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"No effects of MRI scan on male reproduction hormones."

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Title: No effects of MRI scan on male reproductive hormones

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Keywords: MRI, reproductive hormones, male, electromagnetic field, inhibin B, testosterone, spermatogenesis, cross-over design

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Manuscript Region of Origin: NORWAY

Abstract: Magnetic resonance imaging (MRI) is increasing around the world and the possible adverse effects on reproductive health of electromagnetic fields (EMF) in MRI are not previously studied. A prospective randomized balanced cross-over study using a head scan in real MRI with whole-body transmitting coil and sham MRI among 24 healthy male volunteers was conducted. Serum-blood samples of inhibin B, testosterone, prolactin, thyrotropin, luteinizing hormone, follicle stimulating hormone, sex-hormone binding globulin and estradiol were taken before and after the different scans. Neither immediately after, nor after 11 days were there seen any differences in the hormone levels comparing real and sham MRI. The lack of effects of EMF on male reproductive hormones should be reassuring to the public and especially for men examined in MRI. Adverse effects on other endpoints than male reproduction or possible chronic effect of multiple MRI scans have not been investigated in this study.

Abstract (150 words)

~~The use of m~~Magnetic resonance imaging (MRI) is increasing around the world and the possible adverse effects on reproductive health of electromagnetic fields (EMF) in MRI are not previously studied. ~~We conducted a~~A prospective randomized balanced cross-over study using a head scan in real MRI with whole-body transmitting coil and sham MRI ~~scan~~ among 24 healthy male volunteers was conducted. Serum-blood samples of inhibin B, testosterone, prolactin, thyrotropin, luteinizing hormone, follicle stimulating hormone, sex-hormone binding globulin and estradiol were taken before and after the different scans. Neither immediately after, nor after 11 days were there seen any differences in the hormone levels comparing real and sham MRI. The lack of effects of EMF on male reproductive hormones should be reassuring to the public and especially for men examined in MRI. Adverse effects on other endpoints than male reproduction or possible chronic effect of multiple MRI scans have not been investigated in this study.

Keywords (max 8)

MRI, reproductive hormones, male, electromagnetic field, inhibin B, testosterone, spermatogenesis, cross-over design

UNIVERSITY OF BERGEN

Department of Public Health and Primary Health Care
Occupational and Environmental Medicine

Dear
Editor Reproductive Toxicology

December, 2011

SUBMISSION OF PAPER

We hope you will consider the submitted manuscript « No effects of an MRI scan on male reproductive hormones», for publication as an article in Reproductive Toxicology. The article is interesting because it is to our knowledge the first article looking at how male reproductive hormones may be influenced by the exposure received in MRI. We confirm that this work is not submitted or accepted for publication elsewhere, and that all authors have participated substantially. The first author planned and carried out the field work, analysed the data and wrote the draft. Moen, Baste, Magerøy participated as supervisors in planning, data analysis and in the writing process. Neto and Ersland planned the MRI sequences and has also participated in the writing process. Bjørge, Torjesen has given valuable insight into the reproductive aspect and helped in both the planning and writing process. Oftedal and Hansson Mild is experts on radiation and has given valuable insight in this and a lot of help in the writing process. All authors consent to publication in Reproductive Toxicology. There are no conflicts of interest in the work being submitted. The ethical committee in Western Norway approved the study.

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Sincerely,

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No effects of MRI scan on male reproductive hormones

Reproductive Toxicology

Dear Mr. Knudsen, PhD

Receiving Ed/Office

Reproductive Toxicology

Thank you for reviewing this manuscript for possible publication in Reproductive Toxicology.

Your reviewers have given us valuable comments which my coauthors and I hope to have addressed properly in this letter and in the revised manuscript. We have described our response in the letter and given reference to where in the revised manuscript the changes are. We have also highlighted the changed text in the revised manuscript.

We hope you will consider this revised manuscript. Do not hesitate to contact me if anything is unclear. Thank you.

Yours sincerely

Ole Jacob Møllerløkken

Institute of Public Health and Primary Health Care

University of Bergen

Bergen – Norway

Reviewer #1:

GENERAL COMMENTS:

This is an interesting manuscript with relevance to human patients. The authors conducted a randomized balanced cross over study using real and sham MRI scan with 24 healthy male volunteers. The exposure was approximately 20 minutes and blood samples were collected to determine male hormone levels. The study is easy to read and to understand.

ANSWER:

Thank you.

SPECIFIC COMMENTS:

1) The results were to be expected because the public is aware that that the acute uses of MRI do not pose major health hazards; otherwise these instruments would never be used in clinical settings.

ANSWER:

A good and correct comment, the public is aware of the safety of the MRI in regards to the given guidelines that are used (International Commission on non-ionizing radiation protection, ICNIRP). But even so, the public is probably not aware of details about these guidelines. E.g. for the radio frequency components, ICNIRP is based on the known damaging effects caused by acute thermal heating of the body, it is based on a time-averaging exposure and says very little about the exposure you for instance receive in the MRI machine where you instead of a continuously exposure are exposed for pulses which alone causes very high maximum SAR levels. But since the guidelines averages over time these high peaks are accepted. Possible chronic health effects of this type of exposure are not considered to the same extent, and are the main reason for our research. We found it important to explain some more on this issue and have added some information about ICNIRP and MRI pulses in the manuscript.

