II. ÜREME TIBBI DERNEĞİ
KONGRESİ
01- 04 Ekim 2009
Gloria Golf Resort Belek, Antalya

# PCOS'de in vitro maturasyon

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**Üreme Endokrinolojis Bilim dalı**
**Izmir**

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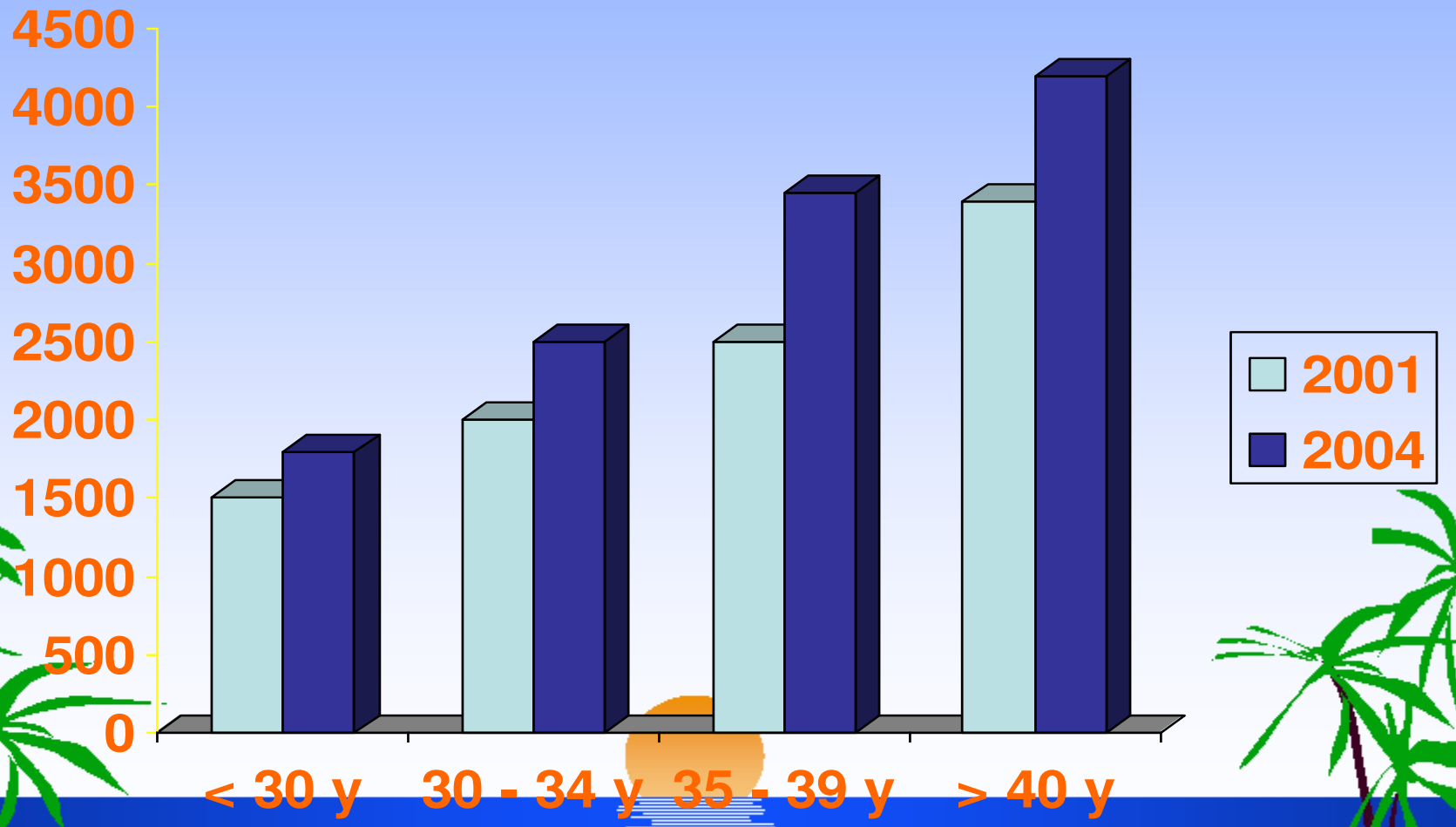
# ART için ovarian stimulasyonu ve ovulasyon indüksiyonundaki problemler

- Aşırı cevap verenler (OHSS dahil)
- Kötü cevap verenler
- Zaman, monitorizasyon
- Maliyet
- Yan etkiler
- Riskler

# Geleneksel IVF'deki 2001 / 2004 ORTALAMA TOTAL İLAÇ MALİYETİ

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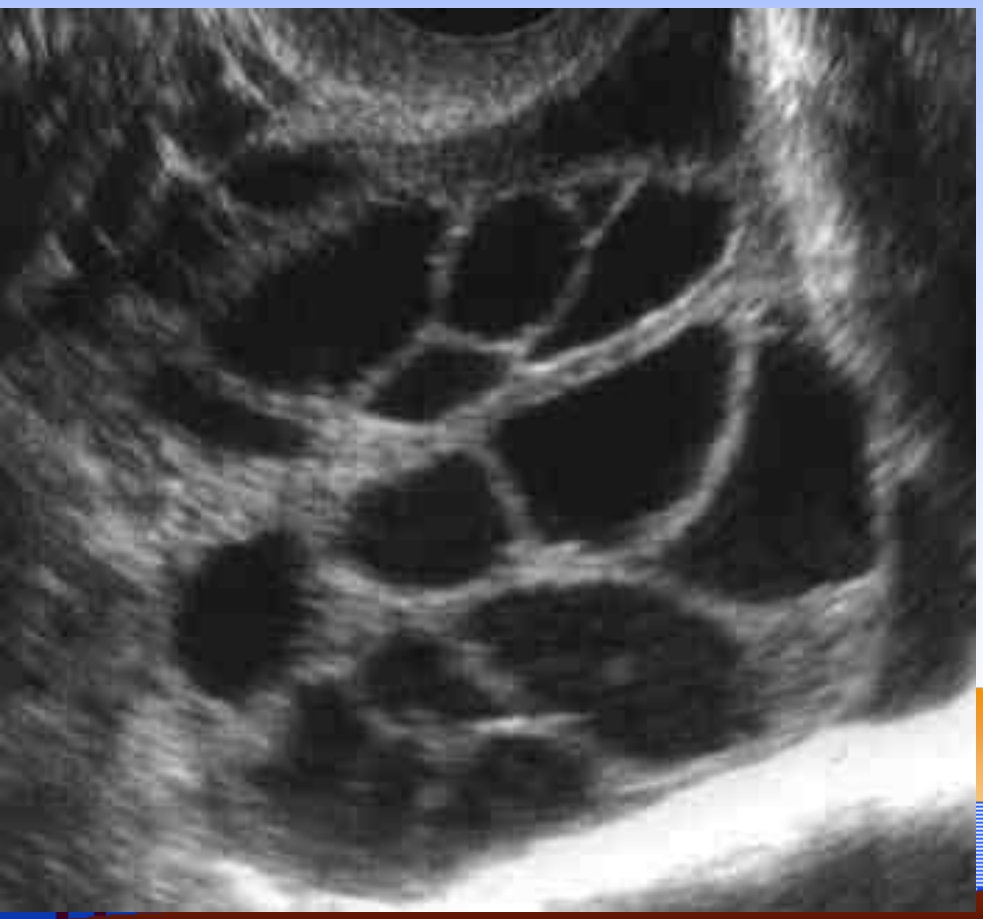
# Riskler / Yan etkiler

