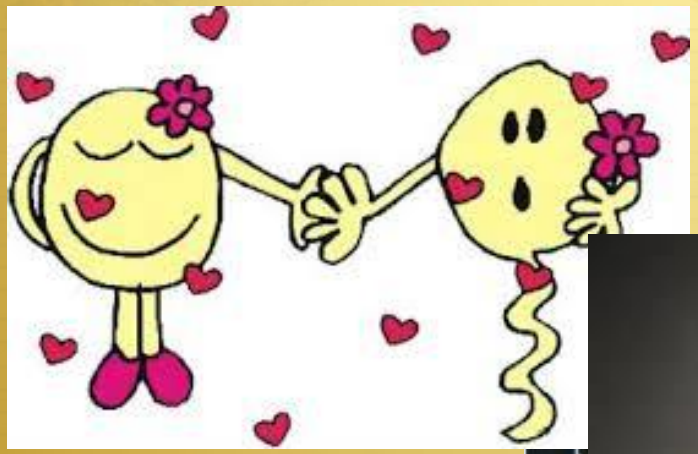
Dra. Adriana Zabala
Médica Especialista en Ginecología y Medicina Reproductiva.
Docente Cátedra "A" de Ginecología de la Facultad de Ciencias Médicas de la UNLP.
Médico de Plata a cargo del Área de Medicina Reproductiva del Servicio de Ginecología del HIGA Gral. San Martin de La Plata.

"Fertilidad después de los 40”

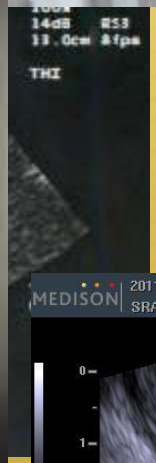
1er Curso Universitario de Postgrado de Formación en Climaterio. aapec.

Dra. Adriana Zabala
Medica Especialista en Ginecología y Medicina de la Reproducción.
Docente Cátedra “A” de Ginecología de la UNLP
Coordinadora del Área de Fertilización Asistida del HIGA San Martin de La Plata.
Provincia de Buenos Aires.

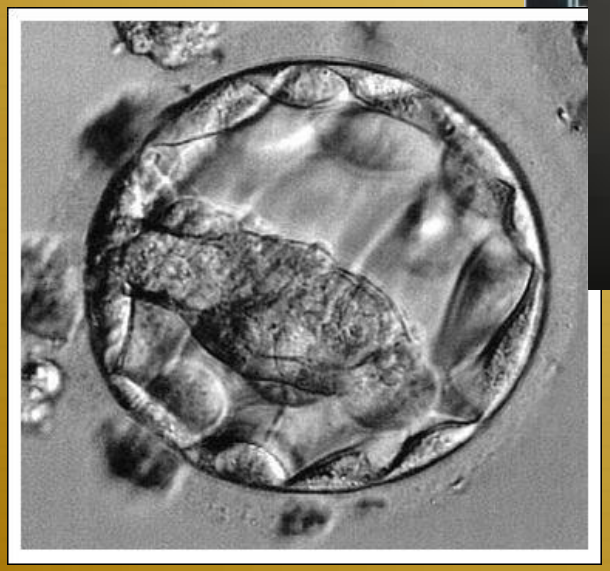
Fertilidad después de los 40 años tiene múltiples focos de análisis…….



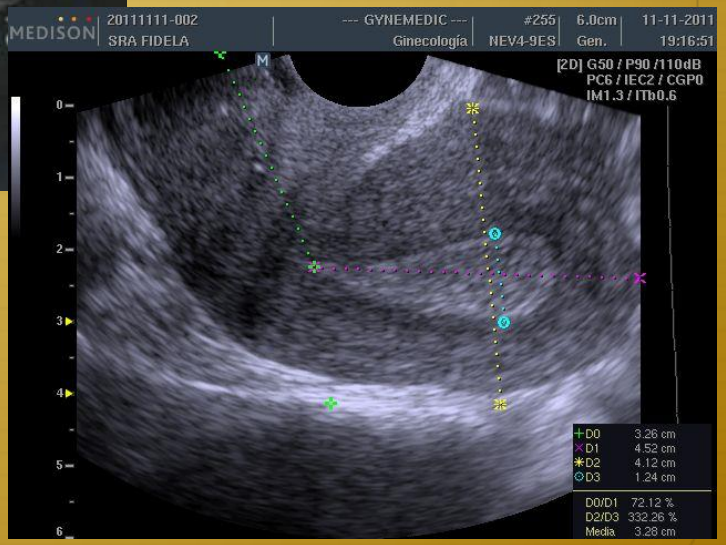
Biológicos



Sociológicos
Demográficos
Psicológicos



Económicos….



TENDENCIA FASHION.....?

TENDENCIA SOCIOCULTURAL.....?

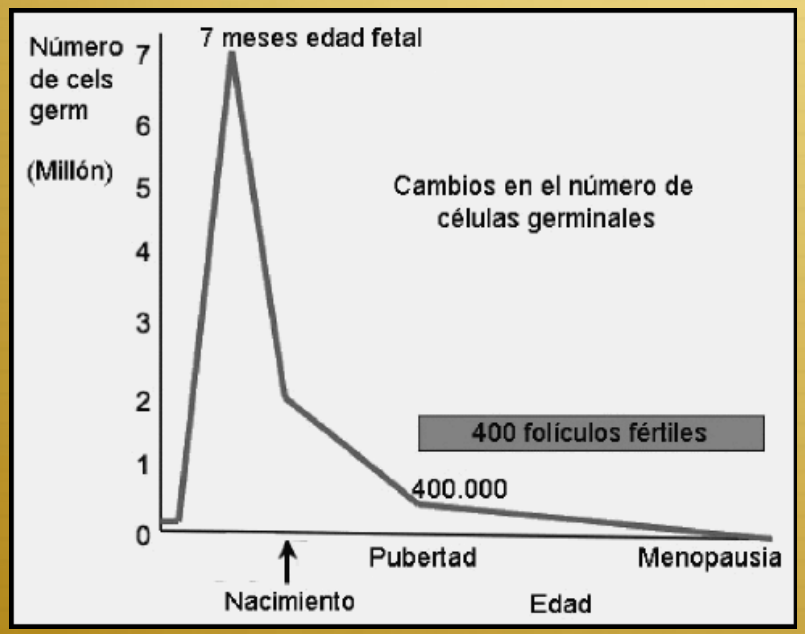
Edad & Fertilidad Femenina

- ✧ Ageing Ovárico
- ✧ Ageing Uterino
- ✧ Resultados materno-fetales de los embarazos luego de los 40 años.

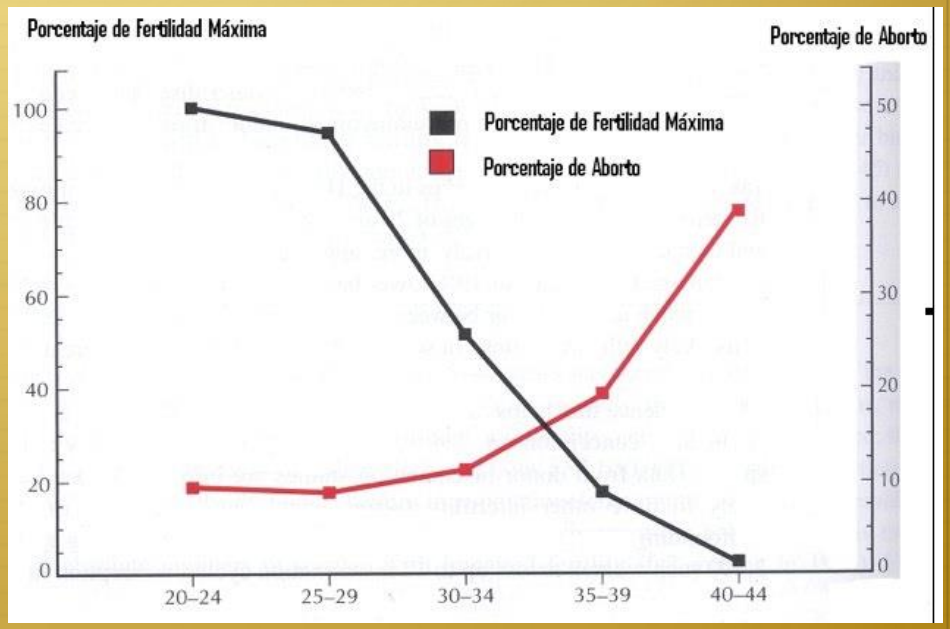
Hally Berry

Ageing Ovárico

Pool de folículos primordiales finito



Calidad & cantidad



El concepto de reserva ovárica limitada en cuanto a cantidad y calidad de ovocitos es el mas importante de la reproducción humana natural y asistida. Últimos hallazgos lo han puesto en discusión pero aun considerado como la verdad absoluta.

Depleción de un recurso agotable??

Molecular Human Reproduction, Vol.15, No.7 pp. 393–398, 2009
doi:10.1093/molehr/gap036

MHR

COMMENTARY

Purification of germline stem cells from adult mammalian ovaries: a step closer towards control of the female biological clock?

