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*

INSTITUT DE VEILLE SANITAIRE

Recent semen data from France

Pre course Eshre 07.07.2013

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

INSTITUT
DE VEILLE SANITAIRE

Objectives

- To briefly describe the background of epidemiologic knowledge on semen quality trends
- To explain the methods used in our recent study published in *Human Reproduction*
- To show and discuss the results

Background

Available source populations to study semen quality trends

1. Semen donor centres: fertile selected men
   - Decreasing quality in Paris: 1973-1992 (Auger, 1995), not in Toulouse (Bujan 1996)
   - Geographic variations in France between 8 centres, 1973-1993 (Auger, 1997)

2. Infertility clinics: men from infertile couples
   - Numerous studies, various methods, large samples

3. Young conscripts: closer to the general population, but low participation rate
   - Danish study : small increase from1996 et 2010 (Jorgensen, 2012)
   - Finish study : decrease from 1998 to 2006 (Jorgensen, 2011)

4. Others (partners of pregnant women, pre-vasectomy…)
   - Geographic variations in Europa (Jorgensen 2001)
   - Geographic variations in USA (Swan, 2003)

Background

Semen quality studies :

- No perfect source population
- Various methods used
- Geographical variations
- Studying sperm trends is very difficult
- A public health issue

Human Reproduction, Vol.28, No.2 pp. 462–470, 2013
Advanced Access publication on December 4, 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

M. Rolland[1], J. Le Moal[1,*,†], V. Wagner[1], D. Royère[2], and J. De Mouzon[3]

[1]Environmental Health Department, Institut de Veille Sanitaire (InVS), F-94415 Saint Maurice, France [2]Fivnat, Reproductive Biology Unit, CHU Bretonneau, 37000 Tours, France [3]Fivnat and Inserm, Paris-Descartes University, Reproductive Medicine Unit, CHU Cochin-Port Royal, 75014 Paris, France

*Correspondence address. E-mail: j.lemoal@invs.sante.fr

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

† Joint first authorship.

InVS
INSTITUT
DE VEILLE SANITAIRE

The Fivnat database

- Built by the Fivnat association
- Most of assisted reproductive technology (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

