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par Morgane ROGIER

Thermal Male Contraception: A Systematic Review of Efficacy, Reversibility, Safety and Acceptability.

Contraception masculine thermique: Une revue systématique de son efficacité, réversibilité, sécurité et acceptabilité.

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To those who have accompanied me on the adventure of life and made me the woman I am,
Those who are still here or those who have left us:
I thank you and I love you. I can never say it enough.

À Mamoune qui ne parle pas anglais ☺ : Je t'aime.

To my cats who don't speak human: Meow.

To Life, no matter what form it takes, and to all laws of Universe:
Thank you for making this world an exceptional place of complexity and perpetual wonder.

♪

Please finish reading this thesis by listening to the song "Victory celebration" by John Williams.

♪

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INTRODUCTION

The idea of influencing fertility has always been a human concern**.** Contraceptive methods have continuously improved from antiquity to the present day (1–3). In the 1960's, it became a medical matter with the arrival of intrauterine devices (IUDs) and contraceptive pills. Utilisation of the latter is considered to be a contraceptive revolution and allowed a feminine control over health and sexual life of women. At this period, if condom kept its position for contraceptive and preventive function for venereal diseases, the withdrawal method, once very popular, became less used and outdated (4,5). The offer of female hormonal contraception expanded in the 2000 with the arrival of implant, patches and vaginal ring.

In France, about 71% of stable relationship use exclusively a feminine method (6), which repartition in population vary depending on age (7). But the large number of contraindications to available options, the high frequency of adverse effects (which led to 40% of discontinuation in a study (8)) and a general growing distrust towards hormonal contraception since the 2012's pill crisis (9–11) can make it difficult to provide an adequate solution for each couple. Additionally, what has been a feminine emancipation tool in the 60s can turns, for some women, into a burden on mental load (12). The shared choice of the method by both women and men is not common in Europe and concern mostly the mature married couples with high instruction level (13). Therefore, this leads to ask the role and responsibility of men in family planning.

There are only three options available for men. Although male condom and withdrawal method are used by 21% and 5% of couples worldwide respectively, their Pearl Index are not fully satisfying (13 and 20 in common practice) (14,15). Vasectomy, underused compared to woman sterilization, is quick and reliable (Pearl index 0,15) but has to be considered as definitive (16) and cannot be truly considered as contraception method. There is no other validate male contraceptive to this day.

The idea of new means of male contraception seems well received across the world. Women would be theoretically ready to share contraceptive burden and a majority of them would trust their partner for the use of a male pill (17,18). For men, acceptability of male contraception range from 13% to 79%, the more acceptable methods for them being the hormonal contraception, probably thanks to an already existing reference in women, and the reversible occlusion of vas deferent (19–22), although they can show some ambivalence between an interest upon it and difficulties to make the leap (23). Some of them express some concerns notably about side effects and make analogies with female methods (24). Interest to try new male contraceptive is related to ages over 30 years old, and to having ever been tested to HIV (22), which could correspond to men in a stable relation, with already an interest upon their sexual health. Those results globally shows the interest and the willingness for new safe methods accessible for men.

Among all leads in male contraception investigated over the last decades (25–27), Thermal Male Contraception (TMC) is rather unknown with little public awareness. Indeed, French studies shows that only 3% of new fathers and 15 to 30% of general practitioners have notions about TMC. Among the latter, 5% know precisely how it works, especially GP practicing in urban areas or with an additional formation in family planning (28,29). Most of them would be interested in accompany men in this direction, provided that research produce some robust evidences (28,29).

For men interviewed on a potential use, the reception is lukewarm. TMC, with its particular appearance, seems at first sight surprising, incongruous and almost ridiculous. Concerns about daily discomfort and constraints, as well as interrogations upon long-term side-effects like testicular cancer are raised, but the device's simplicity and the absence of chemical or hormonal substances are also brought up (30) and the rate of interest for trying TMC ranges from 13% to 59% (21,29,31).

CONTEXT

I. USEFUL NOTIONS OF TESTICULAR PHISIOLOGY

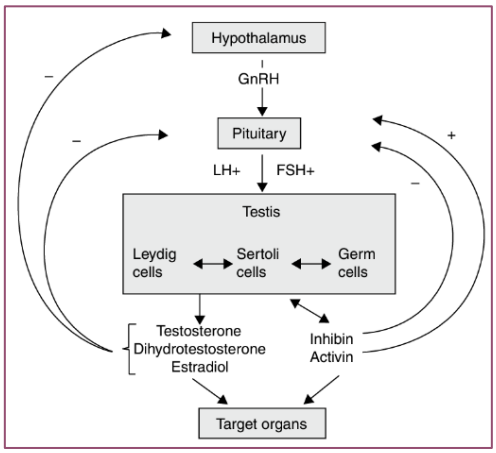

Figure A. Diagram of the hypothalamic–pituitary–testis axis (33)

1 – Hormonal axis

In healthy men, the hormonal axis which regulate spermatogenesis necessitate a pulsatile release of GnRH by the hypothalamus. Consecutively, the anterior pituitary secretes the LH and FSH. FSH stimulates spermatogenesis in Sertoli cells, and LH acts on the production of testosterone on Leydig cells (which comes with estradiol and 5-a-dihydrotestosterone (DHT)). This hypothalamo-hypophyseal axis is inhibited by testosterone *via* a negative feedback (**Figure A**). (32)

2 – Spermatogenesis

Spermatogenesis is the succession of steps leading to haploid male gametes (spermatozoa) from diploid stem cells (spermatogonia). It lays in the semeniferous tubules, which epithelioma include stem cells located near the basement membrane, germ cells (spermatozoa's precursors) and the large Sertoli cells that surround all of them, which role is to support and nourish them (**Figure B**).

Under the influence of FSH and testosterone, spermatogonial stem cells (2n) will perform mitotic division which will lead to the production of a spermatogonia A (for refilling the stem cells stock) and a spermatogonia B which will continue its journey to turn into primary spermatocytes (2n). The latter will become two secondary spermatocytes (n) through meiosis, each of them divides into spermatids (n) by another meiosis. At this point begins the spermiogenesis, which consist in the transformation of spermatids to mature spermatozoa. All this process starts close to the basement membrane and cross the Sertoli cell to reach the semeniferous tubule's lumen, and last between 74 and 120 days (3 months being the most common estimation). The spermatozoa are then stored in the epididymis.

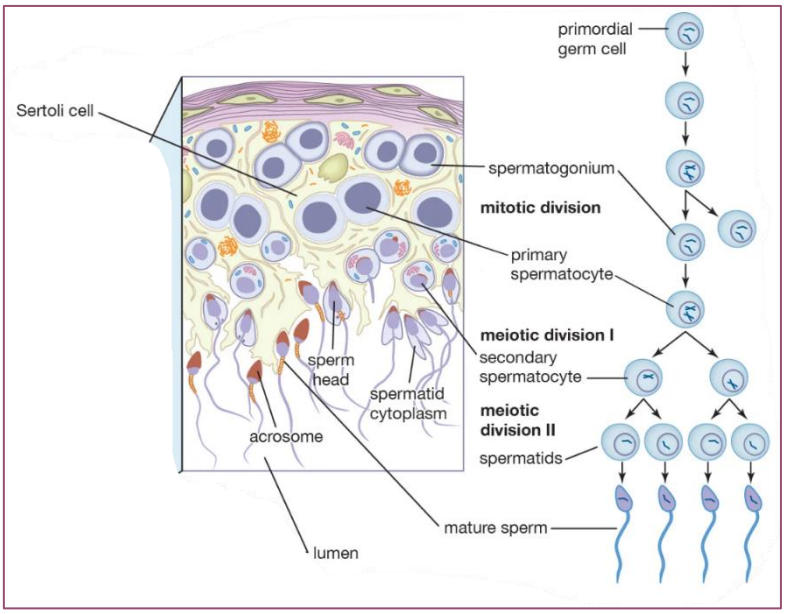

Figure B. Spermatogenesis in seminiferous tubules (34)

3 – Testicular thermoregulation

In men and some mammal species, the testicular temperature must be 2 at 4°C lower than body temperature to achieve a normal spermatogenesis. In a healthy man, scrotal temperature is about 32,5 to 34,9°C, and testicle temperature from 31,8° to 34,5°C. This balance can be maintained by 2 thermoregulation system which are passive but involve dynamic adaptations (35,36).

The first element which allow such low temperature is the scrotum itself (**Figure C**). Thanks to its absence of subcutaneous fat, its surface's variability permitted by the dartos muscle, and its vascularisation, the scrotum allows the excessive temperature coming from the blood vessels, to escape into the external environment (35). When environmental temperature is low, the muscles (dartos and cremaster) tighten up, bringing testicles closer to the abdominal warm and preventing heat loss, and reversely they relax when temperature is high. The scrotal sudation also allows this heat loss. This one occurs, by reflex arcs to medulla, thalamus and cerebral cortex, when external temperature exceed the cutaneous thermoreceptors thresholds (37).

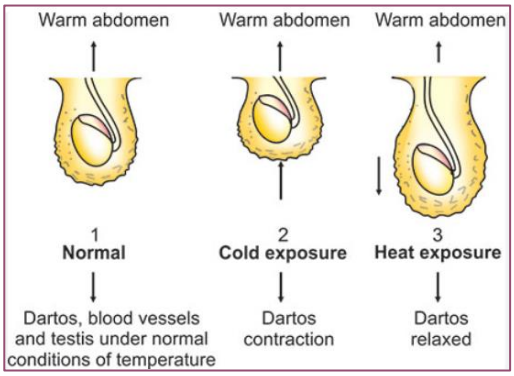

Figure C. Scrotal thermoregulation to environmental temperature (38)

The second constituent of this homeostasis is the spermatic cord, which contain vascular system and notably the pampiniform veinous plexus, in which the heat is transferred from the incoming artery to the outgoing veins (**Figure D**). In doing so, the blood from artery is already cooled before arriving to the testicle. This system is only possible when the scrotum regulation is operative, as it requires the vein to be cooler than artery after its passage through the scrotum.

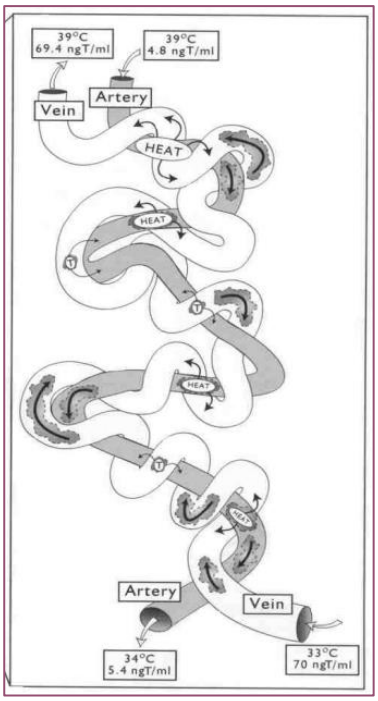

Figure D. The pampiniform plexus: a countercurrent heat exchanger (39)

II. QUICK OVERVIEW OF RESEARCH FOR MALE CONTRACEPTION

Research shows promising perspectives for male contraception and various methods have been examined by scientists worldwide over the last decades (25–27), although none of them has yet been validated.

1 – Male non-hormonal contraceptive methods

Some leads have unfortunately witnessed grave adverse effects or permanent infertility. For instance, gossypol, a large molecule of cotton which had effect on fertility, was studied on more than 8000 men with a 90% efficacy rate on pregnancy. The trials have been stopped due to the permanent infertility in about 20% of cases and to severe adverse effects such as hypokalaemia (40–42). Compounds blocking the adhesion of spermatids to Sertoli cells are tested on animals since the 2000's (43,44). One of them, Adjudin, was effective but the prevention of its severe adverse effect (liver inflammation) seemed to be too expensive for a contraception (45,46). A derivative product, Gamendazole, was also tested on rats but was not reversible (47).

Several products are still tested on animals, with potential efficacy and reversibility. Triptonide, a molecule used for rheumatoid arthritis in Chinese medicine, alterating sperm count and mobility, is studied on mice and monkeys (48,49). Inhibition of the Eppin protein, necessary for sperm motility, by immunological way (using an Eppin-antibody), is on development on monkeys (50–52). The Bromodomain testis-specific protein (BRDT), required for meiosis, has been inhibited in rodents, leading to an effective reversible infertility. However further studies are necessary to increase affinity and specificity of the inhibitor, as some side-effects have been found in other organs (53). The inhibition of a sperm-specific calcium channel (CatSper) suppress sperm motility in-vitro (54,55). The only in-vivo study in mice suggested that it could be effective for contraception (56).

Other methods are currently evaluated on human trials, or are going to be. The inhibition of vassal peristalsis has been investigated, through cation channels antagonists (57) or already known alpha1-antagonists (phenoxybenzamine, tamsulosin, alfuzosin…) (58,59). Recent small size studies on men showed efficacy of tamsulosin, causing reversible anejaculation, but with inconvenient side effects (dizziness and orthostatic hypotension) (60,61). The blockade of retinoic acid receptors, which is an essential part for sperm production, seems promising in rodent studies with a well-tolerated reversible infertility (62–64) and a clinical trial in human was planned for 2022 (65). The reversible occlusion of vas deferens by injection of polymers (RISUG, Vasalgel), have moved from animals (66–70) to human clinical trials phase II (with an on-going phase III), which found good efficacy over a 1-year period, but the reversibility has not yet been proved (71–76). Only one study of reversible occlusion in men, at our knowledge, retrieved 100% of sperm parameters and allowed pregnancies after removing polyurethane plugs (77).

2 – Male hormonal contraception

Among all these researches, the most known and publicized method is probably hormonal male contraception (78), which consists in providing exogenous testosterone to block the hypothalamo-hypophyseal axis by negative feedback, inhibiting in doing so the release of LH and FSH, the stimulation of the Leydig and Sertoli cells and ultimately the spermatogenesis to a certain extent of sperm concentration called contraceptive threshold.

It appears to be effective and reversible. Either testosterone alone or testosterone associated with progestin have been evaluated on more than 2400 men before 2016 with a Pearl index between 0 and 2.8 depending on the studies (79). The semen recovery was achieved within 6 to 7 months. Though, these trials brought to light some limitations. Indeed, 5 at 10% of men fail to achieve the contraceptive threshold and some men had "sperm rebound" (presence of sperm above the cut-off, after an azoospermia period). In addition, oral formulation of testosterone failed to suppress spermatogenesis (79–83).

Side effects seemed mostly acceptable and similar to those experienced by women with contraceptive pills. They were related to alteration of hormonal pathway: acne, weight gain, reduced or increased libido, mild or moderate mood disorders or to pain at the injection site (79). Serious adverse effects were not frequent, however, a large efficacy study in 2016 has been terminated early (details were not disclosed). In that study, adverse effects included a high rate of mood disorders (31%, most described as mild or moderate) and a suicide case among participants (but that was not associated with the trial) (84). Another point to note is the interdiction of anabolic steroid in sports, leading to a difficulty for athletes to use hormonal contraception.

Most recent studies are focusing on new ways of administration such as transdermal gel, actually on human phase II trial in 2023 (85–88), and on different testosterone/progestin combinations that may be used (89–94). Some other groups work on a molecule with both androgenic and progestogenic activity (95–98)

3 – Spermatogenesis inhibition and contraceptive threshold

Hormonal and thermal approaches are both based on reversible spermatogenesis inhibition (26). Complete azoospermia (meaning no sperm identified in semen analysis) being difficult to reach (58-77% of cases (80,81)), it was necessary to determine an achievable goal of sperm count that could not lead to a pregnancy. Such number is named contraceptive threshold. It has been admitted, in some studies and later in a 2007's consensus, the acceptable contraceptive threshold of <1million/ml of sperm concentration in the ejaculate (26,78,99) with an associated Pearl Index less than 1.

4 – Criteria for spermatogenesis inhibition researches

To guide the research, criteria have been established in a 2007 consensus for the development of male contraception (99). Initially for hormonal methods, those requirements also appear to be appropriate for other methods based on inhibiting spermatogenesis inhibition, such as thermal male contraception:

1. For efficacy criteria, the goal of sperm concentration should be ≤1 million/mL.
2. Reversibility should be assessed for each participant, by a return to sperm concentrations of at least 20 million/mL.
3. Participants with known or suspected infertility should not be enrolled in clinical efficacy studies.
4. Open-label, non-comparative contraceptive efficacy studies are acceptable if the primary endpoint is not susceptible to bias (eg, pregnancy rate).
5. For contraceptive efficacy, 2 independent phase III trials for one year, beginning when the male volunteer has suppressed to ≤1 million sperm/mL, should be completed by 200 men or couples per trial.
6. For safety assurance for a new chemical entity, trials are required to involve at least 300–600 men for 6 months at the intended combination and dose, 100 men exposed for one year, and a total of 1500 men in phase I—III studies at the minimum.
7. Long-term safety will be monitored by postmarketing surveillance.
8. The necessary laboratory investigations, especially semen analysis, need to be made under strict quality control.

III. PRINCIPLES OF THERMAL MALE CONTRACEPTION

1 – Impact of temperature on spermatogenesis

Unlike other organs that can be damaged at high temperature, the testicle's exocrine function (spermatozoa's production) is damaged by only a slight elevation of heat, at body temperature. Impact of heat upon the spermatogenesis has long been known. The first evidence appears to date from 1893, when Griffiths noted in dogs with artificial cryptorchidism that the testicles' size reduced and that the spermatozoa "were not forthcoming" (100). Dr Crew in 1922 (101) and Dr Moore in 1924 (102) both formulated the hypothesis that the mechanism was related to a higher temperature. Further studies in animals (rat, rabbit, guinea pig, rams, bulls, boars, dogs…) corroborate these theories: the scrotum temperature is lower than abdominal temperature and the interruption of this thermoregulation leads to abnormal spermatogenesis (103–113). The reversibility of heat induced abnormal spermatogenesis is proved in 1926 on guinea pigs after 5 months of treatment (105,107).

It is interesting to note how were conducted those experimental studies on animals. Indeed, different means to obtain heat exposition were used: local scrotal heating by artificial cryptorchidism, scrotal insulation, water bath over 40 (often 43°C), infrared, microwave or ultrasounds, and whole body heating by elevated air temperature. The studies used either mild heating (at abdominal temperature), or high heating (via an external heat source).

Thereafter, relation between heat and human fertility has been largely studied and several risk factors of infertility have been sought for (114,115). The wearing of tight underwear instead of boxer shorts tend to impair sperm quality (116–119), though this conclusion is not shared by all studies (120). Diapers were also scrutinised, and whereas the ones with protective plastic cover indeed increase temperature (121), there is no evidence that this may have an impact in adulthood spermatogenesis.

Occupational exposures to heat such as drivers, welders and bakers, are suspected to extend the period of pregnancy occurrence, but without definitive conclusions (and possible confounders) (122–124). On the other hand, sedentary work position and use of laptops, although moderately rising scrotal temperature, does not seem to affect sperm quality (125–127).

In 1940, a study investigated the side-effects of diathermy (electromagnetic current known for sexual disturbance treatment) and found a negative impact on spermatogenesis after six treatments (128). More recent experimental studies reproducing sauna exposure or febrile illness (129–132) retrieve a significant decline of sperm count and normal sperm morphology about 30 days post-exposure, which return to baseline values within 40 to 90 days after the end of exposition. Varicocele is a well-known risk factor for spermatogenesis impairment an its treatment often allows improvement of semen parameters and pregnancy rate (133,134).

Multiple studies are still trying to elucidate mechanisms behind spermatogenesis impairment by heat. Several alterations are noticed in molecular biology, protein expression, DNA, oxidative stress and enzymes activity, with the final step being germ cell apoptosis (135–138).

2 – Thermal Male Contraception devices

It appears that there is no clear definition of thermal male contraception (TMC). If papers or websites refers to it as a "slight elevation of testicular temperature about 2°C" (26,139,140), these descriptions are mostly relying on one particular device (described below). In this study, we decided to think about TMC as "an induced elevation of testicular temperature for contraceptive purpose". Therefore we are going to consider in that review all type of scrotal heating method, no matter the intensity of temperature, exception made of total body heating.

Currently, the TMC's landscape in society is quite poor but exists**.** It is not a contraceptive method medically recommended by health authorities. At this date, there is no thermal contraceptive device commercially available, because of an absence of European certification and marketing authorization. However, some devices can be found on the market and are already used by some men, being medically followed or not. Associations (141,142), notably through social medias, play great role

in information, support and devices' accessibility for those men willing to implicate themselves in the "contraceptive load". (143)

- The Toulouse underwear developed and dispensed by Dr Mieusset is perforated underpants allowing to hold the testicles on a supra-scrotal position. It has to be worn during waking hours (15 hours a day). However, Dr Mieusset cannot accept all demands and alternatives emerged. Several "Do It Yourself" tutorials are available on internet to enable the self-fabrication from a classic underwear, a jockstrap or a bra (144).

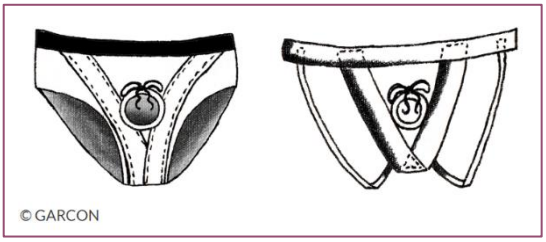

Image 1. Perforated underwear and jockstrap (144)

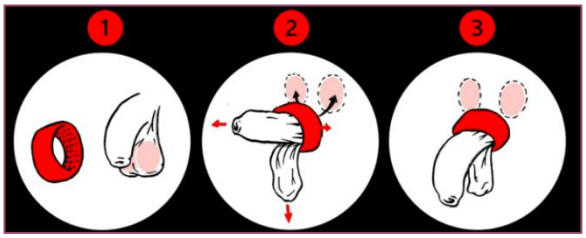

Image 2. Silicone ring, Androswitch (147)

- Silicone rings, such as Androswitch, are inspired by the Toulouse underwear and follow the same wearing protocol. French authorities prohibited the sale of Androswitch in 2021 (145) and, in response, a safety trial is planned for 2024 in order to obtain certification in 2028 (146). In the meantime, some workshops allow men to create their own device.

- A heating underwear with external battery, named SpermaPause (148), is available online. The website claims its efficacy for 4h a day without giving references. It seems there is no certification to this device.

- "Coso", a german scrotal hot bath based on ultrasounds is on development (149).

Image 3. SpermaPause (148)

3 – Successive steps in spermatogenesis inhibition

The spermatogenesis inhibition based methods, here TMC, have no direct impact and its use implicate different phases:

- Pre-heating phase: the man ensure he can use TMC. TMC's contraindications are established as: cryptorchidism or ectopic testicle (treated or not), inguinal hernia (treated or not), testicular cancer, grade 3 varicocele and severe obesity. The pre-heating semen analysis must be normal (sperm concentration above 15millions/ml, progressive motility above 32% and normal morphology) (139).

- Inhibition phase: the man starts using TMC, and the sperm count decreases gradually. Another mean of contraception must be used during this time. Semen analysis should be done monthly until the 6th month, and then every two months.

- Contraceptive phase: the sperm count reaches the threshold of <1 million/ml of spermatozoa on two semen samples (performed three weeks apart). From this moment, TMC is considered effective and can be used as the only contraceptive mean. It is advised to continue regular semen analysis.

- Recovery phase: After the device is stopped, semen analysis must be controlled to ensure a return to baseline values.

ARTICLE

Thermal Male Contraception: A Systematic Review of Efficacy, Reversibility, Safety and Acceptability.

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I. INTRODUCTION

Mankind has always been interested in influencing fertility (1–3). In both France and worldwide, female contraception remains the primary method of choice for most couples (6,7,14). However, finding a suitable solution for each couple can be challenging due to the large number of contraindications to available options, the high frequency of adverse effects and a general growing distrust towards hormonal contraception since the 2012's pill crisis (8–11). This raises questions about the role and responsibility of men in family planning. The three available options for men, namely male condoms, withdrawal and vasectomy, are not fully satisfying (14–16). The idea of new means of male contraception seems to be well received across the world by both women and men (17–22).

Thermal male contraception (TMC) is one of the numerous male contraceptive methods that have been studied over the last decades (25–27). Its principle relies on the reversible inhibition of spermatogenesis induced by heat on the testicles, which involves different phases. After the inhibition phase when sperm count gradually decreases, the sperm concentration reaches the admitted goal of <1million/mL, called contraceptive threshold (99). From this moment, TMC is considered effective and can be used as the only contraceptive mean. Currently, TMC is not widely used or medically recommended by health authorities (145). However, some devices can be found and are already used by some men, being medically monitored or not. Associations (141,142), particularly through social medias, play a significant role in providing information, support and accessibility to devices for men who are willing to implicate themselves in the "contraceptive load" (143). In France, TMC is regularly reported and commented in the press (150–153).

TMC is rather unknown with little public awareness. Indeed, rare are the men and general practitioners to have more than vague notions about TMC. Most of general doctors would be interested in accompanying men in this direction, provided that research produce some robust evidences (28,29). For men interviewed on a potential use, the reception is lukewarm. Concerns about daily discomfort and constraints, as well as interrogations upon long-term side-effects are raised, but the device's simplicity and the absence of chemical or hormonal substances are also brought up (30). The rate of interest for trying TMC ranges from 13% to 59% according to the study (21,29,31).

