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PROLACTIN AND SEXUAL DYSFUNCTION IN WOMEN

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ABSTRACT

Raised serum prolactin levels have been associated with sexual dysfunction in both men and women. The papers reporting this association using a sexual dysfunction clinic data base have mostly been done on men, and those few studies done on women have had a number of deficiencies. The current investigation involved studying serum prolactin levels in 48 women who presented to a Sexuality Clinic with a primary diagnosis of sexual dysfunction. The criteria for the specific types of sexual dysfunction were based on the *Diagnostic and statistical manual of mental disorders* (3rd ed) (DSMIII). The prevalence of hyperprolactinemia as well as the mean prolactin level of this group were compared to those of a control group of 93 women. One out of the 48 women (2.1%) in the study group was found to have hyperprolactinemia. However, the differences in both prevalence of hyperprolactinemia and mean prolactin levels, between study and control groups, were not statistically significant. No significant differences were found in mean prolactin levels among subgroups of women with different sexual diagnoses or in those with single vs. multiple sexual diagnoses. However, the presence of hyperprolactinemia may increase the probability of a woman having multiple sexual diagnoses. Larger studies with differently comprised control groups are indicated to confirm or disprove the present investigation's results.

PROLACTIN AND SEXUAL DYSFUNCTION IN WOMEN

Jeffrey P. Reiss

Hyperprolactinemia, independent of etiology, has been associated with both problems of sexual desire and of sexual performance for both men and women. Specifically, in men, hyperprolactinemia has been associated with inhibited sexual desire,[1-7] impotence[1, 3, 5-20] and ejaculatory disturbances.[2, 5, 18, 20] In women, the association has been made with inhibited sexual desire,[1, 20-22] arousal dysfunction,[22] and orgasmic difficulties.[19, 20, 23] Hyperprolactinemic men can have problems with libido and/or impotence even when their testosterone levels are normal.[4, 6, 11, 12, 24] There is ample evidence to show that after successful treatment of hyperprolactinemia with bromocryptine,[1, 7-9, 18, 22, 25, 26] other dopaminergic agonists,[27] or with surgery for pituitary adenomas,[8, 15] that the sexual dysfunction, in both sexes, improves in the majority of cases. This may be so even when testosterone levels remain low after prolactin levels have diminished, in the cases of impotence.[7] So, even though prolactin excess seems to have an effect on sexuality independent of its testosterone lowering effect, the recommmendation of assessing prolactin levels in cases of male sexual dysfunction has been made most often only after testosterone has been found to be low[5, 11, 12] for supposed cost-effectiveness or other, unexplained, reasons. However, there are others who feel that every impotent man should have prolactin assessed as a first line of investigation.[16, 19, 20] In women with sexual dysfunction, the recommendation of assessment of prolactin levels has

been recommended only for those who have failed to respond to a course of sexual therapy,[22] but guidelines for assessing prolactin levels as part of an initial evaluation are lacking.

The various physiological mechanisms that have been invoked to explain how prolactin interferes with sexual functioning include: an effect on hypothalamic gonadotropin-releasing hormone release, damage to pituitary gonadotrophs (by tumour), peripheral effects including interference with gonadal androgen production and a disturbance in the metabolic conversion of testosterone to dihydrotestosterone, and a direct central disruption of prolactin on libido.[28] The possibility that raised prolactin levels may just be a reflection of increased central serotonin activity, and that the latter may be the actual cause of sexual dysfunction, has also been raised.[29]

One of the problems with the literature to date is that there is too little information on prolactin and female sexual dysfunction as most of the studies have been done on men. This is so, even though it is commonly believed that hyperprolactinemia is more prevalent in women.[30] A second problem is that while the clinical implications of hyperprolactinemia and sexual disorders have been made, as described above, these have been derived mostly from reports and studies of people who had suspected or known hormonal problems rather than based on a population of people presenting with sexual complaints to their physicians or to a sexual dysfunction clinic. The studies that have assessed prolactin levels on a sex clinic population have mostly been done on males and have estimated the prevalence of hyperprolactinemia associated with impotence to be from 0-17%.[5, 10-12, 16, 17, 19, 20, 31]

One study[5] combined impotence and/or ejaculatory incompetence to yield a prevalence of hyperprolactinemia of 8.1% and all of those men had decreased libido as well. Another one of these studies[20] found moderate hyperprolactinemia in 10% of the men presenting with premature ejaculation.

