LUND UNIVERSITY

Effects on fetal and maternal temperatures of paracetamol administration during labour: a case-control study.

Lavesson, Tony; Akerman, Fernanda; Källén, Karin; Olofsson, Per

Published in:
European Journal of Obstetrics, Gynecology, and Reproductive Biology

DOI:
10.1016/j.ejogrb.2012.12.033

2013

Link to publication

Citation for published version (APA):
Lavesson, T., Akerman, F., Källén, K., & Olofsson, P. (2013). Effects on fetal and maternal temperatures of paracetamol administration during labour: a case-control study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *168*(2), 138-144. https://doi.org/10.1016/j.ejogrb.2012.12.033

Total number of authors:
4

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Effects on fetal and maternal temperatures of paracetamol administration during labour. A case-control study

Tony Lavesson [a*], Fernanda Åkerman [a], Karin Källén [b], Per Olofsson [a]

[a]Institution of Clinical Sciences, Department of Obstetrics and Gynecology, Skåne University Hospital, Lund University, Malmö, Sweden

[b]Center for Reproductive Epidemiology, Tornblad Institute, Lund University, Lund, Sweden

[*]Corresponding author at: Department of Obstetrics and Gynecology, Skåne University Hospital, S-205 02 Malmö, Sweden.

Tel.: +46 40 331000; fax: +46 40 962600.

E-mail address: tony.lavesson@med.lu.se

Running foot: Effect of paracetamol on temperature in labour

CONDENSATION

Paracetamol given to febrile parturients halts an increasing trend and stabilises the fetal temperature.

Effects on fetal and maternal temperatures of paracetamol administration during labour. A case-control study

Tony Lavesson, Fernanda Åkerman, Karin Källén, Per Olofsson

ABSTRACT

OBJECTIVE: To study the effect of paracetamol (acetaminophen) on maternal and fetal temperatures in labour.

STUDY DESIGN: From a cohort of 185 women with continuous maternal axillary and fetal scalp temperature recordings in labour, 18 women treated with 1000 mg paracetamol orally for pyrexia and 36 untreated controls matched for parity, cervical dilatation, and epidural analgesia were selected. Electronically stored temperature data were analysed offline *post hoc*. The dual temperatures recorded every 30 min from 60 min before (T-60) paracetamol administration (T0) until delivery, were noted. Longitudinal data were compared with Wilcoxon matched-pairs signed-ranks test and cross-sectional data with Mann-Whitney *U* test. Shapes of the temperature curves were compared with mixed-effect models statistics for repeated measurements. The main outcome measures were temperature changes after paracetamol. A two-tailed $P < 0.05$ was considered significant.

RESULTS: Prior to T0 maternal and fetal temperatures increased in the paracetamol group, but after T0 no significant changes ($P \geq 0.1$) were seen when compared with Wilcoxon signed-ranks test. In the control group, both temperatures increased from T-60 and onwards. Delta-temperatures (fetal minus maternal temperature) remained unchanged in both groups. The mixed-effect models analyses showed a significant difference ($P = 0.01$) in the shape of fetal temperature curves between the paracetamol and control groups, but no significant difference ($P = 0.4$) in maternal temperature curve shapes.

CONCLUSION: In febrile parturients, neither maternal nor fetal temperatures dropped after paracetamol. However, paracetamol halted an increasing trend and stabilised the fetal temperature. The effect of paracetamol on maternal temperature was inconclusive.

KEY WORDS:

Fever in pregnancy

Acetaminophen

Paracetamol

Fetal hyperthermia

Maternal temperature

INTRODUCTION

The maternal body temperature increases during labor and the increase is greater in primiparae than in multiparae (1, 2). The fetus has a 0.24 °C higher temperature than the mother when measured as fetal skin and maternal uterine wall temperatures (3, 4). Due to uterine and skeletal muscle strain, long labor, infection after early amniorrhexis, and epidural analgesia, maternal pyrexia in labor is not uncommon.

Maternal fever in labor increases the risk of cesarean section and assisted vaginal delivery (5). In cases of pyrexia and chorioamnionitis the neonate runs an increased risk of developing encephalopathy and subsequent cerebral palsy (6-8). Pyrexia might aggravate fetal hypoxia because of an increased tissue oxygen consumption and a shift of the oxygen dissociation curve to the right. In epidural analgesia-induced fever, the rate of low Apgar scores, neonatal hypotonia, assisted ventilation and early-onset seizures increases with the degree of maternal temperature elevation (9).

Rudelstorfer et al. (10, 11) demonstrated an inverse relation between fetal head heat flux during delivery, i.e. conductive and convective heat transfer, and pH in fetal scalp blood and umbilical arterial blood at birth. Thus, there is evidence of a direct relation between fetal temperature and acid-base status.

The possibilities to lower the body temperature in febrile parturients are limited. Opioids reduce the physiological increase in temperature during delivery (12) but should not be used for temperature regulation purposes. Non-steroidal anti-inflammatory drugs are contraindicated during the third trimester. Paracetamol (acetaminophen) is a widely used analgesic and antipyretic drug, and its effectiveness is comparable to that of aspirin and other

NSAIDs. It has an onset time of 30-60 min, a half-time of 2 h, and a duration of 8 h after oral administration (13). It is considered safe during all parts of pregnancy. However, the effectiveness of paracetamol therapy on maternal and fetal temperatures during labour is not well documented. In a double-blind placebo-controlled study, prophylactic paracetamol did not prevent epidural-induced fever in nulliparous women (14).

The aim of the study was to investigate the effect of paracetamol on maternal and fetal temperatures when given to febrile parturients. Our hypothesis was that paracetamol would result in a decrease in both maternal and fetal temperatures.

MATERIAL AND METHODS

One-hundred and eighty-five women in the first stage of labour at Helsingborg Hospital, Sweden, were continuously monitored with maternal axillar and fetal scalp temperatures in addition to regular monitoring with cardiotocography (CTG) and fetal ECG ST segment analysis (STAN^{TM}) (Neoventa Medical AB, Mölndal, Sweden). The study was consecutive in the sense that when one of the authors (T.L.) was present eligible women were asked to participate. The Research Ethics Committee at Lund University, Sweden, approved the study (LU 88-03) and all women gave their oral and written consent to participate. The electrode was applied after rupture of the membranes by one of the authors (T.L.) or two specially trained midwifes. The membranes ruptured either spontaneously, or were artificially ruptured to augment labour or to apply a scalp electrode for better electronic monitoring signal quality. Exclusion criteria were inability to understand oral and written information, non-cephalic lie, fetal face or forehead presentation, maternal hepatitis or HIV infection, suspicion of fetal coagulopathy, or other contraindications for applying a scalp electrode.

