Mild induced labour prior to planned caesarean delivery to improve neonatal and maternal outcome – a randomized trial

This study is organized by PD Dr. med. Tilo Burkhardt, UniversitätsSpital Zürich
The clinic of obstetrics, Kantonsspital Winterthur is one of six study sites.

Dear expectant mother,

Today we ask for your participation in a clinical trial.
The most important facts and outlines of the study are presented below

Summary

1	**Aim of the study** With this study we intend to find out if the induction of mild, controlled contractions before elective cesarean section increases the level of stress hormones in the child as it usually happens with a vaginal delivery and whether or not this leads to a reduction in the incidence of problems in respiratory adaptation for the child at birth.
2	**Recruitment** We are asking you to participate in the study because you chose to deliver by planned cesarean section or because your physician recommends a planned cesarean section as the mode of delivery.
3	**Study information** This is an international study that is conducted in six centers in Switzerland and Germany. In total, 1450 pregnant women will be included. The participants will be randomized to two different groups: one group will receive an infusion with low-dose oxytocin while the other group will receive an infusion with NaCL-Laktat, which is the standard infusion used here before cesarean section. The oxytocin infusion (Syntocinon®) has been used in obstetrics for decades and is approved for the use in pregnant women.
4	**Study Organization** On the day before the planned cesarean section, you will have an appointment in the hospital as preparation for the cesarean section. We routinely take your blood for a blood count (hemoglobin, hematocrit); this information is for the study as well. On the day of delivery, you will have to come to the delivery unit about one hour earlier if you participate in the study. Every woman routinely receives an i.v. infusion before cesarean section. If you participate in the study, there is no extra venous puncture. Oxytocin will be administered via this i.v. infusion. We will start oxytocin infusion on a low dose and will increase the dose until the tocogram shows contractions or until contractions are palpated through the abdomen. As soon as you have regular contractions, the oxytocin infusion is stopped. For additional analysis we will collect 5 ml of the umbilical cord blood.
5	**Study benefit** The measurement of stress hormone levels does not have a benefit for the treatment. If the hypothesis of the study proves to be correct, children would have a lower risk for problems in respiratory adaption after delivery after oxytocin-treatment. Thanks to your study participation, the results could be available for other pregnant women and children.

6	**Rights** You take part voluntarily and your decision will not have an influence on your medical care. You do not have to justify your decision.
7	**Duties** As study participant we ask you • to follow the instructions of the investigator and adhere to the study plan • to inform the investigators on any side effects, adverse effects or diseases that might be diagnosed during conduction of the study.
8	**Risks** The contractions that are induced by the oxytocin infusion are much milder than contractions during a normal delivery. The induced contractions are a little bit stronger than natural contractions that you might have experienced during the last weeks before the cesarean section. Sometimes women may feel mild discomfort or even pain by the induced contractions. In rare cases, it might induce spontaneous rupture of membranes.
9	**Other methods of treatment** If you do not want to participate in the study the cesarean section will be conducted as usual and there will be no administration of oxytocin. Umbilical cord blood donation still is available outside of the study.
10	**Results** You will be informed on results of the study if they are medically relevant to you. If you wish not to have any information on the results of the study please inform the study investigator.
11	**Data handling and protection of the privacy** We are following legal requirements for data privacy and all investigators are bound to medical confidentiality. Your personal and medical data and your samples (blood, stool, milk etc.) are coded and secured. The samples are not used for other research unless you give a separate consent.
12	**Withdrawal** You can withdraw consent at any time. Data, which has already been assessed, will be used for the results of the study**.**
13	**Recompensation** There is no monetary compensation for participation in the study.
14	**Liability** The University Hospital Zurich and the sponsors (PD Dr. T. Burkhardt, Prof. S. Wellmann) will compensate for any occurred damages that you might have during the clinical trial. For this reason, the University Hospital Zurich has contracted an insurance in your interest.
15	**Financing** The study is financed by the Family Larsson Rosenquist Foundation and by the participating hospitals.
16	**Local contact** Dr. med. Leila Sultan-Beyer: Frauenklinik, Kantonsspital Winterthur, Brauerstrasse 15, Postfach 834, 8401 Winterthur leila.sultan-beyer@ksw.ch 052 266 2761 24h reachability: 052 266 3030

Detailed information

1. Aim of the Study

With this study we want to find out whether mild controlled and limited induction of contractions before elective cesarean section increases the level of stress hormones in the child. Regular vaginal delivery is associated with relevant stress for the mother and the child and leads to massive increase of stress hormones, which help to initiate different processes that support a good maternal and fetal transition after delivery. This natural release of stress hormones into the blood of the newborn after vaginal delivery is unique in life and is lower if the delivery occurs per elective cesarean section without prior contractions. In this context, it is known that the children that are born via elective cesarean section have a higher incidence of transitory respiratory problems after delivery.
The oxytocin challenge test has been used for decades in obstetrics and is an established method to test placental function in high risk pregnancies. During the oxytocin challenge, test contractions are induced via an infusion with oxytocin until the tocogramm shows regular contractions over a period of 10 minutes or until they can be palpated on the maternal abdomen.
After delivery, two stress hormone levels will be measured from the umbilical cord blood left in the placenta. The results will be compared with those from children which also had a delivery via elective cesarean section but without a prior oxytocin challenge test.

