

An Integrative Approach to Diagnosing and Treating Unexplained Infertility

Abstract

Up to 30 per cent of couples trying to conceive worldwide are thought to have unexplained infertility, yet the diagnosis, treatment and management of these cases are often ill-defined, inconsistent and erroneous. A true diagnosis of unexplained infertility, which is considered a diagnosis of exclusion, requires a skillful clinician and appropriate diagnostic testing. Lack of consistent and standardised diagnostic protocols for couples trying to conceive frequently leads to non-identification of explainable causes and therefore couples do not receive proper treatment and lose valuable time. Finding no identifiable cause for infertility does not mean that one does not exist. Careful investigation of the male and female must be undertaken in order to properly diagnose unexplained infertility. Even after an exhaustive exploration, typical Western interventions are limited, costly and frequently ineffective. Integrating traditional Chinese medicine (TCM) with orthodox medical diagnostics and procedures, or using TCM alone often offers the most successful approach to achieving a healthy pregnancy and birth in cases of unexplained infertility. This article explores unexplained infertility from an integrative perspective, and provides a diagnostic approach and treatment suggestions for TCM practitioners who wish to help patients and couples who have received this diagnosis.

By: Katherine
Alexander
Anderson

Keywords:
Unexplained
infertility,
infertility, male
factor, Chinese
medicine, TCM,
acupuncture,
semen analysis,
oxidative
stress, DNA
fragmentation.

I. Introduction/Background

Up to 30 per cent of couples trying to conceive worldwide are thought to have unexplained infertility (Sadeghi, 2015). In the U.S., one third of all infertility is due to female factors, another third is due to male factors and the remaining third is due to some combination of the two (ASRM Reproductive Facts, 2017). At least 10 per cent of all female infertility problems (Speroff et al., 2010) and 40 to 45 per cent of male factor infertility is diagnosed as unexplained or idiopathic (Schattman, 2016). However, the incidence of unexplained infertility is highly dependent on reporting criteria, the clinician's skill and their understanding of what 'unexplained' truly means.

The current consensus is that unexplained infertility occurs in 'couples in whom routine semen analysis is within normal reference values, and a definitive female infertility factor has not been identified' (Schattman, 2016). This means there must be both unexplained male infertility and unexplained female infertility present. Three factors must be therefore be ruled normal before a couple can be considered to have a diagnosis of unexplained infertility: 1) the sperm analysis has been ruled 'normal' and tested at least twice, 2) ovulation is occurring regularly, and 3) the fallopian tubes are open.

It is important to point out is that although the terms 'unexplained' and 'idiopathic' are often used interchangeably, this is not technically accurate.

'Unexplained' refers to a situation in which testing has not revealed a known disease, whereas 'idiopathic' acknowledges a known pathology but with unknown aetiology. Thus although 'idiopathic' is similar in meaning to 'unexplained', in clinical practice when a medical provider refers to 'idiopathic infertility' this means they have already identified a problem - therefore this is technically not unexplained at all. For example, if we know that the shape of the sperm (morphology) or its ability to swim about (motility) do not fall within normal limits, then we have identified a potential cause of the infertility (although we still have not identified the cause of this cause). This situation should technically be termed 'idiopathic' rather than unexplained as male factor infertility is the known cause. Also, in TCM terms, poor motility and/or morphology would be viewed as a symptom, and therefore the 'branch' of the disease, and identifying this does not mean we have identified the root of the problem; we have identified an irregular parameter but do not know how it came to be. Men with unexplained infertility have normal semen parameters and those with abnormal semen analyses are often idiopathic (Schattman, 2016). Low anti-Müllerian hormone (AMH) in a young female or ovulatory issues are also often considered idiopathic rather than unexplained. Low levels of this hormone (less than 1.0 ng/ml) are assumed to show a dwindling egg supply and decreased fertility. When this occurs in

a female less than 35 years old, it is considered idiopathic. That is, we know that it is not normal and is likely to be contributing to infertility, but we do not know the cause of this cause.

Although the terms ‘unexplained’ and ‘idiopathic’ are often used interchangeably, this is not technically accurate.

The question then becomes how do we best treat cases of unexplained infertility, given that we may not be able to clearly identify what is happening? It is estimated that between 44 and 73 per cent of infertile couples will seek consultation for a fertility evaluation (Schattman, 2016). Patients are searching for answers and the ‘expectant management’ (i.e. do nothing and wait and see) approach may not be prudent. Telling a patient to ‘just keep trying and see what happens’ tends to leave them feeling isolated and disconnected as well as wasting valuable time in cases where there is something wrong that could be addressed. As educated TCM providers, we can forensically search out causes, refer to Western medical providers when appropriate, while offering natural solutions that may garner higher pregnancy rates than modern allopathic approaches.