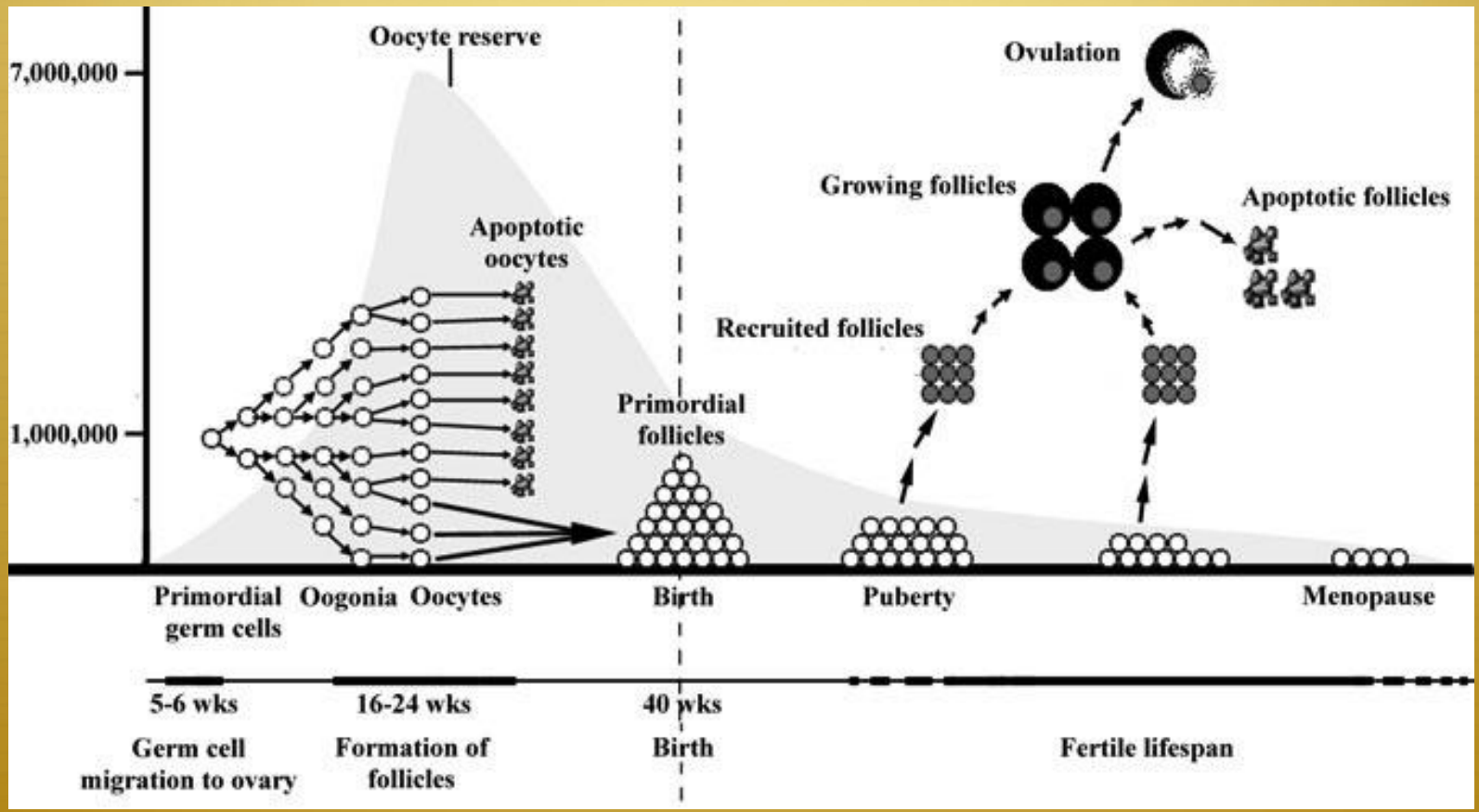
Jonathan L. Tilly[1,2,4] and Evelyn E. Telfer[3,4]

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bone Marrow Transplantation Generates Immature Oocytes and Rescues Long-Term Fertility in a Preclinical Mouse Model of Chemotherapy-Induced Premature Ovarian Failure

Ho-Joon Lee, Kaisa Selesniemi, Yuichi Niikura, Teruko Niikura, Rachael Klein, David M. Dombkowski, and Jonathan L. Tilly


Oocyte reserve
7,000,000
1,000,000
Apoptotic oocytes
Primordial follicles
Ovulation
Growing follicles
Apoptotic follicles
Recruited follicles
Primordial germ cells
Oogonia
Oocytes
Birth
Puberty
Menopause
5-6 wks
16-24 wks
40 wks
Germ cell migration to ovary
Formation of follicles
Birth
Fertile lifespan

DINÁMICA FOLICULAR

A. GOUGEON

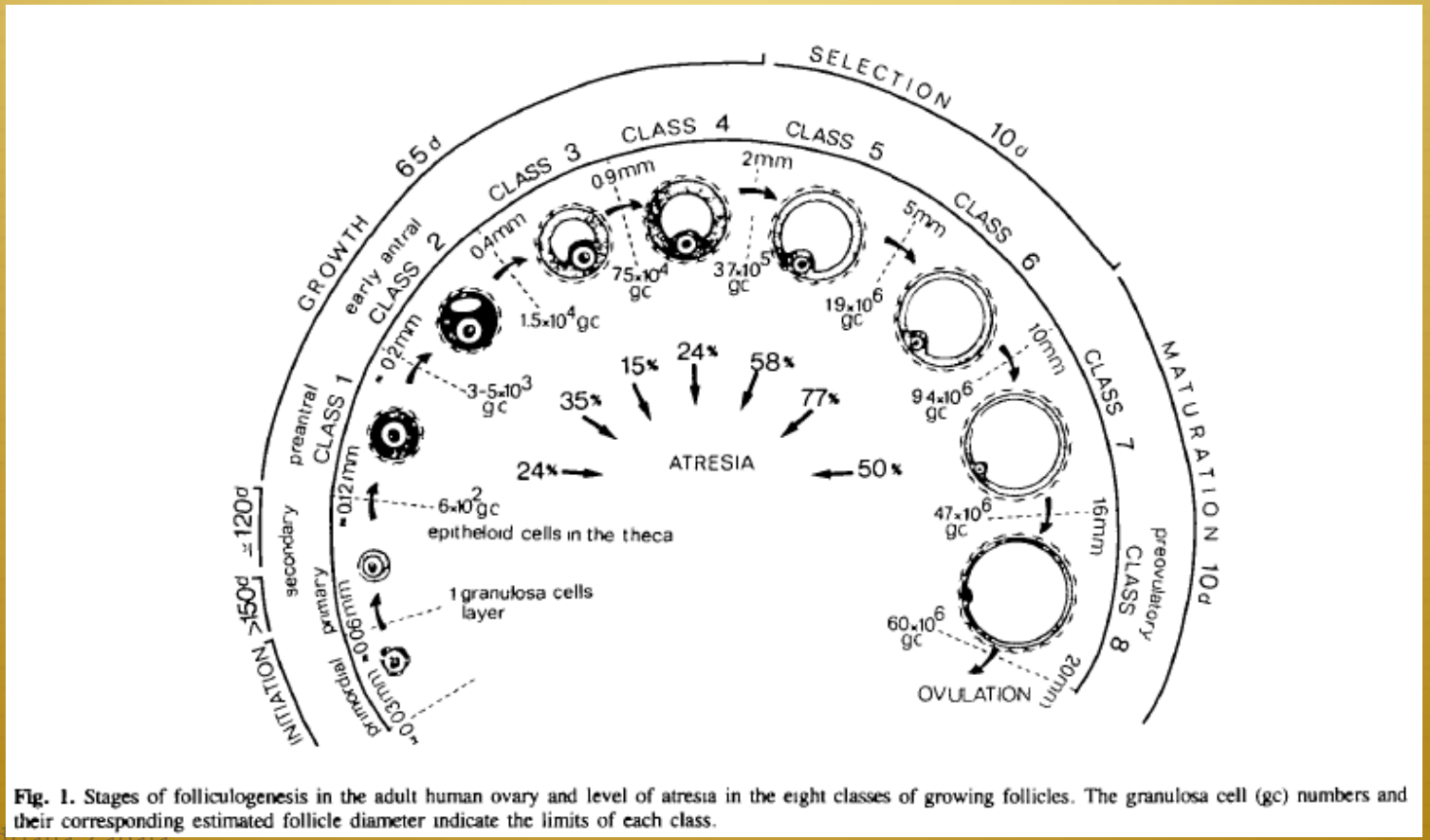


Fig. 1. Stages of folliculogenesis in the adult human ovary and level of atresia in the eight classes of growing follicles. The granulosa cell (gc) numbers and their corresponding estimated follicle diameter indicate the limits of each class.

Ageing uterino

- *Menor tasa de embarazo / implantación.*
- *Mayor tasa de aborto.*
- *Peores resultados perinatales.*

Human Reproduction Update, Vol.19, No.1 pp. 67–83, 2013

The ageing ovary and uterus: new biological insights

S.M. Nelson[1,*], E.E. Telfer[2], and R.A. Anderson[3]

1-Deterioro en el desarrollo placentario y desidualización:

⌘Demostrado por estudios básicos en ratas.

