Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

The European Journal of Medical Sciences

Original article | Published 19 September 2013, doi:10.4414/smw.2013.13864

Cite this as: Swiss Med Wkly. 2013;143:w13864

Origin and outcome of multiple pregnancies in Bern, Switzerland, 1995–2006 and the current proposal of the Swiss parliament to revise the Swiss law of reproductive medicine: Switzerland quo vadis?

Dorothea Wunder[a], Eva-Maria Neurohr[b], Mohamed Faouzi[c], Martin H. Birkhäuser[d]

[a] Department of Obstetrics and Gynaecology, University Hospital CHUV, Lausanne, Switzerland

[b] Department of Internal Medicine, Kantonsspital Baden, Switzerland

[c] Department of Epidemiology, University Hospital CHUV, Lausanne, Switzerland

[d] Department of Obstetrics and Gynaecology, University Hospital Inselspital Bern, Switzerland

Summary

INTRODUCTION: Infertility treatments are a major source of the increase in multiple pregnancies (MPs).

AIMS: The aims of the present study were (1.) to investigate the origin and maternal/neonatal outcomes of MP and (2.) to review the different measures that can be adopted to reduce these serious complications.

METHODS: The study included all women with multiple births between 1 January 1995 and 31 December 2006 at the University Hospital of Bern, Switzerland. The outcomes associated with the various origins of MP (natural conception, ovarian stimulation [OS] – *in-vitro* fertilisation [IVF-ICSI]) were analysed using a multinomial logistic regression model.

An analysis of the Swiss law on reproductive medicine and its current proposed revision, as well as a literature review using Pubmed, was carried out.

RESULTS: A total of 592 MP were registered, 91% (n = 537) resulted in live births. There was significantly more neonatal/maternal morbidity in MP after OS compared with natural conception and even with the IVF-ICSI group. With a policy of elective single embryo transfer (eSET), twin rates after IVF-ICSI can be reduced to <5% and triplets to <1%.

CONCLUSIONS: After OS, more triplets are found and the outcome of MP is worse. MP is known to be associated with morbidity, mortality, and economic and social risks. To counteract these complications (1.) better training for physicians performing OS should be encouraged and (2.) the Swiss law on reproductive medicine needs to be changed, with the introduction of eSET policies. This would lead to a dramatic decrease in neonatal and maternal morbidity/mortality as well as significant cost reductions for the Swiss healthcare system.

Key words: *ovarian stimulation; infertility treatment; IVF-ICSI; intrauterine insemination; multiple pregnancies; Swiss law on reproductive medicine; elective single embryo transfer*

Introduction

In recent decades, the number of twins and triplets has been continually rising with a simultaneously decreasing birth rate. In Switzerland, the incidence of twin deliveries increased from 127.6 per 10,000 (1.3% of all live births) in 1996 to 160 per 10,000 (1.6% of all live births) in 2004. This is equivalent to a rise of 25% in only 8 years. In contrast to this, the number of live births per 1,000 inhabitants in the same study period (1995 to 2006), declined from 11.7 to 9.8 [1]. But these observations are not specific to Switzerland. A summary of studies from different European countries and North America show that, for example, in France twin deliveries increased between 1972 and 1998 from 8.9 per 1,000 deliveries to 14.4 which is equivalent to an increase of 62% [2]. In contrast to the continually rising occurrence of twins, the rise in triplet deliveries is phenomenal. Again in France, in addition to the 62% increase in twins, a rise of 310% for triplets (0.09 per 1,000 live births in 1972 and 0.33 in 1989) was observed [2].

