Timed intercourse in infertile couples doing more harm than benefits in terms of sexual dysfunction and time to pregnancy: a cohort study

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Abstract

Objective: To study the differences in sexual dysfunction (SD) and time to pregnancy (TTP) between infertile couples pursuing timed intercourse (TI- around the time of ovulation) and regular intercourse (RI- at least twice a week). Design: Prospective cohort study Setting: Infertility clinics of Kolkata over three years Population or Sample: Infertile couples pursuing TI (n=283) or RI (n=88), having no preexisting sexual or psychiatric illness, and no medical contraindications to frequent intercourse. Methods: At the first visit, SD of both the partners was assessed using the Arizona Sexual Experiences Scale (ASEX) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). The couples for whom natural conception was possible were followed up to determine TTP using Kaplan Meier Analysis. Main Outcome Measure: Differences in SD and differences in TTP. Results: TI significantly increased the risk of SD than RI for both males (Odds ratio [OR] 15.24, 95% confidence interval [CI] 7.96-29.15) and females (OR 5.52, 95% CI 2.38- 12.78). This difference persisted even after adjusting for age, medical disorders, obesity, smoking, cause of infertility, and previous assisted reproductive techniques. TI carried a higher risk of developing ED, premature ejaculation, male hypoactive sexual dysfunction, female sexual interest-arousal disorder, and female orgasmic disorder. IIEF-5 score was significantly better in the RI group than in the TI. The TTP for natural conception was similar between them (Log-rank p= 0.1365). Conclusions: TI increased the risk of sexual dysfunction without accelerating the time to achieve pregnancy, compared with RI.

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Tweetable abstract

Timed intercourse increased the risk of sexual dysfunction without improving the time to pregnancy

Main Document

Introduction

Human reproduction is a relatively inefficient process, with the chance of conception per act of intercourse estimated between 0.1% and 9.7%.[1] Theoretically, pregnancy is possible only if adequate numbers of healthy sperms (with adequate motility and morphology) are present in the female genital tract around the time of ovulation.[2,3,4,5] Therefore, "timed intercourse" (TI), which is basically "targeting" the SI around the period of ovulation ("fertile period"), has been hypothesized to maximize the chance of conception.[3,6,7,8.]

However, we cannot overemphasize that procreation is not the sole purpose of human sexuality.9 Sex is one of the basic human instincts. Unfortunately, sex becomes a "necessity" when a couple struggles to conceive.[9,10,11] Infertility is a risk factor for sexual dysfunction (SD).[9,10,11,12,13,14,15,16,17,18,19,20] TI adds to SD in both the partners by forcing them to engage in sex around the fertile period.[7,9,13,21,22,23]

In contrast, regular intercourse (RI) two to three times a week had been recommended for the couples trying to conceive.[12,24]This would translate into one to two episodes of SI in the fertile window.[25,26] There was no evidence to suggest impairment of sperm-quality by frequent intercourse.[3,4,24,27,28]

Studies directly comparing TI with RI were sparse.[22,33] Many studies showed that TI increased the risk of SD, but they did not weigh against RI.[7,9,21]Even the Cochrane review did not mention SD as the "adverse effects" of TI.[8]

Most of the studies showing the beneficial role of TI in improving the chance of pregnancy did not compare TI with RI.[4,6,8,29,30,31,32] Additionally, most of them included the couples trying for pregnancy for a shorter period and therefore, were not actually "infertile".[4,29,30,31,33] None of the studies followed up the individuals beyond six cycles.[29,30,31,32,33] The Cochrane review found that the quality of evidence supporting TI was low to very low with a high risk of bias.[8]

We were mindful of the potential morbidity of SD on infertile couples and sought to identify if TI could cause more harm than good. Therefore, we tried to compare TI with RI in terms of different types of SD in both male and female partners of the infertile couples and the chance of pregnancy after extended follow-up. The primary objective of our study was to find out differences in SD between the individuals engaged in TI and RI. The secondary objective was to see differences in time to pregnancy (TTP) between these them.

