

**Cryopreservation of human sperm: efficacy and use of a new nitrogen-free controlled rate freezer versus liquid nitrogen vapour freezing.**

[Andrologia](#). 2011 Dec;43(6):392-7.

[Creemers E](#), [Nijs M](#), [Vanheusden E](#), [Ombelet W](#).

**Source**

Genk Institute for Fertility Technology, Ziekenhuis Oost Limburg, Belgium.  
eva.creemers@zol.be

**Abstract**

Preservation of spermatozoa is an important aspect of assisted reproductive medicine. The aim of this study was to investigate the efficacy and use of a recently developed liquid nitrogen and cryogen-free controlled rate freezer and this compared with the classical liquid nitrogen vapour freezing method for the cryopreservation of human spermatozoa. Ten patients entering the IVF programme donated semen samples for the study. Samples were analysed according to the World Health Organization guidelines. No significant difference in total sperm motility after freeze-thawing between the new technique and classical technique was demonstrated. The advantage of the new freezing technique is that it uses no liquid nitrogen during the freezing process, hence being safer to use and clean room compatible. Investment costs are higher for the apparatus but running costs are only 1% in comparison with classical liquid nitrogen freezing. In conclusion, post-thaw motility of samples frozen with the classical liquid nitrogen vapour technique was comparable with samples frozen with the new nitrogen-free freezing technique. This latter technique can thus be a very useful asset to the sperm cryopreservation laboratory.

**Correlation between male age, WHO sperm parameters, DNA fragmentation, chromatin packaging and outcome in assisted reproduction technology.**

[Andrologia](#). 2011 Jun;43(3):174-9.

[Nijs M](#), [De Jonge C](#), [Cox A](#), [Janssen M](#), [Bosmans E](#), [Ombelet W](#).

**Source**

Genk Institute for Fertility Technology, Ziekenhuis Oost Limburg, Genk, Belgium.  
martine.nijs@zol.be

**Abstract**

In the human, male ageing results in reproductive hormonal and cellular changes that can influence semen quality (volume, motility, concentration and morphology) and ultimately result in a reduced fertilising capacity and a longer 'time to pregnancy' for ageing men as well as an increased risk for miscarriage. This prospective cohort study of 278 patients undergoing a first in vitro fertilisation or intracytoplasmic sperm injection treatment was undertaken to examine whether patient's age was reflected in sperm motility, concentration, morphology as well as in DNA fragmentation (DFI) and immature chromatin (unprocessed nuclear proteins and/or poorly condensed chromatin) as measured by the sperm chromatin structure assay. This study also investigated the possible influence of male age (after correcting for female age) on their fertilising capacity, on obtaining a pregnancy and a healthy baby at home. Logistic regression analysis did not reveal any male age-related influences on sperm parameters like concentration, motility or morphology. No significant male age-related increase in DFI or immature chromatin was demonstrable for these patients. Elevated male age, after correcting for female age, was not related to lower fertilisation rates or significant decreases in the chance for a healthy baby at home.

**The addition of GnRH antagonists in intrauterine insemination cycles with mild ovarian hyperstimulation does not increase live birth rates--a randomized, double-blinded, placebo-controlled trial.**

[Hum Reprod.](#) 2011 May;26(5):1104-11.

[Cantineau AE](#), [Cohlen BJ](#), [Klip H](#), [Heineman MJ](#); [Dutch IUI Study Group Collaborators](#).  
[Collaborators \(11\)](#)

[Hoek A](#), [Lambalk CB](#), [Hamilton CJ](#), [Van Bommel PF](#), [van Dop PA](#), [van der Heijden PF](#), [de Sutter P](#), [D'Hooghe T](#), [Manger PA](#), [Ombelet W](#), [Santema JG](#).

**Source**

Department of Gynecology, University Medical Center Groningen, 9700 RB Groningen, The Netherlands. [aepcantineau@gmail.com](mailto:aepcantineau@gmail.com)

**Abstract**

*Background*

This multicenter, double-blinded RCT investigated the efficacy of GnRH antagonists in cycles with mild ovarian hyperstimulation (MOH) followed by IUI in subfertile women.

*Methods*

Couples diagnosed with unexplained, male factor subfertility or associated with the presence of minimal or mild endometriosis were randomized with a computer-generated list of numbers by a third party in a double-blinded setting to receive either a GnRH antagonists or a placebo in 12 institutional or academic hospitals. All women were treated with recombinant FSH in a low-dose step-up regimen starting on Day 2-4 of the cycle. A GnRH antagonist was added when one or more follicles of 14 mm diameter or more were visualized. When at least one follicle reached a size of  $\geq 18$  mm, ovulation was induced by hCG injection. A single IUI was performed 38-40 h later. Couples were offered a maximum of three consecutive cycles. The primary outcome of the trial was live births. Secondary outcomes were pregnancy rates, multiple pregnancy rates, miscarriages and ovarian hyperstimulation syndrome rate.

*Results*

A total of 233 couples were included from January 2006 to February 2009, starting 572 treatment cycles. Live birth rates were not significantly different between the group treated with GnRH antagonist (8.4%; 23/275) and the placebo group (12%; 36/297) ( $P = 0.30$ ). Three twin pregnancies occurred in the GnRH antagonist group and two twin pregnancies in the placebo group.

*Conclusions*

Adding a GnRH antagonist in cycles with MOH in an IUI program does not increase live birth rates. Dutch Trial Register no: NTR497.

**Relationship between hyaluronic acid binding assay and outcome in ART: a pilot study.**

[Andrologia.](#) 2010 Oct;42(5):291-6.

[Nijs M](#), [Creemers E](#), [Cox A](#), [Janssen M](#), [Vanheusden E](#), [Van der Elst J](#), [Ombelet W](#).

**Source**

Genk Institute for Fertility Technology, Ziekenhuis Oost Limburg, Genk, Belgium.  
[martine.nijs@zol.be](mailto:martine.nijs@zol.be)

**Abstract**

The sperm-hyaluronan binding assay (HBA) is a diagnostic kit for assessing sperm maturity, function and fertility. The aim of this prospective cohort pilot study was to evaluate the relationship between HBA and WHO sperm parameters (motility, concentration and detailed morphology) and possible influence of sperm processing on hyaluronic acid binding. A cohort of 68 patients undergoing a first combo in vitro fertilisation/intracytoplasmic sperm injection treatment after failure of three or more intrauterine insemination cycles were included in the study. Outcome measures studied were fertilisation rate, embryo quality, ongoing pregnancy rate and cumulative pregnancy rate. HBA outcome improved after sperm preparation and culture, but was not correlated to detailed sperm morphology, concentration or motility. HBA did not provide additional information for identifying patients with poor or absent fertilisation, although the latter had more immature sperm cells and cells with cytoplasmic retention present in their semen. HBA outcome in the neat sample was significantly correlated with embryo quality, with miscarriage rates and ongoing pregnancy rates in the fresh cycles, but not with the cumulative ongoing pregnancy rate. No threshold value for HBA and outcome in combo IVF/ICSI treatment could be established. The clinical value for HBA in addition to routine semen analysis for this patient population seems limited.

### **Gender differences and factors associated with treatment-seeking behaviour for infertility in Rwanda.**

[Hum Reprod.](#) 2010 Aug;25(8):2024-30.

[Dhont N](#), [Luchters S](#), [Ombelet W](#), [Vyankandondera J](#), [Gasarabwe A](#), [van de Wijgert J](#), [Temmerman M](#).

#### **Source**

International Centre for Reproductive Health, Ghent University, Ghent, Belgium.

[dhontnathalie@gmail.com](mailto:dhontnathalie@gmail.com)

#### **Abstract**

##### *Background*

This study examines perceptions of infertility causes, treatment-seeking behaviour and factors associated with seeking medical care in an urban infertile population in Rwanda, as well as the response of health providers.

##### *Methods*

Between November 2007 and May 2009 a hospital based survey was conducted among 312 women and 254 male partners in an infertile relationship.

##### *Results*

Infertility causes based on a medical diagnosis were mentioned by 24% of women and 17% of men. Male infertility awareness was low in both sexes with 28% of men and 10% of women reporting male-related causes. Seventy-four per cent of women and 22% of men had sought care for their infertility in the past. Seeking treatment in the formal medical sector was associated with higher income, being married and infertility duration of more than 5 years in both sexes. In women, higher education and being nulliparous and in men blaming oneself for the infertility was also associated with seeking formal medical care. Participants reported a wide array of treatments they received in the past, often including ineffective or even harmful interventions.

### *Conclusion*

Health authorities should invest in improving information, education and counselling on issues pertaining to causes and treatments of infertility, and in drawing up guidelines for the management of infertility at all levels of health care.

### **Chromomycin A3 staining, sperm chromatin structure assay and hyaluronic acid binding assay as predictors for assisted reproductive outcome.**

[Reprod Biomed Online](#). 2009 Nov;19(5):671-84.

