# “Just relax and you’ll get pregnant”
# Is there a link between stress and infertility?

Never Stand Still | Medicine | School of Women’s and Children’s Health

William Ledger

Professor of Obstetrics and Gynaecology

# Declaration of interest

This work was supported by SPD Development Company Ltd

WLL is a member of the SPD international advisory board


# Of course stress causes infertility:

# Of course stress causes infertility:

Clinically recognised forms of stress related reproductive dysfunction include

- functional hypothalamic amenorrhoea
- anorexia nervosa (bulimia)
- grief reaction
- sexual dysfunction

Growing recognition that each of these syndromes develops in response to exposure to psychogenic and metabolic stressors

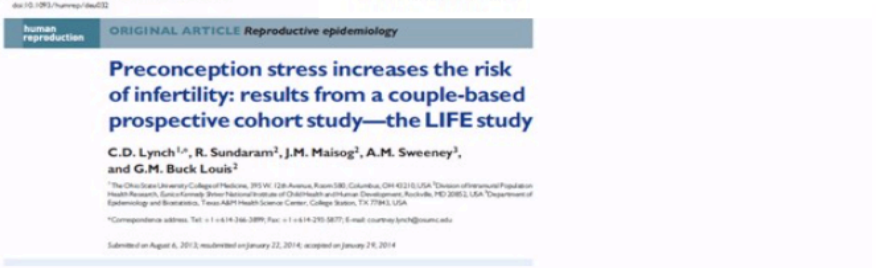
# But its not as simple as it seems:

J Assist Reprod Genet (2013) 30:35–41
DOI 10.1007/s10815-012-9904-x

ASSISTED REPRODUCTION TECHNOLOGIES

**Relationship between psychological stress and reproductive outcome in women undergoing in vitro fertilization treatment: Psychological and neurohormonal assessment**

Yuan An · Zhuangzhuang Sun · Linan Li · Yajuan Zhang · Hongping Ji



Human Reproduction, Vol.29, No.5 pp. 1067–1075, 2014

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

**Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study—the LIFE study**

C.D. Lynch[1,*], R. Sundaram[2], J.M. Maisog[2], A.M. Sweeney[3], and G.M. Buck Louis[2]

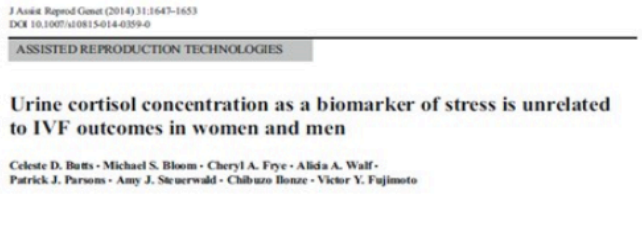
Human Reproduction, Vol.24, No.5 pp. 1092–1098, 2009
Advanced Access publication on January 28, 2009 doi:10.1093/humrep/den491

human reproduction

ORIGINAL ARTICLE *Psychology and counselling*

**Anxiety and depression have no influence on the cancellation and pregnancy rates of a first IVF or ICSI treatment**

A.M.E. Lintsen[1,5], C.M. Verhaak[2], M.J.C. Eijkemans[3], J.M.J. Smeenk[1,4], and D.D.M. Braat[1]



J Assist Reprod Genet (2014) 31:1647–1653
DOI 10.1007/s10815-014-0359-0

ASSISTED REPRODUCTION TECHNOLOGIES

**Urine cortisol concentration as a biomarker of stress is unrelated to IVF outcomes in women and men**

Celeste D. Butts · Michael S. Bloom · Cheryl A. Frye · Alicia A. Walf · Patrick J. Parsons · Amy J. Steuerwald · Chibuzo Ilonze · Victor Y. Fujimoto

**Human Reproduction, Vol.29, No.5 pp. 1067–1075, 2014**
doi:10.1093/humrep/deu032

human reproduction

**ORIGINAL ARTICLE** ***Reproductive epidemiology***

# Preconception stress increases the risk of infertility: results from a couple-based prospective cohort study—the LIFE study

**C.D. Lynch[1,*], R. Sundaram[2], J.M. Maisog[2], A.M. Sweeney[3], and G.M. Buck Louis[2]**

[1]The Ohio State University College of Medicine, 395 W. 12th Avenue, Room 580, Columbus, OH 43210, USA [2]Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Rockville, MD 20852, USA [3]Department of Epidemiology and Biostatistics, Texas A&M Health Science Center, College Station, TX 77843, USA

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Enrolled women collected saliva the morning following enrollment and then the morning following their first observed study menses for the measurement of cortisol and alpha-amylase, which are biomarkers of stress. TTP was measured in cycles. Covariate data were captured on both a baseline questionnaire and daily journals.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Among the 401 (80%) women who completed the protocol, 347 (87%) became pregnant and 54 (13%) did not. After adjustment for female age, race, income, and use of alcohol, caffeine and cigarettes while trying to conceive, women in the highest tertile of alpha-amylase exhibited a 29% reduction in fecundity (longer TTP) compared with women in the lowest tertile [fecundability odds ratios (FORs) = 0.71; 95% confidence interval (CI) = (0.51, 1.00); $P < 0.05$]. This reduction in fecundity translated into a >2-fold increased risk of infertility among these women [relative risk (RR) = 2.07; 95% CI = (1.04, 4.11)]. In contrast, we found no association between salivary cortisol and fecundability.

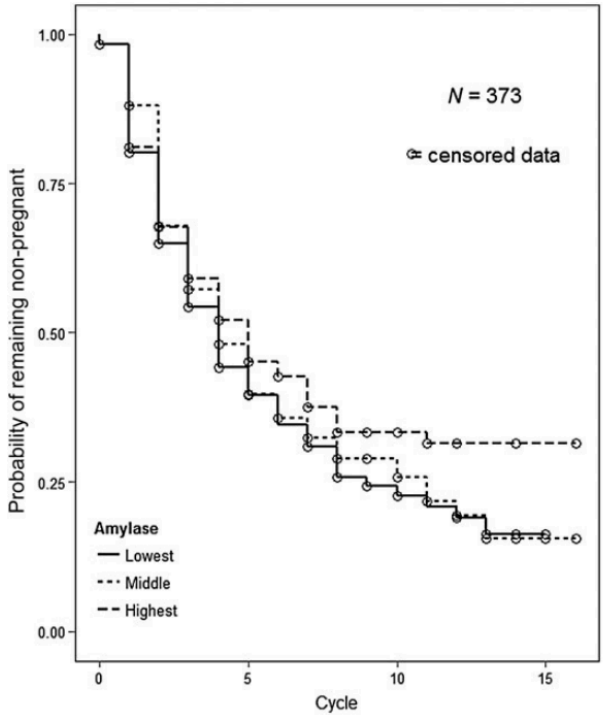
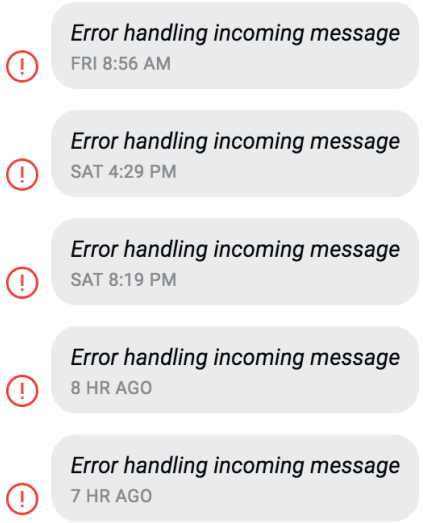



