

Use of complementary and alternative medicines associated with a 30% lower ongoing pregnancy/live birth rate during 12 months of fertility treatment

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BACKGROUND: There seems to be little discussion between patient and physician about the use of complementary and alternative medicines (CAMs), perhaps because they are not perceived to have adverse effects on fertility. We therefore compared ongoing pregnancy and live birth rate in spontaneous users and non-users of CAM during a 12-month period of assisted reproduction technique (ART) treatment. Consent was by questionnaire return.

METHOD: This was a prospective observational cohort study with a 12-month follow-up period, sampling consecutive patients attending five ART clinics in Denmark. $N = 728$ women about to have ART for the first time completed self-report assessments prior to treatment (Time 1, T1) and at 12-month follow-up (Time 2, T2). Data from treatment records were also available for $n = 590$.

RESULTS: About 30.6% ($n = 223$) of women used CAMs during the observation period. At T2 the ongoing pregnancy and live birth rate was 31.3% lower in CAM users (42.2%) compared with non-users (61.4%). Adjusted odds of pregnancy/live birth remained lower in CAM users versus non-users, odds ratio = 0.467 (95% confidence interval 0.306–0.711) after controlling for prognostic indicators (age, parity, years infertile).

CONCLUSIONS: Concurrent use of CAM during treatment with ART was associated with a 30% lower pregnancy rate that could not be explained by poor prognosis or life style factors. The mechanisms that could account for this association were discussed. Concurrent CAM use should be monitored during ART. A main limitation was that we could not ascertain which type of CAM was most associated with lower pregnancy rates.

Key words: complementary and alternative medicine / IVF / pregnancy / psychology / poor prognosis

Introduction

About 30–60% of infertility patients use complementary and alternative medicines (CAMs) (Zini *et al.*, 2004; Coulson and Jenkins, 2005; Stankiewicz *et al.*, 2007). The National Institutes of Health, National Center for Complementary and Alternative Medicines defines CAM as: ‘... a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine’ (see <http://nccam.nih.gov/health/whatisacam>). Nutritional and herbal medicines, acupuncture and reflexology are the most frequently used CAMs (Zini *et al.*, 2004; Coulson and Jenkins, 2005; Stankiewicz *et al.*, 2007). There seems to be little information exchange between patient and physician about CAM usage. About 42% of patients do not report CAM use to their fertility doctor and

less than 1% of fertility doctors enquire about its use (Stankiewicz *et al.*, 2007). The lack of exchange is due, in part, to the fact that complementary therapies are not perceived to have adverse effects on fertility (Domar, 2006). However, we do not have much information about this issue. None of the surveys on spontaneous CAM users have examined pregnancy or live birth rates with treatment (Zini *et al.*, 2004; Coulson and Jenkins, 2005; Stankiewicz *et al.*, 2007). Existing randomized controlled trials (RCTs) show evidence of both benefit and harm, e.g. meta-analyses of the acupuncture literature in IVF conclude that there are positive (Manheimer *et al.*, 2008), nil (Cheong *et al.*, 2008) or mixed (El-Toukhy *et al.*, 2008) effects of acupuncture on clinical pregnancy rates in assisted reproduction techniques (ARTs). RCTs for other CAMs (e.g. reflexology) or spontaneous patterns of use (e.g. simultaneous use of more than

one CAM) do not yet exist for assisted conception. In other health contexts spontaneous CAM users have been shown to have a poorer prognosis with conventional treatment (Sirois, 2008), which could explain their use of complementary therapies but differences in prognosis have not been adjusted in existing fertility studies of spontaneous CAM users versus non-users.

The aim of the present prospective observational cohort study was to examine associations between ongoing pregnancy and live birth rates among spontaneous CAM users and non-users for a 12-month period of treatment with ARTs. To control for differences in prognosis, only couples without prior experience of IVF/ICSI were examined, and odds ratios (ORs) for treatment success were adjusted for pre-treatment and concurrent IVF indicators of prognosis to examine the independent association between CAM use and ongoing pregnancy and live birth rates.