⌘Mayor peso placentario por hipertrofia compensatoria.

⌘Reducción de los receptores de estrógeno y progesterona con incremento de la fibrosis y del colágeno.

2- Alteración de la función miometrial:

⌘Mayor riesgo de cesárea intraparto y parto operatorio en mujeres mayores de 40 comparadas con las menores.

⌘Correlación negativa entre edad materna y actividad espontanea.

⌘Cambios ultraestructurales de la fibra del musculo miometrial con inclusiones citoplasmáticas, disociación de micro filamentos, destrucción mitocondria y del Retículo endoplasmatico.

Los autores hipotizan que la exposición a ciclos de alza y caída de los esteroides sexuales es lo que lleva a un deterioro de la función miometrial / endometrial y serian la base biológica para los resultados observados en mujeres mayores de 40 años.

Ageing Uterino & resultados

Clinical factors affecting endometrial receptiveness in oocyte donation cycles

Sérgio Reis Soares, M.D.,[a] *Juan Antonio Garcia Velasco, M.D.,*[b] *Manuel Fernandez, M.D.,*[b] *Ernesto Bosch, M.D.,*[b] *José Remohí, M.D.,*[b] *Antonio Pellicer, M.D.,*[b,c] *and Carlos Simón, M.D.*[b]

[a] IVI-Lisboa, Avenida Infante Dom Henrique, 333-H, 1800-282, Lisboa, Portugal; [b] Instituto Universitario IVI, Universidad de Valencia, Valencia; and [c] Hospital Universitario Dr. Peset, Valencia, Spain

Fertility and Sterility® Vol. 89, No. 3, March 2008

- *Edad de la mujer receptora.*
- *Índice de masa corporal.*
- *Habito del tabaco.*
- *Preparación endometrial.*
- *Presencia de hidrosalping y endometriosis-adenomiosis.*

TABLE 1

Factors influencing endometrial receptiveness in oocyte donation cycles.

	Cutoff point	PR	MR	MPR	References
Recipients age (y)	>45	↓	↑		Yaron et al. (4), Moomjy et al. (5), Legro et al. (6), Paulson et al. (7), Noyes et al. (8), Cano et al. (9), Toner et al. (10), Soares et al. (1)
BMI (kg/m^2)	>30	↓	↑		Wattanakumtornkul et al. (17), Styne-Gross et al. (18), Bellver et al. (19), Bellver et al. (20)
Endometrial priming					
Thickness		No effect			Noyes et al. (8), Soares et al. (11), Garcia-Velasco et al. (23), Shapiro et al. (24), Abdalla et al. (25), Borini et al. (26), Remohí et al. (27), Coulam et al. (28)
Serum E_2 levels		No effect			Noyes et al. (8), Soares et al. (11), Garcia-Velasco et al. (23), Michalas et al. (31), Remohí et al. (34)
Duration (wk)	>7	↓			Soares et al. (11), Michalas et al. (31), Yaron et al. (32), Younis et al. (33), Remohí et al. (34), Borini et al. (35)
Oral vs. transdermal		No available data			
Progesterone		No effect			Daya et al. (48), Manno et al. (49), Lightman et al. (50), Gibbons et al. (51)
Pituitary suppression		No effect			Simon et al. (53), Dal Prato et al. (54), El-Toukhy et al. (55)
Smoking habit	>10/day	↓		↑	Soares et al. (65)
Hydrosalpinx		↓			Camus et al. (68), Andersen et al. (69), Strandell et al. (70), Strandell et al. (71), Meyer et al. (72), Bildirici et al. (73), Seli et al. (74), Johnson et al. (75), Stadtmauer et al. (76), Hurst et al. (77)
Endometriosis		No effect			Simón et al. (85), Sung et al. (86), Díaz et al. (87)
Adenomyosis		No available data			

Note: PR = pregnancy rate; MR = miscarriage rate; MPR = multiple pregnancy rate.

Soares. Clinical factors relevant to egg donation. Fertil Steril 2008.

J Hum Reprod Sci. 2012 Sep;5(3):252-7.

A study of recipient related predictors of success in oocyte donation program.

Gupta P, Banker M, Patel P, Joshi B. Department of Reproductive, Medicine and Endoscopy, The Pulse Women Hospital Pvt. Ltd. Ahmedabad, Gujarat, India.

Table 1: Clinical pregnancy, implantation rate and ongoing pregnancy rates relative to the age of recipients

Age of recipient (years)	Clinical pregnancy rate (%)	Ongoing pregnancy rate %	Implantation rate %	Singleton/twin/ triplet (S/tw/tri)	Miscarriage rate
<35	29/79 = 36.70[a]	28/79 = 31.64[b]	45/229 = 19.65[c]	16/10/3	1/29 = 3.4[d]
35-39	34/81 = 41.97[a]	31/81 = 38.37[b]	58/235 = 24.68[c]	14/16/4	3/34 = 8.8[d]
40-44	25/78 = 32.05[a]	20/78 = 24.64[b]	25/228 = 12.28[c]	15/10/0	5/25 = 20[d]
≥45	7/32 = 21.87[a]	6/32 = 18.75[b]	12/91 = 13.18[c]	3/3/1	1/7 = 14.8[d]
*P value	0.209	0.001	0.001	NA	0.195

*P = non significant for a and d, significant for band c

……..This might be due to reduced uterine blood flow with increased age.[6,7] or a decreased sensitivity to progesterone effects. [8] Histologic, ultrastructural, and biochemical changes like subepithelial extracellular matrix deposition, stromal angiosclerosis, which become more common with age.[2,6] ……

Edad materna & resultados perinatales.

Advanced Maternal Age and Adverse Pregnancy Outcome: Evidence from a Large Contemporary Cohort

Louise C. Kenny[1], Tina Lavender[2], Roseanne McNamee[3], Sinéad M. O'Neill[4], Tracey Mills[2], Ali S. Khashan[1,5]*

PLOS | ONE February 2013 | Volume 8 | Issue 2 | e56583

>riesgo de muerte fetal, pretermino, bajo peso, macrosomia, extremadamente grande para la EG, cesárea.

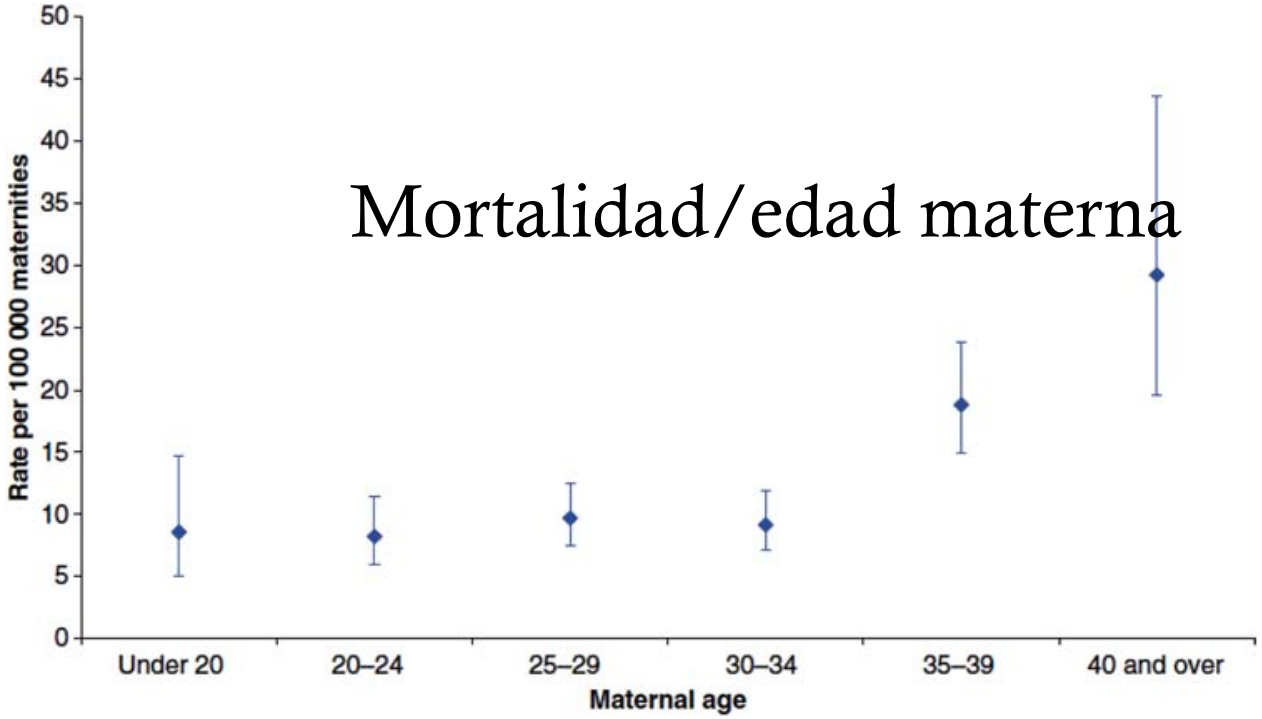
ades have witnessed an increase in mean maternal age at childbirth in most high-resourced rnal age has been associated with several adverse maternal and perinatal outcomes. Although on this topic, data from large contemporary population-based cohorts that controls for own to influence perinatal outcomes is limited.

population-based cohort study using data on all singleton births in 2004–2008 from the North based at The University of Manchester, UK. We compared pregnancy outcomes in women aged rs with women aged 20–29 years using log-linear binomial regression. Models were adjusted for parity, ethnicity, social deprivation score and body mass index.