- Huy değişiklikleri
- Baş ağrısı
- Depresyon
- Mastalji
- Şişme (bloating) / kilo artışı
- Pelvik ağrı
- Enjeksiyon yerinde ağrı
- Bulantı / kusma
- Allerjik reaksiyonlar

# Riskler / Yan etkiler

## Ciddi OHSS



**Assit**
**Plevral effüzyon**
**tromboz**

## PCO / PCOS x 3-4

MacDougall et al, 1990

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# In Vitro Oosit Matürasyonu (IVM)

Doğal siklusda stimule edilmemiş overlerden germinal vezikül (GV) aşamasındaki oositleri toplamak

In vitro 24 - 48 saatte matür (M-II evresi) hale getirdikten sonra IVF / ICSI uygulamak

# Oosit maturasyonu nedir?

Oosit maturasyonu germinal vesikül (GV) evresinden metafaz –II (M-II) evresine geçişteki birinci meiotik bölünmenin tamamlanması, ve bu sürece  fertilizasyon ve erken embryonik gelişim için gerekli olan sitoplazmik maturasyonun eşlik etmesi olarak tanımlanır

# IVM Potansiyel Biolojik Avantajları

- **Gonadotropinlerin çok az ya da hiç olmaması**
  *Anöploidi oranına etkisi ?*
- **Oositin doğal seçilmiş olması**
  *Daha iyi embryo gelişimi ve seçimi ?*
- **GnRH analoglarının olmaması**
  *Oosit / Endometrium üzerine etkisi ?*
- **NET SONUÇ**
  *Ovarian / uterin fizyolojiye minimal müdahale*
  Oosit ve endometriumda maksimum uyum

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# IVM Potansiyel Dezavantajları

1. **Daha az sayıda oosit**

   *Gerçekte ne kadara ihtiyaç var ?*

2. **Mayotik spindle oluşumu esnasında yapay bir çevrede bulunmanın etkisi**

   *Li et al 2006 IVM vs IVF oositlerinde daha yüksek oranda anomal spindle ve kromozom anomalisi rapor etmişlerdir*

# IVM – Klinik Güçlükler

- **Hasta seçimi**
- **Gonadotropin stimulasyonu**
- **hCG tetiklenmesi (priming)**
- **Endometrial hazırlık –** erken mi yoksa geç mi estrojen vermek? Hangi kalınlık?
- **IVF veya ICSI ?**
- **IVM kültür mediumu ?**

# Hasta seçim kriterleri -IVM

1. PCO veya PCOS hastaları, irregular ya da regular- siklusu olanlar
2. Antral follikül sayısı (AFC) >20
3. Yaş <35

4. Overleri normal olan hastalarda IVM; erkek faktörlü hastalar ve Unexp inf. – *kabul edilebilir gebelik oranları (Suikkari, Finland)*
5. Diğer ***(IVF kötü cevap verenler, oosit bağışı ve kanser hastalarında fertilitenin korunması)***

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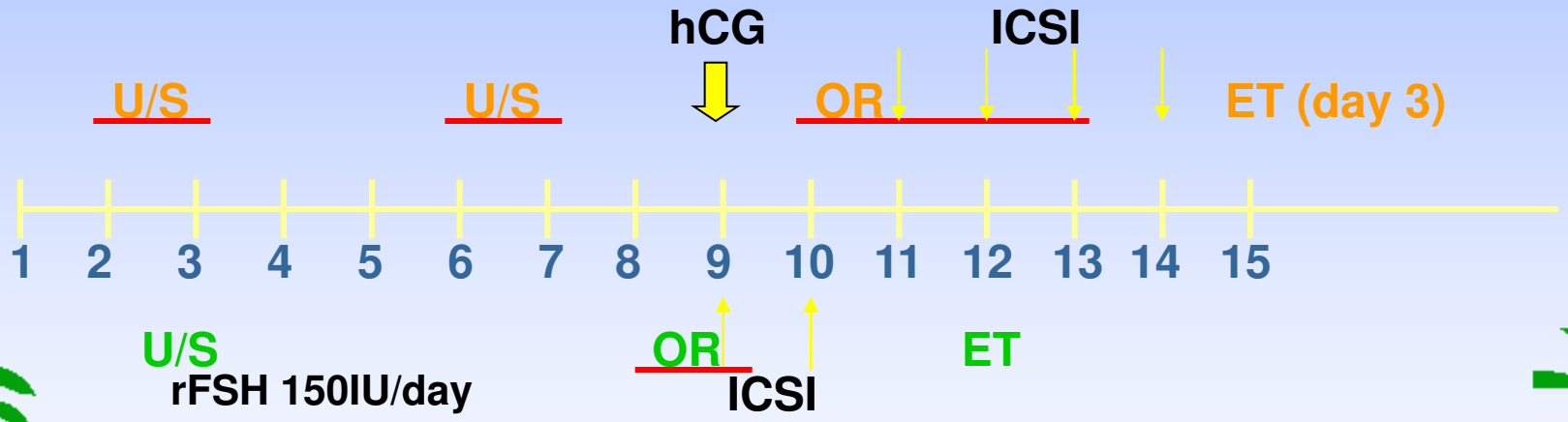
# IVM hastalarının klinik hazırlanması