All those elements manifest the interest of men themselves but also of general practitioners for TMC. Literature on the subject is rather fragmented, offering several propositions, making difficult for interested practitioners that may not have time to develop an expertise, to look to the whole data and to appreciate their quality. A practical guide was published in 2012 (139), and in 2022, 44% of 244 general practitioners interrogated about it reported that the lack of formation, not compensated by the guide, was an obstacle to accompany men in this area (154).

This systematic review aims to synthetize the available data on TMC and to provide a clear and exhaustive overview regarding efficacy, reversibility, safety and acceptability criteria – that should be answered by all contraceptive means – for interested clinicians and to offer some leads to improve future research. Therefore, our research's questions are the following: is thermal male contraception an **[1]** effective, **[2]** reversible, **[3]** safe and **[4]** acceptable contraceptive method?

II. METHOD

Protocol and registration

This systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (155). The review protocol was registered on the International Prospective Register of Systematic reviews (PROSPERO: CRD42023464033) the 30/09/2023 (156).

***Search strategy**:*

A comprehensive literature search was completed until October the 20th, 2023 in the following databases: PubMed, EMbase, Cochrane, Web of Science, Lissa, Sudoc, CisMeF and Google scholar. The latter, according to recent recommendations, has been limited to the first 300 records (157). Search terms were related to three main concepts: contraception, male and thermal. They were limited, when the database allowed to do so, to title, abstract and keywords. The detailed search queries are provided in **Annex n°1**. In addition, the references' lists of included articles and excluded reviews were searched for potential relevant unidentified contributions, and other publications from the interest' authors were screened using ResearchGate.

Study's selection:

The Rayyan program (158) has been used for all selection's stages. First, records were screened for duplicates and those latter were removed. Then, titles and abstracts of records retrieved by the search strategy have been screened independently by two team members with double-blind strategy according to the inclusion and exclusion criteria (see **Table 1**). Discrepancies were solved through discussion between the reviewers. After this step, the full text of selected records were downloaded and, again, screened independently by the two reviewers. When the complete text was not available, the corresponding author was emailed for request.

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
- Population: Humans; men **- Intervention:** Use of a TMC device defined as "the induced elevation of testicular temperature for contraceptive purposes" **- Outcomes:** Research of at least ONE of the following outcomes : Efficacy (pregnancy occurrence or contraceptive threshold's reaching **(99)**); Reversibility (pregnancy occurrence or return of sperm concentration to its baseline value or above >20millions/ml); Safety (occurrence of clinical, biological or histological adverse-effects); Acceptability (satisfaction, cessation rate) **- Studies:** Clinical trials of any type; case-controls; cross-sectional studies; case reports; epidemiological studies; cohort. (retrospective, prospective or transversal data)	**- Population:** Not human; female; children <15 years old **- Intervention:** TMC combined with another method; whole body heating; the potential use of a TMC device; studies of infertility risk factors or passive exposition to elevation of temperature. **- Studies:** Not an original paper (paper reporting data of another study, review); other language than French or English

Frontiers are thin between trials for TMC and research on spermatogenesis. Studies often have the same protocol and outcome, but not for the same reasons. Therefore, some papers which purpose was not exactly contraceptive were included, the doubt benefiting to inclusion. However, we excluded publications with a clearly different purpose (128,159) although their protocols could be considered similar. We did not consider the research on mechanisms of TMC as adverse-effects, thus proteomics analysis and molecular mechanisms were not included for outcomes (136,138). The initial PROSPERO protocol excluded microwaves and ultrasounds as we considered them to be half-heat and half-waves based methods. However after discovering the Coso device (160) we finally decided to include them. Search queries were modified according to this change.

Data extraction:

Data has been extracted by the main author using the Excel software. Afterwards, another team member checked the correctness of the extracted data to minimize the probability of errors. For studies investigating several groups of men, we only extracted data for male thermal contraception groups, as our goal was not to make comparison with other contraceptives.

The authors extracted general and methodological characteristics about the studies. The following information regarding the outcomes were extracted:

- Efficacy: pregnancy occurrence, the number of exposure cycles, the Pearl Index value, the number of men reaching the contraceptive threshold, the mean and range time to achieve it and the number of sperm rebound afterward. Pearl Index, if not directly given by the study, was calculated using the following equation, where exposure cycles are estimated as the number of months:

$$Pearl\ Index = 1200\ x \frac{number\ of\ pregnancy}{number\ of\ exposure\ cycles}$$

- Reversibility: pregnancy occurrence with additional information on the outcome of pregnancy and child's health, the number of recovery of sperm parameters and the necessary time for it to happen.

- Safety: the name of clinical adverse effect and its frequency rate, the name of biological adverse effect and its before/after values (the "after" being the lowest or highest value), the description of biopsy analysis.

- Acceptability: declared satisfaction and number of drop-out for reasons related to the devices.

For better clarity and homogenisation, some results given in days or weeks were converted in the correspondent values in months: days by dividing by 30.5, and weeks by dividing by 4.28.

Quality and risk of bias assessment:

The quality and bias assessment of the included studies was performed by the main author and, again, checked by a second member. These operations were carried out using a combination of different quality assessment tools, according to the type of studies' designs:

- The Cochrane risk of bias (ROB2) for randomized trials, after attending a specific formation from Cochrane France for the use of this tool (161).
- The Newcastle Ottawa Scale (NOS) for non-randomized trials and cohort studies (162), as proposed by Cochrane as a valid alternative to the ROBINS-1 tool (163).
- The Joanna Briggs Institute (JBI) for cross-sectional studies. (164).

In addition to these scores, a descriptive and detailed biases analysis was carried out.

Data analysis and synthesis methods

All studies were eligible for data report and narrative analysis. No meta-analysis was performed due to heterogeneity of data measurements and the multiplicity of devices and study designs.

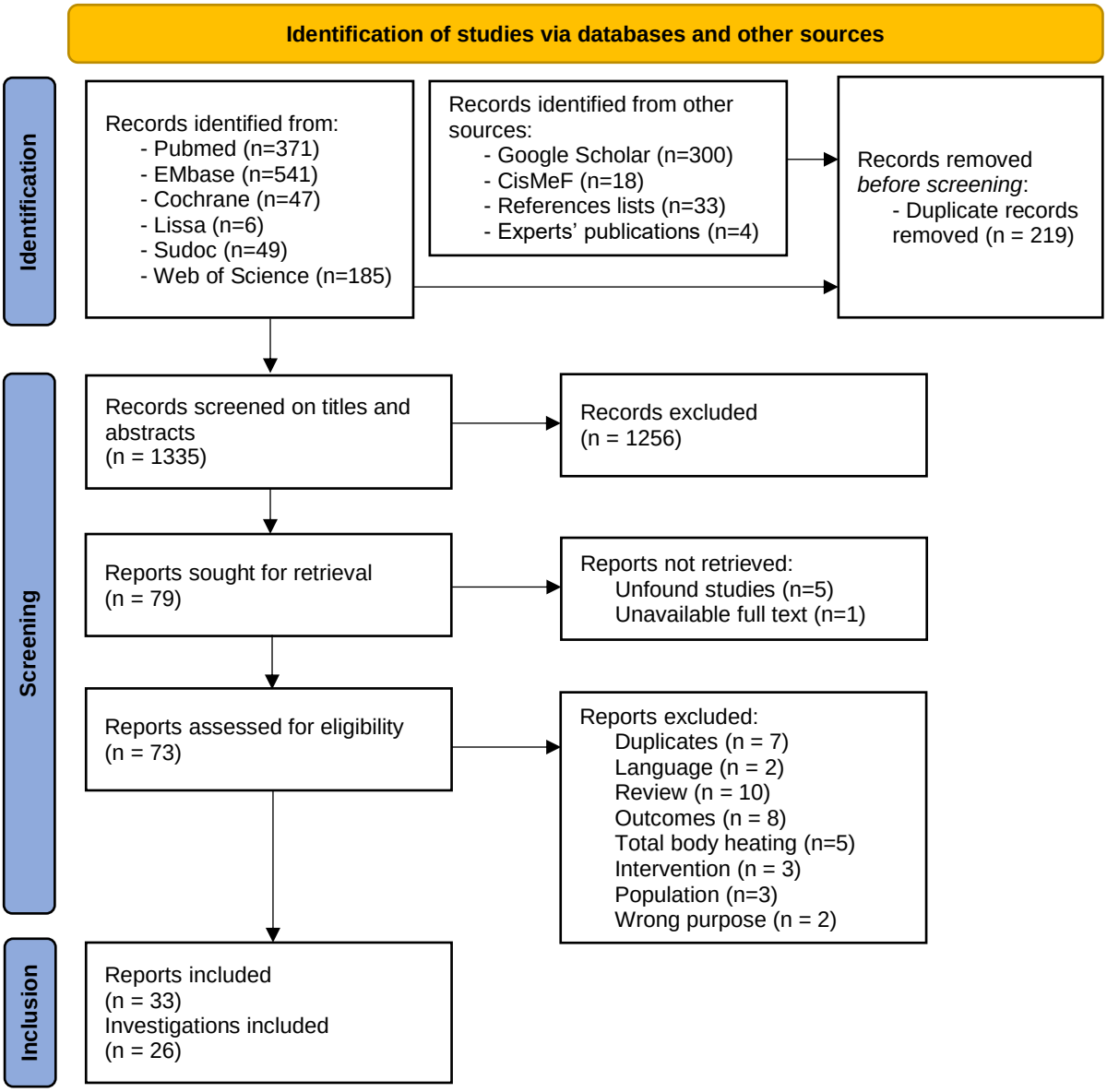
III. RESULTS

1 – RESULTS OF THE SELECTION PROCESS

The whole process of identification and selection is summarized in **Figure 1**. From an initial pool of 1554 records and after the removal of duplicates, 1335 were screened for title and abstract, 79 for full text and finally 33 were included in this systematic review. A list of the excluded reports on full text and the reasons for exclusion is provided in **Annex n°2**.

Several papers described different stages or outcomes of the same experiment whereas others reported several studies in a single publication. Actually, the 33 included contributions report data brought by 26 different investigations (see **Figure 1 – Inclusion**).

Figure 1. Flow chart summarizing the whole process of the identification and selection of studies.

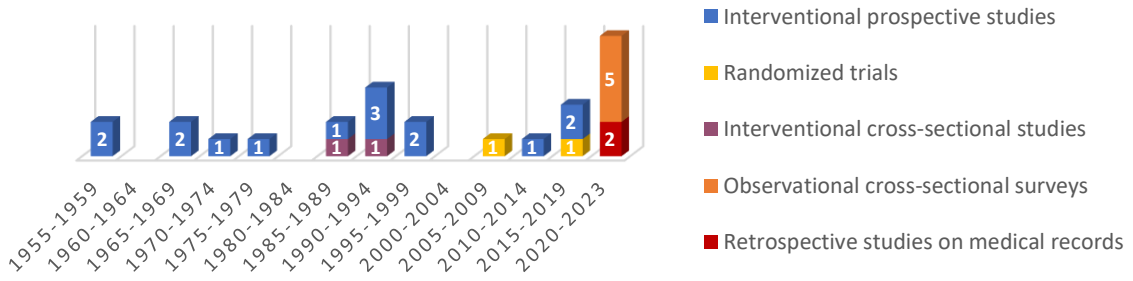


Adapted from PRISMA 2020 (165).

Overview of the main characteristics of the included studies

All studies were conducted between 1956 and 2023 (**Figure 2**.) in several countries, including France, the United States of America, China, Egypt, Indonesia, India, and Japan.

FIGURE 2. MALE THERMAL CONTRACEPTION : TIMELINE OF THE 26 INVESTIGATIONS



From the 26 investigations included (**Figures 1 and 2.**), 19 were interventional. Fourteen were prospective studies with a cross-over design. In these studies, volunteers acted as their own control in three different phases: before, during, and after the application of heat. Semen analysis and other relevant parameters (according to the study) were performed throughout the experimentation. An additional study provided complementary analyses to one experiment, using another group control. Two randomised trials were conducted. One compared different protocols of thermal male contraception (TMC), whereas the second compared hormonal contraception, TMC, and the combination of the two methods. Each group of randomised trials followed the same cross-over design as previously described for prospective studies. Two studies were interventional cross-sectional studies, evaluating long-term effects after exposition to TMC by microwaves, using another group control. Seven studies were observational. Five cross-sectional studies analysed surveys sent to real-life TMC's users with both cross-sectional and retrospective data. Two of these papers simultaneously conducted retrospective studies on medical records.

Of these papers, four of the five cross-sectional surveys, the two retrospective studies and one interventional non-randomised study were unpublished. In addition, part of the study conducted by Ahmad (2011, 2012) was only available as a thesis. All others were published in journals or books dealing with urology, andrology, fertility, contraception, obstetrics, gynaecology, bioelectricity or general medicine.

Out of the 26 investigations, 12 (including five unpublished papers) did not specify the absence of grants or conflicts of interest. Seven had no conflicts of interest. Eleven reported having received a grant from either a national institute, university, or hospital, and one reported having received financial support from an American electronic company.

The 26 investigations analysed a total of 1675 men. The interventional studies had varying sample sizes, ranging from 5 to 35 healthy adult men, often fathers, aged between 18 and 52 years old. Fahim (1977) examined four men aged 52 to 65 years old with prostate carcinoma who were scheduled for orchiectomy. The cross-sectional surveys had sample sizes ranging from 21 to 970 men.

Description of TMC methods

To increase testicular temperature, various approaches were used that can be classified into two categories depending on the heat source: the man's own body or an external heat source. **Table 2 and Table 3** summarize the type, sample size, groups and duration of each study based on the applied technique. A detailed description of the different techniques is available in **Annex n°3**.

Table 2. Use of body as source of heat				
Study	**Type**	**Device and protocol**	**Population size**	**Exposure duration**
Testicular suspension or "artificial cryptorchidism" (+ 1-2°C)				
Total : 11 studies – 4 IP, 5OCS, 2 Retro			**IP: 63; OCS: 1347; Retro: 52 men**	**IP: 4-49 m; OCS: 3-118 m; Retro: 3-15 m**
Mieusset, 1985, 1987a, 1987b, 1991 (166–169)	IP	Perforated underwear (beta) Every day on waking hours (15h/day)	13	6 to 24 months
		Perforated underwear Every day on waking hours (15h/day)	8	6 to 24 months
Mieusset, 1994 (170)	IP	Perforated underwear (beta) Every day on waking hours (15h/day)	3	24 to 38 months
		Perforated underwear Every day on waking hours (15h/day)	6	7 to 49 months
Shafik, 1991 (171)	IP	Surgical suspension	15	12 months
		Suspensory sling with balls Every day (24h)	13	12 months
Ahmad 2011, 2012 (172,173)	IP	Perforated underwear Every day on waking hours (15h/day)	5	4 months
Abdelhamid 2019a, 2019b (174,175)	IP			
Guidarelli, 2023 (176)	OCS	Ring (androswitch) Every day on waking hours (15h/day)	931	970 (rotation between devices) / 6 to 118 months
		Perforated underwear Every day on waking hours (15h/day)	25	
		Others DIY Every day on waking hours (15h/day)	56	
Lalieux, 2022 (177)	OCS	Ring (androswitch) Every day on waking hours (15h/day)	20	3 to 15 months
Lalieux, 2022 (177)	Retro		22	3 to 15 months
Rouanet, 2021 (178)	OCS	Ring (androswitch) Every day on waking hours (15h/day)	233	3 to 18 months
Joubert, 2022 (179)	OCS	Perforated underwear Every day on waking hours (15h/day)	63	Not described
Béraud, 2023 (180)	OCS	Ring (androswitch) Every day on waking hours (15h/day)	49	0 to 4 years
		Perforated underwear Every day on waking hours (15h/day)	4	
		Ring (androswitch) + Perforated underwear Every day on waking hours (15h/day)	6	
Béraud, 2023 (180)	Retro	Unknown	32	3 to 8 months
Testicular suspension with Polyester (+ 0,8 to 2°C)				
Total : 3	**3 IP**		**45 men**	**6-12 months**
Shafik, 1992 (181)	IP	TS + Polyester sling underwear Every day (24h)	14	12 months
Moeloek, 1995 (182)	IP	TS + Polyester sling underwear Every day (24h)	10	6 months
Wang, 1997 (183)	IP	Every day (22-24h) TS + Athletic supporter lined with… ... one polyester layer	7	12 months
		... one polyester layer + one layer of polyester impregnated with aluminium	7	
		... two polyester layers	7	
Insulating underwear (+ 0,3 to 1,1°C)				
Total : 2	**2 IP**		**17 men**	**6-14 weeks**
Rock, 1965 (184)	IP	Various types of underwear insulated with layers of oilcloth, surgical plastic and paper tissue. Every day (24h).	7	6 to 14 weeks
Robinson, 1967 (185)	IP	Athletic supporter insulated with layers of oilcloth and paper tissues. Every day on waking hours.	10	6 to 11 weeks
Voluntary control by meditation and biofeedback (+ 0,9 to 4,5°C)				
Total : 1	**1 IP**		**5 men**	**5 days**
DJ French, 1973 (186)	IP	Meditation – 15 min – Once a day	1	5 days
		Meditation – 30min – Once a day	4	

IP=Interventional Prospective, OCS=Observational Cross-sectional, ICS=Interventional Cross-sectional, Retro=Retrospective, Rando=Randomized trial, TS=Testicular suspension

Table 3. Use of external source of heat				
Study	**Type**	**Device and protocol**	**Population size**	**Exposure duration**
Scrotum immersion in hot bath, or wet heat (40-47°C)				
Total : 5 studies – 3 IP, 2 Rando			**112 men**	**1 day to 28 weeks**
Voegeli, 1956 (187)	IP	Hot baths – 46,6°C – 45min Consecutive days – Once a day	9	3 weeks
Watanabe, 1959 (188)	IP	Hot baths – 43-47°C – 30min Consecutive days – Once a day	27	1 to 12 days
		Hot baths – 43-47°C – 30min Repetitions after an interval of 3 or 4 weeks	8	9 to 28 weeks
Wang, 2007 (189)	Rando	Hot baths – 43°C – 30min Consecutive days – Once a day	18	6 days
Zhang, 2015a, 2015b, 2018a, 2018b (190–193)	IP	Belt with water warming bag – 40-43°C – 40min 2 consecutive days per week	30	3 months
Rao, 2015, 2016 (194,195)	Rando	Hot baths – 43°C – 30min – Once a day	10	10 days
		Hot baths – 43°C – 30min – Once every 3 days	10	30 days
Dry heat				
Total : 2 studies – 1OCS, 1 Retro			**1 man**	**12 months**
Lalieux, 2022 (177)	OCS	Heating underwear (Spermapause) Every day (3-5h)	1	12 months
Lalieux, 2022 (177)	Retro			
Microwaves (40-42°C)				
Total: 2	**2 ICS**		**29 men**	**13 to 176 treatments**
Liu, 1988 (196)	ICS	Microwaves (2,45GHz, 20-30 W) – 40-42°C – 30 min. Once or twice every 3 weeks	16	13 to 60 treatments
Liu, 1991 (197)	ICS		13	14 to 176 treatments
Ultrasounds				
Total: 1	**1 IP**		**4 men**	**Unknown**
Fahim, 1977 (198)	IP	Ultrasounds 1w/sq – 10 min Testis in water cup	4	Not described

IP=Interventional Prospective, OCS=Observational Cross-sectional, ICS=Interventional Cross-sectional, Retro=Retrospective, Rando=Randomized trial

2 – RISK OF BIAS

The main results of risk of bias evaluation are presented in **Table 4** for each study and each evaluation criterion. The details are shown in **Annex n°4**.

Table 4. Risk of bias assessment

Evaluation criteria	Contraceptive threshold	Pregnancy occurrence	Sperm concentration	Pregnancy occurrence	Global sperm concentration	Clinical adverse effects	Biological adverse effects	Histological adverse effects	Cessation rate	Satisfaction
	Efficacy		Reversibility			Security			Acceptability	
Non-randomized interventional prospective studies : Newcastle Ottawa Scale – TOTAL /9 ★										
Voegeli (1956)	/	/	/	3 ★	3 ★	3 ★	3 ★	/	/	/
Watanabe (1959)	/	/	6 ★	/	/	/	6 ★	/	/	/
Rock (1965)	/	/	6 ★	/	6 ★	4 ★	6 ★	/	/	/
Robinson (1967)	/	/	6 ★	/	7 ★	6 ★	7 ★	/	/	/
French (1973)	8 ★	/	8 ★	/	/	/	8 ★	/	/	/
Fahim (1977)	/	/	/	/	/	5 ★	/	7 ★	/	/
Mieusset (1985, 1987a, b, 1991)	/	/	/	8 ★	6 ★	5 ★	7 ★	/	/	/
Mieusset (1994)	7 ★	8 ★	7 ★	8 ★	/	6 ★	/	/	/	/
Shafik (1991)	7 ★	8 ★	7 ★	8 ★	/	7 ★	7 ★	7 ★	/	/
Shafik (1992)	7 ★	8 ★	7 ★	8 ★	/	6 ★	7 ★	6 ★	/	/
Moeloek (1995)	/	/	/	/	7 ★	6 ★	7 ★	/	/	/
Wang (1997)	/	/	/	/	7 ★	6 ★	7 ★	/	/	/
Ahmad (2012a, 2012b)	/	/	/	/	7 ★	/	8 ★	/	/	/
Abdelhamid (2019a, 2019b)	/	/	/	/	/	/	6 ★	/	/	/
Zhang (2015a,b, 2018a,b)	/	/	/	/	8 ★	7 ★	8 ★	/	/	/
Randomized interventional prospective studies = Rob2 – Low risk, Some concerns or High risk of bias										
Wang (2007)	SC	/	SC	/	/	SC	SC	SC	/	/
Rao (2015, 2016)	/	/	SC	/	SC	/	SC	/	/	/
Interventional cross-sectional studies : Joanna Briggs Institute – TOTAL										
Liu (1988)	/	/	/	/	/	/	5/8	/	/	/
Liu (1991)	2/7	/	2/7	3/7	/	2/7	/	5/8	/	/
Observational cross-sectional surveys : Joanna Briggs Institute – TOTAL /8										
Guidarelli (2023)	4	5	4	/	/	4	/	/	7	7
Lalieux (2022)	/	/	/	/	/	4	/	/	7	7
Rouanet (2021)	/	/	/	/	/	4	/	/	7	/
Joubert (2022)	4	4	/	/	/	4	/	/	7	7
Béraud (2023)	4	4	/	/	/	4	/	/	7	7
Retrospective studies on medical records = No evaluation scale (description below)										
Béraud (2023)	HR	/	/	/	/	/	HR	/	/	/
Lalieux (2022)	HR	SC	HR	SC	/	/	HR	/	/	/

SC= Some concerns, HR=High risk

Interventional prospective studies were evaluated with Newcastle Ottawa Scale and share several similarities in biases:

Selection bias: the use of volunteers is usually considered as an auto-selection bias. However, in the particular case of contraception, they are also representative of the target population which is composed of men willing to try the investigated method. Only one study (Moeloek (1995)) selected 10 volunteers with the highest sperm count inducing a recruitment bias that likely led to underestimate the efficacy. Watanabe (1959) selected volunteers from a unique centre (medical students), causing a recruitment bias.

Classification bias: if the blinding of patient or assessors was not possible in that kind of investigation, only one of the non-randomized studies specified having called on a biologist unaware of the use of TMC (Zhang 2015a,b, 2018a,b). Therefore, for all others, the evaluation of sperm parameters or biological adverse effects might have been impacted by evaluation bias (probably in a way that overestimate the alterations). However, several studies specified having the same biologist for all men, limiting the inter and intra-individual variations. Pregnancy, being an objective outcome, was unlikely to be subject to that type of bias. The measurement of clinical side effects was rarely described and might have been underestimated. The protocols using devices that needed to be worn at home could not check the proper compliance of the volunteers. This may have affected outcomes in both directions (men could wear it on shorter period due to the constraint, or wear it longer due to fear of inefficacy)

Confounding bias: they were well controlled by the cross-over like design. Abdelhamid's study (2019a, 2019b) is the only one to compare its outcomes (biological side effects) to another control group. All studies applied an abstinence period before semen analysis, to limit cofounders of sperm count decrease. However, only French (1973) recorded other sources of heat (such as the use of sauna or fever period…) that could also alter sperm parameters. Watanabe (1959) called on 18 volunteers for realising 35 interventions: some men were "used" multiple times after an undescribed "necessary rest". These repetitions of heating could have lead to overestimate alterations. Additionally, treatments or medical conditions that could potentially reduce fertility in women were not taken into consideration for outcomes regarding pregnancy occurrence, at the exception of Shafik's study (1992).

Voegeli's study (1956) was sent to The Lancet but never published. It reports blurred description of the experiment and no proper objective results. It is therefore considered to have a high risk of bias.

Power: The population samples were small (under 30 volunteers), and therefore the power of all studies has been considered as low.

Randomized studies were evaluated with ROB2, thanks to the Excel tool algorithm, after a specific formation from Cochrane France. They share multiple biases with non-randomised trials.

The study of Wang (2007) presents a recruitment bias, all volunteers coming from a unique glass factory. The biopsies were not realized on random patients but on men who already completed their families, and thus probably older than other volunteers. The risk of evaluation bias is low for biological outcomes as blinding was established for biologists and the questionnaire for clinical outcomes was validated. The study of Rao (2015, 2016) did not use blinding, but the results were read by two different biologists. For both studies, the confounding factor of abstinence was controlled, but the occurrence of fever or other heat exposure was not sought for.

