

PROF.DR.MEHMET ÇOLAKOĞLU
NEU MERAM TIP FAK KONYA
İNFERTİLİTE VE TEKRARLAYAN DÜŞÜKLER

20-23 NİSAN
2019

**KONYA
AİLE
HEKİMLİĞİ
ETKİNLİK
DERNEĞİ
1. ULUSAL KONGRESİ**

EĞİTİM
KENDİNİ GELİŞTİRME
AİLE HEKİMLİĞİ SORUNLARINI
PAYLAŞIM VE ÇÖZÜM ÖNERİLERİ

YENİLİĞİN
GELİŞİMİN
ÇÖZÜMÜN
PARÇASI
OLUN

İNFERTİL HASTA BEKLENTİLERİ

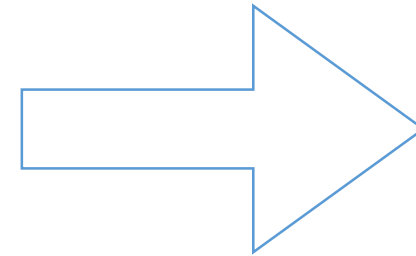
- 1) EN KISA ZAMANDA GEBE KALMAK
- 2) MALİYETİ DÜŞÜK TUTMAK
- 3) KOMPLİKASYONLARI MİNİMAL OLMAK
- 4) AZ TAKİPDE KALMAK
- 5) MÜMKÜN OLDUĞUNCA GİZLİ KALMAK
- 6) BAZEN ÇOĞUL GEBE KALMAK

İNFERTİL HASTA TEDAVİ EDEN DOKTOR BEKLENTİLERİ

- 1) BAŞARILI OLUP KISA ZAMANDA GEBE BIRAKMAK
- 2) KOMPLİKASYONSUZ VEYA MİNİMAL KOMPLİKASYONLU TEDAVİ
- 3) MİNİMAL TAKİP
- 4) MİNİMAL MALİYET
- 5) BAŞARILI OLDUĞUNDA HASTANIN DOKTORUNU TAKDİR ETMESİ
- 6) BAŞARISIZ OLDUĞUNDA DOKTORUNU KOLAY KOLAY BIRAKMAMASI

İnfertilite Tedavisi

- Ovulasyon indüksiyonu
- Kontrollü over hiperstimülasyonu (COH)
- İntrauterin inseminasyon (IUI)
- IUI & COH
- Gamete İntrafallopian Transfer (GIFT)
- Zigot İntrafallopian Transfer (ZIFT)
- İn Vitro Fertilizasyon (IVF)
- İntrasitoplazmik Sperm İnjeksiyonu (ICSI)
- TESE TESA MESA



Nadir olarak yapılır

İNFERTİLİTE TEDAVİSİ YAPARKEN :

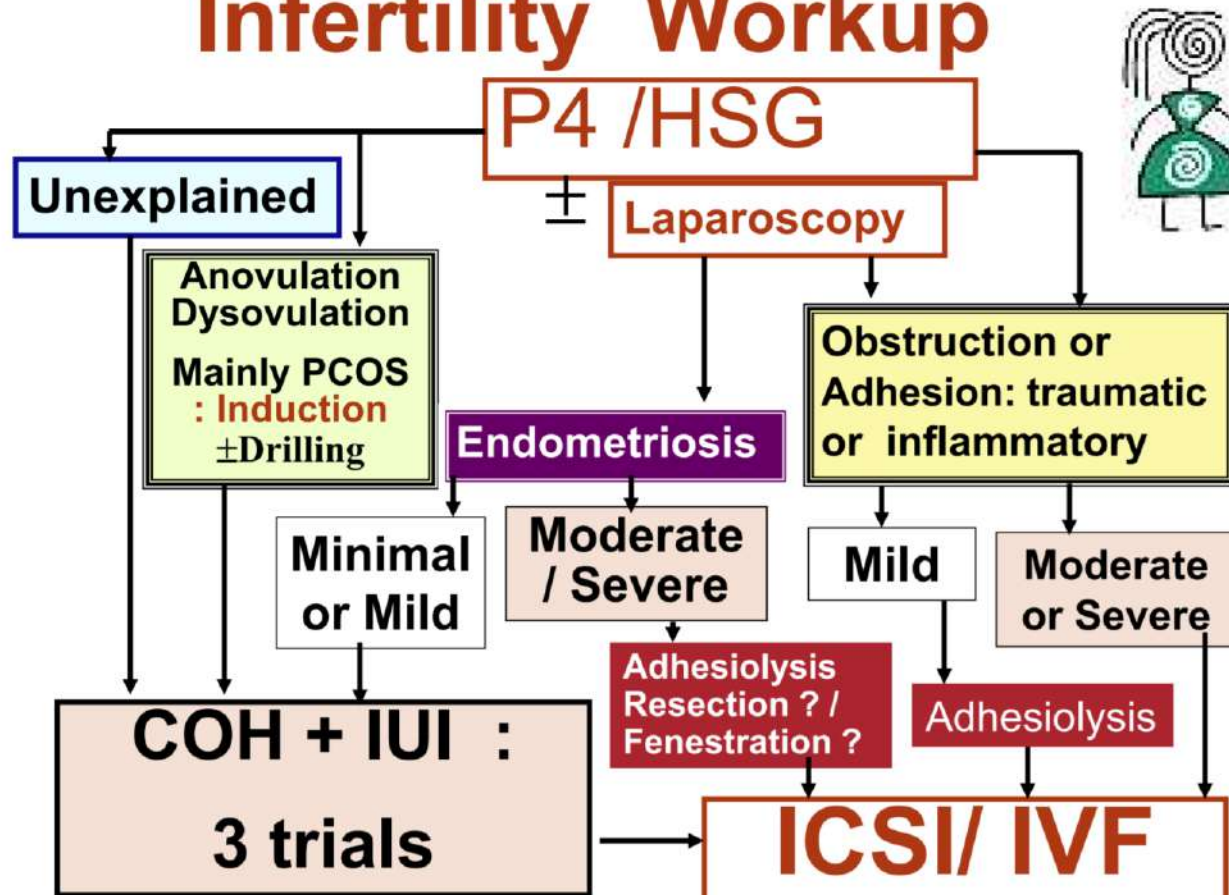
- 1)İNFERTİLİTE SEBEBİ
- 2)İNFERTİLİTE SÜRESİ
- 3)KADIN YAŞI
- 4)DAHA ÖNCEKİ GEBELİK ÖYKÜSÜ
- MALİYET DİKKATE ALINMALIDIR

- Özellikle genç kadınlara gereksiz ART önermek hem akıllıca hem de etik değildir.

ART'nin maliyetini ve komplikasyonlarını göz önüne alın.

Ancak özellikle ileri kadın yaşı ve ileri erkek infertilitesinde TÜP BEBEK yaptırmak için hastalar cesaretlendirilmelidir

Infertility Workup



IVF Recommendation

IVF is recommended for women who have failed to achieve a pregnancy after undergoing a 2 or 3 cycles of IUI.

