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Kinderwunsch-Anhörung A 04-10.10.2013

LANDTAG
NORDRHEIN-WESTFALEN
16. WAHLPERIODE

STELLUNGNAHME
16/1093

Alle Abg

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Kinderwunsch-Anhörung A 04-10.10.2013

Sehr geehrte Damen und Herren,

vielen Dank für die Gelegenheit, als reproduktionsmedizinischer Sachverständiger zu den Fragen des Kataloges vom 29.07.2013, sowie zu dem Antrag der Fraktion der CDU und der Fraktion der FDP (Drucksache 16/2624) Stellung nehmen zu dürfen! Die Originale der zitierten Veröffentlichungen sind als PDF-Dateien beigefügt.

Wie Sie meinem beigefügten Lebenslauf entnehmen können, bin ich sowohl als Leiter des größten universitären Kinderwunschzentrums Deutschlands UniKiD als auch in meinen Funktionen als Mitglied des Wissenschaftlichen Beirates der Bundesärztekammer, als Vorstand des Deutschen IVF-Registers (D.I.R) und als Vorstandsmitglied der Deutschen Gesellschaft für Reproduktionsmedizin in klinischer, wissenschaftlicher und berufspolitischer Hinsicht tief in die Materie eingearbeitet.

Der Antrag (Drucksache 16/2624) ist aus meiner Sicht uneingeschränkt zu unterstützen, die dort genannten Fakten sind korrekt und die emotionale Belastung der Kinderwunschpaare ist treffend dargestellt. Die finanzielle Belastung der gesetzlich versicherten Kinderwunschpaare hat tatsächlich mit Inkrafttreten des GMG am 01.01.2004 zu einem Rückgang der in vitro Fertilisationsbehandlungen (IVF) und Behandlungen mittels intrazytoplasmatischer Spermiuminjektion (ICSI) in Deutschland um >50% geführt (Abb. 1).

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Universitäres Interdisziplinäres Kinderwunschzentrum Düsseldorf

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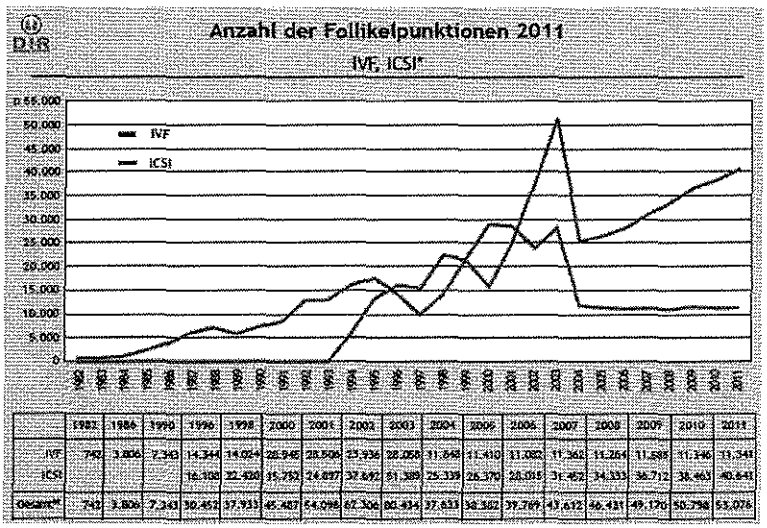
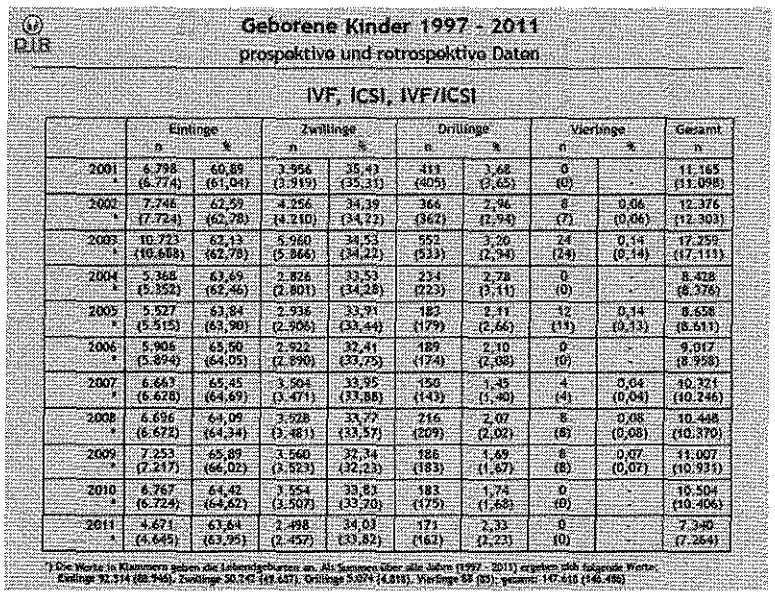


	1982	1986	1990	1996	1998	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IVF	742	3.806	7.343	14.344	14.024	26.945	28.506	25.936	22.050	11.849	11.410	11.082	11.362	11.264	11.688	11.146	11.341
ICSI				16.100	22.420	35.792	24.697	32.692	51.389	25.339	26.370	28.015	31.452	34.333	36.712	38.463	40.641
Gesamt*	742	3.806	7.343	30.452	37.933	45.487	54.098	67.306	80.434	37.633	38.362	39.799	43.612	46.431	49.176	50.798	53.076

Abb. 1: Fallzahlen IVF und ICSI pro Jahr anhand des D.I.R. Rückgang der Zahlen von 80434 in 2003 auf 37633 in 2004. Aus: J Reproduktionsmed Endokrinol 2012: 9(6)15

Weiterhin lässt sich anhand der Daten des Deutschen IVF-Registers (D.I.R) klar belegen, dass die Zahl der nach Inkrafttreten des GMG am 01.01.2004 durch IVF oder ICSI geborenen Kinder in Deutschland im Jahr 2004 um 8735 (=51,05%) im Vergleich zum Vorjahr zurückgegangen ist (Abb. 2).



	Einlinge		Zwillinge		Drillinge		Vierlinge		Gesamt
	n	%	n	%	n	%	n	%	n
2001 *	6.798 (6.774)	60,89 (61,04)	3.956 (3.919)	35,43 (35,31)	411 (405)	3,68 (3,65)	0 (0)	-	11.165 (11.098)
2002 *	7.746 (7.724)	62,59 (62,78)	4.256 (4.210)	34,39 (34,22)	366 (362)	2,96 (2,94)	8 (7)	0,06 (0,06)	12.376 (12.303)
2003 *	10.723 (10.658)	62,13 (62,78)	5.960 (5.866)	34,53 (34,22)	552 (533)	3,20 (2,94)	24 (24)	0,14 (0,14)	17.259 (17.111)
2004 *	5.368 (5.352)	63,69 (62,46)	2.826 (2.801)	33,53 (34,28)	234 (223)	2,78 (3,11)	0 (0)	-	8.428 (8.376)
2005 *	5.527 (5.515)	63,84 (63,90)	2.936 (2.906)	33,91 (33,44)	182 (179)	2,11 (2,66)	12 (11)	0,14 (0,13)	8.658 (8.611)
2006 *	5.906 (5.894)	65,50 (64,05)	2.922 (2.890)	32,41 (33,75)	189 (174)	2,10 (2,08)	0 (0)	-	9.017 (8.958)
2007 *	6.663 (6.628)	65,45 (64,69)	3.504 (3.471)	33,95 (33,88)	150 (143)	1,45 (1,40)	4 (4)	0,04 (0,04)	10.321 (10.246)
2008 *	6.696 (6.672)	64,09 (64,34)	3.528 (3.481)	33,77 (33,57)	216 (209)	2,07 (2,02)	8 (8)	0,08 (0,08)	10.448 (10.370)
2009 *	7.253 (7.217)	65,89 (66,02)	3.560 (3.523)	32,34 (32,23)	186 (183)	1,69 (1,67)	8 (8)	0,07 (0,07)	11.007 (10.931)
2010 *	6.767 (6.724)	64,42 (64,62)	3.554 (3.507)	33,83 (33,70)	183 (175)	1,74 (1,68)	0 (0)	-	10.504 (10.406)
2011 *	4.671 (4.645)	63,64 (63,95)	2.498 (2.457)	34,03 (33,82)	171 (162)	2,33 (2,23)	0 (0)	-	7.340 (7.264)

*) Die Werte in Klammern geben die Lebendgeburten an. Als Summen über alle Jahre (1997 - 2011) ergeben sich folgende Werte: Einlinge 92.314 (88.946), Zwillinge 50.176 (49.457), Drillinge 5.074 (4.818), Vierlinge 88 (85); gesamt: 147.618 (146.486)

Abb. 2: Geborene Kinder nach IVF und ICSI pro Jahr aus anhand des D.I.R. Rückgang der Zahlen von 17111 in 2003 auf 8376 in 2004. Aus: J Reproduktionsmed Endokrinol 2012: 9(6)29

Ein weiterer negativer Effekt der Gesundheitsreform und der damit verbundenen Einschränkung der Leistungen für gesetzlich Krankenversicherte ist der nachweisbare Anstieg des Alters der Patientinnen und Patienten bei Behandlung in einem Kinderwunschzentrum (Abb. 3).