Materials and Methods

Participants

The sample consisted of 728 women undergoing treatment at one of the five clinics in Denmark and participating in the first (Time 1, T1) and 12 month follow-up assessment (Time 2, T2) of the Copenhagen Multi-centre Psychosocial Infertility (COMPI) research programme.

In total, 1407 questionnaires were distributed to eligible women at the first assessment. Of these, 1169 (83.1%) were returned. All these T1 women were mailed the follow-up questionnaire 12 months later and 1024 (87.6% of T1 sample) returned questionnaires (see Schmidt, 2006 for detailed analysis of distribution and response rates for T1 and T2 assessment).

Of those returning at both T1 and T2 ($n = 1024$), only 728 were retained for final analyses in the present study. Women who were excluded were those women who became parents through adoption ($n = 9$) or who did not have any treatment (1.6%, $n = 16$) between T1 and T2 or where the outcome of treatment could not be ascertained from participant responses or medical records (1.9%, $n = 20$). In order to ensure all groups had similar expectations of success prior to and during treatment, women who already had IVF/ICSI at T1 (13.2%, $n = 135$) and those who did not do a fresh IVF or ICSI cycle during the study period (10.4%, $n = 107$) were also excluded. One patient, who was an outlier on the number of T1 treatments (i.e. 17), was also excluded. Finally, eight women were missing data on demographic variables. The final sample was $N = 728$ (71.1% of women returning T1 and T2 questionnaires).

The overall COMPI study was powered to investigate various outcomes with adequate power ($\beta = 0.80$) to detect medium effects ($\omega = 0.30$) for the chi-square goodness-of-fit test reported in the present analyses (Cohen, 1992).

Materials

The COMPI questionnaire booklet contains numerous questions about stress and coping with infertility (see Schmidt 2006; Boivin and Schmidt 2005, for a detailed description of materials). Only those questions relevant to the present study are described.

T1 assessment

Demographic and medical information

These questions were used to obtain demographic (e.g. age, years married) and medical (e.g. years infertile, parity) information as well as information about the number of and types of fertility treatments women had prior to study entry.

T2 assessment (12 month follow-up)

CAM use

On the 12 month follow-up questionnaire women detailed their CAM use by indicating which of the following interventions they had used to try to become pregnant: acupuncture, reflexology, kinesiology, homeopathy, healing, herbal supplements or state other interventions. Women were assigned to the CAM user group if they reported using at least one type of CAM during treatment and to the CAM non-user group if they did not report any CAM use.

Medical treatment cycles and outcome

On the 12 month follow-up questionnaire participants indicated the types and total number of medical treatment cycles they had undergone, whether they had achieved a pregnancy and if they had, whether they were currently pregnant or had delivered. Women who had become pregnant but did not fall into either of the latter categories were considered to have had a pregnancy failure (e.g. miscarriage, ectopic pregnancy).

IVF prognosis

In 590 (81.0%) women it was possible to obtain IVF/ICSI medical records to collect cycle specific data about ovarian response (number of oocytes retrieved), fertilization and embryo transfer (number embryos created, transferred and cryopreserved) and treatment outcome (non-pregnant cycles, spontaneous miscarriage and live birth). In some medical files ($n = 112-401$, depending on variable) data about semen quality (trial sperm volume and count, sperm wash motility) and life-style factors (BMI ≥ 30 , World Health Organization, 2000), smoking status or alcohol consumption, yes/no was also available, but this information was not consistently recorded during the study period as it would be today.