- Advanced maternal age of a woman – typically, over 35 years of age
- Blocked or damaged fallopian tubes
- Endometriosis
- Ovulation disorders – premature ovarian failure or uterine fibroids
- Lack of fallopian tubes due to surgical removal
- Genetic disorder
- Male factor infertility, including blockage, decreased sperm count or motility
- Unexplained infertility

In the United States, the live birth rate for each IVF cycle started is approximately:

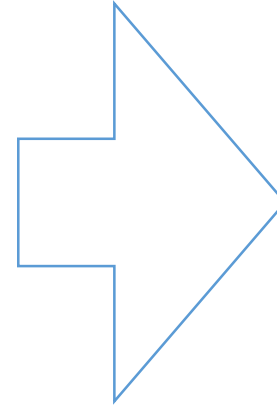
- **41-43% for women under age 35.**
- **33-36% for women ages 35 to 37.**
- **23-27% for women ages 38 to 40.**
- **13-18% for women ages over 40.**

İVF/İCSI HAZIRLIĞINDA

- 1)ANAMNEZ
- 2)BASAL VAGİNAL US
- 3)ENDOKRİN DEĞERLENDİRME VE OVER REZERV TESTLERİ
- 4)HSG vs HİSTEROSKOPİ
- AYRICA
- *ERKEK DEĞERLENDİRMESİ
- *GENEL DEĞERLENDİRME
- *HAZIRLIK TEDAVİSİ YAPILMALIDIR

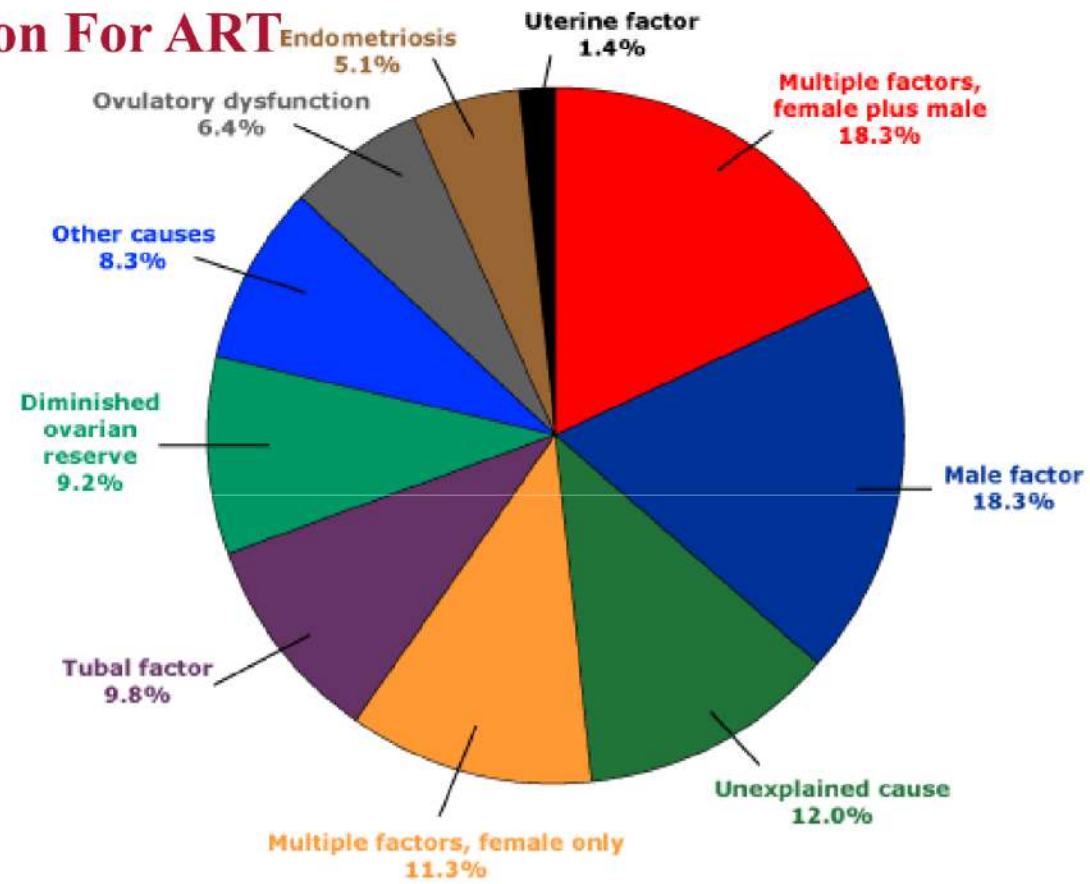
IVF Endikasyonları

- IVF için standart endikasyonlar;
- Tubal faktör.
- Endometriozis.
- Açıklanamayan infertilite.
- Orta derecedeki erkek faktör vakaları.
- PCO
- İLERİ ANNE YAŞI?
- Tek Gen hastalıkları
- Akraba Evliliğine bağlı önceki anomalili doğum



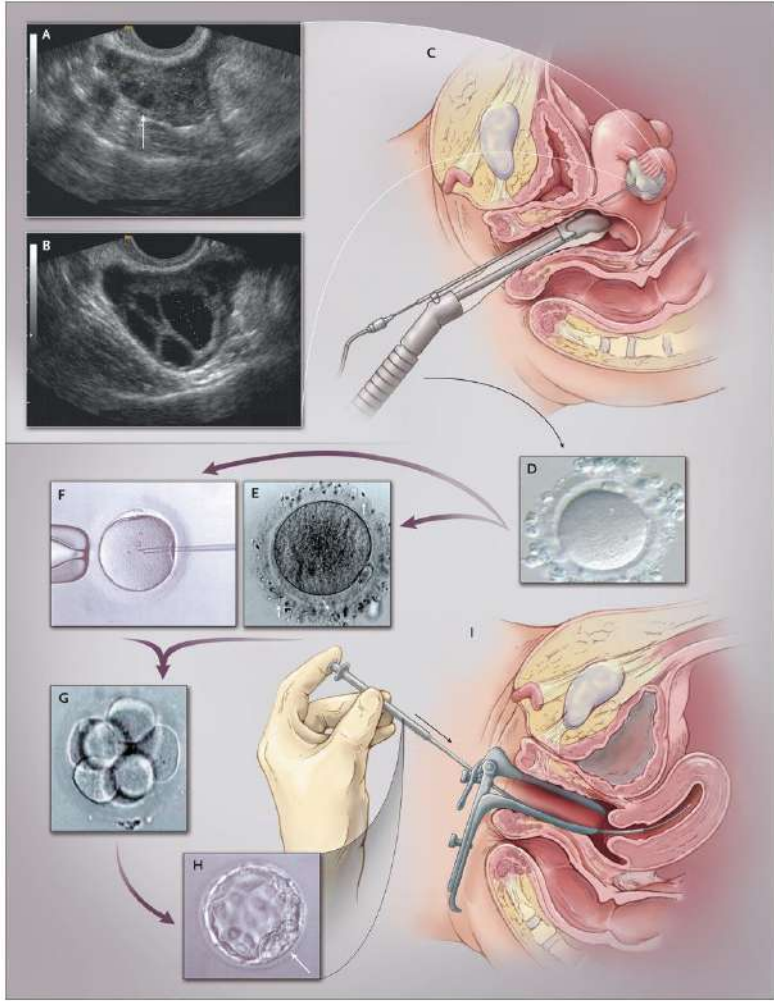
Daha az invaziv bir
tedavi
başarısızlığından
sonra