[Nijs M](#), [Creemers E](#), [Cox A](#), [Franssen K](#), [Janssen M](#), [Vanheusden E](#), [De Jonge C](#), [Ombelet W](#).

#### **Source**

Genk Institute for Fertility Technology (GIFT), Ziekenhuis Oost Limburg, Genk, Belgium.  
martine.nijs@zol.be

#### **Abstract**

Functional sperm tests such as the sperm chromatin structure assay (SCSA), chromomycin A3 staining (CMA(3)) and hyaluronic acid binding assay (HBA) have been suggested as predictive tests of fertility in vitro. This study aimed to define the clinical role of these functional parameters in assisted reproduction in a prospective cohort study. Conventional sperm diagnosis (motility, morphology and concentration) as well as SCSA, CMA(3) and HBA tests were performed on 205 semen samples [74 IVF, 94 ICSI and 37 combined IVF/intracytoplasmic sperm injection (ICSI)]. Main outcome parameters were fertilization rate, clinical pregnancy rate and take-home baby rate. The study showed that each of the three functional sperm tests was related to one or more conventional and one or more functional sperm tests, indicating that spermatozoa from patients with abnormal conventional semen parameters have a higher likelihood for multiple functional abnormalities. Only SCSA and CMA(3) staining were shown to have a limited predictive value when IVF or combined IVF/ICSI was applied. The proposed threshold value of  $\leq 15\%$  for predicting good fertilization rates and obtaining a pregnancy in IVF could only be confirmed for percent HDS (high DNA stainability in SCSA). ICSI outcome was not influenced by any of the conventional or functional sperm parameters.

### **Influence of freeze-thawing on hyaluronic acid binding of human spermatozoa.**

[Reprod Biomed Online](#). 2009 Aug;19(2):202-6.

[Nijs M](#), [Creemers E](#), [Cox A](#), [Janssen M](#), [Vanheusden E](#), [Castro-Sanchez Y](#), [Thijs H](#), [Ombelet W](#).

#### **Source**

Genk Institute for Fertility Technology, Ziekenhuis Oost Limburg, Genk, Belgium.  
martine.nijs@zol.be

#### **Abstract**

Mature human spermatozoa have at least three specific hyaluronic acid (HA) binding proteins present on their sperm membrane. These receptors play a role in the acrosome reaction, hyaluronidase activity, hyaluronan-mediated motility and sperm-zona and sperm-oolemmal binding. Cryopreservation of spermatozoa can cause ultrastructural and even molecular damage. The aim of this study was to investigate if HA binding receptors of human spermatozoa remain functional after freeze-thawing. Forty patients were enrolled in the study. Semen samples were analysed before and after cryopreservation. Parameters analysed included concentration, motility, morphology and hyaluronan binding. Samples were frozen

in CBS straws using a glycerol-glucose-based cryoprotectant. HA binding was studied using the sperm-hyaluronan binding assay. Freeze-thawing resulted in a significant decline in motility: the percentage of motile spermatozoa reduced from 50.6 to 30.3% ( $P < 0.001$ ). HA binding properties of frozen-thawed spermatozoa remained unchanged after the freeze-thawing process: 68.5 +/- 17.1% spermatozoa of the neat sample were bound to HA, as were 71.3 +/- 20.4 of the frozen-thawed sample. This study indicates that freeze-thawing did not alter the functional hyaluronan binding sites of mature motile spermatozoa, and therefore will not alter their fertilizing potential.

**Reproductive healthcare systems should include accessible infertility diagnosis and treatment: an important challenge for resource-poor countries.**

[Int J Gynaecol Obstet.](#) 2009 Aug;106(2):168-71.

[Ombelet W.](#)

**Source**

Department of Obstetrics and Gynecology, Genk Institute for Fertility Technology, 3600 Genk, Belgium. [willem.ombelet@telenet.be](mailto:willem.ombelet@telenet.be)

**Abstract**

Infertility is a central issue in the lives of many couples who suffer from it. In resource-poor countries the problem of childlessness is even more pronounced compared with Western societies owing to different sociocultural circumstances. It often leads to severe psychological, social, and economic suffering, and access to infertility treatment is often limited to certain procedures and certain costumers. The issue of infertility in resource-poor countries is underestimated and neglected, not only by local governments but also by the international nonprofit organizations. Simplification of the diagnostic and therapeutic procedures, minimizing the complication rate, and incorporating fertility centers into existing reproductive healthcare programs are essential measures to take in resource-poor countries if infertility treatment is to be accessible for a large part of the population. For reasons of social justice, a search for strategies to implement simplified methods of infertility diagnosis and treatment in resource-poor countries is urgently warranted.

**A cost per live birth comparison of HMG and rFSH randomized trials.**

[Reprod Biomed Online.](#) 2008 Dec;17(6):756-63.

[Connolly M,](#) [De Vrieze K,](#) [Ombelet W,](#) [Schneider D,](#) [Currie C.](#)

**Source**

Market Access, Ferring International Centre, St. Prex, Switzerland. [mark@mmasoln.com](mailto:mark@mmasoln.com)

**Abstract**

To help inform healthcare treatment practices and funding decisions, an economic evaluation was conducted to compare the two leading gonadotrophins used for IVF in Belgium. Based on the results of a recently published meta-analysis, a simulated decision tree model was constructed with four states: (i) fresh cycle, (ii) cryopreserved cycle, (iii) live birth and (iv) treatment withdrawal. Gonadotrophin costs were based on highly purified human menopausal gonadotrophin (HP-HMG; Menopur) and recombinant FSH (rFSH) alpha (Gonal-F). After one fresh and one cryopreserved cycle the average treatment cost with HP-HMG was lower

than with rFSH (HP-HMG euro3635; rFSH euro4103). The average cost saving per person started on HP-HMG when compared with rFSH was euro468. Additionally, the average costs per live birth of HP-HMG and rFSH were found to be significantly different: HP-HMG euro9996; rFSH euro13,009 ( $P < 0.0001$ ). HP-HMG remained cost-saving even after key parameters in the model were varied in the probabilistic sensitivity analysis. Treatment with HP-HMG was found to be the dominant treatment strategy in IVF because of improved live birth rates and lower costs. Within a fixed healthcare budget, the cost-savings achieved using HP-HMG would allow for the delivery of additional IVF cycles.

**Reprotoxicity of intrauterine insemination and in vitro fertilization-embryo transfer disposables and products: a 4-year survey.**

[Fertil Steril.](#) 2009 Aug;92(2):527-35.

[Nijs M](#), [Franssen K](#), [Cox A](#), [Wissmann D](#), [Ruis H](#), [Ombelet W](#).

**Source**

Genk Institute for Fertility Technology, Ziekenhuis Oost Limburg, Genk, Belgium.

[martine.nijs@zol.be](mailto:martine.nijs@zol.be)

**Abstract**

*Objective*

To test consumables and other products used during oocyte collection, sperm preparation, IUI, embryo culture, and IVF-embryo transfer for their possible reprotoxic properties.

*Design*

A prospective 4-year survey of reprotoxicity testing of consumables and other products used in assisted reproductive technologies (ART).

*Setting*

Private infertility center in a university-affiliated teaching hospital.

*Intervention(s)*

Thirty-six products of 72 different brands, including plastics, syringes, tubing, and surgical gloves were analyzed for their reprotoxicity in 350 human sperm survival tests (SpST).

*Main Outcome Measure(s)*

The SpST index: percentage progressive motility of test sample/percentage progressive motility of control sample after 24 and 96 hours.

*Result(s)*

Thirteen of 36 products were found to be reprotoxic: an SpST index  $<0.85$  was noted 24 and 96 hours after exposure. These products included eight brands of unpowdered surgical gloves, two types of hysterometers and one type of tubing attached to the oocyte collection needle, one type of ovum pickup procedure needle, and one type of embryo transfer catheter. One type of condom used for ultrasound, one type of sterile Pasteur pipette and petri dish, as well as the cover of a specimen container, were reprotoxic.

*Conclusion(s)*

The SpST is an inexpensive, easy, and reliable method to identify potential reprotoxic

products and consumables used in ART procedures. These data underline the importance of the inclusion of the SpST in a continuous quality control (QC) program of ART outcome.

**Infertility and the provision of infertility medical services in developing countries.**

[Hum Reprod Update](#). 2008 Nov-Dec;14(6):605-21.

[Ombelet W](#), [Cooke I](#), [Dyer S](#), [Serour G](#), [Devroey P](#).

