PRE-CONGRESS COURSE 2

Is male fertility decreasing? The latest news suggests not...

Special Interest Group Andrology
London - UK, 7 July 2013

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Is male fertility decreasing? The latest news suggests not…

London, United Kingdom
7 July 2013

Organised by
The ESHRE Special Interest Group Andrology

Contents

Course coordinators

Sheena E.M. Lewis (United Kingdom) and Jackson Kirkman Brown (United Kingdom)

Course description

This course will present the latest research on male reproductive health and debate two issues: whether male fertility is declining and secondly if ART is a solution to Europe's demographic demise

i) The impact on ART on falling birth rates on European Society
ii) The economic benefits of ART on European Society
iii) Factors causing the increase in couples seeking ART year on year
iv) The health of children conceived with surgically retrieved sperm

Target audience

Clinicians, paramedical staff, embryologists and andrologists with an interest in male reproduction and the differing schools of thought on male fertility public health issues

Scientific programme

Is male reproductive health decreasing?
Chairman: Sheena E. M. Lewis - Ireland

09:00 - 09:20 Recent semen data from France
Joelle Le Moal - France
09:20 - 09:40 Male reproductive health: Its impacts in relation to general wellbeing and low European fertility rates
Stefan Schlatt - Germany
09:40 - 10:00 Trends in global semen parameters
Harry Fisch - U.S.A.
10:00 - 10:30 Discussion

10:30 - 11:00 Coffee break

Factors that may causing the increase in couples seeking ART each year
Chairman: Stefan Schlatt - Germany

11:00 - 11:30 Effect of lifestyle and environment
Richard Sharpe - United Kingdom
11:30 - 11:45 Discussion
11:45 - 12:15 Increasing patient age
Lone Schmidt - Denmark
12:15 - 12:30 Discussion

12:30 - 13:30 Lunch

Debate: We believe that ART is an important part of the solution to Europe's demographic demise
Chairman: Jackson Kirkman-Brown - United Kingdom

13:30 - 14:00 For the motion
Søren Ziebe - Denmark
14:00 - 14:30 Against the motion
Egbert R. te Velde - The Netherlands
14:30 - 15:00 Discussion

15:00 - 15:30 Coffee break

Chairman: Willem Ombelet - Belgium

15:30 - 16:00 Costs matter, but so do benefits: The economic benefits of ART to Society
Georgina Chambers - Australia
16:00 - 16:15 Discussion
16:15 - 16:45 How will ART children from infertile fathers affect the health of European Society in the future?
The latest child health data
Anja Pinborg - Denmark
16:45 - 17:00 Discussion

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Recent semen data from France

Pre course Eshre 07.07.2013

J. Le Moal, MD, MPH
Institut de Veille Sanitaire, France

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Conflict of interest

- *I work for a French public agency, InVS (French Institute for public health surveillance)*
- *I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content*

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Objectives

- Briefly describe the background of epidemilogic knowledge on semen quality trends, their potential link with endocrin disruptors, and methods usually used
- Explain the methods used in our recent study published in *Human Reproduction*
- Present and discuss the results

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BACKGROUND

- 1992 : Meta-analysis by Carlsen *et al.*, global decrease in human semen quality since 50 years in developed countries ► Numerous studies trying to confirm or invalidate these alarming results
- 1996 *Our stolen future* (Colborn T *et al.*): reproductive troubles observed in wild life around polluted sites (Guillette, Jr. *et al.*) ; alligators exposed to pesticides, seals exposed to PCB; birds exposed to DDT; snakes exposed toTBT etc.
- 2001. N. Skakkebaeks' hypothesis :
  - Fetal exposure to environmental endocrine disruptors (ED) could cause a testicular dysgenesis syndrome (TDS)
  - Troubles of genital development : urogenital malformations (cryptorchidies, hypospadias), low semen quality, testis cancer
  - Discordances between Denmark and Finland
- 2000-2013: growing data showing the impact of ED at low doses on animals, biological evidences, emerging concept of DOHaD, importance of epigenetic processes to account for environmental effects
- 2013 : new report UNEP/WHO: State of the Science : Endocrine disrupting chemicals-2012.

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Epidemiologic knowledge on semen quality

► Semen donor studies:
  - Decreasing quality in Paris: 1973-1992 (Auger, 1995), not in Toulouse (Bujan 1996)
  - Geographic variations in France between 8 centres, 1973-1993 (Auger 1997)
  - Only one recent study in France since the 90s' : Tours, (Splingart, 2012)
  - Geographic variations in Europa (Auger 2001, Jorgensen 2001)
  - Geographic variations in USA (Swan, 2003)

► Infertility clinic studies : men involved in ART attempts
  - France (De Mouzon 1996): decrease from1989 to1994, birth date dependent
  - USA, Israël, Inde, Espagne, Tunisie : various methods used, very difficult to compare. Some recent ones seem to show a debcrease, but not all.

► Young conscript studies :
  - Danish study : small increase from1996 et 2010 (Jorgensen, 2012)
  - Finish study : decrease from 1998 to 2006 (Jorgensen, 2011)

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Human Reproduction, Vol.28, No.2 pp. 462–470, 2013
Advanced Access publication on December 9, 2012 doi:10.1093/humrep/des415

human reproduction ORIGINAL ARTICLE Reproductive epidemiology

Decline in semen concentration and morphology in a sample of 26 609 men close to general population between 1989 and 2005 in France

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Submitted on June 14, 2012; resubmitted on October 22, 2012; accepted on November 1, 2012

†Joint first authorship.

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The Fivnat data base

- Built by the Fivnat association from 1985 in France
- Most of ART attempts in Metropolitan France
- One record for each attempt of a couple with data on men and women involved, especially the spermiogram
- Period : 1989-2005
- Huge number of records:> 440 000
- Estimated exhaustivity: 40 à 80% of the french ART centres

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The Fivnat data base

- On each record, two spermiograms available per man:
  - ► Check-up spermiogram carried out during a fertility check-up in a specialized laboratory within 6 month before the attempt
  - ► Attempt spermiogram carried out at the ART centre the day of the oocyte retrieval

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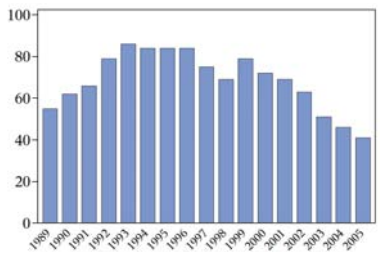
The Fivnat data base



Number of ART centres sending ART records to the Fivnat data base between 1989 and 2005

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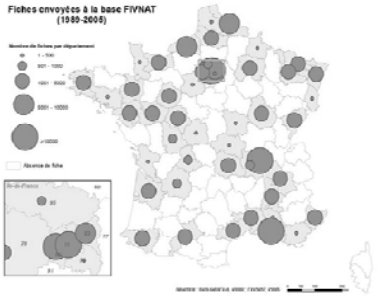
The Fivnat data base



Geographic cover of the ART centres included in the Fivnat data base from 1989 to 2005: number of records/county

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Methods

- The source population
- Men involved in a first attempt of standard IVF or ICSI recorded in the Fivnat data base between the 1st january 1989 and the 31st december 2005.
- Freshly ejaculated sperm
- Available data on age, ART technique, date of oocyte retrieval and spermiogram
- Azoospermic excluded
- The study population
- Men from couples where the woman had both tubes either blocked or absent, thus naturally infertile : no selection about the man's fertility

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Methods

- 3 indicators :
  - concentration (millions of sperm/ml)
  - total motility (% of motile sperm)
  - morphology (% of morphologically normal forms)
- Attempt spermiogram
- Statistical analysis :
  - 3 indicators regressed on time, controlling for men's age and season (penalized spline)
  - Generalized additive model allowing to consider non linear relationships between the indicators and the explanatory variables
  - Box-Cox transforming for concentration, no need transforming for motility and morphology

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Methods

- Sensibility analysis:
  - Adjustment for the ART centre (to confirm that non particular centre impacted the global trends)
  - Analysis on the check-up spermiogram (intra–subject variation and laboratory practice diversity)
  - Ajustment on ART technique and introduction of an interaction time/technique (in order to test if the decrease could be due to the inclusion of men made eligible for ART following the introduction of ICSI)
  - Analyses on another subsample of fertile men (not impacted by a possible tubal infection)
  - Analyses on men <50 ans (to test for an overselection of older men)
  - Analyses excluding centres that did not declare using the Kruger method for morphology (lower values when using the method)

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Results

	Source population * N=154 712			Study population ** N=26 609		
Indicator	Concentr.	Mob	Morph	Concentr.	Mob	Morph
Complete attempts***	**121 702**	**120 635**	**59 457**	**21 055**	**21 102**	**11 416**
IVF	73.90%	74.30%	77.40%	94.60%	94.70%	95.50%
ICSI	26.10%	25.70%	22.60%	5.40%	5.30%	4.50%
Age average ; percentile 25 ; median ; percentile 75	**35.2**; 31; 34; 38			**35.2**; 31; 34; 39		

Table 1: Number of men in the source and the study population, for each sperm parameter analysis and each ART technique, with age distribution

*Men involved in in couples undergoing their first ART cycle, registered in the Fivnat database, using freshly ejaculated semen
** Parners of women with both tubes absent or blocked
***age, technique, date and infertility factor completed

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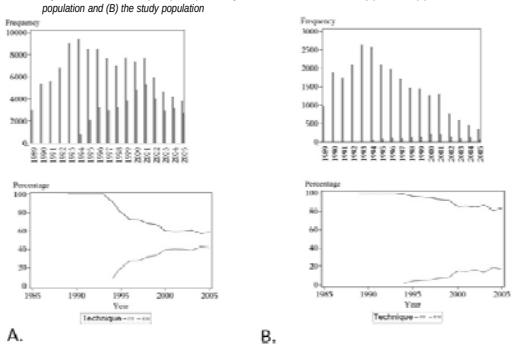
Results

Fig 1: Evolution of the frequency and percentage of IVF and ICSI over the study period for (A) the source population and (B) the study population



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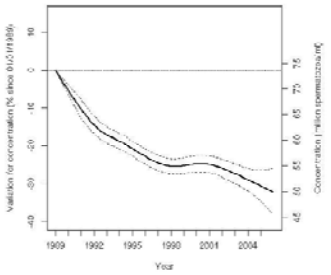
Results



- 32.2% [26.3-36.3]
- 1.9%/year, -1.4M/year
In 1989 : 73.6Mz/ml [69.0-78.4]
In 2005 : 49.9Mspz/ml [43.5-54.7]

Left axis: Variation in % for concentration since the 1st january 1989 for a 35-years-old man in metropolitan France, with $CI_{95\%}$
Right axis: Projected values in millions sperm per milliliter, with $CI_{95\%}$

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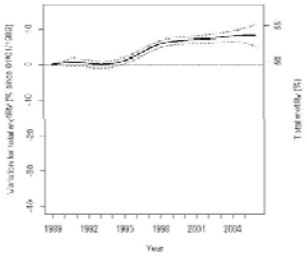
Résultats



Stability, then + 5.6%, from 1994 to 1998, then stability
In 1989 : 49.5% spzm [48.2-50.8]
In 2005 : 53.6% spzm [52.2-55.2]

Left axis : Variation in % of total motility since the 1st january1989 for a 35-years old man in metropolitan France with $CI_{95\%}$
Right axis : Projected values in % motile spermatozoa, with $CI_{95\%}$

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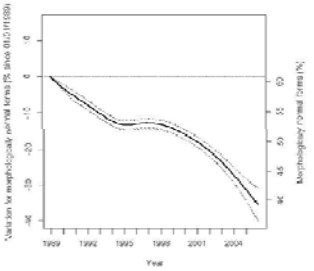
Résultats



-33.4% from 1989 to 1995, stability, then -34.6% from 1998 to 2005

Left axis: Variation in % morphologically normal forms since the 1st january 1989 for a 35-years-old man in metropolitan France, with $CI_{95\%}$
Right axis : Projected values in % morphologically normal forms, with $CI_{95\%}$

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Results

- Sensibility analysis : robust results
  - No centre effect
  - Similar trends for the 3 indicators with le check-up spermiogram and with the subsample of fertile men
  - Results in the study population not impacted by the arrival of ICSI
  - No overselection of men > 50 years
  - Same results on morphology when excluding centres which did not declare using Kruger method, but too much lacking data (97,5%)

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Discussion

- Extrapolation of the results to the general population:
  - Minimum selection bias concerning men's fertility
  - Not truncated distribution
  - Geographic diversity reflecting the whole of France
  - No bias about age
  - Bias linked to socio-economic status (more educated : Moreau, 2010)?
    - Tobacco consumption and overweight less likely in more educated men
    - In the study period, % of overweighted men has less increased in educated men than in the general population in France (Sasco, 1994 et de Saint Pol, 2009). ⇨ *In the general population, probably lower values and stronger decrease*

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Discussion

- Limits
  - No adjustment for abstinence time, but no reason for thinking that a continous change in abstinence time have occured
  - No data on the diversity of laboratory practises, but 2 spermiograms performed in separate laboratories give same trends
  - Evolution in laboratory methods : no main change during the study period for concentration et motility, yes for morphology
  - No adjustment for other factors involved in intra-individual variability: stress, temperature…but analysis of the 2 spermiograms gives similar results

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Conclusion 1

- To our knowledge, the bigest sample close to the general population studied in the world, at the scale of a whole country
- Non-linear model, controling for season and age, minimizing usual bias
- Decrease in sperm concentration of 1.9%/year along 17 years, concording results with french past studies and some in other countries
- Average concentration for a 35-years-old (49,9 M spz/ml) in 2005 above the WHO infertility reference value but below the threshold which is expected to impact the time to procreate (Slama et al., 2002)
- Decrease in morphologically normal sperm, not quantifiable

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Conclusion 2

- Sperm quality is a sentinel biomarker, correlated to life expectancy (Jensen, 2009). Possible impact on next generation's health (DOHaD) via genetic and epigenetic ways
- These results constitute a serious public health warning
- Sustain etiologic research : ED and other potential causes
- Need to implement gametes quality monitoring systems

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Aknowlegments

The ART centres involved in Fivnat

VICHY LA PERCOLA
NICE CHU
NICE St Georges
NICE Sainte Marie
CHARLEVILLE MEZIERES CH
MARSEILLE CONCEPTION
MARSEILLE PAYS PROVENCE
MARSEILLE LA.M.A.
MARSEILLE Renaissance
MARSEILLE BELLE DE MAI
MARSEILLE CONCEPTION (Aculife)
CAEN CHU
GRASSILLE Polyclinique
LA ROCHELLE LE MAIL
MIMIZAN St Gonzalo
AJACCIO CH
DIJON CHU
DIJON SAINTE MARTHE
INSTITUT FERTILITE PERIGORD
BESANCON CHU
BESANCON LES CHADONNES
VALENCE AUGUSTINICE
VALENCE AUGUSTINICE
DIEULIT CH
BREST CHU
BREST PASTEUR
NIMES CHU
NIMES ST-JOSEPH
TOULOUSE CHU**
TOULOUSE ST JEAN
TOULOUSE L'UNION
BORDEAUX PELLEGRIN Bion
BORDEAUX ARIEGARD
BORDEAUX PELLEGRIN (Lang)
BORDEAUX PELLEGRIN (Dalby)
MONTPELLIER CHU
MONTPELLIER Clinique SAINT-ROCH
RENNES CHU
RENNES LA SAGESSE
TOURS CHU
TOURS GEST
GRENOBLE CHU
GRENOBLE BELLEDONNE
GRENOBLE EAUX CLAIRES *
SAINT-PRIEST JUREZ CESFIV
SAINT-PRIEST JUREZ CESFIV
SAINT ETIENNE MICHELET
C.H.G. FIRMINY
ROANNE CH
NANTES CHU
NANTES POLYCLINIQUE ATLANTIQUE
NANTES Nice DAME DE BRUCE
ANGERS CHRU
CHOLET POLYCLINIQUE
EQUEURDREVILLE CLINIQUE COTENTIN
REIMS CHU
REIMS COURLANCY
NANCY CHU
NANCY Majorelle
LONVENT Etoile
LONVENT Ste Brigitte
METZ Claude Bernard
METZ Bon secours
METZ SAINTE-CROIX
METZ MERCEAUX
DIEZIZE CH
LILLE HURIEZ/ JEANNE DE FLANDRE
LILLE EPIAP Dubois
ROUBAIX CHU
DUNKERQUE Les Bateaux
LILLE CHR PAV. OUSSER
LOMME SAINT PHILIBERT
LILLE SALENGRO
SAINT SAULVE Le Parc
LENS CH
LENS Bois Bernard
CLERMONT-FERRAND CHU
BAYONNE PIV C.BASQUE
PAU LAGRANGE
SCHILTIGHEIM CMCO
MULHOUSE Diaconat
LYON ECULLIES MERIEUX
LYON BRON MADELEIN
LYON CMIS
LYON PERTUY MONTPLAISIR
LYON MONTPLAISIR
LYON CROIX ROUSSE
LE MANS TERTRE ROUGE
LE MANS St. DAMIEN
PARIS TENON
PARIS MARMOUN
PARIS BAUDELOCQUE
PARIS PORT-ROYAL
PARIS CITE UNIVERSITAIRE
PARIS PITIE
PARIS DIACONESSES
PARIS HOTEL-DIEU
PARIS Bichat
PARIS MILETTE/ MARGNAN
PARIS SAINT-ANTOINE
PARIS ST VINCENT DE PAUL
PARIS Blanis
PARIS Spantini
ROUEN CHU
ROSS-GUILLAUME
LE HAVRE JINES
POISSY CHR
VELIZY LES CHENES
LE CHESNAY PARIS13
MAISON LAFITTE Sully
AMIENS CHU
AMIENS APATIS SAINTE THERESE
AMIENS SAINTE CLAIRE
DRAGUIGNAN CH
TOULON ST MICHEL
AVIGNON LIMBAUV
POITIERS - CHU
LIMOGES CHU
CLAMART BECLERE
SAINES CHU
NEUILLY Bois&Alm
NEUILLY HOP. AMERICAIN
NEUILLY CHR REST
COURBEVOIE CH
BONDY - CHU
RAINCHLET LE DAUTE
BLANC-MESNIL Clinique
AUBERVILLIERS ROSERAIE*
VITRY Nucleis
PONTOISE CH
CORBEILLES / FORGES
ENGHIEN Polyclinique
LES ABYMES GARPHAG

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Aknowlegments

- *D. Royère et J. De Mouzon (Fivnat)*
- *InVS colleagues: F. De Bels, A. LeTertre, Y. Le Strat, D. Eilstein, E. Bertrand, P. De Crouy-Chanel, N. Velly, A. Lefranc, G.Salines.*
- *Pr C. Poirot (hop. Tenon)*

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EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

SCIENCE POLICY BRIEFING • September 2010 40

Male Reproductive Health

Its impacts in relation to general wellbeing and low European fertility rates

Contents

Foreword

Research in the area of male reproductive health has in the past focused mainly on birth control and family planning in non-developing countries, contraception, and sexually transmitted diseases such as HIV. Only little attention has been paid to male reproductive health disorders that lead to impaired fertility resulting in lower birth rates especially in industrialised countries. There is therefore an urgent need for better understanding the status of male reproductive health, especially in Europe and in industrialised countries where lifestyle and environmental factors may have a negative impact.

This Science Policy Briefing is the first to highlight this important issue which could have a dramatic impact on future birth rates and demographic changes in industrialised countries. It summarises the various exogenous and endogenous factors which can have an impact on male reproductive health and provides policy advice to national and European funding institutions.

