The possible relation between poly-and perfluoroalkyl substances (PFAS) pollution and the presence of in- or subfertility in industrialised countries

Master Thesis proposed to achieve the degree of master in medicine by Laurens De Ridder and Jolien De Ridder

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AR	Androgen receptors
EFSA	European Food Safety Authority
ER	Estrogen receptors
ERalfa	Estrogen receptor alfa
ERbeta	Estrogen receptor beta
HBM-I	Human Biomonitoring I value
HBM-II	Human Biomonitoring II value
HTA	Health technology assessment
IF + group	Group of subjects with the presence of infertility factors
IF - group	Group of subjects without the presence of infertility factors
LH	Luteinizing hormone
LOD	Limit of detection
MeSH	Medical subject heading
PCOS	Polycystic ovary syndrome
PFAS	Per-and polyfluoroalkyl substance
PFBS	Perfluorobutane sulfonic acid
PFDA	Perfluorodecanoic acid
PFDoA	Perfluorododecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHxS	Perfluorohexane sulfonate
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic Acid
PFOS	Perfluorooctane Sulfonate
PFOSA	Perfluorooctane sulfonamide
PFUA	Perfluoroundecanoic acid
PFUnA	Perfluoroundecanoic acid
pH	Potential of hydrogen
POP	Persistent organic pollutants
PPAR	Proliferator-activatedreceptors
PPARgamma	Proliferator-activatedreceptor gamma
PXR	Pregnane X receptor
ROS	Reactive oxygen species
TTP	Time to pregnancy
The MIREC Study	The Maternal-Infant Research on Environmental Chemicals
USA	United states of America

ABSTRACT

Background
PFAS is a collective term for pollutants like PFOA and PFOS. These are manmade chemicals that are used in household products, textile and fire-fighting foam. Because of their high thermal stability and durability they do not easily biodegrade and can stay in the environment. Via our food chain and air transmission humans can be exposed to PFAS and therefore it may influence our health and fertility.
Objectives
The aim of our study is to investigate the possible influence of PFAS on human in- or subfertility in industrialised countries. Furthermore, we want to provide an answer to possible questions people might have about this topic when visiting their general practitioner.
Design
We searched in the present literature for appropriate articles that could answer possible frequently asked questions about PFAS and the influence on fertility.
Results
Our literature search in 9 different databases led to 21 included articles. Both for women and men ambiguous answers were found about whether PFAS have a clear influence on human fertility. We found that men have a higher level of PFAS in their blood compared to women because of a lower clearance. The major source of exposure for humans was by the consumption of contaminated food or drinking water.
Conclusion
Human beings are constantly exposed to a lot of environmental factors, the so called exposome. It is almost impossible to have no confounders when studying the influence of PFAS on fertility rates. There is need to do further research, in order to understand the isolated influence of PFAS and the correlation to human subfertility.

INTRODUCTION

PFAS are a class of organic molecules used in everyday products such as water- and oil-repellents, coatings for cookware, insecticides, cleaning agents, carpets and textiles. PFAS have different kind of remarkable characteristics: they are colourless, odourless, have a high thermal stability, a low chemical reactivity and high durability (1)(2). High availability combined with low production cost makes them interesting chemicals to use in our industrial and commercial economy. Due to these specific properties they bioaccumulate in our food chain, which is considered as the primary source of human exposure to PFAS (1). The two most common PFAS in the USA are PFOS and PFOA (3). Which are also the most returning PFAS in European studies (4)(5). Therefore PFOA and PFOS are the most relevant PFAS in this paper. In most Western countries, PFOA and PFOS are not allowed to be used in manufacturing processes, but they still appear in our commerce via products manufactured in China (3).

In the past 2 years, PFOS has received great attention in the Belgian media after discovering large quantities of PFOS in the soil around the 3M factory in Zwijndrecht during the 'Oosterweelproject'. 3M produced PFOS in Zwijndrecht until the production stopped in 2002. There is a general concern that during the 'Oosterweelproject' the contaminated soil will cause numerous health risks for the people working on the project and for the people in the vicinity of Zwijndrecht. A blood test was taken on 796 persons around the 3M factory and tested for PFAS. After analysis, PFOS was the most frequently found PFAS in the blood, 59% of the participants had concentrations higher than the HBM-II and 10% even had several times higher values. HBM-II is considered as the concentration of PFOS which may lead to health problems when exceeded. The majority (90%) of the participants exceeded the HBM-I limit (6). HBM-I and HBM-II are values of PFAS concentrations determined by the German Human Biomonitoring Commission. These values are based on the current knowledge of PFAS and its effects on human health. HBM-I corresponds to the concentration of PFAS which, when not exceeded, causes no adverse health effects. For PFOA, the HBM-I value is determined at 2ng/ml and for PFOS at 5ng/ml. In the blood analysis around Zwijndrecht, only 9% of the participants had values below the HBM-I (7).

Although PFAS is linked with numerous health problems, for this paper we focussed on in- or subfertility. Infertility is a common and growing problem in developed countries, implying a greater demand for assisted reproduction (2). In the USA, 2% of women of reproductive age had an appointment with a doctor concerning infertility problems and 8% of women had an infertility related visit in the past (8). In Belgium 1 in 6 couples are suffering from reduced fertility (9). It can have a significant negative psychological impact on couples that experience subfertility and this can cause stress and anxiety and therefore impair the mental health (10). Once in the circulatory, PFAS may act as endocrine disruptors and lead to genital disorders, impaired spermatogenesis, reproductive defects and anti-androgenic driven conditions (e.g. testicular dysgenesis syndrome) (1). Infertility or fertility impairment is defined as failure of getting pregnant after 12 months of regular sexual intercourse without any protective measures. Most studies report the prevalence of infertility on average around 9-12% in developed countries with approximately 56% of those couples seek medical attention (11)(12).

With growing concern about the (long term) health effects of PFAS and, as discussed before, its characteristic to bioaccumulate in the human body, we wanted to investigate the possible relationship between PFAS and in- or subfertility in these industrialised countries (1). We believe that the increasing media attention about PFAS pollution in Belgium will cause an increase in questions and concerns about the effects on in- or subfertility.

METHODS

We searched the recent literature for suitable articles to answer the question: “Is there a correlation between PFAS pollution and the presence of infertility in industrialised countries?”. We experienced that the knowledge about the damaging effects of PFAS were discovered relatively recently. Therefore it was not needed to exclude articles based on their publication date.

