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Effect of male age on fertility: evidence for the decline in male fertility with increasing age

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Objective: To evaluate the effect of men's age on time to pregnancy (TTP) using age at the onset of pregnancy attempts, adjusting for the confounding effects of women's age, coital frequency, and life-style characteristics.

Design: Observational study.

Setting: Teaching hospital in Hull, United Kingdom.

Patient(s): Two thousand one hundred twelve consecutive pregnant women.

Intervention(s): A questionnaire inquiring about TTP, contraceptive use, pregnancy planning, previous subfertility, previous pregnancies, age, and individual life-style characteristics of both partners.

Main Outcome Measure(s): Time to pregnancy, conception rates, and relative risk of subfecundity for men and women's age groups.

Result(s): As with women's age, increasing men's age was associated with significantly rising TTP and declining conception rates. A fivefold increase in TTP occurred with men's age >45 years. Relative to men <25 years old, those >45 years were 4.6-fold and 12.5-fold more likely to have had TTP of >1 or >2 years. Restricting the analysis to partners of young women revealed similar effects of increasing men's age. Women >35 years were 2.2-fold more likely to be subfertile than women <25 years. The results were comparable, whether age at conception or at the onset of pregnancy attempts was analyzed, and they remained unchanged after adjustment for the confounding factors.

Conclusion(s): Evidence for and quantification of the decline in men's fertility with increasing age is provided. (Fertil Steril® 2003;79(Suppl 3):1520–7. ©2003 by American Society for Reproductive Medicine.)

Key Words: Fertility, fecundity, men's age, women's age, life-style, time to pregnancy

Half of the couples trying for pregnancy succeed within 3 months, increasing to over 85% by end of the first year (1). Subfertility is defined by an unsuccessful waiting time to pregnancy (TTP) of >12 months, despite frequent unprotected intercourse (2). One in six couples is subfertile (3), 30% of subfertile couples have no identifiable medical cause (4), and over 70% of these conceive within a further 24 months of trying without medical help (5). Differences in individual and life-style characteristics have been suggested to have a role in the cause of subfertility (6–9) and in the success of treatment (10–12).

The effect of women's age on fertility is well recognized (13–17). Indeed women's age is one of the two most important factors influencing the probability of conceiving without medical intervention in cases of unexplained subfertility; the other is the duration of trying for pregnancy (18–20). Furthermore, studies of donor insemination, donor oocyte, and in vitro fertilization (IVF) programs have demonstrated the important role that women's age has in the success of the treatment (21–28).

Men's age effect on fertility, on the other hand, remains uncertain (29). Evaluation of standard sperm and/or endocrine parameters in age groups has been inaccurate, as these parameters do not reflect the sperm fertilizing capacity or fecundability. Studies investigating the age effect on fecundity have been criticized on methodological grounds for using age at conception or for not taking account of the confounding factors (e.g., female age, coital frequency). Increasingly, couples with career ambitions delay having children till later age (30); demographic changes have meant older

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TABLE 1

Variation in life-style characteristics of women and men according to their age groups.