Methods

The study was conducted on the infertile couples presenting to our infertility clinics over three years (from January 2016 to December 2018). It was a prospective cohort study.

After obtaining the clearance from the Institutional Ethics Committee and informed consent from all the participants, we included the couples trying for pregnancy for more than one year. Excluded were the couples with any partner having pre-existing sexual problems (present before they started planning for pregnancy), previously/ currently being treated for psychiatric disorders, medical contraindications to frequent intercourse (like HIV affected serodiscordant couples, severely compromised heart disease, etc.), and who were reluctant to disclose the sexual problems.

As per our clinic-protocol "standard fertility-consultation" (**Figure 1**) was conducted by taking a detailed medical history, reviewing previous medical records, offering further investigations when appropriate, and discussing further possible treatment options. We used the term "assisted reproductive techniques" (ART) to describe the fertility-treatment apart from vaginal intercourse, which included intrauterine insemination, in vitro fertilization, and intracytoplasmic sperm injection.[12] "Natural conception" was defined as pregnancy resulting after unprotected vaginal intercourse (including after ovulation induction [OI]).

The pattern of sexual intercourse

In the first visit to our clinic, all the couples were asked about their intercourse pattern since they started planning for pregnancy. Based on the frequency of penile-vaginal intercourse, the couples were finally divided into two groups-

TI group (SI limited around the ovulation-time, based on different methods of ovulation-prediction) and

RI group (at least two times a week on average, without ovulation-prediction).

None of these couples were advised to change their coital frequency (TI/ RI) throughout the study period.

Arizona Sexual Experiences Scale (ASEX)

At the first visit, both the partners of all the couples were separately asked to fill up the ASEX Questionnaire (**Figure 1**). The ASEX consists of 5 questions (sex-drive, arousal, penile erection or vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm) with a 6-point Likert Scale, ranging from 1 (hyperfunction) to 6 (hypofunction).[34] Total scores ranged between 5 and 30, with a higher score signifying severe sexual problems. SD (ASEX Score positive) was defined as a total ASEX score [?]19, score in any one of the five questions [?]5 and score in any three questions [?]4.[34] The individuals with SD were offered specialist-referral, appropriate investigations, and treatment.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)

In all the individuals, irrespective of the ASEX score, the presence or absence of SD was defined according to the DSM-V at the first consultation (**Figure 1**). For male partners, the disorders included male hypoactive sexual dysfunction (MHSD), erectile dysfunction (ED), premature ejaculation (PE), and delayed ejaculation (DE).[35] Female sexual dysfunction (FSD) comprised female sexual interest-arousal disorder (FSIAD), genito-pelvic penetration-pain disorder (GPPPD), and female orgasmic disorder (FOD).[35] A particular SD was diagnosed only if that was present on at least 75% of sexual encounters for at least six months.[35] As we excluded individuals with pre-existing sexual dysfunction, all the individuals having SD in our study were having "acquired" sexual dysfunctions only, not from "lifelong" dysfunction.

International Index of Erectile Function-5 (IIEF-5)

Men having ED were asked to fill up the IIEF-5 questionnaire (**Figure 1**). It consists of 5 questions; each scored 1-5, with a lower score meaning more inferior erectile function.[36,37]

Follow up

In the second part of the study, the TTP was determined for the couples having the possibility of "natural conception" (at least one fallopian tube patent, total motile sperm count (TMSC) 5 million or more, and ovulating naturally or after OI). As our study was completed in December 2018, to allow at least one year for follow-up, we excluded the couples whose date of the first visit to our clinics was after December 2017 (**Figure 1**).