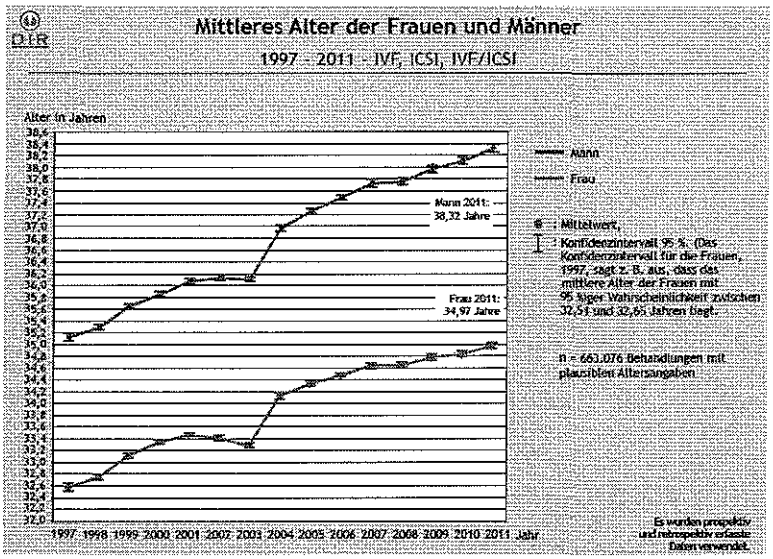


Abb. 3: Anstieg des durchschnittlichen Alters der Behandelten. Nach Inkrafttreten des GMG ist das Alter sprunghaft angestiegen. Aus: J Reproduktionsmed Endokrinol 2012: 9(6)26

Dieser Altersanstieg wiederum hat unmittelbare negative Auswirkungen auf den möglichen Behandlungserfolg, da die Schwangerschaftswahrscheinlichkeit nach reproduktionsmedizinischer Behandlung mit zunehmendem Alter der Patientin dramatisch abnimmt (Abb. 4). Der negative Effekt des Alters der Frau ist hierbei sowohl auf die abnehmende Anzahl der Eizellen (Verminderung der ovariellen Reserve), als auch auf die Zunahme von genetischen Störungen während der meiotischen Reifeteilung der Eizellen zurückzuführen.

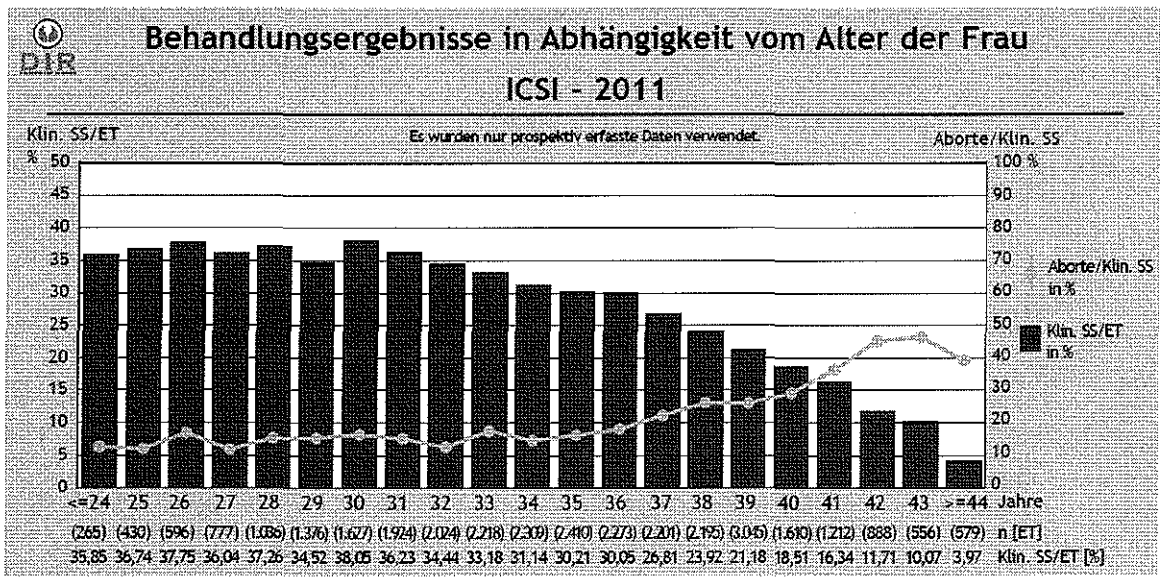


Abb. 4: Abnahme der Schwangerschaftswahrscheinlichkeit und Zunahme des Fehlgeburtrisikos abhängig vom Alter der Patientin. Aus: J Reproduktionsmed Endokrinol 2012: 9(6)22

Der Fragenkatalog enthält einige Fragen, welche sich offensichtlich an Sachverständige aus anderen Gebieten richten. Die Fragen, zu denen ich in meiner Funktion als Reproduktionsmediziner fundiert Stellung nehmen kann, beantworte ich wie folgt:

Frage 1: *Welche Unterstützung brauchen Menschen mit unerfülltem Kinderwunsch? In welcher Form und von welcher Seite sollte Ihnen Beratung und Unterstützung gegeben werden?*

Paare mit unerfülltem Kinderwunsch sind häufig in einer emotional, finanziell, sozial und logistisch stark belastenden Situation. Der Wunsch nach einem Kind ist sehr intensiv und dominant. Andererseits ist die ungewollte Kinderlosigkeit in Deutschland ein Tabuthema, über das kaum offen gesprochen wird. Kinderwunschpaare fürchten eine Stigmatisierung, wenn Sie sich anderen Menschen anvertrauen. Dies betrifft sowohl die Familie und Freunde, als auch die Arbeitskolleginnen und Kollegen. Kinderwunschpaare brauchen Unterstützung auf allen Ebenen. Hilfreich wären z.B.:

- Kampagnen zur Enttabuisierung des unerfüllten Kinderwunsches analog z.B. zur Darmkrebsvorsorge
- Finanzierung der Kinderwunschbehandlung aus öffentlichen Mitteln, um den Paaren zumindest die finanzielle Belastung zu nehmen
- Unterstützung von Selbsthilfegruppen, psychosozialen Beratungsstellen

Frage 2: *Wie bewerten Sie das Angebot an Beratung und Betreuung im Rahmen der Behandlung derzeit?*

Das Angebot ist formal ausreichend, wird aber von den Patientinnen häufig nicht wahrgenommen oder nicht in Anspruch genommen. Auch kommen hier unter Umständen weitere finanzielle Belastungen auf die Paare zu.

Der Bekanntheitsgrad der Angebote müsste gesteigert werden.

Frage 3: *Welches sind in der Beratungspraxis die größten Probleme der von unerfülltem Kinderwunsch betroffenen Paare? Wie bewerten Sie die psychische Belastung der Frauen, welche durch eine IVF/ICSI-Behandlung besteht?*

Die größten Probleme sind:

- Angst davor, dass Arbeitgeber oder Kollegen (m/w) von der Erkrankung „unerfüllter Kinderwunsch" erfahren
- Finanzielle Belastung durch die Behandlungskosten

Das Ausmaß der psychischen Belastung ist individuell stark abhängig von Faktoren wie Leidensdruck, Erfolg/Misserfolg der Behandlung, ausreichende Möglichkeit für Fragen und Arztkontakt, Empathie des betreuenden Fachpersonals etc..

Frage 4: *Welche grundsätzliche Haltung haben die christlichen Kirchen zur künstlichen Befruchtung und den unterschiedlichen Verfahren in diesem Bereich?*

Ich betrachte mich nicht als kompetenten Ansprechpartner für diese Frage.

Meines Wissens nach lehnt die römisch-katholische Kirche die Maßnahmen der assistierten Fortpflanzung strikt ab, die evangelische Kirche nicht.

