

## **Treatment of Male Infertility Using Some Prostaglandin Synthetase Inhibitors**

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### **ABSTRACT**

*Indomethacin administration at a dose of 25 mg, three times a day for ninety days to a group (n: 20) of oligospermic men caused an increase in sperm count and motility, a higher level of plasma testosterone and a lower seminal prostaglandin E than the corresponding values before drug intake. The pregnancy rate was 15% (3 out of 20). The present result indicates that indomethacin could be helpful in the treatment of some cases of male infertility.*

### **INTRODUCTION**

Prostaglandins have an inhibitory effect on testicular steroidogenesis and spermatogenesis *in vivo*, as well as on sperm motility *in vitro*. These observations suggest a negative regulatory effect of prostaglandins on testicular and spermatozoal function and conclude a potential beneficial effect of prostaglandin inhibition on fertility.<sup>(1-2)</sup>

Human seminal fluid contains large amounts of prostaglandins (PGs) and their corresponding isomers<sup>(3)</sup>

Statistical correlation between PGs concentration in semen and the degree of fertility has been demonstrated<sup>(4)</sup>. Based on experimental studies, PGs have had an inhibitory effect on testicular steroidogenesis<sup>(5)</sup>, and spermatogenesis *in vivo*<sup>(6)</sup>, and on sperm motility *in vitro*<sup>(7)</sup>. These observations agree with the deleterious effects of PGs on fertility potential and suggest the possible effective role of

prostaglandin synthetase inhibitors in treated subfertile men.<sup>(8)</sup>

The present study aimed at shedding a light on the role of a prostaglandin synthetase inhibitor, namely indomethacin, on fertility and sperm quality among oligospermic patients as well as its effect in changing the plasma levels of luteinizing hormone (LH), follicular stimulating hormone (FSH) and testosterone (T) in the same patients.

### **SUBJECTS & METHODS**

Twenty oligospermic individuals having the age range from 20-35 years, with a sperm count of  $1 \times 10^6$  to  $19 \times 10^6$ /ml and sperm motility less than 60% were included in the study. The duration of their infertility ranged from 2 to 4 years (mean = 2.8 year) despite of their regular sexual contact with their wives and despite of the fact that their wives had normal biphasic cycles with ovulation and their hormonal pattern and

hysterosalpingiography were normal. None of these oligospermic patients had received hormonal therapy (e.g. anti-oestrogen or androgens) or any drugs affecting spermatogenesis<sup>(9)</sup>, (e.g. caffeine, thyroxine, sulphasalazine, spironolactone .. etc.) during the last three months before their participation on the present study. Smokers were excluded.

Indomethacin was taken at a dose of 25mg, after meal, three times a day for three months (90 days). Seminal prostaglandin E (PGE) level was estimated by radio-immuno assay using Radioimmuno-assay kit (RIA), Cataglo No 8-6223, lot 401248, advanced magnetics incorporation (16- Money street, Cambridge, MA 02138, U.K).

Control group (20 patients) with the same experimental conditions received 50mg sucrose in capsules orally BID as placebo served as control group. This group was subjected to the same above mentioned laboratory procedures.

## RESULTS

Results were evaluated using paired "t" test.<sup>(10)</sup>

Patients receiving indomethacin showed:

- A statistically significant ( $P < 0.05$ ) increase in sperm count and motility in semen specimens obtained on day 90 was reported as compared to the same parameters in semen samples obtained on day 0 (Table 1). The pregnancy rate among which was 15% (3 out of 20).
- A statistically significant ( $P < 0.05$ ) higher mean plasma testosterone (T) levels on day 90, than the mean plasma (T) levels in blood specimens obtained on day 0. (Table 2).
- A rather statistically insignificant difference in plasma FSH & LH levels in specimens obtained on day 90 compared to their corresponding level in day 0. (Table 2).

