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Extended Analyses of the German IVF Registry (D-I-R): Andrological Aspects, Medical-Economical Assumptions Related to the Shift From IVF to ICSI and Stimulation with Gonadotropins

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In addition to the annual report of the German IVF Registry (D-I-R) the database of 498,784 ART cycles between 1998 and 2008 was analysed for aspects regarding andrology, medical and economical aspects of ICSI and stimulation with gonadotropins. The indication for an ICSI procedure is related to the retrieval of sperm. Seven percent of all ART cycles in the DIR are already performed with epididymal or testicular sperm due to azoospermia. The analysis of cycles with testicular sperm revealed that fertilisation and pregnancy rates are reduced in comparison to ejaculated or frozen sperm, but miscarriage and birth rates do not increase. The data recording of lifestyle parameters can be valuable in the future. The analysis of the D-I-R data demonstrates that restrictions on the reimbursement for ART cycles have significant impact on the use of IVF and ICSI treatments. Medical indications rather than economic reasons seem to be responsible for the increase in ICSI treatment. Since the commercial launch of GnRH antagonists in 1999 and 2000 more than 90 % of IVF and ICSI protocols in Germany are now performed with GnRH agonists (54.8 %) and GnRH antagonists (31.5 %). Approximately 90% of the IVF and ICSI cycles in Germany are performed with recombinant FSH (rFSH), highly purified menotropin (HP-hMG) or a combination of both. Non-medical factors can influence the choice of gonadotropins for stimulation. Women beyond the age of 34 probably have better IVF or ICSI outcome when the stimulation is performed with rFSH. **J Reproduktionsmed Endokrinol 2010; 7 (1): 40–4.**

Key words: German IVF Registry (D-I-R), azoospermia, lifestyle, reimbursement, intracytoplasmic sperm injection (ICSI), GnRH analogues, gonadotropin

■ Practical Aspects

Medical indications rather than economic reasons seem to be responsible for the increase in ICSI treatment. Seven percent of ICSI cycles are performed with testicular or epididymal sperm. In these cases miscarriage and birth rates are not reduced. GnRH antagonist protocols play an increasing part in routine ART cycles.

■ Introduction

For the second time, a lunch symposium was held during the annual meeting of the German IVF groups in Freiburg in November 2009 with the presentation of the special statistical evaluations in addition to the annual report of the German IVF Registry (D-I-R). The data were presented by members of the directorial board and the board of trustees. In the 2008 lunch symposium, a detailed analysis of ART cycles for regional differences in success rates, clinical aspects of GnRH agonist and antagonist protocols and IVF quality had been assessed anonymously for individual IVF centers [1]. The topics of the current symposium were male infertility, ICSI treatment and

stimulation with urinary or recombinant gonadotropins in clinical routine.

■ Indications and Results of ART Cycles for Male Infertility

ICSI cycles have been registered in the D-I-R since 1994 [2]. By 1999, all D-I-R

centers in Germany practiced both IVF and ICSI techniques and between 2001 and 2004 one or two centers only documented ICSI cycles. The ESHRE European IVF Monitoring (EIM) recorded the trend in IVF practice with ICSI cycles exceeding the frequency of IVF cycles in 2002 in Europe [3]. In the current analysis of andrological aspects in

Table 1: Retrieval of sperm for ART cycles in the German IVF Registry (D-I-R) 1998–2008.

	Frequency (n)	Cumulative frequency (n)	Percentage (%)	Cumulative percentage (%)
Not specified	7202	7202	2.38	2.38
Antegrade ejaculation	267,572	274,774	88.48	90.86
Retrograde ejaculation	229	275,003	0.08	90.94
Cryopreserved sperm	5,337	280,340	1.76	92.70
Microsurgical epididymal sperm aspiration (MESA)	185	280,525	0.06	92.76
Cryopreserved sperm after MESA	624	281,149	0.21	92.97
Percutaneous epididymal sperm aspiration (PESA)	32	281,181	0.01	92.98
Cryopreserved sperm after PESA	15	281,196	0.00	92.98
Testicular sperm extraction (TESE)	4,260	285,456	1.41	94.39
TESE of cryopreserved testicular tissue	16,143	301,599	5.34	99.73
Electro-ejaculation	41	301,640	0.01	99.74
Artificial spermatocele	11	301,651	0.00	99.75
Donor sperm	762	302,413	0.25	100.00

