THERAPY IN ANDROLOGY

Pharmacological, Surgical and Psychological Aspects

Editors:

G.F.Menchini Fabris

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Therapy in Andrology

Pharmacological, Surgical and Psychological Aspects

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PREFACE

Andrology is a comparatively new multidisciplinary field, that gathers various aspects from branches such as endocrinology, urology, dermatology, psychiatry, neurology, genetics and pediatrics. The data coming from the individual specialist in any one field carries the risk of a biased and fragmentary approach to any problem regarding the male reproductive system. Andrology, therefore, expresses the need for a unitary and global approach to this subject. Nowadays, Andrology is structured as an autonomous science with its own University chairs, clinics and schools. The problem facing people coming from different backgrounds is therapeutic. Therapy in Andrology needs, obviously, a multidisciplinary approach, since the endocrinologist must know the indications and the limits of the urological operation, and vice versa.

Hence, the necessity and the opportunity to meet and to confront, on a unique occasion, the experience and results from the three main aspects of andrological therapy: pharmacological, surgical and psychological. This comparison will allow the integration of individual views concerning therapy, since different treatment methods often interact with each other.

This has been the policy followed by the Postgraduate School of Andrology in organizing this Congress which has been sponsored by the International Society of Andrology and the Italian Society of Andrology.

We wish to express our special thanks to the distinguished scientists who with their contribution have made this Congress possible and successful.

We hope that the Congress has provided a clearer insight into the therapeutic possibilities in Andrology and has proved to be a culturally deepening experience for all the people working in the andrological field. We also hope that this volume maintains the spirit that enlivened the Congress.

Prof. F. TRONCHETTI
Dean of the Postgraduate School of Andrology of Pisa

Prof. A. FABBRINI
President of the Italian Society of Andrology

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G.F. Menchini Fabris
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DEFINITION AND GOALS OF ANDROLOGY. OPENING ADDRESS BY THE PRESIDENT OF THE INTERNATIONAL SOCIETY OF ANDROLOGY

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On behalf of the International Society of Andrology I would like to welcome you to this congress, the first international congress devoted exclusively to "Therapy in Andrology". I would like to take this opportunity to talk about the definition, role and tasks of andrology.

WHAT IS ANDROLOGY ?

Andrology is a very young field and has only recently gained recognition as a discipline in its own right. Andrology can be defined as those branches of science and medicine dealing with the physiology and pathology of male reproductive functions. This implies that andrology is an interdisciplinary field in which basic scientists, veterinarians and clinicians participate.

The interdisciplinary character of andrology is one of the obstacles to establish this field. Other new disciplines came into existence by fragmentation of large established fields. In this way, for example, orthopedics and neurosurgery separated from surgery, neurology and dermatology separated from internal medicine. Andrological work, however, is done in many disciplines: urology, internal medicine, gynecology, dermatology, physiology, biochemistry, genetics, immunology and even psychology. This means that andrology needs to be synthesized out of various disciplines and synthesis is always a much more difficult process than fragmentation. Many disciplines and many people have to contribute to create andrology, and many individials are afraid of losing something through the establishment of andrology as a field in its own right.

Some people in fact feel that andrology is not a field as such, and its subject should only be considered in reference to the partner, in reference to the female. They believe "Reproductive Medicine" encompassing both male and female would be preferable to a field of gynecology on one side and andrology on the other. Ultimately this opinion may prevail and a discipline such as reproductive medicine may replace the other two. At the moment, however, we must deal with two unevenly developed counterparts. While gynecology is a highly advanced field, andrology appears to be far behind. Compared to the female our

knowledge about the male is rather limited. In order to close this gap, andrology needs to be developed, needs input and impetus. And when both partners are equal, reproductive medicine may emerge as a new entity from gynecology and andrology to deal with reproduction in both sexes.

In this phase of juvenile growth, andrology - like a pubertal child - needs understanding and protection from the adults, i.e. from academic medicine as well as from the medical profession. The universities have to allow development of andrology departments and should be proud of forwardlooking scientists and clinicians who see the need to create such departments. The medical associations have to recognize andrology as a field in its own right and should not be opposed to this important new development.

WHAT IS THE TASK OF ANDROLOGY ?

