

PhD THESES

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Medical and sociological factors contributing to increasing rates of Cesarean sections

(Acute phase reaction and alterations of iron homeostasis during delivery and gynecological interventions)

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In general, having a Cesarean section does not affect adversely the quality of life and later family planning that it is performed with adequate techniques. However, the question whether the high rate of Cesarean sections is really justified raises from time to time. Is it sure that there are

no early changes in maternal body that adversely affect the quick adaptation following the parturition? During my PhD work I as a practicing obstetrician addressed some issues in this field.

In the first phase of my work I analyzed the possible role of some factors contributing to the steadily increasing Cesarean section rate in Hungary. As a result I could identify several factors that may be present in the everyday practice of obstetrics.

In the second phase of my work I evaluated the impact of the way of delivery on maternal body from two aspects. From one hand, I evaluated the magnitude and nature of sterile inflammation following delivery with a multiplex cytokine measuring biochip. On the other hand, I related the levels of hepcidin, a recently identified iron-lowering polypeptide to iron homeostasis and the way of delivery on the day of delivery and three days later. The techniques used made an opportunity to collect some preliminary data about inflammation and iron homeostasis in women undergoing gynecologic intervention.

Aims

During my PhD work I aimed to address the following questions:

Evaluation of factors with a possible impact on the tendency to perform a Cesarean section

1. Analyzing the possible association between date of delivery, maternal age and the risk of performing a Cesarean section in deliveries occurred in Uzsoki street Hospital during the last decade.
2. Using a national database I analyzed the association between the increasing rate of Cesarean sections and the number of deliveries in each hospitals, the experience of obstetrician and maternal age.

Investigation of cytokine levels

3. Comparison of cytokine levels measured at the time of delivery and three days later in women with vaginal delivery or Cesarean section.
4. Comparison of cytokine levels measured at the time of intervention and three days later in women subjected to gynecological surgery.

Investigation of iron homeostasis

5. Comparison of hepcidin levels and other parameters of iron homeostasis measured at the time of delivery and three days later in women with vaginal delivery or Cesarean section.
6. Comparison of hepcidin levels and other parameters of iron homeostasis measured at the time of intervention and three days later in women subjected to gynecological surgery.

Methods

Evaluation of factors with an impact on the risk of having a Cesarean section

Data collection

We have collected data from 12 Hungarian hospitals with a department of Obstetrics (these institutions are responsible for the obstetric care of 15% of Hungary). The way of delivery (i.e. Cesarean section or vaginal birth) was related to the calendar year of delivery, maternal age and the experience of obstetrician at the time of delivery. (For the estimation of this parameter we used the first two digits of the professional ID No. of practitioner who led the delivery.) The analyzed data included just those deliveries that were complicated with any medicinal condition, the documentation revealed abnormal fetal position or twin pregnancy, or the delivery occurred before the 37th week of gestation.

In total, databases contained data about 171,523 deliveries between January, 1999 and June, 2009; of those, 11,662 were excluded according to exclusion criteria mentioned above. Finally, we analyzed data about 159,861 deliveries.

In Uzsoki Hospital we evaluated the data of 9465 deliveries fulfilling criteria above; of those, 2169 deliveries were terminated by Cesarean section (22.9%). We made an additional analysis with the database of Uzsoki street Hospital. We evaluated separately the possible association between the way of delivery and the month of delivery and whether the delivery occurred on a working day.

Data analysis

The impact of analyzed factors on the risk of Cesarean section was assessed by multiple regression analysis approach. As a basis the calendar year 1999, January and physicians with '1' as the first digit in practitioner's Id No were used.

Measurements of cytokine levels and iron parameters during and after deliveries and gynecological interventions

Delivering women

We enrolled 40 delivering women (age of gestation [median, range]: 40 (37 – 41) week); 25 of those delivered vaginally; while an elective Cesarean section was performed in 15 anesthetized with spinal anesthesia. Blood was taken just before the delivery, then 3 days later.

Women undergoing gynecological intervention

This patient group included 17 women subjected to different gynecological interventions. Blood was taken just before the intervention, then 3 days later again.

Local vaginal surgery	4
Cystectomy due to an ovarian cyst with laparoscopy	2
Salpingectomy due to extrauterine gravidity with laparoscopy	3
Hysterectomy due to fibroma with laparotomy	7
Vaginal hysterectomy due to prolapsed uterine	1

Hysterectomies and laparoscopic interventions were performed in general anesthesia, while local vaginal surgery was performed in local anesthesia.

Laboratory investigations

Complete blood cell count (platelet-, red blood cell and white blood cell counts) was assessed with a Sysmex K4500 hematological automated analyzer using Diagon reagents. Latent iron binding capacity, serum transferrin and iron levels were measured using Olympus 640 laboratory automated analyzer with available Olympus kits; ferritin levels were measured using ABBOTT AxSYM instrument with an Abbott kit. These investigations were done in the Central Laboratory Department of Uzsoki street Hospital.

Measurement of cytokine levels

For the measurement of serum cytokine levels, the BioRad biochip system was used in the Central Laboratory Department of Semmelweis University. We determined the levels of the following cytokines and growth factors: interleukin (IL)-1 α , IL-1 β , IL-2, IL-6, IL-8, IL-17, IL-12, TNF- α , IFN- γ , IL-4, IL-10, IL-5, IL-13, IL-7, macrophage inflammatory protein (MIP)-1 β , granulocyte-colony stimulating factor (GCSF) and granulocyte-macrophage colony stimulating factor (GMCSF).

