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# THE ABC OF INFERTILITY MANAGEMENT REVISITED

#### Sunday, 14 June I Organised by the Middle East Fertility Society

#### Course coordinators

Johnny Awwad (Lebanon) and Mohammad Aboulghar (Egypt)

#### Course type

Basic and advanced

#### Course description

While most advances in the field of human reproduction have focused on reproductive technologies, much less has been vested in the basic management of infertility. Many related practices remain as an old heritage of the past, without ever being revisited on the basis of emerging evidence.

The process of counselling any subfertile couple involves the following:

- A diagnostic assessment plan
- A pre-intervention conception prognosis estimate
- A proposed intervention with improved conception estimate

The final management of subfertility is subject to a shared patient-physician decision. The counseling process should therefore take into account the couple's sense of urgency as it relates to personal choice, culture and/or beliefs. A clear knowledge of the conception prognosis estimates pre- and post- proposed intervention is therefore essential for proper decision-making on the basis of sound risk-benefit and cost effectiveness analysis.

This pre-congress course will discuss some of these parameters from an evidence-based perspective for the purpose of establishing an updated platform for infertility management more reflective of the current status of the evidence.

#### **Target audience**

- Reproductive endocrinologists and fertility specialists
- Biologists involved in assisted reproductive technologies
- General gynaecologists
- Infertility nurses
- Policy regulators and representatives of third party stakeholders

#### Educational needs and expected outcomes

At the completion of this pre-congress course, participants should be able to:

- Re-define infertility in relation to women's reproductive characteristics
- Re-explore the benefits of simple ovulation monitoring and timed intercourse in the context of subfertility
- Understand to what extent ovarian reserve testing may influence natural conception
- Critically assess whether laparoscopy, endometrial biopsy and semen mucus interaction testing should remain an essential component of every subfertility work-up
- Understand to what extent an abnormal semen analysis, the presence of anti-sperm antibodies and varicoceles may affect natural conception in a couple with subfertility
- Determine optimal ovulation protocols to improve outcome in subfertile couples
- Critically evaluate whether intrauterine insemination should remain the bridge between ovulation induction and assisted reproduction
- Design a fertility management algorithm and a fertility counselling platform for subfertile couples on the basis of the above



# SCIENTIFIC PROGRAMME

09:00 - 09:25	Re-defining infertility: Adjustment for ovarian and chronological age – Johnny Awwad (Lebanon)
09:25 - 09:50	The roles of ovulation documentation and timed intercourse in increasing the likelihood of pregnancy in women trying to conceive – Robert W. Rebar (U.S.A.)
09:50 - 10:15	How would ovarian reserve testing influence the probability of natural pregnancy in women with subfertility? – Thomas D'Hooghe (Belgium)
10:15 - 10:30	Discussion
10:30 - 11:00	Coffee break

#### Chairman: Michel Abou Abdallah (Lebanon )

11:00 - 11:25	Laparoscopy: Should it remain an essential component of the fertility work up – Cindy M. Farquhar (New Zealand)
11:25 - 11:50	Does measurements of sperm-mucus interaction (Post-coital Test) influence the chances of conception? – Thomas D'Hooghe (Belgium)
11:50 - 12:15	The value of endometrial biopsy in modern fertility management – Johnny Awwad (Lebanon)
12:15 - 12:30	Discussion
12:30 - 13:30	Lunch break

#### Chairman: Johnny Awwad (Lebanon)

13:30 - 13:55	The value of basic semen analysis in altering early fertility management – Craig Niederberger (U.S.A.)
13:55 - 14:20	Anti-sperm antibodies: Any role for screening in modern fertility management? – Robert W. Rebar (U.S.A.)
14:20 - 14:45	Would the presence of varicocele alter fertility management of couples? – Craig Niederberger (U.S.A.)
14:45 - 15:00	Discussion
15:00 - 15:30	Coffee break

#### Chairman: Mohamed A. Aboulghar (Egypt)

15:30 - 15:55	Oral ovulation induction agents (clomiphene, letrozole): when to start and for how long? – Johnny Awwad (Lebanon)
15:55 - 16:20	Intrauterine insemination: Is it still the bridge between ovarian stimulation and in vitro fertilization in unexplained subfertility – Richard Reindollar (U.S.A.)
16:20 - 16:45	How would a cost-effective fertility management algorithm look like? – Cindy M. Farquhar (New Zealand)
16:45 - 17:00	Discussion



#### Re-defining infertility: Adjustment for ovarian and chronological age

Johnny Awwad, MD Professor of Obstetrics and Gynecology American University of Beirut Medical Center

#### No Conflict of Interest

#### Objectives

- Review the various definitions of infertility in the medical literature
- Re-evaluate the definition of infertility while adjusting for
  - Ovarian age
  - Chronological age

PRECONGRESS COURSE 14 I	LISBON,	, PORTUGAL - 14 JUNE 2015	

#### Definition of "infertility"

The Practice Committee of the American Society for Reproductive Medicine American Society for Reproductive Medicine, Birmingham, Alabam

Infertility is a disease.\*\* The duration of the failure to conceive should be twelve or more months before an inves-tigation is undertaken unless medical history and physical indings dictate earlier evaluation and treatment.

Approved by the Practice Committee of the American Society for Reproductive Medicine (Formerly The American Fertility Society), March 27, 1993.

ommittee Opinion
Fertility Society), March 21, 1993.

Fertility Society), March 21, 1993.

Approved by the Board of Directors of the American Society for Reproductive Medicine, 1200 Marigoriney Highway, firminglant, Adamsa SOCH.

Fertility Society), July 17, 1993.

Infertility revisited: The state of the art today and tomorrow\*

#### The ESHRE Capri Workshop

#### Infertility

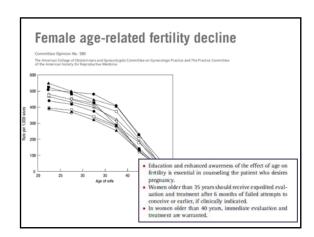
#### Definitions

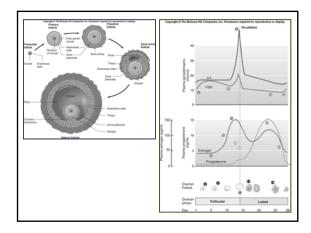
Definitions

Fertility: Based on the distribution of fecundity observed in a 'normal' population, normal fertility was defined by the ESHRE Group as achieving a pregnancy within 2 years by regular coital exposure.

Steriity, subfertility: infertility: Those couples who do not achieve a pregnancy within 2 years include the sterile members of the population, for whom there is no possibility of natural pregnancy, and the remainder who are subfertile. Together, these comprise the infertile population. The term sterile may refer to either the male or the female, whereas the term subfertile refers to the couple.

## Table I Published definitions of infertility. Organization Definition Infertility should be defined as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of known reproductive pathology Infertility is a disease defined by failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse Earlier evaluation and treatment may be justified based on medical history and hybical findings and is warranted after 6 months for women over age 35 years Infertility (clinical definition): a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse National Institute for Health and Clinical Excellence guideline 2004<sup>a</sup> International Committee for Monitoring Assisted Reproductive Technology (ICMART), and World Health Organization 2009<sup>c</sup> Demographic definition<sup>d</sup> Inability of a non-contracepting, sexually active woman to have a live birth \*NCE guideline (UK) (2004). \*Phatoice Committee of the American Society for Reproductive Medicine. Fertal Steril 2008/90 (5 Suppl):560. \*Zegers-Hochschild et al. (2009). \*Quarter (2005).





 Re-defining infertility Advanced chronological age Advanced chronological age Irregular cycles Shorter cycles Prolonged unexplained infertility Previous ovarian surgery

- Juul et al., 1999, 2000 and Jensen et al., 2001 only recorded Time To Pregnancy TTP retrospectively among pregnant women using questionnaires to measure fertility, by assessing exposures related to semen quality, age or environment.
- Their study design does not estimate real fecundity, because infertile couples were excluded. Therefore, effects on the proportion of truly infertile couples cannot be assessed.

- Wang et al. (2003) prospectively observed 518 newly married Chinese textile workers (20–34 years of age) trying to conceive.
- They recorded vaginal bleeding, sexual intercourse and collected daily first-morning urine specimens for up to 1 year or until a clinical pregnancy was achieved.
- In their cohort of women, about 50% became clinically pregnant in the first two cycles and more than 90% in the first six cycles.
- They found that the monthly fecundity varied between 30 and 35%.

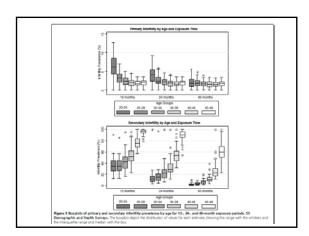
# TABLE 1 TABLE 1 Willa Larsen, Ph.D. Table 1 Subsequently infertile and wanting a child wanting a child wanting a child wanting a child wanting of contraception. Subsequently infertile and wanting a child wanting a child wanting a child contraception. Subsequently infertile and wanting a child wanting or contraception. Subsequently infertile and wanting a child wanting or contraception. Estimated from information about date of last birth, date of first a regression wanting or contraception. Subsequently infertile and wanting a child wanting or contraception. Subsequently infertile and wanting a child wanting a child wanting or contraception. Estimated from information about date of last birth, date of first arrange, if childrens (i), and current use of contraception. Estimated from information about date of last birth, date of first arrange, if childrens (i), and in the quantion of wanting and the quantion wanting and the quantion wanting and the quantion of primary infertility (is lifetime measure).

	nfertility	,.				4 1-4470		
			_			n of infertilit	_	sequently
	of it Study sample (N		elf-report conce infertility leas N = 1120; (N		eive for at t 2 years = 993; = 68)	infertile and wanting a child (N = 720; n = 59)		
Characteristic	%	±95% CI	%	±95% CI	%	±95% CI	%	±95% C
Age at interview								
20-29	50.3	3.3	52.5	8.8	40.8	13.1	19.0	9.5
30-39	38.3	3.1	36.4	9.5	43.2	13.4	64.5	12.0
40-44	11.5	2.0	10.9	5.3	16.0	10.0	16.5	9.9
Parity								
0	9.1	2.1	28.3	7.6	26.7	11.9	16.5	9.1
1-3	65.4	3.2	62.3	9.2	61.8	12.1	70.0	15.9
4-5	19.3	2.5	8.3	5.6	9.0	6.3	12.4	10.1
6+	6.2	1.5	1.0	1.9	2.4	3.3	1.2	2.3
Ever conceived								
Yes	93.6	3.5	79.2	7.9	76.1	11.7	86.3	8.8
No	6.4	3.5	20.8	7.9	23.9	11.7	13.7	8.8
Ethnic group								
Chagga	49.1	4.6	37.4	10.9	46.2	12.8	49.6	15.7
Pare	13.8	2.8	22.2	10.3	19.0	10.7	18.6	15.2
Other	37.2	4.0	40.4	10.5	34.9	11.3	31.8	13.0
Education								
Primary, 0-8 years	77.0	3.1	81.0	7.6	81.9	9.7	84.5	8.9
Secondary, 9+ years	23.0	3.1	19.0	7.6	18.1	9.7	15.5	8.9
Religion	34.7	4.6	37.5	10.7	38.3	12.0	36.1	15.7
Muslim Catholic	34.7	4.6	37.5 36.1	9.6	38.3	12.0 11.4	36.1 40.8	15.7 15.3
Protestant	24.0	4.1 3.2	21.9	9.6 8.2	23.1	10.7	40.8 15.9	10.9
Other or none	4.1	1.5	4.5	5.3	5.8	4.8	7.2	5.9

In clinical practice, it is important to know v	whather on	TABLE 2					
individual woman has had difficulties in conce	iving or in	Prevalence of infertility and 95% confidence interval (CI) by five different definitions.					
carrying a pregnancy to term; however, the failur child is the salient question in social science resea		Definition of	Pi	revalence			
the individual women and men who are affected		infertility	%	95% CI			
ity. This divergence in focus partly explains the discrepan- cies in the previous infertility definitions used in research and clinical practice. On this basis, we recommend that primary infertility be estimated from women who have never conceived and secondary infertility from women who have		Self-report of infertility Unprotected intercourse for at least 2 years	y 10.3 12.1	8.4-12.2 9.4-14.8			
		Tried to conceive for at least 2 years	6.9	5.2-8.6			
conceived; we also recommend asking "How Ion		Subsequently infertile		9.2-13.7			
tried to get pregnant?", following the WHO recommenda-		Subsequently infertile and wanting a child		3.9-7.1			
tion,		Larsen. Which definition should w		2005.			
tion. ABLE 3				2005.			
ABLE 3	y by differen	Larsen. Which definition should w		2005.			
1000		Larsen. Which definition should w	e use? Fertil Steril ;	ondary			
ABLE 3  Prevalence of primary and secondary infertility		Larses. Which definition should we to definitions.	e use? Fertil Steril ;	ondary			
ABLE 3  Prevalence of primary and secondary infertility  Definition of infertility	P	Larsen. Which definition should we t definitions.	se une? Fertil Steril :	ondary			
ABLE 3 Prevalence of primary and secondary infertilit Definition of infertility Self-report of infertility	P %	t definitions.	Sec	ondary 95% C 6.0–8.8			
ABLE 3 Prevalence of primary and secondary infertilit  Definition of infertility Self-report of infertility Unprotected intercourse for at least 2 years	P %	t definitions.  rimary  95% CI  1.9–3.9	Sec %	ondary 95% C 6.0–8.8			
ABLE 3  Prevalence of primary and secondary infertility  Definition of infertility  Self-report of infertility  Unprotected intercourse for at least 2 years  Tried to conceive for at least 2 years	P %	t definitions. rimary  95% CI  1.9–3.9 1.5–3.5	Sec % 7.4 9.6	95% C 6.0–8.8 7.3–11.9 3.5–6.5			
ABLE 3 Prevalence of primary and secondary infertilit  Definition of infertility  Self-report of infertility Unprotected intercourse for at least 2 years Stubsequently infertile	P %	t definitions. rimary  95% CI  1.9–3.9 1.5–3.5	Sec % 7.4 9.6 5.0	95% C 6.0–8.8 7.3–11.9 3.5–6.5			
ABLE 3	P %	t definitions. rimary  95% CI  1.9–3.9 1.5–3.5	Sec % 7.4 9.6 5.0 11.1	95% CI 6.0–8.8 7.3–11.9 3.5–6.5 9.8–12.4			

Mascarenhas et al. Population Health Metrics 2012, 10:17 http://www.pophealthmetrics.com/content/10/1/17	POPULATION HEALTH METRICS		
RESEARCH	Open Access		
Measuring infertility in pop standard definition for use reproductive health survey:	with demographic and		
Maya N Mascarenhas <sup>1</sup> , Hoiwan Cheung <sup>2</sup> , Colin D Mathers <sup>3</sup> an		_	

Reference	Definition
International Committee for Monitoring Technology and World Health Organization, 2009 Revised Glossary on ART Terminology [15]	infertity iclinical definitions in a disease of the reproductive system defined. by the failure to achieve a clinical pregnancy after 12 or more months of regular unprotected sexual intercourse.
American Society for Reproductive Medicine, 2008 Definitions of infertility and recurrent pregnancy loss [16]	infertity is a disease, defined by the failure to achieve a successful prognancy after 12 months or more of regular unprotected inecourse. Earlier evaluation and treatment may be justified based on medical history and physical findings and a warranced after as minorful for women over age 35 years.
National Institute for Health and Clinical Excellence guideline 2004 [17]	infertility should be defined as the failure to conceive after regular unprotected sexual intercourse after two years in the absence of a known reproductive gathology.
World Health Organization, 2001 Reproductive Health Indicators for Global Monitoring [9]	Percentage of women of reproductive age (15–49) at risk of pregnancy (not pregnant, sexually active, noncontracepting, and nonfactating) who report trying for a pregnancy for two years or more.
World Health Organization, 1985 Manual for the investigation and diagnosis of the infertile couple (19)	infectility, primary. The woman has never conceived despite conhabitation, imposses to pregnancy, and the with to become pregnant for at least 12 months, infecting, secondary the woman has previously conceived but it is subrequently variet to conceive despite conhebitation, exposure to pregnancy, and the with to become pregnant for at least 12 months if the woman has bransfied a previous riffact, then exposure to pregnancy should be calculated from the centre of regular mentational following deleney.
Demographic definition, 1985 The dictionary of demography [19]	The inability to positive a live birth. The term usually refers to women, but men or couples can be the foot of steriors. Used without qualification, sterility models inversibility, but the term semporary seelily is sometimes used. A distinction is made between primary sterility where a woman has mere been able to have a child, and secondary sterility, which occurs after the birth of at-least one offspire.
Wold Health Organization, 1975 The Epidemiology of Infestility – Report of a WHO Scientific Group (8)	Firmary infertality. The seconan has never conceived despite cohabitation and exposure to pregnancy for at lets two years, Secondary infertility. The seconal has previously conceived but its subsequently unable to conceive despite conductation and exposure to pregnancy for a period of two years, if the seconal has treasfied a previous infant, then exposure to pregnancy should be calculate from the end of the period of lacational amenoration.



	20-24	ent, and outco	30-34	35-39	40-44	45-40	Age-standardized
Age group	20-24	25-29		y infertility	40-44	45-49	Age-standardized
Contraception*	9.2	5.8	4.3	0.0	0.0	0.0	5.5
	(0:0, 31.9)	(0.0, 192)	(00, 13.2)	(-0.1, 68)	(-0.1, 3.5)	(0.0, 0.0)	(2.7, 14.9)
Intent <sup>b</sup>	0.0	0.0	0.0	2.2	2.1	11.4	4.1
	(-0.1, 0.0)	(0.0, 1.5)	(0.0, 3.3)	(0.0, 6.8)	(0.0, 12.7)	(0.0, 20.3)	(1.7, 7.7)
Outcome <sup>c</sup>	-10.1	-4.6	-1.5	0.0	0.0	0.0	-3.4
	(-16.7, 0.0)	(-91, 0.0)	(-6.2, 0.0)	(-1.4, 00)	(0.0, 0.0)	(0.0, 0.0)	(-5.2, -1.7)
			Seconda	ary infertility			
Contraception*	129.9	102.1	54.1	236	12.0	5.3	20.7
	(73.1, 331.5)	(\$7.6, 169.6)	(32.4, 80.3)	(12.4, 39.9)	(6.9, 23.8)	(2.4, 103)	(126, 26.9)
Intent <sup>b</sup>	4.5	29.1	41.3	844	104.9	37.9	58.2
	(0.0, 28.2)	(16.8, 34.8)	(27.0, 60.8)	(59.6, 106.8)	(65.9, 131.7)	(20.8, 53.5)	(443, 67.9)
Outcome <sup>c</sup>	-16.7	-2.8	-0.B	0.0	0.0	0.0	-0.7
	(-50.0, 0.0)	(-5.9, 0.0)	(-3.0, 0.0)	(-0.5, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(-1.1, -0.3)

b. Not using the others of this interference of the control of

## Time to pregnancy: results of the German prospective study and impact on the management of infertility

#### C.Gnoth<sup>1,4</sup>, D.Godehardt<sup>1</sup>, E.Godehardt<sup>2</sup>, P.Frank-Herrmann<sup>1,3</sup> and G.Freundl<sup>1</sup>

Table L Cumulative probability of conception (CPC) for all couples and the truly fertile subgroup of women who finally conceived

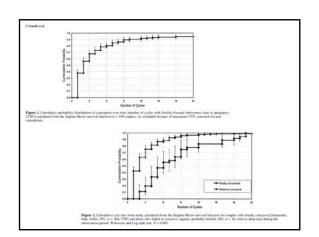
Patient group	No. of cycle	No. of cycle					
	1	3	6	12			
All couples <sup>a</sup> Truly fertile couples <sup>b</sup>	0.38 (0.026) 0.42 (0.028)	0.68 (0.026) 0.75 (0.025)	0.81 (0.022) 0.88 (0.018)	0.92 (0.017) 0.98 (0.009)			

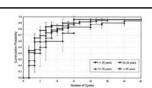
Values in parentheses are SEM.

h = 340; six couples excluded due to inaccurate time to pregnancy.

h = 304 couples; six couples excluded due to inaccurate time to pregnancy.

Couples with a good prognosis (unexplained infertility, no tubal or male factor and no signs of reduced ovarian reserve) should be advised to wait as they have a reasonably good chance (>60%) of conceiving s spontaneously during the next 36 months.





(425 years, n = 50; 26-30 years, n =

Taking into account the results of the overall conception rates for all couples, among when the substitution of the couples are substitutionally as the coupless are substitutionally as the couples are substitutionally as t

The Hidden Infertile: Infertile Women without Pregnancy Intent in the United States

Arthur L. Greil, Ph.D. [Professor of Sociology], Alfred University Alfred, New York

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The University of Nebraska at Lincoln Lincoln, Nebraska jmcquillan2@uninotes.unl.edu

Katherine Johnson, M.A. [Doctoral Candidate]. The Pennsylvania State University University Park, Pennsylvania kmj165@psu.edu

The reconsystems State University University Park, "entropyrems and proggous our Katherine Slauson, M.A. [Doctoral candidate], and The University of Nebraska at Lincoln Lincoln, Nebraska kolauson@unisenve uni edu Karina M. Shreffler, Ph.D. [Assistant Pressor in Human Development and Family Science] Oklations Satio University Tuta, Oklationna harma shreffler@okstate edu

According to commonly accepted medical criteria for infertility, women are categorized as infertile if they experience a year of unprotected intercourse without conception.

Using this definition, the National Survey of Family Growth (NSFG) estimates that 7.4 percent of married U.S. women were infertile in 2002. It makes no explicit reference to intent to conceive, but, given the availability of contraception, this definition implies that women meeting the criteria for infertility were *trying to conceive*.

Data from the National Study of Fertility Barriers (NSFB) reveal that there are a large number of women who at some point in their lives fit the NSFG definition of infertility but who do not describe themselves as having tried to become pregnant at that time.

