Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Annales d'Endocrinologie 75 (2014) 115–117

Annales d'Endocrinologie
Annals of Endocrinology

Journées Klotz 2014

Male fertility preservation, where are we in 2014?

Préservation de la fertilité masculine, où en sommes-nous en 2014 ?

Ellen Goossens *, Herman Tournaye

Research group biology of testis, department of embryology and genetics, Vrije universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium

Abstract

Male fertility preservation receives growing attention in the field of reproductive medicine. The first clinical programs were established to preserve reproductive potential in men needing gonadotoxic treatment. Sperm cryopreservation is now a standard procedure. Since a few years, several centres offer testicular tissue cryopreservation to prepubertal boys. This method is still experimental and further research is needed to implement the transplantation techniques in the clinic. With the aim to preserve or restore fertility in patients affected by other diseases (Klinefelter syndrome, *Sertoli cell only syndrome*), techniques for in vitro spermatogenesis are being developed.

Keywords: Fertility preservation; Gonadotoxic treatment; Klinefelter; Spermatogenesis; Spermatogonial stem cell

Résumé

La préservation de la fertilité chez l'homme reçoit une attention croissante dans le domaine de la médecine de la reproduction. Les premiers programmes cliniques ont été créés pour préserver le potentiel de reproduction chez les hommes ayant besoin d'un traitement gonadotoxique. La cryoconservation du sperme est maintenant une procédure standard. Depuis quelques années, plusieurs centres offrent la cryoconservation de tissu testiculaire pour les garçons prépubères. Cette méthode est encore au stade expérimental et d'autres recherches sont nécessaires pour mettre en œuvre les techniques de transplantation en clinique. Dans le but de préserver ou de restaurer la fertilité chez les patients atteints par d'autres maladies (syndrome de Klinefelter, Sertoli cell only syndrome) des techniques de spermatogenèse in vitro sont en cours d'élaboration.

Mots clés : La préservation de la fertilité ; Le traitement gonadotoxique ; Klinefelter ; Spermatogenèse ; Cellules souches spermatogoniales

1. Male infertility

Male fertility depends on the production of qualitatively and quantitatively normal sperm. In many European countries, fertility is affected in more than 20% of men. These men exhibit semen quality below the lower WHO reference levels (volume < 1.5 mL; sperm concentration < 15.10^6/mL; motility < 40%; vitality < 58%; > 96% of sperm cells with abnormal morphology) [1]. Only for a small fraction of these patients, the cause of their infertility can be diagnosed (e.g. cryptorchidism,

DOIs of original articles: http://dx.doi.org/10.1016/j.ando.2014.03.007, http://dx.doi.org/10.1016/j.ando.2014.04.010, http://dx.doi.org/10.1016/j.ando.2014.03.004, http://dx.doi.org/10.1016/j.ando.2014.04.006, http://dx.doi.org/10.1016/j.ando.2014.04.011, http://dx.doi.org/10.1016/j.ando.2014.03.008, http://dx.doi.org/10.1016/j.ando.2014.03.010, http://dx.doi.org/10.1016/j.ando.2014.04.002, http://dx.doi.org/10.1016/j.ando.2014.04.004, http://dx.doi.org/10.1016/j.ando.2014.03.001, http://dx.doi.org/10.1016/j.ando.2014.03.003, http://dx.doi.org/10.1016/j.ando.2014.03.009, http://dx.doi.org/10.1016/j.ando.2014.04.001, http://dx.doi.org/10.1016/j.ando.2014.04.003, http://dx.doi.org/10.1016/j.ando.2014.04.005, http://dx.doi.org/10.1016/j.ando.2014.03.002, http://dx.doi.org/10.1016/j.ando.2014.03.005
* Corresponding author.
E-mail address: ellen.goossens@uzbrussel.be (E. Goossens).

