Aus der Klinik für Geburtsmedizin
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Perinatal medicine in transition
Three challenges in perinatal medicine: advanced maternal
age, rupture of membranes before viability and termination of
pregnancy in case of maternal-fetal complications

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Content:

1. Abstract

1.1. German Abstract

Einführung

Die Perinatalmedizin befindet sich im Wandel, mit immer besserer Schwangerenvorsorge und Diagnostik und rasch voranschreitender Optimierung der neonatologischen Versorgung. Dennoch konnte die Frühgeborenenrate nicht substanziell gesenkt werden. Darüber hinaus hat sich mit dem steigenden Alter der Schwangeren und den Entwicklungen in der Reproduktionsmedizin (z. B. durch eine höhere Mehrlingsrate) das Komplikationsspektrum ebenfalls verändert.

Material und Methoden

Seit Januar 2000 wurden Daten von Patientinnen der Charité Universitätsmedizin Berlin, Campus Charité Mitte und Campus Virchow Klinikum erhoben. Es wurde eine retrospektive Analyse der geburtsmedizinischen und neonatologischen Patientenakten, Laborbefunden und Bildgebungen durchgeführt. Die Datenbank des Bundesamtes für Statistik und eine ausführliche Literaturrecherche wurden verwendet.
Aus den erhobenen Daten wurden drei individuelle Veröffentlichungen erstellt.

Ergebnisse

"Pregnancies in Women Aged 45 Years and Older – a 10-Year Retrospective Analysis in Berlin":
Ein maternales Alter >45 Jahre birgt ein signifikant erhöhtes Risiko für Schwangerschaftskomplikationen: Gestationsdiabetes, Präeklampsie, Frühgeburt und Sectio-Raten.

"Perinatal outcomes after previable preterm premature rupture of membranes before 24 weeks of gestation":
Feten aus einer Schwangerschaft mit einem Blasensprung vor der 24 Schwangerschaftswoche haben insgesamt 51% Überlebenschance, und eine 80% Überlebenschance nach Lebendgeburt. Das neonatale Outcome hängt vom Schwangerschaftsalter bei Geburt und nicht vom Schwangerschaftsalter bei Blasensprung ab.

"A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center":

Die Gründe für einen medizinisch indizierten Schwangerschaftsabbruch nach der 14. Schwangerschaftswoche sind vielfältig und kommen in jedem maternalen Alter und in jeder Schwangerschaftswoche vor.

Diskussion

Das erhöhte Risiko für Schwangere >45 Jahren ist nicht nur Teil der Beratung in der Reproduktionsmedizin, sondern auch ein Leitfaden für den behandelnden Arzt, auf welche potentiellen Komplikationen vermehrt geachtet werden muss.

Blasensprünge vor Erreichen der Lebensfähigkeit bleiben eine medizinische und ethische Herausforderung. Eine Arbeit, die sich mit dem Outcome betroffener Schwangerschaften beschäftigt hat kann als Beratungsgrundlage für betroffene paar dienen.

Es ist denkbar, dass die Anzahl der Schwangerschaftsbeendigungen nach Erreichen der Lebensfähigkeit durch ein differenziertes und allgemein zugängliches Ultraschallscreening verringert werden könnten. Die Beratung der betroffenen Patientinnen kann durch eine Übersichtsarbeit erleichtert werden.

Um die Beratungssituation zu verbessern, werden repräsentative Daten benötigt. Da die Entscheidungen, die in der Geburtsmedizin von Arzt und Patient getroffen werden müssen, oft sehr individuell sind und auch über das Leben des ungeborenen Kindes entscheiden können die hier präsentierten Daten nicht randomisiert und prospektiv erhoben werden.

1.2. <u>English Abstract</u>

Background

Perinatal medicine is changing rapidly. On one hand neonatal care is advancing, as well as prenatal care diagnostics. On the other hand, reproductive medicine increases the rate of high-risk pregnancies and the accompanying complications.

As a result, preterm birth rates are not decreasing, even in the western world.

Materials and methods

The patient files from the Department of Obstetrics, Charité Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow-Klinikum since January 2000 were collected.

A retrospective analysis was performed from perinatal, obstetric and neonatal files, including laboratory and imaging results. Data was also pulled from the German Federal Statistical Office and a thorough research of the literature was performed.

Three individual papers were created from the results.

Results

"Pregnancies in Women Aged 45 Years and Older – a 10-Year Retrospective Analysis in Berlin":

Maternal age >45 years poses a significantly increased risk of pregnancy complications e.g. gestational diabetes, preeclampsia and preterm delivery; and an increased rate of cesarean sections.