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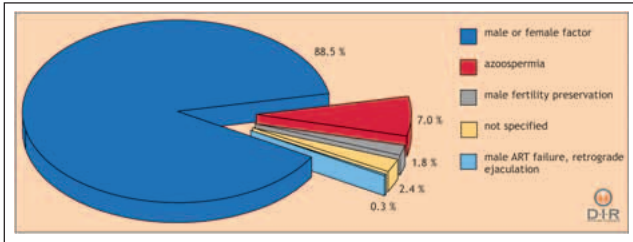


Figure 1: Indications for ART-related diagnosis according to the kind of sperm retrieval 1998–2008 (302,413 ART cycles).

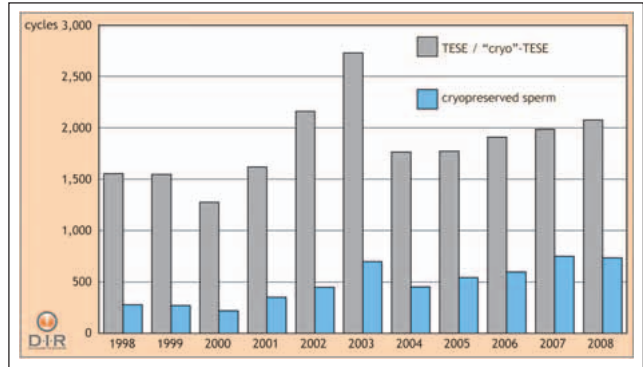


Figure 2: Increase in annual numbers for ART cycles with cryopreserved ejaculated sperm or fresh or frozen testicular sperm (TESE/"cryo"-TESE) 1998–2008 (total 25,740 ART cycles).

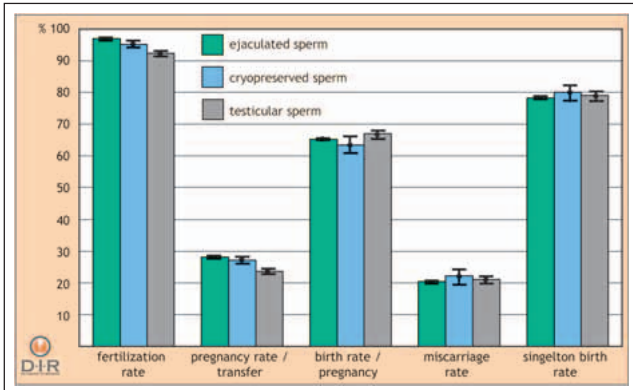


Figure 3: Means (± 95% confidence interval [CI]) for fertilization rate, pregnancy rate, birth and miscarriage rate and singleton pregnancy rate for ejaculated, cryopreserved or testicular sperm in percent (%), 293,312 ART cycles 1998–2008, lost for follow-up 13.7%.

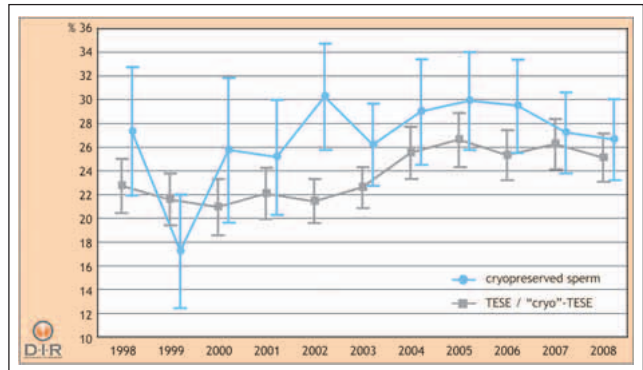


Figure 4: Annual pregnancy rates (%) for cryopreserved ejaculated sperm and fresh or frozen testicular sperm (means ± 95% CI), $p < 0.05$ in 2002; 1998–2008 (total 25,740 ART cycles).