## Protokol 1
(no stimulation)




## Protokol 2
(stimulation)

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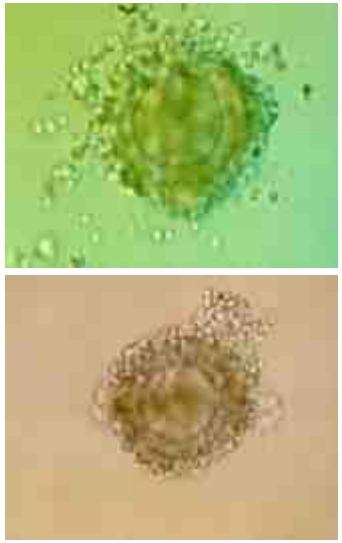
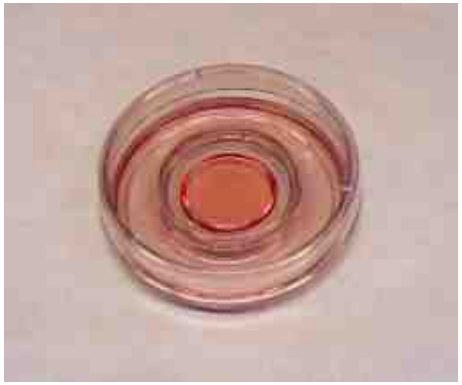
# IVM oositleri – laboratuar işlemleri



Immature oocytes

Oositler yıkanır

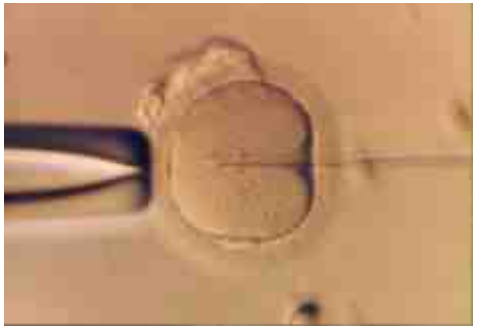


Maturasyon mediumda oositler kültüre edilir

24 – 48 st kültür

Mature oosit (M-2)

Inseminasyon



Inseminasyon (ICSI)

16-18 saat

Fertilize oositler (2PN)

Klivaj

Transfere hazır embryolar

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The NEW ENGLAND JOURNAL of MEDICINE

◄ Previous Volume 341:1624-1626 November 18, 1999 Number 21 Next ►

# Priming with Human Chorionic Gonadotropin before Retrieval of Immature Oocytes in Women with Infertility Due to the Polycystic Ovary Syndrome

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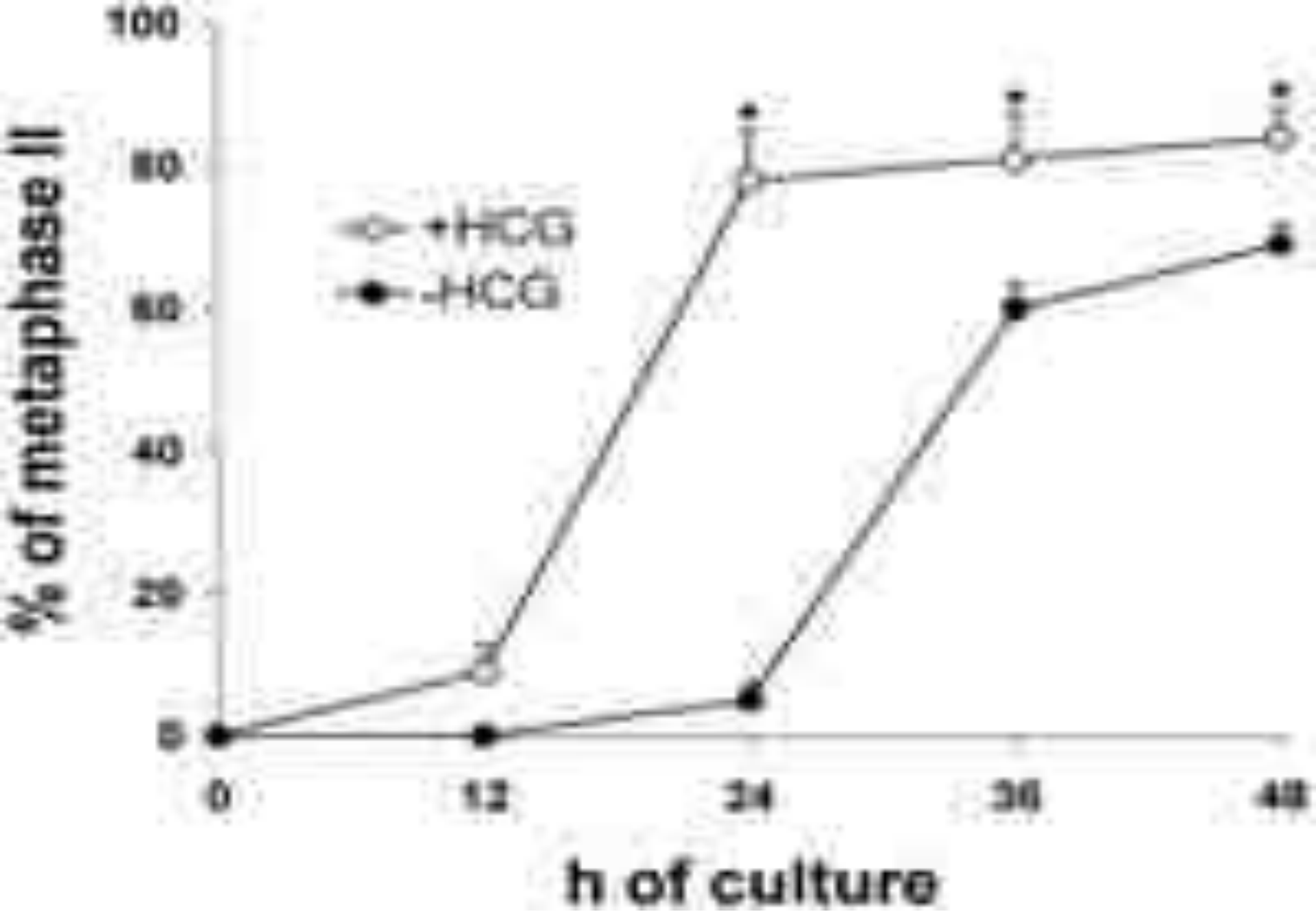
**TABLE 1.** RESULTS OF IN VITRO MATURATION AND FERTILIZATION OF OOCYTES FOLLOWED BY EMBRYO TRANSFER IN 20 WOMEN WITH THE POLYCYSTIC OVARY SYNDROME.*

| VARIABLE | VALUE |
|---|---|
| Cycles of in vitro fertilization | 25 |
| Age — yr | 35.4±4.7 |
| Oocytes retrieved — no. | |
| Total | 249 |
| Mean | 10.3±5.4 |
| Oocytes matured — no. (%) | 209 (84) |
| Oocytes fertilized — no. (%) | 182 (87) |
| Embryos cleaved — no. (%) | 173 (95) |
| Embryos transferred — no. | |
| Total | 73 |
| Mean | 2.9±0.6 |
| Clinical pregnancies — no. (%) | 10 (40) |
| Implantation — no. (%) | 8 (32) |

*Plus–minus values are means ±SD.




