IVF Pregnancy in the over 40s

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Items Addressed

-Proportion of women over 40s in IVF programs.

-Causes of decline of fertility in the over 40s.

-Factors affecting IVF pregnancy in the over 40s.

-Clinical applications and recommendations.

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Objectives of the presentation

1- Be aware of the magnitude of the problem.

2- Identify causes of decline of fertility in the above 40s.

3- Identify factors affecting pregnancy and live birth rates in the above 40s.

4- Be able to counsel and advise patients above 40s in IVF programs.

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Declaration of conflict of Interest

This presentation does not have any direct or indirect industry support and does not include discussion of any particular commercial products or services.

4

There has always been interest in the reproductive capacity of older women. Recently the numbers of women delaying childbearing into their late 30s and 40s have markedly increased particularly in developed countries for various social reasons.

Speroff L. Curr Opin Obstet Gynecol. 1994;6:115-20

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ART Surveillance USA 2005
134265 IVF & ICSI cycles

Age	
> 35 Year	45%
35 – 37 Y	24%
38 – 40Y	19%
40 – 42Y	8%
> 42Y	4%

Wright et al 2008. National Center for Chronic disease prevention and health Promotion

ART in Europe 2004

Age	IVF cycle	ICSI cycle
	114672	167192
40 – 44Y	13.7%	11.3%
≥ 45 Y	1%	1.2%

ESHRE Report Nyboe et al., Hum Reprod. 2008 23, 4, 756-771

Middle East

Mansour & Abousetta. Midd. East Fertil. & Steril J 2006. 11,3,145-154	*IVF/ICSI* *16293*	Age >40	% 9.3
Sills et al J. Exp.& Clin AR,2007. 4:3,1-6 13 Centers	263-4000/ center	≥ 41	8.7

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However the proportion of IVF patients above 40s varies markedly in individual centers depending upon the policy of the center and availability and acceptability of egg donation programs.

9

Fertility declines with age, specially after 41 years of age, both in normally cycling women and in patients undergoing reproductive technology.

- Menken J etal. Science 1986, 233:1289-94; Tan S-L et al. Lancet, 1992; 339:1390-4; Devroey P et al. Hum Reprod 1996; 11:1324-7; Hull GRM et al . Fertil Steril 1996; 65:783-90; Marcus S F and Brindson PR. Lancet 1996 ; 348:1402-6; Templeton et al. Lancet 1996.

Fertility and Age

Age	Decline in Fertility
20 – 24	Fertility peaks
25 – 29	4 – 8%
30 – 34	15 – 19%
35 – 39	26 – 46%
≥ 40	95%

Maroulis G. et al., (2005) Hum. Reprod. 17, 1519

Possible causes of decline of fertility in 40s

- **Decline in frequency of intercourse .**
  (Leeton J. Obstet Gynecol 1992; 6:217-27).
- **Decreased number of primordial follicles.**
  (Richardson SJ et al. J Clin Endocrinol Metab 1987;65:1765-8)
- **Poorer quality oocytes**
  (Wallach EE. Fertil Steril 1995:63:12-4)
- **Decreased uterine receptivity.**
  (Abdalla HI et al. Hum Reprod 1990;5:1018-22)
- **Embryo loss from chromosomal abnormalities.**
  (Munne S et al. Fertil Steril 1995;64:382-91)

Decline in Frequency of Intercourse and sperm quality

The treatment of > 2000 women by donor insemination showed clearly that the decline in pregnancy rate can be solely attributed to the increasing age of the female patient, independently of sperm quality or reduced frequency of intercourse.

CECOS Federation . N Engl J Med 1982; 306:404-6.

No of Primordial Follicles

	No. of oocytes
7th Month of gestation	**7.000.000**
At Birth	**2.000.000**
Age of seven year	**300.000**
Puberty	**40.000**
Released by ovulation	**400 – 500**

Erickson GF 2000, Adashi EY (ed) N. Y. 31-48

Gougheon A, (2004) in Leung PK et al., (ed) San Diego 25-43.

