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Prolactin and aggression in women with fertility problems

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This study tested the hypothesis that women with higher prolactin feel more hostility, anger and aggression. A total of 66 women with moderate fertility problems were grouped into the 50% who had the highest and the 50% who had the lowest levels of prolactin. Levels of hostility, aggression and anger were compared. Women with higher prolactin levels did not report significantly increased hostility. After Bonferroni correction, women with lower prolactin showed non-significantly increased scores on two measures of state anger, and on a measure of trait temper. When comparing those with the highest and lowest 20% of prolactin levels, those with lower prolactin had non-significantly higher scores on trait temper and outward expression of anger, and non-significantly lower scores for control of anger. Although non-significant, these findings run counter to those of earlier studies on this topic. Implications for future research and patient care are discussed.

Keywords: Aggression, anger, hostility, infertility, polycystic ovary syndrome, prolactin

Introduction

Some animal research suggests that prolactin promotes the protective behaviour known as maternal aggression (Numan 1988). Placental mammals typically exhibit maternal behaviours, and it is plausible that women experience subtle changes in behaviour after childbirth. Prolactin levels increase steeply during pregnancy and decrease in the weeks after delivery (Battin et al. 1985). During lactation, prolactin stimulates milk production (Del Pozo et al. 1979), and prolactin is released at intervals in response to each occasion that the infant suckles (Uvnäs-Moberg et al. 1990b). The mechanism for the effect of prolactin on brain and behaviour might be related to the presence of prolactin receptors in the hypothalamus, where binding is especially high in females (Di Carlo et al. 1992). Many studies have found that the hypothalamus is implicated in the control of aggression in humans (Siegel and Victoroff 2009).

Anger, aggression and hostility

Research on the relationship between prolactin and aggression-related affect in humans has tended to focus mostly on hostility rather than anger or aggression. Although it should be noted that these three constructs are highly intercorrelated, Miller et al. (1996) offer distinctions between the three, which may be useful: aggression is an overt behaviour, which may be expressed verbally or physically; anger is an unpleasant emotion varying in intensity from mild irritation to rage, and may be experienced cognitively and/or physiologically; and hostility is a cognitive state, consisting of negative beliefs and attitudes about other people, principally mistrust, cynicism and suspicion that others' motives are malign.

Prolactin and hostility

Seminal studies on prolactin and hostility in human participants found that women with higher prolactin levels were more hostile than women with normal levels of prolactin (Fava et al. 1981; Mastrogiacomo et al. 1982; Kellner et al. 1984; Fava et al. 1988). More recently, a study found moderately more hostility in hyperprolactinaemic women than female control patients with normal prolactin levels (Reavley et al. 1997).

Infertility is clinically defined as being unable to conceive within 12 months (Abma et al. 1997) and has been associated with increased distress, for women more so than for men (Wright et al. 1991). Grief-like responses to lacking reproductive success are common among infertile women (Lee et al. 2010). Because the prolactin/aggression link is commonly associated with maternal aggression and the postpartum period, it could be suggested that women who are experiencing reduced reproductive health or who are infertile, might not experience the expected relationship between prolactin and aggression. However, findings from a study of amenorrhoea (Fava et al. 1981) and a study of infertility (Csemiczky et al. 2000) suggest that infertility by itself does not have an impact on the expected relationship between prolactin and hostility.

One of the most common causes of infertility is polycystic ovary syndrome (PCOS), which affects 5–10% of women (Franks 1995). Because elevated testosterone is often seen in PCOS, it has been hypothesised that aggression will be higher among women with PCOS. However, research evidence has found that although women with PCOS may experience mildly elevated anxiety and depression (Barry et al. 2011b), findings of outward aggression are either absent (Barry et al. 2011a) or not particularly strong (Elsenbruch et al. 2003), suggesting that testosterone does not increase aggression in women with PCOS.