In the INTRODUCTION, Section 1, lines 11 - 25

2) Lack of exposure levels. It is not clear how much radiation was emitted during the 20 minutes MRI scan performed to these volunteers. Measuring the radiation levels in these volunteers and then correlating the exposure with lack of hormonal effects would have provide much reliable data

ANSWER:

Thank you for addressing an issue of, in our opinion, special importance in this field of research. Many articles evaluating electromagnetic field and possible influence on humans do not take into consideration the exposure classification and levels. The MRI machine calculates the SAR the subjects are exposed too during the different sequences (Table 1). This estimate is based upon the volunteer's weight and the specific parameters of the sequence used and are the estimates that the staff and the machine use to avoid over-exposure of the subjects (in accordance with ICNIRP guidelines). Measuring exposure levels in the volunteers is impossible. There are some research groups working on human models (made of different plastic materials) to measure just what the referee ask for here, especially the Swiss Federal Institute of Technology, which works on making "virtual families", models of humans that can be implanted with detectors to investigate exposure levels when for instance doing a MRI investigation. They focuses for instance on how the exposure is if you have an implanted hip and similar. We have added some information on this in the text.

In the SUBJECTS AND METHODS, section 2.2.1, lines 4 – 8.

3) I think testing the hormonal effects of the technical staff conducting the MRI routinely would have provided much better data. These individuals are chronically exposed.

ANSWER:

To our knowledge, the MRI staff is usually not exposed to the gradient magnetic fields or the radiofrequency fields which we wanted to investigate in this study. The only exposures they receive are from the static magnetic field when they enter the room to guide the patient to or from the machine. They stay very, very seldom at the machine when the patient is examined, only on specific occasions when for instance a frightened

child must be examined, but even then they normally have a parent or nurse from the bed-ward who sits with the child. Outside the machine, in the control room the levels of exposure are similar to a normal office due to extensive shielding of the MRI room. However if they need to assist the patient/volunteer during a scan they will be exposed to all fields. A study of this personell would of course be of interest, but will need another aim and another design than we have in the present study. We have not commented on this in the manuscript, and hope that it is all right.

4) Minor comment: please clarify the volume of blood collected per volunteer

ANSWER:

The amount of blood collected per volunteer is: 6 ml x 3 glasses per blood sample, and a total of 5 blood samples, which adds up to 90 ml blood. This is added in the article.

In the SUBJECTS AND METHODS, section 2.3, line 2

Reviewer #2:

GENERAL COMMENTS:

The rationale for performing this study as rather low level. The possibility that a conventional head MRI scan would significantly affect hormone levels in males seems extremely remote. That said, the findings of no effect will presumably be reassuring to patients and operators.

The manuscript is well written, the English expression could be improved editorially but it is a quite readable and understandable as it is.

ANSWER:

As mentioned in the answer to Reviewer nr.1 and added in the manuscript, INTRODUCTION, section 1, lines 11-25, there are, despite what one might think, very few studies done on MRI and possible influences on humans. We have, as earlier explained, now tried to make this information more clear in the introduction. We think it is important to underline that we did not use a MRI which only gives exposure to the head although it took a head scan. This MRI machine (as most of these types of machines on the market) gives you a full-body exposure to static magnetic, gradient magnetic and radiofrequency fields, but the picture (the scan) is only of the head. It uses a full-body transmitting coil to deliver the exposure and then it uses a head only receive coil to receive the radiation emitted by the body after the RF exposure, thereby creating a picture of the head. To make this totally clear, we have added a sentence in the article.

In the SUBJECTS AND METHODS, section 2.2.1, lines 4 – 5.

SPECIFIC COMMENTS:

The power of the study to detect changes in hormone levels should be discussed more fully. If I understand it correctly it was powered to detect a 20% change. This impacts on the presentation of the results. For example, the Abstract states "the lack of effect of EMF on male reproductive hormones". If the study was only powered to detect a 20% change, then that

should be stated in the Abstract. Presumably to get ethical approval for this study the authors needed to present a power calculation of what changes could be detected.

ANSWER:

Thank you for a very good comment. We did power calculations before getting ethical approval. We did not expect any major changes, as you previously has mentioned and it is known from the literature that Inhibin B normally in infertile men is given around 110 pg/ml, while fertile men often has levels around 220 pg/ml. We chose to calculate a study sample that would detect a possible change of Inhibin B of 20 pg/ml (that is a change of approximately 9 %). This change would not be of clinical importance, but could indicate an influence of electromagnetic fields. We find it difficult to include a statement of this in the abstract, given the word limit of only 150 words, but we have included a paragraph on this in the discussion.

In the DISCUSSION, section 4, subsection 5, lines 3 - 7

Also I think it should be stated in Abstract that this was a head MRI scan only.

ANSWER:

We have changed the abstract to accommodate this.

In the ABSTRACT, lines 1 - 5

Reviewer #3:

GENERAL COMMENTS:

This is particularly well-designed study. I would add the word prospective to the Phrase "(prospective) randomized balanced cross-over study" to clarify the unique strength of this human study. I am especially impressed that the authors included a Sham MRI and cross over design. The results are believable.

