



AN EVALUATION OF THE USE OF G-CSF AS AN ADJUNCT TO IVF IN WOMEN WITH MULTIPLE PREVIOUS FAILED ATTEMPTS WITH IVF

Dr Tasneem Mohamed, Prof. Yasmin Adam, Dr Mohamed Iqbal Cassim

INTRODUCTION

Infertility is a common presenting problem in the practice of Obstetrics and Gynaecology with approximately one in six couples being affected.¹ In Vitro Fertilisation (IVF) is a procedure commonly used in the management of infertility. For some, pregnancy by standard IVF is still not achieved, even if ovulation induction and embryo development is successful. This may be due to defective implantation. A thin endometrium is associated with implantation failure. Studies show that improved endometrial thickness increases the probability of successful IVF.^{2,3}

BACKGROUND

G-CSF and its use in Assisted Reproductive Technology (ART)

Granulocyte Colony Stimulating Factor ("G-CSF") was initially identified as a growth factor for neutrophils. In recent years, many additional effects of G-CSF on cell mediated immunity have been uncovered.⁴ G-CSF has been shown to have an important role to play in human reproduction and this has been the basis for studies which have combined the use of G-CSF and ART. G-CSF through its action on neutrophilic granulocyte proliferation and macrophages of decidual cells has been shown to positively affect implantation.^{5,6}

The effect of endometrial thickness on fertility

The measurement of endometrial thickness is an indirect measure of endometrial receptivity and is measured by transvaginal ultrasound.^{7,8} There is no evidence to state what is considered an exact ideal endometrial thickness, but it is thought to be between 7mm and 14mm. There are studies that show that an endometrial thickness of < 7mm or > 14mm correlates negatively with implantation rates.^{7,9}

OBJECTIVES

To evaluate the effects of G-CSF as an adjunct to IVF in the treatment of infertility. The study looked at the influence of G-CSF on achievement of pregnancy as well as its effects on the endometrium.

METHODS

This was a retrospective cross-sectional study of a subgroup of women attending BioART Fertility Centre, who had two or more failed IVFs previously. These women underwent a procedure of transcervical instillation of G-CSF in addition to their IVF protocol. Endometrial thickness was not a criterion for its use.

- There were a total number of 49 women reviewed. Their ages ranged between 28 and 51.

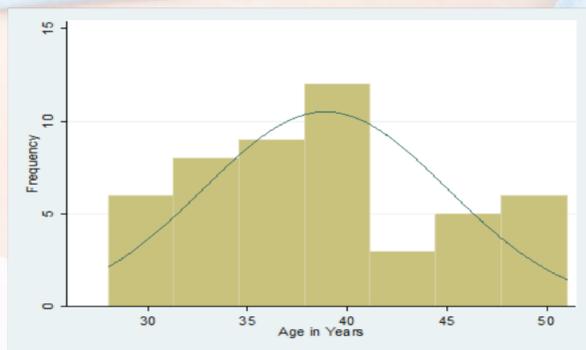
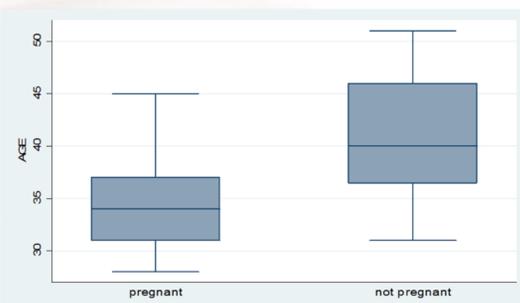


Table 3 showing comparison of pregnancy outcomes related to demographics, fertility history and cycle specific data