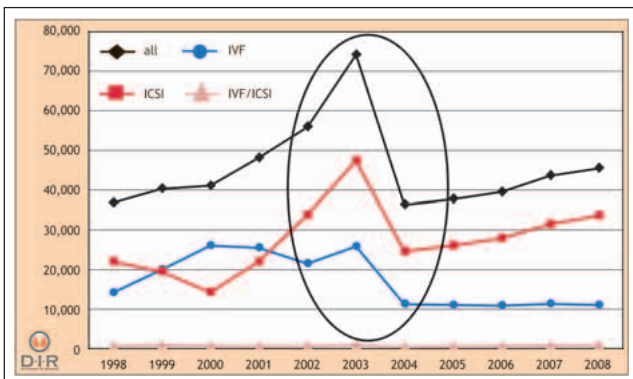


Figure 5: Annual development of ART cycles in Germany 1998–2008 ($n = 498,784$). IVF/ICSI cycles are fresh cycles in which oocytes are divided for both IVF and ICSI treatment.

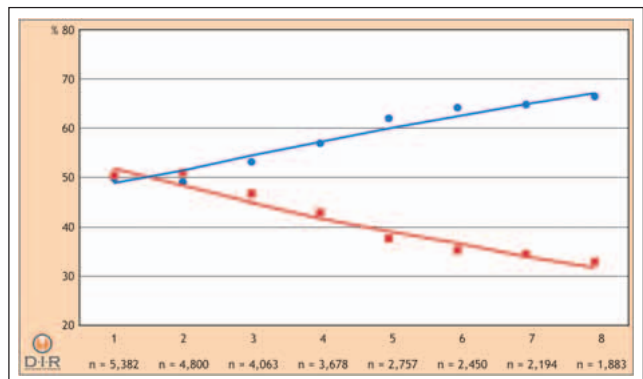


Figure 6: Percentage of fertilisation failure in IVF (line with filled circle) or ICSI cycles (line with filled quad) plotted against the number of oocytes available for fertilisation (1999–2001).

ART, 302,413 cycles registered between 1998 and 2008 by the D-I-R were analysed.

Sperm Retrieval for ART Cycles

The indication for an ICSI procedure is related to the retrieval of sperm in the mandatory field in the D-I-R database (Tab. 1). Indications for IVF or ICSI treatment can be derived from the origin of sperm for ART (Fig. 1): male factor (poor sperm quality, antegrade ejaculation), obstructive or non-obstructive

azoospermia (MESA, PESA, TESE or artificial spermatocele), retrograde ejaculation (sperm retrieved from urine, electro-stimulation or antegrade ejaculation after medication), male fertility preservation (cryopreserved sperm) or male ART treatment failure (cryopreserved donor sperm). Seven percent of all ART cycles in the German registry were performed with epididymal or testicular sperm due to azoospermia. But no differentiation can be carried out between non-obstructive and obstructive

azoospermia and fertilization and pregnancy results cannot be distinguished between cycles with intracytoplasmic injection of motile and immotile testicular sperm (no mandatory fields). The number of ART cycles with testicular or cryopreserved ejaculated sperm is increasing (Fig. 2). Fluctuations in the numbers of treatment cycles in 2000 and 2004 are due to changes in the reimbursement of ICSI cycles by the public health insurance. 20,403 TESE cycles and 5,337 cycles with cryopreserved

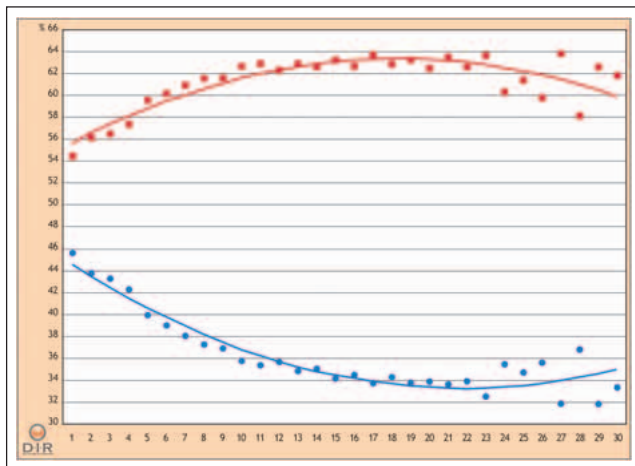


Figure 7: Percentage of IVF (line with filled circle) and ICSI (line with filled quad) cycles (n = 488,174) performed plotted against the number of oocytes available for fertilisation (1998–2008).

