Editorial—Recent Developments in Clinical Medicine: Reproductive Health

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There is no doubt; we are living in an extraordinary era from many aspects, but especially from the aspect of reproductive sciences. In the last few years, especially in the third millennium, new and fascinating data have put old dogmas into equivocal perspectives and doubtful uncertainty… I shall briefly address just a few of these, almost revolutionary topics.

The era of assisted reproduction technology [ART], starting just thirty years ago, with the birth of the first IVF baby, Louise Brown, after the pioneering studies of Steptoe and Edwards have given way to an enormous scientific advance, in addition to blessed fertility to millions of childless infertile couples. But the dogmas and state of the art is constantly changing. Whereas just a few years ago we all strived to retrieve and generate many ova and many embrya, to provide for as many as possible embryo transfers, the recent data and studies suggest that sometimes, "less is more". Indeed, Murray et al. [1] have recently found that in an *in vitro* cultured mouse follicle system, the oocytes from follicles exposed to high estrogen levels had lower fertilization, regardless of high androgen concentrations. This information supports the recent tendency to avoid the high pharmacologic estrogen concentrations and many follicles development in ART/IVF cycles and prefer the more "soft" or friendly COH protocols. Indeed, this is in keeping to our old publication [2,3], whereby growth hormone-binding protein [GH-BP] levels, reflecting the GH-receptor levels, may be a mediator and put forward a possible explanation to the detrimental effect of highly supraphysiologic estrogen concentrations on the results of COH.

Another "hot" issue in the last decade is the preservation of fertility and possibly ovarian function despite chemo- and/or radiotherapy in young women, for either malignant or non-malignant autoimmune diseases exposed to gonadotoxic chemotherapy [4,5]. The necessity for fertility preservation in the future evokes from the increased prevalence of cancer in the young, combined with improved long term survival after improved treatment outcome. None of the suggested modalities: IVF and cryopreservation of embrya or unfertilized ova, ovarian tissue cryopreservation for later auto-, hetero-, or zenotransplantation, or *in-vitro* maturation [IVM], or GnRH-agonists administration in parallel to chemotherapy, is perfect, and none of these potential avenues guarantees future fertility [4,5]. Fortunately, recent progress and encouraging data have been published in the last year regarding several of the suggested avenues for future preservation of fertility in these young women. Although the results of a large prospective randomized study is still awaited, recent publications support the effectiveness of GnRH-a in minimizing the chemotherapy associated gonadotoxicity [5,6]. Furthermore, Telfer et al. [7] have recently found that a two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin, suggesting that improved technology may, in the not far future, enable the IVM of metaphase II, fertilizable human ova, from the uncommitted stage of primordial follicles, cryopreserved in ovarian tissue biopsies from before chemo- or radiotherapy administration. They have demonstrated that under defined conditions, it may be possible to accelerate human oogenesis and folliculogenesis from primordial and primary follicles. This provides the first encouraging step towards achieving full in vitro growth of human oocytes [7]. Such a technical breakthrough may indeed increase the safety of achieving fertility, without the risk of reimplantation of malignant cells possibly existing in the ovarian biopsies retrieved before treatment [8,9]. The Gene expression profiling of human oocytes following *in vivo* or *in vitro* maturation is the subject of intense recent investigation [10].

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Another fascinating issue which is equivocal today but may possibly turn real in the future is the generation of human gametes from stem cells [11–14]. Stem cells, with their pluripotentic unlimited self-renewal characteristic and capability to differentiate into almost every mature cell type in the body, have enormous research and therapeutic potential [11–14]. Whether the ability of embryonic stem cells to form germ cells in vitro can be translated into clinical generation of gametes for azoospermic men and young women suffering premature ovarian failure is a question of tremendous clinical and scientific impact. We all are eager and are almost impatient to wait and see…

Another related issue of ubiquitous interest is the revolutionary equivocal question of whether germinative stem cells can be de-novo generated in the adult mammal. Johnson and Tilly [15–17] have raised this intriguing question a few years ago challenging the long accepted dogma of fixed endowment of oocytes at birth, raising skeptical responses and generating fierce arguments within the scientific community [18–20].