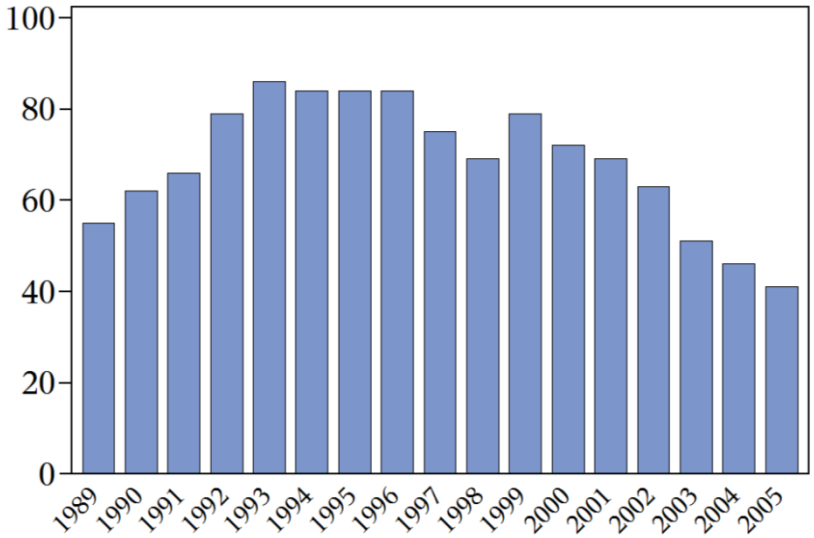
The Fivnat database

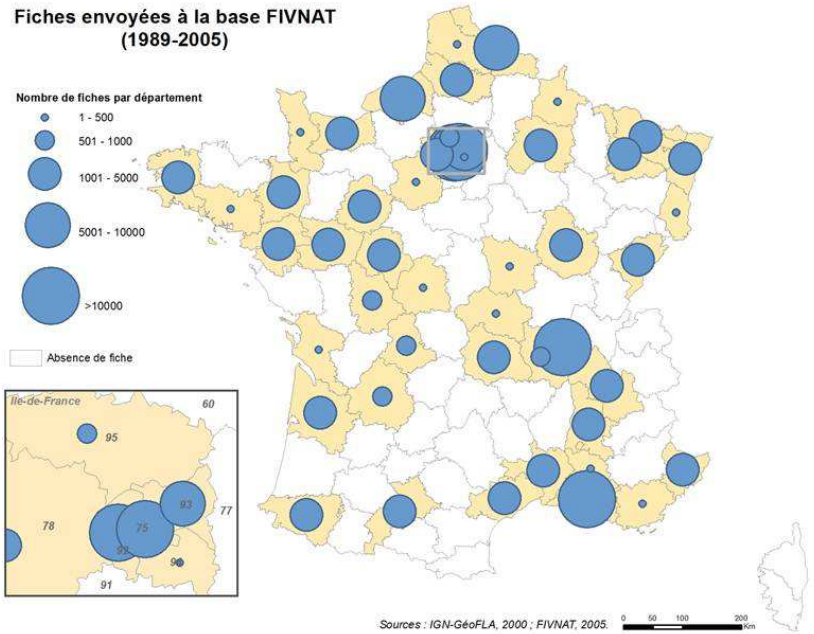
On each record, two spermiograms available per man:

- Check-up spermiogram carried out during a fertility check-up in a specialized laboratory within 6 months before the attempt

- Attempt spermiogram carried out at the ART centre the day of the oocyte retrieval

The Fivnat database





Number of ART centres sending records to the Fivnat database each year.
No more than 100 centres available at the same time in France.

Geographic covering of the ART centres included in the Fivnat database in the study period: number of records/county

INSTITUT DE VEILLE SANITAIRE

Methods

The source population

- Men involved in a first attempt of standard IVF or ICSI recorded in the Fivnat database between January 1989 and December 2005.
- Freshly ejaculated sperm
- Available data on age, ART technique, date of oocyte retrieval and spermiograms
- Azoospermic excluded

The study population

- Men whose female partner had both tubes either blocked or absent, thus naturally infertile : no selection about the man's fertility

Methods

Attempt spermiogram (date available)

3 indicators

- concentration (millions of sperm/ml)
- total motility (% of motile sperm)
- morphology (% of morphologically normal forms) (mainly David's classification)

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

Methods

Sensitivity analysis	
1- Adjustment for the ART centre	To confirm that no particular centre impacted the global trends
2- Analysis on the check-up spermiogram	To test the robustness of the results for intra-subject variation and laboratory practice diversity
3- Adjustment on ART technique and introduction of an interaction time/technique	To see if a decrease could be due to the inclusion of men newly eligible for ART with the introduction of ICSI in 1994
4- Analyses on another subsample of fertile men	Not impacted by a possible shared tubal infection
5- Analyses repeated on men <50 years	To test for an over selection of older men
6- Analyses restricted to centres that did not declare using the Kruger classification for morphology	Lower values when using the Kruger classification

