

## A STUDY ON THE ROLE OF ELEVATED SERUM PROLACTIN IN PRIMARY FEMALE INFERTILITY

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### ABSTRACT

#### BACKGROUND

Infertility affects large number of couples both globally as well as in India. Primary infertility is a common, preventable, but neglected reproductive health problem in developing countries like India. The present study was undertaken in an attempt to find out the role of hyperprolactinaemia or elevated prolactin level in the development of primary infertility in female and analyse its effect in folliculogenesis.

#### MATERIALS AND METHODS

In this study, 52 female subjects with the complaint of primary infertility in the child bearing age group who have attended Obstetrics and Gynaecology, Outpatient Department, Gauhati Medical College and Hospital, Guwahati, for treatment were taken as the cases.

#### RESULTS

The incidence of hyperprolactinaemia, i.e. serum prolactin levels >25 ng/mL in the infertile women was 42.31%, whereas in the control group of fertile females, the incidence of hyperprolactinaemia was 13.46%. Anovulatory cycles were detected in 51.92% of the infertile group, whereas in the control group, it was detected in 7.69%. Galactorrhea was present in 9.62% of the infertile women. Menstrual disorders observed in the infertile and control groups were 61.54% and 17.31%, respectively. The results of the study were statistically analysed.

#### CONCLUSION

There is a high incidence of hyperprolactinaemia in infertile women. Percentage of anovulatory/delayed ovulatory cycles were also found to be higher in the infertile group than the fertile females.

#### KEYWORDS

Anovulatory Cycles, Hyperprolactinaemia, Primary Infertility.

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#### BACKGROUND

Infertility affects large number of couples both globally as well as in India. It may not be a threat to physical health, but carries with it extremely adverse social and psychological implications. As a result, they suffer physical and mental abuse, neglect, abandonment, economic deprivation and social ostracism as well as deprivation from certain social activities and traditional ceremonies.<sup>1</sup>

It is estimated that 60-80 million couples suffer from infertility every year of which probably between 15-20 millions (25%) are in India alone.<sup>2,3</sup> Infertility is acquiring a proportion of global epidemic with the prevalence rate of approximately 8-12%.<sup>4</sup>

World Health Organization (1991) defines infertility as failure to conceive despite one year of cohabitation and exposure to pregnancy. If the couple has never conceived, despite cohabitation and exposure to pregnancy for a period of one year, it is called primary infertility.<sup>5</sup> Globally, most infertile couples suffer from primary infertility. The WHO estimates the overall prevalence of primary infertility in India to be between 3.9 and 16.8 percent. Estimates of infertility vary widely among Indian states from 3.7 percent in Uttar Pradesh, Himachal Pradesh and Maharashtra to 5 percent in Andhra Pradesh and 15 percent in Kashmir.<sup>6</sup> Moreover, the prevalence of primary infertility has been shown to vary across tribes and castes within the same region.

Hormonal disorders of female reproductive system is comprised of a number of problems resulting from aberrant dysfunction of hypothalamic-pituitary-ovarian axis. These relatively common disorders often lead to infertility. Difficulty to conceive or subfertility constitute a major psychological burden. Proper evaluation of these disorders involves a multidimensional diagnostic approach.<sup>7</sup>

Hyperprolactinaemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH (gonadotropin releasing hormone) and hence interfering

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with ovulation.<sup>8,9</sup> This disorder has been implicated in menstrual and ovulatory dysfunctions like amenorrhoea, oligomenorrhoea, anovulation, inadequate corpus luteal phase and galactorrhea.<sup>10,11</sup>

Estimation of serum prolactin levels is recommended in women with unexplained infertility, any menstrual irregularity with or without amenorrhoea, luteal phase defects, anovulation, anovulatory bleeding and delayed puberty. Apart from these groups of women, infertile women with regular menses also may have hyperprolactinaemia.<sup>12</sup>

The aim of the study is to find the incidence of hyperprolactinaemia in primary female infertility and analyse its effect in folliculogenesis.

### Aims and Objectives

1. To identify the risk factors associated with primary female infertility and compare it with that of healthy fertile controls.
2. To find the incidence of hyperprolactinaemia in the infertile females and their controls.
3. To investigate the impact of hyperprolactinaemia on the fertility of the subjects by follicular study.