Given the overall evidence from previous research, the present study hypothesised that higher levels of prolactin would be associated with greater hostility, anger and aggression.

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Materials and methods

This study was a cross-sectional independent groups design. It was conducted with the approval of and in accordance with the guidelines of the Research Ethics Committees of participating clinics. Additional permission to assess prolactin levels was granted by the Queen's Square Research Ethics Committee, London. Participants were identified only by a code to ensure anonymity. Written, informed consent was given by all participants prior to their inclusion in the study.

Participants

All women were examined by an endocrinologist or gynaecologist. They were recruited as part of a previous study (Barry et al. 2011a), and the present study describes a subset of these women, for whom data on prolactin were available.

A total of 33 women with PCOS were recruited from London gynaecology clinics (the Royal Free Hospital, University College London Hospital, Guy's Hospital and the Centre for Reproductive and Genetic Health). Inclusion criteria were: (1) diagnosis of PCOS by the Rotterdam criteria (Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group 2004); (2) aged 18–45 years. Exclusion criteria were: (1) any condition other than PCOS-affecting hormones (with the exception of well-controlled hypothyroidism), e.g. menopause, congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome; (2) being treated with any drugs that affect hormones (other than thyroid hormone or drugs used to treat PCOS, e.g. Metformin or Dianette); (3) history of psychotic illness; (4) because questionnaires were used, participants who were not fluent in English were also excluded.

A total of 33 women with fertility issues not related to PCOS were recruited from the same London gynaecology clinics as the PCOS participants. Women who would qualify for a diagnosis of PCOS according to the Rotterdam criteria were excluded from the control group. All other inclusion and exclusion criteria for the PCOS group were also applied to the selection of the control group.

Information on diagnosis and medication use were confirmed from hospital records.

Allocation to groups: high–normal vs low–normal prolactin

The participants were allocated to high–normal or low–normal prolactin groups, by dividing the observed prolactin values into the top 50% and bottom 50%. The 50th centile (midpoint) was 250 mIU/l. The normal range for prolactin is roughly 100–500 mIU/l. To increase sensitivity to any effects of prolactin on hostility, the groups were additionally grouped as the top 20% of prolactin values ($>$ 353 mIU/l) vs the bottom 20% ($<$ 165 mIU/l).

Questionnaires

The Aggression Questionnaire (AQ)

The Aggression Questionnaire (Buss and Perry 1992) uses 19 items to measure four aspects of trait aggression: physical aggression, verbal aggression, anger and hostility. Items are measured on a five-point scale from 'extremely uncharacteristic of me' to 'extremely characteristic of me'. An example of items from the Hostility subscale were: 'At times I feel I have got a raw deal out of life'; 'Other people always seem to get the breaks'; and 'I am suspicious of overly friendly strangers'. The subscales can be added to give a total AQ score.

The State − Trait Anger Expression Inventory (STAXI)

The STAXI (Spielberger 2010) uses 44 items to measure various aspects of current (state) and long-term (trait) personal expression of anger. The five subscales are: state anger, trait anger, anger-in (anger suppression), anger-out (anger expression), anger control and extreme problems in dealing with anger.

The Framingham Anger Measure

The Framingham Anger Measure (Haynes et al. 1978) uses 12 items to measure four aspects of anger: anger symptoms (e.g. 'get tense or worried'); anger-in (e.g. 'keep it to myself'), anger-out (e.g. 'take it out on others') and anger discuss (e.g. 'talk to a friend or relative').

Control measures

PCOS Quality of Life (QoL) Questionnaire (PCOSQ)

The PCOS Questionnaire (Cronin et al. 1998) uses 26 items to assess the impact of: emotions, hirsutism, weight, infertility, menstrual problems and acne on the patient's QoL. Lower scores indicate a worse QoL.

Socioeconomic classification (SEC) was defined by the Office for National Statistics three-class hierarchy of: managerial and professional, intermediate occupations and routine and manual jobs (ONS 2010).