"Perinatal outcomes after previable preterm premature rupture of membranes before 24 weeks of gestation":

The fetal survival rate is approx. 51% overall. In case of a live birth, the neonatal survival rate is approx. 80%. The neonatal outcome depends on the gestational age at delivery, not on the gestational age at rupture of membranes.

"A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center":

The medical reasons for a termination of pregnancy after the 14th week of gestation are multifarious and not depending on gestational or maternal age.

Discussion

The patient has to be informed of the increased risk for pregnant women >45 years of age, already when considering reproductive medicine. The knowledge of the most important risk factors during pregnancy can be a guideline for the treating physicians during the pregnancy and around birth.

Rupture of membranes before viability will continue to be a medical and ethical challenge. A retrospective outline of the outcomes can help couples and physicians in the decision-making process.

The reduction of a portion of terminations of pregnancy beyond viability may only be achieved by a comprehensive and accessible ultrasound screening for all patients.

A review of a representable case number can ease the counseling and decision-making for physicians and patients.

In order to support the quality of the consultation and patient information representable data is needed.

Patients and physicians have to make individual decisions not only affecting the parents' life but also the unborn child's'. These decisions and outcomes cannot be forced into a randomized prospective trial, so often the supportive data can only be excerpted from retrospective evaluations.

2. <u>Introduction</u>

From the advances in reproductive medicine, invasive/non-invasive screening and intrauterine treatment to neonatal care, perinatal medicine is a wide and fast developing field.

With the implementation of antenatal corticosteroids for fetal maturation came a substantial reduction of postnatal mortality, neonatal respiratory distress syndrome and intraventricular hemorrhage(1). In combination with postnatal surfactant therapy, antenatal steroids led to a reduced viability cut-off.

The limits of viability are currently considered to be at 24+0 weeks of gestation in Germany, 22+0 to 23+6 weeks being a grey area in which the treating physician and the parents can opt for fetal lung maturation (2). Neonates born after viability receive full up-to-date intensive care treatment and if necessary resuscitation.

Even though the medical possibilities in perinatal medicine are expanding, so are the challenges.

Through reproductive assistance the maternal age is continuously rising (see Table 1) (3).

Maternal age (n)	2012	2013	2014	2015	2016	2017
Live born	673 544	682 069	714 927	737 575	792 131	784 884
< 18 years	2 920	2 823	3 071	3 041	3 415	2 842
18 – 40	635 983	645 043	676 297	698 243	748 967	741 511
≥ 40	34 641	34 203	35 559	36 291	39 591	40 437

Table 1: German live births grouped by maternal age. Adapted from the official website of the German Federal Statistical Office(4).

Maternal medical conditions, which used to be a contraindication to pregnancy are now mere obstacles: cervical cancer (5), renal transplants (6) or cardiac disease (7).

However, with great possibilities come great challenges. Maternal age, maternal diseases, fetal malformations and pregnancy complications bring up medical and ethical treatment decisions.
Because of social, financial and medical circumstances, ethical, and religious believes the treatment in perinatal medicine is always an individual decision.

The research presented in this thesis is derived from retrospective analyses of large patient cohorts at the Charité Universitätsmedizin Berlin, Department of Obstetrics. Three challenges were discussed in three separate papers: Advanced maternal age beyond 45 years, preterm rupture of membranes before viability and the medical background of terminations of pregnancy after 14 weeks of gestation.

3. Materials and Methods

Data sources
The patient cohorts were collected from the Charité Universitätsmedizin Berlin, Campus Charité Mitte and Campus Virchow-Klinikum. The electronic databases ViewPoint (GE General Electric Healthcare, Chicago, USA) and SAP (Systems, Applications & Products in Data Processing, Walldorf, Germany) were used to identify patients, and excerpt obstetric and neonatal charts, laboratory results and ultrasound records. We also reviewed the patient hard copy files if the data was not sufficiently digitalized.

Women with a maternal age ≥ 45 years were collected from both campuses between January 2004 and May 2015. Women aged 29, who had given birth within the same period, were randomly selected in a 1:1 ratio.

The patient contingent with previable preterm premature rupture of membranes (pPPROM) was collected from Campus Charité Mitte records from January 2010 to March 2016.

Women who opted for termination of pregnancy in Campus Charité Mitte and Campus Virchow-Klinikum, were identified between January 2000 and December 2017. The German national birth and termination data, without medical causes, was extracted from the official website of the German Federal Statistical Office (8).

Study design

Maternal-fetal outcomes of pregnancies in advanced maternal age or complicated by pPPROM were analyzed (9, 10). The maternal-fetal medical diagnoses of pregnancy terminations after 14 weeks of gestation were examined (11).

Ethic approval from the responsible independent IRB (Institutional Review Board, Ethics Committee) was obtained for the analysis of pPPROM and TOP cases separately.

