Outcome of stimulated in vitro fertilisation (SIVF) using clomiphene citrate and human menopausal gonadotropin in different infertility groups

F. Zayed, *M.R.C.O.G., M.D.*

Sheffield Fertility Centre and Univ. Dept. of Obstetric & Gynaecology, Jessop Hospital for Women, Sheffield, UK
Jordan University of Science and Technology, Dept. of Obstetrics & Gynaecology, Jordan

Summary

A prospective study was undertaken to evaluate the efficacy of stimulated in vitro fertilisation (SIVF) using Clomiphene Citrate and hMG in different infertilities. The analysis was applied to the first 81 cycles over a period of 9 months in the years 1994-1996 in Sheffield Fertility Centre (SFC). The female patients included in this study were under 40 years of age, and their FSH and LH values were <10IU/L. Mild and moderate male factor infertilities were included.

For tubal factor infertility 16 cases were included with an implantation rate of 0%. The unexplained factor infertility included 33 cases with an implantation rate per embryo transfer (ET) of 41%. For male factor infertility there were 18 cases with an implantation rate per ET of 42%. Out of 3 cases in the ovulatory factor group none reached ET with 0% implantation. For multiple factor infertility 11 cases were included with a 0% implantation rate. The overall implantation per embryo transfer was 27%, while the implantation per cycle started was 15%.

We conclude that there are certain infertility factors, i.e. unexplained infertility and mild male factor, which can have good results in IVF using CC/hMG only.

Key words: Stimulated in vitro fertilization (SIVF); Clomiphene citrate; Human menopausal gonadotropin.

Introduction

The birth of Louise Brown, the first child born from natural-cycle in vitro fertilization (NIVF), [1] heralded the genesis of a new treatment which brought hope to countless unfortunate infertile couples. Stimulated in vitro fertilization (SIVF) when replaced by NIVF, improved pregnancy rates mainly as a result of transferring several embryos [2, 3].

Until recently the most common ovarian stimulation regimen used in assisted conception was clomiphene citrate (CC) and exogenous human menopausal gonadotrophin preparations (HMG), where CC as an oestrogen antagonist stimulates the recruitment of a number of small follicles and hMG sustains the growth of this cohort of recruited follicles. The best results using this combination have been achieved in those units where extensive monitoring of endogenous luteinizing hormone (LH) secretion in the late follicular phase is employed. Macnamee *et al.* [4] showed that if LH was detected and supported with HCG administration for timing the egg recovery, then the patient's clinical performance through assisted conception is not compromised. A recent major step in preventing these unwanted phenomena came with the introduction of gonadotrophin releasing hormone analogues (GnRH-a) which abolish the LH surge [5].

The use of CC/hMG induction of ovulation is outmoded in the IVF protocols, however due to the rise in the price of the high purity FSH which is replacing the hMG products, we aimed to study the reuse of CC/hMG in IVF and to assess and compare the various infertility factor outcomes in this prospective study.

Materials and methods

The female patients included in this study were under 40 years of age, and had FSH and LH values of <10IU/L. Mild and moderate male factor infertility were included (normal semen analysis when density >20 millions/ml, motility (I-II)>30%, morphology>25%, Couples with mild male factor (PI) had only one and the moderate male factor had two low parameters in the semen analysis of either a density between 5 and 20 million sperm/ml, a motility (grade I+II) between 5 and 30%, or the normal forms between 5 and 25%.

Ovulation was induced by using clomiphene citrate from day 4 to day 8 of the cycle. Before that, basal FSH, LH, and E2 blood tests were performed at day 2 of the cycle and the treatment was carried on if both FSH and LH were performed at day 2 of the cycle and the treatment was carried on if both FSH and LH were less than 10 IU/L. Patients attended the clinic on day 7 for blood tests of E2 and ultrasound checks for follicles, and accordingly hMG was given IM in doses of 150 IU daily from day 7 to day 9. On the 10th day patients again had blood tests for E2 and ultrasound follicular growth checks and continued hMG daily, being monitored with blood tests for E2 and LH. On alternate days ultrasound checks were done and accordingly the dose of hMG was individually adjusted to the ovarian response till at least 3 follicles of more than 17 mm were achieved with at least 1000 pmol/l E2 for each follicle provided no excessive ovarian stimulation and no premature LH surge occurred. However if a LH surge was detected, timing of HCG followed a designed table plotted from previous experience [6]. HCG 10,000 IU was given IM and egg recovery was planned at 34-36 hours. Ultrasound guided needle aspiration transvaginally

Revised manuscript accepted for publication January 25, 1999

was then performed under sedation, Eggs were given to the embryologists to inseminate with the husband's prepared semen and the development and cleavage was monitored. After 48 to 72 hours no more than 2-3 embryos were transferred transcervically. Patients were given luteal support with progesterone pessaries from d14 of embryo (ET) till a transfer pregnancy test (B-HCG) was performed.