The report was developed by a group of leading European experts. The issue was first raised by Professor Niels E. Skakkebæk during a mini symposium organised at the European Medical Research Councils (EMRC) plenary meeting in Strasbourg in April 2009. A first strategic meeting was held in Copenhagen on 20 May 2009 and the report was then written and finalised by the high level expert group present at this meeting.

This paper aims to increase awareness about the major consequences that reduced male reproductive health can have. It also provides advice on where and how to strengthen research in this area. Male reproductive health has been a low priority for funding agencies in European countries over the last 25 years. This has led to a lack of continuity in funding and a large translational gap between basic scientists and clinicians working with European patients.

The main policy recommendations are as follows:

- Increase awareness of male reproductive health issues
- Strengthen interdisciplinary, translational research in the area of male reproductive health issues
- Implement long-term, epidemiological studies aimed at better understanding the causes and effects of male reproductive disorders
- Target research efforts at preventing/minimising the occurrence of disorders rather than developing drug treatments.

Recommended funding instruments are transdisciplinary research networks which should be implemented at the European and international level to strengthen this highly important research area for the benefit of society.

We would like to thank the members of the high level expert group for their excellent work.

Professor Marja Makarow, ESF Chief Executive
Professor Liselotte Højgaard, EMRC Chair

Introduction

In most European countries fertility rates have declined drastically to below replacement level – the level at which the rate of new births can replace a population (1,2). This decline is primarily due to changes in social and economic conditions, such as wider use of contraception and more women seeking careers and postponing childbirth (1). However, declining fertility rates may also partly result from a decreased ability to conceive. In Europe there is a growing demand for use of assisted reproduction techniques (ART; 3,4), and a growing body of evidence points towards adverse trends in male reproductive health, including reduced semen quality, increased incidence of testicular cancer and increased or an already high incidence of congenital reproductive malformations (cryptorchidism and hypospadias; 5). It is to be expected that poor semen quality in young men, when combined with the high prevalence of increased age at attempting for pregnancy in women (when fertility is already declining), will lead to increased fertility problems in couples and its attendant socio-economic impacts.

Other than cancers, reproductive problems in men are generally not life-threatening, but in the last five years there has been a growing recognition that male reproductive function and risk of cardiometabolic disorders, including abdominal obesity, type 2 diabetes and hypertension are interlinked, as late-onset hypogonadism (low/subnormal testosterone levels) in men is an important determinant and/or consequence of these disorders (6,7). Moreover, the (normal) age-related decline in testosterone levels in men (8) clearly predisposes to such disorders with broad effects on wellbeing and mortality (7,9). Estimates of the incidence of hypogonadism vary from ~10% (10) to nearer 40% in men >45 years (11). The European-wide increase in the proportion of the male population that are of older age

thus carries with it the prospect of an increasing proportion of men with hypogonadism, and thus a progressive increase in prevalence of cardiometabolic disorders in the male population, irrespective of any change in diet and exercise. However, perhaps more worrying is the evidence that these problems may also be emerging in much younger men. Thus, large studies in both Europe and the US document a trend for declining testosterone levels in men (of any age) according to more recent year of birth (12,13), and have shown a clear negative correlation between visceral fat levels and lower testosterone levels (14). At present, it is not clear to what extent it is abdominal obesity that is causing lower testosterone levels and to what extent it is the other way around. The most likely scenario, especially in relation to aging, is that it is a 'vicious circle'. Thus, more research is needed to better understand these mechanisms.

Based on the issues described above, there are cogent reasons for concern about the remarkably poor state of male reproductive health across Europe. Not only does this have implications for population maintenance and replacement, but it also augurs for more pervasive and more life-threatening changes in men's cardiometabolic health, a change that may not just be restricted to the aging population. These changes pose huge financial and healthcare issues for European governments. There is therefore an urgent need for implementation of a common research strategy to better understand the status of male reproductive health in Europe and the causes of its problems and its inter-relations with wider health issues. This is the focus of this report.

Issues and challenges

Declining semen quality

Semen quality has been declining throughout the past half century in industrialised countries (15,16). Studies indicate a significant ~50% decrease in semen quality in men without fertility problems (dropping sperm counts from 113×10^6/ml to 66×10^6/ml; 15). There has been a lot of discussion about these results and different attempts to reanalyse the data within the scientific community (16-18; Figs. 1 and 2). Nevertheless, the question of temporal changes in semen quality still remains controversial, and there are reports of unchanged or even increasing semen quality in some regions (17). However, recent prospective investigations have, in accordance with the reported adverse trend, found a remarkably poor semen quality among young men from general populations in Northern Europe (18,19). Approximately 20% of young men in various European countries had a sperm concentration below the lower WHO reference level ($<20\text{x}10^6$ sperm/ml) and 40% of the men had a sperm concentration below the level that has been associated with prolongation of the waiting time to pregnancy ($40\text{x}10^6$/ml; 20). These trends in semen quality may also have wider implications for health in general, as men with poor semen quality seem to have increased mortality rates and shorter life expectancy (21).

Worldwide studies of fertile men using standardised protocols have shown significant regional differences in semen quality (22-24). Finnish (Turku) men have a 35% higher sperm concentration than do Danish men, while Scottish and French men have sperm counts in between these extremes (22). Similar regional differences in semen quality were found between fertile men from different US cities (23). Japanese fertile men had a sperm concentration at the same low level as Danish men (24) and men from Singapore had even lower concentrations (25). The reasons for these significant geographical differences in semen quality are largely unknown and should be further examined. Similar regional differences in other disorders of the male reproductive system have been observed, including testicular germ cell cancer (TGC) and congenital malformations of the male reproductive tract (5).

One reason for discrepancies in the results of semen quality studies could be insufficient quality management systems in different geographic areas which may affect the validity of the results. To assure comparability of

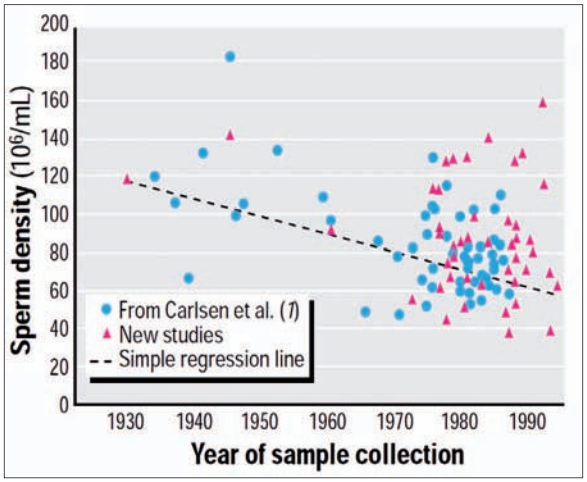

Figure 1. Mean sperm density in 101 studies published between 1934 and 1996 and simple regression line (from ref. 16).

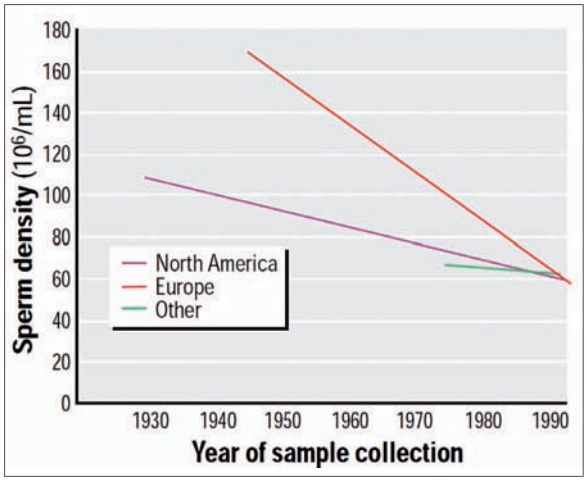

Figure 2. Interactive regression model for mean sperm density by year and geographic region after controlling for proven fertility (from ref. 16).

all endpoints of semen analysis, the WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction provides a basis for global standards. To verify high standards, quality management systems for semen analysis have been implemented by various Andrology Societies in several European countries (e.g. QuaDeGA, Germany; UK NEQAS Andrology; EQA programme, ESHRE). These quality control systems have been running successfully for years and provide a good basis and training for all participants to harmonise and maintain a high standard of analysis. It will be important for the field to maintain quality control programmes and to extend these schemes throughout Europe.

Testicular germ cell cancer (TGC)

TGC is the commonest cancer in young men in many countries. It is well documented to be associated with impaired semen quality (26) and lower fertility rates, even prior to development of the cancer (27). The incidence of TGC has been increasing over the past 40 to 50 years in the majority of industrialised countries (28-30; Fig. 3) coincident with the declining trend in semen quality. The aetiology of TGC is unknown, but there is abundant evidence that cancer *in situ* of the testis, which is a precursor for TGC, is generated during fetal development and TGC therefore has a prenatal origin (31,32). The regional differences in TGC incidence in Europe follow the same pattern as observed for semen quality, as semen quality in high-risk TGC areas is lower than in low-risk TGC areas (33). As an example, studies in Denmark and Finland indicate that the age-standardised incidence rates of TGC in 1995 were 15.4 per 10^5 and 3.1 per 10^5, respectively, following the pattern of lower semen quality among Danish men compared to Finnish men. These studies have to be expanded at European level to better understand these results.

Congenital malformations (see also TDS section below)

Cryptorchidism (undescended testis) and hypospadias (incomplete fusion of the urethral folds that form the penis) are among the most common congenital malformations in human males. These two congenital abnormalities share common risk factors (34,35) and are both associated with reduced fertility (36,37). Cryptorchidism is also associated with poor semen quality (36) and a considerably increased risk of TGC (38). The incidence of these malformations appears to have been increasing in the Western world over recent decades, with an apparent levelling off in hypospadias incidence in most European countries during the 1980s (39). At present there is only a limited number of studies available. Recent prospective, cohort studies in Denmark and in the UK indicate that the incidence of cryptorchidism at birth may be far higher than had been supposed (40,41) although a much lower incidence was found in Finland. A similar difference in the incidence of hypospadias was also found between Denmark and Finland (42). Thus, the geographic difference in incidence of both cryptorchidism and hypospadias parallels the pattern for TGC and semen quality in these countries. Much more research is needed to better understand these health problems and their relationships.

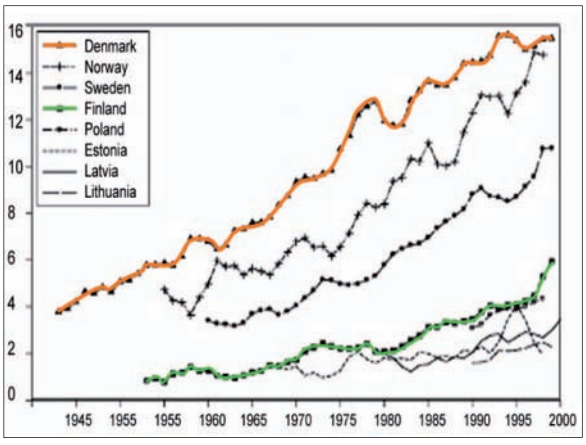

Figure 3. Trends in incidence of testicular cancer in Northern Europe. Age-standardised (world standard population) incidence of testicular cancer by year of diagnosis, country and histological type (from ref. 30).

Fertility and fecundity

The crucial question is whether semen quality among young men in Europe is now so low that it has reached a threshold at which fertility rates may be affected. In a recent study of pregnancy rates among native Danish women born between 1960 and 1980 (43), a 'total natural conception rate' (TNCR) was calculated, which included both the total number of births and induced abortions, and excluded births after the use of ART. Among the younger cohorts, who had not finished their reproductive career, projections were used to estimate their future fertility. Younger Danish cohorts of women had progressively lower TNCR, while the use of ART substantially increased, partly compensating for the decline in TNCR. The results suggest a cohort-related decline in fecundity (ability to conceive). Due to the partly prognostic nature of the study the results are, however, hedged with a degree of uncertainty, and new studies including the most recent registry data will be informative to examine the precision of the projections. On the other hand, the findings are consistent with a growing demand for ART in Denmark. It has been estimated that more than 7% of all children born in 2007 in Denmark were conceived by use of ART, which includes *in vitro* fertilisation, intracytoplasmic sperm injection (ICSI), and intrauterine insemination (44). Poor semen quality may be part of the reason for the increasing use of ART, which is confirmed by the increasing use of ICSI. Dependency on ART would dramatically influence society, since only limited resources are available for state-supported healthcare and those who do not qualify to receive free ART have to pay for the possibility to have children. The high costs of ART will certainly put people in an unequal position for their chances to conceive. Thus more research at international level is needed to provide information from other countries and to implement a common strategy to improve the situation.

Declining serum testosterone levels in American Men

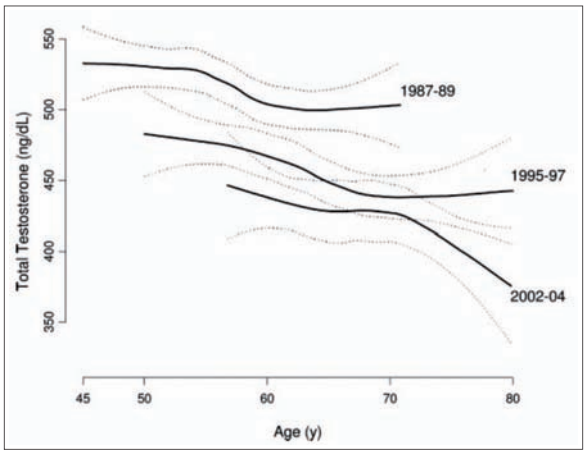

Figure 4. A substantial age-independent decline in testosterone that did not appear to be attributable to observed changes in explanatory factors, including health and lifestyle characteristics such as smoking and obesity. The estimated population level declines were greater in magnitude than the cross sectional declines in testosterone typically associated with age (from ref. 12).

Testosterone levels

Testosterone is the major driver of male reproductive development and function and suppression of its levels within the adult testis shuts down spermatogenesis (the process by which mature sperm cells are formed) and induces infertility. Testosterone levels within the testis are around 200-fold higher than in peripheral blood. However, lower intratesticular testosterone levels can sustain spermatogenesis. Studies of men with idiopathic infertility and low sperm counts often show evidence for abnormal function of Leydig cells (cells that produce testosterone) when compared with normospermic fertile men, such that their blood testosterone levels are either low or show evidence of 'compensated failure' – a situation in which increased luteinising hormone drive to the Leydig cells is required to maintain testosterone levels within the normal range (45,46). It is suspected, but unproven, that such compensation will predispose to more overt Leydig cell failure during aging (46), with its attendant health consequences, as outlined above.

The fact that across Europe the prevalence of oligozoospermia (low sperm numbers) in young men (18-25 years) is of the order of 20% (see above) could suggest that the prevalence of Leydig cell dysfunction in this population may also be high or may occur with high frequency as the men begin to age, thus predisposing them to cardiometabolic disease. Abdominal obesity is clearly associated with reduced testosterone levels (6,14) and it is also established that obesity (BMI >25) is associated with an approximate 20% reduction in sperm counts (47), although it is not clear if it is the obesity that causes the low sperm counts or whether there is an underlying common cause for both conditions. As mentioned earlier, studies in both Denmark and the US indicate a birth cohort-related decline in testosterone levels in men (12,13; Fig. 4), echoing the similar decline in sperm counts.

Testicular dysgenesis syndrome (TDS)

In Europe there has been a synchronised upward trend in incidence of TGC and congenital reproductive tract malformations at the same time as a downward trend in semen quality and testosterone levels (although there are only data for the latter in Denmark). In addition, most of these disorders share common risk factors and are risk factors for each other. It has been proposed (5) that these conditions may represent a syndrome of disorders, a testicular dysgenesis syndrome (TDS; Fig. 5) caused by a common underlying entity, which results in a disturbance of the development of the testes during fetal life. Resulting from TDS one or more of the following symptoms may occur: cryptorchidism, hypospadias, decreased spermatogenesis and TGC. The aetiology of TDS is unclear, but the apparent rapid increase in male reproductive health problems during a few generations suggests that changes in lifestyle and/or in environmental factors are more likely causes than genetic factors (see sections above).

Endocrine disrupting chemicals (EDC)

EDC are exogenous substances that alter one or more functions of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations (WHO, International Programme on Chemical Safety, IPCS).

Scientific focus has in particular been directed towards EDC as possible contributing factors to the rise in incidence of TDS disorders (49). EDC have the potential capability of interfering with the sexual organs in early fetal life. The process of a fetus developing into a male

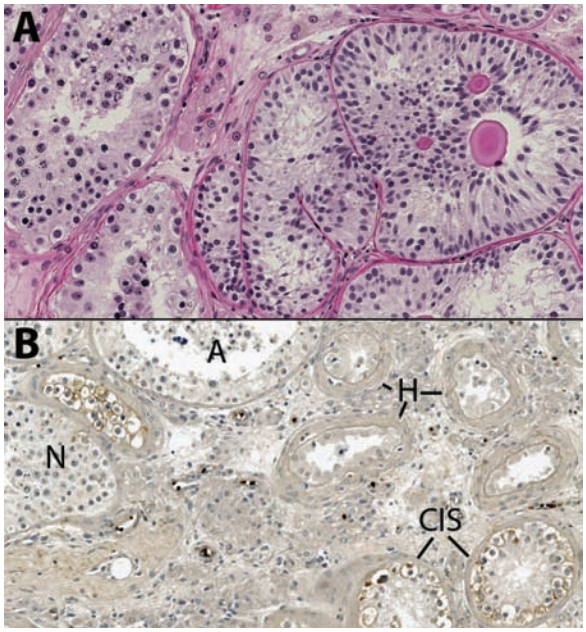

Figure 5. Testicular specimens from patients with TDS. A) Infertile man. Note abnormal spermatogenesis (left) and tubules containing only undifferentiated Sertoli cells and intratubular microliths (right). B. Mixed pattern with normal (N) and abnormal (A) spermatogenesis, hyalinised tubules (H) and tubules with carcinoma *in situ* (CIS).

involves a complex cascade of events. This is initiated by sex-determining genes, which activate the process of testis formation, which is a hormone-independent process. In contrast, subsequent steps in masculinisation, which include formation of the external genitalia and descent of the testes into the scrotum, are hormone-dependent (48). Three hormones are involved, anti-Müllerian hormone, testosterone and insulin-like factor 3, but of these testosterone (an androgen) has the widest ranging effects. Androgens are responsible for masculinisation of the external genitalia and final testis descent into the scrotum, events which are programmed or induced during the first trimester of pregnancy, so the timing of testosterone secretion is critical for normal development of the reproductive organs. Impairment of action of androgens in a male fetus leads to undermasculinisation, while exposure of a female fetus to androgens will cause masculinisation (49). EDC with anti-androgenic and estrogenic (e.g. diethylstilboestrol) and possibly other properties may therefore potentially disturb the development of reproductive organs during fetal life.

Animal experiments have shown that certain EDC can cause adverse effects in the male reproductive system that resemble the disorders described in human TDS, except for TGC (50). Wildlife exposed to environmental contaminants also exhibit abnormal reproductive development (51). The list of chemicals that have been identified as having endocrine disrupting properties in animal studies is growing and includes numerous substances found in household and consumer products; e.g. phthalates in many domestic, commercial and personal care products, and dioxin in fish and milk products (see examples in Table 1).

