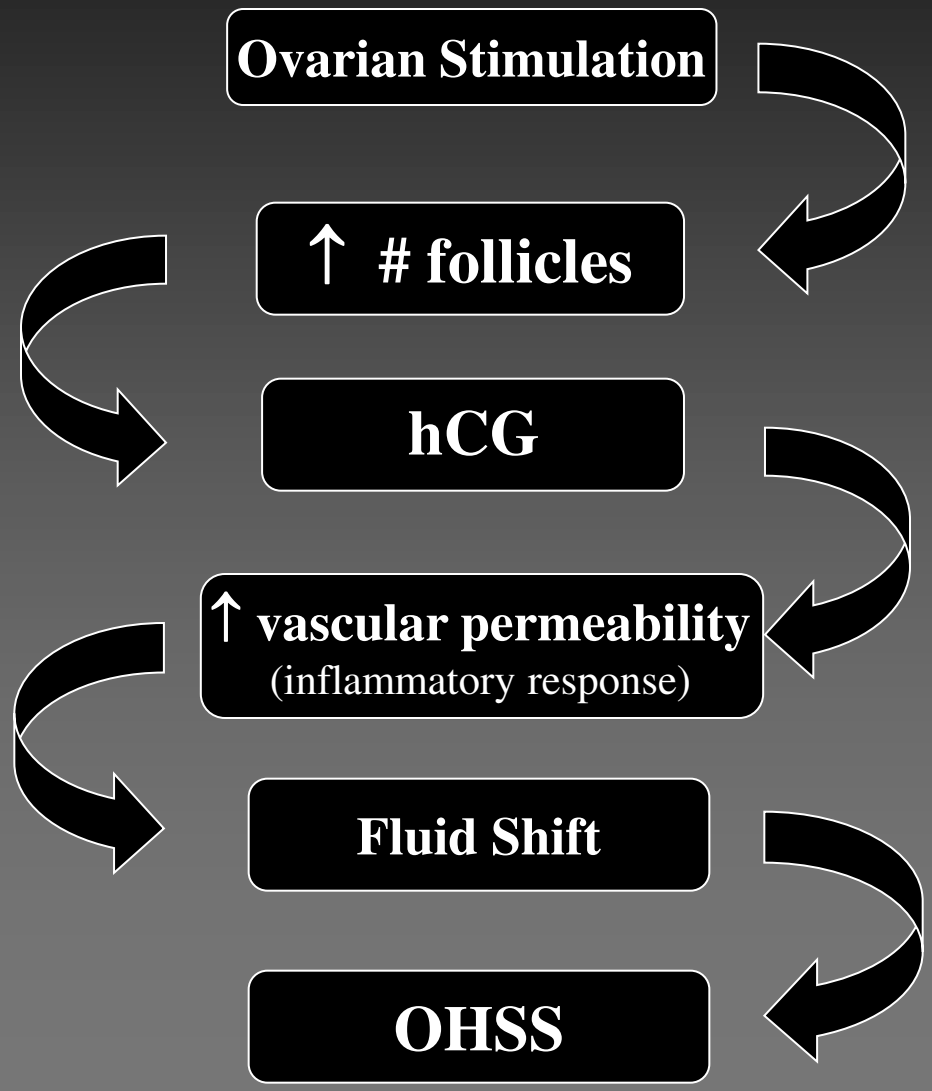
- OHSS önleneblir bir komplikasyondur
- İnsidansı kullanıcının OI filozofisini hastanın özelliklerine göre uygulamasına bağlıdır
- Stimulasyon protokollerinin hastaya özel kişiselleşmesi OHSS önlemesi için en kritik noktadır

KEEP ON GOING R.Edwards

OHSS: Strategies for Prevention

Mechanism (Pathophysiology)



Strategies for preventing OHSS

- **Individualization** (lowest gonadotropin doses)
- **Ovarian suppression** (OCP/GnRHa, GnRHa, GnRH antagonists)
- **Cycle cancellation**
- **Coasting**
- **↓ hCG dosage**
- **Antagonist + GNs + GnRHa as ovulatory stimulus**
- **Albumin,hydroxyethyl starch?**
- **Specific inflammatory antagonists?**
- **Paracentesis**
- **Supportive therapy (maintain fluid balance)**
- **Heparin**
- **Albumin, hydroxyethylstarch**
- **Dopamine agonists?**