

High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2)

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BACKGROUND: Medical induction of ovulation using clomiphene citrate (CC) as first line and exogenous gonadotrophins as second line forms the classical treatment algorithm in normogonadotrophic anovulatory infertility. Because the chances of success following classical ovulation induction are not well established, a shift in first-line therapy can be observed towards alternative treatment. The study aim was to: (i) reliably assess the probability of singleton live birth following classical induction of ovulation; and (ii) construct a prediction model, based on individual patient characteristics assessed upon standardized initial screening, to help identify patients with poor chances of success. **METHODS:** A total of 240 consecutive women visiting a specialist academic fertility unit with a history of infertility, oligomenorrhoea or amenorrhoea, and normal FSH and estradiol serum concentrations (WHO group 2) was prospectively followed. The women had not been previously treated with ovulation-inducing agents. All patients commenced with CC. Patients who did not ovulate within three treatment cycles of incremental daily doses up to 150 mg for 5 consecutive days or ovulatory CC patients who did not conceive within six cycles, subsequently underwent gonadotrophin induction of ovulation applying a step-down dose regimen. The main outcome measure was pregnancy resulting in singleton live birth. Cox regression was used to construct a multivariable prediction model. **RESULTS:** Overall, there were 134 pregnancies ending in a singleton live birth (56% of women). The cumulative pregnancy rate after 12 and 24 months of follow-up was 50% and 71% respectively. Polycystic ovary syndrome (PCOS) patients (49%), clearly non-PCOS patients (13%) and the in-between group did not differ in prognosis ($P = 0.9$). The multivariable Cox regression model contained the woman's age, the insulin:glucose ratio and duration of infertility. With a cut-off value of 30% for low chance, the model predicted probabilities at 12 months lower than this cut-off for 25 out of 240 patients (10.4%). **CONCLUSIONS:** Classical ovulation induction produces very good results in normogonadotrophic anovulatory infertility. Alternative treatment options may not be indicated as first-line therapy in these patients, except for subgroups with poor prognosis. These women can be identified by older age, longer duration of infertility and higher insulin:glucose ratio.

Key words: anovulation/clomiphene citrate/hMG/pregnancy rate/prognosis

Introduction

Anovulation is a common cause of infertility, and is diagnosed in at least 25% of couples with fertility problems. In the great majority of these women the underlying cause is described as 'pituitary-ovarian disbalance', where serum FSH and estradiol (E_2) levels are within normal limits [also described as World Health Organization (WHO) group 2] (World Health Organization, 1993; The ESHRE Capri Workshop Group, 1995). Patients suffering from polycystic ovary syndrome (PCOS) are considered a subgroup of WHO 2 (Laven *et al.*,

2002). Since the early 1960s, patients have been treated effectively with the anti-estrogen clomiphene citrate (CC), as well as exogenous gonadotrophins. CC is generally applied as first-line treatment in these women, due to low costs and minor chances of side effects or complications. Traditionally, exogenous gonadotrophins (especially FSH) are considered second-line therapy in case of failure to ovulate or conceive following CC. This treatment modality requires frequent monitoring due to inherent risks of multiple follicle development resulting in increased chances for ovarian hyperstimula-

tion syndrome (OHSS) and multiple gestation, especially in PCOS patients (Messinis and Milingos, 1997; Legro, 1998). Over the years, numerous (mainly retrospective) studies have established the overall effectiveness of either CC (Hammond *et al.*, 1983; Kousta *et al.*, 1997) or FSH (White *et al.*, 1996; Fauser and Van Heusden, 1997; van Santbrink and Fauser, 1997) in varying groups of patients. However, data concerning a prospective follow-up of a coherent CC and FSH treatment strategy in a well-defined group of patients are not yet available.

Over the past 10 years, increased attention has focused towards alternative treatment options such as the insulin-sensitizing agents (Glueck *et al.*, 2002; Heard *et al.*, 2002; Nestler *et al.*, 2002), aromatase inhibitors (Mitwally and Casper, 2001), laparoscopic surgery of the ovaries (Cohen, 1996; Farquhar *et al.*, 2001) or assisted reproduction such as intrauterine insemination (IUI) or IVF (Buyalos and Lee, 1996; Child *et al.*, 2001). Most promising results of up to 80% pregnancies have been reported by individual studies, but the majority of these reports involved a limited number of selected patients and were retrospective and uncontrolled. It is often suggested that the multiple birth rate is reduced in comparison with ovulation induction, but reliable information on multiple births is mostly lacking.