Bluman Reproduction Vol.20, No.2 pp. 1144-2147, 2000 Advance Access publication March 16, 2000

#### DEBATE-CONTINUED

Definition and prevalence of subfertility and infertility

C.Gnoth<sup>1,5</sup>, E.Godehardt<sup>2</sup>, P.Frank-Herrmann<sup>5</sup>, K.Friol<sup>1</sup>, Jürgen Tigges<sup>1</sup> and G.Freundl<sup>4</sup>

Table I. Definition and prevalence of subfertility and infertility

central cycles About 20% at least slightly subfertile couples

About 5% nearly complete infertile couples

Chains to conserve operationswith in the fature 50% of these conjugates will conceive spectaneously in the next six cycles, the reaching are moderarly subferrise [Equivalent to slightly reduced fartility reaching are moderarly subferrise [Equivalent to slightly reduced fartility 10% of these couples will conserve spectaneously in the next 16 months, the remaining are newly complete irestific [Equivalent to moderate/spectarly couples with only specialic spectaneous conceptions [Equivalent to startle couple (Edelenters et al., 2018).

Subfertility must be raised after six cycles of unprotected intercourse without conception—regardless of age because most of the women less than 30 years of age should have conceived.

For women after the age of 35 years—if treatment (e.g. IVF) will be necessary the chance of a live birth will decrease rapidly.

nan Reproduction Update, Vol.17, No.5 pp. 575-588, 2011 human reproduction update Defining infertility—a systematic review of prevalence studies S. Gurunath <sup>1</sup>, Z. Pandian <sup>2</sup>, Richard A. Anderson <sup>3</sup>, and Siladitya Bhattacharya <sup>1,\*</sup> BACKGROUND: Existing definitions of infertility lack uniformity, rendering comparisons in prevalence between countries or over time problematic. The absence of an agreed definition also compromises clinical management and undermines the impact of research findings. Demographers tend to define infertility as childlessness in a population of women of reproductive age. Epidemiological definition is based on 'trying for' or 'time to' a pregnancy, generally in a population of women exposed to the risk of conception.

There is considerable variation in terms of the duration of 'trying for pregnancy', the age of women sampled and their marital or cohabitation status. This leads to inconsistencies in determining the numerator and denominator used to calculate the prevalence of infertility.

#### References

- C.Gnoth, E.Godehardt, P.Frank-Herrmann, K.Friol, Jurgen Tigges and G.Freundl. Definition and prevalence of subfertility and infertility. Human Reproduction Vol.20, No.5 pp. 1144–1147, 2005.
- Wang X, Chen C, Wang L, Chen D, Guang W and French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril (2003) 79,577–584.
- Gnoth C, Frank-Herrmann P, Freundl G, Godehardt D and Godehardt E. Time to pregnancy: results of the German prospective study and impact on the management of infertility. Hum Reprod (2003) 18,1959–1966.
- Arthur L. Greil, Julia McQuillan, Katherine Johnson, Katherine Slauson, Karina M. Shreffler. The Hidden Infertile: Infertile Women without Pregnancy Intent in the United States. Fertil Steril. 2010 April ; 93(6): 2080-2083

#### References

- Juul S, Karmaus W, Olsen J. Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. The European Intertility and Subfecundity Study Group. Hum Reprod (1999) 14,1250–1254.
- European Infertility and Subfecundity Study Group. Hum Reprod (1999) 14,1250–1254. Juul S, Keiding N, Tvede M. Retrospectively sampled time-to pregnancy data may make age-decreasing fecundity look increasing. European Infertility and Subfecundity Study Group. Epidemiology (2000) 11, 717–719. Jensen TK, Slama R, Ducot B et al. Regional differences in waiting time to pregnancy among fertile couples from four European cities. Hum Reprod (2001) 16,2697–2704. S. Gurunath, Z. Pandian, Richard A. Anderson, Sliaditya Bhattacharya. Defining infertility—a systematic review of prevalence studies. Human Reproduction Update, Vol.17, No.5 pp. 575–588, 2011

- Ulla Larsen. Research on infertility: which definition should we use? Fertil Steril 2005;83:846 –52
- Maya N Mascarenhas, Hoiwan Cheung, Colin D Mathers, Gretchen A Stevens.

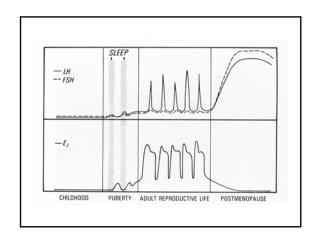
  Measuring infertility in populations: constructing a standard definition for use with demographic and reproductive health surveys. Population Health Metrics 2012, 10:17

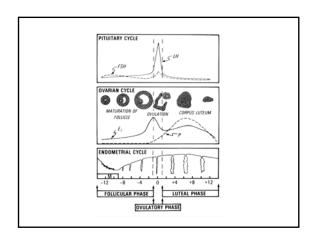
The Roles of Ovulation Documentation and Timed Intercourse in Increasing the Likelihood of Pregnancy in Women Trying to Conceive

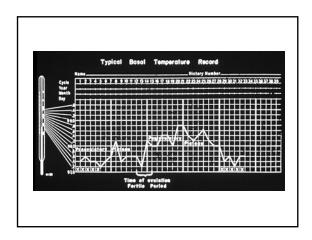
Robert W. Rebar, M.D.
Professor and Chair,
Department of Obstetrics and Gynecology
Western Michigan University Homer Stryker M.D. School of
Medicine

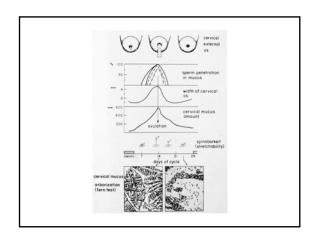


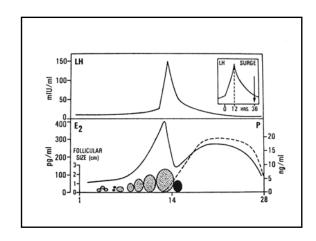
Disclosures	]
•I serve on multiple Data Safety Monitoring Boards for randomized trials; write summaries for <i>Journal Watch</i> , a non-profit publication of the Massachusetts Medical Society; and am Deputy Editor of the	
journal <u>Contraception</u> .  •I receive no monies from any commercial	
source.	
•Any opinions I express are mine alone and do not represent the views of any	
organization.	
At the conclusion of this presentation, participants should be able to:	]
• Describe the biophysical and hormonal changes	
that typically occur during the normal menstrual cycle.	
•Summarize the data from studies documenting the "fertile window" and presumptive ovulation.	
• Discuss how the frequency of intercourse affects the pregnancy rate.	
<ul> <li>Discuss advantages and disadvantages of using ovulation monitors and timed intercourse.</li> </ul>	

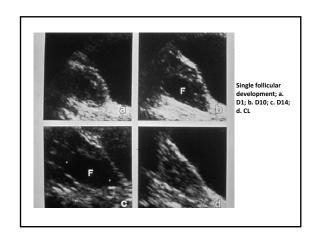


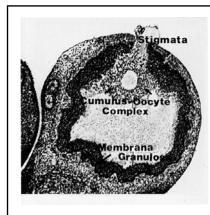




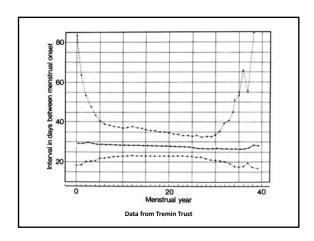


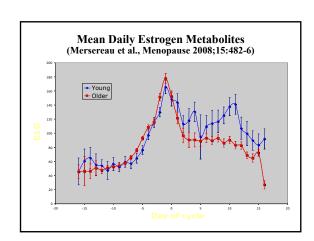


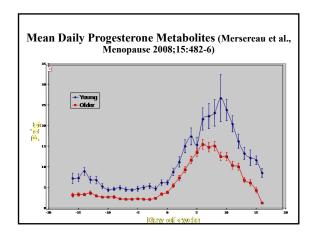




Ovulation of the cumulusoocyte complex through the stigma (Erickson GF. Semin Reprod Endocrinol 1986;4:233)







Urinary Metabolites (Averaged over cycle phases) (Mersereau et al., Menopause 2008;15:482-6)						
		Younger (20- 34 yrs) n=28	Older (35-50 yrs) n=78	p value**		
	Total*	11.2 ± 4.5	6.6 <u>+</u> 3.1	<0.001		
PdG	Follicular*	5.6 <u>+</u> 2.2	2.7 <u>+</u> 1.3	<0.001		
	Luteal*	18.1 <u>+</u> 8.9	11.0 ± 5.2	<0.001		
	Total*	97.2 <u>+</u> 39.8	89.2 ± 32.7	0.469		
E1G	Follicular*	81.7 <u>+</u> 32.9	88.5 <u>+</u> 37.3	0.431		
	Luteal*	115.4 <u>+</u> 56.1	90.4 <u>+</u> 33.6	0.035		

#### **Documentation of Ovulation**

- Ovulation only can be proven in any given menstrual cycle by a resulting pregnancy or by physically observing ovulation; even then there is no way to identify if the oocyte is normal.
- Virtually no study "documenting" ovulation has confirmed its occurrence.
- Surrogates for ovulation are typically used: measurement of progesterone or its metabolites (sometimes after an elevated LH or in association with measurement of estrogen or its metabolites), evidence of follicle collapse on ultrasound, endometrial biopsy, and changes in biophysical parameters such as BBT and cervical mucus.

Findings of one study of ovulation (Blackwell et al., Hum Reprod 2013;28:3306)

- Prospective uncontrolled cohort study of 62 fertile women with apparently normal menstrual cycles
- Daily urine samples collected for 2 cycles and assessed for E1G and PdG
- •Concluded that 80.5% of cycles were potentially fertile and that 19.5% had some luteal defect (LUF, deficient luteal phase, short luteal phase)
- •The "luteal defects" were arbitrarily defined and were not proven to be associated with inability to become pregnant during that cycle.

Findings of another study of ovulation (Hambridge et al., Hum Reprod 2013;28:1687)

- Prospective uncontrolled cohort study of 250 regularly menstruating (21-35 d) women aged 18-44
- Serum LH, E2, & P were measured in blood samples obtained in up to 16 visits over 2 cycles.
- •87.6% of the women had 2 normal cycles with P > 5 ng/ml; 9.6% had 1 ovulatory cycle; 2.8% had two anovulatory cycles.
- •The unproven presumption was that cycles with P ≤ 5 ng/ml were anovulatory.

Summary findings from 8 studies of ovulation (Blackwell et al., Hum Reprod 2013;28:3306; Hambridge et al., Hum Reprod 2013;28:1687; van Zonneveld et al., Gyn Endocrinol 1994;8:169; Malcolm & Cumming, Obstet Gynecol 2003;102:317; Miller & Soules, Obstet Gynecol 1996;87:13; Rudy & Estok, J Obstet Gynecol Neonatal Nursing 1992;21:407; Rollason et al., Int. J Women's Health 2014;6:657; Manders et al., Cochrane Database 2014; issue 9)

- Eight studies including 2411 subjects
- Presumptive anovulation rates in 3 studies ranged from 3.7-12.8%; one study found a 19.5% incidence of luteal phase defect.
- •There was insufficient evidence to designate any gold standard; the presumed standard is serum Progesterone.

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These newer data are consistent with reports from the 1960s and 1970s that approximately one in every 12 menstrual cycles appeared anovulatory on the basis of hormonal changes.	
Despite the absence of definitive proof, it	
appears reasonable to conclude that ovulation occurs essentially monthly in regularly	
menstruating women with cycle length between 24 and 35 days.	
It would seem unlikely that documentation of ovulation, generally by measurement of serum	
progesterone in the luteal phase, would provide any additional assistance even though mid-	
luteal progesterone levels correlate with pregnancy by identifying those women who are anovulatory.	
	]
An Evidence-Based Assessment of Diagnostic Tests Used in Evaluating Infertility (JA Collins, 1995)	
•Test results correlating with pregnancy	
Semen analysis     Tubal patency testing by HSG or	
laparoscopy  •Mid-luteal progesterone levels	
ivila-luteal progesterone levels	

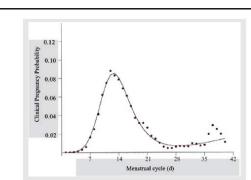
# The Probability of Pregnancy and the Frequency of Intercourse A retrospective study of almost 9500 semen specimens found that, in men with normal semen quality, sperm concentration, and motility, sperm concentration and motility remain normal even with daily ejaculation (Levitas et al., Fertil Steril 2005;83:1680). After abstinence intervals of ≥ 10 days, semen parameters begin to deteriorate (Check et al., Arch Androl 1995;27:93). In 221 presumably fertile couples attempting pregnancy, daily intercourse resulted in the highest cycle fecundability (37%), but the pregnancy rate was comparable with intercourse on alternate days (33%); the likelihood of pregnancy decreased to 15% with intercourse only weekly (Wilcox et al., NEJM 1995;333:1517). These data imply that couples should be informed that the likelihood of pregnancy increases with the frequency of intercourse and is highest with intercourse at 1 to 2 day intervals; however, couples should be advised that the optimal frequency of intercourse during midcycle is best defined by their own preferences so as to reduce any stress. 1.2.2.1 People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. [NICE Fertility Guidelines, 2004, amended 2013]

#### **Additional NICE Fertility Guidelines**

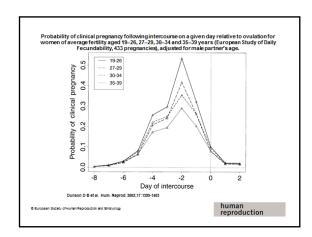
- 1.3.4.1 Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating. [2004]
- 1.3.4.2 Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. [2004, amended 2013]
- 1.3.4.4 The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended. [2004]

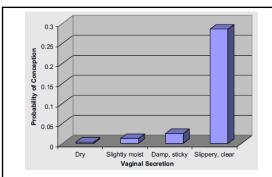
# The "Fertile Window" and the Probability of Pregnancy

- •The so-called "fertile window" can be defined as the 6-day interval ending on the day of ovulation; pregnancy is most likely with intercourse during the 3 days prior to ovulation (Wilcox et al., NEJM 1995;333:1517; Brosens et al., Sex Reprod Menopause 2006;4:13).
- The likelihood of pregnancy decreases with increasing age.
- •The likelihood of pregnancy can be maximized by increasing the frequency of intercourse from the end of menses through ovulation in midcycle.



Probability of pregnancy with a single act of intercourse. Modified from Wilcox et al. Contraception 2001;63:211.





Probability of pregnancy according to vaginal secretion observations on the day of intercourse. Data from Scarpa et al., Eur J Obstet Gynaecol Reprod Biol 2006;125:72.

#### **Documentation of Ovulation**

- Commercial approaches to determining when ovulation occurs include among others:
  - Basal Body Temperature (BBT)
  - Urine LH kits such as Ovuquick® and First Response™
  - Clearplan/Clearblue Easy Fertility Monitor® of urinary LH and estrogen metabolites
  - ${\bf \cdot}$  Duofertility  ${\bf ^{TM}}$  monitor of temperature and heat flow
  - OvuSense™ Fertility Monitor of vaginal temperature
  - OvaCue™ Fertility Monitor of electrolyte changes in saliva and cervical mucus
- All tests have false positives and false negatives.

Documentation of Ovulation (cont.)  •It is also possible to document ovulation by:  •Serial ultrasound (relatively precisely and expensively)  •Fertility awareness based methods, including cervical mucus and BBT changes and calendars (imprecisely)  •Menstrual cycle charting (very imprecisely)	
Data indicate that stress associated with trying to become pregnant can reduce sexual esteem, satisfaction, and frequency of intercourse; moreover, stress can be further increased by utilizing ovulation predictor kits or following a strict schedule (Lenzi et al., J Endocrinol Invest 2003;26:72; Andrews et al., Fertil Steril 1992;57:1247).	
Timed intercourse was found to be the most emotionally stressful activity in the initial infertility evaluation (Kopitzke et al., Fertil Steril 1991;55:1137).	

#### Timing of Intercourse

- BBT is known to be a poor predictor of the day of ovulation (Templeton, Penney, & Leader, Br J Obstet Gynaecol 1982;89:985)
- While hormonal ovulation detection kits are better at predicting ovulation, they are expensive and there is no evidence their use improves pregnancy rates.
- In one study 105 couples with unexplained infertility and 45 couples with asthenozoospermia were randomized to timed intercourse with an LH detection kit or advice for timing intercourse, pregnancy rates were not significantly different (Leader, Russell, & Stenning, Aust N Zeal J Obstet Gynaecol 1992;32:158).

Timed Intercourse for Couples Trying to Conceive (A New Cochrane Review) (Manders et al., In Press)

- Conclusion: "There was insufficient evidence to draw definite conclusions on the effectiveness of timed intercourse for live births, adverse events or clinical pregnancy in couples trying to conceive."
- •There may be a higher pregnancy (including self-reported pregnancies, especially for women trying for <12 months, BUT "the overall quality of the evidence is low to very low" and "the size of the benefit is small."</p>

Ovulation detection kits may be of benefit to couples who have intercourse sporadically, perhaps because they travel extensively or work in different cities, and to those who wish to use them, but there are no data documenting that they increase the likelihood of pregnancy.

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	Might it be just as effective to ask couples to record menses and days when intercourse occurred retrospectively?			
•		ı		
I	Summary and Conclusions			
I	Normal ovulation can only be documented by a resulting pregnancy.			
I	Surrogate markers for pregnancy involve measuring various biophysical and hormonal parameters.     It appears that perhaps 3-12% of menstrual cycles of normal length			
I	may be anovulatory, but there is no evidence that women with regular menses are more than seldom anovulatory.			
I	<ul> <li>Intercourse at intervals of 1-3 days from the end of menses through midcycle appears as effective as any monitoring in</li> </ul>			
I	resulting in pregnancy.  In today's complicated world ovulation monitors may be of assistance to some couples, but there is no evidence from			
I	controlled studies that they increase pregnancy rates.			
l				
		·		
I	Summary and Conclusions (cont.)			
I	<ul> <li>Large scale randomized controlled trials are required to document any benefit for the</li> </ul>			
	different methods for timing intercourse versus spontaneous intercourse and versus each other.			
I	•The economic impact of the different			
	ovulation prediction methods— as well as the impact on the emotional health of the			
	couple – should also be assessed, as this must be considered in recommending any			
	method.			







#### How would ovarian reserve testing influence the probability of natural pregnancy in women with subfertility

Prof Dr TM D'Hooghe, MD, PhD1 Prof Dr D. De Neubourg, MD, PhD<sup>2</sup>

KU Leuven/University of Leuven (B)  $^{\rm 1,\,2}$ Yale University (USA)1 Institute Primate Research (WHO CC), Nairobi, Kenya<sup>1</sup> "ESHRE Pre-congress Course PCC14:

MEFS exchange course: the ABCs of infertility management revisited." June 14<sup>th</sup>, 2015, Lisbon, Portugal

1)150	

- Fundamental Clinical Investigator for endometriosis, Belgian Research Foundation (1998-2009), Leuven University Hospital Clinical Research Fund (2010-2015)
- Co-Chair WHO Infertility Guidelines Development Group Steering Committee
- Board Member European Endometriosis Liga (EEL)
- Council Member Society Gynecol Investigation (SGI)
- Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya (WHO-CC)
- Grants from Merck Serono, Ferring, MSD, Besins, WERF
- Consultancy/KOL for Merck Serono, Ferring, MSD, Bayer, Abbott, Abbvie, Preglem, Gedeon Richter, Pharmaplex, Uteron Pharma, Roche, Proteomika

#### Learning objectives

- What is the role of AMH as a test for ovarian reserve?
- Can ovarian reserve tests (AMH, FSH, AFC) predict the probability of natural pregnancy in an infertile population?

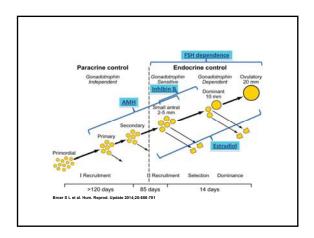
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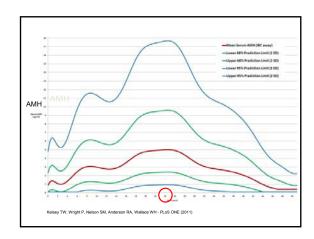
#### AMH (Anti-Mullerian Hormone)

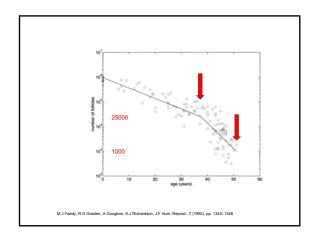
Produced by small pre-antral, large pre-antral and antral follicles

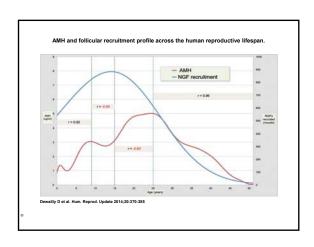
Plasma concentration: 1-7ng/ml dependent on type of test and lab

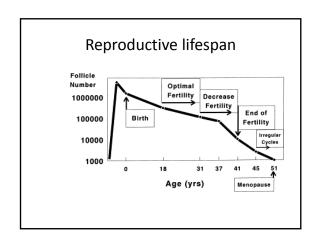
Reproductive age : 0.65 - 12.60 ng/ml Postmenopausal phase : < 0.08 ng/ml

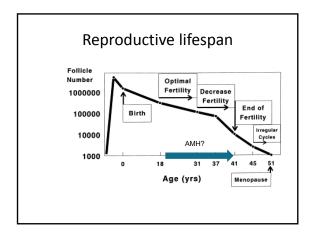






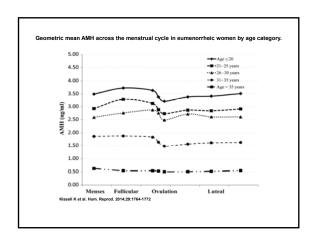






#### Serum AMH determination

- = parameter for ovarian reserve
- One assessment is suffcient
- Independent of cycle phase and consistent over several cycles
- Independent of intake of oral contraception or GnRH agonists during short duration. (In case of long duration: reduction with 20%).



#### **AMH** determination

- = parameter for ovarian reserve
- Lower in women who smoke
- Lower in women with increased BMI?
- Increased (2-3x) in women with PCOS

# PCO PCO: †AMH

#### Can serum AMH predict



- Ovarian reserve and function (N)?
- Egg quality (Q)?
- Pregnancy (N&Q)?
- Menopause (N&Q)?