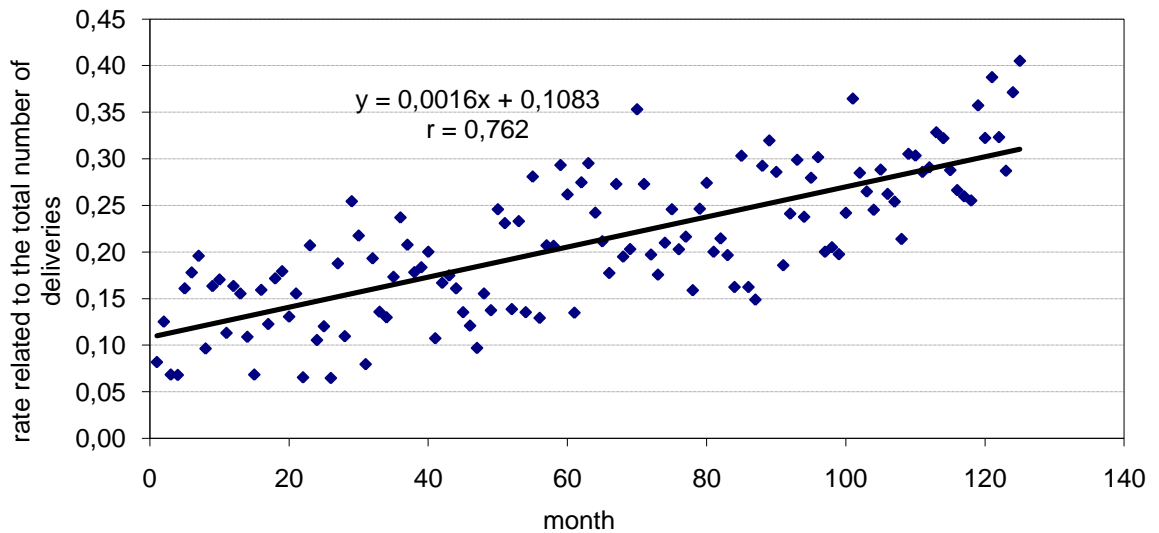
Determination of serum hepcidin levels

Serum hepcidin levels were measured in the Screening Laboratory of Metabolic Disorders of the First Department of Pediatrics, Semmelweis University with a mass spectrometry method developed here for this purpose.

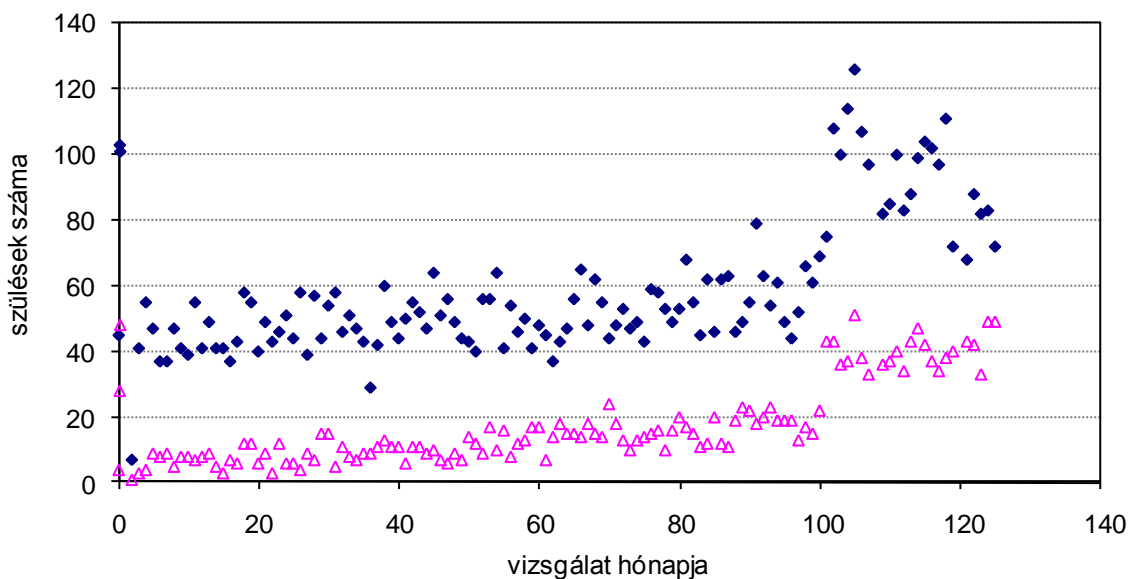
Results

Analyzing risk factors of performing a Cesarean section: obstetric data regarding the last decade in the Uzsoki street Hospital

Over the time period analyzed the rate of Cesarean sections steadily increased. The Cesarean section rate did not depend on actual number of deliveries.



Monthly rates of Cesarean sections in Obstetric Department of Uzsoki street Hospital between 1st January, 1999 and 30th June, 2009



Number of Cesarean sections (Δ) and vaginal deliveries (\blacksquare) in each month between 1st January, 1999 and 30th June, 2009 that occurred on the Department of Obstetrics and Gynecology in Uzsoki Hospital.

During the period between 1st January, 1999 and 30th June 9465 deliveries were managed in our Department; of those, 7296 were vaginal delivery; while 2169 deliveries were terminated by Cesarean section (22.9%). There was a 2.5 fold increase in Cesarean section rate during this period (12.9 vs. 28.3 per cent in 1999 and 2008, respectively.) Maternal age also increased during this period by 2.5 years in average; this was alone responsible for a 5% increase in Cesarean section rates. The risk of Cesarean section rate increased in working days and June and December; this finding indicates that some of Cesarean sections were performed in an elective manner.

