Fertility treatment in women with WHO type II ovulation disorder

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CHAPTER 2

TREATMENT STRATEGIES AND CUMULATIVE LIVE BIRTH RATES IN WHO-II OVULATION DISORDERS

Braam SC, de Bruin JP, Buisman ETIA, Brandes M, Nelen WLD, Smeenk JMJ, van der Steeg JW, Mol BWJ, Hamilton CJCM.

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ABSTRACT

Objective: To assess the live birth rate in women with WHO II anovulation and the proportion of women that need second or third line treatments if the initial therapy fails.

Study design: In this multicenter cohort study we included couples with unfulfilled child wish who were referred to three fertility clinics in the Netherlands and selected women with a WHO II ovulation disorder as the only final infertility diagnosis (n = 468).

Results: The cumulative live birth rate of the total group was 82% (383/468). The majority started with clomiphene-citrate as first-line treatment (n = 378) resulting in 180 (48%) live births. There were 153 couples (40%) who underwent a second-line treatment (recombinant-FSH or laparoscopic electrocoagulation of the ovaries, LEO) and 52 couples (14%) a third-line treatment (IVF/ICSI), resulting in 44% and 63% treatment dependent live births rates, respectively. Of all couples, 92 (20%) conceived naturally, 186 (40%) after clomiphene-citrate, 60 (13%) after recombinant-FSH, nine (2%) after LEO and 36 (8%) after IVF.

Conclusion: Subfertile women with a WHO II ovulation disorder have a good prognosis on live birth, and most did so after ovulation induction with clomiphene-citrate. If first-line ovulation induction has failed ovulation induction with gonadotrophins or IVF still result in a live birth in about half of the cases.
INTRODUCTION

In women with WHO-II anovulation, i.e. normogonadotropic normoestrogenic anovulation, clomiphene-citrate (CC) or letrozole is the treatment of first choice.\textsuperscript{1,2} CC-resistant women can be effectively treated with gonadotrophins or electrocoagulation of the ovaries, whereas the effectiveness of metformin and naltrexon is uncertain.\textsuperscript{3-5}

The effectiveness of the different individual treatment modalities for ovulation induction has been assessed in many studies.\textsuperscript{5-8} Most studies report on pregnancy chances per cycle or the cumulative pregnancy chances for a specific treatment modality. However, frequently patients will undergo multiple treatments; if first-line ovulation induction is unsuccessful, other treatment modalities follow. Little is known neither about the overall live birth rate of such treatment strategies, nor about the relative contribution to the pregnancy rate of the individual treatment modalities within a treatment strategy. Yet, this information is essential for doctors to counsel infertile women with ovulation disorders properly, specifically in an IVF dominated area.

The objective of our study was to get insight in the different types of treatment applied in women with a WHO II ovulation disorder and the contribution of each of these treatments to the overall live birth rate. Therefore, we studied an unselected cohort of infertile women with a WHO II ovulation disorder as single diagnosis.

MATERIAL AND METHODS

Study population and setting

We used two datasets. The first dataset was derived from a longitudinal multicentre cohort study for couples starting fertility treatment in three Dutch fertility clinics between 2002 and 2006 (n = 2476) as previously described by Brandes et al., 2011.\textsuperscript{9} From this study, we could include 319 women with WHO-II anovulation as a single subfertility diagnosis. The second dataset was derived from couples with anovulation WHO-II starting fertility treatment in the Jeroen Bosch Hospital between 2007 and 2009 (n = 149).