The mechanisms via which synthetic chemicals affect hormone action during masculinisation are only known for a few compounds. Some substances have been identified as being anti-androgenic because they bind to, but do not activate, the androgen receptor (AR), e.g. p,p'-DDE, which is a metabolite of the pesticide DDT, and the fungicide vinclozolin (52). In contrast, certain phthalate esters (e.g. diethylhexyl phthalate and di-n-butylphthalate) interfere with androgen biosynthesis in the fetal testis, resulting in anti-androgenic effects (49). Other chemicals exhibit estrogenic activity, and the adverse effects of estrogens in male animals are to an extent similar to those of anti-androgens (49). An example of an estrogenic chemical is bisphenol A, which in the 1930s was identified as a weak synthetic estrogen (53). Bisphenol A exerts estrogenic effects through binding to estrogen receptors (54,55) but it may also exert effects that are not estrogen-mediated. Some chemicals can act through multiple mechanisms, for example the fungicide prochloraz, which acts both by blocking the AR and by inhibiting fetal androgen production (56).

The effects of EDC are usually studied in animals at (maternal-fetal) exposure levels higher than those to which humans are typically exposed. However, in several studies exposure to mixtures of between three and seven chemicals with anti-androgenic properties, at doses at which each chemical alone was without significant effect, caused major impairment of masculinisation and occurrence of hypospadias (57,58). As humans are exposed to a complex cocktail of environmental chemicals (59), it is assumed that similar additive effects will also occur. This being the case, it introduces enormous complexity to identifying the causal contribution to TDS disorders of individual chemicals. The administrative regulation of such chemicals presents similar complexity (60).

Some human studies have found associations between exposure to EDC and malformations of the male urogenital tract. Higher concentrations of persistent pesticides (61) and flame retardants (62) in human breast milk as well as maternal occupational pesticide exposure early in pregnancy have also been found to be related to increased risk of cryptorchidism among the offspring (63).

Few studies have examined the effects of prenatal exposure to EDC on future semen quality and risk of testicular cancer, probably due to the challenging lag time between exposures and the occurrence of these disorders, which do not manifest until after puberty (64).

The epidemiological evidence of current exposure to EDC on semen quality is also still sparse (65), but a number of studies have found associations between PCBs and reduced semen quality.

In relation to the marked Danish-Finnish difference in incidence of male reproductive disorders described above, it is of note that Danish mothers have higher concentrations of several persistent chemicals in breast milk compared to Finnish mothers (66,67). In addition to

Table 1. Examples of endocrine disrupters and human exposure sources

Endocrine disrupters	Human exposure sources
Polychlorinated biphenyls (PCBs)	Transformers, cutting oils, plastic, paint, food
Phthalates (e.g. diethylphthalate, dibutyl phthalate)	Paint, plastics, food wrapping, cosmetics, food, dust
Brominated flame retardants	Building materials, electronic equipment, food
Parabens (e.g. butylparaben, propylparaben)	Preservatives in food and cosmetics
Bisphenol-A (e.g. polycarbonate)	Baby and water bottles, electronic equipment, food
UV-filters (e.g. 3-(4-methylbenzylidene)-camphor, hydroxylated benzophenones)	Sunscreens, coloured industrial products
Dioxin (e.g. 2,3,7,8-tetrachlorodibenzo-p-dioxin)	By-product from combustion processes, food
Polyfluorinated chemicals (e.g. PFOA, PFDoA)	Paints, impregnation of clothes and footwear, waxes for floors and cars, air
Pesticides (e.g. vinclozolin, dieldrin, hexachlorobenzene, DDT/DDE)	Food

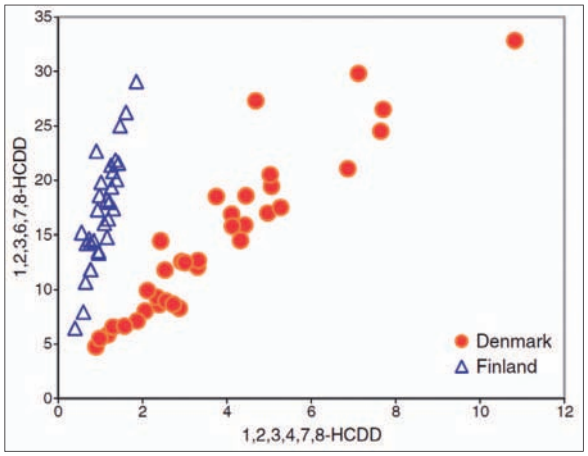

Figure 6. A 2-dimensional scatter plot showing the concentration of the two chemicals, 1,2,3,4,7,8-HCDD (x-axis) and 1,2,3,6,7,8-HCDD (y-axis), in each breast milk sample (pg/g lipids). The Danish (red) and Finnish (blue) samples are completely separated into two distinct groups. In each country, the two chemicals are clearly linearly correlated. However, the slopes are different in the two groups (from ref. 67).

quantitative differences in the exposure levels, the Danish and Finnish children have qualitatively distinct exposure patterns, typical chemical signatures that exemplify differences in their environmental impacts (Fig. 6) indicating a higher exposure for Danish infants, and presumably also indicating higher exposure during fetal life.

Although there is probably enough evidence overall to support the conclusion that exposure to EDC, probably during fetal life, may have contributed to the increase in male reproductive health problems, this evidence does not provide grounds for concluding that this is the sole causal factor (64). On the other hand, the complexity of current human exposure to environmental chemicals and the likelihood for additive effects of similarly acting chemicals, as seen in animal studies, means that identifying the importance of the role played by EDC in human male reproductive disorders is quite difficult. Despite this difficulty, there is a strong incentive to improve our understanding in this area, as it is certainly feasible to take steps to minimise exposure to identified causal agents, and this can only have positive effects in terms of improving reproductive health.

Epidemiological studies at an international level are urgently needed to provide a definitive association, or its lack, between exposure to individual environmental chemicals and any of the male reproductive disorders in humans (64). As described above the impact on male reproductive health can be very high.

Lifestyle factors

Lifestyle factors may also contribute to the observed adverse trends in male reproductive health. During the past 50 years huge changes in Western lifestyle have occurred; for example obesity is reaching epidemic proportions worldwide (68,69) and the prevalence of smokers has increased and then more recently declined in many Western countries (70). Several studies among men from the general population or infertile men (71-74) have shown that male obesity is associated with reduced semen quality. Smoking has also been found to impair semen quality. A meta-analysis published in 1994 based on 20 studies (75) found that smokers had a significant reduction in sperm concentration and a recent Danish study among men from the general population found a dose–response relationship between smoking and sperm motility and total sperm count (76). Interestingly, maternal smoking during pregnancy has a quite pronounced negative impact on semen quality among the offspring indicating that prenatal exposures are also important (77-80). Maternal smoking in pregnancy has also been shown in some (but not all) studies to increase the risk of hypospadias (81) and cryptorchidism (82,83) in male offspring. On the other hand, a meta-analysis has shown that maternal smoking during pregnancy is not associated with increased risk of TGC in sons (84). Nevertheless, the considerable increase in smoking prevalence among young women in most European countries in recent years can only exacerbate the incidence of male reproductive problems as some of these women will continue to smoke during pregnancy.

Genetic factors

There is growing evidence that genetic and epigenetic factors play a pivotal role for male reproductive health (85,86,87). The presence of a supernumerary X chromosome leads to Klinefelter syndrome (47, XXY), which is the most frequent chromosomal aneuploidy with an incidence of 1:400 male births and is characterised by hypergonadotropic hypogonadism and infertility. Recent studies clearly show that methylation and genetic polymorphisms are impacting the highly variable phenotype of Klinefelter patients. Moreover, further development of microsurgical techniques has led to the recovery of spermatozoa from these patients, which in principle allows them to father children. However, in more than 50% of the patients no sperm can be recovered, indicating that the same chromosomal background could have significantly different effects on spermatogenesis.

Familial aggregation of TDS disorders indicates that genetic factors may be involved in the aetiology. For example, the risk of developing TGC is markedly increased among brothers and sons of patients with TGC (88), and likewise cryptorchidism as well as hypospadias aggregate among male twin pairs and first-, second- and third-degree relatives (89). Besides rare point mutations (e.g. SRY mutation) and abnormal chromosome constitutions (e.g. 45X/46, XY), which are associated with increased risk of TGC, little is known about the role that specific genes play in the aetiology of TDS disorders. Mutations in the AR gene or in the gene encoding the 5-α-reductase type II enzyme, are associated with cryptorchidism and/or hypospadias, but these mutations are also extremely rare. Furthermore, there is, to date, virtually no evidence for the existence of specific genotypes predisposing to adverse effects of environmental or lifestyle factors (90). Racial differences in TDS, however, indicate a genetic component. US white men exhibit a markedly higher incidence of TGC than both Afro-American and other non-white US men (91). Geographical differences in TDS disorders, e.g.

between Danish and Finnish men as described above, could also reflect genetic differences in susceptibility to induction of these disorders by EDC and/or lifestyle factors or a combination of both. In this regard, several Scandinavian studies have shown that the incidence of TGC among Finnish first generation immigrants to Sweden is comparable to the country of origin, whereas among second generation immigrants it resembles that of the host country. This strongly suggests that environmental factors are an essential component in many TGC cases (92,93). Further research at international level is needed to get more knowledge about these severe reproductive health problems. As with many diseases it seems likely that the risk of developing male reproductive disorders/TDS will involve interplay between genes and the environment.

During recent years numerous candidate genes for male infertility have been screened for mutations. However, it turns out that mutations in autosomal genes are rare and do not play a substantial role in male infertility, while in 2% of oligo- or azoospermic men, microdeletions in the male-specific region of the Y chromosome can be detected (94,95). Our knowledge about X-chromosomal genes and their role in spermatogenesis is scant and should be improved.

A new concept has recently been proposed predicting that single nucleotide polymorphisms (SNPs) either alone or in combination with other SNPs are associated with modulation of spermatogenesis. In the worst scenario these polymorphisms may cause male infertility. Finally, epimutations leading to aberrant methylation of imprinted genes are considered a clear-cut phenomenon in men with impaired spermatogenesis. Several studies have convincingly shown that sperm morphology and sperm counts are significantly associated with the degree of normal methylation patterns of imprinted genes (96). Genetic alterations of the male germline are specifically relevant for patients undergoing ART. It will be of great importance to ensure that the sperm used for ICSI or IVF procedures is as well selected in terms of DNA integrity as under natural conception. It is biologically plausible, and preliminary data indicate, that children conceived by ART procedures show an increased risk of developing DNA methylation-specific diseases such as Beckwith-Wiedemann- or Angelman syndrome (97). Whether these genetic changes are associated with the disturbed genetic background of infertile couples or with the IVF procedures remains uncertain at present and has to be clarified.

Thus the research field of epigenetic changes has great importance for male reproductive health and needs to be more deeply explored as it brings qualitative aspects of male germ cells into the centre of attention which are highly relevant for the health of offspring conceived through ART procedures.

Conclusions

During recent years we have witnessed significant adverse trends in reproductive health problems in ***young*** men, with large geographical variations. In many European countries at least 20% of young men exhibit semen quality below the lower WHO reference level and this will most likely affect their fertility. The increasing use of ART also indicates that infertility is a growing problem. These widespread male reproductive health problems may contribute to decreasing birth rates, and the attendant socio-economic consequences. A significant proportion of men with TGC, poor semen quality, cryptorchidism and hypospadias may have a TDS of prenatal origin. The recently observed rapid increase in male reproductive disorders indicates that they are caused by environmental factors or changes in our lifestyle rather than genetic factors; this means that such disorders are intrinsically preventable, provided that the cause(s) can be identified. Of concern is also the mounting evidence that these male reproductive disorders may be associated with, and may contribute causally to, the explosive increase in cardiovascular and metabolic diseases in men, possibly via effects on testosterone levels. The recent recognition of the dynamic interplay between testosterone levels and abdominal obesity and its sequelae in men, in combination with the evidence for a secular decline in testosterone levels in men, suggests that the parallel increases in male reproductive and cardiometabolic health disorders may to some extent be interrelated. Our present understanding of the origin, and especially of the causes, of human male reproductive disorders is unfortunately very poor. Increased understanding would not only improve our ability to prevent or treat male reproductive disorders, but would also have a much wider impact on aspects of men's health that look set to dominate the European scene for the coming decades. From a socio-economic perspective, the impact of deteriorating male reproductive health in Europe thus looks pervasive.

Thus action is needed to improve national and international collaborative research in the field of male reproductive health to resolve the many remaining questions.

Recommendations for a common research strategy in male reproductive health

There is an urgent need to strengthen and to interlink research in male reproductive health at the national, European and international levels. This should take into account other factors which could interact with reproductive health at various levels, such as, for example, the growing obesity-related health issues across Europe or the influence of EDC. As mentioned above there remain many open questions both at the molecular and at the population/patient level so that it is generally important to strengthen translational research to better understand the consequences of certain disorders and their underlying mechanisms.

The **main recommendations** are therefore the following:

- **Increase awareness of male reproductive health issues**
  Currently, reproductive health of young men is not considered an important issue (other than sexually transmitted infections), despite growing evidence that it has a major influence on the frequency of male infertility and subsequent need for ART. In addition poor male reproductive health may be intrinsically linked to general health and life expectancy. It is therefore important to increase awareness of the major consequences that can arise from reduced male reproductive health.
- **Strengthen interdisciplinary, translational research**
  Male reproductive health might be influenced by different factors. As an example there is growing evidence that modern lifestyle not only causes obesity, it may also adversely affect both sperm counts and blood testosterone levels in men. However, the mechanisms involved and the long-term health implications are largely unknown. The susceptibility to develop infertility and reproductive dysfunction/diseases can start during testicular development as a result of exposure of pregnant women to environmental chemicals. Indeed there is the possibility, shown in animal models, that subferfility may be transmitted through several generations. In light of the current low birth rates and high need for ART, interdisciplinary, translational research is needed to better understand the different interacting factors which can have adverse effects on male reproductive health.
- **Implement long-term, epidemiological studies**
  To truly understand the etiology of poor male reproductive health, it will be critical to mechanistically understand the genetic and environmental contributions and their interactions in male reproductive health. Since environment, as opposed to genetics, can be changed, there is the possibility to intervene to prevent infertility and other reproductive diseases as well as co-morbidity factors by reducing environmental exposures. Therefore it is necessary to conduct long-term epidemiological studies to better understand the interacting mechanisms in male reproductive disorders.
- **Target research efforts**
  Better understanding of the mechanisms involved in these processes will provide paths forward for improving male reproductive health and will also likely have an impact on wider aspects of general health because of the emerging interconnections between these. It is envisaged that the results of such a research effort will be to identify the means of preventing/minimising occurrence of the disorders rather than the lengthy and costly development of drug treatments.

Proposed funding instruments

- **Strengthen national funding**
  Transdisciplinary, translational national research networks in human male reproductive health and fertility/infertility should be established as a focus area by national research councils and should be part of and contribute to the European network described below.
  National funds needed will vary with size of country, probably between 1 and 5 million euros per country per year.
- **Establish a European transdisciplinary, translational 'Research Network of Excellence' in male reproductive health**
  The role of such a network would be to evaluate the causes and consequences of the current low European fertility rates. The network should include expertise in andrology, endocrinology, management of infertility (IVF, ICSI), EDC, environmental health sciences, experimental systems, demography, sociology, epidemiology and bioinformatics/statistics. This network should use this multidisciplinary expertise to **establish robust methods** for accurately determining the extent of involuntary infertility across Europe, especially male-mediated infertility, and the **importance of societal factors** including **exposures to environmental chemicals** (individually and in mixtures), and **genetic background**. It should **utilise available methods, birth and adult cohorts**, to tease apart the relative importance of developmental versus adult causes of low sperm counts/infertility; this should take into account and make use of established geographical differences in sperm counts/related male reproductive disorders within Europe. The network should maintain quality control schemes to establish high and consistent standards of analytical methodology and patient care and include a **scientific advisory board** to assess progress and integration. Suggested funding level: 5 million euros per year for 10 years.
- **Establish links between the proposed European research network and similar networks in the US, Asia and other parts of the world**
  Such transnational cooperation would enable coordination of research, intervention and prevention efforts across the globe. The links should result in the formation of an effective international taskforce to tackle the alarmingly low fertility rates and other male reproductive diseases/dysfunctions in industrialised countries across the world, including all European countries, Japan, South Korea, Singapore as well as the US and developing countries. It is expected that the international groups will depend on their own core funding. However, running the taskforce activities (workshops, exchange of young scientists, common publications) are estimated to cost 1 million euros per year (European share: 25%).

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Abbreviations

ART: assisted reproduction techniques
EDC: endocrine disrupting chemicals
ICSI: intracytoplasmic sperm injection
IVF: *in vitro* fertilisation
TDS: testicular dysgenesis syndrome
TGC: testicular germ cell cancer
TNCR: total natural conception rate

Definitions

Testicular Germ Cell Cancer
- Commonest cancer in young men
- Associated with impaired semen quality and lower fertility rates
- Aetiology unknown

Congenital Malformations
- Cryptorchidism: undescended testis
- Hypospadias: incomplete fusion of the urethral folds

Total Natural Conception Rate
- Includes total number of births and induced abortions
- Excludes births after the use of ART

Endocrine disrupting chemicals (EDC)
Definition by WHO, International Programme on Chemical Safety (IPCS):
Exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub)populations

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Trends in Global Semen Parameters

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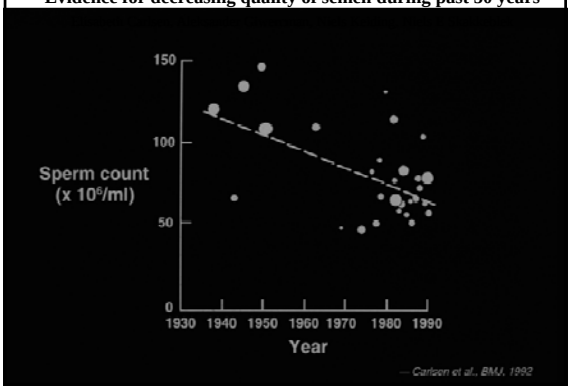
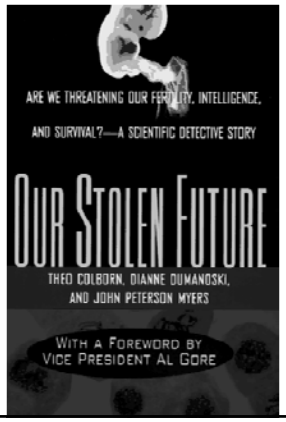
I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content.

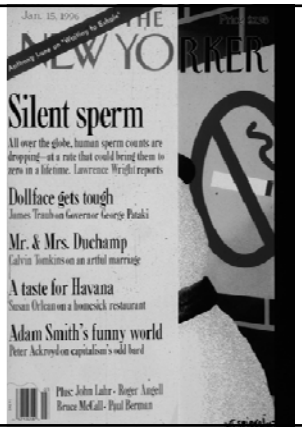
Evidence for decreasing quality of semen during past 50 years





"Although scientists are just beginning to explore the implications of this research, initial animal and human studies link these chemicals to myriad effects, including **low sperm counts**; infertility; genital deformities; hormonally triggered human cancers , such as those of the breast and prostate gland……

Vice President Al Gore , 1996



UN Report Calls Hormone Disrupting Chemicals Global Threat

21 February 2013

According to the UN **research** team, artificial chemicals **present** in daily use products are causing major increase in the serious health adversities. The report was compiled by the United Nations Environment **Programme** (UNEP) and the World Health Organization (WHO).

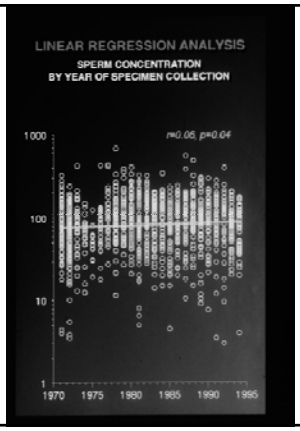
HUFFPOST GREEN
March 7th, 2013
Chemical Creep: How Toxic Chemicals Are Sneaking Into Your Food, And Your Body.