Commercially available fetal scalp CTG electrodes (Goldtrace^{TM}, Neoventa Medical AB, Mölndal, Sweden) were modified to also record the fetal scalp temperature. In the center of the plastic case of the electrode, a small hole was drilled and a pointed bi-metal thermocouple temperature sensor (Medexxa GmbH, Hasloh, Germany) glued into the hole (Fig. 1). The pointed pin sensor projects approximately 2 mm above the plastic surface to penetrate the fetal scalp when the spiral electrode is applied.

We have previously validated the device in an animal study, showing a close correlation between fetal subcutaneous scalp temperature and intracranial temperature (15).

The room temperature was routinely set to 23.0-24.0 °C and regularly checked with a mercury thermometer.

The maternal temperature was recorded non-invasively by taping a 'naked' bi-metal temperature sensor, i.e. a sensor without the CTG spiral electrode, in the axilla. A thermal isolator pad with a heat-reflecting surface facing towards the skin was used to fix the maternal electrode to the skin.

Cables connected the fetal scalp and maternal skin temperature sensors to a Milou™ Temperature Monitoring System instrument (Medexa Diagnostisk Service AB, Limhamn, Sweden). Temperature data were displayed on the computer screen online but were also stored in the system hard disc for *post hoc* offline analyses. With a digital movable 'vertical ruler', any point of time during the recordings could be chosen to display the maternal and fetal temperatures in °C with two decimals.

The CTG and STAN™ information was transmitted by cable from the STAN™ machine to the Milou™ Temperature Monitoring System, and displayed together with the thermal information (Fig. 2). Displayed temperature data were not used for clinical management. The equipment has a measurement precision of ± 0.0 grades ˚C. The CTG and STAN™ information were stored in the system hard disc for offline analysis together with the temperature data.

Eighteen women whom received paracetamol were retrospectively identified from data in medical charts and partograms. According to the maternity unit's written instructions, all 18 women received 1000 mg paracetamol (Panodil®, GlaxoSmithKline AB, Solna, Sweden)

orally. The indication for paracetamol administration was an ear temperature ≥38.0 ˚C to be repeated every 6 h if needed.

For each paracetamol case, two control cases without paracetamol were chosen by scrolling the 185 women data register, and matched for parity, use of epidural analgesia, and opening of the cervix ± 1 cm. Maternal age, gestational age and oxytocin administration were not matched for. For each paracetamol case and control, a case report form (CRF) was filled in with the dual temperature recordings noted 60 min before paracetamol administration (called time T-60), 30 min before paracetamol (T-30), time of paracetamol administration as determined from notes in the medical chart and/or partogram (time T0), and then every 30 min until delivery. T0 in controls corresponds to cervical dilatation ± 1 cm at T0 in the respective paracetamol case. For each T time dual temperature recording, the vertical ruler was moved on the computer screen and placed in between uterine contractions, three times 10 seconds apart, and the mean value of the three recordings was noted as the temperature at time T. The researcher who performed the offline temperature measurements and filled in the CRFs (F.Å.) was blinded to case and control allocation.

The baseline fetal heart rate (FHR) was visually assessed for 20-min windows, starting 10 min before and ending 10 min after each time T, and noted in the CRF. The FHR assessment was also blinded from allocation.

Dichotomous category data were compared with Fisher´s exact test. Continuous data were compared between groups with Mann-Whitney *U* test, and longitudinal data with Wilcoxon matched-pairs signed-ranks test. The difference between the shapes of the temperature curves among the paracetamol and control groups was evaluated using third order mixed-effect

models for repeated measurement data (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA)(16). Since the data included repeated measurements, the mixed-effect models (considering both fixed and random effects) were used in order to address the issue of covariation between measures on the same patient. A two-tailed *P* value <0.05 was regarded statistically significant. Statistical analyses were performed with aid of StatView® computer software (SAS Institute Inc., Cary, NC, U.S.A.), except for the mixed-effect models.

Although non-parametric statistical tests were used, for didactic reasons mean ± standard deviation (SD) values and 95% confidence interval (CI) are reported in addition to median and range values.

RESULTS

Eighteen women received paracetamol and the number of matched controls was 36. In no woman was paracetamol given repeatedly. For one paracetamol case 3-para with epidural analgesia it was not possible to find a perfect match for parity in one of the controls, so a 2-parous woman with epidural analgesia was chosen instead. Demographic data of paracetamol cases and controls are presented in Table 1. Women in the control group were significantly older but no significant differences were found for gestational age, time parameters, mode of delivery, Apgar score, umbilical cord artery pH, and neonatal morbidity.

All women were in the first stage of labor at T0. In the paracetamol group the cervix was dilated 2 cm in one case, 4 cm in one case, 5 cm in two cases, 6 cm in two cases, 7 cm in two cases, 10 cm in nine cases and retracted in one case.

In the paracetamol group13 woman received epidural analgesia (and consequently, 26 in the control group).

Recordings of temperature, CTG and STAN^{TM} were done until delivery. Many recordings lasted for several hours, with a maximum of 570 min. As the women delivered we chose to perform no statistical comparisons, except for the mixed-effect models for repeated-measurement data, when the number of paracetamol cases became fewer then 10. This happened beyond 150 min, with labours and recordings then ongoing in 5 paracetamol cases and 13 controls.

The overall percentage of missing or unreadable temperature values were in the maternal paracetamol group 18%, maternal control group 20%, fetal paracetamol group 15% and in the

fetal control group 13%. The main reason for missing values was that the registration was not ongoing when time T occurred because the woman was visiting the bathroom, took a shower or a walk, etc. In some instances the temperature signal quality was poor and the offline temperature measurements thus disabled. The numbers of valid measurements in paracetamol cases and controls at each time T from T-60 to T150 are displayed on the temperature curves in Figures 3 and 4.

Figure 3 shows mean maternal temperatures with 95% CI. From T-60 to T60 the temperature was higher in the paracetamol group ($P \leq 0.03$). In the paracetamol group there was a significant increase in temperature from T-60 to T-30 ($P = 0.01$), whereupon no temporal changes occurred (T0 versus other T's: $P \geq 0.4$; step-by-step comparisons between T's: $P \geq 0.1$). In the control group the temperature increased gradually from T-30 to T90 after which no further increase occurred (T-60 to T-30: $P = 0.7$; T90-T120: $P = 0.1$; T120-T150: $P = 0.4$).

In Figure 4 the mean fetal temperatures with 95% CI are demonstrated. At all T-times from T-60 to T90 the temperature was higher in the paracetamol group ($P \leq 0.04$). In the paracetamol group, the temperature increased significantly from T-60 to T-30 and from T-30 to T0 (and from T-60 to T0), after which no significant changes occurred (T0 versus T's after T0: $P \geq 0.1$; step-by-step comparisons between T's: $P \geq 0.7$). In the control group there was a gradual increase in temperature, except from T-60 to T-30 ($P = 0.06$).