Data were analysed using statistical analysis where pregnancy rates were included (clinical, abortion, ectopic, and biochemical). Implantation was considered as B-HCG levels above 10 IU/L, with a live birth after 28 weeks' gestation. Statistical analysis with the Student's t-test and Mann-Whitney test were used when appropriate and on discrete results the X^2 was used and also the Fischer exact test when appropriate.

Results

The analysis was applied on the first 81 cycles over a of period of 9 months in Sheffield Fertility Centre (SFC). The preliminary results showed (Table 1) that in tubal factor infertility in 16 cases there was 71% of good quality eggs out of the 76 eggs collected, 61% were fertilized and on 10 occasions embryos were transferred with an implantation rate of 0%. In the unexplained factor infertility in 33 cases 174 eggs were retrieved and there was 56% of good quality eggs with a fertilization rate of 46%; on 22 occasions embryos were transferred with an implantation rate per cycle started of 27%. In the male factor infertility in 18 cases there was 64% of good quality eggs out of the 89 eggs collected; the fertilization rate was 23% and on 7 occasions the embryos were transferred with an implantation rate per cycle started of 17%. In the ovulatory factor group in 3 cases there was 70% of good quality eggs out of 23 eggs collected and the fertilization rate was 44%; none reached ET with a 0% implantation. In the multiple factor infertility in 11 cases 60 eggs were retrieved and only 72% were good quality eggs; the rate of fertilization was 47% with embryos transferred on 6 occasions but with a 0% implantation rate.

In this study (Table 2) 81 cases of SIVF were started, 12 cycles were abandoned and 12 cycles ended in no fertilization, 6 in the male factor, 2 in the tubal factor, and 4 in the unexplained factor. However, two cycles had hyperstimulation where the eggs were all frozen for further management with frozen embryo replacement. The overall implantation per embryo transfer was 27%, while the implantation per cycle was 15%.

Table 1. — *Outcome of SIVF.*

Diagnosis (n)	No.eggs (E/C)	Good eggs (%)	Fert. egg (%)	Impl/ET	Impl/CS
Unexpl(33)	174(6.7)	98(56)	80(46)	9(41)	27%
Tubal(16)	76(6.3)	54(71)	46(61)	0%	0%
Male(18)	89(6.8)	57(64)	20(23)	3(42)	17%
P1(6)	*17*	*13*	*6(46)*	*2(67)*	*33%*
Multiple(11)	60(7.5)	43(72)	28(47)	0%	0%
Ovulat(3)	23(7.7)	16(70)	10(44)	0%	0%
Total(81)	422(6.8)	268(64)	184(44)	27%	15%

Male factor = mild and moderate male factor
P1=mild male factor
Pregnancies: (12) = 9 clinical pregnancies (8 ongoing and 1 abortion) and 3 biochemichal

Table 2. — *Results of the cycles started in SIVF.*

	Unexpl (%)	Tubal (%)	Male (%)	Multiple (%)	Ovul (%)	Total (%)
Cycle started	33	16	18	11	3	81
Cycle reached Aspirat.	26(79)	12(75)	13(72)	8(73)	3(100)	62(77)
Cycle reached ET	22(67)	10(63)	7(39)	6(55)	0	45(56)
Abandoned cycle	3	4	2	3	0	12
Converted to IUI	4	0	3	0	0	7
Failed fertilization	4	2	6	0	0	12
Cycle Freeze all	0	0	0	2	1	3
Pregnancy	9	0	3	0	0	12

Discussion

Up-to-date the information available on the utilisation of a GnRH-a/hMG combination for ovulation induction within an IVF programme does appear to have some advantages over the clomiphene citrate CC/hMG regimen by improving the treatment cycle management. The personnel in an IVF centre can more effectively control the timing of egg retrieval and the daily routine is restricted to normal working hours; however the usage of hMG is doubled or tripled, so it is much more expensive than the CC/hMG regimen and may be not necessary in all indications for IVF as in ovulatory cycling women, i.e. unexplained infertility [7].