Results

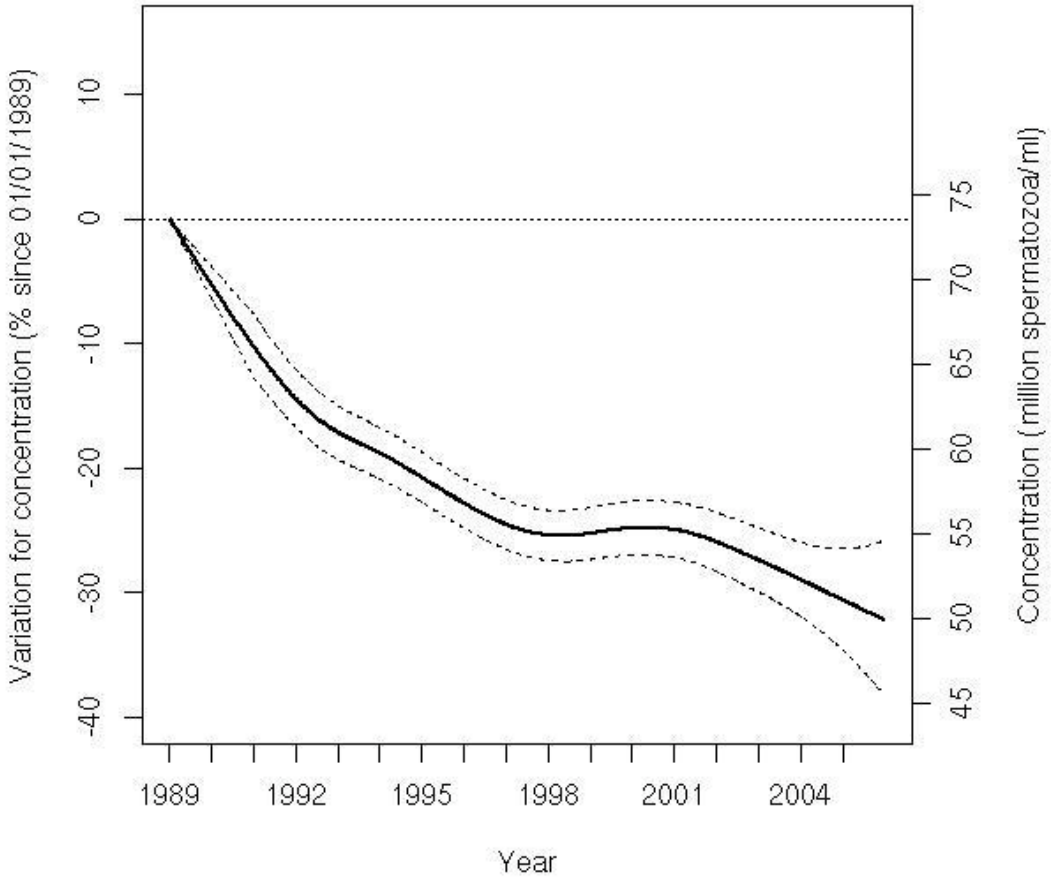
	Source population * **N=154 712**			Study population ** **N=26 609**		
Indicator	Concentr.	Mob	Morph	Concentr.	Mob	Morph
Complete attempts***	**121 702**	**120 635**	**59 457**	**21 055**	**21 102**	**11 416**
IVF	73.90%	74.30%	77.40%	94.60%	94.70%	95.50%
ICSI	26.10%	25.70%	22.60%	5.40%	5.30%	4.50%
Age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

Number of men in the source and the study population, for each sperm parameter analysis and each ART technique, with age distribution (source : Human Reproduction)