ANSWER:

Thank you very much for a very nice comment. The word prospective is added:

In the ABSTRACT, line 3

SPECIFIC COMMENTS:

The main problem is included in the author's statement "To prevent the same mistake to be made with MRI technology, continued studies of acute and chronic health effects from the MRI examinations are needed." Most endocrine disruptors have been shown not to change hormone levels at all. More importantly, the main concerns (even with radiation exposure) developed after chronic exposure or with large delays. Epigenomic changes may accompany brief exposures and these can lead to a host of problems later on. Even neurotoxicity secondary to acute exposure often shows very late onset. Thus, the failure of this study to show any hormone changes acutely is a reassuring first step but should not cause anyone feel complaisant about potential risks of MRI.

Regarding the statement: "The lack of effects of EMF on male reproductive hormones should be reassuring to the public and especially for men examined in MRI". Fetal phthalate exposures are known to alter sperm counts and sperm health indices in prepubescent boys(seven years after exposure). (Hormone levels are unaffected). Thus, we should be very cautious about using this study to justify some greater sense of safety. None of the males has yet had sperm morphology measures, or follow-up brain volumes (or cognitive tests). They have not reached an age when premature dementia might be seen. As such, the authors have taken the least vulnerable subjects, not studied their most vulnerable reproductive parts (spermatozoa), and stated that

"The lack of effects of EMF on male reproductive hormones should be reassuring to the public and especially for men examined in MRI." I would be very cautious about this level of reassurance.

I would perhaps like to see another statement of humility at the end of this paper. The extreme toxicity of X-Irradiation would likely have been missed using this study as a test of safety. Thus, the authors might suggest that lack of acute hormonal changes does not imply that reproductive effects won't be detected in other studies nor has epigenetic-induced endocrine disruption been at all ruled out by this study.

ANSWER:

These comments are particularly valuable and we agree that this is important to clarify. We also feel that more has to be done in this type of research. We have contacts with some research groups that are currently investigating some other endpoints and are waiting anxiously for their results. As you say, and if you will let us, we have borrowed your expression, this is a good first step, but not the whole story. We have removed some lines and added some other lines addressing this issue in the article:

In the INTRODUCTION, section 1, lines 11 – 25 and

In the DISCUSSION, section 4, subsection 8

Finally, there is one additional control session that might have been ethically feasible in this study design. This would have been a Sham-Sham group. There are clear trends in both study groups for increasing and decreasing hormone trends. These could represent time of day effects or stress/situational effects. Testosterone levels can change acutely in response to stress, football and perhaps the gender of the assistant who places the subjects into the MRI machine. A Sham-Sham control would add information without adding risk and might be considered in the study design. The nagging question is whether there is a general trend which is more disturbed by MRI than by Sham. Congratulations on the study as it is.

ANSWER:

Thank you again for kind words and valuable comments. The question regarding possible stress/situational effects and time of day effects is always there when one investigates hormones which vary so considerably depending on time of day or shape of the volunteers. However we feel that we had relatively good control of the volunteers, we had information on their weekly activities, their sleeping patterns, exercise patterns and so on. In addition we did the sampling at exactly the same time at each session and even randomly assigned the assistant drawing the sample to avoid possible influence from this. Also the last session (without real or sham MRI) should function as a test whether or not the situation of doing a scan would influence the results, which it did not.

ADDITIONAL COMMENTS FROM THE AUTHORS:

We have discovered some errors in the reference list.

The reference 12 and 13 was in the wrong order in regards to when they were published. Therefore these have changed no. 12 is now no. 13 and vice versa.

Reference no. 9 had some errors in the author section, which is now corrected.

Reference no. 2 had some errors in the author section, which is now corrected.

Table 1. We have changed the number of decimals from 4 to 2.

Discussion has now gotten a section number.

Research highlights

- **No effects of MRI on male reproductive hormones**
- **Cross over design**
- **Controlled exposure setting**
- **Complete set of samples**
- **High statistical power**

No effects of MRI scan on male reproduction hormones

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Abstract (150 words)

~~The use of m~~Magnetic resonance imaging (MRI) is increasing around the world and the possible adverse effects on reproductive health of electromagnetic fields (EMF) in MRI are not previously studied. ~~We conducted a~~A prospective randomized balanced cross-over study using a head scan in real MRI with whole-body transmitting coil and sham MRI ~~scan~~ among 24 healthy male volunteers was conducted. Serum-blood samples of inhibin B, testosterone, prolactin, thyrotropin, luteinizing hormone, follicle stimulating hormone, sex-hormone binding globulin and estradiol were taken before and after the different scans. Neither immediately after, nor after 11 days were there seen any differences in the hormone levels comparing real and sham MRI. The lack of effects of EMF on male reproductive hormones should be reassuring to the public and especially for men examined in MRI. Adverse effects on other endpoints than male reproduction or possible chronic effect of multiple MRI scans have not been investigated in this study.

