

Declining semen quality of French men

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Semen quality studies : source populations

- ▶ **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)
 - Geographic variations in Europa (Auger 2001, Jorgensen 2001)
 - Geographic variations in USA (Swan, 2003)

- ▶ **Infertility clinic studies** : men involved in assisted reproductive technology (ART) attempts
 - France (De Mouzon 1996): decrease from 1989 to 1994
 - USA, Israel, India, Spain, Tunisia : various methods used. Some recent ones seem to show a decrease, but not all.

- ▶ **Young conscript studies** :
 - Danish study : slight increase from 1996 et 2010 (Jorgensen, 2012)
 - Finnish study : decrease from 1998 to 2006 (Jorgensen, 2011)



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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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The Fivnat database

- Built by the Fivnat association from 1985 in France
- 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
- Estimated completeness: 40 to 80% of the french ART centres



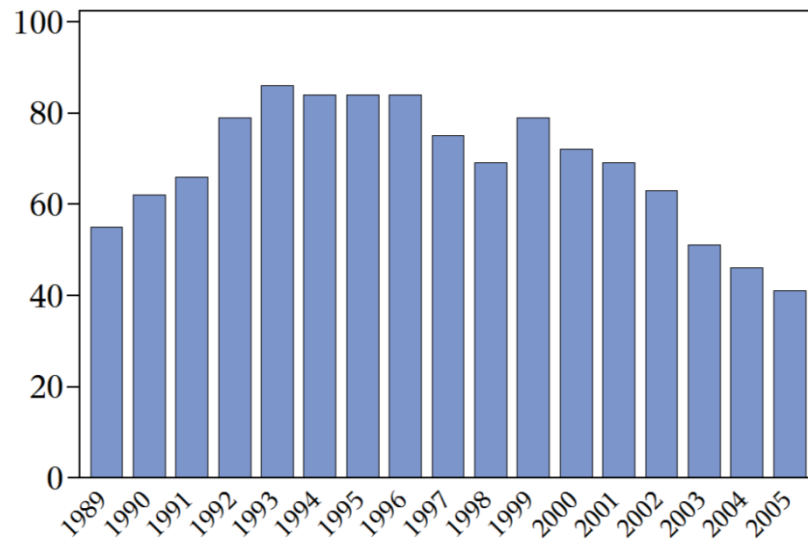
The Fivnat data base

On each record, two spermograms available per man:

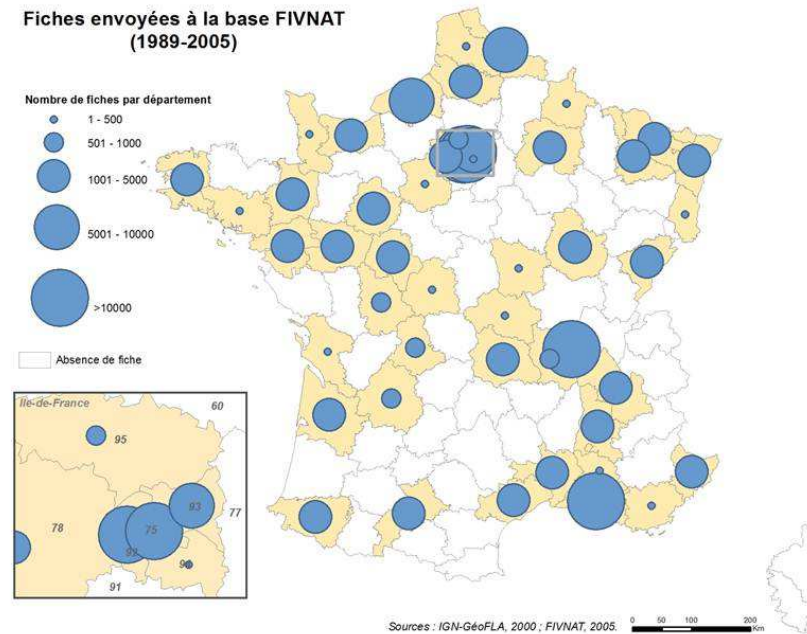
- ▶ **Check-up spermogram** carried out during a fertility check-up in a specialized laboratory within 6 months before the attempt
- ▶ **Attempt spermogram** carried out at the ART centre the day of the oocyte retrieval