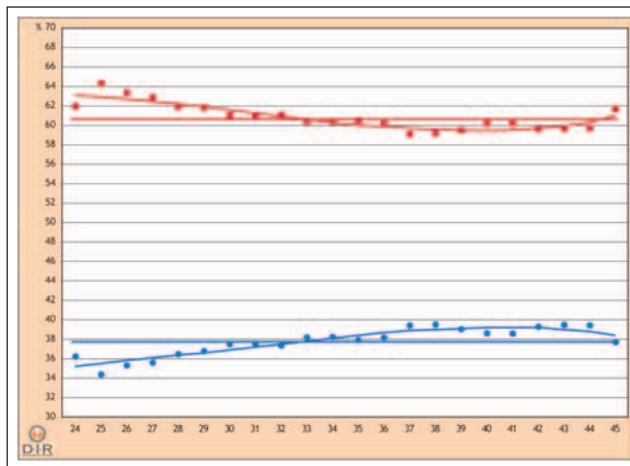


Figure 8: Percentage of IVF (line with filled circle) and ICSI (line with filled quad) cycles (n = 488,174) performed plotted against the female age (1998–2008), means for percent-age of IVF and ICSI treatments are marked by solid lines.

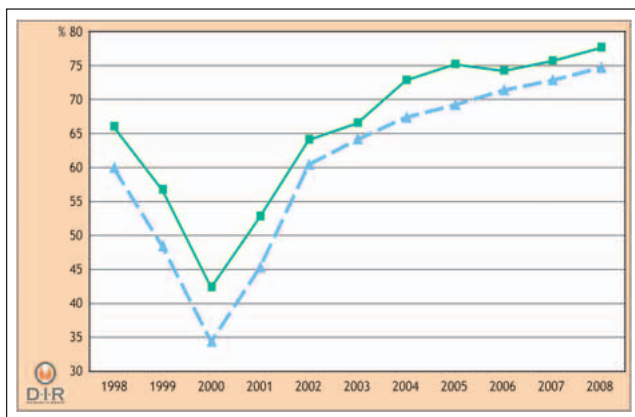


Figure 9: Percentage of ICSI cycles in private fertility centers (dashed line with tri-angle) and public general or university hospitals (solid line with quad) (1998–2008).

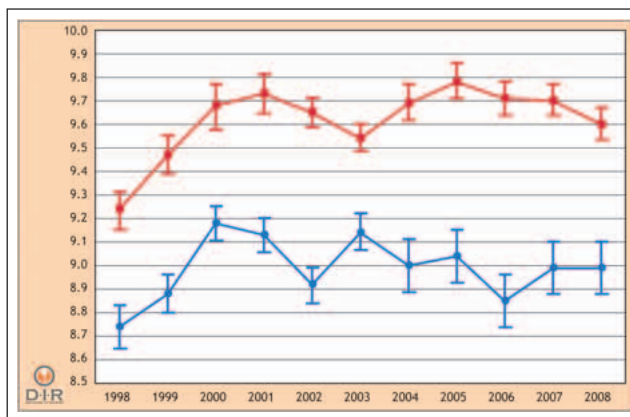


Figure 10: Means (± 95 % CI) for number of oocytes retrieved (n = 4,610,133) in IVF (line with circle) or ICSI (line with quad) cycles (1998–2008).

sperm were performed between 1998 and 2008.

Success Rates and Sperm Retrieval

Lower fertilization and pregnancy rates are expected when ART cycles are performed with poor sperm quality or even testicular sperm. The analysis of 293,312 cycles with ejaculated, cryopreserved or testicular sperm confirmed this assumption. Fertilization and pregnancy rates were lowest with testicular sperm ($p < 0.05$). But when a pregnancy can be achieved the birth rate seems to be highest and the risk for multiple pregnancies lower than with ejaculated sperm (Fig. 3). Although pregnancy rates are higher for cryopreserved ejaculated sperm in comparison to testicular sperm, the annual analysis of 11 years reveals an improvement in pregnancy rates with almost similar success rates for cryopre-served and testicular sperm (Fig. 4).

Lifestyle and ART Cycles

Alcohol, smoking, over- but also under-weight are known risk factors for infertility problems in women and men. Especially the prevalence of obesity and infertility is increasing in the developed world.