**Figure 2** Adjusted* probability of remaining not pregnant by tertile of salivary alpha-amylase.*Adjusted for age of female, difference in age between male and female, income of female (dichotomized), race of female (dichotomized), female's cigarette use, female's caffeine use, and female's alcohol use.

**Table III** RR of infertility by average stress biomarker level in the first two cycles of participation ($n = 299$).

| | RR | 95% CI | Adjusted RR[b] | 95% CI |
|---|---|---|---|---|
| Alpha-amylase[a] | 1.41 | [1.04, 1.90] | 1.46 | [1.08, 1.98] |
| Lowest | — | — | — | — |
| Middle | 0.92 | [0.44, 1.93] | 1.02 | [0.47, 2.19] |
| Highest | 1.75 | [0.91, 3.35] | 2.07 | [1.04, 4.11] |
| Cortisol[a] | 0.24 | [0.03, 2.20] | 0.36 | [0.05, 2.77] |
| Lowest | — | — | — | — |
| Middle | 1.12 | [0.60, 2.08] | 1.33 | [0.69, 2.55] |
| Highest | 0.72 | [0.36, 1.43] | 0.84 | [0.40, 1.76] |

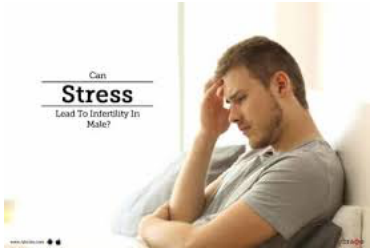
# The Internet is all-knowing




Infertility
How Does Stress
Trigger It?


STRESS
CAUSE OF INFERTILITY


Intended Parents:
Is Stress Causing your Infertility?

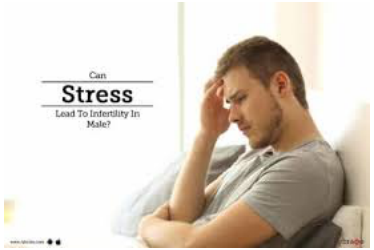

Can
Stress
Lead To Infertility In
Male?


Infertility
How Does Stress
Trigger It?


STRESS
CAUSE OF INFERTILITY


Intended Parents:
Is Stress Causing your Infertility?


Stress
Depression
Anxiety
Savings
Debt
Sick
Time Management
Health
Fear
Headache
Worry
No Sleep


Can
Stress
Lead To Infertility In
Male?


Infertility
How Does Stress Trigger It?

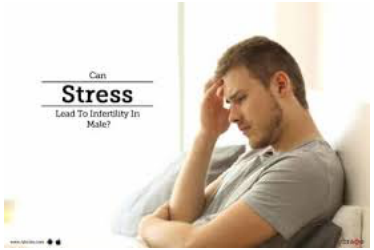

STRESS
CAUSE OF INFERTILITY

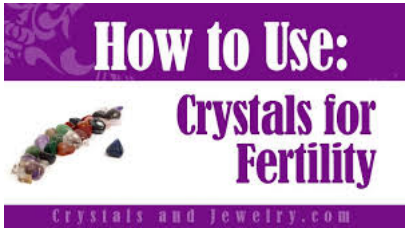

Trailhead
your guide to holistic health
EDUCATIONAL VIDEO
Connection between stress and infertility
Jennifer E Winer, L.Ac. , Dipl. Ac., MSOM, Fertility Expert, Viola Practitioner, founder of Winer Acupuncture in MN, talks about how acupuncture can help us manage stress


Intended Parents:
Is Stress Causing your Infertility?


Stress
Depression
Anxiety
Savings
Debt
Sick
Time Management
Health
Fear
Headache
Worry
No Sleep


Zen
Fertility
Center
858.495.0771

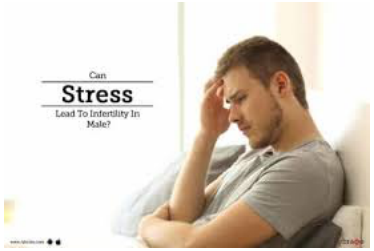

Can
Stress
Lead To Infertility In Male?


How to Use:
Crystals for Fertility
Crystals and Jewelry.com


Infertility
How Does Stress Trigger It?


STRESS
CAUSE OF INFERTILITY


Intended Parents:
Is Stress Causing your Infertility?


Can
Stress
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Stress
Depression
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Savings
Debt
Sick
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Health
Fear
Headache
Worry
No Sleep


I THINK IT'S STRESS!!

# In Utero Exposure to Famine and Subsequent Fertility: The Dutch Famine Birth Cohort Study

*L.H. Lumey, MD, PhD, and Aryeh D. Stein, MPH, PhD*

# In Utero Exposure to Famine and Subsequent Fertility: The Dutch Famine Birth Cohort Study

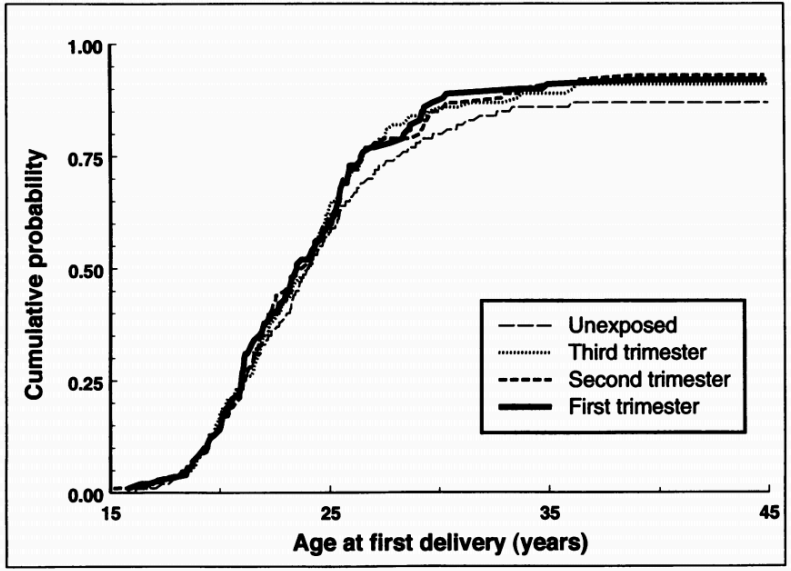
*L.H. Lumey, MD, PhD, and Aryeh D. Stein, MPH, PhD*