The major task of andrology is to contribute to the regulation of male fertility, i.e. regulation of male fertility in the positive as well as in the negative direction. Andrological research and clinical work concentrate on the development of methods for improving disturbed male fertility and also on the development of methods for male fertility control. Both aspects are two sides of the same coin. As this congress will demonstrate, new therapeutic methods for the treatment of male infertility are desparately required. I am convinced that when we have found ways to treat male infertility in a rational fashion, we will at the same time have methods for male fertility control available. Thus andrology contributes to the identification of new methods for family planning. We feel that the burden and the risks of fertility control should be shared evenly between husband and wife.

HOW CAN ANDROLOGY ACHIEVE ITS GOALS ?

One of the most important prerequisites for performing good scientific work is communication and cooperation among the workers in the field. Cooperation is best achieved by exchange of scientists and there are various private, national and international programmes to facilitate this exchange. Furthermore, scientific societies provide a good framework for communication and cooperation. The growing number of national societies of andrology founded over the past decade is an indication of the growing recognition of andrology as a field of research and clinical work. These societies are important for facilitating the exchange of ideas and knowledge.

However, science is international and knows no borders, and therefore it is quite natural that scientists also should unite on an international level. To this end the Comite Internacional di Andrologia (CIDA) was founded in 1971. Under the presidency of Rune Eliasson, CIDA grew from a club to a society, so that in 1981 the name was

changed from CIDA to "International Society of Andrology" (ISA). Today prominent scientists in 39 countries are members of ISA and ISA has 11 affiliated national societies, including the one from Italy.

One of the primary goals of ISA is to disseminate knowledge about andrology. This is best done by bringing together colleagues at a congress. We are very glad that Dr. Menchini Fabris has organized the present congress so that we can all meet and exchange ideas.

THE PRESENT CONGRESS

Dr. Menchini Fabris undertook a heroic task by organizing this congress dealing with one of the unsatisfactory areas of andrology, namely therapy. However, as a clinician Dr. Menchini Fabris recognises that the therapy of diseases is the most important aspect of research for the patient. He has succeeded in covering all aspects of therapy in andrology in the scientific programme, and the congress will summarize our achievements to date. But it will also show the gaps in our knowledge and will indicate where intensified research is required.

We are very happy that this congress is taking place in Pisa, in Tuscany, in Italy, because we all admire Italy. We appreciate its architecture and landscape, its cuisine and wines, and the friends we have here. Italian science has a prominent position and a long tradition in the field of male reproductive functions. I would just like to remind you that in the second half of the 18th century L. Spallanzani first demonstrated that egg and sperm have to get together to form new life by inseminating a spaniel bitch (3). A hundred years later E. Sertoli first described a testicular cell type, whose function is of utmost importance for spermatogenesis and which still carries the name of this famous morphologist (2). The present congress highlights the current Italian contributions to the field of andrology.

Pisa is the place where, in the 13th century, Leonardo Fibonacci introduced Arabic figures to Europe (1). They proved to be of paramount importance for science. Today Pisa is the place where the first Postgraduate School of Andrology was founded. Let us hope that our thoughts about andrology may travel as widely as the arabic figures!

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INTERACTION OF THE TWO PARTNERS OF THE COUPLE

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INTRODUCTION

Numerous publications concerned with human infertility deal with either male or female infertility. In 1941 it was pointed out that an interaction between both partners of a couple is required to produce an offspring (4) and later a "simultaneous study" of the husband and wife was proposed (17,8). However, infertility continued to be managed as if it were a separate disorder of either the male or the female. Recently the importance of a "couple approach" to the management of infertility was emphasized again (9,1) but no data were presented in support of this much discussed and little understood concept.

We suggested (16) and subsequently demonstrated (12,10,7,15) that infertility of each partner of a couple is a relative state and that a complex interaction between the fertility potentials of each partner indeed determines the ultimate fertility potential of the couple.

In this communication we would like to discuss some additional quantitative data in support of the concept of interaction between the two partners of a couple, to discuss the characteristics of this interaction, and to analyze the influence of gamet-pathology in either member of the couple on the outcome of the pregnancy.

RESPECTIVE CONTRIBUTIONS OF EACH PARTNER TO THE FERTILITY POTENTIAL OF A COUPLE

To investigate this question we constructed three models utilizing our infertile couples' population. The first was designed to examine the contribution of the male, the second to investigate the contribution of the female and the third was designed to examine the interaction between the fertility potentials of both members of the couple.

Contribution of the male

In this model the relationships between the motile

TABLE 1. Relationships between motile sperm count, percent pregnancy and time required for conception to occur in 152 couples in whom the male was not treated.