Plastic tubing used during mechanical milking is one likely source of hormone-disrupting chemicals in our food supply.

STUDY POPULATION:

MEN WHO BANKED SPERM BEFORE VASECTOMY
(n=1283)

Sperm Bank	n	Years of Study
New York - Idant Labs	400	1972 - 94
Minnesota - Cryogenic Labs	662	1970 - 94
California - California Cryobank	221	1978 - 94



Fisch et al, Fert Steril 1996

MULTIPLE REGRESSION ANALYSIS
EFFECTS OF AGE, ABSTINENCE AND YEAR OF SPECIMEN COLLECTION ON SPERM CHARACTERISTICS (n=1283)

	Sperm Concentration	Semen Volume	Sperm Motility
Age	N.S.	-0.15 (p<0.001)	-0.17 (p<0.001)
Duration of Abstinence	0.15 (p<0.001)	0.22 (p<0.001)	N.S.
Year of Specimen Collection	0.07 (p=0.03)	N.S.	N.S.

Fisch et al , Fert Steril 1996

SEMEN CHARACTERISTICS BY REGION

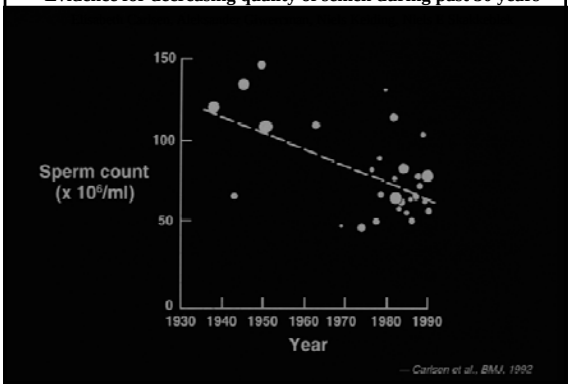
Mean +/- SE

	Sperm Conc (millions/cc)	Motility (%)	Volume (cc)
NY	131.5 +/- 3.5*	58.2 +/- 0.5**	4.0 +/- 0.1
MN	100.8 +/- 2.8*	56.0 +/- 0.5**	4.2 +/- 0.1
CA	72.7 +/- 3.1*	51.4 +/- 1.1**	3.3 +/- 0.1*

*(p<0.01)
**(p<0.05)

Fisch et al, Fert Steril 1996

Evidence for decreasing quality of semen during past 50 years

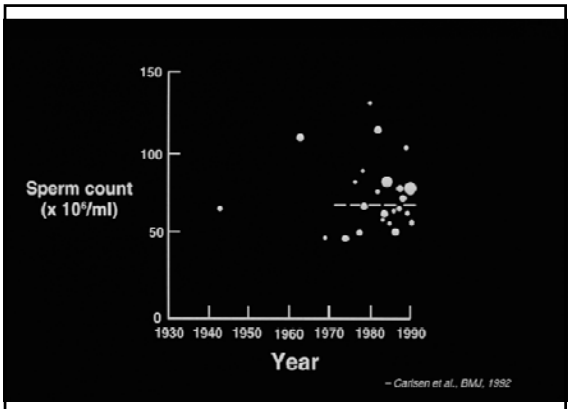


GEOGRAPHIC VARIATIONS IN SPERM CONCENTRATION

Year	Location	Sperm Conc (M/cc)	n
1938	New York	120.6	200
1945	New York	134.0	100
1950	New York	100.7	100
1951	New York	107.0	1000
1963	Washington	110.0	100
1971	Germany	74.4	100
1974	Iowa	48.0	386
1975	New York	79.0	2300
1979	Brazil	67.6	185
1982	Texas	66.0	4435

Year	Location	Sperm Conc (M/cc)	n
1983	France	102.9	809
1983	Libya	65.0	1500
1984	Australia	83.9	119
1984	Greece	72.0	114
1985	Hong Kong	83.0	1239
1986	Thailand	52.9	307
1986	Nigeria	54.7	100
1987	Tanzania	66.9	120
1989	UK	91.3	104
1989	France	77.7	1222

Carlsen, et. al, BMJ 1992.



"Theoretically, selection bias due to geographical and racial differences could account for the decrease in sperm counts."

Evidence for decreasing quality of semen during past 50 years
Elisabeth Carlsen, Aleksander Giwercman, Niels Keiding, Niels E Skakkebæk
BMJ 1992;305:609-13

FERTILITY AND STERILITY
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Geographic variations in sperm counts: a potential cause of bias in studies of semen quality

Harry Fisch, M.D.*††
Erik T. Goluboff, M.D.*

Columbia-Presbyterian Medical Center, and Albert Einstein College of Medicine, New York, New York

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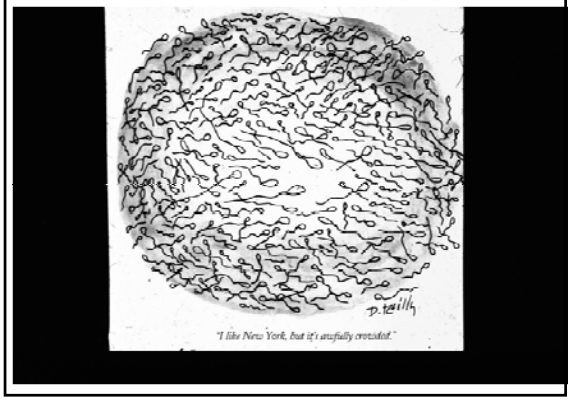
Semen analyses in 1,283 men from the United States over a 25-year period: no decline in quality

Harry Fisch, M.D.*†‡ Joseph Feldshuh, M.D.‖
Erik T. Goluboff, M.D.* Stephen J. Broder, B.S.¶
John H. Olson, M.S.T.§ David H. Barad, M.D.†

Columbia-Presbyterian Medical Center; Albert Einstein College of Medicine, and Idant Laboratories, New York, New York; Cryogenic Laboratories, Roseville, Minnesota; and California Cryobank, Inc., Los Angeles, California



Studies Finding a Decline in Sperm Count

Date	First Author	Sample Size (N)	Study Period	Location
1995	Auger	1351	1973-1992	France
1996	Irvine	577	1984-1995	Scotland
1996	Adamopoulos	2385	1977-1993	Greece
1998	Bonde	1196	1986-1995	Denmark
1999	Bilotta	1068	1981-1995	Italy
2003	Almagor	2638	1990-2000	Israel
2005	Lackner	7780	1986-2003	Austria
2012	Splingart	1114	1976-2009	France
2012	Rolland	26609	1989-2005	France

Total N = **44,718**

Declining Worldwide Sperm Counts: Disproving a Myth Harry Fisch, Urologic Clinics of North America (2008)

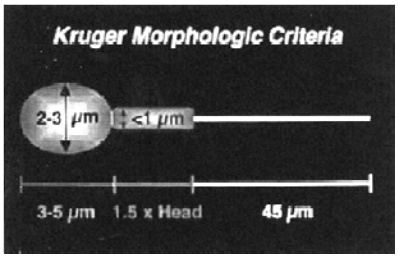
Trends in Global Semen Parameters **Fisch H,** Asian J Androl. **2013**

Studies Finding **an Increase** or **No Decline** in Sperm Count

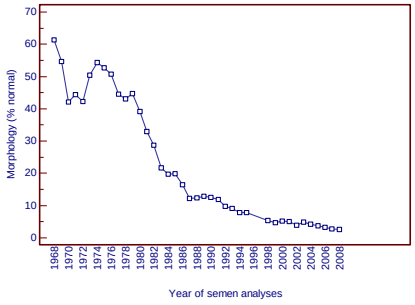
Date	First Author	Sample Size (N)	Study Period	Location
1996	Bujan	302	1977-1992	France
1996	Paulsen	510	1972-1993	US
1996	Vierula	5481	1967 - 1994	Finland
1996	Fisch	1283	1970-1994	US
1997	Berling	718	1985-1995	Sweden
1997	Benshushan	188	1980-1995	Israel
1997	Handelsman	689	1980-1995	Australia
1997	Rasmussen	1055	1950-1970	Denmark
1998	Emanuel	374	1971-1994	US
1998	Younglai	48,968	1984-1996	Canada
1999	Andolz	20,411	1960-1996	Spain
1999	Gyllenborg	1,927	1977-1995	Denmark
1999	Zorn	2,343	1983-1996	Slovenia
2000	Acacio	1347	1951-1997	US
2000	Tae Seo	22,249	1989-1998	Korea
2001	Itoh	711	1975-1998	Japan
2002	Costello	448	1983-2001	Australia
2003	Marimuthu	1176	1990-2000	India
2006	Pal	368	1993 - 2005	India
2011	Axelsson	511	2000/2001 – 2008-2010	Sweden
2012	Elia	1327	1992-2012	Italy

Total N = 112,386

Trends in Global Semen Parameters
Fisch H, Asian J Androl. **2013**
Declining Worldwide Sperm Counts: Disproving a Myth
Harry Fisch, Urologic Clinics of North America (2008)



Overview of declining sperm morphology values over years



Menkveld etal., 1986; Menkveld, 2009

Normal values from WHO manuals, editions 2- 4 and lower reference limits from new 5th WHO manual (2010)

Semen parameter	WHO edition and year			
	2nd - 1987	3rd - 1992	4th - 1999	5th - 2010
Volume (ml)	2.0	2.0	2.0	1.5
Sperm concentration (10^6/ml)	20	20	20	15
Total sperm count (10^6)	40	40	40	39
Motility (% progressive)	50	50	50	28
Vitality (% live)	50	75	75	59
Morphology (% normal)	**50**	**30**	**(15)**	**4**

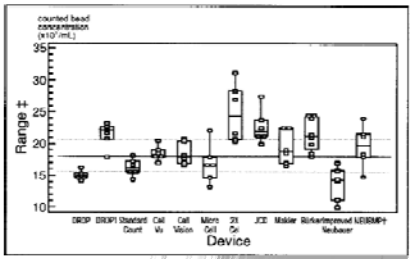
Cooper, 2007 (ESHRE campus meeting)

Geographic Differences in Semen Quality of Fertile US Male

Swan *et al*, EHP 2002

Center	n	Hemacytometer (10^6/mL)	μ-Cell (10^6/mL)
Missouri	176	58.7	53.4
California	124	80.8	69.0
Minnesota	155	98.6	74.6
New York	38	102.9	75.5

The performance of 10 different methods for the estimation of sperm concentration, Comhaire et al 1997



PTS PROFICIENCY Andrology 2012

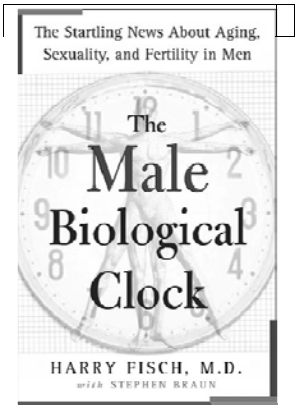
Name	Line No.	Specimen 1 Range & Type		Mean	SD
Sperm Count					
Initial Grouping by Method					
Cell-Vu	1	2.0 - 16.0	C	8.9	2.7
Makler	2	4.0 - 18.0	C	11.4	3.0
Mid Atlantic/Leja Standard	3	3.0 - 17.0	C	9.7	2.3
Mid Antlant/Leja - CASA	4	8.0 - 22.0	C	14.9	19.6
Micro Cell - CASA	5	4.0 - 18.0	C	10.8	4.2
Hemacytometer	6	8.0 - 22.0	C	14.5	3.4
Micro Cell	7	3.0 - 17.0	C	10.3	2.4
Total Population					
Whole Population	8	5.0 - 19.0	C	11.7	5.8

Decline in semen concentration and morphology in a sample of 26,609 men close to general population between 1989 and 2005 in France

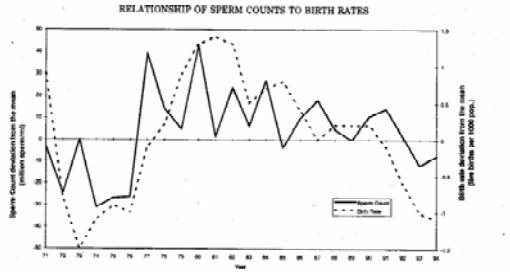
Rolland, Le Moal, Wagner, Royere and De Mouzon

Human Reproduction 2012

"Regarding the measurement methods for concentration and motility, experts have confirmed that the methods have not changed noticeably during the study period."



The relationship of sperm counts to birth rates: a population based study *(Fisch et al J Urol. 1997)*



World Health Organization reference values for human semen characteristics (2010)

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

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

Effect of lifestyle and environment – **Richard Sharpe (United Kingdom)**

Contribution not submitted by the speaker

UNIVERSITY OF COPENHAGEN Department of Public Health

Faculty of Health Sciences

Increasing patient age –

A factor that may causing the increase in couples seeking ART each year

Lone Schmidt
Associate Professor, DMSci, PhD
University of Copenhagen
Department of Public Health
Denmark

PCC 2, ESHRE
London 7 July 2013

Dias 1

UNIVERSITY OF COPENHAGEN Department of Public Health

Conflict of interest

- Research funding from Merck, Sharpe & Dohme for a PhD project

Dias 2

UNIVERSITY OF COPENHAGEN Department of Public Health

Learning objectives

- ❑ Postponement of family formation –
  - fertility
  - family size
  - need for medically assisted reproduction (MAR)
- ❑ Paternal age – time to pregnancy, infertility, miscarriages, outcome of MAR treatment
- ❑ The importance of studying the combined effect of female and male age on reproduction

Dias 3

Postponement of family formation

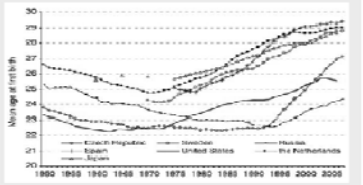


Figure 1 Mean age of mother at first birth, selected countries, 1950–2007. Sources: Council of Europe (2006), Human Fertility Database, and own computations based on Eurostat (2009) and national statistical offices.

Schmidt et al. Hum Reprod Update 2012;18:29-43

Monthly hazard of live birth conception – female age

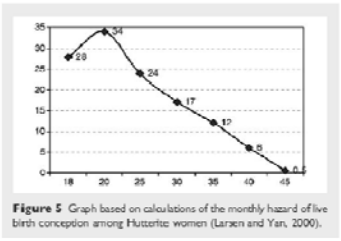


Figure 5 Graph based on calculations of the monthly hazard of live birth conception among Hutterite women (Larsen and Yan, 2000).

Schmidt et al. Hum Reprod Update 2012;18:29-43

Impact of postponement

	Initial population	1st birth → 69 months	Relative change
Mean age first pregnancy attempt	25.1	30.8	22.7%
Mean final number of children	2.004	1.766	- 11.9%
Couples with fewer births than wanted	14.8%	24.0%	62.2%
Couples involuntarily childless	9.8%	15.8%	61.2%
Couples eligible for ART	11.6%	20.8%	79.3%
Couples with more births than wanted	15.8%	10.2%	- 35.4%

Leridon & Slama. Hum Reprod 2008;23:1312-9.

Time to pregnancy and family size

When TTP ≥ 12 months

Age	Significant ORs of no second child	Significant ORs of no third child
All age groups	1.64-2.45	1.47 – 1.83
25-29 years	1.79 – 2.31	1.62 – 1.90
30+ years	3.57 – 8.52	3.22 – 4.71

Joffe et al. Hum Reprod 2009;24:1999-2206.

Paternal age – in fertile study populations

Paternal age and time to pregnancy (TTP)

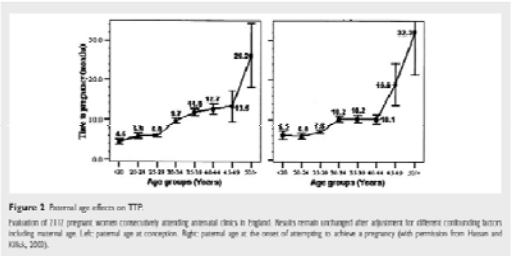


Figure 2 Paternal age effects on TTP.

Evaluation of 7132 pregnant women consecutively attending antenatal clinics in England. Results remain unchanged after adjustment for different confounding factors including maternal age. Left: paternal age at conception. Right: paternal age at the onset of attempting to achieve a pregnancy (with permission from Hassan and Killick, 2003).

Sartorius & Nieschlag. Hum Reprod Update 2010;16:65-79.

Paternal age and TTP ≤12 months

ALSPAC study – 8515 planned pregnancies, ≥ 24 weeks

Adjusted odds ratio of conception ≤ 12 months compared with men < 25 years

Age 30-34 0.62 (0.40-0.98)
Age 35-39 0.50 (0.31-0.81)
Age >39 0.51 (0.31-0.86)

Ford et al. Hum Reprod 2000;15:1703-8.

Paternal age and miscarriage

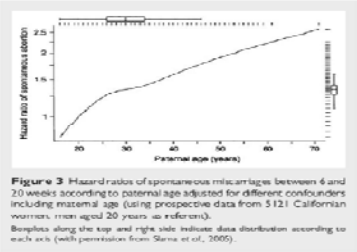


Figure 3 Hazard ratios of spontaneous miscarriages between 6 and 20 weeks according to paternal age adjusted for different confounders including maternal age (using prospective data from 3121 Californian women, men aged 20 years as referent).
Boxplots along the top and right side indicate data distribution according to each axis (with permission from Slama et al., 2005).

Sartorius & Nieschlag. Hum Reprod Update 2010;16:65-79.

Paternal age and fetal death

Danish National Birth Cohort – pregnant women and offspring
> 23,000 pregnancies

Men > 50 years, adjusted hazard ratios

Risk of early fetal death 1.38 (0.66 – 2.88)

Risk of late fetal death 3.94 (1.12 – 13.8)

Nybo Andersen et al. Am J Epidemiol 2004;160:1214-22.

Paternal, maternal age and miscarriage

Adjusted OR for miscarriage

Paternal age	Maternal age 20-29	30-34	35-44
20-29	Standard risk zone	Standard Risk zone	High risk zone
30-34	Standard risk zone	Standard risk zone	2.87 (1.86-4.45)
35-39	Standard risk zone	Standard risk zone	High risk zone
40-64	Standard risk zone	High risk zone	Highest risk zone 5.65 (3.20-9.98)

Dias 13 de La Rochebrochard et al. Hum Reprod 2002;17:1649-56.

Paternal age – in fertility patient study populations

Dias 14

Female age and live births among couples initiating MAR

Complete 5-year follow-up after initiating MAR at a specialised fertility clinic (n= 1338 women)

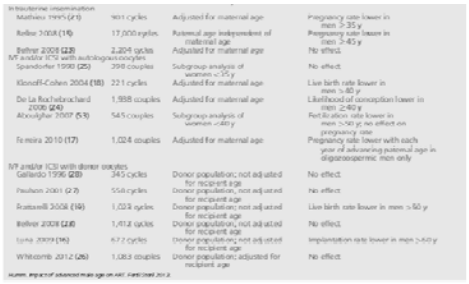
69.4% achieved a live birth

74.9% among women < 35 years when initiating MAR

52.2% among women ≥ 35 years when initiating MAR

Dias 15 Pinborg et al. Hum Reprod 2009;24:991-9.

Male age and MAR



Humm &Sakkas. Fertil Steril 2013;99:30-6.

Male age and IVF conception

Risk of failure to conceive after IVF, n=1938 couples

Adjusted OR

Paternal age

< 30	1.00
30-34	1.52 (1.08-2.14)
35-39	1.32 (0.92-1.89)
> 39	1.70 (1.14-2.52)

De La Rochebrochard et al. Fertil Steril 2006;85:1420-4.