2. Recruitment

We are asking you to participate in the study because you chose to deliver by planned cesarean section or because your physician recommends a planned cesarean section as the mode of delivery. All women with singleton pregnancies who plan to deliver via cesarean section can participate in the study. Women who had more than one prior cesarean section and women carrying twins are excluded.

3. General information on the study

This is a international study, which is conducted in six centers in Switzerland and germany. In total 1450 women will be included. In this study, we investigate if the oxytocin challenge test has an influence on maternal and newborn well-being. The participants will be randomized to two different groups: one group will receive an infusion with low-dose oxytocin (Syntocinon®) (study group) while the other group will receive an infusion with NaCL-Lösung (control group), which is the standard infusion used before cesarean section. If you choose to participate in the study, you will be randomized to one of the two groups automatically. Neither you nor the investigators and physicians can influence this random selection. The oxytocin infusion (Syntocinon®) has been used in obstetrics for decades and is approved for the use in pregnant women.
The study follows all legal requirements in Switzerland. We respect international guidelines. The study was reviewed and approved by the local ethics committee. You can find a description of the study under https://clinicaltrials.gov

4. Study Organization

The day before the planned cesarean section you will routinely have an appointment in the hospital as preparation for the cesarean section on the next day. Blood is taken from you. The results from the blood work (hemoglobin, hematocrit) that are necessary for the cesarean section will be used for the study as well. If you participate in the study, you will have to come one hour earlier than usual to the labor ward before the cesarean section. Every woman routinely receives an i.v. infusion before cesarean section. If you participate in the study there is no extra venous puncture. Oxytocin will be administered via this i.v. infusion, if you should be assigned to the study group. We will start with a low dose of oxytocin and will increase the dose until the tocogram shows regular contractions or until we can palpate contractions on the abdomen. As soon as you have regular contractions, the oxytocin infusion will be stopped. For additional analysis we will collect 5 ml of the umbilical cord blood. The Institute of Clinical Chemistry at the University Hospital Zurich will perform the measurement of the stress hormones in umbilical cord blood. The samples will be encrypted before analysis and destroyed after measurement of the stress hormone.
Furthermore, we will contact you four weeks and one year after birth to ask you questions concerning body measurements of your child, breastfeeding and any antibiotic treatment.

5. Study Benefit

The sole measurement of stress hormone levels does not have a direct benefit for you or your child. If the hypothesis of the study proves to be correct, children would have a lower risk for problems in respiratory adaption after delivery. Thanks to your study participation, the results could be available for other pregnant women and children.

6. Rights

Participation is voluntary. If you do not wish to participate or withdraw your participation later, you do not have to justify your decision at any time. Your medical care is guaranteed regardless of your decision. You can ask questions concerning the study at any time, please use the contact information at the end of this patient information.

7. Duties

As study participant, we ask you

- to adhere to the necessary requirements of the study
- to inform your caregiver on any side effects, adverse effects, diseases and new symptoms or changes in condition that might be diagnosed during conduction of the study (as well after study end, and after the side effects stop)
- to inform the investigator on concurrent treatment and therapy by other physicians and on the medication you take

8. Risks

The contractions induced by the oxytocin infusion are much milder than the contractions during a normal delivery. The induced contractions are a little bit stronger than natural contractions that you might have experienced during the last weeks before the cesarean section. Sometimes women may feel mild discomfort or even pain by the induced contractions. In rare cases, spontaneous rupture of the membranes can occur. In this case, oxytocin infusion is stopped immediately. Rupture of membranes can cause change in the child's heart rate patterns just like in vaginal birth. Contractions itself can cause abnormal heart rate patters in the child. Since induced contractions are much weaker than in normal birth, the risk is very low in normal pregnancies with normal placenta function.
If the fetal heart rate pattern is conspicuous, oxytocin infusion is stopped immediately and the planned cesarean section is performed. Oxytocin has a short duration of action and, if necessary, the effects can be treated with tocolysis. If the induced contractions should continue even after oxytocin is stopped, tocolysis may be needed until the cesarean section is performed. If you are assigned to the control group, there are no additional strains compared to routine procedure before a cesarean section.

9. Other methods of treatment

Participation in the study is voluntary. If you do not want to participate in the study the cesarean section will be conducted as usual and there will be no administration of oxytocin and no samples will be taken. Umbilical cord blood donation still is available outside of the study.

10. Results

The investigator will inform you about all new findings during the study, which may affect the benefit of the study or your safety or your consent to participate in the study. You will receive the information verbally and in writing.