# Can plasma-AMH predict time to pregnancy?

Reference	N patients	Age patients	TTP Time to pregnancy	AMH? FR= fecundability ratio	
Steiner 2011	100	30-44 30% > 35y 5% >40y	63% in 6m	<0.7ng/ml: FR 0.38 (95%Cl 0.08-0.91)	
Hagen 2012	186	26.6 (95% CI: 21.4-31.8)	59% in 6m	Quintile 1 vs Quintile 2-4: FR: 0.81 (95%CI: 0.44-1.40) Quintile 5 vs Quintile 2-4 FR: 0.48 (95%CI: 0.270.85)	
Streuli 2014	87	23-41 31.0±4.5y	82% 6m	Age (r= -0.24; p=0.02) 0.10)	AMH ( r= -

# Do tests of ovarian reserve predict the probability of pregnancy in infertile women?

#### In expectant management populations:

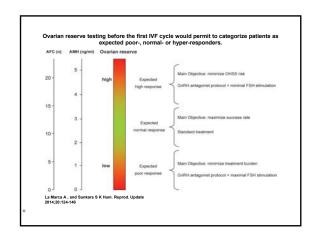
- FSH: Casadei 2013, Haadsma 2008, Van der Steeg 2007
- AMH: Casadei 2013
- AFC: Casadei, Haadsma 2008,
- CCCT: Haadsma 2008

None of these studies found that any of the ORTs assessed had any clinically meaningful value for predicting pregnancy or live birth, either when used alone or when added to a prediction model.

#### Clinical value of AMH testing

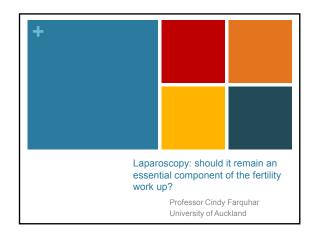
- = parameter for ovarian reserve
- Good prediction of poor response and of exaggerated response in the context of ART treatment
- Potentially useful for ovarian stimulation protocols
  - ✓ Start dose
  - ✓ Adaptation dose
  - ✓ Predict ovarian response

	•	٠	



#### **CONCLUSIONS**

- AMH testing, FSH testing or AFC testing not useful to predict spontaneous conception in subfertile women during expectant management
- AMH testing useful for prediction of ovarian response during ART treatment



#### Declarations

- Co-ordinating editor of the Cochrane Menstrual Disorders and Subfertility Group
- Co-Chair of the Diagnostic section of the WHO Fertility Guidelines 2014-2015
- No commercial conflicts to declare

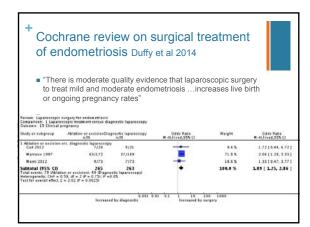
#### Laparoscopy and fertility: learning objectives

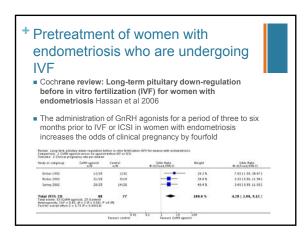


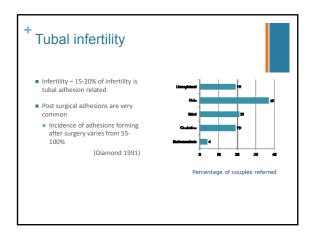
- ■What information is provided by a laparoscopy that assists fertility?
- ■Does having the diagnosis improve outcomes?
- ■What are the alternatives to laparoscopy?
- ■Which women should we offer laparoscopy to?

	WHO is developing guidelines for investigation and treatment of women with infertility	
	<ul> <li>Process – question development</li> <li>Developing a PICO</li> <li>P – patients</li> <li>I – intervention</li> <li>C – comparison</li> </ul>	
	O - outcomes	
	+ Which women should be offered	╗
	laparoscopy at the time of presenting with infertility?	
	P Women of reproductive age with infertility with and without the following clinical flags: painful periods (endometriosis), sisk factors for tubal disease (past history of chlamydia/gonorrhea)	
	history of pelvic surgery (appendicitis/ovarian cystectomy/previous diagnosis of endometriosis)     abnormal clinical examination or imaging     I – laparoscopy (diagnostic)	
	C- no laparoscopy or imaging prior to laparoscopy  O – Outcomes	
	adhesions (underlying infection/endometriosis/postsurgery) and endometriosis     change in previously planned management of women as a result of the findings on diagnostic laparoscopy     pregnancylive birth (either naturally conceived or through fertility treatment)	
	= cost	
	What information is provided by a laparoscopy that assists fertility?	
	■Tubal disease/adhesions secondary to infection, previous surgery, hydrosalpinges	
	■Endometriosis – peritoneal and ovarian, bowel disease	
	■Tubal patency	
J		1

# Harms and benefits of laparoscopy ■Benefits ■ Diagnosis leads to treatment of disease that may improve pregnancy rates and improve success of IVF ■Harms Invasive ■ Potential for injury ■ Days off work ■ Cost <sup>+</sup> Laparoscopy may lead to treatment ■Treatment of peritoneal or ovarian endometriosis ■Removal of hydrosalpinges in preparation for ■Possibility of release of adhesions Endometriosis ■Benefits of diagnosis ■ Surgical removal is associated with better ■ Pre IVF down regulation for 3 months



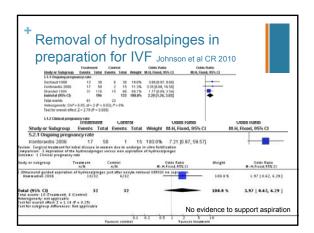




### Tubal adhesions and fertility



- The incidence of tubal infertility following pelvic inflammatory disease (Westrom et al 1980)
  - after 1 episode of pelvic infection is 12%
- 23% after 2 episodes
- 54% after 3 episodes of pelvic infection
- Surgical treatment to restore patency (Techniques for polvic surgery in subfertility Ahmad et al 2006 and Surgery for tubal infertility Pandian et al 2007)
  - But no RCTs and based on cases series
- Adhesions may interfere with assisted reproduction
- Distortion makes monitoring and ovum pick up more difficult



# What are the alternatives to laparoscopy for tubal infertility?



- ■Tubal Disease
- Ultrasound
- HSG/HyCoSY
- CAT
- ■5 Systematic reviews
  - Broeze 2011, Mol 1997, Broeze 2011a, Broeze 2012, Maheux-Lacroix 2014
  - All moderate or good quality

#### Chlamydia Antibody Testing (CAT) vs laparoscopy: 2 SRs



- Prevalence of any tubal pathology was 29% (27 to 30%) and for bilateral tubal pathology was 13% (12 to 15%), as defined by laparoscopy
- Sensitivity and specificity of CAT not pooled
- For any tubal pathology, sensitivity was 12 to 91% and specificity was 35 to 100%
- Broeze 2011: CAT low sensitivities of CAT but high specificities
- high specificitie means that CAT might avoid unnecessary testing in women without tubal pathology
- low sensitivities might be too low to accurately rule out tubal pathology
- Mol 1997:
- CAT is comparable to HSG in the diagnosis of tubal occlusion in the diagnosis of any tubal pathology
- No information on the anatomy of uterus and cervix

#### Hysterosalpingogram vs Laparoscopy: SR Broeze 2011



- 7 primary studies with 7226 women
- Prevalence of any tubal pathology\* was 30% (95% CI 29 to 32%)
   prevalence of bilateral tubal pathology was 15% (95% CI 14 to 17%)
- Pooled sensitivity and specificity of HSG were 53% and 87% for any tubal pathology and 46% and 95% for bilateral tubal pathology
- Diagnostic accuracy of HSG > in women with risk factors of women without risk factors
- In women without risk factors, the sensitivity of HSG was 38% for any tubal pathology compared with 61% in women with risk factors (p=0.005)
- "HSG can be considered equally useful in detecting tubal pathology for all groups of women. Although some women may still benefit from laparoscopy, HSG can be used as a screening test for all infertile couples"
- \*as defined by diagnostic laparoscopy

#### CAT and HSG



- In the comparison of CAT with HSG, the combination of patient history with CAT and HSG testing provided the best estimate of bilateral tubal pathology, compared to either test
- Prevalence rates of chlamdyia infection varies between

### HSG vs HyCoSy

- HyCoSy appears to be a well tolerated procedure when compared to HSG
- No studies were identified which directly compared all diagnostic tests for tubal patency
- Diagnostic accuracy of HSG and HyCoSy were

#### CAT/HSG/Laparoscopy and fertility outcomes



- +ve CAT serology associated with reduced pregnancies
- Keltz 2013
- 70/1279 (5.5%) had a positive chlamydia serology result.
- + CTA more likely to have blocked tubes on HSG (37.5% vs 10.1%, p=0.001) and laparoscopically confirmed damage (85.7% vs 48.9%, p=0.002)
   No spontaneous pregnancies in CAT positive patients with an abnormal HSG
- Verhoeve 2011
- HSG and laparoscopy results were similar wrt spontaneous pregnancy:
   unilateral tubal pathology on HSG and laparoscopy reduced chances of a spontaneous pregnancy and bilateral tubal pathology severely reduced preg
- Positive chlamydia IGC serology was associated with a statistically significant 33% lower probability of an ongoing pregnancy (adjusted fecundity rate ratio 0.66 (0.49 to 0.89).

#### Who should we offer laparoscopy to?



- Why not everyone?
- ■Expensive and invasive
- ■Potential for harm
- ■Should we limit to women with possible underlying pathology
- Those women with clinical flags?
- ■What are the clinical flags?

## \* Clinical flags for pelvic disease

- Endometriosis
- Painful periods new onset of symptoms, requires pain relief >24 hours
- Pain with sex, pain with bowel motions
- Change in symptoms
- ■Tubal Disease
- risk factors for tubal disease (past history of chlamydia/gonorrhea)
- history of pelvic surgery (appendicitis/ovarian cystectomy/previous diagnosis of endometriosis)
- Abnormal clinical examination or imaging

# Evidence for laparoscopy as part of the investigation of infertility



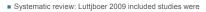
- ■8 studies
- One systematic review (Luttjeboer 2009)
- 3 RCTs (Perquin 2006, Badawy 2010, Tanahatoe 2005)
- One controlled cohort study (Berube 1998)
- One prognostic cohort study (Mol 1999)
- One cost study (Moayeri 2009)

## Description of studies



- One systematic review was identified that provided indirect evidence on the role of laparoscopy
- The remaining studies were RCTs (n=3), cohort studies (n=2), one cross sectional study and a cost effectiveness study
- Four studies were undertaken in the Netherlands (n=4) and one each in Egypt, Canada, USA and Turkey

#### Diagnosis of tubal infertility at laparoscopy 2º to adhesions and endometriosis



- Cohort studies:
- History of complicated appendicitis (OR 7.2, 95% CI 2.2 to 22.8)Pelvic surgery (OR 3.6, 95% CI 1.4 to 9.0)
- PID (OR 3.2, 95% CI 1.6 to 6.6)
- Case control studies:
- History of complicated appendicitis (OR 3.3, 95% CI 1.8 to 6.3)
- PID (OR 5.5, 95% CI 2.7 to 11.0)
- Ectopic pregnancy (OR 16.0, 95% CI 12.5 to 20.4)
  Endometriosis (OR 5.9, 95% CI 3.2 to 10.8)
- Sexually transmitted disease (OR 11.9, 95% CI 4.3 to 33.3)

"Subfertile women reporting a history of PID, complicated appendicitis, pelvic surgery, ectopic pregnancy and endometriosis are at increased risk of having tuboperitoneal pathology. In these women, diagnostic laparoscopy should be offered early in the fertility workup"

#### RCT of HSG then laparoscopy or immediate laparoscopy Perquin 2006



- Average length of infertility = 2 years
- Risk factors were equally distributed between the groups
   3% of each group had a history of PID, 2% and 3% respectively had a history of IUD use, 4% had previous sexually transmitted infection and 1% had previous tubal surgery.
- Coagulation of endometriosis (grade I or II) was performed in 25% and 27% respectively,
- Laparoscopic adhesiolysis in 5% and 4% respectively and laparoscopic cystectomy in 1% of both groups

"Routine use of HSG at an early stage of fertilty workup prior to laparoscopy does not influence cumulative pregnancy rate compared with routine use of laparoscopy with out HSG"

#### + RCTs (2) laparoscopy then OI or IUI or treatment with OI or IUI first then laparoscopy



- Badawy 2010: unexplained infertility (normal HSG)
- Adhesions were identified in 15% to 18% of women
- Endometriosis in 14% to 16% of women
- Pregnancy rate after 6 months Lap +OS = 44.7% cf with OS: 41.7% (NS)
- "laparoscopy could be postponed"
- Tanahatoe 2005 unexplained
- Abnormalities were identified in 48% to 56% of the randomized women
- Endometriosis was found in 44% to 52% and adhesions in 0% to 4% respectively
- Pregnancy rates: lap +IUI = 44%, IUI + Lap = 49% (NS)
- Authors questioned the value of routinely performing a laparoscopy prior

#### Prospective cohort study (Mol 1999)

- Compared the HSG and laparoscopy
- Consecutive subfertile couples (n=794) in 11 Canadian centres who underwent HSG and laparoscopy were included
- Patients with an abnormal HSG underwent laparoscopy without delay but in patients with a normal HSG, laparoscopy was only performed in cases where subfertility persisted for a longer period of time.
- Of those having laparoscopy, 16% of tubal diagnoses showed "other tubal pathology" (included adhesions and phimosis) at laparoscopy and for endometriosis diagnoses, 78% had no endometriosis, 20% had grade 1 or 2 endometriosis and 2% had grade 3 or 4 endometriosis

#### Cross-sectional study Kahyaoglu 2009

- 191 unexplained infertile women in Turkey.
- Women had both primary and secondary infertility, with a mean age of 27 and 29 years respectively.
- All women had HSG and transvaginal ultrasound. Results were as follows:
- 123/191 (64%) of patients had pelvic pathology. 16% had pelvic adhesions, 26% had endometriosis, 13% had pelvic infections and 19% had tubal occlusion. 35% had normal pelvic anatomy.
- Risk factors for infertility included: abnormal HSG, previous pelvic surgery, ectopic pregnancy (for secondary infertility), ovarian surgery and dysmenorrhea/pelvic pain.
- There was no significant difference in the rate of pathology on diagnostic laparoscopy according to whether or not women had prior risk factors: 61% vs 59%.

#### Planning laparoscopy - conclusions



- Women with risk factors appear to have an elevated risk of tubal pathology, including PID and endometriosis
- Other studies found that in women with generally unexplained infertility, the risk of adhesions ranged from 0% to 24% and the risk of endometriosis ranged from 14% to 52%
- It is difficult to extrapolate from these figures, as the populations in the individual studies are likely to have differed, although generally they had either unexplained infertility or were candidates for IUI

#### + Laparoscopy leading to change in management



- RCT Badawy 2010
- randomized with unexplained fertility to laparoscopy plus treatment compared to treatment alone (with laparoscopy if it was unsuccessful)
- 2.3% of patients had a change of management according to laparoscopy findings
- 6/257 patients were found to have moderate and severe adhesions and were referred directly to the IVF/ICSI program
- X-sectional study Kahyaoglu 2009: association between lap and risk factors
- A high rate of pelvic pathology was identified; only 35% of the whole group had normal pelvic anatomy. The authors reported:
   Treatment strategies of 9% (primary) and 13% (secondary) of infertile women without risk factors were changed as a result of laparoscopy findings
  - Treatment strategies of 43%(primary) and 49% (secondary) of infertile women with risk factors changed after diagnostic laparoscopy

- Conclusions There was moderate evidence that women with unexplained infertility and normal HSG findings could delay diagnostic laparoscopy for 6 to 10 months, without influencing their chances of a spontaneous pregnancy.
- There was low quality evidence that diagnostic laparoscopy findings in women with risk factors such as previous surgery, ectopic pregnancy, pelvic pain and abnormal HSG may result in change of their subfertility management in 43% to 49% of the women.
- Abnormal findings at laparoscopy may lead to an alteration in management including correction at surgery and treatment of endometriosis and decisions about fertility treatment

## What do guidelines say?



- ■The 2013 NICE guideline recommends
- ■Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pathology can be assessed at the same time

#### + Laparoscopy: should it remain an essential component of the fertility work up



- It is not an essential component for all women
- Women with clinical flags for tubal disease or endometriosis should be considered for laparoscopy
- Bilateral tubal disease detected by HSG may be so severe that laparoscopy not likely to improve changes of conceiving but removal of the tubes indicated prior to IVF
- Treatment of endometriosis a useful step in treatment

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- Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM. Long-term pitultary down-regulation before in vitro women with endometriosis. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004635. DOI: 10.1002/1455185.CD004635. pub2.
- Diamond et alPostoperative adhesion development after operative laparoscopy: Evaluation at early second-look procedures
   Journal of Gynecology & Obstetrics INT J GYNECOL OBSTET 01/1992; 37(4):328-328. DOI: 10.1016/0020-7292(92)90354
- Weström, L. Incidence, prevalence and trends of acute pelvic inflammatory disease and its consequences in its American Journal of Obstetrics and Gynecology. 1980;138:880–891.
- Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BWJ. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD002125. DOI: 10.1002/14551858.CD002125.pub3.
- Luttleboer FY, Verhoeve HR, van Dessel HJ, van der Veen F, Mol BWJ, Coppus SFPJ. The value of medical history taking as a risk indi for fuboperitoneal pathology: a systematic review. BJOG 2009; 116: 612-625
- Perquin DAM, Dorr PJ, de Craen AJM, Helmerhorst FM. Routline use of hysterosalpingography prior to laparoscopy in the fertility workup: a multicenter randomized controlled trial. Human Reproduction 2006; 21(5): 1227-1231 Badawy A, Khiary M, Ragab A, Hassan M, Sherif L. Laparoscopy – or not – for management of unexplained infertility. Journal of Obstetrics and Gynaecology 2010; 30(7): 712-715
- Tanahotoe S.J, Lambalk CB, Hompes PGA. The role of laparoscopy in intrauterine insemination: a prospective randomized Human Reproduction 2005; 20(11): 3225-3230
- Mol BWJ, Collins JA, Burrows EA, van der Veen F, Bossuyt PMM. Comparison of hysterosalpingography and Japaroscopy in predicting fertility outcome. Human Reproduction 1999; 14(5): 1237-1242
- Berube S, Marcoux S, Langevin M, Maheux R and the Canadian Collaborative Group on Endometriosis. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. Fertility and Sterlitry 1998; 69(6): 1034-1041
- Kahyaoglu S, Kahyaoglu I, Yilmaz B, Var T, Ertas IE, Mollamahmutoglu L, Batioglu S. Should diagnostic laparoscopy be performed initially ond, during infertility management of primary and secondary infertile women? A cross sectional study. Journal of Obstetrics and Gynecological Research 2009; 35(1): 139-144.
- Mosyeri SE, Lee HC, Lathi RB, Westphal LM, Milki AA, Garber AM. Laparoscopy in women with unexplained infertility: a cost efficiency analysis. Fertility and Sterility 2006; 92(2): 471-480







# Does assessment of sperm-mucus interaction (postcoital test) influence the chances of conception?

Prof Dr TM D'Hooghe, MD, PhD¹ Prof Dr D. De Neubourg, MD, PhD²

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Yale University (USA)<sup>1</sup>
Institute Primate Research (WHO CC), Nairobi, Kenya<sup>1</sup>
"ESHRE Pre-congress Course PCC14:

MEFS exchange course: the ABCs of infertility management revisited." June 14<sup>th</sup>, 2015, Lisbon, Portugal

#### Disclosure:

- Fundamental Clinical Investigator for endometriosis, Belgian Research Foundation (1998-2009), Leuven University Hospital Clinical Research Fund (2010-2015)
- Co-Chair WHO Infertility Guidelines Development Group Steering Committee
- Board Member European Endometriosis Liga (EEL)
- Council Member Society Gynecol Investigation (SGI)
- Research Associate and Chair International Advisory Board, Institute of Primate Research, Kenya (WHO-CC)
- Grants from Merck Serono, Ferring, MSD, Besins, WERF
- Consultancy/KOL for Merck Serono, Ferring, MSD, Bayer, Abbott, Abbvie, Preglem, Gedeon Richter, Pharmaplex, Uteron Pharma, Roche, Proteomika

## Learning objectives

- What is the postcoital test?
- What is the added value of the postcoital test?

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# Learning objectives

- What is the postcoital test?
- What is the added value of the postcoital test?

#### POSTCOITAL TEST (PCT)

#### 1. MUCUS SCORE:

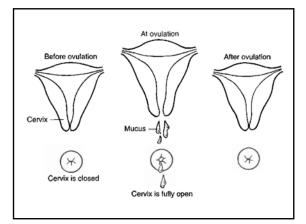
#### Timing:

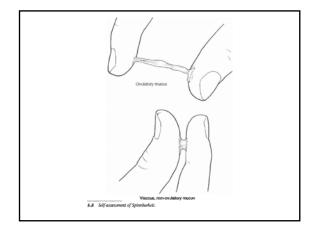
very close to ovulation,

(cycle length, BTC, US dominant ovarian follicle)

#### Mucus aspiration:

- -nonlubricated speculum, tuberculin syringe
- -aspirate mucus 1 cm into endocervical canal
- -put sample on slide
- -assess phase contrast microscope
- -scoring: volume, stretching/spinnbarkeit (10 cm), color, absence of WBCs, Ferning pattern





#### POSTCOITAL TEST

#### Timing:

- close to ovulation (see mucus)
- abstinence of 2 -3 days
- coitus within 8-12 hours prior to PCT (Speroff: 2-8 hours; WHO: 9 to 24 hours)

## Collection (see mucus): - nonlubricated speculum

- aspirate 2 samples
  - from fluid pool in posterior vaginal fornix: microscopic sperms?
  - from endocervical canal (use different tube): endocervical fluid: -
- put 0.1 mL on 1 slide, cover with cover-slip and assess put remaining fluid on 2nd slide and let dry (assess Ferning)

#### POSTCOITAL TEST (PCT) ASSESSMENT

- 1. Report number of spermatozoa/HPF
- 2. Report motility (Rapidly, slowly progressive, non-progressive, immotile)

POSITIVE = 1 or more than 1 fast progressively motile sperm cell/HPF in more than half or in at least 5 HPFs

Unsatisfactory: 1 or more with slow or irregular motility

NEGATIVE: 1 or more nonprogressive or immotile sperm cell

NEGATIVE TEST IS ONLY VALID IF

- A COITUS WITH EJACULATION TOOK PLACE (sperm cells in posterior
- MUCUS SCORE IS MORE THAN OR EQUAL TO 10 (repeat in same cycle if required)
- NEGATIVE RESULTS ARE FOUND IN 2 SEPARATE CYCLES

5	2	

## Learning objectives

- What is the postcoital test?
- What is the added value of the postcoital test?