Variable [μ (CI)]	Women's age groups				Male partners' age groups			
	≤25 years	>25–35 years	>35 years	*P* value[a]	≤25 years	>25–45 years	>45 years	*P* value[a]
Other partner's age (years)	25.7 (25.3–26.0)	32.0 (31.7–32.3)	38.5 (37.7–39.4)	<.001	21.4 (21.1–21.8)	29.0 (28.8–29.3)	34.6 (33.6–35.6)	<.001
Women's weight (kg)	68.0 (67.0–69.0)	70.0 (69.2–70.9)	69.1 (68.0–70.2)	.009	68.1 (66.8–69.4)	69.4 (68.7–70.2)	68.2 (65.5–70.9)	.27
Women's body mass index (kg/m^2)	25.4 (25.1–25.8)	25.9 (25.6–26.2)	25.2 (24.5–25.9)	.14	25.6 (25.1–26.1)	25.7 (25.4–26.0)	25.2 (24.2–26.1)	.5
Women's smoking (cig/day)	4.1 (3.7–4.5)	2.4 (2.0–2.7)	2.3 (1.6–3.1)	<.001	4.8 (4.1–5.4)	2.4 (2.1–2.7)	3.4 (2.3–4.6)	<.001
Men's smoking (cig/day)	9.1 (8.4–9.9)	4.4 (3.8–4.9)	7.4 (5.8–9.1)	<.001	9.1 (8.2–9.9)	5.4 (5.0–5.9)	7.7 (5.3–10.1)	<.001
Women's alcohol (U/week)	1.0 (0.9–1.2)	1.7 (1.5–1.9)	2.2 (1.7–2.6)	<.001	0.8 (0.7–0.9)	1.6 (1.5–1.8)	2.1 (1.5–2.7)	<.001
Men's alcohol (U/week)	7.4 (6.6–8.2)	7.6 (7.1–8.1)	10.7 (9.0–12.4)	<.001	7.3 (6.3–8.3)	7.9 (7.4–8.4)	8.4 (6.3–10.4)	.005
Women's coffee (cup/day)	3.4 (3.2–3.6)	3.8 (3.6–4.0)	4.4 (4.0–4.9)	<.001	3.5 (3.3–3.7)	3.7 (3.5–3.8)	4.9 (4.3–5.6)	<.001
Coital frequency (/week)	2.1 (2.0–2.2)	1.8 (1.7–1.8)	1.7 (1.5–1.8)	<.001	2.3 (2.1–2.4)	1.8 (1.7–1.8)	1.8 (1.6–2.0)	<.001
Age at menarche (years)	12.6 (12.5–12.8)	13.0 (12.9–13.1)	13.2 (12.9–13.5)	<.001	12.6 (12.5–12.8)	13.0 (12.9–13.1)	12.8 (12.4–13.2)	<.001
Deprivation Index	46.2 (44.6–47.7)	34.6 (33.1–36.0)	33.4 (29.7–37.1)	<.001	47.0 (44.9–49.1)	36.0 (34.7–37.3)	37.0 (32.1–42.0)	<.001
Previous pregnancies	0.5 (0.4–0.6)	1.4 (1.4–1.5)	2.1 (2.0–2.2)	<.001	1.3 (1.2–1.4)	1.7 (1.6–1.8)	2.3 (1.5–3.1)	<.001
Contraceptive duration (m)	28.2 (25.8–30.5)	48.3 (45.1–51.5)	44.3 (35.8–52.9)	<.001	22.9 (20.4–25.5)	47.2 (44.4–49.9)	42.8 (32.6–52.9)	<.001

Note: μ = mean; CI = 95% confidence interval.

[a] Kruskal-Wallis test.

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people are more likely to start new relationships and desire more children. The age effect on fertility is certainly clinically relevant. To evaluate and quantify the exclusive effects of women and men's ages on fecundity, we attempted to avoid some of the shortcomings of the previous studies by using the age at the onset of trying for pregnancy (i.e., the time of the couple discontinuing contraception), and by adjusting for the confounding factors.

