

PREGNANCIES FOLLOWING TREATMENT OF INFERTILITY

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SUMMARY

This report relates to 567 conceptions that have been recorded following investigation and treatment of infertility, over a period of 5 years and 6 months. Conception rate, treatment-to-conception interval and pregnancy complications attended with various fertility disorders are highlighted. Based on this comprehensive data, guidelines for approaching the different fertility problems have been evolved.

Introduction

This study, based on my observation of pregnancy behaviour of 567 conceptions resulting following treatment of various fertility disorders over a period of 5 years and 6 months, allows for meaningful decisions to be made on the above mentioned aspects.

Materials and Methods

Beginning in September, 1983, the details of all the conceptions reported following investigation and treatment of infertility in my service have been collected. Uptil March, 1989 (5 years and 6 months) detailed information of 567 conceptions could be recorded. From this data the following have been analysed and

documented in this communication: (i) Number of pregnancies in each form of fertility disorders; (ii) Treatment-to-conception interval; and (iii) pregnancy complications.

Results and Discussions

Among the 567 conceptions, the major infertility factors and their corrections that have yielded good results include: (i) surgical (and also medical) treatment of endometriosis (109 pregnancies), (ii) Induction of ovulation employing various ovulogens (141 pregnancies), and (iii) spontaneous conceptions following infertility evaluation employing basic investigations/HSG/laparoscopy (153 pregnancies). Other significant factors that were contributory to the success rate include: (i) Medical (hormones) and surgical treatment of oligospermia (68 pregnancies), (ii) utero-tubal

TABLE 1
CONCEPTIONS IN DIFFERENT GROUPS OF INFERTILITY FACTORS

Total conceptions: 567		Study period: 5 years and 6 months	
<i>Fertility disorder</i>	<i>Treatment</i>	<i>Conceptions</i>	<i>Percentage of total conceptions</i>
Unexplained infertility	(i) basic evaluation, (ii) HSG, (iii) laparoscopy, and (iv) hysteroscopy	153	26.98
Anovulation	(i) CC, (ii) CC & hCG, (iii) CC & Dex, (iv) CC & Brom, (v) hMG & hCG (vi) FSH & hCG, (vii) Bromocriptine, (viii) Operative laparoscopy, (ix) Wedge resection	141	24.87
Endometriosis	(i) operative laparoscopy, (ii) laparoscopy, (iii) danazol & surgery (iv) danazol alone	109	19.22
Oligospermia	(i) hCG, (ii) hMG & hCG, (iii) CC, (iv) varicocele ligation, and (v) varicocele ligation and hCG	68	11.99
AZospermia and other intractable male factors	A.I.D.	33	5.82
Proximal tubal occlusion	Utero-tubal implantation	21	3.70
Uterine myoma	(i) abdominal myomectomy (ii) vaginal hysterotomy & myomectomy	14	2.47
Other factors	(i) operative laparoscopy, (ii) surgery for PID. (iii) surgery following previous ectopic gestation, (iv) metroplasty, (v) cervical amputation, (vi) excision of vaginal septum, and (vii) counselling for coital problems	28	4.94

implantation for proximal tubal occlusions (21 pregnancies) and (iii) myomectomies (14 pregnancies). The percentage of conceptions contributed by these factors are given in Table I. Evidently, ovulatory disorders and endometriosis remain the commonest fertility disorders of the female; and the ones to respond most favourably to optimal treatment.

The 567 pregnancies studied in this report represent the conceptions achieved following treatment of various types of male and female fertility disorders. A general survey indicates that 30.32% of the conceptions have been achieved by the first month of initiation of investigation/treatment. By 3rd month 58.63% of the conceptions, and by 6th month 77.31% of the conceptions have been achieved. Such of those to conceive following investigation/treatment of infertility, 91.16% have done so within 1 year (Table II). While this is only an overall picture and does not rep-

resent the pregnancy outcome in a particular fertility disorder, the following informations could be deduced: (i) Proper counselling, coital advices and necessary encouragements should be initiated at the first visit itself. Particularly stressed must be the need for frequent coitus in the treatment cycle, and resumption of coitus in the very next cycle of surgical correction of infertility. This is essential because around 1/3rd of the total conceptions are achieved in the very first treatment cycle/month following completion of treatment. (ii) Six months could be an average acceptable period of conception to occur following any form of treatment; and (iii) the couple should be prepared for patient waiting for atleast one year before believing that alternate approach should be adopted. This is of course on general terms for all infertile couples; and the guidelines could vary depending upon the fertility disorder under question.