In the winter of 1944/45, a severe famine occurred in the western Netherlands; this was a society with a well-developed administrative structure and in which the population had generally been adequately nourished. The severity of the famine and its widespread nature have been fully documented. [2–5]

Official food rations were below 1000 calories (4200 J) per person per day from January through April 1945. Pregnant women were allocated some additional food rations, but the extent to which redistribution of these additional rations occurred within families is not known. The famine ceased immediately with liberation in May 1945, when Allied food supplies became abundant. Dramatic effects of the famine on pregnancy weight gain and infant birth size have been documented elsewhere. [6–8]

# In Utero Exposure to Famine and Subsequent Fertility: The Dutch Famine Birth Cohort Study

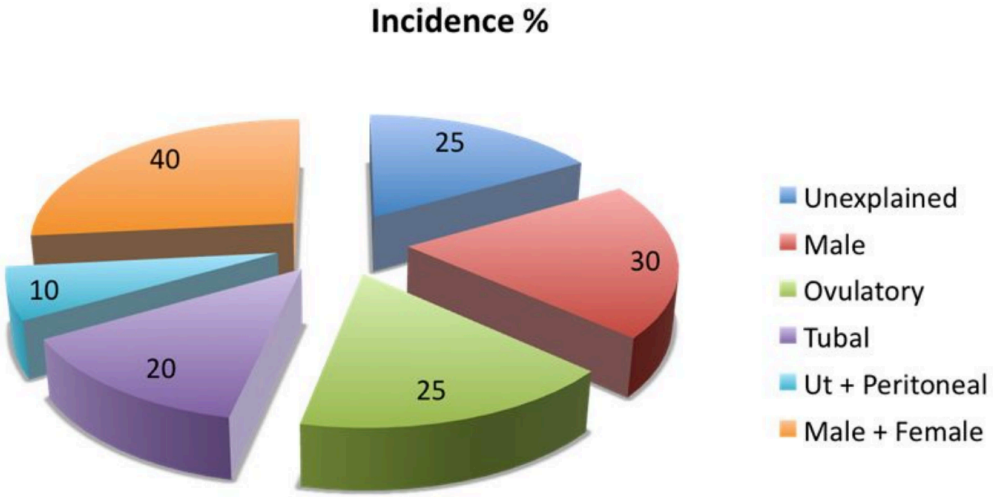
*L.H. Lumey, MD, PhD, and Aryeh D. Stein, MPH, PhD*




*Note.* Famine cohorts overlap: A woman could have been exposed in both the first and the second trimesters or in both the second and the third trimesters. No woman was exposed in both first and third trimesters, and women in the control group had no in utero famine exposure. No statistically significant ($P > .10$ for all comparisons) pairwise differences could be detected by log-rank test.

**Figure 1—Cumulative probability of delivering at least one child, by age at first delivery and maternal trimester of famine exposure, among 700 women born in Amsterdam, the Netherlands, from August 1, 1944, through April 15, 1946, and interviewed between 1987 and 1991.**

# Causes of subfertility




Hull 1985, Thonneau 1991

# Stress, lifestyle and fertility

# The impact of stress on fertility treatment

*Kristin L. Rooney*[a] *and Alice D. Domar*[a,b]

[a]Domar Center for Mind/Body Health, Boston IVF and [b]Beth Israel Deaconess Medical Center, Harvard Medical School, Waltham, Massachusetts, USA

Correspondence to Dr Alice D. Domar, 130 Second Avenue, Waltham, MA 02451, USA. Tel: +1 781 434 6515; fax: +1 781 370 2330; e-mail: domar@domarcenter.com

**Curr Opin Obstet Gynecol** 2016, 28:198–201

CURRENT OPINION

# The impact of stress on fertility treatment

*Kristin L. Rooney*[a] *and Alice D. Domar*[a,b]

## KEY POINTS

- Infertile individuals are more stressed than the fertile population and want help to reduce stress.
- Psychological interventions have a significant impact on infertility patients' well being, especially ones that focus on skills acquisition such as CBT.
- Self-administered interventions may be useful tools at reducing patient stress and decreasing dropout rates.
- It is unclear if stress negatively affects treatment outcomes.

International Journal of Gynecology and Obstetrics 124 (2014) 143–147

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

# A comparison of psychological stress among women with and without reproductive failure

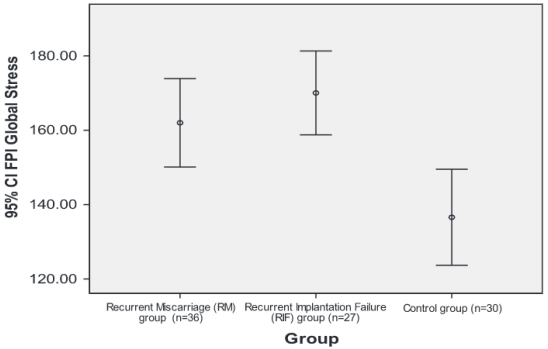
Carol Coughlan [a], Stephen Walters [b], William Ledger [c], T.C. Li [a,*]

27 women with RIF
36 women with RM (3-7)
30 parous controls

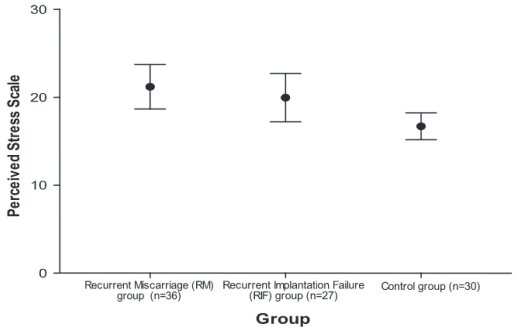
FPI, PSS, PANAS

Fertility Problem Inventory (FPI), the Perceived Stress Scale (PSS) and the Positive and Negative Affect Schedule (PANAS)

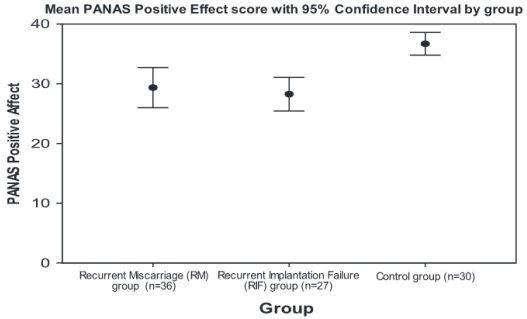
**a) Mean Global Stress Score with 95% Confidence Interval by group**