II. Unexplained infertility and the male

Historically, the woman is implicated when infertility arises: ‘It must be her eggs, or her age or her tubes or her menstrual cycles, or something!’ Further, in TCM school we are typically taught that treating infertility entails regulating the menstrual cycle. Although this may be an important part of treatment, it is only one part and oversimplifies the situation. So why does the woman often get subjected to expensive and invasive testing and treatment before a sperm analysis is ordered, given that male factor infertility either alone or in combination with female fertility issues is a problem up to two-thirds of the time? When a female patient presents in clinic for infertility care I immediately involve the male as I consider him integral to successful treatment. Though prevalence is difficult to discern, it is estimated that male factor infertility is as high as 40 to 50 per cent of all infertility cases worldwide (Kumar & Singh, 2015) compared to the U.S. figures of 33 per cent; 37 to 58 per cent of the time infertility is considered of unknown origin (Hamada & Esteves, 2011). Dr. Paul Turek, reproductive urologist has suggested, ‘Let’s let men lead the infertility dance’ (Turek, 2018). Let us not spend extensive time evaluating and treating the female only to find out - thousands of dollars and months to years later - that male factor was a contributing, or even primary, factor. The tricky part, however, is in the evaluation. Contrary to popular belief, a semen analysis is not

actually a fertility test. A Netherlands study assessed the semen analysis criteria according to World Health Organisation (WHO) classifications and determined that whether men had normal or abnormal sperm did not impact on 1-year pregnancy rates (van der Steeg et al., 2011). Furthermore, ‘40% of infertile men have normal semen analysis parameters’ (Schattman, 2016). Men with a ‘normal’ sperm analysis therefore can still be infertile and men with an ‘abnormal’ sperm analysis can be fertile. This is one of the hardest things to explain to a couple struggling with infertility. I once had a patient tell me that the reproductive endocrinologist they were working with gave her husband a huge grin and a high-five, telling him that his sperm analysis was ‘awesome’, so not to worry. Unfortunately, although this may have made the husband feel proud, it made the wife feel horrible, and ultimately was not necessarily an accurate prognosis of their fertility as a couple.

Why then is the sperm analysis the first test done when a man presents with suspected infertility? Because although it is not a conclusive fertility test, the sperm analysis does provide value when assessed appropriately. In fact, semen quality is considered valuable enough that the National Institutes of Health (NIH) are currently researching how fertility biomarkers act as indicators of overall health in infertility (<https://grants.nih.gov/grants/guide/pa-files/PA-17-091.html>). Misleading information about male fertility is however perpetuated by WHO’s current reference values for semen analysis (see Table 1). Published in 2010, this lowered the previous reference ranges for some sperm characteristics (count, motility, morphology and volume). The study that informed these ranges was based on assessment of sperm of fertile men (who had previously fathered children). However, the more clinically relevant population to assess is *infertile* men (Turek, 2018). Therefore when comparing a patient’s sperm sample to that of the fertile men in the 2010 WHO study, you may be overzealous in your conclusions that nothing is wrong with the man’s fertility.

WHO Semen Characteristics	1999	2010
Volume (mL)	≥ 2	1.5
Sperm count (10 ⁶ /mL)	≥ 20	15
Total sperm count 10 ⁶	≥ 40	39
Total motility (% motile)	≥ 50	40
Progressive motility (%)	≥ 25	32
Morphology (% normal forms)	(14)*	4

* Strict Criteria:

> 14 % normal: (normal; fertilizing capacity excellent)

4-14 % normal: (abnormal; possibly decreased or impaired fertilizing capacity)

0-3% normal: (abnormal; severe impairment or probable inability to fertilize)

Table 1: WHO semen reference ranges in 1999 and 2010 (from Schattman, 2016).

Genetic causes

One major problem with orthodox sperm analysis is that it does not test for some of the most common reasons for unexplained male infertility, such as genetic/epigenetic and immunological causes. A common clinical situation is seen in cases when a female patient has had two miscarriages (rather than the required three before a confirmed diagnosis of recurrent miscarriage can be applied and further testing will be performed), and is told that because she was able to get pregnant her husband's sperm must not be the problem. The implication that 'good' sperm, identified purely on a basic semen analysis, is the only sperm that can fertilise an egg is in itself inaccurate and contradicts the science of reproduction, which has shown that an egg is able to correct male genetic imperfections (Fritz & Speroff, 2015; Turek, 2012). Karyotype testing can be used to evaluate the chromosomes through a simple blood test, which can detect abnormalities, but is often overlooked by family practitioners and gynaecologists. Only once a patient gets to the reproductive endocrinologist and infertility specialist is such testing typically considered.

Assuming a comprehensive health history and a physical examination have been performed, basic lab testing and hormone levels have been checked, and at least two semen analyses have been ruled normal (and I use the word normal lightly - see above), then unexplained male infertility is often concluded. It is at this point that DNA fragmentation should be considered: '80% of couples who are diagnosed with unexplained or idiopathic infertility have a known cause called high sperm DNA damage' (Robinson et al., 2012). Both genetic and epigenetic factors can affect the integrity of the DNA. Cigarette smoking, alcohol, genetic mutations, heat, radiation, pesticides, herbicides and industrial chemicals can all cause oxidative stress which affects the genetic expression of sperm DNA and impairs spermatogenesis and sperm function. It is believed that oxidative stress, an imbalance between reactive oxygen species and pro- or anti-oxidant species is a major culprit. It is known that unexplained male infertility patients have a DNA fragmentation index greater than 30 per cent due to reactive oxygen species (Saleh et al., 2003). Even radio frequency electro-magnetic waves (RF-EMWs) have been found to increase malonyldialdehyde levels and decrease antioxidant levels, whilst cell phone radiation can decrease melatonin (Gorpinchenko, Nikitin et al., 2014) which can affect steroid hormone production (Srivastava & Krishna, 2010). These factors can in turn produce sperm with poor chromatin, the genetic material that makes up the chromosomes.

