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ZUBER J., ANGLICHEAU D., ELIE C., BERERHI L., TIMSIT M.O., MAMZER-BRUNEEL M.F., CIROLDI M., MARTINEZ F., SNANOUDJ R., HIESSE C., KREIS H., EUSTACHE F., LABORDE K., THERVET E., LEGENDRE C.

Sirolimus May Reduce Fertility in Male Renal Transplant Recipients.

Amer. J. Transplant., 8 (7), 1471-1479, 2008 ; (Facteur d'Impact 2007 : **6,423**)

(Services cités : Biostatistique, CECOS, Explorations Fonctionnelles, Transplantation Adulte, Urologie)

Assessment of sex hormones in organ transplant recipients suggests that sirolimus may impair testicular function. The aim of this study was to evaluate the frequency and severity of sirolimus-associated alterations in sperm parameters and their impact on fathered pregnancy rate. An observational study was carried out in male patients aged 20-40 years who received a kidney transplant during 1995-2005. Patients were sent a questionnaire by post, and sperm analysis was proposed. The fathered pregnancy rates according to the immunosuppressive regimen were estimated and compared using the Poisson model. Complete information was obtained from 95 out of 116 recipients. Patients treated with sirolimus throughout the post-transplant period had a significantly reduced total sperm count compared to patients who did not receive sirolimus ($28.6 \pm 31.2 \times 10^6$ and $292.2 \pm 271.2 \times 10^6$, respectively; $p = 0.006$), and a decreased proportion of motile spermatozoa ($22.2 \pm 12.3\%$ and $41.0 \pm 14.5\%$, $p = 0.01$). Moreover, the fathered pregnancy rate (pregnancies/1000 patient years) was 5.9 (95% CI, 0.8-42.1) and 92.9 (95% CI, 66.4-130.0) in patients receiving sirolimus-based and sirolimus-free regimens, respectively ($p = 0.007$). Of six patients in whom sirolimus treatment was interrupted, only three showed a significant improvement in sperm parameters. Sirolimus is associated with impaired spermatogenesis and, as a corollary, may reduce male fertility.

2007

LETUR H.

Current practices of oocyte donation in France and Europe.

J. Gynécol. Obst. Biol. Reprod., 36 (8), 727-737, 2007 ; (Facteur d'Impact 2006 : **X**)

(Services cités : CECOS)

This review aims to evaluate, in France, oocyte donation, an assisted reproductive technique (ART), for which 25 years of experience have shown its efficacy for the palliative treatment of infertility caused by ovarian exocrine failure. Its indications have since been expanded to cover certain genetic diseases and document failures of other ART attempts. Oocyte donation is performed within the framework of French legislation - bioethics laws 94-653 and 94-654 of 29 July 1994, and the revised bioethics law 2004-800 of 6 August 2004. Its main fundamental principles are: voluntary, free, anonymous donation, for which regulated confidentiality is assured and now - judicial decree 2004-606 of 24 June 2004 - and the synchronization of donor-recipient cycles with fresh embryo transfer in accordance with established safety procedures. According to the 2004 results of the French Group for the Study of Oocyte Donation (GEDO) for French centers actively involved in ART, the chance of pregnancy was increased to 43.4% for synchronized cycles with fresh embryo transfers versus 18.7% for deferred cycles with frozen-thawed embryos ($P < 0.01$). In addition, follow-up studies reported the excellent family relationships and physical and psychological development of these children. The major difficulties encountered in the daily practice of oocyte donation concern the recruitment and management of donors, but also, and above all, the lack of optimal means to exercise this medical specialty, due to the lack of recognition of the organizational duties incurred, which are the cornerstone of the character-specific functioning of this type of ART. In comparison, we foresee that the discrepancies of this ART practice in Europe, with its differential facets, will lead to medical nomadism for those couples financially able to do so, when national conditions of access fail because of prohibitions but also as a consequence of insufficient means to perform the inherent tasks. Today, it seems essential to provide information on the particularity and practice of oocyte donation required for the comprehension of its obligations for the different players with the aim of obtaining the means necessary for the perpetuation of its practice.

2005

BRIAT A., DULIOUST E., GALIMAND J., FONTAINE H., CHAIX M.L., LETUR-KONIRSCH H., POL S., JOUANNET P., ROUZIOUX C., LERUEZ-VILLE M.