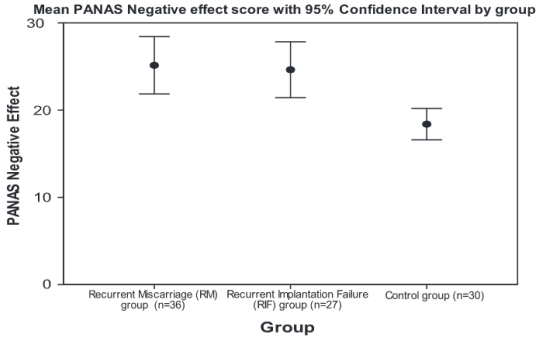

**b) Mean Perceived Stress Score with 95% Confidence Interval by group**

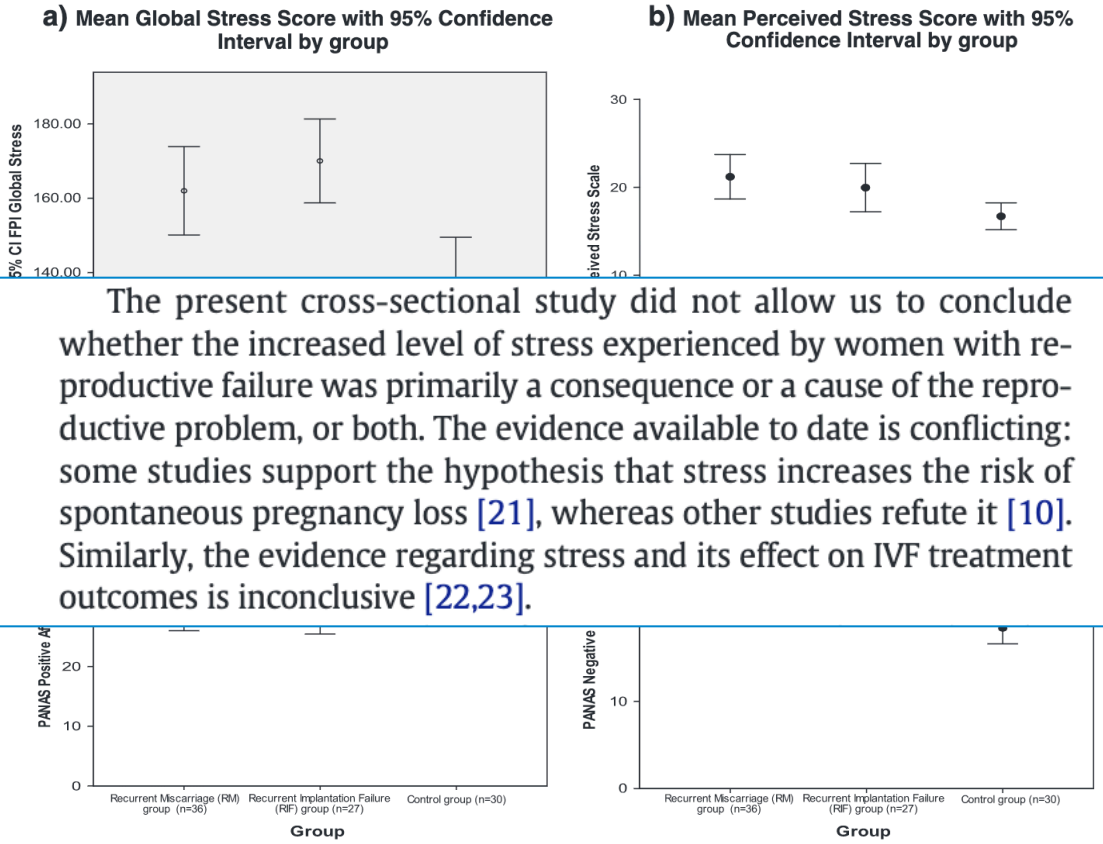



**c) Mean PANAS Positive Affect score with 95% confidence interval by group**




**d) Mean PANAS Negative Affect score with 95% confidence interval by group**






The present cross-sectional study did not allow us to conclude whether the increased level of stress experienced by women with reproductive failure was primarily a consequence or a cause of the reproductive problem, or both. The evidence available to date is conflicting: some studies support the hypothesis that stress increases the risk of spontaneous pregnancy loss [21], whereas other studies refute it [10]. Similarly, the evidence regarding stress and its effect on IVF treatment outcomes is inconclusive [22,23].

**Human Reproduction, Vol.28, No.1 pp. 138–151, 2013**
Advanced Access publication on October 18, 2012 doi:10.1093/humrep/des372

human reproduction

ORIGINAL ARTICLE *Infertility*

# Home ovulation tests and stress in women trying to conceive: a randomized controlled trial

**S. Tiplady[1,*], G. Jones[2], M. Campbell[2], S. Johnson[1], and W. Ledger[3]**

*Primary*

WOMEN'S HEALTH

Women's Health
Volume 15: 1–12
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DOI: 10.1177/1745506519838363
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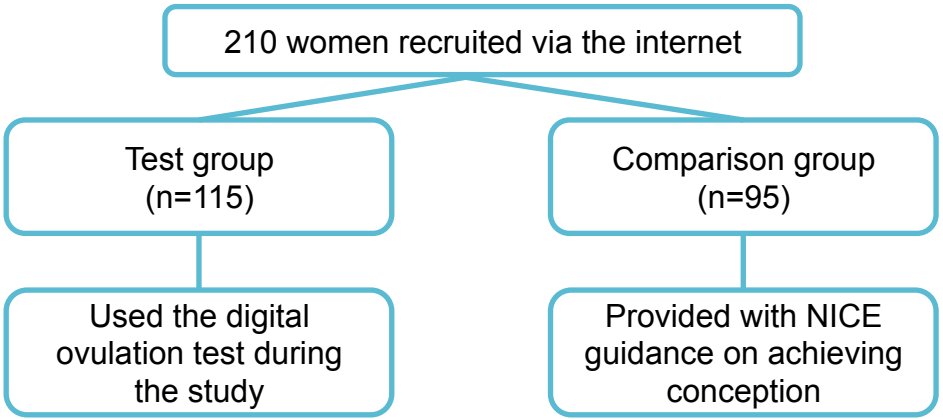
SAGE

# Home ovulation test use and stress during subfertility evaluation: Subarm of a randomized controlled trial

**Sarah Weddell[1], Georgina L Jones[2], Sheila Duffy[3], Cameron Hogg[4], Sarah Johnson[1] and William Ledger[5]**

Original Study: Prospective randomised controlled study comparing women using a digital ovulation test compared with women not using the test




