Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens*

Lam P.Ly, Peter Y.Liu and David J.Handelsman[1]

Departments of Andrology, Concord Hospital & ANZAC Research Institute, University of Sydney, Sydney NSW 2139, Australia

[1]To whom correspondence should be addressed. E-mail: djh@anzac.edu.au

BACKGROUND: Practical hormonal male contraceptive regimens are likely to have delayed onset and offset of reliable contraception dictated by the length of the spermatogenic cycle and clearance rate of pre-formed sperm from the ductular system. While delayed onset of contraceptive efficacy is an accepted feature of vasectomy, reliable time estimates for a hormonal male contraceptive of time to onset and offset of reliable contraception and of resumption of normal male fertility are required. METHODS AND RESULTS: We utilized the sperm output data from three male contraceptive efficacy studies to define quantitative estimates of suppression and recovery rates from an androgen alone (testosterone enanthate) and an androgen/progestin (testosterone/depot medroxyprogesterone acetate) study. Using nearly 14 000 semen samples from World Health Organization (WHO) studies #85921 and #89903 with identical protocols, the rate of suppression of sperm output was best modelled as a two-parameter, single exponential decay function with effective half-time to suppression of 5.5 weeks and times of 6.8 weeks to 10×10^6/ml, 8.7 weeks to 5×10^6/ml, 10.0 weeks to 3×10^6/ml and 13.0 weeks to 1×10^6/ml. The rate of recovery using absolute sperm concentration was best modelled as a three-parameter, sigmoidal curve with effective time to reach half of the recovery plateau of 10.5 weeks and times of 9.0 weeks to 3×10^6/ml, 9.9 weeks to 5×10^6/ml, 11.5 weeks to 10×10^6/ml, and 13.6 weeks to 20×10^6/ml. Using relative sperm output, defined as a percentage of the participants' own baseline, recovery approached an asymptotic plateau of ∼85% of geometric mean pre-treatment sperm concentration. In the combination androgen/progestin study, suppression rate was significantly faster (effective time to reach half maximal suppression of 3.0 weeks) and recovery significantly slower (effective time to reach half of recovery plateau of 14.7 weeks) and less complete (asymptotic recovery plateau of 43% of baseline) than in the androgen-alone WHO studies. CONCLUSION: These findings therefore provide large sample estimates of the suppression and recovery rates from an androgen-alone hormonal male contraceptive regimen as a basis for comparison with other second-generation combination androgen/progestin regimens that are the most promising approach to developing practical male hormonal regimens.

Key words: androgen/contraception/progestin/sperm output/testosterone

Introduction

A hormonal male contraceptive aims to prevent pregnancy by eliminating fertile sperm from the ejaculate by sufficient and reversible suppression of sperm output (Handelsman, 2005). While achieving azoospermia in all men would be ideal for an effective hormonal male contraceptive, all regimens so far fall short of the optimal target of uniform azoospermia (Anderson and Baird, 2002; Kamischke and Nieschlag, 2004). Landmark World Health Organization (WHO) studies have shown that the failure rate of a hormonal male contraceptive is proportional to the sperm concentration remaining in the ejaculate (WHO Task Force on Methods for the Regulation of Male Fertility, 1990, 1996).

Any hormonal male contraceptive must also be reversible to allow predictable resumption of male fertility upon cessation of treatment. The relatively slow clearance of sperm from the post-testicular ductular system as well as the length of the human spermatogenic cycle (∼75 days) are significant limitations on the speed of sperm output suppression and recovery, respectively. Within these constraints, a male contraceptive should have the fastest and most predictable onset and offset possible. The recent proof of principle for practical second generation male hormonal contraceptive regimens based on depot androgen/progestin combinations (Turner *et al.*, 2003) make it feasible to develop practical regimens. This means it is therefore now essential to provide accurate

1733

estimates for the time required for onset and offset of reliable contraception and of post-treatment recovery of male fertility. These considerations require focus on the time-dependence of sperm suppression and recovery and on their determinants, issues which have been of lower priority until recently.

In this study we use the uniquely large WHO dataset from the two male contraceptive efficacy studies to provide estimates of sperm suppression and recovery rates for testosterone-induced sperm suppression and recovery. Using these estimates, we evaluate the rates of suppression and recovery of men who participated in the first contraceptive efficacy study of a depot androgen/progestin combination in order to determine distinctive characteristics of the progestin used, medroxyprogesterone acetate, on suppression and recovery of sperm output.