All women were treatment-naïve, and referred for unfulfilled childwish by a general practitioner, in general after failure to conceive despite 6–12 months of unprotected intercourse.\textsuperscript{10,11}
**Fertility work-up**

All couples underwent a standardized fertility work-up as described previously by Brandes et al. The diagnosis ovulation disorder was based on the absence of dominant follicle growth on serial ultrasound until cycle day 20 and on cycle length, making a distinction between mild oligomenorrhea (35–49 days), severe oligomenorrhea (49–180 days) or amenorrhea (>180 days). Regular cycles (<35 days) were also classified as ovulation disorder if serial ultrasound did not show an ovulation, if the midluteal progesterone seven days after the ovulation was less than 27 nmol/l or if the length of the luteal phase was less than 11 days regardless of the underlying pathology. The latter was classified as a subtle cycle disorder on the basis of a luteal phase defect. In cases of ovulation disorder serum levels of FSH, LH, oestradiol, total testosterone, prolactin and thyroid-stimulating hormone level were measured on cycle day 1–4 after a spontaneous or progestagen induced bleeding.

**Fertility treatment**

All couples were treated according to the national clinical guidelines of the Dutch Society of Obstetrics and Gynaecology. Women with either overweight or underweight were made aware of the importance of weight reduction or weight gain by means of lifestyle changes.

In WHO-II anovulatory women, CC was the first-line treatment. Women received CC 50 mg up to 150 mg a day from cycle day 3 through 7. In case of absent response Metformin or Naltrexone was added in a subsequent cycle. Ovulation was detected by ultrasonographic monitoring and/or a timed midluteal progesterone level. Once women ovulated on a certain CC dose, they continued this dose in subsequent cycles. Patients with a luteal phase defect were also treated with CC 50 mg.

In case of a mucus problem, intra uterine insemination (IUI) was added. A mucus problem was quantified as a negative postcoitum test in an ovulatory CC cycle. Women with an imminent ovarian failure (defined as a basal FSH >10 IU/l) were treated with recombinant-FSH (rFSH) or were offered an IVF/ICSI treatment directly.

Second-line treatment was started if women were clomiphene resistant. Women were then counseled either for ovulation induction with rFSH or laparoscopic electrocautery of the ovaries (LEO). The final choice between rFSH and LEO was based on the preference of the patient.

Second-line treatment with rFSH was also started in case of CC failure, defined as no pregnancy after six to nine ovulatory CC cycles. To prevent multifollicular growth, a
chronic low-dose step-up regimen was applied. IUI was added after six cycles of rFSH, for three cycles. Cycles were cancelled if there were more than two dominant follicles in ovulation induction cycles and more than three dominant follicles in IUI cycles.

Finally, IVF was offered as a third-line treatment if couples were not pregnant after at least 12 ovulatory cycles or in cases with repeated difficulties in attaining monofollicular growth by hormonal treatment.

Drop-out and follow-up

All couples were followed until they achieved an ongoing pregnancy resulting in a live birth or until three years after entering the fertility clinic. The decision to stop fertility treatment, defined as drop-out, could be made either on patients or doctors’ initiative. Ongoing pregnancy was defined as positive heartbeat at ultrasonography at 10 weeks of gestational age. Live birth was defined as a living child at delivery.

Outcome measures

Outcome measure was the cumulative overall live birth rate. We registered baseline characteristics and mode of conception. Secondary outcomes were clinical pregnancy, miscarriage, ectopic pregnancy and multiple pregnancy. We also studied ovulation rates, the impact of different treatments, drop-out rates and details about consecutive treatments and patient flow. Furthermore, we analyzed the number of treatment cycles and success rates. For CC, we reported the dosage at which ovulation was established as well as the percentage of women not responding to the therapy (CC-resistance and CC-failure).

Statistical analysis

Characteristics of patients with and without a live birth were compared using non-parametric tests, Mann Whitney U and Chi Square tests. Actual cumulative pregnancy rates leading to live birth were used instead of survival analyses methods. A p-value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for the Social Sciences 22.0 software for windows.
CHAPTER 2

RESULTS

Study population

From the datasets, we identified 538 women with ovulation disorder as the only final diagnosis. After exclusion of four women with WHO-I anovulation, 21 women with WHO-III anovulation, 15 women with hyperprolactinaemia (2.8%) or hypothyroidism and 30 women with missing data, 468 women (87%) with a WHO-II ovulation disorder remained for analysis. Baseline characteristics are shown in Table 1. The median female age was 29 years with a duration of subfertility of 12 months. 75% of the couples had a primary infertility (352/468).