*Chian RC et al., Hum Reprod 15: 165-170, 2000*

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FERTILITY AND STERILITY®
*VOL. 82, NO. 5, NOVEMBER 2004*


# Randomized, controlled trial of priming with 10,000 IU versus 20,000 IU of human chorionic gonadotropin in women with polycystic ovary syndrome who are undergoing in vitro maturation

Bulent Gulekli, M.D.
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Ri-Cheng Chian, Ph.D.
Timothy J. Child, M.R.C.O.G.
A. Kamal Abdul-Jalil, M.Sc.
Seang Lin Tan, M.B.B.S.
*McGill Reproductive Centre, Royal Victoria Hospital, Montreal, Québec, Canada*

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## TABLE 1

The 24-hour and 48-hour maturation rates (primary outcome measures), the fertilization rate, the cleavage rate, and the cumulative embryo score in the 10,000-IU-hCG and 20,000-IU-hCG groups.

| | 10,000 IU hCG (n = 180) | 20,000 IU hCG (n = 151) | *P* value |
|---|---|---|---|
| 24-h oocyte maturation rate (%) | 56.7 | 53.0 | NS (*P*=.44) |
| 48-h oocyte maturation rate (%) | 70.5 | 74.2 | NS (*P*=.46) |
| Fertilization rate (after ICSI) (%) | 71.7 | 58.9 | *P*=.03 |
| Embryo cleavage rate (%) | 90.1 | 87.9 | NS (*P*=.62) |
| Mean cumulative embryo score | 37.9 | 29.2 | NS (*P*=.25) |

*Note:* NS = not significant.

*Galeldi. 10,000 vs. 20,000 IUhCG for IVM. Fertil Steril 2004.*

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# IN-VITRO MATURATION AND FERTILIZATION OF OOCYTES FROM UNSTIMULATED OVARIES: PREDICTING THE NUMBER OF IMMATURE OOCYTES RETRIEVED BY EARLY FOLLICULAR PHASE ULTRASOUND SCAN

**Tan SL, Child TJ, Gülekli B**

McGill Reproductive Center, Royal Victoria Hospital
Montreal, Canada

*Am J Obstet & Gynecol, 2002 ,186:684-9*

McGill

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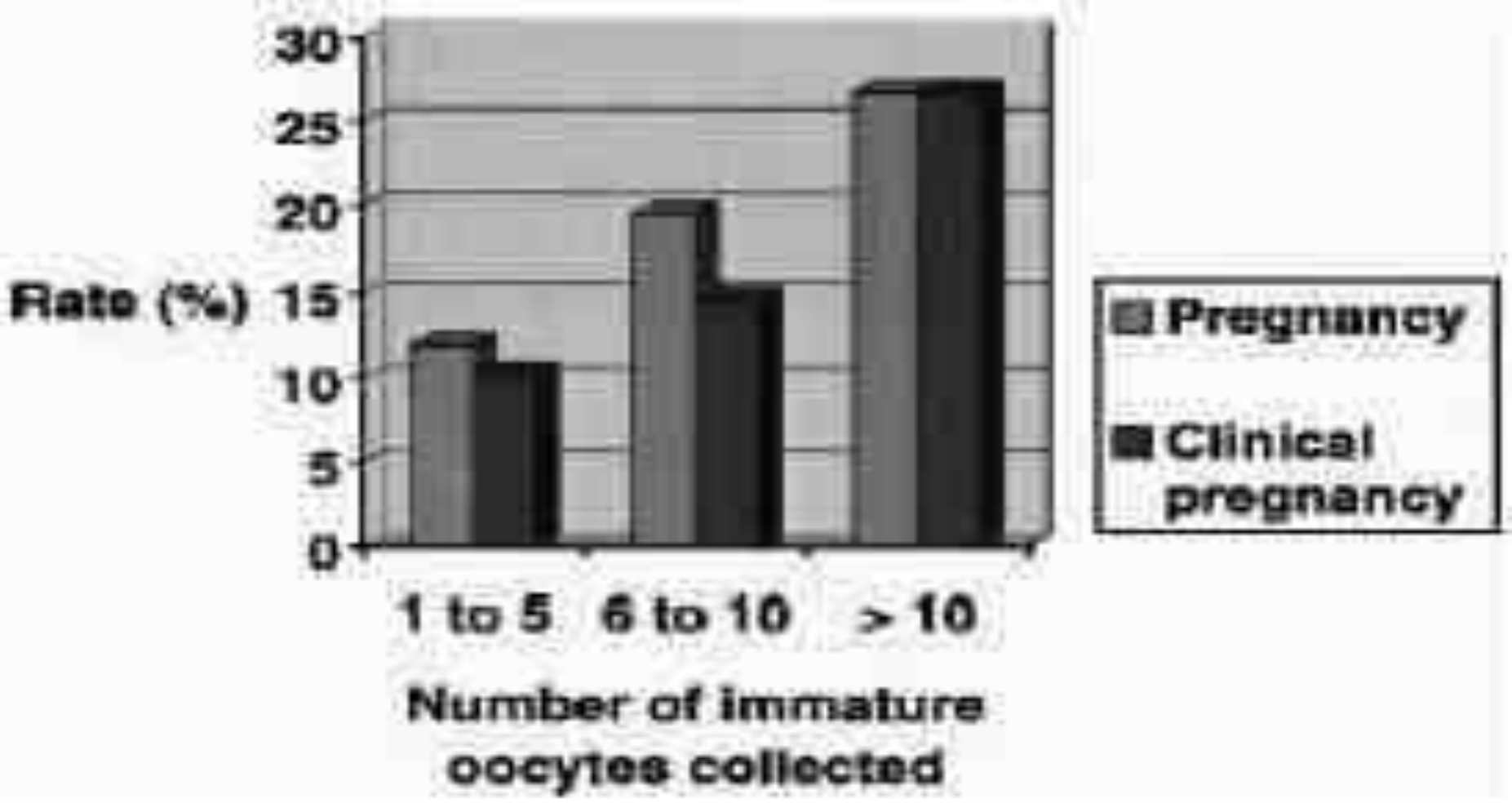


Fig 1. Relationship between numbers of immature oocytes collected and pregnancy and clinical pregnancy rates in 189 consecutive IVM cycles. No immature oocytes were found in 2 cycles. $\chi^2$ test for trend: pregnancy rate by number of immature oocytes collected, $P = .063$; clinical pregnancy rate by number of immature oocytes collected, $P = .023$.

