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ORIGINAL ARTICLE

A concise infertility work-up results in fewer pregnancies

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STUDY QUESTION: Is pregnancy success rate after a concise infertility work-up the same as pregnancy success rate after the traditional extensive infertility work-up?

SUMMARY ANSWER: The ongoing pregnancy rate within a follow-up of 1 year after a concise infertility work-up is significantly lower than the pregnancy success rate after the traditional and extensive infertility work-up.

WHAT IS KNOWN ALREADY: Based on cost-effectiveness studies, which have mainly focused on diagnosis, infertility work-up has become less comprehensive. Many centres have even adopted a one-stop approach to their infertility work-up.

STUDY DESIGN, SIZE, DURATION: We performed a historically controlled cohort study. In 2012 and 2013 all new infertile couples (n = 795) underwent an extensive infertility work-up (group A). In 2014 and 2015, all new infertile couples (n = 752) underwent a concise infertility work-up (group B). The follow-up period was 1 year for both groups. Complete follow-up was available for 99.0% of couples in group A and 97.5% in group B.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The extensive infertility work-up consisted of history taking, a gynaecological ultrasound scan, semen analysis, ultrasonographic cycle monitoring, a timed postcoital test, a timed progesterone and chlamydia antibody titre. A hysterosalpingography (HSG) was advised routinely. The concise infertility work-up was mainly based on history taking, a gynaecological ultrasound scan and semen analysis. A HSG was only performed if tubal pathology was suspected or before the start of IUI. Laparoscopy and hormonal tests were only performed if indicated. Couples were treated according to the diagnosis with either expectant management (if the Hunault prognostic score was >30%), ovulation induction (in case of ovulation disorders), IUI in natural cycles (in case of cervical factor), IUI in stimulated cycles (if the Hunault prognostic score was <30%) or IVF/ICSI (in case of tubal factor, advanced female age, severe male factor and if other treatments remained unsuccessful).
The primary outcomes were time to pregnancy and the ongoing pregnancy rates in both groups. The secondary outcomes were the number of investigations, the distribution of diagnoses made, the first treatment (started) after infertility work-up and the mode of conception.

MAIN RESULTS AND THE ROLE OF CHANCE: The descriptive data, such as age, duration of infertility, type of infertility and lifestyle habits, in both groups were comparable. In group A, more than twice the number of infertility investigations were performed, compared to group B. An HSG was made less frequently in group B (33% versus 42%) and at a later stage. A Kaplan–Meier curve shows a shorter time to pregnancy in group A. Also, a significantly higher overall ongoing pregnancy rate within a follow-up of 1 year was found in group A (58.7% versus 46.8%, respectively, $P < 0.001$). In group A, more couples conceived during the infertility work-up (14.7% versus 6.5%, respectively, $P < 0.05$). The diagnosis cervical infertility could only be made in group A (9.3%). The diagnosis unexplained infertility differed between groups, at 23.5% in group A and 32.2% in group B ($P < 0.001$).

LIMITATIONS, REASONS FOR CAUTION: This was a historically controlled cohort study; introduction of bias cannot be ruled out. The follow-up rate was similar in the two groups and therefore could not explain the differences in pregnancy rate.

WIDER IMPLICATIONS OF THE FINDINGS: Re-introduction of an extensive infertility work-up should be considered as it may lead to higher ongoing pregnancy rates within a year. The therapeutic effects of HSG and timing of intercourse may improve the fertility chance. This finding should be verified in a randomized controlled trial.

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Key word: Infertility / pregnancy / assisted reproduction / epidemiology / cost effectiveness / IVF/ICSI outcome / work-up / post-coital test / hysterosalpingography

WHAT DOES THIS MEAN FOR PATIENTS?

After trying to conceive for more than 1 year, couples can be referred to an infertility clinic. Several fertility tests can be performed. This is called the infertility work-up. In 2014, a new approach or 'lean' infertility work-up was introduced with fewer tests than before. Some tests were thought to be unnecessary to make the right decisions on which fertility treatment to start. This approach aimed to reduce the burden and costs of the fertility work-up. In this study, we compared couples that underwent the traditional, more extensive infertility work-up with couples that underwent this 'lean' infertility work-up. The type of infertility work-up led to a difference in diagnosis made and treatment started. After 1 year of follow-up, we saw that more couples were pregnant after the traditional infertility work-up. Possible explanations are the therapeutic effect of tests or the timing of having intercourse. In view of this effect on outcome it is advisable to discuss the type of work-up with the patient.

Introduction

An infertility work-up should not only provide accurate diagnostic and prognostic information but also should be cost-effective, evidence based and not too cumbersome for patients.

In recent years many cost-effectiveness studies have been performed (Mol *et al.*, 2001; Coppus *et al.*, 2007b; Luttjeboer *et al.*, 2009; Verhoeve *et al.*, 2011). Reproductive societies worldwide have updated their medical guidelines based on these new data.

While in the past couples referred to an infertility clinic would undergo almost all commonly available diagnostic tests, nowadays an infertility work-up must be lean (i.e. concise). Many clinics have adopted a one-stop infertility clinic (Brosens *et al.*, 2002).

Medical history has become the crux of the matter again. For example, if a woman has a regular menstrual cycle, there is a high probability that the cycle is ovulatory, and thus there is no need to explore the cycle (ASRM, 2012; NVOG, 2004).