#### Literature search

- PubMed 16 March 2016
- Key words: "postcoital test", "cervical factor infertility"
- · Reviews and clinical trials
- 14 papers: presented in 3 parts
- Published before Cochrane 2005 SR
- Cochrane 2005 SR
- Original research after Cochrane 2005 SR

#### Papers before Cochrane 2005

Check et al, 1995 RCT

- Couples Unexpl Infert with nl semen analysis and abnl PCT
- Abnl PCT = no progressively forward moving sperm 8-12hrs after intercourse at time of mature follicle
- IUI natural cycle vs sexual intercourse
- Monthly fecundity rate after 1 month: higher after IUI (21%) dan after intercourse (4%)

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#### Papers before Cochrane 2005

Oei et al, HR 1995. When is the PCT normal?

A critical appraisal

- Predictive value nl PCT: 0,37-0,92 and for abnormal PCT: 0,30-0,97
- Sensitivity 0,10-0,90; Specificity 0,30-0,97
- Likelihood ratio 0,77 (nl) and 1,85 (abnl)
- Overall poor discriminating ability
- Recommendation: < 1 sperm/HPF as cut-off point for high specificity and high LHR

5/16/2015

#### Papers before Cochrane 2005

Oei et al, BJOG 1995. EU PCTs: opinion and practice

- Used in 92% of Ob Gyn Departments
- Large differences in timing of the test in relation to
  - -menstrual cycle
  - -coitus
  - -method for analysis
  - -cut-off level for normality
  - -type of treatment offered for abnl test

Conclusion: Added value of PCT unclear

5/16/2015

#### Papers before Cochrane 2005

Oei et al, BJOG 1995. EU PCTs: opinion and practice

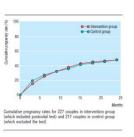
- Used in 92% of Ob Gyn Departments
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  - -menstrual cycle
  - -coitus
  - -method for analysis
  - -cut-off level for normality
  - -type of treatment offered for abnl test Conclusion:

Conclusion: Added value of PCT unclear, even though no negative effect on sexual relationship (Oei et al, 1996 and 1998)

5/16/2015

#### Papers before Cochrane 2005 Oei et al, BMJ 1998

- RCT to investigate impact of PCT on PR among subfertile couples
- 736 consecutive new couples
- PCT standardized 6-18 hrs after intercourse, 14-16 days before menses, negative test (< 1 fwd moving sperm/HPF) only valid if good Q mucus, positive test always valid
- No difference in Cum PR, but more treatment offered in intervention group (54%) than in control group (41%).
   Overtreatment???



5/16/2015

#### Cochrane 2010 (Helmerhorst et al)

- IUI vs Timed intercourse or expectant Mx for cervical hostility in subfertile couples
- Literature updated till Aug 2008
- 6 studies of variable quality → pooling of results in SR not possible
- 5 studies with important flaws regarding method of randomization, failure to conceal upcoming assignment, losses after randomization
- One study (Steures et al, 2007): good Q according to CONSORT guidelines for RCTs
- Overall conclusion: no evidence that IUI is an effective treatment for cervical factor infertility

LI 0 5/16/201

# Expectant management: indications

- Only patients without ovulation disorder, tubal pathology, azoospermia (Hunault et al, 2004) or severe sperm problem (< 3 million TMC, van der Steeg et al, 2007).
- These patients and their doctors may overestimate ART success and underestimate ART risks.
- Based on calibrated and validated Hunault score with good prognostic performance (Hunault et al, 2004; van der Steeg et al, 2007)

5/16/2015

#### **Definitions Hunault score**

- Duration of subfertility: time interval from discontinuation of contraceptive activities until registration at the fertility centre (Hunault et al, 2004).
- Primary and secondary subfertility: subfertility without and with a previous clinical pregnancy (Zegers-Hochschild et al, 2009) in a current or previous relationship (Van der steeg et al, 2007)
- Progressive motility: percentage motile spermatozoa of the first semen analysis (Van der Steeg et al, 2007)

5/16/2015

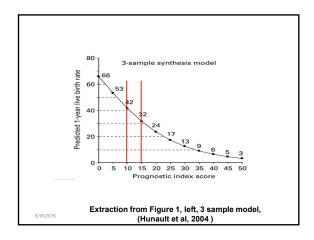
#### **Definitions Hunault score**

- Referral status:
- Referral by general practitioner: **secondary-care** (Hunault et al, 2004)
- Referral by gynaecologist/other medical specialist: **tertiary-care** (Hunault et al, 2004)
- **Self-referral**: secondary-care, but tertiary care if couple has already been investigated or treated by another gynecologist or another medical specialist (andrologists, urologist, geneticist, ...) , even if couple was not specifically referred by this other gynecologist/medical specialist

5/16/2015

SCORING TABLE (adapted from Hunault et al, 2004– 3 sample model)

Woman's age	21-25	26-31	32-35	36-37	38-39	40-41	Score	
	0	3	7	10	13	15		
Duration (Yrs)	1	2	3-4	5-6	7-8			
of Subfertility	0	3	7	12	18			
Type of		Seco	ndary		Prim	ary		
subfertility		0			8			
Sperm	≥60	40-59	20-39	0-19				
Progressive	0	2	4	6			1	
Motility (%)		_		"				
(A+B)								
Referral status	Secondary-care couple			Tertiary-care couple				
	0			4				
	Prognostic index score (sum)							



# Expectant management Belgian consensus

Depends on predicted chances of spontaneous conception within 1 year:

- if > or = 40% (Hunault score 10 or less): Expt Mx for 1 yr, then treatment
- if 30-40% (Hunault score 10-15): choice between Exp Mx and medical/surgical treatment to be discussed with patient (probability, patient preference, and effectiveness/safety of treatment).
- if < 30%: (Hunault score > 15): active medical/surgical treatment recommended.

5/16/201

#### Steures et al, 2007a

- RCT 99 couples with isolated cervical factor infertility and good pregnancy prognosis >30% in next 12/12 (Hunault score)
- IUI natural cycle versus expect Mx for 6/12
- After 6/12: N ongoing pregnancies:
   22 (43%) in IUI group and
   13 (27%) in Expt Mx group

(RR 1.6 (95% CI 0.91-2.8): not significant but interesting trend

5/16/2015

PRECONGRESS COURSE 14	1	LISBON.	PORTUGAL -	14	JUNE	2015

#### Steures et al 2007b

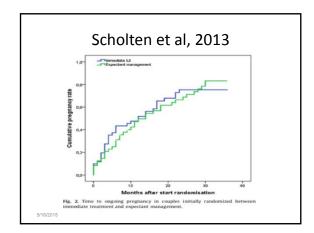
- Added value of ovarian stimulation with IUI in couples with abnormal PCT and poor prognosis (<=30% spt pregnancy in next 12/12)
- IUI (n=132 with COH/n=133 without COH)
- Pregnancy rate after IUI:
   25% with COH (2/26 twins) and
   21% without COH (1/22 twins)

5/16/2015

#### Scholten et al, 2013

- Long term outcome in subfertile couples with isolated cervical factor
- FU for 3 years after conclusion of RCT with 99 participants who had isolated cervical infertility (Steures et al, 2007)
- Local treatment up to 3 years
- Similar cumulative pregnancy rates in both groups

5/16/2015



-	

#### Overall conclusion

- PCT: not standardized, huge variability
- Diagnostic relevance unclear
- Prognostic relevance poor
- Value of treatment with IUI not proven
- Not recommended in clinical practice
- Potentially interesting in a research context (repeat RCT Steures et al, 2007)

#### The value of endometrial biopsy as a diagnostic tool in modern fertility management

Johnny Awwad, MD Professor of Obstetrics and Gynecology American University of Beirut Medical Center

#### No Conflict of Interest

## Objectives

- Evaluate the clinical benefits of routine endometrial biopsy to enhance the reproductive outcome of couples with sub/infertility
  - Diagnostic value luteal phase defect, endometrial pathology
     Prognostic value with and without intervention

#### Background

- The use of endometrial biopsy to assess luteal phase defects has been an essentially component of the routine infertility work-up of women.
- The practice has been largely introduced with little evidence as to its diagnostic and prognostic value.
- · It has been partially abandoned in current fertility practice,
  - Because of the indiscriminate use of luteal supplementation, reducing the need to address its invasive nature and associated costs.
  - Because of the lack of consensus in diagnosing luteal phase defect
  - Because it fails to predict infertility

Incidence of detecting luteal phase defect

- Coutifaris et al
- RCT / mid and late luteal biopsies in fertile and infertile women; n=619
- Luteal phase defect in midluteal phase:
  - Fertile vs infertile couples: 49.4% vs 43.2%; P = NS
- Luteal phase defects in late phase:
  - Fertile vs infertile couples: 35.3% vs 23.0%; P<0.05</li>

Given the high prevalence of luteal phase defect in fertile couples, it calls into question the diagnosis of luteal phase defect as a cause of infertility

or late luteal phase.

Variables	Women of fertile couples (n = 332)	Women of infertile couples (n = 287)	Odds ratio point estimate	Odds ratio estimates 95% Wald CL	P value
OOP>2	42.2%	32.7%	0.68	0.49-0.95	.0248
OOP>3	33.2%	20.9%	0.54	0.37-0.78	.0011°
OOP>4	19.9%	11.2%	0.49	0.31-0.78	.0027*

COOP > Q OOP > 3, and OOP > 4 denotes more than 3, and more than 4 days difference between the postovulatory day and the histological dat using the Noves criteria. To adjust for preplanned multiple comparisons, fertility group differences were considered significant if P = 0.125.

Coutifaris et a

Out of phase biopsy results diagnosing luteal phase defect poorly discriminates between women from fertile and infertile couples in either the midluteal or late luteal phase

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# Incidence of detecting luteal phase defect • Balasch et al Retrospective No significant difference in the incidence of luteal phase defect between infertile and fertile couples (30.6% vs 17.8%, P Incidence of detecting endometrial pathology • Tuberculous endometritis: 1.8 – 3.3% (Sahmay et al, Zawar et al, Coutifaris et al, Nisa et al) • Chronic endometritis and endometrial polyps: 0.23-12% (Sahmay et al, Nisa et al) • Endometrial hyperplasia (typical and atypical) and carcinoma: 0.06 – 4.68% (Sahmay et al, Zawar et al, Kurabayashi et al, • Early pregnancy tissue found inadvertently: 0.21% (Sahmay et Value of improving pregnancy outcome • NICE 2004 Systematic review • No significant benefit of treatment of luteal phase defect was • The relative risk of pregnancy in infertile couples who received treatment with progesterone versus no treatment was RR=1.9 (CI 0.4 to 8.1)

#### Value of improving pregnancy outcome

- Balasch et al. Case control cohort
- No significant difference of the absence or presence of luteal phase defect on: Term delivery and Spontaneous miscarriage

Table IV. Pregnancy outcome according to endometrial histology in the cycle

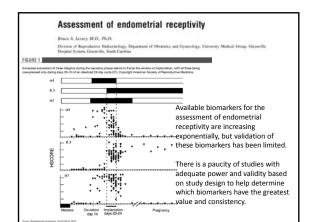
Pregnancy	Endometrial histology		
outcome	In phase <sup>b</sup>	Out of phase	
Term	15 (79%)	4 (21%)	
Spontaneous			
abortion	5 (72%)	2 (28%)	

#### Value of improving pregnancy outcome

- Balasch et al. Case control cohort
- No significant difference in reproductive outcome between treatment and no treatment for luteal phase defect on: Term delivery and Spontaneous miscarriage

Table V. Pregnancy outcome in patients treated for luteal phase deficiency (LPD) and untreated patients\*

Treatment for LPD	Pregnancy outcome	
	Term	Spontaneous abortion
Yesh	14 (78%)	4 (22%)
Noc	27 (77%)	8 (23%)



 $<sup>^{</sup>a}\chi^{2}=0.16;$  P=NS.  $^{b}$ One hydatidiform mole excluded (endometrial histology: in phase).

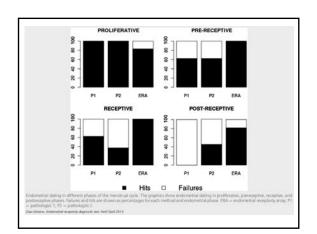
 $a_{\chi}^2 = 0.003$ ; P = NS. bOne hydatidiform mole excluded. Cone ectopic pregnancy excluded

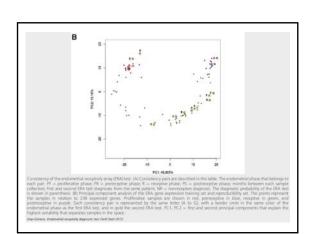
# The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity

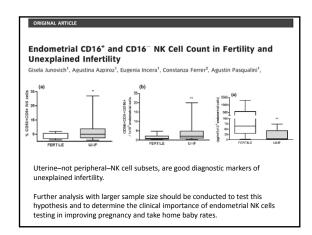
Training stage: predictor training parameters after the cross-validation testing of each machine-learning prediction.

Algorithm	Correct	Uncorrect	Specificity	Sensibility
SVM KNN RF	73 (92.4%) 69 (87.3%) 68 (86%)	6 (7.6%) 10 (12.7%) 11 (14%)	0.83 0.90 0.84	1.00 0.86 0.89

Note: KNN = K-nearest neighbor; RF = random forest; SVM = support vector machine Diaz-Gimeno. Endometrial receptivity diagnostic test. Fertil Steril 2013.







# Conclusions Value of routine endometrial biopsy in diagnosing Unfavorable luteal phase defects Value of routine endometrial biopsy in detecting suspicious endometrial pathology Value of routine endometrial biopsy in predicting Unfavorable Moderate pregnancy outcome

#### Recommendations

- The use of endometrial biopsy to detect luteal phase defects during the routine work-up of women presenting with sub/infertility, should be abandoned because of the lack of supportive evidence for an improvement if reproductive outcome with/without intervention
- The use of endometrial biopsy to detect endometrial pathology during the routine work-up of women presenting with sub/infertility, is associated with a low yield, and should be reserved to women at risk

#### References

- Coutifaris, C., et al., Histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertility and sterility, 2004. 82(5): p. 1264-72.
- acjoj: p. 1204-72. Kurabayashi, T., et al., Endometrial abnormalities in infertile women. Journal of Reproductive Medicine, 2003. 48(6): p. 455-9. Nisa, Z., The value of endometrial biopsy in infertility. JPMA. The Journal of the Pakistan Medical Association, 1983. 33(12): p. 304-305.
- Zawar, M.P., et al., Histopathological study of endometrium in infertility. Indian Journal of Pathology & Microbiology, 2003. 46(4): p. 630-3.
- Balasch, J., et al., The usefulness of endometrial biopsy for luteal phase evaluation in infertility. Human Reproduction, 1992. **7**(7): p. 973-7.

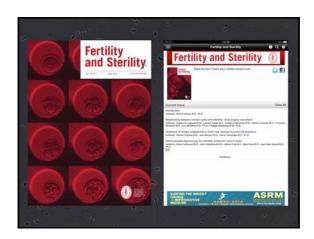
#### References

- Bruce A. Lessey. Assessment of endometrial receptivity. Fertil Steril 2011;96:522-9.
- Patricia Díaz-Gimeno et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril 2013;99:508–17.
- Gisela Junovich et al. Endometrial CD16+ and CD16 NK Cell Count in Fertility and Unexplained Infertility. American Journal of Reproductive Immunology 72013: 0 (2013) 182-189.

# The value of basic semen analysis in altering early fertility management The ABC of infertility management revisited June 14, 2015

	Disclosu	ires
		•
ASRM	Journal Editor	Medical Communications
AUA	Journal Section Editor	Medical Communications
Ferring	Investigator	Scientific Study
IBSA	Investigator	Scientific Study
NexHand	Co-Founder	Medical Device Company
No relations	rip presents a conflict of in	terest with the material in

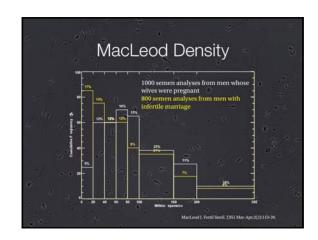
## Learning Objectives At the conclusion of this presentation, the participant will be able to: 1. Summarize the limitations of the predictive value of bulk semen analysis parameters 2. Describe the natural variability of bulk semen parameters ${\bf 3.} \ Explain \ how the \ limit at ions \ and \ variability \ of$ semen parameters affect scientific studies

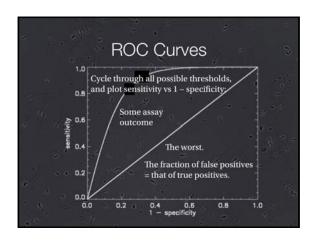


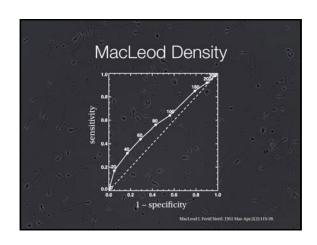


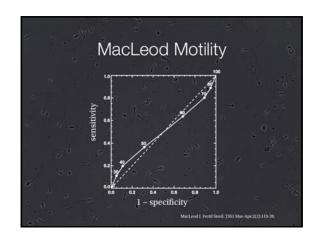


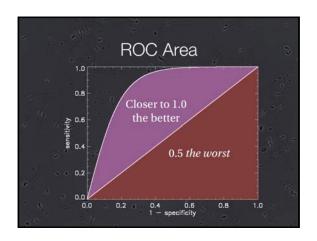




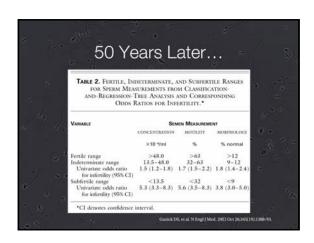






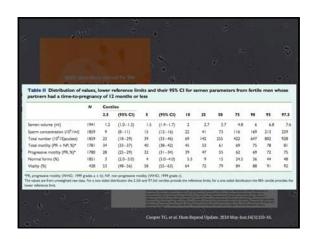


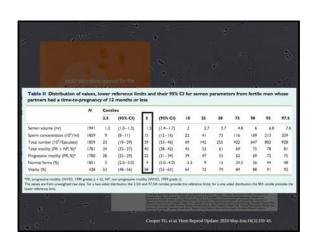




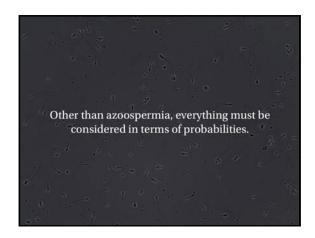


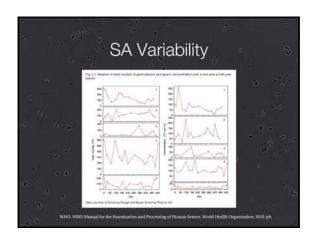




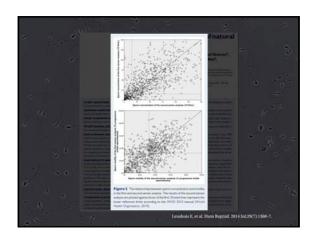




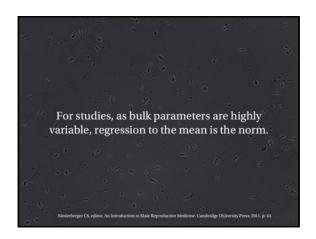




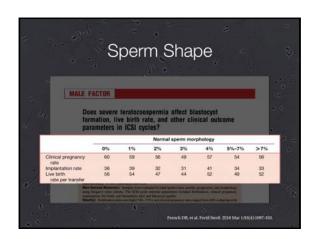








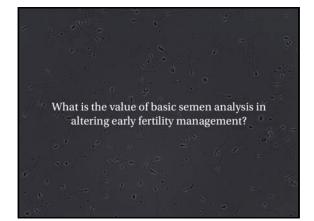




Sperm morphology: classification drift over time and clinical implications
Dean E. Morbeck, Ph.D., <sup>ch</sup> Phoebe H. Leonard, M.D., *Amy L. Weaver, M.S., *Katherine M. Shimek, M.D., d Esther V. A. Bouwsma, M.D., *and Charles C. Coddington, M.D.*
* Department of Obstetics and Gynecology, * Department of Laboratory Medicine and Pathology, * Department of Biomedical Statistics and Informatics, and * Mayo Medical School, Mayo Clinic, Rochester, Minnesota
Objective: To assess sperm morphology with Typerberg (strict) and World Health Organization (WHO) 3rd criteria for intrasterine inseminations UID between two eras to determine if there was a difference in pregnancy rates. Design: Recospective study. Design: Assessment institution. See The Company of t
Result[2, Average sperm morphology was higher in era.1 baners 2 for beth WHO 3et $\Omega T = 13\%$ to $2.5 \pm 10\%$ . Deepancy rates per cycle were $5.9\%$ versus $19.8\%$ in era.1 and $16.7\%$ versus $19.3\%$ in era.2 for couples with WHO 3et morphology $<20\%$ or $<20\%$ , respectively. Pregnancy rates per cycle were $2.7\%$ versus $15.0\%$ in era.1 and $13.3\%$ versus $14.7\%$ in era.2 for couples with strict morphology $<40\%$ or $<24\%$ , respectively.
Conclusion(s): There was a strong relationship between morphology and IUI outcome in era 1 that was not present in era 2. These results suggest that classification drift increased the percentage of men diagnosed with tentoroo- spermia and resulted in a loss of predictive value. (Fertil Steril* 2011;96:1350-4. ©2011 by American Society for Reproductive Molecine.)
Key Words: Intrauterine insemination, male infertility, semen analysis, sperm morphology, Typerberg strict

	Sperm morpholo clinical implicati		drift over time and	6
	Dent E. Markett, Ph.D. ** Phote Faller V.A. Bourema, M.D. * and		re. M.S., Kutherme M. Shimek, M.D.,*	
			s the threshold for	
WH	O 3rd criteria,	31 (25.8%) of	120 patients were	
		ology with Typerburg (selectional We	red with 85 (77.3%)	) of
110	patients in era	2. Similarly, u	vith a strict criteria	
thre	shold of % 4%	normal forms,	24 (31.6%) of 76	
pati	ents were teral	tozoospermic i	n era 1 compared	
with	175 (56.4%) of	f 133 patients in	n era 2."	
			nd IUI outcome in era 1 that was not present	
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		ikis, make interdity, server analysi		
		Morbes	ck DE, et al. Fertil Steril. 2011 Dec;96(6):1350-4.	