Table. Prediction of the number of immature oocytes retrieved on the basis of AFC, ovarian stromal Vmax, and average ovarian volume

| *Characteristic* | *Model 1** *P value* | *Model 2†* *P value* |
|---|---|---|
| AFC | <.001 | <.001 |
| Average ovarian stromal Vmax | .038 | .902 |
| Average ovarian volume | <.001 | .687 |

The number of immature oocytes retrieved, AFC, and average ovarian volume were analyzed on the log scale.

*Based on univariate analysis.

†Based on analysis adjusted for all other variables in the model. Regression equation: log (No. of immature oocytes) = −1.14 + 0.68 × log(AFC) + 0.04 × log(ovarian volume) + 0.01 × ovarian stromal Vmax (see text).

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# A comparison of in vitro maturation and in vitro fertilization for women with polycystic ovaries

*Child TJ, Philips SJ, Abdul-Jalil AK, Gulekli B, Tan SL*

McGill Reproductive Center, Royal Victoria Hospital
Montreal, Canada

***Obstet Gynecol 2002; 100:665-70***

McGill

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**Table 1.** Results of 107 Age- and Diagnosis-Matched IVM and IVF Treatment Cycles in Infertile Women With Polycystic Ovaries

| | IVM | IVF | OR (95% CI) |
|---|---|---|---|
| No. of cycles | 107 | 107 | |
| Age (y) | 32.8 ± 4.2 | 33.1 ± 4.1 | |
| Total injected units (ampoules) of follicle-stimulating hormone | 0 | 2355 ± 833 (31.4 ± 11.1)* | |
| Oocytes collected | 10.3 ± 7.6 | 14.9 ± 6.5* | |
| Metaphase II stage oocytes | 7.8 ± 4.9 | 12.0 ± 5.4* | |
| Fertilized 2PN embryos | 6.1 ± 3.8 | 9.3 ± 4.4* | |
| Cleaving embryos | 5.8 ± 3.7 | 8.6 ± 4.2* | |
| Embryos transferred (range) | 3.2 ± 0.9 (1–5) | 2.7 ± 0.8 (1–6)* | |
| Embryos cryopreserved (range) | 0.8 ± 2.3 (0–14) | 1.2 ± 3.0 (0–16) | |
| Pregnant [*n* (%)] | 28 (26.2) | 41 (38.3) | 0.57 (0.31, 1.06) |
| Implantation rate (%) | 9.5 | 17.1* | 0.51 (0.31, 0.84) |
| Clinical pregnancy [*n* (%)] | 23 (21.5) | 36 (33.7) | 0.54 (0.28, 1.04) |
| Live birth [*n* (%)] | 17 (15.9) | 28 (26.2) | 0.53 (0.26, 1.10) |
| Multiple live births [*n* (% of total live births)] | 7 (41.2) | 10 (37.0) | 1.26 (0.30, 5.11) |
| Twins | 6 | 9 | |
| Triplets | 1 | 1 | |
| Moderate or severe ovarian hyperstimulation syndrome | 0 | 12 (11.2%)* | |

IVM = in vitro maturation; IVF = in vitro fertilization; OR = odds ratio; CI = confidence interval.
Results are means ± standard deviations unless stated.
* $P < .01$.

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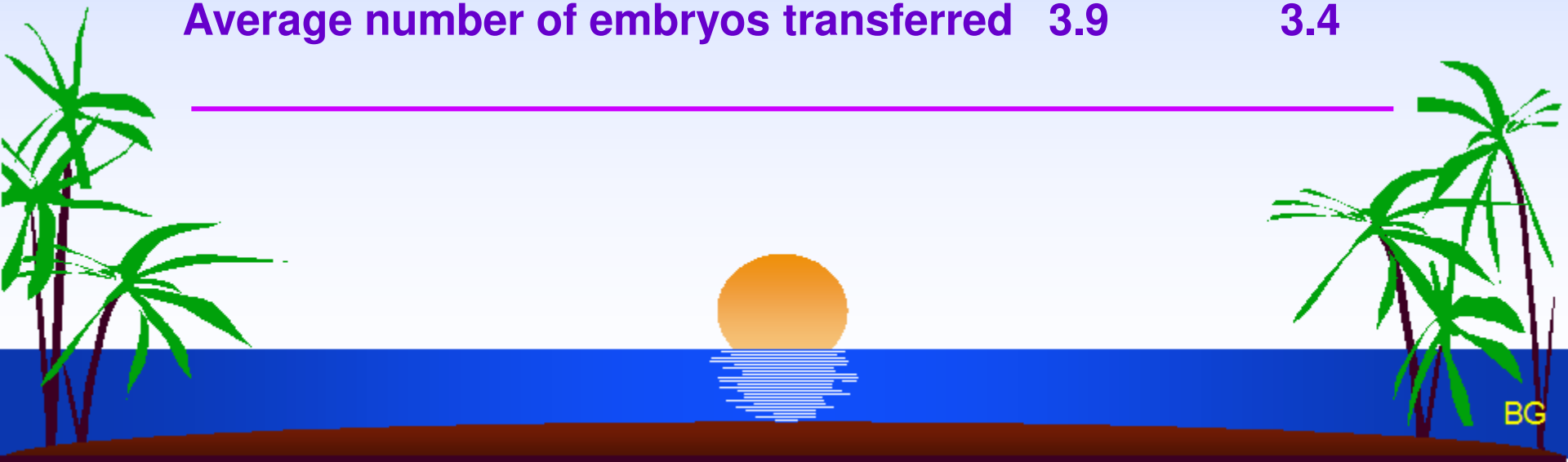
# Embryology data from IVM programmes

| | McGill | DEU |
|---|---|---|
| Average number of oocytes retrieved | 14.2 | 13.4 |
| Percentage of oocytes matured | 76.8% | 65.8% |
| Percentage of oocytes fertilized | 63.1% | 64.2% |
| Percentage of embryos cleaved | 89.0% | 87.5% |
| Average number of embryos transferred | 3.9 | 3.4 |



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# IVM programlarının sonuçları

| Merkez | Vak'a sayısı | Klinik gebe / ET |
|---|---|---|
| Maria Hospital (Korea, '00-'02)[a] | 419 | 32.7% |
| Memorial Hosp. (Taiwan)[a] | 68 | 33.8% |
| Hopital Antoine-B (France, '02-'03)[a] | 17 | 23.5% |
| McGill Rep. Ctr. (Canada, '03)[b] | 66 | 32.3% |
| DEU Izmir | 34 | 28.5% |