Keywords (max 8)

MRI, reproductive hormones, male, electromagnetic field, inhibin B, testosterone, spermatogenesis, cross-over design

1. INTRODUCTION

Every day thousands of persons undergo magnetic resonance imaging (MRI) scans for diagnostic purposes. It is estimated that there are over 20 000 MRI machines worldwide and the number is increasing. The exposure to electromagnetic fields (EMF) is quite high for the persons in MRI (1). The operating staff is mainly exposed to static magnetic (B) field (2). In order to obtain best possible resolution of the images there is a continuously development of MRI scanners with increasing field strengths of both the static B- and the switched gradient B fields, as well as increasingly power of the transmission coils used for the radiofrequency (RF) field. Possible negative health effects of the increased exposure to EMF are not known. It is relevant to remind that X-ray technology in the beginning was praised as a revolutionary way both to diagnose and treat diseases. It was not until several years of use that the negative health effects of X-rays were discovered. Although MRI is monitored and follows the guidelines given by the International Commission on non-ionizing radiation protection (ICNIRP) it is important to have in mind the basis of these guidelines (1;3;4). Concerning the RF fields, ICNIRP (5) is based upon a time-averaging exposure to EMF on a period of 0.1 hours which should not increase the body temperature. It is therefore fundamentally based on a known damaging thermal effect of the EMF exposure which may be irreversible at levels exceeding 4 W/kg. To account for eventual different conditions like high ambient temperature, humidity or physical activity it's limits are lowered by a factor of 10 to the occupational limit of 0.4 W/kg and public limit by another factor of 5 to 0.08 W/kg. However these limits do not take into consideration short intense exposures of several W/kg that you may receive in an MRI that are under the limits given because of time-averaging. Very little data on these exposures exists and on possible influence these exposures may have on humans. It is therefore important to conduct ~~To prevent the same mistake to be made with MRI technology, continued studies of on possible~~ acute and chronic health effects from ~~the EMF exposure under~~ MRI examinations ~~are needed~~(6).

The MRI uses three types of fields; a static B field, a switched gradient B field and a RF field. The static B field is usually of the order of a few teslas (T); the most common machines operate at 1.5 T or 3 T. The switched gradient B field can be in the order of tens of mT with rise and fall times down to tens of microseconds (μ s). The rapid change in the B field strength will give a high value for the time derivative dB/dt. The RF field frequency in MRI is around 63.4 megahertz (MHz) for a 1.5 T device and around 127 MHz for a 3 T device. Limit values

exist for the RF in MRI set by the European committee for electrotechnical standardization (CENELEC), but such limits are mainly related to acute health effects caused by heating from this type of exposure. Limiting factors for the exposure of patients is also peripheral nerve stimulation (PNS) due to induced electric potentials. The International Commission on non-ionizing radiation protection (ICNIRP) has recommended a limit on dB/dt to avoid nerve excitation in the patient (7). The International electrotechnical commission (IEC) standard 60601-2-33 (8), which applies to the design and manufacture of MRI scanners and is harmonized to the Medical Devices Directive, aims to minimize the risk of even mild PNS in patients and workers. The limit values are debated as they do not take into consideration the risk for chronic health effects. Especially the possible presences of chronic health effects related to RF EMF are discussed. A review from 2009 (6) specifically concerning biological effects and safety in MRI concludes that more studies are needed especially on the effects from the combination of all three fields, this is also mentioned in other more general reviews (7;9;10).

There are some studies on adverse health effects related to MRI (11-18). Among the more recent work are two studies indicating a genotoxic potential of MRI in cell cultures (15;16). The causes and consequences of these findings are not known. One cause could be increased number of reactive oxygen radicals, which has been seen as a consequence of RF radiation (19). A consequence of this could be an increased risk of cancer. The latency time of cancer makes this potential outcome difficult to investigate. Other consequences that are easier to examine could be a more acute influence on enzymes, hormones or sperm production controlling the reproductive ability as suggested in previous articles (20;21).

Studies have been conducted of the relationship between exposure for RF EMF and male reproductive health in humans, by examination of both semen parameters and hormonal values. Both central nervous effects on the hypothalamus and the pituitary gland and a direct effect on testis could be present. The results so far have been conflicting and the studies have limitations in the methodology (22-28) especially concerning examination of sperm samples (21). In sperm samples the most used parameter for fecundity is total sperm count, controlled and regulated by the Sertoli cells through hormones. The hormone inhibin B (29-31) is produced by the Sertoli cells and is positively correlated with the total sperm count. It also regulates the production of FSH through negative feedback mechanisms and other male reproductive hormones like luteinizing hormone (LH), follicle stimulating hormone (FSH),

testosterone, sex-hormone binding globulin (SHBG), prolactin (PRL), estradiol (E2) and thyrotropin (TSH). These hormones work together in complex ways to control male reproductive ability, regulated both centrally through the pituitary gland and locally in the gonads (25;29;32-36). A disruption of sperm production as speculated by Gutschi et al (20) might cause a decrease in inhibin B and a corresponding change in the other reproductive hormones. We wanted to examine the relationship between RF EMF and reproduction by investigating if a 20 min standard MRI anatomical head scan had effect on the level of hormones relevant for male reproduction.

2. SUBJECTS AND METHODS

2.1 Participants

Participants among male medical students at the University of Bergen were recruited. They were informed about the study at three short oral information meetings after student lectures and on web-postal. Interested students were given more extensive information at a later joint meeting or through receiving extensive information through mail, and were invited to participate in the study. The inclusion criteria were to be healthy, non-smoking, Caucasian, male medical student in the age range 18 – 40 years, with no previous work exposure to solvents or oil vapor. In addition the participants could not have had previous work with a risk of RF EMF exposure, such as in welding, work aboard fast-patrol boats in the Navy or as members of electronic warfare companies in the army, or involvement in radio-amateur activity. Normal MRI exclusion criteria had to be fulfilled with regards to presence of metals in the body, history of head-, eye-, ear- or heart surgery and claustrophobia. The study was conducted in the fall 2010 and in accordance with the Helsinki declaration. The study was approved by the Regional Ethical Committee of Western-Norway (REK 2010/1271).