There have been two different types of studies that have evaluated the association of prolactin and sexual dysfunction in women based on a sex clinic population. Of the first type of study there have been two reports which have addressed whether there are significant differences in plasma prolactin levels between a group of sexually dysfunctional women and a non-dysfunctional control group. In the first of these two there were significantly greater prolactin levels in the group of 11 women who presented with loss of libido and arousal dysfunction compared to 12 age-matched control women who denied any form of sexual difficulty ($p=0.05$).[22] By contrast, in the second study of this same type, 11 women with global inhibited sexual desire were found not to have a significantly greater mean prolactin level when compared to 11 women who expressed normal sexual desire and had normal sexual functioning.[32] An obvious problem with both these studies is, of course, their small number of subjects.

In the second type of study evaluating the association of prolactin and sexual dysfunction in women based on a sex clinic population, the prevalence of hyperprolactinemia per se was determined. Again, there were only two papers of this type reported in the literature. In the first of these, 5.6% of the women presenting with idiopathic frigidity were found to have moderate hyperprolactinemia.[20]

In the second study of this type, 18.4% of the women presenting with reduced or absent interest in sex and/or reduced or absent capacity for sexual arousal were found to be hyperprolactinemic.[22] This second figure may be somewhat of a high estimate due to two factors. Firstly, 80% of the group consisted of women who had previously been unsuccessful in sex therapy, thus possibly rendering the population biased to a higher prevalence of non-psychogenic dysfunction than would otherwise be expected. In fact, of the remaining 20% for whom this was their first referral, only one woman (4.8% of this group) was hyperprolactinemic. The second reason why the above quoted 18.4% may be a relatively high estimate, would be due to the low upper limit of normal prolactin levels (396 IU/L) used in that study, as compared to other laboratories.[22] Another interesting result of this study was that prolactin levels of the arousal dysfunction group were significantly higher than those of the reduced or absent interest group and the highest prolactin levels were observed in those women with both conditions. In both studies of this second type, there were some diagnostic deficiencies. Neither study used recognized standardized criteria to make their diagnoses. In addition, both studies chose to evaluate a fairly narrow scope of female sexual dysfunction.

In the present study some of the shortcomings of the earlier ones evaluating the association of prolactin and sexual dysfunction in women based on a sex clinic population, were addressed. Firstly, both the mean prolactin level and the prevalence of hyperprolactinemia were studied on the same population of sexually dysfunctional women and were compared to a control group. Secondly, all clinically recognized female

sexual dysfunctions were potentially studied using internationally recognized diagnostic criteria and labels. Thirdly, in this study, as contrasted to the others, the sexual partner, if present, was interviewed as well. This was important in order to obtain a source of collateral history and particularly to aid in sorting out primary from secondary dysfunctions, where there were multiple diagnoses.

In summary, it was the intention of this study to yield information pertaining to the association of prolactin levels with sexual dysfunction in women, as well as to provide suggestive but heuristic information regarding possible associations of prolactin with specific sexual dysfunctions, either individually or with multiple sexual dysfunction diagnoses. It was hoped that a very pragmatic implication of this study would be to provide empirical evidence as to the usefulness of ordering prolactin levels in screening for medical causes of sexual dysfunction.

METHOD

Subjects

Patients and their sexual partner (if any) presenting to the Health Sciences Centre Sexuality Clinic were either self-referred, or, more usually, were referred by their physician or other health professional. All patients had a physical examination and general medical screening (but no prolactin studies) performed by their physician to exclude any woman with a clear organic cause for her sexual problem. Patients were studied on a consecutive presentation basis with the only inclusion criterion being that of having a presentation which would qualify for a *Diagnostic and statistical*

manual of mental disorders, (3rd ed) (DSM III)[33] psychosexual dysfunction diagnosis, except that a functional etiology was not assumed in relation to possible hyperprolactinemia. The specific DSM III psychosexual dysfunctions that could have been potentially studied included: inhibited sexual desire (ISD); inhibited sexual excitement (ISE); inhibited female orgasm (IFO); dyspareunia (DYS); vaginismus (VAG); and atypical psychosexual dysfunction (APD).

A study group of approximately 50 women was initially desired. Fifty-two consecutive women were fully assessed. However, two women were eliminated from the study when it was later established that they did not meet DSM III criteria for a psychosexual dysfunction diagnosis, and two other women were eliminated from the study as insufficient blood was obtained to perform the assays. Thus, a total of 48 women were included in the patient sample. This group ranged in age from 19-60 years.