There seems to be a clear need to firmly establish the success and complication rates of the conventional approach for ovulation induction (involving CC and FSH) in a large unselected cohort of patients. The present report contains an integrated analysis of chances for pregnancies resulting in singleton live childbirth, extending previously reported outcomes separately for CC (Imani *et al.*, 2002a) and FSH (Imani *et al.*, 2002b; Mulders *et al.*, 2003). In addition, a prediction model is presented to help identify patients with poor chances of success. This information may serve as point of reference for future studies involving alternative approaches for ovulation induction.

Materials and methods

Subjects

Between November 1992 and May 1999, a consecutive series of 240 women attending the authors' infertility unit were included in the present study using the following inclusion criteria: (i) oligomenorrhoea (bleeding intervals between 35 days and 6 months) or amenorrhoea (bleeding interval >6 months); (ii) normal serum FSH (1–10 IU/l) and E₂ (150–400 pmol/l) levels (van Santbrink *et al.*, 1997); (iii) normal serum prolactin and thyroid-stimulating hormone levels; (iv) spontaneous menses or positive bleeding response to progestagen withdrawal; (v) a body mass index (BMI: body weight divided by the square of the patient's height) >18 kg/m²; (vi) age between 19 and 40 years; (vii) no previous use of ovulation-induction agents; (viii) a total motile sperm count [TMC = ejaculate volume (ml) × sperm concentration (10⁶/ml) × percentage of progressive motile sperm] of the partner >1 × 10⁶; (ix) a negative history of or screening for any tubal pathology; and (x) no indication for IUI. Institutional review board approval was obtained from the human subjects committee of the Erasmus Medical Center, and informed consent was obtained from all study participants.

The standardized initial clinical, sonographic and endocrine screening took place prior to the initiation of CC ovulation induction, as has been described previously (Imani *et al.*, 2002a). The clinical screening included patient's age, type of infertility (primary or secondary), cycle history (amenorrhoea or oligomenorrhoea), BMI, waist-to-hip ratio (WHR) and previous medication and/or surgery. Transvaginal sonography included assessment of ovarian volume (ml), and total number of follicles, as described previously (Pache *et al.*, 1992). Endocrine screening included serum assays for FSH, LH, E₂, androstenedione, testosterone, sex-hormone binding globulin (SHBG), and fasting insulin and glucose. The hormone assays used, and the intra- and inter-assay coefficients of variation valid for this study, have all been described previously (Imani *et al.*, 2000).

The treatment protocol and assessment of ovarian response and pregnancy after CC administration have also been described previously (Imani *et al.*, 2002a). In brief, the women received initial CC doses of 50 mg/day from cycle day 3 until day 7 after spontaneous or progestagen-induced withdrawal bleeding. In cases of absent ovarian response, the daily dosage was increased to 100 and 150 mg in subsequent cycles. Ovulation after CC or FSH medication was assessed by sonographic monitoring of disappearance of the pre-ovulatory follicle and/or the finding of midluteal progesterone levels >25 nmol/l. In case of CC-resistant anovulation (CRA)—that is, absent ovulation after 3 months, despite stimulation with a maximum daily CC dose of 150 mg—or if pregnancy failed to occur within six ovulatory cycles, ovulation induction with exogenous recombinant FSH (Puregon®; Organon NV, Oss, The Netherlands) was applied as second-line treatment, using a decremental dose regimen as published previously (van Santbrink and Fauser, 1997). The FSH response dose was assessed during the first cycle applying a low-dose, step-up regimen (Imani *et al.*, 2002b; Mulders *et al.*, 2003).

