LETTERS TO THE EDITOR

Allografting ovarian cortex between genetically non-identical sisters: authors’ correction (Donnez et al.)

Sir,

This letter concerns two manuscripts published in Human Reproduction: ‘Restoration of ovarian function after allografting of ovarian cortex between genetically non-identical sisters’ and ‘Livebirth after allografting of ovarian cortex between genetically non-identical sisters’. We wish to draw to the attention of the journal’s readership, two points that have recently come to light.

Firstly, in the latter paper, one of the three cases (Patient II) had ovarian failure with elevated FSH levels after chemotherapy at 15 years of age. In this paper, we reported when she received an ovarian transplant at age 32, the ovarian biopsy did not reveal the presence of any follicles in five serial sections of a fragment measuring 1 mm × 1.5 mm. It has now been shown that another fragment of the same ovary sent to a different lab did contain some primordial follicles (PFs). Recent immunohistochemical studies revealed that these PFs were non-functional (the oocyte being ++ ++ positive for Caspase 3 and the granulosa cells being negative for Ki67).

This presence of ovarian follicles does not change the clinical diagnosis, the indications for surgery or the cause of the restoration of ovarian activity. Since the birth, the sister donor has been identified as one genetic parent of the child. The following points support these conclusions.

(i) The patient had undergone total body irradiation followed by bone marrow transplantation at the age of 15 years. Such treatment, requiring administration of two alkylating agents which are very toxic to the ovary, induces premature menopause in nearly 100% of post-pubertal patients as in this case (Sanders et al., 1996; Teinturier et al., 1998; Meirov and Nugent, 2001; Salooja et al., 2001; Lutchman Singh et al., 2005).

(ii) The patient presented with secondary amenorrhea dating back more than 15 years, with FSH levels >80 mIU/ml and 17β-estradiol values less than 20 pg/ml in the absence of HRT. Her preoperative AMH concentrations were zero.

(iii) Ovarian volume determined by echography was equivalent to that in a woman of more than 60 years of age (14 × 14 mm) (18 × 11 mm) (on 22 August 2007). Antral follicle count was zero at echography.

(iv) Intra-operative laparoscopic views of the recipient ovary showed an atrophic aspect, without any surface follicle deformation or corpus luteum.

(v) Recovery of menstrual cycles 3½ months after grafting, when the patient had not experienced spontaneous menstruation for 10 years, indicates that the origin of amenorrhea was indeed ovarian. Restoration of cyclic ovarian activity was assessed by vaginal ultrasound, high levels of estradiol and development of follicles. The ovaries showed development of a corpus luteum, with high levels of progesterone that the patient had not experienced for more than 17 years.

(vi) Finally, genetic analysis confirmed that the genetic origin of the baby was the donor ovary.

Secondly, in both papers we stated ‘Our protocol was authorized by the Ethics Committee of the Catholic University of Louvain which, back in 1995, had approved such research protocols, including reimplantation of ovarian tissue to preserve or restore fertility in women treated with high doses of chemotherapy, which could induce ovarian failure’.

We considered that this approval back in 1995 covered both autografting and allografting. However, after recent discussions within the University and to avoid any potential misinterpretation in the future, our group has agreed that from here on, we will ensure that specific agreement of the Ethical Committee is sought and obtained, as required by the national and international regulations.

References


Teinturier C, Hartmann O, Valteau-Couanet D, Bénhamou E, Bougneres PF. Ovarian function after autologous bone marrow...

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Allografting ovarian cortex between genetically non-identical sisters: authors’ correction (Englert et al.)

Sir,

In May 2011, we were informed by the Vice-rector of the Catholic University of Louvain that an internal procedure against our colleague Professor Jacques Donnez had driven the University to conclude that an article (‘Livebirth after allografting of ovarian cortex between genetically non-identical sisters’ by Donnez et al., 2011), for which I and two members of my research staff are co-authors, was considered to raise significant problems because ‘it contains statements that are not supported by documented evidence’. We understand that the letter containing this statement has subsequently been withdrawn by Université Catholique de Louvain (UCL), considering that Professor Jacques Donnez acted ‘in good faith’ and that ‘there is no proven intention of scientific fraud’.

Since then, many actions appear to have taken place inside the Catholic University of Louvain, as well as between Jacques Donnez and the journal. In order to clarify the situation, Jacques Donnez proposed a letter with additional information regarding the refutable facts related to the published case. This letter is published in the present issue of Human Reproduction.

As external co-authors of the paper, we would like to stress the fact:

(i) that we could not verify or even imagine that aspects of the case were omitted by our distinguished colleague and that, in any case, our participation to the case was to perform IVF for tubal infertility in a laboratory specific for high viral risk as a standard procedure in that case;

(ii) that we did not take part in the internal inquiry performed by the UCL authorities and are not able to build a personal opinion on the facts themselves.

The letter proposed by Jacques Donnez was unable to convince us that the situation was entirely clarified. Therefore, we maintain our request from May 2011 to be withdrawn as co-authors of the paper.

Intermediate and normal sized CGG repeat on the FMR1 gene does not negatively affect donor ovarian response

Sir,

We applaud Lledo et al. (2012) in their recent attempt to further elucidate the effects of the FMR1 gene on ovarian function. Unfortunately, we cannot agree with the authors’ conclusion that the FMR1 screening should not be considered for predicting responses to ovarian stimulation. Nothing in their data, indeed, supports such a conclusion.

To assess whether CGGn on the FMR1 gene was predictive of ovarian response to stimulation, the authors chose young oocyte donors. While in detail referring to our work (Gleicher et al., 2009a,b,c,d), they, unfortunately, overlooked our most relevant publication on the subject, in which we, indeed, had performed 2 years earlier almost exactly the same study they now reported (Gleicher et al., 2010a).

Had they been aware of our study, they would have noted that young egg donors do not demonstrate evidence for differences in the functional ovarian reserve (FOR), as assessed by anti-Müllerian hormone (AMH), based on CGGn, now referred to as ovarian FMR1 genotypes and sub-genotypes (Gleicher et al., 2010a, Figure 2A, 2010b). We, thus, fully agree with the findings of Lledo et al., or, even more accurately, their findings fully concur with our previously reported findings. As our earlier study, however, also demonstrated, infertile patients do behave differently, and do demonstrate CGGn-associated FOR (Gleicher et al., 2010a, Figure 2B).

In contrast to the statement by Lledo et al. that oocyte donors represent the best possible study population to assess whether CGGn is indeed predictive of ovarian response to stimulation and therefore FOR oocyte donors are probably unsuited for such a study.

Our 2010a paper commented on this by noting that young, carefully selected oocyte donors, even with abnormal ovarian FMR1 genotypes and sub-genotypes, usually still have enough FOR to present with what are considered normal AMH levels and, therefore, by implication, likely normal oocyte yields. Infertile women, especially as

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