Frage 5: *Gibt es gesundheitliche Probleme bzw. Risiken bei künstlichen Befruchtungen für Frauen und Kinder, falls ja, welche (evtl. vorhandene statistische Daten bitte anfügen)?*

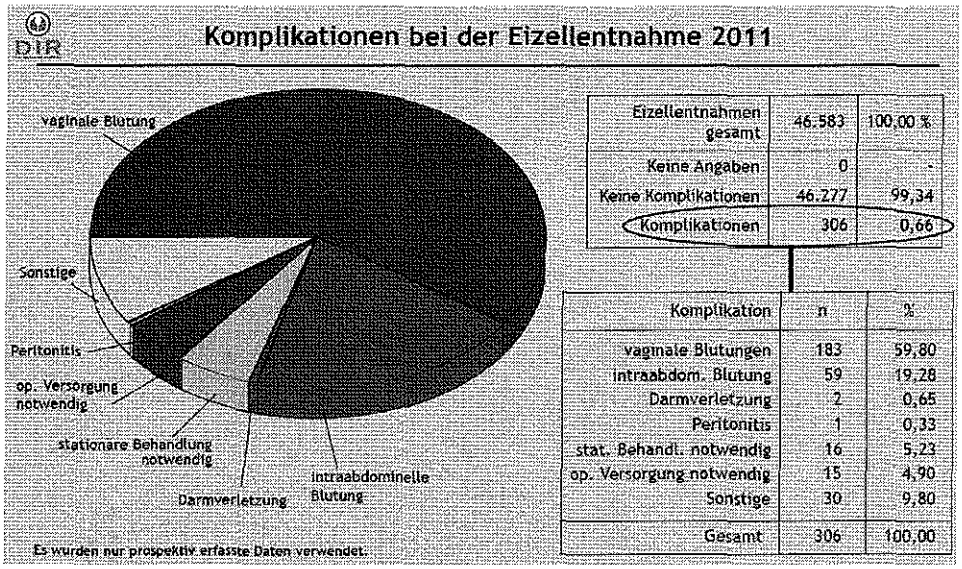
Risiken für Kinder:

- Eine aktuelle Metaanalyse aus 2013, welche systematische Übersichtsarbeiten und große Populationsstudien zwischen 2004 und 2010 untersuchte, fand eine leichte Häufung von Auffälligkeiten im Schwangerschaftsverlauf (z.B. Gestationsdiabetes, leichte Erniedrigung des Geburtsgewichtes, Entbindung vor der 38. Schwangerschaftswoche), jedoch sind die absoluten Zahlen sehr gering (Talaulikar, Eur J Obst Gynecol Reprod Biol 2013(170): 13-19).
- Eine große Metaanalyse aus 2011 (vorangegangen war eine ebensolche Analyse aus 2006), welche die weltweite Literatur in Bezug auf die nach IVF und ICSI geborenen Kinder systematisch untersuchte, fand in der großen Majorität der Studien „keine offensichtlichen Probleme der Kinder nach IVF oder ICSI". Allerdings wurde eine methodenbedingte Häufung von Mehrlingsschwangerschaften beobachtet. Damit assoziiert fanden sich gehäuft Komplikationen wie Frühgeburtlichkeit und niedriges Geburtsgewicht. Die Studie untersuchte weiterhin auf Risiken assoziiert mit der ICSI-Behandlung, Erkrankungen der geborenen Kinder inkl. Fehlbildungen, Krebserkrankungen im Kindesalter, seltene Syndrome und psychologische Auffälligkeiten. Nachdem die Studie aus 2006 zu dem Schluss gekommen war, dass es neben den o.g. Komplikationen bedingt durch Mehrlingsschwangerschaften keine Risiken aus der IVF für die Mütter und Kinder ergeben, fanden sich auch in der aktuellen Auswertung weiterer Daten allenfalls einzelne Fälle von Auffälligkeiten (*case reports*) oder von seltenen Syndromen (Fortunato, Eur J Obst Gynecol Reprod Biol 2011 (154) 125-129). Die Autoren dieser Metaanalysen diskutieren aber auch, dass diese seltenen Auffälligkeiten vermutlich auch durch die der Sterilität zugrundeliegenden Erkrankungen der Eltern verursacht worden sein könnten.
- Eine sehr aktuelle Studie aus Dänemark hat die geburtshilflichen Daten und die Daten der Neugeborenenperiode von 63.854 nach natürlicher Empfängnis geborenen Kindern mit denen von 17.592 Kindern nach IVF, 8.967 Kindern nach ICSI mit ejakulierten Spermien und 466 Kindern nach ICSI mit Spermien aus Hoden- oder Nebenhodenproben verglichen. Diese umfangreiche Studie kam zu dem Schluss, dass die Schwangerschaften, welche mittels der untersuchten Techniken der assistierten Reproduktion entstanden waren, in Hinblick auf die Gesundheit der neugeborenen Kinder und die Rate an Fehlbildungen die gleiche Sicherheit aufweisen, wie Schwangerschaften, welche nach natürlicher Empfängnis entstanden waren (Fedder, Hum Reprod 2013(28)230-240).

Risiken für Frauen:

- Nach derzeitigem Wissenstand gibt es keine erwiesenen Spätfolgen. Es findet sich z.B. keine signifikante Häufung von Krebserkrankungen irgendeiner Form bei Frauen, welche eine oder mehrere IVF- oder ICSI- Behandlungen mit derzeit üblichen Stimulationsprotokollen durchgeführt haben (Brinton, Reprod Biomed Online 2007 (15): 138-44).
- Die Entnahme der Eizellen im Rahmen der IVF oder ICSI erfolgt mittels transvaginaler Punktion. Hierbei werden die Eibläschen (Follikel) innerhalb der Eierstöcke unter Ultraschallkontrolle gezielt punktiert, die Follikelflüssigkeit mit den darin befindlichen Eizellen wird abgesaugt. Bei diesem operativen Eingriff sind

Komplikationen sehr selten. Laut D.I.R kam es in 2011 bei 46.583 Eizellentnahmen nur in 306 Fällen (= 0,66%) zu einer Komplikation, wobei diese meistens (ca. 60% der gemeldeten Komplikationen) in einer Blutung aus den Einstichstellen bestand. Diese lässt sich durch einfache Kompression (ca. 5 Minuten Druck mit einem Tupfer) beherrschen. Ernste Komplikationen, welche eine stationäre Versorgung notwendig werden ließen, kamen nur in 16/46.583 (0,03%) Fällen vor (s. Abb. 5).



Eizellentnahmen gesamt	46.583	100,00 %
Keine Angaben	0	-
Keine Komplikationen	46.277	99,34
Komplikationen	306	0,66

Komplikation	n	%
vaginale Blutungen	183	59,80
intraabdom. Blutung	59	19,28
Darmverletzung	2	0,65
Peritonitis	1	0,33
stat. Behandl. notwendig	16	5,23
op. Versorgung notwendig	15	4,90
Sonstige	30	9,80
Gesamt	306	100,00

Abb. 5: Komplikationen bei der Eizellentnahme.
Aus: J Reproduktionsmed Endokrinol 2012: 9(6)31

- Im Rahmen der hormonellen Stimulationsbehandlung, welche in den ca. 2 Wochen vor der Eizellentnahme dieser voraus geht, kann es zu einer überschießenden Reaktion der Eierstöcke kommen, dem Überstimulationssyndrom (*ovarian hyperstimulation syndrome*, OHSS). Dabei können die Eierstöcke deutlich an Größe zunehmen. Bei einem OHSS °III können unter Umständen Flüssigkeitsansammlungen im Bauchraum (Aszites), Atemnot (Dyspnoe, Orthopnoe), Flüssigkeitsansammlungen im Brustraum (Pleuraergüsse), Übelkeit, Erbrechen und eine Konzentration der festen Blutbestandteile eintreten. In Einzelfällen sind Thrombembolien beschrieben worden, welche lebensbedrohlich sein können. Laut D.I.R handelt es sich dabei aber um ein seltenes Krankheitsbild, in 2011 wurden bei 45.078 Stimulationen in 137 Fällen ein OHSS °III beobachtet (0,3%, vgl. Abb. 6). Seit einigen Jahren ist zur Vermeidung des höhergradigen OHSS ein spezielles Stimulationsprotokoll beschrieben worden (so. Agonist-triggering im Antagonistenprotokoll), welches die Entstehung eines höhergradigen OHSS komplett verhindert, so dass in Zukunft diese ohnehin seltene Komplikation noch weiter in den Hintergrund treten wird.

Überstimulationssyndrom in Abhängigkeit von der Stimulation bei erfolgtem Transfer IVF, ICSI, IVF/ICSI 2011

	Stimulation	%	Zahl gew. Eizellen	OHSS III	OHSS III/Stim %
GnRHa-kurz	3.649	8,09	8,06	3	0,08
nur FSH	1.347		9,39	2	0,15
nur hMG	1.523		7,67	0	-
FSH und hMG	624		6,60	1	0,16
Sonstige	142		6,39	0	-
keine Angaben	13		5,54	0	-
GnRHa-lang	17.674	39,21	10,55	74	0,42
nur FSH	9.615		11,46	40	0,42
nur hMG	3.529		9,32	1	0,03
FSH und hMG	3.741		9,91	31	0,96
Sonstige	1.164		8,74	2	0,17
keine Angaben	125		9,22	0	-
Ohne GnRH-Analoga	4.354	9,66	8,19	6	0,14
nur FSH	1.438		10,07	4	0,28
nur hMG	793		8,81	1	0,13
FSH und hMG	771		9,09	1	0,13
Sonstige	538		6,44	0	-
keine Angaben	814		4,56	0	-
GnRH-Antagonisten	19.401	43,04	8,86	54	0,28
nur FSH	11.068		10,39	45	0,41
nur hMG	3.451		7,15	4	0,12
FSH und hMG	2.282		7,11	3	0,13
Sonstige	2.468		6,19	1	0,04
keine Angaben	132		5,98	1	0,76
Summe	45.078	100,00	9,40	137	0,30

Es wurden nur prospektiv erfasste Daten verwendet.

