

Individual fertility assessment and pro-fertility counselling; should this be offered to women and men of reproductive age?

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ABSTRACT: During the 1970s new contraceptive options developed and legal abortions became accessible. Family planning clinics targeting young women and men provided advice and assistance on contraception. Today, delayed childbearing, low total fertility rates and increasing use of social oocyte freezing create a need for pro-fertility initiatives. Three years ago we established a new separate unit: The Fertility Assessment and Counselling (FAC) clinic. The FAC clinic offers free individual counselling based on a clinical assessment including measurement of serum anti-Müllerian hormone and ovarian and pelvic sonography in women, sperm analysis in men, and a review of reproductive risk factors in both sexes. The FAC clinic includes a research programme with the goal to improve prediction and protection of fertility. Our first proposition is that clinics for individual assessment and counselling need to be established, as there is a strong unmet demand among women and men to obtain: (i) knowledge of fertility status, (ii) knowledge of reproductive lifespan (women) and (iii) pro-fertility advice. Addressing these issues is often more challenging than treating infertile patients. Therefore, we propose that fertility assessment and counselling should be developed by specialists in reproductive medicine. There are two main areas of concern: As our current knowledge on reproductive risk factors is primarily based on data from infertile patients, the first concern is how precisely we are able to forecast future reproductive problems. Predictive parameters from infertile couples, such as duration of infertility, are not applicable, diagnostic factors like tubal patency are unavailable and other parameters may be unsuitable when applied to the general population. Therefore, strict validation of reproductive forecasting in women and men from the general population is crucial. The second main concern is that we may turn clients into patients. Screening including reproductive forecasting may induce unnecessary anxiety through false positive predictions and may even result in overtreatment in contrast to the intended preventive concept. False negative findings may create false reassurance and result in postponement of conceptions.

Key words: prediction fertility / reproductive lifespan / reproductive risk / anti-Müllerian hormone / family planning

Introduction

The United Nations (UN) stated in 1995 that reproductive health implies that people should be able to have a satisfying sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so (United Nations, 1995). This of course implies the use of contraception, but in 2014 with today's low fertility rates, delayed childbearing and a variety of new treatment options, we argue that it is time that fertility experts engage themselves in other pro-fertility initiatives than fertility treatment. One such initiative could be to open clinics for fertility assessment and counselling.

In terms of contraception the developments 40–50 years ago revolutionized our ability to avoid undesired pregnancies (Leridon, 2006). One

of the many initiatives at that time was specialized family planning clinics offering young women and men contraceptive advice and care such as insertion of intrauterine devices, prescription of oral contraceptives (OC) or guidance on barrier methods. Thus, in practice family planning focuses on contraception.

As an analogy to the contraceptive clinics, we established the Fertility Assessment and Counselling Clinic (FAC) with the aim of protecting fertility. The FAC clinic opened in 2011 as an independent unit using the facilities and the professional expertise of the Fertility Clinic. The FAC clinic provides individual assessment and guidance to women and men with no known reproductive problems. Couples with a known reproductive problem who have attempted to conceive for 12 months or more cannot attend the clinic. The concept of the FAC clinic is to

prevent infertility and hopefully diminish the demand for fertility treatments.

By now > 1200 individuals have attended the FAC clinic in Copenhagen. In our experience, women and men wish to extend family planning to what could be called 'full programming of conception' ranging from contraception to pro-fertility behaviour to be able to establish their desired family size at an appropriate time.

The FAC clinic in Copenhagen

The FAC clinic is open for any individual who calls us for an appointment. No referral is needed and attendance is free of charge. All clients are informed that the activity includes an ongoing scientific project with the aim of evaluating our ability to predict, and possibly prevent, future infertility. Each individual is seen by a fertility expert and given 30 min

of consultation. The clinic offers women a review of their risk factors for female subfertility grouped into three risk zones (green, yellow/orange and red) and scored on the risk evaluation form presented in Table I. As seen, the risk evaluation form includes 14 parameters regarding reproductive and medical history and seven lifestyle factors. The risk evaluation form is our construction inspired by the FertiSTAT: a colour-coded tool developed for self-assessment of reproductive risk (Bunting and Boivin, 2010).