11. Data handling and protection of privacy

Your personal and medical data will be collected for this project. Very few people involved in the study will see your unencrypted data, which will be used exclusively to fullfill tasks within the project. Data collected for study purposes will be encrypted. Encryption means, that all data that could lead to your person (name, date of birth) is deleted and replaced by a code. The code-list, which connects your personal data and the code always remains in the local hospital. Persons who do not have access to the code-list cannot draw any conclusions to your person.
The samples from umbilical cord blood will be destroyed after the study. In case you consented for storage and usage of data and samples in upcoming research, samples of stool and breastmilk can be stored.

Publication on the study contents summarize the data, therefore your name will never be published, nor will it appear on the Internet. Sometimes journals require publications raw data. This raw data is always encrypted and therefore allows no conclusions to your person. All people who have access to your data are strictly subjected to confidentiality and all guidelines of data protection will be rigorously adhered to. You, as a participating person have the right to access your data.
This study project may be reviewed by the Ethics Committee or by the institution, which initiated the project. The project manager may need to disclose your personal and medical data for such controls. All person must maintain strict confidentiality. It is possible that your follow-up physician is contacted to give information on your state of health.

12. Withdrawal

You can withdraw from the study at any time. Collected data and samples that already were collected will be evaluated encrypted, because otherwise the whole project will lose its validity. It is not possible to maintain the anonymity of your data samples on withdrawal, which means, the data and samples remain encrypted. Please check whether you agree to this before you participate in the study.

13. Recompensation

There will be no monetary compensation for taking part in the study. There are no costs for you or for your medical insurance.

14. Liability

If you should be harmed by the study project, the institution or company that initiated the project is responsible for its execution and is liable. Law regulates the prerequisites and procedures. If you have suffered any damage, please contact the investigators.

15. Financing

The study is financed by the Family Larsson Rosenquist Foundation and by the participating hospitals.

16. Contact

In case of uncertainties, concerns or emergencies that occur during the project or afterwards, you can reach one of these contacts at any time.

Dr. med. Leila Sultan-Beyer:
Frauenklinik, Kantonsspital Winterthur, Brauerstrasse 15, Postfach 834, 8401 Winterthur
leila.sultan-beyer@ksw.ch
052 266 2761

Dr. med. Elisabeth Kapfhammer-Seltenheim
Frauenklinik, Kantonsspital Winterthur, Brauerstrasse 15, Postfach 834, 8401 Winterthur
elisabeth.kapfhammer-seltenheim@ksw.ch
052 266 2763

24h reachability: 052 266 3030

Informed Consent

Written consent for pregnant women participating in a clinical study

Please read this form carefully. Do not hesitate to ask if you do not understand something or you want to have more information.

BASEC-Nummer (nach Einreichung):	2018-01842
Title of the study (scientific and amateur):	Mild induced labour prior to planned caesarean delivery to improve neonatal and maternal outcome – a randomized trial
Responsible institution (Project leader and address):	PD Dr. med. Tilo Burkhardt, Klinik für Geburtshilfe, UniversitätsSpital Zürich, 8091 Zürich
Study site	Clinic of obstetrics, Kantonsspital Winterthur Brauerstrasse 15, Postfach 834, 8401 Winterthur
Responsible investigator at study site Name and surname in print letters:	Dr. med. Leila Sultan-Beyer
Participant: Name and surname in print letters: Date of birth :	

- I was informed verbally and in writing about the purpose, the progress of the project, the possible advantages and disadvantages as well as possible risks by the signing investigator.
- I voluntarily participate in this project and accept the content of the written information given on the above project. I had enough time to make my decision.
- My questions related to the participation in this project have been answered. I retain the written information and received a copy of my written declaration of consent.
- I was informed about different ways of treatment.
- I agree that the experts responsible for the project management / client of the study and of the ethics committee which is responsible for this project may inspect my unencrypted data for inspection and control purposes, but under strict adherence to confidentiality.
- I will be informed in the case of study results or random findings concerning my health directly. If I do not want that, I will inform my investigator.
- I am aware that my health related and personal data and samples can be passed on only encrypted for the research purposes of this study.
- I can withdraw from the participation at any time without stating any reason, without having any disadvantages with regard to further medical care. The collected data and samples are still used for evaluation.
- The liability insurance institution of the hospital/ institution is liable for any damages.
- I am aware that the obligations stated in the participant information must be complied with. In the interest of my health, the director of the study can always exclude me.

Location, date	Signature of participant

Confirmation of the investigator: I hereby confirm that I have explained to this participant, the importance and scope of the project. I hereby certify that all the obligations relating to this project are in accordance with applicable law. If, at any time during the implementation of the project, I become aware of aspects that could affect the participant's readiness to participate in the study, I will inform her/him immediately.

Location, date	Name and first name of the informing investigator in print letters Signature of the investigator