The Fivnat database



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



Geographic covering of the ART centres included in the Fivnat database from 1989 to 2005: number of records/county



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 spermiogram
- 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 spermogram

3 indicators

- concentration (millions of sperm/ml)
- total motility (% of motile sperm)
- morphology (% of morphologically normal forms)

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

- Adjustment for the ART centre (to confirm that no particular centre impacted the global trends)
- Analysis on the check-up spermogram (intra–subject variation and laboratory practice diversity)
- Adjustment on ART technique and introduction of an interaction time/technique (in order to see if a decrease could be due to the inclusion of men newly 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 years (to test for an overselection of older men)
- Analyses restricted to centres that did not declare using the Kruger method for morphology (lower values when using the method)



Results

	Source population *			Study population **		
	N=154 712			N=26 609		
Indicator	Concent r.	Mob	Morph	Concent r.	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		

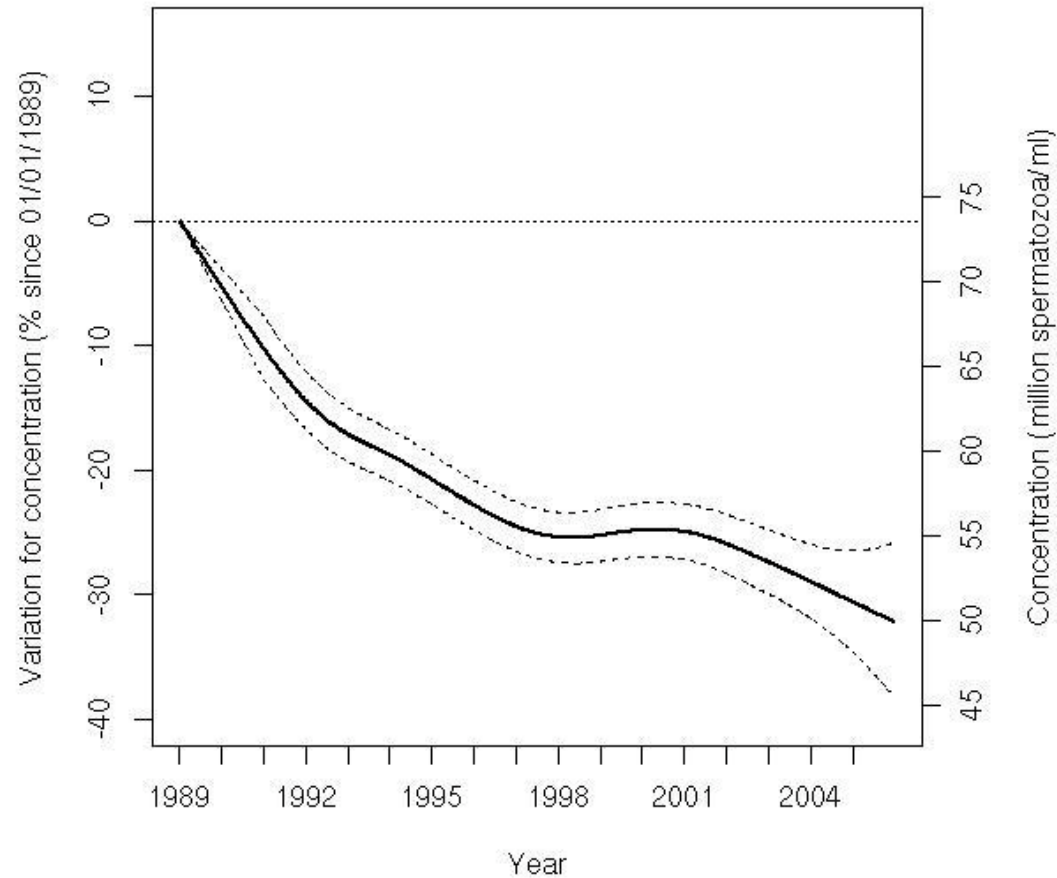
Table 1: Number of men in the source and the study population, for each sperm parameter analysis and each ART technique, with age distribution (source : Human Reproduction)