Materials and methods

Data were obtained from three previously published contraceptive efficacy studies, the two WHO Male Contraceptive Efficacy studies #85921 (WHO Task Force on Methods for the Regulation of Male Fertility, 1990) and #89903 (WHO Task Force on Methods for the Regulation of Male Fertility, 1996) and an Australian study using a depot androgen/progestin combination (Turner *et al.*, 2003). The two WHO studies used identical protocols for treatment using weekly i.m. injections of 200 mg testosterone enanthate (Primoteston; Schering) and monitoring, differing only in the entry criterion to the efficacy phase. Briefly, eligible men with apparently normal fertility, sperm output and blood reproductive hormone levels entered the suppression phase after receiving their first testosterone injection and provided at least monthly semen samples throughout the study. After 3 months in the suppression phase, they provided fortnightly semen samples until three specimens reached the criteria for entry to the efficacy phase. In the first WHO study (#85921), men were required to be azoospermic to enter efficacy phase whereas in the second WHO study (#89903) men could enter efficacy with a sperm concentration of $< 5 \times 10^6$ (later 3×10^6) per ml. Those who discontinued for non-suppression or other reasons as well as those completing the efficacy phase continued to provide monthly semen samples until recovery. Unit data comprising all individual semen analysis results for all participants, regardless of entry to efficacy phase, together with date and time since start or stop of treatment was provided from all studies. Data from all participants in the two WHO studies were combined for these analyses as their study protocols were identical with regard to analysis of sperm suppression and recovery rates. The 16 centres in the WHO studies were divided into six predominantly Chinese centres (Beijing, Nanjing, Chengdu, Singapore, Beijing2, Bangkok) and 10 non-Chinese centres (Stockholm, Szeged, Sydney, Seattle, Melbourne, Turku, Edinburgh, Manchester, Torrance, Paris).

Data analysis

Sperm concentrations were cube-root transformed to achieve near-gaussian distribution while also preserving appropriate handling of zeros (azoospermia) which are frequent in these data and crucial to the quantitative analyses (Handelsman, 2002). Log transformation (Berman *et al.*, 1996) was less suitable, as the arbitrary offset required for zeros would systematically influence regression estimates.

The start of treatment was defined as the date of first hormone administration. The end of treatment was defined as the date of the last treatment plus the time of one treatment administration

(i.e. the date of the first missed hormone treatment). This was 1 week after the last weekly testosterone enanthate injection, 3 months after the last DMPA injection and 4 months after the last testosterone implant. In the combination study, where the end of two concurrent treatment cycles did not coincide, the later date was defined as the end of treatment. For analysis, because the exact date when samples were provided was known, each semen sample was pooled into the closest time-period (week, month) based on the number of days from start or end of treatment.

To estimate quantitatively the suppression and recovery rates, time was calculated from the start of treatment with the fall or rise of sperm output fitted by non-linear regression. Rate estimates were calculated according to two definitions of sperm output: one analysing the absolute sperm concentration and the other as the relative sperm concentration, defined as a proportion of the man's own geometric mean baseline (pre-treatment) sperm concentration.

Inspection of the data indicated that a non-linear regression was required, that the suppression was asymptotic and the recovery involved substantial delay followed by an increase to a plateau. Among families of non-linear curves (polynomial, peak, sigmoid, exponential, hyperbola, waveform, power, rational), the most suitable were exponential regression for suppression and a sigmoidal curve for recovery. Preliminary analysis balancing parsimony in model parameters against degrees of freedom (guided by the Akaike Information Criterion, AIC) aiming for the model to maximally reduce data entropy, we chose a three- rather than four- or five-parameter sigmoid and one-component rather than two- or more component exponential forms. These choices were confirmed by an analysis with TableCurve, which simultaneously evaluates 3665 in-built functional forms, including all non-linear curve families.

For suppression rate, the data were fitted by a two-parameter, single exponential non-linear regression that provided a rate coefficient which was back-transformed into an estimate of half-time for suppression. The recovery data were fitted by a three-parameter sigmoidal curve that provided estimates of a half-time to, and plateau of, recovery. Confidence intervals (CI) were estimated from the appropriate SE. Differences between categorical variables (study centres) were evaluated as main effects in log-linear regression for suppression rates and logistic regression for recovery rates using SPSS version 12 software. Non-linear regression was performed using Sigmaplot 8.0 software.