The calculation with mixed-effect models for repeated-measurement data was done from T0 until delivery in all paracetamol cases and controls. There was no significant difference in curve shapes between the maternal paracetamol and control groups ($P = 0.4$) (Fig. 5), whereas the curve shapes for fetal temperatures were significant different ($P = 0.01$) (Fig. 6).

The difference between fetal and maternal temperatures (delta temperature) was calculated for all paracetamol and control cases at each time T from T-60 to T300. There were neither in the paracetamol group (T0 versus other T's: $P \geq 0.2$, step-by-step comparisons between T's: $P \geq 0.07$) nor in the control group (T0 versus other T's: $P \geq 0.09$, step-by-step comparisons between T's $P \geq 0.06$) any significant changes in delta temperatures, except for T0 to T240 ($P = 0.03$) in the control group. In the paracetamol group, the mean delta temperature varied from 0.47 ˚C (T270) to 0.79 ˚C (T0), and the maximum and minimum differences recorded were 2.29 ˚C (T30) and -0.49 ˚C (T120). The mean delta temperature in the control group varied from 0.47 ˚C (T300) to 0.73 ˚C (T180); the maximum and minimum differences recorded were 1.98 ºC (T-30) and 0.04 ºC (T90).

The basal FHR was at each time T positively correlated with fetal temperature when calculated in the total material ($P \leq 0.006$). At group comparisons the basal FHR was significantly higher in the paracetamol group at all T times ($P \leq 0.047$). In the paracetamol group there were significant increases in the basal FHR from T-60 to T-30 ($P = 0.02$), T-30 to T0 ($P = 0.02$) and from T-60 to T0 ($P = 0.008$). After T0 there were no significant changes in basal FHR in the paracetamol group, neither in comparisons between T0 and other T times ($P \geq 0.2$) nor in stepwise comparisons ($P \geq 0.2$). In the control group there was a significant increase in the basal FHR from T-60 to T-30 ($P = 0.045$) and from T-60 to T0 ($P = 0.049$). For other comparisons there were no significant changes in the basal FHR, neither in comparisons between T0 and other T times ($P \geq 0.2$) nor in stepwise comparisons ($P \geq 0.3$).

COMMENT

This study showed that the ongoing increases in fetal temperatures in febrile women in labour were halted by 1000 mg paracetamol (acetaminophen) orally, but the fetal temperatures did not decrease after paracetamol. As a result of paracetamol medication the fetal temperatures stabilised, i.e. showed no further increases. Since in the control group the fetal temperatures increased by advancing time of labour, the findings indicate an antipyretic effect of paracetamol even if the temperatures did not fall. We consider this a robust conclusion since continuous temperature curves were read frequently (every 30 min) and the results were unambiguous when assessed with different statistical tests. The stable fetal temperatures lasted for at least 150 min after paracetamol, after which the effect could not be evaluated since many women were in advanced labour and when they delivered the material became too small (N <10) for statistical analyses.

The different statistical evaluations of maternal temperatures showed no unanimous results. Longitudinal comparisons with the non-parametric Wilcoxon matched-pairs signed-ranks test showed patterns similar to the fetal temperatures, i.e. increases in the control group and a halt of the ongoing increase in the paracetamol group. However, trend analysis with the mixed-effects models, a robust analytical technique to distinguish between the degree of variation across time in longitudinal data for both within-individual-variation and between-individual-variation, showed that in the paracetamol group there was no significant difference in the shapes of individual temperature curves in comparisons with temperature curves in the control group. This latter finding indicates that paracetamol had no effect on maternal temperatures in the paracetamol group.

Since it is biologically not feasible that paracetamol had an effect on fetal temperatures without affecting maternal temperatures, and the fetal-maternal delta temperatures did not change significantly over time in any group, the difference in statistical outcomes might be a consequence of the differences in observation time between the statistical tests and the fairly small number of paracetamol cases and controls. In fact, the maternal temperature increase in the control group lasted, when assessed with longitudinal comparisons, only until 90 min after time T0; this period of increase was probably too short to show a difference in curve shapes when the maternal paracetamol case and control curves were assessed with the mixed-effect models analysis covering the considerably longer time elapsing till delivery in many paracetamol cases and controls.

The maternal axilla temperature sensor sometimes came off and had to be fixed again. A maternal rectal temperature probe would probably show a temperature curve of better quality, but due to long-lasting recordings and anticipated discomfort for the woman we chose not to use a rectal probe. Moreover, we noted that the maternal ear temperature in general was higher than the axilla temperature. This explains why some women getting paracetamol had a fairly normal axilla temperature at T0.

It is well known that there is a positive correlation between maternal temperature and FHR. The present study confirmed this relation, with a higher basal FHR among the febrile women. Paracetamol interrupted the increasing FHR in the paracetamol group, but since the same pattern was found in the control group we can only conclude that paracetamol had no lowering effect on baseline FHR. This is logic since the temperature did not drop either.

The documentation of the effectiveness of paracetamol on maternal and fetal temperatures in labor is sparse. Kirshon et al. (17) treated eight febrile parturients with 650 mg rectal suppositories and found a mean decrease in temperature with 1.2 °C (2.2 °F). No data were reported on the effect in individual cases, which is needed for evaluation in such a small series. In a placebo-controlled study, Goetzl et al. (14) showed that 650 mg prophylactic paracetamol administered rectally every four hours did not prevent maternal epidural-induced fever. Since paracetamol acts at the hypothalamic thermoregulatory set point, the finding indicates that epidural fever is not modulated through a direct effect at this site. There is evidence of an inflammatory basis for epidural fever (18, 19) and the failure of paracetamol to prevent epidural-induced fever may thus be explained by the weak anti-inflammatory effect of paracetamol.

In summary, this study showed that administration of 1000 mg paracetamol orally to febrile women in labour did not lower the fetal scalp temperature, but it interrupted an increasing trend and stabilised the temperature. Since in the control group the fetal temperatures increased by progression of labour, the results indicate that paracetamol had an anti-pyretic effect in fetuses of labouring febrile women. Regarding maternal temperatures the statistics were not unanimous, showing no difference in temperature curve shapes at trend analysis between febrile women and controls, but a stabilising effect of paracetamol at non-parametric longitudinal comparisons. These conflicting results might be a consequence of differences in observation time in a fairly small series, where the trend analysis covered a considerably longer time in many cases and controls. Thus, the possibility of a type II statistical error cannot be excluded and it remains an open question whether paracetamol can have an anti-pyretic effect in the fetus without affecting maternal temperature.