Statistics

After data transfer in anonymous form to MS Excel (Microsoft Corporation, Redmond, USA), analysis was performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism V8 software (San Diego, CA, USA). A p value of < 0.05 was considered statistically significant.

4. <u>Results</u>

The result section was sorted by publication to increase clarity.

4.1.   Paper: "Pregnancies in Women Aged 45 Years and Older – a 10-Year Retrospective Analysis in Berlin" (12)

In the period study period, 186 patients were aged 45 years and older at the time of delivery. The average amount of patients over 45 years per year increased from four in 2004, with an average of 12 cases between the years 2004-2009, to an average of 19 women per year until 2015.

The maternal age, gravidity/parity and comorbidities for both study groups can be extracted from Table 2.

The outcome data was grouped by fertility treatment, delivery mode, gestational age at preterm delivery and maternal-fetal pathological outcomes (see Table 3). Only 34% of the patients reported to have used reproductive medicine measures, of which one third included egg donation.

Of importance are the statistically significant differences between the study and control group in cesarean section rate (59% in the study group vs. 29% in the control group, $p<0.001$), the occurrence of pregnancy complications such as preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome (17 vs 5 cases, $p=0.022$) and the incidence of gestational diabetes (23 vs. 4 cases, $p=0.001$).

No differences were shown for intrauterine growth restriction (IUGR), placental abruption or intrauterine fetal death (IUFD).

Multiple gestations occurred in 16% (n=30) of the study group, of which 80% were derived from IVF treatment. These included two triplet, one quadruplet and two triplet pregnancies, which were selectively reduced to twin pregnancies.

In the control group 5% of the pregnancies were multiple gestations, 40% derived of in-vitro fertilization (IVF) treatment.

	Study group (n = 186)	Control group (n = 186)	
Maternal age (years, range)	46.56 ± 2.66 (45–65)	29	$p < 0.001$
Gravidity (range)	4.2 ± 2.6 (1–16)	2.3 ± 1.5 (1–8)	$p < 0.001$
Parity (range)	2.8 ± 2.1 (0–13)	1.8 ± 1.1 (0–7)	$p < 0.001$
Co-morbidities			
▪ Hypertension	13	0	$p < 0.001$
▪ Enucleation of uterine fibroids	10	0	$p < 0.001$
▪ Depression	2	1	$p = 1.000$
▪ Breast cancer	2	0	$p = 0.498$
▪ HIV	2	0	$p = 0.498$
▪ Hepatitis B	4	1	$p = 0.371$
▪ Epilepsy	2	1	$p = 1.000$
▪ Cervical conization	4	3	$p = 1.000$
▪ Cardiac arrhythmias	3	3	$p = 1.000$
Cesarean section in a previous pregnancy	33 (18%)	20 (11%)	$p = 0.074$

Descriptive statistics of the patient characteristics are given as mean ± standard deviation for continuous variables and as frequencies (%) for categorical data. N = 186 subjects aged ≥ 45 years were compared to a control group of women aged 29 years at the time of giving birth. Continuous variables were compared with the two-tailed Student's t-test. Frequencies were compared using the χ^2-test or Fisher's exact test as appropriate. The level of significance was two-tailed at 0.05.

Table 2, Overview maternal characteristics and co-morbidities. Copied from Table 1 "Patient characteristics and co-morbidities for the study and control groups" R. Rendtorff et al. (13)

	Study group (n = 186)	Control group (n = 186)	
Gestational age at delivery	37 ± 4	39 ± 3	$p < 0.001$
Fertility treatment			
▪ IVF/ICSI	63 (34%)	6 (3%)	$p < 0.001$
▪ Egg donation	20 (32%)	0	$p < 0.001$
Delivery mode			
▪ Spontaneous	75 (40%)	117[#] (62%)	$p < 0.001$
▪ Cesarean section	109 (59%)	55 (29%)	$p < 0.001$
▪ Vacuum extraction	2 (1%)	12[#] (6%)	$p = 0.006$
▪ Forceps	0	3 (3%)	$p = 0.082$
Preterm delivery	52 (28%)	20 (11%)	$p < 0.001$
▪ <24 + 0 weeks	2	1	
▪ 24 + 0–33 + 6 weeks	30	8	
▪ 34 + 0–36 + 6 weeks	20	11	
Premature rupture of membranes	18	3	$p = 0.001$
Multiple pregnancy	30 (16%)	9 (5%)	$p < 0.001$
▪ After IVF treatment	24/30 (80%)	4/9 (40%)	$p = 0.085$
Fetal birth weight	2875 ± 908 g	3178 ± 740 g	$p = 0.001$
Blood loss	459 ± 246 ml	391 ± 258 ml	$p = 0.558$
Preeclampsia	14	5	$p = 0.022$
Gestational diabetes	23	4	$p = 0.001$
HELLP syndrome	3	0	$p = 0.248$
IUGR	5	3	$p = 0.724$

Descriptive statistics of the patient characteristics and outcome variables are given as mean ± standard deviation for continuous variables and as frequencies (%) for categorical data. Continuous variables were compared with the two-tailed Student's t-test. Frequencies were compared using the χ^2-test or Fisher's exact test as appropriate. The level of significance was two-tailed at 0.05.

