Title of the study: Prospective validation of the ADNEX Model for discrimination between benign and malignant adnexal masses in pregnancy: International Ovarian Tumour Analysis in pregnancy study ('p-IOTA study')

Sponsor of the study: UZ Leuven, Herestraat 49, 3000 Leuven.

Medical Ethics Committee: Ethische Commissie onderzoek UZ / KU Leuven, Herestraat 49, 3000 Leuven.

Local investigators: prof. Dr Wouter Froyman - prof. dr. Dirk Timmerman - prof. dr. Thierry Van den Bosch: Department of Gynaecology and Obstetrics, UZ Leuven, Herestraat 49, 3000 Leuven.

I Information vital to your decision to take part

Introduction

Dear madam

You are being invited to take part in a multicentre observational clinical study, called **'Prospective validation of the ADNEX Model for discrimination between benign and malignant adnexal masses in pregnancy: International Ovarian Tumour Analysis in pregnancy' ('p-IOTA study**'). In this trial we want to assess the reliability of the "ADNEX"-model, which is used in non-pregnant women during ultrasound to distinguish between benign and malignant adnexal (at the level of the ovaries or fallopian tubes) tumours, in pregnant women.

This is a study commissioned by UZ Leuven and conducted under the supervision of the IOTA research group (coordinated from KU Leuven). At UZ Leuven, this study is led by physician-investigator prof. Wouter Froyman. This is a '*multicentre'* trial which means that this research will be done by gynecologists in different hospitals in different countries. We would like to include about 855 patients over a period of 3 years.

We use the term '*observational'* study to indicate that we are only asking your permission to collect data from your medical file. We will combine your data with data from other patients receiving the same examination/treatment in order to statistically process them for research purposes. We will not propose you any additional procedure for diagnosis or follow-up in this study. The examination/treatment that is offered to you was prescribed in the usual way, in accordance with the conditions of good medical practice and regardless of your possible participation in this study.

Before you agree to take part in this study, we invite you to take note of its implications in terms of organisation, to allow you to make a decision with full awareness of the implications. This is known as giving "informed consent".

Please read these few pages of information carefully and ask any questions you want to the investigator or his representative.

There are 3 parts to this document: the information essential to your decision, your written consent and supplementary information (appendices) detailing certain aspects of the basic information.

If you take part in this study, you should be aware that:

- The treatment offered to you by the investigator in accordance with current recommendations will not be altered if you take part in the study.
- This clinical study is being conducted after having been reviewed by one ethics committee.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after having signed this document, you can stop taking part by informing the investigator.
- The data collected on this occasion are confidential and the protection of your identity is guaranteed during publication of the results.
- Insurance has been taken out in case you should suffer any damage in connection with your participation in this clinical study.
- You may contact the investigator or a member of his/her team at any time should you need any additional information.

Further information about your "Rights as a participant in a clinical study" can be found in appendix III.

Background

Adnexal masses are common in woman of reproductive age. This are cysts on the organs that belong to the uterus, such as the ovaries or the fallopian tubes. Often these cysts are discovered incidentally via imaging in women who do not experience any symptoms. In pregnant women, screening via the standard "first trimester ultrasound" increases the detection of cysts. The majority of these cysts are benign and may disappear spontaneously. However sometimes a cyst may show suspicious features and raise concerns about an underlying malignancy. Therefore it is important to correctly distinguish between benign and malignant cysts. Especially for pregnant women, given the risks of surgery during pregnancy

The decision to proceed with surgery and removal of the cyst is usually made for two reasons: concern about a possible malignancy and to reduce the risk of complications associated with cysts,

such as an ovarian twist (torsion) or rupture of a cyst. Traditionally, surgery was recommended. Nowadays, a wait-and-see policy is preferred for cysts that look benign on an ultrasound scan. After all, there are risks attached to surgery during pregnancy, both for the mother as the for the unborn baby. Furthermore it appears that a torsion, rupture of the cyst or a potentially malignant cyst is rather rare. The choice for a wait-and-see policy or the decision to proceed with surgery must be supported by a reliable determination of the nature of the cyst.

