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**MODERN TRENDS**

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# Effects of male age on semen quality and fertility: a review of the literature

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**Objective:** To review the literature on the association between male age and semen quality (semen volume, concentration, motility, and morphology) and fertility status (pregnancy rate and time to pregnancy/subfecundity).

**Method(s):** Review of English language–published research over the last 20 years from January 1, 1980, through December 31, 1999, using MEDLINE and Biosis databases. Studies with insufficient numbers of subjects, case reports, case series, or anecdotal data were excluded.

**Result(s):** Among the methodologically stronger studies, decreases in semen volume of 3%–22%, decreases in sperm motility of 3%–37%, and decreases in percent normal sperm of 4%–18% were likely when comparing 30-year-old men to 50-year-old men. Most studies examining fertility status suggest a relationship between male age and fertility, but the results are most likely confounded by female partner age. Among studies that did control for female age, comparisons between men under 30 and men over 50 found relative decreases in pregnancy rates between 23% and 38%. A comparison of the various age categories showed that the increased risks for subfecundity ranged from 11% to 250%.

**Conclusion(s):** The weight of the evidence suggests that increased male age is associated with a decline in semen volume, sperm motility, and sperm morphology but not with sperm concentration. (Fertil Steril® 2001; 75:237–48. ©2001 by American Society for Reproductive Medicine.)

**Key Words:** Human male, age, semen, volume, concentration, motility, morphology, pregnancy, fertility, review

Infertility has a major public health impact, with approximately 15% of couples of reproductive age in the United States receiving infertility services at some point in their lives (1), and approximately 7% of married couples not being able to conceive after trying for a year (2). Reduced fertility typically occurs among women in their late 30s to early 40s, when there is a sharp decrease in oocyte production (3). However, 25% or more of infertility is attributed to male factors (1).

Since 1980, there has been in the United States a 16% increase in the birth rate for fathers over age 35 (4). Unlike women, who are more fertile below the age of 40, men can conceive children well beyond their 40s and there is no known critical threshold with respect to sperm production in men. Nevertheless, it is important to know whether advanced paternal age is associated with diminished semen quality and a higher risk of infertility.

Rats and mice are good animal models for investigating the mechanisms of reproductive aging in males (5, 6). Aging of rodents appears to be related to histologic changes in the testes and in declines in sperm quality. Tanemura et al. (5) reported that vacuoles appeared in germ cells and cell numbers decreased in older mice (18 months old), resulting in a thinner seminiferous epithelium. Spermatids and spermatocytes essentially disappeared in very old mice (33 months old), as spermatogenesis was severely interrupted. Parkening et al. (7) found that older mice had atrophied testes, fewer motile sperm, and degenerated seminiferous epithelium and failed to mate when paired with young females. Wang et al. (6) reported significantly reduced total sperm production among older rats (22 and 30 months old).

Aging may also contribute to infertility via increased preimplantation losses. Preimplantation losses that were seen when older rats were mated may have been indicative of a decreased ability of sperm to fertilize or degeneration of embryos before implantation (8). Finally, mutation frequencies (9) and aneuploidy in sper-

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matids (10) were increased in older mice, which may also contribute to male-mediated infertility as well as genetic defects in offspring.

There has been no comprehensive review of the effects of male aging on semen quality and fertility in humans. We have conducted a review of the scientific literature of the past 20 years to evaluate the weight of the evidence for reproductive aging among men.

## METHODS

We included all research on humans published in English from January 1, 1980, through December 31, 1999. Two electronic database sources were searched: MEDLINE from 1980 and Biosis from 1988. We excluded studies with insufficient numbers of subjects ($n<20$), case reports, case series, and anecdotal data. The following reproductive outcomes were evaluated: semen volume, sperm concentration, sperm motility, sperm morphology, pregnancy rate, and time to pregnancy/subfecundity.

We emphasized analytic epidemiological studies, evaluating each study by whether the authors [1] adjusted for duration of abstinence (conventional semen quality studies) or age of female partner (fertility status studies), [2] clearly defined their criteria for selection of the study population, [3] provided data in the paper, [4] provided concurrent control data, and [5] adjusted for other potential confounders (e.g., smoking, parity). In summary paragraphs for each outcome where data allowed this, we calculated relative changes in the outcome with age. For example, if semen volume decreased from 4.1 mL in the younger age group to 3.2 mL in the older age group, then the relative decrease was 0.9/4.1, a 22% decrease in volume with increased age. Whenever possible, we summarized the differences between younger men (i.e., ages $\leq$30 years) and older men (i.e., ages $\geq$50 years).

## RESULTS

### Conventional Semen Quality

#### *Semen Volume*

Sixteen studies examined the relationship between male age and semen volume (Table 1). The study settings and populations were heterogeneous, with more than half based on infertility clinic or assisted conception populations, while the others used volunteers recruited from advertisements or sperm banks.

Among the 11 studies that reported decreases in semen volume with increased age (11–21), the study with the statistically strongest findings (12) reported a 30% decrease in volume from the young (mean age, 31 years) to the old age group (mean age, 54 years). Two other studies (11, 20) reported statistically strong findings, even after adjustment for potential confounding by duration of abstinence. These studies examined age as a continuous variable and found decreases of 0.15% (11) to 0.5% (20) for each increase in year of age. Several of the remaining studies that reported that volume decreased with increasing age found large differences in semen volume (ranging from 0.6 to 0.9 mL) between the youngest and the oldest age group(s) (13–16). However, only one of these studies adjusted for potential confounding by duration of abstinence.

Among the four studies that found no relationship between age and volume (22–25), only one adjusted for duration of abstinence, by restricting analyses to $\leq$5 days of abstinence (22). This study reported an inverse U-shaped curve with similar low volumes in both the youngest (21–25 years) and oldest (46–50 years) age groups and higher volumes in the age groups in between (26–45 years).

The one study (26) that reported a slight increase (0.01 mL/year) in volume with increased age showed that this effect disappeared after adjusting for year of birth in the final regression model. This study suggests that factor(s) related to time, other than aging, may be responsible for the findings.

Most of the studies listed in Table 1 did not adjust for potential confounding (e.g., smoking, type of infertility among clinic patients). Few studies adjusted for or assured a similar length of abstinence, although there is good evidence in the literature that an increased duration of abstinence increases volume in a time-dependent fashion (27–29). A longer duration of abstinence among older men would be likely to bias toward finding no association or a positive association (an increase in volume with an increase in age). Overall, this may have contributed to a bias toward the null in results across studies. Four (11, 14, 19, 20) of the five (11, 14, 19, 20, 22) studies that did control for duration of abstinence showed a decrease in volume with increased age.

The weight of the evidence suggests that there is a decrease in semen volume with increasing age, most notably among men over 50 years of age. In those studies that report a decrease, the relative decrease ranges between 3% and 30% for men less than 30 years old compared with men $\geq$50 years old, with most of these studies reporting a change of approximately 20%–30%. The methodologically stronger studies (11, 14, 20) found more modest decreases of 3%–22% comparing men in these age groups.

#### *Sperm Concentration*

Twenty-one studies examined the relationship between age and sperm concentration (Table 2). There is little consensus on the nature of this relationship.