The controls utilized in this study were a group of women whose sera were used as part of the process in establishing normative values, by the Health Sciences Centre, Department of Endocrinology and Metabolism, Clinical Investigation Unit. Specifically, these data were obtained from 93 female adult blood donors who ranged in age from 18-61 years, were in good general health, neither pregnant, post-partum, or breast feeding, were on no medication, and did not receive any remuneration for donating their blood.

Procedure

All participants in this study were initially screened over the telephone to exclude obviously inappropriate subjects (eg. psychotic)

and to ascertain their ability to understand and participate in the study. Following this the patients were sent for serum analysis which was followed by general psychosexual assessment interviews, using DSM III diagnostic criteria, of both the patient and the partner, if applicable. All blood samples were taken between 8 and 9 a.m., to control for diurnal fluctuations in prolactin levels. The blood was drawn 20 minutes after intravenous puncture to ensure that the patient was in a rested state at the time of actual blood sampling, as venipuncture induced stress has been shown to transiently induce elevated prolactin levels.[28] Prolactin determinations were done by the Delphia kit fluoroimmunoassay method. Results were considered normal if they were ≤ 15 μg/L, as this was the standard determined previously by the Health Sciences Centre, Department of Endocrinology and Metabolism, Clinical Investigation Unit. If the results of any blood test were abnormal or if clinically indicated, the test was repeated to confirm the initial result. Following this, if test results remained abnormal the referring physician was notified with the recommendation for further endocrinological investigation and treatment, with the Health Sciences Centre Endocrinology Clinic being available for this service. If a test was repeated, then the average result was used for statistical purposes.

The parametric and non-parametric procedures used in the comparison of age differences between the patient and control groups were the Student's t test (two-tailed), and the Mann-Whitney U test (Wilcoxon two-sample test, two-tailed), respectively.

The statistical analysis of differences between groups for the

occurrence of hyperprolactinemia was done by the Fisher exact test. The Student's t test (two-tailed) and one-way analysis of variance (ANOVA) were used to compare mean prolactin levels among respective groups. A procedure correcting for non-homogeneity of variances was utilized as appropriate when the Student's t test was used. The Student-Newman-Keuls procedure was used in the post hoc analysis of the ANOVA.

RESULTS

Table 1 (p. 12) reveals that the patient and control groups were quite comparable in age range (19-60 vs. 18-61 years), median (both 35 years), and means (35.1 vs. 36.5 years). Furthermore, whatever difference in age that did exist between the two groups was found not to be significant by parametric and non-parametric tests.

In Table 2 (p. 13), a breakdown of the various primary diagnostic groups represented is found. The two largest groups that make up 93.8% of the patient population are the ISD and IFO ones with 54.2% and 39.6% representation, respectively. There were too few patients with a primary diagnosis of DYS (n=2) or VAG (n=1) for statistical purposes, so only the ISD and IFO groups were used for diagnosis specific calculations.

From Table 3 (p. 14), it can be seen that both the patient and control groups had one woman each with an abnormally elevated prolactin level. In the control group this one level was mildly elevated at 16.3 μ g/L (normal $\leq$15). The prolactin level of the woman in the patient group was considerably elevated at 57.0 μg/L (the average of two assays). Her primary sexual diagnosis was ISD along with secondary

diagnoses of: ISE, IFO, and DYS. Further investigation of patient #25's hyperprolactinemia ruled out primary hypothyroidism although the possibility of a pituitary microadenoma could not be excluded, so she continues to be monitored closely. Although the prevalence of hyperprolactinemia was twice as great in the patient group (2.1%) as it was in the control group (1.0%), using the Fisher exact test, this difference was not statistically significant.

Table 4 (pp. 15, 16) is a summary of the various comparisons of prolactin levels between two different groups. In this regard there was no significant difference between the patient and control populations. Although there appeared to be a non-significant trend for the patient group to have higher prolactin levels, this effect was removed when patient #25's score was eliminated from the sample, leaving almost identical mean prolactin levels for the two groups. In addition, there was no significant difference in prolactin levels between the subgroups of patients with ISD and IFO as primary diagnoses. Initially it would have appeared as if the ISD subgroup had a non-significant trend towards having higher prolactin levels. However, when patient #25 was removed from the sample or further when the patients who had both ISD and IFO as diagnoses were eliminated, if anything the reverse was the case with the IFO subgroup having the higher mean prolactin levels, though not being statistically significant. Finally, those patients with a single sexual dysfunction diagnosis had their prolactin levels compared to the patients with more than one diagnosis. As was the case in the patient vs. control comparison, any difference was virtually eliminated with the removal of patient #25 from the sample.