The IOTA research group has already developed some ultrasound-based tools, such as the ADNEX model, to distinguish between benign and (potentially) malignant adnexal masses. The term ADNEX stands for 'Assessment of Different NEoplasias in the adneXa" or 'the assessment of benign and malignant cysts in the adnexa'. You can think of ADNEX as a diagnostic model that uses a kind of checklist to help the doctor determine the nature of the tumour we are dealing with. The reliability of this diagnostic tool has already been demonstrated in non-pregnant women. The strength of the ADNEX model in assessing cysts has not yet been evaluated in pregnant women. Previous research shows that the ultrasound characteristics of malignant cysts in pregnant women who received ultrasound before surgery are similar to the characteristics of malignant cysts in non-pregnant women.

Objectives and course of the study

During this study, clinical and ultrasound data will be collected from patients with ovarian cysts known before pregnancy or diagnosed during pregnancy. These data will be used for statistical analysis to facilitate the recognition of the different types of ovarian cysts and especially to distinguish benign from malignant cysts. All women aged 18 years or older with an adnexal mass found in ultrasound at any gestational age can participate in this study. The physician-investigator will explain the study and give the opportunity to ask questions. If the patient decides to participate in the study, the 'informed consent' document must be signed.

Your participation in the p-IOTA trial does not chance your standard follow-up of the pregnancy or your standard care. The study investigator will perform a standard ultrasound scan. This examination does not use radiation and is not known to have harmful effects. For the aim of this study, the ultrasound findings and measurements will be described and registered in a standardised way.

This examination will not take longer than a standard one. If chosen for watchful waiting, another follow-up ultrasound scan will be performed 0-90 days after delivery. If you agree to it, we will also like to scan you a number of times during pregnancy to see how the mass is evolving. Ovarian cysts are monitored during and after pregnancy in standard care . There are no additional examinations in this trial compared to the standard care.

Description of risks and benefits

No special risks are related to the gynaecological ultrasound scan. There are no additional charges, nor for you nor for your healthcare insurance, as this examination is a normal, standardised procedure in gynaecological practice.

No direct personal benefits are foreseen. As the study is not commercial and no compensation is provided. However, your participation in this study is highly appreciated, as it will contribute to the development of scientific improvements, which will lead to a better insight in the behaviour of ovarian cysts during and after pregnancy and to a better diagnosis and a better treatment of patients with ovarian masses.

Withdrawal of consent

Your participation in this study is voluntary and will have no influence at all on your treatment and appropriate medical care. You can decide to withdraw your participation at any time without obligation to justify your decision. Therefore, you only have to contact your doctor.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor

If you agree to participate in this trial, we ask you:

- to keep this information form and sign the consent form.
- to cooperate fully in the smooth running of this study
- not to conceal anything such as information relating to your state of health, the medication you are taking or the symptoms you are experiencing.
- to inform your doctor if you are asked to take part in another study to discuss with him/her the possibility of taking part in this study and to see whether you should then stop taking part in the present study.

Contact

If you need further information regarding participation, but also if you have problems or concerns, you can contact one of the physician-investigators (prof. dr Wouter Froyman, prof. dr. Dirk Timmerman or prof.dr. Thierry Van den Bosch) on the following telephone numbers

- during consultation hours: +0032 (0)16 34 36 42 (ultrasound) or +0032 (0)16 34 51 25 (secretary's office)
- out of consultation hours: +0032 (0)16 34 08 03 (assistant physician with on-call duty)

If you have any questions relating to your rights as a participant in a clinical study, you can contact the patient rights ombudsman of your institution on this telephone number: +32 16 34 48 18. If necessary, he/she can put you in contact with the ethics committee.