TABLE II
PREGNANCIES FOLLOWING TREATMENT OF INFERTILITY
TIME TAKEN FOR ACHIEVING CONCEPTION IN VARIOUS FERTILITY DISORDERS

Fertility disorder	Total pregnancies	Treatment-to-conception interval in months (cumulative percentage)				
		Treatment cycle	1 month	3 months	6 months	12 months
Anovulation	141	nil	43.65	78.57	94.44	99.21
A.I.D.	33	nil	38.71	70.97	90.32	93.55
Endometriosis	109	3.92	21.57	54.90	78.43	92.16
Unexplained infertility	153	8.73	35.71	63.49	77.78	95.24
Utero-tubal implantation	21	nil	5.56	33.33	55.56	72.22
Uterine Myoma	14	nil	46.15	53.85	53.85	76.92
Male factor (oligospermia)	68	nil	10.34	20.69	46.55	77.59
Other factors	28	nil	16.67	41.67	66.67	75.00
All factors	567	3.01	30.32	58.63	77.31	91.16

TABLE III
PREGNANCIES FOLLOWING TREATMENT OF INFERTILITY
PREGNANCY COMPLICATIONS

Total conceptions: 567		Study period: 5 years and 6 months			
Fertility disorder	Total pregnancies	Abortion	Ectopic gestation	Multiple births	Fetal anomaly
All factors	567	58	6	4	2
70 / 567 = 12.34%		10.23%	1.06%	0.71%	0.35%
Anovulation	141	18	1	4	2
25 / 141 = 17.73%		12.77%	0.71%	2.84%	1.42%
Unexplained Infertility	153	9	5	nil	nil
14 / 153 = 9.15%		5.88%	3.26%		
Endometriosis	109	5	nil	nil	nil
5 / 109 = 4.59%		4.59%			
Utero-tubal implantation	21	4	nil	nil	nil
4 / 21 = 19.04%		19.04%			
Uterine myoma (myomectomy)	14	4	nil	nil	nil
4 / 14 = 28.57%		28.57%			
Oligospermia	68	9	nil	nil	nil
9 / 68 = 13.24%		13.24%			
A.I.D.	33	4	nil	nil	nil
4 / 33 = 12.12%		12.12%			
Other factors	28	4	nil	nil	nil
4 / 28 = 14.28%		14.28%			

The overall pregnancy complications in infertile couple do not appear to be different from that of general population. (Table III). There have been 70 pregnancy complications reported for the 567 conceptions (12.35%). Pregnancy abortions are the commonest complication encountered on 58 occasions (10.23%). Tubal ectopic gestations have been recorded in 6 subjects (1.06%), multiple pregnancy (including triplets) in 4 subjects (0.71%), and fetal anomalies in 2 subjects (0.35%). Blighted ovum (anembryonic pregnancy), missed abortion, and midtrimester losses were the different types of abortions encountered. It is remarkable that molar gestations were not encountered in pregnancies

conceived following investigation and treatment of infertility. Since ectopic gestation is a very prominent pregnancy complication it is preferable to initiate pregnancy surveillance at the earliest. I employ ultrasound and beta hCG studies as early as 31st to 33rd day of LNMP. Currently, my preference is for transvaginal sonography for the earliest confirmation of pregnancy.

Induction of Ovulation : (Table IV)

Around 25% of the total conceptions in this group have been following induction of ovulation. Among the 141 pregnancies nearly 50% have been conceived in the first treatment cycle itself, 2/3rds by the

TABLE IV
PREGNANCIES FOLLOWING INDUCTION OF OVULATION

Treatment of anovulation	Pregnancies	Cumulative conception rate based on treatment-to-conception interval			
		1st cycle %	3rd cycle %	6th cycle %	12th cycle %
Clomiphene citrate (CC) CC & Dex, and CC & Brom	86	39.73	82.19	95.89	100.00
CC and hCG	23	82.61	95.65	100% by 4th cycle	
Gonadotropins hMG and hCG, FSH and hCG	10	20.00	70.00	90.00	100.00
Bromocriptine	8	12.50	50.00	62.50	100.00

second cycle, 3/4th by the third treatment cycle, and within 6 months, practically all conceptions (about 95%) have been realised. Two significant observations emerge out of this study: (i) Ovulation induction significantly contributes a major share to the success rate of infertility treatment; and (ii) Practically, within a short period of 6 months the results could be definitely known.