MATERIALS AND METHODS

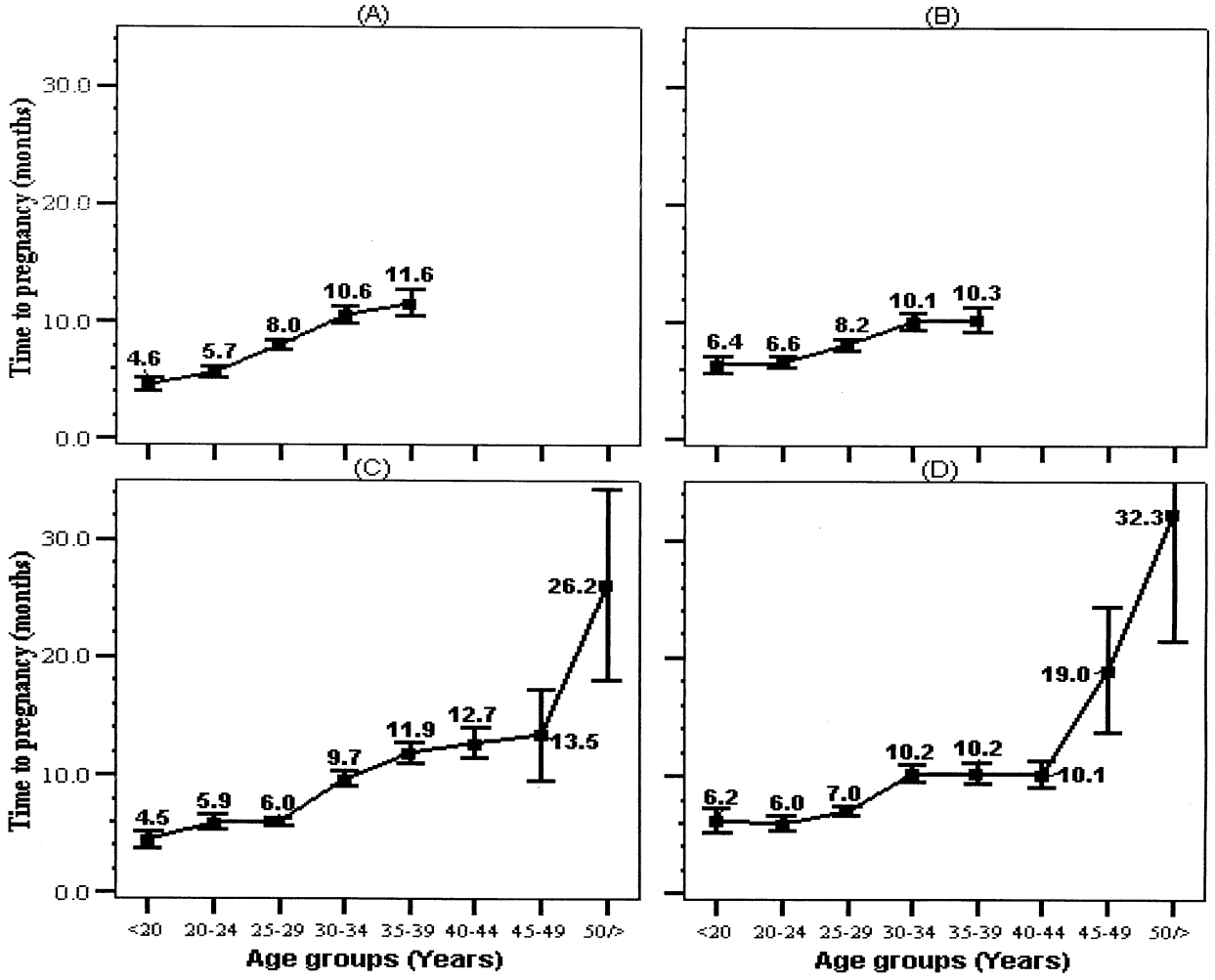
A survey was conducted in Hull and East Yorkshire (September 2000 to May 2001). Consecutive women in the antenatal clinics were asked to self-complete a questionnaire inquiring about TTP (the interval of exposure to unprotected intercourse from discontinuing birth control methods till conception), contraceptive use, pregnancy planning, previous fertility problems/pregnancies, gynecological disease/surgery, and individual life-style factors, including the woman's age, weight, height, smoking, alcohol consumption, coffee and tea intake, recreational drug use, and the partner's age, smoking, alcohol consumption, drug use, known fertility/health problems and surgery, and the couple's coital frequency. The postal address code, linked to the Index of Deprivation, was used as an indicator of the living standard (31).

The questionnaire was piloted. An independent assessor interviewed women in the clinic after the women had self-completed the questionnaire to ensure that the respondents had understood exactly what information was required from each question. Another group was asked to complete the same questionnaire on two occasions, 2 weeks apart, to ensure that their answers were consistent. Approval was obtained from the local research ethics committee (the U.K. equivalent of the institutional review board). There were no conflicts of interest. The questionnaire was anonymous and confidentiality was preserved. The response was over 99%. The sample included 2,112 completed questionnaires.

Data analysis was carried out using the SPSS computer package (SPSS, Inc., Chicago, IL). Outcome measures were the mean (± SD) TTP, conception rates, and relative risk (RR) of subfecundity for age groups, using age at the onset of the couple attempting to achieve pregnancy (at discontinuing contraception) after adjustment for the confounding factors. Women and men's ages were correlated to TTP (Spearman) then grouped. Differences in individual and life-style variables among age groups were evaluated (Kruskal-

FIGURE 1

The effect of increasing age, presented as age groups in years, on fecundity expressed as time to pregnancy (TTP) in months. Women's age effect on TTP was calculated using the (**A**) age at conception and (**B**) the age at the onset of attempting to achieve pregnancy. Men's age effect on TTP was calculated using (**C**) the age at conception and (**D**) the age at the onset of attempting to achieve pregnancy. Values in each figure represent the mean TTP for the age groups; the error bars represent the standard error of the mean. ($P<.001$ for all calculations.)