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II Informed consent

Participant

1. I declare that I have read the information for the patient regarding the use of gynaecological ultrasound features for the p-IOTA study. I have been informed of the nature of the study, its purpose, its duration and what is expected of me. I have taken note of the information document and the appendices to this document.
2. I received a dated and signed copy of this consent form and a copy of the patient information form. I have had sufficient time to think about it and discuss it with a person of my choice (GP, relative). I have had the opportunity to ask any questions that came to mind and have obtained a favourable response to my questions.
3. I know that this study is approved by the Ethics Committee Research of UZ Leuven
4. My participation in this study is voluntary, and I have the option to end participation at any time without obligation to justify my decision and without experiencing any disadvantage in my further medical treatment.
5. I understand that data about me will be collected throughout my participation in this study and that the investigator and the sponsor of the study will guarantee the confidentiality of these data in accordance with applicable European and Belgian legislation. My medical data, name and address will remain confidential. I understand that the performance of this study by UZ Leuven serves the general interest and that the processing of my personal data is necessary for the performance of this study.
6. I agree to my GP or other specialists in charge of my health being contacted if required to obtain additional information about my health.

I, the undersigned (*Surname, first name*)……agree to participate in the p-IOTA study

Date and signature of the participant:

……

Witness/Interpreter

I was present during the entire process of informing the patient and I confirm that the information on the objectives and procedures of the study was adequately provided, that the participant (or his/her legal representative) apparently understood the study and that consent to participate in the study was freely given.

Surname, first name and qualification of the witness/interpreter:……

Date and signature of the witness/interpreter: ……

Investigator

I, the undersigned,……investigator/clinical research assistant, confirm that I have verbally provided the necessary information about the study and have given the participant a copy of the information document. I confirm that I have explained satisfactorily the aim of this study to the participant. I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required.

I confirm that I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law of 7 May 2004 related to experiments on humans.

Surname, first name, date and signature of the investigator:

……

Surname, first name, date and signature of the investigator's representative:

……

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III Supplementary information on the protection and rights of the participant in a clinical study

Ethics Committee

This study has been reviewed by an independent Ethics Committee, namely the Ethics Committee of Ethische Commissie Onderzoek UZ/KU Leuven, which has issued a favourable opinion. It is the task of the Ethics Committees to protect people who take part in a clinical trial. They make sure that your rights as a patient and as a participant in a clinical study are respected, that based on current knowledge, the study is scientifically relevant and ethical.
You should not under any circumstances take the favourable opinion of the Ethics Committee as an incentive to take part in this study.

The study will be performed according to the guidelines for good clinical practice (ICH/GCP) and to the Declaration of Helsinki, protecting people who participate in clinical studies.

Voluntary participation

Before signing, do not hesitate to ask any questions you feel are appropriate. Take the time to discuss matters with a trusted person if you so wish.

Your participation in the study is voluntary and must remain free of any coercion: this means that you have the right not to take part in the study or to withdraw without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or the quality of your future therapeutic care.

If you agree to take part in this study, you will sign the informed consent form. The investigator will also sign this form to confirm that he/she has provided you with the necessary information about the study. You will receive a copy of the form.

Costs associated with your participation

You will not receive any compensation for your participation in this study. Furthermore, the study will not involve any additional costs for you.

Guarantee of confidentiality

Your participation in the study means that your personal data are collected by the investigator and used in an encoded form by the study sponsor for research purposes and in connection with scientific and medical publications.

The processing of your personal data is necessary to achieve the scientific research purposes as set out herein. The conduct of scientific research is one of the core missions of UZ Leuven as defined by law. As a university hospital, part of KU Leuven, UZ Leuven is indeed required to support research and education in the public interest. We would therefore like to inform you that the necessity of the processing for the conduct of scientific research as a task of public interest constitutes the lawful basis on which we process your information in the context of the study in which you are participating. UZ Leuven is also subject to specific legal requirements which require the processing of your personal in the context of safety reporting (such as for example the notification of adverse events to the regulatory authorities).

All your data will be treated confidentially; besides your personal doctor and his/her staff, only authorised researchers, maintaining their professional secrecy, will have access to your data. All medical data will be coded and saved electronically in a secured database. Coded data can be exchanged with (inter)national academic or other research groups. In this case, and when the results of the study will be published, measures will be undertaken to guarantee your privacy. No other data than those necessary for the study will be collected.