Abb. 6: Häufigkeit eines Überstimulationssyndroms.
Aus: J Reproduktionsmed Endokrinol 2012: 9(6)31

- Mehrlingsschwangerschaften sind im Vergleich zu einer natürlich entstandenen Schwangerschaft (Häufigkeit hier ca. 1:85 Geburten) bei der künstlichen Befruchtung deutlich häufiger. Das Embryonenschutzgesetz (ESchG) schreibt vor, dass maximal 3 Embryonen pro Transfer in die Gebärmutter der Frau übertragen werden dürfen (§1(1)3 ESchG), faktisch ist die Anzahl der übertragenen Embryonen in Deutschland auch seit vielen Jahren rückläufig (Abb.7).

  Dennoch wird eine Mehrlingsschwangerschaft billigend in Kauf genommen, die betroffenen Paare entscheiden sich in den misten Fällen dazu, 2 Embryonen transferieren zu lassen. Dies führt dazu, dass nur 64% der Geburten nach IVF oder ICSI in Deutschland Einlingsgeburten sind. Erfreulicherweise ist aber durch die Verbesserung der Kulturbedingungen und durch die Möglichkeit, entwicklungsfähige Embryonen zu identifizieren, die Rate an Einlingsgeburten in den letzten Jahren sukzessive gestiegen (Abb. 8). Auch ist die Rate an höhergradigen Mehrlingsschwangerschaften (insbes. Drillinge), welche in besonderem Maße risikobehaftet sind, deutlich gesunken (Abb. 8).

Transferierte Embryonen/Zyklus (MW*) und Kinder IVF, ICSI 1997 - 2011
(prospektiv und nicht prospektive Daten)

		1997	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IVF	Transf. Embryo.	2,49	2,29	2,25	2,19	2,17	2,15	2,11	2,08	2,08	2,06	2,03	2,01	1,99
	Kinder/Transfer	0,21	0,23	0,24	0,22	0,23	0,23	0,24	0,25	0,25	0,24	0,24	0,22	0,15
	Kinder/Geburt	1,31	1,28	1,27	1,26	1,26	1,25	1,23	1,23	1,24	1,24	1,22	1,24	1,26
ICSI	Transf. Embryo.	2,56	2,39	2,30	2,21	2,17	2,15	2,11	2,09	2,08	2,08	2,06	2,05	2,02
	Kinder/Transfer	0,22	0,23	0,24	0,22	0,23	0,23	0,24	0,24	0,24	0,23	0,23	0,22	0,15
	Kinder/Geburt	1,29	1,26	1,23	1,23	1,23	1,22	1,22	1,20	1,21	1,22	1,21	1,21	1,22
Kryo -ET	Transf. Embryo.	2,34	2,25	2,20	2,14	2,12	2,14	2,10	2,10	2,07	2,07	2,05	2,04	2,02
	Kinder/Transfer	0,10	0,12	0,12	0,12	0,12	0,12	0,14	0,14	0,14	0,14	0,14	0,14	0,10
	Kinder/Geburt	1,14	1,16	1,16	1,16	1,16	1,17	1,16	1,16	1,16	1,15	1,16	1,16	1,18

Abb. 7: Rückgang der Anzahl übertragener Embryonen seit 1997.
Aus: J Reproduktionsmed Endokrinol 2012: 9(6)20

DIR

Geborene Kinder 1997 - 2011
prospektive und retrospektive Daten

IVF, ICSI, IVF/ICSI

	Einlinge		Zwillinge		Drillinge		Vierlinge		Gesamt
	n	%	n	%	n	%	n	%	n
2001 *	6.798 (6.774)	60,89 (61,04)	3.956 (3.919)	35,43 (35,31)	411 (405)	3,68 (3,65)	0 (0)	- -	11.165 (11.098)
2002 *	7.746 (7.724)	62,59 (62,78)	4.256 (4.210)	34,39 (34,22)	366 (362)	2,96 (2,94)	8 (7)	0,06 (0,06)	12.376 (12.303)
2003 *	10.723 (10.688)	62,13 (62,78)	5.960 (5.866)	34,53 (34,22)	552 (533)	3,20 (2,94)	24 (24)	0,14 (0,14)	17.259 (17.111)
2004 *	5.368 (5.352)	63,69 (62,46)	2.826 (2.801)	33,53 (34,28)	234 (223)	2,78 (3,11)	0 (0)	- -	8.428 (8.376)
2005 *	5.527 (5.515)	63,84 (63,90)	2.936 (2.906)	33,91 (33,44)	183 (179)	2,11 (2,66)	12 (11)	0,14 (0,13)	8.658 (8.611)
2006 *	5.906 (5.894)	65,50 (64,05)	2.922 (2.890)	32,41 (33,75)	189 (174)	2,10 (2,08)	0 (0)	- -	9.017 (8.958)
2007 *	6.663 (6.628)	65,45 (64,69)	3.504 (3.471)	33,95 (33,88)	150 (143)	1,45 (1,40)	4 (4)	0,04 (0,04)	10.321 (10.246)
2008 *	6.696 (6.672)	64,09 (64,34)	3.528 (3.481)	33,77 (33,57)	216 (209)	2,07 (2,02)	8 (8)	0,08 (0,08)	10.448 (10.370)
2009 *	7.253 (7.217)	65,89 (66,02)	3.560 (3.523)	32,34 (32,23)	186 (183)	1,69 (1,67)	8 (8)	0,07 (0,07)	11.007 (10.931)
2010 *	6.767 (6.724)	64,42 (64,62)	3.554 (3.507)	33,83 (33,70)	183 (175)	1,74 (1,68)	0 (0)	- -	10.504 (10.406)
2011 *	4.671 (4.645)	63,64 (63,95)	2.498 (2.457)	34,03 (33,82)	171 (162)	2,33 (2,23)	0 (0)	- -	7.340 (7.264)

*) Die Werte in Klammern geben die Lebendgeburten an. Als Summen über alle Jahre (1997 - 2011) ergeben sich folgende Werte: Einlinge 92.314 (88.946), Zwillinge 50.242 (49.637), Drillinge 5.074 (4.818), Vierlinge 88 (85); gesamt: 147.618 (146.486)

Abb. 8: Häufigkeit von Mehrlingsgeburten nach IVF und ICSI
Aus: J Reproduktionsmed Endokrinol 2012: 9(6)29

Frage 6: Gibt es Gründe für eine Beschränkung auf verheiratete Paare? Wenn ja, welche wären das? Welche medizinischen Gründe gibt es, Reproduktionsmedizin auf bestimmte Paare zu beschränken?

Ein grundsätzlicher Ausschluss von Männern und Frauen unter 25 Jahren sowie von Frauen über 40 Jahren und Männern über 50 Jahren zur Bezahlung von Maßnahmen der künstlichen Befruchtung erscheint medizinisch und sozial nicht zeitgemäß.

Eine Begrenzung des Bezahlungsmodus auf den Ehestatus ist politisch und sozial ebenfalls nicht zeitgemäß.

Aus medizinischer Sicht gibt es keinerlei Gründe, eine reproduktionsmedizinische Behandlung auf verheiratete Paare zu beschränken.

Frage 7: *Wie stellt sich die Situation für gleichgeschlechtliche Paare dar, die sich ein Kind wünschen und dazu auf künstliche Befruchtung angewiesen sind? Erhalten sie eine finanzielle Unterstützung seitens der GKV oder aus dem Bundesprogramm?*

Nein. Auch wenn die heterologe Insemination oder IVF, also die Behandlung mit Fremdsperma, in Deutschland prinzipiell erlaubt ist, erhalten diese Paare keinerlei finanzielle Unterstützung seitens der GKV oder aus dem Bundesprogramm. Eine Behandlung gleichgeschlechtlicher Paare wäre in Deutschland aufgrund des Verbotes der Eizellspende und der Leihmutterschaft aber nur bei lesbischen Partnerschaften möglich.

Frage 8: *Wie stehen Sie zu einer Ausweitung der Regelung unter Einbeziehung unverheirateter und gleichgeschlechtlicher Paare?*

Uneingeschränkt positiv bei Anwendung innerhalb der legalen Möglichkeiten!

Allerdings wären familienrechtliche Fragen zu klären, so dass dem geborenen Kind später auf Wunsch die genetische Herkunft bekannt gemacht werden kann, ohne dass es zu einer möglichen Unterhalts- und Erbschaftspflicht kommen kann.

