

DEBATE—continued

Investigation of the infertile couple: a basic fertility work-up performed within 12 months of trying to conceive generates costs and complications for no particular benefit

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The current approach of the basic fertility work-up has been questioned recently in this journal. Based on new data on human fecundity, the authors advocated starting the fertility work-up after just 6 months of trying to conceive instead of the usual 12 months. In women younger than 39 years and with a regular cycle, there are several arguments why the basic fertility work-up should not be done earlier than after 12 months of child wish. Firstly, 50% of couples who have tried to conceive for 6 months without success will conceive in the next 6 months without any treatment. Secondly, the prevalence of fertility diseases is lower in couples who have been trying to conceive for 6 months as compared with those who have been trying for 12 months. Performance of a fertility work-up at this stage will lead to an increase in false-positive diagnoses compared with performing them at 12 months of subfertility. Thirdly, fertility treatment will have fewer additional effects in couples with good spontaneous conception prospects (6–12 months child wish), compared with subfertile couples who have poor prospects. At present, none of the available fertility treatments have success rates comparable with no intervention in these women, and postponement of treatment in such couples will prevent complications such as ovarian hyperstimulation syndrome and multiple pregnancies. We argue that the fertility work-up should not be offered to couples with a duration of child wish of <12 months, except for women with ovulation disorders and women of 39 years and older.

Key words: complications/fertility work-up/subfertility/timing/treatment/

Introduction

The current fertility work-up, for example as recommended in the National Institute for Clinical Excellence (NICE) guidelines, is performed in couples who have an unfulfilled child wish for at least 12 months (National Collaborating Centre for Women's and Children's Health, 2003). Since recent prospective studies on fecundity have shown that ~80% of all couples conceive within 6 months after discontinuation of contraception, and that only 10% of the initial group will conceive within the next 6 months, the timing of the fertility work-up has been debated (Gnoth *et al.*, 2003; Wang *et al.*, 2003). Brosens *et al.* (2004) advocated that female subfertility should be investigated after 6 months of child wish. One of their arguments was that the current definition of subfertility is based on a probability to conceive of 20% per cycle or ~85% per year. According to the new data, this point is already reached at 6 months, in contrast to previous, mostly retrospective studies, which reported a cumulative pregnancy rate of ~85% at

12 months (Hull *et al.*, 1985; Snick *et al.*, 1997; Evers 2002; Brosens *et al.*, 2004). Gnoth *et al.* (2003) also advocated performing the basic fertility work-up at an earlier stage, stating that after six cycles of unprotected intercourse without conception, every second couple is probably subfertile.

In the following sections, we explore four arguments why the fertility work-up should not be offered to couples with a child wish of <12 months.

The 'spontaneous pregnancy' argument

In the studies by Gnoth *et al.* (2003) and Wang *et al.* (2003), 80% of the couples conceived successfully within 6 months, whereas only 10% of patients conceived in the 6 months thereafter. The results of these studies were used as an argument for the early evaluation of the reproductive capacity of couples who had not conceived after 6 months, since 50% of those that had not conceived after 6 months would not conceive in the

next 6 months. Now let us flip the coin, and look at it from the other side. The same data implicate that 50% of couples who had not conceived after 6 months will conceive in the next 6 months. Pregnancy rates as high as 50% are rarely reported in reproductive medicine. As a matter of fact, we are not aware of any treatment that has such pregnancy rates, without generating harm, side effects and costs. Thus, whereas used as an argument for starting a diagnostic work-up, the data of Gnoth *et al.* and Wang *et al.* are a strong motive for reassurance of couples who did not conceive after 6 months, to aim for natural conception for another 6 months.

The ‘false-positive diagnosis’ argument

The recently published NICE guidelines recommend performance of ovulation detection, semen analysis as well as hysterosalpingography (HSG) in couples who do not conceive within 12 months (National Collaborating Centre for Women’s and Children’s Health, 2003). Apparently, these tests are valuable for couples who have tried to conceive for >12 months. What will happen if we perform these tests after 6 months of unfulfilled child wish? As an example, we use HSG. For HSG, the sensitivity is known to be 65% for a specificity of 83% (Mol *et al.*, 1996). When these tests are used in a population of subfertile couples who have been trying to conceive for at least 12 months, the prevalence of tubal pathology in this group will be ~20% (Mol *et al.*, 1997). Table I shows the two-by-two table that can be constructed if we perform a test with a sensitivity of 65% and a specificity of 80% in a population of 1000 fictitious subfertile couples, where the prevalence of tubal disease is 20%. Out of 200 patients with tubal pathology, HSG will identify 130 cases, whereas out of 800 couples without tubal pathology, HSG will incorrectly point out 160 as having tubal pathology. This means that if we assume all patients with an abnormal HSG are scheduled for subsequent laparoscopy to assess their tubal status in detail, 130 out of 290 patients that will undergo laparoscopy indeed have tubal pathology (44.8%), whereas 55.2% have not.

Now let us consider what happens when the HSG is applied among couples who have been trying to conceive for 6 months rather than 12 months. From the studies of Gnoth *et al.* (2003) and Wang *et al.* (2003), we know that of those couples who are not pregnant after 6 months, 50% will conceive and have an ongoing pregnancy within the next 6 months. These couples will not have relevant tubal pathology and, as a consequence, the prevalence of tubal pathology in a cohort of couples who

Table I. Test results of HSG when it is performed only in subfertile couples (trying to conceive for at least 12 months)

		Laparoscopy		
		Tubal pathology	No tubal pathology	
HSG	Tubal pathology	130	160	290
	No tubal pathology	70	640	710
		200	800	1000

Test properties: sensitivity 65% for a specificity of 80%.
Prevalence of tubal pathology is assumed to be 20%.