We used 7 medical databases. We started our search with Pubmed. On Pubmed we used two different approaches. Primarily we searched by using ‘Mesh’ terms. Following terms were utilized “(perfluorocarbons[MeSH Terms]) AND ((female subfertility[MeSH Terms]) OR (male subfertility[MeSH Terms]))”. This research resulted in 19 articles of which we excluded 8. Our exclusion criteria were population, design, intervention and outcome. Based on population we excluded 4 articles, all of them were solely animal studies. Based on design we excluded 2 articles, one was a narrative review, the other was a letter. Based on intervention we excluded 1 article because the main focus of the article was a method to optimise fertilisation. Based on outcome we excluded 1 article, because it did not study fertility. Secondly we did a free text-search on Pubmed. The free terms “PFOS PFOA Infertility“ gave us 16 articles from which we excluded 9 articles, 6 of them were double. Based on population we excluded 2 articles, one article was only about babies, the other was specifically about women who underwent IVF therapy. Based on outcome we excluded 1 article that was too focused on ovarian reserve only. The last pubmed search with the free terms “female subfertility male subfertility infertility pfos pfoa” resulted in 5 articles, all of them were double.

On Embase we found 13 articles whereof 10 were excluded. We searched on title or abstract containing the words “PFAS” and “infertility”. Five articles were double. Based on design 2 were excluded because the set-up of the study was differing from the aim of our study. Based on outcome 1 article was excluded because it concerned IVF fertilisation. Based on population, 1 study about rats was excluded. Another article was excluded because it had an invalid article ID.

In Medline we did multiple searches with the terms “infertility”, “PFAS”, “PFOS”, “PFOA”. We only included 5-star articles and all of them were double. On TRIP database we searched with the free text: “PFAS infertility” and we only found one double article. In Cochrane library, Dare database and HTA database we did not found any relevant article with the search terms “Pfas” and “infertility” used separately or together.

All the exclusions were based on reading the full article. We had a total of 57 articles. After deleting the doubles, 37 articles remained. We divided these 37 articles between the two of us. At the end, we both reviewed the excluded articles together, in which we reached a consensus. Finally 21 articles remained after exclusion of 16 articles based on design [4], population [7], intervention [1], outcome [3], and one deleted article [1]. In figure 1 there is a compact overview of the process of exclusion.

RESULTS

We would like to give you an overview of the answers to relevant questions that may be asked by patients about PFAS and in- or subfertility in the general practice.

How is PFAS entering our bodies, where is it stored and how is it excreted?

PFAS have been used in a wide range of industrial products (e.g. textiles, paper, cleaning agents, paints and insecticide formulations), leading to their widespread presence in the environment. PFAS is widely present in our drinking water, waste water, stormwater and groundwater (13). Consequently PFAS accumulate in our food chains, especially in fish (2). According to the EFSA, fish and other seafood are the main source of PFAS exposure in adults in Europe. Even in some cases up to 86% of the total exposure to PFAS (14). Although filtration of our drinking water may reduce the amount of PFAS, we can still be exposed. The major source of exposure for humans is by the consumption of contaminated food or potable water (15). For example, in populations in Ronneby (Sweden), up to one third of households are exposed to PFAS contaminated drinking water. Apart from our dietary intake, PFAS can also be inhaled by contaminated indoor air and dust (from furniture) (13). Some studies even report that the indoor environment could account up to 50% of the contamination (14).

Blood is considered the matrix of choice for compounds like PFOS and PFOA. PFAS can also be measured in seminal plasma (2). PFAS bioaccumulates in humans and have a half-life of several years (13). Acknowledging that blood is a storage place for PFOS and PFOA, blood loss can reduce plasma levels of PFAS. The study of Zhang *et al*. (16) described menstrual bleeding as an important route of excretion besides pregnancy and lactation.

Who is exposed to the highest PFAS concentrations?

In the study of La Rocca *et al.* (17) they investigated the presence of endocrine disruptors in the blood from men living in a metropolitan area, an urban area and a rural area. When they compared the blood samples of fertile and infertile men they saw that PFOA was found in over 75% of the study subjects in the rural area compared to 47% in people living in urban areas and 7% in metropolitan areas. PFOS was detected in about 30% of the subjects in each area. The highest concentration for PFOS and PFOA were found in the rural area, followed by the urban area and the lowest concentrations were found in the metropolitan area. Examination of the quantity of PFAS in the semen showed the same trend (2). As to women, they found that infertile women from urban and rural areas had higher PFOA levels in their blood, compared to infertile women from the metropolitan area (18).

A study of Zang *et al.* (16) examined PFAS concentrations in the residents of Wenzhou (city in East-China). They saw that in 50 samples of employees working in a leather-industry there was no difference in PFOA and PFOS levels whether they worked on making chemical solutions, coating the leather or gluing the multiple layers of leather together. In addition this study showed a gender effect by showing higher concentrations of PFOS (not PFOA) in male workers vs. female workers. No age-effect was seen. In the same study in Wenzhou they examined the PFAS concentration in 55 umbilical cord serum samples. Compared with other studies, their PFOS concentration in the umbilical cord serum was similar to those concentrations found in Canada. However the umbilical cord concentrations found in China were higher than in Japan and the USA. The PFOA levels in Wenzhou were higher than in Germany and another Chinese city; Shengyang. Other American studies confirmed PFAS having a sex-dependent pharmacodynamic profile with men having much higher accumulation and lower clearance. Last, they saw a tendency of

higher levels of PFOS in umbilical cord serum with increasing age of the mother and male sex of the unborn baby (16).

Is there a correlation between PFAS and infertility in women?

Several studies investigated the correlation between PFAS exposure of infertile women and of fertile women.

The study of La Rocca *et al*. showed that there was no significant difference between the presence of PFOS and PFOA in the blood of 110 infertile women in comparison with 43 fertile women living in the same area (18). A study from Caserta *et al.* (19) that compared 48 infertile and 13 fertile women from Rome (Italy), could not find a statistically relevant difference in serum levels of PFOA and PFOS between the two groups. Another study of Caserta *et al.* (20) with a bigger study population confirmed the previous results. Vélez *et al*. (3) showed us that higher PFOA and PFHxS concentrations in maternal blood were associated with reduction in fecundity. With each standard deviation increase of PFOA level and PFHxS level, the odds of infertility increases with 31% (odds ratio (OR) = 1.31; 95% CI 1.11–1.53) and 27% (OR = 1.27; 95% CI 1.09–1.48) respectively. This was not observed for PFOS. It was a study of 2001 women from Canada and the model was adjusted for maternal age.