Male age and IVF conception

Adjusted OR for failure to conceive after IVF –
with maternal/paternal age interaction

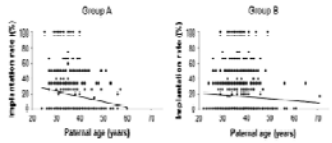
Paternal age	Maternal age 35-37	38-40	> 40
35-39	1.33 (0.80-2.22)	3.05 (1.44-6.48)	2.16 (0.89-5.20)
≥ 40	2.00 (1.10-3.61)	2.03 (1.12-3.68)	5.74 (2.16-15.23)

De La Rochebrochard et al. Fertil Steril 2006;85:1420-4

Male age and ICSI conceptions

Group A: Oligozoospermic patients
Group B: Normozoospermic patients

Implantationrates



Ferreira et al. Fertil Steril 2010;93:1870-4.

Dias 19

Male age and oocyte recipient cycles – live births

1392 oocyte donor cycles in 1083 female recipients and male partner

OR and adjusted OR for achieving a live birth

Factor	OR	Adjusted OR
Male age < 50	1.55 (1.04-2.30)	1.36 (0.90-2.06)
50+	1	1
Female age < 45	1.52 (1.15-2.00)	1.44 (1.09-1,92)
45+	1	1

Whitcomb et al. Fertil Steril 2011;95:147-51.

Dias 20

Male age and MAR - reviews

- "Insufficient evidence to demonstrate an unfavorable effect of paternal age on ART outcome"
  (Dain et al. Fertil Steril 2011;95:1-8)

- Only one prospective study- Klonoff-Cohen et al., 2004
  "Each additional year of paternal age was associated with a 12% increased odds of not having a successful live birth (p=.01)"
  (Humm & Sakkas. Fertil Steril 2013;99:30-6)

Dias 21

UNIVERSITY OF COPENHAGEN Department of Public Health

Importance of combined effect of male and female age on reproduction

- Women in average is seeking to establish a family with men that are older than themselves
- The combined effect of female and male age is of importance for fertility/infertility, miscarriage rates, outcome of medically assisted reproduction
- Present additional results for combined age effect – not only results adjusted for age effect of one of the partners

Dias 22

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Take-home messages

- Advanced paternal age is a risk factor for prolonged time to pregnancy, infertility, and miscarriages in fertile populations
- The lower paternal age limit for increased risks not yet clear – > 40 or > 45 or >50?
- Advanced paternal age is a potential risk factor for decreased successrates after MAR
- Combined effect of paternal and maternal age increases risks of reduced fertility

Dias 23

UNIVERSITY OF COPENHAGEN Department of Public Health

Is increasing patient age a cause of more people seeking MAR?

YES –

- Postponement of family formation increases the risk of more couples seeking medically assisted reproduction treatment
- Even high-quality MAR treatments cannot overcome the impact of increased female and male age on treatment outcome

Two important messages for the public

Dias 24

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Pinborg A et al. Prospective longitudinal cohort study on cumulative 5-year delivery and adoption rates among 1338 couples initiating infertility treatment. Hum Reprod 2009;24:991-9.

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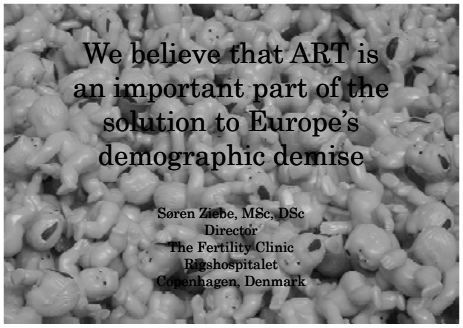
Whitcomb BW et al. Contribution of male age to outcomes in assisted reproductive technologies. Fertil Steril 2011;95:147-51.



Disclosure:

I have nothing to disclose

Learning points:

-10 % is important

-We help young couples, families and society

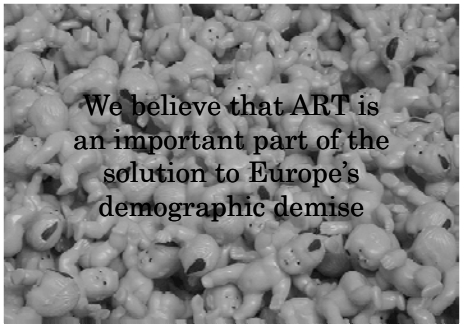
-Prevention is better than cure

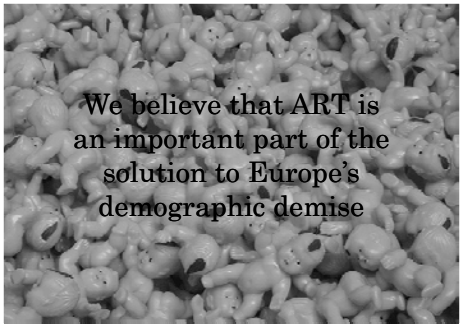
-We do better than nature

-We are far from utilizing the full potential of ART

-We should use our effort on preventing people becoming infertile

- not on preventing infertile from having treatments


We believe that ART is an important part of the solution to Europe's demographic demise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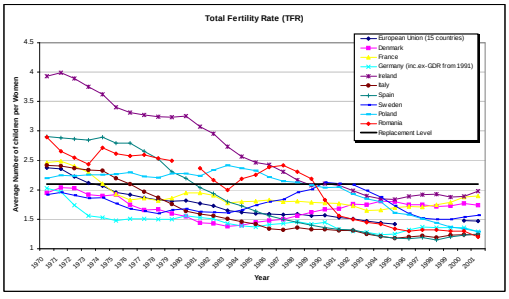
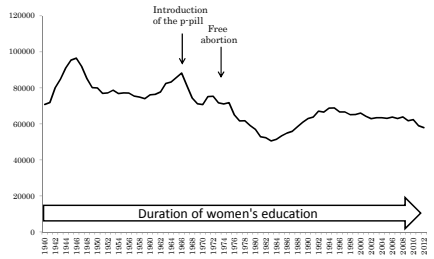
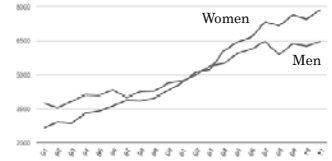

Total Fertility Rate (TFR)
European Union (15 countries)
Denmark
France
Germany (inc.ex-GDR from 1991)
Ireland
Italy
Spain
Sweden
Poland
Romania
Replacement Level
Average Number of children per Women
Year

Birth cohort in Denmark



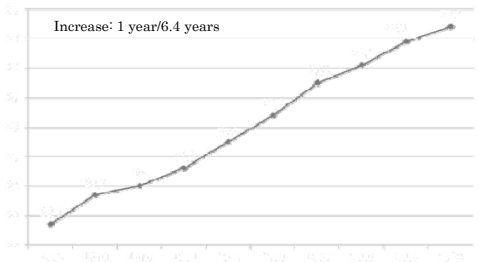
Longer education in Denmark – especially for the women



"Your father and I will strongly advice you not to have children until you finished your education"

"But then it may be too late Mom!"

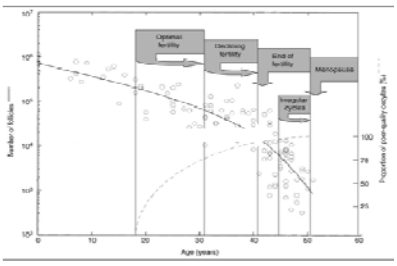
Age at first birth in Denmark 1965-2012



Danmarks Statistik Online: www.dst.dk

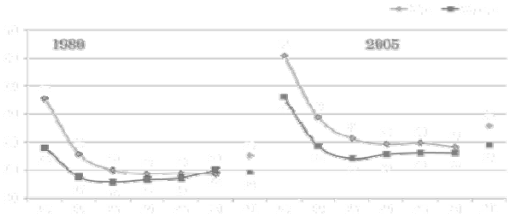
IGNORING OUR BIOLOGY

We are moving our reproduction from the optimal period to the declining period of our life



Broekmans et al.
Trends in Endocrinologi & Metabolism, 2007

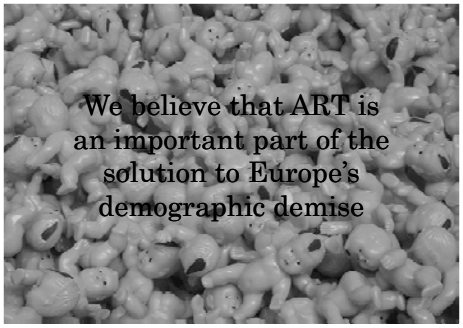
The proportion (%) of Danish women and men living single in 1980 and 2005 according to age



Age

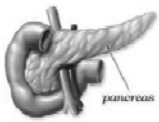
Motivating young couples to start having children at a earlier stage and to have more children is almost never part of any strategy addressing the demographics challenges

Preventing infertility is almost never part of any strategy addressing the fertility issues
We as ART professionals and societies like ESHRE and ASRM have failed immensely in addressing this issue



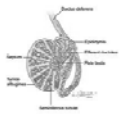
Two men - Two sick glands
but different public perception

John



If you are sick in the pancreas and have diabetes nobody will question if you are sick and should have insulin

Robert



If you are sick in the testicles and have an affected sperm production it is often not considered a disease

Infertile or Subfertile – Some things simply just takes time ……

Table II – percentages of pregnancies in each subgroup and theoretical delays necessary to obtain 100 % pregnancy rates considering all couples as potentially fertile

Sperm concentration	Pregnancies in 12 years	Percentage	Comparative theoretical delays for 100 % pregnancies (considering all couples as potentially fertile)
0.1-1 mill/ml	9/104	8.65 %	138 years
1-5 mill/ml	29/109	26.6 %	45 years
5-10 mill/ml	70/204	34.3 %	35 years
10-15 mill/ml	213/364	58.5 %	20 years
15-20 mill/ml	118/510	81.96 %	15 years

Schoysman and Gerris 1983

Denial ?

How long is it reasonable to wait?

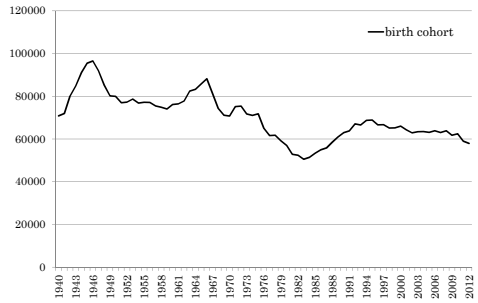
Fertility desires in Europe

Countries	Average desired number of children (women)	Average desired number of children (men)
Austria	1.84	1.78
Belgium	1.86	1.81
CZ Republic	1.97	2.02
Estonia	2.16	2.09
Finland	2.18	2.14
Germany	1.75	1.59
Italy	1.92	1.86
Netherlands	2.13	1.98
Slovenia	2.01	2.02

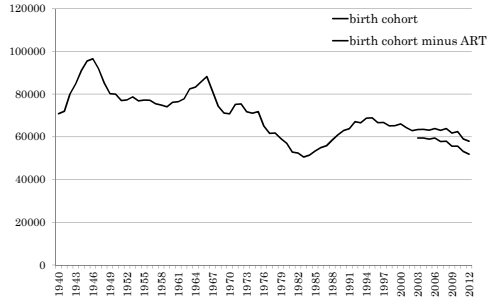
Federal Institute for Population Research: DIALOG (http://www.bosch-stiftung.de/content/language1/downloads/PPAS_en.pdf). The Demographic Future of Europe – Facts, Figures, Policies. Results of the Population Policy Acceptance Study (PPAS)

Slide from Mark Connolly

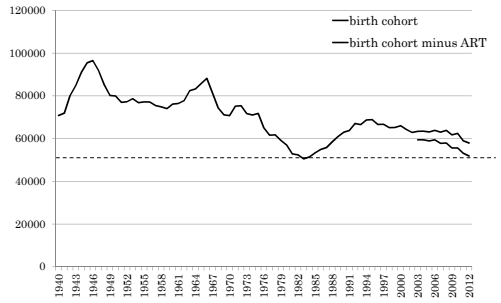
Birth cohort in Denmark



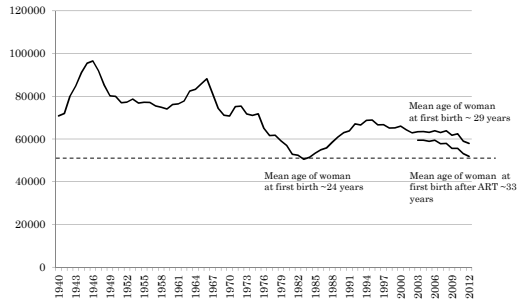
Birth cohort in Denmark



Birth cohort in Denmark



Birth cohorts in Denmark



Number of children – by age of the first child

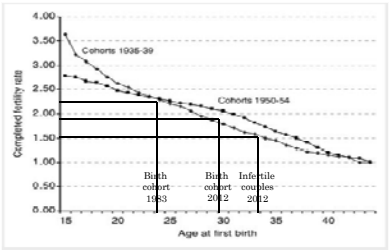
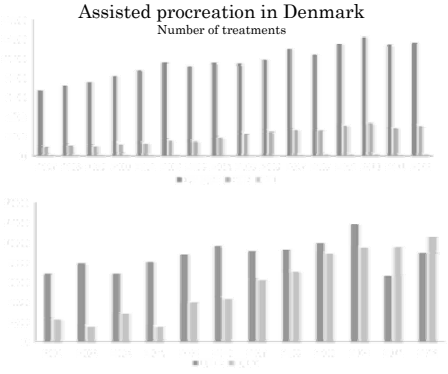


Figure 4 Age at first birth and completed fertility rate, Swedish women born in 1935–1939 and 1950–1954. Source: Andersson et al. (2008: 49, Table 12d).

Assisted procreation in Denmark

Number of treatments



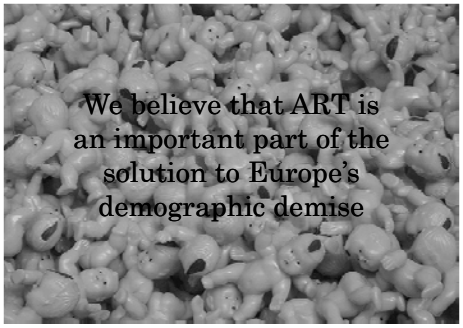
Assisted procreation in Denmark 2012

	No. of Cycles	Ongoing Pregnancies	Multiple pregnancies	Number of Children
IVF/ICSI <40 year	9.112	2.276	15,1%	2.629
IVF/ICSI >40 year	2.595	242	10,7%	268
FER	3.084	501	13,6%	569
DONATION	194	54	25,9%	70
ART	14.985	3.073	14,7%	3.536
IUI-H	8.989	1.096	10,4%	1.219
IUI-D	10.612	1.193	6,5%	1.284
IUI	19.601	2.289	8,4%	2.503
ART + IUI	**34.586**	**5.362**	**12,0%**	**6.039**

Total birth cohort 2012 in Denmark 57.916

8.4-10.4 % OF ALL CHILDREN BORN IN DENMARK IN 2012 IS A RESULT OF ASSISTED PROCREATION

10 % of the annual national birth cohort is important to any society!

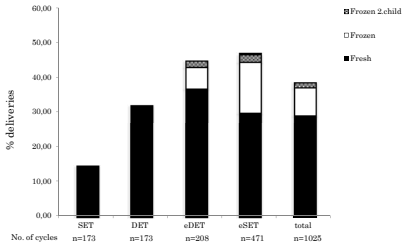


Cumulative outcome in a consecutive cohort of 1025 first treatment cycles

COHORT STUDY
(PRELIMINARY DATA – Fresh transfer with 5 years follow up of frozen embryos)

Number of treatment cycles:	1025
Resulting in a live birth	394 (38%)
Not resulting in a live birth	647 (62%)
Number of oocytes retrieved:	8854
Number of embryos transferred:	2366
Fresh cycle 1406	
Frozen cycles 960	
Transferrable embryos	26,7 %
Total number of children born	452

Cumulative outcome in a consecutive cohort of 1025 first treatment cycles



Cumulative outcome in a consecutive cohort of 1025 first treatment cycles

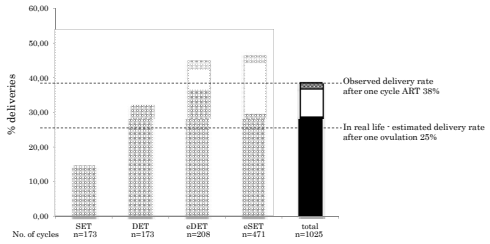
CONCLUSSION:

IN 62 % OF ALL ASPIRATIONS THERE WHERE NO OOCYTES THAT COULD DEVELOP INTO A CHILD

19 % OF TRANSFERRED EMBRYOS CAPABLE OF DEVELOPING INTO A CHILD

ONLY 5,1 % OF THE OOCYTES HAD THE COMPETENCE TO DEVELOP INTO A CHILD

Cumulative outcome in a consecutive cohort of 1025 first treatment cycles



The full biological potential in a single cycle

Cumulative outcome in a consecutive cohort of 1025 first treatment cycles

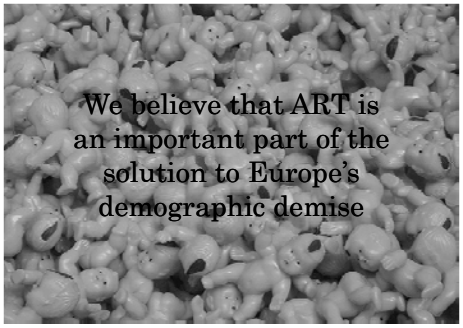
SPECULATIONS:

	ART	NATURAL CYCLE
No. of cycles	1025	1025
No. of oocytes	8854	1025 (IGNORING TWINS)
No. of children	452	256 (with 25 % delivery rate)
% oocytes resulting in children	5%	25%

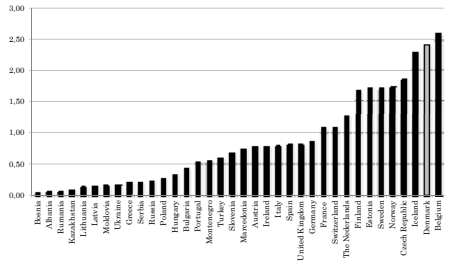
Difference: 196 extra children (~75%) after ART in "*the same number of cycles*"

WE CAN "MAKE" 75% MORE CHILDREN THAN NATURE…

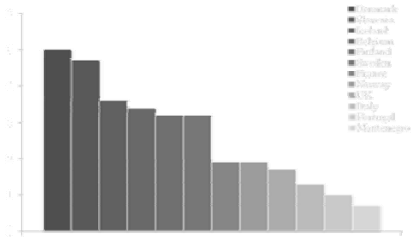
HUMANS ARE NOT USING THE FULL BIOLOGICAL POTENTIAL IN A SINGLE CYCLE



Number of reported ART cycles per 1000 inhabitants
EIM 2008



Percentage of infants born after ART
Europe, 2007. (Countries with complete recording)



ESHRE EIM, Human Reproduction, 2010.

Can we evaluate a technique when we deliberately is not using its full potential?