- **The decrease in the number of primordial follicles significantly accelerates around the age of 37 years on average.**
- **Most women reach menopause by their 50s.**

HFEA, (1996); Patient Guide to DI and IVF clinic London (1988), Br. Med. J., 296:1765-8.

Poor quality of Oocytes

Age	Genetic aberrations
< 34 years	24%
35 – 39 years	52%
≥ 40 year	95.8%

Hull M et al., (1995) Fertil & Steril 63, 979-83.

Impairment of implantation

Which factor quality of oocyte or impairment of implantation has a more negative effect on the chance to establish a pregnancy remains a perennial question. Probably both elements are equally important.

17

Large studies have shown a significant decrease in implantation and pregnancy rates in women aged 40-49 years compared with women aged < 40 years in oocyte donation program.

- Flamigni C. (1993) Hum Reprod, 8:1343-4
- Borini A. et al. (1996) Fertil Steril, 65:94-7

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Impaired Implantation

- **Past pelvic infections.**
- **Damage to the endometrium.**
- **Reduced vascular perfusion of the uterus.**
- **Increased frequency of fibroids and / or endometriosis.**

Crow J, et al., (1994)Hum Reprod. 12:2224-33.
Goswamy P K et al., (1988), Hum Reprod, 3:955-9.

Aneuploidy

Pregnancy loss is significantly increased with advancing maternal age. The major underlying cause of these losses seem to be chromosomal aneuploidy.

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Cytogenetic Analysis of 74 Losses

Abnormal Karyotypes	**52/74**	**71.2%**
≥ 40 years Chromosomally abnormal fetuses		**82%**
< 40 years Chromosomally abnormal fetuses.		**65%**
OR 3.35;95 C1, 0.96-11.97		

Spandorfer SD et al., (2004) Fertil & Steril 81, 5, 1265-9

Factors affecting IVF pregnancy in the over 40s

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Prediction of ovarian response

Declining fertility in the over 40s is an individual event that cannot be predicted accurately before ART cycle is undertaken.

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All available ovarian reserve tests detect the quantity rather than the quality of the follicular pool.

Broekmans et al. *Hum Reprod Update* 2006;12:685-718.

Ovarian reserve tests may predict ovarian response to stimulation in elderly patients but they cannot predict the pregnancy rate in these patients.

Broekmans et al. *Hum Reprod Update* 2006;12:685-718.

Ovarian reserve tests may help in determing the dose of HMG/FSH and the protocol of stimulation to be used but they are poor predictors of the pregnancy rate.

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Ovarian response in over 40s

-High dose and duration of HMG/FSH stimulation.

-High cancellation rate.

-Fewer oocytes are obtained.

-High percentage of poor quality oocytes.

-Number of oocytes collected or embryos available do not correlate significantly with implantation rate.

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Dose and duration of FSH according to age in IVF/ICSI

Variable	Age of patient y											
	41		42		43		44		>45		Total	
	IVF	ICSI	IVF	ICSI	IVF	ICSI	IVF	ICSI	IVF	ICSI	IVF	ICSI
No. of cycles	72	70	54	56	23	45	8	25	12	11	169	207
No. of hMG ampules	45.2[a]	43.8[b]	54.3	53.2	59.2	56.3	58.7	54.2	56.8	55.3	53.2[a]	51.8[b]
No. of days of hMG	12.8	12.4	14.2	12.1	15.9[a]	14.1	14.9	15.1[a]	12.0	13.1	13.9[a]	13.3[a]

Note: Values are means. There were no statistically significant differences between the IVF and ICSI groups

a P < .01

b P < .02

Ron- El R. et al. (2000) Fertil Steril; 4, 3, 471-475

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Total number of hMG ampoules and IVF outcome in 1000 initiated IVF cycles

No. of ampoules	No. of cycles	Age (Y)	E_2 level (pmol/L)*	No. of Oocytes *	Fertilization Rate (%)	No. of clinical pregnancies (%)+
≤ 60	497	41.1	6,645	8.1	56	94 (18.9)
61 – 100	232	41.5	4,931	5.2	54	24 (10.3)
>100	111	41.7	3,868	3.7	51	5(4.5)

*** P< .001 between each group**

+ The pregnancy rate was significantly lower in patients who required medium or high doses of hMG (P <.002).