In the study of Fei *et al*. (8) they assessed the association between TTP and PFOA and PFOS serum levels in 1240 women that contributed in the Danish national birth cohort. In comparison with women that became pregnant in the first 6 months of trying, women that had a longer TTP also had higher serum levels of PFOA and PFOS independent to parity. The odds of impaired fecundability were 70-134% higher for women in each of the highest exposure categories (quartiles) of PFOS and 60-154% for PFOA, compared to the lowest exposure groups. The study of Bach *et al.* (21) who observed the same cohort, could not find an association between present serum levels of PFAS and longer TTP or reduced fecundability in nulliparous women. Remarkably, in an review of the previous article (update from the Danish National Birth cohort) of Bach *et al.* (22) they observed a new sample from the same cohort. In the new sample, there was an association between longer TPP and exposure to PFOA in parous but not in nulliparous women, furthermore there was no association between PFOS and TTP.

The influence of PFAS in follicular fluid is also examined. In a limited study of Governini *et al.* (23) they investigated the follicular fluid of 18 women undergoing IVF. The follicular fluid of half of the included subjects contained PFAS (not specified which). The contaminated group had significant lower fertilisation rate in comparison to the control group with no PFAS contamination.

With PCOS taught to be one of the most common gynaecological endocrine disorders (24) and being an important cause of infertility in women, the study of Wang *et al.* (25) examined the relation between PFAS exposure and PCOS-related infertility. This study showed that the concentration of PFDoA in the blood was higher in infertile women diagnosticated with PCOS vs. infertile women without PCOS or another endocrine disease. However there was no significant relation between the blood concentration of other PFAS and PCOS-related infertility. The study of Heffernan *et al.* (26) showed a higher serum concentration of PFOS in women with PCOS vs. controls and in women with irregular menstrual cycles vs. women with regular menstrual cycles. This was not seen for other observed PFAS. Endometriosis, another frequent cause of infertility, was correlated with exposure of one particular PFAS namely PFBS compared with those without the disease. Although PFOS and PFOA, the concerning PFAS of this review, were not associated with increased risks of endometriosis-related infertility (27).

Is there a correlation between PFAS and infertility in men?

In the study of La Rocca *et al.* (2) they noticed that in the metropolitan area PFOS levels in the blood of infertile men were significantly higher than in the blood of fertile men. They did not observed the same results for PFOA. No significant correlation was seen in the plasma of semen. PFOS and PFOA exposure have been associated with poor semen quality. In the study of Zhang *et al.* (16) they showed that men accumulate higher PFAS levels than women. However they did not see a correlation between sperm density and PFAS serum concentration. In the study of Di Nisio *et al.* (1) they characterized the androgenic action of PFAS and its capacity to alter the testosterone with its specific AR. The plasma serum of exposed men (high degree of pollution in that area defined by regional authorities) showed higher PFOS and PFOA. Only higher PFOA was seen in the semen of exposed men. After adjustments, subjects from the exposed group showed a lower mean testicular volume, shorter penile length, shorter anogenital distance and lower semen quality. This lower semen quality means higher semen pH, lower sperm progressive motility and immotile sperm. Exposed men had higher levels of testosterone and LH in serum and seminal fluids. The stated results above of seminal and genital alterations are suggestive of an impairment of androgenic signalling in the gonadalpituitary axis. With an in vitro test they confirmed the putative inhibitory effect of PFOA on AR, partly explaining the higher circulating testosterone levels in the exposed men. Tarapore *et al.* (13) concluded in their review that the results of all the epidemiological studies about PFAS and male reproductivity are controversial. Most studies showed some degree of association between PFOS or PFOA and male reproductive parameters, but some other groups found that PFAS exposure was not significantly associated with reproductive hormone levels or semen quality.

Most of the studies investigated a possible correlation of PFAS contamination and classical semen parameters, but the study of Governini *et al.* (28) focused on whether PFAS can affect sperm chromosome segregation and DNA integrity. A total of 95 men (age range 27-45years) were included whom 58% were positive for PFAS contamination. They found that in whole blood PFOS was detected more frequently than PFOA. The opposite was true in seminal plasma were PFOA was found in 75% of samples and PFOS in 25% of cases. No PFAS contaminations were seen in sperm cell fraction. Of the PFAS positive men, 100% had decreased sperm motility and 82% had morphological alternations with different extent. The main abnormalities detected in men with deviant classical semen parameters were abnormal nuclear shape, empty and irregular acrosome, disorganized axoneme and swollen and defectively assembled mitochondria. Thereby gonosome disomies and the diploidy rate were significantly increased in the PFAS-positive group. Also important to mention is the fact that of the 95 observed male patients attending the centre for couple sterility at the univertity hospital of Siena (Italy), 46 men were oligoasthenoteratozoospermic.

Bonato *et al.* (29) is an overview article that discusses detrimental effects of PFAS on humans. In males, PFAS can act as a endocrine disruptor that interferes with the hormonal mechanisms. This interference can lead to problems in growth and development of tissues, both pre- and postnatal. Endocrine disruptors can do this by mimicking the natural hormones like oestrogens and androgens. Endocrine disruptors can also lead to an inflammatory response that generates about 100 times more ROS than normal. Disbalance in ROS and antioxidants can lead of disruption of the normal physiology of the Leydig cells. The Leydig cells are important for the testis development and masculinization during the fetal life. Interruption in this period can thus lead to infertility. (15)

Is there a correlation between PFAS and infertility in both men and women?

La Rocca *et al.* (17) (Previeni project) did a research in 53 couples who were infertile. They divided the couples in the IF - group and the IF + group. The IF + group showed higher blood levels of PFOS. In this IF+

group, women had higher PFOS levels than men but there were more men with values overlapping the LOD. PFOA levels were generally below the LOD in the IF+ group. The study of La Rocca *et al.* (17) and the study of Fei (8) searched for a correlation between a higher PFOS or PFOA level and fecundability in couples could not find a statistically significant result. Neither did the study of Jørgensen *et al*. (30), they included couples of 3 different geographical areas; Greenland, Ukraine and Poland and they studied PFAS exposure to both of the partners in relation to TTP.