#### Other Current Metrics? Clinical Relevance Unknown Computer-assisted semen analysis (CASA) Nuclear morphology (MSOME) Nuclear DNA structure (Comet, TUNEL, SCSA, Raman microspectroscopy) Metabolic activity Surrogate IVF outcomes (Hamster Ova)





Anti-Sperm Antibodies (ASA): Any Role for Screening in Modern Fertility Management?

Robert W. Rebar, M.D.
Professor and Chair, Department of Obstetrics and
Gynecology

Western Michigan University Homer Stryker M.D. School of Medicine Kalamazoo, Michigan



#### **Disclosures**

- I serve on multiple Data Safety Monitoring Boards for randomized trials; write summaries for *Journal Watch*, a non-profit publication of the Massachusetts Medical Society; and am Deputy Editor of the journal <u>Contraception</u>.
- I receive no monies from any commercial source.
- Any opinions I express are mine alone and do not represent the views of any organization.

At the conclusion of this presentation, participants should be able to:

- Briefly discuss the antigenicity of the male and female reproductive tracts.
- List conditions associated with antisperm antibodies.
- Discuss current tests for antisperm antibodies and their difficulties.
- Discuss current treatment for antisperm antibodies.

#### **Can Immune Infertility Exist?**

- The antigenicity of sperm and seminal plasma components has been recognized since the turn of the 20<sup>th</sup> century.
- Experimental evidence has documented the immune responsiveness of the female genital tract at all levels.
- Antibodies against a variety of antigens common to sperm, such as blood group and HLA antigens, are present in cervical mucus and may prevent recognizing sperm as "foreign".

#### Can Immune Infertility Exist? (cont.)

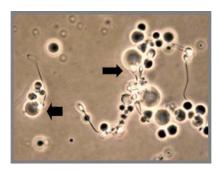
- A "blood-seminiferous tubule barrier" exists that prevents recognition of developing sperm as "foreign"; this barrier is needed because developing sperm acquire new surface antigens after puberty while immunological tolerance to self antigens arises during embryological development.
- Any breach of this barrier can lead to the development of sperm antibodies in the male.

#### Immune Infertility

- ASA have been found in both males and females.
  - Reported in up to 9-12.8% of infertile couples (Ayvaliotis et al., Fertil Steril 1985;43:393; Collins et al., Hum Reprod 1993;8:592)
  - Present as well in 1-2.5% of fertile men (Heidenreich et al., Am J Reprod Immunol 1994;31:69; Sinisi et al., Int J Androl 1993;16:311) and in 1.4% of fertile women (Clarke & Baker, Fertil Steril 1993;59:463)
- No available test identifies a specific antigen that may be associated with infertility.

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#### **Conditions Historically Associated with ASA in Males** (Adapted from Walsh & Turek, 2009) Obstruction - Vasectomy, CBAVD, idiopathic epididymal obstruction, ejaculatory duct obstruction Inflammation - Orchitis, venereal disease, prostatitis, cancer Thermal - Varicocele, cryptorchidism, hot baths Trauma Torsion, coital, testis biopsy, oral or rectal trauma Genetic - Thymic maldevelopment, HLA-B28 haplotype Some clinicians maintain that ASA should be sought when: • Semen Analysis (SA) shows sperm agglutination or clumping in the absence of infection • There is poor sperm motility and a history of testis injury or surgery · There are increased leukocytes on SA · There is unexplained infertility (There is poor penetration of mucus on postcoital testing) (Sperm "shaking" is observed on sperm-cervical mucus contact testing) **ASA Testing: Immunobead Test** The direct immunobead test (IBT) has been used most frequently and uses polyacrylamide beads coated with antibodies against human immunoglobulin to bind antibodycoated sperm. A second antibody uses smaller beads and rabbit antibodies to human Ig to bind any sperm-bead complexes and result in agglutination of sperm and beads. IBT can identify the classes of ASA (IgG, IgA) and the sites on sperm affected. IgA are believed to be more detrimental than IgGs to sperm function; IgMs are not believed to have any significant role. Generally the IBT is first done with all classes of immunoglobulins; if more than 20% show binding, then each immunoglobulin class can be tested separately. If IgA are positive, then some clinicians suggest intrauterine insemination (IUI) to bypass cervical mucus.



**Positive ASA with Immunobead Testing** 

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- The direct MAR test can use sperm from unwashed or washed ejaculates.
- Either IgG-coated latex particles or IgG-sensitized erythrocytes are placed on a microscope slide with antiserum against IgG and sperm and observed for agglutination.
- If ≥20% sperm are agglutinated, further testing, first with the better characterized IBT.

#### **Intrauterine Insemination for ASA**

- There are no controlled prospective studies of IUI for the treatment of ASA.
- The studies that have been done are largely retrospective and involve small numbers of patients.
- In these small uncontrolled studies, pregnancy rates have ranged from 5% to 25% per cycle (Margalloth et al., Fertil Steril 1988;50:441; Ulstein, Acta Obstet Gynaecol Scand 1973;52:5; Shulman et al., Fertil Steril 1978; 29:309; Confino et al., Fertil Steril 1986;46:55; Kremer et al., Int J Fertil 1978;23:270; Agarwal, Arch Androl 1992;29:207).

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Informal discussions with andrology laboratories in the **United States indicates that** almost no tests for ASA have been ordered in the last 15 years.

Immunoglobulin G antisperm antibodies do not predict spontaneous pregnancy (Leushuis et al., Fertil Steril 2009;92:1659)

- Dutch prospective cohort study involving 1794 consecutive ovulatory infertile couples, 16% of whom had a spontaneous pregnancy within one
- 3% of couples had a positive mixed agglutination reaction (MAR) for IgG ASA
- In multivariable analysis, a positive MAR (≥50%) did not predict the likelihood of spontaneous pregnancy (hazard ratio 0.99; 95% CI, 0.4-2.4)

#### **ASA Are Not Associated with Pregnancy Rates** after IVF and ICSI: A Meta-Analysis

(Zini et al., Hum Reprod 2011;26:1288)

- Included 16 studies with 4209 treatment cycles (1508 IVF; 2701 ICSI)
- The overall (IVF + ICSI) combined OR for failure to achieve a pregnancy was 1.08 (95% CI, 0.85-
- · ASA cutoff values were heterogeneous

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#### **Summary and Conclusions**

- Although it appears that some ASA cause or contribute to infertility, current diagnostic techniques fail to distinguish between antibodies that cause and those that do not cause infertility.
- None of the tests identify specific antigens: available tests are heterogeneous and more qualitative than quantitative.
- Experiments have generally been uncontrolled and poorly conducted.
- Because of the success of IVF + ICSI, there have been very few advances in the last two decades.

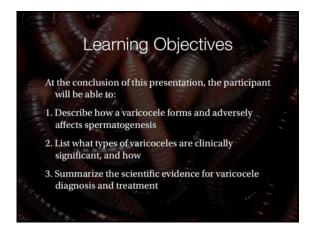
#### **Summary and Conclusions (cont.)**

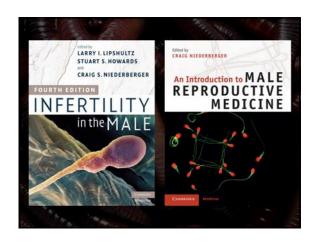
 Because it appears unlikely that immunemediated infertility is common and because of the inability to diagnose the disorder, let alone to treat it specifically, it would seem most prudent to rule out all other causes of infertility before considering immune infertility
 – and even then to treat the couple with IVF + ICSI.

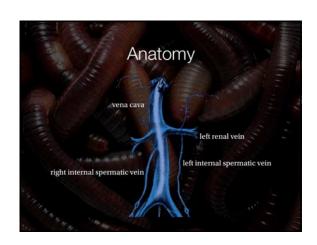
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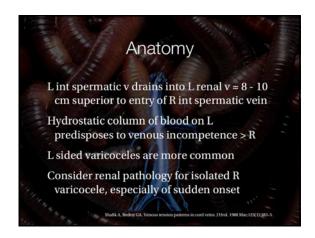


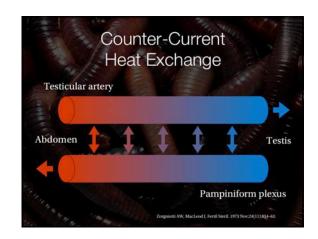


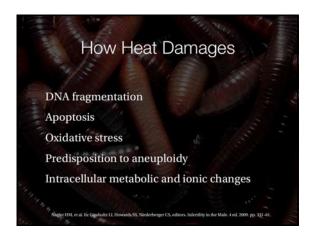






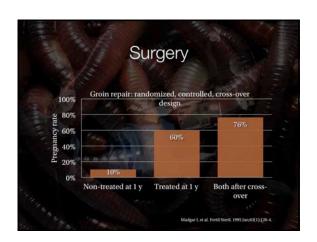


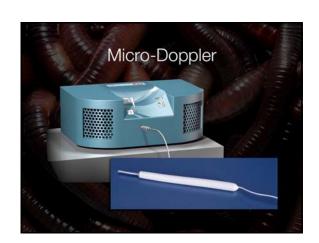
















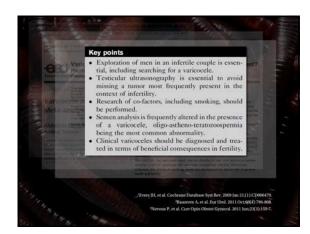




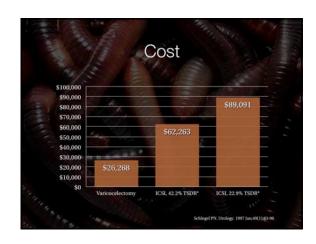


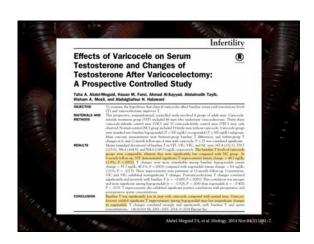
Varicocele repair is clearly associated with a significant improvement in sperm concentration as well as total and progressive sperm motility. Varicocele repair also appears to reduce seminal oxidative stress and sperm DNA damage and to improve sperm ultramorphology. However, there is insufficient evidence at present to demonstrate a beneficial effect of varicocele repair on spontaneous pregnancy rates. Although the various methods of repair are all viable options, microsurgical repair appears to be associated with better outcomes and lower complication rates. Presently, the data suggest that subclinical varicocele repair for male factor infertility is not beneficial."<sup>2</sup>

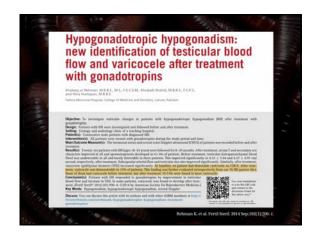


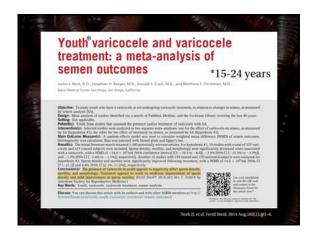


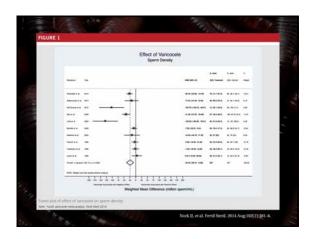


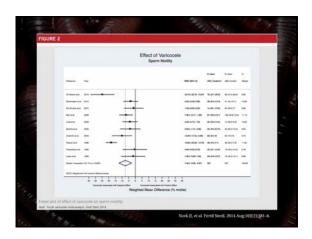


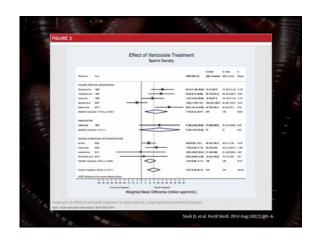


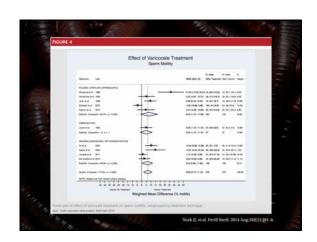


















### Oral ovulation induction agents: When to start and for how long?

Johnny Awwad, MD Professor of Obstetrics and Gynecology American University of Beirut Medical Center

Nο	Conflict	of Interest

#### Objectives

- Review the various recommendations for the use of oral ovulation induction agents in the context of infertility
- Review of algorithms for dose adjustments
- Evaluate the benefits of prediction models in clinical practice
- Evaluate cancer risks from prolonged use of some oral induction agents

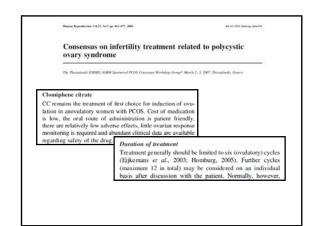
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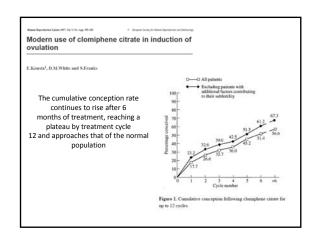
- Normogonadotropic anovulation
- Clomiphene citrate (CC) is first-line treatment, antiestrogen MRL-41, (Greenblatt et al., 1961)
- NICE guidelines: CC should be used for up to twelve months. But, lacking evidence for this recommendation
- Gonadotropins? More expensive, higher risk of multiple pregnancies

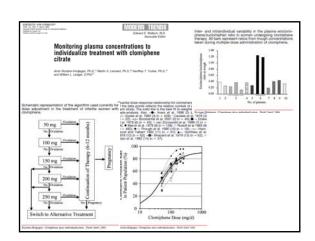
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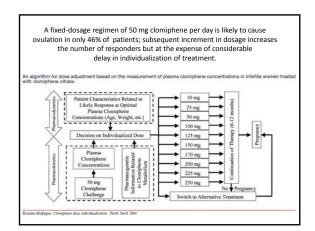
- CC is safe and convenient with limited chances for complications
- Multiple pregnancy
- Ovarian hyperstimulation syndrome
- About 60% to 85% of PCOS women starting ovulation induction with CC ovulate
- Life-table analysis indicates a conception rate of up to 22% per cycle in those ovulating on CC (Hammond 1983; Kousta 1997; Eijkemans 2003)
- The cumulative live birth rate within 12 months has been estimated to be 42%

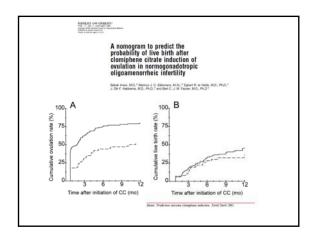
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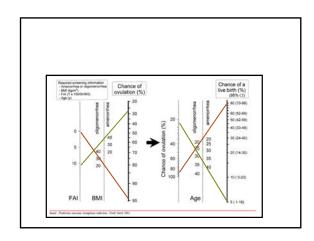


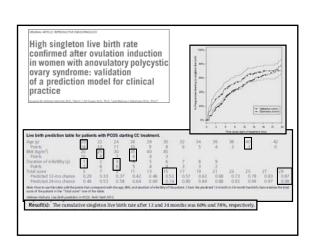


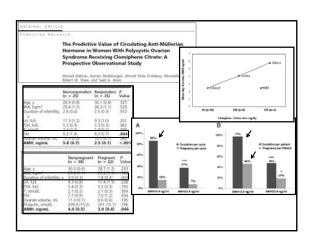
- After receiving CC, 98 (38%) women conceived, leading to live birth. The Arter receiving CC, 98 (35%) women conceived, leading to live birth. The cumulative live birth rate within 12 months was 42% for the total study population and 55% for the ovulatory women who had received CC. Factors predicting the chances for live birth included free androgen index (testosterone/sex hormone—binding globulin ratio), body mass index, cycle
- history (oligomenorrhea versus amenorrhea), and the woman's age.

Odds ratios IOR of initial screening characteristics in relation to the occurrence of outsition in the entire group of normogonalistropic oliginamenomies: infertile scores p. s = 184 of 259 or two birth in outsitroy women after CC (n = 96 of 194).

Sorming characteristics	Ovalation following CC	Live both in ovolstary women following CC
Clearal	Maria No.	ranomitiku *
Age (per ys)*	1.05 (0.98-1.12)	0.90 (0.83-0.94)
Primary vs. secondary infertilety <sup>2</sup>	1.23 (0.04-2.34)	6.71 (0.44-1.15)
Oligomenedas ys. appropries****	434 (2.34-8.85)	0.77 (0.47-1.26)
Biredag asterral to case of elegenessordes be		
3-4 weeks	#30 (3.29-20.9D)	0.65-(0.36-1.16)
6-9 weeks	3.64 (1.75-3.39)	0.87 (0.50-1.51)
9-26 works	2.90 (3.25-6.73)	0.83 (0.42-1.63)
BMC Garw'Y	0.92 (0.58-0.96)	100(0.97-1.04)
Wast to-Jup ratio (WHR per 0.1) <sup>b</sup>	0.60 (9.40-0.89)	1.00 (0.83-1.42)
Eudocrine		
DE GULP	0.97 (0.91-1.00)	1.04 (1.00-1.09)
TATE	0.83 (0.78-0.89)	1.06 (1.01-1.11)
Programbiogramus (elevated T and/or AD)*	0.54-(0.20-0.87)	1.67(1.19-2.50)
InvolutionCLP	6.95 (0.92-0.98)	0.99 (0.97-1.02)
Sandar photos saturi	6.87 (0.77-0.97)	E 99 (0.90-LOE)
Indultes B (egr.L.P	1.00 (0.99-1.01)	1.00(0.99-1.01)
Free IGE-1 (sarred.)*	0.91 (0.77-4.99)	1.10 (0.96-1.29)
Lenta (ne/nf.)	0.97 (0.95-0.96)	1.02 (1.00-1.01)
Descript		
PCO terror son PCOFF	0.39 (0.29-1.27)	0.98 (0.45-1.54)
Spens parameters		
Total number sperm count 10° 5	_	1.00 (0.81-1.25)







Nahuis et al. BMC Women's Health 2013, 13:42 http://www.biomedcentral.com/1472-6874/13/42 STUDY PROTOCOL



The M-OVIN study: does switching treatment to FSH and / or IUI lead to higher pregnancy rates in a subset of women with world health organization type II anovulation not conceiving after six ovulatory cycles with clomiphene citrate – a randomised controlled trial

Marleen J Nishus<sup>2</sup>, Nierike S Weiss, Fu'co van der Veen, Ben Willem J Mol, Peter G Hompes, Jur Oosterhuis Nils B Lambalk, Jesper MJ S'menerk, Carolien AM Kols, Ron JT van Golde, Joop SE Laven, Ben J Cohlen, Kathrin Fleischer, Angelique J Goverde, Marke H Gerards, Nicole F Kiljn, Lilska CM Nekrul, Ilte AJ van Rooj, Diederik A Hoozemans and Madelon van Wely

- A multicentre RCT in the Netherlands
- Women with WHO type II anovulation
- Low risk of damaged Fallopian tubes
- Randomization after six ovulatory cycles with CC
- Outcome: live birth



mer JAM, Nelen WLDM, Farq	shar C								
	subf	Letrozole appears to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to clomiphene citrate. [The quality of this evidence is low]							
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Line	Sirth care	100 per 1000	270 per 1008 (314 to 321)	00 till (1,00 till)	CD Parks	MCCC W			
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trozole versus cl ertility: A syster							
ni Liu <sup>1</sup> , Chao Zheng <sup>2</sup> , Ju	nzhe Lang	and V	Venbing Chen				
ozolo is as offe	ctive :		minhon	. in		with unexplained	Linfortility
ozole is as elle	ctive	15 CIC	imphen	e III w	omen	with unexplained	i iiilertiiity.
	letroze	de.	clomiphene	eltesta		Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events		Weight	M-H. Random, 95% CI	M-H. Random, 95% GI
Badawy 2009a	76	205	74	207	25.4%	1.04 [0.80, 1.34]	+
Badawy 2009b	36	269	77	420		0.73 (0.51, 1.05)	-
Fouda 2011	40	106	24	105		1.65 [1.08, 2.53]	-
Fozan 2004	13	74	11	80	12.9%	1.28 (0.61, 2.67)	-
Brahim 2012	30	130	14	131	16.3%	2.16 [1.20, 3.88]	-
Sammour 2001	4	25	1	24	2.6%	3.84 [0.46, 31.94]	
Total (95% CI)		809		967	100.0%	1,26 (0.89, 1.80)	•
Total events	199		201				
Heterogeneity: Tau* =	0.11; Ch <sup>2</sup>	= 15.0	3. df = 5 (P = 0	0.01): P =	67%	E	1 0.1 1 10 100
Test for overall effect:	Z = 1.29 (	P = 0.2	5)			0.0	01 0.1 1 10 100 iphene citrate letrozole
Figure 2 Clinical pr interval: M-H, Ma			r letrozole v	ersus ele	miphene	in women with unexpla	ined infertility: CI, confidence

	Efficacy of infertility	treatment for	unexplained	
Aggregate data	David S. Guzick, M.I. Marcelle I. Cedars, A Michael P. Steinkam for each treatment.	LD. SRichard J. Falk, M.D. I pf, M.D.**	I, M.D., <sup>†</sup> G. David Adamson, M.D., <sup>‡</sup> Edwin P. Peterson, M.D., <sup>‡</sup> and	
Treatment		No. of studies	No. (%) of pregnancies per mitated cycle	Percent of quality-adjusted pregnancies per initiated cyc
Control groups		- 11	64/3.539 (1.8)	13
Control groups, ran	idomized studies	6	23/597 (3.8)	4.1
CC		1	17/617 (6)	5.6
		5	21/315 (6.7)	8.3
		13	139/1,806 (7.7)	7.7
		14		
CC + RUI MMG MMG + RUI RVF GEFT		13		

Syst Biol Reprod Med. 2014 Apr;60(2):105-11.
Endometrial receptivity markers in infertile women stimulated with letrozole compared with clomiphene citrate and natural cycles.
Ganesh A, Chauhan N, Das S, Chakravarty B, Chaudhury K.