Statistical analysis

Using the SAS 9.4 software, we applied the chi-square test or Fisher's exact test (if the cells in the corresponding 2x2 table have at least one expected frequency <5) for categorical data. For continuous data Shapiro-Wilk test was used to check for normal distribution, and accordingly, Student's (unpaired) t-test or Mann-Whitney U-test were applied

Multiple logistic regression analysis was performed to identify different factors associated with SD. The following parameters were put in the analysis:

1. Frequency of intercourse (TI or RI)
2. Age (35 years or more in a female and 40 years or more in a male)
3. Medical disorders (treated or untreated conditions like diabetes, hypertension, hypothyroidism, dyslipidaemia, and other chronic systemic co-morbidities)
4. Obesity (body mass index [BMI] 30 Kg/M2 or more)
5. Smoking (current user or who quitted <12 months ago)
6. Cause of infertility: for male partners presence and absence of male factor infertility [defined as the abnormal semen analysis results as per World Health Organization, 2010 recommendation] and for female partners presence or absence of female factor infertility [defined as anovulation, fallopian tube pathology, and/or endometriosis]
7. Previous treatment with ART

The odds ratio (OR) and 95% confidence interval (CI) were calculated. Further regression analysis was done whenever required.

The survival analysis was performed to calculate the TTP using Kaplan Meier (KM) method with the log-rank test. The starting point was when a couple started trying for pregnancy (as stated by them). For natural conception, the end-point was the first day of the last menstrual period (LMP) in which "clinical pregnancy" (the ultrasound evidence of gestational sac) took place by natural conception. The couples were censored at the starting date of the ART in case of ART-conception and at the date of the last visit if they were lost to follow up (defined as no visit after June 2018) or were still under treatment. Therefore, to calculate the total duration of trying for pregnancy (T), the following formula was applied:

T= x +y

x= the duration of trying before coming to us

y = the interval between the first visit to our clinic and

1. the LMP (in case of clinical pregnancy)
2. or last visit (when lost to follow up or still under treatment and not conceived naturally)
3. or starting date of ART (when conceived by ART).

Unless otherwise mentioned, the two-tailed test was used for testing the null hypothesis. The threshold for type I error was set at 5%. P-value <0.05 was considered statistically significant.

Results

Out of the 432 couples seeking infertility treatment over the study period, we included 371 of them, of which 283 (76.28%) and 88 (23.72%) were doing TI and RI, respectively (**Figure 1**). Nearly 56% of the couples pursuing TI received that advice from their doctors, whereas 7.42% were "compelled" to follow TI because of the inability to meet regularly as the partners used to stay at separate places. The calendar method was the most common method used for ovulation-prediction (95.41%).

Sexual dysfunctions

Significantly more men and women suffered from SD (defined as ASEX score positive) in the TI group than in the RI (**Table 1**). The incidences of MHSD, ED, PE, FSIAD, and FOD were significantly higher in the TI group. However, there were no differences in the occurrence of DE and GPPPD between the two groups. In males, ED was the commonest sexual dysfunction, followed by PE, whereas in females, FSIAD was the most frequent complaint.

IIEF-5 Score

As the samples were not normally distributed (Shapiro-Wilk test; p-value 0.0001 and 0.0052 for TI and RI, respectively), the Mann-Whitney U-test was applied. The mean ($\pm$ standard deviation) scores of TI and RI groups were 12.06$\pm$ 5.61 and 16.85$\pm$ 4.76. Not only was there a significant difference in scores between these groups (two-sided p-value 0.0009), but also the RI group had a significantly better score (one-sided p-value 0.0005). Therefore, ED was more severe in men doing TI than those doing RI.

Logistic regression

For male and female partners, TI increased the risk of SD (ASEX score positive) by 15.235 and 5.519 times, respectively (**Figure 2**). Most of the logistic regression parameters did not increase the risk of sexual dysfunction in males and females. However, obesity and previous ART increased the risk of SD in men in women, respectively. Therefore, considering obesity in males and prior ART in females as potential confounders, we adjusted them with the stratification method taking the different strata in the process. Significant differences in SD between the TI and RI group were still observed even after stratifying for obesity present (OR 13.943, 95% CI 4.371- 44.480, p-value $<$0.0001) and absent (OR 15.281, 95% CI 7.059-33.084, p-value $<$0.0001) in men. Similarly, in women, significant differences between the TI and RI were still observed even after stratifying for previous ART done (OR 6.576, 95% CI 1.217-35.525, p-value 0.0286) and not done (OR 5.137, 95% CI 1.989-13.270, p-value 0.0007).