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## TABLE 2

Clinical outcome of IVM cycles in women with normal ovaries and regular cycles.

| First author and year published (reference citation no.) | No. of cycles | Priming | Average no. of oocytes retrieved | % Maturation (duration of culture in h) | % Fertilization (type of insemination) | % Cleaved embryos | Average no. of embryos transferred | PR (%) per ET | IR (%) | No. of live births | % SAb |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Child 2001 (36) | 56 | hCG | 5.1 | 78.4 (48) | 72.5 (ICSI) | 93.1 | 2.6 | 4 | 1.5 | 1 | 50 |
| Mikkelsen 1999 (50) | 10 | None vs. | 3.7 | 76 (36) | 62 (ICSI) | 54 | 1.8 | 33.3 | 18.8 | 4 | 20 |
| | 10 | FSH × 3 d | 4 | 85 (36) | 65 (ICSI) | 62 | 1.9 | 22.2 | 11.8 | | |
| | 5 | FSH × 3 d, vs. | 4.2 | 71 (48) | 61 (ICSI) | 48 | 1.4 | 20 | 14.3 | 1 | 0 |
| | 7 | FSH × up to 6 d | 2.4 | 71 (48) | 61 (ICSI) | 59 | 1.1 | 0 | 0 | | |
| Mikkelsen 2000 (48) | 87 | None | 6.1 | 60 (28–36) | 77 (ICSI) | 87 | 2.0 | 17.4 | 8.8 | 9 | 18.9 |
| Mikkelsen 2001 (49) | 132 | None | 3.8 | 60 (28–36) | 73 (ICSI) | 87 | NA | 18 | NA | 12 | 20 |
| Soderstrom-Anttila 2005 (12) | 91 | None | 6.3 | 66.9 (30–48) | 35.9 (IVF) vs. | 84.8 | 1.4 | 31 | 22.6 | 12 | 33.3 |
| | 100 | None | 6.5 | 54.5 (30–48) | 67.1[a] (ICSI) | 85.8 | 1.5 | 21 | 20.0 | 15 | 16.7 |
| Yoon 2001 (47) | 63 | None | 9.0 | 40.7/71.5/74.3 (24/48/56) | 72.6 (IVF and ICSI) | 89 | 3.6 | 17.6 | 6.5 | 6 | 33.3 |

*Note:* NA = not available; PR = pregnancy rate; IR = implantation rate; SAb = spontaneous abortion.

[a] Statistically significant difference compared with the other arm of that study.

18.4 %

*Jurema. In vitro maturation of human oocytes. Fertil Steril 2006.*

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## TABLE 1

Clinical outcome of IVM cycles in PCO and PCOS patients.

| First author and year published (reference citation no.) | No. of cycles | Priming | Average no. of oocytes retrieved | % Maturation (duration of culture in h) | % Fertilization (type of insemination) | % Cleaved embryos | Average no. of embryos transferred | PR (%) per ET | IR (%) | No. of live births | % SAb |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cha 2000 (41) | 94 | None | 13.6 | 62.2 (48) | 68 (ICSI) | 88 | 4.9 | 27.1 | 6.9 | 20 | 20 |
| Cha 2005 (51) | 203 | None | 15.5 | NA | NA | NA | 5.0 | 21.9 | 5.5 | 24 | 37 |
| Chian 2000 (38) | 13 | hCG vs. | 7.8 | 78.2/85.2 (24/48) | 90.7 (ICSI) | 94.9 | 2.8 | 38.5 | 16.6 | 3 | 40 |
| | 11 | none | 7.4 | 4.9[a]/68.0[a] (24/48) | 83.9 (ICSI) | 95.7 | 2.5 | 27.3 | 14.8 | 3 | 0 |
| Child 2001 (36) | 53 (PCO) vs. | hCG | 10.0 | 76 (48) | 76.3 (ICSI) | 94.8 | 3.3 | 23.1 | 8.9 | 9 | 40 |
| | 68 (PCOS) | hCG | 11.3 | 77 (48) | 79.3 (ICSI) | 91.3 | 3.2 | 29.9 | 9.6 | 10 | 52.3 |
| Child 2002 (40) | 107 | hCG | 10.3 | 76 (48) | 78 (ICSI) | 74 | 3.2 | 21.5 | 9.5 | 17 | 26.1 |
| LeDu 2005 (10) | 45 | hCG | 11.4 | 54.2/63 (24/48) | 70.1 (ICSI) | 96.3 | 2.5 | 22.5 | 10.9 | 6 | 40 |
| Lin 2003 (39) | 35 | FSH + hCG vs. | 21.9 | 43.2/76.5 (24/48) | 75.8 (ICSI) | 89.4 | 3.8 | 31.4 | 9.7 | 21 | 13 |
| | 33 | hCG | 23.1 | 39.2/71.9 (24/48) | 69.5 (ICSI) | 88.1 | 3.8 | 36.4 | 11.3 | | |
| Mikkelsen 2001 (37) | 12 | None vs. | 6.8 | 44 (24) | 69 (ICSI) | 64 | 1.7 | 0 | 0 | 0 | 0 |
| | 24 | FSH | 6.5 | 59 (24)[a] | 70 (ICSI) | 56 | 1.8 | 33[a] | 21.6 | 3 | 62.5 |
| Soderstrom-Anttila 2005 (12) | 20 (PCO) vs. | None | 9.3 | 54.9 (30–48) | 35.0 (IVF, 13) | 85.7 | 1.7 | 22.2 | 13.3 | 2 | 0 |
| | | | | | 72.4 (ICSI, 7) | 61.9 | 2.0 | 0 | 0 | 0 | 0 |
| | 28 (PCOS) | None | 14.3 | 58.2 (30–48) | 43.8 (IVF, 18) | 82.5 | 1.7 | 52.9 | 34.5 | 6 | 33.3 |
| | | | | | 78.4 (ICSI, 10) | 70.9 | 1.8 | 22.2 | 12.5 | 1 | 50 |

*Note:* NA = not available; PR = pregnancy rate; IR = implantation rate; SAb = spontaneous abortion.

[a] Statistically significant difference compared with the other arm of that study.

