

PCOS'da OHSS'yi Önleme Stratejileri



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Yıldız

29 EKİM CUMHURİYET BAYRAMI

KUTLU OLSUN!

OHSS

- Çok sayıda follikül elde etme amacıyla verilen gonadotropinlere cevapda aşırılık sonucunda ortaya çıkan yaşamı tehdit edici potansiyelde iyatrojenik bir komplikasyondur.
- Yardımcı Üreme Tedavilerinde daha sık
- Nadiren spontan,CC, GnRHa ile bildirilmiştir

OHSS: Ana bulgular

- Çok sayıda follikül gelişimi
- Bilateral ovaryan büyüme
- Vaskuler permeabilite artışı
- Üçüncü boşluklara ani sıvı geçişi
- İntravaskuler volum azalması
- Hemokonsantrasyon

OHSS Sınıflaması

Severity	Mild	Modarate	Severe
Baker (1982) ¹⁰	Grade 1: Estrogen > 150 µg/24h and progesterone > 10 mg/24h Grade 2: Grade 1 + enlarged ovaries and possibly palpable cysts	Grade 3: Grade 2 + confirmed palpable cysts and distended abdomen Grade 4: Grade 3 + vomiting and possibly diarrhea	Grade 5: Grade 4 + ascites and possibly hydrothorax Grade 6: Grade 5 + changes in blood volume, viscosity and coagulability etc.
WHO (1973) ¹¹	Grade 1: Variable ovarian enlargement sometimes associated with small cysts; urinary estrone levels > 150 µg/24h and progesterone excretion rate > 10 mg/24h	Grade 2: Additional symptoms of a variable nature: abdominal distension, nausea, vomiting and diarrhea	Grade 3: Large ovarian cysts, ascites and sometimes hydrothorax; hemocoagulation with increased blood viscosity and coagulability abnormalities may appear
Schacter (1978) ¹²	Grade 1: Estrogen > 150 µg/24h and progesterone > 10 mg/24h Grade 2: Grade 1 + enlarged ovaries, sometimes small cysts	Grade 3: Grade 2 + abdominal distension Grade 4: Grade 3 + nausea, vomiting and/or diarrhea	Grade 5: Grade 4 + large ovarian cysts, ascites and/or hydrothorax Grade 6: Marked hemocoagulation + increased blood viscosity and possibly coagulability abnormalities
Schwartz (1981) ¹³	Lower abdominal distention; ovaries slightly enlarged, but no larger than 5 x 3 cm, and no marked weight gain	Ovaries enlarged up to 10 x 10 cm, some ascites, and weight gain of up to 10% (kg)	Ovaries extremely enlarged and easily palpated; abnormally ascites, pleural effusions, oliguria, hemocoagulation, hypotension, anorexia and electrolyte imbalance occur; increased blood coagulability and weight gain of more than 10 kg are common
Golan (1989) ¹⁴	Grade 1: Abdominal distension and discomfort Grade 2: Grade 1 + nausea, vomiting and/or diarrhea, enlarged ovaries > 12 cm	Grade 3: Grade 2 + US evidence of ascites	Grade 4: Grade 3 + clinical evidence of ascites and/or hydrothorax and breathing difficulties Grade 5: Grade 4 + hemocoagulation, increased blood viscosity, coagulability abnormality and distended renal perfusion
Kayir (1992) ¹⁵			Severe OHSS: variable enlarged ovary; massive ascites & hydrothorax; Hct > 63%, WBC > 12000, oliguria; creatinine > 1.0-1.5 mg/dL; uremia; hematocrit > 30 mL/dL; liver dysfunction; anasarca Critical OHSS: variable enlarged ovary; severe ascites & hydrothorax; Hct > 63%, WBC > 25000, oliguria; creatinine > 1.0, uremic encephalopathy > 30 mL/min renal failure; thrombocytopenia; disseminated intravascular coagulation Grade A: Dyspnea, oliguria, nausea, vomiting, diarrhea, abdominal pain, clinical evidence of ascites, marked distension of abdomen or hydrothorax, US showing large ovaries and marked ascites, normal biochemical profile Grade B: Grade A + massive reactive ascites, markedly enlarged ovaries, severe dyspnea and marked oliguria, increased Hct, elevated creatinine and liver dysfunction Grade C: Complications such as respiratory distress syndrome, renal shutdown or acute thrombosis
Wak (1994) ¹⁶		Distention, pain, nausea, diarrhea, US evidence of ascites and enlarged ovaries, normal hematological and biological profiles	

• Hafif

- Grade 1 Abdominal gerginlik, rahatsızlık
- Grade 2 Bulantı, kusma 4+-diare, Overler 5-10cm

• Orta

- Grade 3 Hafif form + US'da assit

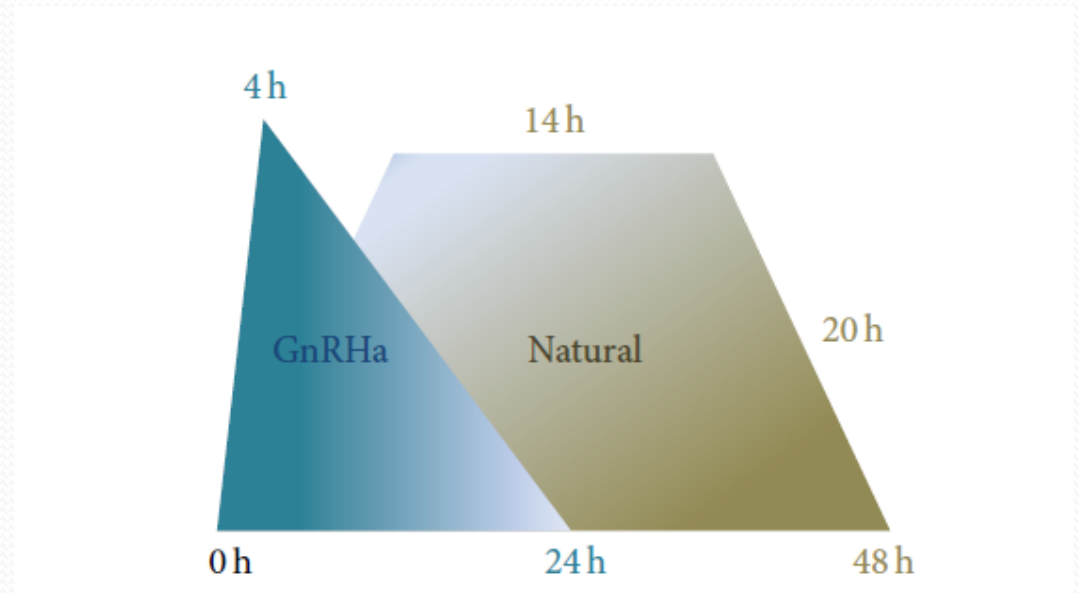
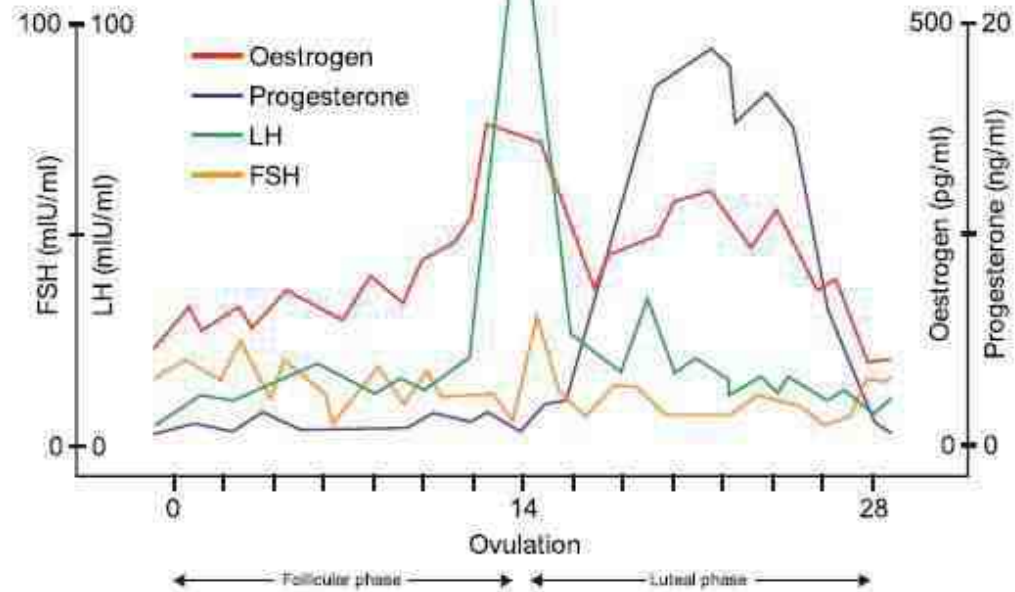
• Şiddetli

- Grade 4 Orta form + klinik assit + - hidrotoraksa bağlı dispne
- Grade 5 Grade 4 + azalmış kan hacmi, hiperkoagulopati ve bozulmuş renal fonksiyon

Şiddetli-Kritik OHSS

Severe OHSS	Critical OHSS
Variably enlarged ovary	Variably enlarged ovary
Massive ascites ± hydrothorax	Tense ascites ± hydrothorax
Hematocrit >45%	Hematocrit >55%
White blood cell count >15,000	White blood cell count >250,000
Oliguria	Oliguria
Creatinine 1.0–1.5 mg/dl	Creatinine >1.6 mg/dl
Creatinine clearance ≥50 ml/min	Creatinine clearance <50 ml/min
Liver dysfunction	Renal failure
Anasarca	Thromboembolic phenomenon
	Acute respiratory syndrome

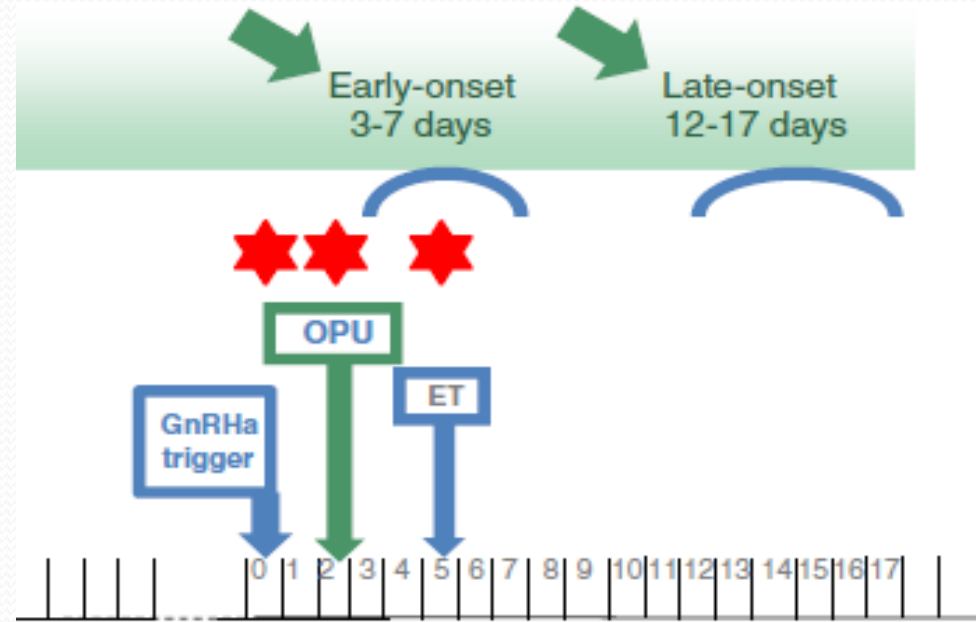
Tetikleyici Faktör: hCG (yö:2.32 gün)



OHSS Başlangıcı

Study/Event	Early	Late
Lipson (1994) ¹	OHSS occurring 3-7 days after hCG administration	OHSS occurring 12-17 days after hCG administration
Quinn (1997) ²	OHSS occurring within 10 days after hCG administration	OHSS occurring from Day 11 onwards after hCG administration
Mattar (2004) ³	OHSS occurring within 11 days after hCG administration	OHSS occurring from Day 12 onwards after hCG administration
Tapanainen (2005) ⁴		
Tapanainen (2007) ⁵		
Palomaa (2006) ⁶	OHSS occurring within 7 days after hCG administration	OHSS occurring from Day 10 onwards after hCG administration
Carver (2008) ⁷		
Pau (2008) ⁸	OHSS in women who did not become pregnant	OHSS prevented in women who became pregnant

Only first number of each study is given. hCG, human chorionic gonadotropin; hA, hatched; GA, clinical; WBC, white blood cell count.