Immunological causes

The immune system is designed to protect us, yet can also turn against us and be a complicating factor in infertility. In the male, the blood-testis barrier that protects

developing spermatozoa can become compromised due to trauma, varicocele, vasectomy or epididymitis, allowing anti-sperm antibodies (ASA's) to develop. These ASAs are particularly associated with low sperm motility; it is thought that up to 40 per cent of male unexplained infertility may be due to ASA's (Schattman, 2016). Although a controversial subject, some experts believe ASAs should be suspected in all cases of unexplained male infertility and especially when other conditions such as varicocele or trauma to the testes has occurred.

Unexplained male infertility patients have a DNA fragmentation index greater than 30 per cent ...

Orthodox treatment

Typical orthodox treatment strategies for the male are limited and include medications or Intracytoplasmic sperm injection (ICSI). In males, follicle stimulating hormone (FSH) and luteinising hormone (LH) from the pituitary are responsible for increasing sperm production and steroidogenesis (Fritz & Speroff, 2015). Clomiphene citrate is sometimes used to inhibit the negative feedback of oestrogen thereby increasing FSH and LH. Aromatase inhibitors (letrozole) have been shown to prevent testosterone to oestrogen conversion for those with low testosterone levels and high oestrogen (Ring et al., 2016). Sometimes these options work, but often they do not.

TCM and male unexplained infertility

What does all this mean in TCM terms? Many TCM practitioners are always asking for the 'secret sauce' for treating unexplained infertility, in terms of acupuncture point prescriptions or herbal medicine formulas. It should go without saying that there is no such thing. Accurate differential diagnosis is obviously primary when treating male unexplained infertility, although there are certain TCM patterns that present more frequently in clinic in male factor unexplained infertility cases. Whilst there is not space in this article to document all clinical possibilities in the treatment of male unexplained infertility, let us take an illustrative example of a man whose semen analysis appear normal and no other contributing factor has been found, other than erectile dysfunction. Whilst we should consider the role of DNA fragmentation and oxidative stress as contributing to erectile dysfunction (Barassi et al., 2009), we should not rely on just this information. If the libido was low, then it is likely to more of a Kidney yang deficiency and *You Gui Wan* (Restore the Right Kidney Pill) would be an appropriate base formula. If the libido was high, then perhaps there is likely to be some Kidney yin deficiency as well and *Zhi Bai Di Huang Wan* (Anemarrhena, Phellodendron, and Rehmannia

Pill) would be indicated. Although yin deficiency may not typically present as erection issues, there may be a situation of both yin and yang deficiency; modifying the formula to the patient's presentation is critical. If Liver qi stagnation or blood stasis were present, there may also be sperm liquefaction issues, then *Ge Xia Zhu Yu Tang* (Below the Diaphragm Dispel Stasis Decoction) may be clinically appropriate. In the clinic, damp-heat in the lower jiao may also present in unexplained infertility.

III. Unexplained infertility and the female

Unexplained female infertility is considered a diagnosis of exclusion. Controversy exists as to what should constitute standard testing, but when the fallopian tubes have been deemed open via a hysterosalpingogram (HSG) and ovulation and the sperm analysis are 'normal', then unexplained infertility is typically assumed. However, all too frequently I have seen female patients diagnosed with unexplained infertility when, a) the sperm has not been tested at all, b) the sperm has been tested and considered abnormal, or c) a full diagnostic work up of the female has not yet been performed. This work up should include (but often does not), assessment of the quality of the cervical mucus and the frequency and timing of intercourse: 'Timed intercourse during the 6-day window before and including the day of ovulation (the fertile window) is significantly more likely to result in conception' (Evans-Hoeker et al., 2013).

One potential cause of infertility that becomes obscured behind a diagnosis of unexplained infertility is endometriosis, often called 'subtle endometriosis' in cases where the patient does not present with the classic symptoms of painful periods (Schattman, 2016). If a laparoscopy has not been performed there is no way to definitively diagnose this condition, and although it is an invasive and costly procedure, this can often be the missing piece of the infertility puzzle. Mild endometriosis is associated with lower progesterone production due to inefficiency of steroidogenesis in the granulosa cells surrounding the oocyte (Gupta et al., 2008). Oocyte quality may be adversely affected and its maturation impaired, as the follicular fluid is subject to greater oxidative stress in patients with endometriosis. Longer follicular phases with smaller dominant follicles are also associated with endometriosis patients when studied in IVF (in-vitro fertilisation) (Gupta et al., 2008).

In order to ovulate, a certain amount of oxidative stress is needed ...

Oxidative stress and female reproduction

The prevailing current wisdom is that oxidative stress is

bad and that antioxidants are good. However, the truth is just not that simple. Reactive oxygen species can be both helpful and a hindrance for the body. As ovarian follicles grow each month, they are protected by the hypoxic environment of the granulosa cells surrounding the follicle. It is this hypoxic condition which regulates the balance between pro-oxidant and reactive oxygen activity, and it is the very insufficiency of oxygen which activates follicular blood flow. In addition, during cell division there is a complex dance of reactive oxygen species in meiosis I that is balanced by antioxidant regulation during meiosis II (Shkolnik et al., 2011). The bottom line is that in order to ovulate, a certain amount of oxidative stress is needed (Shkolnik et al., 2011). But how much is enough? Unfortunately the research is inadequate at this stage to definitively answer this question. We know that factors including poor diet and lifestyle can influence epigenetic changes and increase reactive oxygen in vivo, and anything that disrupts this homeostatic environment - especially endocrine disruptors - can cause metabolic cellular stress. There are many stressors to consider such as bisphenol A (BPA) in plastics, dioxins in chlorinated products and polychlorinated biphenyls (PCBs) in animal fats and some seafood. Without testing (oxidative stress analysis is widely available) to determine how distressed the patient's internal environment is, recommending supplements to your patient may actually disrupt the oxidative balance in their body.