DISCUSSION

Our goal was to investigate the relationship between PFAS pollution and in- or subfertility. Numerous studies already suggested a link between PFAS contamination and different health effects, for example an increased risk on diabetes type 2 (31). We focussed in this paper on in- or subfertility because it is a growing problem in the developed countries and environmental pollution is one possible cause of this increase (2). We also believe that the people living in the highly contaminated areas will be worried about the possible health effects of PFAS and can possibly cause an increase in consultations at the (family) doctor.

Is there a relationship between PFAS exposure and sub- or infertility in men and women?

As we collected the data from our 21 included articles, it quickly became clear that the outcomes are heterogenous or contradictory. A good example are the articles about the Danish National Birth Cohort. Fei *et al.* (8) showed that higher PFOS and PFOA levels were associated with longer TTP. However Bach *et al.* (22) wanted to confirm this association in a new sample from the same Cohort but in this new sample no association was found between PFOS levels and longer TTP. Only in the pooled sample, a combination of the sample used in Fei *et al.* (8) and the new sample, there was a tendency towards longer TTP with increasing PFOS levels. And in the MIREC study of Vélez *et al.* (3), a retrospective study carried out in Canada, only PFHxS was found to be associated with longer TTP.

La Rocca *et al.* (17)(18)(2) was the main author of three articles about de role of exposure to different kind of endocrine disruptors and infertility in men and women from three different areas in Italy. The main conclusion of all three articles was that neither PFOA or PFOS were risk factors for infertility. Although tendencies of higher PFOS or PFOA concentrations were found in groups affected by infertility, the authors concluded that PFOS exposure did not represent a risk factor.

Nor the study of Zhang *et al.* (16) found a causal correlation. There was no significant relationship between the presence of PFAS in serum and an altered sperm density of samples from infertile men. They did found a gender difference in the presence of PFOS in worker serum samples. All the workers in this study were employed in a leather factory but had different job assignments (solution preparation, coating and gluing). The authors suspected that a gender effect could be seen among the different job types but in their study they did not observe any work related PFOS elevation in their serum (16). It is not known if this was caused because of an equal gender distribution between the different jobs or because there was no PFOS elevation caused by doing the different jobs. The other suggestion of this gender effect was that women have different mechanisms of excretion, for example menstrual bleeding, lactation and pregnancy. While menstrual bleeding is considered to be the most important excretion mechanism among women, in men urinary excretion is seen as the main excretion route (32). Other PFAS did not show this gender effect.

What makes the results of these studies so contradictious and heterogenous?

The numerous pollutants that we are exposed to every day in our lives, the so called exposome, is difficult to investigate. It is complex to investigate a sole pollutant and its effect on a single subject or a group of subjects. For example in the study of Tarapore *et al*. (13), they mentioned that contradictory findings about PFAS and their effect on sperm quality could be a consequence of the difference in composition and concentration levels of various PFAS with the exposure mixture, racial differences, the difference in diet and/or the receptive windows of exposure between two studies aiming to search the same link. The articles of La Rocca *et al*. (18) (2) also examined the influence of other endocrine disruptors on subfertility which showed that subjects were never exposed to one single endocrine disruptor.

TTP was often used as an indicator for in- or subfertility. Although TTP is not considered as the best parameter to determine infertility because a variety of factors (not only other pollutants) can have an influence on a longer TTP. All of the studies above were retrospective studies which collected data from questionnaires after conception. This meant that we have little evidence or control from the months preceding conception. No data was collected about frequency and timing of intercourse or about the use of birth control in the period before wanting to become pregnant (22). TTP itself did not indicate if a delayed conception was caused by female or male factors (16). Furthermore neither of these studies collected data about the male partner exposure. However male factors determine about 40-50 % of the infertility in couples and TTP is a measure of fertility in couples and not only in women (33). The article of Bach *et al*. (22) described the fact that they assume that the pollutants of the father were similar to the mother due to similar home and lifestyle environment. However the modern parent spends a lot of time at work, which can make the working environment and thus the exposome of men and women different. Not including data from the male partner can cause an over- or underestimation of the influence of PFAS on TTP. Cofounders such as socio-occupational status, maternal age and women with already irregular menstrual cycles are additional parameters that should be taken into account to determine TTP. (8)

The articles concerning TTP usually included both nulliparous and parous women in their study groups, but this can cause a wrong interpretation of the results. Nulliparous women may have a higher level of PFAS in their serum compared to women who recently gave birth since pregnancy is an important excretion route of PFAS. Women with shorter inter-pregnancy intervals may be recorded with lower PFAS levels then parous women with a longer inter-pregnancy interval (16). Because of the previous stated reasons, the article of Bach *et al.* (21) considered it necessary to only include nulliparous women. They devoted the found associations between PFAS and TTP in other studies to reverse causation among parous women or confounding related to previous pregnancy's. Reverse causation in this case meant that parous women with longer TTP had a higher level of PFAS because of a longer inter-pregnancy interval. The higher levels of PFAS were thus caused by the longer TTP, and not the other way around.

In our literature study we observed there was no uniformity in the concentrations or LOD of PFAS found in bloodserum or other fluids. This makes comparing articles more difficult. There was also a heterogeneity in observing the presence of a dose-response effect. For example the article of Wang *et al.* (25) mentioned in their sensitivity analysis a dose-response manner of PFDoA- levels and the risk of developing PCOS-related infertility. The study of Wang B. *et al.* (27) showed similar results. However the article of Tarapore *et al.* (13) mentioned non-monotonic dose responses for endocrine disruptors including PFAS. There is need for a new meta-analysis of the different studies that takes into account the dose-response effect and the ambiguity of the PFAS levels.

There are many ways by which the concentration of PFAS can be influenced. Blood is the matrix of choice for PFOS and PFOA (2), but biodistribution can occur in liver tissue, brain tissue, follicular fluid, breastmilk and seminal fluid (28). Pregnancy, breastfeeding and menstrual bleeding have an influence on female PFAS plasma concentration. The blood of a pregnant women gets diluted because of the increasing plasma volume which causes a reduction in PFAS concentration. Also trough breastfeeding a women can excrete pollutants, so these levels are inversely associated with the duration of lactation. Furthermore menstrual bleeding can also be a route of excretion for PFAS and therefore they assume a lower level of PFAS in women. This last argument can be the reason that women with PCOS have a higher level of PFAS because they suffer more often from oligomenorrhoea or amenorrhea (26). Ignoring this can lead to a wrong interpretation of the findings.