Data from 143 volunteers were re-analysed with an exit status of:

Not pregnant n=100

Pregnant n=43

Subjective stress measured with PANAS (positive and negative affect schedule) and PSS (Perceived Stress Scale )
General health measured with Short-Form 12 health survey

Urinary cortisol was measured as a biochemical marker of stress

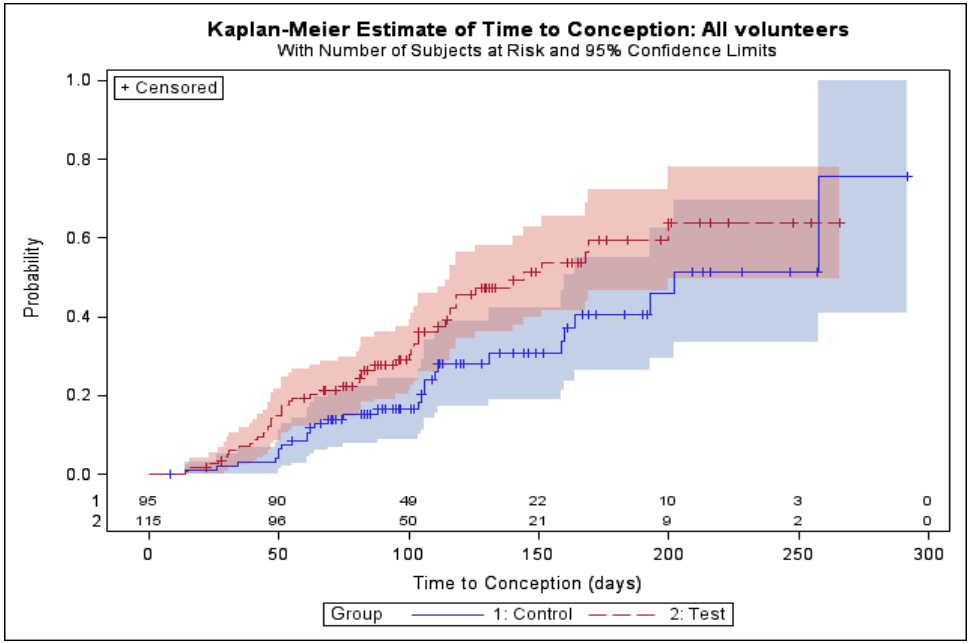
Data were collected at 1) baseline before next menstrual cycle, 2) day 6 in next cycle and 3) day after ovulation in next cycle

The study lasted for 2 complete menstrual cycles with pregnancy confirmed via positive digital home pregnancy

Stress levels were compared between those who conceived (n=43) with those who did not (n=100)

The data were re-analysed to determine whether stress levels were related to likelihood of pregnancy (regardless of randomisation group)

# Cycle tracking reduces time to pregnancy




Odds ratio 1.77 (95% CI: 0.999, 3.16)

# How to measure stress?

Stress levels were objectively measured at specific time points over 2 menstrual cycles by:

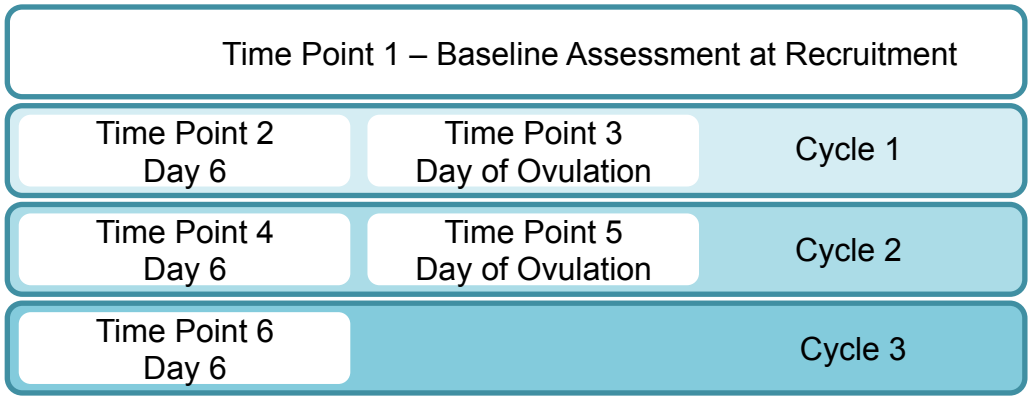
- **Questionnaire**

  Perceived Stress Scale and Positive And Negative Affect Score: ALL timepoints

  SF-12: Timepoint 1 and 6

- **Biochemical marker**

  Urinary cortisol: Timepoint 2, 3, 4, 5 and 6




For this analysis data were assessed from Time Points 1, 2 and 3 only (cycle 1) as the emotional impact of failing to conceive for a further cycle may impact findings in the Not Pregnant cohort