Furthermore, if the medical history is uneventful as far as sexually transmitted diseases, pelvic infections or surgery are concerned, the likelihood for tubal pathology is low, and thus no urgent need exists to test the patency of the tubes (Coppus *et al.*, 2007b; Luttjeboer *et al.*, 2009; NVOG, 2004; Verhoeve *et al.*, 2011). Many doctors have abolished the postcoital test (PCT) in view of its presumed lack of predictive value (Oei *et al.*, 1998; NICE, 2013; NVOG, 2004) although this has been questioned by others (Eimers *et al.*, 1994; Hunault *et al.*, 2004; van der Steeg *et al.*, 2004; Hessel *et al.*, 2014). Chlamydia serology has only limited prognostic value, and if a screening test for tubal pathology is necessary, the hysterosalpingography (HSG) is preferred (ASRM, 2012).

Guidelines have been updated, but an overall evaluation has not taken place (ASRM, 2012; NVOG, 2004). The question is whether the concise infertility work-up can be introduced without missing essential diagnoses and subsequent indicated treatment. Does it indeed lead to the same diagnoses, the same prognostic information, and will as many couples as after a traditional work-up achieve their desired pregnancy and in the same time frame? To answer these questions, we performed a historical controlled study and compared the two strategies.

Materials and methods

In the run-up to the implementation of the new Dutch infertility guidelines, the concise infertility work-up was introduced in the Centre for Reproductive Medicine in the Jeroen Bosch hospital, 's-Hertogenbosch, the Netherlands in January 2014. In this historically controlled cohort study, the findings of all new infertile couples referred in 2012 and 2013, who were screened in the traditional way (group A), were compared with those of all new couples referred in 2014 and 2015, who received the concise infertility work-up (group B). All couples were referred by their general practitioner, as is mandatory in the Netherlands.

The primary outcome measures of the study were the cumulative ongoing pregnancy rate (COPR) after 1 year and time to pregnancy.

In case of infertility, which was defined as a failure to conceive despite 12 months of unprotected intercourse, couples were referred to secondary care. In case of female age above 38 years, oligo- or amenorrhoea or known bilateral tubal block, patients with the wish to conceive could be referred to secondary care before these 12 months.

Couples were excluded when a pregnancy was already established at the time of first visit or before the initiation of fertility testing. Couples were also excluded if insufficient data were available, for example, when no result of the semen analysis was known. All infertility investigations, treatments (including the time to start the first treatment and the number of cycles per treatment), and ongoing pregnancies were documented within a follow-up of 1 year. The time to pregnancy after an HSG or PCT was registered.

Baseline variables were collected to evaluate whether both groups were comparable at the start of the infertility work-up. Data on costs were not collected in this study.

Data were registered prospectively in an electronic patient record (LSFD© Landelijk specialistisch fertiliteitsdossier, STB, Houten, the Netherlands), and continuously monitored for completeness.

The traditional infertility work-up

The traditional infertility work-up consisted of a medical history, physical examination and a transvaginal ultrasound scan to diagnose

gynaecological pathology. Variables collected in the medical history were female age, male age, duration of infertility, type of infertility, obstetric and general medical history, familial diseases, menstrual cycle history, symptoms of endocrinopathy, dysmenorrhoea, pelvic inflammatory disease, sexually transmitted disease, surgery, sexual functions, female and male smoking and drinking habits or the use of drugs, and female BMI.

Furthermore, the work-up generally consisted of cycle monitoring by ultrasound, a timed PCT, and a timed mid-luteal progesterone. A PCT was not performed in case of pregnancy or in case it was immediately clear that IVF or ICSI was indicated.

In case of irregular menstrual cycles, hormonal screening was performed to distinguish between the World Health Organization (WHO) groups of ovulation disorders, thyroid disease and hyperprolactinaemia. This hormonal screening consisted of FSH, thyroid-stimulating hormone, LH, prolactin, testosterone and 17-beta-estradiol. Tubal disease was screened with the chlamydia antibody test (CAT). An HSG with a water-based contrast medium, followed by flushing the tubes with an oil-based contrast medium for its therapeutic effect was advised. Not every couple underwent an HSG. The HSG was postponed for 3 months in cases where ovulation induction (OI) was started first or was not performed at all in case of pregnancy, or in case of a clear indication for IVF or ICSI. A laparoscopy was performed only if indicated, i.e. in case of abnormal findings on ultrasound or HSG, or based on a specific finding in the medical history, such as pelvic inflammatory disease, sexually transmitted disease or tubal surgery.

A semen analysis was carried out according to the WHO laboratory manual for the examination and processing of human semen (WHO, 2010).

The concise infertility work-up

The concise infertility work-up consisted of a medical history and physical examination as described above and a single transvaginal ultrasound scan. If the menstrual cycle was between 25 and 35 days and the difference between the shortest and longest cycle was no longer than 7 days, the cycle was considered ovulatory and no further cycle monitoring was performed. Serial ultrasound (i.e. cycle monitoring) was only used in case women had cycle durations with a maximum of 35–40 days.

A PCT and assessment of the cervical mucus did not take place. Progesterone was only determined when an ovulatory disorder was suspected. If the medical history revealed a pelvic inflammatory disease, peritonitis, complicated appendicitis or abdominal surgery, or in case of abnormal ultrasound findings tubal pathology was suspected, an HSG was performed. If not, the HSG was postponed for 6 months or until OI with gonadotrophins, or IUI, was started. The CAT was not performed on a routine basis. A laparoscopy was performed in case of abnormal HSG. In case of clear abnormal findings on ultrasound, a laparoscopy was performed without performing an HSG.

If no severe dysmenorrhoea and/or signs of endometrioma at the pelvic ultrasound scan were present, the likelihood of endometriosis was considered low. In case of severe dysmenorrhoea and abnormal findings on ultrasound, a laparoscopy was performed. The diagnosis endometriosis was based on laparoscopic findings. A semen analysis was carried out according to the WHO laboratory manual for the examination and processing of human semen (WHO, 2010).