### MATERIALS AND METHODS

The cases consists of 52 female subjects in the child bearing age group with the complaint of primary infertility who have attended Obstetrics and Gynaecology Outpatient Department, Gauhati Medical College and Hospital, Guwahati for treatment. The male partners were verified with recent semen analysis and relevant questions and only the female partners were taken into consideration for further study.

The inclusion criteria for the selection of cases are-

- Diagnosis of primary infertility.
- Age between 20-35 years.
- Duration of marriage more than one year.

The exclusion criteria that were adopted during case selection are male factor infertility and among the female factors are tubal factor and any congenital anomaly of the urogenital tract or any obvious organic lesions. Any history of tuberculosis, thyroid disease or previous thyroid surgery or being on thyroid medication were also amounted to exclusion from the study. The protocol for infertility workup in the women included a detailed medical history on a prepared questionnaire, a clinical examination, an ultrasonography, estimation of serum prolactin level and follicular study by transvaginal sonography. The same number (52 nos.) of healthy fertile females (parous, nonpregnant, nonlactating) of Gauhati Medical College and Hospital with similar age range and socioeconomic status were enrolled as controls.

The participants were enrolled after signing on informed consent. For prolactin estimation, a fasting mid-morning venous sample in follicular phase was taken. Serum was separated and the levels determined using ELISA technique. The normal range of serum prolactin taken was 2-25 ng/mL. These values were used to confirm abnormal cases. The

laboratory works were carried out in the Department of Anatomy, Gauhati Medical College, Guwahati.

Follicular study by transvaginal sonography was carried out on 3<sup>rd</sup>, 11<sup>th</sup>, 13<sup>th</sup> and 15-17<sup>th</sup> day of menstrual cycle in the females with regular menstrual cycle. In women with irregular cycle, the last follicular study was done calculating the mid-cycle period.

The effect of elevated serum prolactin level or hyperprolactinaemia on the fertility of the subjects and its effect in folliculogenesis were analysed.

For the statistical analysis, calculation of Odds ratio was done using MedCalc software and the calculation of risk ratio and Chi-square were done by using Vassarstats software. Univariate analysis of risk calculation was done by Odds ratio with 95% confidence interval.

### RESULTS AND OBSERVATIONS

The study was conducted on a total number of 52 primary infertility patients. The same number of healthy females were taken as controls. The age of the patients and the controls in the present study varied from 20 to 35 years. Maximum number of infertile women belonged to the age between 26 to 30 yrs. (29 cases, 55.77%), 18 cases (34.61%) belonged to the age group 31-35 yrs. and 5 cases (9.62%) belonged to the age between 20-25 yrs. Majority of infertile women were from urban area. The duration of primary infertility in 29 cases (55.77%) were between 2-5 yrs. of marriage, 15 cases (28.85%) were between 6-9 yrs. and 8 cases (15.38%) were married for 10 yrs. and above. In 31/52 (59.62%) cases age at marriage was 25 yrs. and above, whereas in majority of the controls (61.54%), the age at marriage was less than 25 yrs. In about 63.46% of females with primary infertility, the age at menarche was delayed (14 yrs. and above), whereas in 57.69% of the control group, the age at menarche was less than 14 yrs. Majority of the cases (51.92%) passed senior secondary and in case of controls 40.38% passed senior secondary. Most of the infertile women reported their primary occupation to be housewife (73.08%). Only five women with primary infertility reported using alcohol or cigarettes, and among the controls, 7 women reported using alcohol or cigarettes. Out of the total number of females with primary infertility, 31 cases (59.62%) were found to be overweight, whereas in the control group, 26.92% (14/52) were found to be overweight. No patients were found to be obese in our study. Normal menstrual cycles were present in 20 patients with primary infertility (38.46%). The remaining 32 (61.54%) showed some menstrual abnormality. Out of the patients with irregular menstrual cycle, 23 cases (71.88%) showed oligomenorrhoea/hypomenorrhoea. Menstrual irregularities were detected in 17.31% of the controls. Follicular study was done in both the cases and controls by transvaginal sonography. 27/52 (51.92%) cases of primary infertility presented with anovulatory cycles, whereas delayed ovulatory cycles were detected in 2 cases. 27/52 (51.92%) cases presented with stress either at home or at workplace or both. The incidence of hyperprolactinaemia (>25 ng/mL) was 42.31% (22/52) in the primary infertility

patients, whereas in the control group, it was found to be 13.46% (7/52). The mean serum prolactin level in the hyperprolactinaemic women in the infertile group was 60.29