**Source**

Department of Obstetrics and Gynaecology, Genk Institute for Fertility Technology, Schiepse Bos 6, 3600 Genk, Belgium. [willem.ombelet@telenet.be](mailto:willem.ombelet@telenet.be)

**Abstract**

*Background*

Worldwide more than 70 million couples suffer from infertility, the majority being residents of developing countries. Negative consequences of childlessness are experienced to a greater degree in developing countries when compared with Western societies. Bilateral tubal occlusion due to sexually transmitted diseases and pregnancy-related infections is the most common cause of infertility in developing countries, a condition that is potentially treatable with assisted reproductive technologies (ART). New reproductive technologies are either unavailable or very costly in developing countries. This review provides a comprehensive survey of all important papers on the issue of infertility in developing countries.

*Methods*

Medline, PubMed, Excerpta Medica and EMBASE searches identified relevant papers published between 1978 and 2007 and the keywords used were the combinations of 'affordable, assisted reproduction, ART, developing countries, health services, infertility, IVF, simplified methods, traditional health care'.

*Results*

The exact prevalence of infertility in developing countries is unknown due to a lack of registration and well-performed studies. On the other hand, the implementation of appropriate infertility treatment is currently not a main goal for most international non-profit organizations. Keystones in the successful implementation of infertility care in low-resource settings include simplification of diagnostic and ART procedures, minimizing the complication rate of interventions, providing training-courses for health-care workers and incorporating infertility treatment into sexual and reproductive health-care programmes.

*Conclusions*

Although recognizing the importance of education and prevention, we believe that for the reasons of social justice, infertility treatment in developing countries requires greater attention at National and International levels.

**A multi-center prospective, randomized, double-blind trial studying the effect of misoprostol on the outcome of intrauterine insemination.**

[Gynecol Obstet Invest](#). 2008;66(3):145-51.

[Billiet K](#), [Dhont M](#), [Vervaeet C](#), [Vermeire A](#), [Gerris J](#), [De Neubourg D](#), [Delbeke L](#), [Ombelet W](#), [De Sutter P](#).

**Source**

Department of Obstetrics and Gynaecology, Ghent University Hospital, Ghent, Belgium.

**Abstract**

*Background*

Because seminal prostaglandins play a role at natural fertilization, it was hypothesized that vaginal supplementation of prostaglandins at the time of intrauterine insemination (IUI) might enhance chances of conception. We investigated the effect of misoprostol, a prostaglandin analogue, on the success rate of IUI.

*Methods*

A multi-center double-blind randomized controlled trial, using a cross-over design with alternating sequence, was designed. Vaginal tablets of misoprostol or placebo were used in conjunction to intrauterine insemination. In total, 199 women, comprising 466 cycles, were analyzed. Main outcome measures were pregnancy rate and prevalence of vaginal bleeding and uterine cramps.

*Results*

The misoprostol group accounted for 146 cycles with 19 pregnancies, whereas the placebo group cycles totaled 164 cycles with 21 pregnancies (13.0 vs. 12.8%, not significant). There was a statistically significant increase in vaginal bleeding (12.3 vs. 1.8%; OR 7.55; 95% CI 2.31-24.48) and abdominal cramping rates (15.1 vs. 4.3%; OR 3.98; 95% CI 1.68-9.39) after application of misoprostol. Due to these severe adverse events the study was prematurely terminated.

*Conclusion*

Although prostaglandins surely play a role in natural human reproduction, vaginal administration of misoprostol at the time of IUI is associated with a high rate of side effects and does not seem to enhance the outcome.

**The ISMAAR proposal on terminology for ovarian stimulation for IVF.**

[Hum Reprod.](#) 2007 Nov;22(11):2801-4.

[Nargund G](#), [Fauser BC](#), [Macklon NS](#), [Ombelet W](#), [Nygren K](#), [Frydman R](#); [Rotterdam ISMAAR Consensus Group on Terminology for Ovarian Stimulation for IVF](#).

**Source**

Department of Reproductive Medicine, St George's Hospital and Medical School, London, UK. [geetanargund@gmail.com](mailto:geetanargund@gmail.com)

**Abstract**

IVF is performed with oocytes collected in natural and stimulated cycles. Different approaches to ovarian stimulation have been employed worldwide. Following the introduction of GnRH antagonists and strategies to reduce multiple births such as single embryo transfer, there is a genuine scientific interest in the revival of natural cycle and mild approaches to ovarian stimulation in IVF. Recent evidence suggests that application of natural and mild IVF is patient-centred, aimed at reducing the cost of treatment, patient discomfort and multiple



pregnancies. However, there seems to be no consistency in the terminology used for definitions and protocols for ovarian stimulation in IVF cycles. Following the recent International Society for Mild Approaches in Assisted Reproduction (ISMAAR) meeting and communication with interested international experts, this article has recommended revised definitions and terminology for natural cycle IVF and different protocols used in ovarian stimulation for IVF. It is proposed that these terms are adopted internationally in order to achieve a consistency in clinical practice, research publications and communication with patients.

**Affordable IVF for developing countries.**

[Reprod Biomed Online](#). 2007 Sep;15(3):257-65.

[Ombelet W](#), [Campo R](#).

**Source**

Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Genk, Belgium. willem.ombelet@telenet.be

**Abstract**

Worldwide, more than 80 million couples suffer from infertility; the majority are residents of developing countries. Residents of developing countries encounter a lack of facilities at all levels of health care, but especially infertility diagnosis and treatment. Infertility defined as a disease has a much stronger negative consequence in developing countries compared with Western societies. Social isolation, economic deprivation and violence are commonly observed. Tubal infertility due to sexually transmitted diseases, unsafe abortion and post-partum pelvic infections are the main causes of infertility in developing countries. Very often those conditions are only treatable by assisted reproductive technologies. Although preventative measures are undoubtedly the most cost-effective approach, not offering assisted reproduction is not an alternative. This study proposes a specially designed infertility care programme leading to cost-effective simplified assisted reproduction as a valid treatment protocol in developing countries when prevention or alternative methods have failed. Special attention should be given to avoid adverse outcomes such as ovarian hyperstimulation and multiple embryo pregnancy.

**Relative contribution of ovarian stimulation versus in vitro fertilization and intracytoplasmic sperm injection to multifetal pregnancies requiring reduction to twins.**

[Fertil Steril](#). 2007 Oct;88(4):997-9.

[Ombelet W](#), [Camus M](#), [de Catte L](#).

**Source**

Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Genk, Belgium. willem.ombelet@telenet.be

**Abstract**

The proportion of twins resulting from multifetal pregnancy reduction of higher-order multiples is increased in pregnancies resulting from hormone stimulation when compared with twins following in vitro fertilization/intracytoplasmic sperm injection treatment. These reduced twin pregnancies may carry a higher perinatal risk compared with other twin pregnancies, which should be taken into account when assessing the perinatal outcome of twin pregnancies after assisted reproduction.

**Coming soon to your clinic: patient-friendly ART.**

[Hum Reprod.](#) 2007 Aug;22(8):2075-9.

[Pennings G](#), [Ombelet W](#).

**Source**

Bioethics Institute Ghent, Ghent University, Blandijnberg 2, 9000 Gent, Belgium.

[guido.pennings@ugent.be](mailto:guido.pennings@ugent.be)

**Abstract**

The current practice in medically assisted reproduction is still too exclusively focused on effectiveness and success rates. This has a number of considerable, and more importantly, avoidable drawbacks. Single embryo transfer was an important move away from this model to include safety and welfare of mother and child. Patient-friendly ART goes one big step further. It is composed of a mix of four criteria: cost-effectiveness, equity of access, minimal risk for mother and child and minimal burden for patients. All four components have a strong normative ethical basis: cost-effectiveness relies on the optimal use of community resources to maximise well-being; equity of access is based on justice, minimal risk is founded on the fundamental non-maleficence rule and minimal burden is largely based on the autonomy principle. The inclusion of the four criteria in decision-making about treatment would express these values in clinical practice.

**Perinatal outcome of 12,021 singleton and 3108 twin births after non-IVF-assisted reproduction: a cohort study.**

[Hum Reprod.](#) 2006 Apr;21(4):1025-32.

[Ombelet W](#), [Martens G](#), [De Sutter P](#), [Gerris J](#), [Bosmans E](#), [Ruyssinck G](#), [Defoort P](#), [Molenberghs G](#), [Gyselaers W](#).

**Source**

Scientific Board of the Flemish Society of Obstetrics and Gynaecology, St Niklaas, Brussels.