Pregnancy was defined as a positive urinary pregnancy test (Clearview, hCG II; Unipath Ltd, Bedford, UK) at least 3 days after the expected menses. Ongoing pregnancy was defined as sonographic assessment at 12 weeks amenorrhoea of an intrauterine gestational sac with a positive heartbeat. Live birth was defined as the delivery of a baby after at least 28 weeks gestational age. Information regarding deliveries and the health condition of the babies born was collected using hospital records. In cases of home delivery, the information was collected directly from the patient and her general practitioner or midwife.

Statistical analysis

The Kaplan–Meier method was used to estimate the cumulative pregnancy rate leading to singleton live birth. The period from the start of CC treatment until the first pregnancy leading to live birth was the time variable in this analysis. Conceptions that ended in miscarriage were ignored by the analysis, and in these cases follow-up continued until pregnancy resulting in singleton live birth occurred. Patients who had a pregnancy ending in premature birth, stillbirth or multiple live birth, were considered censored at conception. Patients who did not become pregnant were censored at their time of last treatment. Spontaneous pregnancies resulting in singleton live birth that occurred during the first or second month after the end of treatment were also included in the analysis.

Cox regression was used for univariable and multivariable analysis relating initial screening characteristics to the cumulative pregnancy rate leading to singleton live birth. In univariable analysis the log-rank test was used, and a *P*-value < 0.05 was considered to be statistically significant. A multivariable prediction model was constructed using a backward stepwise elimination method with *P* < 0.15 for exclusion of predictors, corresponding to Akaike's Information Criterion (Akaike, 1973). Predictor variables with univariable *P* < 0.5 were candidate

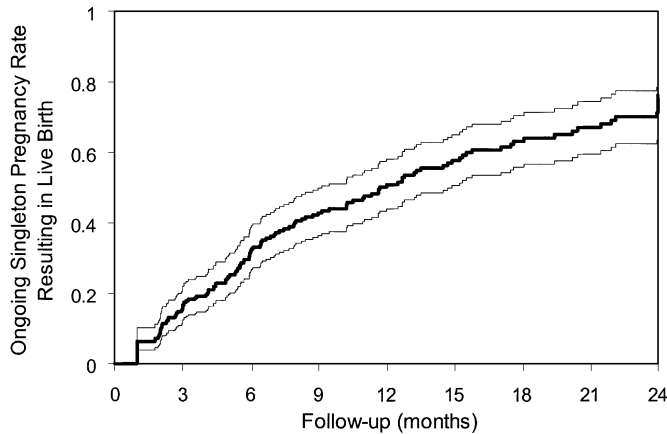


Figure 1. Cumulative pregnancy rate resulting in singleton live birth of a consecutive series of 240 normogonadotrophic anovulatory infertile women undergoing classical ovulation induction (CC as first-line, followed by FSH as second-line therapy if required), calculated by the Kaplan–Meier method, with 95% confidence interval.

variables for the multivariable model. These ‘liberal’ P -values were chosen because the resulting model may be expected to have a better predictive performance in new patients than when the strict $P < 0.05$ criterion is used (Harrell *et al.*, 1996). The prediction model was corrected by a shrinkage factor, determined by a bootstrapping technique with 200 replications, to provide better predictions in new patients (Van Houwelingen and Le Cessie, 1990; Harrell *et al.*, 1996). The discriminative ability of the prediction model was assessed by the c-statistic, which is similar to the area under the receiver operating characteristic (ROC) curve for dichotomous outcomes, and can range from 0.5 to 1.0 (Harrell *et al.*, 1985). The bootstrap technique was used again, this time to correct the optimism in the apparent c-statistic (Harrell *et al.*, 1996). Missing values occurred for some screening characteristics. The technique of multiple imputation was used to avoid loss of information due to missing data in multivariable analyses (Little, 1992). Missing data occurred in the WHR (45% missing), semen analysis (25% missing) and insulin:glucose ratio (26% missing). Statistical analyses were performed with SPSS for Windows (version 10) and S+ 2000.