Frage 9: *Wie erfolgreich ist die Behandlung im Vergleich mit dem natürlichen Weg für ein Paar schwanger zu werden?*

Dieser Vergleich ist nicht ganz einfach. Die Behandlungsdaten jeder einzelnen IVF und ICSI in Deutschland werden dem Deutschen IVF-Register prospektiv übermittelt und dort auf Plausibilität überprüft und ausgewertet. Für natürlich entstehende Schwangerschaften gibt es zwar naturgemäß keine Datenbanken in diesem Umfang, aber einzelne Studien zu dieser Fragestellung erreichen auch eine repräsentative Zahl an überwachten Zyklen. Eine deutsche Arbeitsgruppe, welche sich mit natürlicher Familienplanung beschäftigt, hat in 2003 eine Auswertung von 346 Paaren mit bis zu 21 Zyklen publiziert (Gnoth, Hum Reprod 2003(18)1959-166). Hierbei zeigten die in Abb. 9 demonstrierten Schwangerschaftswahrscheinlichkeiten:

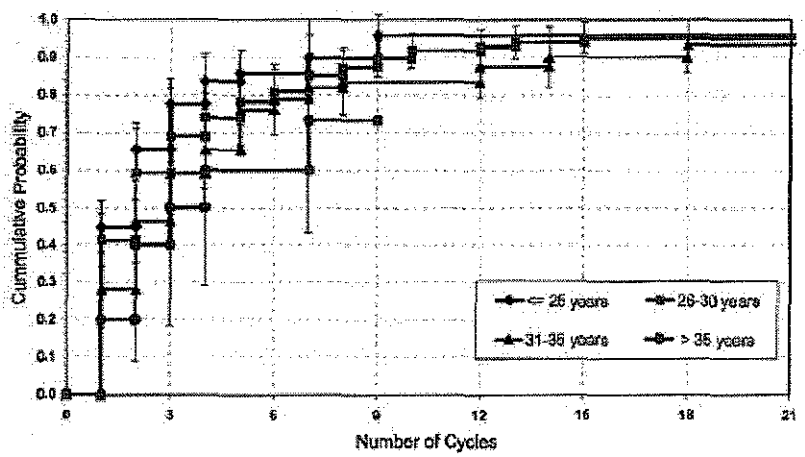


Abb. 9: Kumulative Schwangerschaftsrate abhängig von der Anzahl der Zyklen und Alter der Frauen. Aus: Hum Reprod 2003 (18) 1963

Die Wahrscheinlichkeit einer reproduktiv gesunden Frau im Alter zwischen 31 und 35 Jahren innerhalb von 4 Zyklen, in denen das Paar zum optimalen Zeitpunkt Verkehr hat, schwanger zu werden, liegt danach bei ca. 60%, nach 6 Zyklen bei ca. 75%.

Die gleiche Arbeitsgruppe konnte 2011 zeigen, dass die kumulative **Lebendgeburt**rate nach künstlicher Befruchtung in derselben Altersgruppe nach 4 Zyklen bei ebenfalls ca 60% lag (Abb. 10). Die **Schwangerschafts**rate nach 6 Zyklen assistierter Reproduktion wird von den Autoren dieser Studie mit 79% angegeben (Gnoth, Hum Reprod 2011)

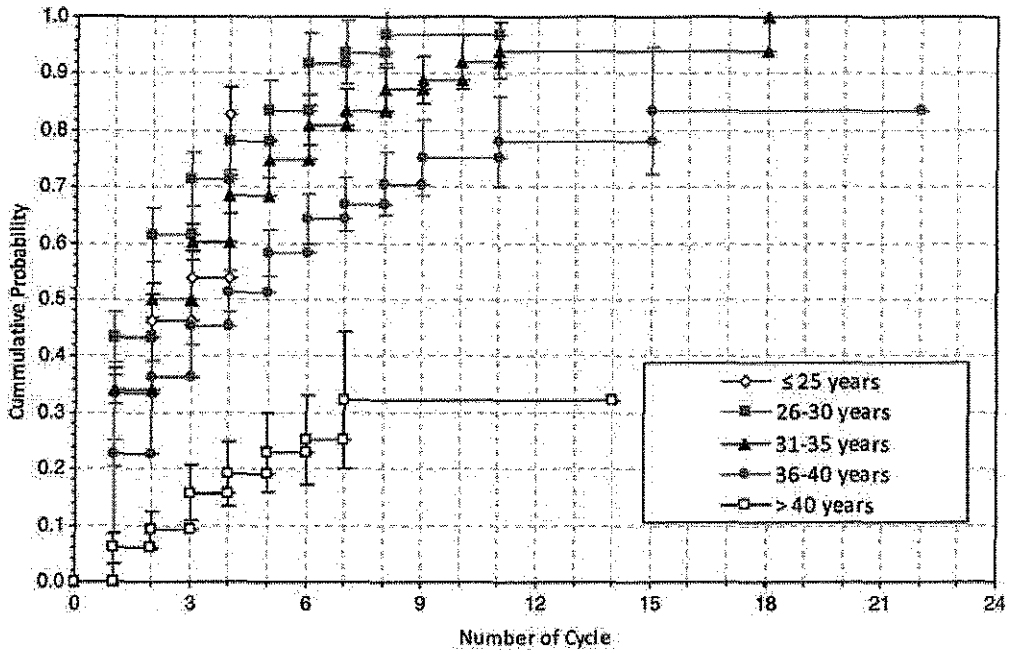


Abb. 10: Kumulative Schwangerschaftsrate abhängig von der Anzahl der Zyklen und Alter der Frauen. Aus: Hum Reprod 2011 (26) 2242

Damit sind die Schwangerschaftsraten annähernd vergleichbar.

Frage 10: *Warum ist die Zahl der von der Gesetzlichen Krankenversicherung anteilig finanzierten assistierten Reproduktionen auf 3 begrenzt? Wie hat sich die Zahl der Behandlungen seit der Kappung der Finanzierung durch die GKV von 4 auf 3 Behandlungen entwickelt?*

Es gibt, gerade auch bei Kenntnis der Daten aus Abb. 10 keinerlei medizinische Gründe für eine Beschränkung der von der Gesetzlichen Krankenversicherung anteilig finanzierten assistierten Reproduktionen auf 3 Behandlungen. Wenn eine Patientin nach 3 Behandlungen ohne Eintritt einer Schwangerschaft die Behandlung beendet, wird ihr dadurch die weiterhin hohe Chance auf eine Schwangerschaft genommen.

Die Anzahl der Behandlungen insgesamt hat seit 2004, also auch seit der Kappung der Finanzierung durch die GKV von 4 auf 3 Behandlungen, deutlich (vgl. Abb. 1, anfänglich um mehr als 50%) verringert.

Frage 11: *Die hier diskutierte Unterstützung der ungewollt kinderlosen Paare aus Steuermitteln ist mit Kosten für das Land Nordrhein-Westfalen verbunden. Wie bewerten Sie das?*

Die Kosten für die diskutierten Maßnahmen sind vergleichsweise gering und daher aus meiner Sicht absolut vertretbar. Schließlich ist es aus demografischer Sicht zwingend geboten, die Bevölkerungszahl durch eine Steigerung der Geburtenrate zu erhöhen. Eine Studie aus den U.S.A. (Connolly, Am J Manag Care 2008 (14) 598-604), in denen die reproduktionsmedizinische Behandlung deutlich (bis zu 5x) teurer ist als in Deutschland konnte zeigen, dass der Staat über Steuereinnahmen selbst in der ungünstigsten Konstellation eine deutlich positive Bilanz erreicht (Abb. 11).

■ **Table 1.** Discounted Lifetime NetTax Contributions and Breakeven Ages Based on Average Employment and on Full Employment[a]

Method of Conception and Age of Mother, y	Age-adjusted Cost per Live Birth Using IVF, US $[b]	Average Employment		Full Employment (ages 20-64 y)	
		Breakeven Age, y	Discounted Lifetime Net Tax Contribution, US $	Breakeven Age, y	Discounted Lifetime Net Tax Contribution, US $
Natural, all ages	Not applicable	37	190,515	34	292,285
IVF					
<35	27,373	40	160,540	36	266,310
35-37	32,041	40	155,870	37	257,640
38-40	43,509	41	144,405	38	246,175
41-42	158,225	44	116,240	40	218,007

IVF indicates in vitro fertilization.
[a]The average employment model assumes that individuals graduate from high school and then follow the average higher education, employment, and unemployment trends. The full employment model assumes full-time education from ages 6 to 19 years, with full-time employment from age 20 years until retirement at age 65 years. The breakeven point is the age at which the financial position between an individual and the state becomes positive in favor of the state.
[b]Derived from the mean IVF cost per cycle divided by the age-adjusted probability of live birth.

Abb. 11: Aus: Am J Manag Care 2008 (14) 589-604

Frage 12: *Wie sind die Erfahrungen in anderen Bundesländern mit dem Bundesprogramm zur künstlichen Befruchtung?*

Zu dieser Frage kann ich keine fundierte Auskunft geben.

Frage 13: *Wie hoch sind die Kosten der Behandlung und können sich ärmere Paare die auf sie entfallende anteilige Finanzierung leisten?*

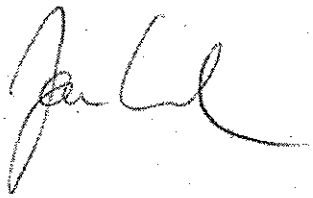
Der 50% Eigenanteil der gesetzlich versicherten Paare, welche die Leistungsvoraussetzungen erfüllen, beträgt - abhängig von der benötigten Dosis der Medikamente für die ovarielle Stimulationsbehandlung - ca. 1.500€ für eine ICSI-Behandlung. Dies liegt in vielen Fällen weit oberhalb der finanziellen Möglichkeiten der Paare, wodurch ein großer zusätzlicher Druck aufgebaut wird.