A prospective randomised placebo-controlled trial would more unambiguously than the present case-control study show the effectiveness of paracetamol in febrile parturients. However, randomising febrile women to treatment with placebo is ethically doubtful, but might be feasible in cases of slight maternal temperature elevations and for a short time of withholding active treatment, and in the absence of fetal distress.

DISCLOSURE OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

CONTRIBUTION TO AUTHORSHIP

TL: conception, planning, carrying out, analysing and writing the article.

FÅ: analysing and writing the article.

KK: analysing and writing the article.

PO: conception, planning, carrying out, analysing and writing the article.

DETAILS OF ETHICS APPROVAL

The Research Ethics Committee at Lund University, Sweden, approved the study 12 February 2003 (reference number LU 88-03).

FUNDING

This study was supported by grants from Lund University, Region Skåne, General Maternity Hospital Foundation, The Gorthon Foundation, The Zoéga Foundation, and The Segerfalk Foundation.

REFERENCES

1. Marx GF, Loew DA. Tympanic temperature during labour and parturition. Br J Anaesth1975;47:600-2.

2. Schouten FD, Wolf H, Smit BJ, Bekedam DJ, de Vos R, Wahlen I. Maternal temperature during labour. BJOG2008;115:1131-7.

3. Wood C, Beard RW. Temperature of the Human Foetus. J Obstet Gynaecol Br Commonw1964;71:768-9.

4. Macaulay JH, Randall NR, Bond K, Steer PJ. Continuous monitoring of fetal temperature by noninvasive probe and its relationship to maternal temperature, fetal heart rate, and cord arterial oxygen and pH. Obstet Gynecol1992;79:469-74.

5. Lieberman E, Cohen A, Lang J, Frigoletto F, Goetzl L. Maternal intrapartum temperature elevation as a risk factor for cesarean delivery and assisted vaginal delivery. Am J Public Health1999;89:506-10.

6. Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full-term infants. BMJ1995;311:598-602.

7. Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. JAMA1997;278:207-11.

8. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA2003;290:2677-84.

9. Greenwell EA, Wyshak G, Ringer SA, Johnson LC, Rivkin MJ, Lieberman E. Intrapartum temperature elevation, epidural use, and adverse outcome in term infants. Pediatrics2012;129:447-54.

10. Rudelstorfer R, Simbruner G, Sharma V, Janisch H. Scalp heat flux and its relationship to scalp blood pH of the fetus. Am J Obstet Gynecol1987;157:372-7.

11. Rudelstorfer R, Simbruner G, Bernaschek G, Rogan AM, Szalay S, Janisch H. Heat flux from the fetal scalp during labor and fetal outcome. Arch Gynecol1983;233:85-91.

12. Negishi C, Lenhardt R, Ozaki M, Ettinger K, Bastanmehr H, Bjorksten AR, et al. Opioids inhibit febrile responses in humans, whereas epidural analgesia does not: an explanation for hyperthermia during epidural analgesia. Anesthesiology2001;94:218-22.

13. Pharmaceutical specialities in Sweden. The Swedish Association of the Pharmaceutical Industy. Available at: http://www.fass.se. Retrieved 1 Aug 2012.

14. Goetzl L, Rivers J, Evans T, Citron DR, Richardson BE, Lieberman E, et al. Prophylactic acetaminophen does not prevent epidural fever in nulliparous women: a double-blind placebo-controlled trial. J Perinatol2004;24:471-5.

15. Lavesson T, Amer-Wahlin I, Hansson S, Ley D, Marsál K, Olofsson P. Continuous monitoring of fetal scalp temperature in labour: a new technology validated in a fetal lamb model. Acta Obst Gynecol2010;89:807-12.

16. Cheng J, Edwards LJ, Maldonado-Molina MM, Komro KA, Muller KE. Real longitudinal data analysis for real people: building a good enough mixed model. Stat Med2010;29:504-20.

17. Kirshon B, Moise KJ, Jr., Wasserstrum N. Effect of acetaminophen on fetal acid-base balance in chorioamnionitis. J Reprod Med1989;34:955-9.

18. Goetzl L, Evans T, Rivers J, Suresh MS, Lieberman E. Elevated maternal and fetal serum interleukin-6 levels are associated with epidural fever. Am J Obstet Gynecol2002;187:834-8.

19. De Jongh RF, Bosmans EP, Puylaert MJ, Ombelet WU, Vandeput HJ, Berghmans RA. The influence of anaesthetic techniques and type of delivery on peripartum serum interleukin-6 concentrations. Acta Anaesthesiol Scand1997;41:853-60.

LEGENDS TO FIGURES

Figure 1.

Fetal scalp electrode for cardiotocography and fetal ECG ST segment analysis with a pointed bi-metal thermocouple temperature sensor mounted in the middle.

Figure 2.

Example of registration from the Milou™ Temperature Monitoring System. Graphs from above indicated by numbered arrows: fetal temperature (1), maternal temperature (2), fetal heart rate (3), tocogram (4) and fetal ECG ST segment analysis (T/QRS ratio) (5).

Figure 3.

Maternal axillary temperature from 60 min before (T-60) administration of paracetamol (T0) to 150 min after (T150). The figure shows mean temperatures with 95% confidence intervals in the paracetamol group (filled squares) and the control group (filled circles), number of cases recorded at each T, and statistically significant differences compared to T0 (* $p<0.05$, ** $p<0.01$ and *** $p<0.001$, calculated with the Wilcoxon matched-pairs signed-ranks test).

Figure 4.

Fetal scalp temperature from 60 min before (T-60) administration of paracetamol (T0) to 150 min after (T150). The figure shows mean temperatures with 95% confidence intervals in the paracetamol group (filled squares) and the control group (filled circles), number of cases