http://dx.doi.org/10.1016/j.ando.2014.03.011
0003-4266/

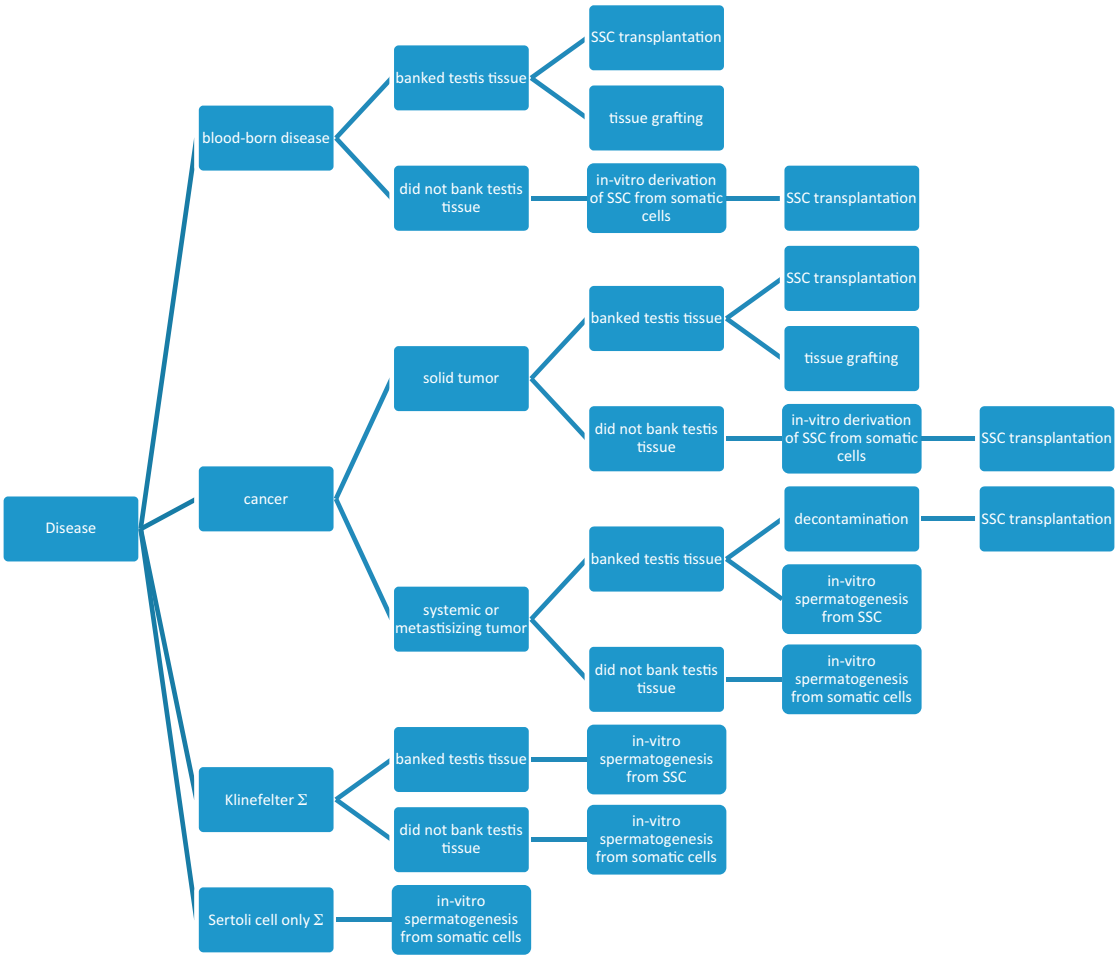

Fig. 1. Decision tree to find the best fertility preservation strategy for each individual patient.

treatment for cancer or infection, chromosomal/genetic aberration). For most infertile men, the reason of their infertility is idiopathic.

As long as spermatogenesis occurs, even if it is only focally, techniques are available to retrieve sperm from semen, by microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE). The spermatozoa may then be used for assisted reproductive technologies such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). However, not all infertile patients can benefit from these possibilities [2].

While spermatogenesis is the motor of male fertility, the spermatogonial stem cell (SSC) is its driving force. Absence, loss or dysfunction of SSCs results in male infertility and can occur "naturally" (e.g. Sertoli cell only syndrome, 47,XXY Klinefelter syndrome) or can be "iatrogenic" (e.g. after chemotherapy to treat cancer) [3]. Increasing evidence points out that also the somatic environment in which the SSCs reside – the so-called SSC niche – plays a significant role on the quality of spermatogenesis. Currently, for men with non-obstructive azoospermia, no options are available to father their genetically own child.

2. Male fertility preservation prior to gonadotoxic treatment

For patients undergoing gonadotoxic treatments (chemotherapy, irradiation), SSCs might be depleted resulting in life-long infertility. However, the so-caused non-obstructive azoospermia can be circumvented by fertility preservation strategies. Adult men are proposed to bank one or more semen samples prior to the start of the cancer treatment. If necessary, the stored semen samples can be used for assisted reproductive techniques (ICSI) [4]. One large study showed a use rate of 9.6% of cryopreserved semen during 57 months of follow-up [5].

Also, adolescents can preserve their fertility by semen banking. If no semen sample can be delivered, the patient can be offered testicular tissue banking. In this case, a small testicular biopsy will be taken under local or general anaesthesia. One half of the biopsied fragments will be stored according to a protocol for sperm freezing, while the other half will be cryopreserved with the intention to preserve SSCs.

For prepubertal boys in whom spermatogenesis has not yet started, the strategy of first choice would be testicular tissue cryopreservation. When the child grows up healthy and wishes

to have children, the stored tissue might be thawed and transplanted. Two transplantation methods are under investigation: spermatogonial stem cell transplantation (SSCT) and testicular grafting. Whereas SSCT might be offered to cancer patients after removal of malignant cells from the biopsy, grafting can only be proposed to patients suffering from non-malignant diseases (e.g. patients needing total body irradiation as a preconditioning treatment for bone marrow transplantation). Although the cryopreservation and auto-transplantation of SSCs are still considered to be experimental, this strategy is very promising. Up till now, the UZ Brussel has stored testicular tissue from more than 50 prepubertal boys. Other centres in Europe and abroad are starting similar fertility preservation programs. The transplantation of testicular tissue or SSCs has not been reported yet [3].