[willem.ombelet@pandora.be](mailto:willem.ombelet@pandora.be)

**Abstract**

Perinatal outcome of pregnancies caused by assisted reproduction technique (ART) is substantially worse when compared with pregnancies following natural conception. We investigated the possible risks of non-IVF ART on perinatal health. We conducted a retrospective cohort study with two exposure groups: a study group of pregnancies after controlled ovarian stimulation (COS), with or without artificial insemination (AI), and a naturally conceived comparison group. We used the data from the regional registry of all hospital deliveries in the Dutch-speaking part of Belgium during the period from January 1993 until December 2003 to investigate differences in perinatal outcome of singleton and twin pregnancies. 12 021 singleton and 3108 twin births could be selected. Naturally conceived subjects were matched for maternal age, parity, fetal sex and year of birth. The main outcome measures were duration of pregnancy, birth weight, perinatal morbidity and perinatal mortality. Our overall results showed a significantly higher incidence of prematurity (<32 and <37 weeks), low and very low birth weight, transfer to the neonatal intensive care unit and most neonatal morbidity parameters for COS/AI singletons. Twin pregnancies resulting from COS/AI showed an increased rate of neonatal mortality, assisted ventilation and respiratory distress syndrome. After excluding same-sex twin sets, COS/AI twin pregnancies were at increased risk for extreme prematurity and very low birth weight. In conclusion, COS/AI singleton and twin pregnancies are significantly disadvantaged compared to naturally conceived children.

**Perinatal outcome of ICSI pregnancies compared with a matched group of natural conception pregnancies in Flanders (Belgium): a cohort study.**

[Reprod Biomed Online](#). 2005 Aug;11(2):244-53.

[Ombelet W](#), [Peeraer K](#), [De Sutter P](#), [Gerris J](#), [Bosmans E](#), [Martens G](#), [Ruyssinck G](#), [Defoort P](#), [Molenberghs G](#), [Gyselaers W](#).

**Source**

Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Genk, Belgium. willem.ombelet@pandora.be

**Abstract**

A retrospective cohort study was conducted with an intracytoplasmic sperm injection (ICSI) group and a naturally conceived comparison group. A total of 1655 singleton and 1102 twin ICSI births were studied with regard to perinatal outcome. Control subjects (naturally conceived pregnancies) were selected from a regional registry and were matched for maternal age, parity, place of delivery, year of birth and fetal sex. The main outcome measures were duration of pregnancy, birth weight, Apgar score <5 after 5 min, neonatal complications, perinatal death and congenital malformations. Twin births, when compared with singletons, carry a much higher risk of poor perinatal outcome. For both ICSI singletons and ICSI twins, no significant difference was found between ICSI and naturally conceived pregnancies for all investigated parameters. After excluding like-sex twin pairs, ICSI twin pregnancies were at increased risk for perinatal mortality (OR = 2.74, CI = 1.26-5.98), prematurity (OR = 1.38, CI = 1.10-1.75) and low birth weight (OR = 1.34, CI = 1.06-1.69) compared with spontaneously conceived different-sex twin pairs. In conclusion, the perinatal outcome of ICSI singleton and twin pregnancies was very similar to that of spontaneously conceived pregnancies in this large cohort study. After excluding like-sex twin pairs, ICSI twins were at increased risk for prematurity, low birth weight and higher perinatal mortality compared with the natural conception comparison group.

**Obstetric and perinatal outcome of 1655 ICSI and 3974 IVF singleton and 1102 ICSI and 2901 IVF twin births: a comparative analysis.**

[Reprod Biomed Online](#). 2005 Jul;11(1):76-85.

[Ombelet W](#), [Cadron I](#), [Gerris J](#), [De Sutter P](#), [Bosmans E](#), [Martens G](#), [Ruyssinck G](#), [Defoort P](#), [Molenberghs G](#), [Gyselaers W](#).

**Source**

Scientific Board of the Flemish Society of Obstetrics and Gynecology, Belgium. willem.ombelet@pandora.be

**Abstract**

A total of 3974 IVF and 1655 ICSI singleton births and 2901 IVF and 1102 ICSI twin births were evaluated. Pregnancies after both fresh and frozen transfers were included. IVF and ICSI singleton pregnancies were very similar for most obstetric and perinatal variables. The only significant difference was a higher risk for prematurity (< 37 weeks of amenorrhoea) in IVF pregnancies compared with ICSI pregnancies (12.4 versus 9.2%, OR = 1.39, 95% CI = 1.15-1.70). For twin pregnancies, differences were not statistically different except for a higher incidence of stillbirths in the ICSI group (2.08 versus 1.03%, OR = 2.04, 95% CI = 1.14-3.64). Intrauterine growth retardation with or without pregnancy-induced hypertension was observed more often in the ICSI group. Regression analysis of the data with correction for parity and female age showed similar results for twins. For singletons, this analysis showed

similar results with the exception of low birth weight babies (< 2500 g), which were also observed more often in IVF pregnancies (9.6 versus 7.9%, OR = 0.79, CI = 0.65-0.98, P = 0.03). This large case-comparative retrospective analysis showed that the obstetric outcome and perinatal health of IVF and ICSI pregnancies is comparable.

**Pregnancy after ICSI with ejaculated immotile spermatozoa from a patient with immotile cilia syndrome: a case report and review of the literature.**

[Reprod Biomed Online](#). 2004 Dec;9(6):659-63.

[Peeraer K](#), [Nijs M](#), [Raick D](#), [Ombelet W](#).

**Source**

Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium.

**Abstract**

This study presents a case of intracytoplasmic sperm injection (ICSI) with ejaculated immotile spermatozoa from a patient with immotile cilia syndrome. Semen analysis of the patient suffering from immotile cilia syndrome revealed an extreme oligoasthenoteratozoospermia (OAT: count <math>1.4 \times 10^6</math>/ml, 0% motility and 3% normal morphology). Electron microscopy of sperm flagella showed the absence of inner and outer dynein arms. During the ICSI cycle, the hypo-osmotic swelling test (HOS) was used for the identification of viable spermatozoa in the pool of immotile spermatozoa for ICSI. A normal fertilization rate was found in eight out of the 12 oocytes. A first fresh double embryo transfer resulted in a late miscarriage at 21 weeks. A second healthy singleton pregnancy occurred after transfer of two frozen-thawed embryos from the same ICSI procedure. Although only one successful ICSI case of the immotile cilia syndrome combined with HOS is described here, HOS might be a simple but valuable tool to obtain normal fertilization and pregnancy for patients suffering from immotile spermatozoa.

**Hemangiopericytoma of the ovary.**

[JBR-BTR](#). 2004 Sep-Oct;87(5):229-30.

[Verswijvel G](#), [Termote B](#), [Sannen G](#), [Ombelet W](#), [Palmer Y](#).

**Source**

Dep. of Radiology, Ziekenhuis Oost Limburg, Campus St Jan, Genk, Belgium.

**Abstract**

We report on a case of hemangiopericytoma in the pelvis occurring in the left ovary. The tumor was found in a 33-year-old woman with left iliac fossa pain. The lesion was well demarcated and had a diameter of approximately 10 cm. It was surgically resected. Computed tomography and ultrasound revealed an aspecific lesion with round lesion with a smooth contour and intratumoral necrosis. To our knowledge, radiological features of hemangiopericytoma of the ovary have not been reported yet.

**Multiple gestation and infertility treatment: registration, reflection and reaction--the Belgian project.**

[Hum Reprod Update](#). 2005 Jan-Feb;11(1):3-14.

[Ombelet W](#), [De Sutter P](#), [Van der Elst J](#), [Martens G](#).

**Source**

Genk Institute for Fertility Technology, Department of Obstetrics and Gynaecology, Genk, Belgium. [willem.ombelet@pandora.be](mailto:willem.ombelet@pandora.be)

**Abstract**

Multiple pregnancies associated with infertility treatment are recognized as an adverse outcome and are responsible for morbidity and mortality related to prematurity and very low birthweight population. Due to the epidemic of iatrogenic multiple births, the incidence of maternal, perinatal and childhood morbidity and mortality has increased. This results in a hidden healthcare cost of infertility therapy and this may lead to social and political concern. Reducing the number of embryos transferred and the use of natural cycle IVF will surely decrease the number of multiple gestations. Consequently, optimized cryopreservation programmes will be essential. For non-IVF hormonal stimulation, responsible for more than one-third of all multiple pregnancies after infertility treatment, a strict ovarian stimulation protocol aiming at mono-ovulation is crucial. Multifetal pregnancy reduction is an effective method to reduce high order multiples but carries its own risk of medical and emotional complications. Excellent data collection of all infertility treatments is needed in our discussion with policy makers. The Belgian project, in which reimbursement of assisted reproduction technology-related laboratory activities is linked to a transfer policy aiming at substantial multiple pregnancy reduction, is a good example of cost-efficient health care through responsible, well considered clinical practice.

**IUI and evidence-based medicine: an urgent need for translation into our clinical practice.**

[Gynecol Obstet Invest](#). 2005;59(1):1-2.

[Ombelet W](#).

**Influence of the abstinence period on human sperm quality.**

[Fertil Steril](#). 2004 Jul;82(1):57-65.

[De Jonge C](#), [LaFromboise M](#), [Bosmans E](#), [Ombelet W](#), [Cox A](#), [Nijs M](#).

