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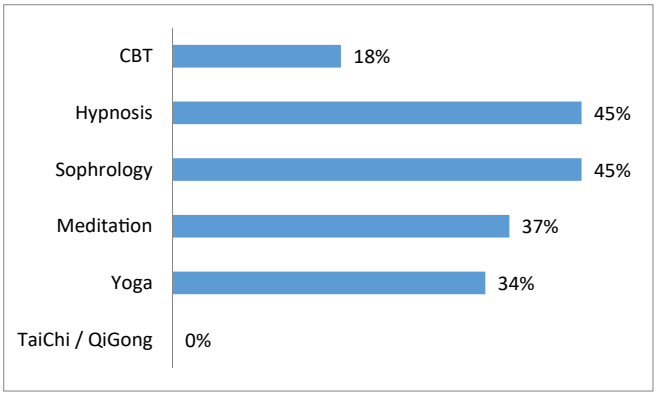

Figure 4: Bar chart showing the percentage use of different types of MBI in our population (n=38), CBT: Cognitive Behavioral Therapy.

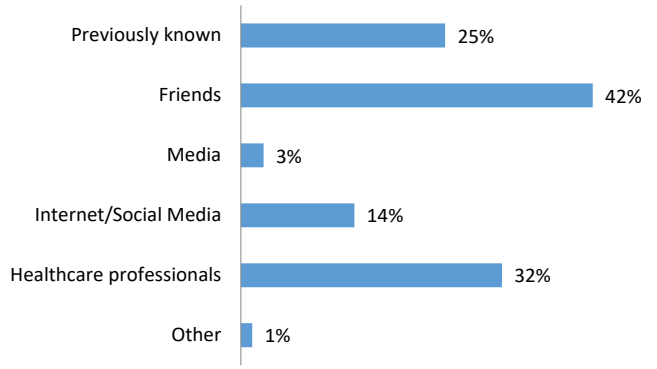

Figure 5: Bar chart showing the various means of CP information used by our patients.

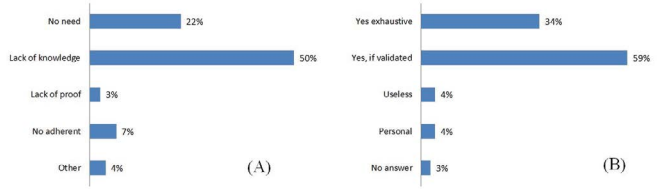

Figure 6: (A) Bar chart showing the main reasons why a part of our population doesn't use CP (n=76). **(B)** Bar chart showing the desire of patients in our population to be informed about CP, whether or not they use them (n=150).

from the physicians at the fertility unit. Most frequently, they want the information to be based on scientific proof, but a large part wants exhaustive information

Discussion

Complementary and alternative medicine is defined by the World Health Organization (WHO) as a "broad set of health care practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant health care system" (9). The WHO counts more than 400 complementary and alternatives medicines, including methods based on natural products (phytotherapy, aromatherapy), techniques based on manipulation (osteopathy, chiropractic…), mind-body interventions (hypnotherapy, meditation, sophrology…), or complete systems based on specific theories (Traditional Chinese Medicine, homeopathy…). These practices are quite heterogeneous, and it is impossible to discuss them as a single homogeneous group. The use of these complementary practices is widespread in certain medical fields, most notably oncology. However, in the field of infertility, and more specifically during ART, their use is yet to be fully analyzed, on a French national or international level.

Infertility can be caused by chronic pathologies with mainly biologic determinants, but also environmental and psychosomatic linked to an important emotional charge in patients. CP offer a different form of accompaniment for these patients during their infertility journey, by offering support, helping them relax, and making them feel capable of maximizing their chances of success (10). Our study has shown that a considerable number of women (48.7%) (Figure 1) have recourse to CP, a finding concordant with the literature. Indeed, the HEFA 2018 study had shown a 50% rate of recourse to CP among women treated for infertility (11). Likewise, an Australian study reported a 66% rate (12) while an American study of 428 couples reported a 29% rate (13). The main purposes, behind the recourse to CP, were to improve the pregnancy rates, and reduce the stress and fatigue associated with infertility treatments (Figure 2). It is worth noting that the utilization rate was higher among women undergoing IVF-ICSI treatment, which is widely known to be a long and arduous process (Figure 3). The most commonly employed CP were the ones based on body manipulation, mind-body interventions, and TCM (especially acupuncture) (Figure 4).