The Recent Life Changes Questionnaire (RLCQ)

The RLCQ (Miller and Rahe 1997) measures the amount of stress experienced due to life changes over the past 12 months in relation to: health, work, home and family, personal and social and finances. Life Change Unit (LCU) totals of 500 and above indicate high recent life stress.

Hospital Anxiety and Depression Scale (HADS)

The HADS scale (Zigmond and Snaith 1983) uses 14 items to measure state anxiety and depression in medical outpatients. Scores of 8–10 indicate a mild problem.

Hormone assays

All of the serum prolactin concentrations were measured using a two-step, sandwich electrochemiluminescence immunoassay (ECLIA), supplied in kit form by Roche Diagnostics and performed on Roche Modular Elecsys systems (E170, 2010, 1010; Roche Diagnostics, Indianapolis, IN). The same assay method was used at all four participating clinics. A total of 49 (74%) of the samples came from the Royal Free London Hospital; 15 (23%) from UCLH; one (1.5%) from Guy's Hospital and one (1.5%) from the Centre for Reproductive and Genetic Health. The inter-assay and intra-assay coefficients of variation were all less than 2%. Reference intervals for women for this assay are 102–496 mIU/l. The analytical range is 1–10,000 mIU/l.

Procedure

Patients who met the inclusion criteria were identified by the consultant or other attending doctors at the participating clinics.

Blood collection

Blood was taken with a 21-gauge needle by the clinic's phlebotomist. Serum samples were transferred to 10 ml gel activator clotting tubes. Samples were centrifuged and then frozen until assayed.

Statistical analysis

The statistical package SPSS for Windows (version 20) was used for all statistical analyses. Comparisons were made using independent group *t*-tests. Where *t*-tests failed, Levene's test of equality of variances, the 'equal variances not assumed' statistics are reported.

Demographic variables were assessed by independent *t*-tests and χ^2-tests (or Fisher's exact tests, where an expected frequency was lower than 5). For demographics and control variables, the significance threshold was $p < 0.05$. For the measures of aggression, in order to reduce the chance of type 1 error due to the multiple testing of using 18 subscales, the significance threshold was adjusted, using the Bonferroni correction (α/n tests), to $p < 0.0028$ (i.e. 0.05/18). All significance levels reported are two-tailed.

Results

For the 66 participants, 8.44% of data were missing on the psychometric variables included. Little's *Missing Completely at Random* (MCAR) test indicated that the missing data did not show a significant pattern ($\chi^2 = 244.224$, df $= 267$, $p < 0.838$), thus missing data were not considered problematic.

Table I shows descriptive statistics and statistical comparisons for the background variables of the high–normal and low–normal prolactin groups.

The two groups were similar in terms of background variables. For example, the groups were similar in terms of age, BMI and stress, and scored similarly for the QoL impact of fertility problems and menstrual problems, both indicating 'some problems' to 'moderate problems', with fertility and menstrual functioning.

Table II compares the scores of the high and low prolactin groups on the various measures of aggression. Also presented are two subgroups of women with the lowest and highest 20% of prolactin levels.

In the groups split at 250 mIU/l, after Bonferroni correction the low–normal prolactin group scored non-significantly higher on the AQ (trait) anger, STAXI trait anger and STAXI trait temper. When comparing scores of those with the highest and lowest 20% of prolactin levels, those with lower prolactin had non-significantly higher scores on STAXI trait temper and STAXI outward expression of anger, and non-significantly lower scores for STAXI control of anger.

Discussion

In this study of women who experienced moderate levels of fertility problems, lower levels of prolactin were associated with statistically non-significantly higher levels of anger and non-significantly higher hostility and aggression after Bonferroni correction. Although the differences between groups in hostility and aggression were statistically non-significant, the results show an overall trend towards higher hostility, anger and aggression in the women with lower prolactin levels.

