

INDUCTION OF OVULATION IN HYPERANDROGENISM

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SUMMARY

This study offers for an endovaginal sonographic discrimination of PCO from the PCOD subjects, without a recourse to any of the endocrine studies. It is argued that this classification is not only simple but also mandatory, because the therapeutic strategy is planned according to the sonographic ovarian morphology.

PCO subjects are ideally treated with clomiphene citrate, anticipating a pregnancy rate of 55.77%. Whereas, PCOD subjects are better primarily treated by laparoscopic ovarian diathermy, since they are poor responders to CC (16.67% conception rate) and achieve 45.45% conception rate for the former treatment. This strategy is further fortified by the fact that among those conceiving following CC induction 78.38% were PCO subjects, and by contrast, of those conceiving following ovarian diathermy 75.00% were PCOD subjects. Hyperglycemic PCOD subjects have 25% conception rate with insulin therapy.

Hyperandrogenism a state of increased androgen production and action is a common cause of anovulatory infertility. In more than 90% of cases a specific etiologic cause could not be identified

(Barbieri, 1990). The full-blown syndrome of hyperandrogenism, namely, polycystic ovarian syndrome (PCOS), presenting with typical somatic features of hyperandrogenism and overproduction of ovarian androgens with high LH:FSH ratio is relatively less common (Nobels and Dwailly, 1992). A more common

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condition is Polycystic ovaries (PCO), which is detected in patients with more subtle clinical and endocrinological expression (Franks, 1989). Inclusion of this group results in dramatic increase in the prevalence of the disease (Nobels and Dwailly, 1992). In fact the PCO subjects, who have been described as the 'hypothalamic anovulatory group', from the missing link between the normal ovulatory subjects and the full-blown hyperandrogenic state of PCOD.

The purpose of this communication is to classify the hyperandrogenic

anovulatory infertile subjects based on endosonographic discriminatory landmarks, and, on this classification, to design individual ovulation induction protocols for the PCO and PCOD subjects.

**STUDY DESIGN -
ENDOSONOGRAPHIC DISCRIMINATION (Table I)**

Polyfollicular appearance with at least 5 round echoless regions of < 10 mm in size per single ovarian slice could be common for normal ovulatory subjects before the 7th day of the cycle, hypotha-

**Table I
Endosonographic Diagnosis of Polyfollicular Pattern**

TVS findings	P.C.O.D.	P.C.O.	↑ PRL	Normal ≤ 7 days
size of ovary	> 10 cms ²	normal	normal	normal
ovarian	roundness			
characteristics	index: > 0.7/ necklace pattern/ hyperechoic follicle wall	normal with transonic follicles	normal with transonic follicles	normal with transonic follicles
follicle size	8 to 10 mm	8 to 10 mm	8 to 10 mm	8 to 10 mm
follicle nos.	> 10	≥ 5	≥ 5	≥ 5
follicular morphology	homogeneous	heterogeneous	heterogeneous	heterogeneous
follicular dominance	nil	nil	nil	initiated
ovarian stroma	increased	normal	normal	normal
endometrial morphology	hyper-plastic/ proliferative	proliferative > 6 mm	hypoestrogenic < 6 mm	midproliferative > 6 mm

lamic anovulation (PCO subjects), PCOD and in hyperprolactinemia (Ardaens et al, 1991). Each condition is sonographically discriminated by the following criteria:

PCOD : (1) Number of microcysts (< 10 mm) is > 5 or usually > 10 and the microcysts are almost homogeneous in appearance; (2) presence of and abnormal ovarian stroma is almost exclusively diagnostic of PCOD; The stroma is considered abnormal when (i) it is hypertrophied and mainly central with the microcysts pushed towards the periphery (necklace pattern), and/or (ii) when the stroma is dense and infiltrating the microcysts enhancing the contrast between the cysts whose walls appeared thickened and hyperechogenic; (3) increase in ovarian size is also a sign of PCOD, with a cross sectional area of > 10 cms²; (4) follicular dominance is not evidenced, and consequently both ovaries are equally prominent; (5) uterine width: ovarian length = < 1; (6) excessive ovarian roundness index (ovarian width/ovarian length > 0.7).

The endometrium is usually estrogenized, either atleast midproliferative or hyperplastic, and seldom hypoestrogenic. 'In general, > 10 microcysts of < 10 mm size per ovarian slice is almost specific for PCOD' (Adams et al., 1986). In fact, abnormal ovarian stroma in combination with a polycystic criterion > 10 is more diagnostic of PCOD than endocrine data (Conway, et al., 1989)

PCO : In hypothalamic anovulation there are multifollicular ovaries with ≥ 5 follicles (< 10 mm in size) per single ovarian slice. There is no evidence of

follicular dominance in follow-up scans, with both ovaries remaining equally active. However, the stroma is not abnormal, and the ovarian size is relatively normal. The Polyfollicular ovaries evidence heterogeneity of the follicular size. The endometrium is reasonably estrogenized, and is usually in the midproliferative phase. This endometrial characteristics will differentiate PCO from hyperprolactinemia which is usually attended with hypoestrogenic endometrial picture; and hence routine prolactin estimation does not have added advantage in PCO subjects.