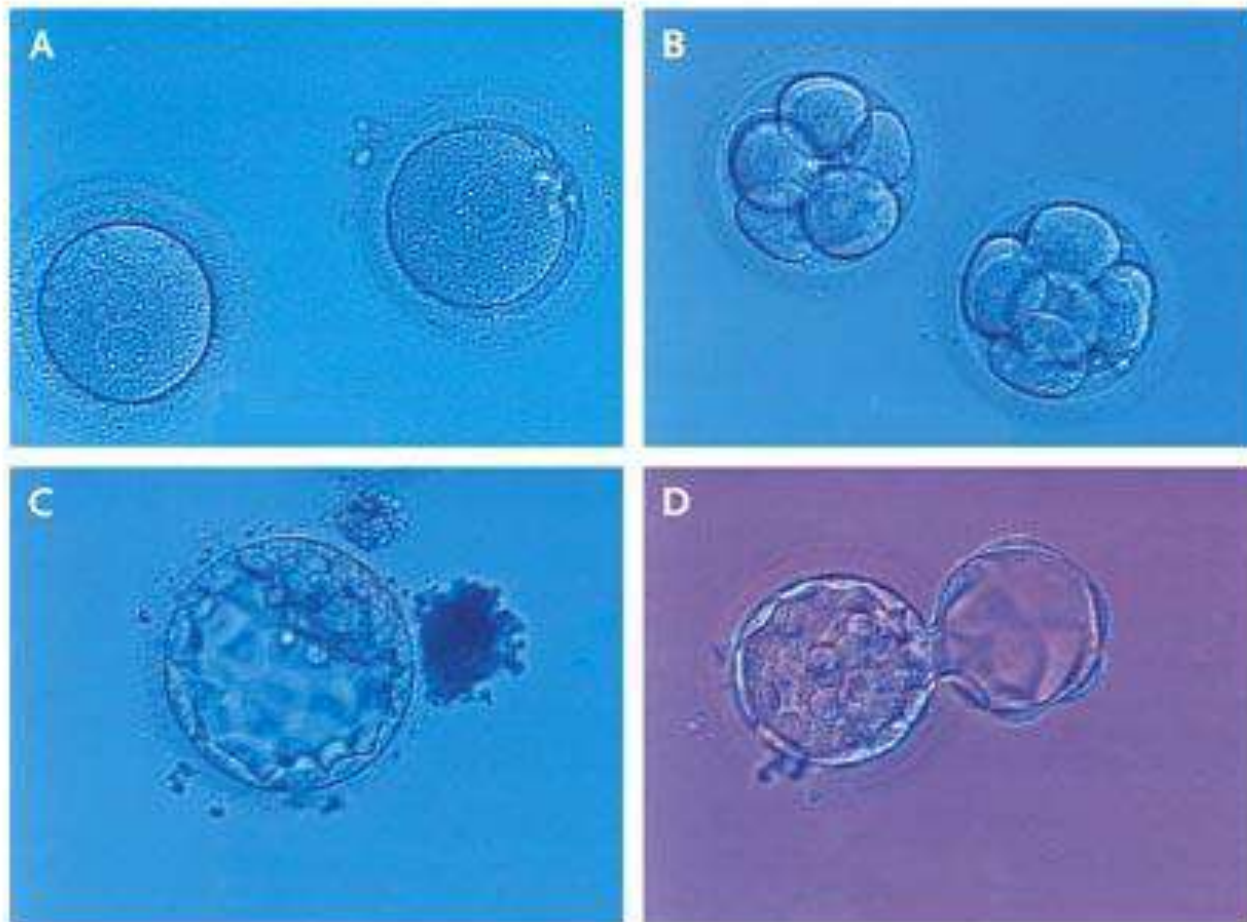
Indication For ART

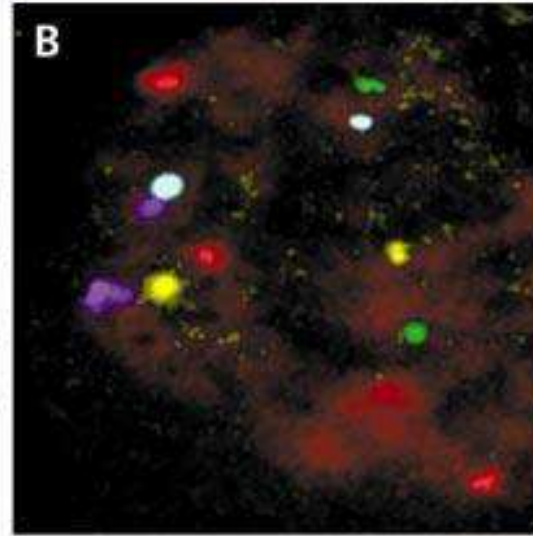
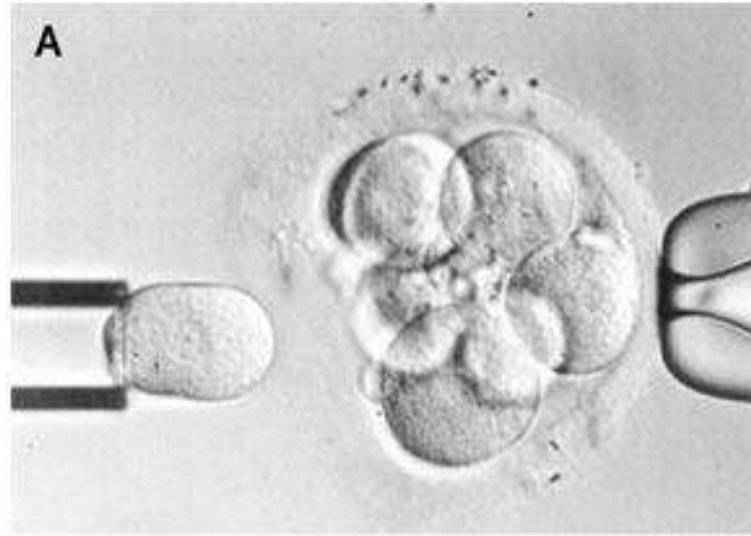