Unexplained infertility and ageing

According to orthodox medical thinking, a woman trying to conceive over the age of 35 years is considered to be of 'advanced maternal age.' Data indicates that the chances of conception decreases with age, although scientists are recently discovering more about human conception and the multitude of factors influencing one's ability to conceive with ageing. The telomere theory of reproductive ageing proposes that telomeres, the repetitive nucleotide sequences at the end of chromosomes, are a primary determinant of reproductive ageing in women. Thus, the shortening of telomeres provides a reasonable explanation for oocyte ageing and the associated deterioration in quality, and could be an important underlying factor in unexplained infertility (Kalmbach et al., 2015). Shorter telomere length has also been identified in the sperm of idiopathic infertile men (Thilagavathi et al., 2013), although this is not associated with abnormal sperm morphology (further casting doubt on sperm analysis as a fertility test; it may be factors such as telomere length rather than macroscopic sperm characteristics that primarily affect fertility).

The epigenetic theory of ageing confirms that our telomeres can be damaged by free radicals from harmful environmental toxins, poor lifestyle choices and other oxidative stressors (Moskalev et al., 2014). TCM doctors

Avoid Harm	Slow rate of telomere loss
No excesses	
Promote Health	Maintain & prevent telomere loss, gradually lengthen telomeres
Good food, emotions, sleep, rest, friends	
Nourish Life	Significantly lengthen telomeres
Good mind, breathing, food limitations	
Supplements?	

Table 2: The yangsheng approach to preserving fertility

have long known that lifestyle and environment can influence healthy ageing. Through the practice of yangsheng (nourishing life), we can essentially manipulate our telomeres. According to Peter Deadman (2016), the principles of yangsheng can be organised into three categories: avoiding harm, promoting health and nourishing life. My interpretation of how yangsheng integrates with the telomere theory of ageing is that by avoiding harmful practices in life such as smoking and drinking excessively, the rate of loss of telomere length can be slowed down, and by incorporating a healthy lifestyle with good food, stable emotions, adequate sleep and a supportive social network, we can maintain our telomeres (see Table 2). And if we can truly 'nourish life' according to the highest Daoist principles of a peaceful mind and proper breathing we may even be able to lengthen our telomeres for optimal ageing (Alda et al., 2016; Epel et al., 2009; Jacobs et al., 2011).

Unexplained infertility and orthodox treatment

The first line of testing typically begins when a woman visits her gynaecologist (who may or may not have in-depth knowledge and experience of reproductive issues). The current standard is that if the female patient is over 35 years old, her doctor will want her to wait to do any testing until she has been officially trying to conceive for at least six months. If she is under 35 years old, the doctor will want her to wait one year. This initial testing includes blood work for a basic hormone panel, an HSG and a sperm analysis. If everything is normal with these three criteria, the patient is usually prescribed clomiphene citrate (Clomid) or letrozole (Femara) for ovulation induction with or without an intra-uterine insemination (IUI), even though the patient may already be ovulating regularly. Though used for decades and insufficiently validated with conclusive literature, Clomid is routinely prescribed as a first-line treatment regardless of whether a woman is ovulating simply because the physician does not know what else to do and/or has no other options in their toolbox. This approach is something like 'throwing spaghetti against the wall to see what sticks' - a reckless trial and error approach to unexplained infertility, especially

Through the practice of yangsheng (nourishing life), we can essentially manipulate our telomeres.

given its low success rates (see below) and potential risks of decreasing endometrial perfusion (Omran et al., 2018), thinning the uterine lining and decreasing cervical mucus (Yilmaz et al., 2018). Clomiphene-controlled ovarian stimulation alone or IUI alone as routine treatments for unexplained infertility are not supported by evidence (Reindollar, 2010). Why then are these still the standard Western medical approach? In the Fast Track and Standard Treatment Trial (FASTT - Reindollar, 2010), women younger than 40 years old that used clomiphene or letrozole for up to three cycles in conjunction with IUI experienced improved pregnancy rates, lower costs and fewer treatment cycles (and therefore fewer risks, in my opinion). This literature demonstrated a 40 per cent increased rate of pregnancy, which sounds impressive, yet do not be confused by the data. This is not to say that 40 per cent of couples conceived but that the time in which they conceived was faster. The per cycle pregnancy success rate was only 7.6 per cent for combined clomid and IUI, versus 6.0 per cent without the treatment (Sozou & Hartshome, 2012). Given the risks elaborated on above, this treatment may not be the right solution for everyone. The 'Forty and Over Treatment' trial (FORT-T) demonstrated that female unexplained infertility patients over 40 years of age should go straight to IVF after only two Clomid/IUI treatments in order to achieve faster pregnancy rates; the Clomid/IUI results were only 6.7 per cent per treatment cycle for this age cohort. Though these two landmark studies have had reproductive endocrinologists jumping for joy, the results of such orthodox treatment seem less than stellar. Furthermore, some experts contend that, 'Successful use of CC [clomiphene citrate] for UI [unexplained infertility] is a contradiction because it is only successful if the cause is suboptimal ovulation'; in addition, if sperm count and motility are normal then IUI does not increase the pregnancy rate (Schattman, 2016).