A counterintuitive result was seen in the study of La Rocca *et al*. (18). They studied 3 different geographic Italian areas i.e. a rural area, a metropolitan area and an urban area. The presence of PFOS in the subjects living in the 3 areas was equally distributed, but PFOA was more prevalent in the rural areas. It is highly remarkable that subjects living in the rural area had the highest amount of PFOA in their blood, while we expected this to be in the metropolitan area with the largest industry. This suggested that there must be an external source of exposure. In the article they hinted to the river "Po" deriving pollutions from industrial sources, so this finding may be a site-specific problem. This suggested that PFAS pollution can be a local problem, with certain hotspots.

What can be the focus of further investigation?

In several studies of La Rocca *et al*. (2), Caserta *et al.* (20) and Rashtian *et al.* (34) they saw that there was an influence of PFAS presence on expression of certain nuclear receptors. For example ERalfa, ERbeta, AR, AhR and PXR. Mostly the presence of PFAS led to a higher expression of the nuclear receptors. Some data showed a higher expression of nuclear receptors in infertile subjects. This was just an observation in their studies, there was a lack of information about the relevance of the influence on infertility. It is suggested that the presence of the nuclear receptors can act as a biomarker for exposure to PFAS. There is need for further investigation about this possible correlation.

CONCLUSION

It is very challenging to isolate one possible disruptor and examine its effect on infertility. Infertility is not caused by one single external factor. During our research we observed several associations between exposure of PFAS and sub- or infertility but no uniformity was seen between the different articles. This suggests that there could be an influence of PFAS, although further research is needed to see consistent results. We are in need for more prospective cohort studies and the newly upcoming exposome studies (35). These kind of studies will give us an insight of all the causes at play when a couple is experiencing infertility. With our current research we cannot show a clear causal relationship between PFAS and infertility.

FIGURES

Figure 1.

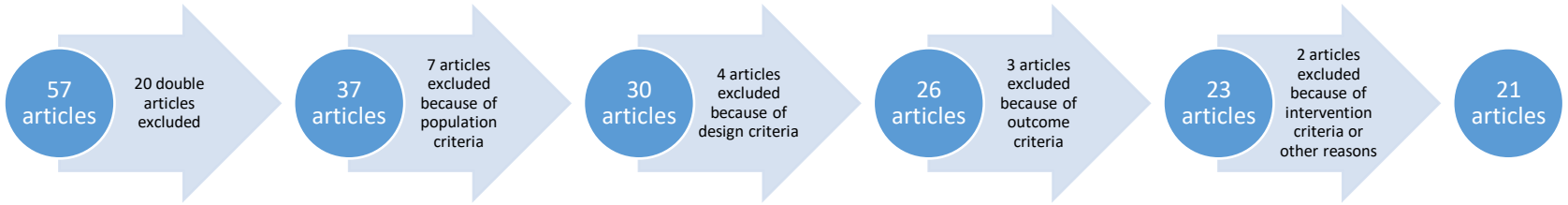


Figure 2.

Author	Titel	Exposure	Dose	Impact on	Conclusion
Wei Wang etal.	Perfluoroalkyl substances exposure and risk of polycystic ovarian syndrome related infertility in Chinese women. (Case-control)	PFOS, PFOA en PFDoA	The LOD was ranging from 0.009 ng/mL to 0.12 ng/mL for the different PFAS. The median concentration of PFOA was 5.07 ng/mL and 4.05 ng/mL for PFOS.	367 Chinese nulliparous women, 180 diagnosed with PCOS, 187 healthy women.	Only the PFDoA concentrations were significant higher in the PCOS group. This could indicate that PFDoA contamination is correlated with PCOS related infertility. No significant correlations between other PFAS and PCOS related infertility.
Andrea Di Nisio etal.	Endocrine Disruption of Androgenic Activity by Perfluoroalkyl Substances: Clinical and Experimental Evidence (cross-sectional observationele)	PFOS en PFOA	The mean concentration of PFOA and PFOS together was 14.99 ng/mL in the exposed group and 4.71 ng/mL in control subjects.	212 exposed young men vs. 171 nonexposed controls. Study performed in Veneto region in Italy.	Elevated concentrations of PFAS in plasma and seminal fluid is positively correlated with circulated testosterone and with reduction in semen quality, testicular volume, anogenital distance and penile length. PFOA has a possible antagonistic effect on the binding of

					testosterone on its natural receptor.
Bin Wang etal.	Perfluoroalkyl substances and endometriosis-related infertility in Chinese women (case control-China)	PFDoA, PFUA, PFDA, PFNA, PFOSA, PFOS, PFOA, PFHpA, PFHxS, PFBS	The LOD was ranging from 0.009 ng/mL to 0.12 ng/mL for the different PFAS. The mean concentration of PFBS was < 0.1 ng/mL.	173 women diagnosed with endometriosis related infertility vs 196 controls (the controls did not have any reproductive disorders).	Only PFBS exposure was significantly associated with risk of endometriosis related infertility. Exact mechanism is not known.
Cathrine Carlsen Bach etal.	Serum perfluoroalkyl acids and time to pregnancy in nulliparous women (Cohort study, Denmark)	PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnA	The median level of PFOS was 8.3 ng/mL, The median level of PFOA was 2.0 ng/mL. Median levels of other PFAAs were less than 1 ng/mL	1372 nulliparous women from Denmark.	No statistical significant association was found between PFAS in the maternal serum and TTP.
Pheruza Tarapore etal.	Perfluoroalkyl Chemicals and Male Reproductive Health: Do PFOA and PFOS Increase Risk for Male Infertility? **(**Epidemiological Evidence Linking PFOS and PFOA to Human Male Reproductive Health p.5 and p.6)	Conclusion of all the discussed articles. It is difficult to show a relationship between PFAS exposure and parameters of male reproductive health. In contrary of the most toxic agents who show a linear response, endocrine disruptors (including PFAS) show a non-monotonic dose response.			
L Governini etal.	Chromosomal aneuploidies and DNA fragmentation of human spermatozoa from patients exposed to perfluorinated compounds	PFOA, PFOS	The LOD for PFOS and PFOA were	95 (age range 27-45) healthy non-smoking	PFAS contamination was present in 58% of the subjects. PFAS