Table I Comparison of the infertility work-up between Group A and B.

	Group A	Group B
Medical history	+	+
Physical exam	+	+
Transvaginal ultrasound scan	+	+
Semen analysis	+	+
Cycle monitoring by ultrasound		
In regular cycles	+	−
In irregular cycles	+	+
Timed postcoital test	+	−
In case of irregular menstrual cycle hormonal screening	+	+
Mid-luteal progesterone	+	If indicated
Chlamydia antibody titre	+	If indicated
Hysterosalphingography*	+	If indicated
Laparoscopy	If indicated	If indicated

Group A = traditional work-up, Group B= concise work-up.
*Recommended per protocol but not always performed in view of exceptions, patients' choice and non-medical reasons.

Table I shows a summarized comparison of the two types of infertility work-up.

According to the local protocol, the aim was to perform all investigations for all new couples. In daily practice, investigations can be postponed or not performed at all because of patients' choice or for non-medical reasons.

Diagnosis

In the concise work-up, an ovulation disorder was diagnosed in case of an irregular menstrual cycle, i.e. if the cycle was anovulatory or had a duration of <25 or more than 35 days. In the traditional infertility work-up, an ovulation disorder was diagnosed in case of an irregular menstrual cycle or abnormal ultrasound or laboratory findings during cycle monitoring.

If the mid-luteal progesterone was lower than 26 nmol/L or if the luteal phase was shorter than 11 days, luteal insufficiency was diagnosed. Patients with luteal insufficiency were diagnosed with an ovulation disorder. The diagnoses poor ovarian reserve and polycystic ovary syndrome are included in the diagnostic category of ovulation disorder.

Tubal disease was diagnosed as abnormal findings from HSG or laparoscopy. Severe tubal disease was diagnosed in case of bilateral tubal pathology and/or severe adhesions. Suspicion of endometriosis was raised if there was a history of severe dysmenorrhoea or if ultrasound showed the presence of endometriotic cysts. The diagnosis of endometriosis was verified by laparoscopy. Severe endometriosis was classified as endometriosis of at least stage II, according to the revised American Society for Reproductive Medicine classification of endometriosis (ASRM, 1997). Sexual dysfunction was defined as the inability to have regular intercourse with intravaginal ejaculation.

Depending on the total motile sperm count (TMSC; i.e. volume multiplied by concentration, multiplied by proportion of progressive motile sperm), male factor was diagnosed as mild (TMSC of 1–10 $\times$ 10^6 spermatozoa before preparation) and severe (TMSC of $<1 \times 10^6$ spermatozoa before preparation).

Cervical factor was based on the findings at PCT. A negative PCT was defined as <1 motile spermatozoa seen per high power field (400×), despite normal semen quality or if too little mucus was found, or the pH was not favourable for spermatozoa (pH < 6.6). In the group that underwent the concise work-up, the diagnosis cervical factor was not made as this item was not investigated. In cases with no other abnormalities, couples were diagnosed as unexplained infertility.

A couple could have more than one diagnosis. In the traditional work-up, unexplained infertility was diagnosed if all tests were normal, including the cycle-related investigations. In the concise work-up, unexplained infertility was diagnosed if the cycle was considered ovulatory, if there was no suspicion for tubal disease and endometriosis, and if the semen analysis was normal.

A different type of infertility work-up may lead to a different distribution of couples in diagnostic categories such as ovulation disorder, unexplained infertility and cervical factor.

Management

The type of treatment after both the traditional and the concise work-up was dependent on the findings in the work-up.

In case of an ovulation disorder, hormonal screening was performed to classify the disorder. The results determined the type of OI. Couples with WHO III ovulation disorder were offered oocyte donation.

Couples with cervical factor were treated with IUI in a natural cycle. The treatment for couples with the diagnosis unexplained infertility or male factor with a TMSC of $>3 \times 10^6$ spermatozoa before preparation was based on the prognosis as assessed with the prediction model of Hunault (Hunault *et al.*, 2004). This prospective validated model is incorporated in the Dutch national guidelines on fertility investigation (Hunault *et al.*, 2005; NVOG, 2004). Depending on whether a PCT is performed, the model of Hunault including the PCT or without the PCT is used to calculate the prognosis. If the prognosis was above 30%, expectant management for 6 months was chosen, followed by six cycles of controlled ovarian stimulation (COS) with IUI and eventually IVF. If the prognosis was below 30%, COS-IUI was offered directly. In case of severe male factor, ICSI was advised. In case of unexplained infertility and female age above 40 years often IVF was offered, in view of the influence of higher female age on prognosis.

In cases of mild and severe tubal factor, surgery was considered or IVF was offered.

Depending on the severity of endometriosis, ablative surgery was performed or the couple was treated with IVF directly.

Every diagnosis resulted in a treatment strategy in which it was possible that couples received several types of treatment over time. For example, couples with unexplained infertility could start with expectant management, and, if unsuccessful, this was followed by controlled ovarian hyperstimulation-IUI (COH-IUI) and IVF .

In daily practice, the treatment strategy and time to start treatment can be influenced by patients' choice and non-medical reasons.

Follow-up

The follow-up period was 1 year after the first visit. If the outcome after 1 year was unknown, couples were contacted by email or phone to find out whether they had undergone any fertility investigations or treatment elsewhere and/or whether they had conceived. If so, the mode of conception was documented. Drop-out was defined as discontinuation of care within the follow-up of 1 year, which could happen either before the start of treatment or before the standard number of therapeutic attempts had been completed.

Outcome parameters

The primary outcome measures were time to pregnancy and COPR within a follow-up of 1 year after the first visit. An ongoing pregnancy was defined as a viable intrauterine pregnancy of at least 12 weeks of duration confirmed on an ultrasound scan.