Frage 14: *Aus welchen Gründen haben Bundesregierung und Bundestagsmehrheit das vom Bundesrat 2012 beschlossene Kinderwunschförderungsgesetz (Bundesrats-Drucksache 478/11) zu einer bundesgesetzlich verbindlichen finanziellen Entlastung von einkommensschwachen Paaren mit unerfülltem Kinderwunsch abgelehnt?*

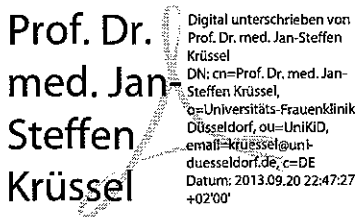
Zu dieser Frage kann ich keine fundierte Auskunft geben.

Für Rückfragen stehe ich gerne zur Verfügung!

Mit freundlichen Grüßen



Professor Dr. med. Jan-Steffen Krüssel



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Review

Maternal, perinatal and long-term outcomes after assisted reproductive techniques (ART): implications for clinical practice

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ABSTRACT

The use of assisted reproductive techniques (ART) is on the rise throughout the world and the number of babies born as a result of ART has reached an estimated total of 5 million since the world's first, Louise Brown, was born in 1978. Data from many prospective and retrospective studies have suggested increased risks of adverse maternal, perinatal and long-term outcomes after ART compared to natural conception. Recent research suggests that underlying maternal factors rather than ART methods themselves play a significant role in causing such outcomes. Couples attempting ART need to be provided with accurate and reliable information on risks of adverse reproductive outcomes and reassured that absolute risks appear small. Clinicians need to remain vigilant about increased risk of pregnancy complications and formulate a plan of care for the woman, from periconception to the puerperium, which aims to prevent or minimise maternal and perinatal morbidity. This review attempts to summarise the available data on reproductive outcomes after ART and provide guidance to the obstetricians and primary care physicians about management of ART pregnancies.

Contents

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1. Introduction

Assisted reproductive techniques (ART) include all fertility treatments in which the gametes (egg and sperm) are handled outside the human body with the aim of achieving a healthy conception. Common ART procedures include in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI), fresh or frozen embryo transfer, and IVF with donor oocytes. Since the birth of the first IVF baby in 1978, the use of ART has increased tremendously and 1.7–4.0% of all children born today in developed countries are conceived through the use of ART [1–3]. Advances in ART procedures, increased access to fertility services and delayed child bearing are all factors contributing to a rise in the use of ART services.

Since the early reports in 1985, several cohort and case control studies have reported increased risks of pregnancy complications such as miscarriage, ectopic pregnancy, congenital anomalies, preterm birth, low birth weight, gestational diabetes and pre-eclampsia in ART pregnancies compared to naturally conceived pregnancies [4–13]. A number of systematic reviews, meta-analyses and large population-based studies have also supported findings of an increased risk of adverse obstetric outcomes from ART conceptions, especially for singleton pregnancies compared to twin pregnancies (Table 1) [14–20]. It is important, however, to remember that the absolute risks appear small and the majority of births after ART are uncomplicated.

The reasons for this observed increase in the risk of adverse reproductive outcomes are unclear. It is not know whether it is the technology (hormonal stimulation, gamete manipulation, cryopreservation and in vitro culture) or the underlying maternal factors which play a greater role in causing adverse outcomes. While some studies have pointed out a role for controlled ovarian hyperstimulation or cryopreservation in altering pregnancy outcome [21–23], others have suggested that maternal factors such as age, ethnicity, medical conditions or cause of subfertility are more important determinants [24,25].

2. Maternal outcomes

2.1. First trimester

Several studies have reported a higher incidence of ectopic pregnancies and spontaneous miscarriage (17–32.6%) in ART pregnancies compared to naturally conceived pregnancies, with possible causes being tubal disease, uterine anomalies, increasing maternal age and chromosomal abnormalities in the conceptus [5,26,27].

2.2. Second and third trimesters

2.2.1. Gestational diabetes and hypertension in pregnancy

Studies have reported an increased risk of gestational hypertension, pre-eclampsia, gestational diabetes and abruption in ART conceptions [5,14,27–30]. A significantly increased risk of pre-eclampsia in singleton pregnancies after single embryo transfer (SET) and double embryo transfer (DET) including fresh and cryopreserved cycles has been reported when compared with singleton pregnancies in the general population. Maternal age, subfertility, underlying chronic conditions or abnormal placentation may contribute towards the increased risks.

2.3. Low lying placenta

A three- to six-fold increased risk of placenta praevia has been reported in ART pregnancies [31] and it has been suggested that this may be related to embryo transfer into the lower part of uterine cavity.

2.4. Obstetric interventions

Many authors have reported an increased rate of caesarean delivery rate in IVF pregnancies [5,32]. The increased rates may be attributed to patient anxiety and physician preference regarding the mode of delivery rather than an increase due to obstetric indications alone.

3. Perinatal outcomes

3.1. Low birth weight and preterm birth

Several systematic reviews and meta-analyses have repeatedly reported higher rates of low birth weight, preterm birth and perinatal mortality in ART pregnancies compared to spontaneous conceptions (Table 1). This excess risk of adverse outcomes stems not only from higher rates of multiple pregnancies in ART births, but it is noted even when singleton ART pregnancies are compared with natural ones.

3.2. Congenital birth defects

In ART children the risk of congenital anomalies is slightly increased (by 15–40%) compared with spontaneously conceived children after adjustments for relevant confounders. Conflicting evidence exists, however, and the absolute numbers remain small. The scientific paper by Royal College of Obstetricians and Gynaecologists (RCOG) in United Kingdom (UK) has suggested that IVF is associated with a 30–40% increased risk of major congenital anomalies compared with natural conceptions [33]. The possible increase in birth defects after ART may be related to the hormonal treatment or the techniques, but subfertility or parental factors may also play a role. A recent large Australian study found that the increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors. The risk of birth defects associated with ICSI remained increased after multivariate adjustment, although the possibility of residual confounding still could not be excluded [34].

Table 1
Systematic reviews and large population based studies comparing reproductive outcomes between ART and natural conceptions.

Study	Study population/s and sample size	Findings
Jackson et al. [14]	Meta-analysis involving studies which compared singleton pregnancies following IVF with spontaneous conceptions. Fifteen studies comprising 12,283 IVF and 1.9 million spontaneously conceived singletons.	Significantly higher odds of each of the perinatal outcomes in ART group: perinatal mortality (OR 2.2, 95% CI 1.6–3.0), preterm delivery (OR 2.0, 95% CI 1.7–2.2), low birth weight (OR 1.8, 95% CI 1.4–2.2), very low birth weight (OR 2.7, 95% CI 2.3–3.1) and small for gestational age (OR 1.6, 95% CI 1.3–2.0).
Helmerhorst et al. [15]	Systematic review on perinatal outcomes in singleton and twin pregnancies comparing natural and assisted conceptions including IVF and IUI (studies between 1985–2002). Twenty-five studies were included of which 17 had matched and 8 had non-matched controls.	For singletons, studies with matched controls indicated a relative risk (RR) of 3.27 (95% CI 2.03–5.28) for very preterm and 2.04 (1.80–2.32) for preterm birth in pregnancies after ART. Relative risks were 3.00 (2.07 –4.36) for very low birth weight, 1.70 (1.50–1.92) for low birth weight, 1.40 (1.15–1.71) for small for gestational age, 1.54 (1.44–1.66) for caesarean section, 1.27 (1.16–1.40) for admission to a neonatal intensive care unit and 1.68 (1.11–2.55) for perinatal mortality. In matched studies of twin gestations, relative risks were 0.95 (0.78–1.15) for very preterm birth, 1.07 (1.02–1.13) for preterm birth, 0.89 (0.74–1.07) for very low birth weight, 1.03 (0.99–1.08) for low birth weight, 1.27 (0.97–1.65) for small for gestational age, 1.21 (1.11–1.32) for caesarean section, 1.05 (1.01–1.09) for admission to a neonatal intensive care unit and 0.58 (0.44–0.77) for perinatal mortality.
Schieve et al. [16]	Perinatal outcomes among singleton infants conceived with ART in the US. 62551 infants born after ART treatments performed in 1996–2000.	ART infants had elevated risks for all outcomes in comparison with the general population of US singletons: low birth weight standardised risk ratio 1.62 (95% CI 1.49–1.75), very low birth weight 1.79 (1.45–2.12), preterm delivery 1.41 (1.32–1.51), preterm low birth weight 1.74 (1.57–1.90) and term low birth weight 1.39 (1.19–1.59).
McDonald et al. [17]	Systematic review including case-control and cohort studies that compared singleton pregnancies conceived by IVF or ICSI with spontaneously conceived singletons.	Singleton pregnancies resulting from IVF had increased rates of poor obstetric outcome, compared with spontaneously conceived singletons with increases in perinatal mortality (OR 2.40, 95% CI 1.59–3.63), preterm birth at <33 weeks (OR 2.99, 95% CI 1.54–5.80), preterm birth at <37 weeks gestation (OR 1.93, 95% CI 1.36–2.74), very low birth weight (<1500 g) (OR 3.78, 95% CI 4.29–5.75), small for gestational age (OR 1.59, 95% CI 1.20–2.11) and congenital malformations (OR 1.41, CI 1.06–1.88).
Boulet et al. [18]	Perinatal outcomes of twin births conceived using ART (in Massachusetts live birth-infant death records from 1997 to 2000). 1446 ART and 2729 non-ART twin deliveries.	ART twin deliveries were less likely than non-ART to be very preterm (adjusted OR 0.75, 95% CI 0.58–0.97), include a very low birth weight (<1500 g) infant (0.75, 95% CI 0.58–0.95) or infant death (0.55, 95% CI 0.35–0.88).
McDonald et al. [19]	Systematic review of seventeen studies with 31,032 singletons conceived through IVF (±ICSI) and 81,119 spontaneously conceived singletons.	IVF singletons had increased risks of preterm birth (RR 1.84, 95% CI 1.54–2.21) and low birth weight <2500 g (RR 1.60, 95% CI 1.29–1.98). Singletons conceived through IVF or IVF/ICSI also were at increased risk for late preterm birth, moderate preterm birth <32–33 weeks, very low birth weight and intrauterine growth restriction.
McDonald et al. [20]	Systematic review of twelve studies with a total of 4385 twins conceived after IVF or IVF/ICSI and 11,793 spontaneously conceived twins.	IVF twins had increased risks of both preterm birth (RR 1.23, 95% CI 1.09–1.41) and low birth weight <2500 g (RR 1.14, 95% CI 1.06–1.22). They were at increased risk for preterm birth <32–33 weeks, although the risks of late preterm birth, very low birth weight, extremely low birth weight and intrauterine growth restriction were not statistically significantly increased compared to spontaneously conceived twins.