Results

WHO studies: suppression rate

The WHO dataset of 13 994 semen samples comprised 8506 samples (16–383 per time-point) during suppression and efficacy and 3419 samples (6–202 per time-point) during recovery.
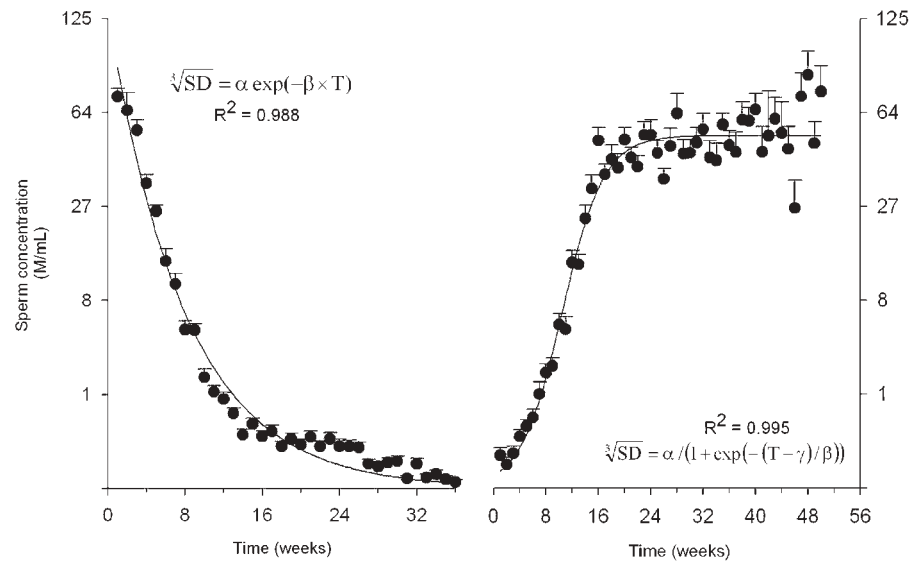
The rate of suppression (Figure 1) was well fitted by a two-parameter, single exponential decay curve:

$$SD = \alpha \times \exp(-\beta \times T).$$

With regression coefficient (SD = cube-root of sperm concentration, T = time in weeks):

$$\alpha = 5.086 \pm 0.103 \quad \beta = 0.1254 \pm 0.0034 (R^2 = 0.988).$$

This provided an estimated time to reach half of maximal suppression of 5.5 weeks (95% confidence interval 5.2–5.9

Figure 1. Plot of suppression (left panel) and recovery (right panel) of sperm output from WHO studies #85921 and #89903 including ~ 14 000 semen samples from men in 16 centres and 10 countries. Data-points represent mean and SE (error bar) of semen samples grouped within weeks with between six and 383 samples per time-point. Note cube-root scale on *y*-axis. For suppression, the smooth line is the two-parameter, single term exponential decay function plotted to fit the data by non-linear regression. For recovery, the smooth line is the three-parameter sigmoidal curve plotted to fit the data by non-linear regression.

weeks) for suppression. Estimated times to reach specific sperm output thresholds were 5.0 weeks (20×10^6/ml), 6.8 weeks (10×10^6/ml), 8.7 weeks (5×10^6/ml), 10.0 weeks (3×10^6/ml) and 13.0 weeks (1×10^6/ml).

There were significant differences between the 16 centres ($F = 16$, $P < 0.001$) in suppression rates. Although this appeared largely attributable to faster suppression by men in Chinese versus non-Chinese centres ($F = 83.8$, $P < 0.001$), there was also significant between-centre variability within Chinese ($F = 13$, $P < 0.001$) and non-Chinese ($F = 11.3$, $P < 0.001$) centres. From fitted regression curves to pooled data from centres by region, the six Chinese centres had shorter time to reach half suppression than the 10 non-Chinese centres but there were no systematic differences between the two Australian and the other eight Western centres in suppression rates (Table I). However, the differences between Chinese and non-Chinese centres in time to half suppression were small in magnitude (5.3 versus 5.6 weeks respectively).

WHO studies: recovery rate

The rate of recovery was determined in regard to absolute (Figure 1) and relative (Figure 2) sperm output. Using the absolute sperm outputs, the recovery rate was estimated well by a three-parameter sigmoid:

$$SD = \alpha / \{1 + \exp[-(T - \gamma)/\beta]\}$$

with coefficients (SD = cube-root of sperm concentration, T = time in weeks):

$$\alpha = 3.752 \pm 0.046 \quad \beta = 3.174 \pm 0.274$$

$$\gamma = 10.46 \pm 0.3 (R^2 = 0.997)$$

The asymptotic plateau recovery was to a sperm concentration of 53×10^6/ml and the estimated time to reach half of the recovery plateau was 10.5 weeks (95% CI 9.9–11.1

Table I.