TCM Diagnosis	Biomedical associations
Kidney deficiency (jing, qi, yin, yang)	PCOS, hypothyroid, genetic, advanced maternal age, diminished ovarian reserve, male factor sperm count/motility, obesity, oral contraceptive use, endometriosis, fibroids
Qi and/or blood stagnation	hormone imbalance, abnormal menses prolactinemia, erectile dysfunction, endometriosis, fibroids
Cold uterus (yang deficiency)	oral contraceptive use, luteal phase defect, recurrent miscarriage, delayed ovulation
Damp phlegm	obesity, PCOS, tubal obstructions
Qi and blood deficiency	hypothyroidism, scanty menses, hypothalamic anovulation secondary to excessive weight loss especially in athletes, vegetarianism
Damp-heat	yeast infections, sexually transmitted diseases, prostatitis
Shen disturbance	trauma, depression, anti-depressant usage

Table 3: Correlations between TCM patterns and biomedical disease labels

TCM and unexplained female infertility

In Chinese medicine the menstrual cycle is generally considered the foundation of fertility. However, it is important for the practitioner to recognise that it is not the only factor, and not be fooled into thinking that simply regulating the cycle will solve everything and result in conception.

A good practitioner should know when they are working outside of their limitations and when it is appropriate to refer to a fertility specialist, whether orthodox or TCM. If a female patient with unexplained infertility presents with what I would consider a 'normal' cycle - 28 to 31 days long, moderate red bleeding for three to five days, soaking a normal size tampon or pad every four hours for a total blood loss of 60 to 100 millilitres per period free of clotting and with minimal cramping, minimal premenstrual symptoms and good quality cervical mucus at ovulation - what else should we look for? The most common biomedical reasons that I uncover when treating unexplained female infertility include undiagnosed PCOS, hypothyroidism and endometriosis. Whilst it can be dangerous to convert biomedical diagnoses directly into TCM patterns - especially in light of the traditional aphorism, 'One disease - many patterns; one pattern - many diseases' - loose associations can be made. It is beyond the scope of this article to document all diagnostic possibilities (and as mentioned above, there is no 'secret sauce' available to provide the right answer), but Table 3 gives possible correlations between TCM patterns and biomedical disease labels. For example, PCOS patients typically present with damp phlegm accumulation with underlying Kidney jing, qi, yin or yang deficiency, Spleen qi deficiency and Liver qi stagnation; hypothyroid patients often present with Kidney yin/yang imbalances (it is not always Kidney yang deficiency); endometriosis patients tend to present with qi and blood stasis with underlying Kidney and/or Spleen qi deficiency.

IV. Integrative treatment

Evaluating and treating unexplained infertility from an integrative perspective requires finesse and diagnostic prowess. At a minimum, the following should be confirmed: that the male has had at least two normal semen analyses, that there are no female factor issues, that coital frequency and timing is appropriate and that a thorough history has been taken, including assessment of previous and current medical conditions, surgeries, developmental delays, occupational hazards, medication use, previous infections and social habits. Weaving the information from a thorough TCM assessment with modern diagnostic markers can help us understand impediments to conception. We should not fear using current day tools to augment or confirm our understanding of the patient. These tools can sometimes save us from doing the patient harm, for example thinking we can help a couple conceive when the fallopian tubes are completely blocked, or when there is an underlying condition of azoospermia and we have not found out whether the sperm has been tested.

One of the simplest assessment tools to incorporate is that of basal body temperature (BBT) charting. Many medical doctors dismiss this valuable tool even though the American Society for Reproductive Medicine (ASRM) states, 'Though it is cumbersome and not routinely recommended, charting your basal body temperature (BBT) is a simple, inexpensive way to see if you are ovulating.' (ASRM, 2012). There are many resources for analysing BBT charts according to the TCM paradigm including the works of Jane Lyttleton as well a previous article in the *Journal of Chinese Medicine* (Karchmer & Krassowski, 2016). I have summarised the other essential factors in my assessment into a checklist.

The checklist.

As a fertility detective, I am an ardent advocate of the checklist when presented with an unexplained infertility

case. Checklists are used extensively in sophisticated technical operations such as in aviation and operating rooms, as well as for relatively simple and mundane procedures such as cleaning hotel rooms or public restrooms. Serving as a reminder for critical steps, the checklist reduces the unreliability of the human multitasker. There are two main checklists I employ when assessing unexplained infertility patients. The first is used to double-check exactly what medical testing has been performed. 'It's normal' is not an acceptable patient response in my clinic - I will always ask for the actual medical reports. Even if a basic female hormone panel and semen analysis have been completed and deemed satisfactory, I will review them. After this I check six aspects: ovulatory function, insulin resistance, thyroid function, androgens, semen and tubal patency (see Table 4). If these have not been properly evaluated, then a diagnosis of unexplained infertility is premature. Ovulatory disorders including polycystic ovarian syndrome (PCOS) are common reasons for infertility and often overlooked. In the past year alone, I have referred at least a half dozen patients to their gynaecologist for further testing after suspecting PCOS, which was subsequently confirmed. Insulin resistance can affect lean PCOS patients as well as non-PCOS patients. Therefore fasting insulin and glucose levels should be checked. I also consider androgen levels when other testing has been inconclusive and PCOS is suspected, especially if there is hirsutism. Correct androgen levels, including dihydrotestosterone (DHT), and DHEA sulfate (DHEA-S), are essential to ensure adequate oestrogen levels. Insufficient androgens means not enough oestrogen, whilst too many androgens means either too much oestrogen or excess androgens due to lack of conversion.