3.3. Multiple pregnancy

Multiple pregnancies are associated with significant maternal and perinatal risks, and there is a substantial increase in multiple births after IVF compared with natural conception. Single embryo transfer is becoming increasingly recommended in ART clinics to reduce the adverse outcomes associated with multiple pregnancies. In UK, the Human Fertilisation and Embryology (HEFA) report indicates that the overall multiple pregnancy rate decreased between 2009 and 2010. The figures show that in 2008, 23.6% of fresh and frozen IVF and ICSI cycles resulted in a multiple birth, but since then clinics have been working hard to reduce this number. Data for the first half of 2009 show the figure dropped to 22.0% [3,35]. The decrease is most pronounced in women aged 18–34 years, who saw the greatest increase in elective single embryo transfer over the same period. The scientific opinion paper from the RCOG suggests that although multiple pregnancy per se is a risk factor for preterm birth; there is an additional small but statistically significant 23% increase in the relative risk of preterm birth in IVF twins compared with natural twins and that the relative contribution of spontaneous or elective preterm birth has not been identified [33]. Most data from systematic reviews and large studies (Table 1) suggest relatively better outcomes for ART twins than natural twins, in contrast to comparison of ART singletons with natural singletons. This may be due to the variation in relative proportion of dichorionic versus monochorionic twins in ART populations or simply to an effect of smaller sample sizes in twin comparison studies.

4. Long-term outcomes

4.1. Cerebral palsy

A number of studies have reported increased risks of cerebral palsy with ART [34,36], but the majority of studies reviewing neurocognitive outcomes in ART children do not suggest that ART itself leads to adverse neurological outcomes after adjustment for confounding factors such as low birth weight and prematurity.

4.2. Childhood malignancies

An increased risk of malignancies has been suggested in ART populations due to increased prevalence of structural chromosomal abnormalities in infertile men and women, and exposure to ART techniques. Confounders, however, such as increased maternal age and underlying parental factors, may play a significant role. The literature reveals conflicting reports: some studies report increased incidence of neuroblastoma, retinoblastoma, histiocytosis, acute lymphocytic leukaemia and non-Hodgkin's lymphoma while others have failed to demonstrate an increased risk [37–40]. The current evidence therefore remains inconclusive and large long-term follow-up studies are necessary to clearly define the risks of childhood cancer in the ART population and whether this risk persists or increases with age.

4.3. Epigenetics and imprinting disorders

There is evidence suggesting a link between ART and epigenetic alterations leading to DNA modifications and imprinting disorders [41,42]. Imprinting is an epigenetic modification of the genome by which genes in only one of the parental alleles are expressed. Several reports have suggested a possible link between ART and various imprinting disorders including Beckwith–Wiedemann Syndrome (BWS), Angelman Syndrome (AS) and maternal hypomethylation syndrome [43]. The cardinal features of BWS are pre- and post-natal overgrowth, abdominal wall defects, visceromegaly, macroglossia and neoplasias. The typical features of AS comprise microcephaly with mental/motor retardation, epilepsy, ataxic gait or complete inability to walk, muscle hypotonia, protruding jaw and tongue, occipital depression and hypopigmented eyes. Based on current evidence however, the absolute risk of imprinting disorders after ART remains small and does not warrant routine screening. Large prospective, multicentre studies are necessary to ascertain whether this association is definitive.

4.4. Growth characteristics and cardiovascular health

As regards patterns of growth in ART children, the majority of studies evaluating height, weight, and body mass index have not found significant differences between ART and naturally conceived children but some studies have indicated differences in adiposity by measuring skinfolds and dual X-ray absorptiometry [44].

It has been hypothesised that epigenetic mechanisms in early pregnancy, as well as higher rates of low birth weight and preterm birth in ART babies, may predispose them to cardiovascular and metabolic problems in future life. While some studies have provided evidence for increased blood pressure among children conceived by IVF/ICSI [45–47], conflicting data exist and long-term studies with large sample sizes are needed to explore these findings further.

5. Recommendations for clinical practice

5.1. Periconceptional period

5.1.1. Counselling, ovulation induction and embryo transfer

From a clinician's point of view, it is very important that appropriate information is provided to the patients about the benefits and adverse effects of different ART treatments. This should assist the couple in making informed decisions about the various ART treatments available to them. A thorough history should be obtained to recognise any pre-existing medical conditions or fetal abnormalities in the family in order to facilitate referral to appropriate medical team or genetic counselling. All men with severe oligozoospermia or azoospermia should be offered genetic counselling and karyotyping for chromosomal abnormalities and cystic fibrosis before attempting IVF–ICSI. They should be made aware of the availability of tests for Y chromosome micro-deletions. Couples considering IVF–ICSI for male factor infertility should receive information, and if necessary genetic counselling, about the increased risk of chromosomal abnormalities associated with their condition. Prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis should be offered to these couples if they conceive [48].

Ovulation induction in the woman should be monitored carefully in order to achieve monofollicular stimulation. The ovarian stimulation strategies should avoid maximising oocyte yield (avoid hyperstimulation), but aim to generate a sufficient number of chromosomally normal embryos by reduced interference with ovarian physiology. Many clinics now recommend low-dose gonadotrophin protocols to achieve this. A recent study suggested that elective cryopreservation of all embryos in patients with elevated peak serum oestradiol, for subsequent cryothaw embryo transfer in cycles with a better physiologic hormonal milieu, may reduce the odds of small for gestational age babies and pre-eclampsia in IVF singleton deliveries [49]. Greater emphasis should be placed on single embryo transfer. The use of elective single embryo transfer combined with cryopreservation of spare embryos can minimise multiple pregnancies.

5.1.2. Optimising maternal health

Opportunity should be taken to optimise the woman's health and control preventable risk factors before embarking on a pregnancy.

Diet and supplementation: Women should be given information on the benefits of a healthy diet before and during pregnancy. The advice must be based on individual woman's circumstances but should include the following if possible: five portions of fruit and vegetables a day and one portion of oily fish (for example, mackerel, sardines, pilchards, herring, trout or salmon) a week [50]. Dietary advice should also include avoidance of raw or partially cooked eggs, meat and pâté, to avoid food borne infections. Folic acid reduces the risk of neural tube defects in the fetus by up to 75%, and 400 micrograms daily is recommended for all women from 12 weeks prior to conception until 12 weeks of pregnancy. A higher dose of 5 mg per day may be necessary in women with history of neural tube defects in the past or the family, obesity, diabetes, anticonvulsant therapy, alcohol abuse and malabsorption. National Institute for Health and Clinical excellence (NICE, UK) guidelines recommend vitamin D supplementation (10 micrograms per day) for all women during pregnancy and while breastfeeding. Those at particular risk include women who are obese, have limited skin exposure to sunlight or who are of South Asian, African, Caribbean or Middle Eastern descent [51].

Lifestyle modifications should be advised, to control risk factors such as obesity, smoking and alcohol abuse. Pregnant women should avoid smoking or drinking because of their association with adverse pregnancy outcomes. Women who choose to drink alcohol during pregnancy are advised not to drink more than 1–2 UK units once or twice a week (1 unit equals half a pint of ordinary strength lager or beer, or one shot [25 ml] of spirits. One small [125 ml] glass of wine is equal to 1.5 UK units) [51].