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Lass A. et al. (1998) Fertil & Steril 70, 6, 1030-1034.

Number of oocytes retrieved and pregnancy rate

1-4 oocytes				≥ 5 oocytes			
Age	No. of cycles	Preg. No.	%	No. of cycles	Pregn. No.	%	
40-41	172	8	4.6	189	35	18.5	<0.0001
42-43	195	16	8	148	22	15	0.04
44-45	127	2	1.6	100	8	8	0.016

Tsafrir A., RBM online, 2007 . 14,3,348-355

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Cancellation and implantation rates

Age group (Y)	No. of patients	No. of initiated cycles	cancellation rate*%	Implantation rate (%)
40	182	429	13	10.9
41	123	282	18.5	10.8
42	70	161	29	9.1
43	36	91	28	5.0
44	36	74	25.6	3.2
45- 48	24	51	33.3	1.6

* The cancellation rate was higher in women ≥ 42 years of age than in women < 42 years of age (P < .001)

+ The pregnancy rate was higher in women < 42 years of age than in women ≥ 42 years of age (P < .001)

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Lass A. et al. (1998) Fertil & Steril, 70, 6 , 1030-1034.

Pregnancy and live birth rate

Source	No.	Age	Preg. Rate %	LBR %
Canadian Register, Gunby et al . Fertli & Steril, 2007, 88,3,550-9	179	>40	15.8	9.2
Australian Register Wang et al . Hum. Reprod. 2008, 23, 7, 1633-8	5669	40-44	-	6.4
	471	≥45	-	0.2
USA Register , Wright et al. NC Ch, dis. Prev. Health promotion,2008	6414	41-42	-	14.9
	3214	>42	-	5.8
ESHRE, Nyboe et al. Hum. Reprod, 2008. 2,3,4,756-71	>33000	40-44	-	-
	>3000	≥45	-	-

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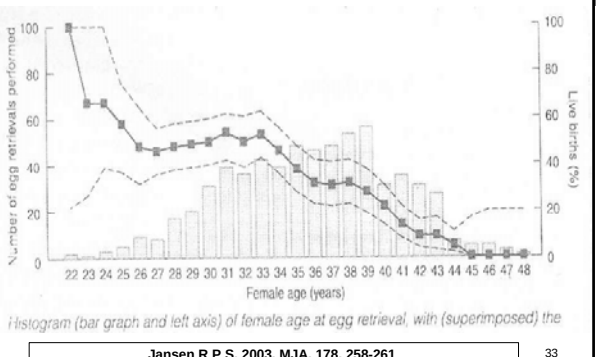
Egg retrievals for in vitro fertilization (IVF), age of the women, and percentage of live births (95% CIs) from single IVF attempts



Histogram (bar graph and left axis) of female age at egg retrieval, with (superimposed) the

Jansen R P S, 2003, MJA, 178, 258-261.

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Clinical pregnancies and deliveries in women ≥ 40s IVF/ICSI cycles

Variable	Age of patient (y) 41Y No.	%	42Y No.	%	43Y No.	%	44Y No.	%	≥45	Total
IVF pregnancies (%)	10/72	14	5/54	9	6/23	26	0/8		0/12	21/169 (12.4)
Deliveries (%)	5	7	1	2	3	13				9/169 (5.3)
ICSI pregnancies (%)	11/70	14	5/56	9	7/45	16	1/25	4	0/11	24/207 (11.6)
Deliveries (%)	5	7	1	2	2	4	0			8/207 (3.9)
Total No. of pregnancies (%)	21/142	15	10/110	9	13/68	19	1/33	3	0/23	45/376 (12.0)
Total No. of deliveries (%)	10/142	7	2/110	2	5/68	7	0		0	17/376 (4.5)

Ron-El R. et al., (2000) Fertil. – Steril., 4, 3, 471-475.

No pregnancy could be achieved among women aged ≥ 45 years when using homologous oocytes.

No pregnancy reached delivery in patients aged ≥ 44 years. The results are similar in IVF and ICSI cycles.