			1.5 and 3 ng g^(-1) fresh weight respectively.	male patients were selected.	exposure disrupts meiotic segregation and DNA integrity.
Cinzia La Rocca etal	Exposure to Endocrine Disruptors and Nuclear Receptors Gene Expression in Infertile and Fertile Men from Italian Areas with Different Environmental Features (2015)	Different kind of ED's were examined but for our study only PFOS and PFOA are important.	The limit of detection (LOD) for both PFOS and PFOA were 0.4 ng/mL	In total, 153 men were enrolled in the study from 3 different kind of areas of Italy (metropolitan, urban and rural areas). 70 infertile men and 83 controls.	In Metropolitan area PFOS blood concentrations in infertile men were significant higher in comparison to fertile men. But exposure to PFOS seems not to be a risk factor for infertility. No association was found between PFOA or PFOS concentration in blood and in semen and infertility. PFOA concentration in blood seems to be correlated to PFOA concentration in semen in infertile men.
Cinzia La Rocca etal	Exposure an effective dose biomarkers for perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in infertile subjects: preliminary results of the PREVIENI project	PFOS and PFOA	LOD = 0.5 ng/g wet weight (ww)	53 couples affected by infertility were studied. In the urban area of Rome.	In comparison to the group not affected by infertility, in the group affected by infertility the number of persons with a PFOS concentration higher

					than LOD was higher for both genders (50% out of 26 male and 63% out of 30 female subjects).
Cinzia La Rocca etal	Exposure to endocrine disrupters and nuclear receptor gene expression in infertile and fertile women from different Italian areas (2014)	Different kind of ED's were examined but for our study only PFOS and PFOA are important.	The LOD for both PFOS and PFOA was 0.4 ng/mL	110 infertile and 43 fertile women from 3 different area's	In the urban area there was a significant increase of PFOA level in blood in comparison with the metropolitan area. Concentrations of PFOA and PFOS were not associated with fertility (in neither of de 3 areas)
Laura Governini etal.	The impact of environmental exposure to perfluorinated compounds on oocyte fertilization capacity	PFAS	No LOD was mentioned in de study	18 infertile women undergoing IVF	The group of women that had PFAS contamination in the follicular fluid had significant lower fertilisation rate in comparison to the control group with no PFAS contamination. Al the women were infertile and were undergoing IVF treatment.
Björvang R.D etal.	Persistent organic pollutants and the size of ovarian reserve in reproductive-aged women	POP. For our study we looked mainly at PFAS pollution. 9	The LOD ranged from 10 pg/mL to	145 women undergoing elective	PFAS seems not to be associated with follicular density (=

		kind of PFAS were determined in serum.	20 pg/mL.	caesarean section. In Stockholm, Sweden.	determinant of ovarian reserve).
Bonato M etal.	Pfas environmental pollution and antioxidant responses: An overview of the impact on human field	Review article that discusses detrimental effects of PFAS on humans. In regard to infertility, PFAS in the human body can act as an endocrine disruptor which leads to the disruption of the normal endocrine homeostasis. PFAS can also induce an inflammatory response that leads to the production of ROS (=reactive oxygen species). ROS is known for its cytotoxic effects on cells. In women PFAS pollution seems to be associated with PCOS related infertility.			
Rashtian J. etal	Water and soil pollution as determinant of water and food quality/contamination and its impact on female fertility	Review article that concludes that in men, there is little evidence of an association between PFAS exposure and semen quality and the effect on androgen receptors and the derangement of the hypothalamic-pituitary axis. Within this research domain there are a lot of conflicting results.			
Chunyuan Fei etal.	Maternal levels of perfluorinated chemicals and subfecundity	PFOS and PFOA.	Median plasma level of PFOA was 5.3 ng/ml and 33.7ng/ml for PFOS. (among the planned or partly planned pregnancies). Among the unplanned pregnancies, the median level of plasma for PFOA was 4.8 ng/ml and 30.0 ng/ml	1240 women were selected from the Danish National Birth Cohort.	The odds of infertility were 70-134% higher in the each of the higher quartiles for PFOS and 60-154% for PFOA. So higher PFOS and PFOA levels were associated with longer TTP.

Cathrine Carlsen Bach etal.	Perfluoroalkyl acids and time to pregnancy revisited: An update from the Danish National Birth Cohort	PFOS and PFOA	The median PFOS serum level was 27.9 ng/ml and the media PFOA serum level was 4.0 ng/ml.	2 samples were studied from the Danish National Birth Cohort. First sample consisted of 440 participants. The second sample contained 1161 participants.	In the second sample and in de pooled analysis of both samples there was an association between higher PFOS/PFOA concentrations and longer TTP. In the first (new) sample, no association was found between PFOS and TTP. For PFOA there was a tendency for longer TTP in parous women.
M P Vélez etal.	Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study	PFOA, PFOS and PFHxS	The geometric means in the maternal plasma of PFOA was 1.66 ng/ml, of PFOS was 4.59 ng/ml and of PFHxS was 1.01 ng/ml	A cohort study of 2001 women recruited before 14 weeks of gestation in 10 cities across Canada between 2008 and 2011.	Increasing concentrations of PFOA or PFHxS in maternal plasma were associated with reduced fecundability and infertility. No relationship between present plasma concentration and TTP was seen for PFOS.
Wei Zhang etal.	Perfluorinated chemicals in blood of residents in Wenzhou, China	PFOA, PFOS, PFHxS and PFBS	3) Mean values of serum concentration	1) 50 serum samples of workers in a leather factory	There is no significant relationship between presence of PFAS in

			of PFOS, PFOA, PFHxS and PFBS was 10.96 ng/ml, 3.43 ng/ml, 0.22ng/ml, 0.1 ng/ml respectivily.	2) 55 umbilical cord serum samples 3) 15 serum samples of infertile men.	the serum and sperm density of samples from the infertile men.
Kristian T Jørgensen etal.	Perfluoroalkyl substances and time to pregnancy in couples from Greenland, Poland and Ukraine	PFOA, PFOS, PFHxS and PFNA	The LOD; PFOA 0.04 ng/ml, PFOS 0.2 ng/ml, PFHxS 0.02 ng/ml and PFNA 0.03 ng/ml.	938 pregnant women from Greenland, Poland (Warshaw) and Ukraine (Kharkiv).	PFOS, PFOA and PFHxS were not consistently associated with TTP (time to pregnancy). Higher PFNA levels seemed to be associated with longer TTP (especially in women from Greenland), but in a sensitivity analysis these associations could not be replicated.
Donatella Caserta etal.	The influence of endocrine disruptors in a selected population of infertile women	PFOS en PFOA	The LOD is 0.4 ng/ml for PFOS and PFOA	48 women aged 18–40 years living in Rome, affected by infertility and examined at the Assisted Reproduction Center of Sant'Andrea	There was no significant difference found between the percentage of patients with detectable PFOS and PFOA concentrations in the infertile patients compared with fertile subjects.