Some previous research has found that higher prolactin is related to more hostility (Fava et al. 1981; Mastrogiacomo et al. 1982; Fava et al. 1988; Kellner et al. 1984; Reavley et al. 1997; Csemiczky et al. 2000) and the results of the present study seemingly do not support the findings of previous research. In fact, the findings for anger, aggression and hostility tend to go in the opposite direction of that predicted. What might explain these unexpected findings? The answer might lie in the methodology of the present study, which differs in four main ways from the meth-

Table I. Demographic and background data, showing means (and standard deviations) and independent-groups tests (*t*-tests, χ^2 or Fisher's exact tests) for the lower prolactin (PRL $<$ 250 mIU/l) compared with higher prolactin (PRL $>$ 250 mIU/l) group.

Variable	PRL $<$ 250 mIU/l ($n = 33$)[a]	PRL $>$ 250 mIU/l ($n = 33$)[a]	Test statistic
Prolactin (PRL) (mIU/l)	181.54 (40.54)	430.52 (309.16)	-4.587***,[b]
Age (years)	30.03 (5.49)	29.85 (5.88)	0.129
BMI	28.08 (8.48)	26.60 (6.71)	0.727
QoL Menstrual	3.99	3.77	0.542
QoL Infertility	3.31	3.89	-1.12
Life stress (LCUs)	400.14 (229.6)	381.82 (214.5)	0.747
Anxiety (HADS)	9.61 (5.14)	9.88 (4.35)	-0.224
SEC			
Professional	11 (42%)	12 (41%)	1.98[d]
Intermediate occupation	2 (8%)	6 (21%)	
Routine/Manual	13 (50%)	11 (38%)	
Ethnic Group[a]			
White	15 (56%)	17 (61%)	0.572[d]
Black	3 (11%)	3 (11%)	
Asian	2 (7%)	3 (11%)	
Chinese	1 (4%)	1 (4%)	
Mixed race	5 (19%)	1 (17%)	
Other	1 (4%)	3 (11%)	
Fertility group			
PCOS	23 (70%)	24 (73%)	0.074[c]
Other subfertile	10 (30%)	9 (27%)	
Medication			
E2–promoting[e]	16 (64%)	11 (55%)	0.375[c]
No medication	9 (36%)	9 (45%)	

Significance values are 2-tailed; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. PRL, prolactin; BMI, body mass index; QoL, Quality of life; SEC, socioeconomic class; PCOS, polycystic ovary syndrome; LCUs, life change units; HADS, Hospital Anxiety and Depression Scale.
[a]Group sizes varied slightly across tests.
[b]*t*-test with 'equal variances not assumed' correction.
[c]χ^2-test.
[d]Fisher's exact test.
[e]Contraceptive pill or fertility-enhancing treatments are medications known to stimulate E2 or reduce androgens.

Table II. Descriptive statistics (mean and SDs) and between groups tests (*t*-tests, χ^2-tests or Fisher's exact tests) for comparing aggression outcomes in the groups based on prolactin levels. The lowest and highest 20% are represented by the < 165 and > 353 groups.