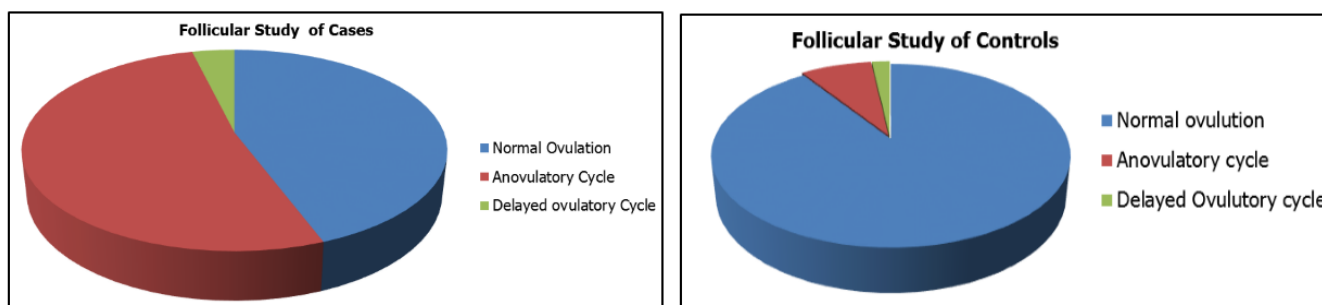
ng/mL. 17/22 (77.27%) high prolactin cases showed anovulatory/delayed ovulatory cycles.

Risk Factor	Cases n=52 (%)	Controls n=52 (%)	Z Statistics	P value	OR	Confidence Limit
<b>Age at Marriage</b>						
≥25 years	31 (59.62)	20 (38.46)	2.141	0.0323*	2.3619	1.0745-5.1874
<25 years	21 (40.38)	32 (61.54)				
<b>Education</b>						
≥Senior secondary	27 ( 51.92)	21 (40.38)	1.177	0.2390*	1.5943	0.7335-3.4654
<Senior secondary	25 (48.08)	31 (59.62)				
<b>Occupation</b>						
Working	14 (26.92)	28 (53.85)	2.754	0.0059	0.3158	0.1391-0.7172
Housewife	38 (73.08)	24 (46.15)				
<b>Overweight</b>						
Yes	31 (59.62)	14 (26.92)	3.293	0.001*	4.0068	1.7541-9.1526
No	21(40.38)	38 (73.08)				
<b>Stress</b>						
Yes	27 (51.92)	23 (44.23)	0.784	0.4329	1.3617	0.6295-2.9459
No	25 (48.08)	29 (55.77)				
<b>Menstrual Pattern</b>						
Irregular	32 (61.54)	9 (17.31)	4.380	<0.0001*	7.6444	3.07672-18.9935
Regular	20 (38.46)	43 (82.69)				
<b>Age at Menarche</b>						
≥14 years	33 (63.46)	22 (42.31)	2.14	0.0320*	2.3684	1.0768-5.2092
<14 years	19 (36.54)	30 (57.69)				
<b>OCP Intake</b>						
Yes	24 (46.15)	25 (48.08)	0.196	0.8443	0.9257	0.4285-1.9997
No	28 (53.85)	27 (51.92)				

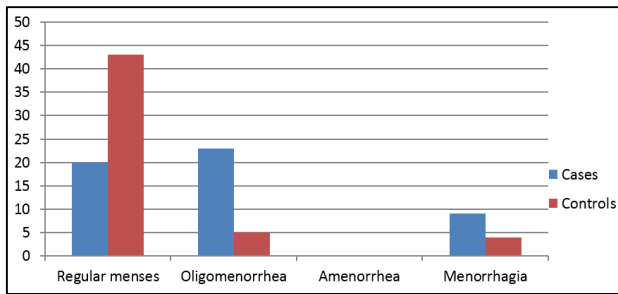
**Table 1. Association of Risk Factors with Cases of Primary Infertility and Controls**

\*Significant, OR = Odds Ratio.