# Data analysis

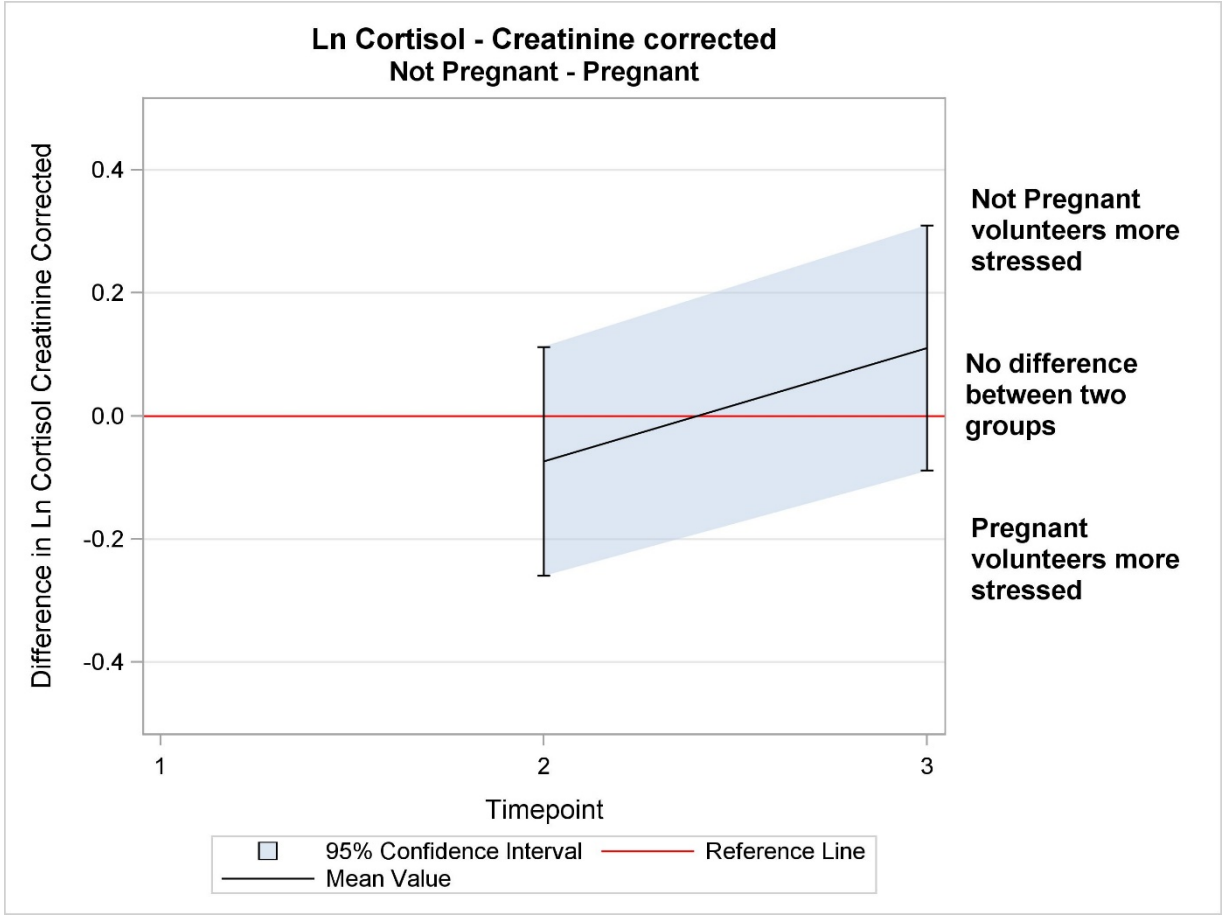
Two-sample t-tests were conducted comparing the Pregnant and Not Pregnant cohorts for each measurement of stress

Comparisons were also made for the following demographic data:

- Age
- BMI
- Weight (kg)
- Height (m)
- Total pregnancies
- Number of live births
- Months trying to conceive
- Units of alcohol per week
- Hours of exercise per week

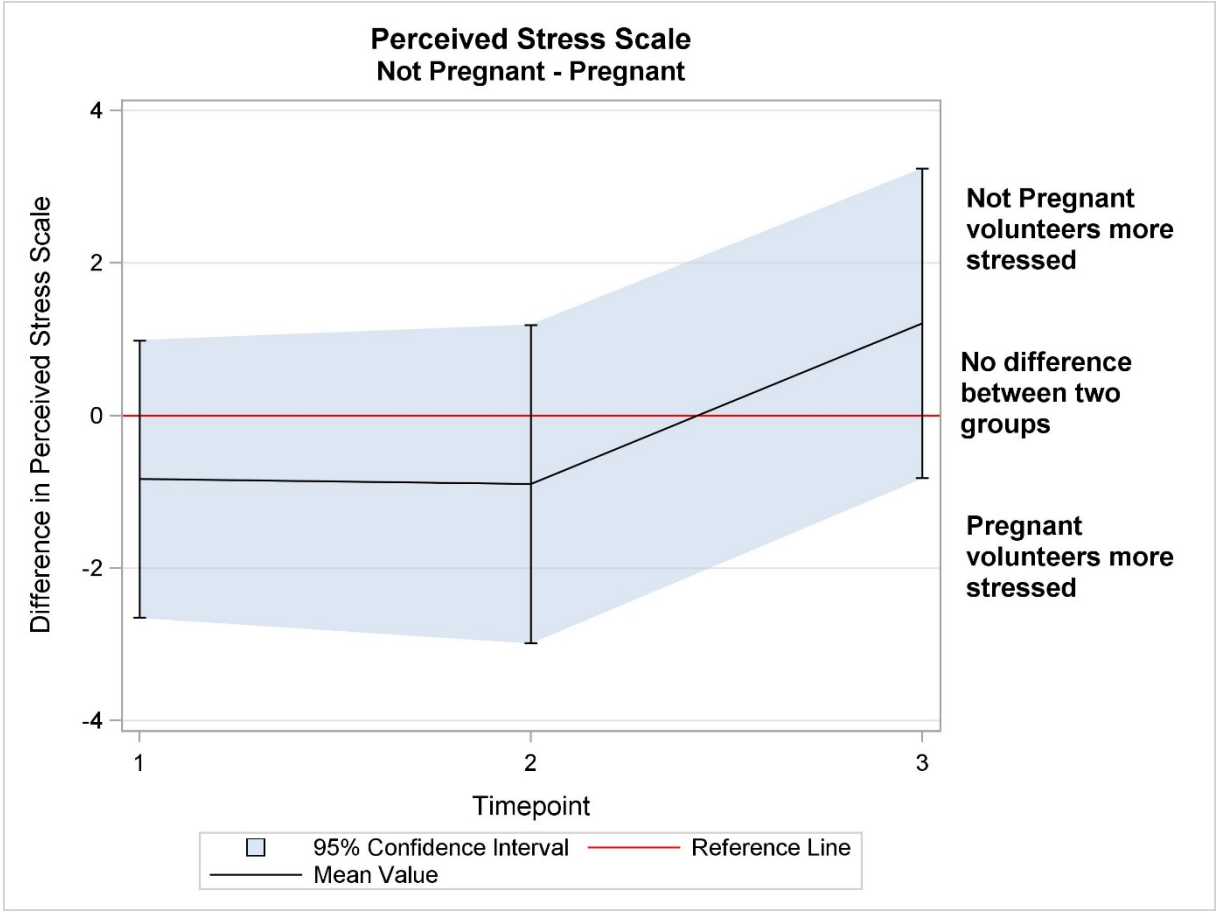
No significant difference was detected in baseline cortisol levels in women who became pregnant versus those who did not become pregnant