ART ONLY

Countries from EIM 2008

Denmark:

5.568.854 inhabitants
13.476 cycles of ART– 2.42 cycle / 1000 inhabitants
3.004 children (4.49 cycles per child)

ART ONLY

Countries from EIM 2008

Denmark:

5.568.854 inhabitants
13.476 cycles of ART– 2.42 cycle / 1000 inhabitants
3.004 children (4.49 cycles per child) GOLDEN STANDARD

ART ONLY

Countries from EIM 2008

Denmark:

5.568.854 inhabitants
13.476 cycles of ART– 2.42 cycle / 1000 inhabitants
3.004 children (4.49 cycles per child) GOLDEN STANDARD

The Nederlands

16.696.700 inhabitants
40.406 cycles (if 2.42 cycle / 1000 inhabitants)
8.999 children per year (if 4.49 cycles per child)

EIM 2008

21.164 cycles (~52 % of utilisation in Denmark)
4.487 children

ART ONLY

Countries from EIM 2008

Denmark:

5.568.854 inhabitants
13.476 cycles of ART– 2.42 cycle / 1000 inhabitants
3.004 children (4.49 cycles per child)

GOLDEN STANDARD

The Nederlands

16.696.700 inhabitants
40.406 cycles (if 2.42 cycle / 1000 inhabitants)
8.999 children per year (if 4.49 cycles per child)

EIM 2008

21.164 cycles (~52 % of utilization in Denmark)
4.487 children

European countries total (EIM 2008)

808.340.815 inhabitants
1.956.182 cycles (if 2.42 cycle / 1000 inhabitants)
435.675 children per year (if 4.49 cycles per child)

EIM 2008

532.260 cycles (~27 % of utilization in Denmark)
107.383 children

Assisted procreation

Countries from EIM 2008

Denmark:

Children after assisted procreation in 2008

ART	3.004 children (57 %)
IUI	2.266 children (43 %)
Total	5.270 children

Assisted procreation

Countries from EIM 2008

Denmark:

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GOLDEN STANDARD

Assisted procreation
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ART	3.004 children (57 %)
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Total	5.270 children

GOLDEN STANDARD

The Nederlands

ART	8.999 children (57 %)
IUI	6.788 children (43 %)
Total	15.787 children
EIM 2008	**4.487 children (IUI not reported)**

LOST POTENTIAL IN THE NEDERLANDS 2008: **11.300 CHILDREN**

Assisted procreation
Countries from EIM 2008

Denmark:

Children after assisted procreation in 2008

ART	3.004 children (57 %)
IUI	2.266 children (43 %)
Total	5.270 children

GOLDEN STANDARD

The Nederlands

ART	8.999 children (57 %)
IUI	6.788 children (43 %)
Total	15.787 children
EIM 2008	**4.487 children (IUI not reported)**

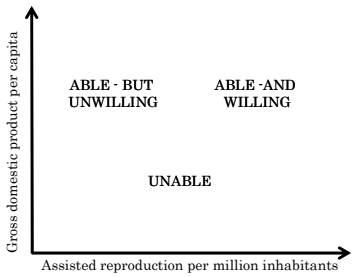
LOST POTENTIAL IN THE NEDERLANDS 2008: **11.300 CHILDREN**

European countries total (EIM 2008)

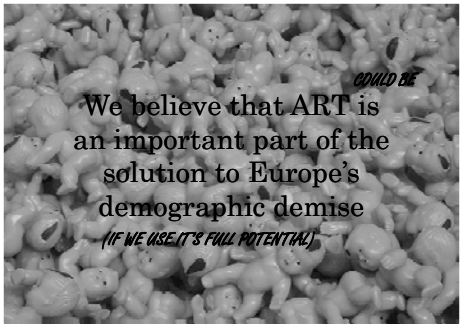
ART	435.675 children (57 %)
IUI	328.667 children (43 %)
Total	764.342 children
EIM 2008	**107.383 children**

LOST POTENTIAL IN EUROPE 2008: **656.959 CHILDREN**

Assisted Reproduction – A question of recourses and priority in society



Modified from Arne Sunde



COULD BE

We believe that ART is an important part of the solution to Europe's demographic demise

(IF WE USE IT'S FULL POTENTIAL)

ART is the best investment a society can do…

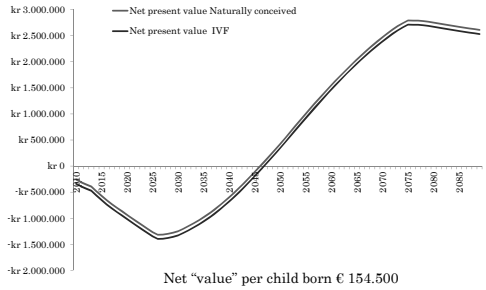
The long-term fiscal impact of funding cuts to Danish public fertility clinics

Mark P Connolly [a,b,*], Maarten J Postma [a], Simone Crespi [c], Anders Nyboe Andersen [d], Søren Ziebe [d]

Table 2 Discounted lifetime tax benefits per IVF/ICSI-conceived and naturally conceived child.

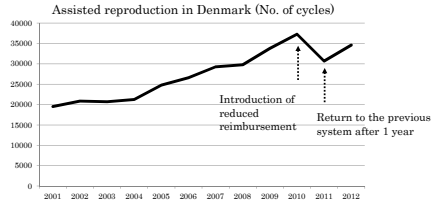
	Cost per live birth (€)	Year 25 (€)	Year 50 (€)	Breakeven age
Naturally conceived	0	−145,150	165,200	39
Assisted-conceived child, mother aged <40	11,078	−155,900	154,500	39
Assisted-conceived child, mother aged ≥40	26,100	−170,500	139,900	41

Net Present value of child in Denmark (2010)



Net "value" per child born € 154.500

Financial potential to Society – but financial burden to the couple



Conclusion:

What do ART do:
- Helps a lot of people to have normal children
- Helps a lot of families to have grandchildren, nephews, nieces
- Highlights risk factors for decreased fertility
- Mask the "natural" fertility rate by compensating with ART children
- Generates a huge financial surplus to society for a very low "investment"

We should use our effort on preventing people becoming infertile - not on preventing infertile from having treatment!

Conclusion:

We believe that ART is an important contribution to the solution to Europe's demographic demise

We believe that ART is an important part of the solution to the infertile patient and their families

References:

Danmarks Statistik Online: www.dst.dk

Broekmans et al,
Trends in Endocrinologi & Metabolism, 2007

Federal Institute for Population Research: DIALOG (http://www.bosch-stiftung.de/content/language1/downloads/PPAS_en.pdf).
The Demographic Future of Europe – Facts, Figures, Policies. Results of the Population Policy Acceptance Study (PPAS)

Danish Fertility Society www.fertilitetsselskab.dk

ESHRE EIM, Human Reproduction, 2010

M. Connolly, M. Postma, S. Crespi, A. Nyboe Andersen, S.Ziebe "*Public investments in Assisted Reproductive Technology in Denmark: The long-term fiscal impact of funding cuts to Danish public clinics*" Reproductive BioMedicine Online, Volume 23, Issue 7, 830–837, 2011

Schoysman and Gerris "Twelve-year follow-up study of pregnancy rates in 1291 couples with idiopathically impathically impaired male fertility" Acta. Eur Fertil 1983 Jan-Feb;14(1):51-6.

The motion of my honourable opponent ***'ART is an important part of the solution to Europe's demographic demise'*** is based on misconceptions (version sent end of March)

Egbert te Velde emeritus professor Reproductive Medicine, University Utrecht; Department of Public Health, University Medical Centre Rotterdam

Disclosures

- I declare that I have no commercial or financial interests or potential conflicts pertaining to the subject of this presentation or its content.

Lessons to be learnt

- The term fertility in demography has a different meaning from fertility in reproductive medicine
- No awareness of this difference is a source of confusion
- There is no demographic demise in Europe, instead there is a demographic recovery
- ART contributes little to this demographic recovery

- Synonyms of demise: decease, expiration, termination or death: my opponent seems to suggest we are in the middle of a demographic catastrophe
- Cheer up opponent: it is not that bad!
- How to assess demographic trends?

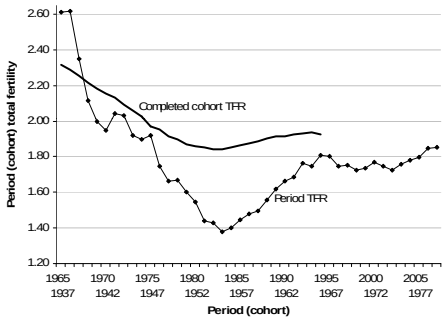
The period Total Fertility Rate (TFR) and the Cohort Total Fertility Rate (C-TFR) are the measures used to assess demographic trends

- TFR is a the mean number of children women will have in a certain country during a calendar year. If she would continue to have the present TFR until the end of her reproductive period it would be her total number of children. Is most commonly used.
- The C-TFR is the mean number of children women have delivered at the end of their reproductive period in a certain country.
- Both terms have nothing to do with the term fertility as used in common language and reproductive medicine e.g. the ability of a woman, man or couple to have one or more children.
- Fecundity and fecundability are the terms used in demography when fertility is used in reproductive medicine
- The different meanings in reproductive medicine and demography for the meaning of fertility is a source of confusion

What is the relation between Period Total Fertility Rate and Cohort Total Fertility Rate?

	Period Total Fertility Rate (TFR)	**Cohort Total fertility Rate (C-TFR)**
Definition	The mean no. of children/woman per year in a certain country	The mean no. of children women have delivered at age 45 in a certain country
Availability	Easy: count no. of births (numerator) and no. of women 15-45 y. (denominator)	Difficult: only available if a cohort of women has passed age 45 (cohort 1968 in 2013)
Stability	Very sensitive to socio-economic and political change. Unstable.	Much more stable
How is it understood?	By lay people often understood as the C-TFR.	Demographers: TFR causes a lot of misunderstanding. Should we stop using it?
Importance	Unstable trends from year to year. No conclusions possible.	Is what we really want to know

An example: The relation between Period TFR (1965-2007) and cohort TFR (1937-1967) in Denmark



Lessons to be learnt

- The term fertility has completely different meanings in demography and reproductive medicine
- As population trends are expressed in demographic terms, all persons involved in reproduction have to be aware of the demographic meaning of the term fertility
- If Total Fertility Rates are declining in a country this does not mean that the reproductive potential in that country is decreasing. And *vice versa.*

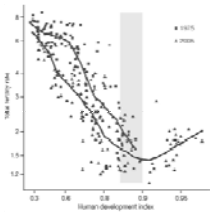
Misconception 1: Demographic demise in Europe?

- There is no demographic demise in Europe!
- There is only demographic recovery!

TFR recovery from lowest TFR in representative EU countries (Goldstein et al. 2009)

Country	Lowest TFR (year)	TFR 2008	Recovery
Northern Europe			
Denmark	1.38 (1983)	1.89	0.51
Sweden	1.50 (1999)	1.91	0.41
Western Europe			
France	1.65 (1993)	2.00	0.35
UK	1.63 (2001)	1.96	0.33
Southern Europe			
Italy	1.19 (1995)	1.41	0.22
Spain	1.16 (1998)	1.46	0.30
Central Europe			
West Germany	1.28 (1985)	1.38	0.10
Austria	1.33 (2001)	1.41	0.08

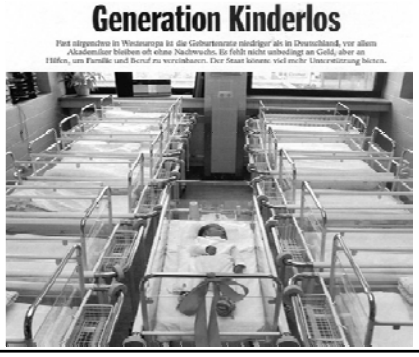
Relation between the TFR in a country and its Human Development Index. 1975 compared to 2005.



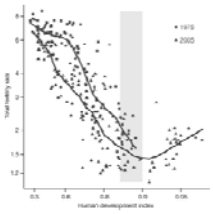
M Myrskylä *et al. Nature* **460**, 741-743 (2009) doi:10.1038/nature08230

nature

Until the end of the 1990s there was indeed a demographic demise.



Above a certain threshold HDI this trend reversed since the beginning of the 2000s: TFRs started to rise in most well-developed EU countries.



M Myrskylä *et al. Nature* **460**, 741-743 (2009) doi:10.1038/nature08230

nature

DEMOGRAPHY

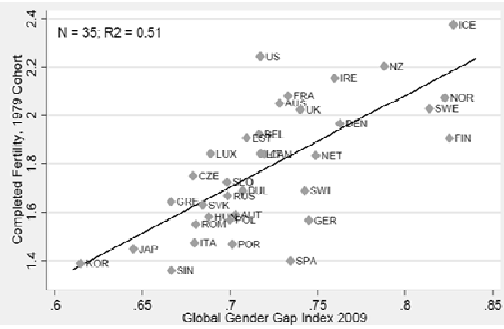
Babies make a comeback

Shripad Tuljapurkar

The population of some wealthy countries is shrinking because of a declining birth rate. It comes as a surprise, and one with policy implications, that after a certain point of development that trend can reverse.

nature

The Global Gender Gap Index, a measure of gender equality. The higher male female equality in a country the more children are born (Myrskylä et al. 2013)



Lessons to be learnt

1. There is no demographic demise in Europe, instead there is a demographic recovery
2. This recovery is related to the social and economic development of a country as reflected by the Human Development Index and the Global Gender Gap Index
3. The recovery is spectacular in the Scandinavian countries where these indices are highest

Question: What is the contribution of ART to the demographic recovery of the last decade?

Misconception 2: ART has much contributed to the demographic recovery of the last decades

- The biggest misunderstanding: all children born after ART directly contribute to the TFR of a country; without ART they would never have been born.
- Rising use of ART may prevent/decrease the decline in period and cohort TFRs
- In times of demographic demise ART is good for a country

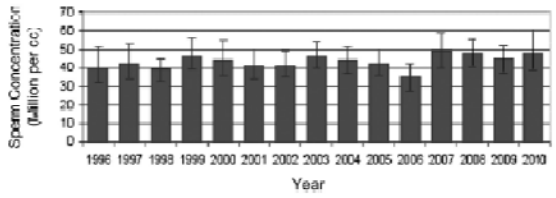
Misconception 2: ART should be used to influence Total Fertility Rates

- Increased availability of ART is a "cost-effective measure to cope with declining fertility rates" (Sunde 2007).
- "Fertility treatment plays a major role in battling negative population growth" (Thaele and Uszkoreit 2007).
- "Adopting ART as a population policy is comparable with those of existing policies used by governments to influence fertility" (Hoorens et al 2007)
- "Assisted reproductive technologies are an integrated part of national strategies addressing demographic and reproductive challenges" (Ziebe and Devroey 2008)

Arguments in favour of misconception 2:

1. The increasing use of ART treatments in Europe indicates that the level of infertility is growing (Lassen et al. 2012)
2. Male reproductive health is deteriorating in Denmark and probably also in Europe (Anderssen et al. 2008))

Male reproductive health is not deteriorating in Denmark? (Bonde et al. 2011)



Misconception 2: ART has much contributed to the baby-come-back trend of the last decades. Arguments in favour:

1. The rise of ART treatments in Europe indicates an increasing need (Lassen et al. 2012).
2. Male reproductive health is deteriorating in Denmark and probably also in Europe (Anderssen et al. 2008)
3. Couple fertility is declining in Europe because of increasing age of parenthood (Te Velde et al. 2012)

Positive and negative trends having an impact on population fecundity

Positive trends

- Less smoking
- Safer sex and better treatment for STDs
- More fertility awareness and knowledge; better timing of intercourse
- Stricter regulations on reproduction-toxic chemicals
- Wider availability of ART

Negative trends

- Increasing postponement of first childbirth
- The growing obesity pandemic
- Environmental pollution

What is the net effect of positive and negative trends? Measures of fecundity in population studies comparing past and present.

Author	Outcome measure	Method	Period or birth cohort	Trend
Joffe 2000	Time-to-pregnancy	Interview survey	1961-1993	Fecundity improved
Jensen et al. 2005	Time-to-pregnancy	Interview survey	Birth cohorts 1931-1993	Fecundity improved
Stephen and Chandra 2006	1-year infertility	Interview survey	1965-2002	Fecundity improved
Scheike et al. 2008	1-year infertility	Nationwide birth register	1983-2002 Birth cohorts 1949-2002	Fecundity improved
Oakly et al. 2008	Lifetime infertility	Postal survey	Birth cohorts 1945-1962	Fecundity unchanged
Mascarenhas et al. 2012	5-year infertility	Household surveys in 190 countries-WHO	2010 compared to 1990	Fecundity unchanged or improved

- Although the concern about environmental pollution is justified there are no signs yet of declining sperm quality in prospectively conducted research
- The net effect of positive and negative trends affecting couple fecundity indicates there has been no change in couple fecundity over the last decades

The crux of misconception 2 is that children born after ART would not have existed otherwise and directly contribute to the TFR of a country. Twin deliveries contribute double. However..

- Only a minority of the couples coming for ART are sterile; most of them are subfertile with a fertility potential varying from almost sterile to almost normal (Leushuis et al. 2008)
- Many subfertile couples still achieve a spontaneous pregnancy after 1 year or even 2 years of infertility (Collins et al. 1983, Dunson et al. 2004, Spira 1986, O'Connor et al. 1986, Van Balen et al. 1997, Tietze 1950)
- Many subfertile couples resort too early to ART; if waited longer many of them would have achieved a spontaneous pregnancy (Habbema et al. 2009)
- Now Single Embryo Transfer (SET) increasingly is becoming the standard, less women deliver twins. Consequently, the contribution of ART to the TFR of a country becomes less important

Crude and estimated net effect of ART on the cohort fertility of Danish women born in 1975 correcting for spontaneous pregnancies and declining twinning rates (Sobotka et al. 2008)

Actual C-TFR in 2008 in Denmark	**1.914**
Crude ART effect assuming that all ART children would not have existed otherwise	0.093
Hypothetical TFR without ART	1.821
Assumed TFR rise due to ART	**~ 0.1**
Correction for spontaneous conceptions Correction for decline in twinning rates Estimated TFR without ART **Estimated TFR rise due to ART** **TFR rise since 1983**	- 0.27 - 0.017 1.865 **~ 0.05** **~ 0.50**

Conclusions

- Misconception 1: there is a demographic demise in Europe.
  No: in all European countries there is demographic recovery.
- This recovery varies from 0.5 TFR in the Nordic countries to 0.1 TFR in Central Europe.
- This recovery is mainly related to social-economic determinants and the level of gender equality in a country
- Misconception2: ART plays an important role in the demographic recovery.
  No: the contribution to this recovery is comparatively small, but not negligible.

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Costs matter, but so do benefits:

The economic benefits of ART to Society

Never Stand Still

School of Women's and Children's Heath

Dr Georgina Chambers PhD MBA

Senior Research Fellow
National Perinatal Epidemiology Research Unit

virtus HEALTH

UNSW AUSTRALIA

Australian Government
Australian Research Council

Conflict of Interest

I declare that The University of New South Wales (UNSW) receives a government/industry partnership grant from the Australian Government Research Council (ARC) and Virtus Health (comprising IVFAustralia, Melbourne IVF and Queensland Fertility Group) to fund the following project of which I am Chief Investigator and Senior Research Fellow:

ARC Grant No: LP10020065 Economic Impact and Policy implications of assisted reproductive technologies in Australia.

Learning Objectives

1. Review how economic benefits and 'value for money' in healthcare are measured.
2. Understand the challenges of using traditional health technology evaluation tools for ARTs.
3. Assess the long-term human capital / fiscal impact of ART children on government accounts.
4. Examine trends in population demographics in Europe and explore whether ART has a role in increasing fertility rates.

1. Defining Economic Benefit … "Value for Money"….in health care

1. Economic efficiency: Maximising health benefits with a fixed amount of resources.

   Health needs are unlimited, but resources are finite.