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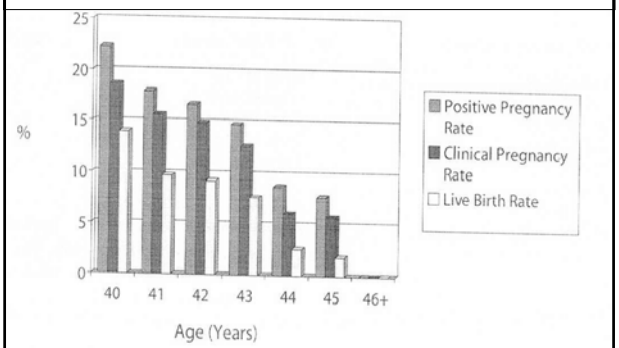
Effect of age on positive pregnancy rate, and live birth rate per cycle start



Klipstein et al Fertil Steril 2005, 84, 2, 435-445

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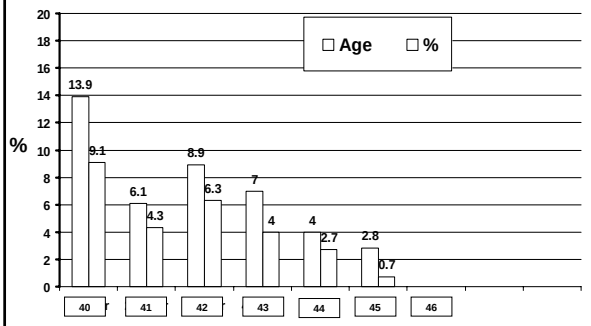
Pregnancy and delivery rates per initiated cycle in 1217 cycles



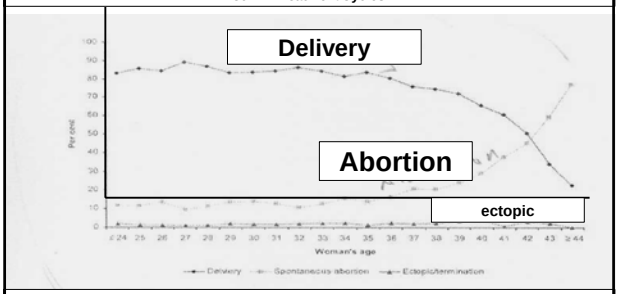
Tsafrir A RBM online , 2007,14, 3, 748-355

Overall Pregnancy loss

Author	Age	Miscarriage
Lass A. et al 1998 Fertil & Steril, 1998, 70,6,1030-1034	≥ 40	27%
Spandorfer S D et al., (2004) Fertil & Steril 81, 5, 1265-9	> 40 Y	22.2%
Klipstein et al 2005. Ferti. & Steril,48,2,435-45	≥ 40	44%
Spandorfer S D et al., (2007) Fertil & Steril 87, 1, 74-76	> 44	85.3%
Serour et al., (2008) (under publication)	>40	33%
Abdulla et al,(1993) Hum. Reprod. 8;1512-17	Donor's age 20-24 y >35 y	14% 44%

Pregnancy outcome following first autologous fresh cycles by woman's age in Australia, 2002 – 2005,

36412 Treatment Cycles



Wany et al., Hum Reprod 2008 23,7,1633-1638

Pregnancy loss

Age	Pregn./initiated cycle	Pregnancy loss No.	%
41	118/661	54	45.8
42	98/590	44	44.9
43	56/380	27	48.2
44	20/230	14	70
45	4/52	3	75
>45 -	No/17	-	-

Klipstein et al. Ferti & Steril 2005, 84,2,435-45

Number of embryos transferred in 1217 treatment cycles & pregnancy rate

1-2 embryos				> 3 embryos			
Age	No. of trans-fers	Pregnancy No.	%	Age	No. of trans-fers	pregnancy %	
40-41	127	8	(7 %)	163	35	(21%)	<0.0001
42-43	136	15	(11 %)	129	20	(15%)	NS
44-45	86	2	(2.3%)	94	8	(8.5%)	NS