A total of 36 women were included in the study out of which 16 women were diagnosed with primary unexplained infertility and the other 20 women with severe oligoasthenozoospermic/azoospermic male partners. Endometrial samples were collected on the seventh day post-ovulation and analyzed. In women with unexplained infertility treated with letrozole and CC, epithelial and stromal expression of  $\alpha\nu\beta$ 3 integrin, L-selectin, leukemia inhibitory factor (LIF), and pinopod formation was found to be significantly higher as compared to controls. Stimulation with letrozole and CC appears to enhance endometrial receptivity in women with unexplained infertility. However, letrozole and CC did not have any significant effect on the endometrial receptivity markers of women with severe male factor infertility

Edward Hughes, Julie Brown, John J Collins, Patrick Vanderkerchove. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev. 2010 Jan 20;(1).

- Fourteen potentially relevant trials were identified of which seven were included in this review.
- There was no evidence that clomiphene citrate was more effective than no treatment or placebo for live birth (odds ratio (OR) 0.79, 95% CI 0.45 to 1.38; P = 0.41) or for clinical pregnancy per woman randomised both with intrauterine insemination (IUI) (OR 2.40, 95% CI 0.70 to 8.19; P = 0.16), without IUI (OR 1.03, 95% CI 0.64 to 1.66; P = 0.91) and without IUI but using human chorionic gonadotropin (hCG) (OR 1.66, 95% CI 0.56 to 4.80; P = 0.35).

#### Treatment of Unexplained Infertility With Aromatase Inhibitors or Clomiphene Citrate

A Systematic Review and Meta-Analysis

Nikolom P. Polyma, MD, Spyridon Tainen, MD, PhD, 1

Devide Marth, MD, Martin Toupin, MD, Hyan Cortinoris, PhD, 9

Lamprist Toll, MD, and Girvannic Canazze, PhD.

. ....

Pregnancy rates with aromatase inhibitors or clomiphene in women with unexplained infertility are comparable

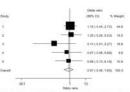
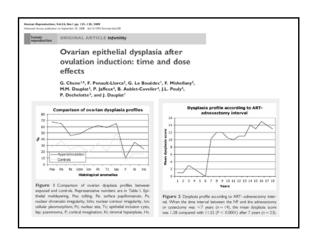
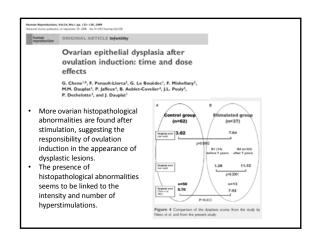


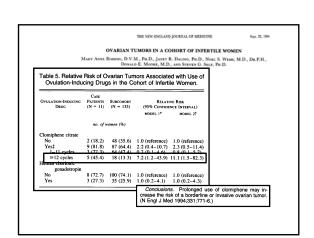
Fig. 2. Meta-analysis of the pregnancy rate with accordate infection versus compleme in women with unexplained infertity. Each study (1) Al Foson et al. 2) Bureaso et al. 3) Sipe et al. 4. Each study (1) Al Foson et al. 2) Bureaso et al. 3) Sipe et al. 4. Each study (1) Al Foson et al. 2) Bureaso et al. 3) Sipe et al. 4. Each study (1) Al Each study (

#### Ovulation and cancer risk

- Epithelial ovarian cancer is the most fatal gynecological malignancy. Its severity is essentially the result of delayed diagnosis at advanced stage in two-thirds of cases, which implies a poor prognosis with a survival rate lower than 20%.
- Cited risk factors for ovarian cancer include the hypothesis of incessant ovulation (Fathalla, 1971) with potential implications for ovarian stimulation
- Such role of ovarian stimulation has been suggested (Harris et al., 1992; Whittemore et al., 1992), but not confirmed.







# Induction of ovulation and ovarian cancer: a critical review of the literature Ali Mahdavi, M.D., a Tanja Pejovic, M.D., and Farr Nezhat, M.D. 408 (7.1) informa ART Fertility drug use and risk of ovarian tumors: a debated clinical challenge

Author	Study	Patients	Risk of overtan tumor			
Franceschi et al. [15]	Case-control study (1992-1993)	195 EOC cases vs. 1335-controler	1355-controle*		18 (0.2-3.7)	
Mosgaard	Case-control study	484 overlan tumoro:	OR (95%-CD) of overtain terrior			
et al. [19]	(1989-1994)	Epithelial = 595 Stromal = 24 Gorm cell = 23	Treated infertile ultip untreated infertile to	Dipurous	0.8 (0.4-2.0)	
		Unspecified = 5 Unclassifiable = 141721 controls	Treated infertile pure untreated infertile pu	28 YS. 1048	0.6-(0.2-1.3)	
Mosquard et al.	Case-control study	231 BOT cases	OR (95%-CD of BOT			
[20] (1990)	(1989-1994)		Treated infertile multiparous vs. untreated infertile no	liperous .	1.5 (0.51-4.50)	
		1721 controls	Treated infertile puro untreated infertile par	28 YS. 1088	1.46 (0.56-3.81)	
Modan	Cohort study	2496 infertile women?	SER (95% CE) of DOC			
et al. [21]	C1946-1974D	(O cancer of any shot 2 DOC	Total treated (n = 1300)		1.7 (0.6-3.0)	
		MINISTER DECK.	Clomiphene citrate (n 900)		2.7 (0.97-5.8)	
			Untrouted (n = 1167)		1.6 (0.6-3.5)	
Venn et al. [24]	Cobort study (1981-1995)	29700 referred for TVF	Exposed to		SER (95%-CE) of overlan tumo	
	(1961-1995)	(including both EOC and BOT)	Any FD (n = 20 656		0.88 (0.42-1.84)	
			Clomiphene		2.46 (0.35-17.5)	
			Cloniphene + HMG		0.77 (0.19-3.07)	
			HMG		1.14 (0.016-8.10)	
			HMG + GnRH		0.48 (0.07-3.38)	
			Not exposed to FD (n = 9044)		1.16 (0.52-2.90)	
New et al. [6]	Eight case-control studies (1989-1990)	5207 ovarian tumor cases (including both EOC and	Pts	FD	OR (95% CI) of ovarian turn	
	semmer (Tago, Tako)	Encluding both EOC and BOT)	All	240	1.0	
		7705 controls		Ties	0.97 (0.76-1.25)	
			Never pregnant	No	1.0	
				Yes	1.60 (0.90-2.87)	
			Ever pregnant	No	0.82 (0.42-1.09)	
Resine	Case-control study	378 creation famor cases	OR (1975; CD) for creation		0.82 (0.82-1.00)	
et al. [26]	(1994-1990)	(including both EOC and BOT)		harnor		
		1637 controls	Ever used any FD			
			Nulliparous Parous		0.840.4-3.0) 0.840.4-1.60	
			Farous Ever used clomiphene		0.8 (0.4-1.6)	
			Ever used clomophone Nulliparous		12 (0.4-35)	
			Parous		0.8 (0.4-1.6)	
dos Santos	Cobort study	7.855 somer with	Parous		SIR (95% CD of TOC	
Silva et al. [35]	(1963-1990)	ordatory disorders	All (n = 7317)		0.97 (0.40, 1.40)	
- Ind		21 BOC	Proceined FD (a = 3)		1.00 (0.57-1.40)	
			Prescribed FD (n = 3) Not recorded FD (n		0.78 (0.34-1.53)	

#### References

- G. Chene, F. Penault-Llorca, G. Le Bouedec, F. Mishellany, M.M. Dauplat, P. Jaffeux, B. Aublet-Cuvelier, J.L. Pouly, P. Dechelotte, and J. Dauplat. Ovarian epithelial dysplasia after ovulation induction: time and dose effects. Human Reproduction, Vol.24, No.1 pp. 132–138, 2009.
- Ali Mahdavi, Tanja Pejovic, and Farr Nezhat. Induction of ovulation and ovarian cancer: a critical review of the literature. Fertil Steril2006; 85:819

- -26.
  Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. N Engl J Med 1994;331:771–6.
  Roy Homburg. Clomiphene citrate—end of an era? a mini-review. Human Reproduction Vol.20, No.8 pp. 2043–2051, 2005.
  Amin Rostami-Hodjegan, Martin S. Lennard, Geoffrey T. Tucker, and William L. Ledger. Monitoring plasma concentrations to individualize treatment with clomiphene citrate. Fertil Steril 2004;81:118793.

#### References

- Babak Imani, Marinus J. C. Eijkemans, Egbert R. te Velde, J. Dik F. Habbema, and Bart C. J. M. Fauser. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. Fertil Steril2002;77:91–7 E.Kousta1, D.M.White and S.Franks. Modern use of clomiphene citrate in
- induction of ovulation. Human Reproduction Update 1997, Vol. 3, No. 4 pp. 359-365
- Ganesh A, Chauhan N, Das S, Chakravarty B, Chaudhury K. Endometrial receptivity markers in infertile women stimulated with letrozole compared with clomiphene citrate and natural cycles. Syst Biol Reprod Med. 2014 Apr;60(2):105-11.

#### References

- Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev. 2010 Jan 20;(1).
- Nikolaos P. Polyzos, Spyridon Tzioras, Davide Mauri, Maria Tsappi, Ivan Cortinovis, Lamprini Tsali, and Giovanni Casazza. Treatment of Unexplained Infertility With Aromatase Inhibitors or Clomiphene Citrate A Systematic Review and Meta-Analysis. OBSTETRICAL AND GYNECOLOGICAL SURVEY Volume 63, Number 7, 2008

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## Intrauterine insemination: Is it still the bridge between ovarian stimulation and in vitro fertilization in unexplained subfertility

Richard H. Reindollar

Adjunct Professor, Departments of Obstetrics and Gynecology

Geisel School of Medicine at Dartmouth and UAB

Executive Director, ASRM

#### Disclosure statement:

Richard H. Reindollar, M.D. has no relevant financial relationships with any manufacturers of pharmaceuticals, laboratory supplies, or medical devices.

This presentation is my personal interpretation of the literature and not the opinion of American Society for Reproductive Medicine.

#### **Learning Objectives**

At the conclusion of this presentation the participant will consider the couple with unexplained infertility, the female partner ≤ 40 years, and be able to:

- 1. List the most important factors to be considered;
- 2. Describe key studies that provide evidence for and against the use of specific treatments;
- 3. Discuss whether IUI strategies are useful treatments.
- 4. Describe a treatment paradigm that is supported by the literature.


# **UI Rx: Factors for Consideration**

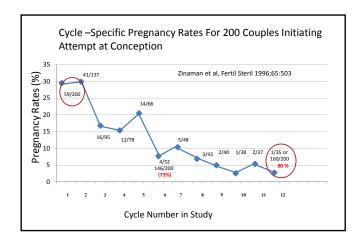
- 1. The chance for pregnancy without and with Rx (evidence for improved success with Rx)
- 2. Access to treatment (availability, cost, etc..)
- 3. Safety/ Adverse Events (e.g., multiples)
- 4. The need (and ability) for some couples to "have any treatment" and others to do "less invasive treatments."

# What is the Evidence? U. S. Preventive Services Task Force Levels of Evidence

- I: Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or meta-analysis of homogeneous RCTs
- II-1: Well-designed controlled trial without randomization
- · II-2: Well-designed cohort or case-control analytic study
- II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
- III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

# What is the Evidence?

- · Level of Evidence (Levels I, II, and III)
- RCT (Gold Standard)
  - Treatment Comparisons (Rx 1 vs. Rx 2)
  - Treatment Paradigm Comparisons (Strategy 1 vs. Strategy 2, may not address specific Rx)
- Absence of Evidence: "What is most appropriate treatment, if any?"
  - Cost, risks, gains
  - Accurate counseling



# **Unexplained Infertility Treatment Successes**

( Mean Reported)

	Before 1995*	1995	2004
No Rx	(1.5 – 4%)	NC	NC
Clomiphene/	8.3%	NC	NC
IUI			
Gonadotropin/	17.1%	NC	NC
IUI			
IVF	20.7%	24%	36.9%†

\* Guzick et al, Fertil Steril 1998 70: 207; † 2004 CDC National Summary, females ≤ 35

# Rationale for UI Treatments: "Upping the Ante"

- Expectant Management: Coitus (maximum 200 sperm) + Monofollicular ovulation (baseline aneuploidy)
- · Upping the Ante
  - IUI alone (more sperm)
  - COS alone (more euploid oocytes)

<ul><li>– IUI + COS</li><li>– IVF (more euploid embryos)</li></ul>	_		
	_		

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  - IUI + COS
  - IVF (more euploid embryos)

# Studies Often Quoted

- NCRMN RCT (Guzick 1999): ICI vs. IUI vs. FSH/ICI vs. FSH/IUI;
- Bhattacharya, RCT Scotland (2008): Clomiphene (cc) vs. IUI vs. expectant management;
- Steures, RCT Lancet (2006): COH/IUI vs. expectant management;
- FASTT Trial (Reindollar 2010): Conventional Rx vs. Fast Track to IVF.

# SART CORS Clinic Summary Report US IVF Success Rates 2012

Fresh Embryos From Non-Donor Oocytes

Number of cycles

Percentage of cycles resulting in

Percentage of cycles resulting in live births

	<35	35-37	38-40	41-42	>42
	38662	19599	18410	10167	6224
	46.7	37.8	29.7	19.8	8.6
	40.7	31.3	22.2	11.8	3.9
`					/

# Immediate IVF

- US success rates clinically higher than for other Rx options, <u>but</u>-twins and HOM remain 20 30% and 0.7 1.1%, respectively;
- Number of Level II, paucity of Level I studies comparing IVF to other Rx.
  - Most of studies showing no difference, before 2000 (IVF 15 20% / cycle success).
     Aboulghar 99, Berg 94, Custers 11, Zayed 97, Abu-Heija 95, Crosignani 91, Simon 91.
  - Cochrane Review of literature up to 2010: "Any effect of IVF relative to expectant management, CC, IUI with and without stimulation and GIFT in terms of live-birth rates for couples with unexplained subfertility remains unknown (Pandian 10)."
- FASTT computer simulation: conventional approach vs. immediate IVF, no difference cost-wise (because of IVF twin pregnancy rate at time).
- Mild stimulation IVF over 3 4 cycles = 1 US IVF cycle, but higher patient satisfaction (some parameters), lower cost, lower multiples.

IVF will be a reasonable option for routine initial treatment of Unexplained Infertility when:	
includity when.	
<ul> <li>treatment is routinely available / accessible;</li> <li>costs are affordable to "all" couples;</li> </ul>	
multiple pregnancy rates are appreciably lower	
by standard practice;	
(except, for those couples seeking less invasive initial strategies).	

Until then, the appropriate question is: "Which alternative treatment(s) meet sufficient criteria for efficacy and / or an acceptable multiple birth rate to warrant a place in a routine treatment paradigm?"	
	1
The Choices: How does IUI fare compared to the other options?	
<ul> <li>IUI alone?</li> <li>Clomiphene (cc) COS alone?</li> <li>Gonadotropin (Gn) COS alone?</li> <li>CC COS + IUI?</li> <li>Letrozole COS + IUI?</li> </ul>	
Gonadotropin COS + IUI?	
IUI Alone	
<ul> <li>2012 Cochrane review, 14 RCTs: "there is evidence that IUI with OH increases the live birth rate compared to IUI alone (Veltman-Verhulst 2012)."</li> <li>NCRMN RCT (Guzick 1999): only 18% of 234 couples pregnant over 4 cycles of IUI alone (4.5% / cycle).</li> <li>Bhattacharya, RCT Scotland (2008), 23% of couples in IUI only arm pregnant over 6 cycles (3.8% / cycle)</li> </ul>	

# The weight of the cumulative literature –no support for IUI alone as a routine Rx for UI.

Except, of course, for sexual dysfunction and neurological disorders.

# Clomiphene COS Alone

- Cochrane review of 7 trials, 5 CC with coitus (Hughes 2010). Pregnancy rates not enhanced.
- Most noted study of Bhattacharya 2008 (cc, IUI, expectant management over 6 cycles): cc alone no better than expectant management but-
  - Only 56% of 167 couple not pregnant from cc received 6 Rx cycles;
  - 4% of cycles cancelled for "hyperstimulation;"
  - 2 couples IUI, not CC

Currently, studies in the literature do not demonstrate benefit from **clomiphene COS alone---**

but, the literature begs better RCTs (particularly using US Rx protocols).

# Gonadotropin (Gn) COS Alone · No studies that have compared Gn COS to expectant management for UI, except-· 2 of 4 arms of NCRMN Trial 1. Gn with intracervical insemination (4% / cycle) 2. Intracervical insemination alone (2% / cycle) - AND, Gn Rx associated with 1 set of quads, 1 set of triplets, ≥ 20% twins + OHSS

The use of Gonadotropin COS alone in couples with UI not justified by any literature.

# Clomiphene COS + IUI

- Systematic review of literature, 8.3% / cycle compared to 4% / cycle untreated patients (Guzick 1998).
- Meta-analysis, 6 RCTs (cc/IUI vs. natural cycle/coitus), 4 5 X higher pregnancy rate for cc/IUI. "Clomiphene and IUI is an effective early treatment option (Costello 2004)."
- 2012 Cochrane Review, 14 RCTs: "there is evidence that IUI with OH increases the live birth rate compared to IUI alone (Veltman-Verhulst 2012)."
- FASTT Trial: all 503 couples cc/IUI, 1294 prospective cycles, sustained pregnancy rate 7.6% / cycle, 25% / 3 cycles (8% multiples, 1 triplet) (Reindollar, 2010).

# NIH RMN AMIGOS RCT

Daimond,MP et al, Presented 2014 ASRM Annual Meeting

### Gn/IUI vs. CC/IUI vs. Letrozole/IUI:

- Up to 4 cycles each for 300, 301, 299 couples with UI, the female partner 18 – 40 years;
- Live birth rates in 32%, 23%, 18.7%\* of cycles;
- Multiple births in 31.8%\* (24 twins, 10 triplets), 9.4% (twins), 13.4% (twins)

Live births for Letrozole lower and multiple births intermediate between Gn and CC/IUI.

CC/IUI remains first line Rx for UI

Clomiphene COS + IUI remains a reasonable first line treatment option for couples with UI.

# Letrozole COS + IUI

 Prior literature suggested that Letrozole cos / IUI had similar efficacy when compared to cc cos / IUI

# NIH RMN AMIGOS RCT

Daimond, MP et al, Presented 2014 ASRM Annual Meeting

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- Up to 4 cycles each for 300, 301, 299 couples with UI, the female partner 18 - 40 years;
- Live birth rates in 32%, 23%, 18.7%\* of cycles;
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Live births for Letrozole lower and multiple births intermediate between Gn and CC/IUI.

CC/IUI remains first line Rx for UI

# Gonadotropin COS + IUI

- Initial systematic review: 20.7% / cycle (Guzick 1998)
- · Initial studies plagued with multiples
  - Gleicher (2000): 441 pregnancies, 88(20%) twins, 22(5%) triplets, 10(2.3%) quadruplets, 5(1.1%) quintuplets, 2(0.5%) sextuplets.
  - Dickey (2001): 294 pregnancies, 41(14%) twins, 20(68%) "higher order multiples" - at least 1 quintuplet.
- NCRMN RCT, Gn/IUI 9% / cycle: twins, triplets, quadruplets (Guzick 1999).
- FASTT RCT, Gn/IUI 10% / cycle (Reindollar 2010)

## NCRMN Trial for FSH/IUI:

Only stimulation of FSH (150 IU) with IUI had a significantly improved success rate (but associated with HOM and high twin rate)

Success rates over 4 cycles:

• ICI 10% • IUI 18%

19% (1 quad, 1 triplet) • FSH/ICI FSH/IUI 33% \* (2 quads, 3 triplets)

\* 9 % /cycle

Guzick et al, NEJM 1999; 340:177.

# FASTT: Pregnancy Rates Per Treatment Cycle Initiated (Reindollar 2010)

Rx Conventional		Fast Track		All		
(N cycles)	All N (%)	Sustained N (%)	All N (%)	Sustained N (%)	All N (%)	Sustained N (%)
CC/IUI (N = 1,294)	55 (8.5)	45 (7.0)	68 (10.5)	53 (8.2)	123 (9.5)	98 (7.6)
FSH/IUI (N = 439)	50 (11.4)	43 (9.8)	-	-	50 (11.4)	43 (9.8)
IVF (N = 622)	95 (36.4)	73 (28.0)	145 (40.2)	118 (32.7)	240 (38.6)	191 <b>(30.7)</b>

# Mild Stimulation Gn COS + IUI

- Steures (2006), COS (mostly Gn) /IUI: no difference than expected management.
- Dankert (2007), CC/IUI (10%/cycle and 28% couples) vs. Gn/IUI (8.2%/cycle and 27% couples).