TTP analysis

In the KM analysis, we included 186 and 56 couples in the TI and RI groups, respectively, who had the ability of "natural conception" and whose first visit to our clinic was till the end of December 2017. Out of them, 43 pursuing TI, and 17 doing RI conceived naturally (**Figure 1**). The probability of conception was similar between the two groups (log-rank p-value 0.1365) (**Figure 3**). Therefore, TI did not improve the TTP compared with RI.

Discussion

Main findings

For male and female partners of infertile couples, TI increased the risk of SD by 15.24 times and 5.52 times, respectively, compared with RI. Secondly, after applying logistic regression, we found that the differences in SD between the TI group and the RI group persisted even after adjusting for age, obesity, smoking status, medical disorders, cause of infertility, and previous ART treatment. Thirdly, after applying the DSM-V definition for different types of SD, TI was found to increase the risk of MHSD, ED, PE, FSIAD, and FOD. The IIEF-5 scores were worse in men practising TI than those doing RI. Finally, after following the couples for more than one year using KM analysis, TI did not accelerate the TTP compared with RI.

Strengths and limitations

This was the first study conducted on the infertile population to the best of our knowledge, assessing two critical aspects of reproduction: SD and TTP. For both the aspects, the effects of TI were directly compared with a control group, unlike previous studies.[4,6,7,8,9,21,29,30,31,32] Although two papers compared TI with RI, one[22] concentrated mainly on FSD and another[33] mainly on the TTP.

Published studies showing the effects of TI on SD did not take both the partners into consideration.[7,9,21,22] In contrast, our study analyzed different aspects of sexual functions in both men and women using structured definitions. We preferred the ASEX because it was less time-consuming, easily understandable, and useful to diagnose SD in a bimodal scale in the clinical set up with minimum embarrassment for the individuals.[34,38] It was already applied in the Indian population.[38,39] However, the ASEX measured only the basic, but not all components of SD.[34]Therefore, applying the ASEX as a screening test, we used the DSM-V for all the individuals to categorize the SDs.[35] Additionally, the severity of ED was assessed by the IIEF-5 score, which was short and user-friendly.[36] We also applied logistic regression to confirm that the increased risk of SD induced by TI could not be explained by the presence of the "confounding factors."

Using KM analysis, we found that TTP was similar between TI and RI. In the literature, two studies used KM analysis showing the beneficial effect of TI on TTP.[30,33] However, one study did not have a control group,[30] and another included women without fertility problems.[33] Additionally, unlike previous studies, [29,30,31,32,33] we followed the couples for a longer time.

One of the limitations of our study was that it was not a prospective randomized one. Because of concerns about completing the detailed questionnaires, the couples were asked to fill up abbreviated questionnaires (ASEX and IIEF-5). Therefore, this self-reported information was recalled data, which was less reliable than intercourse diaries.[40] Again, the starting point of TTP was when the couples started planning for pregnancy, which was again recall-based. We did not assess psychological stress and live birth. Finally, the study population was mainly based on Indian couples presenting to particular clinics. The SD may differ according to ethnicity and culture.[41]

Interpretation

Theoretically, programming the intercourse in the "fertile window" (comprised of six days ending on the day of ovulation) should increase the chance of conception.[4,5,8,25] To identify that fertile window, most of the women in our study used the calendar method. However, the calendar method was unreliable because only 30% of women would have their fertile window between day10 and day17 of the cycle.[3,25] Few women in our study used the urinary luteinizing hormone (LH) test, which again had fallacies.[3,42] Basically, TI based on available methods can miss the actual fertile window.[24,26]