Multiple pregnancies (MP) have serious adverse effects on neonatal and maternal health, such as increased morbidity (physically, psychologically) and mortality as well as social and economic consequences. Maternal mortality rates rise two to three fold in women with multiple pregnancies [3]. In some studies, the risk of depression even several years after delivery is very high [2, 4–6]. There is also a high divorce rate among multiple birth parents [7]. Furthermore, the economic consequences of multiple births due to infertility treatments are substantial: [8]. Nearly all triplets are

born with a birth weight below 2,500 g and the risk of having a birth weight under 1,500 g increases with twin and triplet pregnancies [2]. Low birth weight is associated with increased adult incidence of cardiovascular disease and associated disorders such as hypertension and diabetes mellitus. The future costs of these complications also should not be neglected. Moreover, premature birth and low birth weight are associated with a lower rate of reproduction in adulthood [9–11]. The risk of cerebral palsy in MP is also increased [12] and the foetal anomaly rate (minor and major) is known to be significantly higher in twin compared to singleton pregnancies [13, 14]. Moreover, not only morbidity but mortality is also substantially increased (intrauterine death, neonatal mortality, infant mortality) [2]. The most important causal factor for the rise in multiples is infertility treatment [2]. Infertility affects 10–15% of couples and nowadays, 1% to 4% of the newborn are conceived due to assisted reproductive technologies (ART) [14]. Two different forms of infertility treatments are specified: ovarian stimulation with/without intrauterine insemination (OS) and *in-vitro* fertilisation (IVF) – intracytoplasmic sperm injection (ICSI).

OS has already been in use since the seventies. The most frequently used therapies to enhance oocyte maturation are anti-oestrogen clomifene and/or gonadotrophins. However, due to inappropriate application of these treatments, quadruplets and quintuplets were already occurring in the seventies [1]. In the USA, there are approximately 12% twin pregnancies after IVF–ICSI, 21% after ovarian stimulation (with/without IUI) and 67% after natural conception [15]. Unfortunately, in most countries (including Switzerland), a national register exists for IVF-ICSI treatments only, but not for OS. Consequently, precise outcomes of these therapies are unknown.

In Switzerland, IVF-ICSI treatments as well as sperm donation are regulated by the Swiss Law of Reproductive Medicine [16]. Embryo cryopreservation is forbidden; only fertilised oocytes in the pronuclear stage can be cryopreserved. Up to three embryos can be transferred according to the Swiss law. A change of certain articles of the Swiss law is currently under discussion.

The aims of the present study were (1.) to investigate the origin and the maternal/neonatal outcomes of MP in the different groups and (2.) to review the different measures that can be adopted to reduce these serious complications of OS and IVF-ICSI treatments.

Materials and methods

Study design and study population

This is a retrospective cohort study that was approved by the local ethics committee. All registered multiple deliveries between 1 January 1995 and 31 December 2006 at the University Hospital Bern, Department of Obstetrics, were included.

Methods

Data were collected exclusively at the University Hospital Bern, Department of Obstetrics. A total of 592 MP were registered during the study period. Ninety one percent were

Table 1: Characteristics of the mothers and maternal outcome according to the different modes of conception.