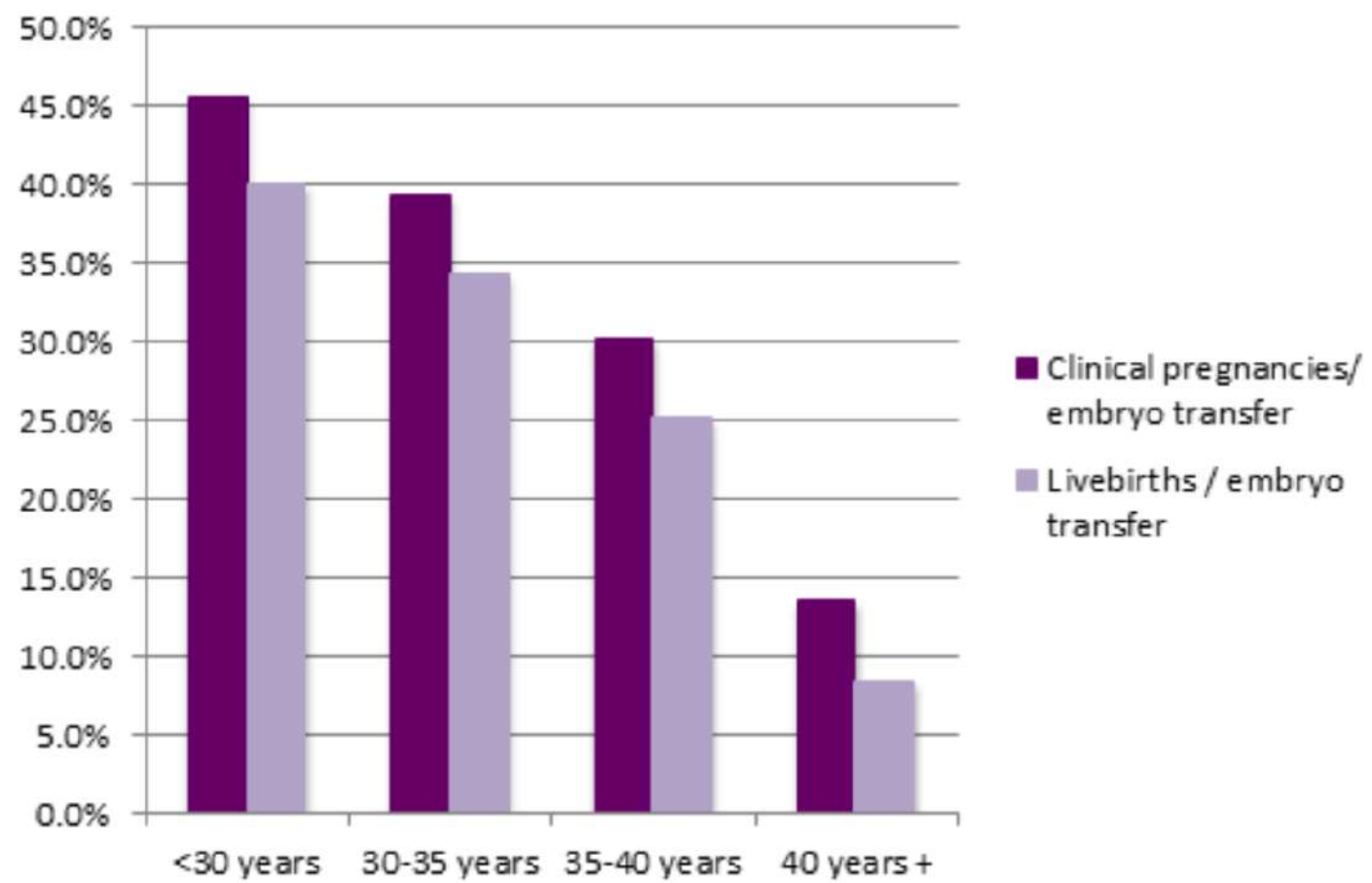
KESİN ENDİKASYONLAR İVF İCSI TESE TESA

- 1) TUBAL TIKANIKLIK
- 2) İLERİ ERKEK FAKTÖRÜ
- 3) EREKSİYON VE EJAKULASYON PROBLEMİ









EŞLİK EDEN DURUM YÖNETİMİ

- 1)OBEZİTE
- 2)ENDOMETRİOZİS/ENDOMETRİOMA
- 3)HİDROSALPENKS
- 4)FİBROİD/POLİP
- 5)PKOS

The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis FREE

Sesh Kamal Sunkara ✉, Mohammed Khairy, Tarek El-Toukhy, Yacoub Khalaf, Arri Coomarasamy

Human Reproduction, Volume 25, Issue 2, 1 February 2010, Pages 418–429,
<https://doi.org/10.1093/humrep/dep396>

RESULTS

We identified 19 observational studies comprising 6087 IVF cycles. Meta-analysis of these studies showed a significant decrease in the live birth (RR = 0.79, 95% CI: 0.70–0.88, $P < 0.0001$) and clinical PRs (RR = 0.85, 95% CI: 0.77–0.94, $P = 0.002$) in women with non-cavity-distorting intramural fibroids compared with those without fibroids, following IVF treatment.

CONCLUSION

The presence of non-cavity-distorting intramural fibroids is associated with adverse pregnancy outcomes in women undergoing IVF treatment.

Hydrosalpinges Prior To IVF

**Laparoscopic salpingectomy
should be considered for all
women with hydrosalpinges prior
to IVF treatment.**

NICE Guideline 2004 Infertility

Johnson et al (2004) *Cochrane Systematic Reviews* 2009 Issue 4

Office Hysteroscopy (OH) & IVF

When to be done ?

- **At the time of laparoscopy**
- **For those not screened by HSG or SIS**
- **Before IVF/ICSI**
- **After one ART implantation failure**
- **After repeated implantation Failure**

Uterine Abnormalities

hysteroscopy should be done if there is a further question of uterine disease.

hysteroscopic excision of small (mean 16 mm) **polyps, underlining**

Perez-Medina et al Hum Reprod 2005; 20:1632.



myoma-like polyp



(i) sessile polyp



Functional polyp

PCOS /PCOS

- More oocytes retrieval
- Lower fertilization rate.
- Pregnancy rate is as other IVF cases
- success rate significantly increased only in normal weight
- High incidence of OHSS
- Metformin ↓ of OHSS

So : Reduction of Wight & Metformin

Balen e t al. Hum Reprod 1993; 8:959

Stadtmauer. Reprod Biomed Online 2002; 5:112.

Meldrum in David & Gardner In Virto Fertilization A Practical Aproch Informa 2008.

PCO & IVF/ICSI

- IVF ilk seenek bir tedavi deęildir.
- Aęırlıklı olarak řu durumlarda endikedir;
- Ovulasyona raęmen gebelik elde edilemeyen PCOS'lu kadınlar (spontane yada asiste ovulasyon olsada)