The number of investigations, the distribution of diagnoses made, the first treatment started after infertility work-up and the mode of conception were registered, as well as the COPR per diagnostic group. In case a natural pregnancy occurred, we distinguished between a natural pregnancy during expectant management or a treatment-independent pregnancy, i.e. a pregnancy during infertility work-up or in between treatments. We calculated the time to start treatment and the total number of cycles per treatment. We calculated the time to pregnancy after a combination of cycle monitoring and PCT. We also calculated the time to HSG after intake and time to pregnancy after an HSG.

Statistics

Patient characteristics, both demographic and infertility-related, were given for couples referred to the medical specialist in 2012 and 2013 (group B) and in 2014 and 2015 (group B). For comparison between the groups, the independent Student's *t*-test or χ^2-test were used. A *P*-value of <0.05 was used to indicate a statistical significance.

Calculations of the total number of investigations, diagnoses made and first treatment started were based on the total cohort, including the couples that were lost to follow-up.

Baseline variables, the total number of investigations, the distribution of diagnoses made, the first treatment started and time to start treatment were calculated for both groups in a univariate way.

The ongoing pregnancy rates were calculated for both groups and analysed in a Kaplan–Meier curve. In this way, a time to pregnancy could be calculated.

To complete the data of couples that were lost to follow-up, we applied imputation in this calculation.

All analysis and calculations were performed with IBM SPSS statistics version 21.0 (IBM Corp, 2012).

Results

In the study period, 1646 new couples were referred by their general practitioner for infertility work-up. In 2012 and 2013, a total of 852 couples underwent the traditional work-up, whereas in 2014 and 2015, 794 couples underwent the concise work-up. Couples with a pregnancy at the time of the first visit (n = 30 in group A and n = 26

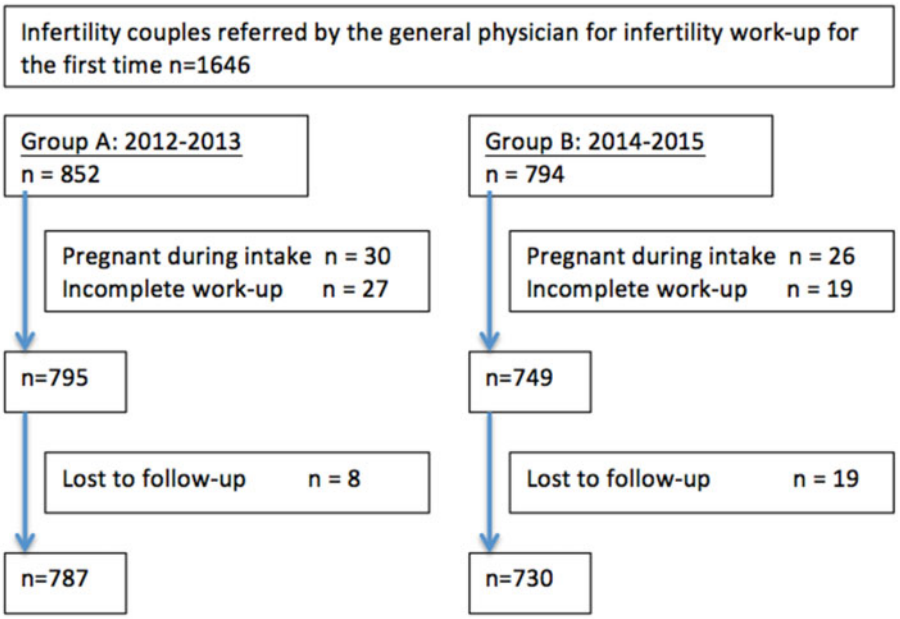

Figure 1 Flowchart of couples assigned to group A or B for infertility work-up. Group A: traditional work-up, Group B: concise work-up.

in group B) were excluded (Fig. 1). Also, couples with an incomplete work-up, most often because the semen analysis had not been performed, were excluded (n = 27 in group A and n = 19 in group B), leaving 795 and 749 couples for analysis in groups A and B, respectively.

Table II shows the baseline variables including female age, duration and type of infertility, lifestyle habits and female BMI. There are no significant differences between the two groups.

In group A, eight couples (1.0%) were lost to follow-up within 1 year and could not be contacted, while in group B this number was 19 (2.5%) (Fig. 1).

Table III shows the number of investigations performed per couple in each group. In group B, fewer ultrasound investigations and fewer laboratory tests were performed, particularly fewer progesterone measurements and fewer CAT determinations. The concise work-up often comprised only two visits.

Primary outcome

Figure 2 shows the Kaplan–Meier curves for the cumulative probability of ongoing pregnancy. It shows the difference in time to pregnancy. After 1 year of follow-up, 58.7% of the couples in group A had achieved an ongoing pregnancy, compared to 46.8% in group B. This difference is statistically significant ($P < 0.001$).

Secondary outcomes

Table IV shows the distributions of the diagnoses. The majority of couples had only one diagnosis. One hundred and eleven couples (14.0%) in group A and 81 (10.8%) couples in group B had two or more diagnoses. The combination of male infertility and ovulation disorder and the combination of cervical factor and ovulation disorder were most common.

In group A, cervical factor was diagnosed in 9.3% of the couples of which 6.3% had cervical factor as the only diagnosis. This diagnosis was not made in group B as the PCT was abolished in this work-up. As a result, more couples were diagnosed with unexplained infertility in group B. Other diagnoses were equally distributed.