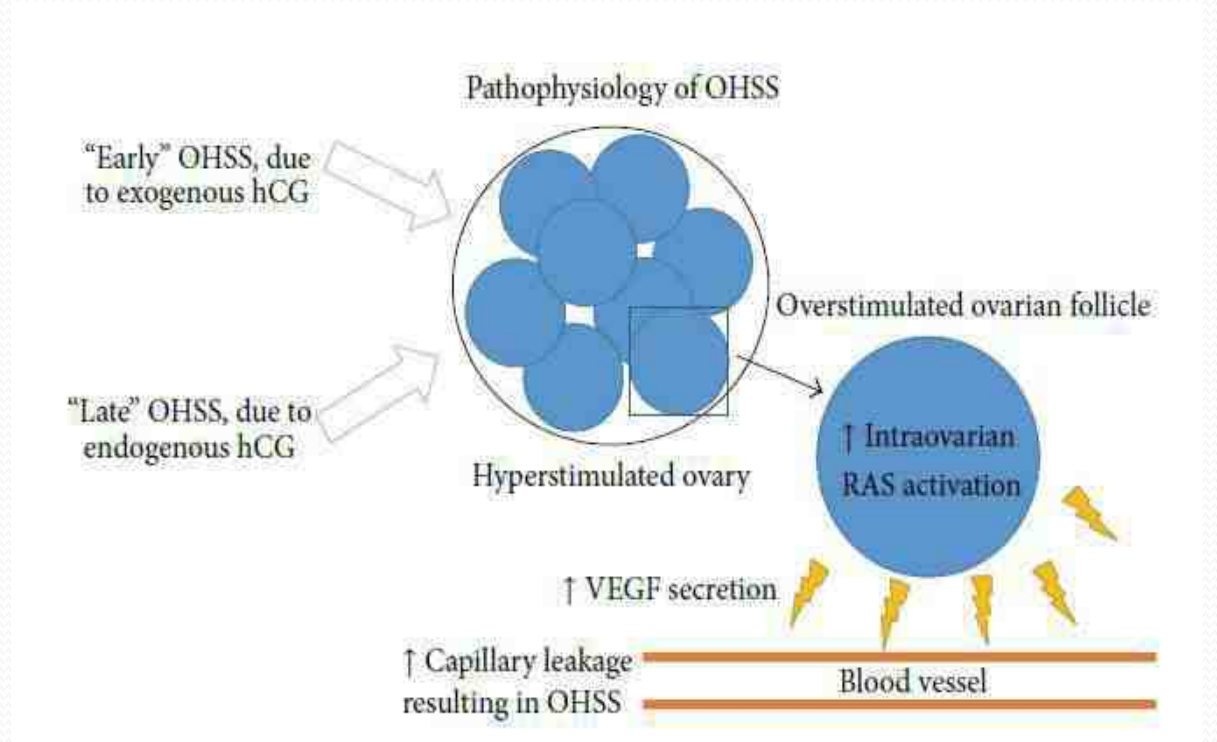


Erken OHSS < 10 gün < Geç OHSS

Patofizyoloji:

- Rol alan Faktörler:

- Angiotensin II
- IGF-I
- **VEGF**
- Interleukin-6 vb



VEGF-A, VEGFR-2 etkileşimi

İnsidans

- OHSS
 - Hafif : % 7-33
 - Orta : % 2-8
 - Şiddetli: <%2
- Orta-Şiddetli OHSS
 - Az riskli grup : % 3-8
 - Çok riskli grup: % 20

OHSS Risk Faktörleri- Bazal

- Genç yaş <30
- Zayıflık
- OHSS geçmişi
- PCOS (>24 follikül)
- Yüksek doz gonadotropin

Primer Belirteçler

- AMH :
 - ≤ 1.26 ng/mL, Normal cevap ≥ 4 oosit (Gnoth C, 2008)
 - > 3.36 ng/mL, OHSS (Sensitivity %90.5, Specificity %81.3) (Lee T 2008)
- AFC:
 - ≥ 24 oosit o-ş OHSS: %8.6
 - < 24 oosit o-ş OHSS: %2.2 (Jayaprakasan K,2012)
 - ≥ 12 oosit OHSS riski artar (Papanikolaou E, 2010)

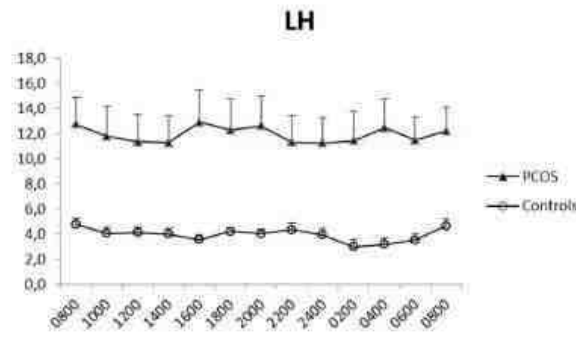
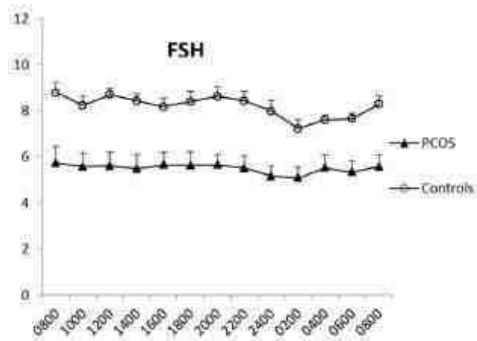
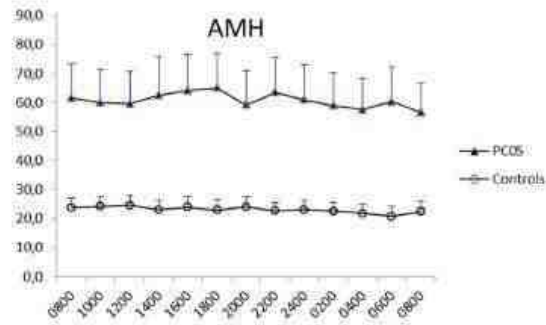
OHSS Risk Faktörleri -Takip

- Hızla yükselen E2 seviyeleri
- Çok sayıda folikül gelişimi (≥ 11 mm follikül)
- Ovulasyon tetiklenmesinde hCG kullanımı
- Luteal destekde hCG kullanımı
- Gebelik oluşması
- Çoğul gebelik önlemi: SET

PCOS

- Üreme çağında %6-8 insidans
- Kronik Anovulasyon
- Oligomenore
- Hiperandrojenemi
- US'da PCO görüntüsü

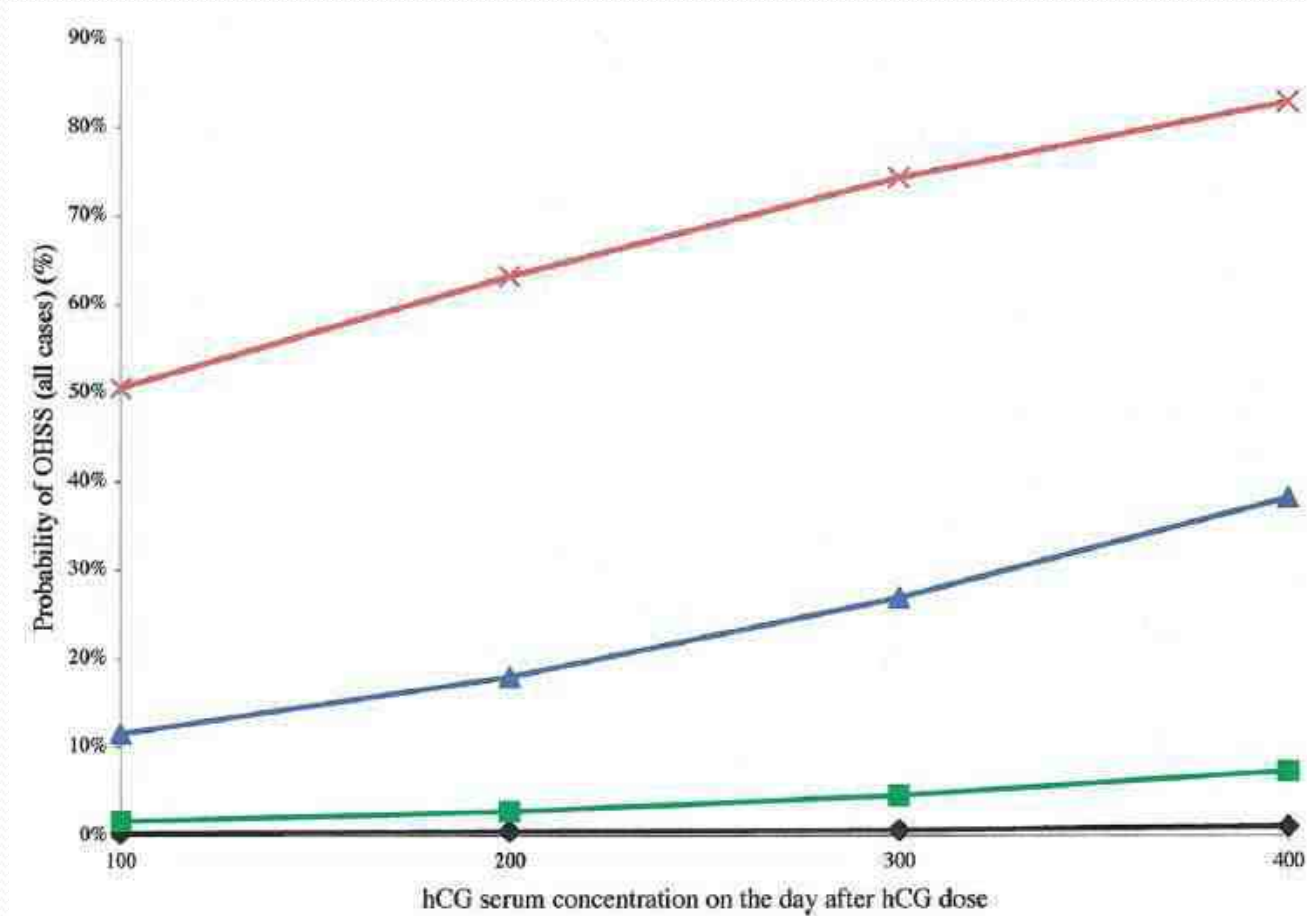
The Circadian Variation in Anti-Müllerian Hormone in Patients with Polycystic Ovary Syndrome Differs Significantly from Normally Ovulating Women