Procedure

All clinics contacted ($N = 5$) agreed to distribute questionnaires as well as pre-addressed, stamped envelopes for the return of completed questionnaires to consecutive couples. T2 questionnaires were sent 12 months after delivery of T1 questionnaires. Participants who did not wish to participate returned an enclosed non-participating form. If the questionnaires or non-participating forms were not received, participants were sent a maximum of two reminders at 10-day intervals. T1 data were collected between January 2000 and August 2001 and T2 data between January 2001 and August 2002. Data about IVF cycle characteristics were collected from medical records after treatment. The study was assessed by the Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities and linkage to medical records approved by this committee. The research was also approved by the Danish Data Protection Agency.

Data analysis

Chi-square and t-test analyses were used for comparisons on demographic and reproductive history variables. Logistic regression was used to examine the association between CAM use and ongoing pregnancy and live birth rates in CAM users and non-users. Unadjusted ORs \pm 95% confidence intervals (CI) were initially presented and then adjusted for age, years infertile and number of treatment cycles prior to study entry (T1), total number of fresh IVF/ICSI cycles and mean IVF characteristics (i.e. mean number of oocytes retrieved, embryos created and embryos transferred) per fresh cycle during the 12-month study period. The significance level was $P < 0.05$.

Table I Demographic and reproductive history at study entry according to CAM user group

Baseline variable (T1)	CAM non-user (n = 505)	CAM user (n = 223)	t or χ^2 value
<i>Demographic</i>			
Female age: M (SD)	31.39 (3.55)	31.62 (3.71)	0.81
Years together: M (SD)	7.85 (3.75)	7.31 (3.54)	0.3
n (%) Ever delivered	34 (6.7)	14 (6.3)	0.05
<i>Social position n (%)</i>			
Outside workforce	14 (2.8)	10 (4.5)	1.95
Manual/unskilled	79 (15.6)	31 (13.9)	
Skilled/white collar	375 (74.3)	168 (75.3)	
Professional executive	37 (7.3)	14 (6.3)	
<i>Reproductive history</i>			
Years trying to conceive	4.32 (2.29)	3.99 (2.08)	1.84
Mean (SD) Nr of treatments (at T1)	2.14 (2.63)	2.80 (3.05)	2.96 ^a
n (%) Insemination	234 (46.3)	119 (53.4)	3.06
n (%) Surgery	40 (7.9)	23 (10.3)	1.21
n (%) No previous treatment	225 (44.6)	83 (37.2)	3.40

Note. Nr, number; CAM, complementary and alternative medicine; M, mean.
^a $P < 0.01$.

Table II Medical and CAM interventions in 12-month observational study period

Variable	CAM non-user (n = 505)	CAM user (n = 223)	t or χ^2 value
<i>Medical intervention</i>			
Mean (SD) Nr of treatments (T1–T2)	1.95 (1.24)	2.49 (1.31)	5.24 ^c
n (%) > 3 IVF cycles	47 (9.3)	38 (17.0)	8.97 ^b
<i>CAM intervention</i>			
Type CAM used ^a n (%)			
Reflexology		121 (54.3)	
Herbal and aroma		112 (50.2)	
Acupuncture		40 (17.9)	
Kinesiology		14 (6.3)	
Homeopathy		13 (5.8)	
Healing		14 (6.3)	
Other		16 (7.2)	

Note. T2, 12 month follow-up assessment.

^aPercentages do not add to 100 because multiple CAM use possible.

^b $P < 0.01$.

^c $P < 0.001$.

Results

Socio-demographic and reproductive characteristics at T1

Table I shows background characteristics of CAM users ($n = 223$) and non-users ($n = 505$) and shows that the two groups were similar on demographic and reproductive variables; however, CAM users had undergone significantly more fertility treatments (mean = 2.80) than non-users (mean = 2.14) at the start of the study period (T1).

Medical treatment and CAM use at T2

Table II shows medical treatment and CAM use during 12-month study period. CAM users reported undergoing significantly more treatment cycles and a higher percentage had more than three IVF/ICSI cycles than non-users. The average number of different CAMs used in the 12-month period of treatment was 1.47 (SD = 0.69), with 61% of CAM users using only one type, 31.8% two and 7.1% three or more types of CAMs. The most frequently used CAM interventions were reflexology, herbal supplements and acupuncture.