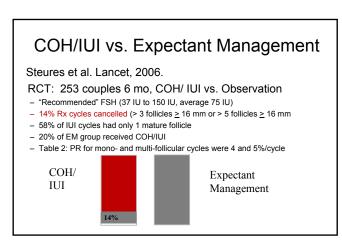
# COH/IUI vs. Expectant Management

Steures et al. Lancet, 2006 The Netherlands

RCT: 253 couples 6 mo, <u>COH/ IUI</u> vs. <u>Exp. Manag.</u>
Pregnant 42/127 (33%) 40/126 (32%)
Ongoing Preg 29/127 (23%) 34/126 (27%)

**CONCLUSION**: IN THIS STUDY, COH/IUI WAS NO DIFFERENT AS A TREATMENT THAN NO TREATMENT (Expectant Management).

# COH/IUI vs. Expectant Management Steures et al. Lancet, 2006. RCT: 253 couples 6 mo, COH/ IUI vs. Observation - "Recommended" FSH (37 IU to 150 IU, average 75 IU) 127 126 COH/ IUI Expectant Management



# COH/IUI vs. Expectant Management Steures et al. Lancet, 2006. RCT: 253 couples 6 mo, COH/ IUI vs. Observation - "Recommended" FSH (37 IU to 150 IU, average 75 IU) - 14% Rx cycles cancelled (> 3 follicles ≥ 16 mm or > 5 follicles ≥ 16 mm - 58% of IUI cycles had only 1 mature follicle - 20% of EM group received COH/IUI - Table 2: PR for mono- and multi-follicular cycles were 4 and 5%/cycle COH/ IUI Expectant Management

# COH/IUI vs. Expectant Management Steures et al. Lancet, 2006. RCT: 253 couples 6 mo, COH/ IUI vs. Observation - "Recommended" FSH (37 IU to 150 IU, average 75 IU) - 14% Rx cycles cancelled (> 3 follicles ≥ 16 mm or > 5 follicles ≥ 16 mm

Expectant

Management

- 58% of IUI cycles had only 1 mature follicle
- 20% of EM group received COH/IUI
- Table 2: PR for mono- and multi-follicular cycles were 4 and 5%/cycle

IUI 72 % 80%

### COH/IUI vs. Expectant Management Steures et al. Lancet, 2006. RCT: 253 couples 6 mo, COH/ IUI vs. Observation - "Recommended" FSH (37 IU to 150 IU, average 75 IU) 14% Rx cycles cancelled (> 3 follicles ≥ 16 mm or > 5 follicles ≥ 16 mm - 58% of IUI cycles had only 1 mature follicle - 20% of EM group received COH/IUI - Table 2: PR for mono- and multi-follicular cycles were 4 and 5%/cycle COH/ Expectant IUI Management 80%

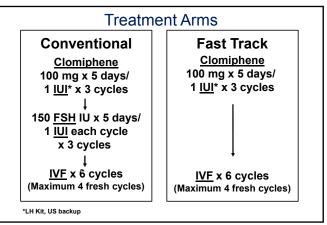


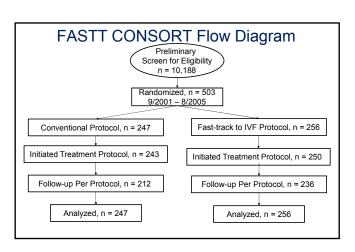
The Fast Track and Standard Treatment (FASTT) Trial NIH/NICHD R01 HD38561\*

\* Reindollar et al. Fertil Steril 2010. 94(3): 888-899.

# **Study Characteristics**

- Treatment Naive
- Met definition of unexplained infertility (FASTT, 1 year)
- Age
  - FASTT: < 40<sup>th</sup> birthday, (mean age 33 yrs);
- Normal ovarian reserve before and during trials: (FSH < 15 mIU/mI, E2 < 100 pg/mI;</li>





# Cycle Characteristics

	Conventional	Fast Track	Total
Patients Randomized	247	256	503
Patients With ≥1 Cycle	243 (98)	250 (98)	493 (98)
Total CC/IUI Cycles	646	648	1294
Total FSH/IUI Cycles	439		
Total IVF Cycles [Incl. Thaw Cycles]	261 [32]	361 [29]	622 [61]
Total Cycles	1346	1009	2355

<sup>\*</sup> NOTE **337 (25%)** FEWER CYCLES IN FAST TRACK COMPARED TO CONVENTIONAL ARM

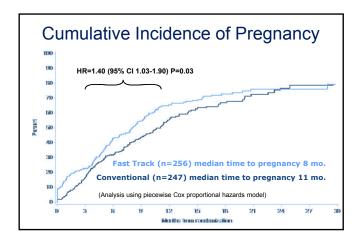
# Sustained Pregnancy Rates Per Couple

	Conventional	Fast Track	All
	N (%)	N (%)	N/ total * (%)
СС	45 (19)	53 (22)	98/475 (21)
FSH	43 (25)	-	43/169 (25)
IVF	73 (66)	118 (69)	191/283 (68)
Subtotal	161 (66)	171 (68)	332/493 (67)
CIP†	24 (10)	28 (11)	52/503 (10)
Total	185 (75)	199 (78)	384/503(76)

 $<sup>^{\</sup>star}$  Total couples undergoing treatment;  $\,^{\dagger}$  Cycle Independent Pregnancies

# Pregnancy Rates Per Treatment Cycle Initiated

Rx Conventional		Fast Track		All		
(N cycles)	All N (%)	Sustained N (%)	All N (%)	Sustained N (%)	All N (%)	Sustained N (%)
CC/IUI (N = 1,294)	55 (8.5)	45 (7.0)	68 (10.5)	53 (8.2)	123 (9.5)	98(7.6)
FSH/IUI (N = 439)	50 (11.4)	43 (9.8)	-	-	50 (11.4)	43(9.8)
IVF (N = 622)	95 (36.4)	73 (28.0)	145 (40.2)	118 (32.7)	240 (38.6)	191 (30.7)



# **Total Charges Per Delivery**

Includes outpatient, inpatient, ER, and medication charges for women, and infant inpatient charges obtained from Insurance Companies.

Arm	Couples N*	Sum Total Charges	Couples with a live birth delivery N	Charge Per Delivery
Conventional	215	\$9,424,646	132	\$71,399
Fast Track	233	\$9,606,269	156	\$61,553

<sup>\*</sup> Insurance data available for 448 (89%) of 503 couples

# Multiple Births of Sustained Pregnancies

	Conventional				Fast Track		
	CC	FSH	IVF	Total†	CC	IVF	Total†
Twins	5 (11)	7 (16)*	21 (29)	37 (20)†	3 (6)	37 (31)	42 (21) <sup>†</sup>
Triplets	0	1 (+1)*	0	1 (+1)*	1	2	3
> 3	0	0	0	0	0	0	0
Total	5 (11)	8 (19)	21 (29)	38 (21)	4 (8)	39 (33)	45 (22)

<sup>\*</sup> Includes 1 reduced from triplets; † includes cycle independent (CIP) Unknown multiple status for 5 CIP and 1 IVF ongoing pregnancies

# Conclusions

- Gonadotropin /IUI treatment does not add value to a contemporary treatment paradigm
- An accelerated approach to IVF (that eliminates FSH/IUI but starts with CC/IUI) results in an equivalent percentage of pregnancies with:
  - a 40% increased rate of pregnancy (between 3 and 11 months of treatment) that is statistically significant;
  - fewer treatment cycles; and,
  - at an estimated lower cost.
- IVF would have to cost \$17,749 for conventional treatment to have a lower cost per delivery than accelerated therapy

## NIH RMN AMIGOS RCT

Daimond,MP et al, Presented 2014 ASRM Annual Meeting

### Gn/IUI vs. CC/IUI vs. Letrozole/IUI:

- Up to 4 cycles each for 300, 301, 299 couples with UI, the female partner 18 – 40 years;
- Live birth rates in 32%, 23%, 18.7%\* of cycles;
- Multiple births in 31.8%\* (24 twins, 10 triplets), 9.4% (twins), 13.4% (twins)

Live births for Letrozole lower and multiple births intermediate between Gn and CC/IUI.

CC/IUI remains first line Rx for UI

Weight of the evidence suggests that there is no role for **Gonadotropin COS + IUI** in the routine treatment of UI.


# Treatment of UI Summary

- IVF is the most successful Rx, but costs, access, and multiple currently limit its use for initial routine Rx.
- Mild stimulation IVF is an acceptable alternative treatment with intermediate success and costs and improved patient satisfaction by some parameters.
- IUI alone, CC COS alone, or Gn COS alone do not improve outcome over no treatment.
- The literature supports CC COS + IUI but not Gn COS + IUI for an initial routine treatment.

Management of Unexplained
Infertility: numerous studies world-wide.

Observation (4%/cycle)

Clomiphene/IUI (8%/cycle)

How to fill the gap?

IVF (40%/cycle)

Management of Unexplained Infertility: numerous studies world-wide

Observation (4%/cycle)

Clomiphene/IUI (8%/cycle)

Mild stimulation IVF (+/- 20%/cycle)

IVF (40%/cycle)

# References

- Guzick et al, Fertil Steril 1988 70: 207;
  2004 CDC National Summary, females ≤ 35
  NCRMN RCT (Guzick 1999); Icl vs. IUI vs. FSH/ICI vs. FSH/IUI:
  Bhattacharya, RCT Csocliand (2008); Comiphene (cc) vs. IUI vs. expectant management;
  Steures, RCT Lancet (2006); COHIVIII vs. expectant management;
  Steures, RCT Lancet (2006); COHIVIII vs. expectant management;
  FASTT Trint (Rotrollosiz 2010); Coventional Rvs. vs. Fast Track to IVF
  Systematic review of Iterature, 8.3% / cycle compared to 4% / cycle untreated patients (Guzick 1998).
  Meta-analysis, RGT (acc) IVI vs. matural cycle/cionus, 4 5 X higher pregnancy rate for cc/IUI. 'Comiphene and IUI is an effective early treatment option (Costello 2004), 4 5 X higher pregnancy rate for cc/IUI. 'Comiphene and IUI alone (Vetiman-Verhulat 2012). 'There is evidence that IUI with OH increases the live birth rate compared to IUI alone (Vetiman-Verhulat 2012). 'There is evidence that IUI with OH increases the live birth rate compared to IUI alone (Vetiman-Verhulat 2012). 'Salo Cospellar 2010, 1924 prospective cycles, sustained pregnancy rate 7.6% / cycle, 25% / 3 cycles (8% FASTT Triat al 303 Cospellar 2010). 'Salo Cospellar 2010, Scurick et al, NEJM 1999; 340-177. 'Salures (2006), COS (mostly of) IUI: no difference than expected management.
  Dankert (2007), CO/IUI (10%/cycle and 28% couples) vs. Gn/IUI (8.2%/cycle and 27% couples). Reindolar et al. Fertil Steril 2010, 94(3): 888-899.



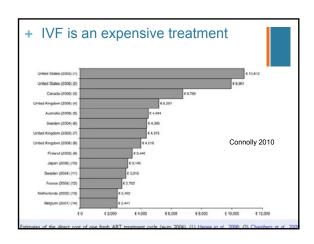
# **Declarations**

- Coordinating editor of the Cochrane Menstrual Disorders and Subfertility Group
- Co-Chair of the Female Diagnostic section of the WHO Fertility Guidelines 2014-2015
- No commercial conflicts to declare

# Learning objectives

- ■Cost effectiveness and fertility treatments why?
- How to develop the costs of an algorithm?
- ■What does a cost effective algorithm look like for female investigation?

# Costs and fertility ■The bottom line – can we afford it? ■ High stakes – how can we not afford it? ■Time is short – want it now! Who is paying? ■Third party ■ Government, insurance ■Self paying ■Co-payment Cost effectiveness and fertility treatments - why? ■ Evidence based medicine can not be isolated from cost Economic approaches are central to informing advice and decisions by guideline developers and funders Safety needs to be taken into consideration ■ To get the best from funding We must be able to express results as a form of benefit and the cost to the population Simple questions – what is the cost of one live birth from a fertility treatment



# + Cost and success rates in IVF

- Live birth rates after one initiated cycle and fresh transfer only arou the globe usually vary from 20-35% per initiated cycle
- Difficult to assess SET and DET if only use fresh transfers
- Should cost include the neonatal care
- If an IVF cycle costs \$10,000 (fresh transfer only)
- Optimistic: likelihood of a live birth is 33% per fresh transfer then the cost of one live birth is \$30,000
- Pessimistic: likelihood of live birth = 10%, then cost of live birth is \$ 100,000

# Health system payer

- There are never enough resource to meet all potential uses
- Decisions about what will be funded (and at what level) and what will not be funded need to be made
- Opportunity costs
- Once the resource is used it can never be used for anything else
  What else might that resource have been spent on
- Allocating resources to one option incurs the cost that some benefit will be lost because resources were not allocated to another opion.....
- Maximise benefits and minimise opportunity costs
- In order to do that you need data on resources (costs) and benefits (effectiveness)

# Economic evaluation is important when.... ...significant amounts of health care resources are at stake; and where trade-offs between costs and outcomes, or between different types of outcomes, are likely ■ Lowest cost and maximal effectiveness and safety also important for self funding couples Rely on advice to make decisions Matrix linking "new treatment" effectiveness with cost Decreasing effectiveness → Improved No difference effective- in effectiveness Not enough Less effectiveness evidenc Increasing costs Cost savings ? No difference # in costs Increased ? costs Not enough evidence NO ? Maybe #neutral + Challenges in developing cost effective algorithms? Variation in health systems Who is paying? Access to treatment Variable drug costs Variable protocols Safety

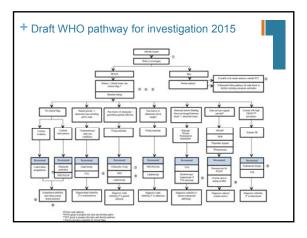
Investigating the infertile woman and man

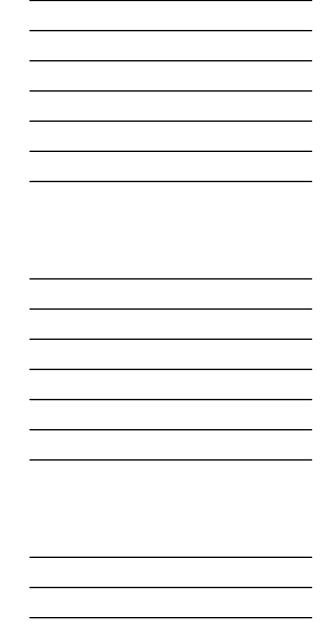


# + The work up – 4 questions?



- Serum progesterone
- or just take a history....
- ■Normal semen analysis?
  - WHO criteria
  - Role of post coital testing
- Is there a satisfactory passage for fertilisation and implantation to occur?
  - CAT or HSG or laparoscopy?
- Clinical flags for pelvic pathology ?
- Additional or alternative testing





# \* Confirming ovulation

- Mid luteal phase progesterone test or mid cycle urinary LH/estrone testing is usually recommended
   Low cost
- A clinical history of regular menstrual cycles is also sufficient

# Ovarian reserve testing

- h- m
- Evidence summary 11 studies, 4 SRs + 7 prospective studies
- SRs: low-moderate evidence that ORTs assessed had no clinically meaningful predictive value for pregnancy or live birth
- Most studies were in women with regular cycles
- Expectant management and IUI (mostly)
- There are studies reporting extremely low AMHs and pregnancies (Yarde 2013)
- Main role is in ovarian stimulation protocols

# + Tubal testing – CAT, HSG or laparoscopy?



- Two scenarios tested cost effectiveness:
- Verhoeve 2013 HSG followed by tailored treatment or diagnostic laparoscopy if HSG shows no tubal patency was also considered cost effective
- Mol 1999 Chlamydia antibody titre (CAT) if they had good fertility prospects but should have immediate HSG if poor fertility prospects (clinical flags for pathology)
- Laparoscopy is indicated if there are clinical flags for tubal disease or endometriosis.... but
- If HSG suggests severe tubal disease & no symptoms then IVF
- Treatment of endometriosis is useful step

## Post coital testing

- 5 studies (n=8709)
- SR + 4 cohort studies\*
- PCT has a poor predictive value on pregnancy rate both naturally conceived and through fertility treatment (low quality evidence)
- PCT result correlates with semen quality
- positive PCT in the presence of severe male factor infertility results in a higher chance of spontaneous ongoing pregnancy (very low quality
- Total absence of visualized motile sperm in a PCT may help to detect those couples who are infertile secondary to significant male factor infertility, or due to coital technique (very low quality evidence)

NICE SR 2004, Leushuis 2011, Hessel 2013, Hwang 1987, Rege 1978

# Post coital testing - recommendations

- The PCT should not be offered in the investigation of the infertile/subfertile couple because it doesn't predict the likelihood of pregnancy
- For couples where the woman has a normal evaluation for infertility factors and the male refuses semen analysis, the PCT can be used to suggest that further evaluation of male factor infertility and/or coital technique is indicated.

# Keeping costs down in investigation pathway

- Laparoscopy can be avoided in many cases
- Bilateral tubal blockage IVF not tubal surgery unless very experienced surgeon or to clip tubes
- Abnormal scan and pelvic pain main indication
- Tubal testing chlamydial antibody test first, if negative continue trying, if positive, then HSG
  - The most cost –effective strategy for tubal pathology in couples whose 3 year chance of conception was >14%
  - If the chance of conception was < 14% then HSG first (Mol et al 1999)
- Low cost items could be stopped eg. Post coital tests, ovarian reserve testing, ovulation testing, endometrial biopsy, others...

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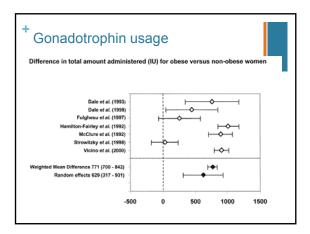
Can we ignore lifestyle factors?	
What about life style factors that we encounter at the time of the first consultation	
+ Patient selection for IVF	
■Maximise success rates and reduce drug costs ■ Avoid high BMIs	
■ Non smokers ■ Age < 42	
+	
It's true	
"Don't step on it it makes you crs."	

# Role of BMI and success of an IVF cycle

- Maheshwari et al 2007: infertility women undergoing IVF
   If BMI >25 then OR for pregnancy = 0.71 (CI 96% 0.62-0.81)
   If BMI >30 then OR for pregnancy = 0.68 (CI95% 0.55-0.83)

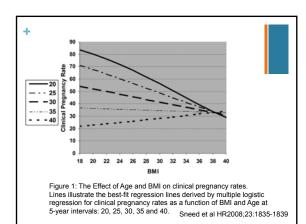
# Resource usage increases

Study	BMI	Resource issue
Lewis 1990	-	Reduced oocytes recovered
Crosignani 1994	> 29	Greater use of gonadotrophins
Ramzy 1996		Greater use of gonadotrophins
Lashen 1999	>28	No impact
Wittemer 2000	BMI > 26	Increased no. ampoules, ↓ oocytes
Spandorfer 2004	BMI > 27	Increased cycle cancellation
Dokras 2006	BMI > 39	Increased cycle cancellation
Engel 2003	-	Greater use of gonadotrophins
Fedorscak 2004	BMI > 30	Greater use of gonadotrophins



# \*Weight and Age

- Sneed et al found BMI did not appear to have a significant effect on IVF outcome (Hum Repro 2008;23:1835-1839)
- However compounded with combination of obesity and age
- At young age, sig BMI had a pronounced neg effect on fertility which reduced with age.
- After 36 yrs, BMI had minimal impact



# \*Role of maternal age and number of treatment attempts

- Australian cost –effectiveness analysis using ANZARD data from 2002 (Griffiths et al, 2010)
- A treatment program included one fresh cycle and a variable number of frozen cycles
- 30-33 yo
- cost per LB \$27373 \$31986 on 1st and 3rd program
- 42-45 yc
- cost per LB \$130951 \$187515 on 1st and 2nd program
- Overall these costs were not affected by the inclusion of costs of OHSS or multiple births (20% at 30-33 yo and 12% at 42-45yo)

All costs Australian \$

# Women and Cigarette Smoking

- ■Meta-analysis (11,000 smokers, 20,000 nonsmokers) Homan, G.F. et al. Hum Reprod Update 2007 13:209-223;
- Increased risk of infertility OR 1.60 (CI= 1.34-1.91)
- Dose related
- Earlier menopause by 1-4 yrs

# \* Smoking and Fertility Treatment



- ■MA of 21 studies (Waylen et al, HRU, 2009)
- OR livebirth/cycle if smoked =0.54 (CI= 0.30- 0.99)
- Spontaneous misc OR= 2.65 (CI= 0.1.33-5.3)
- Ectopic OR = 15.69 (CI= 0.2.87-85.76)
- ■Canadian Retrospective study (Neal et al HR 2005)
- Passive smoking also important
- preg rates smokers (19.4%)
- passive smokers (20%)
- non-smokers (48.3%)

# **Smoking Cessation**



- ■Beneficial for chances of conception, healthy pregnancy and healthy environment for child to grow up in.
- ■Observational data suggests negative effect reversed within 1 yr of cessation

# + Treatment choices for couples with unexplained infertility ■ Continue trying ■ Intrauterine insemination ■ In vitro fertilisation + Calculate the probability of a spontaneous ongoing pregnancy within 1 year (leading to live birth). Previous pregnancies (in current or other partnerships)? Ves : Duration of subfertility in years The calculated probability of a spontaneous ongoing pregnancy within one year is: 66.4% This model has been validated between 2002-2004 in 38 hospitals in the Netherlands by Van der Steeg et al. In the Colaborative Effort of Clinical Evaluation in Reproductive Medicine (CECEBM). The models showed to predict accurately IUI or IVF Pandian et al Cochrane review 2015 ■ 9 RCTs: 2 compared IVF with expectant management ■ 2 RCTs compared IVF with unstimulated IIUI • 6 RCTs compared IVF with stimulated IUI (FSH or CC) ■ Moderate to very low – poor reporting. imprecision

## + IUI versus IVF: live birth rates

- IVF versus expectant management: Live birth rate per woman was significan higher with IVF (45.8%) than EM (3.7%) (odds ratio (OR) 22.00, 95% confidence interval (CI) 2.56 to 189.37, 1 RCT, 51 women
- IVF versus unstimulated IUI: significantly higher with IVF (OR 2.47, 95% CI 1.19 to 5.12, 2 RCTs, 156 women), 40.5% with IVF versus 18.3% with unstimulated IUI.
- IVF versus stimulated IUI: no evidence of a difference between the groups among treatment-naive women (OR 1.11, 95% CI 0.95 to 1.30, 4 RCTs, 745 women), 46.3% with IVF versus 41.7% with IUI+SO
- ! RCT comparing IVF and IUI+CC: There was no evidence of a significant difference in live birth rate between IVF (31.3%) and IUI+CC (15.6%), (OR 2.46, 95% CI 0.94 to 6.41, 1 RCT,102 women).
- No evidence of difference between treatment groups for multiple pregnancy and OHSS

Pandian et al Cochrane review 2015

# † IUI versus expectant management



- Two RCTs:
- Bhattacharya 2008: unstimulated IUI had similar rates of live birth to expectant management
- Steures et al 2006: couples with prediction scores between 30 and 40% had similar live birth rates with IUI + FSH and expectant management

Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Library 2012

# IUI stimulation protocols



- ■RCT of 900 women up to 4 cycles of IUI
- ■outcomes of LBR, MPR
- Clomiphene 23.3%, 1.3%
- Letrozole 18.7%, 2.7%
- FSH 32%, 10.3%
- Letrozole was significantly lower than CC and FSH for LBR
- No high order multiple in CC and Letrozole but 10 sets of triplets in the FSH group
- "CC and IUI remains first line therapy for couples with unexplained infertility
- Diamond et al Abstract ASRM 2014

# An assisted reproduction cycle is a series of individual steps....





- Complex with interactions between steps
- Benefits and harms can take place with each step
- Trade-offs may be necessary
- Two patients to considermother and baby

# + Steps in an ART cycle – where are the cost savings?

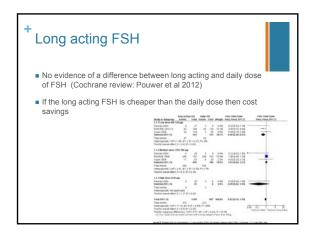


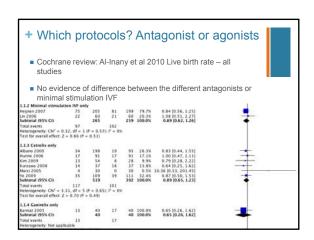
- Gonadotropins urinary/recombinant/depot
- Oral stimulation protocols
- Antagonist cycles
- Modified natural cycle IVF
- Minimal monitoring ultrasound
- Triggering
- Freeze all cycles
- Ovum pick up
- The transfer SET, ultrasound guidance
- Length of embryo incubation
- Luteal phase support

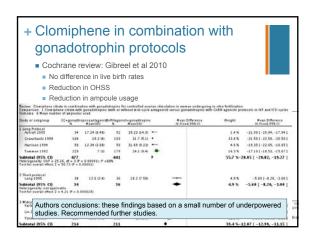
# Which gonadotrophin – urinary or recombinant?