Five studies (12, 17, 21, 23, 28) reported decreases in sperm concentration with increased age. The study (28) with the largest decline in sperm concentration with age included duration of abstinence and year of birth as independent

## TABLE 1

Male age and semen volume.

| Reference | Population | Male age definition (range/mean/group)[a,b] | Semen volume, mL[a,b] | Direction of effect with increasing age[c] | Data quality[d] |
|---|---|---|---|---|---|
| (12) | Infertility clinic ($n$ = 555) | I. 31 (0.2)<br>II. 54 (4.2) | 30% decrease from I to II | ↓ ($P<.0005$) | 2, 3 |
| (11) | Sperm donors ($n$ = 1,283) | 34.3 (0.2) | 0.15% decrease per year of age | ↓ ($P<.001$) | 1, 2, 3, 4, 5 |
| (20) | Infertility clinic ($n$ = 20,411) | 31.9 (5.4)<br>15–74 | 0.5% decrease per year of age | ↓ ($P<.001$) | 1, 2, 3, 4, 5 |
| (13) | Assisted conception ($n$ = 821) | I. ≤39<br>II. 40–49<br>III. ≥50 | I. 2.7 (0.1)<br>II. 2.5 (0.1)<br>III. 2.1 (0.2) | ↓ ($P<.05$) | 2, 3,4 |
| (16) | Assisted conception ($n$ = 345) | I. ≤30<br>II. 31–40<br>III. 41–50<br>IV. 51–64 | I. 3.1 (0.6)<br>II. 2.6 (1.4)<br>III. 2.3 (2.0)<br>IV. 2.2 (0.9) | ↓ (NS) | 2, 3, 4 |
| (14) | Infertility clinic ($n$ = 78) | I. <30 (matched by year of attendance)<br>II. <30 (matched by wives' ages)<br>III. >50 | I. 4.1 (1.6)<br><br>III. 3.2 (1.9) | ↓ (NS) | 1, 2, 3, 4 |
| (21) | Andrology lab ($n$ = 2,065) | 33.6 (5.8)<br>19–67 | Age correlation with volume ($r$ = −.04) | ↓ (NS) | 2, 3, 4 |
| (15) | Volunteers responding to advertisement ($n$ = 43) | I. 29 (3.2)<br>II. 67 (7.8) | I. 4.0 (1.7)<br>II. 3.2 (1.9) | ↓ (NS) | 2, 3 |
| (19) | Infertility clinic ($n$ = 3,437) | 19–63 | Age-dependent decrease in semen volume | ↓ | 1, 2, 4 |
| (17) | Volunteers ($n$ = 445) | I. <40<br>II. 40–60<br>III. >60 | Gradual decrease after age 40 | ↓ | 4 |
| (18) | Sperm donors with counts >200 $\times 10^6$/mL ($n$ = 1,299) | I. 34.6 (6.4)<br>II. 35.2 (9.4)<br>III. 38.4 (12.5) | I. ≥6<br>II. 1–5<br>III. <1 | ↓ | 3 |
| (22) | Semen donors ($n$ = 809) | I. 21–25<br>II. 26–30<br>III. 31–35<br>IV. 36–40<br>V. 41–45<br>VI. 46–50 | I. 3.2 (1.6)<br>II. 3.7 (1.2)<br>III. 3.6 (1.3)<br>IV. 3.6 (2.1)<br>V. 3.6 (1.7)<br>VI. 3.1 (2.1) | ↔ (NS) | 1, 2, 3, 4 |
| (23) | Older men planning further children ($n$ = 64) | I. 32.2<br>II. 50.3 | I. 3.2 (1.5)<br>II. 3.2 (1.7) | ↔ (NS) | 3, 4 |
| (24) | Infertility clinic ($n$ = 718) | 21–54 | Age correlation with volume ($r$ = .06) | ↔ | 2, 3, 4 |
| (25) | Family planning clinic ($n$ = 1,239) | 19–53 | No correlation with age | ↔ | 2, 4 |
| (26) | Sperm donors ($n$ = 577) | 18–53 | .01% (−.01, .03)[e] increase per year of age | ↑ (NS) | 2, 3, 4, 5 |

[a] Roman numeral groups in the third column correspond with roman numeral groups in the fourth column.
[b] Mean (SD).
[c] NS = not statistically significant at $P<.05$; no $P$ value indicates that no statistical testing was done; ↓ = decrease in volume with increase in age; ↔ = no relationship; ↑ = increase in volume with increase in age.
[d] Data quality: 1 = adjusted for duration of abstinence; 2 = clearly defined their criteria for selection of the study population; 3 = provided data in the paper; 4 = used concurrent controls; 5 = adjusted for other potential confounding factors.
[e] 95% confidence interval.

*Kidd. Effects of male age on semen and fertility. Fertil Steril 2001.*

variables in a multiple regression model. This study reported a decrease in sperm concentration of 3.3% per year of age, or about a 66% decrease in concentration from age 30 to 50. The other four studies did not adjust for potential confounders. Two of these studies compared men in younger (≤30) and older (≥50) age groups. One study (23) found nearly half the sperm concentration in the older group, and the second (12) found almost a 3-fold increase in the percentage

**TABLE 2**

Male age and sperm concentration.

| Reference | Population | Male age definition (range/mean/group)[a,b] | Sperm concentration, $\times 10^6$/mL[a,b] | Direction of effect with increasing age[c] | Data quality[d] |
|---|---|---|---|---|---|
| (28) | Semen donors ($n$ = 1,351) | 19–59 | 3.3% (−0.8, −4.7)[e] decrease per year of age | ↓ ($P<.001$) | 1, 2, 3, 4, 5 |
| (23) | Older men planning further children ($n$ = 64) | I. 32.2<br>II. 50.3 | I. 115.1 (103)<br>II. 66.9 (67) | ↓ ($P=.01$) | 3, 4 |
| (21) | Andrology lab ($n$ = 2,065) | 33.6 (5.8)<br>19–67 | Age correlation with concentration ($r$ = −.06) | ↓ ($P<.02$) | 2, 3, 4 |
| (12) | Infertility clinic ($n$ = 555) | I. 31 (0.2)<br>II. 54 (4.2) | I. 5.6% <5<br>II. 15.4% <5 | ↓ ($P<.05$) | 2, 3 |
| (17) | Volunteers ($n$ = 445) | I. <40<br>II. 40–60<br>III. >60 | Gradual decrease after age 40; considerable decrease after age 60 | ↓ | 4 |
| (22) | Semen donors ($n$ = 809) | I. 21–25<br>II. 26–30<br>III. 31–35<br>IV. 36–40<br>V. 41—45<br>VI. 46–50 | I. 77 (57.0)<br>II. 92 (64.3)<br>III. 95 (64.2)<br>IV. 90 (67.5)<br>V. 94 (67.5)<br>VI. 81 (61.9) | ↔ (NS) | 1, 2, 3, 4 |
| (13) | Assisted conception ($n$ = 821) | I. ≤39<br>II. 40–49<br>III. ≥50 | I. 22.7 (1.3)<br>II. 24.7 (2.4)<br>III. 19.8 (4.5) | ↔ (NS) | 2, 3, 4 |
| (33) | Infertility clinic ($n$ = 570) | I. 22–30<br>II. 31–40<br>III. 41–50<br>IV. >50 | I. 71 (66)<br>II. 87 (79)<br>III. 84 (57)<br>IV. 76 (61) | ↔ (NS) | 2, 3 |
| (30) | Volunteers responding to advertisement ($n$ = 187) | 19–47 | No association between age and concentration | ↔ (NS) | 2, 3 |
| (24) | Infertility clinic ($n$ = 718) | 21–54 | Age was not correlated with concentration ($r$ = .03) | ↔ | 2, 3, 4 |
| (31) | Meta-analysis of semen donors ($n$ = 14,947) | 17–64 | No trend of mean concentration with age | ↔ | 2, 4 |
| (25) | Family planning clinic ($n$ = 1,239) | 19–53 | No correlation with age | ↔ | 2, 4 |
| (32) | Infertility clinic ($n$ = 200) | I. ≤35<br>II. >35 | No difference between groups | ↔ | 2, 4 |
| (26) | Sperm donors ($n$ = 577) | 18–53 | 2.1% (1.9, 2.4)[e] increase per year of age | ↑ ($P<.001$) | 2, 3, 4, 5 |
| (20) | Infertility clinic ($n$ = 20,411) | 31.9 (5.4)<br>15–74 | 0.7% increase per year of age | ↑ ($P<.004$) | 1, 2, 3, 4, 5 |
| (15) | Volunteers responding to advertisement ($n$ = 43) | I. 29 (3.2)<br>II. 67 (7.8) | I. 78 (51)<br>II. 120 (101) | ↑ ($P<.05$) | 2, 3 |
| (11) | Sperm donors ($n$ = 1,283) | 34.3 (0.2) | 0.03% increase per year of age | ↑ (NS) | 1, 2, 3, 4, 5 |
| (14) | Infertility clinic ($n$ = 78) | I. <30 (matched by year of attendance)<br>II. <30 (matched by wives' age)<br>III. >50 | I. 44 (55.3)<br>III. 56 (90.1) | ↑ (NS) | 1, 2, 3, 4 |
| (34) | Sperm donors ($n$ = 302) | 21–44 | 3.3% (0.7, 6.1)[e] increase per year of age | ↑ (NS) | 2, 3, 4, 5 |
| (16) | Assisted conception ($n$ = 345) | I. ≤30<br>II. 31–40<br>III. 41–50<br>IV. 51–64 | I. 52.3 (59.0)<br>II. 54.2 (62.8)<br>III. 56.6 (72.3)<br>IV. 57.2 (38.5) | ↑ (NS) | 2, 3, 4 |
| (18) | Sperm donors with <1 mL volume ($n$ = 1,299) | I. 31.4 (7.8)<br>II. 33.9 (10.5)<br>III. 31.6 (10.0)<br>IV. 38.4 (12.5) | I. 0.1–20<br>II. 20–100<br>III. 100–200<br>IV. >200 | ↑ | 3 |

