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Clomiphene Citrate (CLOMID) and Pregnancy

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Eugene Pergament, MD, PhD; Amy Schechtman, MS, CGC; Aimee Tucker, BS

Current trends in parenthood find a shift upward in the age of first-time parents. With this increase there has been a corresponding increase in use of ovulation induction agents. Questions arise about such infertility treatments, their effects on the women receiving them, and the pregnancy they enable. This RISK||NEWSLETTER explores clomid, a common ovulation induction agent, and possible teratogenic risks associated with its use.

CLOMID

Clomid is an estrogen receptor agonist/antagonist. Treatment with clomid involves oral doses of 50-100 mg per day for a five-day period in 40-day cycles until pregnancy is achieved or the regimen is discontinued. Rosa (1990) estimated that approximately 1% of women of reproductive age undergo ovulation induction. Successful induction of ovulation can be achieved in 70-90% of patients with conception rates ranging between 30-40% (Scialli, 1986). These success rates fail to mention the number of treatment cycles required. However, this number may be of significance in determining the teratogenicity of clomid. With a half-life of 5-7 days, it is possible that clomid, after inducing a successfully fertilized ovulation, remains in the mother's system well into the initial weeks of pregnancy. Mikkelsen et al. (1986) suggested that with repeated treatment cycles, clomid and its metabolites might build up, resulting in considerable exposure for the fetus. However, the estrogen receptors necessary for interaction with clomid are not present until the fetal stage of pregnancy (56 days post-conception) (Cunha et al., 1987). Furthermore, multiple gestations occur in 8-13% of pregnancies after use of clomid (Adashi et al., 1979; MacGregor et al., 1968; Harlap, 1976; Hack et al., 1972; Karrow et al., 1968). These studies also do not consider deformations due to multiple gestations.

ANIMAL STUDIES

Clark and McCormack (1980) studied the effects of clomid on the reproductive tract of fetal and neonatal mice. They found that a wide number of abnormalities occurred due to the intense and sustained estrogenic stimulation of the tract's epithelial lining during its development. The number of abnormalities was related to the dosage and animal's age, as the number of estrogen receptors increases as mice age. Laufer et al. (1982 and 1983) found that high doses of clomid in vitro might lead to degeneration of rat oocytes. In looking at this effect in vivo, they found that clomid exposure in preovulatory mice was associated with a decrease in the number of ova and a diminished fertilization potential. Dziadek (1993) found that preovulatory administration of clomid to mice was associated with lower implantation rates and IUGR in surviving fetuses. A higher incidence of exencephaly was also noted in these offspring. The degree of effect was dependent on dosage and timing in relation to ovulation. Implant rate was lowest and IUGR highest with injection before ovulation. Administration in

the pre-implantation period led to complete inhibition of implantation, while post-implantation exposures led to small decreases in fetal weight. Finally, transfer of exposed blastocysts to unexposed foster mother mice showed that effects were mediated by clomid on the mother's reproductive system and not directly on the embryo.

HUMAN STUDIES

Effects on the Reproductive Tract

Dlugi et al. (1985), in an in vivo analysis of oocytes released via clomid treatment, demonstrated no impairment in terms of quality and number of oocytes that occurred subsequently implanted. Clomid may alter the development of the human reproductive tract (Cunha et al., 1987). Tissue culture exposure of fetal tissues to clomid demonstrated the occurrence of estrogenic proliferation. This only developed in tissues of 16 weeks gestation or greater. Again, this is likely due to the absence of estrogen receptors until the 11th week of gestation. The authors suggested that earlier exposures do not have a comparable effect.

Spontaneous Abortion (SAB) and Other Pregnancy Loss

Several reports suggest a possible association between pre-ovulatory clomid use and increased frequency of pregnancy loss. Toshinobu et al. (1979) found a 24% SAB rate post-clomid use compared to a control group rate of 8.9%. Garcia et al. (1977) found a 25% SAB rate for pregnancies conceived after previous clomid use but which had been discontinued before conception. In a study of subclinical loss, Bateman et al. (1992) presented information suggesting that such loss is more common in clomid-treated pregnancies. Subclinical loss is defined as hCG > 0.5 IU/L in the luteal phase with luteal phase of normal length (14 days + 2). A review of the literature on clomid and SAB by Shoham et al. (1991) indicated that 16-22% of clomid-assisted pregnancies were lost as SABs. A review by Venn et al. (1994) cited this range to be between 8.7 and 27%. While the percentages of loss varied, the association between clomid and SAB was apparent. Scialli (1986) and numerous other authors pointed out, however, that all studies of such nature were biased by the scrutiny under which pregnancies achieved via fertility treatment were placed. These pregnancies were detected earlier than pregnancies from the general population, and reports of their higher susceptibility to SAB were likely to be biased by surveillance. Scialli did point out, however, that there might be an association between miscarriage rates and cycle timing and duration of clomid treatment. The author stated that one-half of all SABs occurring in clomid-treated patients had undergone treatment for greater than 6 months. Perhaps Mikkelsen's accumulation theory (1986) is applicable to understanding these findings.

Venn (1984) also reviewed other forms of pregnancy loss and their associations with clomid use, suggesting a 0.7-7% perinatal mortality rate and a 0.5-4% ectopic pregnancy rate (general population ectopic pregnancy rates estimated at 0.7-0.8% (Weiss et al., 1975) and 0.3-1.3% (Martinez et al., 1986)). Venn does state that in much of the literature reviewed, report rates may be biased by levels of surveillance, inadequate comparison groups and small population sizes.