Region	Suppression			Recovery			
	α	β	R^2	α	β	γ	R^2
All	5.086 ± 0.103	0.1254 ± 0.0034	0.988	3.752 ± 0.046	3.174 ± 0.274	10.46 ± 0.3	0.997
Chinese	5.315 ± 0.2155	0.1298 ± 0.0070	0.936	3.735 ± 0.360	3.327 ± 1.140	12.38 ± 1.9	0.976
Non-Chinese	4.955 ± 0.1345	0.1245 ± 0.0045	0.965	3.720 ± 0.343	3.204 ± 1.325	9.58 ± 1.8	0.974
Australian	4.797 ± 0.1756	0.1221 ± 0.0059	0.946	4.268 ± 0.3813	3.368 ± 1.226	10.37 ± 1.8	0.977
Western	4.932 ± 0.1363	0.1238 ± 0.0045	0.963	3.365 ± 0.3191	3.012 ± 1.359	9.03 ± 1.8	0.955

Tabulation of fitted regression coefficient for models described in the text for the WHO studies.
The data are analysed according to geographical region comprising the six Chinese and 10 non-Chinese centres, the latter also divided into two Australian and eight other Western centres. For both suppression and recovery, sperm concentration was in cube-root transformed scale and time is in weeks. The model goodness of fit is indicated by the coefficient of determination (R^2).
For the suppression phase, the non-linear regression used a single component, two-parameter curve fit for which α represents the *y*-axis (sperm concentration) intercept and β the exponential rate coefficient, from which the time to half maximal suppression is calculated as $\log_e 2/\beta$.
For the recovery phase, the non-linear regression is a three-parameter sigmoidal curve where α represents the upper plateau (asymptotic recovery of sperm concentration), β represents the slope factor and γ the time to reach half plateau recovery of sperm concentration.
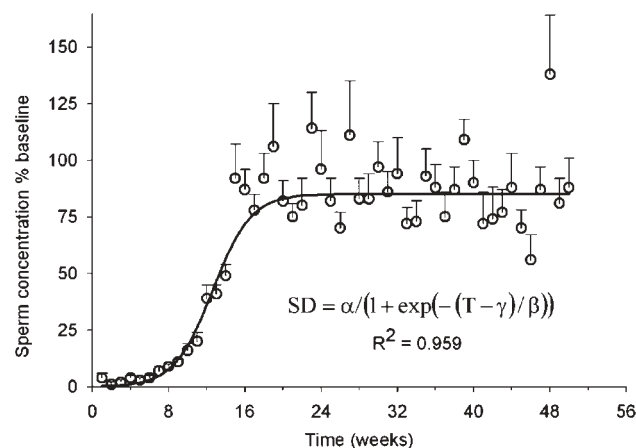
Figure 2. Plot of recovery of relative sperm output (expressed as a percentage of geometric mean pre-treatment baseline) from WHO studies #85921 and #89903 including 3419 semen samples from men in 16 centres and 10 countries. Data-points represent mean and SE (error bar) of semen samples grouped within weeks with between six and 202 samples per time-point. Smooth line is the three-parameter sigmoidal curve plotted to fit the data by non-linear regression. Note that plateau of recovery is 85% of pre-treatment baseline.

weeks). This provided estimates of 9.0 weeks to a sperm concentration of 3×10^6/ml, 9.9 weeks to 5×10^6/ml, 11.5 weeks to 10×10^6/ml and 13.6 weeks to 20×10^6/ml.

There were significant differences between the 16 centres ($F = 2.1$, $P = 0.007$) in recovery rates. This was attributable to slower recovery by men in Chinese versus non-Chinese centres ($F = 14.3$, $P < 0.001$) and there was no significant difference between centres among Chinese ($F = 1.8$, $P = 0.103$) or non-Chinese ($F = 1.1$, $P = 0.389$) centres. The time to reach half recovery plateau was longer in the six

Chinese centres compared with the 10 non-Chinese centres but there were no significant difference between the two Australian and other Western centres (Table I).