The overall pregnancy complications could not be considered more frequent in this series, even though certain complications such as ectopic gestation, multiple pregnancy and fetal anomalies have been significantly observed following induction of ovulation (Table III). Hence early pregnancy surveillance and frequent sonographic monitoring becoming mandatory for this group of subjects.

Among the infertile anovulatory subjects certain groups deserve a special mention. Those subjects who are ideally treated with clomiphene citrate (CC), when the follicular dynamics are monitored by

sonography and hCG administration is optimally timed, achieve a very high success rate. Moreover, of the 23 conceptions that followed CC and hCG combination, 19 (82.61%) were achieved by the first treatment cycle, 22 (95.65%) by the 3rd treatment cycle, and all conceptions by the 4th cycle. This has to be contrasted with the figures for CC alone, namely, 39.73%, 82.19% for the 1st and 3rd treatment cycles respectively. It is also important that addition of hCG to the CC regimen has not increased the pregnancy complications. Thus, it could be concluded that optimally timed hCG administration in subjects undergoing induction ovulation employing CC benefits the patient by a remarkable increase in pregnancy rate at the cost of minimal treatment cycles with no untoward problems.

Among the 10 pregnancies conceived following hMG/hCG or FSH/hCG treatment 7 were conceived by the 3rd treatment cycle, and all except one were conceived by 6 cycles of treatment. This group

recorded 3 abortions and 2 multiple gestations (twins and triplets).

It is the hyperprolactinemic subjects treated with bromocriptine who take longer duration to achieve the results; nonetheless the pregnancy rate is remarkably high. Only 50% of the conceptions are recorded by 3 months, and 62.50% by 6 months, and all conceptions have been achieved within 12 months of treatment. Two subjects in this group reported neurological symptoms during pregnancy; but the pregnancy complications were not very significant, except one abortion in the first trimester.

There have been 16 subjects who have remained resistant to CC therapy, but successfully managed by laparoscopic follicular puncture-coagulation, laparoscopic mini-ovarian biopsy or classical ovarian wedge resection. These conceptions were achieved either spontaneously following the surgery or with CC or gonadotropin back-up, within 1 to 6 months of surgery.

Endometriosis : (Table V)

About 20% of the conceptions recorded in this study have resulted following treat-

ment of endometriosis, essentially by surgical approach which included conservative surgery and operative laparoscopy (with a post or pre-operative danazol back-up in severe degrees). On an average 2/3rds of the 109 conceptions were achieved following laparotomy corrective surgeries, and 1/3rds following operative laparoscopy. About 10% of conceptions had been following danazol supplementation, and 4 pregnancies were conceived following medical treatment employing danazol. This observation highlights the prominent role of operative laparoscopy (an extension of the diagnostic procedure) in the management of endometriosis. It was also observed that the conception rate is certainly 10% more for danazol and surgery, than surgery alone. However, there is not much difference in the pregnancy rate between pre-operative and post-operative administration. This study emphasizes that danazol alone (following diagnostic confirmation at laparoscopy) also has a place in the treatment of infertility in endometriosis.

Treatment-to-conception interval has not been influenced by the treatment

TABLE V
PREGNANCIES FOLLOWING TREATMENT OF ENDOMETRIOSIS

<i>Treatment modality</i>	<i>No. of pregnancies</i>	<i>Percentage of the total 109 pregnancies</i>
Laparotomy	59	54.13
Laparotomy and danazol	8	7.34
Operative laparoscopy	31	28.44
Operative laparoscopy & danazol	2	1.83
Danazol alone	4	3.67
17-alpha OH progesterone	1	0.92
Expectant management	4	3.67

Total conceptions studied: 567

Total conceptions following treatment of endometriosis : 109
(19.22% of the total pregnancies)

modality of endometriosis. On an average, 21.57% of the total 109 conceptions have been achieved in the next month itself, 38.24% by 2 months, 54.90% by 3 months, 78.43% by 6 months and 92.16% by 12 months. Since more than 1/2 of the conceptions are realised within 3 months of surgery or cessation of danazol, and around 4/5th of the conceptions are realised by 6th month we urge the need for earlier institution of coitus (from the very next cycle itself). We advocate an average waiting period of 6 months to achieve the results, if not one year; and before completion of this duration we do not advocate repeat surgery or alternate therapeutic approaches.