Tsafrir A. RBM online, 2007, 14,3,348-355

Number of embryos transferred & LBR in 2705 initiated cycles

	40Y		41 Y		42 y		43 y		44 y	
No. of Et[a]	No.	LBR %	No.	LBR %	No.	LBR %	No.	LBR %	No.	LBR%
1	2/75	(2.7)	1/67	(1.5)	0/47	(0)	0/36	(0)	0/27	(0)
2	12/110	(10.9)	5/85	(5.9)	4/78	(5.13)	2/53	(3.77)	1/26	(3.85)
3	28/136	(20.6)	10/91	(11.0)	10/84	11.90	8/58	(13.79)	0/21	(0)
≥4	62/258	(24.0)	44/22	(19.3)	38/198	(19.2)	16/126	(12.7)	4/74	(5.4)
Mean no. of ETs	3.1			3.3		3.4		3.4		3.5

[a] P< .001

Klipstein et al., Fertil Steril 2005, 84, 2, 435-445

In a Retrospective Study it was found that women over 40s having five or more embryos transferred had significantly increased pregnancy rates and live birth rates and significantly decreased miscarriage rates compared with fewer than five embryos transferred.

-Combelles C et al., Fertil & Steril, 2005, 84, 6, 1637-1642.

Number of embryos transferred and live birth rate

No. of transferred embryos	No. of cycles	No. of live births	Live birth rate (%)
1	57	1	1.8[a]
2	100	2	2.0[a]
3	112	7	6.7[a,c]
4	123	5	4.2[a]
5	142	30	26.8[b]
6	105	18	20.7[b]
7	131	33	33.7[b]
8	22	2	10.0[a,b]
9	22	3	15.8[a,b]
10	46	8	21.1[b,c]
11	3	0	0

Note: Values with different superscript letters are statistically different (P < .05)

Combelles et al, 2005 Fertil & Steril, 84, 6, 1637-1642

In women over 40s five embryos is the optimum number to transfer and transferring more than five does not confer any additional benefit to the clinical outcome.

-Combelles C et al., Fertil & Steril, 2005, 84, 6, 1637-1642.

Risk of Multiple Pregnancy

eSET , to avoid the risks of multiple pregnancy is not applicable in patients over 40s because of low implantation rate.

M P in over 40s

Author	No. ET	Twin	Triplet
Svendsen TO et al ,(1996) Fertil steril 65:561-5	3	NA	0.3 %
Less et al, 1998	3	7.1	0
Serour et al., (2008) (under publication)	≥ 3	2.6%	0%

Vanishing Twin in MP detected at 7th weeks' gestation

	No. delivered (%)			
Fetal hearts at 7-wk ultrasound	**SAB**	**Singleton**	**Twin**	**Triplet**
Twins	**5.4**	**15.0 %**	**78.9%**	**0.8[a]**
Triplets	**4.3**	**6.5%**	**34.2%**	**54.9 %**

[a] Five patients initially thought to have a twin gestation at 7 wk were later found to have triplets.

Spandorfer SD et al. (2004) Ferti Steril, 81, 5, 1265-1269

Pregnancies in which multiple implantations exist or cycles with a large number of embryos available for transfer and cryopreservation are more likely to deliver at least one live born infant when compared with age-matched controls with a singleton pregnancy documented by fetal cardiac activity at a 7 week vaginal ultrasound examination

Spandorfer SD et al. Ferti Steril 2004; vol. 81, No.5
Klipstein et al., Fertil & Steril 2005, 84, 2, 435-445

Cumulative delivery rate /3 cycles

Cycle No.	No. of initiated cycles	No. of deliveries	Delivery rate (%)	Cumulative delivery rate (%)
1	471	38	8.7	8.7
2	194	13	6.7	14.8
3	67	5	7.5	21.2
4	24	1	4.2	25.5
5	6	0	0	25.5
6	4	0	0	25.5

Lass A. et al., (1998), Fertil & Steril. 70, 6, 1030-1034.