In Table 5 (p. 17), serum prolactin levels between single diagnosis, multiple diagnosis, and control groups were compared using an ANOVA technique. A significant difference ($p=0.035$) was obtained with the post hoc analysis revealing that the multiple diagnosis subgroup of patients had a significantly higher mean prolactin level ($p \leq 0.05$) than either the single diagnosis subgroup of patients or the control group. However, with the elimination of patient #25 from the sample, no significant difference in mean prolactin levels was found and the values did not even suggest an identifiable non-significant trend.

TABLE 1

Comparison of Age (In Years) Between Patient and Control Groups

	N	Range	Median	Mean	Standard Devaiation	Probability (Parametric and Non-Parametric)
Patient	48	19-60	35	35.1	8.6	N.S.
Control	93	18-61	35	36.5	11.3	

N.S.=Not Significant, $p>0.05$

TABLE 2

Patient Diagnostic Groups

Primary Diagnosis:	ISD	IFO	DYS	VAG	ISE	APD	TOTAL
	26	19	2	1	0	0	48

TABLE 3

Number, Prolactin Category, Range, and Median for Patient and Control Groups

	N	Prolactin ≤15 µg/L	Prolactin >15 µg/L	Range	Median
Patient	48	47	1	2.6-57.0	6.0
Control	93	92	1	2.1-16.3	5.8

TABLE 4

Comparison of Serum Prolactin Levels Between Different Groups

	N	Prolactin (μg/L)	Standard Deviation	T value	Probability	Notes
Patient	48	7.32	7.91	<1	N.S.	
Control	93	6.13	2.76			
Patient	47	6.26	3.03	<1	N.S.	Without pt. #25 (PRL-57.0)
Control	93	6.13	2.76			
ISD	26	7.88	10.36	<1	N.S.	
IFO	19	6.69	3.53			
ISD	25	5.92	2.68	<1	N.S.	Without pt. #25
IFO	19	6.69	3.53			
ISD	21	5.73	2.61	<1	N.S.	Without patients with both ISD & IFO as combination diagnoses including pt. #25
IFO	16	6.64	3.75			
Single Diagnosis	34	6.27	2.98	<1	N.S.	
Multiple Diagnoses	14	9.88	13.92			

Table 4 (Cont'd)

	N	Prolactin (µg/L)	Standard Deviation	T value	Probability	Notes
Single Diagnosis	34	6.27	2.98	<1	N.S.	Without pt. #25
Multiple Diagnoses	13	6.25	3.27			

N.S.=Not Significant, p>0.05
ISD =Inhibited Sexual Desire
IFO =Inhibited Female Orgasm

TABLE 5

Comparison of Serum Prolactin Levels Between Single Diagnosis, Multiple Diagnoses, and Control Groups

	N	Prolactin µg/L	Standard Deviation	F Ratio	F Probability	Post Hoc Analysis
Single Diagnosis	34	6.27	2.98			Group 2 is significantly different at the 0.05 level from both Groups 1 & 3
Multiple Diagnoses	14	9.88	13.92	3.43	0.035	
Control (No Diagnosis)	93	6.13	2.76			
Single Diagnosis	34	6.27	2.98			No two groups are significantly different at the 0.05 level
Multiple Diagnoses without pt. #25	13	6.25	3.27	<1	N.S.	
Control (No Diagnosis)	93	6.13	2.76			

N.S.=Not Significant, $p>0.05$

DISCUSSION

It is not surprising that the vast majority of women presenting for this study were found to have either ISD or IFO as the primary diagnosis as this finding is consistent with the clinic's historical experience and it is generally acknowledged that these problems are the most common female psychosexual dysfunctions.[34, 35]

Hyperprolactinemia was detected in one patient out of 48 yielding a prevalence of 2.1% in this sexually dysfunctional group. In the earlier quoted French study[20] the prevalence was 5.6% and in the British study,[22] even though the overall prevalence was 18.4%, of the women for whom this was their first referral (ie. not treatment resistant) the prevalence was 4.8%. When differences in laboratory techniques and standards are considered in addition to the fact that prevalence rates in relatively uncommon conditions will be more subject to variation unless the sample populations are very large, this study's finding, while somewhat lower, is not entirely dissimilar from the previous ones.