Results: The final study cohort consisted of 215,344 births; 122,307 mothers (54.19%) were aged 20–29 years, 62,371(27.63%) were aged 30–34 years, 33,966(15.05%) were aged 35–39 years and 7,066(3.13%) were aged ≥40 years. Women aged 40+ at delivery were at increased risk of stillbirth (RR = 1.83, [95% CI 1.37–2.43]), pre-term (RR = 1.25, [95% CI: 1.14–1.36]) and very pre-term birth (RR = 1.29, [95% CI:1.08–1.55]), Macrosomia (RR = 1.31, [95% CI: 1.12–1.54]), extremely large for gestational age (RR = 1.40, [95% CI: 1.25–1.58]) and Caesarean delivery (RR = 1.83, [95% CI: 1.77–1.90]).

Conclusions: Advanced maternal age is associated with a range of adverse pregnancy outcomes. These risks are independent of parity and remain after adjusting for the ameliorating effects of higher socioeconomic status. The data from this large contemporary cohort will be of interest to healthcare providers and women and will facilitate evidence based counselling of older expectant mothers.

Human Reproduction Update, Vol.19, No.1 pp. 67–83, 2013



gure 1 Maternal mortality rates by age group (years); UK: 2006–2008. Reproduced with permission from Cantwell *et al.* (2011).

Mayor riesgo de diabetes gestacional, Preeclamcia, hemorragia postparto, obesidad, etc.

Human Reproduction, Vol.27, No.3 pp. 896–901, 2012
Advanced Access publication on January 16, 2012 doi:10.1093/humrep/der469

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Association between oocyte donation and maternal and perinatal outcomes in women aged 43 years or older

C. Le Ray[1,2,*], S. Scherier[1], O. Anselem[1,2], A. Marszalek[2,3], V. Tsatsaris[1,2], D. Cabrol[1,2], and F. Goffinet[1,2]

[1]Port Royal Maternity, Department of Obstetrics and Gynaecology I, Cochin-Broca-Hotel Dieu Hospital, Assistance Publique des Hôpitaux de Paris, 123 Bd de Port-Royal, 75014 Paris, France [2]Paris Descartes University, Sorbonne Paris Cité, Paris, France [3]Reproductive, Endocrine and Infertility, Department of Obstetrics and Gynaecology II, Cochin-Broca-Hotel Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France

*Correspondence address. Tel: +33-1-58-41-31-36; Fax: +33-1-58-41-21-05; E-mail: camille.le-ray@cch.aphp.fr

Submitted on September 22, 2011; resubmitted on November 27, 2011; accepted on December 7, 2011

METHODS: This retrospective study covered all women, aged 43 or more, who gave birth between 2008 and 2010. Univariate and multivariate analyses with logistic regression models were used to compare maternal and perinatal outcomes as a function of mode of conception: without IVF, with IVF using own oocytes or with IVF and oocyte donation.

RESULTS: The study included 380 women, including 40 who had IVF without oocyte donation (10.5%) and 104 who had both (27.4%). There were 326 singleton and 54 multiple pregnancies. Overall, the complication rate was high: 8.7% pre-eclampsia, 6.1% gestational diabetes, 20.2% preterm delivery and 8.2% very preterm delivery (before 33 weeks), 44.8% Cesarean sections and 7.4% severe postpartum hemorrhage (PPH). The pre-eclampsia rate differed significantly between the groups (3.8% after no IVF, 10.0% after IVF only and 19.2% after IVF with oocyte donation, $P < 0.001$). After adjustment, the risk of pre-eclampsia was significantly higher in women with donated oocytes compared with pregnant women without IVF [adjusted OR = 3.3 (1.2–8.9)]. The rate of twin pregnancy was significantly higher in women with IVF and oocyte donation (39.4 versus 15.0% with IVF only and 2.5% without IVF, $P < 0.001$). Twin pregnancy was significantly associated with the risk of preterm delivery [adjusted OR = 8.9 (4.0–19.9)] and PPH [adjusted OR = 3.5 (1.3–9.5)].

CONCLUSION: In women aged 43 years or older, pregnancies obtained by IVF with oocyte donation are associated with higher rates of pre-eclampsia and twin pregnancies than those obtained without IVF or with IVF using their own oocytes.

Table II Complications according to mode of conception: univariate analysis.

	No IVF (n = 236)	IVF without oocyte donation (n = 40)	IVF with oocyte donation (n = 104)	P
Pre-eclampsia	9 (3.8)	4 (10.0)	20 (19.2)	<0.001[a]
Gestational diabetes	12 (5.1)	3 (7.5)	8 (7.7)	0.494[a]
Cesarean[c]	86 (37.9)	16 (42.1)	62 (61.4)	0.001[b]
PPH	11 (4.7)	2 (5.0)	15 (14.4)	0.008[a]
Preterm delivery <37 weeks[c]	34 (15.0)	10 (26.2)	30 (29.7)	0.006[b]
Preterm delivery <33 weeks[c]	15 (6.6)	2 (5.3)	13 (12.9)	0.152[a]
Birthweight <1000 g[c]	5 (2.1)	0	6 (4.2)	0.340[a]
Birthweight <2500 g[c]	40 (17.2)	14 (31.8)	54 (38.0)	<0.001[b]
IUFD[d]	5 (2.1)	1 (2.5)	1 (1.0)	0.728[a]

IUFD, *in utero* fetal death; TOP, termination of pregnancy.
[a]Fisher's exact test comparing the three modes of conception.
[b]χ^2 test comparing the three modes of conception.
[c]IUFD and TOP excluded.
[d]Onset in at least one fetus in each multiple pregnancy.

Los autores postulan un factor inmunológico como causa de estos resultados: embrión como implante alogenico total.

Table I Population characteristics according to mode of conception.

	No IVF (n = 236)	IVF without oocyte donation (n = 40)	IVF with oocyte donation (n = 104)	P
Maternal age (mean ± SD)	44.1 ± 1.4	44.0 ± 1.4	46.2 ± 2.9	<0.001
43 years (n, %)	102 (43.2)	18 (45.0)	19 (18.3)	
44 years	70 (29.7)	14 (35.0)	14 (13.5)	
45 years	35 (14.8)	2 (5.0)	14 (13.5)	
46 years	13 (5.5)	3 (7.5)	17 (16.5)	
47 years and older	16 (6.8)	3 (7.5)	40 (38.5)	<0.001
Geographic origin (n, %)				
France	118 (50.0)	24 (60.0)	70 (67.3)	
Other European countries	21 (8.9)	4 (10.0)	10 (9.6)	
Africa	66 (28.0)	6 (15.0)	12 (11.5)	
Asia	5 (2.1)	2 (5.0)	4 (3.9)	
Other	26 (11.0)	4 (10.0)	8 (7.7)	0.051
Parity (mean ± SD)	1.4 ± 1.4	0.9 ± 1.1	0.3 ± 0.6	<0.001
Nulliparity (n, %)	78 (33.2)	16 (40.0)	82 (78.9)	<0.001
Type of pregnancy (n, %)				
Singleton	230 (97.5)	34 (85.0)	62 (59.6)	
Twin	6 (2.5)	6 (15.0)	41 (39.4)	
Triplet	0	0	1 (1.0)	<0.001

The aged uterus: multifetal pregnancy outcome after ovum donation in older women

Michal J. Simchen[1,3], Adrian Shulman[2], Amir Wiser[2], Eran Zilberberg[1], and Eyal Schiff[1]

Human Reproduction, Vol.24, No.10 pp. 2500–2503, 2009

Table I Maternal characteristics: ovum recipient pregnant women aged ≥40 years and controls (women with twin pregnancies)

	Ovum recipient women with twins (*n* = 42)	Ovum recipient women with singletons (*n* = 83)	*P*-value (study twins versus study singletons)	Controls (*n* = 417)	*P*-value (study twins versus control twins)
Mean maternal age (years ± SD)	49.2 ± 4.3	49.3 ± 4.7	NS	31.6 ± 6.5	<0.001
Diabetes	13 (31%)	24 (29%)	NS	30 (7.3%)	<0.001
Hypertension	21 (50%)	35 (42%)	NS	38 (9.1%)	<0.001
Hospitalization	29 (69%)	39 (47%)	0.03	58 (13.9%)	<0.001
Cesarean delivery	41 (98%)	75 (89%)	NS	273 (65.5%)	<0.001

SD, standard deviation; NS, not significant.

Mayor incidencia de Hipertensión y DBT gestacional en ambas poblaciones. Mayores tiempos de hospitalización en gemelares.