Overall outcome

Of the total group of 468, 405 women (87%) had conceived within 3 years. Among the 405 women who conceived, 66 (16.3%) had a miscarriage in the first pregnancy, and 21 of these patients never achieved an ongoing pregnancy, be it with or without more miscarriages. There were 384 women who had at least one ongoing pregnancy (82%), resulting in 383 (81.8%) of them to deliver a live born baby. One woman had her pregnancy terminated because of congenital anomalies.

Women who eventually had a live birth had a significant lower age at presentation (median 28.9 vs 31.1, p < 0.001), and shorter duration of subfertility (median 11.0 vs. 16.5 months, p = 0.005) compared to women without a live birth (Table 1).

![Table 1. Patient characteristics, WHO II ovulation disorder group and live birth or no live birth.](image)

<table>
<thead>
<tr>
<th></th>
<th>Total n = 468</th>
<th>Live birth n = 383 (81.8%)</th>
<th>No live birth n = 85 (18.2%)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female age, median (range)</td>
<td>29.0 (18–44)</td>
<td>28.9 (18–40)</td>
<td>31.1 (18–44)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Duration of subfertility in months, median (range)</td>
<td>12.0 (0–70)</td>
<td>11.0 (0–70)</td>
<td>16.5 (1–69)</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Female BMI (range)</td>
<td>23.3 (16–48.6)</td>
<td>23.3 (16–48.6)</td>
<td>23.4 (17–44)</td>
<td>p = 0.467</td>
</tr>
<tr>
<td>Prim. infertility n (%)</td>
<td>352 (75.2%)</td>
<td>290 (82.6%)</td>
<td>62 (72.9%)</td>
<td>p = 0.592</td>
</tr>
<tr>
<td>Sec. infertility n (%)</td>
<td>116 (24.8%)</td>
<td>93 (24.3)</td>
<td>23 (27.1%)</td>
<td></td>
</tr>
<tr>
<td>Semen quality (Total Motile Count, range)</td>
<td>77.3 (4–947)</td>
<td>74.9 (11–650)</td>
<td>83.0 (4–947)</td>
<td>p = 0.247</td>
</tr>
</tbody>
</table>

Female age in years at time of first visit, duration of subfertility in months at time of first visit. BMI, body mass index (kg/m²); TMSC, total motile sperm count (10⁶). *Univariate analysis, comparison between ‘live birth’ and ‘no live birth’.
The cumulative live birth rate in the total WHO-II ovulation disorder group is shown in Fig. 1. There were 186 live births after treatment with CC (40%), including eight live births after CC combined with IUI. Also, 92 women (20%) had a live birth after a spontaneous conception, 60 (13%) after rFSH, including 16 pregnancies conceived by rFSH combined with IUI, nine live births after LEO (2%), while 36 couples (8%) conceived by IVF. Among the 384 ongoing pregnancies, there were 361 singleton and 23 twin pregnancies (6%). The 13 born twins were conceived by CC (13/186, 7.0%), four after rFSH (4/60, 6.7%), four after IVF/ICSI (4/36, 11%), while two twins occurred spontaneously (2/92, 2.2%). Within this multiple pregnancy group, there was one stillbirth of one of the children.

Figure 1. Cumulative live birth rate and mode of conception for the WHO-II ovulation disorder group, from day of first visit. CC, clomiphene-citrate; rFSH, recombinant FSH; IVF/ICSI, assisted reproductive treatment including IVF and ICSI; LEO, laparoscopic electrocoagulation of the ovaries.