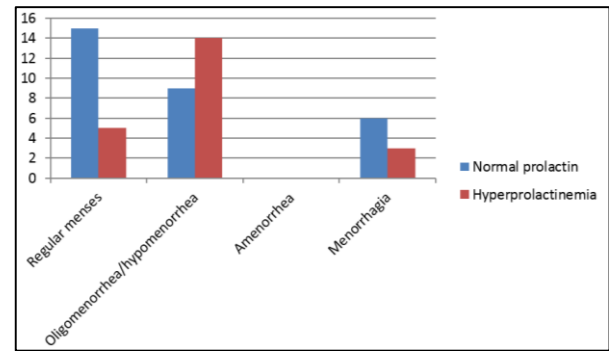
- The present study showed that 59.62% of infertile female married after age twenty five as compared to control 38.46% with an estimated Odds Ratio (OR) of 2.3619 (95%, CI- 1.0745 to 5.1874).
- Approximately, 51.92% of primary infertility cases received education of senior secondary and above compared to 40.38% of the controls and estimated OR of 1.5943 (95%, CI- 0.7335-3.4654).
- Occupation other than housewives were observed in 26.92% of cases compared to 53.85% of controls with an estimated OR 0.3158 (95%, CI- 0.1391-0.7172).
- 59.62% of cases were found to be overweight compared to 26.92% controls with an estimated OR 4.0068 (95%, CI- 1.7541 to 9.1526).
- Stress was reported in 51.92% of primary infertility cases compared to 44.23% of controls with an estimated OR 1.3617 (95%, CI- 0.6295 to 2.9459).
- About 61.54% of cases presented with irregular menstrual pattern compared to 17.31% of controls, OR 7.6444 (95%, CI- 3.076 to 18.99).
- In 63.46% of infertile females, age of menarche was ≥14 years as compared to 42.31% in the controls with an estimated OR 2.368 (95%, CI- 1.0768-5.2092).
- OCP intake was reported in 46.15% of primary infertility cases against 48.08% of controls, OR 0.9257 (95%, CI- 0.4285-1.9997).



**Figure 1. Pie Diagram Showing the Percentage Distribution of the Primary Infertility Cases and Controls According to their Ovulatory Status**



**Figure 2. Bar Diagram Showing Menstrual Disturbance in the Primary Infertility Cases and Controls**



**Figure 3. Bar Diagram Showing the Relation of Menstrual Disturbance and Hyperprolactinaemia in the Infertile Group**

Clinical Condition	Cases (n=52)		Controls (n=52)	
	Number	Percentage	Number	Percentage
Regular menses	20	38.46	43	82.69
Oligomenorrhoea	23	44.23	5	9.62
Amenorrhoea	0		0	
Menorrhagia	9	17.31	4	7.69
<b>Total</b>	<b>52</b>	<b>100</b>	<b>52</b>	<b>100</b>

**Table 2. Menstrual Disturbance in the Primary Infertility Cases and Controls**

Clinical Condition	Primary Infertility (n=52)		Normal Prolactin Level (n=30)		Hyperprolactinaemia (n=22)	
	Number	Percentage	Number	Percentage	Number	Percentage
Regular menses	20	38.46	15	50	5	22.73
Oligomenorrhoea/hypomenorrhoea	23	44.23	9	30	14	63.63
Amenorrhoea	0		0		0	
Menorrhagia	9	17.31	6	20	3	13.64
<b>Total</b>	<b>52</b>	<b>100</b>	<b>30</b>	<b>100</b>	<b>22</b>	<b>100</b>

**Table 3. Menstrual Disturbance and Hyperprolactinaemia in Infertile Group**

Serum Prolactin (ng/mL)	Primary Infertility (n=52)	Percentage	Controls (n=52)	Percentage	Pearson's Chi-square	P Value	Risk Ratio
0-25	30	57.69	45	86.54	10.76	0.00227	2.48
26-50	13	25	6	11.54	5.43	0.0197	0.78
51-100	9	17.31	1	-	-	0.0077	0.8011
101 and above	Nil	0	Nil	0	-	-	-
<b>Total</b>	<b>52</b>	<b>100</b>	<b>52</b>	<b>100</b>			

**Table 4. Serum Prolactin Levels in Primary Infertility Cases and Controls**

Interpretation- It was found that in women with normal serum prolactin (0-25 ng/mL) the risk ratio is more, i.e. less chance of infertility and in women with high serum prolactin level (>25 ng/mL) the risk ratio is less, i.e. more chance of infertility.