[a] Roman numeral groups in the third column correspond with roman numeral groups in the fourth column.

[b] Mean (SD).

[c] NS = not statistically significant at $P<.05$; no $P$ value indicates that no statistical testing was done; ↓ = decrease in concentration with increase in age; ↔ = no relationship; ↑ = increase in concentration with increase in age.

[d] Data quality: 1 = adjusted for duration of abstinence; 2 = clearly defined their criteria for selection of the study population; 3 = provided data in the paper; 4 = used concurrent controls; 5 = adjusted for other potential confounding factors.

[e] 95% confidence interval.

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of men with sperm concentration less than 5 million/mL in the older group.

Six studies (13, 24, 25, 30–32) found little or no association between age and sperm concentration, and two studies (22, 33) noted an ambiguous relationship between age and sperm concentration among age categories. That is, the youngest age groups had lower sperm concentrations than age groups in between, but the concentrations were similar to those of the oldest age group, suggesting inverse U-shaped data distributions.

Eight studies (11, 14–16, 18, 20, 26, 34) reported that sperm concentration increased with age. Several studies (11, 20, 26, 34) reported linear increases, with findings ranging from a 0.03% increase to a 3.3% increase in sperm concentration per year of age. These studies adjusted for some potential confounding, although the two (11, 20) that adjusted for duration of abstinence had findings of more modest increases. Of the remaining studies with positive associations, one (15) found a large increase in sperm concentration (from 78 to 120 million/mL) from the youngest to oldest age group.

Few studies controlled for duration of abstinence (11, 14, 20, 22, 28) or any other potential confounding factors (26, 34). Even among studies that controlled for duration of abstinence, the findings remained inconsistent. The weight of the evidence from the literature does not suggest that sperm concentration decreases with increasing age.

### *Sperm Motility*

Nineteen studies examined the relationship between age and sperm motility (percent motile) (Table 3). Sperm motility was typically assessed visually using a light microscope. Only two studies (21, 33) used computer-assisted sperm analysis.

Most studies (13 of 19) found a decrease in sperm motility with increasing age. Those studies that adjusted for duration of abstinence (11, 14, 22, 28, 35) reported statistically significant effects. In the study by Auger et al. (28), there was a 0.6% decrease in percent motile sperm for each year of age, which would translate into a 12% decrease in motility comparing a 50-year-old man with a 30-year-old man. Several studies reported negative linear relationships, with correlations ranging between $-.08$ (21) and $-.37$ (35) and decreases in motility ranging from 0.17 %(11) to 0.6% (28) for each year of age. Seven studies (13–17, 22, 23) that examined changes across age groups found lower fractions of motile sperm in the oldest age groups.

Four studies (24, 32, 33, 36) found no association between age and sperm motility. Check et al. (33) reported an inverse U-shaped distribution of the proportion of subjects with >50% motility. Some studies (32, 36) may have failed to show a difference across age groups because they did not compare age extremes.

Two studies reported a positive correlation ($r = .14$) (25) and a modest 0.06% increase in percent motility for each increase in year of age (26).

Thus, there is strong and consistent evidence across the majority of studies for a decrease in sperm motility with increasing age. This relative decrease across age groups comparing men approximately 50 years of age or older to those 30 years of age and younger is within the range of a 3%–37% decrease in motility. Among the methodologically stronger studies (11, 14, 22, 28), decreases of 3%–37% were also reported for comparisons of 30-year-old men with 50-year-old men.

### *Sperm Morphology*

Fourteen studies examined the relationship between age and sperm morphology (Table 4), with nine of these studies reporting an age-related decrease in percent normal sperm (14, 16, 20-23, 28, 37, 38). Auger et al. (28) reported that the percent normal sperm decreased by 0.9% for each year of age, controlling for year of birth and duration of abstinence in a linear regression model. Thus, an average 50-year-old man had an 18% decrease in the percent normally shaped sperm compared with the average 30-year-old man. Schwartz et al. (22) noted that coiled tails and microcephalic heads increased with age, although a statistically significant trend across age groups remained after excluding these two types of abnormalities.

Five studies found no association between percent normal sperm and age (13, 24, 30, 32, 39), but no data were presented in four of these studies to support the null findings.

The variable morphology criteria used across studies prohibit easy comparisons of the magnitude of the age-related decline between studies. For example, the WHO criteria (40) count more tail abnormalities than the David criteria (37) and generally count different head abnormalities. Different criteria would be especially relevant if different abnormalities were directly related to age. Unfortunately, in nearly all of the studies one could not examine directly the impact of differing criteria because the analyses did not list out the different sperm forms by age or age group.

In conclusion, there is good evidence that percent normally shaped sperm decreases with age. In most of the studies using age as a categorical variable (14, 16, 22, 23, 37, 38), there was a consistent trend toward decreasing percent normal sperm with increasing age groups. There was between a 4% and 22% decrease in percent normally shaped sperm for men $\geq$50 years of age compared with those $\leq$30 years of age. The relative percent change when comparing these age groups was roughly 4%–18% among the methodologically stronger studies (14, 20, 28).