It has been observed that atleast 2 subjects have conceived while they were on danazol (100 mg, 4 times a day for 3 months), and both pregnancies are continuing normally and mid-trimester sonography has excluded major fetal anomalies. Consequent to this we advocate the couple to avoid conception while the female partner is for danazol therapy. Only pregnancy complication encountered in subjects with endometriosis is first trimester abortion, in 4.59%. It is noteworthy that surgery for endometriosis is not contributing to tubal ectopic gestations.

Utero-Tubal Implantation

Proximal tubal occlusions managed by implantation of ampullary segment through a transverse posterior wall uterine incision has been popularly employed by me. In this report 21 conceptions have been documented, with first trimester abortion rate of 19.04%. Within 6 months of surgery 55.56% of conceptions are realised, and 72.22% within 1 year. The longest surgery-to-conception interval has been 22 months. We advocate review HSG if conception has not resulted in one year.

Unexplained Infertility (Table VI)

More than 1/4th of the total conceptions (153 numbers) in this study have been recorded following investigations for infertility such as (i) basic evaluation, (ii), HSG, and (iii) Diagnostic laparoscopy. Thus, it is evident that spontaneous conceptions following infertility evaluation constitutes the majority of conceptions that occur in infertile subjects. Hence, the popularly designated 'therapeutic effect' of various investigative procedures must be properly recognized and due weight given to this phenomenon.

Equally significant is that more than 1/3rd (35.71%) of these conceptions are registered by the next month following

TABLE VI
SPONTANEOUS CONCEPTIONS IN 'UNEXPLAINED INFERTILITY'

Total pregnancies: 567		Conceptions following infertility evaluation : 153 (26.98% of the total pregnancies)	
<i>Investigative procedure:</i>	<i>No. pregnant</i>	<i>Percentage of the total 153 conceptions</i>	
Basic investigations	62	40.52	
Laparoscopy	53	34.64	
H.S.G.	38	24.84	

investigation, about 2/3rds (63.49%) by 3 months and 3/4th (77.78%) by 6 months. Among them 40.52% were following basic evaluations, 34.64% following diagnostic laparoscopy, and 24.84% following HSG.

From these interesting observations we infer that if the basic investigations reveal no explainable cause for infertility, young subjects with short period of infertility could optimistically wait for spontaneous conception to occur. If the female partner is above 25 years of age and or married for more than 3 years we would advocate a diagnostic laparoscopy and hysteroscopy. If these investigations fail to unearth any etiological factor certainly optimistic waiting should be advocated.

The duration of optimistic waiting is evident from this study. With frequent coitus instituted from the very next month, 6 months will be a good enough interval to gain the maximum benefit. If the subject is young we could advocate an interval of upto 1 year. The couple should be carefully counselled on the greater potential for conception, and encouraged to await the results; the couple should also temporarily forget their fertility problem and should have casual and frequent sex during this period of expectation.

High incidence of ectopic gestation among these subjects, particularly following laparoscopy (4 for 53 conceptions - 7.55%) and HSG (1 for 38 pregnancies - 2.63%) is a real concern. Probably the therapeutic effect of these procedures in

subjects with minimal (and unrecognised) tubal luminal pathology may be responsible for this catastrophe. Hence we exercise extreme degree of caution and advocate very early pregnancy surveillance.

Oligospermia

Treatment modalities employed for oligospermia, such as hCG, hMG and hCG, CC, and varicocele ligation, take a considerably longer period to achieve the results. By 6 months of treatment only 46.55% of the 68 conceptions have been realised, and about 1/4th of the conceptions occur only after 1 year of treatment. Hence a longer duration of waiting should be advocated for couple treated for oligospermia. It also should be recognised that the treatment of male disorders yield a poor pregnancy rate as compared to that of female fertility problems (Table I). Among the 567 pregnancies studied correction of oligospermia has contributed only 68 conceptions (11.99%).

Spontaneous Conceptions

Spontaneous conceptions, without any form of specific treatment, has been observed in endometriosis (6 nos.) anovulation (7 nos.), and oligospermia (4 nos.). In the unexplained infertility group 7 of the 38 conceptions (18.42%) following HSG have been conceived in the cycle of investigation. But no pregnancy complications, including abortions have been reported in this group. Hence HSGs are performed in early follicular phase and we allow coitus in the same cycle.