[#] A total of n = 187 births because in a twin pregnancy a vacuum extraction was performed for one twin with spontaneous delivery of the second twin.

Table 3: Fetomaternal outcome. Copied from Table 2: Outcome variables such as delivery mode and fetomaternal complications for the study and control groups (14).

4.2. Paper: "Perinatal outcomes after previable preterm premature rupture of membranes before 24 weeks of gestation" (15)

73 cases of pPPROM were collected and the patients opting for expectant management (72.6%, n=53) analyzed (Table 3).

27.4% (n=20) patients opted for termination of pregnancy and were excluded from further analysis.

The gestational age at pPPROM was not predictive for the outcome of expectant management, also not when grouped into gestational ages (GA) < 18 weeks, 18-22 weeks and 22-24 weeks. Neither were the inflammatory markers at admission. Neonatal outcome of the 44 live born infants could not be predicted by length of latency period or maternal inflammatory markers at the time of delivery, even though signs of intra-amniotic infection (IAI) are commonly the indication for immediate delivery.

	Proceeding to live birth	Spontaneous miscarriage
Weeks GA at pPPROM, median (range)	21+4 (15+0 - 23+5)	18+2 (16+0 - 22+4)
Singleton gestations, median (range)	21+4 (15+0 to 23+5)	18+2 (16+0 to 22+4)
Multiple gestations, median (range)	22+2 (16+0 to 23+3)	19+5 (15+6 to 21+6)
Weeks GA at end of pregnancy/delivery, median (range)	25+3 (22+0 to 34+0)	20+5 (16+1 to 24+2)
Singleton gestations, median (range)	26+0 (22+6 to 32+6)	20+5 (17+1 to 24+2)
Multiple gestations, median (range)	27+5 (22+4 to 34+0)	20+6 (17+1 to 22+2)
Latency period, median (range)	38 (1–126)	2.5 (0–40)
Singleton gestations, median (range)	37 (1–114)	7 (0–40)
Multiple gestations, median (range)	38 (2–126)	1.5 (0–31)

Table 3: Comparison of GA at pPPROM and birth, adapted from Kiver at al. Table 2 (16)

The overall survival rate (without TOP) was 51.5%, the neonatal survival rate was 79.5%. The neonatal survival was statistically significantly dependent on the gestational age at delivery (p=0.0495).

The most common neonatal sequelae respiratory distress syndrome (100%), connatal infection (56.8%; n = 25) and pulmonary hypoplasia (29.5%; n = 13).

Intact survival defined as discharge without: oxygen therapy, intraventricular hemorrhage (IVH) Grade III° or IV°, retinopathy of prematurity (ROP) requiring surgery, or necrotizing enterocolitis (NEC) was 45.5%. Connatal infection was not predictive of intact survival.

4.3. Paper: "A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center"

In Germany pregnancy terminations are decreasing, but terminations after 14 weeks, and more notably after viability (24+0 weeks of gestation) are increasing since 2010. The distribution of the 1746 TOPs at the study center is fluctuating. See Table 4. The main medical causes of TOP were divided into 23 groups and details are presented in Table 5, the incidences for diagnoses within the groups are presented in the paper (17). Main cause of TOP was trisomy 21 (15.5%, n=270), followed by neurological malformations (11.1%, n=193) and malformations of the heart and the great vessels (7.7%, n=135).

