Predictors of Successful conception in a clinical trial of 30 patients with primary amenorrheic hypogonadotrophic hypogonadism treated by ovulation induction

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Summary:

Objectives: *A clinical trial was designed to assess the association between the treatment of infertile females with Hypogonadotrophic Hypogonadism and their fertility state considering conception as the desired outcome. Serum hormones, LH, FSH and estradiol, endometrial thickness and count of active ovarian follicles were assessed by U/S to evaluat their role in anticipating a successful conception.*

Materials and Methods: *Standard protocols of ovulation induction were used in a clinical trial (historical cohort design) of 30 patients with primary hypogonadotrophic hypogonadism. For ethical reasons no attempt was made to fix the number of induction courses given to the female patient (such a variability is suspected to confound the result to a limited extent), so a female was followed up with several courses of ovulation induction (according to the advice of the physician in charge) for a median duration of 1 year with conception as the final outcome of interest. Four serum hormonal markers (FSH, LH, Prolaction and estradiol) were assessed before and 12-14 days after initiating therapy. Transvaginal U/S was done to measure endometrial thickness and the number of dominant follicles in both ovaries after 12-14 days of treatment.*

Results *Serum estradiol concentration, endometrial thickness and number of dominant follicles were significant predictors of successful conception. Using endometrial thickness as a decision rule to predict successful conception at a cutoff value of 7 mm, considering the rule as positive if equal or greater than 7 mm, resulted in a positive predictive value (PPV) of 50% (Relative risk of having conception was 4.3 times). The confidence in a positive rule was increased to 71.4% (PPV =11.4%) when the cutoff value was set higher at 8 mm endometrial thickness. Using the number of dominant follicles as a decision rule at a cutoff value of 4 resulted in a PPV of 60%. This PPV was further increased to 72.7% %) when the cutoff value was set higher at 5. An U/S finding of 5 or more dominant follicles increased the . .probability of having conception by 12.6 times. A serum estradiol concentration at day 12 of 114 pgm/ml and higher predicted successful conception with a PPV of 50% (relative risk of having conception was 7), increasing this cutoff value of serum estradiol to a maximum of 498.5 pgm/ml increased the PPV to 66.7%.*

Conclusions and Recommendations: *a clinician can predict successful conception after the first 2 weeks of initiating therapy with a moderate degree of confidence depending on serum estradiol, endometrial thickness and number of dominant follicles in the ovary. Other factors however need to be considered to increase the confidence of prediction, such as the type of insemination technique, sperm count of husband. A larger sample size and a survival analysis design is needed to assess the èxact risk of having conception after each course of treatment.*

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Introduction

The initiation of puberty depends on a complex series of events that occur within the brain and appears to require interactive participation of neuronal circuits and glial networks, as well as the peripheral endocrine metabolic signals, and the progression of the pubertal development and maturation in girls is marked by the onset of menstrual period. One of the most important causes of primary amenorrhea is Hypogondotrophic hypogonadism that constitutes about 22.9%) of all the primary amenorrhea cases [1].

Hypogondotrophic hypogonadism (H.H), is absent or decreased gonadal function **in** the male (testis) or female (ovaries) resulting from the absence of the gonadal stimulating pituitary hormones FSH (Follicle Stimulating hromone) and LFI (Leutinizing hormone) [2]. A deficient pulsatile GnRH, LFI and FSH secretion leads to delayed puberty and sexual infantilism. GnRH deficiency may be due to genetic or developmental defect of the hypothalamus or to destructive lesions such as tumors, inflammatory processes, vascular lesions or trauma [1].

Since FSH and LH are hormones released by the pituitary glands, these hormones stimulate the ovaries (female) and testis (male) to secrete hormone that are responsible for

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normal development in puberty. Decreased level of FSH and LH may occur in association with damage to or absence of the pituitary gland (Flypogonadism) or hypothalamus. In the absence of the gonadal stimulation by FSH and LFI, puberty does not take place and the secondary sexual characteristics do not develop. This may also occur as a result of hypothalamic abnormalities. The hypothalamus produce gonadotropin releasing hormone (GnRH) that stimulate the pituitary to release FSH and LH, if GnRH is absent FSH and LH will be absent(3).

With proper diagnosis and selection of treatment ovulation induction is an option for anovulatory women, specialized skilled, knowledge and resources as well as patients and physician commitment are prerequisites to the appropriate application, support and access to the health care team to maximize success. Current therapeutic options include the use of clomiphenc citrate, bromocriptinc, gonadotropins and GnRH. Importantly, each and every one of these agents is best applied only in the appropriate clinical circumstances in keeping

with the patient's individual's needs, whereas clomiphene citrate is particularly suited for the management of women with normal levels of FSH and Prolactine and adequate levels of estrogen. Gonadotropins, therapy may be applied to both women with low levels of estrogen and gonadotropins as well as those with normal levels (4).