Association between CAM use and pregnancy at 12-month follow-up

In total 55.5% of women were either currently pregnant ($n = 183$) or had delivered ($n = 221$) at T2. About 146 of the ongoing pregnancies (79.8%) were beyond the first trimester. The pregnancy rate was 31.3% lower in CAM users (42.2%, $n = 94$) compared to non-users (61.4%, $n = 310$). The odds of ongoing pregnancy/live birth in CAM users was 0.73 whereas it was 1.59 in non-users with an unadjusted OR at 12-month follow-up of 0.414 (95% CI 0.290–591, $\chi^2(1) = 23.59$, $P < 0.001$).

We examined IVF treatment data in the sub-sample ($n = 590$) for whom we could access medical records. Demographic and reproductive variables for this sub-sample were as for the overall sample (data not shown). There were significant differences in terms of IVF cycle data for the 12-month treatment period (see Table III). CAM users underwent significantly more fresh IVF cycles, required marginally more I.U. units of gonadotrophins for optimal stimulation and produced significantly more embryos per fresh IVF/ICSI cycle than did non-users but they had a significantly lower pregnancy rate (44.6%, $n = 82$) than did non-users (65.9%, $n = 267$) ($\chi^2 = 23.91$, $P = 0.001$). The OR for CAM use on ongoing pregnancy/live birth rate adjusted for IVF cycle data was very similar to the unadjusted odds, and was 0.467 (95% CI 0.306–0.711, Wald(1) = 12.58, $P < 0.001$; $\chi^2(8) = 178.49$, $P < 0.001$).

Although we did not have complete data on sperm quality and life style factors, what was available (see Table III) showed that partners of CAM users and non-users were similar with respect to semen volume and sperm count for the trial sperm analysis and for the percentage motile sperm in the IVF/ICSI sperm sample wash. Furthermore, the

Table III Average IVF/ICSI cycle characteristics in sub-sample of CAM users and non-users with IVF/ICSI medical records ($n = 590$) for 12-month observational study period

Variable	CAM non-user ($n = 406$)	CAM user ($n = 184$)	t or χ^2 value
Average cycle characteristics	Mean (SD)	Mean (SD)	
Nr fresh IVF/ICSI cycles	1.84 (1.00)	2.20 (1.02)	4.08 ^c
Average total I.U. of stimulation ^a	1915.35 (664.31)	2014.48 (691.28)	1.65
Nr oocytes retrieved	9.51 (4.47)	10.01 (4.78)	1.20
Nr embryos produced	5.81 (3.53)	6.54 (3.80)	2.28 ^b
Nr embryos transferred	1.82 (.38)	1.81 (.37)	0.417
Partner semen characteristics ^a			
Sperm concentration ($\times 10^6$ /ml)	64.60 (106.18)	68.91 (95.21)	0.45
% Motile (after wash)	74.45 (31.98)	73.32 (33.03)	0.311

Note. Sample size (n) for CAM non-users: I.U. stimulation ($n = 401$); sperm concentration ($n = 363$); motility ($n = 220$). For CAM user: I.U. stimulation ($n = 182$); sperm concentration ($n = 164$); motility ($n = 112$).

^aSample size differed according to variable.

^b $P < 0.05$.

^c $P < 0.001$.

CAM users and non-users did not differ significantly on percentage of women who, at T1, had a BMI greater than 30 (12.2 and 12.7%, respectively, $\chi^2(1) = 0.02$, $P = 0.882$); smoked (33.3 and 36.3%, respectively, $\chi^2(1) = 0.34$, $P = 0.556$) or consumed alcohol (61.5 and 64.2% $\chi^2(1) = 0.10$, $P = 0.749$).