## Fertility Status

Since semen quality is only an indirect measure of the probability of pregnancy, we also examined the literature for

**TABLE 3**

Male age and sperm motility.

| Reference | Population | Male age of definition (range/mean/group)[a,b] | Sperm motility (% motile)[a,b] | Direction of effect with increasing age[c] | Data quality[d] |
|---|---|---|---|---|---|
| (15) | Volunteers responding to advertisement ($n$ = 43) | I. 29 (3.2)<br>II. 67 (7.8) | I. 68 (14)<br>II. 50 (19) | ↓ ($P<.0005$) | 2, 3 |
| (28) | Semen donors ($n$ = 1,351) | 19–59 | 0.6% (−0.4, −0.8)[e] decrease per year of age | ↓ ($P<.001$) | 1, 2, 3, 4, 5 |
| (11) | Sperm donors ($n$ = 1,283) | 34.3 (0.2) | 0.17% decrease per year of age | ↓ ($P<.001$) | 1, 2, 3, 4 |
| (21) | Andrology lab ($n$ = 2,065) | 33.6 (5.8)<br>19–67 | Age correlation with motility ($r$ = −.10)<br>Age correlation with motile concentration (millions motile sperm/ml) ($r$ = −.08) | ↓ ($P<.001$)<br>↓ ($P<.002$) | 2, 3, 4 |
| (35) | Infertility clinic and healthy donors ($n$ = 90) | 22–57 | Age correlation with motility ($r$ = −.37) | ↓ ($P<.001$) | 1, 3, 4 |
| (38) | Infertility clinic ($n$ = 77) | I. <26<br>II. ≥26 | Motile sperm concentration, $\times 10^6$/mL<br>I. 55.2 (32.3)<br>II. 32.8 (10.9) | ↓ ($P<.01$) | 2, 3, 4 |
| (30) | Volunteers responding to advertisement ($n$ = 187) | 19–47 | Total percent motility decreased with increasing age | ↓ ($P$ = .01) | 2, 3 |
| (22) | Semen donors ($n$ = 809) | I. 21–25<br>II. 26–30<br>III. 31–35<br>IV. 36–40<br>V. 41–45<br>VI. 46–50 | I. 70.2 (8.8)<br>II. 71.9 (7.4)<br>III. 70.5 (12.0)<br>IV. 69.1 (9.3)<br>V. 70.8 (8.7)<br>VI. 64.8 (16.7) | ↓ ($P<.02$) | 1, 2, 3, 4 |
| (23) | Older men planning further children ($n$ = 64) | I. 32.2<br>II. 50.3 | I. 30.4 (14.5)<br>II. 23.1 (13.7) | ↓ ($P$ = .04) | 3, 4 |
| (14) | Infertility clinic ($n$ = 78) | I. <30 (matched by year of attendance)<br>II. <30 (matched by wives' age)<br>III. >50 | I. 41 (25)<br>III. 26 (22) | ↓ ($P<.05$) | 1, 2, 3, 4 |
| (13) | Assisted conception ($n$ = 821) | I. ≤39<br>II. 40–49<br>III. ≥50 | I. 36.5 (0.9)<br>II. 35.3 (1.4)<br>III. 34.9 (4.3) | ↓ (NS) | 2, 3, 4 |
| (16) | Assisted conception ($n$ = 345) | I. ≤30<br>II. 31–40<br>III. 41–50<br>IV. 51–64 | I. 43.8 (34.5)<br>II. 45.9 (29.3)<br>III. 42.2 (30.7)<br>IV. 40.7 (20.6)) | ↓ (NS) | 2, 3, 4 |
| (17) | Volunteers ($n$ = 445) | I. <40<br>II. 40–60<br>III. >60 | Gradual decrease after age 40 | ↓ | 4 |
| (33) | Infertility clinic ($n$ = 570) | I. 22–30<br>II. 31–40<br>III. 41–50<br>IV. >50 | Percent motility >50%<br>I. 39 (20)<br>II. 49 (19)<br>III. 44 (20)<br>IV. 34 (14) | ↔ (NS) | 2, 3 |
| (24) | Infertility lab ($n$ = 718) | 21–54 | No correlation with age ($r$ = .04) | ↔ | 2, 3, 4 |
| (36) | Infertility clinic ($n$ = 566) | I. <30<br>II. ≥30 | Motile sperm $\times 10^6$<br>I. 25.7 (28.0)<br>II. 24.8 (32.6) | ↔ | 2, 3, 4 |
| (32) | Infertility clinic ($n$ = 200) | I. ≤35<br>II. >35 | No difference between groups | ↔ | 2, 4 |
| (25) | Family planning clinic ($n$ = 1,239) | 19–53 | Age was correlated with motility ($r$ = .14) | ↑ ($P<.05$) | 2, 4 |
| (26) | Sperm donors ($n$ = 577) | 18–53 | 0.06% (−0.1, 0.2)[e] increase per year of age | ↑ (NS) | 2, 3, 4, 5 |

[a] Roman numeral groups in the third column correspond with roman numeral groups in the fourth column.
[b] Mean (SD).
[c] NS = not statistically significant at $P<.05$; no $P$ value indicates that no statistical testing was done; ↓ = decrease in motility with increase in age; ↔ = no relationship; ↑ = increase in motility with increase in age.
[d] Data quality: 1 = adjusted for duration of abstinence; 2 = clearly defined their criteria for selection of the study population; 3 = provided data in the paper; 4 = used concurrent controls; 5 = adjusted for other potential confounding factors.
[e] 95% confidence interval.

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**TABLE 4**

Male age and sperm morphology.

| Reference | Population | Male age definition (range/mean/group)[ab] | Sperm morphology (% normal)[ab] | Direction of effect with increasing age[c] | Data quality[d] |
|---|---|---|---|---|---|
| (28) | Semen donors ($n$ = 1,351) | 19–59 | 0.9% (−0.7, −1.1)[e] decrease per year of age | ↓ ($P$<.001) | 1, 2, 3, 4, 5 |
| (20) | Infertility clinic ($n$ = 20,411) | 31.9 (5.4)<br>15–74 | 0.2% decrease per year of age | ↓ ($P$<.001) | 1, 2, 3, 4, 5 |
| (22) | Semen donors ($n$ = 809) | I. 21–25<br>II. 26–30<br>III. 31–35<br>IV. 36–40<br>V. 41–45<br>VI. 46–50 | I. 54.6 (15.4)<br>II. 61.9 (11.6)<br>III. 61.6 (11.1)<br>IV. 60.8 (12.5)<br>V. 58.5 (11.4)<br>VI. 54.9 (10.2) | ↓ ($P$<.001) | 2, 3, 4 |
| (37) | Sperm donors ($n$ = 210) | I. 20–25<br>II. 26–30<br>III. 31–35<br>IV. 36–40<br>V. 41–45<br>VI. 46–50 | I. 75<br>II. 75.2<br>III. 71.8<br>IV. 72.2<br>V. 69.2<br>VI. 70.3 | ↓ ($P$<.001) | 2, 3, 4 |
| (38) | Infertility lab ($n$ = 77) | I. ≤40<br>II. >40 | I. 78.5 (2.9)<br>II. 72.3 (1.3) | ↓ ($P$<.01) | 2, 3, 4 |
| (14) | Infertility clinic ($n$ = 78) | I. <30 (matched by year of attendance)<br>II. <30 (matched by wives' age)<br>III. >50 | I. 31 (17)<br><br><br>III. 26 (18) | ↓ (NS) | 1, 2, 3, 4 |
| (16) | Assisted conception ($n$ = 345) | I. ≤30<br>II. 31–40<br>III. 41–50<br>IV. 51–64 | I. 61.3 (32.8)<br>II. 52.9 (39.1)<br>III. 48.5 (50.5)<br>IV. 53.2 (20.2) | ↓ (NS) | 2, 3, 4 |
| (21) | Andrology lab ($n$ = 2,065) | 33.6 (5.8)<br>19–67 | Age was correlated with morphology ($r$ = −.05) | ↓ (NS) | 2, 3, 4 |
| (23) | Older men planning further children ($n$ = 64) | I. 32.2<br>II. 50.3 | I. 26.5 (13.9)<br>II. 20.7 (16.2) | ↓ (NS) | 3, 4 |
| (13) | Assisted conception ($n$ = 821) | I. ≤39<br>II. 40–49<br>III. ≥50 | No significant differences in morphology | ↔ (NS) | 2, 3, 4 |
| (30) | Volunteers responding to advertisement ($n$ = 187) | 19–47 | No association between age and morphology | ↔ (NS) | 2, 3 |
| (24) | Infertility clinic ($n$ = 718) | 21–54 | Age was not correlated with morphology ($r$ = .03) | ↔ | 2, 3, 4 |
| (32) | Infertility clinic ($n$ = 200) | I. ≤35<br>II. >35 | No difference between groups | ↔ | 2, 4 |
| (39) | Assisted conception ($n$ = 100) | No age data | Poor correlation with age | ↔ | 1, 4 |