Thyroid function is also often overlooked by orthodox medical doctors who are only looking at the thyroid stimulating hormone (TSH) levels while ignoring the functions of free T3 and T4 and thyroid antibodies. In one study of couples who had experienced three or more failed clomiphene citrate/IUI procedures, hypothyroidism was found in five per cent of cases (Schattman, 2016). TSH levels greater than 2.5 mIU/L, though in the normal range for general health, are considered abnormal by most reproductive endocrinologists for optimal fertility. I prefer to see them at 2.0 mIU/L or less, whilst keeping in mind the context of the full thyroid panel.

Endometrial lining and adequate cervical mucus are the other two major items on my orthodox medical checklist. 'Conception and delivery rates are highest when endometrial thickness was greater than or equal to 9 mm' (Schattman, 2015). Some fertility labs I work with claim they see implantation success with uterine linings less than this, but this is not the norm in my clinic. Adequate quantity and quality of cervical mucus is also necessary for the sperm to reach its destination, yet this is often ignored in orthodox investigations. If oestrogen levels are

inadequate or excessive, cervical mucus will be impaired; when oestrogen levels are in the optimal range, the cervical mucus becomes stretchy like egg-white and gives the sperm the best chance of reaching the egg (Bigelow et al., 2004). The Sims-Huhner post-coital test (PCT), used to evaluate mucus quality as well as the sperm's ability to survive, is rarely employed nowadays based on studies which have shown it does not increase fertility. If cervical mucus is insufficient, oestrogen levels are likely to be inadequate, and a cascade of other factors may not be aligned for conception to occur. Perhaps the PCT should not be utilised as routine testing, but in unexplained infertility, I would not rule it out when all else is considered normal.

Ovulatory function
Insulin resistance
Thyroid function
Androgens
Semen
Tubal patency
Endometrial lining
Cervical mucus

Table 4: Checklist 1 - basic aspects

The second checklist (see Table 5) is a general collection of prompts that remind me to ask about things that may seem obvious but which I have seen influence a couple's ability to conceive. For example, has the patient seen a medical doctor and had basic testing? Are lubricants being used during intercourse (which may be hostile to sperm)? How many and which supplements or medications is the patient taking? Also, with the increase in marijuana legalisation in the United States, it is common for patients to assume that because it is legal it must be safe. Men with daily marijuana use have significantly lower sperm concentration and counts (Eisenberg, 2015).

Is IUI/IVF/ICSI the answer for unexplained infertility?

The Centers for Disease Control have reported that of all fresh IVF non-donor cycles with a diagnosis of 'unknown origin' in 2015, only 29 per cent resulted in a live birth (CDC, 2018). Further, the major reason IVF cycles were cancelled during this same time period was due to poor egg production. In a Dutch study of couples with unexplained infertility that had tried to conceive for almost two years, 60 per cent conceived naturally without treatment after consulting a reproductive specialist (Kamphuis et al., 2016; Brandes et al., 2011). Some studies have shown that intervening too quickly in couples with unexplained infertility (within three years) is both unnecessary and costly, especially in younger women who may conceive naturally within this time period (Mol et al., 2000).

Research shows these treatments are most successful in

The Unexplained Infertility Checklist			
General	Labwork	Female	Male
Seen gynaecologist?	FSH _____	Over/under weight	Fathered a child?
Seen fertility specialist?	LH _____	Egg white cervical mucus	Sperm analysis high or low?
Cigarettes?	Estradiol _____	Make up? Hair dye?	Ejaculation frequency
Marijuana?	AMH _____	Lotions? Skin products	Work exposure?
Sauna, hot tub?	AFC _____	Cleans own house?	Testosterone use?
Car seat heater?	Progesterone _____	EWG.org	Handyman?
	Prolactin _____	Acne/hair growth?	Get/sustain erection?
Medications	TSH _____	Celiac? Leaky gut?	Electronics near testicles?
HBP?	InhibinB _____	Nipple discharge	Kidney disease
Statins?	Sperm analysis x 2 ?	Lubricants or saliva for intercourse?	
Clomid?	Ultrasound?	Sexual frequency?	
Letrozole?	Sonohystogram?	#/type of supplements	
SSRI's?	Laparoscopy?	# alcoholic drinks/week	
Pesticides?	HSG?	How many vegetables?	

Table 5: Checklist 2 - other aspects

cases of anti-sperm antibodies, DNA damage, fertilisation defects and oxidative stress (Aktan et.al., 2013); yet these are routinely offered to unexplained infertility patients. Moreover, as with most medical treatment, there are risks. One specific risk is that ICSI eliminates the natural protection mechanisms employed by the body as sperm travels organically to meet the egg. Natural selection is non-existent in ICSI, yet many infertility patients are desperate and therefore do not consider these factors, and unquestioningly trust their doctor's recommendations. In many cases of ICSI, fertilisation may occur, and implantation may even happen, but is this ideal if the pregnancy does not progress to a live birth? The answer to the question then is that IUI/IVF/ICSI is not always the solution for women with unexplained infertility, especially in the early days of trying to conceive. In such cases, TCM treatment can instead be considered to nourish the follicular environment and reduce oxidation of the developing oocytes (see below).

Improving DNA fragmentation is one of the major ways TCM can enhance fertility and offer hope.