The examination involves obtaining a sample for assessment of serum anti-Müllerian hormone (AMH) and a transvaginal sonography including antral follicle count (AFC) and ovarian, uterine and pelvic pathology. These parameters are also grouped into three categories as seen on the risk evaluation form (Table I).

For the men, we use a similar risk evaluation form with known risk factors for male subfertility. The man brings a sperm sample and a

Table I Risk evaluation form used for structured risk evaluation of female clients attending the Fertility Assessment and Counselling Clinic (FAC) at Rigshospitalet, Copenhagen University Hospital, Denmark.

Name:		Personal ID:		
Risk factors	Parameter	Low risk	Medium risk	High risk
Female age				
Age	Age, years	Under 35	35–39	40 or above
Ovarian reserve and cycle length				
Cycle length	Days	23–35	More than 35	Less than 23
Antral follicle count (Sum of both ovaries)	N	11–30	5–10 or more than 30	Less than 5
Anti-Müllerian hormone	pmol/l	10–50	5–9 or higher than 50	Lower than 5
Gynaecological history and general health				
Months of trying to conceive	Months	Less than 6	6–12	Longer than 12
Pelvic inflammatory disease	N	0	1–2	3 or more
Ectopic pregnancy	N	0	1	2 or more
Endometriosis	Yes/no	No	Yes	Endometriomas
Pelvic surgery	Yes/no	No	Intestinal surgery	Surgery in ovaries/tubes
Uterine fibroids (submucosal/intramural fibroids)	Major diameter	0	Less than 3 cm	More than 3 cm
Intraperitoneal fluid/uterine malformation/hydrosalpinx	Yes/no	No		Yes
Previous chemotherapy	Yes/no	No		Yes
Genetic dispositions and intrauterine exposure				
Maternal age at menopause	Age, years	Above 50	45–50	Less than 45
Mother smoked during pregnancy	Yes/no	No		Yes
Lifestyle factors				
BMI	Kg/m ²	20–30	Lower than 20 or 31–35	More than 35
Waist/hip ratio		0.8 or lower	Higher than 0.80	
Smoking	Number per day	0	1–10	More than 10
Alcohol	Drinks per week	0	1–6	7 or more
Caffeinated beverage	Cups per day	Less than 6	More than 6	
Physical activity		Mild/moderate	Excessive	
Work environment factors				
Stress		None/moderate	Highly	

sperm analysis is performed including volume, concentration, total sperm count, percentage motility and progressive motility. Morphological criteria are not included. The results are presented to the client during the consultation.

Serum, blood and semen are stored in a biobank and the procedure is approved by the Ethical Committee of the Capital Region of Denmark (Project ID: 29262). A sister function, using the same concept, is operating at the centre for Reproductive Medicine in Malmö, Sweden as part of an European Union funded project.

Who attend the clinic and what are their motives?

Table II shows demographic characteristics as well as motives for seeking a consultation based on the first 916 women and 280 men attending the

FAC clinic from August 2011 through June 2014. The mean female age was 33.4 years with an age-range of 19–46 and the mean male age was 32.5 years with an age-range of 19–63. Of the female clients, 38% were single, whereas 3% of the male clients were single. Single women had a mean age of 35.2 years and were thus significantly older than women in a relationship. Clients were generally well-educated; the large majority were in employment and had a relatively high household income.

Clients were asked to state their reasons for making an appointment. Overall, 28% of the women and 48% of the men stated that they were currently trying to conceive and wanted an estimate of their present chance of doing so. Half of the clients wanted to know how to preserve or optimize their future chance to have a family and as many as 70% of the women wanted an estimate on how long they could safely postpone childbearing.

Table II Demographic characteristics of women and men examined at the Fertility Assessment and Counselling Clinic (FAC) from August 2011 through June 2014 including motives for attending the FAC clinic.