Table II Pregnancy outcome for advanced age women after ovum donation (*n* = 42) compared with 417 controls

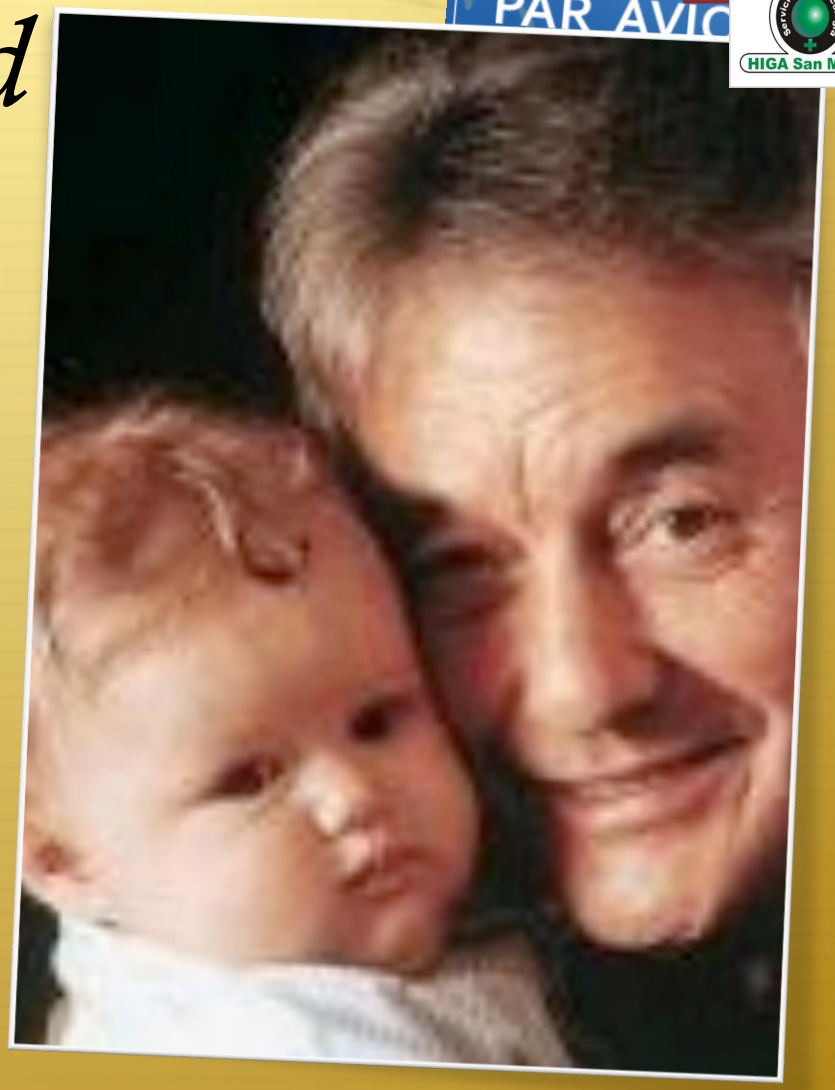
	Study group (*n* = 42)	Control group (*n* = 417)	*P*-value
Gestational age at delivery (wks ± SD)	35.19 ± 2.3	35.67 ± 2.6	0.039
Delivery ≤34 weeks	15 (35.7%)	91 (21.8%)	0.06
Mean birthweight (g)	2149 ± 474	2289 ± 585	0.02
Low birthweight <2500 g	53/83 neonates (77.1%)	503/834 neonates (60.3%)	0.004
Very low birthweight <1500 g	6/83 neonates (7.2%)	78/834 neonates (9.4%)	NS
SGA	14/83 neonates (16.9%)	89/834 neonates (10.7%)	NS
At least one SGA infant	12 (28.6%)	83 (19.9%)	NS

wks, gestational weeks; SD, standard deviation; SGA, small for gestational age, birthweight less than the 10th percentile corrected for multiplicity and gender (Dollberg *et al.*, 2005); NS, not significant.

Menor peso al nacer gemelares vs gemelares de población gral.

Edad & fertilidad masculina

- Fertilidad masculina natural
- Resultados de los ciclos de FIV según edad paterna.
- Asociación a patología genética o epigenetica.
- Mecanismos de alteración en la fertilidad masculina.



Maturitas 78 (2014) 22–29

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

How to overcome male infertility after 40: Influence of paternal age on fertility

Stephanie Belloc[a,1], Andre Hazout[a,1], Armand Zini[b,2], Philippe Merviel[c,3], Rosalie Cabry[c,3], Hikmat Chahine[d,4], Henri Copin[c,3], Moncef Benkhalifa[c,*]

[a] Eylau/Unilabs Laboratory, Reproductive Biology Unit, 55 Rue Saint Didier, 75016 Paris, France
[b] Department of Surgery, McGill University, St. Mary's Hospital, Montreal, Quebec, H3T 1M5 Canada
[c] Reproductive Medicine & Medical, Cytogenetics Department, Regional University Hospital & School of Medicine, Picardie University Jules Verne, CGO, 124 Rue Camille Desmoulins, 80054 Amiens, France
[d] Andrology Unit, ForteBio Laboratory, 16 Rue Fusilllés, 40100 Dax, France

- Asociación entre edad paterna y peores parámetros seminales (volumen, conteo espermático, motilidad y morfología), función endocrina y sexual.
- Menor tasa de embarazo e incremento de la tasa de aborto en embarazos espontáneos y logrados por Inseminaciones intrauterinas.
- En ciclos de FIV y Ovodonación, se observo menor porcentaje de desarrollo embrionario a 5to día en hombres mayores de 55 años. Asociado al daño del ADN espermático.
- Asociación de la edad paterna a defectos genéticos y epigeneticos.
- Estrategia medicas podrían mejorar la fertilidad masculina?

Role of increased male age in IVF and egg donation: is sperm DNA fragmentation responsible?

Kathryn C. Humm, M.D.,[a,b] and Denny Sakkas, Ph.D.[a]

VOL. 99 NO. 1 / JANUARY 2013

- *Revisión de los efectos de la edad paterna en la fertilidad, tratamientos de fertilidad y salud de los hijos.*
- *Resultados controvertidos: pareciera que los efectos del ageing paterno se potencian o no según la edad materna.*
- *Volumen seminal seria el parámetro seminal afectado por el avance de la edad y molecularmente los mecanismos podrían ser el daño del ADN espermático, metilación del ADN espermático y estrés oxidativo.*
- *Asociación entre edad paterna y enfermedades genéticas/ epigeneticas/ multifactoriales que son foco de estudio en la actualidad.*

TABLE 1

Brief overview of selected studies examining the effect of paternal age on outcomes in both natural conception and assisted reproductive technologies as well as the reported paternal age threshold of interest.

Study	Number	Maternal age	Observed paternal age effect	Age threshold (y)
Natural conception				
Ford 2000 (11)	8,515 couples	Adjusted for maternal age	Time to conception greater in men ≥40 y	≥40
Dunson 2002 (13)	782 couples	Adjusted for maternal age	Fertility lower in men >35 y	>35
Hassan 2003 (12)	2,112 pregnant women	Adjusted for maternal age and subgroup analysis of women <25 y	Men >45 y with longer time to conception	>45
Intrauterine insemination				
Mathieu 1995 (21)	901 cycles	Adjusted for maternal age	Pregnancy rate lower in men ≥35 y	≥35
Belloc 2008 (15)	17,000 cycles	Paternal age independent of maternal age	Pregnancy rate lower in men ≥45 y	≥45
Bellver 2008 (23)	2,204 cycles	Adjusted for maternal age	No effect	–
IVF and/or ICSI with autologous oocytes				
Spandorfer 1998 (25)	398 couples	Subgroup analysis of women <35 y	No effect	–
Klonoff-Cohen 2004 (18)	221 cycles	Adjusted for maternal age	Live birth rate lower in men >40 y	>40
De La Rochebrochard 2006 (24)	1,938 couples	Adjusted for maternal age	Likelihood of conception lower in men ≥40 y	≥40
Aboulghar 2007 (53)	545 couples	Subgroup analysis of women <40 y	Fertilization rate lower in men >50 y; no effect on pregnancy rate	>50
Ferreira 2010 (17)	1,024 couples	Adjusted for maternal age	Pregnancy rate lower with each year of advancing paternal age in oligozoospermic men only	–
IVF and/or ICSI with donor oocytes				
Gallardo 1996 (28)	345 cycles	Donor population; not adjusted for recipient age	No effect	–
Paulson 2001 (27)	558 cycles	Donor population, not adjusted for recipient age	No effect	–
Frattarelli 2008 (19)	1,023 cycles	Donor population; not adjusted for recipient age	Live birth rate lower in men >50 y	>50
Bellver 2008 (23)	1,412 cycles	Donor population; not adjusted for recipient age	No effect	–
Luna 2009 (16)	672 cycles	Donor population; not adjusted for recipient age	Implantation rate lower in men >60 y	>60
Whitcomb 2012 (26)	1,083 couples	Donor population; adjusted for recipient age	No effect	–

Humm. Impact of advanced male age on ART. Fertil Steril 2013.