[a] Roman numeral groups in the third column correspond with roman numeral groups in the fourth column.
[b] Mean (SD).
[c] NS = not statistically significant at $P$<.05; no $P$ value indicates that no statistical testing was done; ↓ = decrease in morphology with increase in age; ↔ = no relationship; ↑ = increase in morphology with increase in age.
[d] Data quality: 1 = adjusted for duration of abstinence; 2 = clearly defined their criteria for selection of the study population; 3 = provided data in the paper; 4 = used concurrent controls; 5 = adjusted for other potential confounding factors.
[e] 95% confidence interval.

*Kidd. Effects of male age on semen and fertility. Fertil Steril 2001.*

male age-related changes in fertility. Several indicators for fertility were used: the pregnancy rate (i.e., the percent of male subjects whose partners achieve a pregnancy over a period of time), time to pregnancy (i.e., the amount of time attempting pregnancy), and subfecundity (i.e., the percent of couples remaining infertile at a defined time point). In contrast to studies of semen quality, reproductive history (e.g., parity, contraceptive use) and habits (e.g., smoking, frequency of intercourse) of the female partner are important determinants of fertility, with female age known to be a strong independent predictor of achieving pregnancy (41).

## Pregnancy Rate

Nine studies examined the relationship between male age and pregnancy rate. All studies selected participants from infertility and assisted conception clinics (Table 5).

**TABLE 5**

Male age and pregnancy rate.

| Reference | Population | Male age definition (range/mean/group)[a] | Pregnacy rate (%)[a] | Direction of effect with increasing age[b] | Data quality[c] |
|---|---|---|---|---|---|
| (42) | Assisted conception ($n$ = 274) | I. <30 | I. 51.7 | ↓ ($P$<.001) | 1, 2, 3, 4 |
| | | II. 30–34 | II. 40.3 | | |
| | | III. ≥35 | III. 25.0 | | |
| (43) | Infertility clinic ($n$ = 1,025) | I. <24 | I. 15.9 | ↓ ($P$=.02) | 2, 3, 4, 5 |
| | | II. 25–29 | II. 20.6 | | |
| | | III. 30–34 | III. 19.7 | | |
| | | IV. 35–39 | IV. 13.7 | | |
| | | V. 40–44 | V. 8.5 | | |
| | | VI. ≥45 | VI. 14.3 | | |
| (13) | Assisted conception ($n$ = 821) | I. ≤35 | I. 55.5 | ↓ ($P$<.04) | 1, 2, 3, 4 |
| | | II. 36–39 | II. 41.8 | | |
| | | III. ≥40 | III. 44.4 | | |
| (44) | Infertility clinic ($n$ = 394) | I. <31 | I. 82 | ↓ ($P$<.05) | 2, 3, 4, 5 |
| | | II. ≥31 | II. 59 | | |
| (32) | Infertility clinic ($n$ = 200) | I. ≤35 | I. 42 | ↓ ($P$<.05) | 2, 4 |
| | | II. >35 | II. 23 | | |
| (14) | Infertility clinic ($n$ = 78) | I. <30 (matched by year of attendance) | | ↓ (NS) | 1, 2, 3, 4 |
| | | II. <30 (matched by wives' age) | II. 30 | | |
| | | III. >50 | III. 23 | | |
| (45) | Assisted conception ($n$ = 208) | I. <30 | I. 32.1 | ↓ (NS) | 1, 2, 3, 4 |
| | | II. 30–39 | II. 21.9 | | |
| | | III. 40–49 | III. 22.2 | | |
| | | IV. >50 | IV. 20.0 | | |
| (16) | Assisted conception ($n$ = 345) | I. ≤30 | I. 64.5 | ↔ (NS) | 1, 2, 3, 4 |
| | | II. 31–40 | II. 45.6 | | |
| | | III. 41–50 | III. 51.0 | | |
| | | IV. 51–64 | IV. 71.4 | | |
| (36) | Infertility clinic ($n$ = 566) | I. <30 | I. 4.5 | ↑ (NS) | 2, 3, 4, 5 |
| | | II. 30–34 | II. 9.6 | | |
| | | III. 35–39 | III. 10.2 | | |
| | | IV. ≥40 | IV. 9.9 | | |

[a] Roman numeral groups in the third column correspond with roman numeral groups in the fourth column.

[b] NS = not statistically significant at $P$<.05; no $P$ value indicates that no statistical testing was done; ↓ = decrease in pregnancy rate with increase in male age; ↔ = no relationship; ↑ = increase in pregnancy rate with increase in male age.

[c] Data quality: 1 = adjusted/tested for potential confounding by female age; 2 = clearly defined their criteria for selection of the study population; 3 = provided data in the paper; 4 = used concurrent controls; 5 = adjusted for other potential confounding factors.

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Seven of the nine studies found that pregnancy rates declined with increased male age. Two studies reported roughly 50% relative decreases in pregnancy rates in men over 35 compared with men <30 (42) and ≤35 (32). Other studies (13, 14, 43–45) reported decreases in pregnancy rates of lesser magnitude. These studies compared varying age extremes with relative decreases ranging from 20% to 38%.

One study (16) did not find an effect of male age on pregnancy rates when the age of the oocyte donor was restricted to <35 years. Only one study (36) reported an increase in pregnancy rates with increasing age. The pregnancy rate was lower in partners of men under 30 when compared with men 30 and older. This same study reported no differences in motile concentration (millions of motile sperm per milliliter) between younger and older men (Table 3), which is consistent with the pregnancy rate findings.

There was a trend across studies in decreasing pregnancy rate with increasing male age, but nearly half of the studies (32, 36, 43, 44) did not adjust for female age in analyses. Overall, the evidence is suggestive of an association between increased male age and decreased pregnancy rate, but the magnitude of the pregnancy rate may be lessened when the influence of female age is properly controlled for. However, among studies with decreased pregnancy rates with age that also controlled for female partner age, the two (14, 45) that allowed comparison between men under 30 and men over 50 found relative decreases in pregnancy rates of 23% and 38%, respectively. The other two studies (13, 42) that compared

**TABLE 6**

Male age and time to pregnancy/subfecundity.