**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*

Results



Trends:

- 32.2% [26.3-36.3]

- 1.9%/year,
=1.4M/ml/year

Values:

In 1989 : 73.6Msp/ml
[69.0-78.4]

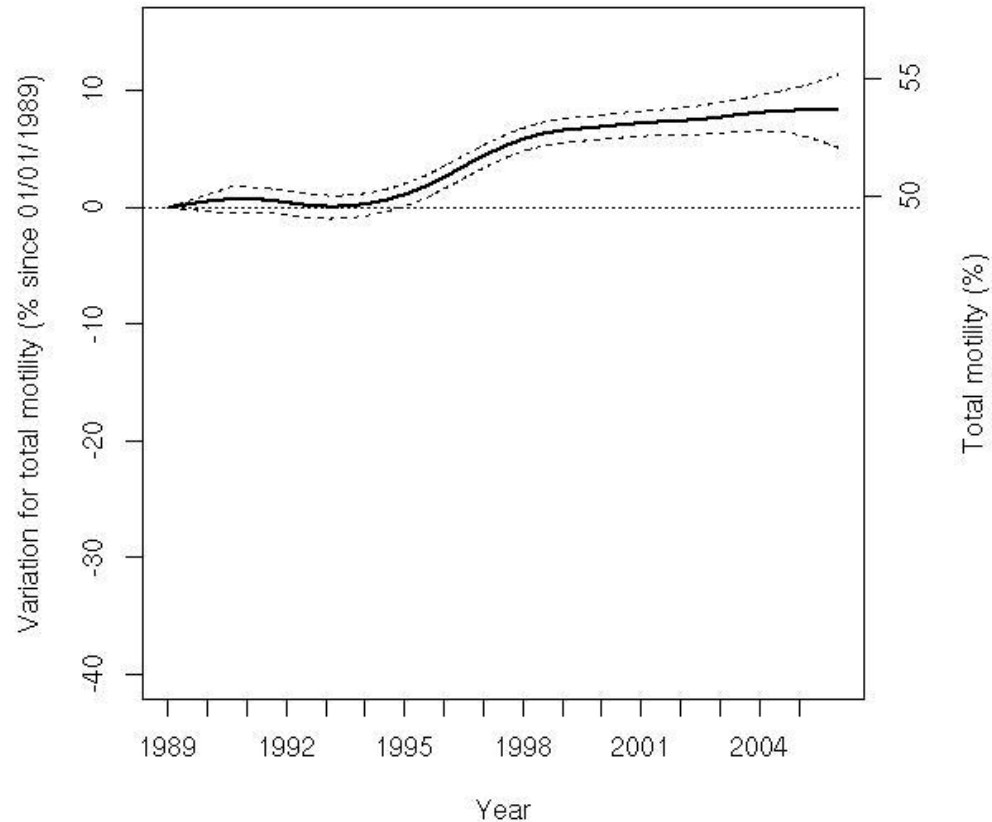
In 2005 : 49.9Msp/ml
[43.5-54.7]

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

Results



Trends:

**Stability, then + 5.6%,
from 1994 to 1998,
then stability**

Values:

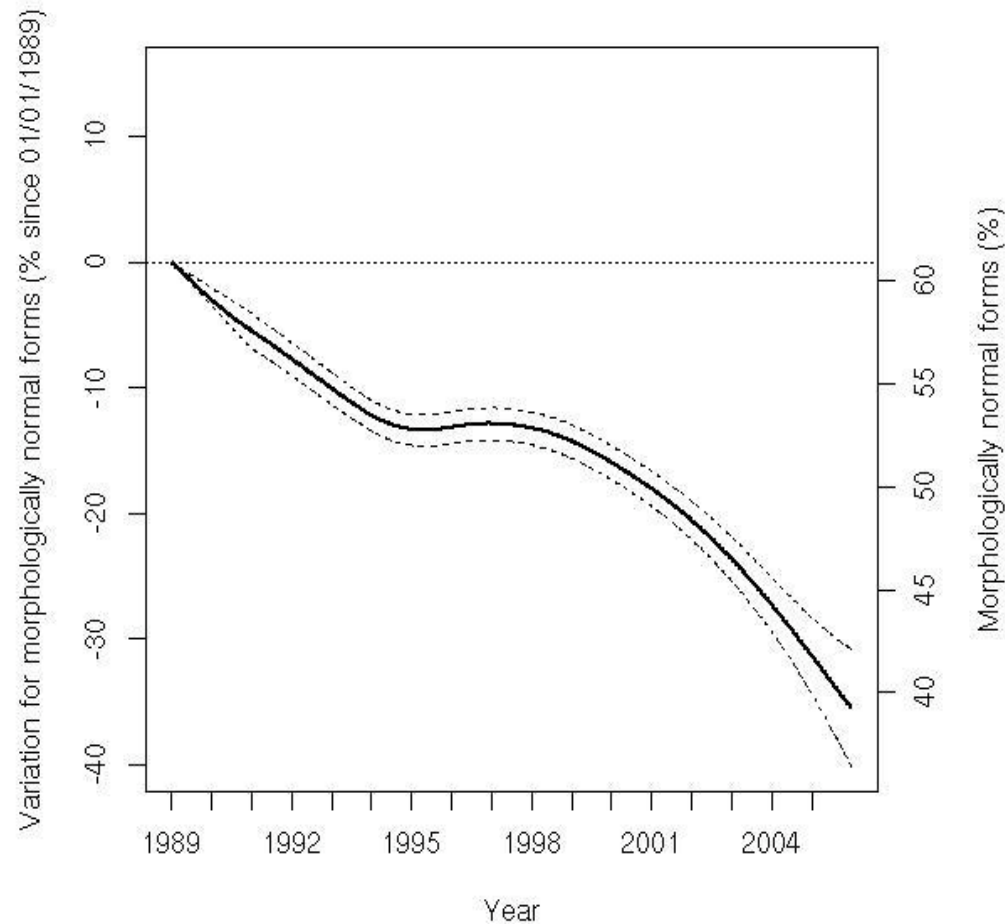
**In 1989 : 49.5% motile
spm [48.2-50.8]
In 2005 : 53.6% motile
spm [52.2-55.2]**

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

Results



Trends :
Biphasic
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



Results

Sensitivity analysis: robust results

- No centre effect
- Similar trends for the 3 indicators with 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 declared using 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 practises, trends observed on alternative spermograms performed in separate laboratories are similar
- Evolution in laboratory methods : no major change documented during the study period for concentration and motility, 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 spermograms 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

- Multiple exposure ways, ubiquity
- Measured in main human matrices (blood, urines, fat,...)
- Substances : in France, high levels of NDL-PCB, pyrethroid and OP pesticides, triclosan particularly...
- Increasing incidence of TDS indicators in France
- Accumulating evidences (UNEP/WHO report): low dose effects, critical development periods, non monotonic dose-response curves, mixture effects...
- Possible effects on all endocrine systems

Lifestyles

- Increasing BMI, sedentariness (TV), testicular heat, stress
- Mother's lifestyle

Others

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

***Various factors
converging toward the
same effects?***



Conclusion on time trends

- 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
- 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**