Interventional cross-sectional studies were evaluated with Joanna Briggs institute for cross-sectional studies.

Selection bias: Liu (1988 and 1991) examined some volunteers who underwent another previous study (unfound) but the selection of these volunteers was not described, neither was the methodology of the original study, therefore its outcomes may have been misestimated.

Classification bias: The use of blinding was not described and the evaluation of outcomes might have been impacted by evaluation bias (probably in a way that overestimate the alterations).

Confounding bias: Both studies of Liu compared their outcome to another control group without information about their characteristics.

Observational cross-sectional surveys were evaluated with Joanna Briggs institute for cross-sectional studies. All those studies can be considered having a high risk of bias.

Selection bias: While Lalieux (2022) and Joubert (2023) had a high participation rate (95 and 94% respectively), Béraud (2023) had only 60% of answers. Apart from the study of Guidarelli (2023), recruitment was done through a unique channel or medical center and was likely to select men still committed in TMC. Additionally, a minimal period of three or six months of use was requested for Guidarelli (2023), Lalieux (2022) and Rouanet (2021) studies, excluding all men that would have undergone bad experiment before that time due to adverse effect or pregnancy occurrence. Therefore efficacy, safety and acceptability might have been overestimated.

Classification bias: users were responding to surveys in total autonomy. A wrong interpretation of the questions and/or answers and therefore a measurement bias are likely to have occurred. Additionally, the surveys touched upon past data, generating a recall bias for all criteria. The subjective outcomes of acceptability and satisfaction could be less susceptible to bias, but the questionnaire was not standardized or validated. Guidarelli (2023) and Rouanet (2021) had no way to ensure that the answers came from real users of TMC.

No proper risk of bias' tool was found to evaluate the two **retrospective studies**, and they hence are described here.

For both studies, a recruiting bias exists due to the data collection from a single medical centre, the population was not representative of general population. The confounders that could have impacted sperm parameters were not sought for. The sample sizes were small. Béraud (2023) had to exclude a large number of semen samples (due to uncomplete data, or to the absence of a second control sample) potentially creating a sampling bias. In contrast, he might have missed samples that were not tagged as "TMC". All included semen samples were identified as "TMC" and thus sperm impairment could have been overestimated by the informed biologist (evaluation bias). In Lalieux' study (2022), the missing data from medical records and the fact that the consultation were not standardized, led to an information and measurement bias.

3 – EFFICACY

Effectiveness was assessed by two means. The ratio of men reaching the contraceptive threshold is given along with the mean time to achieve this threshold and the number of men experiencing a "sperm rebound", i.e. the elevation of sperm concentration above 1million/ml after the threshold being reached. The occurrence of pregnancy is given with Pearl Index and number of cycles exposure when available. Detailed data are given in **Annex n°5**.

- **Testicular suspension**

Several studies, including two interventional prospective studies, three observational cross-sectional studies, and two retrospective studies involving 37, 1089, and 54 men respectively, have evaluated the contraceptive effectiveness of various testicular suspension devices. The results are presented in **Table 5** for contraceptive threshold and **Table 6** for pregnancy rate.

Table 5. Efficacy according to contraceptive threshold of testicular suspension devices

Study	Devices and Population (N)		Contraceptive threshold Number of men (n (%))			Delay in months (mean ± SD)	Rebound in sperm count (n (%)) *
			Reached	Missing data	Unreached		
Interventional Prospective studies							
Mieusset (1994)	PU (beta)	3	2 (67%)	0	1 (33%)	11±3,2	2 (100%)
Mieusset (1994)	PU	6	6 (100%)	0	0	3.5±2,5	2 (33%)
Shafik (1991)	SS	15	11 (73%)	0	4 (27%)	7.6±2,6	ND
Shafik (1991)	SSB	13	8 (61%)	0	5 (39%)	7.6±2,6	ND
Total		***37***	***27 (73%)***	***0***	***10 (27%)***		***4 (44.4%)***
Observational cross-sectional studies							
Guidarelli (2023)	AS, PU, DIY	970	766 (79%)	143 (14.7%)	61 (6.3%)	3.3±1.3	36
Joubert (2022)	PU	60	59 (98.3%)	0	1 (1.7%)	3.4±0,7	2
Béraud (2023)	AS, PU	59	48 (81.3%)	4 (6.8%)	7 (11.9%)	4.2±1,5	ND
Total		***1089***	***873 (80.2%)***	***147 (13.5%)***	***69 (6.3%)***		
Retrospective studies							
Lalieux (2022)	AS	22	11 (50%)	7 (31.8%)	4 (18.2%)	3.8±1.3	1/5 (20%)
Béraud (2023)	Unknown	32	28 (87.5%)	1 (3.1%)	3 (9.4%)	3.3±1	4/15 (26.7%)
Total		***54***	***39 (72.2%)***	***8 (14.8%)***	***7 (13%)***		***5/20 (25%)***

*AS= Androswitch, PU= Perforated underwear, DIY= Other DIY, SS=Surgical suspension, SSB=Suspensory sling with balls, ND= No data; * = number of men who experienced a rebound among men who reached threshold and performed controls*

One pregnancy occurred during Mieusset's study (1994) with perforated underwear (beta version), and 6 pregnancies were reported in Guidarelli's cross-sectional study (2023). This leads to a pearl Index of 2.9 for all testicular suspension devices in trials, and of 0.53 in cross-sectional surveys. All pregnancies were due to failure to the protocol.

Table 6. Efficacy according to pregnancy rate of testicular suspension devices

Study	Devices and Population (N)		Pregnancy occurrence Number of couple (n (%))	Exposure cycles	Pearl Index
Interventional Prospective studies					
Mieusset 1994	PU (beta)	3	1 (33%)	42	28.6
Mieusset 1994	PU	6	0	117	0
Shafik 1991	SS, SSB	28	0	252	0
Total		***37***	***1***	***411***	***2.9***
Observational cross-sectional studies					
Guidarelli 2023	AS, PU, DIY	964	6 (0.6%)	13634	0.53
Joubert 2022	PU	59	0	ND	ND
Béraud 2023	AS, PU	59	0	ND	ND
Retrospective studies					
Lalieux 2022	AS	6	0	28	0

AS= Androswitch, PU= Perforated underwear, DIY= Other DIY, SS=Surgical suspension, SSB=Suspensory sling with balls ND= No data

- **Other thermal male contraception devices**

The efficacy results for other TMC techniques such as testicular suspension with polyester, meditation and biofeedback, SpermaPause (dry heat), microwaves and hot baths (wet heat) are presented in **Tables 7 and 8.** With regard to meditation and biofeedback, one of the men reaching the threshold had a fever at the same time and therefore his result cannot be taken into consideration.

Table 7. Efficacy according to contraceptive threshold of other devices

Study	Design and Population (N)		Men reaching threshold (n (%))	Delay in months (mean ± SD)	Rebound in sperm count (n (%))*
Testicular suspension with polyester					
Shafik (1992)	IP	14	14 (100%)	3.6±0.7	0/14
Meditation and biofeedback					
French (1973)	IP	5	2 (40%)	0.4±0.1 *(11.5±2.5 days)*	ND
SpermaPause					
Lalieux (2022)	Retro	1	1 (100%)	3	0/1
Microwaves					
Liu (1991)	ICS	13	11 (84.6%)	ND	ND
Hot baths (43°C for 30min) on 6 consecutive days					
Wang (2007)	Rando	18	0	ND	ND

** = number of men who experienced a rebound among men who reached threshold and performed controls*; *IP= Interventional Prospective; Retro= Retrospective; ICS=Interventional cross-sectional; Rando= Randomized trial; ND= No data*

Table 8. Efficacy according to pregnancy rate of other devices

Study	Design and Population (N)		Pregnancy occurrence (n (% of men))	Exposure cycles	Pearl Index
Testicular suspension with polyester					
Shafik (1992)	IP	14	0	98	0
SpermaPause					
Lalieux (2022)	Retro	1	0	12	0

IP= Interventional Prospective; Retro= Retrospective

Narrative analysis: Efficacy

Apart from French's contribution (1973), none of the studies recorded confounding factors such as other exposition to heat (baths, sauna, fever…) that might have decreased the sperm concentration. Likewise, the health of female partners was not registered, some conditions might have explained the absence of pregnancy. However, men were excluded if they were known or suspected to be infertile, and a minimum initial sperm concentration of 15 or 20 million/mL was required for participation. Biologists were not blind of the intervention, and the reading of sperm concentration might have been misestimated. It must be kept in mind that those results are then susceptible to biases, and that the population samples are small.

Observational cross-sectional surveys allow the assessment of device performance in real-life situations and provide a larger sample size. However, they are subject to several biases and cannot be taken as evidence of effectiveness. The data provided are based on self-reporting and cannot be verified. Additionally, the selection process excluded men who had used TMC for less than three or six months, which could have resulted in the exclusion of men who stopped using the device due to not reaching the threshold or due to the arrival of pregnancy. Hence efficacy from those study is likely overestimated.

Among studies investigating testicular suspension, trials reported rates between 61 and 100% for threshold's achievement, depending on the device. Each particular device was evaluated for effectiveness in a single interventional study, and results relied on very small population which might explain these differences. In cross-sectional surveys, this rate was 80.2% for all testicular suspension, although this value was probably both underestimated by the large proportion of missing data (13.5%) and overestimated by the selection bias explained above. The relative influence of each of these opposing biases is difficult to estimate. The delay until threshold retrieved in Shafik's study (1991) appears to be longer than others. This difference can be attributed to the different rhythm of semen

analysis, as in Shafik's study (1991) sperm count was only provided at 6 and 12 months, whereas other studies conducted analysis every two months. The improved version of perforated underwear appeared to be more effective than the beta version in Mieusset's study (1994) with a better rate of reaching the threshold in a shorter time.

All men who used meditation and biofeedback experienced a decrease in their sperm count. In addition to the two men whose sperm concentration reached 1 million/ml, one participant was close to the threshold with a count of 4 million/ml. The remaining two participants were either unable to sufficiently raise their testicular temperature or only underwent 15-minutes sessions. Due to the small population size and the fever confounder in one of the participant, it is not possible to conclude.

A Chinese study, which we could not retrieve, evaluated the effectiveness of microwaves as a form of TMC. According to Liu (1988), the study involved 53 patients who underwent microwave treatment once or twice every three weeks. The two included papers of Liu (1988, 1991) provided complementary analyses of some of these men to investigate the long-term effects of the treatment. The presented effectiveness data is incomplete as it does not indicate the selection criteria for the 13 men. Therefore, the results cannot be accurately interpreted.

The results from SpermaPause cannot be generalised as they are based on a single participant.

Others included studies in this review may support these individual data about threshold's attainment, either by reporting overall mean values of decreased sperm concentration, although these cannot be directly used to evaluate contraceptive efficacy, or by giving individual data with no precision about the threshold. Those additional results are given here and detailed in **Annex n°6.**

Mieusset (1987, 1991) reported a significant decrease of 72% and 96.4% from the sperm concentration baseline value after 4 months of using perforated underwear (beta and improved version, respectively). Those diminutions reached 92.6 and 99.6% at the end of the exposition. In Ahmad's study (2011, 2012), two out of five men became azoospermic after wearing perforated underwear for a period of three to four months. One man had a total sperm count of under 2 million (without further precision), while the other two men had a sperm concentration above 2 million/ml. The mean sperm concentration decreased by 99.5% after 3 months.

The results of Shafik's contribution (1992) seem clear regarding polyester testicular suspension's effectiveness. However, the other two studies on the polyester device did not draw the same conclusion. Moeloek (1995), who used the same device as Shafik, found no azoospermia after six months, but all sperm count still decreased to under 20 million/ml, and mean sperm concentration dropped from 80.9 to 13.3 million/ml. If the experiment had lasted longer, some men might have reached the threshold. The difference in results may be attributed to the fact that the volunteers were selected based on their higher sperm count as well as a difference in ethnicity, all men in Moeloek's study being Indonesian. Moreover, Shafik's study lasted longer. Wang (1997) reported different results, but did not present individual data. The overall effect on spermatogenesis did not show a significant decrease in sperm count, suggesting that none of the volunteers likely reached the threshold. The difference in results was hypothesised by the authors to be due to the use of a different device and a smaller temperature increase, along with a more accurate estimation of baseline sperm count levels as a greater number of samples were employed to establish the baseline value, thereby reducing intra-individual variability. Those explanations do not appear entirely satisfying.

Insulating underwear was not examined for its contraceptive efficacy. However, Robinson (1967) observed a significant decrease in the average sperm concentration beginning three weeks after the start of the intervention, which reached 78.2% by the seventh week. Similarly, Rock (1965) reported a significant decrease in sperm concentration, although the exact value was not provided.

Several hot bath protocols have been tested to investigate the effect of heat on spermatogenesis. However, the use of hot baths as a contraceptive method has not been extensively explored. The lack of threshold attainment in Wang's study (2007) is likely due to the short treatment

period of only six days, as it was not the intended outcome of the study. Rao (2015) compared the effects of daily hot baths for ten consecutive days with those of hot baths every three days for 30 days. The study found that 40% of the 20 men experienced a drop in their sperm count to under 5 million/ml. The mean sperm count decrease ranged from 71.1% to 84.5% at week 8, reaching 14.6±3.6 and 7.4±1.1 million/mL for each group, respectively. Zhang (2015, 2018) conducted a three-month study on 30 patients who received two baths per week. One participant (3.3%) was found to be azoospermic, and seven out of 25 (28%) had a sperm concentration below 15 million/ml. The global sperm concentration decreased by 55.6% from the baseline value at the second month. Additionally, Voegeli (1956) described the use of a daily hot bath at 46.6°C for three weeks to maintain infertility and prevent pregnancy for four to six months, but did not provide any numerical data.

4 – REVERSIBILITY

Individual data allowing to answer the reversibility questions were provided by eight studies for the restoration of sperm concentration (to baseline value or above 20 million/ml) in 116 men and by five studies for the pregnancy occurrence in 40 couples, in addition to a retrospective study of one man using Androswitch. Detailed data are in **Annex n°7**.

All methods considered, 95.7% of 117 men attained reversibility within the mean of 1.8 to 4.3 months after the cessation of TMC. The four missing data represented 3.4%. One man (0.9%) did not restore his sperm count, by either criterion, before being lost to follow-up. Data are presented in **Table 9**.

In the cross-sectional study of Guidarelli (2023), which did not initially evaluate reversibility, one man spontaneously reported not having recover his “fertility” after one year of cessation, without any more details.

Table 9. Reversibility according to sperm concentration

Study and Population (N)			Number of men (n (%))			Mean delay in months (mean±SD)	Maximal delay (months)
			Returning to baseline level	Returning over 20 M/L	Missing data		
Interventional Prospective			**Testicular suspension**				
	Mieusset (1994)	8	7 (87.5%)	ND	1 (12.5%)	ND	18
	Shafik (1991)	28	ND	28 (100%)	0	4.1±1.4*	6
			Testicular suspension + Polyester				
	Shafik (1992)	14	14 (100%)	14 (100%)	0	5.22±0.5$ and 3.6±0.3*	ND
			Insulating underwear				
	Rock (1965)	7	7 (100%)	ND	0	3±0.5$	4.2
	Robinson (1967)	10	10 (100%)	ND	0	ND	2.5
			Meditation with biofeedback				
	French (1973)	5	5 (100%)	ND	0	1.8±1$	3.6
			Hot baths				
	Watanabe (1959) (consecutive days)	23	22 (95.7%)	ND	0	3.3±0.7$	4.7
	Watanabe (1959) (with intervals)	8	3 (37.5%)	5 (62.5%)	3 (37.5%)	4.3±1.2$	6
			Microwaves				
ICS	Liu (1991)	13	ND	13 (100%)	0	ND	12
			Testicular suspension (Androswitch)				
Retro	Lalieux (2022)	1	1 (100%)	ND	0	2$	2

*ND= No data, $= mean delay to return to baseline value, *=mean delay to achieve >20M/ml; Retro=Retrospective study; ICS= Interventional cross-sectional*

The occurrence of pregnancy after cessation of TMC was reported by six studies investigating testicular suspension, testicular suspension with polyester, microwaves and SpermaPause. All couples wishing to have a child succeeded. Out of the 41 reported pregnancies, one ended in a miscarriage while the others were carried to term, resulting in the birth of healthy children. In addition, Voegeli (1956) reported the arrival of healthy wanted children in some couples treated with her method of hot baths. Only Shafik (1991) mentioned the delay until pregnancy: all couples conceived within 14 months.

Narrative analysis: Reversibility

The medical records of the retrospective study had no standardised structure and information about other participants related to reversibility might be missing. The absence of blinding for assessment of sperm concentration may have induced a classification bias in either way (overestimation or underestimation). Otherwise, the outcomes for reversibility in interventional studies were unlikely to be subject to other biases and can be considered quite reliable. However, those data incorporate all individual data of men after the cessation of TMC, whether or not they had reach the contraceptive threshold. Their lower sperm count were therefore not equal.

Four men (3.4%) were missing to assess the return to normal of sperm concentration and probably underestimated recovery. The three men who did not return to their baseline values were lost to follow-up. However, their sperm concentration raised and they would have possibly reached that level if the follow-up had been kept up. Indeed, two of them had already a sperm concentration above 20 million/ml.

Data upon pregnancy are homogeneous. With the exception of the man in Guidarelli's study (2023), for whom we ignore details of his "unfound fertility", TMC seems to be reversible either by return to previous values or by the occurrence of desired pregnancies.

Those individual data, which assess reversibility for each participant as recommended (99), are consistent with all other studies from this review that are reporting global data, i.e. recovery of the average sperm concentration of the population sample (**Annex n°6**). The mean sperm concentration of users of perforated underwear returned to its initial value in 2.4 months in Ahmad's study (2011, 2012). Recovery was achieved in 6 to 8 months in Mieusset's trial (1991), but with no numerical data available, making it difficult to explain the different delay between those two studies. The recovery of average sperm count after the use of hot baths was achieved in all studies within 3 to 4 months.

5 – SAFETY

❖ Clinical safety

Thirteen trials with a total of 190 men mentioned clinical side effects, summarized in **Table 10**. Detailed data are available in **Annex n°8**.

Reports of local irritation due to the devices were rare. Shafik (1991) found that a few men experienced post-surgical pain. In Wang's study (1997), a man wearing a polyester device experienced a mycosis recurrence, and in Robinson's study (1967), some men experienced local irritation due to insulating underwear in summer.

None of the experiments highlighted a decrease in libido. Minor changes were reported by five men in Robinson's study (1967), with some experiencing an increase and others a decrease. Wang (2007) described a significantly higher mean sexual pleasure, enjoyment, activity and satisfaction, and more frequent erections.

Seven studies examined testicular size. Among them, two studies (Shafik 1991 and 1992) did not specify the number of men affected but reported a mean decrease in testicular size of respectively

37% and 16.2% at one year, associated with a softer consistency. These effects were reversible in the following year after cessation. On the other hand, Mieusset (1994), Moeloek (1995), Wang (1997) and Wang (2007) found no changes in testicular dimensions.

Table 10. **Clinical side effects of thermal male contraception devices (number of men (n)) in interventional studies**

	Testicular suspension			TS + Polyester			Insulating underwear		Hot baths			Micro-waves	Ultra-sounds
	Mieusset (1991)	Mieusset (1994)	Shafik (1991)	Shafik (1992)	Moeloek (1995)	Wang (1997)	Rock (1965)	Robinson (1967)	Zhang (2018a, 2018b)	Wang (2007)	Voegeli (1956)	Liu (1991)	Fahim (1977)
Population size	21	9	28	14	10	21	3	10	30	18	9+	13	4
Pain	**0**	**0**	**>1**	**0**	**0**	*ND*	*ND*	*ND*	**0**	*ND*	**0**	*ND*	**0**
Severe discomfort	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**0**	*ND*	**0**	*ND*	*ND*
Skin irritation	*ND*	*ND*	*ND*	**0**	*ND*	*ND*	*ND*	**>1**	*ND*	**0**	**0**	*ND*	*ND*
Mycosis	*ND*	*ND*	*ND*	**0**	*ND*	**1**	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Decreased testicular size	*ND*	**0**	**>1**	**>1**	**0**	**0**	*ND*	*ND*	*ND*	**0**	*ND*	**0**	*ND*
Testicular anomaly	*ND*	**0**	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Varicocoele	*ND*	**0**	*ND*	*ND*	*ND*	**0**	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*
Decreased libido	**0**	**0**	**0**	*ND*	**0**	*ND*	**0**	*ND*	*ND*	*ND*	*ND*	**0**	*ND*
Increased sexual satisfaction	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**>1**	*ND*	*ND*	*ND*
Modified libido (up or down)	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**5**	*ND*	*ND*	*ND*	**0**	*ND*
Erectile modifications	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**0**	*ND*	**0**	*ND*	*ND*	**0**	*ND*
Anejaculation	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**0**	*ND*	*ND*	*ND*	*ND*
Dizziness	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**0**	*ND*	*ND*	*ND*	*ND*
Mood fluctuations	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	**0**	**0**	*ND*	*ND*
Bodyweight impact	*ND*	*ND*	*ND*	*ND*	**0**	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*	*ND*

TS= Testicular suspension, ND= No data

The five observational cross-sectional studies explored additional clinical adverse-effects in real-life utilisation. Between them, they included 1345 men using testicular suspension devices (androswitch, perforated underwear from Toulouse or from DIY tutorials) and one man using SpermaPause. The only side-effect noted by the SpermaPause's user is a burning sensation in the groin during the first utilisations. Side-effects of testicular suspension devices are presented with their frequency in **Table 11**. To preserve the values of the original papers, some of the presented results were not merged for homogenisation and may appear fragmented, as effects were entitled differently depending on the study. Thirty-one answers are missing in Rouanet's study (2.3% of pooled population), reducing the population size at 1314.

Table 11. Clinical side effects of testicular suspension devices (number of men and %) in cross-sectional surveys

CLINICAL SIDE EFFECT	TOTAL	Guidarelli (N=970)	Lalieux (N=20)	Rouanet (N=202)	Joubert (N=63)	Béraud (N=59)
Pain (no specified)	**14%** (48/344)	*ND*	7 (35%)	14 (6.9%)	22 (35%)	5 (8.5%)
Testicular pain	**18.5%** (179/970)	179 (18.5%)	*ND*	*ND*	*ND*	*ND*
Pelvic pain	**9.2%** (89/970)	89 (9.2%)	*ND*	*ND*	*ND*	*ND*
Discomfort (no specified)	**23.8%** (82/344)	*ND*	7 (35%)	14 (6.9%)	35 (56%)	26 (44.1%)
Testicular discomfort	**45.8%** (444/970)	444 (45.8%)	*ND*	*ND*	*ND*	*ND*
Pelvic discomfort	**28.7%** (278/970)	278 (28.7%)	*ND*	*ND*	*ND*	*ND*
Discomfort in some activities	**14.9%** (33/222)	*ND*	4 (20%)	29 (14.3%)	*ND*	*ND*
Burning sensation	4 men	4 (/)	*ND*	*ND*	*ND*	*ND*
Skin irritation or itch (no specified)	**36.6%** (126/344)	*ND*	12 (60%)	51 (25.2%)	37 (59%)	26 (44.1%)
Penile skin irritation	**53.1%** (515/970)	515 (53.1%)	*ND*	*ND*	*ND*	*ND*
Scrotal skin irritation	**51.9%** (503/970)	503 (51.9%)	*ND*	*ND*	*ND*	*ND*
Penile itch	**46%** (446/970)	446 (46%)	*ND*	*ND*	*ND*	*ND*
Scrotal itch	**45.1%** (437/970)	437 (45.1%)	*ND*	*ND*	*ND*	*ND*
Excessive sweating	**5%** (3/63)	*ND*	*ND*	*ND*	3 (5%)	*ND*
Mycosis	**1.4%** (14/970)	14 (1.4%)	*ND*	*ND*	*ND*	*ND*
Allergic reaction	**2.7%** (26/970)	26 (2.7%)	*ND*	*ND*	*ND*	*ND*
Hair's irritation	**27.2%** (327/1172)	313 (32.3%)	*ND*	14 (6.9%)	*ND*	*ND*
Foreskin malposition	3 men	3 (/)	*ND*	*ND*	*ND*	*ND*
Decreased libido	**1.8%** (5/281)	*ND*	0 (0%)	5 (2.5%)	*ND*	0 (0%)
Increased libido	**2.5%** (7/281)	*ND*	0 (0%)	7 (3.5%)	*ND*	0 (0%)
Erectile pain or discomfort	**18.9%** (248/1314)	227 (23.4%)	4 (20%)	8 (3.9%)	9 (14%)	0 (0%)
Erection modification (hardness)	**4.8%** (47/970)	47 (4.8%)	*ND*	*ND*	*ND*	*ND*
Erection modification (duration)	**3.9%** (38/970)	38 (3.9%)	*ND*	*ND*	*ND*	*ND*
Erection > 4 hours	**0.1%** (1/970)	1 (0.1%)	*ND*	*ND*	*ND*	*ND*
Erection modification (rapidity)	**2.6%** (25/970)	25 (2.6%)	*ND*	*ND*	*ND*	*ND*
Unusual penile curvature	**0.3%** (3/970)	3 (0.3%)	*ND*	*ND*	*ND*	*ND*
Sexual negative impact	**1%** (11/1068)	10/866 (1.2%)	*ND*	1 (0.5%)	*ND*	*ND*
Sexual positive impact	**51.7%** (553/1068)	544/866 (62.8%)	*ND*	9 (4.5%)	*ND*	*ND*
Ejaculation or sperm modifications	**1%** (2/202) + 4	4 (/)	*ND*	2 (1%)	*ND*	*ND*
Decreased testicular size	**28%** (328/1172)	306 (31.5%)	*ND*	22 (10.9%)	*ND*	*ND*
Testicular induration	**0.3%** (3/970)	3 (0.3%)	*ND*	*ND*	*ND*	*ND*
Testicular torsion	**0%** (0/970)	0 (0%)	*ND*	*ND*	*ND*	*ND*
Urinary modifications	**27.8%** (275/990)	274 (28.2%)	1 (5%)	*ND*	*ND*	*ND*
Unusual delayed last drops	**21.4%** (208/970)	208 (21.4%)	*ND*	*ND*	*ND*	*ND*
Sensation of incomplete urination	**7.9%** (77/970)	77 (7.9%)	*ND*	*ND*	*ND*	*ND*
Blockade sensation (need to push)	**4.1%** (40/970)	40 (4.1%)	*ND*	*ND*	*ND*	*ND*
Delayed start for urination	**3.6%** (35/970)	35 (3.6%)	*ND*	*ND*	*ND*	*ND*
Difficulty to urinate	**1.3%** (13/970)	13 (1.3%)	*ND*	*ND*	*ND*	*ND*
Urine leakage	**0.9%** (9/970)	9 (0.9%)	*ND*	*ND*	*ND*	*ND*
Urinary infections	**0.3%** (3/970)	3 (0.3%)	*ND*	*ND*	*ND*	*ND*
Hematuria	**0.1%** (1/970)	1 (0.1%)	*ND*	*ND*	*ND*	*ND*
Pollakiuria	21 men	21 (/)	*ND*	*ND*	*ND*	*ND*
Overactive bladder	5 men	5 (/)	*ND*	*ND*	*ND*	*ND*
Renal colic	1 man	1 (/)	*ND*	*ND*	*ND*	*ND*
Penis venous thrombosis	1 man	1 (/)	*ND*	*ND*	*ND*	*ND*
Penis oedema	**0.9%** (9/970)	9 (0.9%)	*ND*	*ND*	*ND*	*ND*
Scrotal or testicular oedema	**1.3%** (13/970)	13 (1.3%)	*ND*	*ND*	*ND*	*ND*
Inguinal oedema	3 men	3 (/)	*ND*	*ND*	*ND*	*ND*
Decreased penis sensitivity	**0.1%** (1/970)	1 (0.1%)	*ND*	*ND*	*ND*	*ND*
Dizziness (at first uses)	**12.5%** (121/970)	121 (12.5%)	*ND*	*ND*	*ND*	*ND*
Fainting (at first uses)	**0.1%** (1/970)	1 (0.1%)	*ND*	*ND*	*ND*	*ND*
Depression	**0.5%** (1/202)	*ND*	*ND*	1 (0.5%)	*ND*	*ND*
No adverse effect	**7.2%** (80/1112)	51 (5.2%)	2 (10%)	*ND*	3 (5%)	24 (40.7%)

Notes: ND= No data; Number without percentages are due to spontaneous reports which do not allow to quantify a frequency

Very common ≥10%	*Common 1 – 9.9%*	*Uncommon 0.1 – 0.9%*	*Rare <0.1%*

(199)

Narrative analysis: clinical safety

Clinical safety was not the primary outcome in any of the interventional trials, regardless of the heating technique used. They were often imprecisely described and referred to as 'no complications' or 'no pain or other side-effects'. There is no mention of systematically asking questions to look for the subjective effects, or whether it was based on spontaneous declaration, which may have led to an underestimation of the frequency.