Outcome variable	PRL < 250 mIU/l ($n = 33$)[a]	PRL > 250 mIU/l ($n = 33$)[a]	*t* value	PRL < 165 mIU/l ($n = 10$)[b]	PRL > 353 mIU/l ($n = 15$)[b]	*t* value
AQ Hostile	19.83 (9.26)	18.19 (6.66)	0.80[c]	19.20 (9.45)	17.40 (4.31)	0.57[c]
AQ Physical	18.00 (7.11)	15.50 (5.75)	1.49	21.40 (9.43)	15.00 (5.83)	2.06
AQ Verbal	12.67 (5.18)	12.81 (4.63)	−0.12	13.10 (5.45)	12.86 (5.74)	0.14
AQ Anger	18.86 (7.68)	14.88 (4.64)	2.42[c]	19.33 (8.97)	12.93 (3.51)	2.05[c]
AQ Total	68.61 (22.44)	60.52 (16.16)	1.57	73.89 (26.73)	56.08 (12.15)	1.87[c]
STAXI State anger	12.0 (3.95)	13.36 (6.55)	−0.98	12.80 (6.21)	11.00 (1.30)	0.90[c]
STAXI Trait anger	21.90 (7.66)	18.48 (4.9)	2.07	22.30 (9.37)	17.21 (4.17)	1.61[c]
STAXI Trait temper	8.07 (3.75)	6.23 (1.88)	2.38[c]	9.00 (4.32)	5.64 (1.65)	2.34[c]
STAXI Reactivity	10.13 (3.22)	9.10 (2.72)	1.39	9.40 (3.78)	8.93 (2.74)	0.36
STAXI Anger-in	17.72 (5.71)	17.83 (5.25)	−0.08	16.67 (5.70)	17.80 (5.57)	−0.46
STAXI Anger-out	16.53 (5.28)	14.52 (3.3)	1.78[c]	17.80 (5.57)	13.50 (2.03)	2.33[c]
STAXI Anger control	20.97 (6.17)	23.44 (5.79)	−1.63	20.30 (6.93)	26.00 (5.40)	−2.31
STAXI Extreme	29.31 (13.25)	23.50 (9.29)	1.92[c]	30.44 (15.74)	21.00 (9.64)	1.75
Fram. Anger symptoms	0.50 (0.32)	0.56 (0.28)	−0.71	0.39 (0.34)	0.47 (0.21)	−0.72
Fram. Anger-in	0.43 (0.35)	0.42 (0.29)	0.04	0.35 (0.36)	0.42 (0.27)	−0.50
Fram. Anger-out	0.38 (0.34)	0.28 (0.25)	1.18[c]	0.36 (0.42)	0.25 (0.28)	0.77
Fram. Anger discuss	0.67 (0.30)	0.55 (0.27)	1.64	0.69 (0.34)	0.57 (0.29)	0.93

PRL, prolactin; AQ, Aggression Questionnaire; STAXI, State-Trait Anger Expression Inventory; Fram., Framingham Anger Measure.
[a]Grouped as the upper and lower 50% of values. The midpoint was 250 mIU/l. Where psychometric data were missing, tests have fewer participants (minimum 28 participants in a group).
[b]Grouped as the highest 20% (> 353 mIU/l) vs the lowest 20% (< 165 mIU/l) of prolactin levels. Where psychometric data were missing, tests have fewer participants (minimum 9 participants in the < 165 mIU/l group).
[c]*t*-test with 'equal variances not assumed' adjustment.

odology of some previous research that concluded that prolactin increases aggression.

First, four previous studies assessed hostility using the Kellner Symptom Questionnaire (KSQ) (Fava et al. 1981; Mastrogiacomo et al. 1982; Kellner et al. 1984; Fava et al. 1988). It is possible that this measure may be particularly sensitive to the relationship between prolactin and hostility, but this possibility is not particularly strong, given that the items in the KSQ do not seem very different than items in other hostility questionnaires.

Second, the control groups used in previous studies differ from that used in the present study. The present study compared two groups of subfertile women. Previous research found that women who were infertile and seeking fertility treatment had higher levels of prolactin and hostility than fertile controls (Csemiczky et al. 2000). However, these groups were not equivalent, because the stress of seeking fertility treatment may have been a confounding variable, complicating the relationship between prolactin and hostility. By using only groups of women with comparable levels of infertility in the present study, the stress associated with fertility status was accounted for, thus fertility issues cannot explain the observed relationship between prolactin and anger. It is interesting that, of the four studies that used the KSQ, only one of them compared equivalent groups which differed only on prolactin level (Fava et al. 1988), and this study, it was found that hostility was only non-significantly higher in the high prolactin group. It may have been useful for the present study to have included, if possible, a healthy control group matched on all variables, including PRL, with the PCOS and subfertility group, because this would allow an improved assessment of any effect of infertility on hostility.