Factors	Natural conception (NC)	Ovarian stimulation (OS)	IVF-ICSI (IVF)	OS vs NC RRR CI (95%)	VF vs NC RRR CI (95%)
Mother General Characteristics					
Number of patients, n (%) Total n = 537 (100%)	391 (72.8)	60 (11.2)	86 (16)		
Age, mean (SD)	30.8 (4.8)	30.7 (5)	32.8 (3.9)	0.99 [0.93–1.05]	1.1 [1.04–1.16]
BMI, mean (SD)	23.2 (4.35)	24.86 (6.56)	22.73 (3.53)	1.07 [1.01–1.13]	0.97 [0.91–1.04]
Multiparity (≥2), n (%)	232 (61.5)	22 (40)	31 (38.3)	2.4 [1.35–4.28]	2.58 [1.58–4.23]
Maternal outcomes during pregnancy					
Mean gestational age at delivery (wk), mean (SD)	33.59 (3.6)	31.9 (4.3)	33.04 (4)	0.89 [0.83–0.96]	0.96 [0.90–1.02]
Gestational diabetes, n (%)	9 (2.3)	2 (3.4)	5 (5.8)	1.49 [0.31–7.07]	2.62 [0.86–8.02]
Arterial hypertension, pre-eclampsia, n (%)	44 (11.3)	7 (11.9)	11 (12.8)	1.06 [0.45–2.48]	1.16 [0.57–2.34]
Vaginal bleeding / placenta praevia, n (%)	49 (12.5)	13 (22.0)	17 (19.8)	1.97 [0.99–3.91]	1.71 [0.93–3.16]
Preterm labour, premature rupture of membranes, n (%)	257 (65.7)	45 (76.3)	58 (67.4)	1.68 [0.88–3.16]	1.08 [0.66–1.78]
Intrauterine growth restriction, n (%)	59 (15.1)	8 (13.6)	6 (7)	0.88 [0.39–1.95]	0.42 [0.18–1.01]
Intrauterine death, n (%)	15 (3.8)	3 (5.1)	5 (5.8)	1.34 [0.37–4.79]	1.54 [0.54–4.38]
Amnion infection syndrome, n (%)	29 (7.4)	16 (27.1)	10 (11.6)	4.64 [2.34–9.24]	1.64 [0.77–3.51]
Transfusion syndrome, n (%)	34 (8.7)	3 (5.1)	2 (2.3)	0.56 [0.16–1.89]	0.25 [0.06–1.06]
Cerclage, n (%)	9 (2.3)	1 (1.7)	1 (1.2)	0.73 [0.09–5.88]	0.49 [0.06–3.99]
Antibiotic treatment during pregnancy, n (%)	109 (27.9)	17 (28.8)	33 (38.4)	1.05 [0.57–1.92]	1.61 [0.99–2.62]
Duration of hospitalisation (days), mean (SD)	13.6 (11.5)	16.4 (12.7)	15.5 (12.8)	1.02 [0.99–1.04]	1.01 [0.99–1.03]
Caesarean section, n (%)	303 (77.9)	48 (82.8)	70 (82.4)	1.36 [0.66–2.80]	1.32 [0.72–2.43]

BMI = body mass index; CI = confidence interval; RRR = relative ride ratio SD = standard deviation

twins, 8.4% triplets and 0.6% quadruplets. All MP with live births (91%, n = 537), more precisely 489 twin-, 45 triplet- and 3 quadruplet-pregnancies, were included in the analysis. Medical data were collected from patients' notes. Since the mode of conception was not always noted in the medical records, couples were contacted by letter and requested to complete a questionnaire (mode of conception, type of infertility treatment undertaken, if any embryo reduction had been carried out or not).

The recorded data included maternal age, gestation and parity, pre-existent maternal diseases (diabetes, hypertonia, renal diseases, etc.), history of infertility treatments/embryo reductions, pregnancy complications (past and present), medication intake and toxic agents, mode of delivery, neonatal data with possible postnatal disease and therapies.

An analysis of the Swiss law on reproductive medicine and the proposal of the current revision as well as a literature review using Pubmed was carried out.

Statistical analysis

The statistical data analysis was performed using STATA 12.1 (College Station, Texas 77845 USA). Continuous variables were summarised as mean (SD) and as number (percentage) for categorical data. Comparison of the group "IVF-ICSI" and the group "OS" with the reference group "natural conception" was performed using a multinomial logistic regression analysis. A univariate analysis was done to assess the association of maternal/neonatal factors to the outcome. Significant predictors at the level of 20% were used in a backward procedure to fit a multivariate model.

Results

Characteristics of the mothers and maternal outcome according to the different modes of conception

These are depicted in table 1.

Compared with women in the natural conception group, maternal age was significantly higher only in women undergoing IVF-ICSI. Interestingly, BMI was significantly higher in the OS than in the natural conception group. In addition, parity was significantly different between the groups: nulliparity was more common in the OS and IVF-ICSI treatment groups. It should be noted that, compared with the natural conception group, gestational age was significantly lower and amniotic infection syndrome significantly higher only in the OS, but not in the IVF-ICSI group. No significant differences were detected between the two groups for all the other pathologies listed in table 1.