Hepatitis C virus in the semen of men coinfecting with HIV-1: prevalence and origin.

AIDS, 19 (16), 1827-1835, 2005

(Services cités : CECOS, Laboratoire de Microbiologie, Hépatologie Adulte)

OBJECTIVE:: To compare the prevalence of hepatitis C (HCV) RNA in semen from men infected with HCV and those coinfecting with HIV-1/HCV and to study the origin of HCV shed in semen. **DESIGN::** Two prospective studies (HC EP09 and BINECO) included 120 HCV-positive men, 82 coinfecting with HIV-1; all had positive HCV RNA detection in blood. **METHODS::** Paired blood and semen samples were collected for HCV RNA detection and quantification in seminal plasma and in blood serum; repeated semen samples were obtained for 45 men. HCV RNA was sought in spermatozoa and non-sperm cells. Phylogenetic analysis of the HVR-1 region of HCV compared the quasispecies in blood serum and seminal plasma of two men. **RESULTS::** HCV RNA was more frequently found in the semen of men coinfecting with HIV-1 (37.8%) than in those with only HCV infection (18.4%) ($P = 0.033$). HCV RNA detection in semen was intermittent and was positive in at least one semen sample of 42.8% of HIV-1/HCV-coinfecting men who provided repeated samples. Men with HCV-positive semen had significantly higher HCV load in blood than men with HCV-negative semen ($P = 0.038$). Phylogenetic comparison of HCV quasispecies in blood and in semen showed no evidence of HCV replication in genital leukocytes; however, a phenetic structure was observed between compartments ($P < 0.001$). **CONCLUSIONS::** HCV particles in semen originate from passive passage from blood, with preferential transfer of some variants. Nearly half of HIV-1/HCV-coinfecting men may intermittently harbour HCV in their semen. Recommendations of protected sex for HIV-infected individuals should be reinforced.

2004

AUGER J., LESAFFRE C., BAZIRE A., SCHOEVAERT-BROSSAULT D., EUSTACHE F.

High-resolution image cytometry of rat sperm nuclear shape, size and chromatin status.

Experimental validation with the reproductive toxicant vinclozolin.

Reprod. Toxicol., 18 (6), 775-783, 2004

(Services cités : CECOS)

Recent studies have shown that the complex inter-related processes of sperm chromatin organization and nuclear morphogenesis, both of which are important fertility determinants, may be disrupted by chemicals. A high-resolution image cytometry method has been developed, using the fluorescent dye bisbenzimidazole, for the measurement of 20 features of the sperm nucleus related to size, form and chromatin status in the rat. For the complete set of features measured and from a total of 150 spermatozoa assessed per sample, the overall coefficient of reproducibility was 5%. Then, an experimental validation of the method was carried out in rats chronically exposed to the antiandrogenic reproductive toxicant vinclozolin and control animals. Univariate statistics revealed significant vinclozolin-induced changes for 19 out of 20 morphometric and chromatin

features. Stepwise linear discriminant analysis classified correctly 84.3% of the sperm nuclei with only four features selected. The accuracy and reproducibility of the cytometry assessment of the sperm nuclei together with the results of the experimental validation suggest this method may be a new powerful tool for use in reproductive toxicology.

LETUR-KONIRSCH H., COLLIN G., DEVAUX A., SIFER C., KUTTENN F., MADELENAT P., BRUN-VEZINET F., FELDMANN G., BENIFLA J.L.

Conservation of human embryos in straws: safety in terms of human immunodeficiency virus 1. *Gynécol. Obstét. Fertil.*, 32 (4), 302-307, 2004

(Services cités : CECOS, Endocrinologie & Médecine de la Reproduction)

OBJECTIVE: The possibility of offering assisted reproductive technologies (ART) to HIV-positive couples has revived questions concerning the safety of the gametes and embryos cryopreservation in liquid nitrogen tanks. **PATIENTS AND METHODS:** We evaluated the safety of three types of straws - polyvinyl chloride (PVC), polyethylene terephthalate glycol (PETG) and so-called 'high-security' ionomeric resin (IR) - containing HIV-1 under standard conditions of cryopreservation. Potential HIV contamination was assessed by RT-PCR and then nested PCR. **RESULTS:** Under cryopreservation conditions, the sealed open ends of PVC and PETG straws were not safe. The ultrasound sealing system seems to be the weak link in obtaining total imperviousness of the straws. In contrast, both ends of the IR straws were safe for HIV in the framework of their use for ART. **CONCLUSION:** Sealing cryopreservation straws ultrasonically could incur the risk of not assuring their impermeability. Under standard cryopreservation conditions thermosealing of IR straws appears to be safe for HIV.