**Table (1):** Effect of indomethacin intake on sperm count and motility among oligospermic men.

	<i>n</i>	<i>Day 0</i> <i>Range</i>	$\bar{X} \pm SD$ <i>(A)</i>	<i>Day 90</i> <i>Range</i>	$\bar{X} \pm SD$ <i>(B)</i>	<i>A versus</i> <i>B.</i> <i>column.</i>
<i>Sperm count</i> <i>(million/ml)</i>	20	1-19 × 10 <sup>6</sup>	9.43 ± 6.097	2-32	15.3 ± 8.16	$P < 0.01$
<i>sperm motility</i> <i>(percentage)</i>	20	5-80	31.7 ± 18.3	20-70	43.25 ± 17.11	$P < 0.01$

*Day 0: Before indomethacin administration.*

*Day 90: following indomethacin administration for 90 days.*

*n: number of Cases.*

*x: Mean*

*SD: standard deviation.*

*Sperm count: expressed in term of × 10<sup>6</sup> /ml.*

*Sperm motility: expressed as a percentage.*

*P < 0.05: statistically significant according to the "t" paired test.*

**Table (2):** Effect of indomethacin therapy on testosterone, follicular stimulating hormone (FSH) and lutealizing hormone (LH) in patients.

	<i>n</i>	<i>Day 0</i> <i>Range of</i> <i>plasma</i> <i>level</i>	$\bar{X} \pm SD$ <i>(A)</i>	<i>Day 90</i> <i>Range of</i> <i>plasma</i> <i>level</i>	$\bar{X} \pm SD$ <i>(B)</i>	<i>A versus</i> <i>B.</i> <i>column.</i>
<i>Testosterone</i> <i>(ng/ml)</i>	20	2-11	4.95 $\pm 2.49$	2-12.2	5.97 $\pm$ 2.93	<i>P</i> <0.01
<i>FSH</i> <i>(mIU/ml)</i>	20	5-12.0	8.0 $\pm$ 1.89	4-11	7.76 $\pm$ 2.08	<i>N.S.</i>
<i>LH</i> <i>(mIU/ml)</i>	20	5-15	9.7 $\pm$ 2.83	4-18	9.95 $\pm$ 4.19	<i>N.S.</i>

*Day 0:* before indomethacin administration.

*Day 90:* following indomethacin administration for 90 days.

*n:* number of cases.

*X:* mean

*S.D.:* standard deviation.

*P*<0.05: statistically significant <sup>(10)</sup>.

***N.S.:* Non Significant.**

- A statistically significant (*P*<0.05) higher seminal PGE levels in semen samples obtained from patients at the start of therapy (day 0), than the corresponding levels in semen samples obtained on day 90 (Table 3).

**Table (3):** Effect of indomethacin intake on seminal prostaglandin E (PGE)  $\mu\text{g/ml}$  among oligospermic men

<i>Range of seminal PGE <math>\mu\text{g/ml}</math> among</i> <i>patients on day 0</i>		<i>Range of seminal PGE <math>\mu\text{g/ml}</math> among</i> <i>patients on day 90</i>	
<i>(A): 61-88</i>		<i>(B): 53 - 69</i>	
<i>n</i>	20	20	
<i>X</i>	70.85	61.3	
$\bar{SD}$	6.71	4.4	
<i>Aversus B</i>	<i>P</i> <0.05		

*Day 0:* Before indomethacin intake.

*Day 90:* After indomethacin intake.

*n:* number of patients.

$\bar{X}$ : : mean.

*SD:* standard deviation *P*<0.05 statistically significant.

#### **Subjects receiving placebo (control group):**

Throughout the whole period of experiment, constant values were reported in hormone levels in plasma

specimens, in sperm quality, motility and in PGE levels in semen in specimens obtained on day 0 and day 90.

## DISCUSSION

There have been controversial evidences upon the impact of seminal plasma prostaglandins (PGs) especially PGE on human fertility.

Seminal plasma PGs, by virtue of their smooth muscle relaxing property cause relaxation of human myometrium, cervical muscle and distal position of oviduct,<sup>(11)</sup> thus contributing to the ascent of sperms after ejaculation in the female reproductive tract. On the other hand, in some PGs concentration in seminal plasma<sup>(12)</sup>

Due to the bell-shaped curve of activity of prostaglandins.<sup>(13)</sup> Such as inhibitory on body metabolic processes and spermatogenesis at high concentrations, the inhibitory effect of PGs on testicular function and sperm motility would be an underlying cause in some infertile men. Thus, a question would be raised as to whether or not the suppression of PGs synthesis with the help of an arsenal of non-steroidal anti-inflammatory drugs could be a line of therapy to improve sperm quality and fertility in men.