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Wallis test) to identify factors that might bias the age effect on TTP. Mean (± SD) TTP of age groups were compared and mean (± SD) ages of TTP bands were compared (univariate analysis). Conception rates by the age groups were compared, and the odds for taking TTP >1 or >2 years were calculated. Both the age at conception and at the onset of attempting to achieve pregnancy were used in the analysis. Results were studied before and after correction for the confounding factors (general linear model for regression analysis of TTP and logistic regression for fecundity). Factors in the models were the other partner's age, women's weight, body mass index (BMI), parity, smoking, alcohol consumption, drug use, tea and coffee intake, contraceptive use, menstrual pattern, gynecologic history, age at menarche, and men's smoking, alcohol, drug use, and the couples' coital frequency, living standard, and potential risk factors for subfertility.

RESULTS

Of the women completing the questionnaire, 136 did not report TTP. Of the remaining 1,976 women, 1,128 (57.1%) conceived within 3 months; the number rose to 1,604 (81.2%) by end of the first year. Of the 372 (18.8%) subfecund couples, 190 (9.6%) conceived in the second year. Teenagers comprised 10.6% of the women; 11.9% were >35

TABLE 2

Time to pregnancy for women's and men's age groups, using the age at the onset of attempting to achieve pregnancy, before and after adjustment for the confounding factors.

Variable (n)	Age groups (years)	Unadjusted TTP (months)		Adjusted TTP[a] (months)	
		μ (CI)	Statistical test	μ (CI)	Statistical test
Women's age (1976)	25 or less	6.4 (5.5–7.3)	F = 12.2	5.0 (3.7–6.4)	F = 2.8
	>25–30	8.2 (7.2–9.2)	$P<.001$	5.9 (4.8–6.9)	$P=.037$
	>30–35	10.8 (9.6–12.0)		7.5 (6.1–8.8)	
	>35 years	10.4 (8.5–12.3)		9.5 (6.8–12.1)	
Men's age (1832)	25 or less	6.4 (5.1–7.6)	F = 16.1	7.0 (5.1–8.9)	F = 9.0
	>25–30	7.2 (6.1–8.2)	$P<.001$	6.9 (5.6–8.2)	$P<.001$
	>30–35	10.0 (8.9–11.2)		9.3 (7.9–10.7)	
	>35–40	10.9 (9.3–12.5)		11.4 (9.5–13.4)	
	>40–45	11.9 (8.7–15.1)		12.4 (8.6–16.2)	
	>45 years	31.3 (24.5–38.1)		37.2 (27.1–47.3)	
Age of male partners of women <25 years old (638)	25 or less	5.3 (4.4–6.2)	F = 4.5	4.6 (3.3–5.9)	F = 6.0
	>25–30	6.1 (4.9–7.3)	$P=.001$	6.2 (4.3–8.0)	$P<.001$
	>30–35	5.2 (2.9–7.5)		6.0 (2.8–9.1)	
	>35–40	7.6 (4.5–10.8)		11.5 (7.3–15.7)	
	>40 years	22.5 (14.1–30.9)		23.2 (14.5–31.9)	

Note: TTP = time to pregnancy; n = number, μ = mean, CI = 95% confidence interval; F = analysis of variance.

[a] Factors in the model: age of the other partner, women's weight, body mass index, smoking, alcohol consumption, tea and coffee intake, parity, contraceptive use, menstrual pattern, age at menarche, and men's smoking, alcohol consumption, coital frequency and living standard. Analysis was also performed after excluding those with a gynecologic history, other risk factors for subfertility or conceived after treatment.

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years old. Of the men, 3.0% were teenagers, and 7.9% were >45 years old. Older women, older men, and their partners smoked fewer cigarettes, consumed more alcohol and more tea and coffee, had longer contraceptive use, had less frequent intercourse, and a higher living standard, and had older partners. Older women were heavier, had an older age at menarche, and had a higher parity (Table 1). Older women were more likely to have had a gynecologic history (30.0% v. 21.1%). No statistically significant difference was found in the history of a health problem among younger and older male partners (6.8% and 8.0%, respectively). Of the men reporting a health problem, only three cases had a history of a risk factor for male subfertility (one with varicocele, and two with vasectomy reversal).