We found that 7.42% of the couples practised TI because of difficulty staying together regularly, as noted by others.[3]However, in most of the other cases, the advice for TI came deliberately from the health-care professionals who could make the couples feel "ordered" even if they were not interested in sex.[23]

In our study, 66% and 25% of men and women respectively experienced SD, supporting the concept that infertile couples often perceive sex just as a "mechanical entity" for procreation, losing its erotic component.[9,10,11] However, TI further increased the risk of SD in our study, which conformed to other authors' findings.[7,9,13,21,22]. The reason was forcing "obligatory" sex at a particular time would separate sex from sexuality.[7,10]

We noted ED as the commonest disorder affecting 49% of the male partners. This incidence was much higher than reported by other authors.[10,43,44] The possible explanation was that ED was significantly more common (59% versus 15%) and more severe (IIEF-5 score 12.0599 $\pm$5.6073 versus 16.8462 $\pm$4.7583) in the TI group than in the RI. Similarly, the incidence of "acquired" PE in our study (32%) was much higher than reported in other studies,[10.43,44] because PE was more common in men pursuing TI than those having RI (39% versus 7%). We also found that the risk of MHSD was also increased by TI.

Interestingly, 14 men in our study developed "acquired" DE. Of them, 12 (85.71%) were able to ejaculate during masturbation, as mentioned by other authors,[7,45] possibly because of stress reaction, sexual precon-

ditioning, and the conflict between sexual realities and fantasies. However, the incidences of DE were not significantly different between the TI and the RI group. But this information should be interpreted with caution because of the difficulty in diagnosing DE.[45]

Few papers investigated the relationship between FSD and TI.[13,22,23] We used the DSM-V recommended-term FSIAD, because of difficulty in the differentiation between female hypoactive sexual disorder and arousal disorder.[35,46] Similarly, the term GPPPD used by the DSM-V combined both vaginismus and dyspareunia.[35,46] Our study established the finding of a previous study,[22] showing that TI increased the risk of both FSAID and FOD.[22] Interestingly, similar to what was mentioned by McCabe et al.[46] we noted a higher occurrence of orgasmic problems in females (FOD; 7.5%) than in males (DE; 3.8%). However, the incidences of GPPPD were similar between TI and RI groups, consistent with a previous study.[22]The probable reason was that painful sex often represented organic pathology like endometriosis, rather than sexual performance.[46]

We found that TI increased the risk of SD in males and females by 15.235 and 5.519 times, respectively. Therefore, in a crude way, men were more affected than women by TI, which conformed to a Japanese study.[13] It contradicted the previous studies.[47,48] claiming that infertility induced more SD in women than men. One possible explanation was that men felt it stressful to "utilize" their partners' fertile window.[9,49] Alternatively, women often perceive themselves as the "passive partner" in sex and may not have an awareness of sexual problems.[50]

The term TTP was considered the measure of human fecundity.[40] We failed to find any differences in TTP in clinical pregnancy between the TI and the RI group, as shown in the Cochrane review.[8] Consequently, we inferred that TI was associated with more harm than benefits.

Conclusion

"Insisting" the couples on TI would harm by increasing the risk of different types of SD in both the partners. TI did not confer any benefits to the infertile couples in terms of hastening the TTP. Caution should be practised while offering TI to the couples struggling to conceive.

Disclosure of interests:

None declared.

Contribution to authorship:

Conception and design: SD, PP, and AC.

Data collection: SD and PP.

Data analysis and interpretation: SD, LCF, and AC.

Drafting the article: SD

Critical revision of the article for important intellectual content: LCF, PP, and AC.

Final approval of the version to be published: SD, LCF, PP, and AC.

Responsibility for all aspects of the work in ensuring the accuracy and integrity of the data: SD, LCF, PP, and SD

Details of Ethics Approval:

This study was approved by the Institutional Ethics Committee of RSV Hospital (IEC-15/12/2A) on 23 December 2015. Written informed consent was taken from both the partners of all the couples participating in this study. The study adhered to the World Medical Association Declaration of Helsinki.