Time	8.00am	10.00am	12.00pm	2.00pm	4.00pm	6.00pm	8.00pm	10.00pm	12.00am	2.00am	4.00am	6.00am	8.00am
AMH													
PCOS, pmol/L; mean (SD)	61,6 (35,1)	60,0 (35,1)	59,6 (33,9)	62,5 (40,2)	64,1 (38,0)	65,0 (35,6)	59,1 (36,2)	63,5 (36,8)	61,0 (36,0)	58,9 (34,0)	57,5 (32,9)	60,4 (36,2)	56,7 (30,8)
Controls, pmol/L; mean (SD)	23,8 (10,0)	24,2 (11,3)	24,5 (11,8)	23,0 (10,9)	23,9 (12,6)	22,9 (11,8)	24,0 (11,7)	22,6 (10,0)	23,0 (10,7)	22,6 (10,2)	21,7 (10,9)	20,8* (11,3)	22,4 (12,0)
FSH													
PCOS, IU/L; mean (SD)	5,7 (1,2)	5,6 (1,1)	5,6 (0,8)	5,5 (0,9)	5,6 (1,1)	5,6 (1,2)	5,6 (1,3)	5,5 (1,2)	5,1 (1,3)	5,1* (1,2)	5,5 (0,6)	5,3 (0,7)	5,6 (1,0)
Controls, IU/L; mean (SD)	8,8 (3,1)	8,2 (2,6)	8,7 (2,6)	8,4 (2,7)	8,5 (2,3)	8,4 (2,5)	8,6 (2,0)	8,4 (2,3)	8,0 (1,9)	7,2* (1,9)	7,6* (2,4)	7,7* (2,4)	8,3 (2,2)
LH													
PCOS, IU/L; mean (SD)	12,8 (6,3)	11,8 (7,2)	11,3 (6,6)	11,3 (6,5)	12,9 (7,6)	12,3 (7,5)	2,6 (7,1)	11,3 (6,5)	11,2 (5,0)	11,4 (7,0)	12,5 (6,8)	11,5 (5,6)	12,2 (5,6)
Controls, IU/L; mean (SD)	4,8 (1,6)	4,1 (1,6)	4,1 (1,5)	4,0 (1,4)	3,8 (1,2)	4,2 (0,9)	4,0 (1,2)	4,3 (1,8)	3,9 (1,7)	3,0* (1,9)	3,2* (1,7)	3,5* (1,7)	4,7 (1,7)

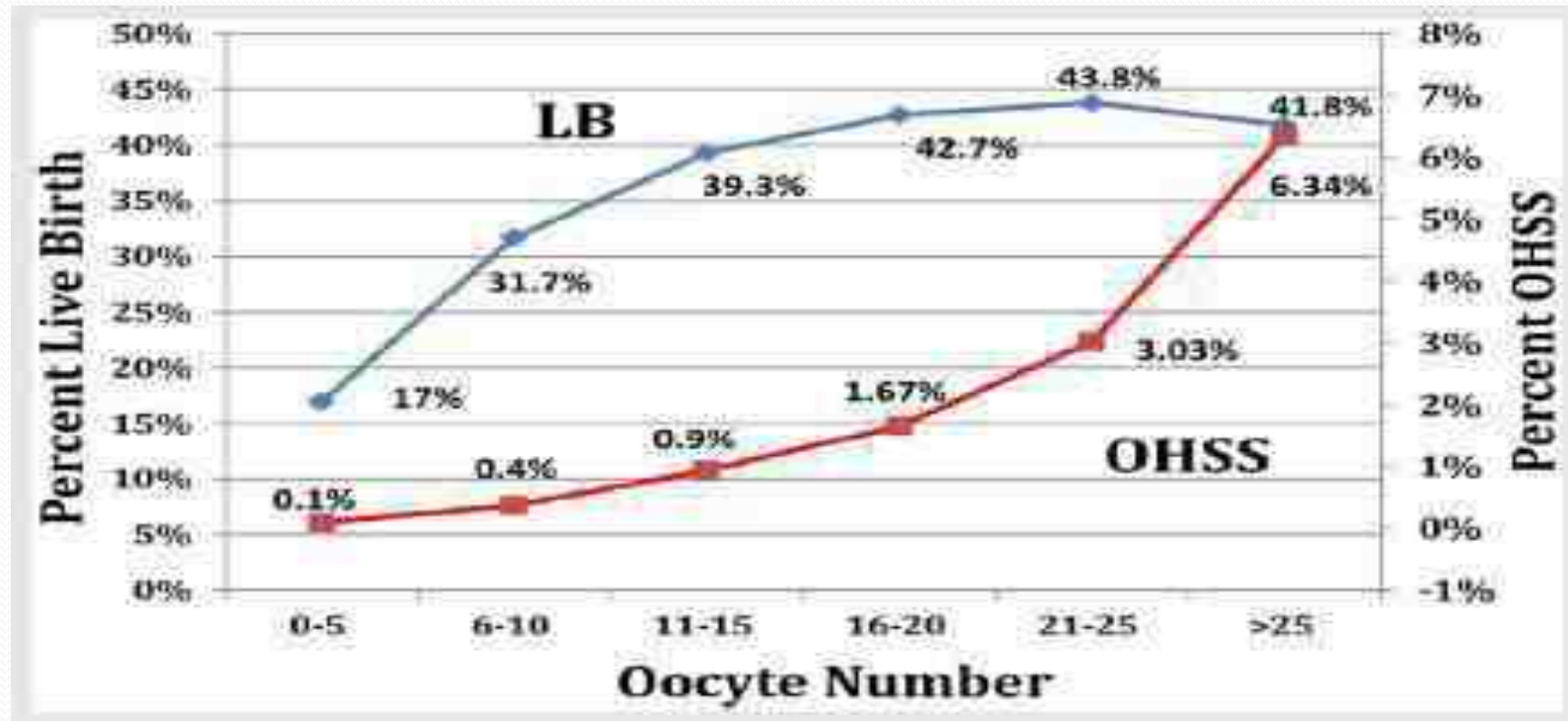
*p<0,05 in comparison to 08.00 a.m. levels.

Folikül Sayısı OHSS Riski



Folikül sayısı
45
35
25
15

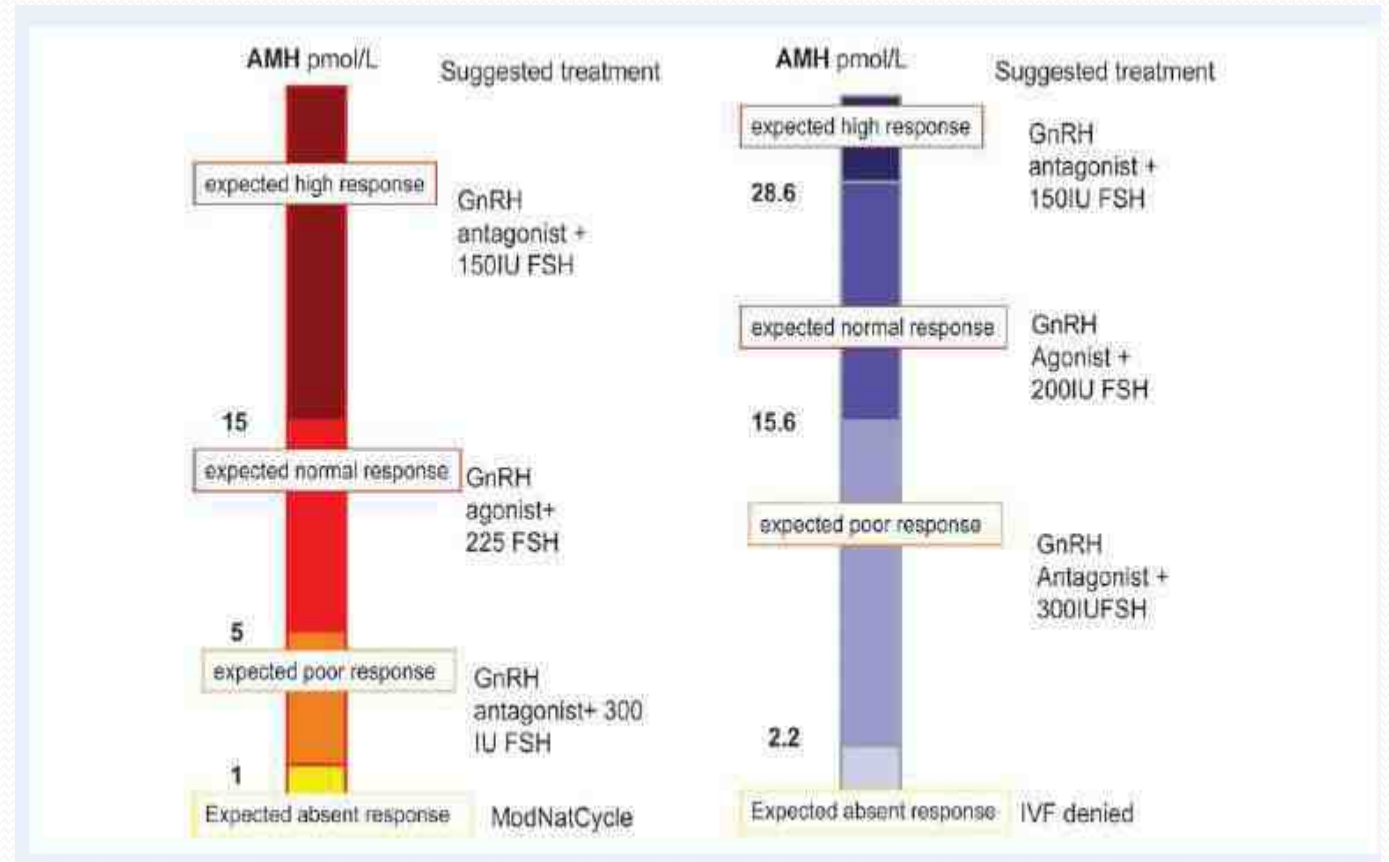
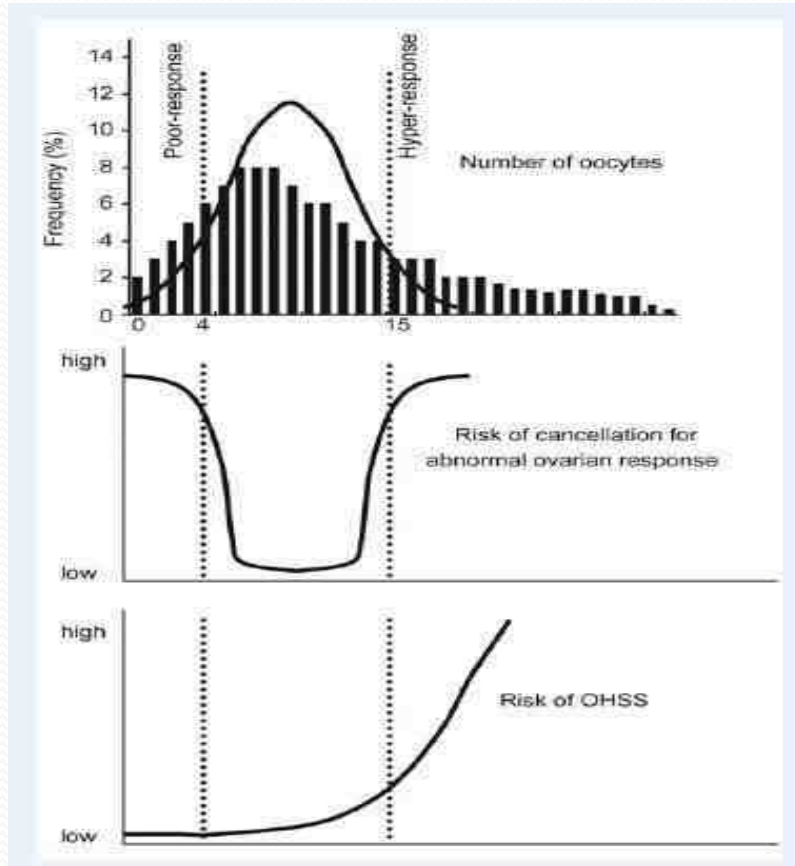
SART 2008-2010