**Source**

Reproductive Medicine Center, University of Minnesota, Minneapolis, Minnesota, USA. [dejonge@umn.edu](mailto:dejonge@umn.edu)

**Abstract**

*Objective*

To determine the influence of ejaculatory abstinence on within-subject semen parameters and DNA fragmentation.

*Design*

Prospective study.

*Setting*

Private infertility institute and university-based research laboratory.

*Patient(s)*

Sixteen consenting male volunteers undergoing infertility investigation.

*Intervention(s)*

None.

*Main Outcome Measure(s)*

Within-subject analysis of World Health Organization semen parameters and sperm DNA fragmentation and chromatin packaging after 1, 3, 5, and 8 days' abstinence.

*Result(s)*

Of 16 men recruited, data for 11 men were included for statistical analysis because 5 men did not strictly comply with abstinence criteria. Duration of abstinence had a statistically significant positive influence on sperm concentration and semen volume. Abstinence had no statistically significant influence on pH, viability, total and grade A motility, or morphology. The percentage of DNA fragmentation remained unchanged relative to abstinence. The percentage of sperm with immature chromatin was statistically significantly increased with 1 day of abstinence.

*Conclusion(s)*

This is the first study to report on within-subject semen parameter, DNA fragmentation, and chromatin packaging variations after specified target days of abstinence. Sperm numbers and semen volume increased with duration of abstinence. Abstinence did not influence pH, viability, morphology, total or grade A motility, or sperm DNA fragmentation. A short (24-hour) abstinence period negatively influenced chromatin quality.

**The presence of abnormal spermatozoa in the ejaculate: did apoptosis fail?**

[Hum Fertil \(Camb\)](#). 2004 Jun;7(2):99-103.

[Sakkas D](#), [Seli E](#), [Manicardi GC](#), [Nijs M](#), [Ombelet W](#), [Bizzaro D](#).

**Source**

Department of Obstetrics and Gynaecology, Yale University School of Medicine, New Haven, Connecticut 06520-8063, USA. [denny.sakkas@yale.edu](mailto:denny.sakkas@yale.edu)

**Abstract**

With the successful use of Assisted Reproduction, in particular intracytoplasmic sperm injection (ICSI), to treat infertile couples we have become less discriminating with the quality of spermatozoa we use to treat our patients. Numerous studies have shown the presence of nuclear DNA strand breaks in human ejaculated spermatozoa. The reason why human spermatozoa, in particular from men with abnormal semen parameters, possess these abnormalities in their nuclear DNA is still not clear. Two processes that have been linked to the presence of nuclear DNA strand breaks in spermatozoa are anomalies in apoptosis during spermatogenesis or problems in the packaging of the chromatin during spermiogenesis. Understanding the mechanisms responsible for producing abnormal spermatozoa in the human will improve our knowledge about certain causes of male infertility. More importantly, the impact of such sperm, if selected to perform ICSI, needs to be better understood so that any detrimental paternal effects can be avoided.

**Endometrial ossification and infertility: the diagnostic value of different imaging techniques.**

[Abdom Imaging](#). 2003 Nov-Dec;28(6):893-6.

[Ombelet W](#), [Lauwers M](#), [Verswijvel G](#), [Grieten M](#), [Hinoul P](#), [Mestdagh G](#).

**Source**

Department of Obstetrics and Gynecology, Ziekenhuizen Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium.

**Abstract**

We present a case of longstanding secondary subfertility caused by endometrial ossification. Of all diagnostic techniques performed, magnetic resonance imaging and hysterosalpingography did not detect the abnormality. Transvaginal ultrasound and computed tomography clearly showed the endometrial pathology. After successful operative hysteroscopy with removal of the osseous tissue, the patient became pregnant spontaneously within 2 months.

**Semen quality and intrauterine insemination.**

[Reprod Biomed Online](#). 2003 Oct-Nov;7(4):485-92.

[Ombelet W](#), [Deblaere K](#), [Bosmans E](#), [Cox A](#), [Jacobs P](#), [Janssen M](#), [Nijs M](#).

**Source**

Genk Institute for Fertility Technology, Schiepse Bos 6, 3600 Genk, Belgium.  
willem.ombelet@pandora.be

**Abstract**

There is good evidence in literature that intrauterine insemination (IUI) is the best first line treatment and most cost-effective procedure for moderate male factor subfertility. It seems very difficult to identify individual semen parameters predicting the likelihood of pregnancy after IUI. This can be explained by a lack of standardization of semen analysis, but many other methodological variables may also influence IUI success rates such as the patient selection, type of ovarian stimulation and number of inseminations per cycle. A review of the literature confirmed that sperm morphology using strict criteria and the inseminating motile sperm count (IMC) after sperm preparation are the two most important sperm parameters to assess the real impact of semen quality on IUI outcome. A universal threshold level above which IUI can be performed with acceptable pregnancy rates has not been determined yet, although IUI success seems to be impaired with <5% normal spermatozoa and an IMC of  $<1 \times 10^6$ . Until now, no method of sperm preparation has been shown to be superior with regard to pregnancy rate after IUI. Whether supplementation of culture media with substances such as antioxidants and platelet activating factor may improve the results remains the subject of further research.

**Intrauterine pregnancy following transperitoneal oocyte and/or sperm migration in a woman with an ectopic (undescended) ovary.**

[Reprod Biomed Online](#). 2003 Jul-Aug;7(1):110-3.

[Ombelet W](#), [Deblaere K](#), [Grieten M](#), [Verswijvel G](#), [Nijs M](#), [Hinoul P](#), [de Jonge E](#).

## Source

Department of Obstetrics and Gynecology, Ziekenhuizen Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. [willem.ombelet@pandora.be](mailto:willem.ombelet@pandora.be)

## Abstract

This is the first report of an intrauterine pregnancy following timed coitus, resulting from transperitoneal sperm and/or oocyte migration as the oocyte originated from an ectopic (undescended) ovary. The patient was treated in the infertility clinic after a history of primary infertility for 2 years. Diagnosis of a moderate teratozoospermia and the presence of a unicornuate uterus with one right-sided normal ovary was made. During the first intrauterine insemination (IUI) treatment cycle with clomiphene citrate stimulation, a discrepancy between oestradiol concentrations and follicular growth was observed. Magnetic resonance imaging (MRI) was carried out because the presence of an ectopic ovary was suspected. The diagnosis of a left-sided undescended ovary was made, containing several follicles, the largest measuring 16 mm in diameter. Because of a spontaneous LH surge 2 days later without substantial follicular growth in the normal right-sided ovary, IUI was cancelled and timed intercourse was planned. Surprisingly, and although the largest follicle in the normally located ovary reached a maximum diameter of only 12 mm on repetitive ultrasound monitoring, this patient became pregnant and gave birth to a healthy baby boy.

## Undescended ovary and unicornuate uterus: simplified diagnosis by the use of clomiphene citrate ovarian stimulation and magnetic resonance imaging (MRI).

[Hum Reprod.](#) 2003 Apr;18(4):858-62.

[Ombelet W](#), [Grieten M](#), [DeNeubourg P](#), [Verswijvel G](#), [Buekenhout L](#), [Hinoul P](#), [deJonge E](#).

## Source

Department of Obstetrics and Gynecology, Ziekenhuizen Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium. [willem.ombelet@pandora.be](mailto:willem.ombelet@pandora.be)

## Erratum in

[Hum Reprod.](#) 2003 Jun;18(6):1362.

## Abstract

### *Background*

Although the association between unicornuate uterus and undescended ovaries is well established, little information is available on this entity, suggesting the possibility that many cases are not recognized at all. Consequently, important clinical information is missed in many patients worldwide.

### *Methods*

During a period of 5 years, eight cases of unicornuate uterus were observed in our infertility clinic. The first three patients received magnetic resonance imaging (MRI) after mild clomiphene citrate (CC) stimulation due to a discrepancy between estradiol levels and follicular growth and because a suspected ectopic ovary could not be visualized on ultrasound. Based on this experience, five consecutive patients were offered MRI after CC stimulation as part of this study.

### *Results*

In five out of eight patients with unicornuate uterus (62.5%) an undescended ovary could be visualized in the upper abdomen. Abdominal ultrasound revealed the ectopic ovary in only two cases. The use of CC stimulation undoubtedly facilitated the diagnosis of the undescended ovary on MRI.



### *Conclusion*

It is suggested that MRI after CC stimulation is an excellent non-invasive method to diagnose undescended ovaries in women with a unicornate uterus.

### **Ectopic ovary and unicornuate uterus.**

[N Engl J Med.](#) 2003 Feb 13;348(7):667-8.

[Ombelet W](#), [Verswijvel G](#), [de Jonge E](#).

### **A novel approach for patients at risk for ovarian hyperstimulation syndrome: elective transfer of a single zona-free blastocyst on day 5.**

[Reprod Biomed Online.](#) 2002 Jan-Feb;4(1):51-5.

