

Abstract

Thesis title: Risk assessment of neurodevelopmental disorders of progenies obtained at advanced paternal age (APA).

Children born to a father of advanced paternal age (APA) are at increased risk of the occurrence of neurodevelopmental disorders (NDDs). APA conception is often associated with the use of assisted reproductive technologies (ART), which has increased in recent years. Both APA and ART are ulterior risk factors that could influence the incidence of the onset of NDDs in progeny. Moreover, embryos obtained with use of ART and from aged parents are characterized by impaired development, which may lead to health alterations later in life. Extended time to implant, for example, by longer embryo culture, which might be used in ART techniques, can positively improve embryo growth. So far, the effects of cumulation of various NDDs risk factors on progeny neurodevelopment and health are not elucidated. In this dissertation, it has been hypothesised, that embryo modifications caused by APA alone or in cumulation with ART, are associated with an increased risk of neurodevelopmental afflictions. Once the hypothesis was confirmed, the next part of the dissertation focused on investigating the possibility of correcting neurodevelopmental alterations in the offspring, by extension of the embryo's time to implant, which is associated with improved embryo quality.

In the first part of the thesis, the effect of APA on the development of the offspring was evaluated as well as social / anxiety behaviour. It was shown that the offspring born to APA fathers is characterised by decreased sociability. These alterations might be a result of dysregulation in genes moderating response to social stimuli and brain development, which were found in adult and foetal brain. Moreover, pups obtained at APA are characterized by lower survival and perturbed growth curves during preweaning period.

In the second part of the experiments, the cumulative effect of APA and ART, which has not been investigated so far, was evaluated by behavioural phenotyping and general development of the progeny. Obtained data shows that APA effect is exacerbated by ART affecting offspring neurodevelopment by increased anxiety, not found in APA progeny. and impairing their social

behaviour. These alterations might be a result of perturbations in expression of the genes regulating response to a stimuli and brain development found in adult brain.

In the third part of the thesis, the possible positive effect of extended time to implantation on the development of offspring was examined by extending its elongation in embryos with an increased risk of developmental changes (embryos from ART). Few days of extension of the time to implant of the blastocyst allowed efficient and long lasting corrections of ART induced alterations in offspring, in terms of behaviour, gene expression in the brain, metabolic status and longevity.

This research opens new scientific horizons for subsequent studies on the cumulative effect of APA and ART, risk factors for offspring development that simultaneously pinpoint the possible positive effect of the extended time to implant the embryo in progeny born with the assistance of ART.