Results

Following the induction of ovulation, 162 pregnancies occurred in 159 patients (66%). In total, 147 (90%) of the pregnancies were ongoing (positive heart action upon ultrasound at 12 weeks amenorrhoea), whereas 15 miscarried within 12 weeks. Of the 147 ongoing pregnancies, 137 were singleton and 10 were multiple (7% of ongoing pregnancies). Of the singleton ongoing pregnancies, two ended in premature birth and one in stillbirth. All other ongoing pregnancies ended in live birth (134 singleton, 10 multiple). The cumulative pregnancy rate resulting in singleton live birth is shown in Figure 1. After 6, 12, 18 and 24 months of follow-up, respectively 32, 50, 63 and 71% of patients presented with a singleton pregnancy resulting in the live birth of a baby. The cumulative chance after 24 months increased to 74% in case multiple live births were included, and to 76% for all ongoing pregnancies. The median time taken to reach pregnancy

resulting in singleton live birth was 11.7 months. The median follow-up of the women who did not reach this end-point was 10 months, with a maximum follow-up of 4 years. Their median duration of CC-treatment was 5.9 (range: 1–18) months, during which time a median of 5.0 (range: 1–13) CC-cycles were performed. The median duration of FSH treatment of the women who did not reach the end-point was 7.0 (range: 1–34) months, with a median number of 5.0 (range: 1–13) FSH treatment cycles.

The fate of the women participating in the study is shown diagrammatically in Figure 2. All 240 women started with CC, and 57 (24%) of them were found to be CRA. CC outcome in the remaining 183 women was 112 pregnancies: 98 ongoing singleton and four ongoing twin pregnancies (4% of CC-pregnancies) resulting in live birth, 11 pregnancies ending in miscarriage (10% of CC-pregnancies) and one ending in stillbirth. There was one additional miscarriage, in a woman who became pregnant again after a first miscarriage. There were 84 women who started FSH induction of ovulation after unsuccessful CC-treatment. In 44 women an ongoing pregnancy was subsequently achieved, and this resulted in 36 singleton, four twin, one triplet and one quadruplet live birth (14% multiple births) and two stillbirths. There were three pregnancies that miscarried (6% of 47 pregnancies). The miscarriage rate was not statistically significant between CC and FSH ($P = 0.7$). Almost 50% (33 out of 71) of the CCF patients did not proceed to FSH treatment and should be considered as drop-outs. They did not differ from the patients who started FSH treatment in any of the screening characteristics, except for the level of endogenous FSH: the mean (\pm SD) level was 4.1 ± 1.7 versus 5.1 ± 1.6 IU/l in the group that started FSH treatment ($P = 0.01$).

The primary screening characteristics are detailed in Table I for women who did and those who did not have a pregnancy that led to a singleton live birth. Successful patients were younger, infertile for a shorter period of time, thinner, had marginally higher FSH, higher LH and lower insulin:glucose ratios. The final column indicates the screening characteristics that had an independent contribution to the multivariable prediction model: age, insulin:glucose ratio and duration of infertility. The distribution of the predicted probabilities calculated by this model (after shrinkage) for the 240 patients in this study is shown in Figure 3. The individual predicted probabilities ranged from 15 to 82%. When a predicted probability at 12 months below 30% was considered as a poor prognosis, the model was able to identify 25 out of 240 (10.4%) as poor-prognosis patients.

In an additional analysis, WHO 2 patients were defined as definitive PCOS in case they presented with an elevated free androgen index (FAI) and polycystic ovaries (Laven *et al.*, 2002) (49% of the 240 patients; in accordance with a recent PCOS consensus meeting), and clearly non-PCOS when the FAI was normal and no signs of polycystic ovaries were present (13% of patients). The remaining women (38% of patients) formed the in-between group of possible PCOS. Kaplan–Meier analysis for pregnancy leading to singleton live birth showed no difference between these groups ($P = 0.9$).