A total of about 60 persons were interested in the study and were given extensive information. Out of these 30 persons agreed to participate in the study, 24 participants and six reserves. All participants had to give their written informed consent at latest before the first session. Three persons withdrew from the study before the first session, and these were replaced by reserves.

2.2 Design

To study the effects of MRI, the participants were examined before and after a real and sham MRI session. A balanced cross-over design was chosen (37). The study consisted of three

sessions with an interval between for each participant (Figure 1). Each session began with a preparation period of 30 minutes, during which the participants relaxed in a chair and filled in a questionnaire. At the first and second sessions the participants had a blood sample immediately before entering the scanner. They were then exposed for real or sham MRI for approximately 20 minutes. After the exposure they were immediately taken outside the scanner room for a new blood sample which completed the session. Session three had no exposure, only a blood sample which was drawn immediately after the preparation period. All participants were randomly divided into having real or sham MRI at their first session. Two researchers organized the sessions and they were also randomly assigned to the real or sham MRI station. The participants were instructed to eat and sleep as normal the nights before the examinations. They had to get up from their bed one and a half hours before arriving at the study site. They should not be involved in night work, drink coffee, tea, caffeine containing or alcohol containing beverages, or use any other central stimulating substance the last 12 hours before the examinations.

2.2.1 Real MRI

Real MRI exposure was given in a 1.5 T GE Signa EXCITE scanner (General Electric, Waukesha, Wisconsin) with Echospeed gradients (33 mTesla/m, 120 Tesla/m/s) located at a local hospital and operated by radiograph technicians employed at the hospital. The scanner had a transmitting body coil and receive only head coil. [This means the scan was taken of the head only, but the whole body is exposed during the procedure.](#) A standard protocol for anatomical head scan was chosen with nine sequences (Table 1). The total sequence time was approximately 20 min. [Since it is difficult to measure individual exposures, -M](#)mean average specific absorption rate (SAR) was calculated [by the 1.5 T GE Signa EXCITE scanner](#) for seven of nine sequences as follows: the SAR for each of the seven available sequences was multiplied with the accusation time. These values were added and the sum was divided with the total time of all nine sequences (20 min). This gave a mean average SAR of 0,29 W/kg which is an underestimation since SAR was not available for the two remaining sequences.

Because of the chance of finding a pathological condition at random when examining healthy volunteers, all MRI images were checked by a neuroradiologist. In case of any pathological finding the participants had to be informed and followed up. There were no pathological findings among the participants in this study.

2.2.2 Sham MRI

Sham MRI exposure was given by a MRI-machine copy produced by Nordic NeuroLab, originally used for training of children and persons with claustrophobia and for testing study designs in MRI-studies. The machine included a car stereo sound system with recorded sounds from the anatomical head scan in the GE Signa scanner used for real MRI exposure. The total sequence time was approximately 20 minutes. The machine was located in a research building with fewer facilities than the real scanner; this therefore made it necessary to inform the participants that this scanner was sham. It was run by the study personnel.

2.3 Blood sampling and analyses

A total of five blood samples consisting of three ethylenediaminetetraacetic acid (EDTA) glasses [of 6 ml volume](#) per sample were drawn from each participant (Figure 1). The hormones investigated were LH, FSH, testosterone, SHBG, inhibin B, PRL, E2 and TSH. To avoid changes due to diurnal variations in hormone levels (35;36) all blood samples were taken in the time period 0700 am – 1000 am. The different samples from each participant were taken at the same time in all three sessions ± 5 min. Inhibin B was analyzed at the Hormone Laboratory, Oslo University Hospital, Oslo, Norway, using the enzyme-linked immunosorbent assay (ELISA) kit from Oxford Bio-innovation, Oxford, UK. Before the ELISA, samples and standards were pretreated with sodium dodecyl sulfate (SDS), heated to 100 °C, and exposed to hydrogen peroxide. These pretreatments enhance the specificity and sensitivity of the ELISA. The total coefficient of variation (CV) was $< 10\%$. TSH was analyzed at the Laboratory for clinical biochemistry, Haukeland University Hospital, Bergen, Norway. Samples were pretreated with antibodies and streptavidin-coated micro particles to form a complex which is then treated magnetically to produce chemiluminescent emission which then is measured (the “Sandwich principle”). The total CV was < 10 . FSH, LH, E2, PRL, SHBG and testosterone were analyzed at the Hormone laboratory, Haukeland University Hospital, Bergen, Norway. The first five of these hormones were analyzed using a solid-phase, two-site chemiluminescent immunometric assay, while testosterone was analyzed by combining liquid-liquid extraction, high performance liquid chromatography and tandem mass spectrometry.