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

INSTITUT DE VEILLE SANITAIRE

Results : concentration

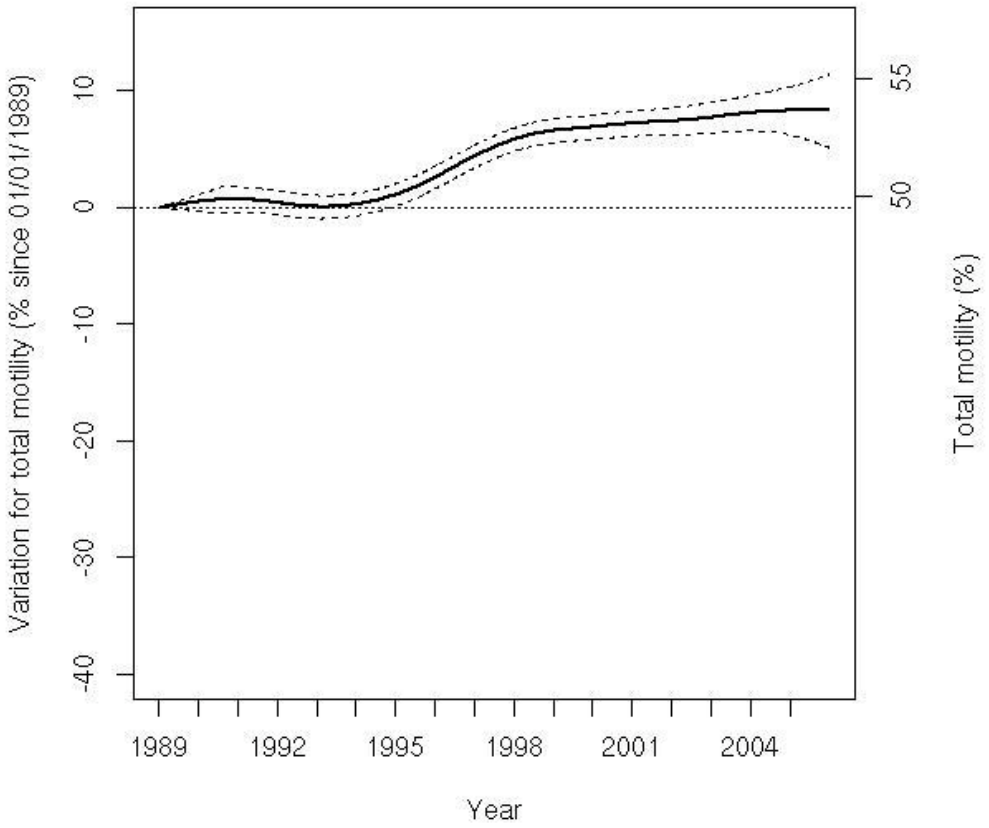


Trends:
- 32.2% [26.3-36.3]
- 1.9%/year,
=1.4M/ml/year
Values:
In 1989 : 73.6Msp/ml [69.0-78.4]
In 2005 : 49.9Msp/ml [43.5-54.7]

Left axis: Variation in % for concentration since January 1989 for a 35-year-old man in metropolitan France, with $CI_{95\%}$
Right axis: Projected values in millions sperm per milliliter, with $CI_{95\%}$
Source : Human Reproduction