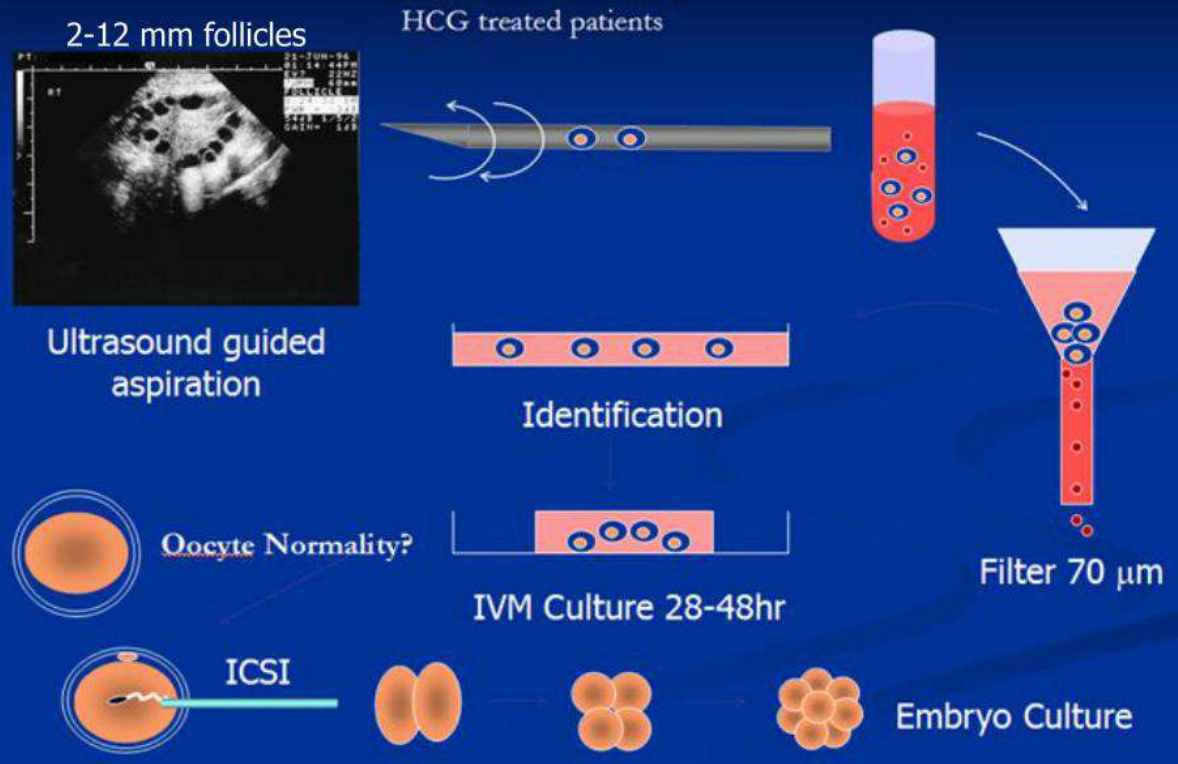
In Vitro Maturizasyon & PCOS

- Güncel bir çalışma: Klinik gebelik oranları %40 / transfer
Zoha et al Fertil Steril. 2009 Jun; 91 (6): 2568-71.
- PCOS lu kadınlarda IVF yada ICSI öncesi IVM yapılmasını öneren hiçbir Randomize klinik çalışma yoktur.

IVM Indications

- PCOS
- High responders
- IVF/IVM
- Fertility preservation
- Donation cycles
- Delayed responders
- Male infertility
- Poor responders

IN Vitro Maturation - IVM

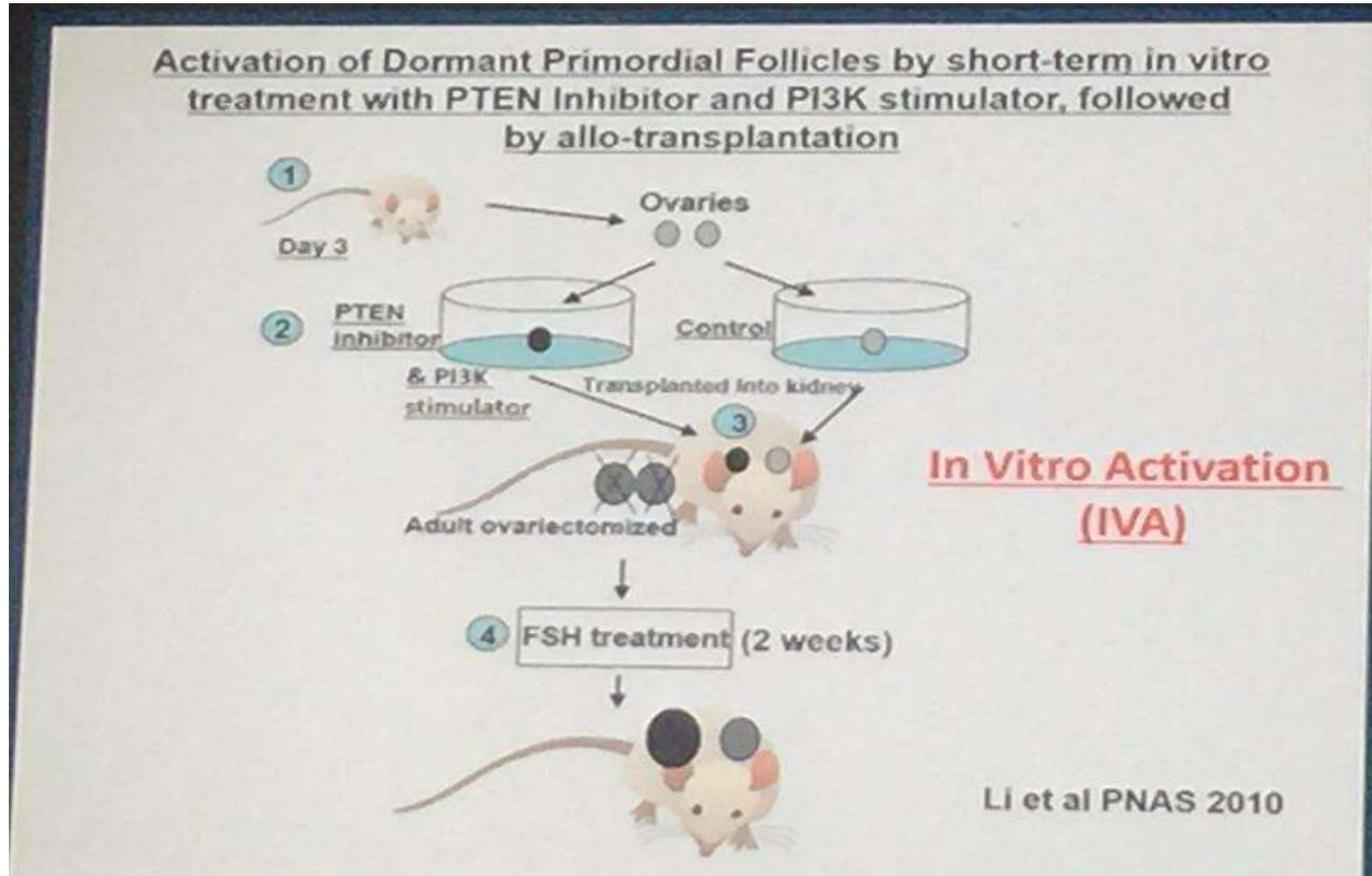


In general

- clinical pregnancy rate 30-35%
- implantation rate 10-15%

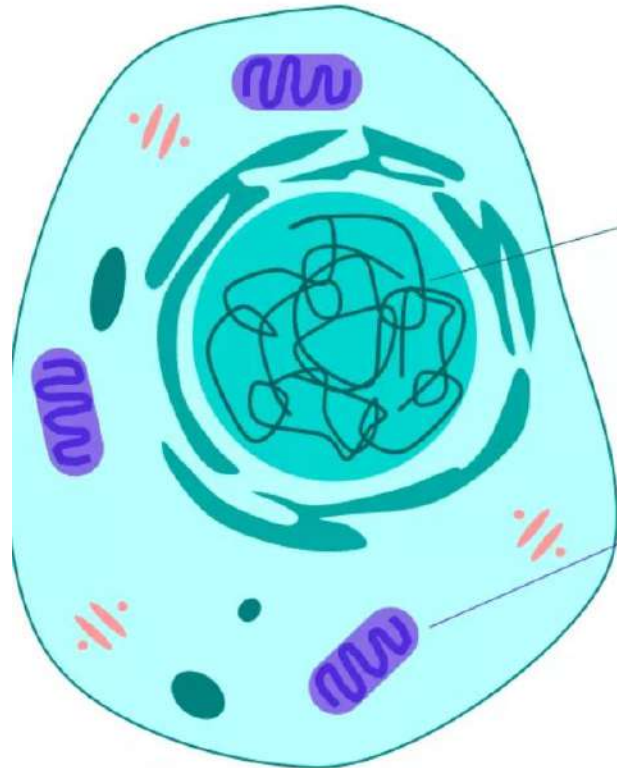
(R.C. Chian RBM Online, 2004)

