Pulsatile GnRH therapy in persistent amenorrheic weight-recovered anorexia nervosa patients: a retrospective study.

A. Fauconnier*[a] (Mlle), B. Galusca[a,b] (Pr), Y. Khalfallah[a] (Dr), A. Wargny[b] (Mlle), JP. Klein[cd] (Dr), C. Papastathi-Boureau[a] (Dr), B. Estour[a,b] (Pr), N. Germain[a,b] (Pr),
[a] Service d'Endocrinologie, CHU Nord de Saint Etienne, Saint Etienne, France , [b] TAPE EA 7423 Université Jean Monnet St Etienne, France, [c] Service d'histologie embryologie, CHU Nord de Saint Etienne, Saint Etienne, Fance [d] Universite de Lyon, Universite Jean Monnet, 42270, Saint Priest en Jarez, France

INTRODUCTION: Anorexia nervosa (AN) is characterized by food intake restriction-induced undernutrition associated with hypothalamic amenorrhea (HA). Weight recovery does not always restore menses and pulsatile GnRH therapy is currently proposed to induce ovulation and pregnancy. So far few specific studies on persistent amenorrheic weight-recovered AN have evaluated pulsatile GnRH therapy and they include small number and under nourished patients. No study has compared recovery AN results with patients with HA from other origins without any eating disorder.

OBJECTIVE: The aim of this study was to compare clinical and hormonal outcomes during pulsatile GnRH therapy between persistent amenorrheic weight-recovered AN and HA from other origins without any eating disorder.

METHODS: 41 patients who underwent GnRH pulsatile therapy in order to achieve pregnancy were included in this retrospective study: 19 amenorrheic weight-recovered AN, BMI> 18.5kg/m^2 without menses recovery (AN), 15 secondary HA patients (SHA) and 7 primary HA patients (PHA).

	AN (n=19)	SHA (n=15)	PHA (n=7)
Age (years)	27.8 ± 0.8	29.1 ± 1.3	25.3 ± 1.4
Weight (kg)	50.7 ± 2.3	57.6 ± 2.7	72.4 ± 4.6*$
Height (m)	1.63 ± 0.12	1.65 ± 0.02	1.64 ± 0.02
Body Mass Index (kg/m^2)	19.1 ± 0.6	21.3 ± 1.1	26.8 ± 1.3*
Leptin (ng/l)	8.1 ± 2.2	14.1 ± 7.2	8.4 ± 2.5
FreeT3 (pmol/l)	3.4 ± 0.4	5.1 ± 1.2	4.0 ± 0.3
24h mean Cortisol (nmol/l)	116.6 ± 53.4	164.2 ± 95.7	156.6 ± 19.6
IGF1 (µg/l)	193.5 ± 24.1	208.1 ± 37.6	177.5 ± 34.6
Estradiol (ng/l)	21.2 ± 2.6	12.3 ± 1.8*	13.6 ± 3.2*
FSH (U/l)	5.8 ± 0.6	5.5 ± 0.8	1.6 ± 0.6*$
LH (U/l)	2.3 ± 0.5	2.8 ± 0.6	1.2 ± 0.8

Table 1: Baseline characteristics. Data are expressed as mean ± SEM. Rec-AN is for persistent amenorrheic weight-recovered Anorexia Nervosa, SHA is for secondary hypothalamic amenorrhea and PHA is for primary hypothalamic amenorrhea Statistics *: p<0.05 vs. Rec-AN and $: p<0.05 vs SHA.