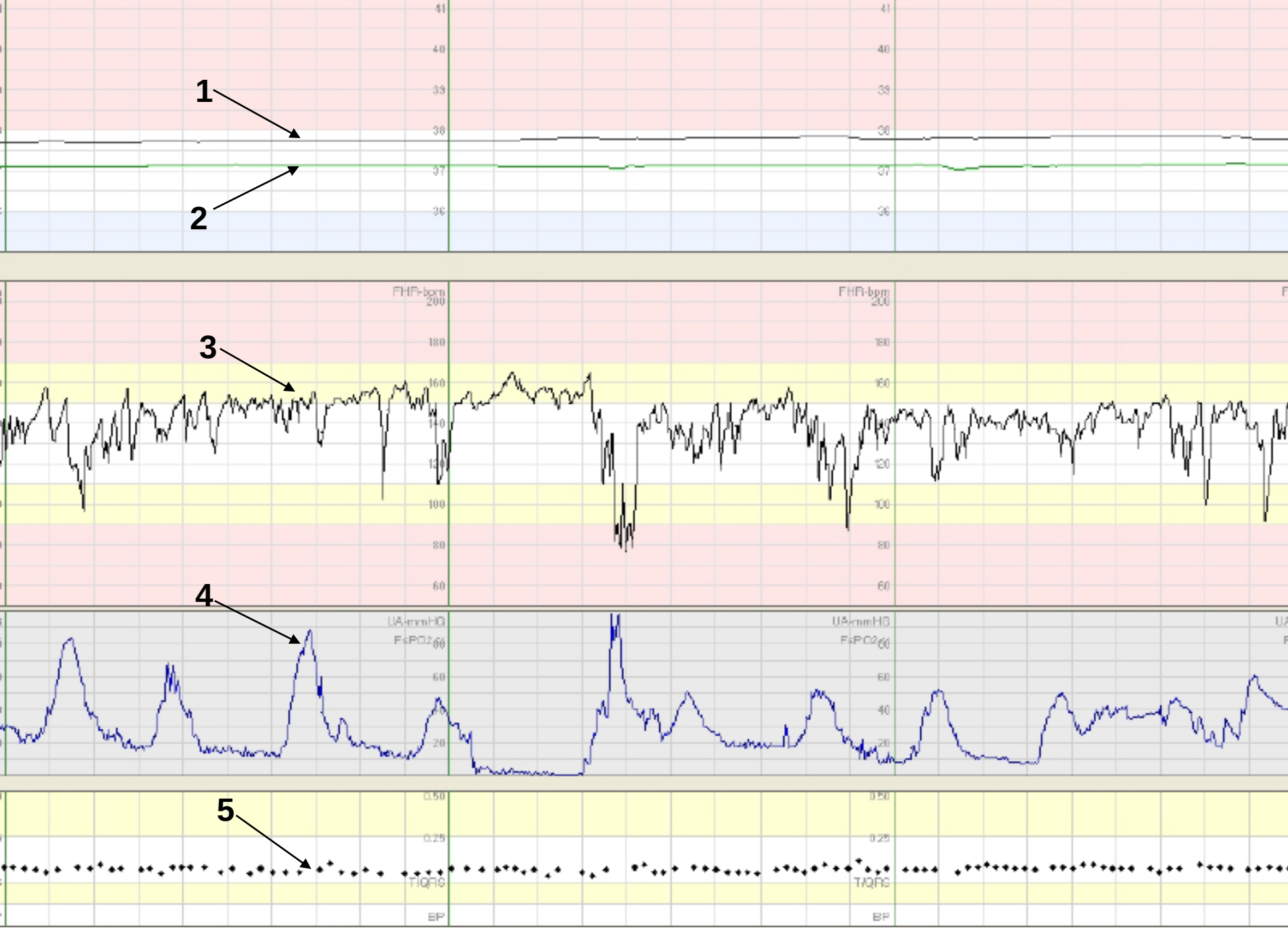
recorded at each T, and statistically significant differences compared to T0 (* $p<0.05$, ** $p<0.01$ and *** $p<0.001$, calculated with the Wilcoxon matched-pairs signed-ranks test).

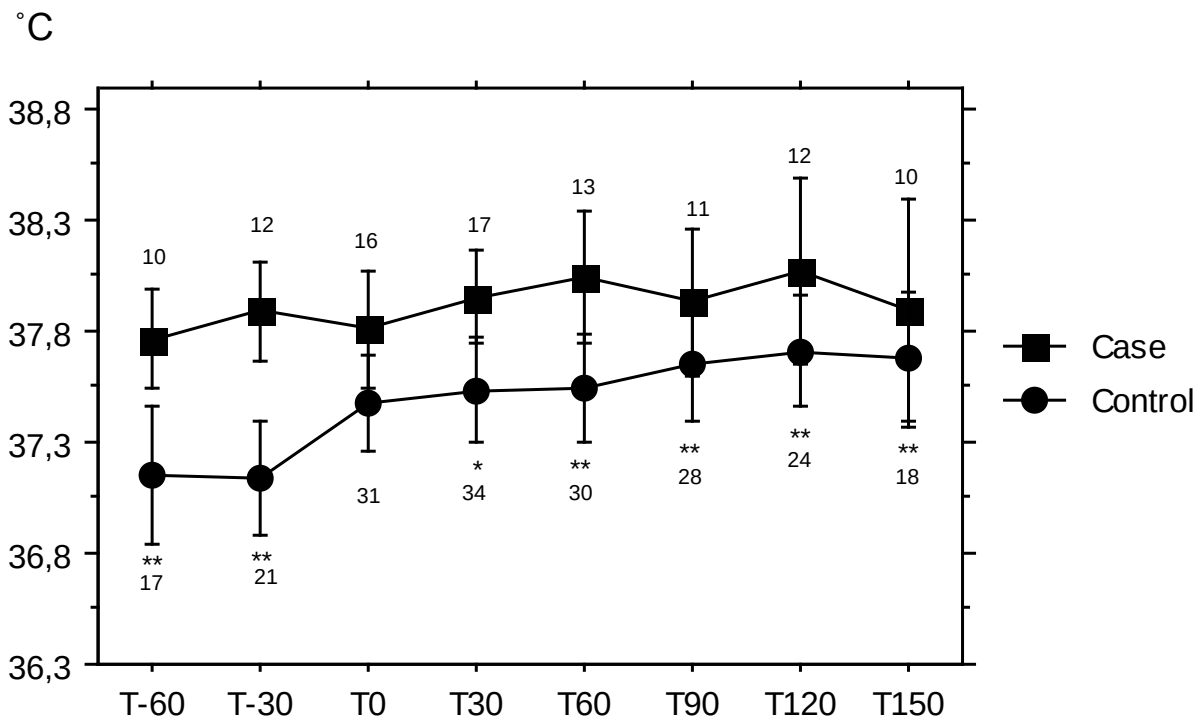
Figure 5.