- Cochrane review van Wely et al 2010:
- Live birth rate: 28 trials, 7339 couples, OR 0.97, 95% CI 0.87 to 1.08
- This suggests that for a group with a 25% live birth rate using urinary gonadotrophins the rate would be between 22.5% and 26.5% using rFSH
- OHSS rate: 32 trials, 7740 couples, OR 1.18, 95% CI 0.86 to 1.61.
- This means that for a group with 2% risk of OHSS using urinary gonadotrophins, the risk would be between 1.7% and 3.2% using rFSH.
- "Clinical choice of gonadotrophin should depend on availability, convenience and costs "
- Connolly 2008: cost difference per cycle €468 (1 fresh and 1 frozen transfer)
- When effectiveness and safety is the same then make decision on cost







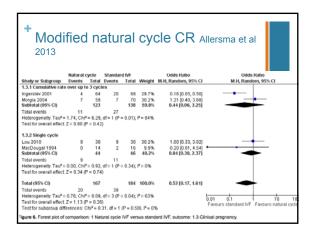
# + Natural cycle or modified NC IVF

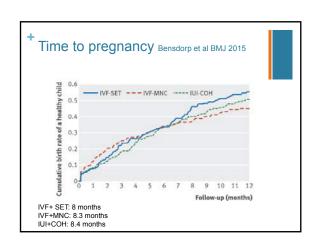
Natural cycle-IVF (NC-IVF)

- No drugs are administered
- When the follicle approaches maturity (10 mm), start monitoring
- Triggering with hCG when the follicle 15 to 20 mm or when the serum estradiol rises, or both

### Modified natural cycle-IVF (MNC-IVF)

- Gonadotrophins for 2-6 days to stimulate follicular growth.
- After maximum six days of FSH or largest follicle is 14 mm, then GnRH antagonists
- When leading follicle is 15 to 20 mm, ovulation is triggered in the same manner as in COH-IVF but only one oocyte is fully grown and retrieved





# Cost of modified natural cycle



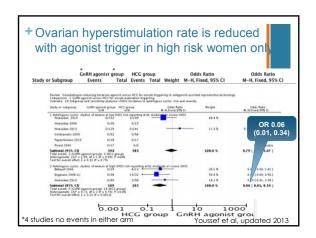
- MNC is cheaper per cycle than COH but also less effective in
- Groen et al 2013: tested different scenarios using observational data from the Netherlands
- "The comparison of simulated scenarios indicates that a strategy of three to six cycles of MNC with minimized medication is a cost-effective alternative for one cycle of COH with strict application of single embryo transfer (SET)"
- Definitely promising.....

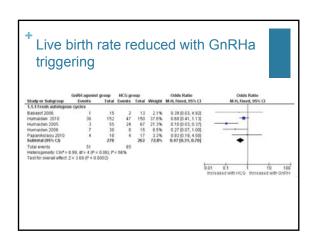
# Cycle Monitoring: Cochrane review Kwan et al 2014 No evidence of a difference between ultrasound and ultrasound plus estradiol levels for clinical pregnancy rate, number of oocytes, OHSS and cycle cancellation Total (9x%-CI) 59 Total events 1 Heteropeneits: Chi\*= 0.31, $\phi$ f = 1 (P = 0.59); P = 0% Text for overall effect Z = 0.55 (P = 0.59)

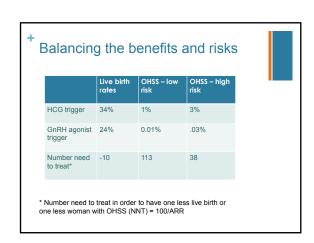
# Triggering – GnRH agonist or hCG?



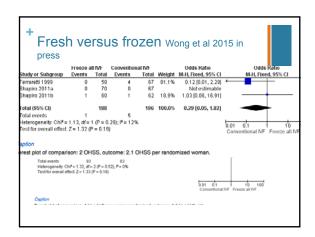
- 17 RCTs
- 9 report OHSS
- 5 report live birth rate
- Risk of bias
- Only 2/17 used blinding
- 4/17 studies stopped prematurely for differing reasons
- All studies were either funded by pharmaceutical companies or did not report their funding



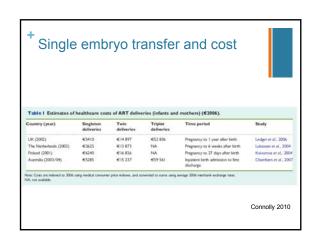




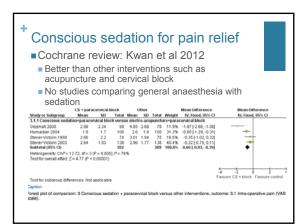
+ Professor Hans Evers Editorial, Human	
Reproduction September 2013	
"As an Editor of this journal, I would whole-heartedly welcome a manuscript on the first sufficiently powered	
RCT of GnRHa triggering in one arm, and traditional hCG triggering in the other; with subsequent secondary	
randomization to a 'freeze-all' strategy or a 'fresh transfer' strategy in either of the two arms. "	
	1
+ Price difference between hCG and	
GnRH agonist trigger	
■\$100 ■Reduced OHSS costs with GnRHa	
But you need to factor in the freezing/thaw and any further stimulation used	
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*Freezing protocols	
■Thaw cycle stimulation protocols	
■Unclear if there is a superior protocol	
	<u> </u>

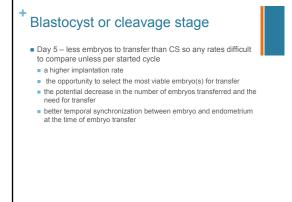


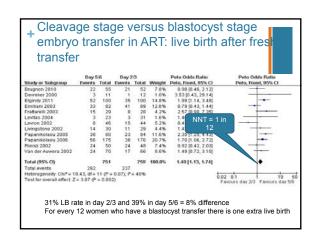
* Single embryo transfer CR Pandian et al 2013					
<ul> <li>Trade off between better live birth rates from one fresh transfer and multiple pregnancy</li> </ul>		Probability of live birth	Probability of multiple pregnancies		
rates  Need to take obstetric and neonatal costs into account – SET delivers considerable savings	Double embryo transfer	41%	29%		
	Single embryo transfer	27%	1.6%		
<ul> <li>DET is the most expensive strategy and only more effective for fresh transfer</li> </ul>	Single embryo transfer + FZET	38%	<1%		

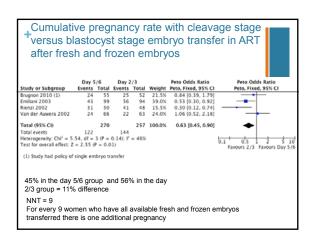


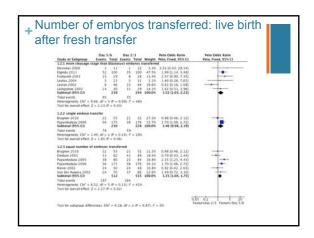
#### Flushing for follicles ■ Follicular flushing: CR by Wongtra-ngan 2010 ■ 3 studies, 164 patients No evidence that follicular aspiration and flushing is associated with improved clinical or ongoing pregnancy rates, nor an increase in oocyte yield ■ The operative time is significantly longer and more opiate analgesia is required for pain relief Ining Odds Ratio Total Weight M-H, Fixed, 95% CI 10 16.4% 1.15 [0.20, 6.74] 15 12.9% 2.67 [0.52, 13.68] 50 70.7% 0.90 [0.36, 2.22] 83 100.0% 1.17 [0.57, 2.38]







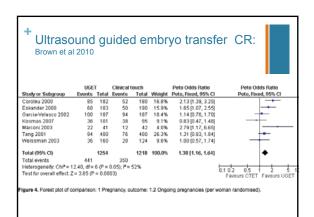




#### Costs - no clear answer re BL and CS

- Better pregnancy rate with fresh transfer
   Lower pregnancy rate with fresh transfer
- Reduced cumulative pregnancy rates
- Reduced no. embryos to transfer
- Reduced embryos to freeze
- Laboratory cost of extended

- Better cumulative rate
- More embryos to freeze



#### Luteal phase support van der Linden et al

- Favours synthetic progesterone without any additions
- ■No specific route
- ■hCG associated with OHSS

#### Topics not covered today

- Laboratory techniques such as oxygen levels, adhesion molecules
- ■Culture media
- ■Time lapse systems
- ■New incubator techniques the walking egg incubator

#### + My version of a cost effective ART cycle

- Which gonadotropin? urinary
- Oral stimulation protocols maybe, not yet
- Antagonist cycles yes
- Modified natural cycle IVF maybe
- Minimal monitoring ultrasound only
- Which trigger? hCG, if no risk factors, GnRHa + freeze all policy if risk factors
- Single embryo transfer yes,
- Length of embryo incubation cleavage stage with transfer of frozen embryos ?
- Ovum pick up sedation, no flushing, adhesion molecules, oxygen concentrations
- Embryo transfer with ultrasound guidance
- Luteal phase support with progesterone

# + A minimalist pathway

#### References for ovulation testing Blackwell LF, Vigil P, Cooke DG, d'Arcangues D, Brown JB. Monitoring of ovarian activity by daily measurement of urinary excretion rates of oestrone glocuronide and pregnamediol glucuronide using the Ovarian Monitor, Part III: variability of normal menstrual cycle profile. Human Reproduction 2013, 28(12): 3366-3315. 3306-3315. Hambridge HL, Mumford SL, Mattison DR, Ye A, Pollack AZ, Bloon MS, Mendola P, Lynch KL, Waclawski Wende J, Schsterman EF. The influence of sporadic annovalation on homone levels in ovulatory cycles. Human Reproduction 2013; 28(6): 1687-1694. 3 additional publications from the same study (Biocycle): Lynch KE, Mumford SL, Schliep KC, Whitcomb BW, Zarek SM, Pollack AZ, Bertone-Johnson ER, Banaher M, Waclawski-Wende J, Gaskins AJ, Schlieman EF. Assessment of anovalation in eumenorrheir women: comparison of ovulation detection algorithms. Fertility and Sterility 2014; 102: 511-516.

- 518.

  Houards RP, Schisterman EF, Wacfareski-Wende J, Reschke JE, Frazer AA, Hovey KM. Timing dinic visits to phases of the mentival cycle by using a fertility monitor: the Blocycle study. American Journal of Epidemiology 2009; 165: 105-112.

  Murnford SL, Steiner AZ, Pollack AZ, Perkins NJ, Filiberto AC, Albert PS, Mattison DR, Wacfawski-Wende JS, Schisterman EF. The utility of mentral acycle length as an indicator of cumulative hormonal exposure. Journal of Clinical and Endocrinological Metabolism 2012; 97(10): 1871-E1879.

  Van Zonneveld P. Velde ER, Ropeschart HPE. Low Higal phase serum progesterone levels in regularly cycling women are predictive of subfe ovulation disorders. Gynecological Endocrinology 1994; 8: 106-174.

- Additionable publication in salite study.
   Van Zonnevley P. Koppeschaar HPF, Habbema JDF, Fauser BCJM, to Velde ER. Diagnosis of subtle ovulation disorders in subfertile women with regular menstrual cycles: cost effective clinical practice?
   Opinecologieal Emodicinelogy 1989, 15, 42-47.
   Matecian CE, Cumming DC. Does anovulation exist in eumenorheic women? Obstetrics and Gynecology 2005, 19(2), 3, 179-38.
- Miller PB, Soules MR. The usefulness of a urinary LH kit for ovulation prediction during menstrual cycles of normal women. Obstetrics and Gynecology 1996; 87(1): 13-17.

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- Pandian Z. Gibreel A. Bhattacharva S. In vitro fertilisation for unexplained subfertility. Cochrane Database of Systematic Reviews 2015
- Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD001838, DOI: 10.1002/14651858, CD001838, pub4.

#### + Ovarian reserve testing

- Broer SL, van Disseldorp J, Broeze KA, et al. Added value of ovarian reserve testing on patient characteristics in the
  of ovarian response and ongoing pregnancy: An individual patient data approach. Hum Reprod Update. 2013;19:Arte
  ms041. ate of Pubaton: January 2013.
- Haadsma ML, Groen H, Fidler V, et al. The predictive value of ovarian reserve tests for spontaneous pregnancy in ovulatory women. Human Reproduction. 2008;23:1800-1807.
- ovulatory women. Human Reproduction. 2005;2:1903–1907.

  J. Biodromitis, Rubey TVW, W.O. Andreson RA. Nelson SM. The predictive accuracy of anti-Mullenian homone for lay after assisted conception: a systematic review and meta-analysis of the literature. Hum Reprod Update. 2014;20:560-570.

  4. Matesharian f. Obreed R. Shattacharya, S. Johnson IVP Journait celss of ovarian reserve: a systematic review of diagnostic accuracy, Reproductive Biomedione Online. 2009;18:717-794.
- van der Steeg JW, Steures P, Eijkemans MJC, et al. Predictive value and clinical impact of basal follicle-stimulating hormone in subfertile, ovulatory women. Journal of Clinical Endocrinology & Metabolism. 2007;92:2163-2168.
- Moolenaar LM, Broekmans FJM, van Disseldorp J, et al. Cost effectiveness of ovarian reserve testing in in vitro fertilization: a Markov decision-analytic model. Fertil Steril. 2011;96:889-U341.
- National declaration and the control of the control
- Erdem M, Erdem A, Guler I, Atmaca S. Role of antral follicle count in controlled ovarian hyperstimulation and intrauterine insemination cycles in patients with unexplained subfertility. Fertil Steril. 2008;90:360-366. Freiesleben NIC, Rosendahl M, Johannsen TH, et al. Prospective investigation of serum anti-Mullerian hormone concentration in ovulatory intrauterine insermination patients: a preliminary study. Peproductive Biomedicine Online. 2010;20:582-587.
   Yarde F, Voorbins M, Dolleman M, Knauff EAH, Ejismana MJC, Brosetmans FJM. Antimutian hormone as predictor of reproductive outcome in subfertile women with elevated basal follicle-stimulating hormone levels: a follow-up study. Pertil Steril. 2013;10:08314-x
- 11. van Rooij I, Broekmans F, Hunault C, et al. Use of ovarian reserve tests for the prediction of ongoing pregnancy in co with unexplained or mild male infertility. Reprod Biomed Online. 2006;12:182-190.
- Casadei L, Manicuti C, Puca F, Madrigale A, Emidi E, Piccione E. Can anti-Mullerian hormone be predictive of spontaneous onset of pregnancy in women with unexplained infertility? *Journal of Obstetrics and Gynaecology*. 2013;33:857-861.
- vines. up regulativity in women with unsupparative intertility? Journal or Unstructs and Gylmaecology; 2013;33:857-861.

  3. Aboudighan M, Saber W, Amin Y, Abuodighan MM, Serour G, Manseuur R, Impact of antimulierian homone assays on the outcomes of in vitro fertilization: a prospective controlled study. Fertility & Sterility. 2014;101:134-137.

  14. Broekmans F, J, Knauff EAH, Velde ETH, Macklon NS, Fauser BC, Female reproductive ageing; current knowledge and future trends. Transfar in Endocrinology and Metabolism: 2017;18:36-86.

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# Reference list for post coital tests NICE SR 2004, Hessel M, Brandes M, de Bruin JP, Bots RSGM, Kremer JAM, Nelen WLDM, et al. Long-term ongoing pregnancy rate and mode of conception after a positive and negative post-coilal test. Acta Obstetricia Et Gynecologica Scandinavica. 2014 Sep.93(9):913-20. Rege N, Haji H, Mekerji P, Vaidya R, Rao S. Semen analysis and its correlation with post coilal tests in infertile couples. Journal of obstetrics and gynaecology of India. 1978 Dec,28(6):1056-61. Hwang MF, Yang SL. Correlation of post-coital test and semen analysis in infertile couples. Talwan yi xue hui za zhi. 1987 Nov.Journal of the Formosan Medical Association. 86(11):1220-6. Leushuis E, van der Steeg JW, Steures P, Roke C, Oosterhuis J, Bourdrez P, et al. Prognostic value of the postcoital test for spontaneous pregnancy. Fertility & Sterility. 2011 May;95(6):2050-5.

Γ	+ References for tubal patency testing
ŀ	Mol BWJ, et al. The accuracy of serum chlamydial antibodies in the diagnosis of tubal pathology. Fertility and Sterility 1997; 67(6): 1031-1037.
ŀ	Broeze KA, et al. Chlamydia antibody testing and diagnosing tubal pathology in subfertile women: an individual patient data meta- analysis. Human Reproduction Update 2011; 17(3): 301-310.
ŀ	Broeze KA et al. Are patient characteristics associated with the accuracy of hysterosalpingography in diagnosing tut an attorious of historical patient data meta-analysis. Human Reproduction Update 2011a; 17(3): 293-300.
ŀ	Broeze KA, et al. Integration of patient characteristics and the results of Chlamydia antibody testing and hysterosalpingography in the diagnosis of tubal pathology: an individual patient data meta-analysis. Human Reproduction 2012; 27(10): 2979-2990.
ŀ	Maheux-Lacroix S, et al. Hysterosalpingosonography for diagnosing tubal occlusion in subfertile women: a systematic review with meta-analysis. Human Reproduction 2014; 29(5): 953-963.
ŀ	Keltz MD, et al. Positive Chlamydia trachomotis serology result in women seeking care for infertility is a negative prognosticator for intrauterine pregnancy. Sexually Transmitted Diseases 2013; 40(11): 842-845.
ŀ	Van Geloven N, et al. Treatment should be considered a competing risk when predicting natural conception in subfertile women. Human Reproduction 2012; 27(3): 889-895.
ŀ	Verhoeve HR, et al. The capacity of hysterosalpingography and laparoscopy to predict natural conception. Human Reproduction 2011; 26(1): 134-142.
ŀ	Coppus SFPJ, et al. Chlamydia trachomotis IgC seropositivity is associated with lower natural conception rates in ovulatory subfertile women without visible tubal pathology. Human Reproduction 2011; 26(11): 3061-3067.
ŀ	Hamilton J, et al. Intrauterine insemination results are not affected if Hysterosalpingo Contrast Sonography is used as the sole test of tubal patency. Fertility and Sterility 2003; 80(1): 165-171.
ŀ	Ayida G, et al. A comparison of patient tolerance of hysterosalpingo-contrast sonography (HyCoSy) with Echovist-200 and X ray hysterosalpingography for outpatient investigation of infertile women. Ultrasound Obstet s
ŀ	Socolov D, et al. International Journal of Gynecology and Obstetrics 2010; 111: 256-259.
ŀ	Mol BWJ, et al. Cost effectiveness of hysterosalpingography, laparoscopy, and Chlamydia antibody testing in subfertile couples. Fertility and Sterility 2001; 75(3): 571-580.
ŀ	Verhoeve HR, et al Cost effectiveness of tubal patency tests. BJOG 2013; 120: 583-593.

# References for IVF Alersma T, Farquhar C, Cantineau AEP, Natural cycle in vitro fertilisation (IVF) for subfertile couples. Communication of Systematic Reviews 2013, Issue 8. Pandina Z, Majoripanska J, Cutruk O, Serour G, Bhattacharya S, Number of embryos for transfer followers of the Vitro fertilisation or intra-cytoplasmic sperm injection. Occhrane Database of Systematic Reviews 2013, Issue 7. Wongtra-ngan S, Vutyavanich T, Brown J. Follicular flushing during oocyte retrieval in assisted reproductive techniques. Cochrane Database of Systematic Reviews 2010, Issue 9. Glujovsky D, Blake D, Bardach A, Farquhar C, Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive techniques. Oscilar AB, Busker M, Ultrascand versus clinical bour of re catheter guidance during embryo transfer in women. Cochrane Database of Systematic Reviews 2012, Issue 7. Brown J, Buckingham K, Farquhar C, Kremer JAM, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database of Systematic Reviews 2011, Issue 10. vaussef MAFM, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M, Gonadotrophin-releasing hormone agonist versus HGG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database of Systematic Reviews 2014, Issue 10. vaussef MAFM, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M, Gonadotrophin-releasing hormone agonist versus HGG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database of Systematic Reviews 2014, Issue 9. vaussef MAFM, Wan I, Burl AL, Thomas J, Vali A, Van der Veen F, Al-lanay HG. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology. Cochrane Database of Systematic Reviews 2011, Issue 1.

 Kwan I, Bhattacharya S, Kang A, Woolner A. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). Cochrane Database of Systematic Reviews 2014, Issue 8.

 Gibreel A, Maheshwari A, Bhattacharya S. Clomiphene citrate in combination with gonadotropins for undergoing in vitro fertilization. Cochrane Database of Systematic Reviews 2012, Issue 11

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■ Cochrane Menstrual Disorders and Subfertility Group		

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