Table II. Test results of HSG where it is performed both in subfertile couples (trying to conceive for at least 12 months) and in couples who are trying to conceive for 6–12 months

		Laparoscopy		
		Tubal pathology	No tubal pathology	
HSG	Tubal pathology	65	180	245
	No tubal pathology	35	720	755
		100	900	1000

Test properties: sensitivity 65% for a specificity of 80%.
Prevalence of tubal pathology is assumed to be 10%.

have not conceived within 6 months of trying is 10%. If we now perform the HSG in 1000 women after 6 months of whom 100 have tubal pathology, the number of patients with tubal pathology that have been identified by HSG will be 65. The number of patients in which a false-positive diagnosis will be made will be 180 (Table II). Thus the percentage of patients in which subsequent laparoscopy will show tubal abnormalities will drop from 44.8% (130 out of 290) to 26.5% (65 out of 245) or, the other way around, the percentage of patients in which laparoscopy is performed and no tubal pathology is found increases from 55.2 to 73.5%.

The above mechanism in which the number of false-positive diagnoses increases due to the fact that the fertility work-up started after 6 months of child wish instead of after 12 months of child wish may also occur in other diagnostic tests, for example the semen analysis. Ombelet *et al.* (1997) demonstrated in a comparison between semen parameters and subsequent pregnancy that the predictive performance of these tests is poor. From the receiver operating characteristic (ROC) curves they provided, it can be derived that for normal count (cut-off value 5.6×10^6), and a sensitivity of 62%, the specificity of semen analysis in the prediction of pregnancy will be ~82%. Other semen parameters are reported to be less specific for a sensitivity of 60%. As a consequence, the example of HSG in the diagnosis of tubal pathology is also true for semen analysis in the diagnosis of male factor subfertility.

The ‘no-benefit from treatment’ argument

The third point is whether early treatment will improve fertility prospects. Virtually all the available evidence on the effectiveness of treatment is based on studies that included couples who were subfertile according to the World Health Organization guidelines, i.e. ‘either a woman’s inability to conceive and bear a live child or a man’s inability to impregnate a woman over a twelve month period of unprotected, regular and normal sexual intercourse.’ (Vayena *et al.*, 2002). We do not know whether this evidence can be transferred to couples who are trying to conceive for 6 months. Let us consider the example of a couple with unexplained subfertility. According to a randomized clinical trial of Guzik *et al.* (1999), treatment of a couple with unexplained subfertility with superovulation and intrauterine insemination (IUI) would increase the probability of an ongoing pregnancy with a relative risk (RR) of 4.4 [95% confidence interval (CI) 2.5–7.9], i.e. from 2.0% per cycle without treatment

to 8.7% per cycle with treatment. Now we offer the same treatment to a couple who have tried to conceive for 6 months. A 50% pregnancy rate per 6 months implies that the spontaneous pregnancy rate per cycle in these couples is 11% [$P=100\% - (100\% - 11\%)^6 = 50\%$]. Consequently, an RR of 4.4 would imply that the pregnancy rate per IUI cycle should be 48%, corresponding to a success rate of 98% after 6 months of IUI treatment, which is virtually impossible.

The 'prevention of complications' argument

Finally, there is the prevention of complications argument. Complications in reproductive medicine are relatively rare but, once present, they can have serious consequences for the individuals who were, apart from their unfulfilled child wish, mostly healthy. An example of such a complication is ovarian hyperstimulation syndrome (OHSS). Many measures have been proposed to prevent OHSS, and recently a recommendation has been made for the prevention of OHSS (Practice Committee of the ASRM, 2003). Among the measures proposed was that the ovulation induction regimens should be highly individualized, careful monitoring should be carried out and minimum dose and duration of gonadotrophin therapy necessary to achieve the therapeutic goal should be used. Unfortunately, a very obvious way to prevent OHSS, i.e. postponement of treatment, was not mentioned at all. The same accounts for what might be the most important side effect these days, i.e. multiple pregnancies (Fauser *et al.*, 2005). Although single embryo transfer (SET) with cryopreservation of the remaining embryos results in a considerable reduction of the multiple pregnancy rate, with an acceptable, although somewhat reduced number of singleton pregnancies, postponement of treatment for 6 months results in a 50% conception rate of singleton pregnancies.

In conclusion, we feel that offering a fertility work-up to couples who did not achieve conception within 6 months of child wish would lead to an unacceptable number of false-positive diagnoses, treatment of couples that would have a considerable chance of conception without treatment, and unnecessary side effects and costs. We plead for careful counselling of those couples who desire a child, with an emphasis on spontaneous conception chances and the relative value of treatment, followed by an adequate diagnostic work-up and careful counselling once pregnancy has not occurred after 1 year. An exception can be made for selected groups of patients, e.g. those couples in whom the female partner does not have a regular menstrual cycle or couples in whom the female partner is over 39 years of age. In the latter group, there is no high quality evidence that the postponement of treatment will harm, but cohort studies suggest a strong decrease of the reproductive capacity in these

women with a further increase of age (Schwartz and Mayaux, 1982; Noord-Zaadstra *et al.*, 1991).

Those who argue that evaluation and subsequent treatment should be performed earlier are invited to demonstrate the value of such interventions in well designed diagnostic and therapeutic studies.

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