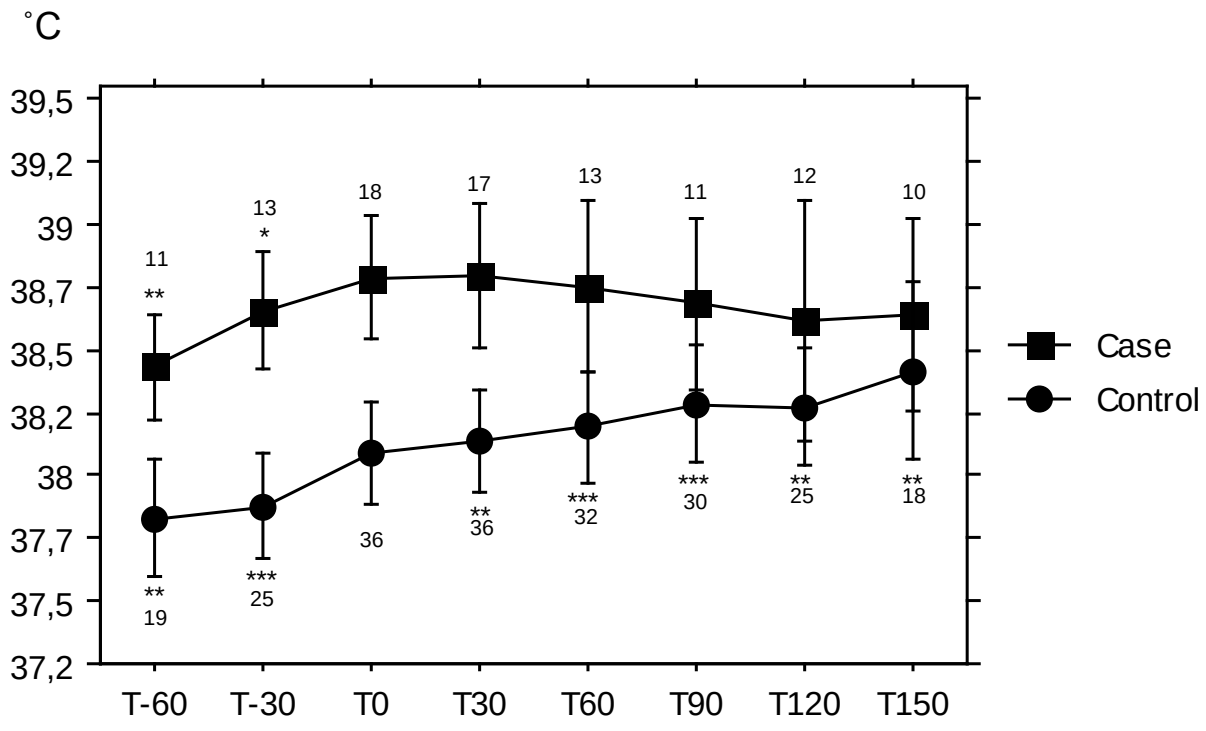
Longitudinal changes during labor of individual maternal axillary temperatures (ºC) after administration of 1000 mg paracetamol orally at time 0 to 18 febrile women (left panel) and 36 matched controls (right panel). The temperatures were recorded continuously and analysed *post hoc* offline with temperature measurements every 30 minutes. The thin lines represent the individual curves, and the thick lines represent the overall estimates. Trend analyses with third degree mixed-effect models showed that the curves were significantly apart (P =0.02) but the curve shapes were statistically not different (P =0.4).

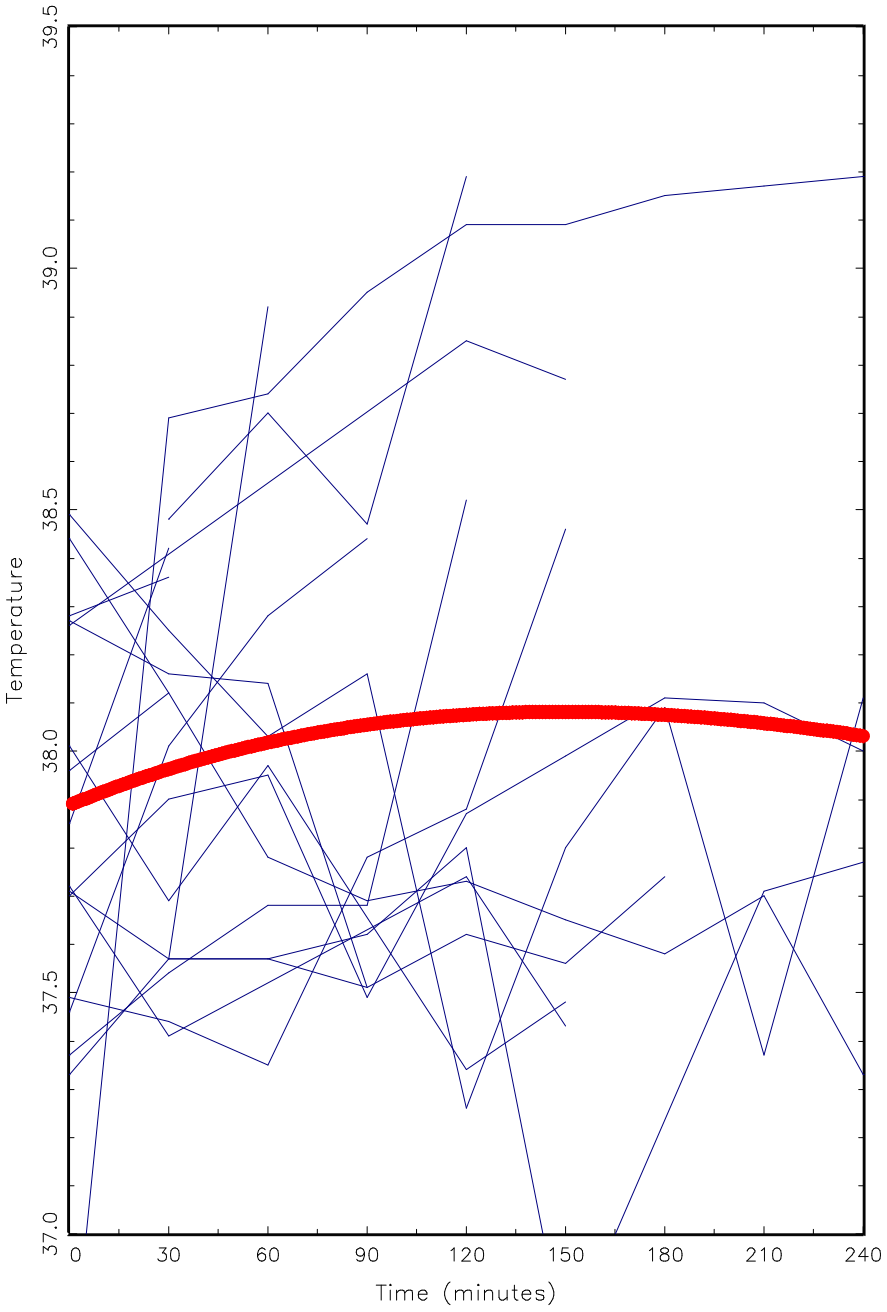
Figure 6.