INSTITUT DE VEILLE SANITAIRE

Results: motility

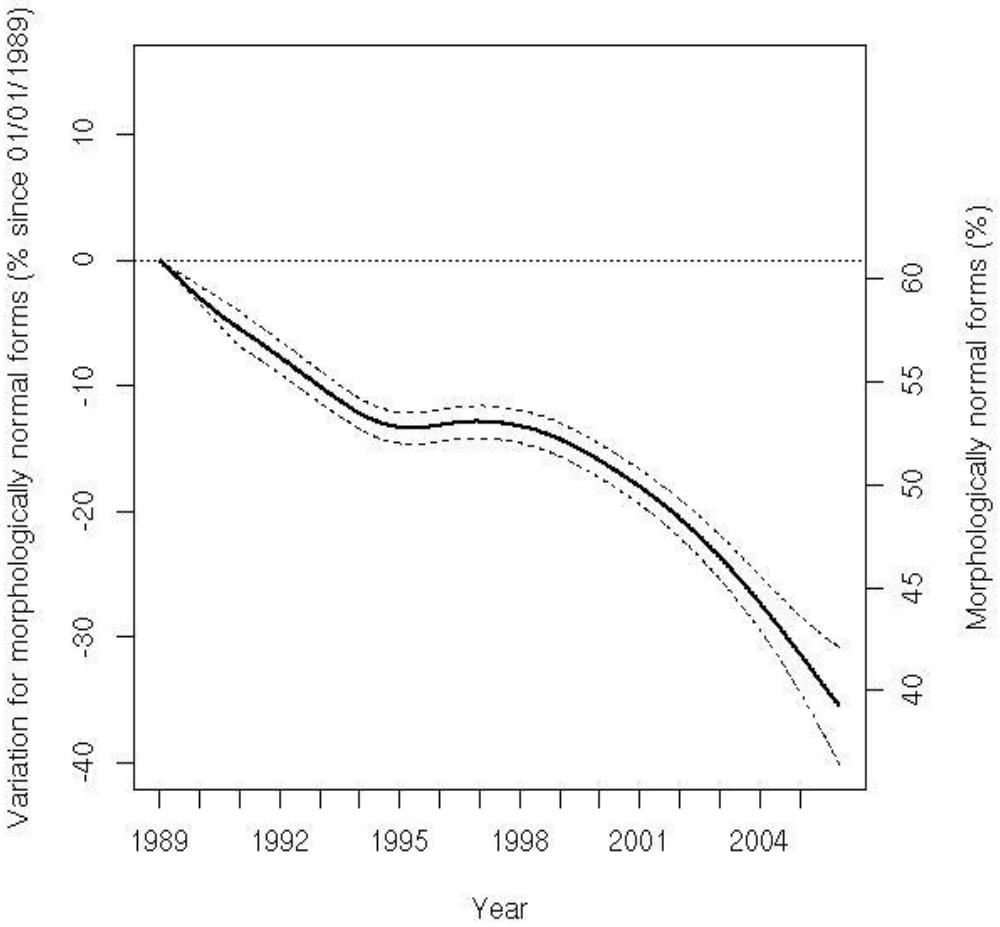


Trends:
Stability, then + 5.6%, from 1994 to 1998, then stability
Values:
In 1989 : 49.5% motile spm [48.2-50.8]
In 2005 : 53.6% motile spm [52.2-55.2]

Left axis : Variation in % of total motility since January 1989 for a 35-year-old man in metropolitan France with $CI_{95\%}$
Right axis : Projected values in % motile spermatozoa, with $CI_{95\%}$
Source : Human Reproduction

INVS INSTITUT DE VEILLE SANITAIRE

Results: morphology



Trends :
Overall decrease:
- 33.4%

Left axis: Variation in % morphologically normal forms since January 1989 for a 35-year-old man in metropolitan France, with $CI_{95\%}$
Right axis : Projected values in % morphologically normal forms, with $CI_{95\%}$
Source : Human Reproduction

INSTITUT DE VEILLE SANITAIRE

Results

Sensitivity analysis: robust results

- No centre effect
- Similar trends for the 3 indicators with the check-up spermiogram and with the subsample of fertile men
- Results in the study population not impacted by the arrival of ICSI
- No over selection of men > 50 years
- Same results on morphology when excluding centres which declared using the Kruger method, but too much lacking data (97.5%)

Discussion

Limits

- No adjustment for abstinence time, but a monotone time trend in abstinence time seems unrealistic
- No data on the diversity of laboratory practices: trends observed on alternative spermiograms performed in separate laboratories are similar
- Evolution in laboratory methods : no major change documented during the study period for concentration and motility, but morphology assessment may have been affected by changes in methods
- No adjustment for other factors involved in intra-individual variability: stress, temperature…but analysis of the 2 spermiograms gives similar results, and monotone time trends in these factors seem unrealistic

Discussion

Extrapolation of the results to the general population

- Minimum selection bias concerning men's fertility
- Distribution not truncated
- Geographic diversity reflecting metropolitan France
- No selection bias on age
- Bias linked to socio-economic status?
  - Tobacco consumption and overweight less likely among more educated men
  - ***In the general population, probably lower values and stronger decrease***

Hypotheses

Endocrine disruptors chemicals

- Measured in main human matrices (blood, urines, fat,…)
- Substances : in France, high levels of NDL-PCB, pyrethroïd and OP pesticides, triclosan particularly…
- Accumulating evidences (UNEP/WHO report): low dose effects, critical development periods, non monotonic dose-response curves, mixture effects…

Lifestyles

- Increasing BMI, sedentariness (TV), stress
- Mother's lifestyle (1950-1970)?