Neonatal outcome according to the different modes of conception

Details are illustrated in table 2.

The number of children was significantly higher after conception by infertility treatments compared with natural conception.

Table 2: Neonatal outcome according to the different modes of conception.

Neonatal outcome	Natural conception (NC)	Ovarian stimulation (OS)	IVF-ICSI (IVF)	OS vs NC RRR CI (95%)	IVF vs NC RRR CI (95%)
Number of pregn. n (%):	391 (100)	60 (100)	86 (100)		
Twins . n (%)	374 (95.6)	44 (73.3)	71(82.6)		
Triplets . n (%)	16 (4.1)	15 (25)	14 (16.3)		
Quadruplets . n (%)	1 (0.3)	1 (1.7)	1 (1.1)	6.6 [3.3–13.4]	4.2 [2.1–8.4]
Mean birth weight (g), mean (SD)	1890 (67)	1540 (71)	1780 (67)	0.93 [0.89–0.96]	0.98 [0.94–1.01]
Postnatal death, n (%):					
Of 1 child	22 (5.6)	1 (1.7)	5 (5.8)		
Of 2 children	5 (1.3)	3 (5)	3 (3.5)		
Of 3 children	0 (0)	3 (5)	0 (0)	2.11 [1.29–3.45]	1.34 [0.77–2.34]
Apgar scores at 5 min, mean (SD)	8.1 (1.6)	8.1 (1.7)	(7.8) (1.8)	1.01 [0.85–1.21]	0.9 [0.79–1.03]
Syndrome of hyaline membranes, n (%):					
In 1 child	84 (21.5)	9 (15)	20(23.3)		
In 2 children	143 (36.6)	23 (38.3)	19 (22.1)		
In 3 children	5 (1.3)	5 (8.3)	8 (9.3)		
In 4 children	1 (0.3)	0 (0)	1 (1.2)	1.20 [0.91–1.59]	1.01 [0.79–1.28]
Cerebral haemorrhage					
In 1 child, n (%)	26 (6.7)	4 (6.7)	5 (5.8)		
In 2 children, n (%)	2 (0.5)	2 (3.3)	0 (0)	1.64 (0.78–3.45)	0.78 (0.31–1.92)
Retinopathy, n (%):					
In 1 child	10 (2.6)	2 (3.3)	1(1.2)		
In 2 children	3 (0.8)	0 (0)	1(1.2)	0.85 [0.24–3.8]	0.89 [0.30–2.59]
Infection, sepsis n (%):					
In 1 child	42 (10.7)	6 (10)	13 (15.1)		
In 2 children	54 (13.8)	10 (16.7)	9 (10.5)		
In 3 children	2 (0.5)	2 (3.3)	1 (1.2)	1.24 [0.89–1.72]	0.99 [0.72–1.36]
Postnatal persistent DAB, n (%):	29 (7.42)	10 (16.6)	11 (12.8)	2.49 [1.15–5.43]	1.83 [0.88–3.83]
Duration of hospitalisation (days): mean (SD)	18.6 (18)	16.9 (15.4)	17.7 (16)	0.99 [0.98–1.01]	0.99 [0.98–1.01]

CI = confidence interval; DAB = ductus arteriosus Botalli; Pregn. = pregnancies; RRR = relative ride ratio; SD = standard deviation;

Compared with the natural conception group, mean birth weight was significantly lower only in the OS, but not in the IVF-ICSI group.
Compared with natural conception, the number of postnatal deaths was significantly increased after ovarian stimulation, but not after IVF-ICSI.
Postnatal persistent ductus arteriosus Botalli was also significantly higher only after ovarian stimulation.
There were no significant differences found for all the other pathologies listed in table 2.