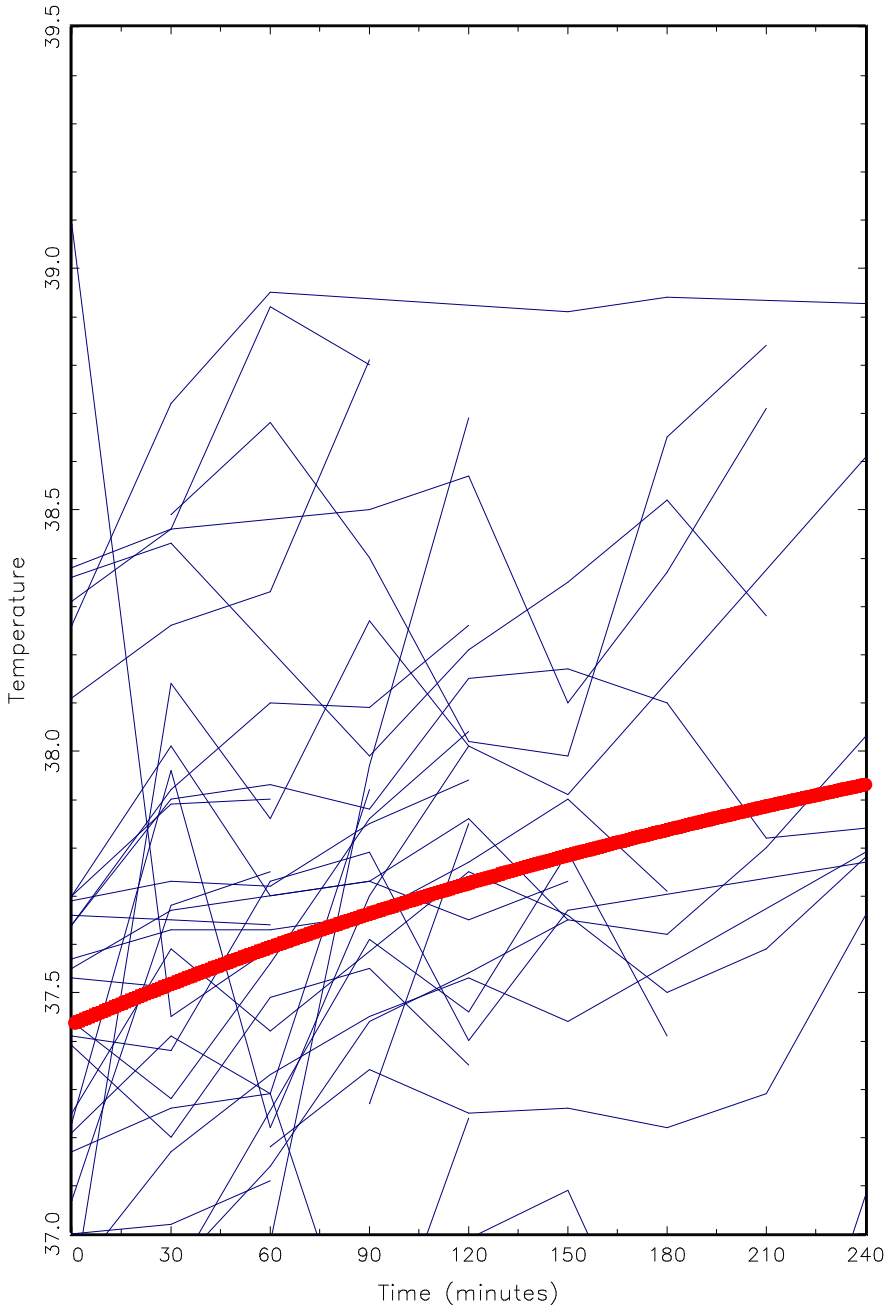
Longitudinal changes during labor of individual fetal scalp temperatures (ºC) after administration of 1000 mg paracetamol orally at time 0 to 18 febrile women (left panel) and 36 matched controls (right panel). The temperatures were recorded continuously and analysed *post hoc* offline with temperature measurements every 30 minutes. The thin lines represent the individual curves, and the thick lines represent the overall estimates. Trend analyses with third degree mixed-effect models showed that the curves were significantly apart (P =0.00006) and the curve shapes were different (P =0.01).

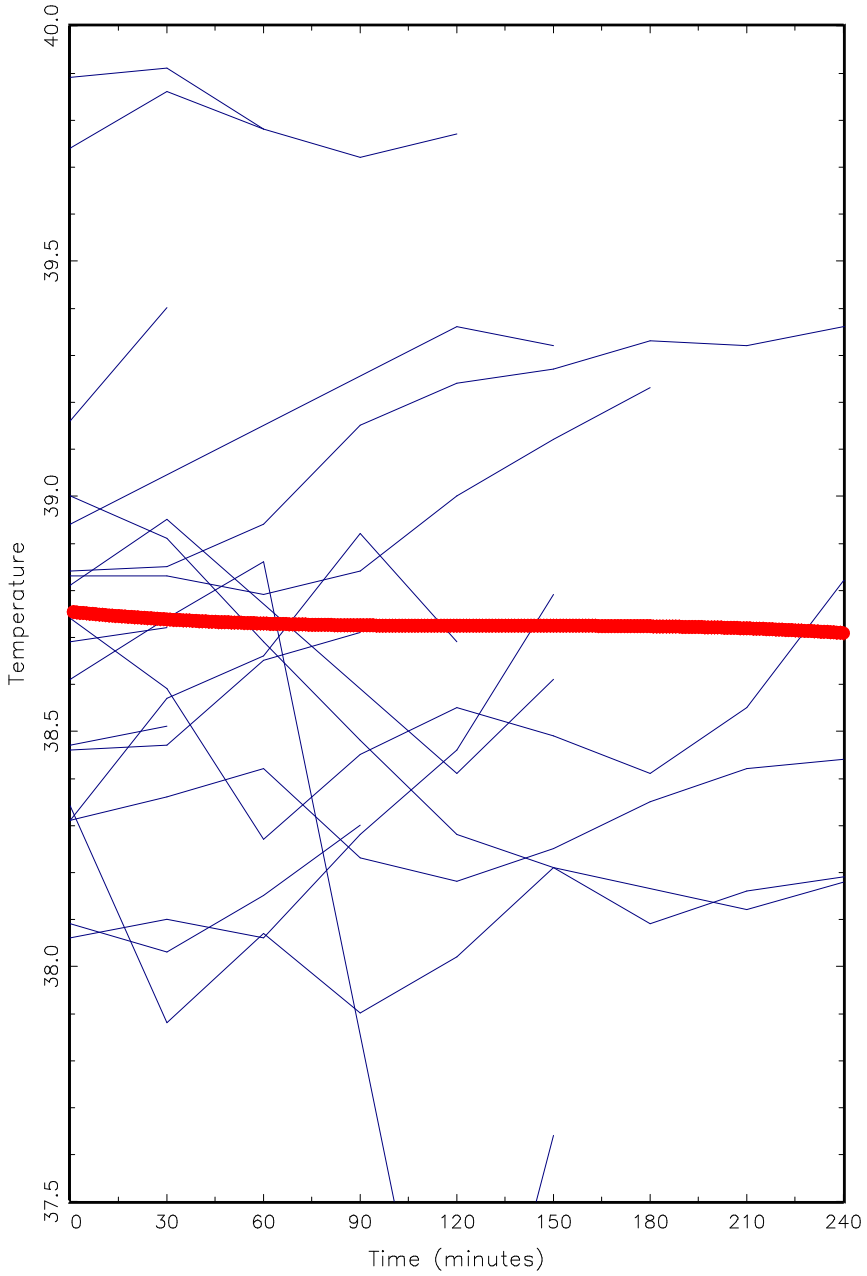

1
2
3
4
5
FHR-bpm
UA-mmHG
FsPO2
T/QRS
BP


˚C
38,8
38,3
37,8
37,3
36,8
36,3
T-60
T-30
T0
T30
T60
T90
T120
T150
10
12
16
17
13
11
12
10
** 17
** 21
31
* 34
** 30
** 28
** 24
** 18
Case
Control