Others

- Non identified factors?
- Late stage of a longer process including intergenerational effects (Joffe, 2010)

Various factors converging toward the same effects?

INSTITUT DE VEILLE SANITAIRE

Conclusion

- To our knowledge, the largest sample close to the general population studied in the world, at the scale of a whole country
- Decrease in sperm concentration of 1.9%/year along 17 years, consistent with French past studies and some in other countries
- Average concentration for a 35-year-old man (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; no global trend for motility

➢ **What is happening to male fertility?**

- 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

➢ **Serious public health warning which need to be addressed**

Aknowlegments

The ART centres involved in Fivnat

VICHY LA PERGOLA

NICE CHU

NICE St Georges

NICE Santa Maria

CHARLEVILLE MEZIERES CH

MARSEILLE CONCEPTION

MARSEILLE FIV-PROVENCE

MARSEILLE I.M.R.

MARSEILLE Renaissance

MARSEILLE BELLE DE MAI

MARSEILLE CONCEPTION (double)

CAEN CHU

DEAUVILLE Polyclinique

LA ROCHELLE LE MAIL

BRIVES St Germain

AJACCIO CH

DIJON CHU

DIJON SAINTE-MARTHE

INSTITUT FERTILITE PERIGORD

BESANCON CHU

BESANCON LES CIGOGNES

VALENCE AUXILIATRICE

VALENCE AUXILIATRICE

DREUX CH

BREST CHU

BREST PASTEUR

NIMES CHU

NIMES ST-JOSEPH

TOULOUSE CHU**

TOULOUSE ST JEAN

TOULOUSE L'UNION

BORDEAUX PELLEGRIN Brun

BORDEAUX IFREARES

BORDEAUX PELLEGRIN (Leng)

BORDEAUX PELLEGRIN (Dallay)