The body mass index (BMI) can be calculated for women and men in the database of the D-I-R because body weight and height are mandatory fields. However, the analysis of these data revealed that the data entered are incomplete or incorrect. According to the analysis of the BMI data only 2.5 % of the infertile men, 6.3 % of the infertile women and 0.7 % of both partners were overweight with a BMI > 30 (expected 17 % for married men and 14 % for married women [4]). Nevertheless, the miscarriage rate for women with obesity was significantly higher in comparison to women with a BMI < 30 and is possibly due to

metabolic disorders [2]. Smoking habits are also recorded in the D-I-R database (mandatory field for pre-existing diseases). The data analysis for nicotine abuse gave invaluable results probably also due to incomplete data collection and data entering [2]. All D-I-R centers should be encouraged to improve their data collection at least for main lifestyle parameters like body weight, height and smoking habits. Thus these D-I-R data can become valuable for the future.

Considerations on the Increase of IVF to ICSI

Reimbursement policies can have significant impact on the accessibility and use of ART treatments, and lack of medical reimbursement will act as a barrier to the use of ART. The analysis of the D-I-R data demonstrate that no reimbursement for ICSI cycles by the public health insurance in the year 2000 re-

Table 2: Percentage of cycles with embryo transfer (ET) and pregnancy rate (PR) in relation to different stimulation protocols and gonadotropin preparations, German IVF Registry (D-I-R) 2008.

Gonadotropin preparation/ Stimulation protocol	uFSH		rFSH		rFSH plus rLH		rFSH plus HP-hMG		Others	n. s.	Total
	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)			
GnRH agonist, short (n)	168	1,573	1,384	85	508	28	3	3,749			
ET (%)	94.6	93.0	92.2	81.2	90.2	96.4	66.7	92.1			
PR (%)	26.4	23.9	23.7	27.5	15.8	15.4	50.0	22.9			
GnRH agonist, long (n)	258	11,973	4,215	1,714	3,327	203	5	21,695			
ET (%)	90.3	92.4	93.6	90.4	93.8	89.7	80.0	92.7			
PR (%)	30.5	32.3	29.3	33.1	32.2	25.8	25.0	31.7			
No GnRH analogues (n)	4	770	333	69	152	183	175	1,686			
ET (%)	75.0	93.5	89.8	91.3	89.5	83.1	76.6	89.4			
PR (%)	33.3	32.9	28.4	22.2	30.2	19.1	9.7	27.9			
Antagonist (n)	93	6,760	2,063	780	1,450	1317	12	12,475			
ET (%)	93.6	92.7	88.6	86.3	90.3	88.4	100.0	90.9			
PR (%)	9.2	29.6	24.2	25.6	23.5	23.5	8.3	27.0			
Total (n)	523	21,076	7,995	2,648	5,437	1,731	195	39,605			
Total (%)	1.3	53.7	20.2	6.7	13.7	4.4	0.5				

Abbreviations: urinary FSH (uFSH), recombinant FSH (rFSH), highly purified menotropin (HP-hMG), rFSH plus HP-hMG, recombinant LH (rLH), not specified (n.s.), short GnRH protocol (microdose flare-up protocol), cycles to embryo transfer (ET), pregnancy rate per embryo transfer (PR)

duced the number of ICSI cycles performed. The 50 % co-payment portion by patients and limitations for the reimbursement e. g., to 3 cycles and to the age of 25–39 for women and 25–49 for men since 2004 dramatically decreased the use of all ART cycles by 50 % (Fig. 5).

Despite the discussion on the decrease in male fertility over the last decades 2 hypotheses were tested: is ICSI preferred to avoid fertilisation failure or is ICSI performed frequently to increase the income of physicians working in reproductive medicine?

Between 1998 and 2004 successful fertilisation and pregnancy rates in IVF and ICSI cycles, IVF cycles with fertilisation failure, the relationship between the number of fertilizable oocytes and IVF or ICSI treatment and cycles in patients with advanced maternal age were analysed to answer the first question. Although pregnancy rates were similar for IVF and ICSI cycles, the rate for successful fertilisation dropped in 2000 for IVF by approximately 7 % (84.8 %). Fertilisation failure in IVF or ICSI cycles depended on the number of oocytes available for fertilisation with an increase in fertilisation failure in IVF cycles with higher numbers of oocytes and vice versa for ICSI cycles (Fig. 6). Against the anticipation that patients with low numbers of oocytes frequently

favour ICSI treatment to optimize their chance for fertilisation, low numbers of oocytes are related to a more frequent performance of IVF than ICSI (Fig. 7). Even in women with advanced maternal age, which is associated with a low number of oocytes, there is a tendency towards the IVF procedure (Fig. 8). This is possibly due to a higher incidence of female infertility factors in the affected couples and the additional cost factor for the ICSI procedure especially for women beyond the age of 39 with no reimbursement for ART by the public health insurance.