Treatment strategies

Of all women in the WHO-II group (n = 468), 46 conceived spontaneously during fertility work up while 14 turned out to be pregnant soon after their first consultation (n=14). There were 17 women who were never treated and dropped out of the program without conception.
**First-line treatment**

The vast majority (n = 378) of couples started with CC treatment (81%). In the other 13 women, CC treatment was not started because of an elevated female age and/or an imminent ovarian failure. Of these patients, 8 started directly with rFSH and 5 directly with IVF. The treatment flow of all patients who started with CC is shown in Fig. 2. IUI pregnancies were grouped under the associated ovulation induction treatment, be it either CC or rFSH.

In the 378 WHO-II patients who started a CC treatment, 180 patients had a conception leading to live birth. On average, 3.1 CC cycles were needed to achieve ongoing pregnancy (range 1–13). Ongoing pregnancy rates were 12% (44/369), 14% (43/303), 18% (41/231), 12% (18/147), 8% (8/103) and 10% (8/79) in cycle 1 till 6, respectively. This resulted in cumulative pregnancy rate of 34.6% (128/369) after three cycles and 43.9% (162/369) after 6 cycles.

Table 2 shows the ovulatory status of women treated with CC. Overall, there were 282 women out of the 378 women (75%) who ovulated of whom 172 had a live birth (61%) after intercourse and another eight after IUI (1%). Eleven women received CC 25 mg a day because multifollicular growth on CC 50 mg, but they were included in the CC 50 mg group for our analyses. Of 16 women, details on CC dosage were missing leading to exclusion of this part of the analysis. There were 105 women who started directly with CC 100 mg a day because of amenorrhea. A total of 35 women (9% of the total CC group) remained anovulatory, after Naltrexone or Metformin was added.

**Second-line treatments**

In case of CC resistance, women could opt for rFSH or LEO as second-line treatment. Some women switched between these therapies. In total, 144 women underwent treatment with rFSH, leading to 60 live births (42%). Of them 21 women (35%) conceived in their first rFSH cycle. On average, women needed 2.9 rFSH cycles to achieve an ongoing pregnancy (range 1–12, missing value n = 2). There were 127 women who had rFSH after a previous unsuccessful CC treatment. Thirty-four women received rFSH because of CC resistance leading to 17 live births (50%), including three live births after rFSH combined with IUI. Furthermore, 89 women received rFSH because of a CC failure which resulted into 37 live births (42%), including 13 live births after rFSH combined with IUI. Of four women details on CC resistance or failure was missing.
**LEO**

In total, 34 women started LEO as a second-line treatment because of CC resistance leading to nine live births (9/34, 26%). They started LEO as a second-line treatment because of CC resistance. Of these 34 women, 26 started LEO directly after CC treatment, while eight women were being treated with rFSH first. Of the 25 women who did not conceive after LEO alone, 16 women underwent a CC treatment again, of whom five conceived and gave birth. Eight women had a rFSH treatment, leading to three live births. The cumulative live birth rate after LEO was 50% (17/34).

**Third-line treatment**

**IVF/ICSI**

In total, 60 women underwent IVF or ICSI leading to 36 live births (60%). Out of the 60 women, five women started IVF treatment without prior first or second line treatment and three started IVF after first line treatment only, all because of higher female age or imminent ovarian failure. Of 11 women who started IVF after undergoing LEO as a second-line treatment (with or without rFSH), six conceived leading to live births (54%). Of 38 women who started IVF after undergoing rFSH as second-line treatment, 23 had a live birth (61%).

**Table 2. Ovulatory status and live birth rate of WHO-II patients treated with CC.**

<table>
<thead>
<tr>
<th></th>
<th>N (patients)</th>
<th>Ovulatory (patients)</th>
<th>Live birth (% of ovulatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC 50 mg/d</td>
<td>242</td>
<td>144 (60%)</td>
<td>89 (62%)</td>
</tr>
<tr>
<td>CC 100 mg/d</td>
<td>211</td>
<td>97 (46%)</td>
<td>51 (53%)</td>
</tr>
<tr>
<td>CC 150 mg/d</td>
<td>88</td>
<td>39 (44%)</td>
<td>19 (49%)</td>
</tr>
<tr>
<td>CC/Metformin or Naltrexone</td>
<td>62</td>
<td>27 (44%)</td>
<td>17 (63%)</td>
</tr>
</tbody>
</table>

*105 patients started with CC 100 mg in their first cycle*
Figure 2. Treatment strategies and outcome in WHO-II patients who started with CC.