Primer Korunma

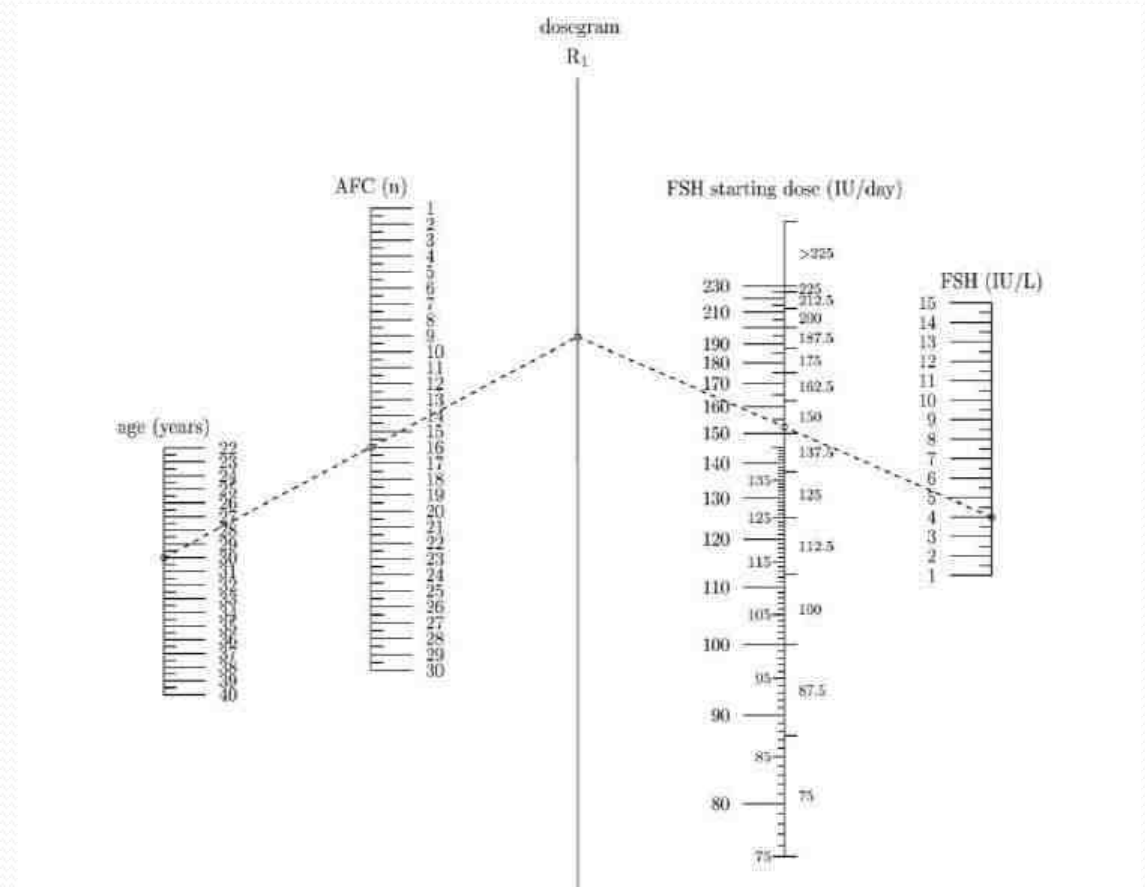
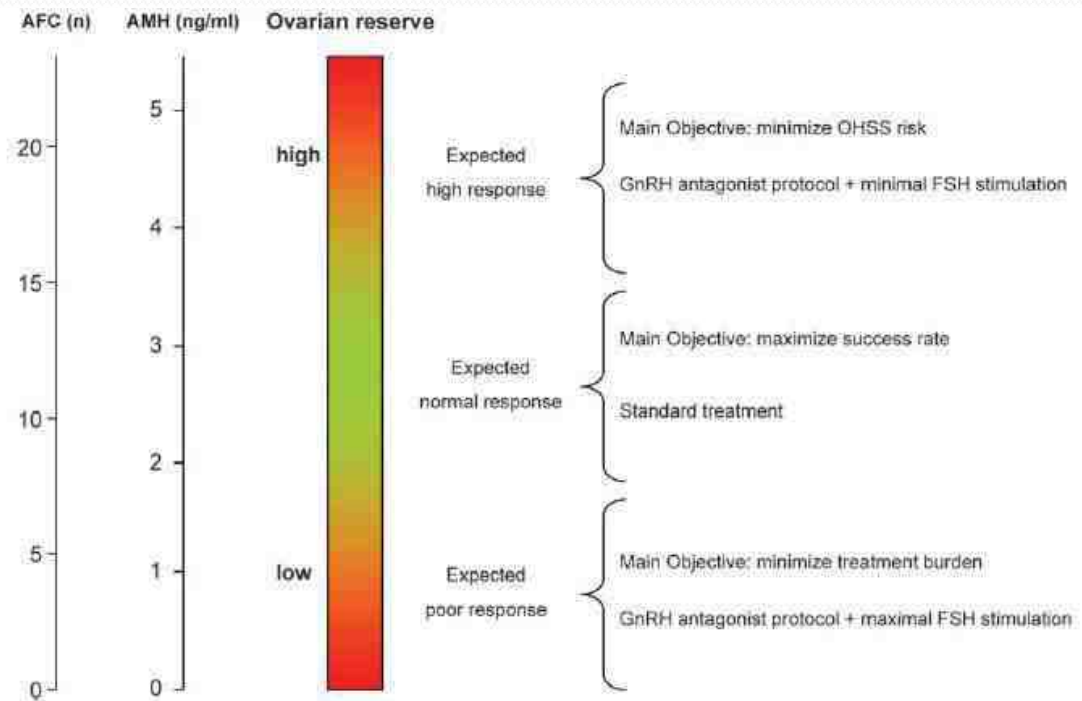
- 1- Bireyselleştirilmiş tedavi şeması (iCOS)
- 2- OK kullanımı
- 3- Siklus tercihi (Agonist X Antagonist)
- 4- Metformin
- 5- Gonadotropin doz ve süresini azaltmak. (FSH türü etkilemez)
- 6- Mild Stimulasyon /Aromataz inhibitörleri
- 7- IVM

Kişiselleştirilmiş Doz



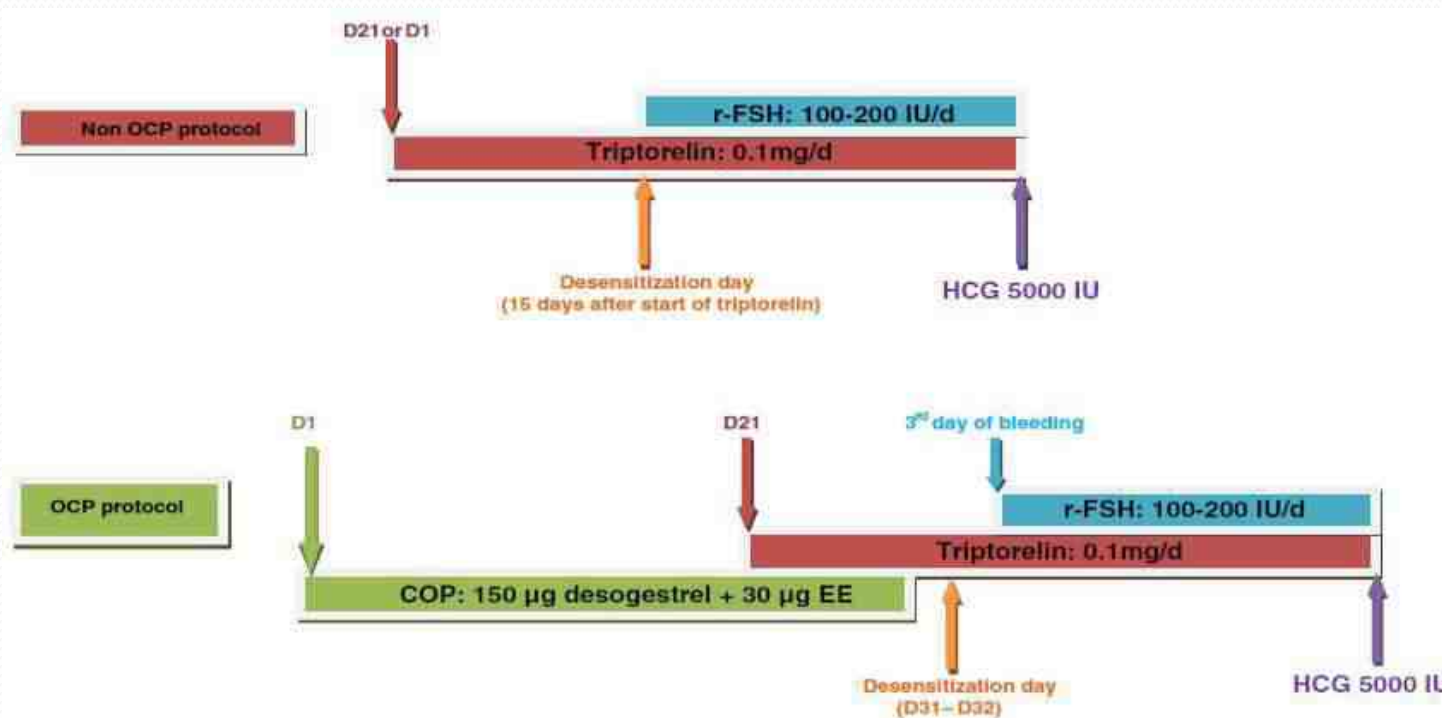
Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice

Antonio La Marca^{1,*} and Sesh Kamal Sunkara²



First intention IVF protocol for polycystic ovaries: does oral contraceptive pill pretreatment influence COH outcome?

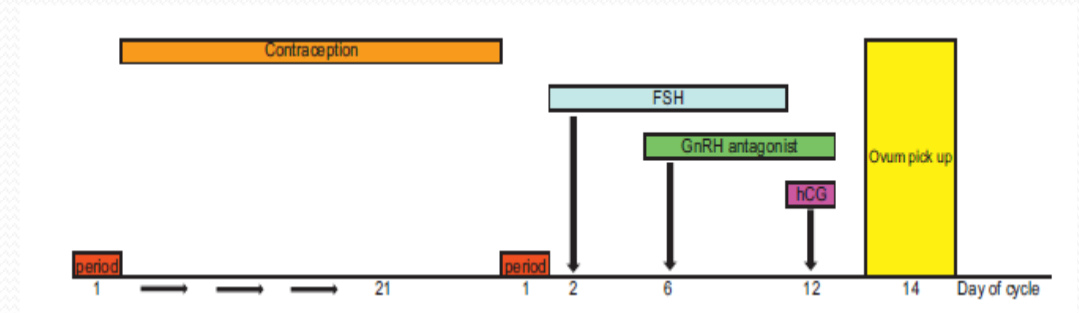
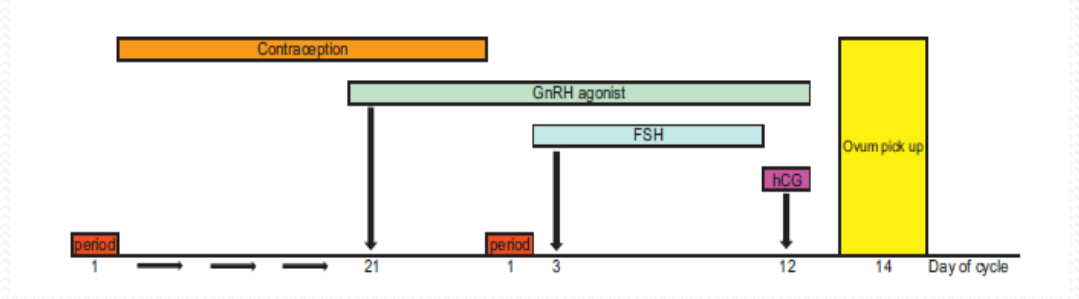
Christine Decanter^{1*}, Geoffroy Robin^{1†}, Patricia Thomas¹, Maryse Leroy¹, Catherine Lefebvre¹, Benoit Soudan², Valerie Lefebvre-Khalil³, Brigitte Leroy-Martin³ and Didier Dewailly¹



In conclusion, extended OCP pretreatment, as a first intention IVF protocol for PCO patients, does not improve the pattern of follicular growth nor the oocyte and embryo quality.