Fertility doctors sometimes are criticised for claiming high costs for infertility treatment. Despite this unjustified critique, employed physicians in clinics in comparison to private fertility centers are less dependent on earning money with IVF and ICSI treatment. Only a few clinics including university hospitals still offer infertility treatment in Germany [5]. However, the percentage of ICSI cycles in clinics is constantly higher compared with private fertility centers (Fig. 9). Thus medical indications rather than economic reasons seem to be responsible for the increase in ICSI treatment. The higher number of oocytes in ICSI compared to IVF cycles emphasize the unrestrained female fertility potential and suggests a severe male fertility disorder (Fig. 10).

■ Stimulation with Gonadotropins

Since the commercial launch of GnRH antagonists in 1999 (cetorelix) and 2000 (ganirelix) stimulation protocols with GnRH antagonists have become routine in ART cycles. Meanwhile > 90 % of IVF and ICSI protocols in Germany are performed with GnRH agonists (54.8 %) and GnRH antagonists (31.5 %) (Tab. 2). This is in accordance with the current trend in ART practice worldwide [6]. Especially in PCOS patients with a higher risk for ovarian hyperstimulation syndrome (OHSS), but also in common ART patients, GnRH antagonists are favoured by more and more clinicians on an individualized patient-centered approach including flexible administration of GnRH antagonists or even the use of a GnRH agonists to trigger final oocyte maturation and ovulation [7, 8]. Pregnancy rates improved for antagonist protocols particularly because less poor responder but more normal or high responder patients with normal ovarian function are treated with this protocol.

Approximately 90 % of the IVF and ICSI cycles in Germany are performed with recombinant FSH (rFSH), highly purified menotropin (HP-hMG) or a combination of both (Tab. 2). In the majority of the GnRH agonist long-protocol cycles rFSH preparations were used. Less than 50 % of the GnRH antagonist cycles were performed with rFSH. In these cycles nearly 40 % were carried out with rFSH in combination with HP-hMG, while in cycles with the long protocol < 20 % were stimulated with the combination of rFSH and HP-hMG. Possibly clinicians try to react to the drop in estradiol concentration due to the suppression of endogenous LH by GnRH antagonists with the administration of exogenous LH by HP-hMG preparations. However, pregnancy rates are only comparable in the GnRH agonist long (32.3 %) and the antagonist protocol (29.6 %) when the stimulation is performed with rFSH.

Pregnancy rates are significantly lower in cycles stimulated with hMG in comparison to rFSH (Fig. 11) independent of further variables such as the stimulation protocol, maternal age or dosage of gonadotropins (no mandatory field for the D-I-R). No general recommendation can



Figure 11: Mean pregnancy rates (\pm 95 %-CI) for stimulated IVF or ICSI cycles with recombinant FSH (rFSH) and urinary menotropin (hMG), 280,394 prospective cycles, D-I-R, 1998–2008.

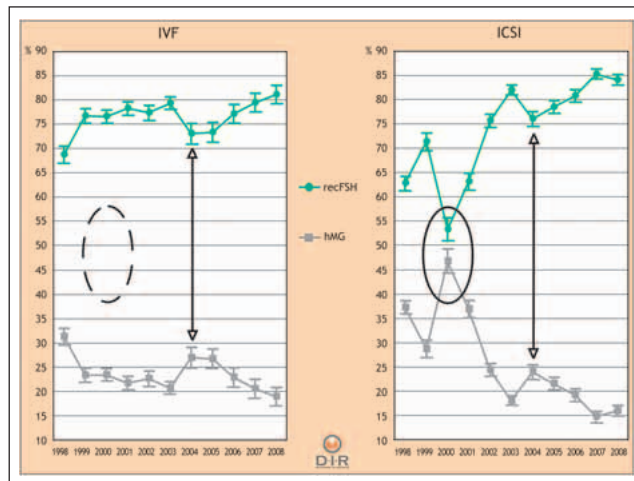


Figure 12: Mean percentage rates (\pm 95 %-CI) of rFSH and hMG application for IVF or ICSI treatment in relation to changes in the reimbursement of ART cycles by the public health insurance, 280,394 prospective cycles, D-I-R 1998–2008.