2.4 Questionnaire

The participants filled in different questionnaires. The first included questions on number of years studied, height and weight, number of biological children, use of cell phone (minutes and number of calls), hours of physical exercise per week and general health on a scale from one to five (very bad – bad – fair – good – very good health). This questionnaire was filled in before the first session only. The second questionnaire was filled in at each preparation, and had questions about transportation to the location (walking, running, cycling and motorized transportation), hours of sleep the preceding night, how the physical exercise, sleep and cell phone use had been. If there were deviations in the cell phone usage, physical exercise and sleep pattern the last week compared to the normal pattern as given in the first questionnaire, the participants were asked to describe if the change was less or more than normal the last week. They were also asked whether or not they had had an infection (yes/no and type of infection), and to confirm that they had not drunken coffee, tea, caffeine containing beverages, alcohol containing beverages or taken any other central stimulating substance the last 12 hours and that they had been awake the last 1.5 hours.

2.5 Data handling and statistical analysis

The “pre” (1, 3, 6 and 8 in Figure 1) relate to the blood samples drawn immediately before receiving the exposure (real or sham MRI). The “post” (2, 4, 7 and 9 in Figure 1) relate to the blood samples drawn immediately after receiving the exposure (real or sham MRI). The “post2” relate to the blood sample drawn after one session interval, but before any next exposure (3 and 10 or 8 and 5 in Figure 1).

2.5.1 In real and sham MRI paired samples T-tests were used in separate analysis to test if mean hormone values changed:

- (a) Between the samples drawn at the beginning of the study and at the end of the study
- (b) Between “pre” and “post”
- (c) Between “pre” and “post2”

2.5.2 Regarding the possible significant differences between real and sham MRI in how the hormone mean levels changed paired samples T-test was used to test this:

- (d) Between “pre” to “post”.
- (e) Between “pre” to “post2”.

2.5.3 It was also tested if there was an effect of the exposure depending on in what order the participants received their exposure. To address this issue the sample was divided and all analyses were done separately among those receiving sham exposure at first session (N = 12) and those receiving MRI exposure at first session (N = 12). T-tests were used to compare continuous variables in the groups and Chi-square tests were used to compare categorical variables. Mean values with 95 % confidence interval (CI) were estimated and calculated p-value of less than 0.05 interpreted as significant. The statistical package from PAWS statistics 18.0 was used.

2.5.4 To calculate the needed number of participants, figures from a previous study (30) on Inhibin B change among volunteers with normal (mean Inhibin B 223 pg/ml $\pm$ 18) and impaired (mean Inhibin B 107 pg/ml $\pm$ 12) spermatogenesis were used. To detect a difference in Inhibin B of 20 pg/ml, a sample of 24 participants gave a statistical power of 96.9 %.

3. RESULTS

All 24 students completed the study with both real and sham MRI examinations, and five blood tests. The study participants were in the age group 19-35 and reported fair health or better. They had no children and their body mass index (BMI) averaged at 23.4 kg/m² (range 18.8 kg/m² – 29.7 kg/m²). Two of the participants fainted during blood sampling. All analyses have been tested with and without these two cases without any difference in the results. In the study design it was planned to have weekly intervals (seven days) between each session. Due to problems with achieving this in each case the intervals deviated some from this with an average of 11 days (minimum one day, maximum 29 days). There was only one interval consisting of less than six days between the sham MRI at first session and the real MRI at second session related to one person. When comparing the group as a whole there was no difference in the average number of days between the different sessions, and no systematic difference in number of days before the sham MRI, the real MRI or the third session.

3.1 Background factors at the different sessions

When investigating the answers to the second questionnaires, the different sessions were found to be very comparable. There was no systematic difference between the different sessions in regards to how much physical activity the participants had performed, their sleep patterns the different weeks and their use of cell phones the different weeks.

3.2 Hormonal values

All hormone levels analyzed in this study were within the normal values given in Norway (38). No significant differences in real or sham MRI were found at separate analysis for any of the hormones in the different settings comparing mean hormone values (Figure 2):

- (a) Samples at the beginning of the study compared with samples at the end of the study
- (b) “pre” levels with “post” levels
- (c) “pre” levels with “post2” levels

No significant differences between real and sham MRI were found for change in hormone mean levels (Table 3):

- (d) Between “pre” to “post”
- (e) Between “pre” to “post2”

4. DISCUSSION

This study found no differences in the hormone levels of follicle stimulating hormone, luteinizing hormone, thyrotropin, prolactin, sex-hormone binding globulin, testosterone, estradiol nor inhibin B before and after a real 20 min standard anatomical head scan in a 1.5 T MRI machine. The same was true for sham exposure. In addition, there were no changes in the hormone levels from before to 11 days after real or sham MRI exposures.

There have been few studies examining possible biological effects of exposure to all three fields in MRI (6) and to our knowledge no one has looked at how male reproductive hormones may be influenced by this type of exposure. Two studies have examined biological effects from MRI exposure, one from Italy (15) and one from the Republic of Korea (16). The Italian study (15) was an in vivo experiment where eight volunteers underwent a standard cardiac scan in a 1.5 T MRI, absorbing energy in the amount of 94.18 Joules (J) (range 18.51, 306.14). Their blood samples were taken and lymphocytes cultured and analyzed at 0, 24, 48, 72, 96 and 120 hours after the scan. This experiment displayed an acute increase in micronuclei frequency after 0 and 24 hours, but the changes normalized after 48 hours. This publication (15) also reports an in vitro investigation where lymphocyte cell cultures derived from eight volunteers were exposed for an increasing time (686 s, 1186 s, 1618 s and 2188 s) in a MRI scanner. A dose dependent increase in micronuclei frequency was found. In the Korean study (16) an in vitro experiment was reported where human lymphocyte cell cultures (derived from one volunteer) were exposed in a 3 T MRI. A significant DNA damage,

increased micronuclei frequency and chromosome aberration was found. The changes increased with increasing exposure time. These findings seem to show other results than in our present study. However, the methods are very different. The cell studies presented might reflect signs of genotoxicity, but whether these findings are related to any disorder or adverse clinical effects, is not shown. The findings in the cell studies might be an acute effect with no further implications, but this is not known.