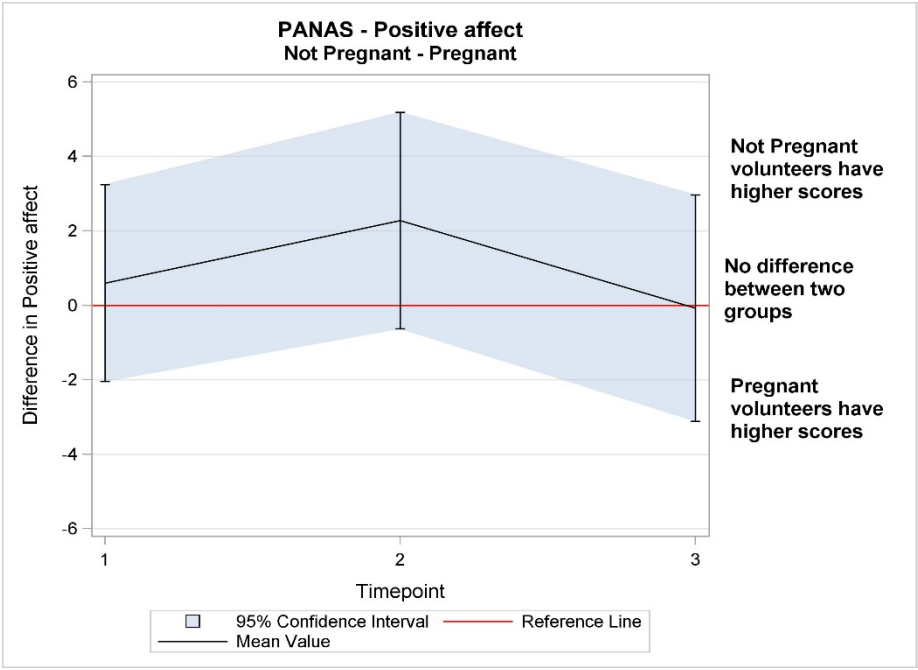
| Time Point | Mean Diff | 95% CI | P |
|---|---|---|---|
| 2 | 0.04 | -0.19 to 0.27 | 0.70 |
| 3 | 0.08 | -0.2 to 0.36 | 0.56 |
| 2 and 3 | 0.06 | -0.11 to 0.24 | 0.48 |

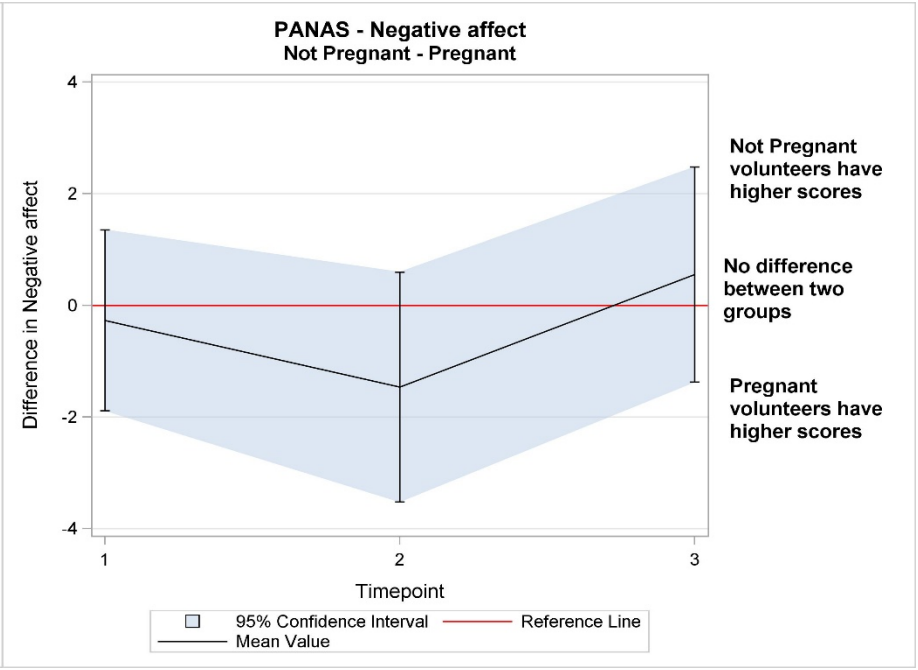


No significant difference was detected in the baseline total stress levels between women who later became pregnant and those who did not

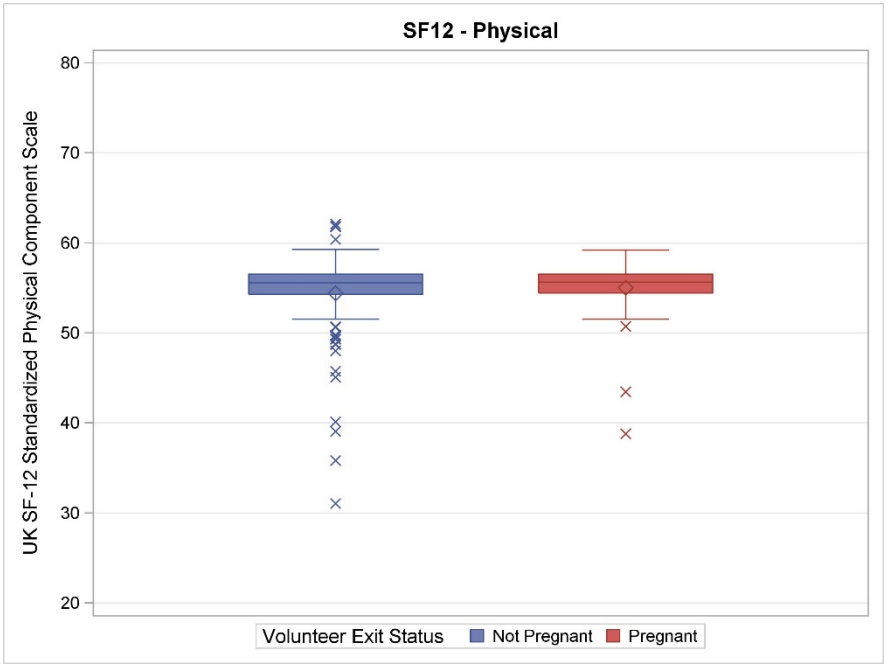
| Time Point | Mean Diff | 95% CI | P |
|---|---|---|---|
| 1 | -0.83 | -2.66 to 0.99 | 0.37 |
| 2 | -0.90 | -2.99 to 1.19 | 0.39 |
| 3 | 1.21 | -0.82 to 3.24 | 0.24 |
| 1 to 3 | -0.22 | -1.35 to 0.91 | 0.71 |