The number of couples in each group who started a specific treatment and the time to start treatment are shown in Table V. In the course of time, couples could have started with more than one treatment. Expectant management was started more often in group B as more couples were diagnosed as unexplained infertility. IUI was started in equal amounts in groups A and B, respectively, 12.3% and 12.5% (not significant). When dividing IUI into IUI in natural cycle and COS-IUI, less IUI in natural cycle and more COS-IUI was started in group B.

Other treatments did not differ significantly. IVF was considered necessary in equal proportions. In group A, a significantly larger proportion of couples did not have to start fertility treatment as they achieved a natural pregnancy during fertility work-up (group A 14.7% versus group B 6.5%). Looking at the time to start treatment, OI was started sooner in group A than in group B.

Table VI shows the number of performed cycles of OI, IUI and IVF/ICSI. In group B, more cycles of COH and IVF-ICSI were performed.

Table VII shows the mode of conception. In group A, more couples achieved a treatment-independent pregnancy, compared to group B. Differences in ongoing pregnancy rates after other treatments are not significant, indicating that the difference in the total ongoing pregnancy rates, as shown in Fig. 2, is mainly caused by the higher rate of natural pregnancies.

Table II Baseline variables of new infertility couples.

	Group A n = 795	Group B n = 749	*P*-value
Female age (years), mean ± SD	31.1 ± 4.7	31.2 ± 4.8	0.78
Type of infertility (women)			
Primary (%)	65.9	68.0	0.39
Secondary (%)	33.8	32.0	0.42
Type of infertility (man)			0.48
Primary (%)	64.6	68.4	
Secondary (%)	35.3	31.6	
Duration of infertility (months)	17.8	17.2	0.17
Female smoking (%)	18.6	17.8	0.22
Male smoking (%)	26.1	27.9	0.31
Female alcohol use (%)	46.1	49.1	0.24
BMI (kg/m^2) Mean ± SD	24.1 ± 4.4	24.6 ± 4.5	0.15

Group A = traditional work-up, Group B = concise work-up.
Female and male age and duration of infertility were calculated at the day of first presentation. For comparison between the groups, the independent Student's *t*-test or χ^2-test were used. A *P*-value of <0.05 was considered as significant.

Table III The number of infertility tests during the first 12 months.

	Group A n = 795	Group B n = 749	*P*-value
Transvaginal ultrasound at first visit	795 (1)	749 (1)	1
Ultrasound for cycle monitoring	2320 (2.9)	271 (0.4)	<0.001
Postcoital test	1119 (1.4)	None	–
Hysterosalpingography	334 (0.4)	246 (0.3)	<0.001
Laparoscopy	47 (0.06)	30 (0.05)	0.09
Laboratory tests	4677 (5.9)	2969 (3.9)	<0.001

Group A = traditional work-up, Group B = concise work-up.
Noted in parenthesis: the average number of infertility tests carried out per couple.
For comparison between the groups, the χ^2-test was used. A *P*-value of <0.05 was considered as significant.

In Supplementary Table SI, we show the first treatment started in relation to the diagnostic groups.

In Supplementary Table SII, we show the mode of conception in relation to the diagnostic groups.

When we compared the COPR in group A and group B by diagnostic group, significant differences existed in male factor, unexplained infertility and cervical factor. The COPR in other diagnostic groups were comparable (data not shown). After 1 year, the COPR in couples with male factor was 50.7% in group A and 40.6% in group B ($P < 0.05$).

Figure 3 shows the differences in COPR in couples with cervical factor and unexplained infertility. Couples diagnosed with cervical factor in group A will probably be diagnosed with unexplained infertility in group B, as this diagnosis was not made in this group.

Initially, the COPR curves of couples with unexplained infertility and cervical infertility in group A were different, but they reached a similar level after 1 year of treatment.

The COPR for couples with unexplained infertility and cervical factor in group A were higher than in the couples with unexplained infertility in group B. After the traditional work-up, 67.6% of couples with the diagnosis unexplained infertility and 70.0% of couples with cervical factor achieved a pregnancy within 1 year after the first visit. After the concise work-up, couples with unexplained infertility had a COPR of 46.2% ($P < 0.001$).

In couples with unexplained infertility in group A who achieved an ongoing pregnancy, 67.9% conceived naturally, and 3.2% became pregnant after IUI. In couples with cervical infertility, 30% became pregnant naturally, whereas 30% became pregnant after IUI: in couples with unexplained infertility in group B, these figures were 51.3% and 10.9%, respectively ($P < 0.001$).

In view of the substantial difference in spontaneous pregnancy rates during work-up between the classical and the concise work-up, we looked into two specific aspects of the work-up in more detail, i.e. the number of HSGs performed and the relation between cycle monitoring and occurrence of pregnancy. In group A, an HSG was performed in 42% of the couples, compared to 33% in group B ($P < 0.001$). In group A, an HSG was also performed sooner after the first visit than in group B (Fig. 4).

At 3 and 6 months after the HSG, respectively, 25.5% and 41.0% of the couples in group A achieved an ongoing pregnancy. At the end of the follow-up period, the ongoing pregnancy rate of the couples that received an HSG in group A was 52%. In group B, these pregnancy rates were 25.8%, 31.1% and 36.6%, at 3 and 6 months after the HSG and at the end of follow-up, respectively.

Despite a similar pregnancy rate after 3 months, the natural pregnancy rate in this period is significantly higher in group A than B (63% versus 36%, respectively).

In the traditional work-up, 628 of the 795 couples underwent cycle monitoring with PCT. Within 1 month after the PCT cycle, 125 pregnancies were achieved of which 102 were natural pregnancies. This resulted in a pregnancy rate of 15.7% per PCT cycle and a natural pregnancy rate of 12.8% per PCT cycle, whereas the average pregnancy rate per cycle in that period was 6%, of which 4.5% was natural.