The difference in prevalence of hyperprolactinemia between the patient group (2.1%) and the control group (1.0%) was found to not be statistically significant. Be this as it may, a number of comments must be made. Firstly, it is certain that a larger patient sample would be required to make this difference in prevalence statistically significant. Stated in another way, especially given that the condition of hyperprolactinemia would seem to be relatively uncommon, this

study's n may not have been large enough to satisfactorily minimize the risk of committing a Type II or beta error. Secondly, it is important to recognize that the control group chosen in this study was potentially biased against finding statisically significant differences between it and the patient group because these lab controls were not assessed as to their sexual functioning status. Hence, for example, it is conceivable that the hyperprolactinemic woman in the control group was sexually dysfunctional herself. Furthermore, while the patient and control groups were similar with respect to age composition, they were not comparable in other ways that could have potentially increased or decreased the likelihood of finding a significant difference in prolactin levels. Differences in blood drawing technique and the lack of a standard time of day for obtaining blood samples from the controls would be examples of this potential effect.

As mentioned earlier, there have been two studies that have addressed the issue of whether there are significant differences in mean prolactin levels between a sexually dysfunctional group and a control group of women, with one study reporting positively[22] and the other study concluding to the negative.[32] In the present study no significant difference was found between the two group's mean prolactin levels. However, the comments made in the previous paragraph apply here as well.

In relation to these above mentioned comments or apparent study design deficiencies, an explanation is required. At the commencement of this project (when funding was requested) there were no studies relating to association of prolactin and female sexual dysfunctions

either published or aware of by the author of this paper. Therefore, this study was to be the first of its type; a sample size of fifty was deemed reasonable as the prevalence of hyperprolactinemia in this group of women was truly unknown; and a control group reflecting the population at large was readily available. Should there have been positive results with this design, then that would have been satisfactory; however negative results (as has occurred) would indicate the need to either increase the sample population and/or use a control group of women who had previously been determined to have no sexual dysfunction and submit them to the identical procedure for blood drawing as the study group. Unfortunately, this ideal proposed study is still lacking in the literature.

One of the earlier mentioned studies[22] reported significantly higher prolactin levels in women with arousal dysfunctions vs. women with reduced/absent sexual interest and the highest prolactin levels being observed in those women with both conditions. This present study yielded somewhat similar results. The IFO (without secondary ISD) subgroup had a higher mean prolactin level (6.64 μg/L) than the ISD (without secondary IFO) subgroup (5.73 μg/L). However, as earlier mentioned, this difference was not significant. As well, in this study the highest prolactin levels were obtained by the women who had more than one sexual diagnosis as compared to one or no diagnosis, and this was statistically significant. However, as mentioned earlier, this effect was entirely attributable to one woman's test results (patient #25). One hypothesis that is supported by both this study and the other,[22] is that the presence of multiple diagnoses may not be

associated with hyperprolactinemia as much as that the presence of hyperprolactinemia may increase the probability of a woman having multiple sexual diagnoses.

While this study did control for stress related and diurnal variations in prolactin levels by blood sampling 20 minutes post venipuncture and at a specific time of day, it could be argued that even more reliable results could be obtained with averaging samples taken on more than one occasion as well as with multiple sampling being done on each separate occasion. Obviously though, this would be an expensive venture that might not be justified.

It was hoped that this study would help provide some empirical evidence as to the usefulness of ordering prolactin levels in screening for medical causes of sexual dysfunction. Clearly there would have been no question in this regard if the prevalence of hyperprolactinemia found in this study had been high; but it was only 2.1%. This taken together with the other studies[20, 22] would indicate that the prevalence of hyperprolactinemia in women presenting for the first time to a sexual dysfunction clinic is of the magnitude of approximately 5% or less. As to whether or not this prevalence rate is high enough to warrant routine prolactin studies, clinical experience and judgement rather than empirically derived data, must be the basis for such a decision. The author suggests that, even though the prevalence may appear to be low, it should be remembered that hyperprolactinemia, in most cases, is readily treatable.[1, 9, 28] Appropriate clinical advice at this time may be to check serum prolactin levels in women presenting with a history of irregular menses, oligo/amenorrhea, or galactorrhea,

or in those who have no clear psychological contributants to the sexual dysfunction, are psychotherapeutically treatment resistant, or have secondary and/or global vs. primary and/or situational sexual dysfunction. Further studies are required to truly validate these recommendations.

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