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Table 1

Sexual dysfunctions in male and female partners in both the groups

Sexual problems	**TI (n =283)**	**RI (n= 88)**	**RI (n= 88)**	**Tests used**	**Tests used**	**p value**	**p value**	**Total (n=371)**	**To (n**
Sexual Dysfunction in male									
ASEX score positive	221 (78.09)	23 (26.14)	23 (26.14)	Chi-square	Chi-square	<0.001*	<0.001*	244 (65.77)	24 (65
Male hypoactive sexual dysfunction	73 (25.76)	4 (4.54)	4 (4.54)	Chi-square	Chi-square	<0.001*	<0.001*	77 (20.75)	77
Erectile dysfunction	167 (59.01)	13 (14.77)	13 (14.77)	Chi-square	Chi-square	<0.001*	<0.001*	180 (48.52)	18 (48
Premature ejaculation	111 (39.22)	6 (6.82)	6 (6.82)	Chi-square	Chi-square	<0.001*	<0.001*	117 (31.54)	11 (31

Sexual problems	**TI (n =283)**	**RI (n= 88)**	**RI (n= 88)**	**Tests used**	**Tests used**	**p value**	**p value**	**Total (n=371)**	**To (n**
Delayed ejaculation	13 (4.59)	1 (1.14)	1 (1.14)	Fisher	Fisher	0.2025	0.2025	14 (3.77)	14
Sexual Dysfunction in female									
ASEX score positive	85 (30.03)	85 (30.03)	7 (7.95)	7 (7.95)	Chi-square	Chi-square	<0.001*	<0.001*	92
Female sexual interest-arousal disorder	72 (25.44)	72 (25.44)	6 (6.82)	6 (6.82)	Chi-square	Chi-square	0.0002*	0.0002*	78
Genito-pelvic penetration-pain disorder	14 (4.95)	14 (4.95)	2 (2.27)	2 (2.27)	Fisher	Fisher	0.3775	0.3775	16
Female orgasmic disorder	27 (9.54)	27 (9.54)	1 (1.14)	1 (1.14)	Chi-square	Chi-square	0.0091*	0.0091*	28

Note: Values are expressed as number (percentage) unless stated otherwise.

ASEX = Arizona Sexual Experience Scale, RI= regular intercourse, TI= timed intercourse

One individual may have more than one sexual dysfunction.

* Significant p value.

Figure Captions List

Figure 1

Flow diagram of the study

ART= assisted reproductive techniques, ASEX = Arizona Sexual Experience Scale, DSM-V= Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, ED= erectile dysfunction, IIEF-5 International Index of Erectile Function-5, NE= not estimated, OI= ovulation induction.

Figure 2

Multiple logistic regression for sexual dysfunctions (defined as positive ASEX score) in male (A) and female (B) partners

ART= assisted reproductive techniques, BMI= body mass index, CI= confidence interval, OR= odds ratio.

a treated or untreated conditions like diabetes, hypertension, hypothyroidism, and other systemic co-morbidities

b current smokers and who quitted <12 month ago

c abnormal semen analysis results as per World Health Organization, 2010 recommendation

d anovulation, fallopian tube pathology, and/or endometriosis

*Significant p value.

Figure 3

Kaplan–Meier estimate of Time to pregnancy (TTP) for the couples having chance of natural conception and whose first visit was till end of December, 2017. The starting point was the time when a couple started trying for pregnancy. For natural conception, the end-point was the first day of the last menstrual period (LMP) in which "clinical pregnancy" took place by natural conception. The couples were censored at the starting date of the assisted reproductive technology (ART) in case of ART-conception and at the date of the last visit if they were lost to follow up (defined as no visit after June 2018) or were still under treatment. Numbers at risk in each group are given along the x-axis at multiple time-points.

RI= regular intercourse, TI= timed intercourse.

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