Immunological Aspects of Fertility Regulation

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Infertility due to immunological factors is recognized in females. This can be due to the presence of either (a) antibodies reacting with sperm (Katsh 1959; Isojima et al. 1968); (b) antibodies curtailing the action of luteinizing hormone (LH) with a slightly shortened cycle; or (c) cell-mediated immune reactions resulting in recurrent abortions (Genetet et al. 1986).

A number of tests based on agglutination or immobilization of sperm help to put in evidence the presence of antisperm antibodies (Kibrick et al. 1952; Franklin and Dukes 1964; Isojima et al. 1968; Shulman et al. 1971; Friberg 1974). The manner in which these antibodies were induced in patients is not known. The response in most cases, however, is of a long-lasting duration, presumably because sperm carry a large number of auto- and isoantigens (Hekman and Rumke 1976). In males antisperm antibody formation is frequently observed in situations where the blood testis barrier is disrupted, which happens in some infections, injury or vasectomy (Wartman 1975; Goldberg 1983). In case pregnancies are desired in women having antisperm antibodies, use of condoms over a period to lower the antibody titers or therapy with corticosteroids are reported to give satisfactory results (Shulman and Shulman 1982; Hargreave and Elton 1982; Alexander et al. 1983).

Infertility by LH cross-reactive antibodies can be induced in experimental animals by immunization with β-oLH (ovine luteinizing hormone) (Thau et al. 1979; Thau and Sundaram 1980) and/or with β-HCG (human chorionic gonadotropin) and β-oLH (Talwar et al. 1986). The animals continue ovulating; the luteal cycle, however, is shortened by about 2 days, and the progesterone production capacity of the corpus luteum is reduced. Long-term safety studies (7 years of repeated hyperimmunization) have not shown any pathological consequences (Thau et al. 1986).

Couples sharing histocompatibility antigens have a higher frequency of recurrent abortions (Beer et al. 1981; Thomas et al. 1985). Transfusion of husband or donor leukocytes to the female has resulted in successful pregnancy in many cases (Taylor and Faulk 1981; Beer et al. 1986; Mowbray 1986). Intricate mechanisms are implicit in the phenomenon (Gill 1983; Johnson et al. 1985).

Birth Control Vaccines (BCVs) are a new class of vaccines. In contrast to traditional vaccines, which are directed against communicable diseases, BCVs seek to intercept a selected physiological process within the body. The rationale of these vaccines is to induce antibodies and/or sensitize cells to interfere in the action of a key reproductive hormone or a reproductive process. Theoretically a number of vaccines are possible. Present research is focussed on the following...
vaccines: gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), LH, and HCG.

1. GnRH: A vaccine directed against the decapeptide GnRH is of potential use in both males and females (Fraser 1983, 1986; Talwar et al. 1984). Other applications of the GnRH vaccine may be found in the treatment of precocious puberty, carcinoma of the prostate, and breast cancer. Immunization against this hormone reduces the production of sex hormones. Bioeffective level of immunization can be achieved without Freund’s complete adjuvant (Shaha et al. 1986).

2. FSH: This vaccine is being developed to control male fertility (Murty et al. 1979; Srinath et al. 1983). The vaccine is currently under evaluation in bonnet monkeys with encouraging results (Moudgal et al. 1986).

3. LH: Thau et al. (1979) have demonstrated the efficacy of immunization of rhesus monkeys with β-oLH for control of fertility. Long-term safety studies in monkeys have shown no side effects (Thau et al. 1986). In another modality β-oLH is used in combination with β-HCG (Talwar et al. 1986).

4. HCG: Vaccines against HCG are at the most advanced stage of development. These are intended to be used in females. Currently four vaccines are in phase I clinical trials; these are: (a) α-oLH-β-HCG-TT/CHB, (b) β-HCG-TT/CHB + β-oLH-TT/CHB, (c) β-HCG-TT, and (d) 37aa CTP-DT.

Broadly speaking, these fall into three categories. The CTP (carboxy terminus peptide) vaccine induces antibodies specific to HCG and is non-cross-reactive with LH (Griffin 1986). The peptide has, however, low immunogenicity and requires the use of adjuvants, emulsifiers and oily vehicle (norMDP, Arlacel A, and squalene). The antibodies are of lower affinity \( K_a = 10^9 \text{M}^{-1} \) than those generated by immunization with β-HCG \( K_a = 10^{10} - 10^{11} \text{M}^{-1} \) (Shastri et al. 1978; Chen et al. 1980). The bioneutralization capacity of the antibodies is also lower (Louvet and Ross 1974; Ramakrishnan et al. 1979). The demand on the quantum of antibodies and their quality for effective control of fertility in humans will only be known when phase II trials with these vaccines are carried out. Immunization with β-HCG has been demonstrated to control fertility in two species of primates by three laboratories (Stevens 1976; Hearn 1979; Talwar et al. 1980). β-HCG is definitely more immunogenic and produces antibodies of high affinity (Thanaval et al. 1979) and with better bioneutralization capacity (Das et al. 1976). The immunogenicity of β-HCG is further improved by its annealing with the α subunit of oLH. The annealed antigen has a conformation akin to the native hormone and produces antibodies with an improved bioneutralization capacity (Talwar 1986). β-HCG and α-oLH × β-HCG also produce antibodies which are cross-reactive to the extent of 10%–50% with LH. This cross-reaction contributes in an additional way to the efficacy of the vaccine, as demonstrated by the extensive studies of Thau et al. (1979) and many other investigators.

Probing clinical trials with β-HCG-TT vaccines were conducted several years ago in Helsinki, Uppsala, Santiago, Bombay, New Delhi, and Bahia. In all, 63 women received the vaccine at an arbitrary dose of 80 μg of β-HCG linked to 10 LF (limit of flocculation) of tetanus toxoid. Four fortnightly injections were given for primary immunization; 61 of these made antibodies against HCG and