| Reference | Population | Male age definition (range/mean/group)[a,b] | Time to pregnancy/subfecundity[a,c] | Direction of effect with increasing age[d] | Data quality[e] |
|---|---|---|---|---|---|
| (50) | Pregnant cohort ($n$ = 10,886) | I. 15–19<br>II. 20–24<br>III. 25–29<br>IV. 30–34<br>V. 35–39<br>VI. ≥40 | Couples (%) with subfecundity (≥1 year)<br>I and II. 10.8<br>III. 11.1<br>IV. 11.9<br>V. 15.2<br>VI. 16.0 | ↑ ($P$<.001) | 1, 2, 3, 4, 5 |
| | | | OR = 1.3 (0.9, 2.0) subfecundity VI vs. I | ↑ (NS) | |
| (46) | Infertility clinic ($n$ = 765) | I. ≤20<br>II. 21–30<br>III. 31–40<br>IV. >40 | Decreased risk for pregnancy before time $t$ (−.0324) | ↑ ($P$<.005) | 2, 3, 4, 5 |
| (49) | Volunteers ($n$ = 274) | 21–51 | Age was associated with infertility at 9 months | ↑ ($P$=.004) | 2, 3, 4, 5 |
| | | I. <35<br>II. ≥35 | OR = 2.3 (1.4, 3.7)<br>Subfecundity II vs. I | ↑ ($P$<.05) | |
| (44) | Infertility clinic ($n$ = 394) | 29.1 (5.2) | Age was related to time to achieve and likelihood of pregnancy | ↑ ($P$<.01) | 2, 3, 4, 5 |
| (42) | Assisted conception ($n$ = 274) | I. <30<br>II. 30–34<br>III. ≥35 | RR = 0.4 (0.3, 0.7)<br>Pregnancy III vs. I | ↑ ($P$<.05) | 1, 2, 3, 4, 5 |
| (43) | Infertility clinic ($n$ = 1,025) | 18–74 | Age was associated with achievement of pregnancy | ↑ ($P$<.05) | 2, 3, 4, 5 |
| (52) | Fertility survey (No $n$ given) | I. <45<br>II. 45–55<br>III. ≥55 | RR of conception<br>I. 1.0<br>II. 0.7–0.9<br>III. 0.8–0.9 | ↑ ($P$<.05) | 1, 3, 5 |
| (14) | Infertility clinic ($n$ = 78) | I. <30 (matched by year of attendance)<br>II. <30 (matched by wives' age)<br>III. >50 | Month before achieving pregnancy, mean (range)<br>II. 66 (25–125)<br>III. 79 (16–187) | ↑ (NS) | 1, 2, 3, 4 |
| (47), (48) | Birth cohort | I. <30<br>II. ≥30 | RR = 0.9 (0.8, 1.0)<br>Time to first birth, II vs. I | ↑ (NS) | 2, 3, 4, 5 |
| (51) | Assisted conception | 25–64 | Mean male age of pregnant group (34.9) similar to nonpregnant group (35.0) | ↔ (NS) | 2, 3, 4 |
| (32) | Infertility clinic ($n$ = 200) | 20–46 | Age and duration of infertility were not correlated ($r$ = .17) | ↔ (NS) | 2, 4 |

[a] Roman numeral groups in the third column correspond with roman numeral groups in the fourth column.
[b] Mean (SD).
[c] OR ( ) = odds ratio (95% confidence interval); RR ( ) = relative risk (95% confidence interval).
[d] NS = not statistically significant at $P$<.05; no $P$ value indicates that no statistical testing was done; ↓ = decrease in time to pregnancy/subfecundity with increase in age; ↔ = no relationship; ↑ = increase in time to pregnancy/subfecundity with increase in age.
[e] Data quality: 1 = adjusted/tested for potential confounding by female age; 2 = clearly defined their criteria for selection of the study population; 3 = provided data in the paper; 4 = used concurrent controls; 5 = adjusted for other potential confounding factors.

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narrower age ranges found relative decreases of 20% and 52%, respectively.

### *Time to Pregnancy/Subfecundity*

Eleven studies examined the relationship between male age and time to pregnancy/subfecundity (Table 6). Nine studies found that time to pregnancy increased with male age. Studies (42, 44, 46, 47) that used a proportional hazard analysis, which adjusts for varying lengths of observation before pregnancy occurs, reported increases in time to pregnancy with increasing male age, although only one study (42) tested for the confounding effects of the age of the female

partner. Mathieu et al. (42) reported a 60% decrease in risk for pregnancy comparing the oldest male age group (≥35 years) with the youngest (<30 years), adjusting for duration of infertility and irregular ovulation (female age was not a confounder). Joffe et al. (48) reported an 11% increase in time to first live birth in the partners of men ≥30 years of age versus <30 years of age, adjusted for male and female smoking and education (there were too many missing values to adjust for female partner age).

Two studies found that older men were less likely to father a pregnancy after engaging in unprotected intercourse for 9 months (49) and for at least 1 year (50). Ford et al. (49) reported that men ≥35 years of age had twice the likelihood of subfecundity than men <35 years of age. Olsen et al. (50) found that the risk of subfecundity for men ≥40 years of age was 30% higher than that of men 15–19 years of age after adjustment for female partner age. There was also a monotonic increase in subfecundity by male age.

One study (51) reported mean male ages that were similar between pregnant and nonpregnant groups, while another (32) did not find a statistically significant correlation ($r=.17$) between male age and duration of infertility (up to 3 years).

Overall, the weight of the evidence supports an association between increased male age and increased time to pregnancy and the frequency of subfecundity. In graphs of the cumulative distribution for time required to conceive, pregnancy rate curves for men with ages >30 (44), ≥35 years (46), and >50 years (14) were 5%–20% lower across time compared with curves for men with ages ≤30, <35, and <30 years, respectively. However, it is unclear to what extent female age and/or other factors may be partly responsible for these associations. Among the studies that controlled for female partner age, increased male age was consistently associated with subfecundity and time to pregnancy. The increased risks for subfecundity in these studies (42, 50, 52) with varying age categories ranged from 11% to 250%, and the relative increase in months to achieve pregnancy (14) was 20%, comparing men >50 years of age with those <30 years of age.

## DISCUSSION

For conventional semen quality, the weight of the scientific evidence suggests that increased male age is associated with a decrease in semen volume, a decrease in percent normal sperm, and a decrease in sperm motility, with no consistent effect on sperm concentration. Among the methodologically stronger studies, decreases in semen volume of 3%–22% (11, 14, 20), decreases in sperm motility of 3%–37% (11, 14, 22, 28), and decreases in percent normal sperm of 4%–18% (14, 20, 28) were likely when comparing 30-year-old men with 50-year-old men. For the two fertility parameters reviewed, most studies found a decrease in fertility with increased male age, but a minority of studies controlled for female partner age, making it difficult to draw definitive conclusions. Among studies that did control for female partner age, the two (14, 45) that allowed comparison between men under 30 and men over 50 found relative decreases in pregnancy rates of 23% and 38%, respectively. The increased risks for subfecundity ranged from 11% to 250%, comparing varying age categories (42, 50, 52), and the relative increase in months to achieve pregnancy was 20%, comparing men <30 years old with men >50 years old (14).

The nature of the data provided does not allow for conclusions about the shape of the relationship (i.e., linearity) between age and these reproductive outcomes or whether there is a critical age threshold where the changes occur. Generally, the data were provided in varying age categories, which restricted our summary by age. However, we were able to focus on comparisons between two age groupings: lower-risk men (ages <30 years) and potentially higher-risk men (ages >50 years). Given the increase in fathering among older men, we wanted to focus on results where biologically important age thresholds may be reasonable and still examine men whose fathering may not be complete (a clinically important age).

A number of mechanisms have been proposed for how aging may affect changes in semen quality. For example, decreased semen volume could be caused by seminal vesicle insufficiency, since seminal vesicle fluid contributes most of the ejaculate volume (53). Changes in the prostate occur with aging, such as smooth muscle atrophy and a decrease in protein and water content, which may affect semen volume and sperm motility (54). Sperm acquire the capacity for vigorous forward motility during transit through the epididymis, which plays an important role in sperm maturation (53). If aging alters epididymal function, this may explain how sperm motility might be affected.