Hyperprolactinemia : Polyfollicular appearance of PCO is equally encountered in hyperprolactinemia, but with one difference, that the endometrial estrogenisation is uniformly subnormal. Endometrium is usually in the inactive phase, to at the most early-mid proliferative phase, and does not cross an interface-to-interface thickness of 6 mm, at any phase of the cycle. Both ovaries are almost equal sized, with no evidence of follicular dominance. The combination of hypoestrogenic endometrium and polyfollicular ovaries is attended with high incidence of hyperprolactinemia and hence mandates a routine serum prolactin study.

Normal Ovulatory Subjects : Normal ovulatory subjects also can have polyfollicular pattern when scanned before the 7th day of the cycle. However, the number of follicles per slice are around 5 and the ovarian stroma is normal. Sooner or later follicular dominance, with contralateral ovarian quiescence will be evident. Endometrial

proliferative changes advance parallel to the development of the dominant follicle.

TREATMENT SCHEDULE

All subjects, whether PCOD or PCO, if found normoprolactinemic, were primarily treated with Clomiphene Citrate (CC), or sometimes a combination of CC and Bromocriptine. Follicular monitoring was routinely performed, and hCG (5000 i.u.) was optimally timed with full follicular maturation and late proliferative endometrium. Those who failed to ovulate on 3 to 6 CC cycles were recruited for operative laparoscopy follicular diathermy and drainage. In the latter half of the study ovarian diathermy was performed following a prior ovarian hyperstimulation employing hMG/hCG regime. Those subjects who were hyperglycemic were treated with human insulin (Actraphene) in a dose beginning with 10 units/day in the morning. Among the subjects remaining refractory to ovarian diathermy majority were treated with hMG or pure FSH and few were considered for prior GnRH agonist (Buserelin) down regulation followed by

gonadotropins. In the former group Buserelin (500 µgm, 2 injections, 12 hours apart) was employed as flare therapy for initiation of endogenous LH surge, and this was aimed at minimizing the risk of hyperstimulation. In the latter group hCG (5000 i.u.) was employed as LH surrogate.

RETROSPECTIVE DATA ANALYSIS

There were 100 subjects in this study group and of them 57 became pregnant following treatment (Table II). All of them had been initially treated with CC, and 37 women achieved a conception. Those 52 subjects who were refractory to CC induction when treated with ovarian diathermy with 20 subjects achieving a conception (38.46%).

There were 52 subjects satisfying the sonographic criteria of PCO and 48 subjects that of PCOD. Among the PCO group, 34 had achieved a conception (58.12%), and in the PCOD group 23 had conceived (47.92%). Considering the overall conception rate for various ovulation induction protocols, it is evident that PCOD subjects are relatively less

Table II
Ovulation Induction in Hyperandrogenic Condition
April 1992 to March 1994 (2 years)

Nature of Treated	No. Treated	No. Pregnant	Percentage
All Patients	100	57	57
Different CC Regimes	100	37	37
Ovarian Diathermy (CC Resistant)	52	20	38.46

fertile than the PCO group (Table III).

Among the 52 PCO subjects, all of whom were treated with CC, 29 achieved a conception with CC regime (55.77%). Among the 19 CC nonresponders, 5 subjects conceived following ovarian diathermy (26.32%). This observations proves that PCO patients are more responsive to CC induction, and hence medical induction of ovulation employing CC should be the first choice (Table IV).

Of the 48 PCOD subjects, when all were exposed to CC induction, only 8 subjects achieved a conception (16.67%), whereas among the 33 CC nonresponders 15 conceived following ovarian

diathermy (45.45%). This impressive response to ovarian diathermy could indicate a primary therapeutic role for ovarian diathermy in PCOD subjects (Table IV). Those PCOD subjects with abnormal G.T.T. values were treated with insulin with 5 conceptions for 20 subjects recruited (25.00%).

Of the total 64 conceptions recorded in infertile subjects over this study period of 2 years, conception following treatment of hyperandrogenism was 62 (38.80%). Of them PCOD contributed 34 conceptions, and PCOD 28, (54.84 and 45.16 percents respectively). This further proves that the fertility for PCO

Table III
Conception Rate in P.C.O. and P.C.O.D.

Ovarian Dysfunction	No. Treated	No. Pregnant	Percentage
P.C.O.	52	34	58.12
P.C.O.D.	48	23	47.92
P.C.O.D. Insulin Treated	20	5	25.00

Table IV
Different treatment Protocols for P.C.O. and P.C.O.D.

Treatment Protocol	P.C.O.		P.C.O.D.	
	No. Treated	Pregnant	No. Treated	Pregnant
Various CC Regime	52	29(55.77%)	48	8(16.67%)
Ovarian Diathermy	19	5(29.32%)	33	15(45.45%)
Insulin			20	5(25.00%)

Table V
Analysis of Total Conceptions in P.C.O. and P.C.O.D.

Treatment	Total Pregnancies	P.C.O.	P.C.O.D.
CC Induction	37	29(78.38%)	8(21.62%)
Diathermy	20	5(25.00%)	15(75.00%)

is more compared to that of PCOD.