Discussion

In this study, we compared the outcomes for couples that underwent a traditional infertility work-up with those of couples that underwent a concise infertility work-up.

The results show significantly higher pregnancy rates within the follow-up period of 1 year and a shorter time to pregnancy in the traditional work-up compared to the concise infertility work-up. This difference cannot be attributed to differences in baseline characteristics or the proportions of couples lost to follow-up. How the components of the traditional infertility work-up precisely contribute to the difference in ongoing pregnancy rates and time to pregnancy is not clear. An important difference in diagnosis is made by the shift from cervical factor to unexplained infertility. Also, in group A, more natural pregnancies were seen, possible a result of the timed intercourse, which was needed to perform the PCT.

A different diagnostic approach apparently results in different diagnoses and accompanying treatment strategies. According to the

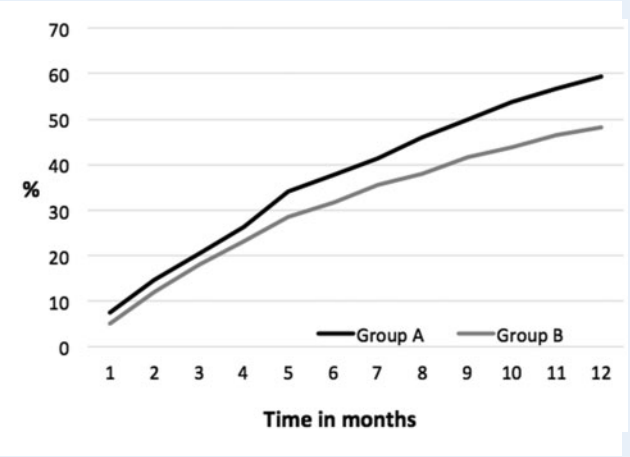

Figure 2 The Cumulative ongoing pregnancy rate in the two groups of infertile couples. The Cumulative ongoing pregnancy rate in Group A (traditional work-up, n = 795) and Group B (concise work-up, n = 745) ($P<0.001$). This is a Kaplan–Meier curve.

Table IV Distribution of diagnostic groups.

Diagnosis	Group A: n = 795 n (%)	Group B: n = 749 n (%)	*P*-value
Unexplained	187 (23.5)	241 (32.2)	$P<0.001$
Ovulation disorder*	264 (33.2)	242 (32.3)	0.707
Cervical factor	50 (6.3)	–	
Cervical factor and ovulation disorder	14 (1.8)	–	
Male infertility	144 (18.1)	133 (17.8)	0.878
Male infertility and ovulation disorder	49 (6.2)	38 (5.1)	0.350
Other combination of diagnoses	48 (6.0)	44 (6.2)	0.870
Severe tubal disease	16 (2.0)	22 (2.9)	0.252
Severe Endometriosis	15 (1.9)	15 (2.0)	0.887
Sexual problems	3 (0.4)	4 (0.5)	0.769
Uterine factor	5 (0.6)	7 (0.9)	0.494

Group A = traditional work-up, Group B = concise work-up. A couple can receive one diagnosis or a combination of diagnoses.
*According to the World Health Organization groups of ovulation disorders I, II and III.
For comparison between the groups, the χ^2-test was used. A *P*-value of <0.05 was considered as significant.

current Dutch guidelines for infertility work-up, less cycle monitoring, fewer HSGs and no PCTs are performed.

Infertility diagnoses such as cervical factor infertility, luteal insufficiency and subtle ovulation disturbances are no longer investigated and diagnosed with the concise work-up. Couples with these diagnoses will presumably be diagnosed as unexplained infertility and will be advised for expectant management, initially followed by IUI after 6 months. Such a policy might result in a different pregnancy chance or time to pregnancy. In a randomized controlled trial (RCT) among couples with cervical factor, Steures *et al.* (2006) showed that treatment with IUI improves pregnancy chances within a follow-up of 6 months. When additional treatments were given afterwards, this difference disappeared in time (Scholten *et al.*, 2013).

It is doubtful whether the prediction model of Hunault should be applied to couples screened in the concise way, as this model was constructed using data from couples who were screened in the traditional way.

As far as treatment is concerned, more expectant management was advised in group B owing to a higher proportion of unexplained infertility. However, the contribution of expectant management to the overall pregnancy rate in groups A and B were the same (Table VII), indicating a lower natural pregnancy rate per couple during expectant management in group B. In group A, more IUI in natural cycle was started and this is probably a result of diagnosing cervical factor in group A.

IVF was considered necessary in equal proportions, but more cycles have been performed in group B with a comparable pregnancy rate.

Slightly more OI was started after the traditional work-up, probably owing to a number of subtle cycle abnormalities found during the cycle monitoring despite regular menstrual cycles. Opponents of the traditional work-up believe that cumbersome tests, such as ovulation detection with ultrasound, will not add much to the correct diagnosis and could easily be omitted.

The most striking differences between groups A and B are the natural pregnancy rate and, more specifically, the natural pregnancy rate during the work-up. Although the exact reason cannot be identified in this historical cohort study, we believe that the therapeutic effects of the HSG and the proper timing of intercourse during cycle monitoring have contributed to this effect.

According to recent studies, an HSG can be postponed if the medical history does not reveal salpingitis, sexually transmitted disease or abdominal surgery (Coppus *et al.*, 2007b).