Multivariate analysis
Results are depicted in table 3.
Age was significantly elevated in the IVF-ICSI-group and BMI significantly elevated in the OS-group compared with the natural conception group.
Vaginal bleeding / placenta praevia and gestational diabetes occurred significantly more often in the IVF-ICSI-group compared with the natural conception group.
There were significantly more amnion infection syndromes in the OS group.
The number of babies was significantly elevated in the OS group (RRR 4.8) and also in the IVF-ICSI-group (RRR 3.97).

Discussion

This study examined the different aetiologies of MP at the university Hospital Bern during a 12-year period. It shows that there is a higher triplet rate after OS. This is confirmed by research undertaken in other countries [15].
Another important point is that, in the current study, the outcome of the MP after OS is worse: there are significantly more amnion infection syndromes compared with natural conception, babies are born at a significantly lower gestational age, they have a significantly lower birth weight and significantly more often a persistent ductus arteriosus Botalli. There are also more postnatal deaths found in the OS group.
Even though in this study there are possible biases due to a university hospital based population, data fit well with published literature and the origin of triplet pregnancies in this study was similar to Swiss results [17]. This recent Swiss study has shown that the incidence of higher-order multiple births in a 20-year interval is still increasing and sufficient control and monitoring is consequently required [17]. According to this study, not only Swiss IVF-ICSI specialists can be made responsible for the important rise of MP in the last decades. Ovarian stimulation treatments with/without insemination in Switzerland are very often carried out by physicians who are not specialised in reproductive medicine, so they equally bear a portion of the responsibility. Furthermore, MP resulting from infertility treatments abroad are also accountable to a certain extent [17]. Consequently, the origin of MP is complex and different measures have to be taken to avoid these complications.
In Belgium, for example, measures have been taken in order to avoid MP after OS: OS is only possible after having achieved a subspecialist training in reproductive medicine at an accredited centre, as established in European countries by ESHRE (European Society of Human Reproduction and Embryology).
In order to lower the occurrence of MP in IVF-ICSI treatments, the number of transferred embryos has to be reduced. The maintenance of equal pregnancy rates with a concomitantly minimal risk of MP is possible with the selection and culture of the best embryo and cryopreservation of the supernumerous embryos, the so called "elective single embryo transfer" (eSET). Many studies have shown that in defined conditions, the cumulative live births after eSET were identical to that of transfer of 2 or even 3 embryos with a dramatic decrease (<5%) in the rate of twin pregnancies and the quasi nonexistence (<<1%) of triplets after IVF-ICSI [18–23]. Moreover, the mean birth weight was shown to be higher and the incidence for preterm birth/low birth weight was clearly reduced [24]. These excellent results have been so convincing that Belgium had elaborated a new concept since 2005: if women with clearly defined criteria get an eSET, the IVF treatment is free of cost for the patient. Thanks to this procedure, MP rates decreased and a dramatic reduction in maternal/neonatal morbidity and costs for the public healthservice ensued [25]. This system stands the test of time and could be taken as a model for other countries.
Owing to Swiss legislation, which prohibits the cryopreservation of embryos, an eSET programme is not possible in Switzerland today [16, 26]. Fortunately, a revision of the current Swiss law plans to legalise preimplantation genetic diagnosis (PGD) and the cryopreservation of embryos. However, instead of giving Swiss infertile couples the optimum chance to avoid MP, the new proposal intends to maintain the maximum number of three embryos which could be cultured to the embryonic state (eight embryos in the case of PGD), notwithstanding numerous explanations by scientific experts worldwide and the Belgium success story. It is incomprehensible that the new proposal will not allow eSET despite scientifically proven lower complication rates and enormous savings for the Swiss health system. In fact, this proposed "pseudo revision" of the Swiss law would not lead to any real changes in reproductive

Table 3: Multivariate analysis.