[Kinet K](#), [Nijs M](#), [Cox AM](#), [Janssen M](#), [Jacobs P](#), [Bosmans E](#), [Ombelet W](#).

#### **Source**

Genk Institute for Fertility Technologies, ZOL, Schiepse Bos 6, B-3600 Genk, Belgium.

#### **Abstract**

In this preliminary prospective randomized study of 420 patients undergoing ovarian stimulation for IVF/intracytoplasmic sperm injection (ICSI), 17 patients (4%) developed moderate to severe ovarian hyperstimulation syndrome (OHSS). Re-evaluation for OHSS on day 4 and 6 after oocyte retrieval identified one patient with continuous risk for severe OHSS, resulting in cancellation of the transfer (1/17, 5.8%). Prospectively, two of three patients had the zona pellucida of the blastocyst removed by pronase exposure prior to transfer. Significantly more patients became pregnant when a zona-free blastocyst was transferred in comparison to transfer of a single zona-intact embryo (9/11 or 82% versus 1/5 or 20%;  $P < 0.01$ ). Higher ongoing singleton pregnancy rates were obtained when the zona pellucida was removed prior to the transfer (6/11 and 1/5 respectively). This preliminary prospective randomized study indicates that by prolonging the evaluation time for patients at risk of developing OHSS for up to 6 days after the oocyte retrieval, those patients at risk for developing severe OHSS can be identified. Transferring a single zona-free day 5 embryo (blastocyst) and freezing of the supernumerary embryos offers the patient with moderate OHSS an optimal chance for a singleton pregnancy, while avoiding the serious maternal complications of ovarian hyperstimulation syndrome.

### **Intracytoplasmic sperm injection in assisted reproductive technology: an evaluation.**

[Hum Fertil \(Camb\).](#) 2000;3(3):221-225.

[Nijs M](#), [Ombelet W](#).

#### **Source**

IVF Laboratory, ZOL, Campus St Jan, Genk 3600, Belgium.

#### **Abstract**

Since the first reports of successful pregnancies in humans after treatment with intracytoplasmic sperm injection (ICSI), intensive investigations have focused on several important aspects of this form of assisted reproductive technology. In addition to the technical

development of ICSI and increasing understanding of the biochemical and biophysical processes involved during fertilization after injection of an immobilized sperm, studies have aimed to define the indications for patients for a first-line ICSI treatment. One of the major concerns is of course the safety of the technique in terms of the health and reproductive life of the babies born after ICSI. The rhesus monkey is an excellent model to investigate all aspects of this micromanipulation technique. This article provides an evaluation of ICSI.

**Cryopreservation of human sperm.**

[Hum Fertil \(Camb\)](#). 2001;4(3):158-63.

[Nijs M](#), [Ombelet W](#).

**Source**

Genk Institute For Fertility Technology, ZOL, Schiepse Bos 6, 3600 Genk, Belgium.

**Abstract**

Freezing of human sperm is considered a routine procedure in assisted reproductive technology (ART) laboratories. This article considers various aspects of cryopreservation of human sperm. Human sperm show a specific cryophysical behaviour and different sperm freezing protocols have been developed to avoid damage to the sperm cells. The damage can range from impaired motility and reduced viability to damage to the cellular organelles and effects at the molecular level, resulting in an impaired fertilizing potential. As testicular sperm are immature and only a small number can be retrieved, special techniques are required for successful freezing and thawing of these samples. Banking of human sperm has to be performed in a safe and controlled way and different guidelines are necessary to ensure that this is achieved.

**Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review.**

[Hum Reprod Update](#). 2001 Sep-Oct;7(5):495-500.

[Van Waart J](#), [Kruger TF](#), [Lombard CJ](#), [Ombelet W](#).

**Source**

Department of Obstetrics and Gynecology, University of Stellenbosch and Tygerberg Hospital, Tygerberg, South Africa.

**Abstract**

The aim of the study was to conduct a structured review of the literature published on the use of normal sperm morphology, as an indicator of male fertility potential in intrauterine insemination (IUI) programmes. Published literature in which normal sperm morphology was used to predict pregnancy outcome in IUI during the period 1984-1998 was reviewed. In total, 421 articles were identified via Medline searches. Eighteen provided data that could be tabulated and analysed. Eight of the analysed studies provided sufficient data for statistical analysis, six studies used the Tygerberg 'strict' criteria, and two the WHO guidelines (1987, 1992). A meta-analysis of the six studies in the strict morphology group yielded a risk difference (RD) between the pregnancy rates achieved in the patients below and above the 4% strict criteria threshold of -0.07 (95% CI: -0.11 to 4.03; P<0.001). The WHO criteria group

(1987, 1992) had insufficient data to be analysed. Meta-analysis showed a significant improvement in pregnancy rate above 4% threshold for strict criteria. Accurate evaluation of normal sperm morphology results should be an integral part of evaluating the male factor.

**Multicenter study on reproducibility of sperm morphology assessments.**

[Arch Androl.](#) 1998 Sep-Oct;41(2):103-14.

[Ombelet W](#), [Bosmans E](#), [Janssen M](#), [Cox A](#), [Maes M](#), [Punjabi U](#), [Blaton V](#), [Gunst J](#), [Haidl G](#), [Wouters E](#), [Spiessens C](#), [Bornman MS](#), [Pienaar E](#), [Menkveld R](#), [Lombard CJ](#).

**Source**

The Genk Institute for Fertility Technology, ZOL-Ziekenhuizen, Belgium.

**Abstract**

Sperm morphology has always been considered an important tool in evaluating a man's fertilizing potential. The objective of this multicentric study was to evaluate intra- and interindividual variability and between-laboratory variation using the same or different criteria of sperm morphology assessment. Semen samples were obtained from 20 males and 32 smears were made of all samples. Eighty coded smears (4 per patient) were sent to 8 laboratories for morphology assessment. The centers applied different classification systems (strict criteria, WHO 1987, Düsseldorf criteria) and participants were asked to analyze the 80 smears twice, with an interval of 1 week between each participant's two analyses. Intraclass correlations between repeats showed that sperm morphology can be assessed with acceptable within observer reproducibility. Expected increases in imprecision were observed up to coefficients of variation of >30% with decreasing morphology scores, regardless of the classification system used. Agreement in correct classification of samples as normal/abnormal was obtained in 80% of cases. Differences in reproducibility between slides may reflect an important source of heterogeneity due to smear preparation. These results emphasize the importance of external quality control systems to improve the value of sperm morphology assessments in the investigation of the male partner in a subfertile couple.

**Sperm morphology assessment: diagnostic potential and comparative analysis of strict or WHO criteria in a fertile and a subfertile population.**

[Int J Androl.](#) 1997 Dec;20(6):367-72.

[Ombelet W](#), [Wouters E](#), [Boels L](#), [Cox A](#), [Janssen M](#), [Spiessens C](#), [Vereecken A](#), [Bosmans E](#), [Steeno O](#).

**Source**

Genk Institute for Fertility Technology, Z.O.L., Belgium.

**Abstract**

This prospective study compared the diagnostic and predictive potential of sperm morphology assessments in a fertile vs. a subfertile population, evaluated in three different laboratories. The fertile population included 144 men who had recently fertilized their partners. As subfertile controls, 136 men with a history of subfertility for more than 12 months were used. All semen samples (280) were evaluated in three different centres in a blind fashion, without

any patient information. The evaluation of sperm morphology was performed according to the criteria normally used in the different laboratories: WHO (1992) criteria for laboratory A, and Tygerberg strict criteria for laboratories B and C. Using ROC analysis, the predictive power of sperm morphology turned out to be different in the three laboratories (area under ROC curve: 69% for lab A, 72% for lab B and 78% for lab C). Using percentile 10 of the fertile population as the cut-off value for normality, we obtained the following results: 2, 1 and 5% for laboratories A, B and C, respectively. Using ROC analysis cut-off values with optimal specificity and sensitivity were 6, 1 and 10%, respectively. Although our data highlight a reasonable predictive power of sperm morphology in centres using different or the same criteria, cut-off values for normality were different, even when the same criteria were applied. These results stress the importance of standardization in sperm morphology evaluation and the need for examining a reference population in estimating the real threshold value in different laboratories.

**Intrauterine insemination after ovarian stimulation with clomiphene citrate: predictive potential of inseminating motile count and sperm morphology.**

[Hum Reprod.](#) 1997 Jul;12(7):1458-63.

[Ombelet W](#), [Vandeput H](#), [Van de Putte G](#), [Cox A](#), [Janssen M](#), [Jacobs P](#), [Bosmans E](#), [Steenoo O](#), [Kruger T](#).

**Source**

Genk Institute for Fertility Technology, Z.O.L. Campus St Jan, Belgium.