				Hospital.	
Donatella Caserta etal.	Correlation of endocrine disrupting chemicals serum levels and white blood cells gene expression of nuclear receptors in a population of infertile women	PFOS and PFOA	The LOD for PFOS and PFOA was 0.4 ng/mL.	Serum samples of 111 infertile women and 44 fertile women.	Between the fertile and infertile group, there was no significant level of PFOS or PFOA.
A L Heffernan etal.	Perfluorinated alkyl acids in the serum and follicular fluid of UK women with and without polycystic ovarian syndrome undergoing fertility treatment and associations with hormonal and metabolic parameters	PFOS, PFOA, PFHxS and PFNA	In the serum the geometric mean of PFOS, PFOA, PFHxS and PFNA were respectively 3.46ng/ml, 2.39 ng/ml, 1.04 ng/ml and 0.57 ng/ml. In the follicular fluid the geometric mean of PFOS, PFOA, PFHxS and PFNA were respectively 2.00 ng/ml, 1.82 ng/ml, 0.88 ng/ml and 0.41 ng/ml.	59 women of whom 30 with PCOS and 29 controls.	Women with PCOS had a higher concentration of PFOS in their blood serum. This was not seen for the other PFAS and no difference in PFAS between the two groups was seen in follicular fluid.

ADDENDUM

Persoonlijke zelfreflectie Jolien De Ridder

Aangezien ik met Laurens quasi elk jaar in een praktijkgroep zat tijdens de gehele opleiding geneeskunde, wist ik op voorhand dat ik goed met hem kon samenwerken. Samen bekeken we de thesisonderwerpen en gelukkig bleek dat vele gemeenschappelijke onderwerpen ons interesseerden. We kozen uiteindelijk voor "Verband tussen gezondheid en milieublootstelling: systematisch literatuur onderzoek." Als onderwerp. Fertiliteit was iets dat mij interesseerde en waar ik reeds in mijn eerste jaar als HAIO toch al af en toe een vraag rond kreeg. Al was dit eerder algemeen over wat mensen konden doen bij bv. het uit blijven van een zwangerschap na één jaar regelmatige coïtus. Kortom, het is een thema dat leeft bij de patiënten. Na kort overleg was Laurens ook akkoord dat we fertiliteit kozen als domein in de "menselijke gezondheid". Initieel zochten we zeer breed "Verband tussen grond-, lucht of waterverontreiniging en fertiliteit". Al gauw merkten we beiden dat deze zoekopdracht te breed was. Toen de PFOS vervuiling in de omgeving van de 3M fabriek een "hot item" was in het nieuws en ik ook wist dat ik in mijn derde jaar in het Antwerpse mijn HAIO-stage ging doen, leek ons dit een goed idee om ons zoekveld te vernauwen.

De kogel was door de kerk en we ging in de literatuur opzoek naar artikels die de mogelijke invloed van PFAS op fertiliteit onderzochten. We lijstten alle titels van de artikels, de auteurs en de reden waarom we het artikel wel of niet zouden includeren op in een gedeeld Excelbestand. We verdeelden de artikels, zodat we elk de helft doornamen. Met kleurtjes duidden we aan welk artikel we even samen moesten bespreken of we het al dan niet gingen includeren. Daarna begon ik met het schrijven van de inleiding en Laurens vulde aan. Ook de resultaten schrijven verliep via een 50-50 verdeling. Tijdens het schrijven van de resultaten nam ik elk artikel ook eens door, aangezien het wel de bedoeling is dat we beide alle artikels hebben gelezen. Ik maakte een boekje waarin in per bladzijde kort elk artikel voor mezelf in het Nederlands samenvatte. De artikels hebben soms een complexe opbouw of soms duurde het even voor ik terug aan de thesis werkte. Doormiddel van dit boekje kon ik snel de draad terug oppikken. Het lijkt mij ook handig om dit mee te nemen naar de thesisverdediging. Initieel herinner ik mij dat ik de methode schreef, maar deze moest achteraf worden aangepast. Hiervoor kwamen we samen omdat ons dit praktischer leek. We wonen niet ver van elkaar en tijdens de uren dat we "live" samen aan de thesis werkten, werd er productief gewerkt. Aangezien dit zo goed ging, hebben we daarna nog een 3 à 4 keer afgesproken om ook de discussie en de bronnen bij te werken en de conclusie te schrijven. Indien na onze bijeenkomsten niet alles klaar was wat er op de planning stond, verdeelden we het werk en spraken we eigen deadlines af tegen wanneer dit klaar moest zijn. Met onze promotor of co-promotor spraken we altijd af via "Microsoft Teams" en dit verliep altijd zeer efficiënt.

Als ik nu terugkijk op het proces denk ik dat we in het begin veel tijd zijn verloren door eerst artikels i.v.m. bodemverontreiniging etc. te gaan zoeken. We hebben pas nadat we vele artikels hadden doorgelezen beslist dat we ons onderzoeksveld toch gingen vernauwen. Het was ietwat teleurstellend toen het duidelijk werd dat er geen artikels waren die een duidelijk causaal verband aantoonden en dat er artikels waren die tegenovergestelde bevindingen rapporteerden. Al was het ontbreken van een causaal verband wel iets wat in de lijn van de verwachtingen lag.

Desondanks heb ik wel het gevoel dat als patiënten vragen zouden hebben over de invloed van PFAS op fertiliteit dat ik ze hierover goed kan informeren. Voor in de praktijk vind ik het relevant dat we dieper zijn ingegaan op hoe men aan PFAS wordt blootgesteld, waar het vooral voorkomt en hoe men het kan uitscheiden.

Momenteel werk ik in de Antwerpse gemeente, Ruisbroek. Samen met Boom en Willebroek zijn het gemeenten in de Rupelstreek die zwaar hebben geleden onder industriële vervuiling. Het is ook al gebeurd dat artsen van in de streek in een groepschat (via Siilo) vragen hoe ze het best een patiënt konden helpen die een vraag had over de invloed van PFAS vervuiling. Ze hadden geen idee waar ze EBM informatie konden vinden i.v.m. dit onderwerp. Ik denk dat deze systematische literatuurstudie toch al zeker op het gebied van fertiliteit een mooie en evidence based samenvatting kan geven over alles wat er tot nu geweten is over de mogelijke invloed van PFAS op dit gezondheidsdomein. Door de tussentiteltjes in onze thesis is het ook mogelijk voor de lezer om enkel het blokje tekst door te nemen van interesse. Het is misschien ietwat spijtig dat er aan de patiënt dan geen zwart-wit antwoord kan worden gegeven op basis van onze thesis, maar geneeskunde is dan ook geen exacte wetenschap. Voorts hoop ik ook dat onze thesis de onderzoekswereld die werkt rond dit thema kan laten inzien dat er nog meer specifiek onderzoek nodig is binnen dit domein.