Apart from its diagnostic value, an HSG can have a therapeutic effect. A recent RCT showed that the effect of an oil contrast medium is more prominent than that of a contrast medium on watery basis (Dreyer *et al.*, 2017). Court *et al.* (2014) also showed that using lipiodol for HSGs improved pregnancy rates for patients with endometriosis and unexplained infertility. It is unclear whether the newly introduced foam ultrasound to test the patency of the tube (Emanuel *et al.*, 2012) has a similar therapeutic effect as the HSG with oil contrast. In our study, fewer HSGs were performed in the concise work-up and at a later stage. Therefore, fewer couples could benefit from the therapeutic effect, resulting in a lower pregnancy rate.

Irrespective of the result of the PCT, the proper timing of intercourse might have contributed to the higher pregnancy rate. A total of 15.7% of the women who underwent a PCT conceived in the monitored cycle, whereas the average ongoing pregnancy rate per cycle for all couples was around 6% in the first 3 months. A study by Wilcox *et al.* (1995) showed that the day of intercourse in relation to the day of ovulation significantly influences the chance to conceive. Gnoth *et al.* (2003) described in an uncontrolled cohort study the time to pregnancy in couples making optimal use of their fertility potential by timed intercourse. A Cochrane analysis on this subject revealed four relatively moderate studies, which showed a weak advantage of timing intercourse, compared to no timing (Manders *et al.*, 2015).

Table V Distribution of first treatment started and time to start treatment in days after fertility work-up.

Distribution of first treatment started				Time to start treatment after fertility work-up		
Treatments	**Group A n = 795 n (%)**	**Group B n = 749 n (%)**	***P*-value**	**Group A n = 795 mean days (95% CI)**	**Group B n = 749 mean days (95% CI)**	***P*-value**
Expectant management	199 (25.0)	255 (34.0)	0.001			
OI	279 (35.1)	235 (31.4)	0.123	53.2 (49.6-56.8)	41.9 (38.5-45.4)	0.027
IUI in natural cycle	39 (4.9)	15 (2.0)	0.002	91.7 (82.3-101.1)	71.4 (57.3-85.6)	0.258
IUI in COS cycle	59 (7.4)	79 (10.5)	0.033	105.0 (96.5-113.5)	109.3 (100.3-118.4)	0.738
IVF/ICSI	97 (12.2)	114 (15.2)	0.086	123.9 (115.3-132.6)	130.3 (123.4-137.1)	0.563
Other (medication/surgery)	5 (0.6)	2 (0.3)	0.381			
No treatment (already pregnant during infertility work-up)	*117 (14.7)*	*49 (6.5)*	*0.001*			

Group A = traditional work-up, Group B = concise work-up.
For comparison between the groups, the χ^2-test was used. A *P*-value of <0.05 was considered as significant.
OI, ovulation induction; COS, controlled ovarian stimulation.

Table VI Number of cycles of OI, IUI and IVF/ICSI.

Treatments	Group A n = 795 n	Group B n = 749 n	*P*-value
OI	773	645	0.005
IUI in natural cycle	139	48	<0.001
IUI in COS cycle	499	520	0.006
IVF/ICSI	168	191	0.038

Group A = traditional work-up, Group B = concise work-up.
For comparison between the groups, the χ^2-test was used. A *P*-value of <0.05 was considered as significant.

Table VII Mode of conception during the first 12 months.

	Group A n = 795 n (%)	Group B n = 749 n (%)	*P*-value
Natural pregnancies			
Treatment-independent pregnancy*	127 (16.0)	60 (8.1)	$P < 0.0001$
During expectant management	92 (11.4)	75 (10.1)	0.411
Ovulation induction	132 (16.6)	118 (15.8)	0.670
IUI natural cycle	12 (1.5)	5 (0.7)	0.134
IUI in COS cycle	47 (5.9)	42 (5.6)	0.800
IVF/ICSI (including TESE and cryo-ET)	52 (6.4)	47 (6.3)	0.936
Other	5 (0.6)	2 (0.3)	0.381
Total	467 (58.7)	349 (46.8)	$P < 0.0001$

Group A = traditional work-up, Group B = concise work-up.
For comparison between the groups, the χ^2-test was used.
A *P*-value of <0.05 was considered as significant.
Exp, expectant management; TESE, testicular sperm extraction; cryo-ET, cryo embryo transfer.
Other is a combination of e.g. surgery or medication other than ovulation induction.
*Treatment independent pregnancy is a natural pregnancy during fertility work up or between fertility treatment cycles.

The role of the PCT is debated heavily in the literature. In the Netherlands, most clinics have abolished the test. This was the result of an RCT by Oei *et al.* (1998) in which the infertility work-up with and without the PCT were compared. According to Oei *et al.* (1998), there was no correlation between the PCT and conception rates. More additional tests and treatments were required if a PCT was done, although a significant difference could only be reached by combining all types of tests and treatments. Unfortunately, the policy on how to act if the test was positive or negative was not stated beforehand (Hull *et al.*, 1999). In their hands, the PCT result had no predictive value for pregnancy. Their conclusion was that the PCT could be omitted. Glazener *et al.* (2000) showed that the PCT is particularly predictive if the test is performed in couples with a relatively short duration of infertility, which usually is the case in couples who are referred to the gynaecologist for the first time and not in couples who are referred to a tertiary care centre. Hessel *et al.* (2014) showed in a large cohort study that 3 years after the PCT is performed, a significant difference in overall pregnancy chance still remains between couples having a positive test and a negative test result, making the PCT a long-term predictor of pregnancy. For this reason, it is difficult to understand why the UK National Institute for Health and Care Excellence guideline states that the PCT has no predictive value on pregnancy rate. Apparently, this is only based on the study of Oei *et al.* (1998). Besides prognostic value, the PCT also has diagnostic value. It can discriminate between cervical and unexplained infertility, each having their own plan of management. But apart from the prognostic and diagnostic value of the PCT, there might be a therapeutic effect, because optimal timing of intercourse may lead to a higher natural pregnancy chance.