Motile sperm count (million/ml)	N	% Pregnancy	Months until conception
< 20.1	76	49%	10
20.1 - 60.0	58	62%	8
> 60.0	18	89%	6
Total	152	59%	8.5

sperm count, the percent pregnancy and the time required for pregnancy to occur were investigated. A total of 152 couples were studied. All couples with azoospermic males were excluded. The female factor was kept relatively constant by excluding couples whose female partners had cervical, uterine, tubal or peritoneal (endometriosis, adhesions, infections, etc.) factors, or ovarian dysfunction not correctable by medical therapy. Since in this model the fertility potential of the male (motile sperm count) varied and the fertility potential of the female was relatively constant, the contribution of the male fertility potential to the couple's fertility could be assessed. The pregnancy rate and the time required for pregnancy to take place were calculated and compared (Table 1). A quantitative direct relationship between the motile sperm count and the percent pregnancy was observed. A quantitative inverse relationship between the motile sperm count and the time necessary for pregnancy to take place was also noted. In couples

TABLE 2. Correlation between motile sperm count and pregnancy rate.

Motile sperm count (million/ml)	N	% Pregnancy
< 5.1	24	37.5%
5.1 - 10.0	19	42.1%
10.1 - 20.0	22	59.1%
20.1 - 40.0	35	62.9%
40.1 - 60.0	15	66.7%
60.1 - 100.0	14	78.6%
> 100.0	11	72.7%

$P < 0.01$ by linear regression analysis.

whose male partners had motile sperm counts of more than 60 million/ml 90% of women conceived in an average of 6 months. In couples whose male partner had motile sperm counts of less than 20 million/ml only 50% of women conceived and an average of 10 months was necessary for pregnancy to occur. These data as well as data presented in Table 2 demonstrate that the motile sperm count is significantly related to the fertility potential of the male. The model also suggests that the fertility potential of the male is a continuum from 0 to 100%. Consequently, demarcation lines between "fertility," "subfertility" or "infertility" on the basis of sperm count may not be feasible.

Contribution of the female

The male factor in this model was kept constant by virtue of the fact that artificial insemination with high quality (motile sperm count > 60 million/ml) donor semen was employed. A total of 238 couples were included in this study. The overall pregnancy rate was 71.4%. The conception occurred after an average of 3.9 $\pm$ 0.3 (S.E.) cycles of insemination. The presence of ovulatory dysfunction (11) decreased the pregnancy rate and increased the number of cycles required for pregnancy to occur (Table 3). In women with normal ovulatory function 86% pregnancy rate was achieved in an average of 2.8 months, while in women with ovulatory dysfunction the pregnancy rate was 62% and an average of 4.8 months was required for pregnancy to occur.

TABLE 3. Influence of ovulatory dysfunction on pregnancy rate and time required for conception to occur in couples with constant male factor.

	N	% Pregnancy	Months until conception
Normal ovulation	91	86%	2.8 $\pm$ 0.3
Ovulatory dysfunction	147	62%	4.8 $\pm$ 0.5
Total	238	71%	3.9 $\pm$ 0.3

Examination of cumulative pregnancy rates in this group of patients (Table 4) showed that in presence of normal ovulation over 90% of all pregnancies occurred within the first five insemination cycles while in women with ovulatory dysfunction 9 cycles of insemination were required to achieve 90% pregnancies. Furthermore after 3 cycles of insemination almost two-thirds of patients

with normal ovulation conceived while less than one-third of patients with ovulatory dysfunction conceived. These data demonstrate the influence of relative fertility dysfunction in the female on the fertility potential of the couple. Similar to the observations made above for the effect of a variable male factor, the presence of a female factor appears to be directly related to the time necessary for conception to take place and inversely related to the pregnancy rate. It is of interest to note that in women with normal ovulatory function undergoing AID in our Department during the last 8 years the average time required for pregnancy to take place has been 1.4 cycles.

TABLE 4. Cumulative pregnancy rates in relation to ovulatory function in couples with constant male factor.