	Women	Men
N	916	280
Age (years) at examination [mean \pm SD]	33.4 \pm 4.4	32.5 \pm 5.6
Civil status [n (%)]		
Single	346 (37.8)	8 (2.8)
In a heterosexual relationship	547 (59.7)	271 (96.8)
In a homosexual relationship	10 (1.1)	0
Other	13 (1.4)	1 (0.4)
Level of educational [n (%)]		
None	1 (0.1)	1 (0.4)
Secondary school	55 (6.0)	33 (11.8)
Training/further education, <3 years	92 (10.0)	51 (18.2)
Further education, 3–4 years	233 (25.4)	51 (18.2)
Further education, >4 years (master's degree)	496 (54.2)	134 (47.8)
Other	39 (4.3)	10 (3.6)
Employment [n (%)]		
In employment	705 (77.0)	230 (82.1)
Unemployed/activation	62 (6.8)	8 (2.9)
Enrolled in education	113 (12.3)	35 (12.5)
Other	36 (3.9)	7 (2.5)
Household income (euro/year) [n (%)]		
Less than 27 000	113 (12.3)	18 (6.4)
27 000–53 000	302 (33.0)	47 (16.8)
53 000–80 000	233 (25.5)	68 (24.3)
More than 80 000	265 (28.9)	146 (52.1)
Unanswered	3 (0.3)	1 (0.4)
Motives for seeking fertility counselling [n (%)] [†]		
(a) I am presently trying to conceive and want an estimate of my pregnancy chance	217 (27.7)	114 (47.9)
(b) I want children and want an estimate on how long I can postpone childbearing	552 (70.4)	100 (42.0)
(c) I am concerned about my ability to have children	491 (62.6)	126 (52.9)
(d) I want information on how to preserve/optimize my chances to have children	372 (47.5)	119 (50.0)
(e) My partner wanted me to come along	18 (2.3)	116 (48.7)

[†]During the spring of 2013, clients were not asked to fill out the evaluation form. Therefore, these data are only available for 784 women and 238 men.

After the consultation, 35% of the women stated that they would advance the decision to become pregnant whereas 19% of the men would do the same. Six per cent of the women and 4% of the men reported that they considered postponing childbearing after having consulted the FAC.

The large majority, 99% of the women and 95% of the men, found the counselling useful. Two-thirds of the clients had increased their knowledge level about the impact of age on female fecundity and 59% of the women and 76% of the men had increased their knowledge level about risk factors for sub-fecundity. Three in four agreed that there is a need for more information to the public about reproductive risk factors.

The FAC clinic is based on self-referral and in our experience fertility assessment and counselling is mainly requested by well-educated women in their thirties of higher socio-economic status, who are particularly prone to delayed childbearing (Mills *et al.*, 2011). Thus, the observed selection bias may increase the benefit of the programme.

To summarize, the key issues that clients at the FAC clinic wish to be informed about are: (i) their present status regarding fertility and (ii) how they can behave in order to achieve their desired family size in the years ahead. This evidently includes an estimate of their reproductive lifespan. Single women in particular attend the clinic at an age where their fertility is already declining. Ideally, these women should have been seen at least 5 years earlier to optimize the usefulness of the guidance.

Why is pro-fertility assessment and counselling needed?

We propose, that clinics for individual fertility assessment and counselling should be established, as there seems to be a strong demand from women and men to have a pro-fertility consultation. The reasons for this demand may relate to several factors.

Firstly, women worldwide are continuously improving their education level which is associated with lower fertility rates at the individual level. It is well known that populations with higher proportions of well-educated women have lower total fertility rates (Lutz and Kc, 2011; Mills *et al.*, 2011). In recent years, several publications have addressed the issues of inadequate fertility awareness (Lampic *et al.*, 2006; Benzie, 2008; Bretherick *et al.*, 2010; Mortensen *et al.*, 2012; Peterson *et al.*, 2012; Hammarberg *et al.*, 2013) and raised concerns about the consequences of involuntary childlessness and smaller families than desired due to postponement of parenthood (Leridon and Slama, 2008; Schmidt *et al.*, 2012).