Using the relative sperm outputs (sperm concentration for each individual as percentage of baseline sperm concentration), the recovery rate was well estimated by a three-parameter sigmoid with coefficients (SD = % baseline sperm concentration, T = time in weeks):

$$\alpha = 85.2 \pm 16 \quad \beta = 2.02 \pm 1.78 \quad \gamma = 12.6 \pm 2.8$$

$$(R^2 = 0.959)$$

The asymptotic plateau recovery was to 85% of pre-treatment baseline sperm concentration with an estimated time to reach half of the recovery plateau of 12.6 weeks (95% CI 7.1–18.1 weeks).

Australian study: suppression and recovery rates

The suppression rate (Figure 3) was significantly faster than in the WHO studies. The regression coefficients (SD = cube-root of sperm concentration, T = time in months) were:

$$\alpha = 3.642 \pm 0.165 \quad \beta = 0.2327 \pm 0.0226 \quad (R^2 = 0.967)$$

This provided an estimated time to reach half of maximal suppression of 3.0 weeks (95% CI 2.5–3.7 weeks) and expected times to reach specific sperm output thresholds of 1.3 weeks (20×10^6/ml), 2.3 weeks (10×10^6/ml), 3.2 weeks (5×10^6/ml), 4.0 weeks (3×10^6/ml) and 5.6 weeks (1×10^6/ml). As indicated by the time to reach half maximal suppression, the suppression rate in this study was faster for
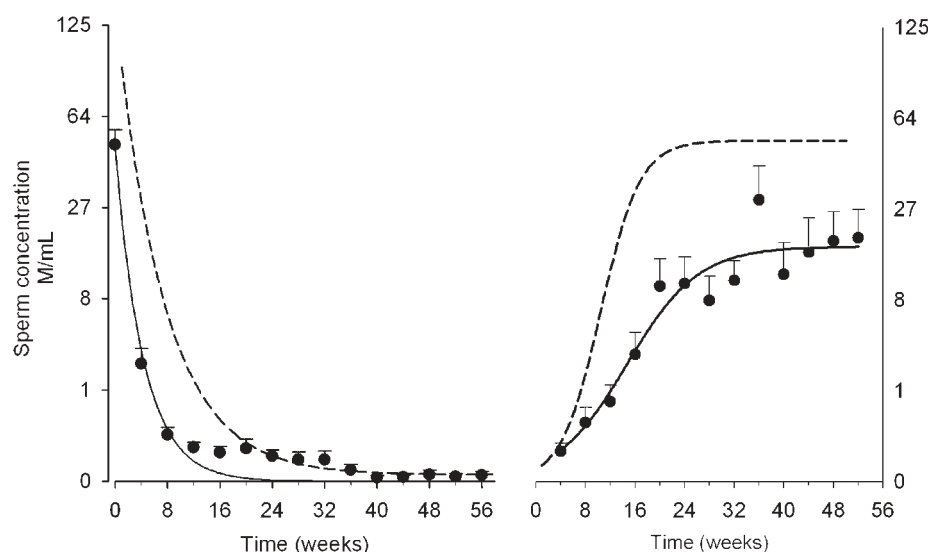
Figure 3. Plot of suppression (left panel) and recovery (right panel) of sperm output from Australian depot combination androgen/progestin study compared with WHO studies. Data-points represent mean and SE (error bar) of semen samples grouped within months. Note cube-root scale on *y*-axis. For suppression, the solid line is the two-parameter, single term exponential decay function plotted to fit the data by non-linear regression. For recovery, the smooth line is the three-parameter sigmoidal curve plotted to fit the data by non-linear regression. For comparison, the dashed line in both panels is the WHO non-linear regression analysis from Figure 1.

men in the two Australian centres than for men in the eight other Western or the 10 non-Chinese centres (Table I).

The recovery rate was significantly slower and less complete than for the WHO dataset and the goodness of fit was significantly inferior judged by coefficient of determination (R^2). Using the absolute sperm outputs (Figure 3), the recovery rate was fitted to a three-parameter sigmoid with coefficients (SD = cube-root of sperm concentration, T = time in months):

$$\alpha = 2.555 \pm 0.71 \quad \beta = 5.71 \pm 5.29 \quad \gamma = 14.7 \pm 7.1$$

$$(R^2 = 0.965)$$

This provided an asymptotic plateau recovery in sperm output of 17×10^6/ml with an estimate of time to reach half of recovery plateau of 14.7 weeks (95% CI 1–29 weeks). As indicated by the time to reach half plateau recovery, the recovery rate in this study was slower than for men in the two Australian centres than for men in the eight other Western or the 10 non-Chinese centres (Table I).