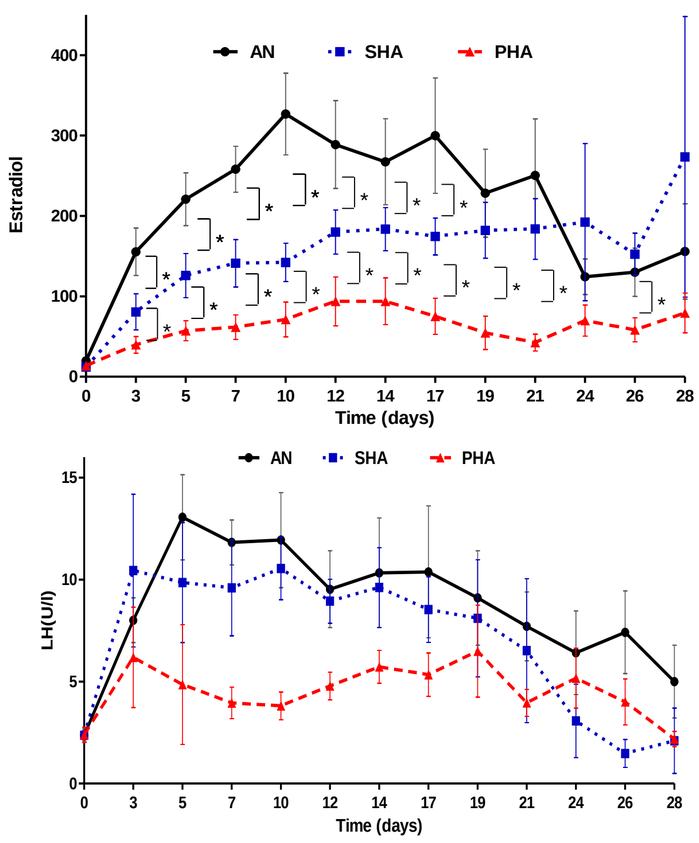

Figure 1: Hormonal monitoring of inductions. Estradiol, LH changes during induction in the three groups of the study with patients with and without pregnancy pooled. AN is for persistent amenorrheic weight-recovered Anorexia Nervosa, SHA is for secondary hypothalamic amenorrhea and PHA is for primary hypothalamic amenorrhea.

RESULTS, BASELINE CARACTERISTICS:
Weight and body mass index in persistent amenorrheic weight-recovered AN group was significantly decreased compared to SHA and PHA (p=0.0001 and p=0.0001 respectively). But no difference was observed for age, height, leptin, free T3, cortisol, ACTH and IGF1 between the groups (table 1).
The gonadotropic initial assessment showed that Estradiol was significantly increased in AN compared to PHA (p=0.0001) and SHA (p=0.001). FSH was also significantly higher in AN than in PHA (p=0.009) (table 1).

RESULTS DURING INDUCTION CYCLES:
The mean plasma level of Estradiol during induction cycles in AN was significantly elevated compared to the two other groups (p=0.0032 vs SHA and p=0.0002 vs PHA). The mean plasma level of Estradiol was also significantly higher in SHA than in PHA (p=0.0053) (figure 1).
The mean plasma level of LH during induction cycles was significantly higher in AN than in PHA (p=0.0013) but similar to SHA (p=0.27).Mean plasma level of LH was higher in SHA than in PHA (p=0.0035) (figure 1).
Cumulative birth rates were 63% in the AN group, 53% in the SHA group and 14% in the PHA group (p=0.03 and 0.01 vs. SHA and AN respectively). **Ovulation rate** was similar between AN and SHA group (p=0.5), but lower in PHA group (p<0.0001 vs. AN and p=0.001 vs. SHA). **Five miscarriages** were observed, two in the AN group and three in the HA groups.

TOLERANCE:
Three AN patients reactivated their eating disorder during pregnancy or after delivery. One episode of excessive response was occurred (≥ 3 ovulatory follicles) and the stimulation was stopped. One twin pregnancies was noted. No other adverse event was found.

CONCLUSION:
This study showed increased gonadal status and higher Estradiol response to pulsatile GnRH therapy in persistent amenorrheic weight-recovered AN than in the other causes of HA.
These results suggest that their individual set-point of body weight allowing a fully functional gonadal axis is not reached yet. Furthermore there must be AN specific factors still abnormal despite weight recovery: insufficient leptin levels and persistent anomalies of kisspeptin path, ghrelin increased, persistent excess of endorphins. The reactivation of three cases of eating disorder in our study shows that it seems important to be able to properly and carefully check on both nutritional and psychiatric status before starting pulsatile GnRH therapy.