**Cycle length**

Table 3 shows the influence of cycle length on the overall outcome. Information on cycle length was not available in six women. Spontaneous pregnancy occurred in all cycle length groups, respectively 20% and 15% in the severe oligomenorrhea and amenorrheic group.
Drop-out

In total, 63 women dropped out during or after fertility treatment. Of them, 25 women dropped out before undergoing IVF. Furthermore, 14 did not conceive after IVF and discontinued further treatment.

Table 3. Mode of conception per cycle length category.

<table>
<thead>
<tr>
<th>Cycle length</th>
<th>Total (n = 468*)</th>
<th>Spontaneous conception</th>
<th>CC</th>
<th>rFSH</th>
<th>IVF</th>
<th>LEO</th>
<th>No live birth/drop out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtle cycle disorder</td>
<td>38 (11%)</td>
<td>4 (11%)</td>
<td>17 (45%)</td>
<td>5 (13%)</td>
<td>4 (11%)</td>
<td>- (21%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>(21–35 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild oligomenorrhea</td>
<td>118 (25%)</td>
<td>29 (25%)</td>
<td>43 (36%)</td>
<td>12 (10%)</td>
<td>6 (5%)</td>
<td>1 (1%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>(35–49 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe oligomenorrhea</td>
<td>175 (20%)</td>
<td>35 (20%)</td>
<td>77 (44%)</td>
<td>19 (11%)</td>
<td>14 (8%)</td>
<td>4 (2%)</td>
<td>26 (15%)</td>
</tr>
<tr>
<td>(49–180 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>131 (15%)</td>
<td>19 (15%)</td>
<td>55 (42%)</td>
<td>20 (15%)</td>
<td>12 (9%)</td>
<td>4 (3%)</td>
<td>21 (16%)</td>
</tr>
<tr>
<td>(&gt;180 days)</td>
<td></td>
<td></td>
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</tbody>
</table>

*aInformation on cycle length was not available in six patients.

COMMENT

In this cohort study among women with a WHO II ovulation disorder, the overall chance on a pregnancy was more than 80%. Most pregnancies were induced by CC, although a considerable proportion still conceived spontaneously. With ovulation induction with CC, rFSH or LEO pregnancies continued to occur until 18 months after the first visit.

The strength of this study is that it was performed in an unselected cohort. The follow-up rate in our study was high resulting in reliable overall live birth rates. This information can be useful for women as well as for doctors working in reproductive medicine. Insight is also given in the proportion of women that has to undergo further treatment steps if the initial treatment fails.

Our study is an observational study with a non-experimental design and this also carries some hazards. It did not follow one single protocol, but rather described daily clinical practice within the boundaries of the Dutch national guidelines, thus resulting in bias-by-indication and influenced partly by women’s own preferences.
First-line treatment was with the use of CC. In case of no response to the initial dose of CC, increasing dosages and adding Metformin led to an ovulatory cycle in approximately 40% of cases. The cumulative pregnancy rate after six ovulatory cycles was 43.9%. This is in line with earlier studies and this simple approach with oral medication is a useful step in the treatment regimen.\textsuperscript{16,17}