Using the relative sperm outputs (sperm concentration for each individual as percentage of baseline sperm concentration, Figure 4), the recovery rate fitted a three-parameter sigmoid with coefficients (SD = % baseline sperm concentration, T = time in months):

$$\alpha = 43 \pm 33 \quad \beta = 5.70 \pm 1.04 \quad \gamma = 18.7 \pm 18.9$$

$$(R^2 = 0.850)$$

This provided an asymptotic plateau recovery of 43% of pre-treatment baseline sperm concentration with an estimate of time to reach half of recovery plateau of 18.7 weeks (95%
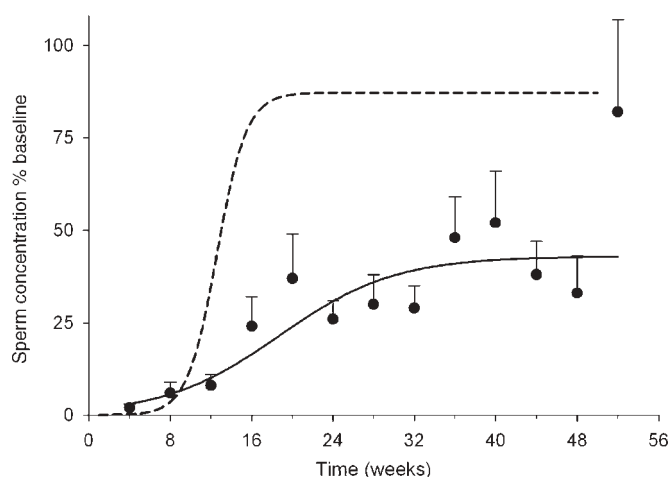
Figure 4. Plot of recovery of relative sperm output from Australian study compared with WHO studies. Data-points represent mean and SE (error bar) of semen samples grouped within months. Note cube-root scale on *y*-axis. The smooth line is the three-parameter sigmoidal curve plotted to fit the data by non-linear regression. For comparison, the dashed line is the WHO recovery data from Figure 3. Note that plateau of recovery is 43% of pre-treatment baseline.

CI 0–56 weeks). The wide CI reflected the unreliability of the time estimates due to incomplete recovery.

Discussion

The rate and extent of suppression and recovery of sperm output are crucial features of any practical hormonal male contraceptive. Some delay in onset and offset of effective contraception is inevitable with any male hormonal method given the length of spermatogenesis (2.5 months; de Kretser and Kerr, 1994) and slow clearance of sperm from the male ductular system (Barone *et al.*, 2003). Yet as delayed onset of effectiveness is an accepted feature of sterilization by vasectomy (Schwingl and Guess, 2000), such delay may be acceptable if accurate estimates for the onset and offset of reliable contraception and for resumption of natural fertility are provided to users so they may plan for adequate coverage during method change-over and avoid delays in subsequent planned pregnancies. Hence the likely time delays in onset and offset of male contraception and their determinants are key issues requiring further elucidation.

Quantitative aspects of sperm suppression and recovery have so far mainly focused on extent of suppression of spermatogenesis, a widely accepted and convenient surrogate variable for selecting the most promising regimens for further evaluation (Anderson and Baird, 2002; Kamischke and Nieschlag, 2004; Handelsman, 2005). Beyond the extent of suppression of spermatogenesis, there has been little quantitative consideration of sperm suppression or recovery rates. This limitation, largely due to the small size of most studies, is overcome by the WHO database which provides a valuable resource to estimate rates of suppression and recovery of spermatogenesis. In this study both suppression and recovery rates differed between centres. This was largely because men in predominantly Chinese centres had faster suppression and slower recovery rates than men in non-Chinese centres. In recovery rates, the differences between centres appeared to be fully accounted for by the geographical factor whereas for suppression rates there remained significant variations between the six predominantly Chinese and between the 10 non-Chinese centres. This indicates that the geographical variations are likely to be multifactorial, consistent with the mixture of ethnic, genetic and environmental factors already identified. The present estimates from those androgen-alone studies suggest that onset of reliable contraception, using the criterion of sperm output of $< 1 \times 10^6$/ml, may take on average 3 months. Similarly, recovery to levels of normal fertility may take 9–13 weeks depending on the definition of 'normal' (see below). As second generation hormonal regimens are now based on androgen/progestin combinations (Anderson and Baird, 2002; Kamischke and Nieschlag, 2004; Handelsman, 2005), the WHO studies provide a convenient benchmark for speed of onset and offset of future combination regimens.