Clinical Condition	Primary Infertility Cases (n=52)		Controls (n=52)	
	Number	Percentage	Number	Percentage
Normal ovulation	23	44.23	47	90.39
Anovulatory cycle	27	51.92	4	7.69
Delayed ovulatory cycle	2	3.85	1	1.92
<b>Total</b>	<b>52</b>	<b>100</b>	<b>52</b>	<b>100</b>

**Table 5. Follicular Study**

	Menstrual Dysfunction		Anovulatory Cycle	
	Number	Percentage	Number	Percentage
Cases (n=52)	32	61.54	27	51.92
Controls (n=52)	9	17.31	4	7.69
<b>Total (n=104)</b>	<b>41</b>	<b>39.42</b>	<b>31</b>	<b>29.81</b>

**Table 6. Distribution of Menstrual Irregularities and Anovulatory Cycles in the Infertile Group and the Controls**

## DISCUSSION

In the present study, the majority of the cases with primary infertility were from urban area. Similar finding was mentioned earlier by Saoji AV<sup>4</sup> and S Shamila et al<sup>13</sup> in their study. Maximum number of infertile women belonged to the age between 26 to 30 yrs. (29 cases, 55.77%) and the duration of primary infertility in majority of women were between 2 to 5 yrs. (55.77%), which were similar to the findings of Dutta S et al.<sup>14</sup> In this study, age at marriage >25 yrs. proved to be a significant risk factor for primary infertility, which is comparable to the findings of Saoji AV<sup>4</sup> and Mokhtar S et al.<sup>15</sup> Obesity and overweight are common conditions that have consequences not only on general health, but also to a great extent on reproductive health. Numerous studies have highlighted the link between obesity and infertility. Some women who are overweight or obese experience hormonal imbalances that can affect their menstrual cycles and prevent ovulation. Overweight proved to be significantly associated with primary infertility in the present study, although no cases were found to be obese in our study. This was similar to the observation of many authors like Seddigh E et al,<sup>16</sup> Sudha G et al<sup>17</sup> and Saoji AV.<sup>4</sup> Education status being the most important variable, women above secondary education had markedly lower average fertility than the less educated. 73.08% of infertile women were unemployed or housewives compared to the control group amongst whom 46.15% were unemployed. These observations were similar to that of S Shamila et al.<sup>13</sup> Menstrual irregularity were also found to be significant risk factor for primary infertility, which was similar to the findings of the study conducted by S Shamila<sup>13</sup> in 2011. In our study, menstrual irregularities were detected in 61.54% of infertile women. Menstrual abnormalities were detected in about 60% of the primary infertility cases in a study done by Goswami B et al,<sup>18</sup> Kumkum et al<sup>12</sup> reported the abnormality to be 57.6% in their study. Saoji AV<sup>4</sup> revealed that females with age of menarche more than 14 years were more risky to develop infertility than those with age of menarche less than 14 years. Our findings were similar to that of Saoji AV.<sup>4</sup> Mokhtar S et al<sup>15</sup> and Komura H et al<sup>19</sup> OCP intake was also found to be nonsignificant with primary infertility in the present study.

A higher occurrence of hyperprolactinaemia (42.31%) was seen in the infertile group as compared to the controls (13.46%) in this study. This is in agreement with the findings of Goswami B et al<sup>18</sup> who found a higher occurrence of hyperprolactinaemia (41%) in the infertile women as compared to the controls (15%). Earlier Kumkum et al<sup>12</sup> in their study depicted an incidence of 49% in the primary infertility group. In our study, 27/52 (51.92%) cases of primary infertility patients presented with anovulatory cycles.

Kumkum et al<sup>12</sup> mentioned that anovulatory/delayed ovulatory cycles were detected in 49% (33/67) of primary infertility patients. In our study, anovulation was detected in 77.27% of the women with hyperprolactinaemia. Goswami B et al<sup>18</sup> mentioned that 58% of infertile women with raised serum prolactin showed non-secretory endometrium

suggestive of anovulation. Kumkum et al<sup>12</sup> showed an incidence of anovulation in hyperprolactinaemia patient to be 73%. K. Mohan and Sultana M.<sup>20</sup> in their study mentioned that both Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) are required for follicle development and oestrogen production. Due to elevated levels of Prolactin, FSH and LH are decreased and causes infertility.

## CONCLUSION

As treatment of infertility is expensive, identifying the risk factors can be of great help to prevent infertility. Hyperprolactinaemia maybe a major contributory hormonal factor in infertility among infertile women, hence estimation of serum prolactin levels is mandatory in the workup of all infertile women especially those presenting with menstrual abnormalities. As the present study was a hospital based one with limited number of cases and controls, a population-based study can be conducted to have a better idea of the impact of hyperprolactinaemia on the fertility of the subjects.

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