Secondly, the possibility of oocyte vitrification and an optimistic public trust in the efficiency of fertility treatments may contribute to the further postponement of childbearing (Molloy *et al.*, 2009; Lockwood, 2011; Mertes and Pennings, 2011; Rienzi *et al.*, 2012; Wyndham *et al.*, 2012). Oocyte vitrification for social reasons, often referred to as social freezing, is advertised on the Internet as 'Eggsurance.com' (6 November 2014, date last accessed) or 'Retrievefreezerelax.com' (6 November 2014, date last accessed), suggesting that women who undergo oocyte vitrification have insurance and can relax after the procedure, as their future fertility will be safe. In a Belgian study among 1024 women of reproductive age, 31.5% would consider social freezing (Stoop *et al.*, 2011) and in a study among American female university students, 79% were interested in learning more about their ovarian reserve and 53% would consider

social freezing if informed that the ovarian reserve was very low (Bavan *et al.*, 2011). So far we do not have any long-term follow-up data showing the true benefit of such social freezing. Further, non-validated commercial home-kits for measuring FSH in urine are available for self-test (Steiner *et al.*, 2011), and Internet sites offer to provide women an Ovarian Reserve Index based on serum-AMH, inhibin-B and FSH, which is then plotted into an age-dependent scale (the PlanAhead test). This simple approach may be useful, but the concept is not validated. The mere presence of such tests and oocyte vitrification for social reasons indicate that there is a demand from individuals to find ways to safeguard their future fertility.

Thirdly, single motherhood by donor insemination is now well-established in many countries. In 2013, almost 1% of the Danish birth cohort was born after donor insemination in heterosexually oriented single mothers (unpublished data from the Danish Fertility Society). Single women seeking this solution are typically above 35 years and as a rule single motherhood is not their dream scenario, but a choice made due to life circumstances (Jadva *et al.*, 2009; Frederiksen *et al.*, 2011). In the FAC clinic, this issue is often addressed by the single women.

Fourthly, the long-term use of OC may conceal the true ovarian reserve. In Western countries, 50–89% of women use OC at some point in their lifetime (Alkema *et al.*, 2013). In our cohort, 27% used OC and many had used OC without any periods of discontinuation since their teenage years. These women will be unaware of anovulation, both due to ovarian failure or due to polycystic ovary syndrome, and this concealment may motivate them towards a clarification of their status. The FAC clinic can help to identify OC users with low ovarian reserve and those with underlying anovulatory disorders.

Based on the above, we conclude that there is a need for pro-fertility initiatives, and as it is a new emerging field critical and evidence-based practice is warranted. This trend strengthens our obligation to gain experience and set up prospective studies to evaluate our ability to predict future fertility and to assess the use of the developed models.

Can we predict fertility in women?

It is well described that in women the optimal fertile period ranges from the early twenties to ~37 years of age (te Velde and Pearson, 2002; Schmidt *et al.*, 2012), and fertility declines rapidly from around 10–12 years before menopause (te Velde and Pearson, 2002). There is a large inter-individual variation in the chronological age at menopause and it would be very useful if we could predict age at menopause and thereby forecast reproductive lifespan in individual women. AMH seems the best currently available method of measuring ovarian reserve in women (Broer *et al.*, 2014), but most data are based on patients treated for infertility.

In terms of predicting natural fecundability, two prospective cohort studies have investigated the potential of AMH as a predictor (Steiner *et al.*, 2011; Hagen *et al.*, 2012). In a cohort of 100 women between 30 and 42 years, an AMH below 0.7 ng/ml (~5 pmol/l) was associated with a significantly reduced fecundability after age-adjustment (Steiner *et al.*, 2011). Hagen *et al.* (2012) did not find low AMH to be predictive of reduced fecundability in a cohort of 186 young women aged 20–35 years, whereas high AMH was associated with reduced probability of conceiving. However, very few of these young women ($n = 15$) had an AMH below 10 pmol/l. In subfertile women with elevated FSH levels

($n = 96$) who had follow-up on treatment-related as well as spontaneous pregnancies, live birth rates increased as AMH increased but only up to an AMH level of $1 \mu\text{g/l}$ ($\sim 7 \text{ pmol/l}$) (Yarde *et al.*, 2013).