Aknowlegments

The ART centres involved in Fivnat

VICHY LA PERGOLA	DREUX CH	SAINT-PRIEST-JAREZ CESFIV	DECIZE CH	LE MANS St. DAMIEN	AMIENS APETS SAINTE THÉRESE
NICE CHU	BREST CHU	SAINT-PRIEST-JAREZ CESFIV	LILLE HURIEZ/ JEANNE DE FLANDRE	PARIS TENON	AMIENS SAINTE CLAIRE
NICE St Georges	BREST PASTEUR	SAINT ETIENNE MICHELET	LILLE EPARP Dubois	PARIS MARIGNAN	DRAGUIGNAN CH
NICE Santa Maria	NIMES CHU	C.H.G. FIRMINY	ROUBAIX CHU	PARIS BAUDELOCQUE	TOULON ST MICHEL
CHARLEVILLE MEZIERES CH	NIMES ST-JOSEPH	ROANNE CH	DUNKERQUE Les Bazennes	PARIS PORT-ROYAL	AVIGNON URBAIN V
MARSEILLE CONCEPTION	TOULOUSE CHU**	NANTES CHU	LILLE CHR PAV. OLIVIER	PARIS CITE UNIVERSITAIRE	POITIERS - CHU
MARSEILLE FIV-PROVENCE	TOULOUSE ST JEAN	NANTES POLYCLINIQUE ATLANTIQUE	LOMME SAINT PHILIBERT	PARIS PITIE	LIMOGES CHU
MARSEILLE I.M.R.	TOULOUSE L'UNION	NANTES Ntre DAME DE GRACE	LILLE SALENGRO	PARIS DIACONESSES	CLAMART BECLERE
MARSEILLE Renaissance	BORDEAUX PELLEGRIN Brun	ANGERS CHRU	SAINT SAULVE Le Parc	PARIS HOTEL-DIEU	SEVRES CHG
MARSEILLE BELLE DE MAI	BORDEAUX IFREARES	CHOLET POLYCLINIQUE	LENS CH	PARIS Bichat	NEUILLY Belvédère
MARSEILLE CONCEPTION (double)	BORDEAUX PELLEGRIN (Leng)	EQUEURDREVILLE CLINIQUE COTENTIN	LENS Bois Bernard	PARIS MUETTE/MARIGNAN	NEUILLY HOP. AMERICAIN
CAEN CHU	BORDEAUX PELLEGRIN (Dallay)	REIMS CHU	CLERMONT-FERRAND CHU	PARIS SAINT-ANTOINE	NEUILLY CHEREST
DEAUVILLE Polyclinique	MONTPELLIER CHU	REIMS COURLANCY	BAYONNE FIV C BASQUE	PARIS ST VINCENT-DE-PAUL	COURBEVOIE CH
LA ROCHELLE LE MAIL	MONTPELLIER Clinique SAINT-ROCH	NANCY CHU	PAU LAGRANGE	PARIS Bluets	BONDY - CHU
BRIVES St Germain	RENNES CHU	NANCY Majorelle	SCHILTIGHEIM CMCO	PARIS Spontini	BAGNOLET LA DHUYS
AJACCIO CH	RENNES LA SAGESSE	LORIENT Bodélio	MULHOUSE Diaconat	ROUEN CHU	BLANC-MESNILClinique
DIJON CHU	TOURS CHU	LORIENT Ste Brigitte	LYON EDOUARD HERRIOT	BOIS-GUILLAUME	AUBERVILLIERS ROSERAIE*
DIJON SAINTE-MARTHE	TOURS GEST	METZ Claude Bernard	LYON BRON RHONALPIN	LE HAVRE -IMES	VITRY Noriets
INSTITUT FERTILITE PERIGORD	GRENOBLE CHU	METZ Bon secours	LYON CRES	POISSY CHR	PONTOISE CH
BESANCON CHU	GRENOBLE BELLEDONNE	METZ SAINTE-CROIX	LYON FERTILY MONTPLAISIR	VELIZY LES CHENES	CORMELLES / PARISIS
BESANCON LES CIGOGNES	GRENOBLE EAUX CLAIRES*	METZ BERCEAUX	LYON MONTPLAISIR	LE CHESNAY PARLY2	ENGHIEN Polyclinique
VALENCE AUXILIATRICE			LYON CROIX ROUSSE	MAISON LAFITTE Sully	LES ABYMES GARFHUG
VALENCE AUXILIATRICE			LE MANS TERTRE ROUGE	AMIENS CHU	



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