| Year | Germany | | | | | | Study center | | |
| | Live births | Total TOPs | TOP >14 weeks | | TOP >24 weeks | | TOP >14 weeks | TOP >24 | |
	N	N	N	(%)	N	(%)	N	N	(%)
2000	766,999	134,609	2.097	1.6	154	7.3	15	8	53.3
2001	734,475	134,964	2.081	1.5	177	8.5	75	21	28.0
2002	719,250	130,387	2.049	1.6	188	9.2	115	30	26.1
2003	706,721	128,030	2.261	1.8	217	9.6	125	27	21.6
2004	705,622	129,650	2.205	1.7	200	9.1	141	39	27.7
2005	685,795	124,023	2.220	1.8	171	7.7	138	25	18.1
2006	672,724	119,710	2.320	1.9	183	7.9	123	18	14.6
2007	684,862	116,871	2.302	2.0	229	9.9	98	15	15.3
2008	682,514	114,484	2.331	2.0	231	9.9	79	10	12.7
2009	665,126	110,694	2.456	2.2	237	9.6	118	28	23.7
2010	677,947	110,431	2.579	2.3	462	10.9	82	27	32.9
2011	662,685	108,867	2.891	2.7	480	16.6	127	29	22.8
2012	673,544	106,815	2.746	2.6	447	16.3	87	22	25.3
2013	682,069	102,802	2.800	2.7	562	20.1	104	33	31.7
2014	714,927	99,715	2.780	2.8	584	21.0	75	26	34.7
2015	737,575	99,237	2.795	2.8	634	22.7	70	18	25.7
2016	792,141	98,721	2.829	2.9	630	22.3	98	32	32.7
2017	784,901	101,209	2.713	2.7	654	24.1	76	17	22.4
Total	12,749,877	2,071,219	44.455	-	6.440	-	1.746	425	-
Mean	708,327	115,068	2.470	2.2	357.8	13.9	97.0	23.6	26.1
SD		12,699	295	0.5	191.8	6.1	31.0	8.2	9.3

Table 4: Overview data Germany and study center year 2000-2017. Adapted from Kiver et al. Table 1 (18).

The mean gestational age, as well as the percentage of TOPs after viability are not evenly distributed between the groups. Diagnoses like Turner syndrome (mean GA at TOP 16.2 weeks) are commonly diagnosed early, while diagnoses like neurological malformations become recognizable later in pregnancy (mean GA at TOP 24.2 weeks). Maternal data was evaluated by group and neither gravidity, parity nor maternal age showed predictive value.

		Cases (n)	Subgroup (%)	Total (%)	Mean GA (week)	>24 weeks (n)	>24 weeks (%)
Genetic causes							
1	Trisomy 21	270	49.36	15.46	19.6	49	18.5
2	Trisomy 18	83	15.17	4.75	20.3	16	19.3
3	Trisomy 13	42	7.68	2.41	20.1	11	26.8
4	Turner syndrome	26	4.75	1.49	16.2	0	0
5	Syndromes with specific mutations	74	13.53	4.24	20.8	18	24.3
6	Genetic mutations	52	9.51	2.98	20.8	11	21.2
Single organ malformations							
7	Neurological malformations	193	24.62	11.05	24.2	100	51.8
8	Neural tube malformations	122	15.56	6.99	22.8	40	32.8
9	Anencephalus	38	4.85	2.18	18.8	5	13.2
10	Heart-/vessel malformations	135	17.22	7.73	21.2	29	21.5
11	Musculoskeletal malformations	96	12.24	5.50	20.6	22	22.9
12	Renal malformations	90	11.48	5.15	21.8	22	24.4
13	Abdominal wall malformations	59	7.53	3.38	18.5	7	11.9
14	Urogenital malformations	26	3.32	1.49	19.4	0	0
15	Special cases	25	3.19	1.43	24.2	14	56
Multiple organ malformations							
16	Complex abnormalities	119	34.29	6.82	21.7	37	31.1
17	Premature rupture of membranes	115	33.14	6.59	19.6	4	3.5
18	IUGR	43	12.39	2.46	23.4	18	41.2
19	Hydrops fetalis	28	8.07	1.60	19.1	4	14.3
20	Connatal infection	19	5.48	1.09	23.6	10	52.6
21	Syndromes w/o spec. mutations	12	3.46	0.69	19.9	1	7.7
22	Monochorial gemini	11	3.17	0.63	21.3	3	27.3
Maternal							
23	Maternal health	68	100.00	3.89	18.5	5	7.4
Total		**1746**		100.00			

Table 5: Grouped diagnosis and prevalence of TOPs at the study center. Adapted from Kiver et al. Table 2+Table 3 (19)

5. <u>Discussion</u>

Reproductive medicine gives many women the opportunity have children later in life. Nevertheless, advanced age poses certain risks for the mother and the unborn child.

In our study group only one third of the patients stated that the pregnancy was the result of reproductive medicine, and of these only 32% reported egg donation. These results are most likely underreported. Spandorfer at al. reported a study with 288 IVF cycles in women over 44: "An overall pregnancy rate of 21.1% (34/161) per retrieval was found. Of these, 85.3% (29/34) experienced a pregnancy loss. The overall delivery rate was 3.1% (5/161) per retrieval." (20).

In populations without contraception and highly multiparous women, studies showed an infertility rate of around 87% after the age of 45 (21-23). Considering these numbers a spontaneous pregnancy rate of 60% seems rather unlikely.