To predict the natural pregnancy rate there are two models described by Hunault. In one model, the PCT is included. The other model is without the PCT. The fact that a PCT was performed in the majority of couples in group A might also have influenced the prognosis calculated by the Hunault model and thus influenced the type of treatment given (Hunault *et al.*, 2004). The prognosis calculated by the

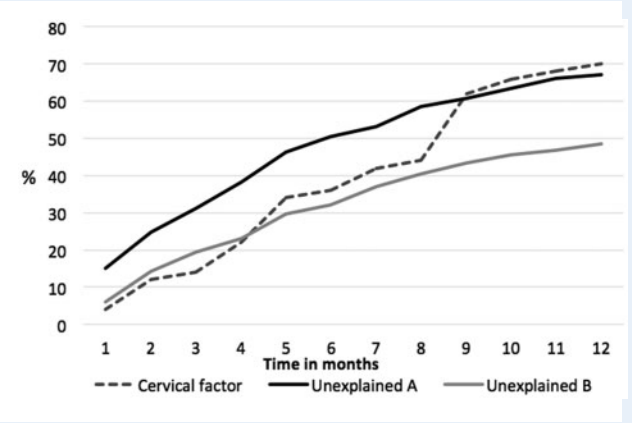

Figure 3 Pregnancy rates for selected diagnoses. Cumulative pregnancy curves (Kaplan–Meier) in couples with unexplained infertility (n = 188) and cervical factor (as the only diagnosis) (n = 50) in group A (traditional work-up) and couples with unexplained infertility in group B (concise work-up) (n = 240). In the concise work-up, the cervical factor was not investigated.

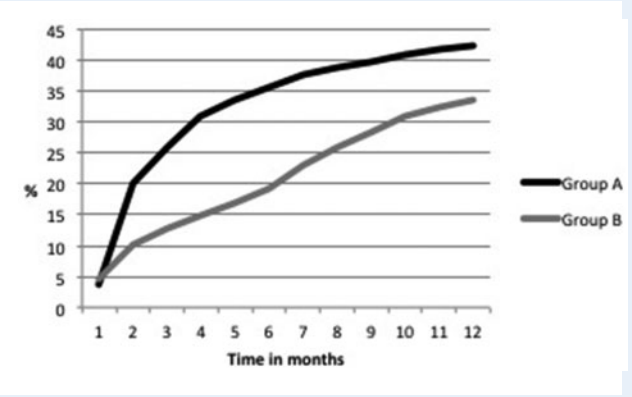

Figure 4 Cumulative percentage of patients in which hysterosalpingography was performed. Group A = traditional work-up, Group B = concise work-up.

model of Hunault which includes the PCT is usually higher if the PCT is positive and lower if the PCT is negative, in comparison with the prognosis calculated for the same couple with the Hunault model without the PCT.

The CAT is a low-cost diagnostic test to screen for tubal pathology. Female patients with a positive CAT are more likely to have tubal pathology than those with a negative result (Punnonen *et al.*, 1979) and despite a blank history, it can be positive. The addition of CAT to a diagnostic model based on patient characteristics increased the area under the receiver operating characteristic curve for the diagnosis of tubal pathology from 0.65 to 0.70, although not significantly (Coppus *et al.*, 2007a).

Study strengths

First, in this study, two relatively large groups of newly referred infertile couples with similar baseline variables were compared. Second, the study was performed in one centre with a limited number of doctors, warranting a good adherence to the pre-defined protocol. Third, all data were collected prospectively in an electronic patient record. Adherence to the protocol could be checked afterwards. Finally, the drop-out rate was extremely low because couples were contacted by email or phone if it was not known whether a pregnancy was achieved.

Limitations of the study

This study was not an RCT but a historically controlled trial. Yet, the groups were comparable and the pre-defined protocol was followed strictly, limiting the chance of bias.

The follow-up was 1 year. It is unknown if this difference in pregnancy rate disappears over time, but we do know that the time to pregnancy is shorter with the traditional work-up. Why this traditional work-up resulted in a higher pregnancy rate after 1 year cannot be explained with our data as too many factors are involved. However, the results of the study justify the need to further explore this difference in RCTs in the future. For example, in one RCT, the policy around cycle monitoring could be kept constant, while the use of HSG is randomized. In another RCT, the use of HSG could be kept constant, while the use of cycle monitoring is randomized.

This study was performed to evaluate the effect on pregnancy rate of the traditional and concise infertility work-up. We did not register data on costs of both work-ups. Yet, Table III gives some insight into this matter by showing the number of tests used: as could be expected, the concise work-up involves fewer infertility tests and would therefore be less costly.

We conclude that the introduction of the concise infertility work-up should be considered with caution as it leads to fewer pregnancies within a follow-up of 1 year. Furthermore, the time to pregnancy is longer with the concise infertility work-up.

The decision to limit the number of HSGs or delay the performance of an HSG should be reconsidered and an RCT should be performed to assess the influence of cycle monitoring on the natural pregnancy rate. A concise work-up is leaner than the traditional work-up but at the expense of a lower pregnancy rate and possibly a longer time to pregnancy.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

C.J.C.M.H. planned and designed the study, J.A.M.H., J.P.D. and J.W.S. were responsible for the data collection. J.A.M.H. conducted the main

part of the analysis, while J.A.M.H., J.P.B., J.W.S. and C.J.C.M.H. contributed to the interpretation of the analysis. J.A.M.H. and C.J.C.M.H. drafted the article, while all authors critically revised the manuscript and approved the final version.

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Conflict of interest

None declared.

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