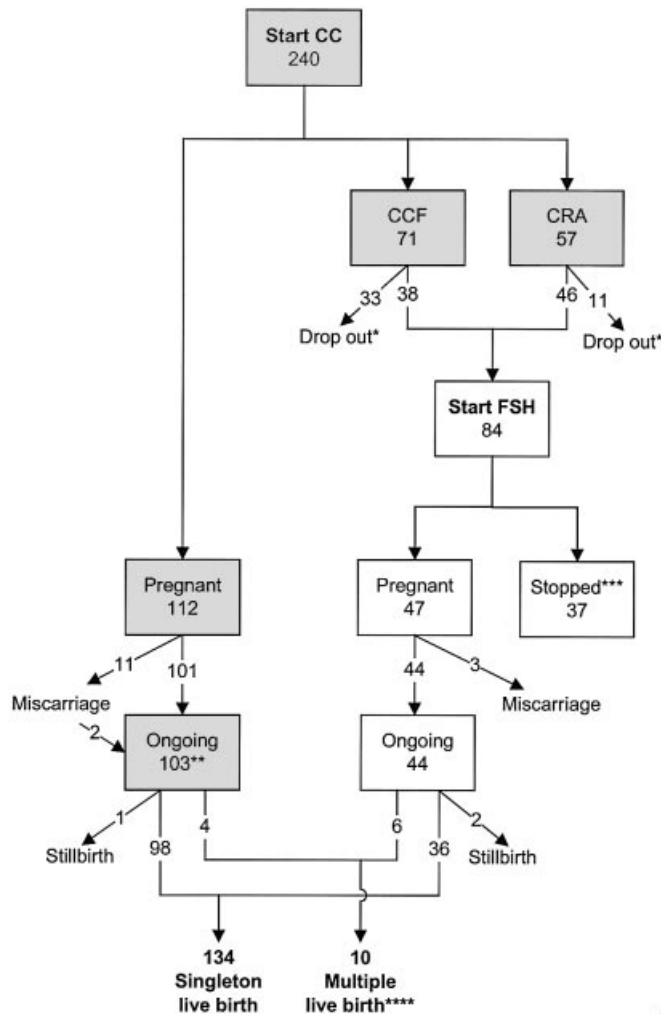


Figure 2. Outcomes during classical induction of ovulation in 240 normogonadotrophic anovulatory infertile women. *Drop-out after CC occurred in 44 patients. In 13 cases because the couple no longer had an active child wish, in seven cases because further treatment was found too burdensome, in nine cases because of medical problems, and in 15 cases because another therapy was started (IVF or IUI). **Two women with miscarriages following CC presented with an ongoing pregnancy after a subsequent second (one patient) or third (one patient) pregnancy with CC. ***FSH treatment was discontinued by 37 patients without their becoming pregnant. In three cases this was because the couple no longer had an active wish for a child, in one case because treatment was found too burdensome, in six cases because of medical problems, and in 22 cases because the couples started another therapy (IVF). Five couples had not yet planned another treatment at the end of follow-up. ****Multiple ongoing pregnancies with CC occurred four times, all of which were twins. With FSH, six multiple live birth occurred (four twins, one triplet, one quadruplet). CCF = CC failure (absence of pregnancy despite ovulatory CC cycles); CRA = clomiphene-resistant anovulation.

Discussion

The current prospective study demonstrated a cumulative chance of pregnancy resulting in singleton live birth of 71% within 2 years of classical ovulation induction (CC medication followed by exogenous FSH as second-line therapy) in a well-defined group of normogonadotrophic anovulatory infertile women (WHO group 2). The chance increased to 74% in case

multiple live births were included, and to 76% for all ongoing pregnancies. Of all live births, only 7% were multiple. These figures compared favourably with the outcome of alternative, more complex treatment algorithms (Child *et al.*, 2001; Heard *et al.*, 2002). Again, many studies involving alternative therapies are retrospective, and involve a small and selected group of patients. Moreover, singleton live birth is rarely used as an end-point. The above-mentioned observations are in favour of the contention that classical ovulation induction should remain the first-line treatment of choice in these women.