OHSS: Agonist / Antagonist Siklus

- Antagonist siklus;
- Daha az
 - Enjeksiyon,
 - Gonadotropin dozu
 - Uygulama süresi
- Agonist tetikleme imkanı
 - hCG uzun luteotropik etkili(8-9 gün)
 - Analog hızlı luteolitik etkili
- Erken OHSS riskinde azalma



Antagonist vs Agonist Siklus

- Cochrane Rev, (Nugent D,2000)
 - Agonist siklusda hiperstimulasyon artar (OR3.15; %95 CI 1.48-6.7)
 - Gonadotropin ihtiyacı, maliyet artar, gebelik oranı sabit
- Cochrane Rev,29RCT (Al-Inany HG,2011)
 - Antagonist siklusda OHSS riski azalır (OR 0.43; %95 CI 0.33-0.57)
 - Gebelik ve canlı doğum oranları aynı

Antagonist+ Metformin

Doldi N et al
(2006)

PCOS affected
(n=20)
Standard short
GnRH-ant protocol
for ovarian
stimulation with
2 month-long
metformin
pretreatment

PCOS affected
(n=20)
Standard short
GnRH-ant
protocol
for ovarian
stimulation

Total r-FSH dose:
GnRH-ant+ M < GnRH-ant, $p < 0.05$
Serum E₂ (hCG day):
GnRH-ant + M < GnRH-ant, $p < 0.05$
No. of mature oocytes:
GnRH-ant+ M > GnRH-ant, $p < 0.05$
No. of cancelled cycles:
GnRH-ant+ M < GnRH-ant, $p < 0.05$
OHSS rate:
GnRH-ant+ M < GnRH-ant, $p < 0.05$
No. of follicles ≥ 14 mm, No. of
oocytes retrieved, Duration of
the stimulation: NS

Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for *in vitro* fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials

S Palomba, A Falbo, GB La Sala

- Metformin PCOS'da OHSS insidansını %70 azaltır (Tso LO, 2014)
- Metformin ovaryan steroidogenez ve intraovarian insulin direncine etki ederek İntraovarian hiperandrojenizmi ve morfolojisini iyileştirir
- Metformin alan PCOS'lu hastalarda serum E2 seviyeleri daha düşük
- 8 hafta önce başlamalı, 3x 500mg
- Sendromsuz PCO'li hastalarda bu yarar izlenmemiştir (RCT,Swanton A 2011)

Mild Protokoller

- Amaç daha ılımlı over uyarısı
- Oral ajanlarla değişik kombinasyonlar
- FSH uygulaması orta –geç foliküler faza ertelenir
- OHSS riski düşer

- Dezavantajları:
 - Siklus iptali artar
 - Düşük gebelik oranları
 - (%15 vs %29 Revelli A 2011, Karimzadeh MA 2010)

In-vitro maturasyon

Uygulama

- I. Uyarılmamış/ minimal uyarılmış follikül (2-12mm)
- II. Endometrium 6-8mm, lider follikül 10-12mm
- III. 7-8.gün End< 6 mm HMG 150IU 3-5 gün
- IV. İmmatur GV oositler 75IUFSH/LH medyumda 24-52 s kültür

Dezavantaj

- I. IVM IVF'e göre optimal değildir
- II. Gebelik oranları daha az
- III. Canlı doğum oranları daha az

Avantaj

- I. Düşük maliyet
- II. Ovaryan stimulasyon gerekmez/ kısmi
- III. Monitorizasyon minimal
- IV. OHSS riski minimal
- V. Genç hastalarda daha başarılı
- VI. PCOS için Alternatif yöntem

In-vitro maturation versus IVF with GnRH antagonist for women with polycystic ovary syndrome: treatment outcome and rates of ovarian hyperstimulation syndrome

Mausumi Das, Weon-Young Son, William Buckett, Togas Tulandi *, Hananel Holzer

Clinical profile	IVF with GnRH antagonist protocol	In-vitro maturation protocol
Number of cycles	60	102
Age (years) (mean ± SEM)	31.7 ± 0.48	30.8 ± 0.3
Body mass index (kg/m ²) ^a	25.5 (21.9-32)	24.5 (21.7-29.8)
Antral follicle count ^a	39.5 (31-45)	40 (34-47)
FSH (IU/L) (mean ± SEM)	5.83 ± 0.2	5.9 ± 0.2
LH (IU/L) ^a	7 (4.5-9)	6.6 (4.3-9)
Oestradiol (pg/ml) ^a	173.5 (133-211)	141.5 (108-202.5)
Progesterone (ng/ml) ^a	3.1 (2.2-9)	2.1 (1.8-3.6)

^aMedian and inter-quartile range. No statistically significant differences were found between the two groups.

	IVF with GnRH antagonist protocol (n = 60)	In-vitro maturation protocol (n = 102)	P-value
Total dose of gonadotrophins used (IU)	1575 (1200-2150)	0 (0-450) (n = 38)	<0.0001
Number of oocytes	17 (10.5-23)	20 (14-26)	0.031
Number of MII oocytes	10 (7-15)	12 (8-17)	NS
In-vitro maturation rate n (%) ^a	NA	1196/1988 (60.2)	
Number of zygotes	8 (4-11)	8 (5-11)	NS
Fertilization rate n (%) ^a	74.2 (56.8-87.9)	71.0 (57.1-85.7)	NS
Number of embryos cleaved	8 (4-11)	7 (4-10)	NS
Number of embryo transfer cycles	59	102	
Number of embryos transferred	1 (1-2)	4 (3-4)	0.0001
Implantation rate n (%) ^a	33/93 (35.5)	50/295 (16.9)	0.002
Clinical pregnancy rate per transfer n (%) ^a	27 (45.8)	33 (32.4)	NS
Multiple pregnancy rate n (%) ^a	6 (22.2)	10 (30.3)	NS
Live birth rate per transfer n (%) ^a	24 (40.7)	24 (23.5)	0.04
Spontaneous abortion rate per transfer n (%) ^a	3 (5.1)	7 (6.9)	NS
Moderate or severe ovarian hyperstimulation syndrome n (%) ^a	5 (8.33)	0	0.006

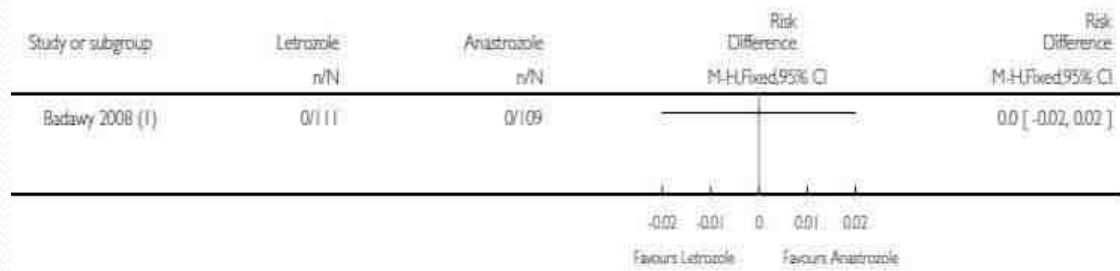
Aromatase inhibitors for subfertile women with polycystic ovary syndrome (Review)

Franik S, Kremer JAM, Nelen WLDM, Farquhar C

Review: Aromatase inhibitors for subfertile women with polycystic ovary syndrome

Comparison: 5 Letrozole compared to anastrozole

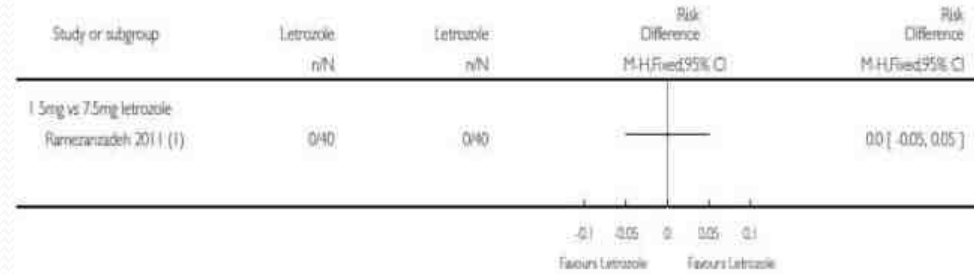
Outcome: 1 Ovarian hyperstimulation syndrome rate



(I) Clomiphene resistant women; Letrozole, 2.5 mg/day versus anastrozole, 1 mg/day

Comparison: 7 Dosage studies of letrozole

Outcome: 1 Ovarian hyperstimulation syndrome rate



(I) No previous ovulation induction treatment

Farklı dozlarda AI uygulamaları ile diğer tedaviler arasında OHSS açısından fark yok

Cochrane 2014

Sekonder Korunma (hCG öncesi)

- 1- Siklus iptali
- 2- Coasting
- 3- Ovulasyon Uyarısında Alternatif uygulamalar,
 - hCG doz azaltması
 - rhLH,
 - GnRHa + iLPS
- 4- Cryo (Freeze- all policy)
- 5- IV Kolloid infüzyonu
 - Albumin
 - HES
- 6- Cabergoline
- 7- Diğer

Coasting

- Hipofizer supresyon
- Gntr kesilmesi
- hCG ertelenmesi (uygun E2 deęerlerine gerileme)

- Genel olarak 3 günden az olmalı
- 4. gün E2 yüksek ise siklus iptali
- OHSS:
 - Risk azalır (Mansour R 2005)
 - Fark yok (D'Angelo A, Cochrane 2011)

Triggering final oocyte maturation using different doses of human chorionic gonadotropin: a randomized pilot study in patients with polycystic ovary syndrome treated with gonadotropin-releasing hormone antagonists and recombinant follicle-stimulating hormone

Efstratios M. Kolibianakis, M.D., Ph.D., Evangelos G. Papanikolaou, M.D., Ph.D., Herman Tournaye, M.D., Ph.D., Michel Camus, M.D., Andre C. Van Steirteghem, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

Cycle outcome in groups of patients randomized to receive 10,000, 5000, or 2500 IU of hCG for triggering final oocyte maturation.