Improving DNA fragmentation is one of the major ways TCM can enhance fertility and offer hope. When a male patient presents with Kidney jing (essence) and/or yin deficiency, or qi and blood stagnation, I suspect oxidative stress with or without DNA fragmentation as a possible contributing factor to the unexplained infertility. *Wu Zi Yan Zhong Wan* (Five Seed Fertility Pill), *Zhi Bai Di Huang Wan* (Anemarrhena, Phellodendron, and Rehmannia Pill) and *Bu Shen Yi Jing Fang* (Supplement the Kidneys and Benefit the Jing Formula) are three excellent base formulas

for these patterns. In addition, Carnitine, Selenium, Zinc, Lycopene, Vitamin E and Vitamin C have all been shown to improve sperm DNA damage, semen parameters, pregnancy and live birth rates (Showell et al, 2014). In my practice, Co-Q10, Zinc, and Vitamin C are standard recommended supplements for male infertility, although whole food sources are ideal.

For the female unexplained fertility patient, the classic formulas used for the male can also be applied depending on pattern identification. Given that oxidative stress can overwhelm the ovaries and adversely influence egg quality, the best defense we have is to use acupuncture and herbs to oxygenate the follicular environment. If a cold uterus is the problem, then *Wen Jing Tang* (Flow-Warming Decoction) is an excellent formula to open the Chong (Penetrating) and Ren (Conception) Vessels and increase blood supply to the ovaries. Given that I see a lot of older patients in my clinic with multiple patterns, I find *Bu Shen Yi Jing Fang* (Supplement the Kidneys Benefit the Jing Formula) to be a well-balanced formula that nourishes the Kidneys and jing while also supplementing and regulating blood and invigorating qi. It also calms the shen which is almost always necessary in unexplained infertility patients, as emotional stress and frustration can cause problems and delay the time to conception.

VI. Conclusion

The treatment of unexplained infertility depends on a proper diagnostic and evaluation system. Though normal sperm parameters are not a guarantee of fertilisation, they may point towards areas which need improvement. In my clinical experience, the most hope for the field of infertility may arise from a better understanding of male factor issues like DNA fragmentation as well as genetic and epigenetic factors affecting egg quality. The orthodox medical community are currently searching for mechanical

interventions to improve the limited fertility rates of current Western interventions. Given the importance of oxidative stress from environmental factors, lifestyle, diet and stress, TCM is the natural choice for improving health and thereby conception.

Does it matter if a patient truly has unexplained infertility or simply idiopathic infertility? To me, it does. If we know the cause, but we just do not know what is causing this cause, then at least we have more information to work with and to provide the patient. Questioning everything reported by the patient and medical providers - including the lab reports - is prudent, to make your own assessment. Using a checklist is not for the weak but for the astute critical reasoner to map out an effective diagnostic framework. Ancient Chinese medicine may not have had the benefit of modern diagnostics, but it does now. One of the biggest stressors I see when working with infertility patients is the

patient's need to control a situation in which they have limited control. Nothing is guaranteed, but at least if I can offer them some information as to what is happening and how we can work to improve it, they can ease into the unknown with a little more direction and clarity.

Katherine Alexander Anderson is a Doctor of Acupuncture and Chinese Medicine, international lecturer and President of the American Board of Oriental Reproductive Medicine (ABORM). Katherine has over 25 years experience in healthcare and takes an integrated and evidence-based approach to care. She has dedicated her practice to reproductive issues and women's health and owns clinics in Maine and New Hampshire, USA. As the President of ABORM, she has been at the forefront of ensuring that Chinese medical practitioners across the globe specialising in infertility receive the highest level of training in Western and Eastern reproductive medicine. She completed her Chinese medical training in the US and in China and also holds an MBA.