	Ovarian stimulation vs Natural conception **RRR** **CI (95%)**	**IVF-ICSI vs Natural conception** **RRR** **CI (95%)**
Maternal age (per 5 years)	1.11 [0.79–1.56]	2.03 [1.47–2.81]
BMI	1.06 [1–1.14]	0.98 [0.91–1.06]
Vaginal bleeding / placenta praevia	2.18 [0.96–4.48]	2.27 [1.08–4.80]
Gestational diabetes during pregnancy	1.39 [0.26–7.43]	3.85 [1.13–13.10]
Amnion infection syndrome	4.01 [1.76–9.15]	0.99 [0.37–2.70]
Number of babies	4.8 [1.95–11.82]	3.97 [1.69–9.28]

BMI = body mass index; CI = confidence interval; RRR = relative ride ratio

medicine in Switzerland: an eSET programme would still be impossible and PGD would quite surely not be practiced in Switzerland, due to much higher costs for couples.

Interestingly, in August 2012, the Strasbourg-based court ordered the Italian Government to pay 17,500 Euros to a couple, as compensation for refusing to screen embryos for cystic fibrosis by PGD in order to avoid abortion of an ill child, which they had had to do twice already. An analogy could be made with couples in Switzerland, who have IVF-twins or -triplets with serious handicaps due to the complications of prematurity. They could be legally entitled to receive compensation from the Swiss state for refusing elective single embryo transfer.

Current practice in infertility treatment in Switzerland is also heavily biased by the reimbursement policy. Whereas OS is covered by the health insurance, all IVF-ICSI treatment must be paid by the infertile couples themselves. The cost-benefit ratio of OS is questionable. In contrast, the cost-benefit ratio of ART has been demonstrated to be in favour of IVF-ICSI. A reversal of the present reimbursement policy, together with a lift of the current ban on cryopreservation of embryos, would drastically modify current practice and lower the present multiple delivery rate.

In conclusion, MP is the most important complication of infertility treatments [2]. Our study results have shown that more triplets originate by OS compared to IVF-ICSI and that the neonatal outcome of multiples conceived by OS is worse compared to spontaneous conception. In contrast, no significant differences concerning neonatal outcome have been observed for neonates conceived by IVF-ICSI. However, as MP (already twin pregnancies) have a much higher maternal and neonatal morbidity/mortality compared with singleton pregnancies, they have absolutely to be avoided. Nonspecialised physicians who perform ovarian stimulation treatments with/without insemination should be encouraged to undergo better specialised training. On the other hand, if the Swiss law on reproductive medicine were changed to allow eSET as an option, a dramatic decrease of MP after IVF-ICSI as well as enormous cost savings in public health care would ensue [18, 24, 25, 27].

Acknowledgement: We warmly thank Eleanore Hickey B.A. (Hons) for her help in the stylistic ameliorations of the English language.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

Correspondence: *Dorothea Wunder, MD, Reproductive Medicine, Department of Gynaecology and Obstetrics, University Hospital CHUV, Avenue Pierre-Decker 2, CH-1011 Lausanne, Switzerland, dorothea.wunder[at]chuv.ch*

References

1 BFS (Bundesamt für Statistik), Bevölkerungsbewegung – Detaillierte Daten, Geburten und Todesfälle 1970–2009. http://www.bfs.admin.ch/

2 B. Blondel, M. Kaminski, The increase in multiple births and its consequences on perinatal health. Gynecol Obstet Biol Reprod. 2002;31:725–40.

3 Canadian Fertility and Andrology Society. Incidence and complications of multiple gestation in Canada: proceedings of an expert meeting. Reprod Biomed Online. 2007;14:773–90.

4 Fisher J, Stocky A. Maternal perinatal mental health and multiple births: implications for practice. Twin Res. 2003;6:506–13.

5 Choi Y, Bishai D, Minkovitz CS. Multiple births are a risk factor for postpartum maternal depressive symptoms. Pediatrics 2009;123:1147–54.

6 Ross LE, McQueen K, Vigod S, Dennis CL. Risk for postpartum depression associated with assisted reproductive technologies and multiple births: a systematic review. Hum Reprod Update. 2010;17:96–06.