**Abstract**

This retrospective study aimed to evaluate the prognostic value of the inseminating motile count (IMC) and sperm morphology (using strict criteria) on success rates after homologous intrauterine insemination (IUI) combined with clomiphene citrate (CC) stimulation. A total of 373 couples underwent 792 IUI cycles in a predominantly (87.4%) male subfertility group. The overall cycle fecundity (CF) and baby take-home rate (BTH) was 14.6 and 9.9% respectively. The cumulative CF and BTH (per couple) after three cycles were 30.6 and 21.1% respectively. Overall, sperm morphology and IMC were of no prognostic value using receiver operating characteristic (ROC) curve analysis, but after classifying the study population into different subgroups according to IMC, sperm morphology turned out to be a valuable prognostic parameter in subgroup 1, i.e.  $IMC < 1 \times 10^6$ . In this subgroup, no pregnancies were seen when the morphology score was  $< 4\%$  and the mean value of sperm morphology was significantly different in the pregnant (8.3%) versus non-pregnant group (5.0%;  $P < 0.05$ ). The cumulative CF and BTH after three IUI cycles were comparable for all couples with the exception of those cases in which the IMC was  $< 1 \times 10^6$  with a morphology score of  $< 4\%$  normal forms. We recorded only two twin pregnancies (2.5%) and no moderate or severe ovarian hyperstimulation syndrome. We conclude that in a selected group of patients without CC resistance and normal ovarian response following CC stimulation [maximum of three follicles with a diameter of  $> 16$  mm at the time of administration of human chorionic gonadotrophin (HCG)], IUI combined with CC-HCG can be offered as a very safe and non-expensive first-line treatment, at least with an IMC of  $> 1 \times 10^6$  spermatozoa. In cases with  $< 1 \times 10^6$  spermatozoa, CC-IUI remains important as a first-choice therapy provided the morphology score is  $>$  or  $= 4\%$ .

## **Treatment of male infertility due to sperm surface antibodies: IUI or IVF?**

[Hum Reprod.](#) 1997 Jun;12(6):1165-70.

[Ombelet W](#), [Vandeput H](#), [Janssen M](#), [Cox A](#), [Vossen C](#), [Pollet H](#), [Steen O](#), [Bosmans E](#).

### **Source**

Genk Institute for Fertility Technology, St Jansziekenhuis, Belgium.

### **Abstract**

This prospectively designed study was aimed at comparing the results of two different treatment protocols in 29 infertile couples with proven male immunological infertility, i.e. a positive (>50%) mixed antiglobulin reaction (MAR) test (IgG and/or IgA). In the first protocol (group I, n = 14) couples were treated with ovarian stimulation/ intrauterine insemination (IUI), followed by in-vitro fertilization (IVF) if no pregnancy occurred after three IUI cycles. In the second protocol (group II, n = 15), patients were treated with IVF as a first choice procedure. The decision to follow protocol 1 or 2 was made by the couples after information about financial costs and expected success rates (according to the literature) for both treatment options. In group I, nine patients (64.3%) conceived after a maximum of three IUI cycles whereas seven patients (46.6%) of group II became pregnant during the first IVF cycle. The take-home baby rate per started IUI or IVF cycle was 27.3% (9/33) and 44.4% (16/36) respectively with a take-home baby rate of 64.3% after three IUI cycles and 93.3% after three IVF attempts. To conclude, both IUI and IVF yielded unexpectedly high pregnancy rates in this selected group of patients with long-standing infertility due to sperm surface (predominantly IgG) antibodies. Since cost benefit analysis comparing superovulation IUI with IVF may favour a course of four IUI cycles, we advocate superovulation IUI as the first line therapy in male immunological infertility.

## **Results of a questionnaire on sperm morphology assessment.**

[Hum Reprod.](#) 1997 May;12(5):1015-20.

[Ombelet W](#), [Pollet H](#), [Bosmans E](#), [Vereecken A](#).

### **Source**

Genk Institute for Fertility Technology, ZOL Campus St Jan, Belgium.

### **Abstract**

This survey describes the results of a questionnaire on the methodology of sperm morphology assessment. A questionnaire form was sent to 410 fertility centres. A total of 170 answer forms (41.5%) from 40 different countries was evaluated. Most responding centres (147 or 86.5%) treat more than 200 new couples per year. According to our results, a wide and complex variation in different methods of sperm preparation, staining procedures and classification systems is observed world wide. WHO recommendations for sperm preparation seem to be poorly followed. Only 86 centres (50.6%) reported the use of a single approach to both semen preparation and sperm morphology evaluation. Our results indicate an urgent need for standardization and consensus on sperm morphology methodology to regain the power of this important sperm parameter.

**Semen parameters in a fertile versus subfertile population: a need for change in the interpretation of semen testing.**

[Hum Reprod.](#) 1997 May;12(5):987-93.

[Ombelet W](#), [Bosmans E](#), [Janssen M](#), [Cox A](#), [Vlasselaer J](#), [Gyselaers W](#), [Vandeput H](#), [Gielen J](#), [Pollet H](#), [Maes M](#), [Steen O](#), [Kruger T](#).

**Source**

Genk Institute for Fertility Technology, ZOL Ziekenhuis, Campus St Jan, Belgium.

**Abstract**

This prospectively designed study was conducted to compare a fertile and a subfertile population so as to define normal values for different semen parameters. Semen analyses were performed according to the World Health Organization (WHO) guidelines, except for sperm morphology (strict criteria). In the fertile population (n = 144), all patients had recently achieved pregnancy, within 12 months of unprotected coitus. As subfertile controls we examined semen samples from 143 consecutive men attending our infertility clinic during the same study period. Couples with tubal factor infertility and/or ovulatory disorders were excluded from our study. Using receiver operating characteristic (ROC) curve analysis we determined the diagnostic potential and cut-off values for single and combined sperm parameters. Sperm morphology scored best, with a value of 78% (area under the ROC curve). Summary statistics showed a shift towards abnormality for most semen parameters in the subfertile population. Using the 10th percentile of the fertile population as the cut-off value, the following results were obtained: 14.3 x 10<sup>6</sup>/ml for sperm concentration, 28% for progressive motility and 5% for sperm morphology. Using ROC analysis, cut-off values were 34 x 10<sup>6</sup>/ml, 45% and 10% respectively. Cut-off values for normality were different from those described in the WHO guidelines. Routine bacterial and non-bacterial cultures turned out to be of little prognostic value.

**The hemizona assay: a simplified technique.**

[Arch Androl.](#) 1997 Mar-Apr;38(2):127-31.

[Janssen M](#), [Ombelet W](#), [Cox A](#), [Pollet H](#), [Franken DR](#), [Bosmans E](#).

**Source**

Genk Institute for Fertility Technology, Belgium.

**Abstract**

The hemizona assay is an important diagnostic tool in assessing human sperm fertilizing potential. Previous hemizona assay results have proven that this functional test is a good predictor of fertilization in vitro and can be used in clinical practice to supply additional information in male factor subfertility cases. The objective of this study was to compare two methods for cutting human zona pellucida into equal halves (manual handcutting versus micromanipulation) in order to examine the necessity of an expensive micromanipulator in performing this assay. Comparable results for recovery rate, diameter size of the hemizonae, and sperm binding were achieved with both methods. According to these results, the use of an

expensive micromanipulator is not essential in performing the hemizona assay.

**Chronobiological fluctuations in semen parameters with a constant abstinence period.**

[Arch Androl.](#) 1996 Sep-Oct;37(2):91-6.

[Ombelet W](#), [Maes M](#), [Vandeput H](#), [Cox A](#), [Janssen M](#), [Pollet H](#), [Fourie FL](#), [Steen O](#), [Bosmans E](#).

**Source**

Genk Institute for Fertility Technology, St.-Jansziekenhuis, Belgium.

**Abstract**

This study examined the seasonal variation in three semen parameters (total sperm count, % grade a progressive motility and sperm morphology according to strict criteria) with an identical abstinence period of 24 h. A total of 340 spermograms of 107 different men enrolled in an intrauterine insemination (IUI) program were examined. To reduce variation due to interindividual disparities in semen quality, differences of each test result from the mean value obtained for that individual were analyzed. Mean values resulted from at least 3 observations during different IUI cycles. Using ANOVA and spectral analysis, no differences in semen parameter results in function of the month of the year were observed. The lack of any significant periodicity may be explained by the large biological variation for individual semen parameters and/or the lack of significant differences regarding light exposure and temperature between summer and winter months in moderate climates.

**Sperm morphology assessment: historical review in relation to fertility.**

[Hum Reprod Update.](#) 1995 Nov;1(6):543-57.

[Ombelet W](#), [Menkveld R](#), [Kruger TF](#), [Steen O](#).

**Source**

Genk Institute for Fertility Technology, Belgium.