Sperm morphology is a good indicator of the status of the germinal epithelium (55, 56). Degenerative changes in the germinal epithelium due to aging may affect spermatogenesis and alter sperm morphology. Although we did not observe a consistent effect of age on sperm concentration, age-related changes in sperm concentration are plausible. With increased age there is narrowing and sclerosis of the tubular lumen, a decrease in spermatogenic activity, degeneration of germ cells, and decreased number and function of Leydig cells (57, 58). However, concentration may be increased with age, as it may be possible that spermatogenesis could be abnormally accelerated because of an impaired responsiveness of the testes to endocrinological influences (18). Age may not only impact semen quality, but also the genetic integrity of the sperm. There is evidence that aging is associated with increased sperm aneuploidy in humans and mice (10, 59–61) and with increases in the incidence of de novo germinal mutations (62–64). Genetically defective

sperm can lead to fetal loss and genetic disease in offspring (56, 65).

Our review of the literature indicates that several methodological issues are important to address, as they impact on the interpretation of studies of semen quality and fertility. Potential confounders were not examined in most studies and could in part explain the age effects observed for some end points. Generally, studies examining semen parameters performed either univariate or bivariate analyses only, disregarding the possibility that other factors besides male age may be responsible for effects observed. In studies examining conventional semen quality, duration of abstinence is a known confounder (27–29), yet in over three-quarters of these studies, there was no attempt to test for potential confounding. In studies examining pregnancy rate and time to pregnancy/subfecundity, female age, an important predictor of fertility (41), was not tested for potential confounding in half of the studies.

Study setting is also an important consideration. Generalizing to the overall male population from clinic-based studies (fertility and assisted conception clinics) must be done cautiously because subfertile men represent a special subgroup of the general population. Clinics may also attract unhealthier men. Given that couples often are not referred until later in their reproductive lives, it may be that younger fertility clinic attendees represent a particularly morbid profile versus older clinic attendees. If this were true, then such studies would have a bias toward finding no association between male age and adverse outcome. Population-based studies (using semen donors and volunteers from advertisements) could also be biased because the men who participate in these studies may be more likely to be healthier and may represent men with greater fertility probability than the entire population of men from which they came.

There were other issues that weaken the study of whether age is associated with poor semen quality and subfertility: criteria for selection of study populations were often not clearly defined; raw data on outcomes were not presented in some of the papers; and historical or nonconcurrent control comparison groups were sometimes used. Many of the studies with negative findings had small age group sizes limiting statistical power, and limited age ranges. If there is a threshold age effect, studies with limited age range may have missed the ages at which the biological effects of aging occur.

Finally, there is some recent interest in whether there is a temporal trend in decreasing semen quality, particularly sperm count or concentration (31, 66) and whether male age may be a surrogate for an exposure(s) that may affect a birth cohort of men across time. For example, older men may be more likely to have been exposed to DDT, an endocrine disruptor that was used up until 1972 in the United States. Thus, any observed associations with male age may not be the direct effects of aging per se, but the cumulative effects of lifelong exposures, and age may only be a proxy for these influences. Only three studies (26, 28, 34) adjusted for year of birth, with mixed findings regarding an independent effect of male age on sperm concentration.

In summary, our review of the literature suggests that the trend toward later fathering appears to come with risks for diminished semen quality and fertility. Future studies examining the relationship between male age and semen quality and/or fertility could improve on the methodological quality of the existing studies by enrolling adequate numbers of men throughout the age spectrum, controlling for the effects of potential confounding factors, and selecting appropriate comparison groups. We have reviewed reproductive end points that predict practical consequences for families, that is, a reduction in pregnancy leading to a less than desired family size. As better biomarkers are developed and used in epidemiological study designs, more knowledge may be gained regarding age and associations with semen quality and fertility, as well as abnormalities in offspring.

## References


1. Templeton A. Infertility—epidemiology, aetiology and effective management. Health Bull (Edinb) 1995;53:294–8.
2. Abma JC, Chandra A, Mosher WD, Peterson LS, Piccinino LJ. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. Vital Health Stat 1997;23:1–114.
3. Lansac J. Delayed parenting. Is delayed childbearing a good thing? Hum Reprod 1995;10:1033–5.
4. Ventura S, Martin J, Curtin S, Mathews T. Report of final natality statistics, 1995. Monthly Vital Stat Rep 1997;45.
5. Tanemura K, Kurohmaru M, Kuramoto K, Hayashi Y. Age-related morphological changes in the testis of the BDF1 mouse. J Vet Med Sci 1993;55:703–10.
6. Wang C, Leung A, Sinha-Hikim AP. Reproductive aging in the male brown-Norway rat: a model for the human. Endocrinology 1993;133: 2773–81.
7. Parkening TA, Collins TJ, Au WW. Paternal age and its effects on reproduction in C57BL/6NNia mice. J Gerontol 1988;43:B79–84.
8. Serre V, Robaire B. Paternal age affects fertility and progeny outcome in the brown Norway rat. Fertil Steril 1998;70:625–31.
9. Walter CA, Intano GW, McCarrey JR, McMahan CA, Walter RB. Mutation frequency declines during spermatogenesis in young mice but increases in old mice. Proc Natl Acad Sci USA 1998;95:10015–9.
10. Lowe X, Collins B, Allen J, Holland NT, Breneman J, van Beek M, et al. Aneuploidies and micronuclei in the germ cells of male mice of advanced age. Mutat Res 1995;338:59–76.
11. Fisch H, Goluboff E, Olson J, Feldshuh J, Broder S, Barad D. Semen analyses in 1283 men from the United States over a 25-year period: no decline in quality. Fertil Steril 1996;65:1009–14.
12. Homonnai ZT, Fainman N, David MP, Paz GF. Semen quality and sex hormone pattern of 29 middle aged men. Andrologia 1982;14:164–70.
13. Spandorfer SD, Avrech OM, Colombero LT, Palermo GD, Rosenwaks Z. Effect of parental age on fertilization and pregnancy characteristics in couples treated by intracytoplasmic sperm injection. Hum Reprod 1998;13:334–8.
14. Rolf C, Behre H, Nieschlag E. Reproductive parameters of older compared to younger men of infertile couples. Int J Androl 1996;19: 135–42.
15. Nieschlag E, Lammers U, Freischem C, Langer K, Wickings E. Reproductive functions in young fathers and grandfathers. J Clin Endocrinol Metab 1982;55:676–81.
16. Gallardo E, Simon C, Levy M, Guanes P, Remohi J, Pellicer A. Effect of age on sperm fertility potential: oocyte donation as a model. Fertil Steril 1996;66:260–4.
17. Dondero F, Mazzilli F, Giovenco P, Lenzi A, Cerasaro M. Fertility in older men. J Endocrinol Invest 1985;8(2):87–91.
18. Singer R, Sagiv M, Levinsky H, Allalouf D. Andrological parameters in men with high sperm counts and possible correlation with age. Arch Androl 1990;24:107–11.
19. Rolf C, Kenkel S, Nieschlag E. Age-dependent changes in semen characteristics of patients attending a tertiary infertility clinic [abstract R-022]. In: Abstracts of the 15th Annual Meeting of the European