In-keeping with the previous point regarding equivalence of groups, not all studies have controlled for other extraneous variables. It is known that anxiety or life stress may elevate prolactin (Reavley et al. 1997; Sonino et al. 2004), as will some types of medication (Del Pozo and Brownell 1979) and pain (Torre

and Falorni 2007). In the present study, relevant characteristics of the women in both groups (age, BMI, socioeconomic status, life stress, anxiety, medication use and quality of life for menstrual and fertility problems) were very similar, and remained similar in the subgroups of women with the highest and lowest prolactin levels. However, not all previous research has been so well controlled. Similarly, in studies where the samples consisted of postpartum women, the hormone oxytocin, which is higher in women postpartum and known to reduce aggression, needs to be controlled in studies of postpartum hostility, though this has not always been done in all previous research in this area (Uvnäs-Moberg et al. 1990a).

Finally, the range of prolactin levels in some previous studies was wider than the range in the present study. Specifically, three previous studies compared normal prolactin levels with prolactin levels above the norm (Fava et al. 1981; Fava et al. 1988; Kellner et al. 1984). By contrast, in the present study, the groups consisted of low–normal to high–normal levels of prolactin, and nearly all levels observed were within the normal range of 102–496 mIU/l (four women had values moderately above the norm but did not show increased scores in the measures of hostility, aggression or anger). Thus, although previous research suggests that, when examining normal vs high prolactin levels, high prolactin is related to more hostility (Fava et al. 1981; Kellner et al. 1984; Fava et al. 1988); by contrast, the present study suggests that, when looking at high–normal vs low–normal levels, low–normal prolactin is related to higher hostility. However, rather than contradicting previous research, the present study is perhaps extending our knowledge of this topic by describing the relationship between prolactin levels within the normal range and anger. Placing side-by-side the evidence from the present study and previous studies (Fava et al. 1981; Mastrogiacomo et al. 1982; Kellner et al. 1984; Fava et al. 1988; Csemiczky et al. 2000), it appears possible that the relationship between prolactin and hostility may possibly be a

weak linear/positive quadratic (J-shaped) correlation. A non-linear relationship between prolactin and psychological factors is plausible, and has been found previously in women (Henry and Sherwin 2012), although not in relation to anger or aggression. The present study may therefore be of importance in telling us something new about the psychobiology of prolactin in the normal range, as opposed to those studies of women for whom high prolactin is caused by a medical condition (Fava et al. 1981; Mastrogiacomo et al. 1982; Kellner et al. 1984; Fava et al. 1988), which may be more relevant to our knowledge of the psychopathology of prolactin.

It is important to note that a complex network of biological factors, notably the neurotransmitter dopamine, affects prolactin levels. Dopamine inhibits the release of prolactin in the pituitary gland (Fitzgerald and Dinan 2008; Ben-Jonathan and Hnasko 2001), and dopamine receptor antagonists are related to increased prolactin levels (Fitzgerald and Dinan 2008). Furthermore, stimulation of dopamine D2 receptors is also related to increased aggression in mammals (Nikulina and Kapralova 1992; Ferrari et al. 2003). Similarly, aggression in humans has been successfully treated by dopamine receptor antagonists (Nelson and Trainor 2007). Thus, the inverse relationship between dopamine and prolactin, as well as the direct relationship between dopamine and aggression found in previous research, supports the finding – albeit non-significant – of increased aggression among those with lower levels of prolactin in the present study.

In conclusion, because prolactin levels are influenced by a number of variables, caution should be taken when interpreting relationships between prolactin and aggression in studies that are not tightly controlled. It appears that the relationship between prolactin and aggression may be weak and complex, with higher levels of anger, hostility or aggression being seen at very low and very high levels of prolactin. Further research should include prolactin samples from as wide a range as possible, so that this apparently complex relationship may be understood more fully.

Acknowledgements

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