A prognostic model based on age of the woman, the insulin:glucose ratio and the duration of infertility predicted probabilities of pregnancy resulting in singleton live birth at 12 months ranging from 15 to 82%. The apparent c-statistic of the model was 0.64, and the optimism-corrected value was 0.61, indicating only a moderate discriminative ability. However, the model was able to identify patients with low chances for success applying classical ovulation induction who may therefore qualify for alternative first-line treatment options such as insulin-sensitizing agents, assisted reproductive technologies or laparoscopic ovarian surgery. For example, a probability lower than 30% was predicted in 25 (10%) out of the 240 patients. However, this cut-off value for low chance of 30% was arbitrarily chosen and other values may be just as valid. In a general infertility setting, the individual choice between several treatment options should depend on the chances of success, the complication rates, the burden to the patient, and costs. Taking these considerations into account, clinicians can choose any desired cut-off value for the chance of success of ovulation induction, and derive from Figure 3 how many patients will be identified as having a low chance of success. In previous studies by the present authors, with regard to outcome following CC-treatment alone, a history of amenorrhoea (as opposed to oligomenorrhoea) was found to be an adverse factor for ovulation (Imani *et al.*, 1998), but a positive factor for pregnancy once ovulation was achieved (Imani *et al.*, 1999). In the present study, amenorrhoea had no effect on outcome, indicating that probably both effects level out, as had been noted previously (Imani *et al.*, 2002a). Additional factors involved in the prediction of live birth following CC treatment included FAI, BMI and female age. Previously identified screening characteristics involved in the prediction of ongoing pregnancy following FSH ovulation induction included concentrations of both insulin-like growth factor-1 (IGF-I) and testosterone, as well as age (Mulders *et al.*, 2003).

Almost 50% of the CC-failure (CCF) patients did not proceed to FSH treatment and should be considered as drop-outs. In general, drop-outs may cause bias in the estimates of outcome when their prognosis differs from the patients who did not drop out ('selective drop-out'), as noted in a previous study (Imani *et al.*, 2002a). However, the screening characteristics that were predictive of success were similar between these patients and the patients who continued with FSH treatment. Only endogenous FSH levels were different, but since that screening characteristic was not associated with outcome in the prognostic model, it can be concluded that there is no

Table I. Clinical, endocrine and ultrasound screening characteristics (mean ± SD) of 240 normogonadotrophic anovulatory infertile women before initiation of classical ovulation induction (CC as first-line; FSH as second-line therapy), and separately for those women who did or did not achieve pregnancy resulting in singleton live birth

Screening parameter	Overall group (n = 240)	Pregnancy resulting in singleton live birth			P ^a	Multivariable Hazard ratio (95% CI) ^b
		No (n = 106)	Yes (n = 134)			
Age (years)	27.8 ± 4.3	28.7 ± 4.5	27.1 ± 4.0	<0.001	0.91 (0.87–0.95)	
Duration of infertility (years)	2.1 ± 2.1	2.5 ± 2.5	1.9 ± 1.6	0.02	0.91 (0.81–1.02)	
% Primary infertility (n)	75% (181)	72% (76)	78% (105)	0.17	–	
% Oligomenorrhoea (n)	78% (187)	79% (84)	77% (103)	0.9	–	
BMI (kg/m ²)	26.9 ± 6.2	27.7 ± 6.8	26.2 ± 5.6	0.02	–	
WHR	0.84 ± 0.10	0.85 ± 0.09	0.83 ± 0.10	0.28	–	
FAI (T × 100/SHBG)	6.2 ± 4.6	6.3 ± 4.7	6.2 ± 4.6	0.5	–	
FSH (IU/l)	4.7 ± 1.5	4.4 ± 1.4	4.8 ± 1.5	0.07	–	
LH (IU/l)	7.6 ± 4.3	7.2 ± 4.0	7.9 ± 4.6	0.04	–	
Estradiol (pmol/l)	240 ± 136	249 ± 139	233 ± 133	0.20	–	
Insulin:glucose ratio	3.4 ± 2.1	3.6 ± 2.4	3.2 ± 1.8	0.04	0.87 (0.79–0.96)	
% Polycystic ovaries (n) ^c	74% (178)	75% (79)	74% (99)	0.8	–	
Total motile sperm count ^d	68 (1–693)	52 (1–662)	80 (1–693)	0.9	–	

^aLog-Rank test.

^bHazard ratios for pregnancy resulting in singleton live birth with 95% Confidence Interval (CI) of the screening characteristics that were selected into the multivariable model. The formula (after shrinkage) to calculate the 12 month predicted probability for a new patient is:

$$1 - \text{EXP}\{-8.3 \times \text{EXP}[-0.072 \times \text{age (years)} - 0.107 \times (\text{insulin:glucose ratio}) - 0.069 \times \text{duration (years)}]\}$$

In this formula, 'EXP' denotes the standard exponential function, which must be applied twice.