2003

LETUR-KONIRSCH H., COLLIN G., SIFER C., DEVAUX A., KUTTENN F., MADELENAT P., BRUN-VEZINET F., FELDMANN G., BENIFLA J.L.

Safety of cryopreservation straws for human gametes or embryos: a study with human immunodeficiency virus-1 under cryopreservation conditions.

Hum. Reprod., 18 (1), 140-144, 2003

(Services cités : CECOS)

BACKGROUND: The possibility of assisted reproductive technology (ART) for couples carrying viruses, especially HIV-1, necessitates consideration of the safety of cryopreserving human gametes or embryos in liquid nitrogen tanks. Following our evaluation of the safety of three kinds of straws containing HIV-1 at 37 degrees C, we have now examined the HIV-1 imperviousness of the same straws under cryopreservation conditions. **METHODS:** Polyvinyl chloride (PVC), polyethylene terephthalate glycol (PETG) and high-security ionomeric resin (IR) straws (24 each) were tested. Each straw was filled with 100 micro l of HIV-1-containing supernatant [reverse transcriptase (RT) activity: 15 000 c.p.m./50 micro l]. Then PVC and PETG straws were sealed ultrasonically only at their free-end, and IR straws were thermosoldered at both ends. Each straw was put in a 15 ml Falcon tube which was capped and submerged in a liquid-nitrogen tank for 7 days. After bleach decontamination or not, the outside of each end of the straw was rinsed with RPMI medium (1 ml) before cryopreservation and after thawing. Viral RNA was extracted from the medium and then amplified by RT-polymerase chain reaction (PCR) followed by nested-PCR using HIV-1 protease-specific primers. **RESULTS:** HIV-1 RNA was detected in some PVC and PETG rinse media, probably resulting from splashing during ultrasonic sealing, but not in the rinse media of thermosoldered IR straws. **CONCLUSION:** Under cryopreservation conditions, IR straws would appear to be safe for HIV-1 storage in ART.

For PVC and PETG straws, as highlighted in this study, the ultrasonic sealing could be the weak safety link.

2000

ALNOT M.O.

Testicular cancer of the testis and male fertility. commentary.

Prog. Urol., 10 (2), 199, 2000

(Services cités : CECOS)

1999

GREWAL R.P., CANCEL G., LEEFLANG E.P., DURR A., MCPEEK M.S., DRAGHINAS D., YAO X., STEVANIN G., ALNOT M.O., BRICE A., ARNHEIM N.

French machado-joseph disease patients do not exhibit gametic segregation distortion: a sperm typing analysis.

Hum. Mol. Genet., 8 (9), 1779-1784, 1999

(Services cités : CECOS)

Segregation distortion has been reported to occur in a number of the trinucleotide repeat disorders. On the basis of a sperm typing study performed in patients of Japanese descent with Machado-Joseph disease (MJD), it was reported that disease alleles are preferentially transmitted during meiosis. We performed a sperm typing study of five MJD patients of French descent and analysis of the pooled data shows a ratio of mutant to normal alleles of 379:436 (46.5:53.5%), which does not support meiotic segregation distortion. To confirm these results, sperm typing analysis was also performed using a polymorphic marker, D14S1050, closely linked to the MJD1 gene. Among 910 sperm analyzed, the allele linked to the disease chromosome was detected in 50.3% of the samples and the allele linked to the normal chromosome was found in 49.6% of the sperm. The difference in frequency of these two alleles is not significant ($P = 0.8423$).

Likelihood-based analysis of segregation distortion in the single sperm data using the SPERMSEG program also showed no support for segregation distortion at the gamete level in this patient population. The previous report on the Japanese patients also suggested that disease allele stability may be influenced by a trans effect of an intragenic polymorphism (987 G/C) in the wild-type allele. All of the French patients were heterozygous for this polymorphism.

However, analysis of the variance in repeat number in sperm from the French MJD patients overlapped significantly with the variance in repeat number observed in the C/C homozygous Japanese patients. [References: 20]