˚C
39,5
39,2
39
38,7
38,5
38,2
38
37,7
37,5
37,2
T-60
T-30
T0
T30
T60
T90
T120
T150
11
**
13
*
18
17
13
11
12
10
**
19
***
25
36
**
36
***
32
***
30
**
25
**
18
Case
Control


39.5
39.0
38.5
38.0
37.5
37.0
Temperature
0
30
60
90
120
150
180
210
240
Time (minutes)


39.5
39.0
38.5
38.0
37.5
37.0
Temperature
0
30
60
90
120
150
180
210
240
Time (minutes)


40.0
39.5
39.0
38.5
38.0
37.5
Temperature
0
30
60
90
120
150
180
210
240
Time (minutes)

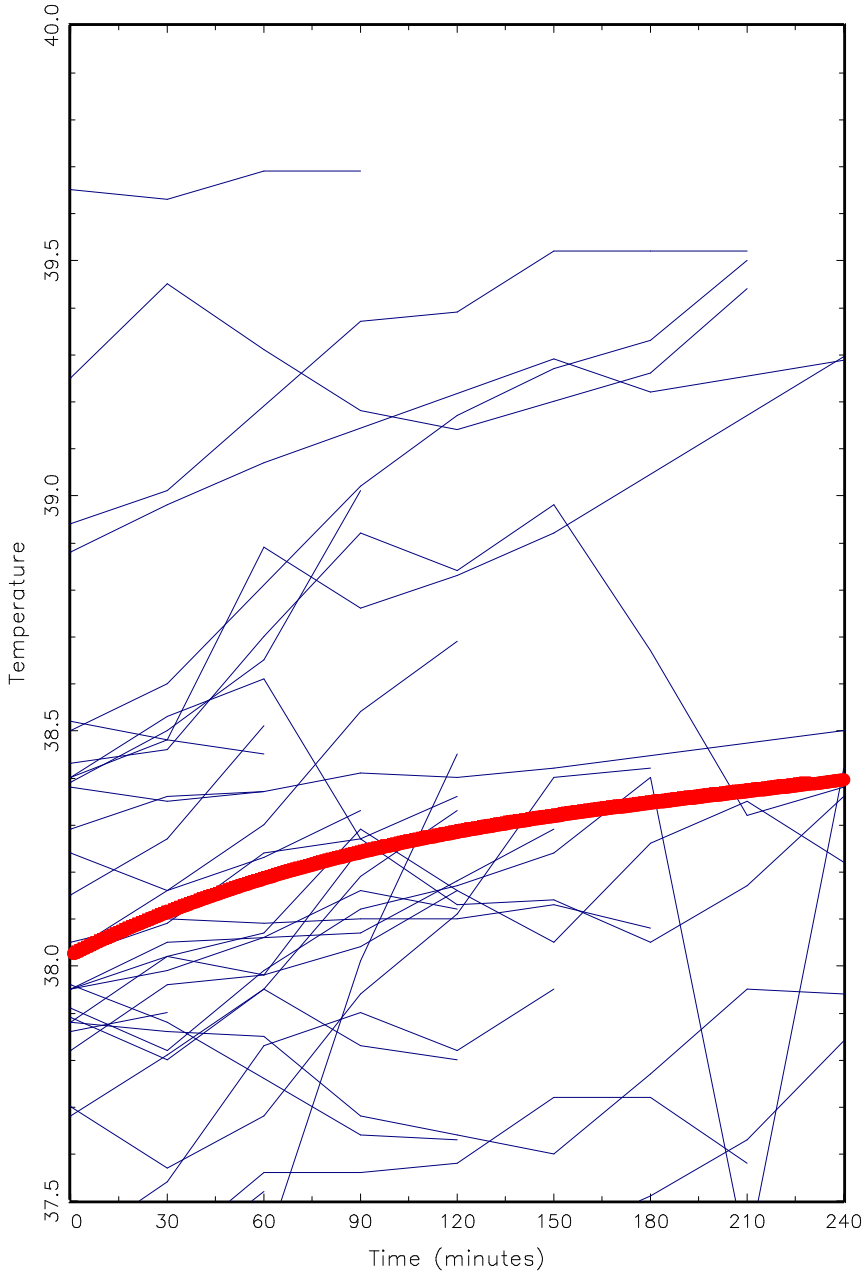

40.0
39.5
39.0
38.5
38.0
37.5
Temperature
0
30
60
90
120
150
180
210
240
Time (minutes)

Table 1.

Demographic data and pregnancy outcome in the paracetamol case and control groups.

	Cases N=18	Controls N=36	Significance of difference (*P*)
Maternal age (years)	26 ± 3.6 (26; 19-32)	29.5 ± 5.1 (29; 17-43)	0.007
Gestational weeks at delivery	39.8 ± 1.2 (40; 38-42)	39.6 ± 1.2 (39; 36-42)	0.6
Time from established labor to T0[a] (min)	427±220 (350; 170-905)	390±214 (355; 135-870)	0.5
Time from T0[a] to delivery (min)	233±162 (174; 40-614)	229±130 (198; 55-570)	0.9
Spontaneous delivery	12	27	0.5[b]
Assisted vaginal delivery	4	7	-
Cesarean section	2	2	0.6[c]
Apgar score <7 at 5 min	1	0	0.3
Umbilical artery pH <7.10	1/15	3/30	1.0
Neonatal morbidity	3[d]	3[e]	0.4
NICU[f]	0	0	-

Values are mean ± SD (median, range) or number of cases. Statistics performed with the Mann-Whitney *U* test or Fisher´s exact test.

a) T0 represents the time when 1000 mg paracetamol was administered
b) non-operative vs operative delivery
c) vaginal delivery vs cesarean section
d) one neonate with pneumonia, one with Erb's palsy, one with collarbone fracture
e) one neonate with respiratory distress, one collarbone fracture, one calcaneovalgus
f) neonatal intensive care unit.