27 %

*Jurema. In vitro maturation of human oocytes. Fertil Steril 2006.*

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# Obstetric Outcomes and Congenital Abnormalities After In Vitro Maturation, In Vitro Fertilization, and Intracytoplasmic Sperm Injection

*William M. Buckett, MD, FRCOG, Ri-Cheng Chian, PhD, Hananel Holzer, MD, Nicola Dean, PhD, Robert Usher, MD, FRCP(C), and Seang Lin Tan, MBBS, FRCOG*

(Obstet Gynecol 2007;110:885–91)

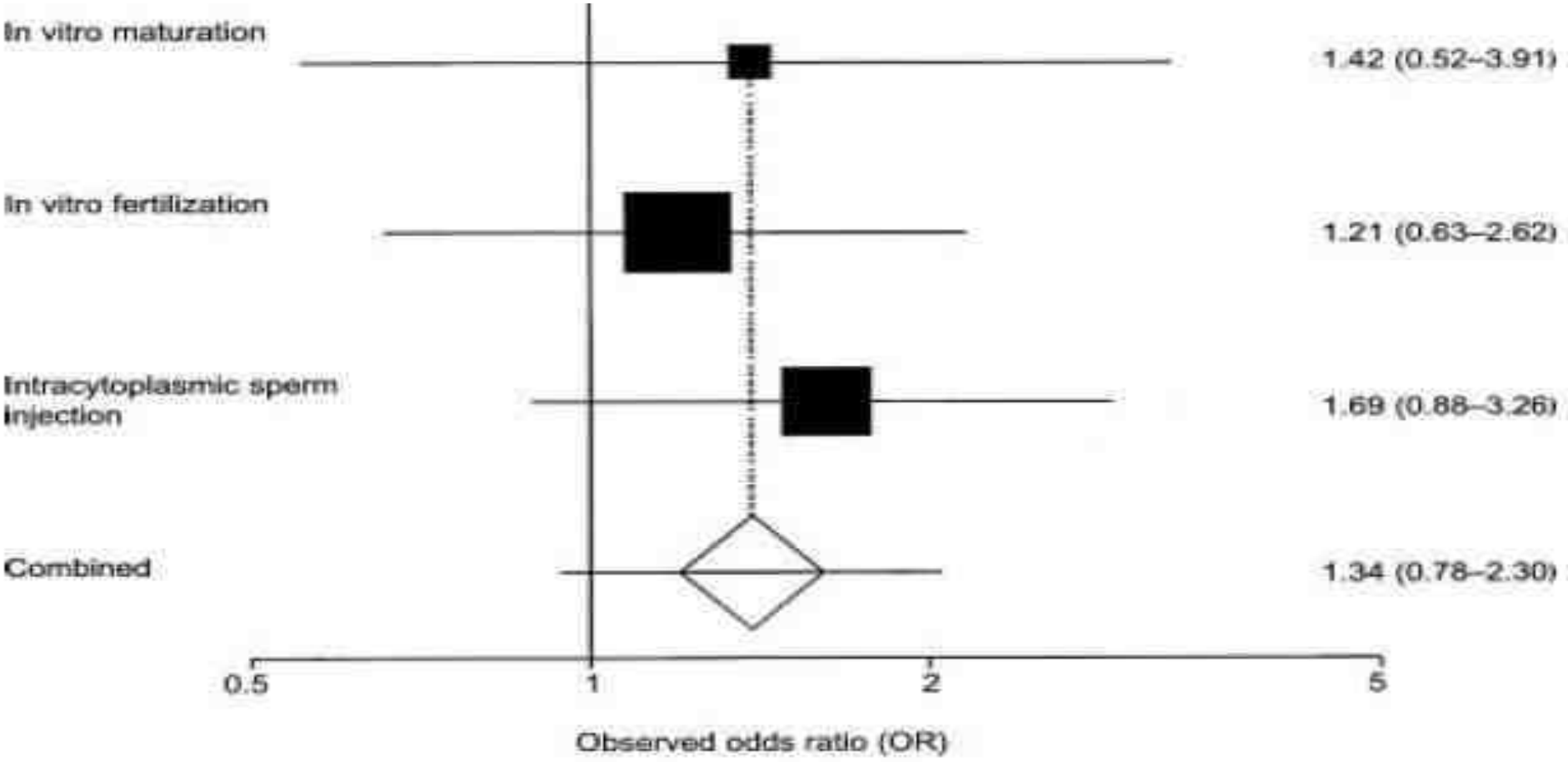



**Fig. 1.** Observed odds ratio for any congenital abnormality after conception with in vitro maturation (IVM), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) compared with age- and parity-matched spontaneously conceived controls.

*Buckett. In Vitro Maturation Pregnancy Outcomes. Obstet Gynecol 2007.*

# Pregnancy loss in pregnancies conceived after in vitro oocyte maturation, conventional in vitro fertilization, and intracytoplasmic sperm injection

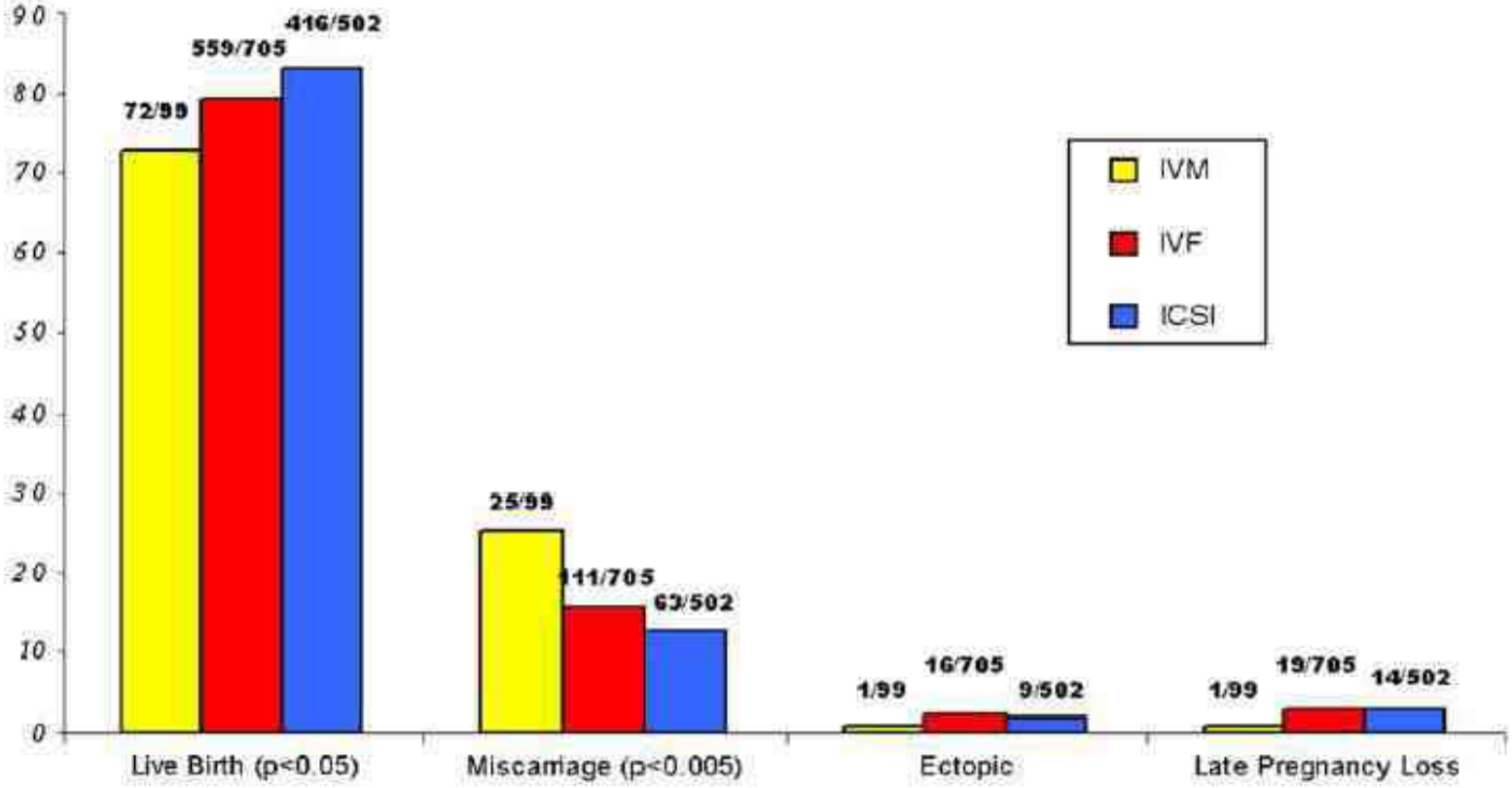
Fertility and Sterility® Vol. 90, No. 3, September 2008