^cPolycystic ovaries defined as mean ovarian volume ≥10.8 ml and/or mean follicle number per ovary ≤10 (van Santbrink *et al.*, 1997).

^dValues are median (range).

BMI = body mass index; FAI = free androgen index; SHBG = sex hormone-binding globulin; T = testosterone; WHR = waist-to-hip ratio

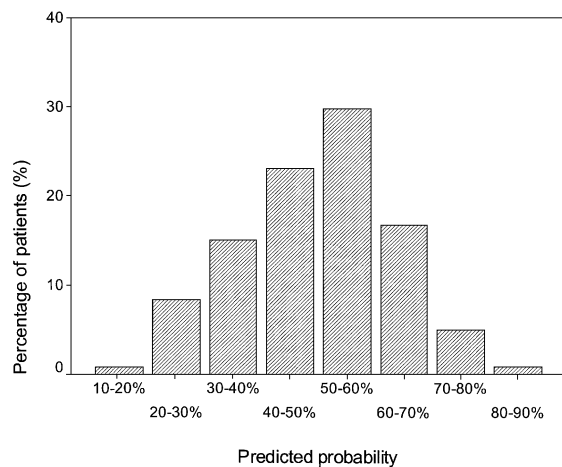


Figure 3. Distribution of predicted probabilities of pregnancy at 12 months resulting in singleton live birth following classical induction of ovulation in 240 normogonadotrophic anovulatory infertile women. Predictions by the Cox regression model with age, insulin:glucose ratio and duration of infertility.

indication of selective drop-out. The 37 women who did not reach the end-point following FSH treatment had received a median number of five treatment cycles, which was close to the standard number of treatment cycles according to protocol. Therefore they were not to be considered as drop-outs.

It is generally perceived that the majority of patients who qualify for exogenous gonadotrophins for ovulation induction suffer from PCOS (White *et al.*, 1996; Fauser and Van Heusden, 1997). However, scientific evidence to support this believe is scant. It has recently been established that 70% of women suffering from normogonadotrophic anovulation pre-

sent with polycystic ovaries as diagnosed by ultrasound, and 61% with endocrine signs associated with PCOS (i.e. hyperandrogenaemia) (Laven *et al.*, 2002). However, insulin resistance—as defined by an increased fasting insulin:glucose ratio—was observed in only 21% of women, whereas 44% were obese. All these clinical, endocrine and ultrasound abnormalities are involved in ovarian dysfunction in PCOS, and may therefore potentially predict response and outcome of ovarian stimulation by exogenous FSH (Balen *et al.*, 1993; Fulghesu *et al.*, 1997). It was surprising therefore to find that none of these features—except for insulin resistance—could be identified in the present study as a predictor of pregnancy in multivariable analysis. Moreover, in case the overall heterogeneous WHO 2 group was classified according to definitive PCOS or definitive non-PCOS (see Results section for details), again no differences in pregnancy chances could be observed. Not even obesity (defined as an elevated BMI) or abnormal fat distribution (indicated by a high WHR) was capable of predicting outcome, despite much emphasis in recent literature on the impact of excess bodyweight (Hamilton-Fairley *et al.*, 1992) and weight reduction (Norman *et al.*, 2002) on the success of fertility therapies in anovulatory women. These discrepancies clearly underline the need for properly designed, prospective studies in a well-defined patient population.

In conclusion, the results of the present study showed that, overall, normogonadotrophic anovulatory women have good prospects of singleton live birth when treated according to the classical induction of ovulation algorithm, including CC as first-line treatment followed by exogenous FSH as second line. Using a multivariate prediction model, individual women with chances for success (far) above or below average can be identified. For women with a predicted low chance, the use of alternative treatment strategies may be appropriate.

Acknowledgements

These studies were supported financially by 'VAZ/CVZ Doelmatigheidsonderzoek' project no. 99201, and 'Stichting Voortplantingsgeneeskunde Rotterdam' (SVG).

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Submitted on April 25, 2003; resubmitted on June 13, 2003; accepted on July 17, 2003