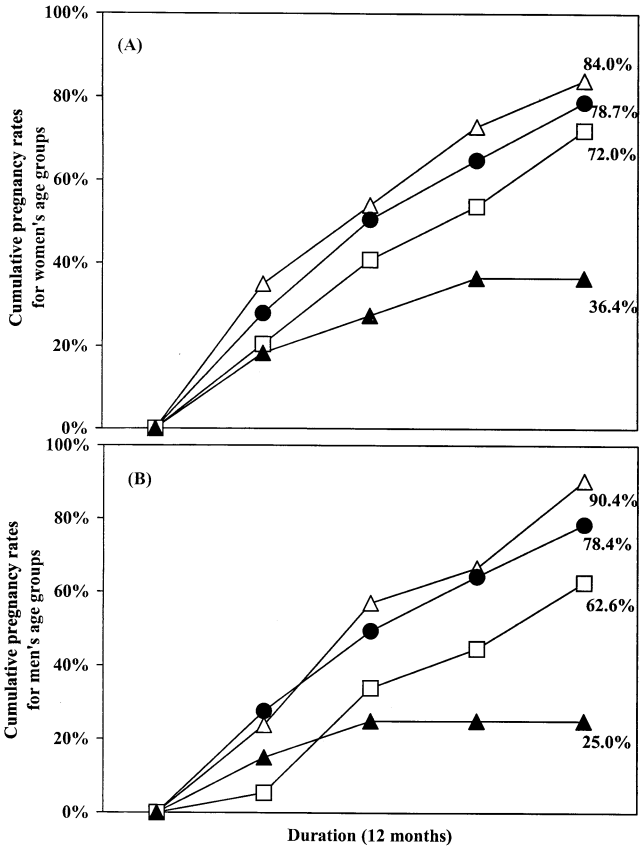
A progressively declining fecundity evident with increasing age of women or men became accelerated when the men's age was 45 years or older (Fig. 1). Women >35 years of age had a TTP twice that of those <25 years. Men >45 years old had significantly reduced fecundity than men <25 years (fivefold longer TTP). By use of regression analysis in a general linear model, the age effect of males on TTP remained unchanged after controlling for women's age, coital frequency, and the other factors affecting both partners, as detailed previously. A similar effect of increasing men's age on TTP was found among male partners of young women, <25 years old (n = 638); couples composed of older male partners and young women had a TTP fourfold that of young couples. This decline in fecundity confirmed that the negative effect of increasing the man's age is independent of the effect of the woman's age (Table 2). The same effect was found when we included planned and unplanned pregnancies, and also those who had risk factors for subfertility or who had conceived following fertility treatments. Similar results were obtained whether the age at conception or the age at the onset of attempting to achieve pregnancy were used in the analysis.

Women who took longer to conceive and men who took longer to impregnate their partners were significantly older at conception (for TTP <12, 12 to 24, and >24 months: mean women's ages 27.2, 27.9, 30.4; and men's ages 30.0, 31.1, 34.3 years, respectively). However, only those who had a TTP >24 months were significantly older at the onset of attempting to achieve pregnancy (women's ages 27.1, 26.9, 28.7; and men's ages 29.8, 30.1, 32.9 years, respectively). The differences in men's ages remained statistically significant after adjustment for the individual and life-style characteristics (adjusted men's ages 30.1, 31.2, 32.3 at conception and 29.8, 30.7, 31.6 years at the onset of attempting to achieve pregnancy, respectively).

Conception rates declined progressively with increasing age (Fig. 2). Within 6 months, 75.5% of women <25 years conceived compared with 58.4% of those >35 years old; 76.8% of men <25 years impregnated their female partners

FIGURE 2

The effect of increasing age among women and men in a pregnant population on the cumulative conception rates during the first year of attempting to achieve pregnancy. (**A**) For women, the cumulative conception rates for each age group are as follows: <20 years old (△), 20 to 34 years old (●), 35 to 39 years old (□), and ≥40 years old (▲). (**B**) For men, the cumulative conception rates for each age group are as follows: <20 years old (△), 20 to 39 years old (●), 40 to 49 years old (□), ≥50 years old (▲). (*P*<.001 for both calculations.)



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compared with 52.9% of men >45 years old. The subfecundity proportions rose constantly with women or men's ages: 13.1% of women <25 years compared with 29.2% of women >35 years; 10.6% of men <25 years compared with 35.3% of men >45 years. Relative to women ≤25 years old, those >35 years were 1.6-fold and 2.2-fold more likely to have a TTP of >1 or >2 years, respectively. The relative risks of TTP >1 or >2 years for couples with male partners >45 years old were 4.6-fold and 12.5-fold, respectively, compared with men ≤25 years. Using conception ages, the corresponding values were 2.8 and 4.4 for women, and 4.6 and 13.3 for men, respectively. Similar results were obtained after adjustment for the factors detailed above using logistic regression (Table 3).