Egg donation and the transfer of more than three embryos is illegal in Germany(24). However, IVF is also a social taboo topic due to the socially perceived time deadlines, the financial burden (health insurance covers only under very limited circumstances only a fraction of the costs) and the high rate of IVF failure.

Nevertheless, not only the challenges of reproductive medicine but also the risks for the resulting pregnancy and birth are an important factor when first discussing treatment options with the prospective parents. Incidences of essential hypertension and insulin resistance are increasing in middle age. The American diabetes association recommends blood glucose level screenings after 45, some suggest it should be even younger(23). Thus increased is the rate of gestational diabetes in our study.

Many factors contribute to the increased risk of preterm birth in our study group. Multiple gestations are in itself a risk factor for preterm birth, PROM and low birthweight. Gestational diabetes and an increased risk of preeclampsia and HELLP syndrome are risk factors for preterm birth and low birth weight.

It is hypothesized that decreased myometrial contractility is the cause of the increased risk of secondary cesarean sections in advanced maternal age pregnancies(25). In our study the rate of elective cesarean sections did not differ (49 vs. 41%) but the rate of secondary cesarean sections was significantly higher in the study group vs the control group.

Physicians taking care of a patient with advanced maternal age need to be aware of the risks, and act preventively and with intensified care.

Prospective parents should be aware of the incidence of a pregnancy in advanced age and the associated risks. But more importantly should educational work about this topic be offered to women in their thirties, to enable them to make informed life choices.

Premature membrane rupture especially before viability and the neonatal outcome has to be discussed in this context.

In our presented study, the overall survival rate in our study was roughly 50%, not counting the pregnancies that were terminated.

Of the life born infants 80% survived, 45% without any serious sequelae associated with prematurity.

So far we could not find markers by which we can identify patients with a favorable outcome after pPPROM. Our study showed that outcome did not depend on time of pPPROM or latency period, but on the gestational age at birth.

In our clinical experience, delivery becomes necessary due to IAI (intra-amniotic infection) promoting labor, but when infection will set in and ascend, cannot be estimated at the time of membrane rupture.

Neonatal outcome and the incidence of intact survival are lacking in predictability, which makes the counseling and decision making process difficult.

In the worst case physical and mental disability are the result of extreme prematurity (26). The impact of prematurity on long-term social-economic status, level of education attained and marital status of the child (6) also factors in.

On the other hand, neonatal outcomes are constantly improving, following the introduction of surfactant and also due to improved neonatal care (27).

Prolonging the latency period in case of pPPROM can result in infection for the mother, and usually in a caesarean section. That any signs of infection, placental abruption or HELLP syndrome/impending eclampsia are an indication for prompt delivery to protect the mother, even if it is too early for the child is part of the initial education of the parents.

Prematurity, especially if it results in disability, increases the parent' socioeconomic load. Some numbers from a Dutch study conducted by Kusters at al. showed a higher divorce rate, financial problems and social isolation. 19 years after the preterm birth 3% of the questioned parents still felt unfavorable effects on their lives (28).

Comprehensive outcome data and risks stratification are important tools in patient counseling. Statistical data can give the patient a much needed frame of reference. Ecker et al. released an important paper for the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine with guidelines surrounding periviable birth (29). They put emphasis on the point of extensive family counseling, the individuality of each decision made surrounding periviable births and the importance of also offering TOP as an option to the patients.

The gestational age until which termination of pregnancy is legal and obtainable for every women varies from country to country. In Germany it ends with the completion of the 14th week calculated from the first day of the last period, confirmed by ultrasound and crown-rump-length.

Termination of pregnancy after this time point are a topic of controversy. Ethical considerations (including religious reasoning) as well psychological consequences for the parents as well as the physicians are much discussed.

In Germany the law states that TOP after 14 weeks of gestation are legal if the life or the well-being of the mother are in danger (§218 StGB) (3).

To add another aspect to the discussion we explored the medical reasons for TOPs after 14 weeks in our study center.

We concluded that TOPs have varying causes and that there are no determining factors like maternal age or how many children a women has given birth to that predict if a women will choose to terminate a pregnancy. This result matches previously released data (18).

When analyzing the German data on terminations of pregnancy, sorted by gestational age it becomes apparent that even though TOPs in general are decreasing in numbers, TOP after 14 weeks and especially beyond viability are constantly on the rise. In the year 2000 154 women had a TOP after viability which equals 7.4% of all TOPs after 14 weeks GA. In the year 2017 it was 654 patients amounting to 24.1% of all late terminations being performed after viability. At our study center the numbers stayed (with the exception of the year 2000) between 20-30 percent. Our interpretation is that our study center has been a center for perinatal care for many years, but our numbers have not changed substantially over the years because with increasing patient numbers, more medical centers have offered perinatal care including TOP.