7 Pinborg A, Loft A, Schmidt L, Andersen AN. Morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families. Hum Reprod. 2003;18:1234–43.

8 Adamson D, Baker V. Multiple births from assisted reproductive technologies: a challenge that must be met. Fertil Steril. 2004;81:517–22.

9 Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ. 1990;301(6746):259–62.

10 Barker DJ, Osmond C, Forsén TJ, Kajantie E. Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med. 2005;353(17):1802–9.

11 Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism? A systematic Review. Diabet Med. 2003;20(5):339–48.

12 Bardis N, Maruthini D, Balen AHB. Modes of conception and multiple pregnancies: a national survey of babies born during one week in 2003 in the United Kingdom. Fertil Steril. 2005;84:1727–32.

13 Pinborg A, Loft A, Nyboe Andersen A. Neonatal outcome in a Danish national cohort of 8602 children born after in vitro fertilization or intracytoplasmic sperm injection: the role of twin pregnancy. Acta Obstet Gynecol Scand. 2004;83:1071–8.

14 Fortunato A, Tosti E. The impact of in vitro fertilization on health of the children: an update. Eur J Obstet Gynecol Reprod Biol. 2011;154(2):125–9.

15 Reynolds MA, Schieve LA, Martin JA, Jeng G, Macaluso M. Trends in multiple births conceived using assisted reproductive technology, United States, 1997-2000. Pediatrics. 2003;111:1159–62.

16 FMedG, Fortpflanzungsmedizingesetz: Bundesgesetz über die medizinisch unterstützte Fortpflanzung vom 18. Dezember 1998: http://www.admin.ch/ch/e/rs/annot/linkss-wisslaw.htmhttp://www.admin.ch/ch/d/sr/8/814.90.de.pdf

17 Arlettaz Mieth R, Ersfeld S, Douchet N, Wellmann S, Bucher HU. Higher multiple births in Switzerland: neonatal outcome and evolution over the last 20 years. Swiss Med Wkly. 2011 Nov 30;141:w13308. doi: 10.4414/smw.2011.13308.

18 McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JC, et al.. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ. 2010;341:c6945.

19 Gelbaya TA, Tsoumpou I, Nardo LG. The likelihood of live birth and multiple birth after single versus double embryo transfer at the cleavage stage: a systematic review and meta-analysis. Fertil Steril. 2010;94:936–45.

20 Thurin-Kjellberg A, Olivius C, Bergh C. Cumulative Live-Birth Rates in a Trial of Single-Embryo or Double-Embryo Transfer. N Engl J Med. 2009;36:1812–3.

21 Van Montfoort AP, Dumoulin JC, Land JA, Coonen E, Derhaag JG, Evers JL. Elective single embryo transfer (eSET) policy in the first three IVF/ICSI treatment cycles. Hum Reprod. 2005;20:433–6.

22 Hamberger L, Hardarson T, Nygren KG. Avoidance of multiple pregnancy by use of single embryo transfer. Minerva Ginecol 2005;57:15-19.

23 Thurin A, Hausken J, Hillensjo T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double embryo transfer in in-vitro fertilization. N Engl J Med. 2004;351:2392–2402.

24 De Sutter P. Single embryo transfer (SET) not only leads to a reduction in twinning rates after IVF/ICSI, but also improves obstetrical and

perinatal outcome of singletons. Verh K Acad Geneeskd Belg. 2006;68:319–27.

25 Ombelet W, De Sutter P, Van der Elst J, Martens G. Multiple gestation and infertility treatment: registration, reflection and reaction – the Belgian project. Hum Reprod Update. 2005;11:3–14.

26 De Geyter C: Assisted reproductive medicine in Switzerland. Swiss Med Wkly. 2012;142:w13569.

27 Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, et al. Born Too Soon preterm prevention analysis group. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet. 2013;381:223–34.