Society of Human Reproduction and Embryology. Tours, France. Hum Reprod, 1999:288–9.
20. Andolz P, Bielsa MA, Vila J. Evolution of semen quality in northeastern Spain: a study in 22,759 infertile men over a 36 year period. Hum Reprod 1999;14:731–5.
21. Centola GM, Eberly S. Seasonal variations and age-related changes in human sperm count, motility, motion parameters, morphology, and white blood cell concentration. Fertil Steril 1999;72:803–8.
22. Schwartz D, Mayaux M-J, Spira A, Moscato M-L, Jouannet P, Czyglik F, et al. Semen characteristics as a function of age in 833 fertile men. Fertil Steril 1983;39:530–5.
23. Haidl G, Jung A, Schill WB. Aging and sperm function. Hum Reprod 1996;11:558–60.
24. Berling S, Wolner-Hanssen P. No evidence of deteriorating semen quality among men in infertile relationships during the last decade: a study of males from southern Sweden. Hum Reprod 1997;12:1002–5.
25. Wang C, Chan SYW, Leung A, Ng RP, Ng M, Tang LCH, et al. Cross-sectional study of semen parameters in a large group of normal Chinese men. Int J Androl 1985;8:257–74.
26. Irvine S, Carwood E, Richardson D, MacDonald E, Aitken J. Evidence of deteriorating semen quality in the United Kingdom: birth cohort study in 577 men in Scotland over 11 years. BMJ 1996;312:467–71.
27. Mortimer D, Templeton AA, Lenton EA, Coleman RA. Influence of abstinence and ejaculation-to-analysis delay on semen analysis parameters of suspected infertile men. Arch Androl 1982;8:251–6.
28. Auger J, Kunstmann JM, Czyglik F, Jouannet P. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 1995;332:281–5.
29. Pellestor F, Girardet A, Andreo B. Effect of long abstinence periods on human sperm quality. Int J Fertil Menopausal Stud 1994;39:278–82.
30. Lemcke B, Behre HM, Nieschlag E. Frequently subnormal semen profiles of normal volunteers recruited over 17 years. Int J Androl 1997;20:144–52.
31. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ 1992;305:609–13.
32. Abramsson L. On the investigation of men from infertile relations. Scand J Urol Nephrol 1988;113(Suppl):7–47.
33. Check JH, Shanis B, Bollendorf A, Adelson H, Breen E. Semen characteristics and infertility in aging. Arch Androl 1989;23:275–7.
34. Bujan L, Mansat A, Pontonnier F, Mieusset R. Time series analysis of sperm concentration in fertile men in Toulouse, France between 1977 and 1992. BMJ 1996;312:471–2.
35. Henkel R, Bittner J, Weber R, Huther F, Miska W. Relevance of zinc in human sperm flagella and its relation to motility. Fertil Steril 1998; 71:1138–43.
36. van der Westerlaken LA, Naaktgeboren N, Helmerhorst FM. Evaluation of pregnancy rates after intrauterine insemination according to indication, age, and sperm parameters. J Assist Reprod Genet 1998;15: 359–64.
37. Bujan L, Mieusset R, Mondinat C, Mansat A, Pontonnier F. Sperm morphology in fertile men and its age related variation. Andrologia 1988;20:121–8.
38. Mladenovic I. Sperm morphology and motility in different age populations. Arch Androl 1994;32:197–205.
39. Hossain AM, Bhaumik D, Selukar R, Huff C, Rizk B, Thorneycroft IH. Assessment of the relationship of sperm morphology with seminal and other clinical conditions of semen donors. Arch Androl 1997;39:111–7.
40. World Health Organization. WHO laboratory manual for the examination of human semen and semen-cervical mucus interaction. Cambridge, UK: Cambridge University Press, 1992.
41. Kline J, Stein Z, Susser M. Conception to birth: epidemiology of prenatal development. New York: Oxford University Press, 1989.
42. Mathieu C, Ecochard R, Bied V, Lornage J, Czyba J. Cumulative conception rate following intrauterine artificial insemination with husband's spermatozoa: influence of husband's age. Hum Reprod 1995; 10:1090–7.
43. Stanwell-Smith R, Hendry W. The prognosis of male subfertility: a survey of 1025 men referred to a fertility clinic. Br J Urol 1984;56: 422–8.
44. Ducot B, Spira A, Feneux D, Jouannet P. Male factors and the likelihood of pregnancy in infertile couples. II. Study of clinical characteristics—practical consequences. Int J Androl 1988;11:395–404.
45. Brzechffa PR, Daneshmand S, Buyalos RP. Sequential clomiphene citrate and human menopausal gonadotrophin with intrauterine insemination: the effect of patient age on clinical outcome. Hum Reprod 1998;13:2110–4.
46. Bostofte E. Prognostic parameters in predicting pregnancy. A twenty-year follow-up study comprising semen analysis in 765 men of infertile couples evaluated by the Cox regression model. Acta Obstet Gynecol Scand 1987;66:617–24.
47. Joffe M, Li Z. Male and female factors in fertility. Am J Epidemiol 1994;140:921–9.
48. Joffe M. Re: male and female factors in fertility [Letter]. Am J Epidemiol 1995;141:1108.
49. Ford J, MacCormac L, Hiller J. PALS (pregnancy and lifestyle study): association between occupational and environmental exposure to chemical and reproductive outcome. Mutat Res 1994;313:153–64.
50. Olsen J. Subfertility according to the age of the mother and the father. Danish Med Bull 1990;37:281–2.
51. Koppers B, Gassner P, Meschede D, Horst J, Behre HM, Nieschlag E. Prognostic value of male diagnostic profiles in intracytoplasmic sperm injection (ICSI). Int J Androl 1998;21:227–32.
52. Goldman N, Montgomery M. Fecundability and husband's age. Soc Biol 1989;36:146–66.
53. Hamilton D, Naftolin F. Basic reproductive medicine. Cambridge, Mass: MIT Press, 1981.
54. Schneider EL. The aging reproductive system. New York: Raven Press, 1978.
55. MacLeod J. Human seminal cytology as a sensitive indicator of the germinal epithelium. Int J Fertil 1964;9:281–95.
56. Wyrobek A. Methods and concepts in detecting abnormal reproductive outcomes of paternal origin. Reprod Toxicol 1993;7:3–16.
57. Bishop M. Aging and reproduction in the male. J Reprod Fertil 1970; 12:65–87.
58. Johnson L. Spermatogenesis and aging in the human. J Androl 1986; 7:331–54.
59. Robbins W, Baulch J, Moore DI, Weire H-U, Blakey D, Wyrobek A. Three-probe fluorescence in situ hybridization to assess chromosome X, Y, and 8 aneuploidy in sperm of 14 men from two healthy groups: evidence for a paternal age effect on sperm aneuploidy. Reprod Fertil Dev 1995;7:799–809.
60. Griffin D, Abruzzo M, Millie E, Sheean LA, Feingold E, Sherman SL, et al. Non-disjunction in human sperm: evidence for an effect of increasing paternal age. Hum Mol Gen 1995;4:2227–32.
61. Martin R, Spriggs E, Ko E, Rademaker A. The relationship between paternal age, sex ratios, and aneuploidy frequencies in human sperm, as assessed by multicolor FISH. Am J Hum Gen 1995;57:1395–9.
62. Martinez-Frias ML, Herranz I, Salvador J, Prieto L, Ramos-Arroyo MA, Rodriguez-Pinilla E, et al. Prevalence of dominant mutations in Spain: effect of changes in maternal age distribution. Am J Hum Gen 1988;31:845–52.
63. Modell B, Kuliev A. Changing paternal age distribution and the human mutation rate in Europe. Hum Gen 1990;86:198–202.
64. Friedman J. Genetic disease in the offspring of older fathers. Obstet Gynecol 1981;57:745–9.
65. Hassold TJ. Chromosome abnormalities in human reproductive wastage. TIG 1986:105–10.
66. Swan SH, Elkin EP, Fenster L. Have sperm densities declined? A reanalysis of global trend data. Environ Health Perspect 1997;105: 1228–32.