Discussion

The principal finding of this large prospective observational cohort study was that the concurrent use of CAM in ART was associated with a 30% lower ongoing pregnancy/live birth rate over a 12-month fertility treatment period despite the fact that CAM users underwent more IVF/ICSI cycles and had on average more embryos than did non-users. From our design we cannot ascertain the direction of causality between CAM use and ongoing pregnancy/live birth rate because these were measured concurrently at the 12-month follow-up. However, the odds of pregnancy remained poorer for CAM users even after controlling for pretreatment failure and concurrent IVF prognostic markers indicating that prognosis could not entirely account for the association observed. Data from IVF/ICSI medical records suggest that CAM use may interfere with the process of implantation and early pregnancy.

Our prospective results are important because they are the first to demonstrate in a large ($n = 728$) representative cohort of people undergoing fertility treatment that CAM use may have adverse effects on the chances of pregnancy and that these forms of intervention may not be as benign as has been previously proposed (Domar, 2006). We applied stringent inclusion criteria to ensure the sample was as homogenous as possible with respect to previous and concurrent fertility treatment experience and we ascertained IVF prognosis and outcome from medical records in about 80% of the sample. Although we did not have complete data, we were also able to show that CAM users and non-users did not differ on key life style characteristics that could have affected the probability of pregnancy. Finally, the pattern of CAM use in this sample was consistent with epidemiological and other surveys indicating that our users were

representative of the cohort of people likely to seek out these types of interventions. Specifically, about 30% of the sample used CAM, almost 40% of people used more than one intervention (Zini *et al.*, 2004; Coulson and Jenkins, 2005; Hanssen *et al.*, 2005; Stankiewicz *et al.*, 2007) and the most common intervention in this Danish population was reflexology, consistent with other reports in this population (Hanssen *et al.*, 2005). Together, these strengths ensure that the associations observed in the present study are reliable and can be generalized to patient populations in other fertility clinics.

The main limitation of the study was that the direction of causality between treatment failure and CAM use could not be determined. A poor prognosis may drive people to use complementary and alternative therapies as has been found in other health contexts (Sirois, 2008). In the present study CAM users started IVF/ICSI treatment with more conventional treatment experience, mainly insemination with husband sperm, and greater failure with these interventions may have encouraged women to seek alternative interventions to improve their chances of success during IVF (Coulson and Jenkins, 2005). According to this perspective, failure precedes rather than follows the use of CAM. Although this remains a possible explanation for future research to explore, further analyses of our own data showed that even if we analysed only data from women who had never had fertility treatment prior to inclusion in COMPI ($n = 258$), the pregnancy rate in CAM users (38%) was still significantly poorer than in non-users (56.1%) ($\chi^2(1) = 6.76$, $P < 0.009$). Thus regardless of whether one includes or excludes people with treatment failure experience (i.e. those with poorer expectations for success) CAM users remained at a disadvantage. Perceived poorer prognosis could in turn cause people more stress, and stress itself could be the causal agent as it is associated with reduced pregnancy rates (Boivin and Schmidt, 2005). Pretreatment stress data on this cohort will be presented in another paper but the OR adjusted for stress was not markedly different from the data presented.

A second limitation was that we could not determine which type of CAM was most associated with treatment failure because c.40% of women used more than one intervention, and single intervention

users were too few to make conclusive statements given they also had to be allocated to their pregnancy group, even in this large sample (i.e. >700 women). It could be argued that the concomitant use of other interventions (whether alternative or medical) compromised the positive effects of individual CAM therapies since some RCTs in the IVF context have shown improved pregnancy rates in acupuncture-only groups compared with controls (Paulus *et al.*, 2002; Dieterle *et al.*, 2006). Further research needs to examine this issue and future RCTs could better reflect spontaneous patterns of CAM use by incorporating mixed CAM user groups in their paradigms.