Earlier studies looking at hormones in response to other exposures for RF EMF have shown inconsistent results (20;25;27). Our study is mainly in line with what was seen in a study performed by Schröder et al, USA (25), where no significant effect on blood-, urine- and semen samples was found among soldiers with potential exposure to radar (N=33), soldiers firing a howitzer (lead exposure, N=57) and unexposed soldiers (N=103). None of the parameters displayed any statistically significant difference among the groups with one exception; artillery-men had lower urine-testosterone than controls. No change was found in serum-testosterone or saliva-testosterone. The strengths of this study were the use of different outcomes; urinary, serum, saliva and semen samples and information on when the urinary samples were taken during the day. A major weakness of the study was no actual measurement of exposure from the potential RF sources. Also the study lacks information about when serum and saliva samples were taken which is a strength when analyzing hormones that vary considerably during the day (35;36;39-41).

Two studies from Austria (20) and USA (27) are not in line with our study, but both studies have important limitations. The study from Austria (20) investigated 2110 men who attended their infertility clinic between the years 1993 to October 2007. The sample study were divided into men using a cell phone (N=991) and men not using cell phone (N=1119). Increased serum-testosterone and decreased serum-LH were found in addition to increased pathological morphology in semen samples among the men using a cell phone. The study however lacks information about actual exposure to EMF, there is neither information of amount- nor duration of cell phone use or type of cell phone. In addition there is no description of the men attending the clinic, what physical state were they in, were they infertile or not, when did they attend the clinic and how was the method for blood- and semen sampling (time of day etc.). The study from USA (27) investigated RF heater operators where increased levels of serum-FSH were found among these operators (N=12) compared to a control group (N=34) and a slightly higher mean semen pH among controls. This study had a description of exposure, but

suffered from other methodological weaknesses. The statistical power was low, vital information about when blood and semen samples were taken was missing and a mix of ethnicity was present among the participants.

Strengths of our present study are controlled exposure setting, complete set of samples, no drop outs, taking of blood samples at fixed times in the morning and analyze of blood samples done in laboratories with high quality. The number of samples [needed to detect a change in Inhibin B of 9 %](#) was sufficient to assure a high statistical power of the analyses; as a consequence, the likeliness of type II error was low. [Although a change in Inhibin B of less than 9 % would not be detected, such a small change would be difficult to separate from the normal variation of the hormone.](#) Also the participants in this study were asked for factors that could influence the normal hormonal profile.

The present study was performed with sham exposure, which adds to the strength of the study. It was hard to do a blinded cross-over study due to difference in facilities surrounding our two scanners. An anticipation of effect of real MRI exposure could have influenced the results, but since no significant differences between the real and sham MRI was found this is irrelevant.

Exposure in this study was done in a 1.5 T GE Excite Scanner and the exposure sequence was set to a standard anatomical head scan which lasted for approximately 20 min. This was chosen because this sequence and this type of scanner is the most commonly used scan in the Western World. Since there have been done few studies looking at adverse effects from MRI's we did not want to expose healthy, young volunteers for anything unusual. Furthermore the GE Excite scanner used in this study had a transmitting body coil and receive-only head coil. This ensures exposure to the whole body from the three fields in MRI, including both brain and gonads. The exposure in MRI is different from what the public may experience in daily life. Compared to cell phones the frequency is lower with 63.4 MHz in a 1.5 T MRI, while cell phones in Europa normally operate in the frequencies 450 MHz – 2100 MHz depending on type of network. The intensity however is greater in the MRI which will give a greater potential for SAR, in this study the SAR is estimated to be 0.29 W/kg on the whole body.

The lack of effects on hormones in this setting ~~should-is a~~ reassuring [first step](#) for the public and for young men experiencing MRI scan in regards to their reproductive hormones. [-but the lack of effects in this study does not rule out that reproductive effects can be](#)

[discovered in later studies investigating other endpoints or with different exposure classification.](#) -The ~~is~~ exposure [in this study](#) represent a higher intensity of EMF compared to what one normally experiences in daily life, but there are differences in frequencies which makes further generalization complicated. The findings must also therefore be interpreted with caution. We [also](#) have only investigated male reproductive hormones. Although extrapolating from our high exposure would indicate small risks for hormonal influence by lower exposure levels, we cannot say anything about possible influence on other endpoints [like epigenomic changes, sperm morphology, neurotoxicity and others](#) ~~nor~~ [on](#) potential chronic effects from repeated exposures to low exposure levels. To evaluate this, further studies should be carried out.