All effects in cross-sectional studies were reported by the users through a questionnaire and therefore could not be clinically objectified nor more clarified on the circumstances of occurrence. The causal relation between the device and the effects could not be confirmed. In addition, the studies conducted by Guidarelli (2023), Lalieux (2022) and Rouanet (2021), which represent the majority of the population sample, excluded men who used TMC for less than three or six months, potentially underestimating the occurrence frequency of side effects.

While adverse effects were rarely reported in trials, they were reported by 92.8% of men in cross-sectional surveys. The discordant results in side effects frequency between trials and cross-sectional surveys might be due to the different methods used to recover the data, as explained above.

The most commonly reported effects for testicular suspension devices were local pain (6.9% to 18.5%), discomfort (14.9% to 45.8%) and irritation (27.2% to 53.1%). The variance in sample sizes of cross-sectional studies and the diversity of used questionnaires and items can explain the large range of values. The exact incidence may be difficult to assess, but those results indicate a very high frequency (>10% (199)) of local benign effects.

Testicular size's reduction was perceived by 28% of men in cross-sectional surveys. The variability in results regarding testicular size among trials could be due to the subjective nature of the evaluation in Mieusset's study (1994) while Shafik (1991 and 1992) used an orchidometer, limiting subjectivity. In addition, the lower effect on spermatogenesis found by Moeloek (1995) and Wang (1997) compared to Shafik may not be sufficient to cause such a reduction in testicle's volume. Wang (2007) found no changes either, but the heat treatment only lasted for 6 days. These findings are suggesting an impact on testicular size.

Erectile functions, urinary functions or oedema were investigated by a single survey. This study had the greater sample size and its findings, although being at risk of biases, are suggestive of damages on the structures nearby the device.

❖ Biological safety

Under the term "biological adverse-effects", we combined all effects not felt by the patient but affecting either blood or other characteristics of semen, spermatozoa and testicles. None of those adverse effects were evaluated through individual data and therefore no frequency rate is available. They have been however studied as global effects in numerous studies. **Table 12** provide an overview of those effects which are detailed below. Extracted data are given in **Annex n°8**.

Table 12. Biological adverse effects of thermal male contraception (1/2)

	Mieusset (1985, 1987)	Shafik (1991)	Moeloek (1995)	French (1973)	Watanabe (1959)	Rock (1965)	Robinson (1967)	Wang (1997)	Ahmad (2011, 2012)	Abdelhamid (2019a, b)	Zhang (2015a, b, 2018a. b)	Béraud (2023)	Lalieux (2022)	Rao (2015, 2016)	Liu (1988)	Voegeli (1956)
Conventional semen parameters																
Semen pH	=	ND	ND	ND	=	ND	ND	ND	=	ND	ND	ND	ND	↘p	ND	ND
Semen volume	↘p	ND	=	=	=	=	=	=	=	ND	=	=	ND	=	ND	ND
Sperm motility	↘p	↘*	=	ND	↘*	ND	ND	=	↘p	ND	↘p	↘p	↘*	↘p	ND	↘*
Sperm vitality	=	ND	ND	ND	ND	ND	ND	=	↘p	ND	↘p	ND	ND	↘p	ND	ND
Abnormal forms	↗p	↗*	↗p	ND	=	=	ND	=	↗p	↗p	↗p	ND	↗*	ND	↗p	ND
Additional semen parameters for sperm functions																
Velocity	ND	ND	↘p	ND	ND	ND	ND	=	ND	ND	ND	ND	ND	ND	ND	ND
Fertilizing capacity	ND	ND	ND	ND	ND	ND	ND	=	ND	ND	↘p	ND	ND	↘p	ND	ND
Epididymal and seminal biochemical markers																
L-Carnitine	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	↘p	ND	ND	ND	ND	ND
NAG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	↘p	ND	ND	=	ND	ND
Fructose	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	=	ND	ND
Zinc	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	=	ND	ND
DNA parameters																
DNA damages	ND	ND	ND	ND	ND	ND	ND	ND	↗p	ND	↗p	ND	ND	↗p	ND	ND
Chromatin maturity	ND	ND	ND	ND	ND	ND	ND	ND	↘p	ND	↘p	ND	ND	ND	ND	ND
Aneuploidy rate	ND	ND	ND	ND	ND	ND	ND	ND	ND	↗p	↗p	ND	ND	ND	ND	ND

*ND= No data, *= Observed results but no statistical analysis performed, ↘p or ↗p = Significant results (p <0.05)*

Table 12. Biological adverse effects of thermal male contraception (2/2)

	Shafik (1991)	Shafik (1992)	Moeloek (1995)	Zhang (2015a, b, 2018a, b)	Rao (2015, 2016)	Wang (2007)
Serum hormonal concentrations						
Testosterone	↘p	=	ND	↘p	=	=
Oestrogens	ND	ND	ND	ND	↘p	ND
LH	=	=	ND	↗p	=	=
FSH	=	=	ND	↗p	=	=
SHBG	ND	ND	ND	ND	=	=
Inhibin	ND	ND	ND	ND	ND	=
Prolactin	↗p	=	ND	ND	ND	ND
Blood parameters						
Liver enzymes	ND	ND	=	ND	ND	=
PSA	ND	ND	ND	ND	ND	=
HDL cholesterol	ND	ND	ND	ND	ND	=
LDL cholesterol	ND	ND	ND	ND	ND	↗p
Haemoglobin	ND	ND	=	ND	ND	↗p
Haematocrit	ND	ND	=	ND	ND	↗p
White blood cells	ND	ND	=	ND	ND	ND
Platelets	ND	ND	=	ND	ND	ND
Creatinine	ND	ND	=	ND	ND	ND
Urea nitrogen	ND	ND	=	ND	ND	ND

ND= No data, ↘p or ↗p = Significant results (p <0.05)

- **Other conventional semen parameters**:

- Sperm pH has been assessed by four studies. While Mieusset (1985), Watanabe (1959) and Ahmad (2012) found no changes throughout their experiments, a significant decrease of mean pH (from 7.7±0.04 to 7.3±0.1) happened in 10 men who underwent hot baths during 10 consecutive days, in Rao's study (2015). This decrease showed no reversibility at the end of the 16 observations weeks. The group which had hot baths every 3 days during one month only showed once this significant decrease, but returned to initial value at the 12th week.

- Sperm volume was reported by 11 studies. Only Mieusset (1985) found a significant decrease (from 3.6±1.2 to 2.8±1.3mL) in a unique occasion at the 4th week, with no significant difference afterwards. Robinson (1967) found high intra-individual variations in both direction. The nine other studies reported no changes.

- Sperm motility (spermatozoa effecting movements) or progressive motility (spermatozoa able to move and progress) were looked for in 11 studies (numerical results are presented in **Table 13)**. Five reported a significant reduction, while four others described a decrease without performing statistical analysis. Lalieux (2022) had ten missing data at the sixth month. Moeloek (1995) and Wang (1997) did not display detailed results, but there was no statistical difference. Watanabe (1959) did not provide numeral values as well, but reported a decrease in motility. Voegeli (1956) reported a decreased motility at 41.6°C and a total suppression at 46.6°C. Whereas return to baseline value was seen in most studies, it was not the case of Zhang (2018) who reported no recovery at 3 months after cessation of heating.

Table 13. Sperm motility variation (% of motile spermatozoa: mean ± SD or median [Q1-Q3])

	Mieusset (1987) Group 1 (N=13)	Mieusset (1987) Group 2 (N=6)	Shafik (1991)	Lalieux (2022) (N=15)	Rao (2015, 2016) Group 1 (N=10)	Rao (2015, 2016) Group 2 (N=10)	Ahmad (2011, 2012) (N=5)	Zhang (2015a, b, 2018a, b) (N=30)	Béraud (2023) (N=32)
	Motility				Progressive motility				
Baseline value (%)	67±5	64±3	>70	54.7±12.6	55.4±2.8	62±3.4	47±1	56.6±13	47.5 [37-55.5]
Minimal value (%)	22±10 ^{p}	5±5 ^{p}	11 *	3.2±4 *	33.4±6.5 ^{p}	35.4±4.7 ^{p}	7.4±3.5 ^{p}	18.8±14.8 ^{p}	0 ^{p}
Time of minimal value (months)	10	10	12	6	1.4	1.4	1.5	2	ND
Max. recovery delay (months)	8	8	9	ND	3.3	2.3	2.4	None at 3	ND

*p= significant difference (p<0.05), *=statistical analysis not performed*

- Vitality (or viability), meaning percentage of living spermatozoa, was assessed by five studies. Different methods were used: the classical staining with eosin-nigrosin, but also hypo-osmotic swelling assay. **Table 14** displays quantitative results. Three studies reported significant decrease during heating. Wang (1997) did not share numerical values and found no modification in vitality.

Table 14. Sperm vitality (% of living spermatozoa: mean ± SD)

	Mieusset (1985) (N=14) EN	Ahmad (2011, 2012) (N=5) EN	Zhang (2015a, b, 2018a, b) (N=30) EN+HOS	Rao (2015, 2016) Group 1 (N=10) HOS	Rao (2015, 2016) Group 2 (N=10) HOS
Baseline value (%)	92±4	73.2±1.7	76.7±7.8	74.9±1.7	80.5±2.1
Minimal value (%)	90±4	20±15 ^{p}	29.2±15.9 ^{p}	46.3±6.3 ^{p}	49±5.5 ^{p}
Time of minimal value (months)	ND	3.2	3	1.4	1.4
Max. recovery delay (months)	8	2.5	2	2.3	2.8

EN= Eosin-nigrosin, HOS=Hypo-Osmotic Swelling; p= significant difference (p<0.05), ND=No Data

- Morphology was evaluated by ten studies during hyperthermia and by one study one year after the cessation of heating by microwaves (Liu (1988)). The latter compared the exposed men to a control group and found a significant increase of cells with nucleated anomalies (4.1±1.9% vs. 1.2±0.4%) and deformed cells (1.4±1% vs. 0.3±0.2%).

Numerical data are given in **Table 15**. Fourteen samples on 15 in Lalieux's study (2022) could not be analysed for morphology and therefore the maximal value is the one of a unique man. 100% of men in Moeloek's trial (1995) had normal forms below 30% (considered as teratozoospermia) at 21 weeks of heating. Wang (1997) and Watanabe (1959) reported no changes in sperm morphology. Rock (1965) did not record change in abnormal forms, except for the man who wore the device for 14 weeks, who showed "a high level of dyspermia" without any more indications.

Table 15. Sperm abnormal forms (mean ± SD)

	Mieusset (1987b) Group 1 (N=13)	Mieusset (1987b) Group 2 (N=6)	Shafik (1991) (N=28)	Ahmad (2011), Abdelhamid (2019b) (N=5)	Zhang (2015a, b, 2018a, b) (N=30)	Moeloek (1995) (N=10)	Lalieux (2022) (N=15)
Baseline value (%)	27±3	27.5±7.5	<40	70	53.3±13.6	42	91.8±3.9
Maximal value (%)	48±6 ^{p}	68±5 ^{p}	88 *	97 ^{p}	97.2±1.7 ^{p}	81 ^{p}	98 *
Time of maximal value (months)	12	10	12	1.5	3	5.6	6
Max. recovery delay (months)	8	8	6	2.4	3	ND	ND

*p= significant difference (p<0.05); *=statistical analysis not performed*

Mieusset (1987b) investigated the different types of morphology anomalies. The deformed cells presented anomalies of the head (elongated, thin, irregular), and of the middle piece of the tail (especially bent tail). Those anomalies did not share the same reversibility's chronology: if tail's anomalies recovered in 12 months, head anomalies remained higher than initial values for 18 months. There were no significant differences in reversibility between men who wore the device for less than one year and those who wore it for more than two years. Ahmad (2011) and Abdelhamid (2019b) reported additional abnormalities such as acrosomal defects, and other anomalies of principal piece of the tail (absent, coiled or multiple).

In addition to percentage of abnormal forms, morphology can be assessed by multiple anomalies index (MAI). Ahmad (2011) and Abdelhamid (2019b) observed in 5 men with perforated underwear an increased MAI as early as the 9th day after beginning of heating, until 45 days after cessation, from 1.9 to more than 2.5. It returned to baseline values at 73 days after cessation. Some check points were not significant, each time because the volunteers had not enough sperm count to observe abnormalities or one sample was missing.

- **Additional semen parameters for sperm functions**:

- Velocity (speed) of spermatozoa was assessed by two studies. Wang (1997) reported no modification. Moeloek (1995) found a significant decrease of speed (from 1.05 to 1.26 seconds for 0.05mm) in all the men of the study.

- Fertilizing capacity, assessed by acrosin activity in two studies, was significantly decreased in Zhang's study (2018) from 66.2±27.5 to 22.5±18.9 µIU/10^{6} and in Rao's study (2015). Recovery occurred in 2 and 3 months respectively for those studies. Additionally, Wang (1997) used the zona-free hamster oocyte penetration test to evaluate this function, but there was no changes.

- **Epididymal and seminal biochemical markers**:

Zhang (2018) reported a significantly decreased seminal plasma concentrations of L-carnitine (from 20.76±4.72ng/mL to 11.51±3.49) until 2 months after cessation. In the same study, neutral α-glucosidase (NAG) was also significantly lower, from 20.76±4.72U/ml to 11.51±3.49 with a recovery at 2 months after cessation. However, it was unchanged in Rao (2015), as well as seminal level of fructose and zinc.

- **DNA parameters**:

- DNA damages to spermatozoa were evaluated in three studies. The chromatin integrity was assessed by four measures: DNA fragmentation index (DFI), High DNA stainability (HDS), DNA fragmentation by TUNEL assay (TUNEL) and DNA denaturation by acridine orange (AO).

The rise in DFI and HDS occurred as early as the 20th day of heating in Ahmad's study (2012). All parameters recovered at 2 or 3 months after the end of heating.

In addition to the numerical values shown in **Table 16**, Rao (2016) reported a significant increase in TUNEL assay and HDS in both group (significantly higher in the group with intervals), with a return to normal at 10th to 12th week post-heating. In the group of hot bath during 10 consecutive days, DFI was significantly higher, whereas in the group with intervals of 3 days during one month, the apparent increase was not significant.

Table 16. DNA damages (%, mean ± SD)

	Ahmad (2012) (N=5)	Zhang (2015a, b, 2018a, b) (N=30)	Ahmad (2012) (N=5)	Zhang (2015a, b, 2018a, b) (N=30)	Zhang (2015a, b, 2018a, b) (N=30)	Zhang (2015a, b, 2018a, b) (N=30)
	DNA fragmentation index (DFI) (%)		High DNA stainability (HDS) (%)		TUNEL (%)	AO (%)
Baseline value	11.9±1.5	11.8±2.4	5.9±0.3	6.7±2.1	11.9±2.4	15±3.9
Maximal value	31.3±5.4 p	68.9±25.1 p	13±1.1 p	33.3±13.2 p	68.9±25.5 p	79.4±19.9 p
Max. recovery delay (months)	2.4	2	2.4	2	3	2

p= significant difference (p<0.05)

- Chromatin immaturity, assessed by aniline blue test, was evaluated in two publications. In the investigation of Ahmad (2011), the tendency was not always significant (due to a small sperm concentration) but normal spermatozoa decreased from 87±0.4 to 77±4%. Zhang (2018) described that normal spermatozoa significantly decreased from 77.3±6.1 to 20.9±21.9%, and reversibility occurred at 2 months after cessation.

- Sperm aneuploidy (abnormal chromosome number) was investigated by two studies on a total of 15 men. Abdelhamid (2019a) observed an increase of aneuploidy among spermatozoa 45 days after cessation of the heating. During the heating phase, at 34 days, no difference was outlined, and FISH analysis could not be done afterwards, due to an insufficient number of spermatozoa. At 45 days after cessation, however, the percentage of spermatozoa with aneuploidy was significantly higher (from median 0.73[0.58-1.19] to 1.93[1.62-2.19]), a consequence of an increase in sex disomic (XY18), sex nullisomic (18) and diploid (XY1818) sperm cells. All five men presented an aneuploidy rate above the 90th percentile of the control group. These results were reversible at 180 days post-heating (6 months).

Zhang (2018) found in ten men a significant increase for all forms of aneuploidy at three months of heating, from mean 1.7 to 13.7%, consequence of an increase of anomalies in both sexual chromosomes and chromosomes 13, 18 and 21. Recovery of those anomalies was not evaluated.

- **Serum hormonal concentrations**:

Five studies controlled plasmatic hormonal concentrations, which results are presented in **Table 17**. Shafik (1991) and Zhang (2018) showed a return to normal levels three months after release.

Table 17. Hormonal concentrations pre and during heating (mean ± SD or median [Q1-Q3])

	Testosterone (ng/mL)		Oestrogens		LH (mIU/mL)		FSH (mIU/mL)		SHBG		Inhibin		Prolactin (ng/mL)	
	Pre	H	Pre	H	Pre	H	Pre	H	Pre	H	Pre	H	Pre	H
Shafik (1991) (N=28)	6.5±1.8	3.4± 1.3 [p]	/	/	NND	NND	NND	NND	/	/	/	/	5.3± 1.6	8.4± 1.9 [p]
Shafik (1992) (N=14)	6.3±1.6	6± 1.8	/	/	5± 1.1	5.4± 1.5	7.4± 2	7.6± 1.9	/	/	/	/	5.3± 1.4	5.8± 1.3
Wang (2007) (N=18)	4.6 [3.5 - 5.1]	NND	/	/	NND	NND	NND	NND	NND	NND	NND	NND	/	/
Zhang (2018) (N=30)	15.3±6.7	8± 5.2 [p]	/	/	5.2± 2	6.9± 2.3 [p]	4.5± 2.3	8± 6.5 [p]	/	/	/	/	/	/
Rao (2015) (N=20)	NND	NND	NND	NND [p]	NND	NND	NND	NND	NND	NND	/	/	/	/

Pre= Pre-heating phase (baseline); H= heating phase, NND= No Numerical Data provided, /= Not evaluated by this study, p= Significant difference (p<0.05)

- **Blood parameters**:

In the two studies evaluating blood parameters, no quantitative data was reported. Moeloek (1995) found no changes in haemoglobin, haematocrit, white blood cells, platelets, liver enzymes, blood urea nitrogen or creatinine. Wang (2007) showed no modifications in liver enzymes, HDL cholesterol or PSA. However, she reported significant but "small" increase in haemoglobin, haematocrit and LDL cholesterol, without giving any values.

Narrative analysis: biological safety

Apart from the studies of Zhang (2015, 2018) and Wang (2007), none of the studies reviewed declared an outcome measurement using blinding. Therefore, subjective outcomes such as semen parameters were susceptible to an evaluation bias, probably in a way which overestimate the alterations. In Rao's experiment (2015, 2016), risks were reduced by the double check by two different biologists. Retrospective studies (Lalieux (2022) and Béraud (2023)) were both susceptible to sampling bias as they may have not include all semen analysis of interest in their studies. Confounding biases were well controlled by the cross-over design. Only Abdelhamid (2019b) and Liu (1988) compared their population to a different control group for morphology outcome. Whereas Abdelhamid checked that the two groups were comparable, Liu did not. Abdelhamid (2019a) employed a cross-over design to compare aneuploidy rate, but used a larger group control in order to determine a percentile limit.

Wang (1997) found no differences in any of the parameters tested, possibly due to the mild heating method used (testicular suspension with polyester) which caused few effect on sperm concentration. Indeed, temperature rise was less than 1°C and this might not have been sufficient to impairs others sperm parameters.

Results mostly agree in indicating that TMC damages spermatozoa's motility, vitality and morphology. However, data regarding the recovery period of those effects are discordant and range from 2.3 to 9 months. This is not especially explained, but the common characteristic of Mieusset (1987) and Shafik's (1991) studies is the one-year duration, while studies with a faster recovery tested TMC for only 3 and 4 months. The initial percentage of normal spermatozoa varied between studies, possibly due to differences in the methods and staining used to assess morphology.

Results upon velocity and fertilizing capacity are few and heterogeneous: once again Wang (1997) found no changes, probably for the reasons explained above.

The epididymis function, necessary for sperm storage and maturation, was evaluated by concentration of seminal molecules or proteins. Zhang (2018a) and Zhang (2018b) reported exactly the same values for L-carnitine and neutral α-glucosidase, therefore we hypothesized an error in the study's writing and we cannot conclude about this effect.

DNA damages were assessed by different measures recommended in the 2021's World Health Organisation (WHO) manual for semen analysis (200). These different methods of assessment allow a record linkage, which is of low risk of bias, despite the absence of blinding by Ahmad (2012). All results, conducted by three studies, are consistent. Results on 15 men suggest similar damages to spermatozoa's chromosomes as the aneuploidy rate significantly increased. The reversibility of this effect is suggested but the power of the study (five men) is insufficient to draw conclusions.

Two studies found a significant decrease in testosterone plasma levels after testicular suspension on a one-year duration, and hot baths during three months. Testosterone concentrations were unchanged in three additional studies, evaluating both hot baths and mild heating with polyester, with different duration as well. There may be a difference in hormonal assay methods, as Wang (2007) and Rao (2015) specified dosing serum testosterone, both free and total, while the other three sources did not provide such details. However, it is unlikely that Shafik used two different measurements between his two studies (1991 and 1992). Therefore no explanation is found to this discrepancy and we cannot reach any conclusion. Results of LH and FSH variations, measured by five studies, were also discordant. Other hormones were evaluated in either one or two studies, which do not allow to draw conclusions. Not enough studies assessed blood parameters to draw a conclusion.

❖ Histological safety

Five studies performed testicular biopsies. Presence or absence of histological anomalies are presented in **Table 18** and details are described below.

Table 18. Presence of testicular histological anomalies during and after thermal male contraception.