In the present study a daily dose of oral indomethacin (75mg/day), given for 90 days to encompass the process of spermatogenesis, induced insignificant change in serum FSH and LH levels and a statistically significant ( $P<0.05$ ) rise in serum testosterone with improvement of sperm count and sperm motility together with a pregnancy rate of 15% (3 of 20) as compared to the corresponding levels and sperm parameters in the same patients before indomethacin administration.

Similarly, a statistically significant ( $P<0.05$ ) lower seminal plasma PGE on day 90, than PGE level on day 0 before the drug intake was shown. As much as placebo therapy could not induce any change in these parameters, when used for 90 days, among placebo group it could be postulated that indomethacin improved fertility potential among these patients. The drug in question could have acted via different mechanisms.<sup>(5-14-15)</sup> Indomethacin might act on hypothalamic – pituitary axis affecting both FSH & LH levels hence testosterone level. The drug could additionally suppress estrogen formation by leydig cells in some oligospermic men.<sup>(16-17)</sup> Moreover, indomethacin increases level of seminal plasma cyclic adenosine monophosphate (cAMP), thus promoting sperm motility.<sup>(18-19)</sup> These results go with the effective action of indomethacin in treating some oligospermic patients and was confirmed by an earlier report of<sup>(6)</sup>

**Barlke et al.**<sup>(6)</sup> and **Rolf et al.**<sup>(20)</sup> in a controlled study examined the effect of indomethacin (75mg/day for 60 days on 100 oligospermic patients). They observed an increase in both FSH & LH with a simultaneous droppage of testosterone level, and decrease in PGs' concentrations in seminal plasma. Also, there was a significant increase in both sperm count and motility. **Barkay et al.**,<sup>(5)</sup> and **Ombelet et al.**,<sup>(21)</sup> had postulated that prolonged stimulation of leydig cell by gonadotropin (LH) could have induced refractivness of these leydig cell and hence a decrease in testosterone production

Similarly, aspirin (2.5-3.6gm/day) caused 50% reversible reduction in seminal plasma PGs.<sup>(22)</sup> adding more to the possible impact of non steroidal anti-inflammatory drugs on sperm quality and semen parameters. However, the possible role of prostaglandin synthetase inhibitors in treating infertility in men warrants further evaluation on a wider scale as these drugs are relatively safe, non toxic, well tolerated and widely used in medical practice.

*Haidl et al.*<sup>(23)</sup> reported that best results are obtained in cases requiring an anti-inflammatory treatment and in patients with an impaired sperm transport. High-dosage administration of FSH is promising new development, aimed particularly at improving the disturbed sperm structure. A careful diagnostic work-up with elucidation of the underlying disease is essential to achieve a successful therapy.

**In conclusion,** Indomethacin drugs have increased sperm count and motility. Though indomethacin offers some hope for the future, improvement of the fertilizing capacity with that drug is still controversial.<sup>(1)</sup>

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## علاج عقم الرجال باستخدام إحدى مثبطات تخليق البروستاجلاندين

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تم استخدام عقار الإندوميثاسين (جرعة ٢٥ مجم/ ٣ مرات يومياً لمدة ٩٠ يوماً) في مجموعة من المرضى (عددهم ٢٠ مريضاً) يعانون من قلة عدد الحيوانات المنوية. لوحظ التحسن في عدد الحيوانات المنوية وحركتها وزيادة ملحوظة في مستوى هرمون الذكورة في الدم وهبوط مستوى البروستاجلاندين (هـ) في السائل المنوي وذلك مقارنة بنفس هذه المعايير فيما قبل العلاج. ولقد وجدت حمل بنسبة ١٥% (٣ مرضى من ٢٠ مريضاً). وهذه الدراسة تؤيد إمكانية استعمال عقار الإندوميثاسين في علاج بعض حالات عقم الرجال.