Future use of clomiphene in ovarian stimulation

Psychic effects of clomiphene citrate

F. Siedentopf and H. Kentenich

Department of Obstetrics and Gynecology, Frauenklinik der DRK-Kliniken Westend, Pulsstrasse 4, 14059 Berlin, Germany

To whom correspondence should be addressed

As Tarlatzis and Grimbizis (1998) mention, after stimulation of the ovaries with clomiphene citrate, ovarian hyperstimulation syndrome can be avoided in most cases. Clomiphene remains the drug of first choice in treating anovulation and inadequate follicular development (Dickey and Holtkamp, 1996); it is also useful for stimulating ovaries during in-vitro fertilization (IVF). Here, an important aspect is to minimize the rates of multiple pregnancy. The psychosocial and physical damage that multiple pregnancy may cause should not be underestimated.

We have to consider that each drug has side-effects. In general, clomiphene citrate is well tolerated. In a study by Kousa et al. (1997), only one of 113 patients dropped out because of side-effects of the drug. What are the psychic effects of clomiphene citrate and what problems can we expect? Within the central nervous system (CNS), as well as being present in the hypothalamus, oestrogen receptors are also present in the limbic system, thereby modulating its activity (Kapfhammer et al., 1990). The binding of clomiphene citrate helps to explain its side-effects on the CNS.

Some of the more frequent side-effects that occur in women undergoing hormonal stimulation treatment are hot flushes (10.4% of the women), complaints caused by enlargement of the ovaries, such as lower abdominal pain (5.5%) and symptoms of the CNS (3.5%). The latter include heightened nervousness, mood swings, sleeplessness, headaches, dizziness and disturbed vision. As a rule the side-effects are dose-dependent and are usually completely reversible once the medication is stopped (Haskell et al., 1977; Derman and Adashi, 1994; Slade et al., 1997). Nevertheless, Purvin (1995) describes three cases of visual disturbances where the visual symptoms persisted after cessation of clomiphene citrate medication. So we should not underestimate the risk of the treatment.

According to our knowledge of current literature, psychiatric complications are described in only four cases (Cashman, 1982; Altmark et al., 1987; Kapfhammer et al., 1990; Siedentopf et al., 1997). When we compared the cases, they demonstrated similarities in the sequence of events: (i) the psychotic reaction appeared while clomiphene was being taken (days 2–7 of stimulation); (ii) there was a paranoid component; (iii) once the medication was stopped, a rapid cessation of the symptoms occurred.

Fortunately, psychoses under clomiphene medication have been described extremely seldom, for they present considerable danger for those affected. Women with a history of psychiatric instability appear to be at greater risk of developing this type of complication. These cases have in common the acute and early occurrence of psychotic symptoms 2–7 days after the start of clomiphene administration. Well-known and more frequent are mood swings induced by clomiphene. In a study by Blenner (1991) in which 14 couples were questioned in detail about the psychic effect of clomiphene, >50% (nine out of 14 patients) mentioned pronounced influences on the emotions. The women described their feelings as uncontrollable. They described themselves as vulnerable, anxious and irritable. They felt that they were at the mercy of their emotions which changed quite suddenly. In contrast to other situations in life, they were no longer in a position to overcome these ups and downs adequately. Significantly, the women reported that their usual coping mechanisms no longer worked. This experience of helplessness certainly leads to an intensification of the distress already in existence due to the unwanted state of childlessness and the treatment itself.

The cause of the symptoms remains unclear. However, in the literature, a parallel with pre-menstrual syndrome has been suggested. Kapfhammer et al. (1990) suspected an aetiological relation to certain post-partal psychoses. When we compare the hormonal situation of the affected women, we notice that each are in states characterized by severe hormonal fluctuations. Consequently the activity within the limbic system became altered due to these hormonal changes. There have been suggestions that oestrogens in particular modulate functions that relate not only to the endocrine system (Altmark et al., 1987). On the hypothalamic and pituitary level clomiphene citrate acts as an anti-oestrogen (Kousa et al., 1997); this may be one explanation for the psychic effects of the substance.

The safety of the administration of clomiphene citrate is an important issue. We should not forget its psychic influence. Before treatment begins, a detailed case history should be completed for each patient which takes the past psychiatric history into account. In this way we can lessen the chance of making the women feel insecure, and the negative effects on the compliance and relationship with the partner can be avoided. Among patients with evidence of psychiatric illness in their case histories, ovulation-inducing substances such as clomiphene citrate should be implemented with particular care. To achieve the best results it requires careful monitoring (Kousa et al., 1997).

References