Role of Traditional Chinese Medicine (TCM)

TCM is a complete medical system that can have a positive impact on a woman's journey through ART, not only by its effects on the gonadotropic axis function (8), but also by its potential effect on the biopsychosocial components associated with the diagnosis of infertility and its treatment. However, and to the best of our knowledge, there are no studies in the literature that looked at its global efficiency. Most studies have been centered around acupuncture or MBI, most probably due to methodological limitations, as well as the difficulties of finding licensed and experienced practitioners of TCM in Western countries.

Acupuncture

Acupuncture is commonly used in the field of infertility, with the HEFA survey reporting a 26% utilization rate among women undergoing ART (11). Acupuncture seems to improve the well-being of patients by decreasing anxiety, and by reducing the pain felt during invasive procedures such as oocyte retrieval or embryo transfer (14). The first randomized

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controlled trials (RCT) on acupuncture in women undergoing infertility treatments are relatively recent. In 2002, a study including 160 women who did or did not undergo an acupuncture session, 25 minutes before and after the embryo transfer, showed a significant increase in pregnancy rates in the acupuncture group (42.5% vs 26.3%, P < 0.03) (15). Two other studies (16,17) also showed a significant improvement in pregnancy rates in IVF patients undergoing acupuncture on the day of embryo transfer. A 2006 study included 225 patients in two groups: the first group received acupuncture according to the TCM principles in the luteal phase, after the transfer, and the second group received a placebo (placebo points) (18). The pregnancy and implantation rates were significantly higher in the acupuncture group (29.4% vs 12.6% and 8.2% vs 3.2%, p<0.01, respectively). A recent study showed that, when compared with estrogen treatment, acupuncture and TCM significantly improved the endometrial thickness and the pregnancy rates in women with thin endometrium (19).

On the other hand, some studies reported contradictory outcomes and failed to show any positive impact of acupuncture. In a series of 150 patients, Domar et al. failed to replicate the results reported in the first 2002 study (20). Similarly, Smith et al. did not show any improvement in pregnancy rates in patients receiving a conventional acupuncture protocol when compared with patients receiving placebo (21). In a multicentric RCT in 2017, Fan et al. did not find any improvement in fertility in women with polycystic ovarian syndrome (PCOS) (22). Likewise, Madaschi et al. did not find any difference in the outcomes of 208 women undergoing IVF/ICSI between the group who had acupuncture and a control group (23). Another 2013 RCT which included 62 women with PCOS undergoing IVF/ICSI showed a significant improvement of embryo quality following acupuncture, but there were no differences in the pregnancy rates after IVF compared with the control group (24). Several systematic reviews and meta-analyses have attempted to synthesize the available data. While some failed to show any benefit (25,26), most of the recent ones, have reported a positive an impact of acupuncture on fertility and IVF outcomes (27–30). In all, and based on the current available evidence, it is difficult to conclude on the impact of acupuncture on the pregnancy rates in ART. The discordance in the results is probably the consequence of the heterogeneity across the studies, most notably in the populations included, the indications, the experience of the practitioners, the choice of acupuncture points, and the whole course of treatment administered. Larger and better defined RCT, using more rigorous methodologies, are needed to confirm any potential positive impact of acupuncture.

Mind-Body interventions (MBI)