	10,000 IU	5000 IU	2500 IU	P ^e
Ongoing pregnancy per patient randomized % (95% CI) (n)	25.0 (12.7–43.4) (7/28)	30.8 (16.5–49.9) (8/26)	30.8 (16.5–49.9) (8/26)	.64
Ongoing pregnancy per hCG/oocyte retrieval % (95% CI) (n)	26.9 (13.7–46.1) (7/26)	30.8 (16.5–49.9) (8/26)	34.8 (18.8–55.1) (8/23)	.55
Ongoing pregnancy per embryo transfer % (95% CI) (n)	29.2 (14.9–49.2) (7/24)	33.3 (17.9–53.3) (8/24)	44.4 (24.6–66.3) (8/18)	.32
Overall cancellation rate ^a % (95% CI) (n)	14.3 (5.7–31.5) (4/28)	7.7 (2.1–24.1) (2/26)	30.8 (16.5–49.9) (8/26)	.12
Cancellation rate following hCG administration ^b % (95% CI) (n)	7.7 (2.1–24.1) (2/26)	7.7 (2.1–24.1) (2/26)	21.7 (9.7–41.9) (5/23)	.19
Ongoing implantation rate % (95% CI) (n)	22.6 (11.4–39.8) (7/31)	33.3 (19.7–50.4) (11/33)	40.9 (23.3–61.3) (9/22)	.15
Early pregnancy loss ^c % (95% CI) (n)	30.0 (10.8–60.3) (3/10)	27.3 (9.7–56.5) (3/11)	27.3 (9.7–56.5) (3/11)	.89
Multiple pregnancies	0	2 ^d	1	

OHSS : A ve B'de birer adet

LH vs hCG

- Aynı reseptörü uyarmalarına rağmen yarı ömürlerindeki farklılık nedeniyle etkinlikleri farklı
- Donör Luteal faz süresi
 - hCG ile ortalama 13 gün
 - GnRha tetiklemesinde dört güne kadar azalır

	LH	hCG
Secreted by	Pituitary	Embryo and placenta
Physiological role	Support follicle development (14 days)	Support implantation and pregnancy (282 days)
Binding affinity	Lower	Higher (2x)
Half-life	Shorter (23 h sc)	Longer (32-33 h sc)
Accumulation	Slight	Significant and down regulation of LH receptor
Stimulation of LH receptor	Physiological	Pharmacological, leading to LH receptor down regulation
Equivalency	6-8 IU of LH	1 IU of hCG
Purity	99%	99% purity for r-hCG and 70% in HP-hMG (39 identified contaminants)
Sources	r-hLH	r-hCG, urinary hCG or hMG
Induction of steroid (testosterone, oestradiol and progesterone) production	Higher LH = higher steroid production	Higher hCG = higher steroid production
Filling system	Filled by mass	Filled by Mass for r-hCG and Filled by IU for hCG/hMG
Gene activation	Differential unexplained	Differential unexplained
Cytokine production	Differential unexplained	Differential unexplained
Embryo quality production	Not objectively proven	Not objectively proven

HCG yerine GnRHa Tetiklemesi

- İlk çalışmalar GnRHa + Standart LPS düşük gebelik oranları
- Yoğun Luteal Destek
- 6 RCT GnRHa vs hCG
 - 3 RCT, (Yüksek doz, E2+P)
 - 2RCT, (P+ düşük doz hCG)
 - 1RCT, (P+ rhLH)
- OHSS : % 0 vs 4.6 (Humaidan P,2011)

HCG vs Analog trigger (Leuprolide 2.5 mg)

Outcome of cycle.	Study group	Control group	Odds ratio (95% CI)	P value
Primary end points				
OHSS (intention to treat)				
Total n, (%)	0/33 (0)	10/32 (31.3)	0 (0–0.26) ^a	<.01
Moderate/severe, n (%)	0/33 (0)	5/32 (15.6)	0 (0–0.74) ^a	.02
OHSS (per protocol)				
Total, n (%)	0/30 (0)	10/29 (34.5)	0 (0–0.26) ^a	<.01
Moderate/Severe, n (%)	0/30 (0)	5/29 (17.2)	0 (0–0.73) ^a	.02
Secondary end point (per protocol)				
Implantation rate, n (%)	22/61 (36)	20/64 (31)	1.18 (0.52–2.65)	.69
Other end points (per protocol)				
Positive pregnancy, n (%)	19/30 (63.3)	18/29 (62.1)	1.06 (0.37–3.0)	.92
Clinical pregnancy rate, n (%)	17/30 (56.7)	15/29 (51.7)	1.22 (0.4–3.4)	.45
Ongoing pregnancy rate, n (%)	16/30 (53.3)	14/29 (48.3)	1.22 (0.4–3.4)	.45

^a The estimates of these odds ratios are zero, because no patient developed OHSS in the study group.

Factors that predict the probability of a successful clinical outcome after induction of oocyte maturation with a gonadotropin-releasing hormone agonist

Nicole Kummer, M.D.,^a Claudio Benadiva, M.D.,^a Richard Feinn, Ph.D.,^b Jessica Mann, M.D.,^a
John Nulsen, M.D.,^a and Lawrence Engmann, M.D.^a

Cycle outcome according to peak E2 level.

Variable	Group 1: E ₂ < 4,000 pg/mL	Group 2: E ₂ ≥ 4,000 pg/mL	P value
Biochemical miscarriage rate n (%)	35/144 (24.3)	6/45 (13.3)	.85
Clinical miscarriage rate n (%)	19/144 (13.2)	6/45 (13.3)	.57
Implantation rate n (%)	120/475 (25.3)	52/143 (34.4)	.03
Clinical pregnancy rate per cycle n (%)	94/247 (38.1)	37/69 (53.6)	.02
Ongoing pregnancy rate per cycle n (%)	82/247 (33.2)	31/69 (44.9)	.07

GnRHa: Luteal Destek Protokolü

- 1-Dual trigger
- 2- Yoğun Luteal Destek
 - A- Yüksek doz E2 ve P, C. Luteum dejenerasyonu
 - B-OPU günü düşük doz hCG ile C. Luteum fonksiyon kurtarması(Luteal Rescue)
 - Progesteron yerine hCG (Luteal rescue, Dual Trigger) kullanımı OHSS riskini arttırır

1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study

Peter Humaidan, M.D.,^a Helle Ejdrup Bredkjær, M.D., Ph.D.,^b Lars Grabow Westergaard, M.D., D.M.Sc.,^c and Claus Yding Andersen, D.M.Sc.^d

- Antagonist siklus
- Normal cevaplı olgu
- hCG vs GnRHa + 1500 IU hCG OPU
- hCG grubunda 2 OHSS
- Luteal Rescue

Pregnancy outcome in GnRHa vs. hCG-group.

Variable	GnRHa	hCG	OR (95% CI)	P Value
Patients, n	152	150		
Rate of transfer, n (%)	130/152 (86)	138/150 (92)	0.5 (0.4–0.7)	.054
Embryos transferred, median (range)	2 (1–2)	2 (1–2)		
Positive hCG per ET, n (%)	63/130 (48)	66/138 (48)	1.0 (0.9–1.2)	.36
Clinical pregnancy per patient, n (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	.29
Ongoing pregnancy per patient, n (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	.16
Early pregnancy loss, n (% of positive hCG)	13/63 (21)	11/66 (17)	1.3 (0.7–1.9)	.36

Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders

Daniel Griffin, M.D., Claudio Benadiva, M.D., Nicole Kummer, M.D., Tara Budinetz, D.O., John Nulsen, M.D., and Lawrence Engmann, M.D.

- Antagonist siklus
- hCG günü E2 < 4000 pg/mL
- GnRHa vs İkili Tetikleme (GnRHa + 1000 IU hCG)

Variable	GnRHa alone	Dual trigger	P value
Biochemical miscarriage rate (%)	14/43 (32.6)	4/26 (15.4)	NS
Clinical miscarriage rate (%)	6/43 (14.0)	3/26 (11.5)	NS
Implantation rate (%)	27/122 (22.1)	26/62 (41.9)	< .01
Clinical pregnancy rate (%)	25/68 (36.8)	20/34 (58.8)	.03
Live birth rate (%)	21/68 (30.9)	18/34 (52.9)	.03
OHSS rate (%)	0/68 (0)	1/34 (2.9)	NS

Note: OHSS = ovarian hyperstimulation syndrome.

Hiperresponder: GnRHa Trigger

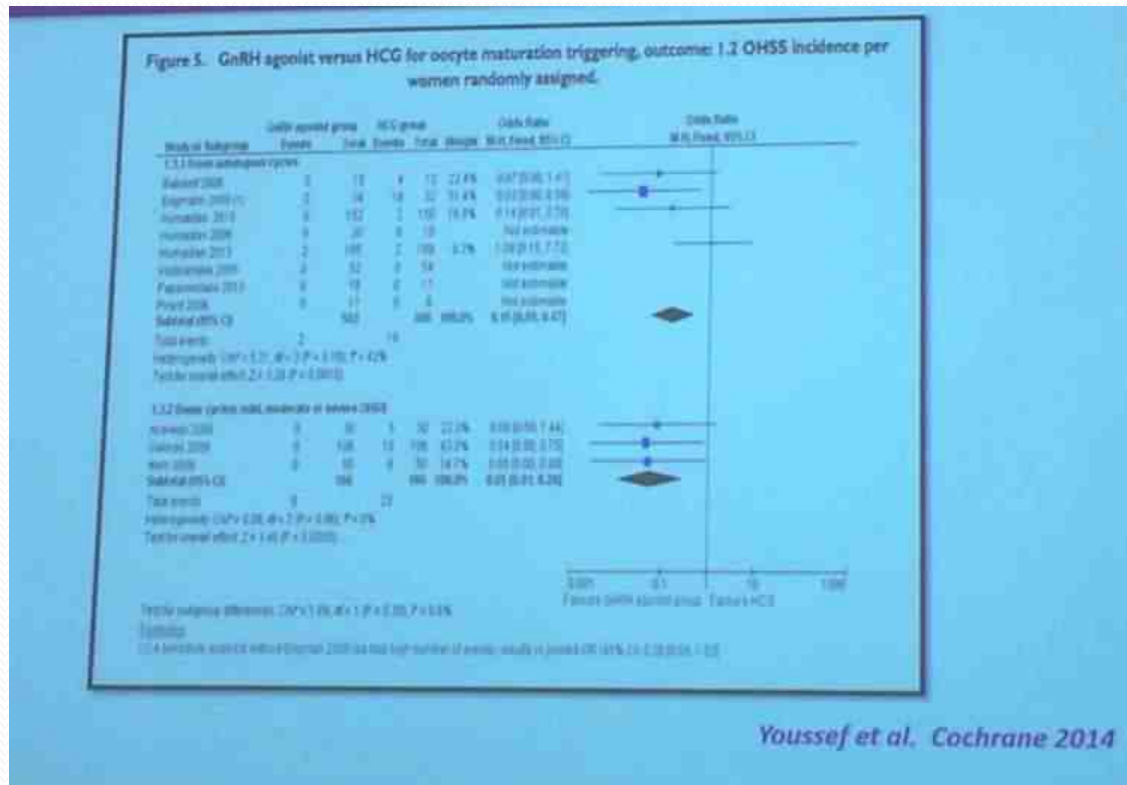
- Avrupa yaklaşımı
 - OPU 1500 IU hCG
 - Küçük doz hCG
- Amerikan yaklaşımı
 - E2<4000 pg/mL
 - Dual Trigger + iLPD
 - E2>4000 pg/mL
 - GnRHa + iLPD

Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology.

[Youssef MA](#)¹, [Van der Veen F](#), [Al-Inany HG](#), [Mochtar MH](#), [Griesinger G](#), [Nagi Mohesen M](#), [Aboufoutouh I](#), [van Wely M](#).