Another practical clinical issue which may possibly bring a breakthrough to the almost asymptotic pregnancy rate of 40%–50% is the local injury to the endometrium found to double the incidence of successful pregnancies in patients undergoing *in vitro* fertilization [21–23]. Whereas initially it raised skepticism, due to lack of scientific explanation, the endometrial injury, performed by *Pipelle* curettage as a simple outpatient procedure increased the pregnancy rate in patients undergoing IVF/ART after several unsuccessful cycles [21, 22]. More recently it has been found, by the same group who initially described the method, that the endometrial biopsy procedure induces gene modulation, supplying the first scientific evidence for the expression of bladder-transmembranal uroplakin Ib [UPIb] gene in human endometrium [21, 23]. The biopsy-induced increase in the expression of UPIb and other genes encoding membrane proteins supports the possible importance of the membrane structure and stability during implantation [23]. Future studies will validate the efficiency of this procedure and supply further evidence by other IVF centers. Furthermore, if this clinical method proves persistently efficient in increasing implantation, it may become, in the future, a common practice in all IVF/ET cycles, not only after several unsuccessful attempts. Thus, we may possibly increase the pregnancy rate and therefore, practicing the transfer of only one embryo for the elimination of multiple gestations and the associated morbidity and neonatal mortality.

We look forward to the publication of new manuscripts regarding these and many other fascinating issues in reproductive sciences in our new journal—***Clinical Medicine—Reproductive Health***.

References

[1] Murray, A.A., Swales, A.K., Smith, R.E., Molinek, M.D., Hillier, S.G. and Spears, N. 2008. Follicular growth and oocyte competence in the in vitro cultured mouse follicle: effects of gonadotrophins and steroids. *Mol. Hum. Reprod.*, 14:75–83.

[2] Blumenfeld, Z., Barkey, R.J., Youdim, M.B., Brandes, J.M. and Amit, T. Nov 1992. Growth hormone (GH)-binding protein regulation by estrogen, progesterone, and gonadotropins in human: the effect of ovulation induction with menopausal gonadotropins, GH, and gestation. *J. Clin. Endocrinol. Metab.*, 75(5):1242–9.

[3] Blumenfeld, Z. and Amit, T. Mar-Apr 1996. The role of growth hormone (GH), GH-receptor and GH-binding protein in reproduction and ovulation induction. *J. Pediatr. Endocrinol. Metab.*, 9(2):145–62. Review.

[4] Blumenfeld, Z. 2007. Debate: How to preserve fertility in young women exposed to chemotherapy? The role of GnRH-agonist in addition to cryopreservation of embryos, oocytes, or ovaries. *The Oncologist*, 12:1044–54.

[5] Blumenfeld, Z., Avivi, I., Eckman, Epelbaum, R., Rowe, J.M., and Dann, E.J. 2008. Gonadotropin Releasing Hormone Agonist Decreases Chemotherapy Induced Gonadotoxicity and Premature Ovarian Failure in Young Female Patients With Hodgkin Lymphoma. *Fertil Steril*, 89:166–73.

[6] Huser, M., Crha, I., Ventruba, P., Hudecek, R., Zakova, J., Smardova, L., Kral, Z. and Jarkovsky, J. 2008. Prevention of ovarian function damage by a GnRH analogue during chemotherapy in Hodgkin lymphoma patients. *Hum. Reprod.*, 23:863–8.

[7] Telfer, E.E., McLaughlin, M., Ding, C. and Thong, K.J. May 2008. A two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin. *Hum. Reprod.*, 23(5):1151–8.

[8] Meirow, D., Hardan, I., Dor, J., Fridman, E., Elizur, S., Ra'anani, H., Slyusarevsky, E., Amariglio, N., Schiff, E., Rechavi, G., Nagler, A. and Ben Yehuda, D. May 2008. Searching for evidence of disease and malignant cell contamination in ovarian tissue stored from hematologic cancer patients. *Hum. Reprod.*, 23(5):1007–13.

[9] Shaw, J.M., Bowles, J., Koopman, P., Wood, E.C. and Trounson, A.O. Aug 1996. Fresh and cryopreserved ovarian tissue samples from donors with lymphoma transmit the cancer to graft recipients. *Hum. Reprod.*, 11(8):1668–73.