The subfecundity proportions for those who had or did not have a gynecologic history in each of the women's age groups showed no statistically significant difference (15.2% vs. 12.5% in young women, and 29.6% vs. 29.0% in older women, respectively). The subfecundity proportions with and without history of a health problem in each male age group showed no statistically significant difference. Exclusion of patients with risk factors for subfertility and of those who had conceived after fertility treatments (3.1%) did not affect the results.

DISCUSSION

Fecundity can be studied using biomarkers such as hormone or sperm data (32), and better results can be achieved by using measures related to the outcome. The measure of choice for studying putative cause of subfecundity is TTP (33), which can be used in studies of pregnant women (34), women in age groups likely to have a pregnancy history (35), or in those planning for pregnancy (36). In contrast with studies of pregnancy planners, we chose an already pregnant population; it was relatively easy to collect a cohort of the relevant size within the study period and no exhaustive follow-up evaluation was required. Also, unlike in retrospective studies, the quality of information derived from studies using time to a current pregnancy was not affected by recall problems or knowledge of the outcome of the pregnancy attempt (37, 38). Recollection of a recent event, such as the onset of attempting to achieve the current pregnancy, is expected to be reasonably accurate. Moreover, asking for the interval from the discontinuation of contraception is probably easier to remember than the initial date of attempting pregnancy, and this permitted inclusion of unplanned pregnancies in the analysis.

Studies using pregnancy-related TTP, however, evaluate only the resolved subfertility, as they exclude those who failed to conceive or gave up an attempt. All the measures thus are calculated conditionally on an already achieved pregnancy (39–41). Such selective sampling is expected to result in underestimation rather than overestimation of the negative effect of rising age on TTP (42) found in this study, as older couples are less likely to persist in trying for pregnancy. Also, older couples are less likely to take adequate contraceptive precautions, but the effect of rising age on TTP, including and excluding the unplanned pregnancies, was similar. The questionnaire was designed for women to respond during the waiting time in the clinics. This was an important factor in the overwhelming response, which would ensure that this sample is truly representative of the large pregnant population, a further advantage of using a pregnant sample for this study.

Data analysis evaluated the exclusive effect of increasing age on fecundity. Couples taking longer TTP are relatively older by the time they conceive; the effect of the age at conception on TTP would thus be flawed. To avoid this bias,

TABLE 3

The effect of increasing women's or men's age at the onset of attempting to achieve pregnancy on the relative risk of subfecundity, before and after adjustment.

Age groups (years)	Subfecundity (TTP >12 months)					TTP longer than 2 years				
	Unadjusted			Adjusted[a]		Unadjusted			Adjusted[a]	
	%	RR (CI)	*P* value	RR (CI)	*P* value	%	RR (CI)	*P* value	RR (CI)	*P* value
Women's age										
25 or less	15.7	1.0		1.0		6.1	1.0		1.0	
>25–30	20.1	1.3 (1.0–1.8)	.04	1.1 (0.6–2.0)	.7	7.7	1.3 (0.8–2.0)	.2	1.6 (0.6–4.6)	.4
>30–35	20.7	1.4 (1.0–1.9)	.04	0.9 (0.4–1.8)	.7	16.0	2.9 (2.0–4.4)	<.0001	4.8 (1.5–16.0)	.01
>35 years	23.2	1.6 (1.1–2.4)	.02	2.2 (0.8–5.8)	.1	12.2	2.2 (1.2–3.8)	.007	7.7 (1.5–38.9)	.01
Men's age										
25 or less	15.7	1.0		1.0		4.8	1.0		1.0	
>25–30	14.1	0.9 (0.6–1.3)	.5	1.1 (0.7–1.7)	.8	5.8	1.2 (0.7–2.2)	.5	1.6 (0.7–3.4)	.3
>30–35	22.7	1.6 (1.1–2.2)	.008	1.8 (1.1–3.0)	.01	13.4	3.1 (1.9–5.2)	<.0001	3.2 (1.5–6.8)	.003
>35–40	23.3	1.6 (1.1–2.4)	.01	2.5 (1.4–4.5)	.001	14.7	3.4 (2.0–6.0)	<.0001	4.6 (2.0–10.7)	.0004
>40–45	28.6	2.1 (1.2–3.7)	.006	3.4 (1.6–7.3)	.001	9.5	2.1 (1.0–5.0)	.09	3.6 (1.2–11.2)	.03
>45 years	46.2	4.6 (2.0–10.4)	.0002	5.2 (1.5–17.4)	.008	38.5	12.5 (5.0–31.0)	<.0001	10.5 (2.3–47.0)	.002

Note: RR = relative risk; CI = 95% confidence interval; statistical test = logistic regression.