Agonist Trigger

- OHSSyi azaltır
 - (Fresh ve donör siklus)
- Fresh siklus: LBR düşer
- Donör siklus: LBR değişmez



Sekonder Korunma

- 1- Siklus iptali
- 2- Coasting
- 3- Ovulasyon Uyarısında Alternatif uygulamalar,
 - hCG doz azaltması
 - rhLH,
 - GnRHa + iLPS
- 4- **Cryo (Freeze-all policy)**
- 5- IV Kolloid infüzyonu
 - Albumin
 - HES
- 6- Cabergoline
- 7- Diğer

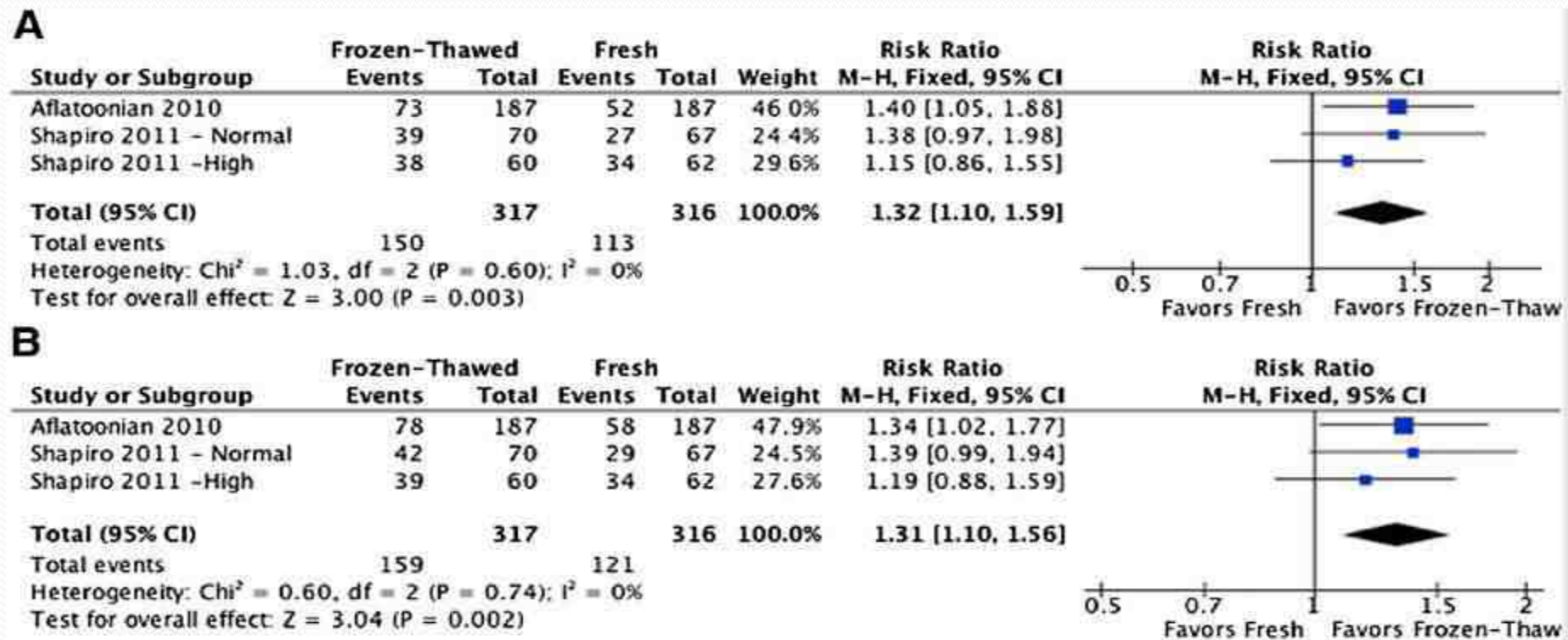
Agonist Triggerda Sorun: Embryo-Endometriyum?

- Fresh sikluslarda PR Düşük
- Oosit ve embryo kalitesi Normal
- FET sikluslarda PR Normal
- Fresh sikluslarda iLFS ile PR Normale döner
- OHSS'siz Klinik: Total Freeze+FET (Ling, Fatemi. Gürbüz 2014)

Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis

Matheus Roque, M.D.,^{a,c} Karinna Lattes, M.D.,^{a,d} Sandra Serra, M.Sc.,^{a,d} Ivan Solà, B.Psych.,^{e,f,g} Selmo Geber, Ph.D.,^{ch} Ramón Carreras, Ph.D.,^b and Miguel Angel Checa, Ph.D.^{b,d}

Freeze- all policy; A-Ongoing PR B-CPR



Sekonder Korunma

- 1- Siklus iptali
- 2- Coasting
- 3- Ovulasyon Uyarısında Alternatif uygulamalar,
 - hCG doz azaltması
 - rhLH,
 - GnRHa + iLPS
- 4- Cryo (Freeze all policy)
- 5- **IV Kolloid infüzyonu**
 - Albumin
 - HES
- 6- Cabergoline
- 7- Diğer

Kolloid İnfüzyonu

- 1-Albumin

- Şiddetli OHSS'yi sınırlı oranda azaltmaktadır (Youssef MA, 2011)
- Şiddetli OHSS'yi azaltmamaktadır (Jee BC,2010)
- Viral enfeksiyon (hepatit B/C/HIV), prion hastalık, anafilaksi riski (Venetis CA,2011)

- 2-HES

- Güvenilirlik ?
- Şiddetli OHSS'yi azaltmaktadır (Youssef MA, 2011, 3RCT)

SOGC Clinical Practice Guideline-2014

Albumin ve diğer plasma genişleticileri OHSS 'den kaçınma amacıyla kullanımı önerilmez

Sekonder Korunma

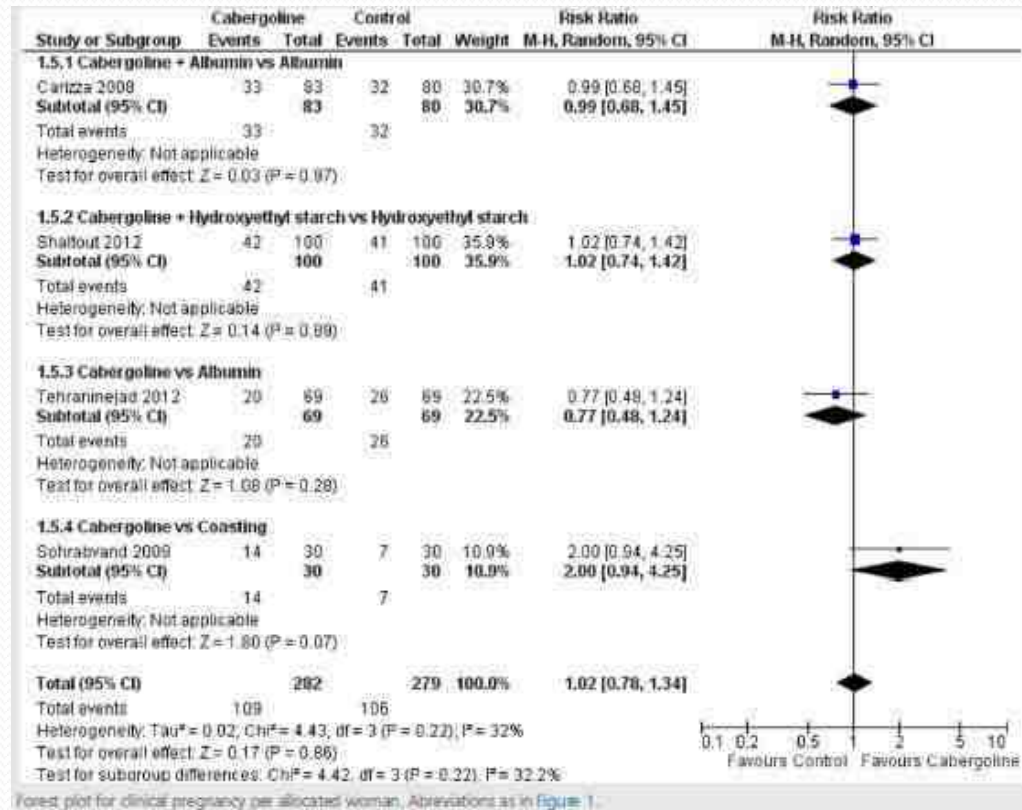
- 1- Siklus iptali
- 2- Coasting
- 3- Ovulasyon Uyarısında Alternatif uygulamalar,
 - hCG doz azaltması
 - rhLH,
 - GnRHa + iLPS
- 4- Cryo (Freeze all policy)
- 5- IV Kolloid infüzyonu
 - Albumin
 - HES
- 6- **Cabergoline**
- 7- Diğer

Cabergoline

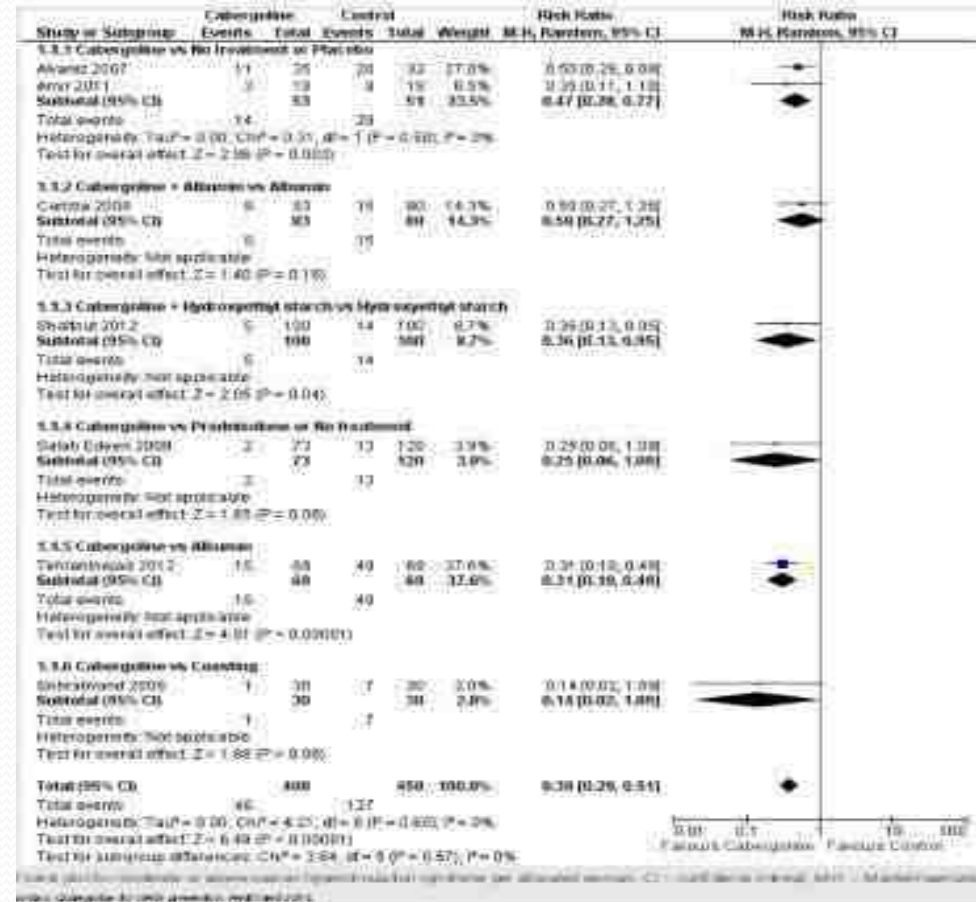
- Dopamin agonistleri vaskuler geirgenlik zerinde anti-anjiojenik ilalarla aynı etkiyi gsterir
- VEGF reseptr-2' nin fosforilizasyonunun kısmi inhibisyonu
- Hayvan deneylerinde permeabilite artışıını engelleyici etki

Cabergoline for the prevention of ovarian hyperstimulation syndrome: systematic review and meta-analysis of randomized controlled trials

Klinik Gebelik



Orta-Şiddetli OHSS



Cabergoline

- 7 RCT
- Cabergoline OHSS insidansını azaltır
- Oosit sayısı, Klinik PR etkilenmemektedir
- Canlı doğum, abortus ve anomali riskleri üzerindeki etkileri bilinmemektedir
- Cabergoline PCOS'lu hastalarda bozulmuş dopaminerjik durum nedeniyle artan anjiogeneze faydalıdır
- Erken OHSS önlemede başarılı
- Gebelerde etkisi yoktur
- Beraberinde Antagonist vb tedaviler uygulanabilir