PAR AVION

Enfoque sociocultural del fenómeno

La postergación de la maternidad es un fenómeno mundial asociado a la participación de la mujer en el mundo laboral, que prioriza su carrera y sus objetivos económicos.

‘Inconvenient biology:’ advantages and disadvantages of first-time parenting after age 40 using *in vitro* fertilization

K. Mac Dougall[1], Y. Beyene[1], and R.D. Nachtigall[1,2,*]

Human Reproduction, Vol.27, No.4 pp. 1058–1065, 2012

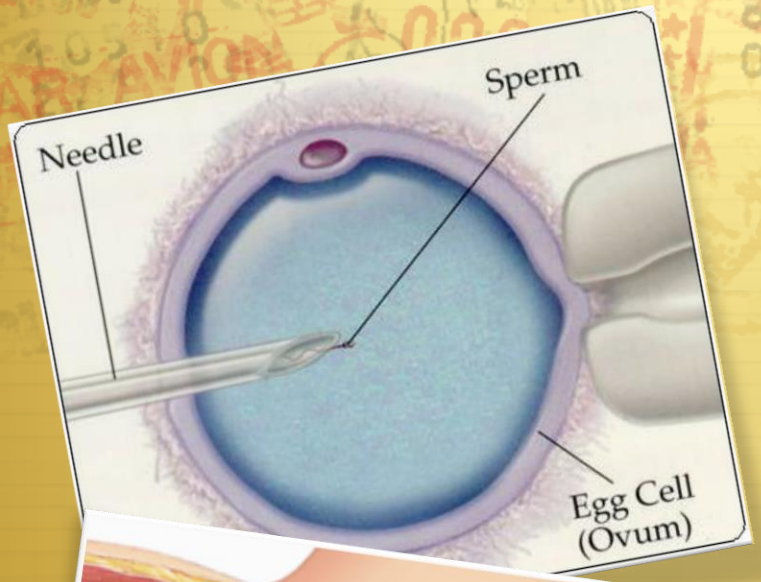
If it weren't for the inconvenient biology, I really think 35 to 45 is agreat time to have kids.

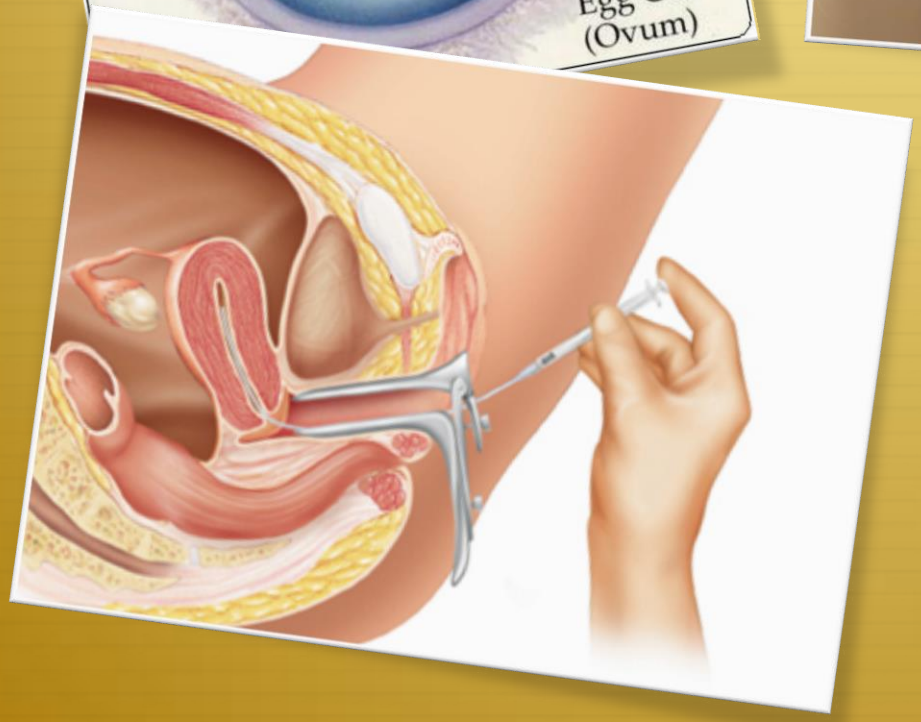
Table II Advantages of first-time parenting over age 40 using IVF.

	Women (n = 65), (%)	Men (n = 42), (%)
Emotional preparedness	72	57
Career/work flexibility	43	31
Financial security	31	36
Perception of strong Partner/ family Relationships	22	12

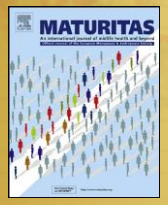
Table III Disadvantages of first-time parenting over age 40 using IVF.

	Women (n = 65), (%)	Men (n = 42), (%)
Infertility and the need for IVF	48	17
Less energy	38	26
Less lifetime with children	31	19
Smaller family size	17	2
Stigma of being ‘Older Parents’	12	19





Posibilidades terapéuticas



Management of infertility in women over 40

Rosalie Cabry[a,1], Philippe Merviel[a,1], Andre Hazout[b,2], Stephanie Belloc[b,2], Alain Dalleac[b,2], Henri Copin[a,1], Moncef Benkhalifa[a,*]

R. Cabry et al. / Maturitas 78 (2014) 17–21

Resultados con IVF

- *Punto de cohorte para la implementación de la técnica los 44 años.*
- *Factor pronostico de embarazo y RN en casa mas importante: n de ovocitos > a 5.*
- *Afianza a los marcadores de reserva ovárica como predictores del número de ovocitos a recuperar mientras que edad sigue siendo el principal factor pronostico de RN en casa.*
- *No determina un esquema de estimulación ovárica como el mas apropiado, recomendando estimulación media en pacientes de pobre respuesta.*
- *Estimula transferencia de mas de 3 embriones para aumentar la tasa de embarazo.*

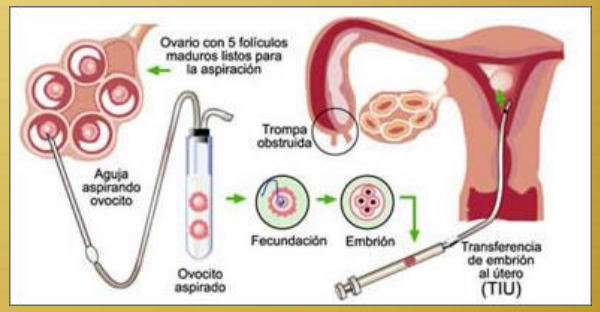


Table 1
Relation between the number of collected oocytes and clinical outcome from patients over 40's after a minimum of 2-repeated IVF/ICI failure.

Number of collected complex cumulus cells	≤5 Oocytes	6–14	≥15
Average maternal age (year)	41.5 ± 1.1a	41 ± 1c	40.7 ± 0.8b
Average paternal age (year)	42.3 ± 5.7	41.7 ± 5.6	41.2 ± 5.9
Infertility duration (year)	3.4 ± 1.8d	4 ± 3.2f	5.5 ± 4e
Day 3 FSH level (UI/l)	8 ± 2.7 g	6.8 ± 2.1i	6.5 ± 1.6 h
Number of cycles	**181**	**260**	**59**
Rank of attempt	2.2 ± 1.3j	2.5 ± 1.5k	2.6 ± 1.5
Total administrated FSH (UI)	5055 ± 1545o	3667 ± 151	2953 ± 1142p
Oestradiol the day of hCG (pg/ml)	1446 ± 363r	2101 ± 960t	2685 ± 375s
Cancellation rate (%)	23.2	11.1	6.7
Completed cycles via OPU	**139**	**231**	**55**
Average collected cumulus	3.4 ± 1.3u	9.3 ± 2.5w	18.8 ± 3.6v
Average métaphase II	2.5 ± 1.4u	7 ± 2.9w	13.7 ± 4.4v
Fertilization rate (%)	46.4	51.6	48.9
Cleavage rate (%) 50.1	50.1	54.4	50.5
Mean transferred embryos/transfer	1.7 ± 1a′	2.2 ± 1c′	2.5 ± 1b′
Clinical pregnancy/transfer (%)	**7.9d′**	**21.7e′**	**18.7**
Implantation rate/embryo (%)	5	10.4	7.4
Ongoing pregnancy/transfer (%)	**3.4f′**	**11.1g′**	**10.4**
Live birth/transfer (%)	**2.2h′**	**10.1i′**	**6.2**

a-c: < 0.0001; a-b: < 10^6; b-c: < 0.02; d-f: < 0.03; d-e: < 0.001; f-e: < 0.01; g-i: < 10^4; g-h: < 10^4; j-k: < 0.05; o-q: < 10 q-p: < 0.001; p: < 10^9; r-t: < 10^9; t-s: < 10^9; r-s: < 10^9; u-w et w-v et u-v: < 10^9;a′-c′: < 0.0001; a′-b′: < 10^4; d′-e′: < 0.01; f′-g′: < 0.05; h′-i′: < 0.05; j′-k′: < 10^9.