Of all women suffering from WHO-II anovulation 40% under- went a second-line treatment with either rFSH or LEO resulting in a cumulative live birth of 42% and 50% respectively. Fourteen% of women proceeded to third-line treatment with IVF/ICSI resulting in 60% cumulative live birth. Live birth rates of rFSH treatment after CC failure or CC resistance were comparable. Furthermore, LEO has shown to be effective in restoring ovulation in almost half of the women who chose for this treatment option. The spontaneous live birth rate after LEO without further ovulation induction (26%) in our study was slightly lower than previously described in literature (34%).\textsuperscript{7} The contribution of IVF to the overall live birth was low, but the chances of live birth were comparable to IVF results performed in couples with other infertility diagnoses.\textsuperscript{18}

Our data indicate that most women with WHO-II anovulation conceived with CC, confirming the role of CC as first line therapy.\textsuperscript{8,16} CC is much cheaper than gonadotrophins and is a simple and patient friendly approach. The cycle fecundability of CC is around 12% in our study with a cumulative live birth rate of approximately 35% after 3 cycles already. Thus the therapeutic effect of this simple drug should not be underestimated. Furthermore the risk of multiple pregnancy is lower in CC than in rFSH. Therefore, although the cycle fecundability in rFSH is higher, in our opinion there is no reason to replace CC with gonadotrophins as first step as suggested in the literature.\textsuperscript{19}

The substantial number of spontaneous pregnancies indicates that despite irregular cycles some women still have late ovulations. We monitored women with serial ultrasound but stopped monitoring if on cycle day 20 still no dominant follicle above 12 mm was visible. It is also known that in women with a WHO-II anovulation, in particular PCOS, menstrual cycle can restore and spontaneous pregnancies can occur at later reproductive ages.\textsuperscript{20,21}

Most spontaneous pregnancies occurred during fertility work up, but a substantial part also occurred even after longstanding fertility therapy. Women with mild oligomenorrhea had the highest spontaneous live birth rate, women with ovulation disorders despite regular cycles had the lowest. The more irregular the cycle, the better the chances to conceive after fertility treatment.
More recently aromatase inhibitors are introduced as a first line infertility treatment in women with WHO II anovulation. There is increasing evidence that letrozole might result in equal or even better pregnancy outcomes than CC. Also, management of anovulation can include lifestyle changes. In the course of time, more attention has been paid to this. Mutsaerts et al. showed that natural conception occurs more frequent and the number of infertility treatments is lower in women who follow a lifestyle intervention aimed at weight loss.

Further research will be needed to determine patient preferences and cost-effectiveness for CC and rFSH treatments, particular focusing on the role of the moment to switch from CC to other treatments. The M-ovin trial recently compared CC versus rFSH as well as the additional role of intra-uterine insemination after six ovulatory cycles with CC. The results have shown that extended ovulation induction with gonadotrophins significantly increased the live birth rate compared to clomiphene citrate. Addition of IUI did not significantly increase the live birth rate compared to timed intercourse.

In WHO-II women, in case of CC resistance, different strategies were applied in different sequences, but the majority started with gonadotrophins. Whether women underwent LEO, rFSH or both, at the end, prospects on live birth are similar. We recently showed that LEO results in a lower number of women needing gonadotrophins (thus potentially lowering the twin rate), a larger number of women that return to spontaneous ovulation and therefore more couples with a second or third child. In women with clomiphene-resistant PCOS, laparoscopic electrocautery of the ovaries results in significantly lower costs per live birth than ovulation induction with gonadotrophins for an at least equal effectiveness.

Treatment related twin pregnancies were proportionally highest after IVF, followed by treatment with gonadotrophins and CC treatment. However, in recent years the use of single embryo transfer in IVF has substantially increased, compared to the years from which the IVF cycles in this study originate.

In summary, overall success rate in couples with a WHO II ovulation disorder is high and CC, in our view, remains the treatment of first choice. In case of absent response on CC, higher dosages and adding Metformin give good prospects on a live birth. About 40% of the women need a second-line treatment. Both FSH and LEO can be considered since they have a comparable overall outcome. Finally, IVF is the third-line treatment in WHO-II ovulation disorder. Only one in six to seven women needs IVF with still good chances for a live birth.
REFERENCES