Cycle of insemination	Percent of total pregnancies		Cumulative pregnancy rate	
	Normal ovulation	Ovulatory dysfunction	Normal ovulation	Ovulatory dysfunction
1	39.7	20.7	34.1	12.9
2	59.0	34.8	50.5	21.8
3	73.1	51.1	62.6	32.0
4	84.6	59.8	72.5	37.4
5	91.0	70.7	78.0	44.2
6	94.9	77.2	81.3	48.3
7	96.2	83.7	82.4	52.4
8	96.7	87.0	82.4	54.4
9	96.2	90.2	82.4	56.5
10	97.4	92.4	83.5	57.8
>10	100.0	100.0	85.7	62.6

Interaction between the male and female factors

This interaction was investigated in couples whose female partners showing either normal ovulation or ovulatory dysfunction were inseminated with either fresh or cryopreserved donor semen (Table 5). In the past we demonstrated diminished fertility potential of cryopreserved semen when compared to fresh semen (14,13). Normally ovulating females inseminated with fresh semen conceived after an average of 1.9 cycles and the pregnancy rate was 88%. The presence of ovulatory dysfunction delayed the occurrence of pregnancy to 3.6 months and decreased the pregnancy rate to 66%. The use of cryopreserved semen in normally ovulating women delayed the occurrence of pregnancy to 4 months and diminished the pregnancy rate to 79%. In women with ovulatory dysfunction inseminated with cryopreserved se-

men there was a further delay in the occurrence of pregnancy (8.7 months) and a further diminished pregnancy rate (44.1%).

TABLE 5. Interaction between the male and female factors.

	Fresh semen AID		Frozen semen AID	
	% pregnancy	Months until conception	% pregnancy	Months until conception
Normal Ovulation	87.9	1.9 ± 0.2	79.3	4.0 ± 0.6
Ovulatory dysfunction	66.0	3.6 ± 0.3	44.1	8.7 ± 1.9

While either male or female factor disturbs the fertility potential of the couple, the presence of both factors appears to cause exaggerated decrease in fertility rate and further delay of the time required for pregnancy to occur. The effects of both factors on the fertility potential of the couple appear to be synergistic rather than additive. These conclusions are supported further when data are analyzed utilizing life table analysis (Table 6).

INFLUENCE OF GAMET-PATHOLOGY IN EITHER MEMBER OF THE COUPLE ON THE OUTCOME OF PREGNANCY

It has been suggested in the past that poor semen quality, particularly increased numbers of morphologically abnormal spermatozoa, may be responsible for spontaneous abortions (2,5). Similarly it has been observed that in women who require treatment of ovulatory dysfunction the spontaneous abortion rates are increased (6,3). To investigate the influence of these factors on pregnancy outcome we analyzed the outcome of 436 consecutive pregnancies in our infertility practice. Spontaneous abortion occurred in 86 cases (19.7%), 348 women carried the pregnancy to term (79.8%) and there were 2 tubal pregnancies (0.5%). In term pregnancies the average birth weight was 7.1 ± 0.1 lbs and the duration of gestation was 280 ± 1 days, both figures similar to those observed in normal populations.

The male factor

Of the 436 pregnancies 131 resulted from AID. The incidence of spontaneous abortion in this group was 21.4%, not significantly different from the abortion

TABLE 6. Cumulative pregnancy rates in women with normal ovulation or ovulatory dysfunction undergoing AID with fresh or cryopreserved semen.

Cycle of insemination	Cumulative pregnancy rate			
	Fresh semen		Cryopreserved semen	
	Normal Ovulation	Abnormal Ovulation	Normal Ovulation	Abnormal Ovulation
	%		%	
1	46.6	17.0	13.8	0
2	65.5	27.4	24.1	2.9
3	74.1	38.7	44.8	11.8
4	81.0	44.3	62.1	17.6
5	84.5	53.8	72.4	17.6
6	87.9	56.6	72.4	26.5
7	----	59.4	72.4	29.4
8	----	62.3	72.4	29.4
9	----	64.2	72.4	32.4
10	----	66.0	72.4	32.4
> 10			79.3	44.1
	% of total pregnancies			
1	52.9	25.7	17.4	0
2	74.5	41.4	30.4	6.7
3	84.3	58.6	56.5	26.7
4	92.2	67.1	78.3	40.0
5	96.1	81.4	91.3	40.0
6	100.0	85.7	91.3	60.0
7	-----	90.0	91.3	66.7
8	-----	94.3	91.3	66.7
9	-----	97.1	91.3	73.3
10	-----	100.0	91.3	73.3
> 10			100.0	100.0

rate in the 305 non AID pregnancies (19.0%). Similarly the durations of gestation and the birth weights were not different in the two groups.

In the 305 non AID pregnancies the semen quality was correlated with the outcome of pregnancy (Table 7). There were no significant differences in sperm count, motile sperm count or percent normal spermatozoa in couples where the pregnancy resulted in miscarriage as compared to full term pregnancy. Furthermore the incidence of varicocele was similar in both groups. These data suggest that abnormal semen quality is not related to the incidence of spontaneous abortions.