Mind-body interventions are based on the interconnexion between the physical (bodily functions), psychosocial (emotions), and spiritual (meaning of life) well-being of a person, all of which play an important role when facing stressful life events. ART are associated with several stressful factors that can significantly affect couples with infertility. This is why the "European Society of Human Reproduction and Embryology" (ESHRE) Psychology and Counselling Guideline Development" recommends psychosocial support as complementary therapy to infertility treatments (31). Besides the discomfort it generates, stress is widely known to have deleterious effects on global health in general and on fertility in particular. Indeed, exposure to stress leads to the activation of certain areas of the brain, such as the prefrontal cortex, hippocampus, and amygdala. That signal is integrated by the hypothalamus which will in turn, via the central nervous system, stimulate the adrenal cortex to secrete adrenaline and noradrenaline and generate an adaptive response that impacts several systems in the body (cardiovascular, respiratory…). In parallel, the hypothalamus releases the corticotropin release hormone which triggers the production of adrenocorticotropin hormone (ACTH) by the pituitary, which will stimulate the production of corticosteroids. Corticosteroids can negatively impact the reproductive tract via several pathways: an interaction with the GnRH producing neurons, which can affect the gonadotropic axis and the production of FSH and LH, and an alteration of ovarian steroidogenesis and the development of the uterine mucosa (32). The clinical studies on the impact of stress on reproduction have produced conflicting results. Some have failed to confirm a negative impact of stress on ART (33,34), while others have clearly demonstrated that negative effect (3,35). In a recent study, Haimovici et al. (36) found that an increase in the levels of stress-specific cytokines in the blood and the follicular fluid on the day of the oocyte retrieval was associated with decreased fertilization, implantation, pregnancy, and live birth rates (36). MBI could modify the activity of the cerebral areas most impacted by stress (Prefrontal cortex, amygdala, hippocampus and hypothalamus). The use of the techniques has been linked to mood improvement and decrease of stress biomarkers. Furthermore, some of the MBI (Mindfulness, Yoga, Tai Chi and Qi Gong) could be able to affect gene expression, leading to an inhibition of the Kappa B pathway which is activated in case of chronic stress (37), as well as certain epigenetic mechanisms (38). Globally, MBI seem to be efficient in reducing stress during ART (32). Several meta-analyses have reported on the significant impact of MBI in reducing the psychological distress of patients undergoing ART, as well as improving the ART outcomes (39,40). A 2016 Cochrane review concluded that the effects of these interventions on pregnancy rates were uncertain due to the very low quality of the evidence, and that there was significant heterogeneity in the studies with regards to the patient population, the techniques and the protocols used

(41). Other meta-analyses reported that these techniques had a significantly positive impact on the psychological health of patients without any improvement in the pregnancy and live births rates (42,43).

Globally, if the positive impact of MBI on ART outcomes (pregnancy and live birth rates) is yet to be definitely established, the literature is unanimous when it comes to their efficiency in improving the well-being of patients undergoing ART, and more specifically in significantly reducing the stress and anxiety levels. The MBI used in the aforementioned studies were quite heterogenous: cognitive behavioral therapy, hypnosis, relaxation, respiration… (32,42,44). Only two studies, both by the same team, used a MBI approach based on TCM that included Tai-chi exercises, meditation and respiration (45). Both studies showed an improvement of the anxiety and well-being score of patients during ART, but did not show any improvement in pregnancy rates (46,47). In our study, despite anxiety and fatigue being a major source of concern for patients, only 38 out of 150 resorted to MBI, and none used Tai-chi or Qi Gong (Figure 5). Tai Chi and Qi Gong combine slow movements and respiration exercises with relaxation and meditation, and are known to have a beneficial impact on the quality of life by reducing stress and anxiety levels, as well as relaxation and fatigue (48,49). These techniques could therefore play an important part in improving the well-being of women undergoing ART, and potentially improve the chances of success.

Knowledge and information about Complementary Practices (CP)

In the current study, most women who resorted to CP were introduced to them by people from their personal network and by patients already using them. In 32% of cases, a healthcare professional was behind the introduction. It is worth noting that in a 2013 USA study, almost 90% of physicians interviewed reported being curious about complementary and alternative medicine, and 75% were interested in adding and integrating these practices to conventional medicine, as well as informing their patients about the methods available (14). The lack of use of CP can be explained by the lack of knowledge and information. Indeed, among women who did not resort to CP, 50% were unaware of them, while a smaller percentage did not believe they needed them, and very few were doubtful and suspicious of their efficacy. Out of the 150 women who answered whether or not they would like the physicians involved in ART to inform them about CP, only 12 thought that it was useless or too personal. The vast majority wanted their physicians to share global information about all these practices, and back it up with scientific proof.

For the physicians involved, the main problem is the large diversity of these methods, and the difficulty of knowing the benefits of each and every one. And even if for many of these techniques, there are several studies available in the literature, they are quite heterogenous and have lots of biases. However, newer and better studies are emerging and offering a better analysis of these practices. In particular, acupuncture and MBI seem to have a beneficial impact, at least in terms of quality of life and well-being of patients undergoing ART. The effect on pregnancy and live births rates remains under investigation.

Conclusion

Our study has shown that women undergoing ART are interested in knowing about and resorting to complementary and alternative practices, with the aim of improving their chances of pregnancy as well as helping them deal with the stress and fatigue associated with ART. Among the different CP available, the ones based on body manipulation, acupuncture and mind-body interventions are the most coveted. Traditional Chinese Medicine includes all these techniques, and even though the jury is still out on its efficiency in improving pregnancy and live birth rates, information about its application and its benefits should be made available to all couples undergoing ART.

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