	Level of significance	Relative risk	Confidence interval
2002	0.049	1.39	1 – 1.93
2003	< 0.0001	1.78	1.29 – 2.45
2004	< 0.0001	2.32	1.71 – 3.16
2005	< 0.0001	1.95	1.43 – 2.67
2006	< 0.0001	2.32	1.71 – 3.15
2007	< 0.0001	2.65	1.99 – 3.55
2008	< 0.0001	3.05	2.29 – 4.06
2009	< 0.0001	4.34	3.17 – 5.93
Maternal age	0.002	1.02	1.01 – 1.03
Working day	< 0.0001	1.67	1.36 – 2.04
June	0.001	1.49	1.18 – 1.88
December	0.013	1.37	1.07 – 1.76

Some parameters with an impact on Cesarean section rates. Results of multiple regression analysis. Basis: 1999, January, Sunday

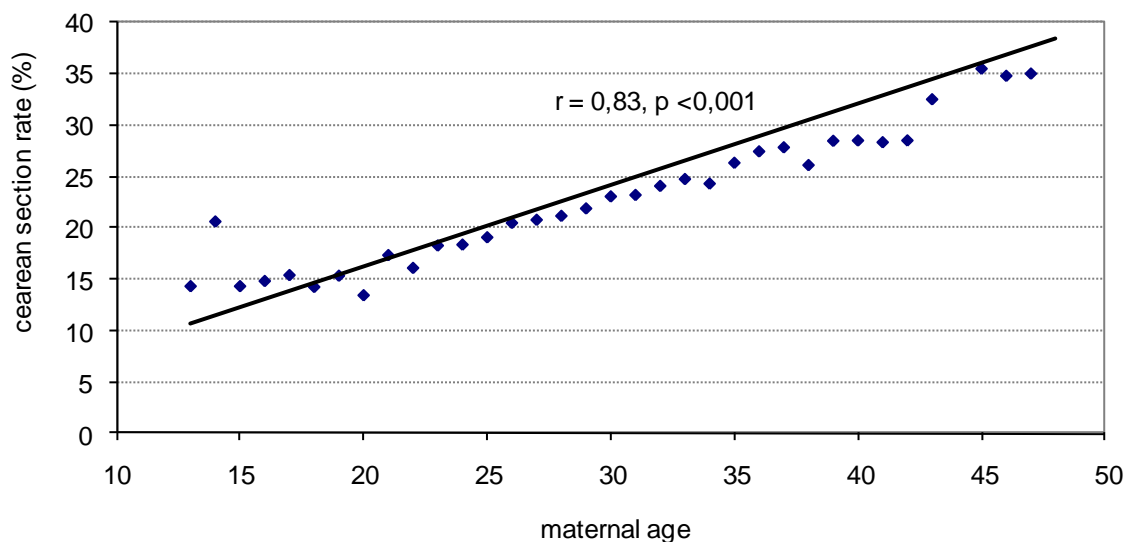
Multiple regression analysis revealed that the risk of performing a Cesarean section depends on calendar year and maternal age. The probability of having a term pregnancy finished with a Cesarean section is higher in December and July and in a working days.

Analysis of deliveries occurred in county and municipality hospitals during one decade

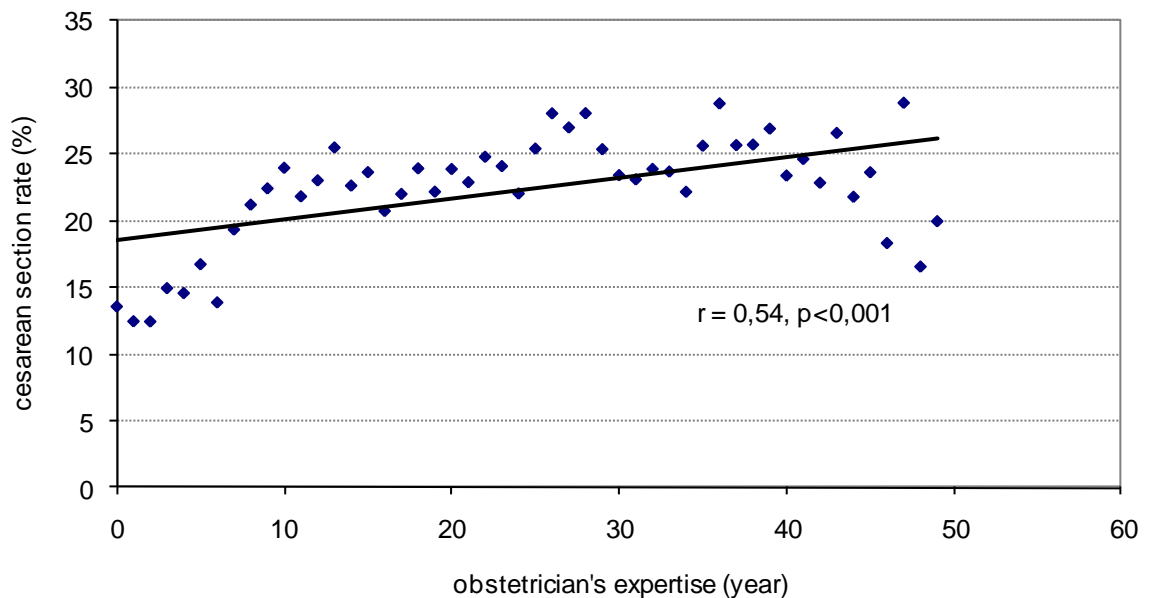
Calendar year had a major impact on risk of performing a Cesarean section. In line with international tendencies the rate of Cesarean sections almost doubled in Hungary between 1999 and 2008 (the incidence increased up to 27.00 per cent from the baseline 14.17 per cent values). This tendency was detected in all institutes participating in our analysis.