References

- Alda, M., Puebla-Guedea, M., Rodero, B. et al. (2016). Zen meditation, Length of Telomeres, and the Role of Experiential Avoidance and Compassion, *Mindfulness*, 7, 3, pp.651-659
- Aktan, G., Doğru-Abbasoğlu, S., Küçükgergin, C. et al. (2013). Mystery of idiopathic male infertility: is oxidative stress an actual risk?, *Fertility and Sterility*, 99, 5, pp.1211-1215
- ASRM (2012). Infertility: An Overview. Available at <<https://www.reproductivefacts.org/news-and-publications/patient-fact-sheets-and-booklets/documents/fact-sheets-and-info-booklets/infertility-an-overview-booklet/>> Accessed online 27 July 2018
- Barassi, A., Colpi, G. M., Piediferro, G. et al. (2009). Oxidative Stress and Antioxidant Status in Patients with Erectile Dysfunction, *The Journal of Sexual Medicine*, 6, 10, 2820-2825
- Bigelow, J. L., Dunson, D. B., Stanford, J. B. et al. (2004). Mucus observations in the fertile window: a better predictor of conception than timing of intercourse *Human Reproduction*, 19, 4, pp.889-92
- Brandes, M., Hamilton, C., van der Steen et al. (2011). Unexplained infertility: overall ongoing pregnancy rate and mode of conception, *Human Reproduction*, 26, 2, pp.360-368
- CDC (2018). Assisted Reproductive Technology National Summary Report 2015. Available at <<https://www.cdc.gov/art/pdf/2015-report/ART-2015-National-Summary-Report.pdf>> Accessed online 27 July 2018
- Deadman, P. (2016). *Live well live long: Teachings from the Chinese nourishment of life tradition*. The Journal of Chinese Medicine: Hove
- Eisenberg, M. L. (2015). Invited Commentary: The Association Between Marijuana Use and Male Reproductive Health, *American Journal of Epidemiology*, 182, 6, pp.482-4
- Epel, E., Daubenmier, J., Moskowitz, J. T. et al. (2009). Can Meditation Slow Rate of Cellular Aging? Cognitive Stress, Mindfulness, and Telomeres, *Annals of the New York Academy of Sciences*, 1172, 1, pp.34-53
- Fritz, M. A. & Speroff, L. (2015). *Clinical Gynecologic Endocrinology and Infertility*. Lippincott Williams & Wilkins: Philadelphia
- Goldman, M. B., Thornton, K. L., Ryley, D. et al. (2014). A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T), *Fertility and Sterility*, 101, 6, 1574
- Gorpinchenko, I., Nikitin, O., Banyra, O. et al. (2014). The influence of direct mobile phone radiation on sperm quality, *Central European Journal of Urology*, 67, 1, pp.65-71
- Gupta, S., Goldberg, J. M., Aziz, N. et al. (2008). Pathogenic mechanisms in endometriosis-associated infertility, *Fertility and Sterility*, 90, 2, 247
- Hamada, A., Esteves, S. C. & Agarwal, A. (2011). Unexplained male infertility: potential causes and management, *Human Andrology*, 1, 1, pp.2-16
- Evans-Hoeker, E., Stanford, J. B., Steiner, A. Z. et al. (2013). Cervical mucus monitoring prevalence and associated fecundability in women trying to conceive, *Fertility and Sterility*, 100, 4, 1033
- Jacobs, T. L., Epel, E. S., Lin, J. et al. (2011). Intensive meditation training, immune cell telomerase activity, and psychological mediators, *Psychoneuroendocrinology*, 36, 5, pp.664-81
- Kalmbach, K., Antunes, D., Kohlrausch, F. et al. (2015). Telomeres and Female Reproductive Aging, *Seminars in Reproductive Medicine*, 33, 6, pp.389-395
- Karchmer, K. & Krassowski, W. (2016). Clarifying the use of Basal Body Temperature Charting in Traditional Chinese Medical Clinical Practice, *Journal of Chinese Medicine*, 112, pp.13-19
- Kamphuis, E. I., Bhattacharya, S., van der Veen, F. et al. (2016). Are we overusing IVF?, *British Medical Journal*, 348
- Mol, B. W. J., Bonse, G. J., Collins, J. A. et al. (2000). Cost-effectiveness of in vitro fertilization and embryo transfer, *Fertility and Sterility*, 73, 4, pp.748-754
- Moskalev, A. A., Aliper, A. M., Buzdin, A., et al. (2014). Genetics and epigenetics of aging and longevity, *Cell Cycle*, 13, 7, pp.1063-1077
- Omran, E., El-Sharkawy, M., El-Mazny, A. et al. (2018). Effect of clomiphene citrate on uterine hemodynamics in women with unexplained infertility, *Women's Health*, 10, pp.147-152
- Reindollar, R. H., Regan, M. M., Neumann, P. J. et al. (2010). A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial, *Fertility and Sterility*, 94, 3, pp.888-899
- Ring, J. D., Lwin, A. A. & Köhler, T. S. (2016). Current medical management of endocrine-related male infertility *Asian Journal of Andrology*, 18, 3, pp.357-63
- Robinson, L., Gallos, I. D., Conner, S. J. et al. (2012). The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis, *Human Reproduction*, 27, 10, pp.2908-17
- Sadeghi, M. R. (2015). Unexplained infertility, the controversial matter in management of infertile couples, *Journal of Reproduction & Infertility*, 16, 1
- Saleh, R. A., Agarwal, A., Nada, E. A. et al. (2003). Negative effects of increased sperm DNA damage in relation to seminal oxidative stress in men with idiopathic and male factor infertility, *Fertility and Sterility*, 79, pp.1597-1605
- Schattman, G. (2016). *Unexplained Infertility*. Springer-Verlag: New York
- Shkolnik, K., Tadmor, A., Nevo, N. et al. (2011). Reactive oxygen species are indispensable in ovulation, *Proceedings of the National Academy of Sciences of the United States of America*, 108, 4, pp.1462-1467
- Showell, M. G., Mackenzie-Proctor, R., Brown, J. et al. (2014). Antioxidants for male subfertility, *Cochrane Database Syst Rev*, 12: CD007411.
- Sozou, P. D. & Hartshorne, G. M. (2012). Time to Pregnancy: A Computational Method for Using the Duration of Non-Conception for Predicting Conception, *Plos One*, 7, 10
- Srivastava, R. K. & Krishna, A. (2010). Melatonin affects steroidogenesis and delayed ovulation during winter in vespertilionid bat, *Scotophilus heathi*, *Journal of Steroid Biochemistry and Molecular Biology*, 118, 1, pp.107-116
- Thilagavathi, J. et al. (2013). Analysis of sperm telomere length in men with idiopathic infertility, *Arch Gynecol Obstet.*, 287:803-7. doi: 10.1007/s00404-012-2632-8
- Turek, P. (2018). Reading the Cards: What the Semen Analysis Really Means, *Integrative Fertility Symposium*, Vancouver
- Turek, P. (2012). It Takes Two to Tango. Available at <<https://www.theturekclinic.com/two-to-tango-sperm-egg-miscarriages-male-infertility/>> Accessed online 27 July 2018
- Van de Steeg, J. W., Steures, P., Eijkemans et al. (2011). Role of semen analysis in subfertile couples, *Fertility and Sterility International Edition*, 95, 3, pp.1013-1019
- Yilmaz, S., Yilmaz, S. N., Gönenç, I. M. et al. (2018). Safety of clomiphene citrate: a literature review. Cytotechnology: Incorporating Methods in Cell Science international, *Journal of Cell Culture and Biotechnology*, 70, 2, pp.489-495