Cumulative live birth rates in 830 women initiating cycles

Age	LB No. of women	Cumulative live birth rate over the first three cycles (%)	Average no. of cycles per woman
40	65/257	25.3	2.40
41	36/195	18.5	2.39
42	34/177	19.2	2.32
43	11/114	9.6	2.24
44	1/62	1.6	2.02
45	1/18	5.6	1.78
46+	0/7	0	1.57

[a] P = NS

[B] P <.02 as compared with ages 40, 41, and 42

[c] P < .01 as compared with ages 40, 41 and 42

Klipstein et al, Fertil Steril 2005, 84,2,435-445

Live birth in women > 45 2002-2004 Australia

	Autologous cycles		Recipient donor cycles	
	No	%	No	%
Initiated cycles	1101		366	
Embryo transfers	639	58.0	295	80.6
Clinical pregnancy	21	1.9	106	29.0
Early pregnancy loss <20 weeks	15	71	34	32
Live birth >20 weeks	6	0.5	70	19.1

Sullivan E et al., 2008 Hum. Reprod. 23,7,1639-1643

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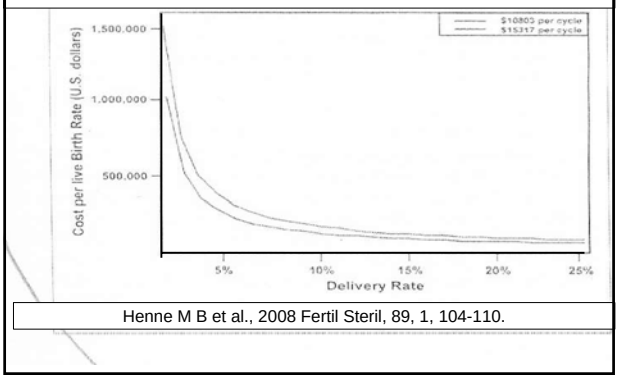
Cost/Live birth

Cost per live birth based on probability of delivery. The Y-axis is the expected cost per live birth using standardized cycle cost. The X-axis is predicted live birth rates



Henne M B et al., 2008 Fertil Steril, 89, 1, 104-110.

Cost per live birth for women aged ≥ 46 years following fresh autologous cycles, Australia 2002-2004[a-b]

Initiated cycles	**1101**
Live births	6
ART treatment costs	€ 4518642
Cost per live birth > 45 years[b]	€753107
Cost per live birth all ages[a]	€ 26021

Sulivan et al. Hum. Reprod. 2008 , 23,7,1639-43

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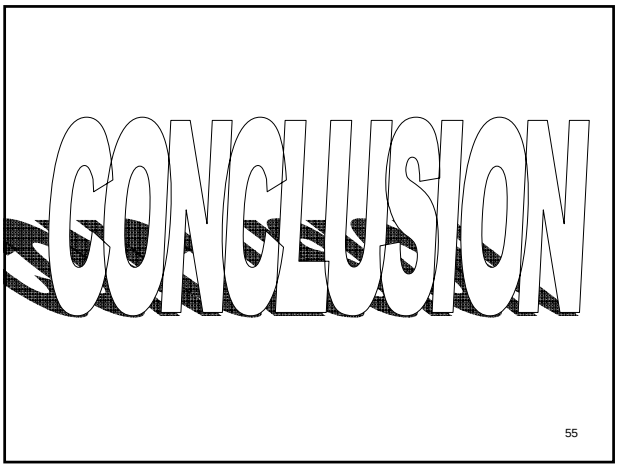

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For physicians to refuse treatment on the arbitrary basis of age alone in women < 44 years of age is illogical. Assessment after the first IVF cycle in the above 40s women is helpful.

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Those with a good response in their first attempt may be encouraged to complete three cycles or more with a modest take home baby rate but a high miscarriage and cogenital anomaly rates.

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Transfer of too many embryos in these patients is not associated with a great risk of MP.

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Women ≥ 44 should be very carefully counselled and discouraged to undergo IVF in favour of egg donation if it is available and ethically acceptable to the couple.

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Other promising alternatives

- Egg donation from young donors.
- Cryopreserved ovarian tissue transplantation.
- Use of own cryopreserved embryos or oocytes.


THANK YOU