We detected a strong correlation between maternal age and Cesarean section rates: the adjusted risk of Cesarean section was increased by 3.9% per maternal year (adjusted odds ratio, 95% CI: 1.039 [1.035-1.043]). As average maternal year increased in the time period tested by almost 4 years (from 26.00 years to 29.76 years), this factor per se may be responsible for the 15% of increase in Cesarean section rates.

The risk of having a Cesarean section is also increased when the delivery was led by an obstetrician with a longer professional experience: each year of practice increased adjusted risk by almost 2 per cent (OR: 1.019 [1.017 - 1.021]). As in 2008 the number of years of experience increased by 4 years compared to 1999 (i.e. from 17.37 ± 10.61 to 21.39 ± 12.15 years, $p < 0.0001$), this may be responsible for a 7.6% increase in Cesarean section rate alone.



Association between the rate of Cesarean sections and maternal age



Association between Cesarean section rate and obstetricians' experience

Cytokine levels after delivery

The levels of the majority of measured cytokines were comparable irrespective of the time of sampling and the mode of delivery. IL-2, IL-4, IL-5, G-CSF, GM-CSF and IFN- γ levels were below the limit of detection in all participants at the first time point and could only be measured in a few women at the second time point at postpartum day 3. Significant time effects were observed just for IL-6 and IL-8 ($P = 0.032$ and $P = 0.044$, respectively); levels of these two cytokines decreased by the third postpartum day only in the Cesarean section group. A significant effect was also observed for IL-7; higher levels of IL-7 were observed in the Cesarean section group at both the first and second time points ($P = 0.031$). No other significant differences were detected between the two groups.

Cytokine levels after a gynecological intervention

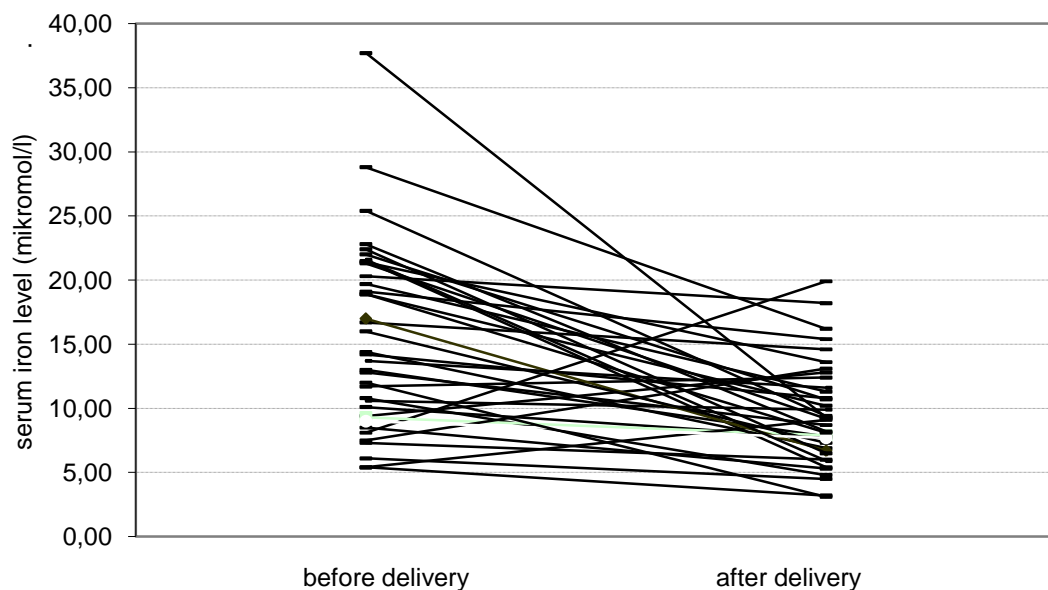
None of the investigated cytokines altered significantly by the 3rd postoperative day. Interventions were grouped according to their extensivity (i.e. laparotomy and laparoscopy) and analyzed separately. Just white blood cell counts were higher in patients subjected to laparotomy; no other difference was observed.

Iron homeostasis after delivery

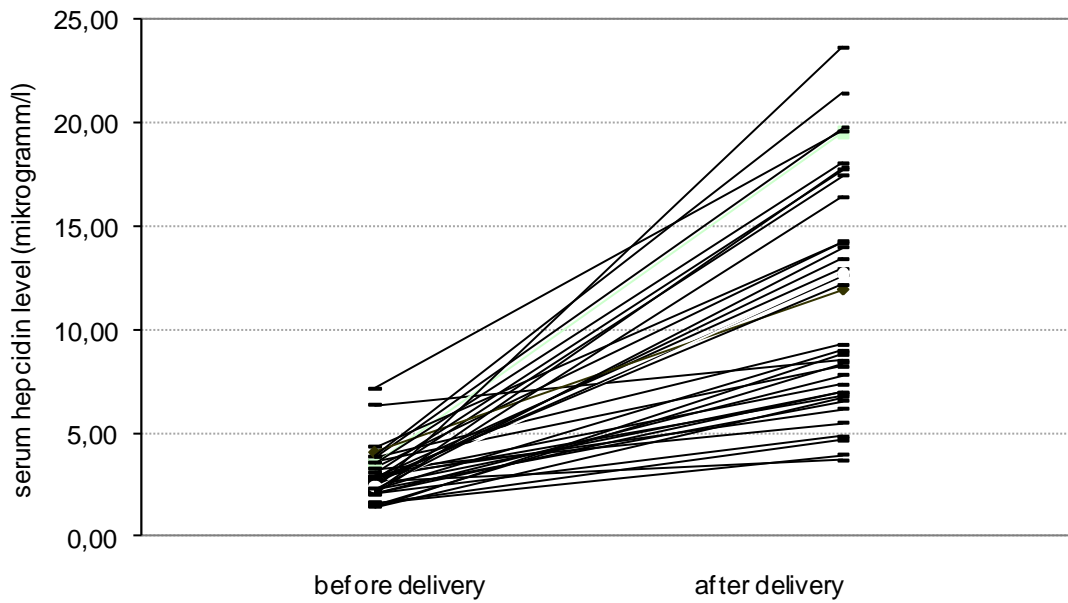
Our results revealed dramatic changes in iron homeostasis. Iron, hemoglobin and hematocrit levels dropped after delivery, while hepcidin levels increased in each woman; however, women with presented with a more marked increase. Iron levels decreased in 35 of 40 women irrespectively of the way of delivery. Ferritin levels increased just in women delivering with Cesarean section.