3. Male fertility preservation in Klinefelter patients

Testicular tissue banking is also offered to Klinefelter patients (1/600 newborn boys). At birth, the testes of these boys have a normal architecture but the testes start to degenerate during puberty. The degeneration and hyalinisation of the seminiferous tubules are followed by hyperplasia of the interstitial tissue and eventually leads to totally sclerotized testes [6].

In 50% of adult KS seeking to father children, spermatozoa can be found after testicular sperm extraction [7,8]. Prepubertal boys could benefit from testicular tissue banking [9]. Because of the degeneration of the testes during puberty, autotransplantation will not be feasible, but in vitro spermatogenesis might be a possibility. The in vitro produced spermatozoa might be used in assisted reproductive techniques.

Although in vitro spermatogenesis has recently been described in rodents [10] resulting in the live birth of healthy pups after ICSI [11], in vitro spermatogenesis from human SSCs has not yet been developed.

4. Future prospective

Next to patients needing gonadotoxic treatment or Klinefelter patients, in the future, fertility preservation strategies might also become available for other patients. An overview of disease-specific strategies is given in Fig. 1. For patients with Sertoli cell only syndrome, SSC banking is not an option. The only possibility for these patients to produce their own genetic sperm is to develop germ cells from somatic cells. As the etiology of Sertoli cell only syndrome pathology is still unknown and might be caused by a deficient microenvironment rather than an intrinsic defect in the SSCs, transplantation of SSCs is not appropriate. In vitro spermatogenesis would probably lead to better results in these patients. Also patients for whom no testicular tissue was banked prior to gonadotoxic treatment and adult Klinefelter patients for whom TESE was unsuccessful might benefit from in vitro production of spermatozoa from patient-specific patient-derived pluripotent cells [12]. The in vitro generated spermatozoa could be used in artificial reproductive techniques.

5. Conclusion

Whereas sperm banking has become a routine procedure for adult cancer patients, the preservation of testicular tissue is still experimental. Worldwide, several reproductive centres are setting up programs for testicular tissue banking. We expect the first patients to come back for transplantation in the near future. In the time being, transplantation protocols are being translated to the clinic.

Recently, researchers started to extend fertility preservation and restoration strategies to other indications, like Klinefelter syndrome and Sertoli cell only syndrome. However, clinical applications are not likely in the first five years to come.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16(3):231–45.
[2] Tournaye H. Surgical sperm recovery for intracytoplasmic sperm injection: which method is to be preferred? Hum Reprod 1999;14(Suppl. 1):71–81.
[3] Goossens E, Van Saen D, Tournaye H. Spermatogonial stem cell preservation and transplantation: from research to clinic. Hum Reprod 2013;28(4):897–907.
[4] Holoch P, Wald M. Current options for preservation of fertility in the male. Fertil Steril 2011;96(2):286–90.
[5] van Casteren NJ, van Santbrink EJ, van Inzen W, Romijn JC, Dohle GR. Use rate and assisted reproduction technologies outcome of cryopreserved semen from 629 cancer patients. Fertil Steril 2008;90:2245–50.
[6] Oates RD. The natural history of endocrine function and spermatogenesis in Klinefelter syndrome: what the data show. Fertil Steril 2012;98(2): 266–73.
[7] Friedler S, Raziel A, Strassburger D, et al. Outcome of ICSI using fresh and cryopreserved-thawed testicular spermatozoa in patients with non-mosaic Klinefelter's syndrome. Hum Reprod 2001;12:2616–20.
[8] Van Saen D, Tournaye H, Goossens E. Presence of spermatogonia in 47,XXY men with no spermatozoa recovered after testicular sperm extraction. Fertil Steril 2012;97(2):319–23.
[9] Gies I, De Schepper J, Goossens E, et al. Spermatogonial stem cell preservation in boys with Klinefelter syndrome: to bank or not to bank, that's the question. Fertil Steril 2012;98(2):284–9.
[10] Stukenborg JB, Wistuba J, Luetjens CM, et al. Coculture of spermatogonia with somatic cells in a novel three-dimensional soft-agar-culture-system. J Androl 2008;29(3):312–29.
[11] Sato T, Katagiri K, Gohbara A, et al. In vitro production of functional sperm in cultured neonatal mouse testes. Nature 2011;471(7339):504–7.
[12] Hayashi Y, Saitou M, Yamanaka S. Germline development from human pluripotent stem cells toward disease modelling of infertility. Fertil Steril 2012;97(6):1250–9.