In this prospective study the number of eggs obtained in this method of ovarian stimulation was similar in all the types of infertility included in the study ranging between 6.3 eggs/cycle in the tubal factor to 7.7 eggs/cycle in the ovulatory factor infertility. The percentage of the good quality eggs were also similar in the tubal, multiple and ovulatory factor infertility (71%, 72%, 70%, respectively) where the unexplained and the male factor infertility had less good quality eggs (56% and 64%, respectively) but with no significant difference. However, the fertilization rates were similar in the ovu-

Table 3. — *Comparison of different SIVF treatments and their outcomes at SFC in (%).*

	SIVF(143) GnRH-a+hMG	SIVF(81) CC+hMG
Cycles reaching aspiration	84	77
Cycles reaching ET	73	56
Cycles with fertilization	78	75
Preg/ET	38	27
Clinical preg/ET	30	20
Preg/cs	28	15
Clinical preg/cs	22	11

latory, unexplained, and multiple factor infertility (44%, 46%, 47%, respectively) where in the tubal factor the fertilization rate was higher (61%) but with no significant difference from the above. However, the fertilization rate of the total male factor infertility was significantly lower (23%) which was expected, but when mild male factor was considered alone the fertilization rate was 46% which is similar to the above factors.

The implantation rates per ET were 0% in the tubal, multiple and ovulatory, but the implantation per ET was 41% in the unexplained factor and 42% in the male factor infertility. Although the numbers are too small to generalise it seems that once fertilization occurred in both groups (unexplained and male) the implantation rate was good and with no problems to hinder the implantation, whereas in the other groups in spite of having similar good quality eggs and similar and even better fertilization than the male and unexplained factor infertility no implantation occurred.

In total the implantation rate per ET for all groups studied was 27% with 15% implantation rate/cycles. Comparing those results with the similar SIVF using GnRH-a and hMG at SFC which were 38% and 28% respectively, shows that the pregnancy rate is roughly doubled when GnRH-a is used and clomiphene citrate is not. It also shows that not all cases of infertility need the latter ovarian stimulation.

The implantation rate was 0% in the ovulatory but it is difficult to make any conclusions from 3 cases only, it was also 0% in the tubal factor which may have had deleterious effects on the implantation from the combination of tubal fluid and CC.

The main problem with the protocol of CC/hMG induction is the premature LH surge in about 30% of patients, either undetected and ovulation occurs before egg retrieval, or even if the eggs were retrieved they would be poor quality so as not to fertilize or be incompatible for implantation [8, 9]. However, in this study those effects did not compromise the outcome in the unexplained and mild male factor infertility.

In spite of the small numbers included in this study we have demonstrated that there are certain infertility factor patients that can get good results in IVF using CC/hMG only, i.e., unexplained infertility and mild male factor.

Acknowledgement

I would like to thank all colleagues and staff at SFC for their cooperation; especially Dr. E. A. Lenton and Professor I. D. Cooke.

References

[1] Steptoe P. C., Edwards R. G.: "Birth after the implantation of human embryo". *Lancet*, *2*, 366, 1978.

[2] Wood C., McMaster R., Rennie G., Trounson A. and Leeton J.: "Factors influencing pregnancy rates following in vitro fertilization and embryo transfer". *Fertil. Steril.*, *43*, 245, 1985.

[3] Testart J., Belaisch-Allart J. and Frydman R.: "Relationship between embryo transfer results and ovarian response and in vitro fertilization rate: analysis of 186 human pregnancies". *Fertil. Steril.*, *45*, 237, 1986.

[4] Macnamee M. C., Edwards R. G. and Howles C. M.: "The influence of stimulation regimes and luteal phase support on the outcome of IVF". *Hum. Reprod.*, *3* suppl., 43, 1988.

[5] Palermo R., Amodeo G., Novat D., Rosenwaks Z. and Cittadini E.: "Concomitant gonadotrophin-releasing hormone agonist and menotropin treatment for the synchronized induction of multiple follicles". *Fertil. Steril.*, *49*, 290, 1988.

[6] Lenton E. A., Cooke I. D., Hooper M., King H., Kumar A. and Verma S.: "In vitro fertilization in the natural cycle". *Balliere's Clin. Obstet. Gynaecol.*, *6*, 229, 1992.

[7] Sengoku K., Tamate K., Takaoka Y., Morishita N., Ishikawa M.: "A randomized prospective study of gonadotrophin with or without gonadotrophin-releasing hormone agonist for treatment of unexplained infertility". *Hum. Reprod.*, *9*, 1043, 1994.

[8] Stanger J. D. and Yovich J. L.: "Reduced in vitro fertilization of human oocytes from patients with raised basal luteinizing hormone levels during follicular phase". *Br. J. Obstet. Gynaecol.*, *92*, 385, 1985.

[9] Homburg R., Armar N. A., Eshel A., Adams J. and Jacobs H. S.: "Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome". *Br. Med. J.*, *297*, 1024, 1988.

Address reprint requests to:
FAHEEM ZAYED, M.D.
Associate Professor in Obstetrics and Gynaecology
Jordan University of Science and Technology
P. O. Box 962106
Amman-11196-Jordan