	Study and device	Shafik (1991) TS	Shafik (1992) TS + polyester	Wang (2007) Hot baths	Fahim (1977) Ultrasounds	Liu (1991) Microwaves
	Population (N)	**28**	**14**	**4**	**4**	**13**
During spermatogenesis inhibition	**Germ cells apoptosis**	Yes	Yes	Yes	Yes	/
	Stem cells apoptosis	Yes	/	/	/	/
	Tubules structure impairment	Yes	Yes	/	Yes	/
	Sertoli's cells damages	/	/	/	Yes	/
	Interstitial tissue damages	Yes	/	/	No	/
	Leydig's cells damages	No	/	/	No	/
	Basal membrane	/	/	/	/	/
After recovery of spermatogenesis	**Germ cells apoptosis**	No	/	/	/	Yes
	Stem cells apoptosis	No	/	/	/	/
	Tubules structure impairment	No	/	No	/	Yes
	Sertoli's cells damages	/	/	/	/	/
	Interstitial tissue damages	No	/	/	/	Yes
	Leydig's cells damages	No	/	/	/	Yes
	Basal membrane	/	/	/	/	Yes

TS = Testicular suspension; / = No data or not specified

Shafik (1991) reported that biopsies carried out during the heating phase (at 6 and 12 months) showed degeneration of spermatogonia and spermatocytes lining the seminiferous tubules. At 12 months, the centres of the tubules were filled with sloughed germ cells. The interstitial tissue was oedematous, but with normal Leydig's cells. Biopsies taken 12 months after the end of the experiment were similar to those taken before treatment.

Shafik (1992) demonstrated degenerative changes in germ cells in 14 men, with some sloughing in the centre of the tubule, six months after the beginning of the heating phase.

Wang (2007) reported a significant increase in germ cell apoptosis in four men two weeks after heating. At nine weeks, when sperm concentration was restored, there were no changes in the diameter or volume of the seminiferous tubule, and the morphological appearance was similar to that of the control group.

Fahim (1977) reported that in four men, two weeks after ultrasounds, there was an impairment of 95% of tubules, with 50% being totally degenerated and hyalinised, 45% composed solely of Sertoli cells, and only 5% of tubules had cells in different stages of spermatogenesis (usually at early stages). The interstitial cells were normal.

Liu (1991) performed testicular biopsies on 13 volunteers, 1.5 years after the end of microwaves treatment. The proportion of normal tubules was conserved between the exposed and control groups, with 16.1% and 14.8% respectively. However, abnormal tubules showed significantly more severe damage in the exposed subjects, with 28.5% being exfoliative tubules (compared to 12.5% in the control group) and 5.2% being severely damaged (compared to 0.4% in the control group). The proportion of simply disturbed tubules was higher in the control group (72.4% compared to 50.2% in the exposed group). There was no correlation between exposure duration and the degree of degeneration. Most of the degenerated germ cells were primary spermatocytes and early spermatids. In the exposed biopsies, 20% of the tubules showed thickening in the basal membrane, reduced lumen tubules, and hyperplasia of fibrous tissue. The majority of interstitial cells were normal, although some were hyperplastic or reduced in number.

Narrative analysis: histological safety

The control group used by Wang (2007) and Liu (1991) did not consist of the same men as those who underwent biopsy. In contrast, the other three studies used a before-after comparison. Furthermore, the biopsies in Wang's study (2007) were not randomly assigned; they were only performed on men who did not desire another child and volunteered for that part of the study, this could have selected older men than the population of interest. Ultrasounds investigated by Fahim (1977) were evaluated in men who do not represent the population of interest for TMC as they were between 52 and 65 years old and had prostate carcinoma (this pathology allowed to perform analysis on orchiectomy pieces). Therefore, those results cannot be generalized.

All of the biopsies were treated with the same protocol before examination. However, the observations and outcomes varied, making comparison difficult.

One result obtained during heating indicate a potential impairment of stem cells, necessary for the retrieval of normal spermatogenesis, indeed Shafik (1991) noted the degeneration of 'spermatogonia' but without specifying which type (A or B). Sertoli's cells were not described as abnormal, except in Fahim's study (1977), where they were found in only 50% of the treated tubules with ultrasounds. The apoptosis of other germ cells and the resulting 'slough' in the tubules should not be considered as adverse effects, but rather as expected effects. Apart from an interstitial oedema in Shafik's description (1991), the extra-tubular tissue, notably Leydig's cells, does not appear to be impacted.

Liu's (1991) findings suggest that although spermatogenesis and sperm concentration had recovered in all subjects, a higher quantity of impaired tubules remained after microwaves treatment. Shafik (1991) and Wang (2007), who investigated devices using only heat mechanisms, did not obtain similar results, but rather observed the reversibility of all histological anomalies. This remaining effect may be attributed to the physical action of microwaves.

6 – ACCEPTABILITY

Two criteria were used to evaluate acceptability: the cessation rate for reasons related to the device, and the declared satisfaction of users. Discontinuation due to personal reasons, such as wish for a child or changes in the relationship, were not considered.

Only the five observational cross-sectional studies explored the acceptability of TMC, and through online surveys. They included 1345 men using a testicular suspension device (androswitch, perforated underwear from Toulouse or from DIY tutorials) and one man using SpermaPause. Some answers are missing for some of the surveys (2.7% of missing data for cessation rate, and 1% for satisfaction). Detailed data are given in **Annex n°9**.

Upon 1345 users of testicular suspension devices, 6.1% (n=82) stopped for reasons linked to TMC, and 2.7% (n=36) did not answer the surveys for this question. The only SpermaPause user did not stopped his contraception for reasons related to the device. The reasons for cessation or dissatisfaction were mainly the clinical adverse effects (43.2%), followed by unacceptable constraints (38.3%), and inefficacy due to an unreached threshold (18.5%).

Satisfaction was assessed differently according to the study. Joubert (2022) reported among users of perforated underwear a global satisfaction of 3.78±0.46 on a maximum score of 4. Guidarelli (2023), Lalieux (2022) and Béraud (2023) ranked their 1049 users according to satisfaction levels **(Figure 3)** showing that an overwhelming majority (84,9%) was highly satisfied. The only user of SpermaPause also declared a high satisfaction with a score of 4/5.

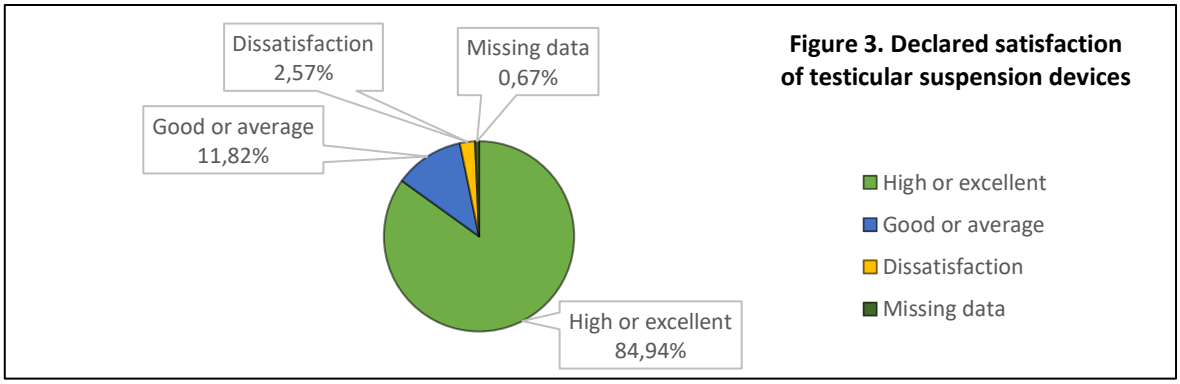


Figure 3. Declared satisfaction of testicular suspension devices

Narrative analysis: Acceptability

Acceptability in users has been investigated by few studies, which mostly focused on testicular suspension devices. Although these results were encouraging, with a low cessation rate of 6.1% and high user satisfaction of 84.9%, they should be interpreted with a degree of caution. The studies conducted by Guidarelli (2023), Lalieux (2022) and Rouanet (2021), which recruited most of the participants for this outcome, excluded men who used TMC for less than three or six months, potentially underestimating cessation rate and overestimating satisfaction. Moreover, respondents who completed the survey were likely to be more committed to using TMC than those who did not respond, which reinforces the same biases.

IV. DISCUSSION

Main results

Included studies: Thirty-three papers reporting data from 26 different investigations conducted between 1956 and 2023, involving 1675 men and eight heating methods, were included. They were essentially at moderate or high risk of bias.

Efficacy: In real life, 80.2% and 72.2% of men in cross-sectional surveys and retrospective studies, respectively, reached the contraceptive threshold (probably underestimated by a large proportion of missing data) with a mean delay of 3.3 to 4.2 months. The Pearl index was 2.9 in trials and 0.53 in surveys. All pregnancies were due to protocol failure. Results for hot baths, polyester and meditation were heterogeneous and inconclusive.

Reversibility: 95.7% of men, probably underestimated due to missing data and loss to follow-up, had a reversible sperm concentration within 1.8 to 4.3 months. All couples wishing a child succeeded.

Clinical safety: 92.8% of real-life users of testicular suspension devices reported adverse effects. Very common effects (incidence >10%) included: local pain and discomfort, decreased testicular size and symptoms of dysuria. Common effects (incidence 1-10%) included local oedema, modification in erection, allergic reaction. Some cases of testicular induration, priapism, phimosis, penile curvature, urinary tract infection and penile venous thrombosis were mentioned.

Biological safety: The results reported significant decreases in motility, progressive motility, viability, normal morphology and fertilizing capacity, reversible within 2.3 to 9 months. DNA damages, chromatin immaturity and aneuploidy rate were significantly increased and recovered within 2 to 6 months. The effects on hormonal concentrations were heterogeneous and questioned a potential impact.

Histological safety: The impairment of germ cells and tubules during heating seemed reversible, except for microwaves, which caused persistent histological abnormalities 1.5 years after cessation. Inconsistent descriptions did not allow to conclude about an impact on Sertoli and Leydig's cells.

Acceptability: 6.1% of users discontinued TMC for reasons related to the testicular suspension devices. 84.9% of users were highly satisfied. These results were probably under and overestimated respectively.

Limitations and strengths of the present review

Limitations: Firstly, one major limitation of our study was the imprecision of some inclusion or exclusion criteria, in particular the definition of the intervention and of adverse effects. The authors have experienced difficulties during the selection process about those criteria that had not been anticipated, and for this reason some changes from the original PROSPERO protocol were made. However, those subtle distinctions were discussed between all reviewers and explained in the method section. Secondly, French medical thesis represented 15% of our included studies. The restriction to English and French databases, although necessary for translation reasons, may have limited the finding of similar unpublished foreign works. In addition, several studies were unfortunately not retrieved and one abstract was unavailable in full text with no respond from the corresponding author. Thirdly, another important limitation was the choice of the contraceptive threshold as an outcome for efficacy. Although it was relevant according to recommendations for assessing efficacy, it was not adapted to most of our studies which did not use it as measurement for their outcome. Finally, the heterogeneity of results did not allow any meta-analysis and prevented the authors from reaching some conclusions.

Strengths: Firstly, this review conformed to the 2020 PRISMA recommendations for protocol (155) and the 2020 PRISMA checklist (**Annex n°10**) for most items. Secondly, the search for contributions was done to be as comprehensive as possible thanks to the multiplicity of databases, the extensive search in bibliography and authors' publications as well as in grey literature and unpublished papers. Thirdly, the double blinded selection process and the check of data enabled to limit the risk of errors. Fourthly, a comprehensive risk of bias assessment was realised, both with validated scores and with complete described analysis. In addition, the main author attended a Cochrane course to be trained at the use the ROB2 tool. Finally, this review presents an overview of the available data on TMC, focusing on the four essential criteria for evaluating any contraceptive method.

Discussion:

The existent results suggest that most men respond correctly to TMC, but still a large number do not experience a satisfactory decrease in sperm concentration. The unreached threshold is the third reason for cessation of TMC. However, unlike other contraceptives where inefficacy is only identified by the occurrence of a pregnancy, TMC allows to evaluate effectiveness through semen analysis. This means that a non-respondent user would be aware of the issue and could take appropriate action (e.g. the use of another contraceptive mean). In addition, the delay for achieving the contraceptive threshold is variable so that no standard delay can be indicated for users. Each man must ensure through sperm analysis that he has reached the threshold and up to that point, another form of contraception must be used by the couple. In addition, some studies have identified sporadic rises in sperm concentration even after reaching this goal, making regular control of semen parameters necessary. The incapacity to reach the threshold for some men and the phenomenon of 'sperm rebound' have also been observed with male hormonal contraception (79) where 72 to 94,9% of men attained the threshold. This could suggest that the ineffectiveness is not necessarily due to the TMC method itself, but rather with inter-individual differences in response to spermatogenesis inhibition factors.

This contraceptive threshold having practical consequences, it seems important to understand how it was established. A 1990's study examined the efficacy of azoospermia (defined as <1 million/ml) consecutive to testosterone injection, with an associated Pearl Index of 0.8. Of the group, 83% of men were completely azoospermic and 17% had a concentration between 0.1 and 1 million/ml (80). However, a complementary study in 1996 has investigated the pregnancy rates for complete azoospermia (<0.1million/ml) and different levels of oligozoospermia. The Pearl index was 0 for azoospermia, and 5.1 for concentrations between 0.1 and 1 million/ml. Above 1 million/ml, it was >14 (81). This statement implies that the threshold, although validated in the 2007's consensus (99), should be interpreted with caution. Men using TMC should be aware that the risk of unplanned pregnancy depends on whether they are azoospermic or not.

The Pearl Index appears to be comparable between thermal and hormonal contraception, as it ranges from 0 to 2.3 for the latter method (79). In the present review, all cases of unplanned pregnancy resulted from incorrect use of the testicular suspension devices and from failure to follow the protocol. In fact, either the device was not worn correctly (less than 15 hours a day or not every day), or the protective measures were not applied during the inhibition phase, such as monitoring semen analysis or the use of a contraceptive protection until the threshold is reached.

Indeed, the required wearing time of 15 hours a day was not respected in 9-13.5% of cases (176,177). According to the users, this recommendation does not allow for any irregularity in sleep schedule and daily routine. Furthermore, the cost of repeated semen tests has not been evaluated and accessibility to medical professionals or laboratories was described as challenging. 14.5% of individuals renounced to perform semen analysis due to this issue (176). Also, 75% of users asked for an improvement in semen analysis follow-up, and 64% were interested in an auto-test (179). Actually, a "home-made" semen analysis protocol was elaborated for this purpose, though this cannot be yet

recommended (201). Those constraints are obstacles for a proper compliance and thus, for effectiveness.

All results and additional data are concordant in showing reversibility of the contraceptive effect after TMC, all devices included. Moreover, it is important to note that even azoospermic men succeeded to recover their fertility. In addition to these results, some studies have shown a reversibility higher than expected and the mean sperm concentration raised until 150 or 238% of baseline values in some studies (169,185). This rise seems to be variable depending on the individuals after exposition to hot baths (188). Due to this particularity, the use of heat on the scrotum was ironically evaluated for treatment of hypofertility in oligospermic men (128,159).

All couples wanting a child conceived after cessation with a miscarriage rate of 2.4%, which is lower than in general population where the miscarriage rate after a confirmed pregnancy ranges from 10 to 20% (202,203). The difference may be attributed to the small population size in our review and differences in the study populations, with most of the users in our included studies already being fathers. Anyway, this information is reassuring regarding to the several anomalies observed in sperm parameters which are all important for fertility.

Most studies showed a significant reduction in sperm motility, progressive motility and vitality as well as an increase of abnormal forms of spermatozoa after TMC. Indeed, these parameters are likely to be impacted by heat as they have been shown to be impaired by high ambient temperature (204), with the exception of sperm vitality. All those parameters are important for male fertility and whereas their modification could be considered an expected effect of TMC, their recovery should be assessed alongside with sperm concentration. Indeed, a recent umbrella review with meta-analysis evidenced the association between progressive motility and recurrent miscarriage, and between sperm morphology and recurrent pregnancy loss (205,206). Multiple Anomalies Index is a factor in fertility assessment: if equal or less than 1.6, it is considered favourable to achieve pregnancy (207). An increase of 0.5 as reported by Ahmad (2011) is negatively associated with pregnancy occurrence (208), independently of the sperm concentration. Although most studies have reported the recovery of all of those parameters (motility, progressive motility, vitality, morphology), the necessary delay for it still needs to be investigated as it varies considerably across studies. A longer delay might be due to a prolonged use of TMC. Liu (1988) found a persistence of abnormal forms one year after cessation of microwaves treatment, suggesting that damages induced by this variety of TMC is partially irreversible (196).

The decrease in fertilizing capacity was assessed by the measure of acrosin activity, a proteolytic enzyme allowing penetration of spermatozoa in the oocyte. This is not the test for acrosome reaction recommended by the WHO in 2021 (200), but this measure is evaluated to be used for medically-assisted procreation (209) as it is a predictive factor of fertilization rate for in vitro fertilization (210). The fact that this index recovered to normal values within three months is reassuring for fertility recovery but would necessitate further investigations.

The impact on DNA integrity occurred early after the beginning of TMC, even before the threshold reaching, when the risk of pregnancy occurrence still exists if no other contraceptive method is used. A meta-analysis of 16 studies on 2969 couples reported a significant increase of miscarriage in patient with high DNA damages, with a risk ratio of 2.16 (1.54-3.03) (211). This result is supported by another meta-analysis which found high correlation between sperm DNA fragmentation and recurrent pregnancy losses (205). Their reversibility is therefore essential for a satisfying return to fertility and fortunately, seems to occur in a mean delay of 2 to 3 months. However, this data has been drawn on studies counting only 55 men, calling for additional studies investigating this issue. Although statistical analysis was not conducted to confirm it, the values of DNA damages (DFI, HDS, sperm immaturity) appear higher in the study by Zhang (2015a,b, 2018a,b) than in Ahmad's study (2012), raising questions about the role of temperature’s intensity in DNA damages.

Studies also found an increased rate of sperm aneuploidy. Such chromosomal anomalies can result in pregnancy loss in case the foetus is not viable, and to the birth of children with aneuploidy in case the anomaly is compatible with life (206,212,213). Increased frequency of aneuploidy spermatozoa may be associated with having a child with chromosomal anomalies (214,215). A 2004's study found an association between abnormal high temperature due to varicocele and meiotic anomalies. Six months after surgery and resolution of the varicocele and the increased heat, no more meiotic abnormalities were present (216). This suggests, in line with Ahmad (2019a), a reversibility of this process. However, this recovery, assessed in only five men, appeared slower than sperm concentration recovery. This could increase the risk of consequences in case of pregnancy occurrence during this delay. It is essential for this issue to be further investigated.

Results on hormonal variation during TMC are discordant and inconclusive through our narrative analysis. A decrease in testosterone, and possibly an increase in LH and FSH through negative feedback, as reported by Zhang (2018), could be explained by an impairment of testicular endocrine functions led by the Leydig's cells. However, the two studies describing histologically Leydig's cells during TMC, including Shafik (1991) who also found a reduction of testosterone level, found them normal. In animals, results are disparate on whether or not testicular endocrine function is altered. The animal studies' designs and protocols are heterogeneous concerning species, type, duration and intensity of exposition, and delay until biological outcome. However, in most experiments, testosterone concentration decreases several days after temperature elevation, or maintains thanks to the compensative effect of LH's elevation (111,217–227). A similar observation has been made in men: indeed, blood rates of LH and FSH were increased in the unfertile male with scrotal hyperthermia compared to unfertile male with normal testicular temperature. The testosterone level was equal across groups (228). Further studies appear necessary to elucidate this point.

No impact on liver, renal and haematological parameters in blood samples were found. The prostate-specific antigen (PSA) only tested in one study was unchanged. However, some clues suggest that ambient temperature can have an incidence on PSA levels (229). Therefore, it could be interesting to investigate the impacts of TMC on these levels, in particular the devices using external heat that could reach the prostate. Indeed, this may lead to false positive in prostatic cancer screening. A slight significant elevation of haemoglobin, haematocrit and LDL-cholesterol was found by Wang (2007), although no quantitative data was detailed. An increase, although insignificant, in testosterone level in that same study was described, and could partially explain these findings. Indeed, testosterone level is significantly correlated to haemoglobin, haematocrit, HDL-cholesterol, but not with LDL-cholesterol (230).

Checking whether testicular heating damages Sertoli's cells and stem cells would complement the argument for the reversibility of this contraceptive method, these cells being responsible for the process of spermatogenesis. Additionally, investigating the preservation of interstitial tissue and Leydig's cells would provide further evidence for the existence or absence of adverse effects, particularly hormonal ones. However, testicular biopsies are invasive and the information they provide can be obtained through less invasive analyses, such as sperm and blood tests. Therefore, the realisation of these investigations for future research upon TMC have to be discussed.

The results regarding acceptability contrast with the high frequency of local clinical adverse effects, such as discomfort, pain, and skin irritation, indicating that these are bearable for most men, although they have led some users to discontinue TMC, being the first cause of cessation (176,177,179). These effects are likely to disappear over time as spontaneously mentioned by eight out of twelve men (177). The frequency of pain and discomfort progressively reduced from 35 and 56% on initial use to 7 and 24% during the contraceptive phase, respectively (179). This suggests that those frequent effects are benign, temporary and well tolerated. Although not reported in those studies, polyester might have a negative impact on sexual functions (231) and its use should be considered with caution. The decrease in testicles' size could be due to the impairment of spermatogenesis and a

decrease in germ cells volume, or to a lower level of testosterone, both of these parameters being related to low testicular volume (232).

A majority of users (even men who have stopped TMC) would recommend this method (177,179) mostly for the repartition of contraceptive mental load in the couple, the method's simplicity (47%), the perception of this method as "natural", due to the absence of chemical products (46%) and the absence of adverse-effect (24%). In addition, they express a high satisfaction for being able to answer their couple contraceptive impasse and for having "rediscover" themselves with the awareness of their own fertility and the control of it (143).

But more serious effects were also reported. The changes in erectile functions were not always commented on, but one man stated that they occurred while wearing the device and that erections were faster, harder, and lasted longer. One case of priapism was reported. These effects are similar to those of a penile ring or cockring, which may cause penis or scrotal strangulation (233,234). Without being as severe as described in literature cases, compression of the nearby structures such as urethra, blood vessels or nerves may conduct to serious injuries. Symptoms of such damages were investigated by Guidarelli (2023) who reported a penis venous thrombosis, oedemas, a decrease in penile sensitivity and symptoms of dysuria that could suggest a mechanism such as urethral obstruction. Complications of such a blockage, notably infections or urine leakage (that could be due to overflow incontinence), though uncommon (<1%) were also reported. No urinary retention was mentioned. Few participants in that study spontaneously reported that the symptoms disappeared with device removal.

Thermal male contraception, specifically the testicular suspension devices, is sometimes called "artificial cryptorchidism". However, that pathology is a well admitted cause of testicular cancer (235,236), and even though its mechanisms are unknown, the role of temperature is suggested as a possibility. A recent thesis investigating a link between heat and testicular cancer could not conclude to such relation for mild heating, but suggested a link between high temperatures scrotal exposure in metal industry and testicular cancer (237). Three TMC's users (0.3%) recorded a testicular induration, without any more precision. This occurrence should be investigated further.

The population size in the studies for assessing efficacy and reversibility are insufficient in regards to the guidelines recommending two independent trials with a one-year contraceptive phase completed by 200 men per trial. For safety, trials involving 300 to 600 men for 6 months, 100 men for one year, and 1500 men for phases I to III are recommended (99). The Androswitch device (silicone ring), forbidden for selling in France (145) due to the lack of data, has a trial planned for 2024 which was made possible by the launch of a participatory campaign (146). The Coso device in development by a German team (160), relies upon both ultrasounds and wet heat. Our results indicate a potential effectiveness of wet heat but highlight the importance of finding the optimal frequency of exposition for men to achieve the threshold. The effectiveness of ultrasounds however has not been evaluated in humans. They were investigated in animals with, at our knowledge, few evidences to support their efficacy or reversibility (109,238–243).

Concerning methodology, TMC is hardly eligible for the blinded randomised trials gold standard. In fact the 2007's consensus upon hormonal contraception (99) proposes the possibility to conduct open-label, non-comparative studies to assess contraceptive effectiveness provided that the primary endpoint is not susceptible to bias. Therefore the outcome could be pregnancy rate or threshold reaching stated with blinding and with systematic research for confounding factors such as abstinence delay, other sources of heat or female partner's health conditions. Volunteers appear to be a suitable recruitment for trial as they are indeed representative of a male population willing to try this contraceptive mean, and the cross-over like design (cohort before/after) allows to overcome any additional confounding biases. Although safety might not be the primary outcome, it could benefit from an assessment through a systematic questionnaire and clinical examination. The lack of power is a supplementary issue, unrelated to methodological problems, and may be difficult to overcome. However, it could be addressed by several studies replicating a similar protocol, making possible a meta-analysis.

IV. CONCLUSION

The small population sizes and the multiplicity of devices and protocol investigated make it difficult to reach decisive conclusions. The available results strongly suggest that thermal male contraception, in particular testicular suspension, might be effective for most men, reversible and acceptable to users. Reasons for ineffectiveness could be inter-individual variations and failures to follow the protocol. In fact, the frequency of local side effects, the wearing duration and the necessity to perform regular semen analysis are obstacles to a proper compliance and are reasons for discontinuation.