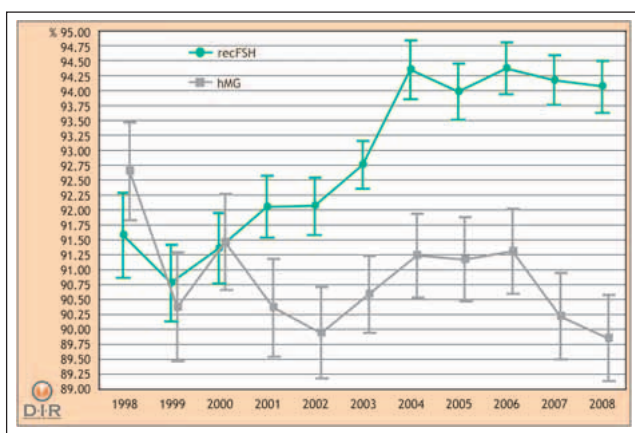


Figure 13: Mean percentage rates (\pm 95 %-CI) of rFSH or hMG stimulated IVF or ICSI cycles leading to oocyte retrieval in women > 34 years, 280,394 prospective cycles, D-I-R 1998–2008.

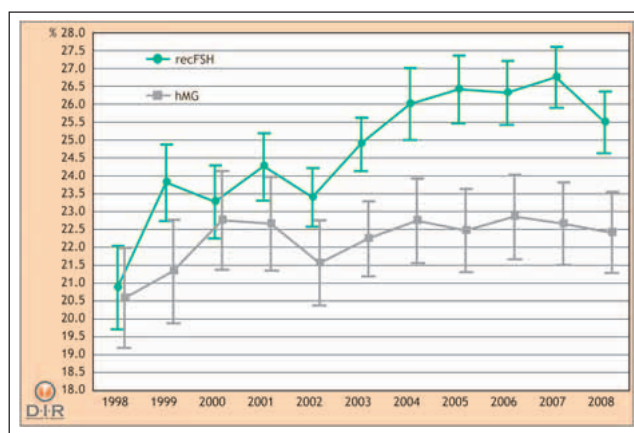


Figure 14: Pregnancy rates per transfer (means \pm 95 %-CI) of rFSH or hMG stimulated IVF or ICSI cycles leading to oocyte retrieval in women > 34 years, 280,394 prospective cycles, D-I-R 1998–2008.

be derived from this fact, because the stimulation of a patient should be individualized which includes the prediction of ovarian response and reduction of the risk for OHSS. Moreover, in a randomized controlled study with oocyte donors no difference was detected between the stimulation with rFSH, hMG or a combination of rFSH and hMG regarding ovarian response and IVF outcome [9]. Interestingly, non-medical factors can influence the choice of gonadotropins for stimulation. Figure 12 demonstrates very clearly the impact of costs for the increase in cycles stimulated with hMG and the decrease in cycles stimulated with rFSH in 2000 for ICSI and 2004 for IVF and ICSI. In those years hMG, not highly purified, was still commercially and considerably cheaper than rFSH. Between 1997 and 2000 ICSI cycles were not reimbursed by the public health insurance and in 2004 the 50 % co-pay-

ment for treatment and medication was established by the public health insurance. Thus patients decided to prefer hMG preparations for ART stimulation. Meanwhile the prices for rFSH and HP-hMG have become similar and non-purified hMG preparations have disappeared from the national and neighbourhood pharmaceutical market.

The analysis of the cycle cancellation rate and pregnancy rate relating to maternal age and rFSH or hMG preparations gives a clear advantage for rFSH in women beyond 34 but not for younger women. Since 2003 the percentage of stimulated cycles leading to oocyte retrieval and the pregnancy rate per transfer have been significantly higher when the stimulation was performed with rFSH (Fig. 13, 14).

The Lunch Symposium was sponsored by Merck-Serono.

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