# Chapter 7
# Clinical Perspectives

The concept of INIM force in the biology of the ovary will generate novel strategies in the treatment of ovarian disorders. As long as ovarian INIM is balanced, it is beneficial for a controlled inflammation and a coordinated remodeling of the periovulatory events. Disorders can be understood as gain or loss of function by either overactivation or inhibition of the TLR signaling cascade. The multifold inflammatory and anti-inflammatory profiles depend on the co-regulation by other receptors and pathways (complement, tachykinin, Wnt). When the Myd88-dependent inflammatory pathway is overactivated in such a way that the high production of VEGF occurs, the hyperstimulation syndrome is generated with a life-threatening general oedema. In this context, the threat of a hyperstimulation syndrome increases with a high number of large-sized follicles at the time of oocyte aspiration (Kahnberg et al. 2009) and likely parallels a high VEGF production. Overactivation could cause the atypical follicle rupture with IOR (Figs. 3.7 and 3.8), which might be clinically hidden behind the unruptured luteinized follicle (LUF) syndrome (Qublan et al. 2006). The true LUF syndrome with high progesterone levels and the failure to become pregnant belong to anovulation disorders such as the PCOS with women suffering from androgen excess (Wild et al. 2010). A majority of women with PCOS are obese and show not only increased levels of oxLDL in the follicular fluid compared to the normal-weight counterparts but also increased levels of the oxLDL-dependent LOX-1 and up to 50% of dead granulosa cells in fresh follicle harvests (Bausenwein et al. 2010; Vilser et al. 2010). An increase in follicle danger signals could be the case in overweight women and explain why lifestyle modification with regular exercise and food restriction can restore ovulations (Rachon and Teede 2010; Thomson et al. 2010). Disorders of menstruation, which accompany puberty and reflect anovular ovarian cycles (Peacock et al. 2010), can be understood as years of education to fine-tune the TLR signaling cascade. Collectively, we assume that anovulation failures correspond with inadequate activation or inhibition of the inflammatory Myd88-dependent TLR signaling cascade being impaired at different levels of molecule activation by co-regulating pathways. Inhibition of the repair signalling then leads to luteinized cysts, which is the outcome of an insufficient connective tissue replacement of the former antrum and a frequent

event in women of reproductive age. In the case of overactivation of the TRIF-dependent pathway, which causes the activation of IRF genes, the so-called IFN mRNA signature should be noted. It refers to inadequate clearance of apoptotic bodies shown, for example, in primary Sjögren's syndrome and systemic sclerosis (Meyer 2009). This connexion could also be correct for the many apoptotic bodies in the luteolytic CL of golden hamsters (Fig. 2.1e) and in regressing antral follicles (Fig. 3.2e, f).

The enormous self-healing potential of the ovary is amazing. It happens in spite of surgical interventions such as wedge resection or ovarian drilling. The strategy has minor effects on the follicle reserve; it is effective in women with PCOS, who have shown resistance to pharmacologically-induced ovulations (Api 2009). How ovarian surgery normalizes endocrine parameters in PCOS women is incompletely understood. Changes seem to be governed by the ovary itself and thus precede the restored feedback to the hypothalamus and pituitary gland (Hendriks et al. 2007). In view of this concept, we assume that INIM function is inhibited in polycystic ovaries and that tissue damage by ovarian drilling repairs blocked INIM interactions. Innate immunity does not stand alone as manager of ovarian functions, but it cooperates with adaptive immunity through DCs (Iwasaki and Medzhitov 2010; Peng et al. 2007; Turvey and Broide 2010). The statement also proves to be correct for the ovary, because T cells are reduced in number in the thecal cell layer of polycystic ovaries (Wu et al. 2007), and because an altered T-cell profile is reported for the follicular fluid of patients with idiopathic infertility (Lukassen et al. 2003). Furthermore, autoimmune damage is known to be responsible of premature ovarian failure diagnosed in women under the age of 40 years. The failure is associated with the alteration of T-cell subsets and T-cell-mediated cell injury (Vujovic 2009). The overall number of T cells is low in the preovulatory follicle and steadily increasing at the time of morphological luteolysis (Brännström et al. 1994b; Best et al. 1996; Bauer et al. 2001). The reports point to a more intense convertion between innate and adaptive immunity at times of luteolysis than of follicle rupture. It is noteworthy that impaired luteolysis never causes a tumor-like body. Another immune-mediated failure appears to be the luteal phase deficiency associated with failed or delayed implantation, infertility and early pregnancy loss (Erlebacher et al. 2004). In detail, when in a murine model the cell-mediated/adaptive response has been blocked by ligating CD40 (TNF receptor superfamily member and critical for adaptive immunity response), INIM is heavily activated, progesterone synthesis impaired and resistance to prolactin stimulation seen. These findings point to the interaction of INIM with the endocrine system. Finally, after menopause and absence of folliculogenesis, the original mission of INIM fades away, and mast cells completely disappear in the medulla and the intersitital cortical tissue (Heider et al. 2001). INIM might become involved in the progression of benign or malignant ovarian tumors. The possibility relates to the immunolocalization of

multiple TLRs in the surface epithelium of human ovaries, in benign and malignant ovarian tumors (Zhou et al. 2009) and to prostate cancer risk associated with gene sequence variants in TLR4 as well as in TLR clusters (Girling and Hedger 2007). In the long run, novel strategies for the therapy of ovarian disorders will cross-react with the field of autoimmune diseases, allergy, transplantation and tumor biology.

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