*William M. Buckett, M.D., Ri-Cheng Chian, Ph.D., Nicola L. Dean, Ph.D., Camille Sylvestre, M.D., Hananel E. G. Holzer, M.D., and Seang Lin Tan, M.B., B.S., M.B.A.*

Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montréal, Québec, Canada

## FIGURE 2

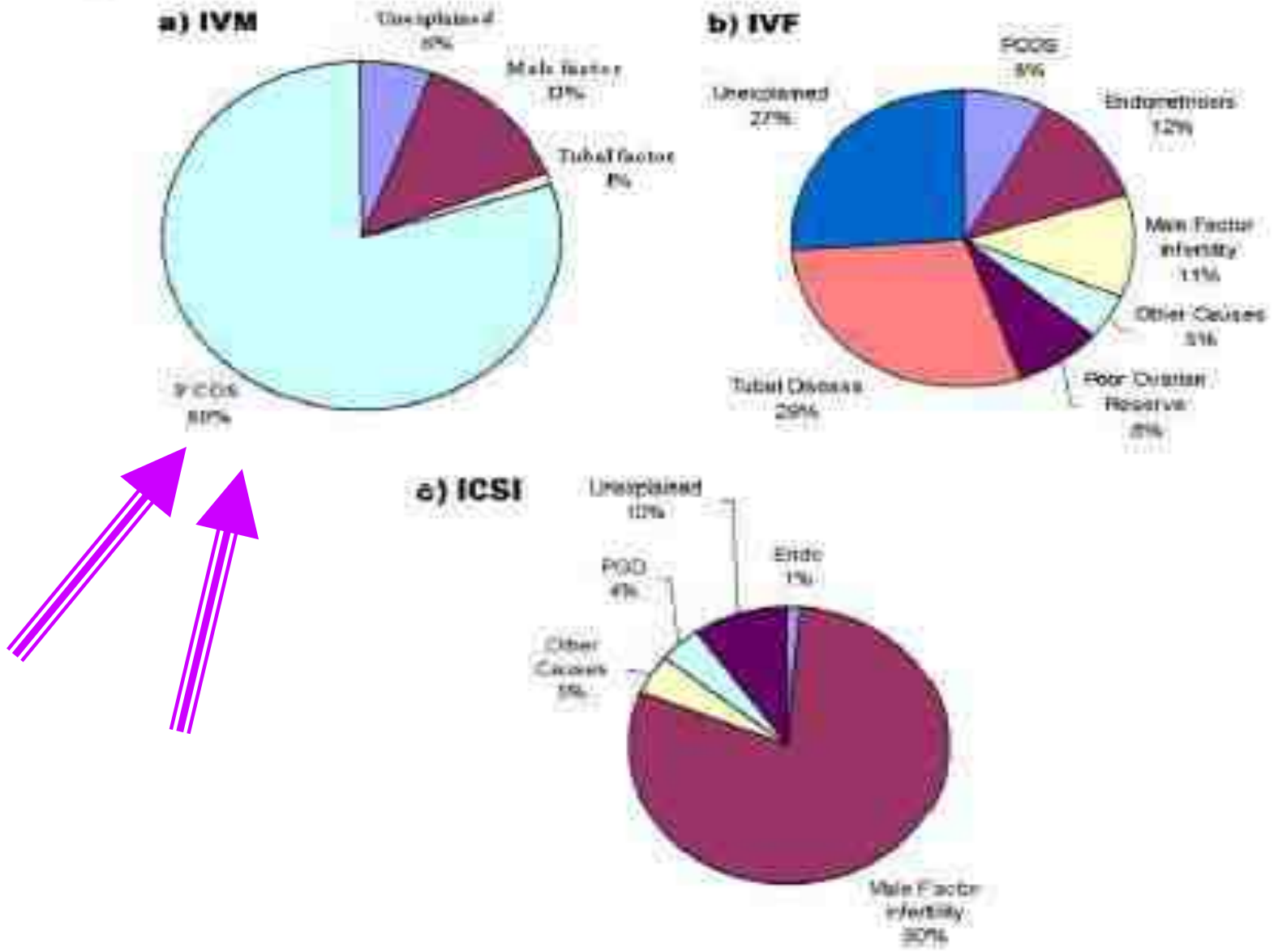
Pregnancy outcomes (%) per clinical pregnancy after IVM, IVF, and ICSI.




*Buckett, Miscarriage and IVM. Fertil Steril 2008.*

FIGURE 1

Primary causes of infertility in pregnancies conceived after (a) IVM, (b) IVF, and (c) ICSI. PGD = preimplantation genetic diagnosis.



# Sonuç

- Ovarian stimulasyona ait risklerden arınmış emin bir tedavi yöntemidir
- Özellikle ART gereksinimi olan PCO / PCOS ‘lu kadınlar için uygun görünmektedir
- Diğer ART yöntemleri kadar güvenlidir
- Daha fazla merkezin sonuçlarına gereksinim vardır

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