Ovo donación

❖Se presenta como el tratamiento con mayores chances de éxito:

53% tasa de embarazo
42 % tasa de recién nacido vivo
94% tasa de embarazo acumulativa luego de 4 transferencias.

Remohi et al .Pregnancy and birth rates after oocyte donation. Fertil Steril 1997

❖Influencia de la edad en la tasa de implantación que se ve reducida en mayores de 45 años.

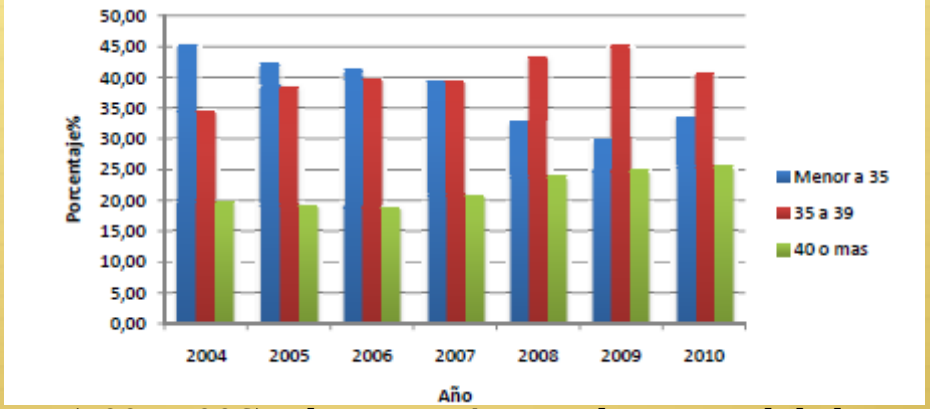
❖ Complicaciones obstétricas por encima de los 50 años rondan el 50 %

❖punto de cohorte para la implementación de la técnica muy difícil de determinar

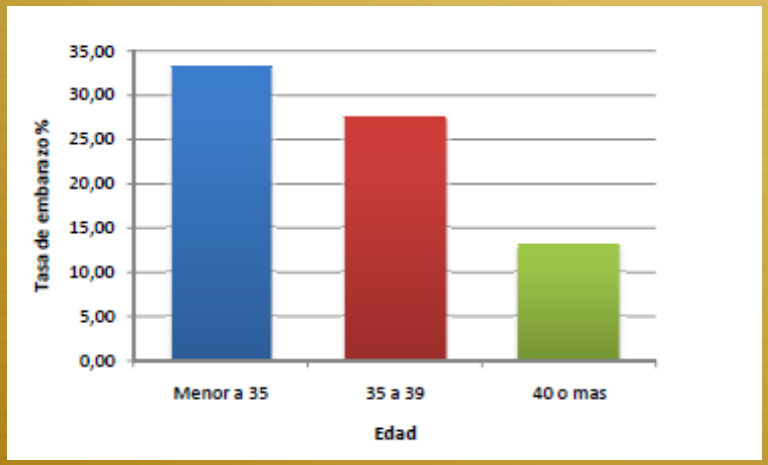
Resultados con la Inseminación Intrauterina

En base a resultados de distintos estudios, siendo del 10 % las mejores tasa de embarazo y mostrando un caída muy importante en esta tasa luego de los 42 años, los autores no recomiendan esta practica como primer estrategia a utilizar en pacientes por encima de 40 años.

Experiencia Argentina. RAFA 2004-2010.



En los primeros años (2004-2006), el grupo más prevalente era el de las mujeres menores de 35 años. Es importante resaltar que el grupo de pacientes mayores de 40 años que realizaron procedimientos de reproducción asistida fue aumentando en forma constante a lo largo del periodo analizado.



Tasa Embarazo < 35 años = 33.3%

Tasa Embarazo 35 – 39 años = 27.5%

Tasa Embarazo > 40 años = 13.1%

Las mejores tasas de embarazo en mayores de 40 años se dieron en los casos de factor masculino.

Experiencia de un Centro Público de Fertilización Asistida

295 pacientes que han consultado con 40 o mas años.

45 pacientes iniciaron Ciclo de Fertilización in vitro (rango de edad 40-44 años):

31 punciones aspiraciones foliculares → 31 % de tasa de cancelación

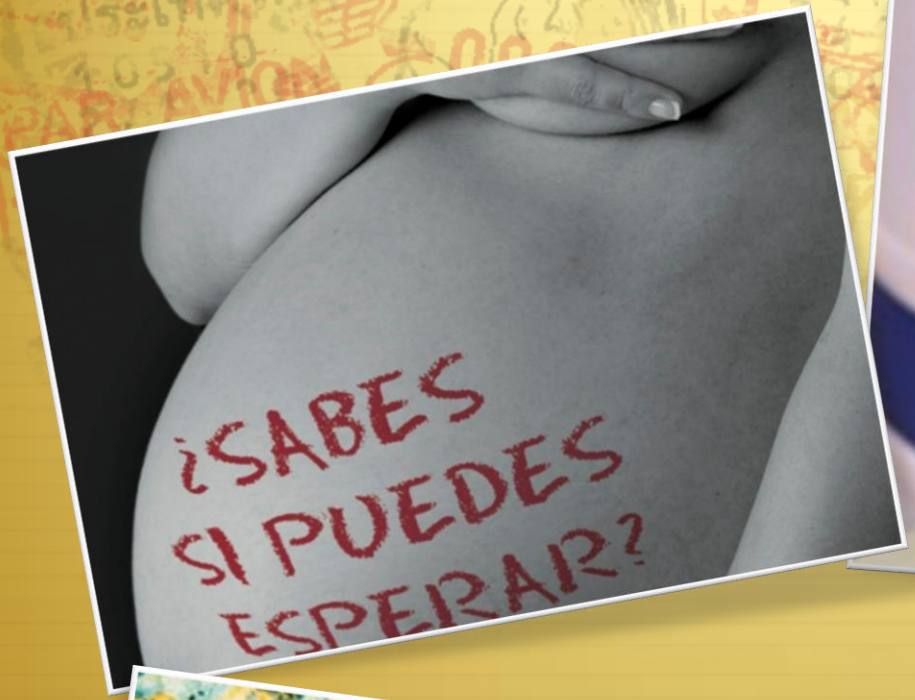
3 fallas de fertilización

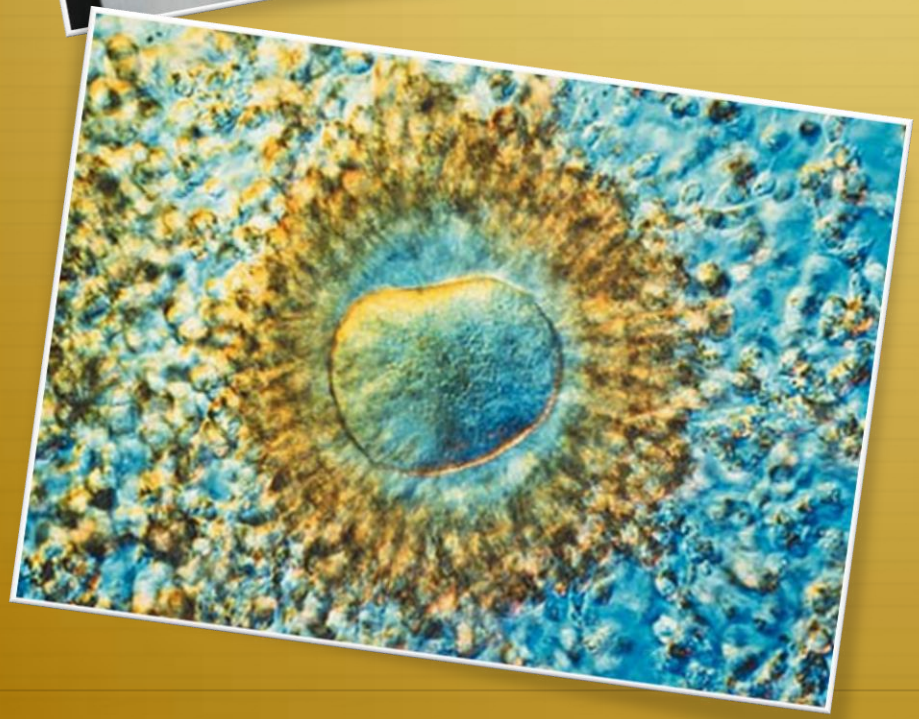
28 Transferencias embrionarias → 37% de tasa de cancelación

3 embarazos bioquímicos

1 embarazo clínico

Tasa de embarazo del 10% aproximadamente, tasa de embarazo evolutivo del 2%.





Previniendo la infertilidad

Preservación de fertilidad y
consejería en planificación familiar.

Vitrificación de ovocitos: banco de óvulos

……..cuando hacerlo?
…….Cuantos óvulos debería congelar para tener chances de un embarazo?
…….cuanto tiempo puedo dejarlos vitrificados?

Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications

Juan A. Garcia-Velasco, M.D.,[a,d] Javier Domingo, M.D.,[b] Ana Cobo, Ph.D.,[c] Maria Martínez, M.D.,[a] Luis Carmona, M.D.,[b] and Antonio Pellicer, M.D.[c]

Fertility and Sterility® Vol. 99, No. 7, June 2013 0015-0282/

Revisión de 1035 pacientes que vitrificaron ovocitos: 560 por motivos no oncológicos y 475 por motivos oncológicos.
Solo 26 del primer grupo y 4 del segundo retornaron en busca de embarazo con sus gametos vitrificados lo que plantea que las preguntas no tienen un respuesta clara en base a la experiencia actual.

Management of infertility in women over 40

Rosalie Cabry[a,1], Philippe Merviel[a,1], Andre Hazout[b,2], Stephanie Belloc[b,2], Alain Dalleac[b,2], Henri Copin[a,1], Moncef Benkhalifa[a,*]

R. Cabry et al. / Maturitas 78 (2014) 17–21

"*According Stoop et al. nearly 22 vitrified metaphase II oocytes are needed to achieve pregnancy in women aged between 23 and 37 years. Knowing that the average number of collected oocytes is 8 per stimulation cycle in this age group, this implies that 2–3 ovarian stimulation and oocyte pick up cycles are needed to achieve a live birth. For patients aged 38–43 years, a minimum of 55 vitrified metaphase II oocytes is needed to achieve a pregnancy. For all ages Cobo et al. recommend that at least 12 metaphase II vitrified oocytes are needed to achieve clinical pregnancy in an oocyte cryopreservation programme*".

Consejería en planificación familiar

Anti-Mullerian Hormone as a Predictor of Time to Menopause in Late Reproductive Age Women

J Clin Endocrinol Metab 97: 1673–1680, 2012

Ellen W. Freeman, Mary D. Sammel, Hui Lin, and Clarisa R. Gracia

Predecir la menopausia para asesorar sobre la planificación familiar.

Context: Anti-Mullerian hormone (AMH) has emerged as a marker of ovarian reserve and a possible surrogate measure of reproductive aging.

Objective: The aim of the study was to evaluate the predictive value of AMH levels in determining the median time to menopause for late reproductive age women and the predictive ability of AMH compared to FSH and inhibin b.

Design and Setting: A 14-yr follow-up in the Penn Ovarian Aging Study, 1996–2010, was conducted for a randomly identified population-based cohort.

Subjects: A total of 401 late reproductive age women participated in the study.

Main Outcome Measure: Observed time to menopause was measured.

Results: All participants were premenopausal, with a mean (SD) age of 41.47 (3.52) yr and a median AMH level of 0.68 ng/ml at baseline. AMH strongly predicted time to menopause; age further improved predictions. Among women with a baseline AMH level below 0.20 ng/ml, the median time to menopause was 5.99 yr [95% confidence interval (CI), 4.20–6.33] in the 45- to 48-yr age group and 9.94 yr (95% CI, 3.31–12.73) in the 35- to 39-yr age group. With higher baseline AMH levels above 1.50 ng/ml, the median time to menopause was 6.23 yr in the oldest age group and more than 13.01 yr in the youngest age group. Smoking significantly reduced the time to menopause (hazard ratio, 1.61; 95% CI, 1.19–2.19; $P = 0.002$). AMH was a stronger predictor of time to menopause than FSH or inhibin b.

Conclusions: AMH is a strong predictor of median time to menopause in late reproductive age women. Age and smoking are significant and independent contributors to the predictions of AMH.

J Clin Endocrinol Metab, May 2012, 97(5):1673–1680

TABLE 3. Median time to menopause by AMH quartiles adjusted for age at baseline

	Age (yr)								
	35–39			40–44			45–48		
	n	Median[a]	95% CI	n	Median[a]	95% CI	n	Median[a]	95% CI
AMH quartiles (ng/ml)									
>1.50	60	>13.01	8.99–NA[b]	41	12.51	10.85–12.88	2	6.23	NA[c]
>0.70–1.50	40	12.63	12.26–12.79	44	10.02	9.08–11.02	9	8.72	6.18–12.05
0.20–0.70	35	12.03	9.28–12.69	47	8.76	8.10–9.52	24	7.99	6.12–8.67
<0.20	14	9.94	3.31–12.73	39	7.99	5.01–9.45	46	5.99	4.20–6.33

NA, Not available.

[a] Median time in years from Kaplan-Meier estimates (n = 401).

[b] No estimate due to ongoing follow-up.

[c] No 95% CI because there were only two subjects in category.

Including age with AMH levels significantly improved the prediction of menopause. Among women with AMH levels less than 0.20 ng/ml, the predicted median time to menopause was approximately 6 yr on average for ages 45– 48 yr, but considerably longer (approximately 10 yr) for women ages 35–39 yr. With higher AMH levels (e.g. 0.70–1.50 ng/ml), the median time to menopause was about 9 yr on average for women ages 45– 48 yr and nearly 13 yr for women ages 35–39 yr.

Human Reproduction, Vol.28, No.1 pp. 247–255, 2013
Advanced Access publication on November 6, 2012 doi:10.1093/humrep/des356

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Maternal menopause as a predictor of anti-Müllerian hormone level and antral follicle count in daughters during reproductive age

J.G. Bentzen[1,*], J.L. Forman[2], E.C. Larsen[1], A. Pinborg[1], T.H. Johannsen[3], L. Schmidt[4], L. Friis-Hansen[3], and A. Nyboe Andersen[1]

STUDY QUESTION: Is the ovarian reserve in a woman at a given age associated with her mother's age at menopause?

SUMMARY ANSWER: We demonstrated a significant, positive association between age at maternal menopause and serum anti-Müllerian hormone (AMH) levels and antral follicle count (AFC) in daughters. The rate of decline in serum-AMH level and AFC is also associated with age at maternal menopause.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS: The association between menopausal age in mothers and daughters has been established through several epidemiological studies. This paper shows that early maternal menopause is related to an advanced depletion of the ovarian reserve and that late maternal menopause is related to a delayed depletion.

STUDY DESIGN AND SIZE: Cross-sectional data were obtained from a prospective cohort study of 863 women. The study comprised 527 participants from this prospective cohort whose mothers' age at natural menopause was known.

PARTICIPANTS, SETTING AND METHODS: Participants were recruited from female health care workers aged 20–40 years employed at Copenhagen University Hospital, Rigshospitalet, and were enrolled in the study between September 2008 and February 2010. The response rate was 52.1%. Endocrine and ovarian parameters related to reproductive ageing (AMH and AFC) were assessed [illegible] transvaginal ovarian sonography on cycle Day 2–5. Data on reproductive history, including age at natural ma[illegible]tained through an internet-based questionnaire. We used an analysis of covariance model with serum-AMH and [illegible]e quantitative predictor and onset of maternal menopause as the categorical predictor, with further adjustments [illegible]ceptives, participants' smoking habits and prenatal smoking exposure.

RESULTS: [illegible]found a significant effect of age at maternal menopause on both serum AMH levels ($P < 0.001$) and AFC [illegible]-AMH concentration declined by 8.6% per year [95% confidence interval (CI): 6.4–10.8%, $P < 0.001$] in the [illegible]enopausal age (≤45 years), by 6.8% per year (95% CI: 5.0–8.6%, $P < 0.001$) in the group with normal maternal menopausal age (46–54 years) and by 4.2% per year (95% CI: 2.0–6.4%, $P < 0.001$) in the group with late maternal menopausal age (≥55 years). Median AFC declined by 5.8% per year (95% CI: 4.0–7.5%, $P < 0.001$) in the group with early maternal menopausal age (≤45 years), by 4.7% per year (95% CI: 3.3–6.1%, $P < 0.001$) in the group with normal maternal menopausal age (46–54 years) and by 3.2% per year (95% CI: 1.4–4.9%, $P < 0.001$) in the group with late maternal age (≥55 years) at menopause.

BIAS, LIMITATIONS AND GENERALIZABILITY: Information on 'age at maternal menopause' was obtained retrospectively and may be prone to recall bias and digit preference. The study population consisted of health care workers, which implies a potential selection bias. Finally, the cross-sectional nature of the data limits the generalizability.

Asociación significativa entre menopausia materna y valores de HAM y FA.

Consideraciones éticas y legales

- Ley 14.208 de Fertilización Asistida de la Provincia de Buenos Aires.

Gametas homologas, limite de edad, limite de tratamientos.

- Ley 26.862 de Reproducción Medicamente Asistida.

Gametas homologas o heterológas, sin limite de edad, no queda claro el limite de tratamientos.

- Postura SAMER ante la edad de la receptora de ovo donación de 50 años o menos.

Reseña histórica de la ovodonación.

- 1984 Inicio en el mundo de la OD (Trounson y cols)
- 1993 Argentina comienzan los ciclos de OD con pacientes que cedieron sus óvocitos luego de tratamientos realizados por ellos mismos.
- 2003 comienzan a hacerse ciclos con donantes exclusivas.
- En algunos centros llega al 35 % de los tratamientos de alta complejidad.

Tasa de embarazo de ciclos frescos: 45 %

ovodonacion

Tipo de Donaciones

Donante anónima.
Donante conocida.
Ovocitos donados por pacientes de FIV.
Banco de óvulos.

Condiciones de la Donación

Única o compartida
Altruista.


…muchas gracias!!!!!!!!