We feel the findings of the present study are relevant despite the inability to isolate the effects of specific CAMs. Publication of contentious associations in reproductive health often leads to important advances and policy changes and we feel our results have the potential to do the same. A prominent example of this is the publication of the association between fertility drugs and ovarian cancer (Whittemore *et al.*, 1992). This paper is now a citation classic (>600 citations) and its publication spawned hundreds of studies investigating the association and the safety of fertility drugs, even though it was an observational investigation like ours that lacked precise details of the types or dosage of drugs that might be implicated in the association or the mechanisms that could account for it. Our findings are important because they show that CAM use 'can' be associated with poorer outcomes and if this is the case then one must identify why this is so. The results should be seen as a cue to stimulate more research into CAM use as it manifests in the population (e.g. specific interventions, multiple CAM use, particular combinations, single doses) and the factors that could explain the association we report.

The mechanism that could account for lower pregnancy rates in CAM users is not clear. One possibility is that a fragmented intervention profile reflects poor commitment to any one intervention, and consequently lower compliance during treatment, as has been shown in other conditions (e.g. cancer McGinnis, 1991). In ART this might mean, for example, poorer adherence to the strict stimulation schedule, which might ultimately compromise the quality of stimulation (Sauer *et al.*, 1994).

If an underlying biological mechanism does account for the association reported then effects at the implantation and early stages of pregnancy seem more likely to be responsible than effects on stimulation. The hormonal response profile of CAM users (see Table III) could be suggestive of a poor response to stimulation in that women in this group required marginally more stimulation. However, Gorgy *et al.* (1997) define a 'poor response' in young women (<37 years) who proceed to oocyte retrieval as a case requiring more than 600 I.U. of stimulation per oocyte retrieved, a ratio which was much higher than that observed in our CAM users (i.e. 201 I.U./oocyte). Furthermore in younger woman a poor response to stimulation is not associated with a lower pregnancy/live birth rate provided oocytes and embryos are obtained, as was the case for CAM-users in the present study (Gorgy *et al.*, 1997). In fact CAM users produced significantly more embryos than did non-users, so it is unlikely that the observed difference in stimulation reflected ovaries that produced poorer quality oocytes that were less likely to be fertilized (Wang *et al.*, 2006). In combination these factors would suggest that negative effects would have occurred later on in the reproductive process (i.e. implantation).

Failure during the implantation period could be due to disrupted embryonic development or impoverished uterine receptivity or a combination of both (Macklon *et al.*, 2002) and such effects have been reported for alternative medicines. Phytoestrogens (e.g. equol, daidzein) in herbal supplements have deleterious estrogenic effects on implantation but such effects vary according to plasma concentrations (Rosselli *et al.*, 2000; Woclawek-Potocka *et al.*, 2005). Acupuncture applied 2 days after embryo transfer (points Sp6 and LI4) was associated with a double chance of early pregnancy loss compared with controls or a single acupuncture session (Westergaard *et al.*, 2006) and Pinborg *et al.* (2008) have recently suggested that such negative effects may occur due to effects on uterine contractility. Sympathetic activation may also be a mechanism for negative uterine effects in reflexology since a recent study showed that after massage participants were psychologically relaxed but physiologically activated (Hatayama *et al.*, 2008). In a recent report there was an increased risk for musculoskeletal malformations in babies of CAM users compared with spontaneously conceiving fertile couples [adjusted hazards ratio: 1.39 (95% CI = 0.58–3.35), Zhu *et al.*, 2006; Zhu, personal communication, August, 16, 2007] suggesting that CAM effects may persist late into pregnancy. More research is needed to identify the mechanisms involved in the effects of different CAMs on reproductive outcome.

Our prospective results are important because they are the first to demonstrate in a large ($n = 728$) representative observational cohort of people undergoing fertility treatment that concurrent CAM use may have adverse effects on the chances of pregnancy. Future research needs to focus on the effects of particular CAM interventions used either exclusively or in combination and on the underlying behavioural or biological mechanisms that could account for the association between the use of CAMs and pregnancy failure in IVF/ICSI cycles. In the meantime, our results indicate the need for better exchange between patients and medical staff about concurrent CAM use during fertility treatment.

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