İN VİTRO AKTİVASYON



MİKONDRIAL DNA İLE GEÇEN HASTALIKLARDA MİTOKONDİRİ TRANSFERİ

The Cell

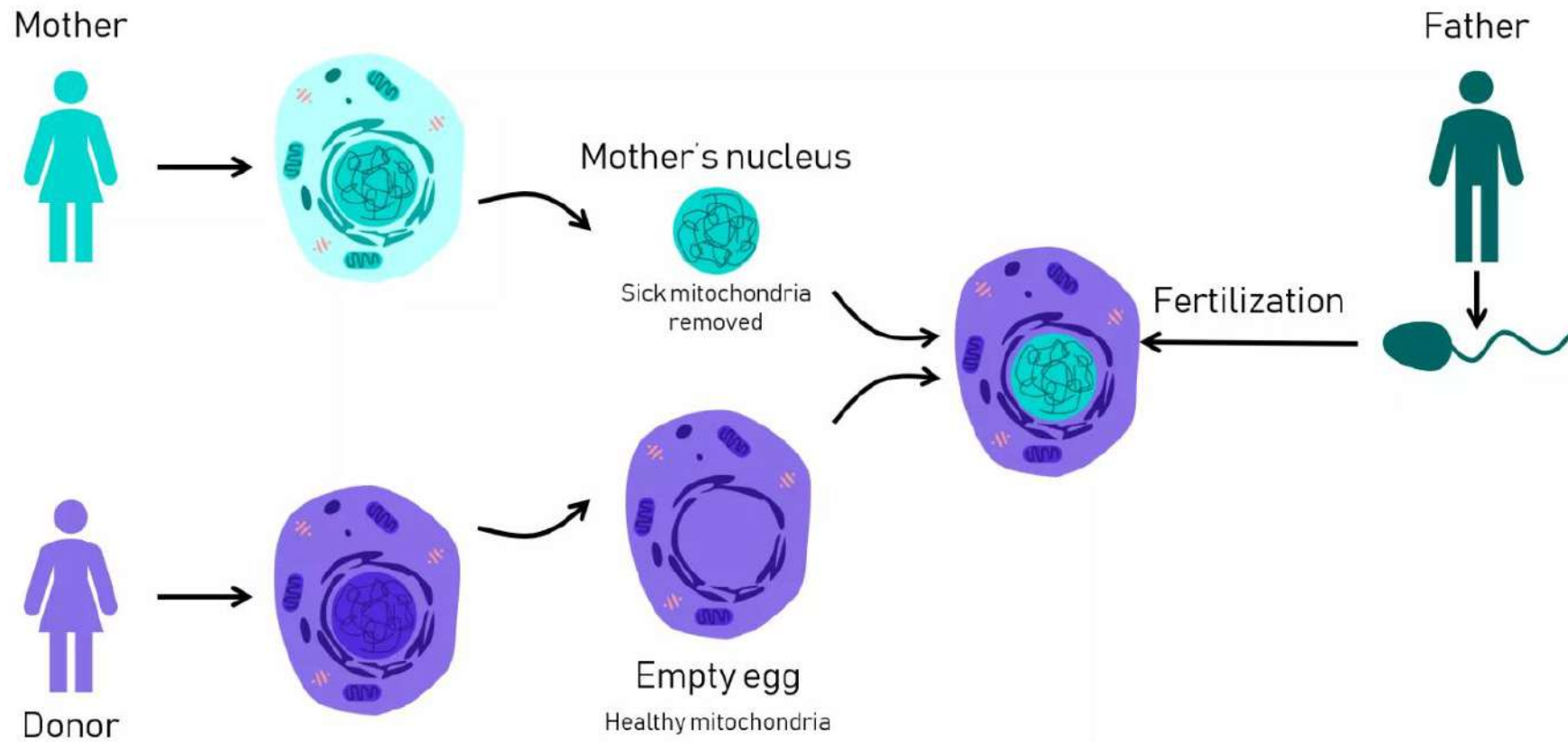


Nuclear DNA

- 20,000 – 40,000 genes
- 99% of total DNA
- Inherited from both mother and father

Mitochondrial DNA

- 37 genes
- 1% of total DNA
- Inherited from mother only



Semen Parameters



WHO 5th Edition-Correlates with Fertility but is this the right cut-off? Why must we have a single cut-off?

Table II Distribution of values, lower reference limits and their 95% CI for semen parameters from fertile men whose partners had a time-to-pregnancy of 12 months or less

| | N | Centiles | | | | | | | | | | |
|-----------------------------------|------|----------|-----------|-----|-----------|-----|-----|-----|------|-----|-----|------|
| | | 2.5 | (95% CI) | 5 | (95% CI) | 10 | 25 | 50 | 75 | 90 | 95 | 97.5 |
| Semen volume (ml) | 1941 | 1.2 | (1.0–1.3) | 1.5 | (1.4–1.7) | 2 | 2.7 | 3.7 | 4.8 | 6 | 6.8 | 7.6 |
| Sperm concentration (10^6 /ml) | 1859 | 9 | (8–11) | 15 | (12–16) | 22 | 41 | 73 | 116 | 169 | 213 | 259 |
| Total number (10^6 /Ejaculate) | 1859 | 23 | (18–29) | 39 | (33–46) | 69 | 142 | 255 | 422 | 647 | 802 | 928 |
| Total motility (PR + NP, %)* | 1781 | 34 | (33–37) | 40 | (38–42) | 45 | 53 | 61 | 69 | 75 | 78 | 81 |
| Progressive motility (PR, %)* | 1780 | 28 | (25–29) | 32 | (31–34) | 39 | 47 | 55 | 62 | 69 | 72 | 75 |
| Normal forms (%) | 1851 | 3 | (2.0–3.0) | 4 | (3.0–4.0) | 5.5 | 9 | 15 | 24.5 | 36 | 44 | 48 |
| Vitality (%) | 428 | 53 | (48–56) | 58 | (55–63) | 64 | 72 | 79 | 84 | 88 | 91 | 92 |

*PR, progressive motility (WHO, 1999 grades a + b); NP, non-progressive motility (WHO, 1999 grade c).

The values are from unweighted raw data. For a two-sided distribution the 2.5th and 97.5th centiles provide the reference limits; for a one-sided distribution the fifth centile provides the lower reference limit.

WHO CRITERIA CHANGE OVER TIME

Table 1. Cut-off values for semen variables as published in consecutive WHO manuals [6–9] and as proposed in the fifth World Health Organization (WHO) manual [1].

| Semen variable | 1980 | 1987 | 1992 | 1999 | 2010 ¹ |
|---|-------------------|---------------------------|-------------------|-------------------|-------------------|
| Volume (mL) | – | ≥ 2.0 | ≥ 2.0 | ≥ 2.0 | 1.5 |
| Concentration (10 ⁶ mL ⁻¹) | 20–200 | ≥ 20 | ≥ 20 | ≥ 20 | 15 |
| Total sperm number (10 ⁶ /ejaculate) | – | ≥ 40 | ≥ 40 | ≥ 40 | 39 |
| Motility (% motile) | ≥ 60 | ≥ 50 (a + b) ² | ≥ 50 (a + b) | ≥ 50 (a + b) | 40 (a + b + c) |
| Forward progression (for 1980 only) | ≥ 2 ³ | ≥ 25 (a) | ≥ 25 (a) | ≥ 25 (a) | 32 (a + b) |
| Morphology (% normal) | 80.5 ⁴ | ≥ 50 | ≥ 30 ⁵ | (14) ⁶ | 4 |
| Viability/vitality (% live) | – | ≥ 50 | ≥ 75 | ≥ 75 | 58 |
| White blood cells (10 ⁶ mL ⁻¹) | < 4.7 | < 1.0 | < 1.0 | < 1.0 | < 1.0 |

¹Lower reference limit. Obtained from the lower fifth centile value. ²Grade a = rapid progressive motility (> 25 $\mu\text{m s}^{-1}$); Grade b = slow/sluggish progressive motility (5–25 $\mu\text{m s}^{-1}$); Grade c = no-progressive motility; Grade d = immotility; Normal = ≥ 50% motility (grades a + b) or ≥ 25% progressive motility (grade a) within 60 min of ejaculation. ³Forward progression on a scale of 0–3, in which 0 = no forward progression. ⁴Mean of a fertile population (range = 48%–98%); modified Bryan Leishman staining. ⁵Arbitrary value. ⁶No actual value given. Multicentre studies in progress refer to > 14% for *in vitro* fertilization (IVF).