2. Perspective: Whose costs , whose benefits?
   - Society
   - Government
   - Patients

4 UNSW

1. Defining Economic Benefit … "Value for Money"….in health care cont

3. Value is subjective
   - Tangible, live-birth rates
   - Intangible outcomes, intrinsic value of human life
   - Reflect personal & societal preferences.

4. Value reflects broader dimensions
   - Equity of access
   - Quality
   - Acceptability

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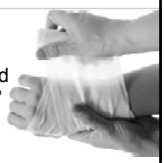
The challenge for policy makers & health economists

Fertility treatments are judged on their ability to create life, rather than to extend or improve the quality of existing life.

Fertility treatments don't fit the standard paradigm used to assess 'Value for Money' in healthcare .



Is this why ARTs are targeted for frequent changes in public funding?

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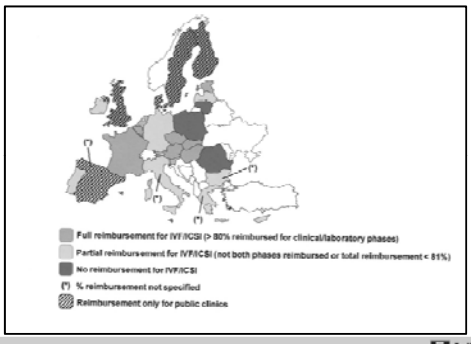
Reimbursement of ART in Europe



7 Source: Comparative Analysis of Medically Assisted Reproduction in the EU ESHRE 2010

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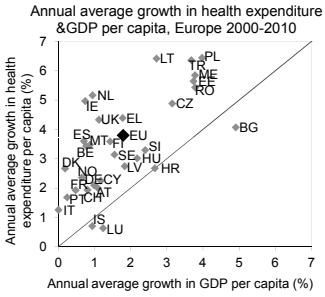
Pressure to demonstrate Economic Benefit / Value for Money in health spending



- Healthcare accounts for ~ 9% of GDP
- Annual growth in healthcare spending per capita ~4%
- Annual growth in GDP per capita ~2%
- Healthcare spending has slowed or fell since the GFC.

8 Source: OECD Health Data 2012; Eurostat Statistics Database; WHO Global Health Expenditure Database.

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2. The health economist's tool box

Health economic evaluations assist decision makers about the most efficient use of health care resources.

i. Cost-effectiveness Analysis (CEA)

ii. Cost Utility Analysis (CUA)

iii. Cost Benefit Analysis (CBA)

9

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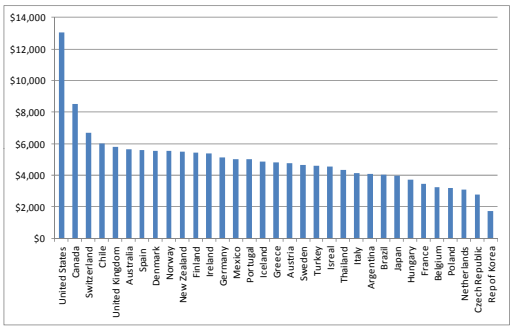
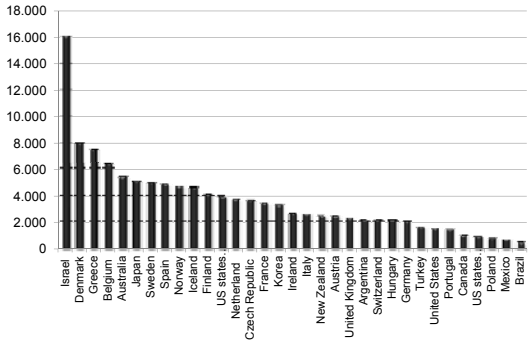
Direct Cost of a fresh IVF cycle before government of third-party subsidization (USD)



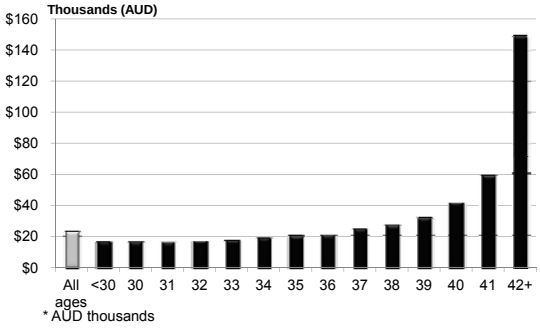
10 Source; Unpublished analysis, various sources. Chambers, GM 2012 ©.

Fresh cycles per million females 19-44 yrs, 2006



11 Source; Unpublished analysis, various sources. Chambers, GM 2012 ©.

Age specific cost per ART live-birth, 2008



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(i) Cost-effectiveness Analyses (CEA)

- Cost per natural units of outcome
- Cost per live-birth from ART treatment
- Incremental cost-effective ratio (ICER):
  - Additional cost needed to achieve one additional live-birth from alternative fertility treatment.

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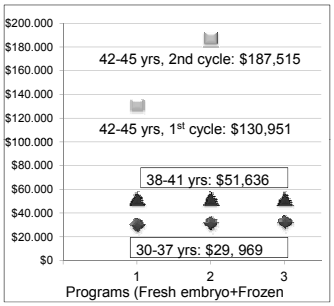
Incremental cost per live birth by maternal age & cycle attempt



Cost-effectiveness depends on maternal age more than number of cycles.

Within reasonable age limits ICERs falls within the threshold of what is considered good value for money.

14

Source: Griffiths A et al. Hum. Reprod. 2010;25:924-931

(ii) Quality Utility Analysis (CUA)

- Cost per Quality Adjusted Life years (QALYs)
- Primary measure in health technology assessment
- QALY = Quality of life + Quantity of life
  - Eg. 2 years in poor health = 1 year in full health
- If cost per QALY saved < WTP threshold ▶ Fund
  - WTP threshold ≈ £20,000-£30,000 (NICE)

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(ii) Quality Utility Analysis (CUA) cont

- The problem with QALYs:
  - Whose QALY? (ART patient or ART child)
  - Is it valid for a life not yet conceived
- On a societal QoL scale*: Death = 0 and Full Health = 1
  ►Life-long infertility = 0.88
- NICE Update to Fertility guidelines: Under most clinically appropriate circumstances access to ART treatment and SET represents good value for money from a societal perspective.

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*** Source: Adapted from Torrance GW Medical Care**

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(iii) Cost benefit analysis (CBA)

- Health outcomes measured in money terms.
- Crude measure to value babies in monetary terms.
  - 'Pricing the priceless'.

1. Willingness-to-pay (WTP) studies
   - Value society places in a baby born from ART.
2. Human Capital / Fiscal Impact of ART children

17

Source: Adapted from Neumann and Johannesson Medical Care

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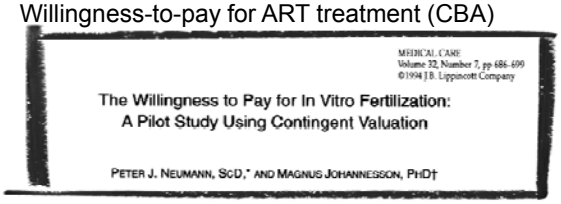
Willingness-to-pay for ART treatment (CBA)



Implied societal willingness-to-pay for a statistical IVF baby:

- $177,000 in the event that infertility status is known.
- $1.8M in insurance premiums to provide access to IVF treatment.
- Lacks empirical evidence

► Society values fertility highly

18

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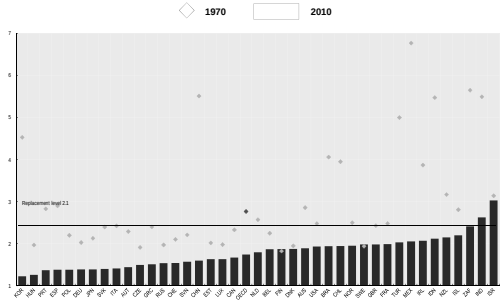
Human Capital / Fiscal Impact of ART children

- Does ART represent a good return of investment by governments?
- Can ART play an role in combating **economic impact** of an Ageing Population?
  - Reduced fertility
  - Greater life expectancy

Population Aging: trends in total fertility rates (TFR)

Number of children born to women age 15 to 49



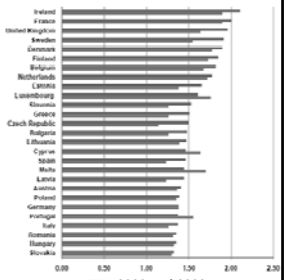
 Source: OECD Factbook 2013 ©

Total Fertility Rate (TFR): EU countries

Number of children born to women age 15 to 49

Recent increase in TFRs in recent years

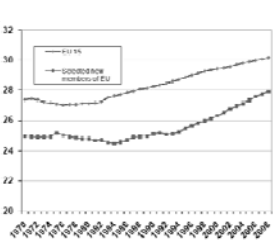
Trends in TFR EU 1970-2008



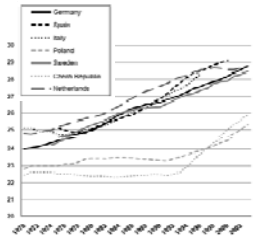
TFR 2000 and 2008 EU countries

 Source: Hoorens et al. RAND Corporation 2011 ©

Maternal age trends: EU Countries



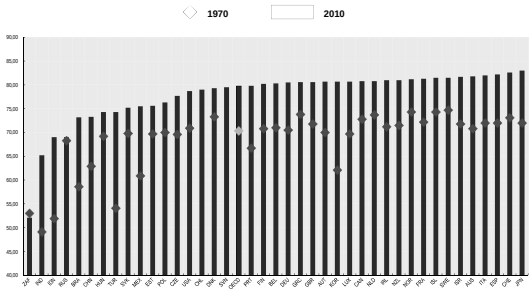
Mean female age at childbirth
EU, 1970-2008



Female age at first child birth
EU 1970-2002

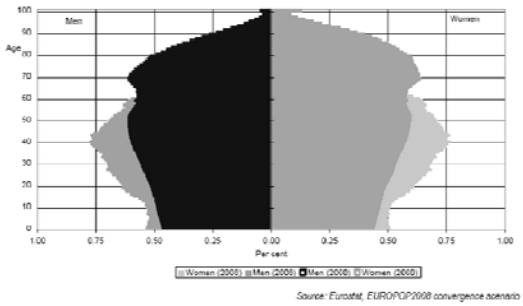
22 Source: Hoorens et al. RAND Corporation 2011 ©

Life Expectancy at Birth: OECD



23 Source OECD Factbook 2013 ©

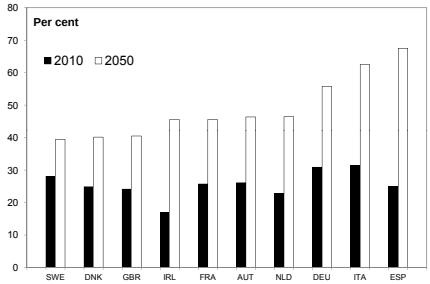
Population Pyramid: EU 27 2008 and 2009



Source: Eurostat, EUROPOP2008 convergence scenario

24 Source: Eurostat, EUROPOP2008

Old age dependency ratio
Selected EU countries



Population 65 years and over divided by 15-64 years population

25 Source: European Commission (DG ECFIN) and the Economic Policy Committee (AWG) ©

Is public funding of ART treatment a good investment of tax payers money?

An example of human capital/ fiscal impact model of ART treatment.

- In 2008, the Australian Government spent $260M of the Medicare budget on ART treatment
- For this there were 9522 ART live births, and 10,341 ART babies
- Investment evaluation uses discounted cash flows to and from the Australian Government by ART children over their life time.

26 Source; Unpublished analysis. Chambers, GM 2012 ©.

Discounted Cash Flow evaluation of public funding
Dynamic life-cycle model of cash flows of 9522 ART live births over their life time.

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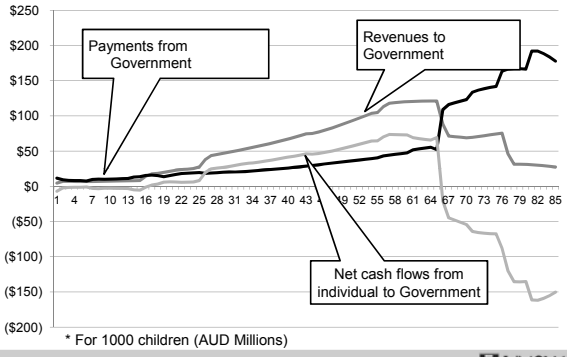
Annual cash flows for all children



* For 1000 children (AUD Millions)

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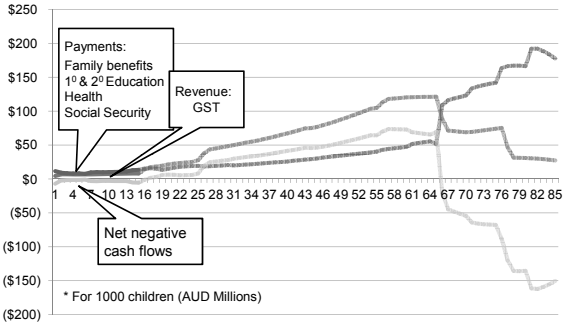
Childhood: 0 to 16 years



* For 1000 children (AUD Millions)

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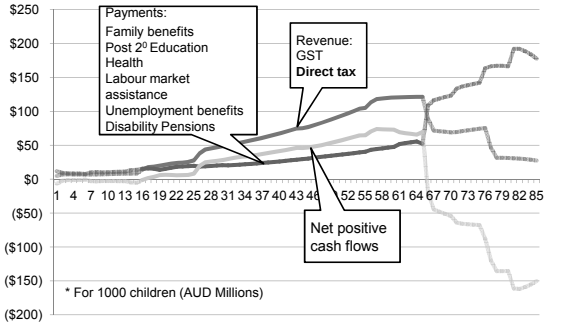
Working years: 17 - 64 years



* For 1000 children (AUD Millions)

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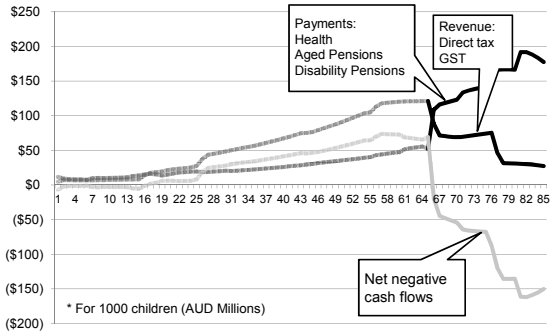
Retirement years: 66 – 85 years



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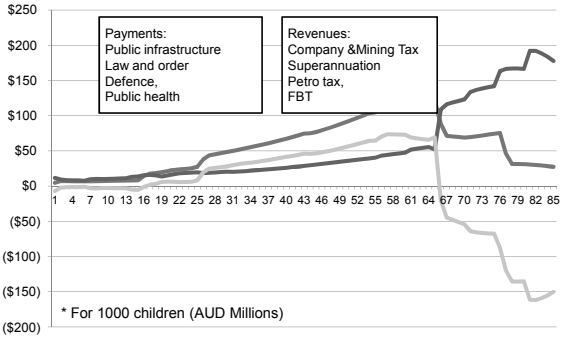
Broader Revenues and Expenses



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Net Present Value (NPV)

- A investment evaluation tool to help decide whether or not investment.
- Discount annual cash flows to one lump sum present value: NPV.
- Discount Rate reflects 'time value of money' & risk premium applied to future cash flows.
  - Base annual Discount Rate applied: 6.25%
- Limitations:
  - Forecast future cash flows requires assumptions.
  - Valuation is sensitive to Discount Rate.

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Maternal age specific NPV for 1000 children

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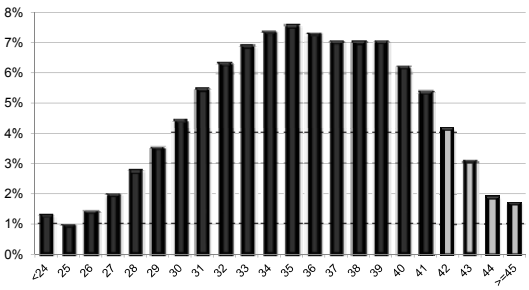
Percentage of ART Government expenditure by maternal age ($260M in 2008)



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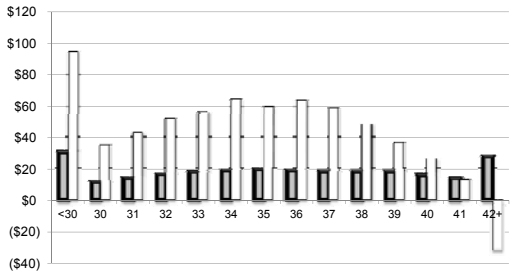
Weighted return on investment for 2008 ART Rx for the 9522 live births



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Discounted Cash Flow evaluation of public funding

The Bottom line:

- The Net Present Value of the $260M government spent in 2008 was $621M.
- Return on investment: 240% over the lifetime of the 'investment'.

▶ART is a positive investment of public money.

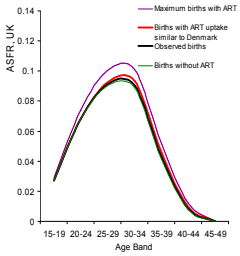
Other estimates of NPV of ART Rx

Country	NPV	RoI	Reference
US	USD 155,870	7 times	Connolly, MP. etal (2008). Am J Man Care, 14, 598.
UK	GBP 109,939	8.5 times	Connolly, MP. etal (2009) Hum Repro, 24, 626.
Sweden	SEK 254,000		Svensson, A etal (2008). Scand J Publ Hth, 36, 841.
Denmark	Euro 154,000		Connolly, MP etal (2011) Repro Bio Online, 23, 830.
Brazil	USD 61,428		Kröger, GB, Ejzenberg, D. (2012) Hum Repro, 27,142.
Australia	AUD 65,000	2.4 times	

▶Breakeven point around 40 years

Contribution of ART to TFR

Effect of tripling the availability of ART in the UK



Triple utilisation: ▲TFR 0.04
▼1.7% old-age depend
Maximum impact: ▲TFR 0.22

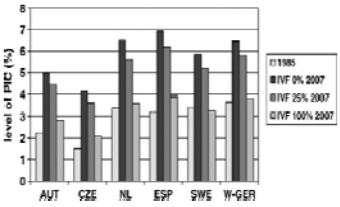
- Assumes all ART children would not have been born without Rx.
- Doesn't account for multiple births.

▶ ART has the potential to influence population structures

Source: Hoorens S et al. Hum. Reprod. 2007

Contribution of ART to TFR and Permanent involuntary childlessness (PIC)

Effect of IVF on PIC rates



Effect of IVF on TFR rates

Full access to IVF after 3 yrs: ▲TFR 0.08

Maximum impact: ▲TFR 0.11

Model assumes naturally conceptions

► At realistic estimates of natural conception and utilisation ART can only have a moderate impact on societal birth rates.

 Sources: Habbema J et al. Hum. Reprod. 2009, te Velde et al Hum. Reprod. 2012

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Pronatalist Policies

► From a societal perspective ART can not compensate for behavioural factors or reduced fecundity.

- Pronatalist policies often ineffective and can result in unintentional consequences.
- Support for education and work-family balance is more important.
- Recent increases in fertility rates not well understood.
- The burden on government accounts from decreased fertility rates and population aging are not clear;
  - Higher labour force participation by women.
  - Increase in pensionable age inline with healthy-life expectancy.
  - Adaptation of the health care system.

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Final Remarks

- Fertility treatments not well suited to the usual health technology evaluation methods.
  - Vulnerable to funding changes
- Parenthood and fertility treatments valued highly by patients and society.
- Within reasonable age limits ARTs are cost-effective.
- The long-term RoI from government investment in ART treatment is positive.
- Evidence is weak that ART has an important role to play in combating economic impact of population ageing.