Giving the patients statistical data might help the counseling and decision making process and might give the patients context for their situation.

But while examining the data another significant assertion emerged: the necessity of a TOP cannot be averted. But the timing and therefore the emotional impact on parents and physicians can be influenced. German maternity guidelines propose three sonographic examinations during the pregnancy in which gestational age, location of the pregnancy and the placenta and later the fetal growth and presentation are controlled. (20)

The maternity guidelines also offer an extended basic screening between 18-22 weeks. For a gynecologist to perform this screening he or she has to complete an online course and exam. In case of any abnormal findings, patients are referred to a specialist.

First trimester screening including nuchal translucency measurements and non-invasive blood biochemistry or a detailed organ screening around the 20th weeks of gestation are not routinely offered to patients. Especially mothers under the age of 35 are considered low risk and have to pay for any of the above mentioned testing unless the basic screening is abnormal.

Considering the increasing number of terminations after viability in Germany this measure seems to not fulfill its intended purpose. Of course not all medical conditions, like neurological malformations, are apparent in early pregnancy. Nevertheless, one has to consider the possibility that a more comprehensive screening, including nuchal translucency measurement and detailed organ screening offered to all patients might reduce the amount of TOPs after viability.

As physicians it is our duty to advise our patients, not based on personal opinion but on medical facts. In perinatal medicine it is often very problematic to present data that fit the individual situation of each patient.

The decision to continue or discontinue a pregnancy cannot be forced into a randomized prospective trial. That makes research and reliable data acquisition difficult. Only large cohorts can try to make up for the lack of prospective, randomized and double-blinded trials.

6. <u>Literature</u>

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7. Eidesstattliche Versicherung

„Ich, Verena Kiver, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: " Perinatal medicine in transition. Three challenges in perinatal medicine: advanced maternal age, rupture of membranes before viability and termination of pregnancy in case of maternal-fetal complications" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst."

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Datum 05.10.2019   Unterschrift

Anteilserklärung an den erfolgten Publikationen

Verena Kiver hatte folgenden Anteil an den folgenden Publikationen:

Verena Kiver, Vinzenz Boos. Anke Thomas, Wolfgang Henrich, Alexander Weichert, Perinatal outcomes after previable preterm premature rupture of membranes before 24 weeks of gestation, Journal of perinatal medicine, 2017

Beitrag im Einzelnen:

Themenfindung (Eigeninitiative). Datenerhebung aus SAP, Geburtenbuch und Viewpoint. Erstellen der Datensheets für die Analyse der Daten. Datenanalyse und Interpretation (in Diskussion mit den Ko-Autoren). Erstellen der Veröffentlichung und Einarbeitung aller Korrekturen der Ko-Autoren, Einreichen der Veröffentlichung.

Rosa Rendtorff, Larry Hinkson, Verena Kiver, Lisa-Antonia Dröge, Wolfgang Henrich, Pregnancies in

Women Aged 45 Years and Older – a 10-Year Retrospective Analysis in Berlin, Geburtshilfe und Frauenheilkunde, 2017

Beitrag im Einzelnen:

Mehrfache inhaltliche Korrekturen und sprachliche Korrekturen, Datenerhebung: neonatale Outcome Daten – aus SAP, welche in der endgültigen Version gestrichen wurden da die Daten nicht vollständig erhoben werden konnten (Pat. nicht mehr an der Charité weiterbehandelt), Patientinnen Akten wurden zusammen mit Fr. Rendtorff durchgesehen und die Daten in Excel Sheets eingefügt. Literaturrecherche und Einfügen in den Text im Rahmen der Korrekturen, erstellen der endgültigen Literaturliste.

Verena Kiver, Judith Altmann, Julian Kamieh-Milz, Alexander Weichert, A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center, Journal of perinatal medicine, 2019

Beitrag im Einzelnen: Themenfindung (Eigeninitiative). Datenerhebung aus SAP, Geburtenbuch und Viewpoint. Erstellen der Datensheets für die Analyse der Daten. Datenanalyse und Interpretation (in Diskussion mit den Ko-Autoren). Erstellen der Veröffentlichung und Einarbeitung aller Korrekturen der Ko-Autoren, Einreichen der Veröffentlichung.

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

8. "Pregnancies in Women Aged 45 Years and Older – a 10-Year Retrospective Analysis in Berlin"

Rendtorff R, Hinkson L, Kiver V, Dröge LA, Henrich W. Pregnancies in Women Aged 45 Years and Older - a 10-Year Retrospective Analysis in Berlin. Geburtshilfe Frauenheilkd. 2017 Mar;77(3):268-275.