ICSI for Diminished Ovarian Reserve

“based on current evidence, the use of ICSI for low oocyte yield does not significantly improve fertilization rates, embryo number and quality, or pregnancy rates”

– ASRM Committee opinion Fertil Steril
2012;98:1395

IUI ENDİKASYONLARI

- 1) SERVİKAL FAKTÖR
- 2) MALE SUBFERTİLİTY
- 3) UNEXPLAINED SUBFERTİLİTY
- 4) VAGİNİSMUS
- 5) ENFEKSIONDAN KORUNMA
- 6) ENDOMETRİOZİS

- PCOS gibi WHO Grup 2 ovulasyon bozukluđu olan kadınlarda 6 ay boyunca klomifen sitrat ile ovulasyon oluřmuř fakat gebelik oluřmamıřsa, hastaya klomifen sitrat ile stimule edilmiř IUI önerilmelidir.

GRADE A

National Institute of Clinical Excellency (NICE) 2004

Determinants Of IUI Outcome

| Female Age | <25 | 25-30 | 30-35 | 35-40 | 40-45 | >45 |
|-------------------------------|---------------|--------------|--------------|--------------|--------------|---------------|
| Pregnancy% / Cycle | 19 | 14 | 12 | 11 | 5 | 0.5 |

| Duration of Infertility | <6 years | > 6 years |
|--------------------------------|--------------------|---------------------|
| Pregnancy % /Cycle | < 20 | < 10 |

Norman, et al · In: Botros et al Infertility & Assisted Reproduction 2008

Tekrarlayan gebelik kaybı

- >3 defa veya 500 g altı gebelik sonlanması ancak en küçük yaşayan çocuk 285 g

Tekrarlayan Gebelik Kayıplarında Risk Faktörleri

1. Epidemiyolojik faktörler:
 - a. Anne yaşı
 - b. Üreme öyküsü
2. Genetik faktörler
3. Anatomik bozukluklar
4. Endokrin faktörler
5. Koagülasyon bozuklukları ve immünolojik faktörler (trombofili, antifosfolipid sendromu,vs)
6. Diğer faktörler (Enfeksiyonlar, çevresel, psikolojik faktörler v.s)

1. Epidemiyolojik Faktörler-Anne yaşı

Geniş prospektif bir çalışmada bilinen gebeliklerde (634.272) yaşa bağımlı riskler şöyle bulunmuştur¹:

| | |
|-------------------|--------|
| 12-19 yaş arası | % 13.3 |
| 20-24 yaş arası | % 11.1 |
| 25-29 yaş arası | % 11.9 |
| 30-34 yaş arası | % 15 |
| 35-39 yaş arası | % 24.6 |
| 40-44 yaş arası | % 51 |
| 45 yaş ve üstünde | % 74.7 |

¹Nybo Anderson AM. BMJ 2000;320:1708-1712 (Danimarka çalışması)

a. Anne Yaşı:

- Obstetrik öyküden bağımsız olarak;
 - Yaşa bağlı artan anormal kromozomlu gebelikler yada
 - Yaşa bağlı azalan over ve uterus fonksiyonları nedeniyle,
- düşük riski artan anne yaşı ile yüksel

1. Epidemiyolojik Faktörler- Parental yaş

- Geniş bir Avrupa çalışması kadınların 35 yaş ve üstü, erkeklerin 40 yaş ve üstü olduklarında düşük riskinin arttığını göstermiştir.

De la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage: Results of a multicentre European study. Human Reprod 2002;17:1649-1656

1. Epidemiyolojik Faktörler

b. Üreme Öyküsü:

- Risk artışı:
 - Bir düşükten sonra: % 16
 - İki ardışık düşükten sonra: % 24
 - Üç ardışık düşükten sonra: % 45
 - Dört ardışık düşükten sonra: % 54 oranlarına çıkmaktadır.

Knudsen UB, et al. Eur J Obstet Gynaecol Reprod Biol 1991;39:31-36

Etiology - Environmental Factors

- Confirmed association
 - Ionizing irradiation
 - Organic solvents
 - Alcohol
 - Mercury
 - Lead
- ▣ **Suspected association**
 - ▣ Caffeine (> 300 mg/day)
 - ▣ Hyperthermia/fever
 - ▣ Cigarette smoking
- ▣ **Unknown association**
 - ▣ Pesticides

Etiology - Environmental Factors

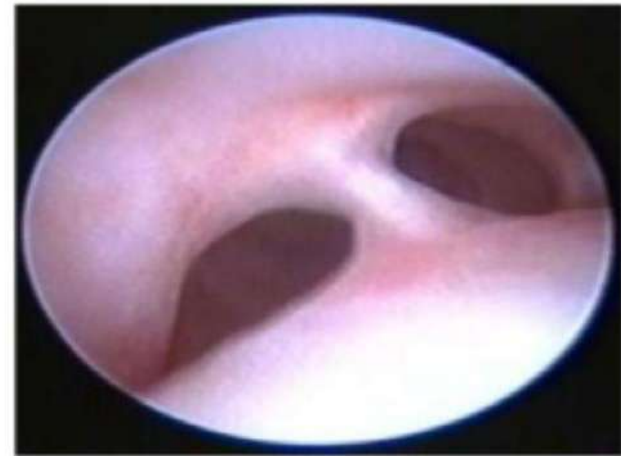
- Diagnostic x-rays
- Air travel
- Microwave ovens
- Diagnostic ultrasounds
- Electromagnetic fields
- Video display terminals
- Aspartame
- Chocolate
- Drinking water
- BGH
- Phytoestrogens
- Phthalates
- Herbicides
- Hair dyes
- Nail polish
- Saccharin

UTERINE FACTORS

- Acquired or congenital anomalies
- Congenital anomalies: 10 -15 % in women with RPL vs. 7 % in all women.
- Abnormal implantation:
 - ↓ vascularity (septum)
 - ↑ inflammation (fibroid)
 - ↓ sensitivity to steroid hormones