Regarding prediction of menopause, our group showed that maternal age at natural menopause was a predictor of the daughter's ovarian reserve in terms of AMH (Bentzen *et al.*, 2013). AMH has been shown to be a better predictor of time to menopause than mother's age at natural menopause (Dolleman *et al.*, 2014). In several population-based studies, AMH has been shown to predict age at menopause (Broer *et al.*, 2011; Freeman *et al.*, 2012; Tehrani *et al.*, 2013, 2014; Dolleman *et al.*, 2014). Among older subfertile women AMH may also predict menopausal transition or menopause (Yarde *et al.*, 2013).

In the FAC clinic, we use AFC and AMH to advise women on their future fertility potential, but we do not forecast a specific age at menopause or a specific fecundability. Even though the full potential of AMH has not yet been elucidated, we consider it possible to make an overall estimate of the woman's reproductive potential. A 35-year-old woman with an AMH of 5 pmol/l will have a poorer chance of achieving the two children she desires within the next 5 years than a 35-year-old woman with an AMH of 25 pmol/l . Obviously, the first woman is pressed for time if she is going to fulfil her wishes.

One of the obstacles is the accuracy of the AMH assays; hence standardized assays and laboratory guidelines are highly needed. Another hurdle is how to counsel users of OC attending the FAC clinic, as OC users have lower AMH levels and AFC than non-users (Bentzen *et al.*, 2012). Thus, serum AMH concentration and AFC may not retain their precision as predictors of the ovarian reserve in women using hormonal contraception. We do not recommend women on OC to cease their contraception, but they are informed that this may influence the result of the assessment. Developing predictive models including an algorithm for OC users is part of the research programme in the FAC clinic.

Individuals attending the FAC clinic are not given a specific prognosis, but we do give them an estimate of their reproductive potential and general information regarding fertility at specific female ages. Additionally, we do identify a number of women with undiagnosed pelvic pathology that may impair their ability to conceive and we counsel clients about life style factors.

Can we predict later infertility in men?

In a prospective population-based study of 430 Danish couples followed for 6 months while trying to conceive it was found that the likelihood of a pregnancy was only 8% per month with a sperm concentration below $10 \times 10^6/\text{ml}$, but 25% per month with a sperm concentration around $40 \times 10^6/\text{ml}$. No further increase in fecundability was observed beyond $40 \times 10^6/\text{ml}$ (Bonde *et al.*, 1998). Semen concentration and percentage motile sperm obtained by computer-assisted semen analysis (CASA) was found to be predictive of fertility potential in men from the general population (Larsen *et al.*, 2000). Zinaman *et al.* (2000) found sperm count and percentage of normal sperm to be associated with fecundity in a cohort of 210 American couples. A recent prospective cohort study followed 501 couples trying to conceive for 1 year and found some semen parameters including per cent motility, sperm concentration and total sperm count to be associated with shorter

time-to-pregnancy (TTP), while other parameters were associated with prolonged TTP (Buck Louis *et al.*, 2014).

We realize that one has to be cautious when estimating a man's fertility from just one semen analysis. If the parameters are below the World Health Organization (WHO) range it may indicate future fertility problems (Bonde *et al.*, 1999) and we recommend contingent screening through a repeat full sperm analysis elsewhere. In men with extreme oligozoospermia, we inform the couple that they should not waste too much time trying to conceive naturally. If known risk factors, such as cryptorchidism, or lifestyle factors that could predispose to male infertility are present, we advise accordingly.

To conclude, we have limited knowledge on prediction of future fertility problems in men from the general population, but values outside the WHO reference range may still be predictive of prolonged TTP or even infertility.

Should fertility experts engage in fertility assessment and counselling?

Fertility assessment and counselling should rely on experienced staff within the field of reproductive medicine. In our experience, providing individualized pro-fertility advice to women and men from the general population is more challenging than treating infertile patients, where we have experience and evidence to facilitate the decision making. In the FAC clinic, we can advise on, for instance, lifestyle factors and known risk factors of sub-fecundity with reasonable confidence, but to forecast reproductive lifespan or to judge the safety of postponing planned pregnancies is still very uncertain. At the present stage of development, we need the highest degree of expertise to guide each individual and in our opinion it should therefore be the responsibility of fertility experts.