MONTPELLIER CHU

MONTPELLIER Clinique SAINT-ROCH

RENNES CHU

RENNES LA SAGESSE

TOURS CHU

TOURS GEST

GRENOBLE CHU

GRENOBLE BELLEDONNE

GRENOBLE EAUX CLAIRES*

SAINT-PRIEST-JAREZ CESFIV

SAINT-PRIEST-JAREZ CESFIV

SAINT ETIENNE MICHELET

C.H.G. FIRMINY

ROANNE CH

NANTES CHU

NANTES POLYCLINIQUE ATLANTIQUE

NANTES Ntre DAME DE GRACE

ANGERS CHRU

CHOLET POLYCLINIQUE

EQUEURDREVILLE CLINIQUE COTENTIN

REIMS CHU

REIMS COURLANCY

NANCY CHU

NANCY Majorelle

LORIENT Bodélio

LORIENT Ste Brigitte

METZ Claude Bernard

METZ Bon secours

METZ SAINTE-CROIX

METZ BERCEAUX

DECIZE CH

LILLE HURIEZ/ JEANNE DE FLANDRE

LILLE EPARP Dubois

ROUBAIX CHU

DUNKERQUE Les Bazennes

LILLE CHR PAV. OLIVIER

LOMME SAINT PHILIBERT

LILLE SALENGRO

SAINT SAULVE Le Parc

LENS CH

LENS Bois Bernard

CLERMONT-FERRAND CHU

BAYONNE FIV C BASQUE

PAU LAGRANGE

SCHILTIGHEIM CMCO

MULHOUSE Diaconat

LYON EDOUARD HERRIOT

LYON BRON RHONALPIN

LYON CRES

LYON FERTILY MONTPLAISIR

LYON MONTPLAISIR

LYON CROIX ROUSSE

LE MANS TERTRE ROUGE

LE MANS St. DAMIEN

PARIS TENON

PARIS MARIGNAN

PARIS BAUDELOCQUE

PARIS PORT-ROYAL

PARIS CITE UNIVERSITAIRE

PARIS PITIE

PARIS DIACONESSES

PARIS HOTEL-DIEU

PARIS Bichat

PARIS MUETTE/MARIGNAN

PARIS SAINT-ANTOINE

PARIS ST VINCENT-DE-PAUL

PARIS Bluets

PARIS Spontini

ROUEN CHU

BOIS-GUILLAUME

LE HAVRE -IMES

POISSY CHR

VELIZY LES CHENES

LE CHESNAY PARLY2

MAISON LAFITTE Sully

AMIENS CHU

AMIENS APETS SAINTE THÉRESE

AMIENS SAINTE CLAIRE

DRAGUIGNAN CH

TOULON ST MICHEL

AVIGNON URBAIN V

POITIERS - CHU

LIMOGES CHU

CLAMART BECLERE

SEVRES CHG

NEUILLY Belvédère

NEUILLY HOP. AMERICAIN

NEUILLY CHEREST

COURBEVOIE CH

BONDY - CHU

BAGNOLET LA DHUYS

BLANC-MESNILClinique

AUBERVILLIERS ROSERAIE*

VITRY Noriets

PONTOISE CH

CORMEILLES / PARISIS

ENGHIEN Polyclinique

LES ABYMES GARFHUG

InVS
INSTITUT DE VEILLE SANITAIRE

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)*

This study was exclusively financed with public funding, by InVS

INSTITUT DE VEILLE SANITAIRE

References

Rapport PNUE/OMS: http://www.who.int/ceh/publications/endocrine/en/index.html

Auger J, Eustache F, Andersen AG, Irvine DS, Jorgensen N, Skakkebaek NE, et al. 2001. Sperm morphological defects related to environment, lifestyle and medical history of 1001 male partners of pregnant women from four European cities. Hum Reprod 16: 2710-2717.

Auger J, Jouannet P. 1997. Evidence for regional differences of semen quality among fertile French men. Federation Francaise des Centres d'Etude et de Conservation des Oeufs et du Sperme humains. Hum Reprod 12: 740-745.

Auger J, Kunstmann JM, Czyglik F, Jouannet P. 1995. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 332: 281-285.

Bernardinelli L, Clayton D, Pascutto C, Montomoli C, Ghislandi M, Songini M ,1995. Bayesian analysis of space-time variation in disease risk, Statistics in Medicine, 14, 2433-2443

Bujan L, Mansat A, Pontonnier F, Mieusset R. 1996. Time series analysis of sperm concentration in fertile men in Toulouse, France between 1977 and 1992. BMJ 312: 471-472.

de Mouzon J., Thonneau P, Spira A, Multigner L. 1996. Declining sperm count. Semen quality has declined among men born in France since 1950. BMJ 313: 43-45.

Joffe M, 2010. What has happened to human fertility?. Human Reprod , 2:295-307

Jensen TK, Jacobsen R, Christensen K, Nielsen NC, Bostofte E. 2009. Goodsemen quality and life expectancy: a cohort study of 43 277 men.

Am J Epidemiol;5:559–565.

Jorgensen N, Andersen AG, Eustache F, Irvine DS, Suominen J, Petersen JH, et al. 2001. Regional differences in semen quality in Europe. Hum Reprod 16: 1012-1019.

Jorgensen N, Joensen UN, Jensen TK, Jensen MB, Almstrup K, Olesen IA, et al. 2012. Human semen quality in the new millennium: a prospective cross-sectional population-based study of 4867 men. BMJ Open 2.

Jorgensen N, Vierula M, Jacobsen R, Pukkala E, Perheentupa A, Virtanen HE, et al. 2011. Recent adverse trends in semen quality and testis cancer incidence among Finnish men. Int J Androl 34: e37-e48.

Slama R, Eustache F, Ducot B, Jensen TK, Jorgensen N, Horte A, et al. 2002. Time to pregnancy and semen parameters: a cross-sectional study among fertile couples from four European cities. Hum Reprod 17: 503-515.

Swan SH, Brazil C, Drobnis EZ, Liu F, Kruse RL, Hatch M, et al. 2003. Geographic differences in semen quality of fertile U.S. males. Environ Health Perspect 111: 414-420.