	Vaginal delivery (n = 25)		Cesarean section (n = 15)	
	At the beginning of delivery	3 days later	Just before	3 days later
White blood cell count (T/L)	11.45 [5.7 – 16.5]	10.8 [4.7 – 13]	9.6 [6.6 – 13.6]	9.2 [4.3 – 12.5]
Red cell count (G/L)	4.155 [3.68 – 4.73]	3.64 [2.18 – 4.32]*	4.23 [3.61 – 4.77]	3.41 [2.99 – 4.29]*
Hemoglobin-level (g/L)	123.5 [106 – 145]	108 [59 – 128]*	125 [108 – 145]	101 [92 – 125]*
Hematocrit (L/L)	0.365 [0.236 – 0.434]	0.315 [0.18 – 0.37]*	0.372 [0.26 – 0.415]	0.298 [0.23 – 0.38]*
Platelet count (T/L)	197.5 [125 – 304]	166 [125 – 287]	173 [125 – 338]	168 [96 – 261]*?
Total iron binding capacity (µmol/L)	77.6 [52.6 – 95.3]	74.3 [55.6 – 88.5]	80.6 [54.6 – 100.7]	70.6 [52.5 – 83.5]
Iron levels (µmol/L)	13.0 [5.4 – 37.7]	9.3 [3.2 – 19.9]*	17 [7.5 – 28.8]	8.1 [3.1 – 18.2]*
Ferritin levels (µg/L)	9.4 [3.1 – 36.4]	14.9 [3.6 – 44]	15.25 [3.9 – 34.5]	38.5 [12.6 – 68]*†
Hepcidin levels (µg/L)	2.02 [0 – 6.65]	7.36 [3.71 – 19.5]**	3.56 [0.81 – 23.21]	17.45 [12 – 23.6]**†

Iron parameter before and 3 days after delivery (data are as median, range). * p<0,01; ** p<0.01 after vs. before delivery; † p<0.05, Cesarean section vs. vaginal delivery



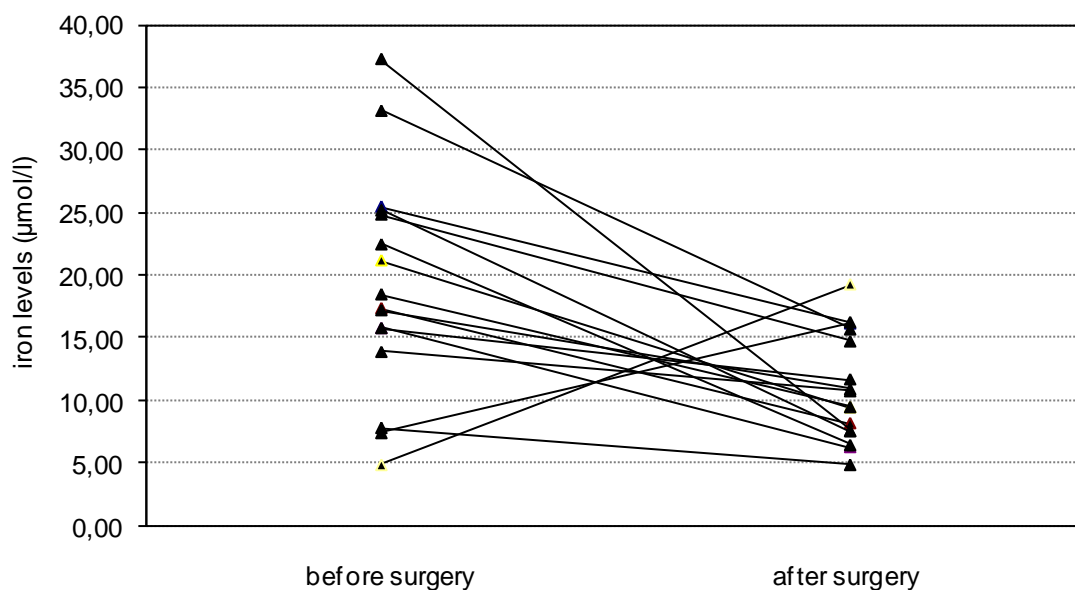
Serum iron levels before and 3 days after delivery (p<0.01)