Estimates derived from the WHO studies are *prima facie* applicable to that study's regimen, weekly i.m. injections of 200 mg testosterone enanthate. Whether these estimates extend to other androgen-alone regimens, such as testosterone

implants (Handelsman *et al.*, 1992, 1996), testosterone undecanoate (Zhang *et al.*, 1999; Kamischke *et al.*, 2000; Gu *et al.*, 2002) or a synthetic androgen such as the nandrolone analogue, MENT (7α-methyl-19-nortestosterone) (von Eckardstein *et al.*, 2003), cannot be considered certain *a priori*. To the extent that androgen-alone regimens work primarily by the common mechanism of gonadotrophin suppression, this is likely to be true. This would be highly advantageous as it is unlikely that any study in the near future will exceed the size of this WHO database, as weekly testosterone enanthate injections were only ever used as a convenient prototype androgen-alone regimen, although it is now considered obsolete for male contraceptive studies. It cannot be excluded, however, that the supraphysiological steady-state blood testosterone levels produced by regular weekly testosterone enanthate injections may produce systematic differences in spermatogenic suppression and recovery (Michel *et al.*, 1985; Meriggiola *et al.*, 2002). By contrast, superior depot testosterone preparations such as testosterone implants or testosterone undecanoate injections maintain more physiological blood testosterone levels. These could lead to differences in spermatogenic suppression, particularly if excessive blood testosterone concentrations counteract the rate or extent of depletion of intratesticular testosterone and thereby delay suppression of spermatogenesis (McLachlan *et al.*, 2002). This hypothesis regarding counter-productive effects of excessive androgen action is plausible because the threshold of testicular testosterone required to support spermatogenesis is remarkably low (Handelsman *et al.*, 1999; McLachlan *et al.*, 2002; Zhang *et al.*, 2003). Nevertheless, previous studies with testosterone implants indicate that, while a better depot may be dose-sparing for systemic androgenic effects, the rate and extent of spermatogenic suppression did not differ significantly from the WHO studies regimen of weekly i.m. injections of testosterone enanthate (Handelsman *et al.*, 1992). Although this suggests that the present estimates may be robust for all androgen-alone regimens, further studies of other androgen-alone regimens are needed to evaluate this proposition. To overcome the consistently small size of these studies, this would require a quantitative summary data analysis.

This study provides the first detailed quantitative information on the effects of a depot progestin, depot medroxyprogesterone acetate (DPMA), on the rate of suppression and recovery of human sperm output in the Australian study. While a limited meta-analysis had previously shown that DMPA demonstrated greater proportionate reduction in sperm output at 1 month after starting treatment (Turner *et al.*, 2003), the present, more detailed, quantitative analysis shows that DMPA effects include not only strikingly faster suppression throughout the suppression phase, but also markedly slower and less complete recovery compared with the testosterone enanthate injections used in the WHO studies. The reasons for these differences are not immediately apparent but may include prolonged depot pharmacokinetics of DMPA with persistent blood MPA concentrations due to secondary fat depots (Ortiz *et al.*, 1977; Lan *et al.*, 1984; Kaunitz, 1994; Mishell, 1996) and/or direct

progestin effects on the testis (Worgul *et al.*, 1979; McLachlan *et al.*, 2004), sperm (Blackmore, 1993; Blackmore *et al.*, 1996; Luconi *et al.*, 1998) or Leydig cells (Pino and Valladares, 1988; El-Hefnawy *et al.*, 2000; Williams *et al.*, 2000). Whether the same accelerated suppression and retarded recovery applies to other depot progestins is not known and will require further analysis.

The rate of suppression of sperm out depends on the stage of spermatogenic cycle most prominently affected (McLachlan *et al.*, 2002) together with the time taken to clear residual pre-formed sperm from the male ductular system. Although sperm transit time through the human epididymis is estimated at < 15 days based on the appearance of labelled sperm in the ejaculate following tracer administration (Rowley *et al.*, 1970) or quantitative estimates of distribution of homogenization-resistant nuclei counts in the testis and epididymis (Amann and Howards, 1980; Johnson and Varner, 1988), recent estimates of sperm clearance rate following vasectomy indicate that clearance to azoospermia may take 3–4 months (Barone *et al.*, 2004; Sokal *et al.*, 2004). The reason for these disparities is unclear but it is possible that surgical manipulation of the vas deferens may slow sperm transit time. Conversely, the similar times to azoospermia after hormonal regimens and vasectomy suggest that the hormonal regimens abolish active spermatogenesis quite rapidly despite ongoing sperm output in the ejaculate, which constitutes a lagging indicator of testicular sperm production. In any case, the time required to clear pre-formed sperm from the ductular system sets a minimum on the time to onset of reliable contraception for any hormonal male contraceptive as it does for vasectomy.