However the results raise some concerns about safety. Testicular suspension devices might cause compression on local structures such as the urethra, blood vessels and nerves. In addition, the effects of heat on the testicles seem to include impairment of additional semen parameters, and damages to spermatozoa's DNA and chromosomes. Uncertainties remain concerning the reversibility's delay of these anomalies, the risk of testicular cancer and the alterations of hormonal profiles.

Thermal male contraception appears to be a promising addition to the contraceptive options for men but some questions remain unanswered. All four criteria – efficacy, reversibility, safety and acceptability – would benefit from additional studies with larger sample sizes or with a similar protocol, so that data can be pooled and meta-analysed to meet the 2007 consensus' recommendations.

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ANNEXES

ANNEX N°1 – Search queries

All search queries have been adapted to the language of each databases, from this equation:

CONTRACEPTION	(contraception) OR (contraceptive) OR (birth control) OR (fertility control) OR (contraception, male[MeSH Terms]) OR (contraceptive devices, male[MeSH Terms])
	AND
MALE	(male) OR (man) OR (masculine) OR (testicular) OR (scrotal) OR (spermatogenesis) OR (contraception, male[MeSH Terms]) OR (contraceptive devices, male[MeSH Terms]) OR (Male Fertility[MeSH Terms]) OR (Spermatogenesis[MeSH Terms]))
	AND
THERMAL	(thermal) OR (temperature) OR (testicular suspension) OR (hyperthermia) OR (contraceptive ring) OR (thermoregulation) OR (heat) OR (artificial cryptorchidism) OR (baths) OR (ultrasounds) OR (microwaves) OR (hot temperature[MeSH Terms]) OR (body temperature[MeSH Terms])

Databases	Search Queries
PUBMED	((contraception[Title/Abstract]) OR (contraceptive[Title/Abstract]) OR (birth control[Title/Abstract]) OR (fertility control[Title/Abstract]) OR (contraception, male[MeSH Terms]) OR (contraceptive devices, male[MeSH Terms])) AND (((male[Title/Abstract]) OR (man[Title/Abstract]) OR (masculine[Title/Abstract]) OR (testicular[Title/Abstract]) OR (scrotal[Title/Abstract]) OR (contraception, male[MeSH Terms]) OR (contraceptive devices, male[MeSH Terms]) OR (Male Fertility[MeSH Terms]) OR (Spermatogenesis[MeSH Terms]))) AND (((thermal[Title/Abstract]) OR (temperature[Title/Abstract]) OR (testicular suspension[Title/Abstract]) OR (hyperthermia[Title/Abstract]) OR (contraceptive ring[Title/Abstract]) OR (thermoregulation[Title/Abstract]) OR (heat[Title/Abstract]) OR (artificial cryptorchidism[Title/Abstract]) OR (hot temperature[MeSH Terms]) OR (microwaves[Title/Abstract]) OR (ultrasounds[Title/Abstract]) OR (body temperature[MeSH Terms]))))))) NOT (("Natural Family Planning Methods"[Mesh Terms])) NOT (condoms[MeSH Terms]))))))))))
CISMeF	Contraception masculine
EMBASE	(contraception:ti,ab,kw OR contraceptive:ti,ab,kw OR 'birth control':ti,ab,kw OR 'fertility control':ti,ab,kw OR ('contraception'/exp AND [male]/lim) OR 'male contraceptive device'/exp OR 'birth control'/exp) AND (male:ti,ab,kw OR man:ti,ab,kw OR masculine:ti,ab,kw OR testicular:ti,ab,kw OR scrotal:ti,ab,kw OR 'male fertility'/exp OR 'spermatogenesis'/exp) AND (thermal:ti,ab,kw OR temperature:ti,ab,kw OR 'testicular suspension':ti,ab,kw OR hyperthermia:ti,ab,kw OR 'contraceptive ring':ti,ab,kw OR thermoregulation:ti,ab,kw OR heat:ti,ab,kw OR 'artificial cryptorchidism':ti,ab,kw OR 'microwaves':ti,ab,kw OR 'ultrasounds':ti,ab,kw OR 'thermotherapy'/exp OR 'thermoregulation'/exp OR 'high temperature'/exp OR 'body temperature'/exp) NOT 'family planning'/exp NOT 'condom'/exp

Databases	Search Queries
COCHRANE	#1 MeSH descriptor: [Contraception] explode all trees #2 ("contraception"):ti,ab,kw #3 (contraceptive):ti,ab,kw #4 ("birth control"):ti,ab,kw #5 ("family planning"):ti,ab,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #7 MeSH descriptor: [Contraceptive Devices, Male] explode all trees #8 MeSH descriptor: [Contraceptive Agents, Male] explode all trees #9 (male):ti,ab,kw #10 (masculine):ti,ab,kw #11 (man):ti,ab,kw #12 (men):ti,ab,kw #13 MeSH descriptor: [Testis] explode all trees #14 (testicular):ti,ab,kw #15 (scrotal):ti,ab,kw #16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #17 #6 AND #16 #18 MeSH descriptor: [Vasectomy] explode all trees #19 (vasectomy):ti,ab,kw #20 MeSH descriptor: [Female] explode all trees #21 MeSH descriptor: [Contraceptive Agents, Female] explode all trees #22 MeSH descriptor: [Ovulation Inhibition] explode all trees #23 MeSH descriptor: [Hormonal Contraception] explode all trees #24 MeSH descriptor: [Natural Family Planning Methods] explode all trees #25 #18 OR #19 #26 #20 OR #21 OR #22 OR #23 OR #24 #27 #17 NOT #25 #28 #27 NOT #26 #29 MeSH descriptor: [Heating] explode all trees #30 MeSH descriptor: [Temperature] explode all trees #31 MeSH descriptor: [Hyperthermia] explode all trees #32 (temperature):ti,ab,kw #33 (hyperthermia):ti,ab,kw #34 (heat):ti,ab,kw #35 (hot):ti,ab,kw #36 ("testicular suspension"):ti,ab,kw #37 (thermal):ti,ab,kw #38 (thermical):ti,ab,kw #39 (ultrasounds):ti,ab,kw #40 (microwaves):ti,ab,kw #41 (baths):ti,ab,kw #42 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 #43 #28 AND #42 #44 (covid):ti,ab,kw #45 (infection):ti,ab,kw #46 #44 OR #45 #47 #43 NOT #46 #48 ("bioequivalence"):ti,ab,kw #49 (injection):ti,ab,kw #50 (placebo):ti,ab,kw #51 (pharmaco*):ti,ab,kw #52 #48 OR #49 OR #50 OR #51 #53 #47 NOT #52
LISSA	((contraception.tl) OU (contraception.mc) OU (contraceptifs.tl) OU (contraceptifs.mc) OU (contraceptifs masculins.tl) OU (contraceptifs masculins.mc) OU (dispositifs contraceptifs.tl) OU (dispositifs contraceptifs.mc)) ET ((masculin.tl) OU (masculin.mc) OU (masculine.tl) OU (masculine.mc) OU (hommes.tl) OU (hommes.mc) OU (Mâle.tl) OU (Mâle.mc)) ET ((thermique.tl) OU (thermique.mc) OU (temperature.tl) OU (temperature.mc) OU (chaleur.tl) OU (chaleur.mc) OU (suspension.tl) OU (suspension.mc) OU (cryptorchidie.tl) OU (cryptorchidie.mc) OU (ultrasons.tl) OU (ultrasons.mc) OU (micro ondes.tl) OU (micro ondes.mc) OU (bains.tl) OU (bains.mc))

Databases	Search Queries
SUDOC	((contraception)) et ((masculine) ou (testiculaire) ou (scrotal) ou (homme)) et ((température) ou (thermique) ou (chaleur) ou (suspension) ou (slip) ou (vêtement) ou (anneau))
GOOGLE SCHOLAR	"thermal male contraception" OR "contraception masculine thermique" OR "remontée testiculaire" OR "testicular suspension" OR "testicular lift" OR "androswitch" OR "hot baths contraception"
Web of science	(((TS=(contraception) OR TS=(contraceptive) OR TS=("birth control") OR TS=("fertility control") OR TS=("male contraception")))) AND (((TS=(male) OR TS=(man) OR TS=(masculine) OR TS=(testicular) OR TS=(scrotal) OR TS=("male contraception") OR TS=(spermatogenesis)))) AND (((TS=(thermal) OR TS=(temperature) OR TS=("testicular suspension") OR TS=(hyperthermia) OR TS=(thermoregulation) OR TS=(heat) OR TS=("artificial cryptorchidism") OR TS=("hot temperature") OR TS=("contraceptive ring") OR TS=("microwaves") OR TS=("ultrasounds") OR TS=("testicular ring"))))

ANNEX n°2 – Excluded reports (on full text) and reasons for exclusion

Reviews (N=10)

- Male fertility regulation by means of ultrasounds, Fahim MS, 1980, Regulation of Male Fertility
- Advances in male contraception, Shafik, 2000, Archives of Andrology
- Biologic response of sperm and seminal plasma to transient testicular heating, Fang ZY, 2019, Frontiers in Bioscience-landmark
- Influence of genital heat stress on semen quality in humans, Jung A., 2007, Andrologia
- Male contraception: Prospects for sound and ultrasound, Sewak, 2017, Medical hypotheses
- Contraception masculine : quelles options actuellement disponibles ?, Gregoris A, 2022, Revue médicale Suisse
- Three new methods for male contraception, Shafik, 1999, Asian Journal of Andrology
- Thermic contraceptive for men, Mieusset R, 1996, Contraception thermique de l'Homme.
- Role of temperature in regulation of spermatogenesis and the use of heating as a method for contraception, Kandeel FR, 1988, Fertility and Sterility
- Acceptabilité de la contraception masculine par les hommes - Revue de littérature, Chaud MA, 2020 (unpublished, thesis)

Wrong outcome (N=8)

- Proteomic analysis of testis biopsies in men treated with transient scrotal hyperthermia reveals the potential targets for contraceptive development, Zhu H, 2010, Proteomics
- Effect of transient scrotal hyperthermia on human sperm: an iTRAQ-based proteomic analysis, Wu YQ, 2020, reproductive biology and endocrinology
- La contraception testiculaire thermique : une méthode contraceptive encore trop peu connue : étude descriptive auprès des médecins généralistes d'Auvergne-Rhône-Alpes par questionnaire auto-administré, Travers F and Vallet W, 2022 (unpublished, thesis)
- Etude qualitative : L'opinion des hommes de 18 à 33 ans sur l'utilisation potentielle d'une contraception masculine thermique par remontée testiculaire, Macé de Gastines E, 2022 (unpublished, thesis)
- Évaluation d'un guide de contraception masculine thermique pour une utilisation pratique en consultation par des médecins généralistes d'Isère, Savoie et Haute-Savoie, Baran C and Sevaz, 2022 (unpublished, thesis)
- Effect of different types of textile fabric on spermatogenesis: electrostatic potentials generated on the surface of the human scrotum by wearing different types of fabric, Shafik, 1992, Archives of Andrology
- Connaissance et appréciation de la contraception masculine thermique chez les 20-35 ans, Vignon, 2023 (unpublished, thesis)
- «Se contracepter» : Une étude phénoménologique auprès des utilisateurs de la contraception masculine par remontée testiculaire, Lacroix M, 2023 (unpublished, thesis)

Duplicates (N=7)

- [Temperature and male fertility], Bujan L and Mieusset R, 1992, Contraception, fertilité, sexualité
- Scrotal suspenders and male infertility, Phadke A, 1966, The Indian practitioner

- Male contraception: what are the currently available options?, Gregoris A, 2022, Revue médicale Suisse
- Male contraception by testicular heating, Bujan L and Mieusset R, 1995, Contraception, Fertilité, Sexualité
- Male contraception by hyperthermia, Bujan L and Mieusset, 1992, Contraception, Fertilité, Sexualité
- Effets de facteurs exogènes sur les gamètes masculins et leur génome: conséquences potentielles d'une élévation modérée de la température des testicules et des épididymes sur la qualité du gamète, Abdelhamid M, 2019 (unpublished, thesis)
- Contraception masculine thermique étude des motivations, choix et satisfaction auprès des utilisateurs, Joubert S, 2021 (unpublished, thesis)

Total body heating (N=5)
- The effect of hyperpyrexia upon spermatozoa counts in men, Macleod J, 1941, Endocrinology
- The effect of a single sauna exposure on spermatozoa, Brown-Woodman PD, 1984, Archives of Andrology
- Seminal and molecular evidence that sauna exposure affects human spermatogenesis, Garolla A, 2013, Human reproduction
- Effects of sauna on sperm movement characteristics of normal men measured by computer-assisted sperm analysis, Saikhun K, 1998, International Journal of Andrology
- Effect of repeated increase of body temperature on human sperm cells, Procopé BJ, 1965, International Journal of fertility

Unfound references (N=5)
- Scrotal suspenders and male infertility, Phadke A, 1966, The Indian practitioner
- Résultats préliminaires d'un essai de contraception masculine par la chaleur, Mieusset R, 1983 (thesis)
- Effect of ultrasound treatment on the human testis of patients with carcinoma of the prostate, Fahim MS, 1979, J Med (in press)
- Contraception masculine thermique, Flambard
- Application of microwave in male contraception, Fang B, 1982, Chinese Journal of Urology

Unavailable full text (N=1)
- Étude de la tolérance de l'anneau de remontée testiculaire porté à visée contraceptive, Foulonneau V, 2022, Progrès en Urologie-FMC

Risk factor of infertility (N=3)
- Temperature and human male fecundity, Bujan L and Mieusset R, 1996, Contraception, fertilité, Sexualité
- Impact of diurnal scrotal temperature on semen quality, Hjollund NH, 2002, Reproductive toxicology
- Diurnal scrotal skin temperature and semen quality, Hjollund NH, 2000, International Journal of Andrology

Animals studies (N=2)
- Testicular suspension: effect on testicular function, Shafik A, 1991, Andrologia
- Magnetic Testis Targeting and Magnetic Hyperthermia for Noninvasive, Controllable Male Contraception via Intravenous Administration, Ding WH, 2021, NanoLetters

Wrong purpose (N=2)
- The effect of diathermy on testicular function, Bauer J and Gutman G, 1940, Urologic cutaneous review
- Control of Human Spermatogenesis by induced changes of intrascrotal Temperature, Robison D, 1968, JAMA

Foreign language (N=2)
- The effect of microwave contraception on human serum testosterone and luteinizing hormone, Hu P, 1985, Reproduction Contraception (China)
- Semen quality in man after genital heat stress, Jung A, 2003, Die samenqualität des mannes nach testikulärer überwärmung

ANNEX n°3 – Description of the different techniques of heat sources investigated as thermal male contraception.

Use of body as source of heat (Table 2.)

- **Testicular suspension or "artificial cryptorchidism"** relies on maintaining testicles on a supra-scrotal position, disrupting its thermoregulation system and using the close abdomen as a source of heat. This suspension can be achieved by the use of several devices:
  - A perforated underwear developed in Toulouse, France, by Dr Mieusset and his team. The penis is placed through the hole with the scrotum while the testicles are pushed back towards abdomen, every day during waking hours (15 hours per day). At a later stage of development, a soft ring was added to help maintaining the position of the testicles throughout the day. This improved version is the one still in use today. For the sake of simplicity, we will, in that review, refer to the final version of this device as "perforated underwear" and to the previous version (without the ring) as "perforated underwear (beta)".
  - Variations inspired from this underwear, following the same wearing protocol, such as a testicular silicone ring (Andro-switch) or self-fabricated devices from a classic underwear, a jockstrap or a bra (with "Do It Yourself" tutorials available on internet) were also evaluated in real life.
  - Surgery was also used by Dr Shafik, an Egyptian urologist. The testicles were hold by stitches which were removed 2 weeks later. The testicles stayed into this position thanks to adhesions to the skin until a second intervention one year later, where they were released. The temperature rise was measured to be +2°C (171).
  - A suspensory with balls pushing up the testis was tested alongside with surgery, and had to be worn every day and night, 24 hours.
- **Testicular suspension using a polyester underwear**, such as a suspensory sling or athletic supporter, combines two mechanisms: a temperature rise and an electrostatic field effect created by friction between the fabric and the skin. The author believes that this field interferes with spermatogenesis as it passes through the scrotum. The device has been studied by three distinct teams. Shafik (1992) and Moeloek (1995) used a similar model consisting of a polyester suspensory that leaves the penis uncovered and lifts the scrotum towards the abdomen, resulting in an increase of +2°C. On the other hand, Wang (1997) used athletic supports lined with one or two layers of 100% polyester or a layer of polyester mixed with aluminium, with an increased temperature measured at +0.8 to 1°C.
- **Insulating underwear**, worn 15 to 24 hours every day, were investigated by an American team as a potential male contraceptive. Several layers of oilcloth, surgical plastic and paper tissue were positioned and held in the underwear, facing the scrotum, disrupting its thermoregulation and causing a slight scrotal temperature elevation (from +0.3 to 1.1°C).
- **Meditation**: men underwent 12 sessions of relaxation training to learn how to increase the temperature of some parts of their body (hands and abdomen) by themselves, thanks to a thermistor providing biofeedback. They were able to increase their scrotal temperature by between 0.9 and 4.5°C during sessions of 15 or 30 minutes every day for 5 days.

External source of heat (Table 3.)

- **Hot baths or "wet heat"** are the first described technique for male thermal contraception (by Dr Voegeli in 1956 who used it in India on multiple men) but are also the easiest way to evaluate impact of heat of spermatogenesis and was used for that perspective. The scrotum or the lower body is immersed in hot water for 30 to 45 minutes with different rhythm and duration protocols

depending on the study. Scrotal temperatures were not measured but the baths were heated from 40 to 47°C.

- **External dry heat** is the direct application of heat on the testicles. SpermaPause is made up of an underwear which is supplied with an electric battery allowing to warm up the scrotal region. This heating device is supposed to be worn 4 hours a day and can be found on internet.
- **Microwaves** were investigated as male contraception in human in China: a specially prepared radiator was installed on an armchair and the scrotum heated until 40-42°C. Two papers which are looking for long-term side effects after microwaves treatments were included.
- **Ultrasounds** have been mostly studied in animals, and was found more effective than hot water for suppression of spermatogenesis in rats (109). The authors assumed that both heat and mechanic explained this effect and an experiment was conducted on humans who were supposed to undergo orchiectomies, to compare testicular histology before and after such a treatment.

ANNEX N°4 – Risk of bias evaluations

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Mieusset et al., 1985, 1987a, 1987b, 1991			
	Efficacy & Reversibility	Reversibility	Security	Security
	Global sperm concentration	Pregnancy occurrence	Clinical AEs	Biological AEs
Selection (maximum one star by item)				
Representativeness of the intervention group	★	★	★	★
Selection of the control group	★	★	★	★
Ascertainment of intervention	0	0	0	0
Demonstration that outcome of interest was not present at start of study	★	★	0	★
Comparability (maximum two stars)				
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★
Outcome (maximum one star by item)				
Assessment of outcome	0	★	0	0
Was follow-up long enough for outcomes to occur?	★	★	★	★
Adequacy of follow up	0	★	0	★
TOTAL /9	**6 ★**	**8 ★**	**5 ★**	**7 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Mieusset and Bujan, 1994				
	Efficacy	Efficacy	Reversibility	Reversibility	Security
	Contraceptive threshold	Pregnancy occurrence	Sperm concentration	Pregnancy occurrence	Clinical AEs
Selection (maximum one star by item)					
Representativeness of the intervention group	★	★	★	★	★
Selection of the control group	★	★	★	★	★
Ascertainment of intervention	0	0	0	0	0
Demonstration that outcome of interest was not present at start of study	★	★	★	★	0
Comparability (maximum two stars)					
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★	★★
Outcome (maximum one star by item)					
Assessment of outcome	0	★	0	★	0
Was follow-up long enough for outcomes to occur?	★	★	★	★	★
Adequacy of follow up	★	★	★	★	★
TOTAL /9	**7 ★**	**8 ★**	**7 ★**	**8 ★**	**6 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Shafik 1992						
	Efficacy	Efficacy	Reversibility	Reversibility	Security	Security	Security
	Threshold	Pregnancy occurrence	Sperm concentration	Pregnancy occurrence	Clinical AEs	Biological AEs	Histological AEs
Selection (maximum one star by item)							
Representativeness of the intervention group	★	★	★	★	★	★	★
Selection of the control group	★	★	★	★	★	★	★
Ascertainment of intervention	0	0	0	0	0	0	0
Demonstration that outcome of interest was not present at start of study	★	★	★	★	0	★	0
Comparability (maximum two stars)							
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★	★★	★★	★★
Outcome (maximum one star by item)							
Assessment of outcome	0	★	0	★	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★	★	★	★	★
Adequacy of follow up	★	★	★	★	★	★	★
TOTAL /9	**7 ★**	**8 ★**	**7 ★**	**8 ★**	**6 ★**	**7 ★**	**6 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Moeloek, 1995		
	Efficacy & Reversibility	Security	Security
	Global sperm concentration	Clinical AEs	Biological AEs
Selection (maximum one star by item)			
Representativeness of the intervention group	★	★	★
Selection of the control group	★	★	★
Ascertainment of intervention	0	0	0
Demonstration that outcome of interest was not present at start of study	★	0	★
Comparability (maximum two stars)			
Comparability of groups on the basis of the design or analysis	★★	★★	★★
Outcome (maximum one star by item)			
Assessment of outcome	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★
Adequacy of follow up	★	★	★
TOTAL /9	**7 ★**	**6 ★**	**7 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Shafik, 1991						
	Efficacy	Efficacy	Reversibility	Reversibility	Security	Security	Security
	Threshold	Pregnancy occurrence	Sperm concentration	Pregnancy occurrence	Clinical AEs	Biological AEs	Histological AEs
Selection (maximum one star by item)							
Representativeness of the intervention group	★	★	★	★	★	★	★
Selection of the control group	★	★	★	★	★	★	★
Ascertainment of intervention	0	0	0	0	0	0	0
Demonstration that outcome of interest was not present at start of study	★	★	★	★	★	★	★
Comparability (maximum two stars)							
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★	★★	★★	★★
Outcome (maximum one star by item)							
Assessment of outcome	0	★	0	★	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★	★	★	★	★
Adequacy of follow up	★	★	★	★	★	★	★
TOTAL /9	**7 ★**	**8 ★**	**7 ★**	**8 ★**	**7 ★**	**7 ★**	**7 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Voegeli M., 1956			
	Efficacy & Reversibility	Reversibility	Security	Security
	Global sperm concentration	Pregnancy occurrence	Clinical AEs	Biological AEs
Selection (maximum one star by item)				
Representativeness of the intervention group	0	0	0	0
Selection of the control group	★	★	★	★
Ascertainment of intervention	0	0	0	0
Demonstration that outcome of interest was not present at start of study	0	0	0	0
Comparability (maximum two stars)				
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★
Outcome (maximum one star by item)				
Assessment of outcome	0	0	0	0
Was follow-up long enough for outcomes to occur?	0	0	0	0
Adequacy of follow up	0	0	0	0
TOTAL /9	**3 ★**	**3 ★**	**3 ★**	**3 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Watanabe, 1959	
	Efficacy & Reversibility	Security
	Global sperm concentration	Biological AEs
Selection (maximum one star by item)		
Representativeness of the intervention group	0	0
Selection of the control group	★	★
Ascertainment of intervention	★	★
Demonstration that outcome of interest was not present at start of study	★	★
Comparability (maximum two stars)		
Comparability of groups on the basis of the design or analysis	★★	★★
Outcome (maximum one star by item)		
Assessment of outcome	0	0
Was follow-up long enough for outcomes to occur?	0	0
Adequacy of follow up	★	★
TOTAL /9	**6 ★**	**6 ★**
General remarks	Annex with detailed tables of result were not retrieved: incomplete data.	