DOI: 10.1055/s-0043-100105

URL: https://doi.org/10.1055/s-0043-100105

9. **"Perinatal outcomes after previable preterm premature rupture of membranes before 24 weeks of gestation"**

Kiver V, Boos V, Thomas A, Henrich W, Weichert A. Perinatal outcomes after previable preterm premature rupture of membranes before 24 weeks of gestation. J Perinat Med. 2018 Jul 26;46(5):555-565.

DOI: 10.1515/jpm-2016-0341

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10. "A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center"

Kiver, Verena I.I., Altmann, Judith, Kamhieh-Milz, Julian and Weichert, Alexander. "A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center" Journal of Perinatal Medicine, vol. 47, no. 8, 2019, pp. 847-856.

11. <u>Lebenslauf</u>

"Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht."

12. **Publikationsliste**

PUBLIKATIONSLISTE DR. VERENA KIVER, STAND 10/2019

JOURNAL PUBLIKATIONEN

Kiver V, Altmann J, Kamieh-Milz J, Weichert A, "A 17-years analysis of terminations of pregnancy ≥14 weeks of gestation in a German level 1 perinatal center", Journal of perinatal medicine. 2019;47(8):847-56.

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Karsten M, Speiser D, Hartmann C, Zeuschner N, Lippold K, Kiver V, Gocke P, Kirchberger V, Blohmer JU. "Web-Based Patient-Reported Outcomes Using the International Consortium for Health Outcome Measurement Dataset in a Major German University Hospital: Observational Study, JMIR Cancer. 2018;4(2):e11373. doi:10.2196/11373

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Impact Factor 2017: 1.558

Rendtorff R, Hinkson L, Kiver V, Dröge LA, Henrich W. "Pregnancies in Women Aged 45 Years and Older - a 10-Year Retrospective Analysis in Berlin." Geburtshilfe Frauenheilkd. 2017 Mar;77(3):268-275. doi: 10.1055/s-0043-100105.

 Impact Factor 2017: 1,291

JOURNAL PUBLIKATIONEN IM REVIEWPROZESS

Altmann J, Kiver V, Henrich W, Weichert A, "Clinical outcome of prenatally suspected cardiac rhabdomyoma of the fetus"

KONFERENZBEITRÄGE UND VORTRÄGE

Kiver V., A. Wulf-Goldenberg, C. Schweiger, P. Jurmeister, B. Brzezicha, O. Gorea, S. Burock, C. Kolberg-Liedtke, J. Hoffmann, J. Blohmer, U. Keilholz, C. Denkert. „Phenotypic and functional characteristics of patient derived murine xenograft models." (Online Abstract) Asco Annual Meeting 2019

Kiver V, Jurmeister P, (…), Keilholz U, Liedtke C, Blohmer JU, "Androgen supplementation in patient derived xenografts in androgen receptor positive breast cancer to increase engraftment and growth rate" (Poster) San Antonio Breast Cancer Symposium 2018

Kiver, V, Gambara, G, Jurmeister, P, Schweiger, C., Fuchs, K., Gorea, O., Burock, S., Liedtke, C., Karsten, M., Bangemann, N., Kußmaul, J., Hoffmann, J., Regenbrecht, C., Denkert, C., Keilholz, U., Blohmer, J. U. „Erfolgreiche Etablierung von präklinischen Brustkrebsmodellen". (Poster) DGGG Annual Meeting 2018

Kiver V, Gambara G, (…), Hoffmann J, Keilholz U, „Successful generation of patient derived xenografts and patient derived 3D cultures as preclinical models for breast cancer" (Poster) ASCO Annual Meeting 2018

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Kiver V, Boos V, Thomas A, Henrich W, Weichert A, "Pregnancy outcomes after previable preterm premature rupture of membranes" (Vortrag) 40. Dreiländertreffen der Deutschen Gesellschaft für Ultraschall in der Medizin 2016

V Kiver, A Thomas, W Henrich, A Bartens, A Weichert. "Exazerbation eines Malabsorptionssyndroms auf Basis eines Magenbypasses in der Schwangerschaft" (Poster) DGGG Annual Meeting 2016

V Kiver, A Bartens, W Henrich, A Nonnenmacher. "Supraventricular tachycardia with aberrancy, first diagnosed on the first day postpartum. A case report" (Abstract) Z Geburtshilfe Neonatol 2015; 219 - P04_8

A Kölle, V Kiver, A Weichert, W Henrich., „Persistierender nicht immunologischer Hydrops fetalis nach intrauteriner Parvovirus B19 Infektion" (Poster) DGGG Annual Meeting 2015

13. <u>Danksagung</u>