Your data will be processed in accordance with the European General Data Protection Regulation (GDPR) and with the Belgian legislation on the protection of natural persons with regard to the processing of personal data. University Hospitals Leuven shall act as data controller for your data. You are entitled to ask the investigator what data are being collected about you and what is their use in connection with the study. This data concerns your current clinical situation but also some of your background (e.g. your age, treatment centre, and country), the results of examinations carried out within the context of care of your health in accordance with the current standards and the results of

examinations required by the protocol. You have the right to inspect these data and correct them if they are incorrect[1].

The investigator has a duty of confidentiality vis-à-vis the data collected.

This means that he/she undertakes not only never to reveal your name in the context of a publication or conference but also that he/she will encode your data before sending them to the manager of the database of collected data (UZ Leuven)

The investigator and his/her team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your medical records[2].

The personal data transmitted will not contain any combination of elements that might despite everything allow you to be identified[3].

For the study data manager designated by the sponsor, the data transmitted will not allow you to be identified. The latter is responsible for collecting the data gathered by all investigators taking part in the study, processing them and protecting them in accordance with the requirements of the Belgian law on the protection of privacy.

To verify the quality of the study, it is possible that your medical records will be examined by third parties (ethics committee, representatives of the study sponsor, external auditors). In any event, this may only take place under the responsibility of the investigator or of one of his/her colleagues and by persons subject to the obligation of professional secrecy.

These (encoded) data will be able to be sent to Belgian or other regulatory authorities, to the relevant ethics committees, to other doctors and/or to organisations working in collaboration with the sponsor.

These doctors and/or organisations can be situated in Belgium and in other countries where the standards in terms of the protection of personal data may be different or less stringent[4].

Your consent to take part in this study therefore also means that your encoded medical data will be used for the purposes described in this information form and may be transmitted to the aforementioned people and authorities.

The sponsor will use the data collected within the context of the study in which you are taking part, but would also like to be able to use them in connection with other research concerning the same

1 These rights are guaranteed by the European Data Protection Regulation (GDPR) and by the Law of 22 August 2002 on patient rights.
2 For clinical studies, the law requires this link with your records to be retained for 20 years.
3 The database containing the results of the study will therefore not contain any combination of elements such as your initials, your gender and your full date of birth (dd/mm/yyyy).
4 The sponsor then undertakes to respect the constraints of the European General Data Protection Regulation (GDPR) and the Belgian legislation on the protection of natural persons with regard to the processing of personal data.

disease as yours and its treatment. Any use of your data outside the context described in this document is only possible with the approval of the ethics committee.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor.

If you have any questions relating to how your data are being processed, you may contact the investigator. The data protection officer in your hospital can be contacted as well: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, e-mail dpo@uzleuven.be.

Finally, if you have a complaint concerning the processing of your data, you can contact the Belgian supervisory authority who ensures that privacy is respected when personal data are processed.

The Belgian supervisory authority is called:
Data Protection Authority (DPA)
Drukpersstraat 35,
1000 Brussels
Tel. +32 2 274 48 00
e-mail: contact@apd-gba.be
Website: https://www.dataprotectionauthority.be

Insurance

In an observational study, the only possible risk would be a flaw in the measures taken to protect the confidentiality of the private information about you. Every participating institution is responsible for appropriate patient care and local data protection. The data are centralized in Leuven without patient identifiers (e.g. patient names; hospital numbers or birth dates). Even without fault, the sponsor accepts responsibility for damage caused to the participant (or his/her dependants) and linked directly or indirectly to participation in this study. In this context, the sponsor has taken out an insurance contract (Amlin Corporate Insurance, polisnr. 299.053.700, contact details insurance broker: Vanbreda Risk & Benefits, Plantin en Moretuslei 297, 2140 Antwerpen)[5]

[5] In accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004)