Neural Tube Defects (NTD)

Perhaps the most controversial issue is the possible association between NTDs and clomid use. Between 1972 and 1990, 368 birth defects arising after clomid use by the mother were reported to the FDA. This number included 35 reports of NTDs (Rosa, 1990). Researchers began looking at this question, because of conflicting and ambiguous results. Czeizel (1989) asked the mothers of 825 children born with NTDs and 18,904 controls about pre-conceptional clomid use. 0.4% of the case mothers reported usage compared to 0.1% of control mothers. The author stated that significance of this finding was unclear. A similar study by Cuckle and Wald (1989) cited 3.7% of case mothers used clomid compared to 2.3% of control mothers. Vollset (1990) combined studies and found an odds ratio

of 2.94% (95% CI 1.32-6.5), indicating that association between clomid use and NTDs was real. Robert (1991) reported a similar odds ratio: 2.36 (95% CI 1.25-4.46).

Mills (1990) questioned this association, citing the limited size of the populations studied, biases because of utilization of maternal recall methods, and publication of only positive results and lack of submission of negative results. Mills found that exposure to clomid during pregnancy was rare and questioned how a pre-ovulatory agent could affect an event occurring 3-4 weeks after conception. In perhaps the most powerful study undertaken, Mills proceeded to compare 571 women with a diagnosis of NTD in her fetus or child, 546 women with the diagnosis of another abnormality and 573 control mothers without diagnosis of an abnormality. Fertility drug use around the time of conception was not common for case mothers compared to mothers of children with other abnormalities or in the case of mothers of children without abnormalities (odds ratio, 1.28 [95% CI 0.39-4.51] and 0.8 [95% CI 0.27-2.27]). Fertility drug use at times other than around conception gave an odds ratio of 1.37 (95% CI 0.70-2.74) for case mothers compared to mothers of children with other abnormalities and 1.05 (95% CI 0.56-1.98) for case mothers in contrast to mothers of children without abnormalities. Other researchers corroborated the results of this study (Lammer, 1995; Shaw, 1995; Milunsky, 1990).

In a meta-analysis undertaken by Schechtman and Pergament at Northwestern University (1996), the conflicting reports of an association between clomid and ONTD were pooled. Meta-analysis of 11 studies (5 showing increased risk, 5 showing no increased risk and one uninterpretable) gave an odds ratio of 1.45 (95% CI 1.10-1.92) ($p=0.01$). There is a need for a large case-control study which considers the following possible confounding factors: the decrease in NTD prevalence rates over time, the termination of affected pregnancies following MSAFP screening, the variance of NTD rates by geography, and the use of different ovulation induction agents in these studies.

Other Abnormalities

The possible association between clomid use and NTDs may be most debated, but it has not been the only association evaluated. Other abnormalities have been studied for their occurrences in births linked to exposure to the ovulation induction agent, clomid. Haring et al. (1992) and Scea et al. (1990) reported cases of acardius acephalus, a rare defect seen in twin pregnancies (1/34,600 deliveries), associated in pregnancies enabled by clomid. There have been reports of neuroectodermal tumors in children whose mothers utilized fertility treatments including clomid. Kurachi et al. (1983) cited previous reports of a 1.1-10.8% incidence of malformations following clomid use. They studied 935 livebirths after clomid treatment and found 21, or 2.3% with visible malformations. This was not increased over the general population frequency or the frequency they found in their control population (1.7%). The types of malformations were similar between groups, and there was no dosage or age correlation. The authors surmised that there were not teratogenic effects linked to clomid. Scialli (1986) found no affect of clomid on fetal growth in terms of length and weight. A comprehensive study detailed the defects that have been found in clomid-treated pregnancies found odds ratios for the following occurrences: microcephaly, 8.4; anorectal atresia, 4.6; hydrocephaly, 3.4; NTDs, 1.2; and, anophthalmia/ microphthalmia, 6.4. Overall, the odds ratio for defects was 0.97 (95% CI 0.55-1.71), indicating no risk for birth defects with clomid use. However, special attention should be paid to the specific defects listed above.

Ovarian Cancer Risk in Women Using Clomid

Although this is a teratogen newsletter, the risk of ovarian cancer in users of clomid should be mentioned. The lifetime risk for ovarian cancer in the general population is 1.8%. Whittemore (1994) cites a 4-5% risk for women treated with clomid. Rossing (1994) evaluated this risk and the lengths of time women were on clomid and found that the relative risk for less than 1 year of treatment was 2.3. However, this risk increased to 11.1 for women treated for 1 year or longer (12 cycles).

SUMMARY

The controversy over clomid use and its teratogenicity is still unresolved. At the present time, the largest studies suggest either no risk or a minimal risk for NTDs and other malformations. Risks for pregnancy loss are clouded by increased surveillance of clomid-induced pregnancies. NTDs can often be identified by ultrasound and MSAFP screening, suggesting that the non-invasive tests can be offered to any woman with concerns about previous clomid use. Commonly, pregnancies enabled with reproductive technologies are followed closely. Perhaps this offers reassurance and early detection to patients with concerns about past or current clomid use. Further studies are needed to definitively decide if clomid is truly a teratogenic agent and, if so, to what extent in the case of specific congenital malformations.