[a] Factors in the model: age of other partner, women's weight, body mass index, parity, smoking, alcohol consumption, tea and coffee intake, contraceptive use, menstrual pattern, and men's smoking, alcohol consumption, coital frequency, and living standard. Analysis was also performed after excluding those with a gynecologic history, other risk factors for subfertility, or fertility treatment.

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we used the age at the onset of trying for pregnancy in our analysis. Differences in the various characteristics of age groups were studied to identify possible confounding factors, for which adjustment in the regression models was carried out so as to evaluate the independent effect of age on fecundity. The age effect was evaluated in two ways. First by comparing the mean TTP for the age groups to identify differences in TTP with increasing age and comparing the mean ages for TTP bands to detect variation in age with rising TTP. Then by comparing the conception rates within 6 or 12 months and estimating the odds ratios for taking TTP >12 or >24 months between the age groups so as to demonstrate whether these would vary with increasing age. Both the ages at conception and at the onset of trying for pregnancy were used in the analysis.

The effect of women's age on fertility is well recognized and was confirmed in our study. Older women took significantly longer to conceive and the conception rates declined progressively with rising women's age. The proportion of subfecundity among women >30 years old was double that for women <20 years. The odds ratios for >12 or >24 months to conceive rose in a statistically significant manner with increasing women's age. Our findings are consistent with the recent evidence indicating that pregnancy probabilities for women aged 35 to 39 years are half those for women <25 years old (43).

Review of the literature on the effect of men's age on fertility reveals contradictory results. Standard sperm parameters or endocrine parameters are not accurate indicators of sperm function, that is, fertilizing capacity (44–46). For example, degenerative forms of germ cells are observed despite normal semen production in aging men (47). Thus, failure to show differences in these parameters with rising age does not indicate absence of an age effect on male fertility. It is less acceptable to study men's age effect on fertility by comparing sperm (48–53) or endocrine parameters (54–57). Studies using a donor-oocyte model (58, 59) failed to demonstrate an association between men's age and sperm parameters, fertilization, or pregnancy rates. Such models do not simulate the in vivo environment under which sperm normally function and do not, therefore, provide an accurate evaluation of the age effect on sperm fecundability. The same applies to studies of men's age effect on fertilization rates with insemination, IVF, or intracytoplasmic sperm injection (ICSI), which also failed to take into account the variation in the maternal factors (e.g., age or oocyte characteristics) (60–62).

It is better to study the effect of age on fecundity using TTP (63–66). Previous studies of TTP have been criticized for using age at conception (67) or for not taking account of the confounding effect of women's age (68). Using age at the onset of attempting to achieve pregnancy and adjusting for the confounding effects of women's age, coital frequency, and other factors of both partners, our study demonstrated a definite statistically significant negative effect of rising men's age on fecundity. A fivefold increase in TTP with men's age of >45 years was detected whether the age at conception or at the onset of attempting to achieve preg-

nancy was used in the analysis. As with women's age, the conception rates within 6 or 12 months declined significantly with increasing men's age. The odds ratios for men taking >1 or >2 years to impregnate their partners rose significantly in older men, whether the age at conception or at the onset of attempting to achieve pregnancy was used in the analysis.

Such an effect of men's age on fecundity could not be attributed to women's age, as the effect remained unchanged after adjustment in the regression models. Also, a similar effect of increasing men's age on TTP was found when the analysis was restricted to the male partners of young women <25 years of age. It cannot be argued that the negative effect of increasing age on fecundity was a result of the higher proportion of couples with potential risk factors for subfertility among older couples, as the effect remained unchanged after excluding these, as well as excluding those who conceived following fertility treatment. The consistency of our results leads to the conclusion that increasing male age is associated with a statistically significant decline in fertility (fivefold longer TTP at age of 45 years), which is independent of women's age, coital frequency, and life-style effect, as well as the effect of other subfertility risk factors.

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