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Thank you

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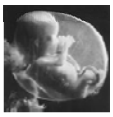
How will ART children from infertile fathers affect the health of European Society in the future? The latest child health data



Anja Pinborg, associate professor, DMSci
Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Denmark

Conflict of interest

I declare that I have no commercial or financial interests pertaining to the subject of this presentation or its content.

Disclosure

There is no commercial relationships or other activities that might be perceived as a potential conflict of interest regarding this lecture

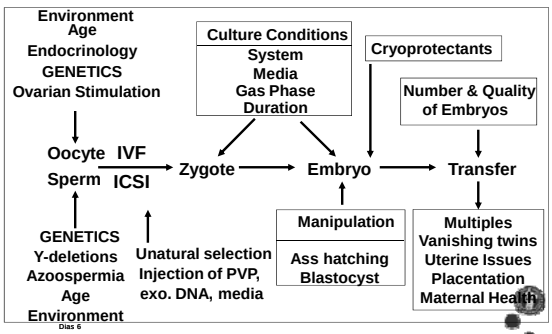
Learning objectives

- Parental subfertility
- Male infertility and genetic risk factors
- ICSI
- Malformations and chromosomal anomalies
- Obstructive and non-obstructive azoospermia
- Male infertility and epigenetic disturbances
- Future generations

ART offspring

- Five million ART children worldwide
- In some countries ART accounts for 5% of the birth cohort
- ICSI accounts for 69% of all fresh ART cycles in Europe
- In Europe the ART twinning rate is 20.7%
- Twinning is still the major health risk for ART children

Causes for adverse outcomes



ART does not heal subfertility

- ART does not heal the causes of subfertility, but makes it possible for subfertile couples to conceive
- ART couples remain *"less reproductive healthy"*

Parental subfertility

- Mean maternal age is higher
- More nulliparous
- Smoking and BMI
- Socio-economic status

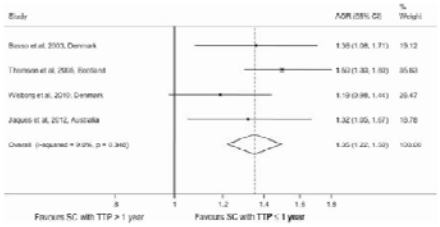
- *One third has male factor infertility*
- Abnormal karyotypes
- Y-chromosome deletions
- Epigenetic disturbances in the spermatozoa

"Time-to-pregnancy" >1 year

	AOR (95%CI)
Preterm delivery	1.5 (1.2-1.8)
Low birth weight	1.8 (1.2-2.7)
Malformation	1.2 (1.1-1.4)
Neonatal mortality	3.3 (1.5-7.5)
SGA	1.2 (1.1-1.4)
Mild cognitive/language delay (18 months)	1.2 (1.0-1.5)

(Basso, Hum Reprod 2003; BMJ 2005; Zhu, BMJ 2006; Obstet Gynecol 2007; Zhu, Paediatr Perinatal Epidemiol 2009; Henriksen, Obstet Gynecol 1997; Draper, Lancet 1999; Pandian, Hum Reprod 2001)

Meta-analysis on preterm birth in women with TTP >1 year *versus* TTP < 1 year



Tau-squared = 0.0010

Pinborg *et al.*, Hum Reprod Upd 2013

Dias 10

Genetic risk factors in men with severe oligozoospermia and azoospermia

- Y-chromosome deletions are seen in 7% of men with oligo- or azoospermia (Van Opstaal et al., 1997)
- Genetic abnormality in 24% of men with motile sperm count < 1 mill/ml (Dohle et al., 2002)
  - 10% Abnormal karyotypes
  - 5% AZF deletions (microdeletions of Y-chromosome)
  - 9% mutations in the CFTR gene
- Increased risk of aneploidy in spermatozoa from patients with testicular failure (Bernadini et al., 2000; Martin et al., 2000; Levron et al., 2001)

Dias 11

ICSI procedure problems

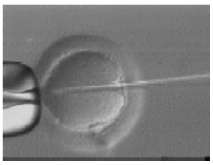
- Microinjection of sperm carrying a chromosomal anomaly (aneuploidy or structural defect)
- Transmission of a genetic defect [such as a Yq deletion or cystic fibrosis(CF) mutation] which is often the origin of male-factor infertility
- Male gamete structural defect
- Anomalies of sperm activating factors
- Potential for incorporating sperm mitochondrial DNA
- Female gamete anomalies (oocyte age-related)

Dias 12

Genetic risks in the ICSI offspring

- Unbalanced chromosome complement
- Male infertility due to Y-chromosome deletions
- Cystic fibrosis if both partners are carriers of the CFTR gene mutation
- Congenital malformations
- Cardiovascular disease

Intracytoplasmatic sperm injection ~ ICSI

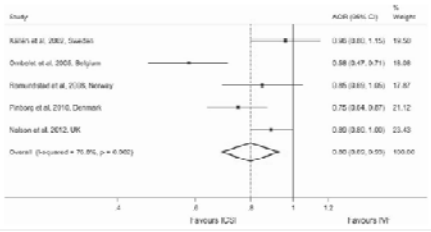


Intracytoplasmatic sperm injection ~ ICSI

- ICSI is increasingly used, 69% of fresh cycles in 2008 in Europe
- Indications have changed over time
- Large geographic differences
- 40-50% of the cycles in the Nordic countries, UK and Holland
- More than 90% of the cycles in many countries

(Nyboe Andersen et al., 2008; Ferraretti et al., 2012)

Meta-analysis on preterm birth in ICSI vs. IVF children



Tau-squared = 0.0232

Pinborg *et al.*, Hum Reprod Upd 2013

ART singletons - malformations

		AOR (95%CI)
Hansen, 2005	Meta-analysis	1.36 (1.28-1.45)
Hansen, 2013	Meta-analysis	1.33 (1.24-1.42)
Källén, 2005	1982-2001	1.33 (1.24-1.45)
Adjusted for years of infertility		1.05 (0.95-1.16)
Källén 2010	2001-2007	1.15 (1.07-1.24)

Zhu et al., 2006: Genital organ anomalies in ART vs. Couples with subfertile couples with TTP > 1 year: HZ 2.32 (95%CI 1.24-4.35)

Congenital malformations ICSI vs. IVF

Meta-analyses

Lie et al., 2005: OR 1.12 (95%CI 0.97-1.28)

Wen et al. 2012: OR 0.95 (95%CI 0.83-1.10)

Cohort studies

Källén et al., 2010: OR 0.90 (95%CI 0.78-1.04)

Davies et al., 2012 OR 1.55 (95%CI 1.24-1.94)

Congenital malformations

Källén, Birth Defects Research, 2010

1.study period 1982-2001	16.280 IVF/ICSI children
2.study period 2001-2007	15.570 IVF/ICSI children
All	AOR 1.15 (1.07-1.24) (5.3 and 4.4%)
All relatively severe	AOR 1.25 (1.15-1.37) (3.7 and 3.0%)
⇑ Cardiovascular	AOR 1.30 (1.13-1.49)
⇑ Limb reduction defects	AOR 1.86 (1.04-3.07)

Hypospadi (ICSI *vs.* IVF):	I.period	AOR 1.9 (1.1-3.4)
	II.period	AOR 0.94 (0.63-1.42)

(Adjusted for year of birth, maternal age, parity, smoking and BMI)

Declining risk of hypospadias in ICSI offspring

- Dilution effect, less men with severe male infertility
- Improvement in the ICSI techniques

Chromosomal anomalies

- Chromosomal abnormalities are increased in ICSI offspring (Aboulghar et al., 2001; Bonduelle et al., 2002; Gjerris et al., 2009)
- Both inherent and do novo

ICSI and chromosomal anomalies

- **430 ICSI babies 3.5% chromosome aberrations (Aboulghar et al., 1997)**
- **1586 ICSI foetoses 3.0% (2.2-3.9%) vs. 0.8-0.9% background population (Bonduelle et al., 2002)**
- **Chromosome anomalies 5.8-13.7% after ICSI, if the father has oligo- or azoospermia**
- **The risk of chromosome anomalies was associated to sperm count and motility**

ICSI and chromosomal anomalies

(Gjerris et al., 2008)

- Prenatal testing: 2.7% (43/1586) with chromosome aberrations
- ICSI vs. IVF: 4.3% vs. 1.9%, P<0.01
- Pre- and post-natally testing: 0.6% (62/9625)
- ICSI vs. IVF: 1.3% vs. 0.5%, P < 0.0001

International collaborative study of ICSI-, IVF- and naturally conceived (NC) 5-year-old child outcomes

Ponjaert-Kristoffersen, Bonduelle, Barnes, Nekkebroeck, Loft, Wennerholm, Tarlatzis, Peters, Hagberg, Berner, Sutcliffe

- 540 ICSI, 538 IVF, 537 NC
- Motor and cognitive development is very similar to naturally conceived (2005)
- Family function and socio-emotional development (2004)
- ICSI and IVF more likely than NC to significant childhood illness, surgical operation, medical therapy and hospital admission. A detailed physical examination revealed no further substantial differences between the groups, however (2005)

International collaborative study of ICSI-, IVF- and naturally conceived (NC) 5-year-old child outcomes

Ponjaert-Kristoffersen, Bonduelle, Barnes, Nekkebroeck, Loft, Wennerholm, Tarlatzis, Peters, Hagberg, Berner, Sutcliffe

- ICSI girls, fewer were left-handed than the NC controls, 7.0%versus 12.4% (P <0.05). Population norm of 8% (2005)
- No indication that growth and cognitive development in ICSI and IVF children differed depending on paternal sperm concentration (2006)

Neonatal outcome of 724 children born after ICSI using non-ejaculated sperm

F. Belva[1,*], F. De Schrijver[1], H. Tournaye[2], I. Liebaers[1,2], P. Devroey[2], P. Haentjens[3], and M. Bonduelle[1]

Table V Outcome parameters of live and stillborns conceived with testicular sperm according to obstructive (OA) or non obstructive (NOA) cause of azoospermia.

	OA (n = 340)	NOA (n = 168)	OR (95% CI) or P-value
Live born singletons	356	117	
Birthweight (g)	2830	2950	0.9
Gestational age (weeks)	38.9	39.0	0.9
Gestational age <37 weeks	16 (7.7)	15 (12.8)	0.2 (0.3 - 1.2)
Live born twins	134	38	
Birthweight (g)	2395	2331	0.9
Gestational age (weeks)	35.8	35.2	0.9
Gestational age <37 weeks	74 (55.2)	24 (63.1)	0.7 (0.3–1.5)
Male gender	183 (51)	78 (46)	1.2 (0.8–1.7)
Children with major malformations	19 (5.2)	7 (4.2)	1.2 (0.5–3.1)
Children with major genital malformations	7	1	0.5 (0.0–1.9)
De novo karyotype anomalies and post-natally detected	3	0	3.8 (0.2–64.3)

Data are presented as numbers (%), OR, odds ratio; 95% CI, 95% confidence interval.

Obstructive (OA) and non-obstructive azoospermia (NOA)

(Belva et al., 2011)

- **No differences in low birth weight, very low birth weight and prematurity rate between testicular, epididymal and ejaculated sperm group**
- **Major malformations, testicular vs. epididymal: 5.0% vs. 3.4% (OR 1.5 [95%CI 0.9-2.4])**
- **Major genital tract anomalies, testicular vs. epididymal: 1.0% vs. 0.3% (OR 3.0 [95%CI 1.0-9.2])**
- **Major malformations, non-ejaculated vs. ejaculated 4.8% vs. 3.4% (OR 1.4 [95%CI 0.9-4.2])**
- **Major genital tract anomalies, non-ejaculated vs. ejaculated: 0.7% vs. 0.3% (OR 2.2 [95%CI 0.7-6.8])**

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Non-ejaculated sperm (Epididymal or testicular sperm)

(Fedder et al., 2012)

Table IV Odds ratios of LBW and PTB for children born after ICSI with epididymal or testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	TESA	ICSI	IVF	NC
Singletons				
LBW (<2500 g)	1.00 (ref.)	1.00 (0.61–1.65)	1.28 (0.68–2.40)	0.58 (0.44–0.77)
Crude				
Adjusted*	1.00 (ref.)	0.97 (0.60–1.58)	1.22 (0.66–2.23)	0.67 (0.50–0.92)
PTB (<37 weeks)	1.00 (ref.)	1.40 (0.67–2.93)	1.83 (0.70–4.79)	0.89 (0.56–1.42)
Crude				
Adjusted*	1.00 (ref.)	1.38 (0.66–2.85)	1.94 (0.70–5.38)	1.02 (0.60–1.74)
Twin children				
LBW (<2500 g)	1.00 (ref.)	1.01 (0.69–1.47)	1.04 (0.72–1.51)	0.94 (0.68–1.32)
Crude				
Adjusted*	1.00 (ref.)	1.04 (0.71–1.53)	1.16 (0.75–1.79)	1.20 (0.77–1.89)
PTB (<37 weeks)	1.00 (ref.)	0.85 (0.59–1.21)	0.70 (0.52–0.95)	0.64 (0.49–0.83)
Crude				
Adjusted*	1.00 (ref.)	0.86 (0.59–1.26)	0.87 (0.59–1.26)	0.84 (0.58–1.20)

The values are OR (95% CI). Binomial regression with adjustment for dependence between twins was done using the robust variance estimation. LBW, low birthweight; PTB, preterm birth.
*Adjusted for mothers' age (<20, 20–24, 25–29 and 40+ years), sex, birth year (1995–1997, 1998–2000, 2001–2003, 2004–2009) and parity (1, 2+).

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Non-ejaculated sperm

(Fedder et al., 2012)

Table V Total rates of congenital abnormalities and possible imprinting-related diseases after ICSI with epididymal or ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D
Total				
Congenital abnormalities	TESA	ICSI	IVF	NC
Neoplasms in bones and joint cartilage, including osteosarcoma				
Singletons				
Congenital abnormalities	21, 7.24 (4.54–10.86)	467, 7.96 (7.28–8.68)	762, 6.89 (6.42–7.38)	1952, 5.77 (5.52–6.02)
Neoplasms in bones and joint cartilage, including osteosarcoma	1, 0.34 (0.01–1.91)	7, 0.12 (0.05–0.25)	29, 0.26 (0.18–0.38)	59, 0.17 (0.13–0.22)

ICSI and epigenetic disturbances

Direct epigenetic alteration of gene expression is the most plausible origin of subsequent aberrations in growth and development

(Thompson et al., 2002)

In mice, ICSI with DNA fragmented sperm resulted in blastocysts with altered methylation pattern of some imprinted genes and in the development of obesity in the adult offspring

(Fernandez-Gonzalez et al., 2008)

Male subfertility

- Epimutations in sperm may be largely associated with impaired male fertility
- Broad epigenetic defect is associated with abnormal semen parameters.
- The underlying mechanism for these epigenetic changes may be improper erasure of DNA methylation during epigenetic reprogramming of the male germ line.

(Houshdaran et al., 2007)

ICSI adolescents
(Belva et al., 2012)

- 217 ICSI and 223 spontaneously conceived singletons
- 14-year old adolescents
- ICSI girls were more prone to central, peripheral and total adiposity compared with SC girls
- ICSI boys with more advanced pubertal development had higher peripheral adiposity
- No increased blood pressure in rest or after stress-test
- Pubertal development equal to SC children
- ICSI girls have less advanced breast development

Human Reproduction, Vol.26, No.2 pp. 430–441, 2011
Advanced Access publication on December 7, 2010 doi:10.1093/humrep/deq340

human reproduction ORIGINAL ARTICLE *Reproductive endocrinology*

Salivary testosterone concentrations in pubertal ICSI boys compared with spontaneously conceived boys

F. Belva[1,*], M. Bonduelle[1], J. Schiettecatte[2], H. Tournaye[3], R.C. Painter[4], P. Devroey[3], and J. De Schepper[5]

CONCLUSIONS: At the age of 14 years, pubertal ICSI boys show testosterone levels comparable to their peers born after SC. ICSI adolescents fathered from men with severely compromised spermatogenesis show testosterone levels comparable to those from fathers with normal spermatogenesis. This notwithstanding, further follow-up of ICSI teenagers into adulthood is mandatory to confirm a normal gonadal function.

Human Reproduction, Vol.25, No.11 pp. 2811–2814, 2010

human reproduction ORIGINAL ARTICLE *Infertility*

Serum inhibin B concentrations in pubertal boys conceived by ICSI: first results

F. Belva[1,3], M. Bonduelle[1], R.C. Painter[2], J. Schiettecatte[1], P. Devroey[1], and J. De Schepper[1]

CONCLUSIONS: The majority of ICSI boys have a significant increase in serum inhibin B, attaining normal values for pubertal status at the age of 14 years. ICSI adolescents from fathers with severely compromised spermatogenesis do not have lower inhibin B levels than those with fathers with normal spermatograms. Further follow-up of the spermatogenic potential of ICSI teenagers up to young adulthood is mandatory to confirm a normal reproductive capacity.

Original Paper

HORMONE RESEARCH

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Testicular Growth and Tubular Function in Prepubertal Boys Conceived by Intracytoplasmic Sperm Injection

Jean De Schepper[a] Florence Belva[b] Johan Schiettecatte[c] Ellen Anckaert[c] Herman Tournaye[d] Maryse Bonduelle[b]

Conclusion: Our data suggest that penile and testicular growth as well as Sertoli cell function are normal in the majority of prepubertal ICSI boys. Serum AMH and inhibin B levels were found to be independent of sperm quality of the father. Further follow-up of these prepubertal children is needed to examine whether normal Sertoli cell markers will be followed by a normal spermatogenesis in puberty.

Take home messages I

- 24% with severe male factor infertility has genetic abnormalities
- 5-10% of men with severe male factor infertility has Y-chromosome deletions
- The rate of chromosome aberrations are increased in ICSI children
- Genetic testing and counselling, if sperm count <2 mill/ml

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Take home messages II

- Malformation rates are similar in IVF and ICSI
- Still controversial if offspring after non-ejaculated sperm has increased risk of chromosome aberrations
- IVF children has increased blood pressure
- Pubertal development seems similar in ICSI children
- Epigenetic changes after ICSI still has to be confirmed

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How will ART children from infertile fathers affect the health of European Society in the future?

- Pubertal development
- Reproductive function
- Cardiovascular disease
- Mortality rates

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Future perspectives

- Twinning is far the most important health risk for ART offspring
- Human ART and epigenetic warrants future caution and continued observation
- Pubertal diseases and reproductive function warrant future research
- CoNARTaS ~ Committee on Nordic ART and Safety
  - 100.000 ART children

Thank you for your attention

You can now register for these upcoming ESHRE Campus events:

- Application and challenges of emerging technologies in preimplantation and prenatal diagnosis
  12-13 September 2013 - Prague, Czech Republic
- Female genital tract congenital malformations: new insights in an old problem
  27-28 September 2013 - Thessaloniki, Greece
- Introducing new techniques into the lab
  4-5 October 2013 - Barcelona, Spain
- Polycystic ovary syndrome: A new look at an old subject
  25-26 October 2013 - Rome, Italy
- Infections from conception to birth: role of ART
  7-8 November 2013 - Berlin, Germany
- Endoscopy in reproductive medicine
  20-22 November 2013 - Leuven, Belgium
- From early implantation to later in life
  28-29 November 2013 - Brussels, Belgium

Mark your calendar for:

- Premature ovarian insufficiency
  6-7 December 2013 - Utrecht, The Netherlands

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