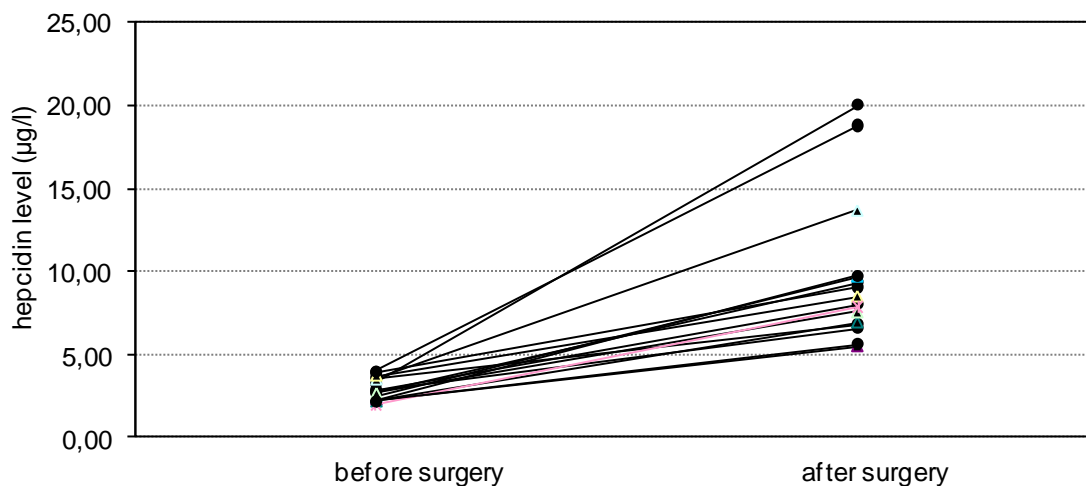
Serum hepcidin levels before and 3 days after delivery ($p < 0.01$)

Iron homeostasis following gynecological surgeries

Three days after delivery hemoglobin level and hematocrit values decreased almost significantly. Serum iron and transferrin levels decreased, while hepcidin levels increased significantly. The type of intervention had no impact on measured parameters.



Serum iron levels before and 3 days after surgery. Serum iron levels decreased in 15 of 17 patients ($p < 0,01$)



Serum hepcidin levels before and 3 days after surgery. Serum hepcidin levels uniformly increased in each patient ($p < 0,0001$)

Discussion

Factors having an impact on Cesarean section rates in Uzsoki street hospital

Our analysis suggests that the steady increase of Cesarean section rates did not cease during the past years in our Department. Possible contributors are the increasing maternal age, repeated pregnancy after a previous Cesarean section and the generally accepted defensive approach to pregnancy and delivery.

The dynamic and continuous increase of Cesarean section rates in our Department is a surprising finding, as – based on data obtained in 1999 Uzsoki street Hospital – Cesarean section rates were lower in our Institute than the national average and the guidelines used in the Department did not change. Finally, in 2009 we reached the rate that was characteristic for university clinics in 2001-2002. Our department takes obstetric care for regional patients; these patients are routinely referred to University hospitals in case of preterm delivery. Therefore in our Department the majority of pregnancies are complication free. It would be interesting to analyze the trend of Cesarean section rates during recent years in Institutes providing tertiary obstetric care and to establish whether it has reached the plateau phase. Our retrospective anonymous database does not allow the identification of factors responsible for increased Cesarean section rates. However, the analysis of some parameters suggests some possible mechanisms.

(1) During the last decade maternal age steadily increased. With advanced age complications of pregnancy and delivery are clearly more prevalent and, therefore, the conditions presenting an indication for Cesarean section are also more prevalent. As our database did not contain any patient identity number we cannot estimate the proportion of delivering women with repeated pregnancies; however, it is reasonable to postulate that women with a Cesarean section in medical history are at more risk to a repeated Cesarean pregnancy. Our analysis indicates that solely the increase of maternal age increased by 5% the rate of Cesarean sections.

(2) Since the beginning of 2007 the number of deliveries dramatically increased in Uzsoki street Hospital, probably as a result of health care reforms. Simultaneously, the medical staff size also increased. However, no sudden alteration was detected in Cesarean section rates. This suggests that the phenomenon detected is not specific to our Institute and the health care reform had no direct impact on Cesarean section rates.

(3) The inter-obstetrician variability in Cesarean section rates was low. Although there should be individual variations, the *lege artis* obstetric care and the guidelines used in our Department to decide whether or not to perform a Cesarean section provide a uniform approach to pregnant women. This finding suggests that instead of targeting obstetric training the establishment of well defined indications would be a way to decrease the frequency of Cesarean sections.

(4) We also observed some cycles in Cesarean section rates supporting that a significant portion of Cesarean sections is performed in an elective manner. (Although medical records use the term 'elective C-section', this term is underused and not suitable to assess the real contribution of elective to the total number of Cesarean sections.) The elective nature is supported by the following observations: (1) working days present a 67% increased risk for Cesarean section and (2) Cesarean section rates are higher in June (before summer holidays) and in December (before Christmas). Of course, this hypothesis should be verified by further analysis and reviewing the hospital records of Cesarean sections done in the period tested.

Factors having an impact on Cesarean section rates: analyzing a national database

Our analysis revealed that the continuously increasing maternal age plays a central role in the doubling of Cesarean section rates during the past decade. Every year of increase in maternal age increased the adjusted Cesarean section risk by 3.9%. As maternal year increased by almost 4 year during the last decade, this factor alone may be responsible for up to 15% increase in Cesarean section rates.

It was a new finding that obstetricians' experience was associated with an increased chance for Cesarean section. (Our original hypothesis was that this factor should be protective). There are several explanations for this observation.

(1) Different levels of decision. In obstetric departments the final decision about Cesarean sections is made by an older obstetrician. As younger and less trained physicians have less access to decide whether or not to do a Cesarean section, they are expected to make a more detailed consideration before they turn to their leaders to allow the surgery.

(2) Different patient populations. Although average age of pregnant women in younger and older obstetricians' practice did not differ and we aimed to exclude complicated pregnancies and deliveries from our analysis, there is still an uncertainty that some of deliveries were classified (incorrectly) as complication free. It is reasonable to postulate that more complicated pregnancies and deliveries are cared by older obstetricians.

(3) Adverse experience. Probably more experience means more adverse experience with pregnancy outcomes and associated legal procedures and this may result in a more careful attitude.