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Rock and Robinson, 1965			
	Reversibility	Efficacy & Reversibility	Safety	Safety
	Sperm concentration	Global sperm concentration	Clinical AEs	Biological AEs
Selection (maximum one star by item)				
Representativeness of the intervention group	0	0	0	0
Selection of the control group	★	★	★	★
Ascertainment of intervention	0	0	0	0
Demonstration that outcome of interest was not present at start of study	★	★	0	★
Comparability (maximum two stars)				
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★
Outcome (maximum one star by item)				
Assessment of outcome	0	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★	★
Adequacy of follow up	★	★	0	★
TOTAL /9	**6 ★**	**6 ★**	**4 ★**	**6 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Rock and Robinson, 1967			
	Reversibility	Efficacy & Reversibility	Safety	Safety
	Sperm concentration	Global sperm concentration	Clinical AEs	Biological AEs
Selection (maximum one star by item)				
Representativeness of the intervention group	0	0	0	0
Selection of the control group	★	★	★	★
Ascertainment of intervention	★	★	★	★
Demonstration that outcome of interest was not present at start of study	★	★	0	★
Comparability (maximum two stars)				
Comparability of groups on the basis of the design or analysis	★★	★★	★★	★★
Outcome (maximum one star by item)				
Assessment of outcome	0	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★	★
Adequacy of follow up	0	★	★	★
TOTAL /9	**6 ★**	**7 ★**	**6 ★**	**7 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	DJ French, 1973		
	Efficacy	Reversibility	Security
	Threshold	Sperm concentration	Biological AEs
Selection (maximum one star by item)			
Representativeness of the intervention group	★	★	★
Selection of the control group	★	★	★
Ascertainment of intervention	★	★	★
Demonstration that outcome of interest was not present at start of study	★	★	★
Comparability (maximum two stars)			
Comparability of groups on the basis of the design or analysis	★★	★★	★★
Outcome (maximum one star by item)			
Assessment of outcome	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★
Adequacy of follow up	★	★	★
TOTAL /9	**8 ★**	**8 ★**	**8 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Fahim, 1977	
	Safety	Safety
	Clinical AEs	Histological AEs
Selection (maximum one star by item)		
Representativeness of the intervention group	0	0
Selection of the control group	★	★
Ascertainment of intervention	★	★
Demonstration that outcome of interest was not present at start of study	0	★
Comparability (maximum two stars)		
Comparability of groups on the basis of the design or analysis	★★	★★
Outcome (maximum one star by item)		
Assessment of outcome	0	0
Was follow-up long enough for outcomes to occur?	0	★
Adequacy of follow up	★	★
TOTAL /9	**5 ★**	**7 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Wang, 1997		
	Efficacy & Reversibility	Safety	Safety
	Global sperm concentration	Clinical AEs	Biological AEs
Selection (maximum one star by item)			
Representativeness of the intervention group	★	★	★
Selection of the control group	★	★	★
Ascertainment of intervention	0	0	0
Demonstration that outcome of interest was not present at start of study	★	0	★
Comparability (maximum two stars)			
Comparability of groups on the basis of the design or analysis	★★	★★	★★
Outcome (maximum one star by item)			
Assessment of outcome	0	0	0
Was follow-up long enough for outcomes to occur?	★	★	★
Adequacy of follow up	★	★	★
TOTAL /9	**7 ★**	**6 ★**	**7 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Ahmad et al, 2011, 2012	
	Efficacy & Reversibility	Safety
	Global sperm concentration	Biological AEs
Selection (maximum one star by item)		
Representativeness of the intervention group	★	★
Selection of the control group	★	★
Ascertainment of intervention	0	0
Demonstration that outcome of interest was not present at start of study	★	★
Comparability (maximum two stars)		
Comparability of groups on the basis of the design or analysis	★★	★★
Outcome (maximum one star by item)		
Assessment of outcome	0	★
Was follow-up long enough for outcomes to occur?	★	★
Adequacy of follow up	★	★
TOTAL /9	**7 ★**	**8 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Abdelhamid 2019a, 2019b
	Safety
	Biological AEs
Selection (maximum one star by item)	
Representativeness of the intervention group	★
Selection of the control group	★
Ascertainment of intervention	0
Demonstration that outcome of interest was not present at start of study	★
Comparability (maximum two stars)	
Comparability of groups on the basis of the design or analysis	★
Outcome (maximum one star by item)	
Assessment of outcome	0
Was follow-up long enough for outcomes to occur?	★
Adequacy of follow up	★
TOTAL /9	**6 ★**

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Zhang et al., 2015a, 2015b, 2018a, 2018b		
	Efficacy & Reversibility	Safety	Safety
	Global sperm concentration	Clinical AEs	Biological AEs
Selection (maximum one star by item)			
Representativeness of the intervention group	★	★	★
Selection of the control group	★	★	★
Ascertainment of intervention	★	★	★
Demonstration that outcome of interest was not present at start of study	★	0	★
Comparability (maximum two stars)			
Comparability of groups on the basis of the design or analysis	★★	★★	★★
Outcome (maximum one star by item)			
Assessment of outcome	★	0	0
Was follow-up long enough for outcomes to occur?	★	★	★
Adequacy of follow up	0	★	★
TOTAL /9	**8 ★**	**7 ★**	**8 ★**

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Liu, 1991				
	Efficacy	Reversibility	Reversibility	Security	Security
	Sperm concentration	Sperm concentration	Pregnancy occurrence	Clinical AEs	Histological AEs
Were the criteria for inclusion in the sample clearly defined?	N	N	N	N	N
Were the study subjects and the setting described in detail?	N	N	N	N	N
Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y
Were confounding factors identified?	N	N	N	N	Y
Were strategies to deal with confounding factors stated?	N	N	N	N	N
Were the outcomes measured in a valid and reliable way?	Unclear	Unclear	Y	Unclear	Y
Was appropriate statistical analysis used?	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Y
TOTAL /8	2/7	2/7	3/7	2/7	5/8

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Liu, 1988
	Security
	Biological AEs
Were the criteria for inclusion in the sample clearly defined?	N
Were the study subjects and the setting described in detail?	N
Was the exposure measured in a valid and reliable way?	Y
Were objective, standard criteria used for measurement of the condition?	Y
Were confounding factors identified?	Y
Were strategies to deal with confounding factors stated?	Y
Were the outcomes measured in a valid and reliable way?	N
Was appropriate statistical analysis used?	Y
TOTAL /8	5/8

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Joubert et al., 2022				
	Efficacy	Efficacy	Security	Acceptability	Acceptability
	Threshold	Pregnancy	Clinical AEs	Cessation rate	Satisfaction
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	N	N	N	N	N
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y
Were confounding factors identified?	N	N	N	Y	Y
Were strategies to deal with confounding factors stated?	N	N	N	Y	Y
Were the outcomes measured in a valid and reliable way?	N	N	N	N	N
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y
TOTAL /8	4	4	4	7	7

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Guidarelli M., 2023					
	Efficacy	Efficacy	Reversibility	Security	Acceptability	Acceptability
	Threshold	Pregnancy	Sperm concentration	Clinical AEs	Cessation rate	Satisfaction
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	N	N	N	N	N	N
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y
Were confounding factors identified?	N	Y	N	N	Y	Y
Were strategies to deal with confounding factors stated?	N	N	N	N	Y	Y
Were the outcomes measured in a valid and reliable way?	N	N	N	N	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y
TOTAL /8	4	5	4	4	7	7

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Lalieux, 2022		
	Security	Acceptability	Acceptability
	Clinical AEs	Cessation rate	Satisfaction
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y
Was the exposure measured in a valid and reliable way?	N	N	N
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y
Were confounding factors identified?	N	Y	Y
Were strategies to deal with confounding factors stated?	N	Y	Y
Were the outcomes measured in a valid and reliable way?	N	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y
TOTAL /8	4	7	7

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Béraud T et al, 2023				
	Efficacy	Efficacy	Security	Acceptability	Acceptability
	Threshold	Pregnancy	Clinical AEs	Cessation rate	Satisfaction
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	N	N	N	N	N
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y
Were confounding factors identified?	N	N	N	Y	Y
Were strategies to deal with confounding factors stated?	N	N	N	Y	Y
Were the outcomes measured in a valid and reliable way?	N	N	N	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y
TOTAL /8	4	4	4	7	7

JOANNA BRIGGS INSTITUTE CRITICAL APPRAISAL CHECKLIST FOR CROSS SECTIONAL STUDIES	Rouanet, 2021	
	Security	Acceptability
	Clinical AEs	Cessation rate
Were the criteria for inclusion in the sample clearly defined?	Y	Y
Were the study subjects and the setting described in detail?	Y	Y
Was the exposure measured in a valid and reliable way?	N	N
Were objective, standard criteria used for measurement of the condition?	Y	Y
Were confounding factors identified?	N	Y
Were strategies to deal with confounding factors stated?	N	Y
Were the outcomes measured in a valid and reliable way?	N	Y
Was appropriate statistical analysis used?	Y	Y
TOTAL /8	4	7

COCHRANE ROB2	Wang, 2007				
	Efficacy	Reversibility	Security	Security	Security
	Threshold	Sperm concentration	Clinical AEs	Biological AEs	Histological AEs
Randomization process					
1.1 Was the allocation sequence random?	NI	NI	NI	NI	N
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	NI	NI	NI	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N
	Some concerns	Some concerns	Some concerns	Some concerns	Some concern
Deviations from intended interventions					
2.1 Were participants aware of their assigned intervention during the trial?	Y	Y	Y	Y	Y
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Y	Y	Y	Y
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N	N	N	N	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	/	/	/	/	/
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	/	/	/	/	/
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y	Y	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to	/	/	/	/	/

analyse participants in the group to which they were randomized?					
	Low	Low	Low	Low	Low
Missing outcome data					
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y	Y	Y	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	/	/	/	/	Y
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	/	/	/	/	/
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	/	/	/	/	/
	Low	Low	Low	Low	Low
Measurement of the outcome					
4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	N	Y	N	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	/	/	Y	/	Y
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	/	/	N	/	N
	Low	Low	Some concerns	Low	Some concerns
Selection of the reported result					
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	NI	NI	NI	NI
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	N	N
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N	N	N	N
	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
OVERALL BIAS	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns

COCHRANE ROB2	Rao, 2015, 2016		
	Efficacy	Reversibility	Security
	Global sperm concentration	Sperm concentration	Biological AEs
Randomization process			
1.1 Was the allocation sequence random?	NI	NI	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	NI	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N
	Some concerns	Some concerns	Some concerns
Deviations from intended interventions			
2.1 Were participants aware of their assigned intervention during the trial?	Y	Y	Y
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Y	Y
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N	N	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	/	/	/
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	/	/	/
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	/	/	/
	Low	Low	Low
Missing outcome data			
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Y	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	/	/	/
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	/	/	/
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	/	/	/
	Low	Low	Low
Measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	N	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the	NI	NI	NI

intervention received by study participants?			
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Y	Y	Y
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N	N	N
	Some concerns	Some concerns	Some concerns
Selection of the reported result			
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI	NI	NI
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	N	N
	Some concerns	Some concerns	Some concerns
OVERALL BIAS	Some concerns	Some concerns	Some concerns

ANNEX N°5 – Data extraction for Efficacy

ANNEX 5 - EFFICACY			
Study	**Device**	**Contraceptive threshold**	**Pregnancy rate**
Mieusset and Bujan, 1994 (170)	Perforated underwear (beta)	!! = **motile** sperm count Group 1: 2 men **(66%) reached threshold** in 7, 11 and 15 months. **Mean delay : 11 months**±3,2 **(7 to 15 months)** Rebound: **2 men (100%)**	Group 1: **42 Exposure** cycles **One pregnancy** (after interruption of the device for 7 weeks) **Pearl Index = 28,6**
	Perforated underwear + soft ring	Group 2: 6 men **(100%) reached threshold**. **Mean delay : 3,5 months**±2,5 (2 to 9 months) Rebound: **2 men (33%)**	Group 2: **117** Exposure cycles No pregnancy. **Pearl Index = 0**
Shafik, 1991 (171)	Surgical suspension Suspensory sling with balls	19 men (67,9%) reached threshold (73% (11) of group 1 + 61% (8) of group 2): - 14 at 6 months - 5 at 12 months **Mean delay : estimated 7,6 months±2,6** 9 didn't reached (22,1%) Rebound: no data No significate difference between the 2 groups	252 exposures cycles (28 men with 9 months of exposition) No pregnancy Pearl Index = 0
Ahmad 2011, 2012 (172,173)	Perforated underwear	**No data for threshold BUT**: Individual values: 2 men (40%) became azoospermic (3 and 4 months). 20% was under <2millions of total sperm count (but with no more precision) 40% were still >2 million total sperm count (since DNA test could be made)	No data
Shafik 1992 (181)	TS + Polyester (+2°C)	**14 men (100%) became azoospermic** at 6 months Mean delay (for 3 azoospermic samples with 2 weeks intervals) = 139,6 days (±20,8) (120 to 160 days) = 4,6 months±0,7 (4 to 5,3 months) → Mean delay (for reaching the first of the 3 azoospermic samples): **3,6** ±0,7 **months** (3 to 4,3 months) Rebound: 0	No indication on the number of exposure cycles. 98 cycles* according to a mean of 7 months (225 days) of exposure for each couple No pregnancy. Pearl Index = 0
Moeloek 1995 (182)	TS + Polyester	**No data for threshold BUT**: Individual values: No azoospermia 10 men (100%) <20millions/ml 3 men (30%) <10millions/ml 1 man (10%) <5millions/ml	No data
DJ French, 1973 (186)	Meditation – 15 min For 5 days	0 (0%) From 75,8 to 15M/ml at 14days	No data
	Meditation – 30min For 5 days	2 men (50%) reached azoospermia (BUT one had fever) at 9 and 14 days → Mean = 11,5 days ±2,5 2 men did not reach the threshold (one was at 4-5 millions/ml, the other succeeded to rise >1°C only 2 times on 5days)	
Zhang, 2015a, 2015b, 2018a, 2018b (190–193)	Hot baths	**No data for threshold BUT**: Individual values: One azoospermic (3%) 7 (on 25) = 24% : Sperm concentration dropped under 15millions/ml	No data
Liu (1991) (197)	Microwaves	- 11 men (84,6%) reached threshold - 2 men (15,4%) were under 2M/ml	No data

Study	**Contraceptive threshold**	**Pregnancy rate**
Wang, 2007	N=18 0 reached threshold (0 were under 3 million/ml)	No data
Rao, 2015, 2016	**N=10** **No data for threshold BUT**: Individual values: 4 men under 5millions/ml	No data
	N=10 **No data for threshold BUT**: Individual values: 4 men under 5millions/ml	No data

Study	**Contraceptive threshold**	**Pregnancy rate**
Guidarelli, 2023	*143 missing data (men who did not realised semen analysis, 14,7%)), N= 827 for this outcome* **766 men** reached the threshold: - 79% among all study population - 92,6% among those who realised semen analysis **Mean delay : 3,3 months±1,3**	*6 missing data, N=964 for this outcome* **6 pregnancies (0,6%)** All pregnancies occurred in inhibition phase, none occurred after reaching the threshold. Pearl Index :

	61 men did not reached threshold: - 6,3% among all study population - 7,4% among those who realised semen analysis *Explanations for unreached threshold: omissions or short worn duration <15h (N=24), testicles malposition (N=19). For 13 men, no explanations is retrieved.* **Rebound** : 36 men experienced an increase in sperm count after reaching the threshold (5,7% of men who did multiple tests)	- Total period (inhibition + contraceptive phases) **= 0,53 (13634 months for 6 pregnancies)** - Contraceptive phase (after reaching the threshold) = 0 (6386 months for no pregnancy)
Joubert, 2022	*N=60 for this outcome (no missing results)* **59 men (98,3%)** reached threshold: - 44 (73,3%) at 3 months - 6 (10%) at 4 months - 9 (15%) at 5 months **Mean delay : 3,4 months±0,7** 1 man (1,7%) did not reached threshold at 5 months. **Rebound** : at least 2 men experienced an increase in sperm count after reaching the threshold	*N=59 for this outcome (no missing results)* During contraceptive phase : 0 pregnancy (No Pearl Index because no number of cycles)
Béraud, 2023 (180)	*4 missing data (6,7%), N = 55 for this outcome* **48 men reached the threshold** (81,3% among all study population / 87,2% among N=55): - 30 less than 3 months - 17 between 3-6 months - 1 >7 months **Mean delay estimated* : 4,2±1,5 months** **7 did not reached the threshold** (11,9% among all study population / 12,7% among N=55)	0 pregnancy (No pearl Index because no number of cycles)

Study	Contraceptive threshold	Pregnancy rate
Lalieux, 2022 **Androswitch**	*7 missing data (semen analysis not retrieved, 31,8%), N=15 for this outcome* **11 men reached threshold** (50% among all study population, 73,3% of N=15): - 8 at 3 months - 3 at 6 months → **Mean delay estimated : 3,8 months ±1,3** **4 (18,2% among all study population, 26,7% of N=15) never reached the threshold** and stopped doing semen analysis at 3 or 6 months. Thought, decrease in sperm count happened and they probably would have reach it if they had continue. **Rebound:** 1 man experienced a rise in sperm count at 12 months. (on 5 men who continued doing semen analysis= 20%)	*N=6 for this outcome (men who used MTC as the only contraceptive)* No pregnancy on 28 cycles Pearl Index = 0
Béraud, 2023	*1 missing data (semen analysis at 10 months not given, 3,1%), N=31 for this outcome* **28 reached threshold** (87,5% among all study population, 90,3% of N=31) - 26 at 3 months - 1 at 6 months - 1 at 8 months **Mean delay estimated : 3,3±1 months** **3** (9,4% among all study population, 9,7% of N=31) **did not reached threshold** at 3 months (but decreased their sperm count over 90%) and were lost of view. **Rebound** : 4 patients (on 15 who did another control = 26,7%) had a rebound over threshold but stayed <5millions/ml	No data
Lalieux, 2022 SpermaPause	N=1 Reached threshold at 3 months	No pregnancy on 12 cycles IP = 0

ANNEX N°6 – Data extraction for global values of sperm concentration

ANNEX 6 – EFFICACY AND REVERSIBILITY : GLOBAL SPERM CONCENTRATION					
Study	**Device**	**Size**		**Global values on sperm concentration**	**Global recovery of sperm concentration**
Mieusset et al. 1985, 1987a, 1987b, 1991 (166–169)	Perforated underwear (beta)	13	21	Global values : Significant decrease Started at 2nd month -72% of baseline value (89±56 to 25±22 M/ml) at 4 months -92,6% of baseline value (89±56 to 6,6±7 M/ml) at nadir 14 months (month 0 being the start of treatment)	Global values: Return to references levels in 6 to 8 months Faster in Group 1 (PU beta)
	Perforated underwear + soft ring	8		Global values : Significant decrease Started at 2nd month -96,4% of baseline value (75±40 to 2,7±3,2 M/ml) at 4 months -99,6% of baseline value (75±40 to 0,3±0,5 M/ml) at nadir 16 months (month 0 being the start of treatment) Significantly lower, faster and longer in group 2	
Ahmad 2011, 2012 (172,173)	Perforated underwear	5		Global values : Significant decrease Started at 34th day (1 month) until the end of treatment (D73 after cessation) -99,5% of baseline value (from 77,6 M/ml to 0,04M/ml) at nadir 95th day (3 months).	Return to references levels at D73 after cessation.
Moeloek 1995 (182)	TS + Polyester	10		Global values : Significant decrease Started at 3rd week until the end of TTT, -83,6% of baseline value (80,9 to 13,3M/ml) at nadir 24weeks	ND

			(week 0 being the start of treatment)	
Wang, 1997 (183)	TS + Polyester One layer	7	Global values : No significant decrease in sperm concentration (despite a decrease in some subjects) No significant difference between groups. (+0,8-1°C)	ND
	One layer + polyester with alu	7		
	Two layers	7		
Rock and Robinson 1965 (184)	Insulating underwear 6 to 14 weeks	7	Global values : Significant decrease, Started at 3rd week (No baseline value to 5-25M/ml) at Nadir between 5th and 9th week (week 0 being the start of treatment) But 1 man (14%) had an initial rise of sperm count, the first 2 weeks of treatment	ND
Robinson and Rock 1967 (185)	Insulating underwear 6 to 11 weeks	10	Global values : Significant decrease, Started at 3rd week -78,2% of baseline value of mean sperm count, at Nadir 7th week (week 0 being the start of treatment), follow by a partial recovery (rebound) then another fall.	ND
Zhang, 2015a, 2015b, 2018a, 2018b (190–193)	Hot water (40-43°C – 40min) 2 days per week 3 months	30	Global values : Significant decrease Started at 1st month until 1 month after cessation, -55,6% (from 87,4 to 38,8 M/ml) at nadir 2nd month.	Return to references levels at 3 months after exposition.

Study	Device	Size	Global impact on sperm concentration	Global recovery of sperm concentration
Wang, 2007 (189)	Hot baths (43°C – 30min) 6 days	18	Significant decrease Started at 3rd week until 12th week, -74% (from 79,3 M/ml to 20,9M/ml) at nadir 6th week. TU+LNG>TU+heat>TU alone>heat alone	Return to references levels at week 12.
Rao, 2015, 2016 (194,195)	Hot baths (43°C – 30min) 10 consecutive days	10	Significant decrease Started at 4th week until 14th week, 28,8% of baseline value (50,6±3,9 to 14,6±3,6 M/ml) at nadir 8 weeks (week 0 being the start of treatment)	Return to references levels at week 14 Group 2 (30 days) : more slowly recovery
	Hot baths (43°C – 30min) Every 3 days during 30 days	10	Significant decrease Started at 6th week until 14th week 15,5% of baseline value (47,8±3 to 7,4±1,1 M/ml) at nadir 8 weeks (week 0 being the start of treatment) --> Significate difference (Group 2>Group1)	

ANNEX N°7 – Data extraction for Reversibility

ANNEX 7 - REVERSIBILITY		
Study	**Return to initial value of sperm concentration (n or % of men) OR over 20millions/ml**	**Pregnancy rate among couple wanting a child**
Mieusset et al. 1985, 1987a, 1987b, 1991 (166–169)	**ND : Global values only** (unclear individual values) *mean recovery in 6 to 8 months / Faster in Group 1*	*(N = 7) for this outcome* 100% pregnancy occurrence No miscarriage, no malformations.
Mieusset and Bujan, 1994 (170)	*1 missing data (lost of view) + 1 continued (N = 7) for this outcome* 7 return to baseline value in 6-18 months	(N = 3) 100% pregnancy occurrence No miscarriage, no pathologies (N = 0) for this outcome
Shafik, 1991 (171)	(N = 28) 18 (64%) were >20M/ml at 3 months post-release 28 (100%) were >40M/ml at 6 months No significant difference between the 2 groups	(N= 19) for this outcome (11 in group 1 and 8 in group 2) 6 (31.6%) occurred between 4 and 6 months 100% of pregnancy occurred in the 14 months post release No fœtal anomalies nor miscarriage.
Shafik 1992 (181)	(N = 14) 100% >20M/L at day 109.6±10.8 100% to baseline value at 156.6±14..8	(N = 5) for this outcome 100% pregnancy occurrence, included 1 miscarriage (20%) and 4 healthy children (80%)
Rock and Robinson 1965 (184)	N = 7 6 returned to baseline at 12th week 1 returned to baseline at 18th week post → **100% recovery** → **Mean delay = 12.9 weeks** ± 2.1 (/4.28 = 3 months ± 0.5) *42% (3 men) had a recovery rise higher than baseline*	ND

Robinson and Rock 1967 (185)	N = 10 **100% returned** higher than baseline level at 10th weeks post-heating (until a group-mean 238% of baseline value)	ND
DJ French, 1973 (186)	100% returned at 21 days → 0,7 months	ND
	100% return to baseline at various delay (28, 42, 65 to 107 days) → Mean delay = 60.5 days ± 29.9 (/30 = 2 months ±1)	
Watanabe, 1959 (188)	*(N = 23) for this outcome (4 had no decrease) – results unclear* - 2 returned to baseline at 10th - 4 returned to baseline between 11 and 13th post heating - 4 returned to baseline at 8 and 11th - 1 did not return to baseline at 10th and then was lost of view - 3 between 13 and 14th - 5 returned at baseline between 11 and 14th - 4 returned to baseline between 17 to 20th → **95.7%** returned to baseline level Mean delay = **14 weeks ±3.1** (/4,28 = 3,3 months±0,7)	ND
	3 missing data, (N = 5) for this outcome **3 (60%)** returned to baseline at 3, 4, 6 months after cessation → **Mean delay 4,3±1,2 months** 2 did not return at 7 and 7,5months and were lost of view afterwards BUT were >20M/ml	ND
Liu 1991 (197)	100% recovery (over 20millions/ml) at 1 year after treatment	(N = 6) 100% pregnancy Normal health
Voegeli, 1956	No numerical data No fertility (pregnancy or sperm count?) for : - 2 to 5 months at 41,6°C - 4 to 7 months at 43,3°C - 6 to 8 months at 46,6°C Except for men with high sperm count : last for only 4 months	No numerical data. Healthy children.

Study	Contraceptive threshold	Pregnancy rate
Guidarelli, 2023	One man declared that he had not regained his "fertility" a year after stopping.	No data

Study	Device	Population size	Contraceptive threshold	Pregnancy rate
Lalieux, 2022	Androswitch	22 men	(N = 1) 100% return to baseline level at 2 months	(N=1) 100%, healthy child
Lalieux, 2022	SpermaPause	1 man	/	/

ANNEX N°8 – Data extraction for Safety

	ANNEX 8.1 – SAFETY : Clinical adverse effects
Study	**Clinical adverse-effects**
Guidarelli, 2023 N=970	- **Discomfort during first utilizations** : 722, 74,5% (45,8% on testicles, 28,7% on lower belly) - **Pain during first utilizations** : 268, 27,7% (18,5% on testicles, 9,2% on lower belly) - **Dizziness during first utilizations**: 121, 12,5% or fating (1, 0,1%) - **Allergic reaction during first utilizations** : 26, 2,7% - **Penis venous thrombosis** : 0,1% (N=1) - **Penis oedema** : 0,1% - **Penis skin affections** : 74,5% (dermal irritation 53,1%, itch 46%, hairs' irritation 32,3%, colour's modification 14,6%, skin texture's modification 8,6%, mycosis 0,8%, oedema 0,9%, affection with necessity of medical care 0,9%, reduced skin feeling 0,1%) - **Scrotal skin affections** : 66,7% (dermal irritation 51,9%, itch 45,1%, colour's modification 3,6%, skin texture's modification 3,7%, mycosis 0,6%, oedema 0,2%, affection with necessity of medical care 0,3%), unusual scrotal pain 0,9% - **Testicular affection** : 40,5% (decrease in testicles' size : 31,5%, Testicular discomfort wearing the device (8,8%) and ongoing after the worn (1,5%), Testicular pain wearing the device (4,7%) and ongoing after the worn (1%), Testicular oedema (0,4%), Testicular induration (0,3%), No testicular torsion) - **Erectile function's affections** : 36,1% (painful or uncomfortable erection when wearing contraception the night (23,4%) or the day (11,8%), or after the worn (0,2%), duration modification during the worn (3,9%), rigidity modifications during the worn (4,8%), delay for erection modification during the worn (2,6%), unusual curved penis (0,3%), priapism (erection >4h) (0,1%) - **Urinary function's affections** : 28,2% (unusual late drops (21,4%), uncomplete urination feeling (7,9%), urination blockage (4,1%), delay (3,6%), urination difficulties on standing (1,3%) or sitting (1,1%) positions, urine leakage (0,9%), urinary infection (0,3%), haematuria (0,1%)), with some of these symptoms disappearing when the device is removed.