Kalsiyum İnfuzyonu

Granuloza lutein Hücre

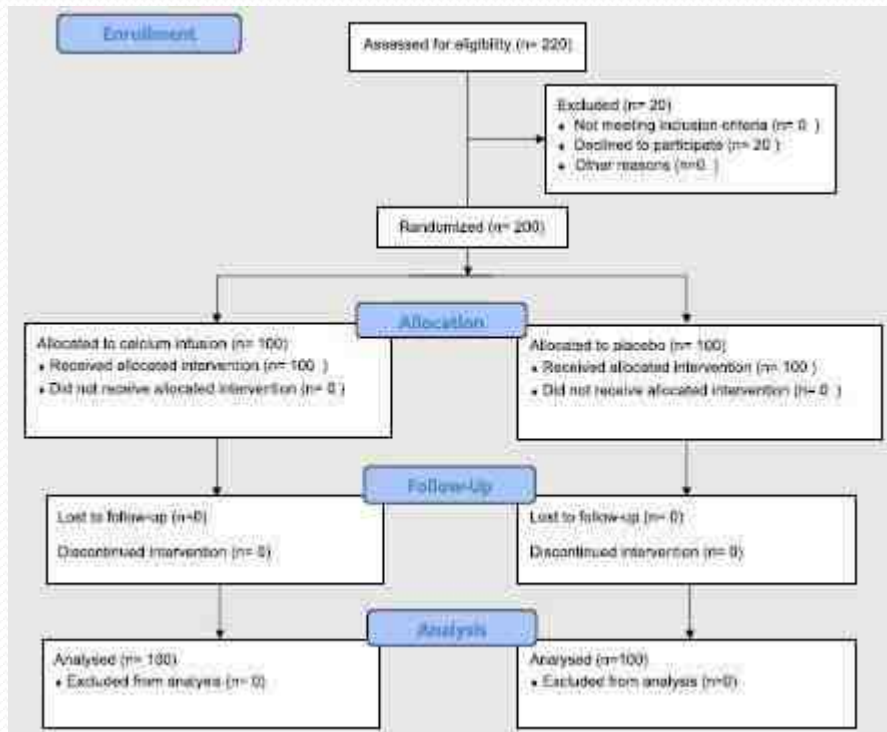
- Kalsiyum artışı
- cAMP bağılı Renin inhibisyonu
- Angiotensin-2
- VEGF mRNA



Klinik Çalışmalar

- Retrospective, 84 hasta
- OHSS %3.6 vs %16
 - Gürgan T 2011
- Randomize, 202 hasta
- OHSS önlemede IV Kalsiyum Cabergoline kadar etkili
 - Naredi N, 2013

Calcium infusion for the prevention of ovarian hyperstimulation syndrome: a double-blind randomized controlled trial



Ovarian stimulation and pregnancy outcomes in both groups.

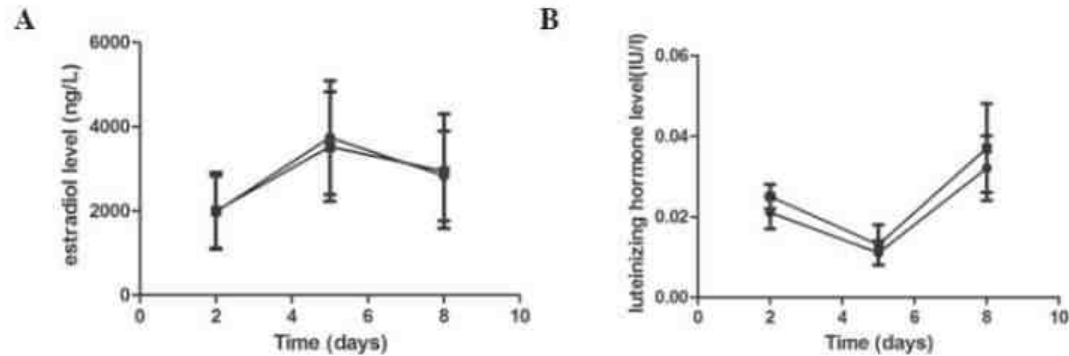
	Calcium group (n = 100)	Placebo group (n = 100)	P value
Amount of total hMG used (IU/L)	2,749.50 ± 392.43	2,658.00 ± 336.31	.078
Length of ovarian stimulation (d)	11.72 ± 0.986	11.92 ± 0.939	.143
Peak E2 on hCG day (pg/mL)	3,847.71 ± 720.82	3,931.71 ± 728.24	.413
Endometrial thickness on hCG day (mm)	10.52 ± 1.202	10.22 ± 1.177	.076
No. of oocytes retrieved (n)	23.95 ± 5.25	23.76 ± 4.99	.794
No. of MII oocytes retrieved (n)	18.96 ± 4.48	18.34 ± 4.41	.326
Fertilization rate (%)	79.41 ± 8.160	77.26 ± 8.612	.072
Implantation rate (%)	30	31	.878
Chemical pregnancy (%)	76 (76)	81 (81)	.389
Clinical pregnancy (%)	59 (59)	65 (66)	.382
Early miscarriage rate (%)	7 (7)	9 (9)	.602
Ongoing pregnancy rate (%)	52 (52)	56 (56)	.570
Live birth rate (%)	52 (52)	56 (56)	.570
OHSS incidence (%)	7 (7)	23 (23)	.002*
Mild OHSS (%)	6 (6)	11 (11)	.205
Moderate OHSS (%)	1 (1)	8 (8)	.017*
Severe OHSS (%)	=	4 (4)	.043*

Note: Values presented as mean ± SD or n (%). MII = metaphase II; OHSS = ovarian hyperstimulation syndrome.
* Statistically significant difference.

Luteal Faz; Aromataz İnhibitörleri (Donör)

	Luteal phase supplementation	Days of administration	Patients (N)	Serum estradiol levels (mean values)			LH levels (mean values)		
				Day 4	Day 7	Day 10	Day 4	Day 7	Day 10
LUTEAL PHASE									
Fatemi 2008 [14]	Letrozole 5 mg	For 14 days from OPU	3	272	229	31	0.2	0.1	0.1
	Placebo		3	749	1457	1308	0.2	0.1	0.1
Garcia-Velasco 2009 [15]	Letrozole 2.5 mg	For 5 days from OPU	15	279	240	40	0.21	0.18	0.40
	Placebo (folic acid)		15	1586	855	448	0.06	0.02	0.16

Cetrotide administration in the early luteal phase in patients at high risk of ovarian hyperstimulation syndrome: A controlled clinical study



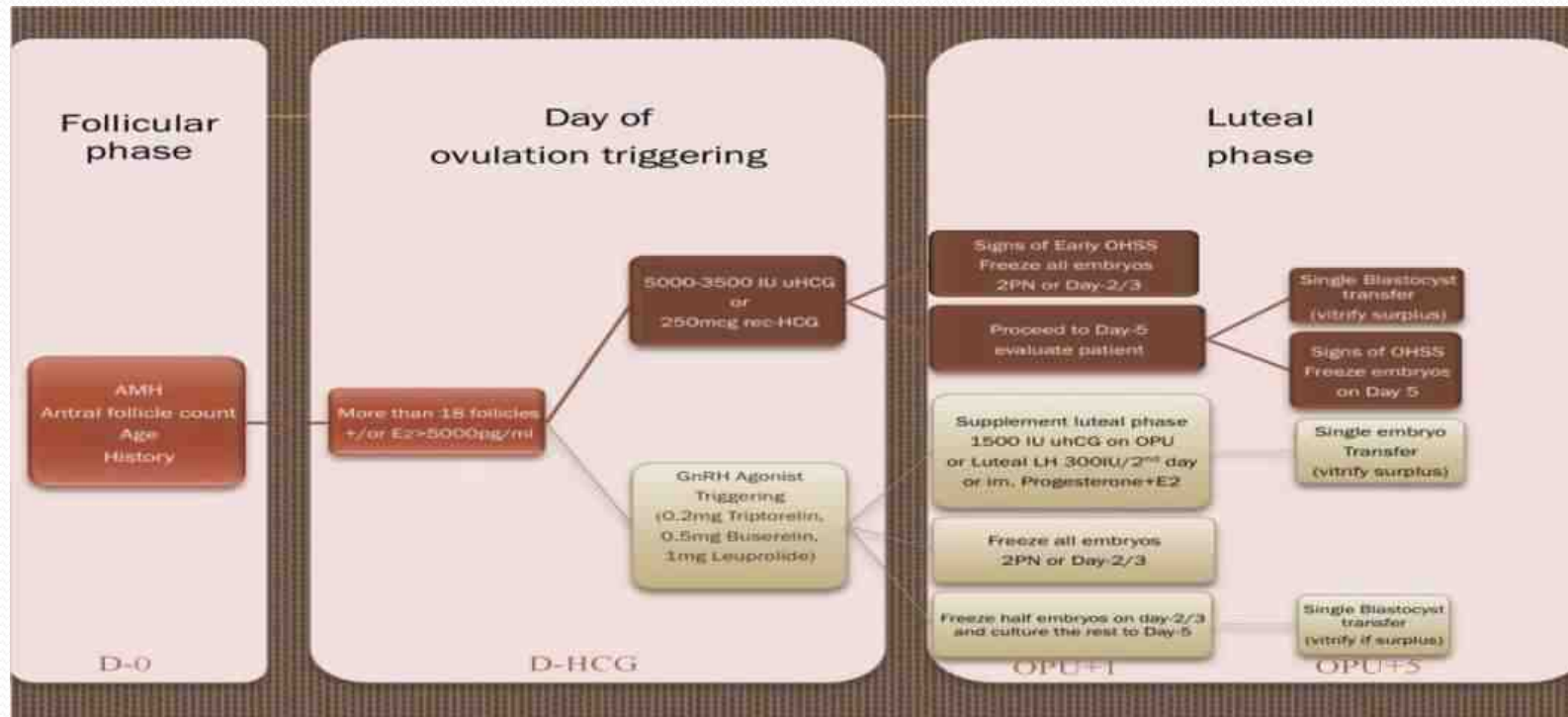
Parameter	Treatment group (n=39)	Control group (n=96)	P-value
Paracentesis, n (%)	7 (17.9)	19 (19.8)	>0.05
Length of hospital stay, days	7.0±2.8	7.3±3.5	>0.05
Severity of OHSS, n (%)			
Mild	19 (48.7)	50 (52.1)	>0.05
Moderate	13 (33.3)	25 (26.1)	>0.05
Severe	7 (18.0)	21 (21.8)	>0.05
Complications, n (%)	0 (0)	0 (0)	
Luteal phase, days ^a	10.7±2.4	11.3±3.0	>0.05

Elde edilen oosit ≥ 25
 serum E2 $\geq 8,000$ pg/ml
 over >10 cm

Faydalı: Lainas TG 2007, Hosseini MA 2012

New algorithm for OHSS prevention

Evangelos G Papanikolaou^{1,7*}, Peter Humaidan², Nikos Polyzos³, Sofia Kalantaridou⁴, Sahar Kol⁵, Claudio Benadiva⁶, Herman Tournaye³ and Basil Tarlatzis⁷



PCOS: Güncel OHSS Risk Minimalizasyonu

- Antagonist protokol
- iCOS- AMH/AFC bireysel en düşük FSH
- Mild stimulasyon CC/FSH
- Metformin
- Düşük doz hCG
- GnRHa trigger + Fresh Transfer + iLPS
- GnRHa trigger + Segmentasyon
- Dopamin Agonist (Cb2) + (Antagonist, IV Ca)
- SET



29 Ekim Cumhuriyet Bayramı
Kutlu Olsun
Prof. Dr. Erkan Alataş