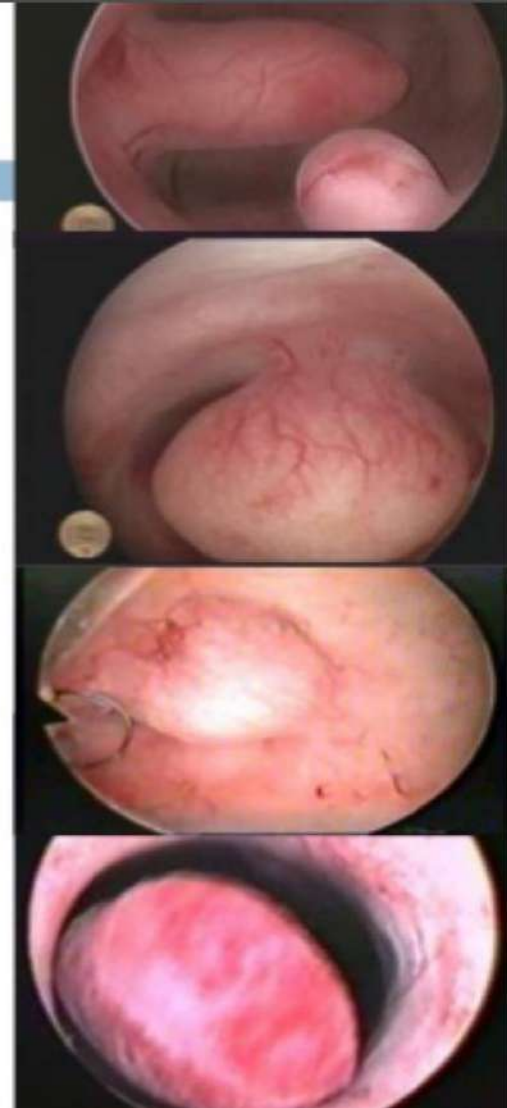
SEPTATE UTERUS

- □ Most common
 - Poorest outcome
 - Miscarriage > 60 %
 - Fetal survival with untreated cases 6 to 28 %
 - The mechanism
 - □ Not clearly understood
 - □ Poor blood supply
- ↓
- poor implantation



LEIOMYOMA

- **Submucous**
- The mechanism -
 - ▣ Their position
 - ▣ Poor endometrial receptivity
 - ▣ Degeneration with increasing cytokine production



OTHER UTERINE CAUSES

- Endometrial polyps
- Intrauterine adhesions
 - ▣ Curettage for pregnancy complications (4/52)
 - ▣ Traumatize basalis layer → granulation tissue
 - ▣ Insufficient endometrium to support fetoplacental growth
 - ▣ Menstrual irregularities (hypomenorrhea, amenorrhea), cyclic pelvic pain, infertility.

OTHER UTERINE CAUSES



- Cervical insufficiency
 - ▣ Recurrent mid-trimester loss
- Other Anomalies
 - DES exposure (T shaped uterus +/- cervical changes)

UTERINE ASSESSMENT

- Sonohysterography (SIS)
 - ▣ More accurate than HSG
 - ▣ Differentiate septate & bicornuate uterus
- Hysterosalpingogram (HSG)
 - ▣ Does not evaluate outer contour
 - ▣ Not ideal for the cavity
- Hysteroscopy
 - ▣ Gold standard for Dx + Rx intrauterine lesions
 - ▣ Reserved for when no Dx is made

UTERINE ASSESSMENT

- Ultrasound
 - ▣ Presence and location of uterine myomas
 - ▣ Associated renal abnormalities
- MRI
 - ▣ Differentiate septate from bicornuate
- Hysteroscopy, laparoscopy, or MRI → second-line tests when additional information is required

TREATMENT

Surgery

- Hysteroscopy
 - Procedure of choice
 - Septum excision, polypectomy
- Laparoscopic myomectomy
 - For fibroids
- Laparotomy

CERVICAL INCOMPETENCE

- **Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should only be considered in women who are likely to benefit.**
- Transabdominal cerclage has been advocated as a treatment for second-trimester miscarriage and the prevention of early preterm labour in selected women with previous failed transvaginal cerclage and/or a very short and scarred cervix

IMMUNOLOGIC FACTORS

Autoimmune

(directed to self)
tissues/cells

- Systemic Lupus Erythmatosus
 - Antiphospholipid Syndrome
- antigen.

Alloimmune

(directed to foreign
antigen)

An abnormal maternal
immune response to
fetal or placental

Antiphospholipid syndrome

■ An Autoimmune disorder having specific clinical & lab criteria.

--**Sapporo criteria**

Diagnosis requires at least one of each.

CLINICAL 1) Thrombotic events-arterial, venous, small vessel
2) Pregnancy loss- ≥ 3 losses at < 10 wks gestation, fetal death after 10 wks, premature birth at < 34 wks associated with severe preeclampsia or placental insufficiency.

LABORATORY 1) Lupus Anticoagulant
2) Anticardiolipin antibodies (IgG or IgM)

Any lab test results must be observed on at least 2 separate occasions 6 wks apart.

APAS

- Treatment
 1. Low Molecular weight Heparin
 - 3000 IU subcu twice a day
 - Expensive treatment
 2. **Un-fractionated Heparin is better option**
 3. Low dose Aspirin
 4. Steroids? Mainly for anti nuclear antibodies
 - 10 – 20 mg prednisolone / day

ANORMAL NK AKTİVİTESİ ve TAKROLİMUS

- many studies are focused on the role of natural killer (NK) cells in normal and pathologic pregnancy because NK cells constitute the dominant cell population in the endometrium and they come in close contact with the allogeneic extravillous trophoblast cells in early pregnancy decidua. The majority of these cells are of CD56^{bright} phenotype. These cells can express killer immunoglobulin-like receptors (KIRs), which, upon recognition of HLA class I molecules (HLA-C and HLA-G) on trophoblasts, may either stimulate or inhibit NK cells to produce soluble factors, and display low cytotoxicity necessary for maintenance of the allogeneic embryo and fetus in the next steps of pregnancy.

ENDOCRINE FACTORS

- Mild endocrine diseases are likely **not** causes for recurrent abortion.

1) Thyroid disease

- Poorly controlled hypo- or hyper-thyroidism
 - Infertility & pregnancy loss
- ↑ thyroid antibody, even if euthyroid.
 - No strong evidence

2) Diabetes mellitus

- ▣ Poorly controlled (\uparrow Blood glucose & HbA1c levels in 1st trimester) \longrightarrow \uparrow risk for loss.
- ▣ Miscarriage risk rises with the level of HbA1c
- ▣ Well-controlled \longrightarrow No \uparrow risk.

3) Polycystic Ovarian Syndrome

Polycystic ovary morphology itself does not predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously (RCOG)

Hyperinsulinemia & ↑ level of Plasminogen Activator Inhibitor activity – implicated as the proximate cause of incidence of loss (30-50%) among PCOS women (Br J Obst Gynecol, 1993)

METFORMIN treatment can reduce or eliminate risk of miscarriage in PCOS women (Fertility Sterility, 2001; J Clin Endocrinol 2002)

4) Luteal phase defect

- ▣ Progesterone is essential for implantation and maintenance of pregnancy
 - A defect in Corpus luteum → impaired progesterone production.
 - However, LPD cannot be diagnosed during pregnancy; a consistently short luteal phase duration is the most reliable diagnostic criterion.

ENDOCRINE FACTORS

- Thyroid Function Tests- T3 ,T4,TSH
- S.Prolactin
- Glucose tolerance test
- HbA1c
- S.FSH
- S.LH
- S.Progesterone

- ◉ Decreased ovarian reserve
 - ▣ Quality and quantity of oocytes decrease
 - ▣ Women with unexplained RPL have a higher D3 FSH and E2 than women with known cause

TORCH HİKAYESİ

PGT-A PGT-M PGT-SR

TEŐEKKÜRLER