	- No frequency available : **higher urination frequency** (N=21), testicles returning to their position despite the device (N=11), increase in testicles size (N=7), foreskin malposition (N=3), inguinal anomaly (N=3), **ejaculation anomalies** (N=5), discomfort in lying position (N=4) **- At least one effect : 94,8%** **- At least one effect (excepting testicle size and skin affections) : 56,6%** - **No sexual dysfunctions** (ASEX questionnaire).
Lalieux, 2022 Androswitch N=20	90% of men described AEs Skin affection (dermal irritation or itch) : N=12 (60%), 66% were temporary Penile, scrotal or testicular pain or discomfort, while wearing : N=7 (35%), 57% were temporary Change of position of testicles (N=2 (10%)) or the ring (N=6 (30%)) Discomfort during physical activities: N=4 (20%) Discomfort during sexual intercourse or erection: N=4 (20%) Urination discomfort while wearing: N=1 (5%) No libido changes N=0
SpermaPause N=1	Groin's burning sensation
Rouanet, 2021 N=233 *31 missing data* *N=202 for this outcome*	Erectile pain: N=8 (3,9%) Night pain: N=9 (4,4%) Transitory discomfort at the beginning: N=13 (6,4%) Pain or discomfort: N=14 (6,9%) Hairs' irritation: N=14 (6,9%) Need to check position: N=16 (7,9%) Discomfort in some activities: N=29 (14,3%) Dermal irritation: N=51 (25,2%), persistent for N=6 (3%) Decrease of sexual sensations: N=1 (0,5%) Depression: N=1 (0,5%) Sperm appearance modification: N=2 (1%) More frequent erections: N=3 (1,5%) Decreased libido: N=5 (2,5%) vs increased libido : N=7 (3,5%) and increased sexual pleasure : N=9 (4,5%) Decreased testicular size: N=22 (10,9%)
Joubert, 2022 N=63	At first utilizations : - Discomfort while wearing: N=35 (56%) - Pain while wearing: N=22 (35%) - Dermal irritation: N=37 (59%) - Testicles movement and malposition: N=34 (54%) - Painful or persistent erections: N=9 (14%) - Excessive sweating: N=3 (5%) Most of those resolved easily (56%) or necessitated a device modification (53%)
Béraud, 2023 N=59	No adverse effects : 40,7% (N=24) Discomfort or irritation : 44,1% (N=26) Pain : 8,5% (N=5) No libido modification 0% (N=0) No erection modification 0% (N=0)

Study	Clinical Adverse-Effects
Mieusset et al. 1985, 1987a, 1987b, 1991	No pain No libido depression
Mieusset and Bujan, 1994	No clinical modification during examination. (Testicles were not measured but evaluated subjectively) No changes in libido and sexual rhythm. No pain or complaint.
Shafik, 1991	Pain in the first days in group 1 (Group 2 tolerated better than group 1) No interferences with activities or sexual intercourse. Decrease testicular size of 20% at 6 months, 37% at one year. Recovery within 1 year.
Ahmad 2011, 2012	No change in duration of abstinence
Shafik 1992	No complications, no reactions to polyester. Mean testicular size decrease from 22ml to 18ml (statistically significant). Reversibility was achieve within 3-5 months.
Moeloek 1995	No pain, no libido changes, no body weight changes, no other side effects reported. Testicular volume unchanged.
Wang, 1997	One recurrence of skin fungal infection.
Rock and Robinson 1965	N = 3 : No effect on libido
Robinson and Rock 1967	Scrotal chafing after several weeks of insulation during summer, in some sweating individuals. Libido: 50% no libido changes. 50% minor variations in libido (up or down).
Voegeli (1956)	No local or general side-effects, physical or psychic. Temperature was comfortably supported. Beneficial on a psychological point of view.
Zhang, 2015a, 2015b, 2018a, 2018b	(N=30) No severe discomfort, no pain, no dizziness, no palpitations, no erectile dysfunction, no anejaculation

Liu (1988, 1991)	No cardiovascular or neurasthenic response to microwave No sexual effects Normal testicular size
Fahim (1977)	No pain or tenderness during or after treatment.

Study	Clinical Adverse-Effects
Wang, 2007	No changes in mood, increase in sexual desire, enjoyment, activity, erection frequency and satisfaction. No immediate scrotal skin changes

ANNEX 8.2 - SAFETY : biological and histological Adverse Effects	
Study	**Sperm parameters and sperm functions**
Mieusset et al. 1985, 1987a, 1987b, 1991	- (N=14) No pH changes (7.4 to 7.4 or 7.5). - (N=14) Significant decrease of volume at 4th week only (3.6+/-1.2 to 2.8+/-1.3) - (N=14) No changes in vitality (92% to 90-92%). - (N=19) Sperm morphology : Significant increase in % of abnormal forms from 30% to 60% within 6-8 months of heating. Significantly higher in Group 2. Recovery at 8 months. Group 1: 27+/-3% to 48+/-6 at 12 months) Group 2: 27.5+/-7.5 to 68+/-5 at 10 months Types of abnormalities: Elongated head, thin head, irregular head (all head x2.4: 13.6% to 35.8%), and bent tail (x2: from 5.5 to 11.8%). No changes in micro or macrocephalic nor duplicate heads. No changes in other tail anomalies. Reversibility of tail anomalies within 12 months after cessation. Head anomalies remains high for 18 months. No statistically difference between men who wore 6 to 12 months, and those more than 24 months. - (N=21) Sperm Motility Group 1 : significant Decrease of 50% after 6 months of heating (from 67+/-5% to 39+/-13, and 22+/-10 at 10 months) Group 2 : significant Decrease of 80% after 3 months of heating (from 64+/-3% to 18+/-13). Minimum: 5±5 at 10 months Recover within 6-8 months after cessation in the 2 groups
Shafik, 1991	No analysis for significant - (N=28) Sperm morphology: Increased abnormal sperm forms from below 40% to 88% at 12 months. Recovery within 6 months post-release for 100% of men. No significant difference between the 2 groups - (N=28) Sperm motility: Decrease of motile sperms from more than 70% to 11% in 12 months. Recovery for 100% of men within 9 months (mean delay: 4.3±1.9 months)
Ahmad 2011, 2012	(N=5) Morphology: - Multiple anomalies index significantly increased from 1,94+/-0.02 to 2,1+/-0.05 at D9 and up to 2.5during hyperthermia, and remained higher until D45 after cessation. Reversibility at D73 post-heating. - Anomalies which increase was significant : head (thin, small head, deformed, acrosomal defects), mild piece (bent: higher but non-significant), tail (absent, coiled, multiple). Recovery of head anomalies at D73 after cessation. (N=5) Semen volume: no significant change (N=5) Progressive mobility (%): significant decrease from 47+/-1 to 7.4+/-3.5 at day 45. Return to baseline at 73th day post-heating. (N=5) Viability (%): from 73.2+/-1.7 to 20+/-15 at day 95. Insignificant after cessation (small N), return to baselin value at day 75 No change in semen pH
Abdelhamid 2019a, 2019b	(N=5) Morphology: - Normal spermatozoa %: Significant decrease in % (from 30 to 3%) of normal spermatozoa during heating from H34 to PH45, and return to baseline at PH73. (H=heating, PH=post-heating)
Lalieux, 2022 Retro	**!! No statistical analysis performed!! numbers from individual semen analysis** (N=15) Mobility (%): decrease from mean 54.7±12.6 to 10.9±17.8 at 3rd month (N=11) and 3.2±4 at 6 months (N=5) (N=15): Normal spermatozoa (%): from 8.2±3.9 at beginning to 2 (N=1) at 6 months. All 14 others could not perform morphology analysis (not enough spermatozoa)
Béraud, 2023 Retro	(N=32) Progressive mobility (%): Significant median decrease from 47.5% (max 68, min 10) to 0 (max 35). Median difference of 46 (IQR 13,25) (N=32) Semen volume: no significant change. From median 3,46 (Q1 2.6 and Q3 4.26, max 7.35, min 0.56) to median 3.55 (Q1 2.7, Q3 5.47, max 8.65, min 1.07)
Moeloek 1995	(N=10) Sperm morphology: Statistically significant increase of abnormal forms (from 42% to 81% at 24 weeks). Teratozoospermia in 100% of men at 21 weeks, defined by <30% of normal morphology. Sperm motility unchanged, not statistically significant. Sperm velocity: Statistically significant decrease (1,05sec to 1,26sec for 0,05mm of distance). 100% of men had abnormal velocity at 21 weeks. No change in semen volume.
Wang, 1997	(N=21) No changes in sperm functions (sperm movement, velocity, hyperactivated motility, and zona-free hamster oocyte penetration test) Insignificant decrease of hyperactivation No changes in semen volume, sperm motility, viability and morphology.
Voegeli, 1956	N=9 : Sperm motility reduced at 41,6°C, Sperm motility disappeared at 46,6°C.
Rock and Robinson 1965	(N=7) Sperm volume: unchanged. (N=7) Sperm morphology: Increase in abnormal forms only in the subject who worn device for 14 weeks

Robinson and Rock 1967	(N=10) Sperm volume: Insignificant changes (with individual variations of fall and rise).
DJ French, 1973	(N=5) No changes in sperm volume
Watanabe, 1959	No changes in volume of semen, pH, morphological differential. Sperm motility decrease
Zhang, 2015a, 2015b, 2018a, 2018b	Semen volume (N=25): no changes Sperm morphology (N=30): Significant decrease of normal forms (46.7±13.6% to 2.8±1.7%). Recovery at 3 months after cessation. Sperm motility (N=30): Significant decrease (from 78.2±14.1% to 20.9±13.7%). No recovery at 3 months after cessation Vitality (N=30): Hypo-osmotic swelling assay + eosin/nigrosine test: Significant decrease of normal spermatozoa (from 76.7±7.8 to 29.2±15.9%). Recovery at 2 months after cessation. Acrosin activity assay (fertilizing capacity): Significant decrease (from 66.2±27.5µIU/10^6 to 22.5±18.9 µIU/10^6). Recovery at 2 months Biochemical markers of epididymis (N=30)/ - Seminal plasma L-carnitine): significant decrease (from 20.76±4.72ng/mL to 11.51±3.49). Recovery at 2 months after cessation - Seminal plasma NAG: significant decrease (from 20.76±4.72U/ml to 11.51±3.49). Recovery at 2 months Oxydative stress (N = 25): Significant increase of levels of NO (nitric oxide) and NOS (NO synthase) in seminal plasma. Recovery at 3 months after. Pro-inflammatory factors (N = 25): Significant increase of macrophage migration inhibitory factor in seminal plasma during heating. Not full recovery at 3 months after. Blood cells (N = 19): Significant increase of white blood cells in semen (0.26 million/ml to 0.76). Recovery at 3 months after.
Rao, 2015, 2016	(N=20) - Hypo-osmotic swelling assay (marker of vitality): significant decrease in Group 1 and 2. Recovery to reference level at week 12 - Total acrosin activity assay (fertilizing capacity): significant decrease in Group 1 and 2. Recovery at week 12 - Semen volume: no changes - Sperm pH: significant decrease in group 2 (from 7.7±0.04 to 7.3±0.1, no recovery at week 16) and only once in group 1 (from 7.8±0.02 to 7.5±0.1, Recovery at week 10.). - Sperm motility: significant decrease (group1: from 63.7±2.5 to 41.8±6.8, Recovery at week 14; group 2: from 68.7±3.2 to 42.8±4.1, Recovery at week 12) - Viability: significant decrease (group 1: from 74.9±1.7 to 46.3±6.3, Recovery at week 10; group 2: from 80.5±2.1 to 49±5.5, Recovery at week 12) - Biochemical markers of epididymis and accessory sex glands (seminal plasma NAG, fructose, zinc) : no changes
Liu, 1988, 1991	(N = 16) Sperm morphology one year after cessation of exposition : Significant increase of abnormal cells - cast-off cells (nucleated anomalies) 4.1±1.9% vs control 1.2±0.43% - deformed cells (head or tail) 1,4±1% vs control 0,3±0.2% with dicephalic, megalocephalic, double-tailed , fork-tailed spermatozoa
Study	**Sperm DNA**
Ahmad 2011, 2012	(N=5) Chromatin immaturity (aniline blue): Tendency to immaturity, but not always significant. Significant from 13+/-0.4 to 23+/-4 at D73. After cessation, insignificant (small N), except at D95. At 180 days post-heating: return to baseline values (N=5) Sperm DNA (chromatin structure assay): DNA fragmentation index (DFI) significantly increases from 11.9+/-1.5% to 31.3+/-5.4%. High DNA stainability (HDS) increase from 5.9+/-0.3 to 13+/-1.1%
Abdelhamid 2019a, 2019b	(N=5) Sperm aneuploidy: significant increase of total aneuploidy. From median 0.73[0.58-1.19] at the beginning. No changes at 34days of heating. No FISH available afterwards until 45days after cessation: median 1.93 [1.62-2.19] (significant). At 180 days post-heating: return to baseline values All 5 men had higher aneuploidy rate than the 90th percentile of control group. Rises start at day 20 of heating phase, and reversibility occurred at day 73 of recovery phase.
Zhang, 2015a, 2015b, 2018a, 2018b	DNA damages (N=30) : - DNA fragmentation index (DFI): Significant increase (from 11.8±2.45% to 68.9±25.1%). Recovery at 2 months after cessation. - DNA fragmentation (TUNEL assay): Significant increase of abnormal spermatozoa (from 11.9±2.4 to 68.9±25.5%). Recovery at 3 months. - HDS: Significant increase (6.7±2.1% to 33.3±13.2%). Recovery at 2 months. - DNA denaturation (Acridine orange): Significant decrease of normal spermatozoa (from 85.0±3.9% to 20.6±19.9%). Recovery at 2 months - Chromatin immaturity (aniline blue + Hypo-osmotic swelling): Significant decrease of normal spermatozoa (from 77.3±6.1% to 20.9±21.9%). Recovery at 2 months Sperm chromosome numbers (N=10): Significant increase of aneuploïdy at 3 months of heating (13.7% vs 1.7% for all forms) (16% vs 1.25% for Ch 13, 18, 21 and 6.7 vs 0.44% for Ch X or Y). No data for recovery.
Rao, 2015, 2016	(N=20) Sperm chromatin structure assay : - DNA fragmentation index (DFI = proportion of denatured DNA) : significant increase in Group 1 / Tendency in group 2 but not significant - DNA fragmentation (TUNEL assay): Significant increase of abnormal spermatozoa (higher in group 2). Recovery at week 12. - High DNA sustainbility (HDS = lack of nuclear condensation): significant increase in both groups. Recovery at week 10-12 (higher and slower in group 2)

	--> Significant difference between group 1 and 2 (higher in group 2)

Study	Blood parameters	Biopsy
Shafik, 1991	(N=28) Hormonal effects: at 3rd month: - Significant decrease of Testosterone (6.5±1.8 to 3.4±1.3) - Significant increase of Prolactin (5.3±1.6 to 8.4±1.9). No changes in FSH or LH. Reversibility at 3 months post-release.	(N=28) Biopsies during heating phase (at 6th and 12th month): germ cells degeneration, reduction of spermatogonia and spermatocytes, interstitial tissue edema, normal Leydig's cells. Recovery within 6 to 12 months post-release (similar at before heating)
Shafik 1992	Hormonal effects :No significant change in hormones serum levels - Testosterone : 6.3±1.6 to 6±1.8 - LH : 5±1.1 to 5.4±1.5 - FSH : 7.4±2 to 7.6±1.9 - Prolactin : 5.3±1.4 to 5.8±1.3	(N=14) Biopsies during heating phase (6th month): degenerative changes of germ cells, some of them had sloughed in the center of the tubule.
Moeloek 1995	(N=10) Blood samples: no changes in values (data not shown) Of: haemoglobin, haematocrit, white blood cells, platelets, liver enzymes, blood urea nitrogen, and creatinine.	ND
Wang, 2007	(N=18) Hormonal serum concentration: Insignificant increase of testosterone (total or free). Unchanged SHBG, LH, FSH and inhibin. (N=18) Blood parameters: No changes in: liver enzymes, HDLchol or PSA. Significant but small increase of: haemoglobin, haematocrit, LDL-chol,	(N=4) Biopsy: Increase of germ cell apoptosis 2 weeks after heating (from 20 to 75 cells for 100 sertoli cells) Morphological appearance 9 weeks after heating shows no difference than control (in tubule diameter or lumen volume). !! Not same men for control and the 2 times of biopsy
Zhang, 2015a, 2015b, 2018a, 2018b	Serum hormonal levels (N=30) : - Significant decrease of testosterone (15.25±6.74 to 8,05±5.22 ng/ml at 3 months) - Significant increase of LH (from 5.19±2.02 to 6.91±2.31) and FSH (from 4.48±2.33 to 7.99±6.46) Recovery at 3 months after cessation for all hormones.	ND
Rao, 2015, 2016	Serum hormones levels : - No change in FSH, LH, Testosterone, free Testosterone, SHGB. - A single time significant decrease in estradiol for Group 1 at week 2	ND
Liu, 1988, 1991	ND	(N = 13) Histological analysis of tubules 1,5 years after cessation of exposition: Significant increase of severe damages (0.052 vs 0.0037 for control) and exfoliative tubules (0.285 vs 0.125 for control). No differences for normal tubules (0.161 vs 0.148 for control). No correlation between exposure time and degree of degeneration. Degenerated primary spermatocytes and early spermatids. 20% of tubules: thickening in basal membrane, reduced lumen tubules, hyperplasia of fibrous tissue. Majority of normal interstitial cells were normal, but some were hyperplastic or reduced in number.
Fahim, 1977	ND	(N=4) Testis biopsies 14 to 17 days after treatment: impairment of 95% of tubules (50% totally degenerated and hyalinised, 45% composed of Sertoli cells, with only 5% left had cells in different stages of spermatogenesis (usually early stages)). The interstitial cells were normal.

ANNEX N°9 – Data extraction for Acceptability

ANNEX 9 – ACCEPTABILITY		
Study	**Cessation for reasons linked to the device (% and number of men N)**	**Declared satisfaction**
Guidarelli, 2023	**4,9% (N=48/970)** (unreached threshold (N=12), adverse effects (N=13), non-acceptable (N=23))	*7 missing data, N=963 for this outcome* Excellent satisfaction : 48,8% (N=470) High satisfaction : 37,7% (N=363) Good satisfaction : 10,9% (N=105) Dissatisfaction : 2,6% (N=25)
Lalieux, 2022	**15% (N=3/20)**	Excellent satisfaction (5/5) : 60% (N=12) High satisfaction (4/5) : 30% (N=6)

	(adverse effects (N=2), unacceptable constraint (wearing length) (N=1))	Good satisfaction (3/5) : 10% (N=2) Average satisfaction (2/5) : 0% (N=0) Dissatisfaction (1/5) : 0% (N=0) 20/21 would recommend MTC without reluctance.
Rouanet, 2021	*36 missing data, N=197 for this outcome* **7,1% (N=14/197)** (Adverse effect or unacceptable constraint)	No data
Joubert, 2022	**7,9% (N=5/63)** Adverse effects (N=4), threshold unreached after 3 semen analysis (N=1)	*4 missing data, N=59 for this outcome* Global satisfaction: 3,78 / 4 (± 0,46) 100% would recommend MTC
Béraud, 2023	**18,6% (N=11/59)** Adverse effects (N=9), threshold unreached (N=2)	High satisfaction : 67,8% (N=40) Good satisfaction : 23,7% (N=14) Average satisfaction : 5,1% (N=3) Dissatisfaction : 3,4% (N=2)
Lalieux, 2022	**0% (N=0/1)**	High satisfaction (4/5) : 100% (N=1)

ANNEX n° 10 – PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	15
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	15
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	16
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	16
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	16
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	60
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	17
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	17
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	17
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	17
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	17

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	17
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	17
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	17
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	17
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	18
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	17
Study characteristics	17	Cite each included study and present its characteristics.	20-21
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	22-24
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	25, 26, 28, 40, 30, 31, 33-37, 38
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	26, 29, 32, 37, 39, 40
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	26, 29, 32, 37, 39, 40
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	41-45
	23b	Discuss any limitations of the evidence included in the review.	41-45
	23c	Discuss any limitations of the review processes used.	41-45
	23d	Discuss implications of the results for practice, policy, and future research.	41-45
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	16
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	16
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	17
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	46
Competing interests	26	Declare any competing interests of review authors.	46
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	60-88

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

ABSTRACT

Thermal Male Contraception: A Systematic Review of Efficacy, Reversibility, Safety and Acceptability.

Objective: To provide a clear synthesis of thermal male contraception regarding efficacy, reversibility, safety and acceptability.

Methods: This review conforms to PRISMA and was registered on PROSPERO (CRD42023464033). A comprehensive search was conducted until October the 20th, 2023 on eight databases. Selection process was made with double blinding. Risk of bias and data extraction were double checked.

Results: Thirty-three records reporting data from 26 different investigations were included. They investigated eight different techniques of thermal male contraception with a total of 1675 men. They were essentially at moderate or high risk of bias. Concerning testicular suspension, 72.2 to 80.2% of men reached the contraceptive threshold and the Pearl Index was 2.9 in trials and 0.53 in surveys. All techniques included, 95.7% of men showed reversible sperm concentration, within 1.8 to 4.3 months, and all couples wanting a child were able to conceive. 92.8% of real-life users of testicular suspension devices reported adverse effects, some of them being rare but serious. TMC reversibly altered additional sperm parameters and spermatozoa's DNA and chromosomes. Microwaves treatment induced persistent morphological and histological anomalies. 6.1% of users discontinued TMC and 84.9% were highly satisfied.

Discussion: The small population sizes and the multiplicity of devices investigated make it difficult to reach decisive conclusions. All results might have been misestimated due to biases. Reasons for ineffectiveness could be inter-individual variations and failure to follow the protocol. Some uncertainty remains about biological damages and local compression.

Conclusion: The results suggest that TMC might be effective for a majority of men, reversible and acceptable for users. However they raise some concerns about safety. To confirm efficacy on a larger population and to investigate security and reversibility of damages, a new trial and a prospective cohort appear necessary.

Keywords: Thermal, Male contraception, Pearl index, Safety, Acceptability,

RÉSUMÉ

Contraception masculine thermique : une revue systématique de son efficacité, réversibilité, sécurité et acceptabilité.

Objectif: Fournir une synthèse claire et complète de la contraception masculine thermique concernant son efficacité, sa réversibilité, sa sécurité et son acceptabilité.

Méthode: Cette revue suit les recommandations PRISMA et a été enregistrée sur PROSPERO (CRD42023464033). Une recherche exhaustive a été réalisée jusqu'au 20 octobre 2023 sur huit bases de données. La sélection des articles s'est faite en double aveugle tandis que le risque de biais et l'extraction de données ont été vérifiés par un autre membre de l'équipe.

Résultats: Trente-trois articles rapportant les données de 26 études ont été inclus. Huit techniques différentes de contraception masculine thermique (CMT) ont été étudiées sur un total de 1675 hommes. Les études avaient principalement un risque de biais modéré ou élevé. Concernant la suspension testiculaire, 72,2 à 80,2 % des hommes ont atteint le seuil contraceptif et l'indice de Pearl était de 2,9 dans les essais et de 0,53 en conditions réelles. Toutes techniques confondues, la réversibilité de la concentration en spermatozoïdes s'est vue chez 95,7 % des hommes dans un délai de 1,8 à 4,3 mois et tous les couples souhaitant un enfant ont rapporté une grossesse. 92,8 % des utilisateurs de suspension testiculaire ont signalé des effets indésirables, dont certains rares et potentiellement graves. La CMT a modifié de manière réversible d'autres paramètres du spermogramme, ainsi que des paramètres génétiques et chromosomiques. L'utilisation de micro-ondes provoquait des anomalies morphologiques et histologiques persistantes. 6,1 % des utilisateurs ont arrêté la CMT et 84,9 % en étaient très satisfaits.

Discussion : La petite taille des échantillons et la diversité des dispositifs étudiés ne permettent pas de conclure de façon formelle. Tous les résultats sont susceptibles à des biais importants. L'inefficacité pourrait s'expliquer par des variations interindividuelles et par le non-respect du protocole. Une certaine incertitude demeure quant aux effets biologiques et à la compression locale.

Conclusion: Les résultats suggèrent que la CMT pourrait être efficace pour une majorité d'hommes, réversible et acceptable pour les utilisateurs. Cependant, ils soulèvent quelques inquiétudes concernant la sécurité d'emploi. Pour confirmer l'efficacité sur une population plus large et pour étudier la sécurité et la réversibilité des effets, un nouvel essai clinique et une cohorte prospective semblent nécessaires.

Mots-clés: Thermique; Contraception masculine; Indice de Pearl; Sécurité; Acceptabilité

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admise dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueuse et reconnaissante envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime si je suis fidèle à mes promesses! Que je sois couverte d'opprobre et méprisée de mes confrères et consœurs si j'y manque!