The FAC clinic uses the facilities and expertise of the Fertility Clinic, but it has been organized as a separate unit open to clients when the Fertility Clinic is closed. This is to ensure that clients who as a rule are reproductively healthy are not mixed with patients. The first reason is that we wish to avoid the suspicion of recruiting subjects for fertility treatment through the FAC clinic. The second reason is that the FAC clinic initially had numerous requests from couples who met the diagnostic criteria for infertility; for such couples, attending the FAC clinic is not relevant, as they require a full infertility diagnostic investigation and possibly treatment.

The problem with false positive and false negative findings

Screening involves the risk of false positive and false negative results. In relation to fertility assessment and counselling, the concern is that if an increased risk of sub-fecundity is identified, how can we avoid that those with a false positive screening take inappropriate actions? One possibility is to apply contingent screening where those identified as having an increased risk in the main screening programme are subjected to further and more conclusive testing. This could involve a selection of the investigations used in infertile couples. However, this is evidently costly and implies further risks of other false positive findings. In our FAC clinic, we have chosen not to proceed with further tests after a positive

identification. The clients are informed about additional tests that could be relevant if, for example, the sperm sample is very poor or infertility occurs in the future. In some cases, clients are advised to seek medical attention earlier than after the usual 12 months of trying to conceive for guidance and possible investigation. As many as one in five stated that they had become concerned about their fertility after the consultation. Some of these concerns may be the result of a false positive finding. The inappropriate consequences for individuals who are falsely identified as having a high risk of future fertility problems may be unnecessary anxiety and possible neglect in terms of contraception; some might even enter fertility treatment, including assisted reproductive technologies (ART), prematurely. Therefore the screening activity could turn reproductively healthy clients into patients.

In terms of false negative findings, the consequences could be that some women (or men) further postpone their parenthood believing that they are safe and have a good prognosis for pregnancy. Indeed, 6% of the women and 4% of the men in our cohort reported that they considered postponing childbearing after having consulted the FAC clinic.

Alternative pro-fertility activities

Whenever there is an unmet demand, the market will respond and try to meet the need and, from a commercial point of view, possibly increase the product range. As addressed above, multiple commercial options are already available including social oocyte freezing.

Other pro-fertility activities focus on increasing the knowledge level of women of reproductive age. In an RCT reproductive-life-plan-based information in contraceptive counselling increased the knowledge of reproduction among young women (Stern et al., 2013), and Wojcieszek and Thompson (2013) found that knowledge of reproduction and ART effectiveness increased in an intervention group exposed to an online brochure on infertility compared with the control group. The FertiSTAT is another approach based on self-evaluation; women tick off their reproductive risk factors and receive standardized guidance according to their personal score (Bunting and Boivin, 2010). Preliminary validation indicated that the FertiSTAT can discriminate between women proven fertile (as they were currently pregnant) and infertile women, and the authors suggest that the tool may enable women to get personalized fertility guidance. Such an approach may be cost effective because it is easily available to everyone, but it is exclusively based on the history. In contrast, the FAC clinic combines sonographic examination and serum-AMH with a structured risk evaluation.

Informing clients on the significance of tests, in particular those investigating ovarian reserve, is sometimes a difficult task that cannot be effectively done in a standardized mathematical manner. Therefore we believe that such a service should be operated by experienced specialists in reproductive medicine. The FAC clinic includes a more comprehensive evaluation than other pro-fertility activities, and hopefully our prospective follow-up study will show that the approach is beneficial.

Conclusion

Modern contraceptives gave women control over their reproduction and the freedom to plan if, when and how often to reproduce. Family

planning clinics successfully provide advice on contraception. However, women and men seek not only advice on how to prevent unwanted pregnancies; they want full programming of reproduction in order to take appropriate action to ensure their desired family. The field is emerging and we encourage fertility experts to embrace the demand for fertility assessment and counselling to ensure the quality of such initiatives. As in all screening programmes, we should be aware of the risk and consequences of false positive and negative findings.

Authors' roles

A.N.A. proposed the concept, H.W.H. and K.B.P. drafted the paper and all authors contributed to the content and revised the drafts.

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Conflict of interest

None declared.

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