tion, and this is of course where prevalence numbers become important.

If, as Tur et al. suggest, the high-order prevalence is indeed only 2.4% of all pregnancies, then ovulation induction does not really have a high-order multiple pregnancy problem, and whatever minor problem there might be could probably be further reduced by more careful patient selection. If, however, as is more likely the case, the high-order multiple pregnancy problem in ovulation induction cycles is closer to 8% of all pregnancies, then a very inefficient treatment (with only a 15% pregnancy rate per cycle) would seem almost prohibitively expensive (especially in the United States, where the cost of gonadotropins is significantly higher than in most of the rest of the world) if cycle cancellation costs have to be added to the calculation of cost-effectiveness. In competent programs, average clinical IVF pregnancy rates now exceed ovulation induction cycle rates, reported by Tur et al. and by us (1, 2), by a factor of at least three.

Responsible IVF transfer policies can prevent high-order multiple pregnancies with almost absolute certainty. The combination of comparatively relatively low pregnancy chances, elevated high-order pregnancy risk (whatever that might be), and relatively high cycle costs with ovulation inductions reaffirms in our opinion our previously voiced opinion that there is very little place in modern infertility care for standard ovulation induction with or without intrauterine inseminations.

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February 14, 2005

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Reply of the Authors:

We thank Dr. Gleicher for his interest in our article (1). He appropriately stresses that the 2.4% triplet rate reported in our study represents less than one third of the high-order multiple pregnancy (HOMP) rate reported in his study (2). This is to be expected, considering that in our study patients with predicted probability of HOMP >6.6% were given the opportunity to cancel the cycle, and a number of them did so. Thus, as many as 77.4% of cycles in which hCG was given had low risk for HOMP according to our prediction model. In contrast, in the study by Gleicher et al. (2), there were patients receiving the hCG injection in spite of having >22 follicles. In fact, as reported in Table 4 in that report (2), in as much as 87.4% of cycles in which hCG was given as a trigger the number of follicles was ≥7, and the remaining patients had ≤6 follicles. Different ovarian stimulation protocols used in the two studies might explain the different response to treatment.

Obviously, IVF is a valid alternative in patients developing multiple follicles during ovulation induction. However, Dr. Gleicher proposes IVF as a first-line therapy of infertility to prevent HOMP. In this regard, it is of note that according to the last Centers for Disease Control and Prevention report on assisted reproductive technology (ART) surveillance in the United States (3), in 2000, among 99,629 ART procedures, the national live-birth delivery per transfer rate was 30.8%. Of the 35,025 infants born, 44% were twins, and 9% were triplet and higher-order multiples. Finally, we agree with Dr. Gleicher that cost-effectiveness studies comparing those different options are warranted.

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Endometrial dating—still room for controversy

To the Editor:

The Reproductive Medicine Network studies (1, 2) recently confirmed what many infertility specialists already accepted more than 2 decades ago, that is that histologic dating of endometrial biopsy timed by the urinary LH peak has no value in evaluating and treating patients with infertility. In addition, the investigators found that the urinary LH peak could be a false-positive sign of ovulation in >7% of women, regardless of their fertility status. Indeed, there is

evidence from earlier studies that serum LH measurements are also not a reliable tool for the exact timing of ovulation, and more particularly, for the onset of the luteal phase in patients with infertility. In the mid 1970s, couples with infertility were investigated according to a comprehensive protocol (3). This included daily recordings of basal body temperature (BBT) for a period of three cycles, with annotation of vulvar mucus changes and occurrence of intercourse. Additional investigations included a postcoital test, hysterosalpingography, and a laparoscopy with endometrial biopsy for histologic dating during the midluteal phase of the third assessment cycle. Simultaneously, to improve dating of the endometrial biopsy, daily blood samples were taken from days 9 to 17 of the cycle and assayed for 17β-E_2, P, prolactin, and LH. The analysis of 82 consecutive patients showed that histologic dating of endometrial biopsies in relation to the midcycle serum LH peak did not differ significantly between patients with tubal or male factor infertility (group I) and patients with unexplained or endometriosis-associated infertility (group II). Endometrial dating correlated with the LH peak, with standard deviations of 1.2 and 1.3 days, respectively, in groups I and II. However, whereas in group I both the BBT and the plasma P were significantly elevated on the first day after the LH peak, the rise of P only occurred on the second day after the LH peak in group II (3). Moreover, in four women the BBT rise occurred 3–5 days after the plasma LH peak, and histologic endometrial dating in these patients was in phase with the BBT rise but not with the LH peak (4). Finally, in two women no LH peak was detectable before the BBT rise, although the luteal phase did occur normally, as determined by serial P assays, endometrial biopsy dating, and a discernible hyperthermic plateau of approximately 12 days. These subtle abnormalities in the relationship between LH peak, 17β-E_2 ovulation, and P, moreover, did not have a relationship with the presence of a luteinized unruptured follicle.

Taken together, these data suggest that the exact periovulatory endocrine relationships are poorly understood in the individual woman. In contrast to the well-documented mean relationship between LH peak and onset of ovulation and luteinization, the interval between LH peak and onset of ovulation and luteinization can occasionally be much longer. If a longer interval were to be a repetitive phenomenon in the individual woman, this would have obvious implications for timing of oocyte retrieval and ET during IVF. We were disappointed decades ago, as the authors are today, that the exact determination of the LH peak did not improve the clinical value of endometrial biopsy dating.

Those looking for clinically useful molecular markers of endometrial defects should remind themselves that the endometrium is primarily a sensitive biological reporter system of ovarian steroidogenesis. In contrast to the persistent belief that subtle peri-ovulatory abnormalities in ovarian steroidogenesis or intrinsic molecular endometrial aberrations are responsible for a substantial proportion of female infertility, the evidence for this intrinsic ovarian or endometrial abnormality still is scanty.

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Reply of the Authors:

We appreciate the author's comments, thank them for drawing our attention to their earlier work, and agree with their conclusions regarding the lack of strong evidence for subtle ovarian or endometrial abnormalities as a substantial cause of female infertility. Dr. Koninckx and colleagues assert: "The Reproductive Medicine Network studies recently confirmed what many infertility specialists already accepted more than 2 decades ago, that is that histologic dating of endometrial biopsy timed by the urinary LH peak has no value in evaluating and treating patients with infertility." The key word in their sentence, of course, is "many." Certainly not all infertility specialists agree. The most recently published edition of a major textbook in the field continues to refer to the timed endometrial biopsy as a method of assessing endometrial histology in the infertile couple (1). The authors also specifically recommend the use of home urine LH kits for the purpose of timing the biopsy. In the chapter on female infertility, endometrial biopsy is listed as a secondary test, along with the postcoital test and diagnostic laparoscopy (2).

This month's issue of a popular journal includes a five-page discussion: "Should endometrial biopsy be part of an infertility evaluation?" in their "Controversies in OB/GYN" section (3, 4).