Conclusion

This study found no effect on hormones relevant for male reproduction in healthy male volunteers after a 20 min standard MRI head scan with whole body exposure.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Table 1
Details regarding the nine MRI sequences used in a study of effects from the electromagnetic fields on male reproductive hormones.

Sequence	TR (ms)	TE (ms)	FOV (mm)	MA (pixels)	TA (s)	SL (mm)	SAR (W/kg)
	Repetition time	Echo time	Field of view	Matrix size	Acusition time	Slice thickness	RF estimation
Fast gradient echo (localizer)	5	1.4	280	256 x 256	4	5	0.27
ASSET calibration	150	1.4	300	32 x 32	12	8	1.70
Sagittal T1 flair	2000	7.9	240	256 x 192	77	5	1.49
Propeller T2	6000	124	240	320 x 320	114	5	Not given
T2 flair propeller	8000	135.5	220	288 x 288	208	5	Not given
Coronar T1 flair	2000	7.9	240	256 x 192	101	3	1.72
T2 diffusion weighted imaging, axial	10000	105	260	128 x 128	64	5	0.19
Magnetic resonance spectroscopy	1500	35	240	1 x 1	132	20	0.22
2D fast gradient echo, axial	550	67	240	256 x 192	243	5	0.004

Table 2

Descriptive statistics of the study population, N = 24

	Mean	RANGE
Age (years)	21	19 – 25
Height (cm)	181	170 – 201
Weight (kg)	77	57 – 104
BMI (kg/m ²)	23	19 – 30
Biological children (no. of)	0	
Cell phone use (min./day last week)	16	1 – 60
Calls made (no. of calls/day last week)	3	1 – 5
Exercise (no. of times/week)	2-3	0 – 7
Self-reported general health *	4	3 – 5

**Scale: 1 – 5 (very bad – bad – fair – good – very good)*

Table 3

Change in mean hormone levels between “pre” and “post” and between “pre” and “post2” for real and sham MRI. Paired samples T-test is used, mean value and 95 % CI is given for the difference between real and sham MRI. N=24.

Hormone	<u>Change in mean hormone levels</u>		<u>Real and sham MRI</u>
	Real MRI	Sham MRI	Difference^a [95 % CI^b]
Thyrotropine			
Pre – Post	-0.04 mIE/l	-0.19 mIE/l	0.015 mIE/l, [-0.04, 0.34]
Pre – Post2	0.09 mIE/l	0.03 mIE/l	0.06 mIE/l, [-0.52, 0.64]
Luteinizing hormone			
Pre – Post	-0.31 IE/l	-0.66 IE/l	0.35 IE/l, [-0.05, 0.75]
Pre – Post2	0.57 IE/l	-0.39 IE/l	0.96 IE/l, [-0.31, 2.24]
Follicle stimulating hormone			
Pre – Post	-0.13 IE/l	-0.22 IE/l	0.08 IE/l, [-0.08, 0.25]
Pre – Post2	0.08 IE/l	-0.21 IE/l	0.29 IE/l, [-0.17, 0.76]
Prolactine			
Pre – Post	-1.38 mIE/l	-29.54 mIE/l	28.16 mIE/l, [-7.99, 64.32]
Pre – Post2	-7.79 mIE/l	-5.67 mIE/l	-2.13 mIE/l, [-44.35, 40.10]
Sex-hormone binding globulin			
Pre – Post	-0.54 nmol/l	-1.33 nmol/l	0.79 nmol/l, [-0.22, 1.80]
Pre – Post2	1.13 nmol/l	-0.63 nmol/l	1.75 nmol/l, [-0.76, 4.26]
Testosterone			
Pre – Post	0.40 nmol/l	0.57 nmol/l	-0.17 nmol/l, [-1.49, 1.15]
Pre – Post2	-0.24 nmol/l	-0.25 nmol/l	0.01 nmol/l, [-2.23, 2.25]
Estradiol			
Pre – Post	-2.00 pmol/l	2.33 pmol/l	-4.33 pmol/l, [-11.07, 2.40]
Pre – Post2	-3.13 pmol/l	-1.21 pmol/l	-1.92 pmol/l, [-10.69, 6.86]
Inhibin B			
Pre – Post	-6.21 pg/ml	3.54 pg/ml	-9.75 pg/ml, [-30.88, 11.38]
Pre – Post2	-3.75 pg/ml	5.58 pg/ml	-9.33 pg/ml, [-41.77, 23.10]

“Pre” = blood sample drawn immediately before exposure

“Post” = blood sample drawn immediately after exposure

“Post2” = blood sample drawn one session interval after exposure, but before any next exposure

^a *Difference between real and sham MRI*

^b *95 % confidence interval of the difference*

Figure One

Figure 1

- = Blood sample
- 1, 3, 6, 8 = “pre” blood samples
- 2, 4, 7, 9 = “post” blood samples
- 3 and 10 = “post2” blood samples related to real MRI
- 8 and 5 = “post2” blood samples related to sham MRI

Figure Two

Figure 2

Mean hormonal values and 95 % confidence intervals of thyreotropine (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactine (PRL), sex-hormone binding globulin (SHBG), testosterone, estradiol (E2) and inhibine B at the different settings, real and sham magnetic resonance imaging.

Pre = blood sample drawn immediately before the exposure

Post = blood sample drawn immediately after the exposure

Post2 = blood sample drawn one session interval after the exposure, but before any next exposure.