	Total N=49	Pregnancy N=17 (34.69%)	No pregnancy N=32 (65.31%)	p-value
Demographics and fertility history				
Age – mean (SD)	38.90 (± 6.11)	34.94 (± 1.15)	41 (± 5.76)	0.0005
Age – median (IQR)	–	34 (31 – 37)	40 (36.5 – 46)	0.0010
Parity - mean (SD)	0.35 (± 0.60)	0.44 (± 0.16)	0.31 (± 0.10)	0.50
Gravidity - mean (SD)	1.04 (± 1.09)	1.06 (± 0.23)	1.03 (± 0.21)	0.93
Paternal age - mean (SD)	42.70 (± 6.96)	41.29 (± 2.15)	43.31 (± 1.14)	0.37
Number of previous IVF's –mean (SD)	3.14 (± 1.77)	3.18 (± 0.40)	3.13 (± 0.33)	0.92
Cycle specific data				
ET pre-GCSF – mean (SD)	7.53 (± 2.69)	7.6 (± 0.72)	7.49 (± 0.46)	0.89
ET post-GCSF – mean (SD)	9.11 (± 2.12)	9.14 (± 0.57)	9.10 (± 0.44)	0.95
Number of Embryos transferred (Fresh/thawed) –mean (SD)	3.37 (± 0.19)	3.82 (± 1.29)	3.13 (± 3.13)	0.08

In our study, the only statistically significant difference noted between those that achieved pregnancy and those that did not, was age (p-value 0.0005).

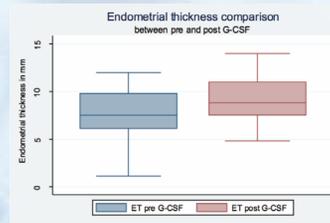


Box plot showing comparison of age between women who achieved pregnancy versus those that did not:

- In order to validate our results, we compared our study's pregnancy rates to pregnancy rates achieved at BioART Fertility Centre in the 12 months preceding G-CSF usage, i.e. 2014 statistics. We also compared it with the United States national 2014 rates as displayed in the summary report on the SART website.

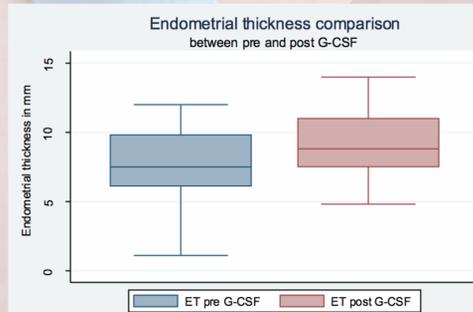
Age	BioART G-CSF	BioART 2014	SART National summary report 2014 ¹⁰
Pregnancy rates (%) (per patient per cycle)			
< 35	62.29	52.00	31.9
35-37	44.44	42.85	26.5
38-40	12.50	32.89	18.3
41-42	33.33	33.33	10.5
>42	8.33	46.42	3.6

- In our study sample, the mean endometrial thickness before G-CSF instillation was 7.35 mm and post-G-CSF instillation, it was 9.11mm. The overall expansion in endometrial thickness post G-CSF was found to be statistically significant. (P-value < 0.001)



- However a comparison of the mean endometrial thickness pre G-CSF and post G-CSF between those that fell pregnant and those that failed to fall pregnant showed no statistically significant difference between the 2 groups. (P-value 0.89 and 0.95 respectively).

- In our study, of the 49 women, 22 had a pre G-CSF endometrial thickness of ≤ 7 mm. By looking specifically at these 22 women, comparisons regarding endometrial expansion post G-CSF were made. From these 22 women, 3 had to be excluded from analysis as the post G-CSF measurement was not recorded in the medical notes. Comparison of the means of pre and post G-CSF endometrial thickness showed statistical significant endometrial expansion. P-value = 0.0004



CONCLUSION

- Results from our study has shown that the use of G-CSF instillation as an adjunct to IVF therapy is associated with improved pregnancy rates in patients under the age of 38 years. We failed to show any evidence for its use in older patients and more studies would be beneficial in this regard.
- In our study, we reported a statistically significant overall expansion of endometrial thickness with the use of G-CSF but failed however to show any association with endometrial expansion and pregnancy outcome.
- The G-CSF may exert its positive effect on pregnancy partly through endometrial thickening as the literature suggests,^{11,12} but also via an as yet uncertain alternative mechanism enhancing implantation.

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