This analysis resolved some methodological issues. One was the definition of the end of treatment raised by the use of depot regimens. Unlike short-acting drugs where there is negligible difference between the time of last administered dose and cessation of drug action, these time-points differ significantly for depot drugs and become troublesome when two or more depot agents with distinctive kinetics are used. We defined the end of treatment as the date of the first missed hormone dose as the most realistic time-point from which to estimate cessation of the last depot dose effects. The use of one dosage interval beyond the last administered dose is justified where there is no drug accumulation, an assumption that may be violated if DMPA has secondary depot effects. A second methodological issue was the use of a power rather than the more conventional log transform. This was a superior approach for quantitative analyses of sperm output where zeros (azoospermia) are important because the log transform requires an arbitrary offset for the zeros which distorts regression estimates. Thirdly, the specific curve-fits we employed may not be optimal or universal. Despite performing very satisfactorily in this analysis, different models may be useful in future studies.

An unexpected and important feature of this analysis is that despite increased sperm output after cessation of treatment, return to the participants' own pre-treatment geometric mean baseline was not achieved consistently. The definition of recovery is crucial to such analyses but no singular

definition is intuitively obvious. We therefore employed both the absolute and relative (to baseline) analyses and both gave concordant patterns. The major reason for the apparently incomplete recovery may be due to the lack of unambiguous criteria for recovery because this requires a definition of 'normal' sperm output. It is well known that there is no satisfactory, evidence-based and widely accepted definition of population-based 'normal' sperm output with or without regard to male fertility. Conventional semen parameters fail to allow clear distinction between men defined as fertile, infertile or the majority who, at any time, may have undefined fertility (MacLeod and Gold, 1951; Meistrich and Brown, 1983; Guzick et al., 2001). The WHO Semen Manual's arbitrary definition of a normal sperm concentration of 20×10^6/ml is based on oracular wisdom rather than empirical evidence and, in the absence of conclusive evidence, it is claimed that this level is too low (Bonde et al., 1998; Zinaman et al., 2000) or too high (Handelsman, 1997; Lemcke et al., 1997; Ombelet et al., 1997; Chia et al., 1998; Andersen et al., 2000). The inability to obtain representative samples from the healthy male community (Handelsman, 2001; Cohn et al., 2002) probably precludes ever arriving at a satisfactory definition of 'normal' by the standards of all other biochemical pathology tests. In our view, the most probable reason for the failure of sperm output to reach the participants' own pre-treatment baseline in the WHO studies is the combined effects of regression to the mean (Bland and Altman, 1994) with unrealistically high WHO norms for sperm concentration. Sperm concentration has high within-subject variability (Schwartz et al., 1979) and if the study entry criterion of 20×10^6/ml is higher than the true, but unknown, community norm, then some men enter the study with higher than their own mean sperm concentration. Subsequently, over time, they would resume a lower mean sperm output regardless of treatment. The alternative interpretation of these data is that hormonal regimens may have mild but irreversible effects in sperm output, an effect that, if true, could increase with prolonged or subsequent courses of treatment. While this latter interpretation seems unlikely, excluding this possibility will require analysis of larger numbers of previous and future studies of hormonal suppression of sperm output.

Male reproductive physiology dictates that some delay is inevitable in the onset and offset of contraception using a male hormonal regimen. Such delay is an accepted facet of vasectomy and is also congruent with likely niches for a male hormonal method. For example, post-partum contraception is a context where hormonal contraceptive treatment can be commenced during pregnancy leaving ample time to establish reliable contraception without risk of conception while assisting mothers to avoid hormonal contraception during lactation. Similarly, delaying vasectomy until the decision for permanent sterilization is well thought out and justified. This may reduce regret and requests for reversal (Holman et al., 2000), just as the use of a reversible hormonal contraceptive is considered a desirable prelude to a permanent decision for female sterilization. Some delay in onset of reliable contraceptive efficacy is also congruent with male

hormonal contraception being primarily directed towards family planning/spacing for couples in stable relationships. By contrast, barrier methods such as the condom are far better suited to men having unplanned sex outside a stable relationship where dual protection against sexually transmitted infections has greater importance. In any case, accurate estimates of time of onset and offset and resumption of normal fertility as well as the criteria to define return to normality require more concerted attention in further studies.

Acknowledgements

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