A ‘sweet’ indication for ovulation induction

Yoav Peled, David Rabinerson, Boris Kaplan, Linda Harel and Moshe Hod

Department of Obstetrics and Gynecology, Rabin Medical Center, Beilinson Campus, Petah Tiqva and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

1To whom correspondence should be addressed: Department of Obstetrics and Gynecology, Rabin Medical Center, Beilinson Campus, Petah Tiqva 49100, Israel

In diabetic patients, euglycaemia at the time of conception is crucial for the success of the pregnancy. In consideration of the difficulty in achieving and maintaining tight glycaemic control for long periods, we administered clomiphene citrate, which is usually indicated in cases of absent or infrequent ovulation, to enhance fecundability in 10 pregestational diabetic patients. All conceived within one to three cycles of the drug, and nine delivered healthy term babies after uneventful pregnancies; one aborted spontaneously in the eighth gestational week. No effect of the drug on the diabetes was noted as based on measurements of glycosylated haemoglobin and fructosamine concentrations and the absence of changes in the patients’ insulin requirements. In the light of these successful results, and in view the importance of euglycaemia at the beginning of diabetic pregnancies, we suggest a new ‘sweet’ indication for the use of clomiphene citrate.

Key words. clomiphene citrate/diabetes mellitus/ovulation induction/pregnancy

Introduction

Pregnancy outcome in women with overt pregestational diabetes is associated with a 7.5–12.9% incidence of major congenital malformations (Miller et al., 1981; Fuhrmann et al., 1983; Ylinen et al., 1984; Steel, 1985; Mills et al., 1988; Greene et al., 1989), a rate 2–5 times that in the general population (Kalter and Warkany, 1983). Reports have indicated that this figure can be effectively reduced if women first undergo meticulous glucose control before conception (Miller et al., 1981; Fuhrmann et al., 1983, 1984; Steel et al., 1988) Normal fecundability, however, is only ~25% (Speroff et al., 1994), and so it may take the average woman 4 months to conceive. Since maintaining tight glucose control is so difficult for such a long period, yet so crucial to a successful pregnancy outcome, we propose that fecundability be enhanced in these patients by the use of clomiphene citrate. The present report describes our preliminary experience with this treatment.

Materials and methods

The Diabetes in Pregnancy Clinic of Rabin Medical Center, Beilinson Campus, Israel, treats 300 patients annually. For purposes of this study, 10 patients with a mean age of 29.5 years (range 23–32 years) with insulin-dependent diabetes mellitus (classes C to RF; White classification, 1974) were offered treatment with clomiphene citrate to enhance fertility. All had achieved tight pregestational glucose control but had not become pregnant after 3 months of unprotected coitus and good coital technique (as proved by post-coital test). Each patient underwent a hormonal profile evaluation prior to clomiphene therapy which included day 3 serum concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin and pelvic ultrasound examination on the same day. Serum concentrations of mid-luteal phase progesterone were also measured. All patients had values within normal range, indicating normal reproductive endocrine function. None was found to have abnormalities of the ovaries on sonographic examination, and no evidence of polycystic ovarian disease was found. Male factor infertility was ruled out by sperm counts. All patients gave informed consent for the study.

Clomiphene citrate was started on the fifth day of the menstrual cycle at a dose of 100 mg/day for 5 days. Patients were requested to have intercourse every other day, from days 12–18 of the cycle. Ovulation was proven by measuring serum progesterone on the 21st day (all measurements were greater than 20 ng/ml). Pregnancy was demonstrated by a serum β-human chorionic gonadotrophin (HCG) concentration of greater than 10 mIU/ml, measured 5 days after a missed period, and later (in the fifth gestational week) by vaginal ultrasonography. Glucose control consisted of strict diet, seven to eight daily self-assessments of capillary blood glucose, and monthly measurement of fructosamine and glycosylated haemoglobin (HbA1c) concentrations.

Results

Five women conceived in the first cycle of treatment, three in the second and two in the third. There were seven singleton term pregnancies, two twin term pregnancies and one singleton spontaneous abortion (in the eighth gestational week). There were no maternal complications. All newborns were healthy and normal; mean birth weight was 3724 ± 325 g, and mean Apgar score at 5 min was 9 (range 7–10). No complications were noted in any of the newborns during their 3 day stay in the Neonatal Department.

Tests revealed no change in blood glucose concentrations during pregnancy or in the patients’ insulin requirements that mandated a revision in the number, timing or dosage of insulin injections from that used before the clomiphene citrate treatment. There was also no change in either fructosamine blood level or HbA1c prior to or after treatment.

Discussion

Clomiphene citrate is indicated for ovulation induction mainly in cases of absent or infrequent ovulation (Speroff et al., 1994). In our preliminary experience with this treatment, all 10 pregestational diabetic patients conceived within one to three cycles of the drug, and nine delivered healthy term babies after uneventful pregnancies; one aborted spontaneously in the eighth gestational week. No effect of the drug on the diabetes was noted as based on measurements of glycosylated haemoglobin and fructosamine concentrations and the absence of changes in the patients’ insulin requirements. In the light of these successful results, and in view the importance of euglycaemia at the beginning of diabetic pregnancies, we suggest a new ‘sweet’ indication for the use of clomiphene citrate.
It is not used to enhance fecundability. Yet, in certain situations, when the timing of conception is critical to the success of another treatment, as in our patients, who were basically normally-ovulating patients with regular menstrual cycles, it seems appropriate to prescribe the drug despite its known possible side-effects, e.g. risk of hyperstimulation and increased rate of multiple gestations. Clomiphene citrate was selected as the drug of choice in our study since it is easy to use in combination with other methods employed for this purpose (such as monitoring the natural cycle combined with intrauterine insemination), has fewer adverse effects than other drugs used for this purpose (such as human menopausal gonadotrophin), and does not necessitate close follow-up with hormone measurements and ultrasound. Although some authors have noted an association between the use of clomiphene citrate and ovarian cancer, they did so only after 12 cycles in which the drug was used and at high doses (250 mg/day) (Rossing et al., 1994). At the doses we used, the risk of adverse effects is minimal and indeed, we did not encounter any, although it should be noted that our sample size was small.

It was reassuring to confirm that clomiphene citrate has no effect on diabetes, as shown by the lack of change in capillary glucose concentrations and insulin requirements in all our patients. Furthermore, it was proved safe in terms of fetal outcome. Although this has already been reported (Shoham et al., 1991; Speroff et al., 1994), it has not been shown in severe diabetics. Since clomiphene citrate was used in our study in normal ovulating women and in order to increase fecundability, it did not seem necessary to monitor these patients by ultrasound prior to ovulation or to enhance it by administering HCG. The 100% success rate with this drug on the one hand and the relatively high number of twin pregnancies (30%) on the other may serve as proof of the effectiveness of clomiphene citrate in fertile ovulating women in comparison with subfertile women, in whom both the success rate and number of twin gestations are lower.

In this study a drug usually used for subfertile women for ovulation induction was used to speed up conception in basically fertile, ovulating women. The relatively short time it took our patients to conceive, the 100% success rate for pregnancy, the lack of drug effect on the diabetes, and the uneventful pregnancy course and good outcome warrant a larger trial with a greater number of patients to establish the efficacy of this method. On the basis of our results, it seems that women with insulin-dependent diabetes under intensive therapy in preparation for a planned pregnancy might be given clomiphene citrate in order to achieve pregnancy while still in tight glycaemic control.

References


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