Among the 37 conceptions following CC induction 29 were in PCO subjects (78.38%), and the remaining 8 (21.62%) were in PCOD subjects (Table V). By contrast, of the 20 conceptions following ovarian diathermy, 15 were in PCOD subjects (75.00%), and only 5 were in PCO subjects (25%). These points further strengthen the idea that PCO subjects are ideally treated with CC, and PCOD are better treated with ovarian diathermy as the primary method of choice.

DISCUSSION

In our infertility practice, all anovulatory subjects who are normoestrogenic and normoprolactinemic are primarily treated with clomiphene citrate (CC). Essentially they are subjects with varying degrees of ovarian hyperandrogenism, ranging from the most subtle variety with no clinical expression of androgen excess to those who have the full-blown signs of hyperandrogenism. Patients failing to respond to various CC regimes, such as CC alone, CC and hCG, or CC and Bromocriptine combinations (after 3 to 6 cycles), are considered for ovarian diathermy at operative laparoscopy.

Failure to respond to ovarian diathermy is considered the indication for gonadotropin induction of ovulation, employing either hMG, or pure FSH. Prior down regulation of the axis employing GnRH agonists has been considered in many subjects undergoing gonadotropin induction. Insulin therapy is preferred in those hyperandrogenic subjects who are hyperglycemic.

In this study 100 consecutive subjects treated with CC have been analyzed, and the pregnancy rate for various CC regimes has been 37%. Among the 52 CC nonresponders 38.46% conceived following ovarian diathermy of whom nearly 50% had post-laparoscopy medical induction with CC or hMG. There were 20 hyperglycemic subjects who responded with 25% pregnancy rate following insulin therapy.

All these patients had a preliminary endosonographic evaluation of their ovarian and endometrial morphology. These sonographic morphometric retrospective data were employed to classify and study the hyperandrogenic subjects with respect to their incidence and response to various ovulation induction protocols. As per the ovarian morphological classification discussed by

Ardaens et al., (1991). The patients were divided into PCO and PCOD subjects. This retrospective analysis tries to identify the different ovarian sonographic morphologies in the responders and nonresponders among the different treatment groups. We individualize and optimise the ovulation induction protocols based on endosonographic ovarian and endometrial landmarks.

Among the total conceptions recorded in infertile subjects 37.80% were contributed by the hyperandrogenic subjects, and of them PCO subjects record higher fertility rate (58.12%) compared to the PCOD subjects (47.92%).

PCO subjects have menstrual delays/ oligomenorrhoea, but do not evidence the typical somatic features of hyperandrogenism. Since they are estrogenized, and seldom are hyperprolactinemic, there is no need for routine PRL estimation, and they respond optimally to CC induction. Primary treatment with CC offers a pregnancy rate of 55.77%, and they poorly respond to ovarian diathermy with a pregnancy rate of 26.32%.

PCOD diagnosed at endopelvic scan significantly correlates with clinical features of hyperandrogenism, such as oligomenorrhoea/amenorrhoea, hirsutism, and obesity; and study of LH:FSH ratio may not further improve the diagnostic accuracy. Such subjects are seldom hyperprolactinemic and hence prolactin estimation is also not mandated. PCOD subjects respond favourably to ovarian diathermy (45.45% conception rate) than to CC (16.67%). Hence normoglycemic PCOD subjects are best treated primarily with ovarian diathermy without a prior

recourse to CC induction. Those who fail to respond to ovarian diathermy should be ideally considered for gonadotropin induction (pure FSH or hMG), preferably after a prior GnRH agonist down regulation. Study of glycemic status (G.T.T.) will be meaningful among the PCOD group, since at least 20 of 48 subjects (41.67%) are hyperglycemic, and 25% conceived following insulin therapy.

The most suitable ovulation induction protocols could be designed for PCO and PCOD subjects purely based on endosonographic ovarian and endometrial morphology, and the routine endocrine studies such as serum prolactin estimation, testosterone assay and LH : FSH ratio do not have additional benefits.

Among the 37 conceptions following CC induction 29 were in PCO subjects (78.38%), and the remaining 8 (21.62%) were in PCOD subjects. By contrast, of the 20 conceptions following ovarian diathermy, 15 were in PCOD subjects (75.00%), and only 5 were in PCO subjects (25%). From these observations it is evident that PCO subjects are better treated primarily with CC, and PCOD subjects by ovarian diathermy. PCOD subjects should be checked for their glycemic status, and if found hyperglycemic they are best treated with insulin.

REFERENCES

1. Ardeans Y., Robert Y., Lemaitre L., Fossati P. and Dewailly D. : *Fertil. Steril* : 55;1062; 1991.
2. Barbieri R.L. : *Clin. Obstet. Gynec.* : 33;640;1990.
3. Conway G.S., Honour J.W. and Jacobs H.S. : *Clin. Endocrinol* : 30;459;1989.
4. Franks S. : *Clin. Endocrinol* : 31;87;1989.
5. Nobels F. and Dewailly D. : *Fertil. Steril.* : 58;655;1922.