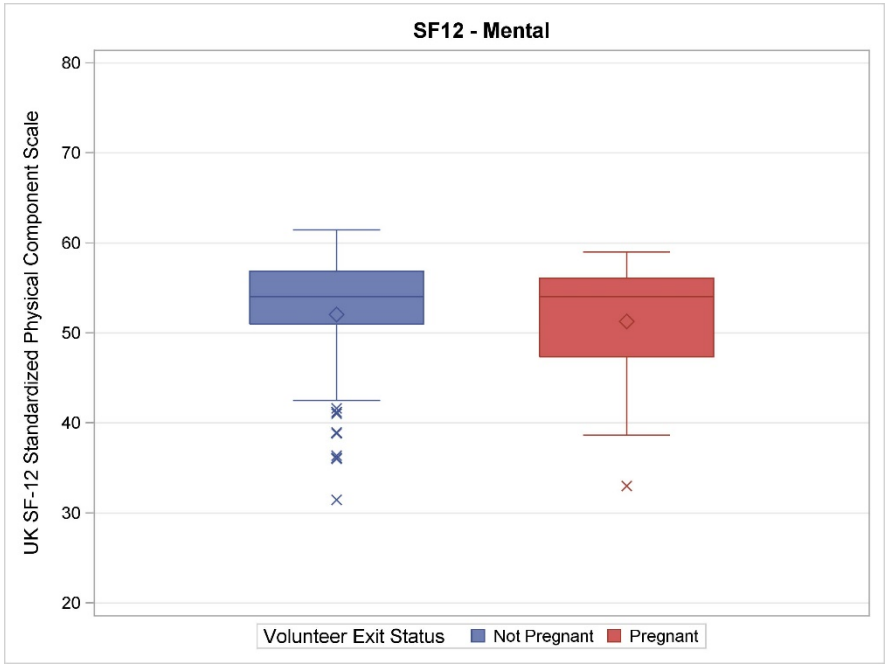





No significant difference was detected in the baseline positive or negative affect scores between volunteers who became pregnant and those who finished the study not pregnant




No significant difference was detected in the baseline physical or mental domains on the SF-12 health survey between volunteers who achieved pregnancy on the study compared to those who failed to conceive

# Demographics

Significant differences were detected for:

Age

Months trying to conceive

Number of previous live births (although this could be confounded by age)

# Conclusion

We found no evidence to suggest that everyday stress reduces likelihood of conception

We did observe some important demographic factors related to likelihood of pregnancy:

- age
- length of time trying to conceive
- BMI
- smoking

Our data support the need for older women to seek advice early when trying to conceive and to adopt healthy lifestyles

But found no evidence that everyday stress is impactful

# Recent studies of ART patients also show no association

# Other recent studies also show no association

## The effects of depression, anxiety and stress symptoms on the clinical pregnancy rate in women undergoing IVF treatment

Saman Maroufizadeh, Behnaz Navid ✉, Reza Omani-Samani & Payam Amini

*BMC Research Notes* **12**, Article number: 256 (2019) | Download Citation ↓

# Other recent studies also show no association

In total, 142 women undergoing IVF treatment participated in this prospective study. The clinical pregnancy rate was 26.8% in this study. Controlling for age, infertility duration, and cause of infertility, there were no relationship between IVF outcome and anxiety (relative risk (RR) = 1.00; 95% CI 0.91–1.09), depression (RR = 0.96; 95% CI 0.88–1.05), and stress (RR = 1.01; 95% CI 0.96–1.07) symptoms. High woman's age and women with both cause of infertility were independent predictors of IVF clinical pregnancy rate. In sum, we found that anxiety, depression, and stress symptoms were not associated with the IVF clinical pregnancy rate.

# But infertility does cause long term emotional stress

Longitudinal studies have shown that female depression increases after unsuccessful treatment

A recent systematic review and meta-analysis found that patients with failed treatments and who ended treatment without achieving parenthood presented poor mental health

However this adjustment tended to improve with time since treatment

Verhaak 2007, Pasch 2012, Gameiro 2014,Gameiro and Finnigan, 2017

**Human Reproduction, Vol.34, No.6, pp. 1065–1073, 2019**
Advance Access Publication on May 15, 2019 doi:10.1093/humrep/dez046

human reproduction

**ORIGINAL ARTICLE** ***Psychology and counselling***

# Infertility-related distress and female sexual function during assisted reproduction

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**PARTICIPANTS/MATERIALS, SETTING, METHODS:** We included 269 consecutive patients with infertility aged 24–45 (37.8 ± 4.0 years). Sexual function outcomes were sexual dysfunction (assessed with the Female Sexual Function Index), sexual distress (evaluated with the Female Sexual Distress Scale-Revised), dyspareunia, and number of intercourses in the month preceding ovarian stimulation. Infertility-related distress was measured with the Fertility Problem Inventory (FPI). The effects of potential confounders such as demographic variables (women's and partners' age and level of education) and infertility-related factors (type and cause of infertility, number of previous IVF cycles, and duration of infertility) were also examined.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Women with higher infertility-related distress were more likely to report sexual dysfunction (odds ratio = 1.02 per point of score; 95% CI, 1.01–1.03; $P = 0.001$). Three FPI domains (i.e. social, relational, and sexual concerns) were correlated with almost all sexual function outcomes ($Ps < 0.05$).

# Infertility can cause long term emotional stress

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## Infertility-related stress and the risk of antidepressants prescription in women: a 10-year register study

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**STUDY DESIGN, SIZE, DURATION:** All women ($n = 1169$) who participated in the Copenhagen Cohort Multi-centre Psychosocial Infertility (COMPI) cohort study in the year 2000 (questionnaire data) were linked with the register-based Danish National ART-Couple (DANAC) I cohort, which includes women and their partners having received ART treatment from 1 January 1994 to 30 September 2009. The study population were among other national health and sociodemographic registers further linked with the Danish National Prescription Registry.

**MAIN RESULTS AND THE ROLE OF CHANCE:** The final sample consisted of 1009 women with a mean age of 31.8 years. At study inclusion, women had tried to conceive for an average of 3.45 years. At 10-year follow-up, a total of 13.7% of women had a first redeemed prescription of antidepressant medication. The adjusted odds ratio (OR) showed that high general physical stress predicted the later prescription of antidepressants (adjusted (adj) OR = 2.85, 95% confidence interval (CI) 1.96–4.16). Regarding infertility-related stress domains, high personal stress (adj OR = 2.14, 95% CI 1.46–3.13) and high marital stress (adj OR = 1.80, 95% CI 1.23–2.64) were significantly associated with the later prescription of antidepressants. Social stress was not significantly associated with the future redeemed prescription of antidepressants (adj OR = 1.10, 95% CI 0.76–1.61). Among women not having achieved childbirth during follow-up, the risk of a first-time prescription of antidepressants associated with infertility-specific stress was higher compared to the risk among women having childbirth during follow-up.

# Conclusions

Fertility matters – a lot!

Women and men are vulnerable to misleading information and are bombarded with Internet based “facts”

Early stage investigations will identify a problem in about 75% of couples (but beware epiphenomena)

Encourage lifestyle modification and regular intercourse (but not too aggressively)

Move at the speed dictated by the couple

Work as a team with nurses, laboratory staff, counsellors and primary care

IVF should often be a last resort.

There is a popular belief that everyday stress reduces chances of natural conception

Most studies on a possible relationship between stress and infertility have focussed on the ART population

We have not found evidence for an impact of everyday stress on fertility in ***women who believed themselves to be healthy***