[10] Jones, G.M., Cram, D.S., Song, B., Magli, M.C., Gianaroli, L., Lacham-Kaplan, O., Findlay, J.K., Jenkin, G. and Trounson, A.O. May 2008. Gene expression profiling of human oocytes following in vivo or in vitro maturation. *Hum. Reprod.*, 23(5):1138–44.

[11] Hübner, K., Fuhrmann, G., Christenson, L.K., Kehler, J., Reinbold, R., De La Fuente, R., Wood, J., Strauss, J.F. 3rd, Boiani, M. and Schöler, H.R. 2003. Derivation of oocytes from mouse embryonic stem cells. *Science*, 300:1251–6.

[12] Toyooka, Y., Tsunekawa, N., Akasu, R. and Noce, T. 2003. Embryonic stem cells can form germ cells in vitro. *Proc. Natl. Acad. Sci. U.S.A.*, 100:11457–62.

[13] Geijsen, N., Horoschak, M., Kim, K., Gribnau, J., Eggan, K. and Daley, G.Q. 2004. Derivation of embryonic germ cells and male gametes from embryonic stem cells. *Nature*, 427:148–54.

[14] Clark, A.T., Bodnar, M.S., Fox, M., Rodriquez, R.T., Abeyta, M.J., Firpo, M.T. and Pera, R.A. 2004. Spontaneous differentiation of germ cells from human embryonic stem cells in vitro. *Hum. Mol. Genet.*, 13:727–39.

[15] Johnson, J., Canning, J., Kaneko, T., Pru, J.K. and Tilly, J.L. Aug 26 2004. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature. 2004 Mar 11; 428(6979):145–50. Erratum in: *Nature*, 430(7003):1062.

[16] Johnson J., Bagley J., Skaznik-Wikiel M, Lee HJ., Adams GB., Niikura Y., Tschudy KS, Tilly JC, Cortes ML, Forkert R., Spitzer T, Iacomini J., Scadden DT, Tilly JL. Jul 29 2005. Oocyte generation in adult mammalian ovaries by putative germ cells in bone marrow and peripheral blood. *Cell*, 122(2):303–15.

[17] Johnson, J., Skaznik-Wikiel, M., Lee, H.J., Niikura, Y., Tilly, J.C. and Tilly, J.L. Nov 2005. Setting the record straight on data supporting postnatal oogenesis in female mammals. *Cell. Cycle*, 4(11):1471–7. Epub Nov 20 2005. Review.

[18] Telfer, E.E., Gosden, R.G., Byskov, A.G., Spears, N., Albertini, D., Andersen, C.Y., Anderson, R., Braw-Tal, R., Clarke, H., Gougeon, A., McLaughlin, E., McLaren, A., McNatty, K., Schatten, G., Silber, S. and Tsafriri, A. Sep 23 2005. On regenerating the ovary and generating controversy. *Cell.*, 122(6):821–2. Review.

[19] Tilly, J.L. and Johnson, J. Apr 15 2007. Recent arguments against germ cell renewal in the adult human ovary: is an absence of marker gene expression really acceptable evidence of an absence of oogenesis? *Cell. Cycle*, 6(8):879–83. Epub Apr 23 2007.

[20] Bukovsky, A., Gupta, S.K., Virant-Klun, I., Upadhyaya, N.B., Copas, P., Van Meter, S.E., Svetlikova, M., Ayala, M.E. and Dominguez, R. 2008. Study origin of germ cells and formation of new primary follicles in adult human and rat ovaries. *Methods Mol. Biol.*, 450:233–65.

[21] Barash, A., Dekel, N., Fieldust, S., Segal, I., Schechtman, E. and Granot, I. 2003. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. *Fertil Steril*, 79(6):1317–22.

[22] Zhou, L., Li, R., Wang, R., Huang, H.X. and Zhong, K. Aug 4 2007. Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates. *Fertil Steril*, [Epub ahead of print].

[23] Kalma, Y., Granot, I., Gnainsky, Y., Or, Y., Czernobilsky, B., Dekel, N. and Barash, A. Mar 18 2008. Endometrial biopsy-induced gene modulation: First evidence for the expression of bladder-transmembranal uroplakin Ib in human endometrium. *Fertil Steril*, [Epub ahead of print].