Objectives:

The study was designed to assess the association between the treatment of females with Hypogonadotrophic Hypogonadism and their fertility state considering conception as the desired outcome. The present study will also determine the predictive power of the following parameters in anticipating successful conception for the treated female, namely: Serum hormones, LIT, FSH and estradiol, endometrial thickness and count of active ovarian follicles assessed by U/S.

Materials and Methods:

Standard protocols of ovulation induction were used in a clinical trial included the use of HMG hormoues as an ovarion stimulating factors (historical cohort design) of 30 patients with primary hypogonadotrophic hypogonadism. The patients were followed up with several courses of ovulation induction for a median duration of 1 year with conception as the final outcome of interest. Four serum hormonal markers (FSFI, LH, Prolaction and estradiol) were assessed before and 12-14 days after initiating therapy. Transvaginal U/S to measure endometrial thickness and count the number of dominant follicles in both ovaries after 12-14 days of treatment was also done.

Results:

A sample of thirty married HH females in their reproductive age has been studied in association to the ovulatory induction programs. The median number of dominant follicles (6) and endometrial thickness (7.7mm) were significantly higher among the group of women who concieved successfully than what was found in the second group who failed to concieve (2 and 6.6 mm respectively), table 1 and 2.

The mean hormonal level, FSH, LH and estradial, after treatment in females who conceived successfully was obviously (though not significant statistically) higher than that in the other group, table 3.

As shown in table 4 and 5, serum estradiol concentration, endometrial thickness and number of dominant follicles were significant predictors of successful conception. Using endometrial thickness as a decision rule to predict successful conception at a cutoff value of 7 mm, considering the rule as positive if equal or greater than 7 mm, resulted in a positive predictive value (PPV) of 50% (Relative risk of having conception was 4.3 times). The confidence in a positive rule was increased to 71.4% (PPV =71.4%) when the cutoff value was set higher at 8 mm endometrial thickness. Using the number of dominant follicles as a decision rule at a cutoff value of 4 resulted in a PPV of 60%. This PPV was further increased to 72.7% %) when the cutoff value was set higher at 5. An U/S finding of 5 or more dominant follicles increased the risk of having conception by 12.6 times. A serum eslradiol concentration at day 12 of 114 pgm/ml and higher predicted successful conception with a PPV of 50% (relative risk of having conception was 7), increasing this cutoff value of serum estradiol to a maximum of 498.5 pgm/ml increased the PPV to 66.7%.

Discussion:

Hypogonadotrophic hypogonadism (HH) ovulatory dysfunction are of central origin mostly anatomic causes of hypothalamic GnRH neuronal dysfunction, such as isolated gonadotrophin deficiency (IGD) which may be of pituitary origin, and Kallman's syndrome, are irreversible and require ovulation induction with GnRH pulastile therapy or controlled ovarian hyperstimulation (COH) with gonadotropins.

In contrast, successful treatment of the underlying cause of functional hypothalamic

amenorrhea (FHA) allows for resumed menses and ovulation in 75% of the patients. So pituitary etiologies of ovulatory dysfunction present as irreversible or reversible HH states (5).

In the present study the positive effect of ovulatory induction treatment for females vith H.H was documented by inducing an increase in number and size of follicles with ncreasing endometrial thickness especially near ovulation time.

The mean hormonal level of FSH, LH and estradial, after treatment in females who conceived successfully was obviously higher, suggesting that human menopausal gonadotropin therapy is a treatment of choice in a variable dosage method of administration. The patient's response to the drugs as measured by serum estradiol levels in addition to other two hormones may serve as an accessory tool to monitor the patient after stimulation (6), table 3.

To predict successful conception as an outcome for ovulatory induction treatment, one would choose the highest predictive value for a positive decision rule for 3 tested parameters, namely: Serum estradiol concentration at day 12 >= 498.5 (PPV =71.4%), an endometrial thickness >= 8 mm (72.7% %) and a count of dominant follicles >= 5 (PPV=66.7%). At best a female with Mil treated by medical ovulatory induction therapy and achieving one of the previous criteria one would expect a successful conception with around 70% confidence.

Conclusions and Recommendations:

A clinician can predict successful conception after the first 2 weeks of initiating therapy with a moderate degree of confidence depending on scrum estradiol, endometrial thickness and number of dominant follicles in the ovary. Other factors however need to be considered to increase the confidence of prediction, such as the type of insemination technique, sperm count of husband. Also a larger sample size and a survival analysis design is needed to assess the exact risk of having conception after each course of treatment.