(4) Control in everyday life. In Western societies anybody (including obstetricians and delivering women) aims to work and live in a planned and controlled manner. The exact timing of vaginal delivery, however, cannot be decided that induces large uncertainty. This uncertainty can be sometimes hardly tolerated by an older colleague and his/her environment.

The enthusiasm of young obstetricians usually decreases by passing years and (s)he decides more easily Cesarean section.

These data may also reflect the change in general view of obstetricians and their patients. It is a common sense that pregnancy should be always finished successfully with a living and healthy newborn; if it is not this case, it may be due to the malpractice. This way of thinking does not allow any risk, as it is reflected by medico-legal procedures and associated costs that sometimes endanger financial basis of the Departments.

On the other side there are the complications associated to Cesarean sections. Their risk is, however, significantly lower compared to that 20 – 30 years before and, usually, they do not emerge immediately by several years later (at a repeated pregnancy).

Based on these considerations it is reasonable to postulate that the trend of increasing Cesarean section rates will further increase in the nearest future; this notion is fully supported by our results.

Investigation of inflammatory response

The mode of delivery and inflammatory response

The key finding of the present study was that, following a normal pregnancy, the reported inflammatory reaction during the peripartum period was probably transient and was not reflected by the cytokine patterns measured 3 days after delivery.

The multiplex cytokine measurement system used in the present study evaluated all of the major pro- and anti-inflammatory cytokines. The only changes in cytokine profiles detected were significant reductions in the IL-6 and IL-8 levels at day 3 postpartum in Cesarean section patients compared with levels at the onset of labor.

As IL-8 is regarded as a pro-inflammatory cytokine, one could speculate that in Cesarean section patients the inflammatory response is skewed toward an anti-inflammatory status 3 days after delivery. This notion may be further supported by the simultaneous decrease of IL-6 regarded as a marker of an acute phase reaction. However, the undetectable anti-

inflammatory cytokine including IL-10 and IL-4 and major pro-inflammatory cytokine levels including IFN- γ and IL-2 in the majority of women at either time point; and the comparable levels of potent inflammatory cytokines (TNF- α , IL-1 β) before and after delivery and the comparable IL-6 and IL-8 levels in Cesarean section and vaginally delivering groups after delivery do not support any skewness into an anti-inflammatory status. Instead, it is more reliable to postulate that the changes in IL-6 and IL-8 observed in Cesarean section occur as a chance because of the high number of comparisons.

The other relevant finding was that the mode of delivery had no systemic inflammatory effects on the third postpartum day reflected by similar cytokine levels in the PV and Cesarean section groups. This finding is similar to a previous study that showed no increase in C-reactive protein levels on the third day after C-section delivery. The only exception was IL-7, which demonstrated significantly higher levels in the patients that underwent a C-section compared with a vaginal birth. IL-7 is a haematopoietic growth factor that stimulates the differentiation of multipotent haematopoietic stem cells into lymphoid progenitor cells and no data are available with regard to its role in delivery. Due to the comparisons of the levels of large numbers of cytokines made in this study and the lack of biological relevance the authors suggest that this result might be also a chance finding.

The absence of an increase in systemic inflammatory cytokines on the third postpartum day and comparable levels in the two groups of women still may have clinical relevance for obstetric practice. Based on these results, it is reasonable to postulate that there is no risk of a persisting systemic inflammatory maternal reaction following an uncomplicated vaginal birth or an elective Cesarean section and this issue need not be considered when making a decision about the mode of delivery.

Inflammatory response after gynecological interventions

The extent and duration of acute phase reactions occurring during elective surgeries are affected by several factors. These include the volume of tissue damage; pain; duration of intervention; clinical characteristics (age, underlying disease, body mass) and perioperative medication used, type of anesthesia, painkillers, antibiotics, anti-inflammatory agents and postoperative complications. For early detection and treatment it is necessary to clinically monitor patients in the postoperative phase (i.e. up to 3 days after the surgery).

We analyzed whether the serum levels of pro- and anti-inflammatory cytokines – that are sensitive and quickly reacting markers of systemic inflammation – are increased on the 3rd postoperative day. There are no literary data regarding to this time point; just one Polish team did a small study in a group of patients after a gynecological intervention and found increased IL-6 levels on the 2nd postoperative day.

As the levels of the 17 cytokines and growth factors became normal by the 3rd postoperative day, it is clear that in common gynecological interventions performed with laparotomy or laparoscopy the systemic acute phase reaction is finished by this time point. In addition we could not detect any difference between patient groups subjected to different interventions suggesting that the impact of surgery on systemic inflammation does not depend on the type of intervention. This is a new and surprising finding as previous data indicated that laparoscopy is associated with less pain and quicker recovery and that early postoperative cytokine levels are lower than those measured after a laparotomy. (To the contrary, all the available data was collected within 48 hours after surgery).

Analyzing these results one should take several factors into account. From one hand, we just measured a dozen of the several hundreds of acute phase reactants; it is reasonable to postulate that some hormones or other proteins with a longer half-life would differ. However, our aim was to characterize the current acute phase reaction. Furthermore, it should also be noted that systemic cytokine levels do not necessarily reflect the local cytokine milieu and the results from the present study do not exclude a localized inflammatory response in the surgical wound and/or damaged tissue 3 days after surgery. It is also worth to emphasize that this study was performed in a population undergoing gynecological surgery.

Summarizing our results we concluded that in common gynecological interventions systemic inflammation is finished in fact by the 3rd postoperative day in patients without complication. These results may help to establish reference values and cut-off levels for the investigated cytokines.