Zelfreflectie van Laurens De Ridder

Van zodra ik hoorde dat de masterthesis in groep mocht gemaakt worden, wilde ik graag met iemand samenwerken. Geen grote groep van drie of vier personen maar maximum met twee om de samenwerking overzichtelijk te houden. Toen ik hoorde dat Jolien De Ridder hetzelfde idee had twijfelde ik niet om met haar samen te werken aangezien we elkaar al lang kennen en veel hebben samengewerkt tijdens de studiejaren. Ik wilde graag met iemand anders aan de thesis werken omdat je dan simpelweg met twee kunt nadenken over problemen die opduiken, omdat je dan een klankbord hebt, samen kunt brainstormen en vervolgens ook samen een plan kunt opstellen. Ook helpt het om elkaar gemotiveerd te houden om de zelfopgelegde deadlines te halen.

Bij het zoeken naar een onderwerp voor de thesis sprong één onderwerp in het oog die bij ons beide interesse opwekte, namelijk: “Verband tussen gezondheid en milieublootstelling: systematisch literatuur onderzoek”. Als domein voor gezondheid kozen wij voor fertiliteit. Jolien is al eerste met dit thema naar voren gekomen omdat dit haar interesseerde en omdat infertiliteit een onderwerp is dat voor veel mensen een psychologische belasting kan zijn en waarover mogelijks veel vragen zijn in de huisartsenpraktijk. Als HAIO heb ik hierover al verschillende vragen gekregen tijdens de raadplegingen. Initieel was het de bedoeling om “milieublootstelling” breed te houden en zowel over lucht- als watervervuiling te spreken maar al snel bleek bij de eerste literatuur zoektocht dat dit niet realistisch was en dat we ons onderzoeksveld moesten vernauwen. Net op dat moment kwam PFOS vervuiling in België prominent in het nieuws en was er veel bezorgdheid over de mogelijke gevolgen van PFOS op de menselijke gezondheid. Wij vonden dit een ideale gelegenheid om de mogelijke invloed van PFOS (en andere PFAS) te onderzoeken op infertiliteit en/of subfertiliteit.

Onze eerste grote deadline was de zoektocht in de literatuur. Hier zijn we vrijwel meteen mee van start gegaan in het 1ste jaar. Bij een systematische review is het van groot belang dat de literatuurstudie correct wordt gedaan en dat alles correct wordt beschreven zodat deze later door onafhankelijke onderzoekers volledig kan gereproduceerd worden. Om onze data en de gebruikte zoektermen goed bij te houden hebben we een online Excel document gecreëerd die we beide konden aanvullen. Door dit vanaf het begin nauwkeurig in te vullen konden we bijna drie jaar na de literatuurstudie nog steeds perfect onze search reproduceren en opnieuw uitvoeren. Vervolgens verdeelden we de artikels gelijk onder ons beide en begonnen we met selecteren op basis van abstract en nadien ook het gehele artikel. Na dit proces (dat ongeveer enkele maanden in beslag heeft genomen) hebben we elkaars artikels

overlopen en besproken. Ik hield ook een apart notitieschriftje bij (net zoals Jolien) met de essentiële resultaten van elke studie om later tijdens het schrijven van de thesis snel iets te kunnen opzoeken.

Na deze literatuurstudie zijn we vrij snel begonnen met het schrijven van de hoofdtekst. De “inleiding” en de “resultaten” hebben verdeeld en apart geschreven om het nadien samen te overlopen. Om de “resultaten” en “discussie” beter te kunnen schrijven besloten we om een grote tabel te maken (die toegevoegd is aan de thesis) met daarin de essentie van alle geïncludeerde artikels. Dit hielp om snel resultaten te kunnen terugvinden aangezien we al snel merkten dat veel resultaten erg heterogeen waren en het gemakkelijk was om het overzicht te verliezen. Voor de “discussie” en “methode” hebben we verschillende keren live afgesproken om er samen aan te kunnen werken. We vonden dat deze manier van werken erg efficiënt verliep en we zo productiever waren. Dit bevestigde ook dat de beslissing om samen te werken de goede beslissing was. De feedback momenten met onze promotor en co-promotor verliepen altijd online via “Microsoft Teams”.

Om ons onderwerp ook voor huisartsen relevant te maken en om rekening te houden met mogelijke vragen die kunnen opkomen bij de patiënten, hebben we in de “discussie” en “resultaten” een onderverdeling gehanteerd met tussentitels zodat de lezer vrij snel naar het deel van zijn/haar interesse kan gaan en niet de gehele paper moet doorlezen. De mogelijke invloed van PFAS op infertiliteit is een redelijk ingewikkeld onderwerp en men kan anders snel interesse verliezen bij het lezen van onze thesis. Wij hebben het gevoel dat we dit hebben kunnen counteren door deze onderverdeling toe te passen. Het is enigszins wel spijtig dat we geen eenduidig antwoord hebben kunnen vinden op onze onderzoeksvraag. We hadden deze outcome op voorhand wel verwacht.

In de meest gebruikte bronnen van huisartsen is er erg weinig EBM terug te vinden over PFOS (of andere PFAS) en hun invloed op gezondheid. Dit kan eigenlijk ook veralgemeend worden naar luchtvervuiling en watervervuiling. Er zijn veel studies die wel mogelijke invloeden hebben gevonden maar een echte conclusie trekken is moeilijk. Dit komt grotendeels door de complexiteit van het exposoom waar we allemaal aan worden blootgesteld. Nochtans is milieuvervuiling een onderwerp dat mensen steeds meer bezig houdt en waar mogelijks vragen over kunnen komen naar ons als arts. Een deel van onze studie was ook om meer te weten komen over PFAS en de verschillende blootstellingsmechanismes en excretiemechanismes. Na het maken van deze thesis heb ik wel het gevoel dat onze studie een duidelijk overzicht geeft over wat tot nu toe gekend is op vlak van PFAS en hun invloed op infertiliteit en ik denk dat de studie gebruikt kan worden door andere artsen of onderzoekers in de toekomst.

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