Table 1; The difference in mean change in endometrial thickness by U/S between the group who failed to conceive and those who conceived successfully.

Endometrial thickness (measured by US) in mm	Mean	SD
Failed to concieve (n=21)	6.6	1.0
Concieved (n=9)	7.7	0.7
P (t-test) = 0.007		

Table 2: The difference in mean change in number of dominant follicles assessed by U/S between the group who failed to conceive and those who conceived successfully

Number of active ovarian follicles	Range	Median
Failed to concieve (n=21)	0-8	2
Concieved (n=9)	4-8	6
? (Mann-Whitney) < 0.001		

Table 3: The difference in mean change in serum hormone levels between the group who failed to conceive and those who conceived successfully.

	Before treatment	After treatment	Change after treatment
1. Serum FSH (miu/ml)			
Failed to concieve			
Mean	1.9	8.7	6.8
SD	1.7	6.5	5.4
Concieved			
Mean	1.8	10.5	8.7
SD	1.6	2.6	3.9
P (t-test) = 0.89^			
2. Serum LH (miu/ml)			
Failed to concieve			
Mean	1.5	6.9	5.4
SD	1.3	5	4.3
Concieved			
Mean	1.3	7.4	6.1
SD	1.3	2.5	3.5
P (t-test) = 0.81^			
3. Serum estradiol (pgm/ml)			
Failed to concieve			
Mean	18.9	171.8	152.9
SD	12.2	207.8	200.2
Concieved			
Mean	24.5	408.6	384.1
SD	19.7	254.2	238.4
P (t-test) = 0.35^			
4. Serum prolactin (ng/ml)			
Failed to concieve			
Mean	14.3	8.9	-5.4
SD	8.5	4.1	7.5
Concieved			
Mean	16.9	9.1	-7.8
SD	10.5	4.7	7.8
P (t-test) = 0.48^			

Table 4: The positive predictive value of 3 lab parameters at different cutoff values after starting ovulation induction therapy in anticipating successful conception of study subjects.

	Conception as an outcome of treatment Negative	Positive	Total	PPV
1. Number of dominant ovarian follicles				
cutoff=4				
Negative (< cutoff) Positive (>= cutoff)	15	0	15	60
	6	9	15	
cutoff=5				
Negative (< cutoff) Positive (>= cutoff)	18	1	19	72.7
cutoff=6	3	8	11	
Negative (< cutoff) Positive (>= cutoff)	18	2	20	78.6
cutoff=7				
Negative (< cutoff) Positive (>= cutoff)	3	7	10	
cutoff=8	19	5	24	66.7
Negative (< cutoff) Positive (>= cutoff) Total	2	4	6	
3. Endometrial thickness (measured by US) in mm cutoff=7				
Negative (< cutoff) Positive (>=cutoff)	20	6	26	75.0
cutoff=8	1	3	4	
Negative (< cutoff) Positive (>=cutoff)	21	9	30	
cutoff=9	12	0	12	50.0
Negative (< cutoff) Positive (>=cutoff) Total	9	9	18	
	19	4	23	71.4
	2	5	7	
	20	8	28	50.0
	1	1	2	
	21	9	30	

Table 4 continued

	Conception as an outcome of treatment Negative	Positive	Total	PPV
3. Serum estradiol (pgm/ml) after treatment				
cutoff = 114				
negative (<cutoff)	13	1	14	50.0
Positive (>=cutoff)	8	8	16	
cutoff = 498.5				
negative (<cutoff)	20	7	27	66.7
Positive (>=cutoff)	1	2	3	
cutoff = 883				
negative (<cutoff)	20	8	28	50.0
Positive (>=cutoff)	1	1	2	
Total	21	9	30	

Table 5: The incidence rate of successful conception by 3 lab parameters.

	Pregnancy as an outcome of treatment Negative N	%	Positive N	%	Total N	%	RR	P
1. Endometrial thickness in mm								
<8	19	82.6	4	17.4	23	100	4.1	0.02
8+	2	28.6	5	71.4	7	100		
2. Number of dominant ovarian follicles								
<5	19	95.0	1	5.0	20	100	14.5	<0.001
5+	3	27.3	8	72.7	11	100		
3. Serum estradiol (pgm/ml) after								
treatment-(cutoff = 114)								
negative (<cutoff)	13	92.9	1	7.1	14	100	7.0	0.28^
Positive (>=cutoff)	8	50	8	50	16	100		
Total	21	70	9	30	30	100		

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