Hepcidin levels 3 days after delivery

Hepcidin is regulated by several factors including blood loss and inflammation. During delivery, these factors are simultaneously present: from one hand, delivery is associated with a significant blood loss that inhibits hepcidin synthesis; on the other hand, delivery triggers inflammatory cytokines, a major stimulus for hepcidin synthesis.

Our study revealed that factors triggering hepcidin synthesis dominate early after delivery in each woman. We just speculate that these factors may include stress associated with and inflammatory cytokines released during and after delivery or Cesarean section. This hypothesis may be reinforced by the lower postdelivery hepcidin levels measured in vaginal delivery compared to Cesarean section women who are subjected to stress associated with surgical intervention additionally to that with delivery.

Interestingly, the level of inflammatory cytokines including IL-6, major trigger factor of hepcidin synthesis did not increase, rather decreased three days after delivery, therefore these factors are probably not responsible for the observed increase in hepcidin. Although theoretically IL-6 levels are still increased in an earlier time-point (i.e. on day 2 after delivery), their impact on hepcidin levels are probably limited by the short half-life of IL-6 and hepcidin. Therefore the increase of hepcidin levels at stable and/or decreasing cytokine levels indicate that a still unclear mechanism is responsible for hepcidin regulation after delivery. Our data may suggest that this may be linked to trauma associated to delivery, as hepcidin levels after Cesarean section were higher compared to those after a vaginal delivery. (Although cytokine levels indicate that the systemic acute phase reaction ceases by the Day 3 after delivery, it is reasonable to postulate that other acute phase proteins with a longer half-life may contribute to the increase in hepcidin levels.

Of note serum hepcidin levels did not correlate to iron homeostasis parameters such as serum iron levels, serum iron binding capacity, iron stores and red cell counts and red cell hemoglobin content. This may indicate that the major determinants of iron homeostasis in periparturition are blood loss and delivery-associated hormonal changes and the role of hepcidin is secondary, if any.

Hepcidin levels following gynecological surgery

Blood loss, transient tissue hypoxia associated with the anesthesia and stress and acute phase reaction may have an impact on hepcidin levels. We have observed a significant increase of hepcidin levels following gynecological interventions. This finding indicates that the factors increasing hepcidin levels dominate in this scenario.

In our study we collected data regarding routine gynecological interventions. Although the conclusions are limited by the small patient number, it is of interest that hepcidin levels increased in each patient and we did not observe any difference between different types of surgery. This makes possible that noxae associated with the surgical intervention (and not the anesthesia used) results in the increase of hepcidin levels.

Summarizing our results we concluded that serum hepcidin levels are increased 3 days following different types of gynecological interventions. This phenomenon was independent of cytokine levels, iron- and transferrin concentration, therefore, based on our data the role of hepcidin in the regulation of postoperative iron homeostasis is still unclear. This issue may be addressed by the follow-up of women subjected to gynecological interventions.

Theses

1. The rate of Cesarean sections steadily increased both in our Institute and in Hungary. This phenomenon may be due to an increase in the average age of delivering women and, probably, to an increase of incidence of elective Cesarean sections.
2. The risk of having a Cesarean section is proportionally increased with the number of years in practice of obstetricians leading the delivery.
3. Unaltered inflammatory cytokine levels support the notion that after a complication free vaginal delivery or Cesarean section a persisting maternal inflammatory response would be present.
4. Systemic inflammation generally occurring with routine gynecological interventions is finished three days after the surgery.
5. Three days after delivery hepcidin levels are increased. This increase is more pronounced in women having a Cesarean section.
6. Three days after gynecological interventions hepcidin levels are increased, irrespectively whether the surgery is done under local or general anesthesia.

Summary

In the first part of my PhD work I evaluated the possible contribution of some factors to the trend of the dramatically increasing rate of cesarean sections in Hungary. Based on data collected about deliveries that occurred in Uzsoki Hospital and other 11 hospitals during the last decade I demonstrated that the increasing average age of pregnant women is responsible alone for the 15% of increase. Another factor is the experience of obstetricians: those with more years after obtaining their medical degree are more ready to perform a cesarean section. In addition, the cyclic nature of cesarean rates suggests a significant contribution of planned elective interventions.

In the second part of my work I investigated the alterations of cytokine levels and iron homeostasis on the third day after a complication free delivery, cesarean section or surgical intervention. Although this time point is of particular clinical importance when one should decide whether or not the patient to be discharged in a few days, there are paucity of literary data collected at this time point.

We enrolled 40 pregnant women at delivery and 17 patients undergoing gynecological interventions. No clinical or laboratory sign or symptom was present in any of them. We measured the levels of 17 different pro- and anti-inflammatory cytokines in blood samples taken at the intervention / delivery and 3 days later. Our results indicated that none of the investigated cytokines increased in any group of subjects. No difference was observed in populations with different ways of delivery or with different types of surgery. This finding suggests that the systemic acute phase reaction is practically ceased on the 3rd postdelivery / postoperative day in patients without complication. These data may help to establish healthy reference cytokine values; cytokine values exceeding this range may warn for systemic inflammation.

For the first time we have demonstrated that the levels hepcidin, a recently described iron-decreasing polypeptide are increased by the 3rd day after delivery / intervention. However, hepcidin levels did not correlate with any of the parameters of iron homeostasis, therefore its contribution to acute decrease of iron levels observed at this time is still unclear.

List of publications related to the Theses

Gyarmati B, Bekő G, Szalay B, Cseh Á, Vásárhelyi B, Treszl A. Maternal cytokine balance on 3rd postpartum day is not affected by the mode of delivery after healthy pregnancies. *Journal of International Medical Research*, 2010 Jan-Feb;38(1):208-13. IF: 0,82

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