**Abstract**

Careful analysis of sperm morphology has always been an important part of a routine semen examination. However, the usefulness of sperm morphology assessment as a predictor of a man's fertilizing potential has often been challenged due to different classification systems, various slide preparation techniques and inconsistency of analyses within and between laboratories. Automated sperm morphology analysis instruments may overcome the subjective nature of visual assessments of sperm morphology, but the technical problems are numerous and the validity of these instruments has still to be proven. Having reviewed the literature, it seems clear that there is general agreement concerning the clinical relevance and predictive value of this single semen parameter in vivo and in vitro. Nevertheless, even in cases of severe teratozoospermia, fertilization may be possible. Studies on the acrosome reaction are very promising for patients with severe sperm morphology abnormalities that do not have major effects on the fertilizing potential. Most promising is the development of intracytoplasmic sperm injection (ICSI) as the treatment of first choice in cases of severe teratozoospermia with failed fertilization in vitro. Normal fertilization and pregnancy rates can be obtained with ICSI in the presence of extreme teratozoospermia, suggesting that sperm morphology may be important in spermatozoa-zona binding, penetration and spermatozoon-

oocyte full in evaluating a patient's fertilizing potential, with the main advantage that the methods used to examine this parameter are easy to learn on equipment found in most laboratories but fails to be of any predictive value once the spermatozoon reaches the cytoplasm of the oocyte. To conclude, accurate and strict sperm morphology assessment is very useful in laboratories.

**Intrauterine insemination: a first-step procedure in the algorithm of male subfertility treatment.**

[Hum Reprod.](#) 1995 Oct;10 Suppl 1:90-102.

[Ombelet W](#), [Puttemans P](#), [Bosmans E](#).

**Source**

Genk Institute for Fertility Technology, St Jansziekenhuis, Genk, Belgium.

**Abstract**

Despite the widespread clinical use of intrauterine insemination (IUI) in the treatment of male subfertility, its therapeutic value remains unclear. The objective of this review was to determine why its efficacy has not been consistently documented in the literature and to give strong evidence supporting the therapeutic merit of ovarian stimulation/IUI in male subfertility treatment. Because (i) this technique is much easier to perform and less expensive than assisted reproduction methods, and seems to be reasonably effective in controlled studies of a male subfertility treatment, and (ii) we may expect that financial resources available for the health care of infertility patients will be limited in the future, we believe that ovarian stimulation/IUI must become the first-line treatment in most cases of male factor subfertility, provided that the multiple gestation incidence can be reduced to an acceptable level.

**Reflections on the way to conduct an investigation of subfertility.**

[Hum Reprod.](#) 1995 Oct;10 Suppl 1:80-9.

[Puttemans P](#), [Ombelet W](#), [Brosens I](#).

**Source**

Department of Obstetrics and Gynaecology, St Elisabeth Hospital, Brussels, Belgium.

**Abstract**

Infertility is a worldwide issue in reproductive health. In view of the World Health Organization's definition of health, the psychological and social consequences of infertility simply cannot be ignored. Prevention of infertility is difficult and does not help the couple seeking medical advice for infertility, whereas efficient treatment for infertility is time consuming, expensive and often unsuccessful. This article reflects on a shortened, yet full investigation of both partners' fertility before any treatment whatsoever, which is indispensable once the decision to help the couple medically has been made. By optimizing the use of modern gynaecological endoscopy within the woman's cycle, an exhaustive infertility investigation can be conducted within the span of two couple-physician contacts, thereby responding to the couple's concern, avoiding loss of time and energy due to inappropriate therapies, and directing the subfertility treatment correctly from the start. Trained gynaecologists can easily conduct this investigation in fertility centres in developed countries, as well as in centres for family planning in developing countries. The investigation can be employed either with an emphasis on diagnosis alone (and then even under local



anaesthesia) or, if the necessary infrastructure is available, in combination with operative endoscopy under general anaesthesia where indicated.

**Teratozoospermia and in-vitro fertilization: a randomized prospective study.**

[Hum Reprod.](#) 1994 Aug;9(8):1479-84.

[Ombelet W](#), [Fourie FL](#), [Vandeput H](#), [Bosmans E](#), [Cox A](#), [Janssen M](#), [Kruger T](#).

**Source**

Genk Institute for Fertility Technology, St.-Jansziekenhuis, Belgium.

**Abstract**

A prospective randomized study was conducted to assess the prognostic value of sperm morphology in an in-vitro fertilization (IVF) programme, using strict criteria. The first group (T, teratozoospermic) included 32 couples with an isolated teratozoospermia in the male partner (morphology < 9% normal). The second group (C, control) contained 36 couples with normal semen parameters, including morphology (> 9% normal, strict criteria). In both groups, 50 IVF cycles were performed. Patients were matched for indication for IVF. There was no difference between the two groups regarding age, duration of infertility, stimulation protocol, catheter used for embryo transfer and different sperm parameters. A statistically significant difference between the T and C groups respectively was observed regarding the fertilization rate (69.2 and 79.4%,  $P < 0.05$ ), pregnancy rate per cycle (12.0 and 42%,  $P < 0.001$ ), the pregnancy rate per transfer (13.9 and 42.0%,  $P < 0.01$ ) and per embryo transferred (6.1 and 14.8%,  $P < 0.05$ ). No pregnancy occurred in the poor prognosis group (morphology < 5% normal). In cases of moderate teratozoospermia, the fertilization rate appeared normal (78.6%) but the conception rate remained low. We concluded that the use of strict criteria in the assessment of sperm morphology is useful in predicting fertilization and pregnancy rate in the human in-vitro model.

**Cytokines in semen of normal men and of patients with andrological diseases.**

[Am J Reprod Immunol.](#) 1994 Mar-Apr;31(2-3):99-103.

[Comhaire F](#), [Bosmans E](#), [Ombelet W](#), [Punjabi U](#), [Schoonjans F](#).

**Source**

University Hospital Ghent, Department of Internal Medicine, Belgium.

**Abstract**

*Problem*

The potential value of assessment of cytokine concentrations for the diagnosis of certain pathological conditions of male reproduction has not been fully evaluated.

*Method*

The concentrations of interleukin 6 (IL-6, pg/mL), its soluble receptor (IL-6 sR, ng/mL), and of interleukin 1 beta (IL-1 beta, pg/mL) have been measured in semen samples of 114 men and 12 corresponding blood sera.

### *Results*

The concentration of IL-6 was unrelated to that of its receptor. Both IL-6 and IL-6 sR were higher in the first (mean: 69 and 31 resp.) than in the second fraction (39 and 13) of split ejaculates, and were within normal limits in vasectomised men. The Interleukin 1 beta concentration presented a strong positive correlated with that of IL-6 ( $r = 0.74$ ,  $P < 0.001$ ). The concentrations of IL-6 and IL-1 beta were unrelated to sperm concentration, motility and morphology, and they were within normal limits in immunological cases. Both IL-6 and IL-1 beta were higher ( $P < 0.01$ ) in cases with accessory gland inflammation.

### *Conclusions*

Measurement of in particular IL-6 in semen may contribute to the diagnosis of inflammatory disease of the accessory sex glands (positive predictive value = 98%, sensitivity = 72%, specificity = 94%), but it is not relevant for the diagnosis of immunological disease.

### **Endometrial ossification, an unusual finding in an infertility clinic. A case report.** [J Reprod Med.](#) 1989 Apr;34(4):303-6.

[Ombelet W.](#)

#### **Source**

Department of Obstetrics and Gynecology, St. Jan's Hospital, Genk, Belgium.

#### **Abstract**

Ectopic bony endometrial tissue was found accidentally during routine diagnostic laparoscopy and curettage that were part of the examination of a woman with a history of primary infertility for seven years. She conceived two months after the second curettage.

### **Advanced extrauterine pregnancy: description of 38 cases with literature survey.** [Obstet Gynecol Surv.](#) 1988 Jul;43(7):386-97.

[Ombelet W](#), [Vandermerwe JV](#), [Van Assche FA](#).

#### **Source**

Department of Obstetrics and Gynecology, St. Jan's Hospital, Genk, Belgium.

#### **Abstract**

An analysis is presented of 38 patients with advanced extrauterine pregnancy. First three typical cases are described that emphasize the marked differentiation of clinical symptoms which these patients present to the doctor. The first patient was referred for induction because of a suspected intrauterine death. The second patient presented an intraligamentous pregnancy with a living fetus. In the third case, the patient was admitted to hospital after 32 weeks of pregnancy because of a persistent oblique lie. At 34 weeks, a normal living fetus was born. In all three cases, ultrasound examination was able to visualize the separate uterus. A literature survey is given with special attention to the specific "clinic" and the problems concerning diagnosis and treatment. It is obvious that sonography is the most important diagnostic technique at present. The decision to remove the placenta by means of a laparotomy is brought up for discussion.