Woman's rubella status also should be checked before the pregnancy. Most women are now immunised in childhood or have natural antibodies due to prior infection. Vaccination should be offered to those who are non-immune. Good control of chronic medical conditions such as diabetes, anaemia, epilepsy and hypertension should be achieved. In diabetic women, good glycemic control reduces the incidence of fetal abnormalities and other complications. Retinopathy and nephropathy screening

and, if required, treatment of retinopathy should be completed before conception to reduce risk of deterioration. Drug therapy for epileptic patients should be optimised so as to utilise the minimum number of drugs required to achieve a good seizure control.

5.2. Early pregnancy

One of the key features of caring for women with pregnancies after ART is developing an effective care plan during the antenatal period.

5.2.1. Risk assessment at beginning of pregnancy

An assessment of risk factors for venous thromboembolism should be undertaken early in pregnancy. Thromboprophylaxis with low molecular weight heparin should be considered for those at high risk, based on scoring as per the RCOG guidelines [52]. NICE guidelines in UK recommend aspirin therapy for women at high risk of pre-eclampsia to prevent or reduce the severity of the condition [51]. As ART pregnancies are at a high risk of pre-eclampsia, women should be advised to take 75 mg of aspirin daily from 12 weeks until the birth of the baby.

5.2.2. Prenatal screening and diagnosis

All women should be offered an ultrasound scan between 10 and 14 weeks of pregnancy to establish viability, check nuchal translucency and for dating of pregnancy. In cases of multiple gestation, the chorionicity and amniocity should be established. The UK National Screening Committee and NICE recommend a dating scan and an 18–20 + 6 weeks fetal structural anomaly ultrasound scan for all pregnant women [51]. Screening for Down's syndrome should be performed by the end of the first trimester but provision should be made to allow later screening for women booking later in pregnancy. NICE recommends the 'combined test' (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) for Down's syndrome screening between 11 and 13 + 6 weeks. For women who book later in pregnancy the most clinically- and cost-effective serum screening test (triple or quadruple test) should be offered between 15 and 20 weeks [51].

If the prenatal tests suggest a significant risk of Down's syndrome, the woman should be referred to a fetal medicine unit for diagnostic tests such as amniocentesis or CVS. Such screening needs to be particularly emphasised in low-resource settings where ART pregnancies should be identified as a group who have a slightly increased risk of congenital anomalies and are therefore in need of these tests.

5.3. Second and third trimesters of pregnancy

Weight should be monitored in the antenatal period in those women with a booking body mass index (BMI) below 20 or above 30 kg/m^2 to assess progress in weight management. Obesity is an increasing problem in obstetrics and needs multidisciplinary input from dietician, anaesthetic, neonatal and the midwifery teams to ensure optimum care.

Multiple pregnancies after ART are particularly at risk of anaemia and should have a full blood count at 20–24 weeks in addition to booking bloods to identify a need for early supplementation with iron or folic acid. Screening should be repeated at 28 weeks as in routine antenatal care.

5.3.1. Monitoring of blood pressure

Keeping in mind the high risk of hypertensive disease in ART pregnancies, blood pressure (BP) should be closely monitored throughout the pregnancy. BP should be measured and urinalysis for proteinuria undertaken routinely at each antenatal visit. BP should ideally be measured in a sitting position with the arm at the level of the heart and a correct size cuff. Hypertension in pregnancy is defined as two readings of 140/90 mmHg or more taken at least 4 h apart, using Korotkoff V for the diastolic sound.

5.3.2. Assessment of fetal growth

The two clinical methods used to assess fetal growth are symphysis-fundal height (SFH) measurement and abdominal palpation. SFH measurements (in centimetres) give a more objective assessment of uterine size and serial measurements give an indication of the fetal growth rate. A discrepancy of 3 or more centimetres from the gestational age in weeks is considered abnormal between 24 and 34 weeks. Although the sensitivity of SFH is low, it is a useful tool requiring minimal equipment, training and time [53]. Both NICE and RCOG guidelines recommend that SFH should be routinely measured from 24 weeks. SFH should be plotted on a customised chart rather than a population-based chart as this may improve prediction of a small for gestational age neonate. Women with a single SFH which plots below the 10th centile or serial measurements which demonstrate slow or static growth by crossing centiles should be referred for ultrasound measurement of fetal size [51,54]. Women in whom measurement of SFH is inaccurate (for example; BMI $>$ 35, large fibroids, hydramnios) should be referred for serial assessment of fetal size using ultrasound [54].

5.3.3. Screening for gestational diabetes and pre-eclampsia

NICE recommends that at the booking appointment, risk factors for gestational diabetes should be determined, including: BMI above 30, previous macrosomic baby weighing 4.5 kg or above, previous gestational diabetes, family history of diabetes (first-degree relative with diabetes, family origin with a high prevalence of diabetes, South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh), Black Caribbean and Middle Eastern (specifically women whose country of family origin is Saudi Arabia, UAE, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt) [51]. A 2 h 75 g oral glucose tolerance test (OGTT) should be offered at 16–18 weeks to test for gestational diabetes if the woman has had gestational diabetes previously, followed by an OGTT at 28 weeks if the first test is normal. NICE advises that an OGTT should be offered at 24–28 weeks if the woman has any other risk factor [51] but given the high risk of diabetes in the ART population, all ART pregnancies should be screened for gestational diabetes with an OGTT at 24–28 weeks even if they do not have any of the above risk factors. If diabetes is detected, the pregnancy should be managed in a joint diabetic clinic with multidisciplinary support.

Although there is a great deal of literature on screening methods for pre-eclampsia, none of these have satisfactory sensitivity and specificity, and therefore they are not currently recommended by NICE. Given the high risk developing hypertension in ART pregnancy, however, screening for pre-eclampsia may help identify women who are potentially high risk of developing severe disease, and they can be offered close blood pressure monitoring and fetal growth surveillance throughout the pregnancy. Abnormal waveforms in the uterine artery, such as increased pulsatility index (PI) with notching on Doppler ultrasound, have been reported to be a good predictor of pre-eclampsia and growth restriction in high risk women (positive likelihood ratio 21) [55,56]. Bilateral uterine artery notching or a mean PI above the 95th centile of the normal range indicates increased impedance of blood flow. It is known that the presence of either of these two factors at 23–24 weeks' gestation in a routine antenatal population identifies 40% of women who later develop pre-eclampsia [57]. Second trimester uterine Doppler screening alone or in combination with pregnancy-associated protein A (PAPP A)

levels is now being offered in many obstetric units as a screening test for pre-eclampsia. The addition of angiogenic factors (sFlt- 1/PIGF ratio) to Doppler ultrasound analysis further improves the power to predict pre-eclampsia in the second trimester, with a sensitivity and specificity of 98% and 95% respectively [58].

5.3.4. Ultrasound and Doppler in ART pregnancies

A second trimester detailed anomaly scan with fetal echocardiography (four-chamber and outflow tract view) is recommended in all patients at 18–24 weeks to rule out any structural anomalies and also to identify any markers of chromosomal abnormalities. If anomalies are detected, woman should be referred to the fetal medicine unit which could provide expert multidisciplinary care and arrange delivery in a unit with specialised neonatal care. The placental site should be established at this scan and if the placenta appears low lying, a rescan should be arranged at 34 weeks to facilitate the planning of mode of delivery. Further ultrasound scans in pregnancy may be performed only if indicated for a clinical reason such as suspected fetal growth restriction (decreased SFH on palpation), abnormal liquor volume or to undertake studies of umbilical artery Doppler and biophysical profile. A low threshold should be maintained for growth scans for suspected fetal growth restriction in view of the higher risk of low birth weight in ART pregnancies. The presence of multiple risk factors besides ART or any clinical suspicion should be followed by serial ultrasound measurement of fetal size and assessment of wellbeing with umbilical artery Doppler from 26 to 28 weeks of pregnancy.

Recent RCOG guidelines suggest that a low level (<0.415 MoM) of the 1st trimester marker PAPP A should be considered a major risk factor for delivery of a small for gestational age neonate [54].

Monitoring for intrauterine growth restriction in multiple pregnancy: Serial ultrasound biometry of twins with adjunctive use of Doppler is necessary to detect abnormal growth or discrepant growth between twins and abnormalities of placentation. Fetal weight discordance should be estimated using two or more biometric parameters at each ultrasound scan from 20 weeks as per NICE guidelines [59]. Scans should be undertaken at intervals of less than 28 days. A 25% or greater difference in size between twins or triplets should be considered a clinically important indicator of growth restriction and the woman should be referred to a tertiary level fetal medicine centre [59].

5.3.5. Cervical length screening

Given the increased incidence of preterm labour in the ART group, cervical length screening may be recommended for high risk women if they have a previous history of late miscarriage before ART. Sonographic assessment of the cervix is usually performed between 14 and 24 weeks of gestation. Selective cervical cerclage and vaginal progesterone therapy (200 mg/day) from the second trimester may be recommended in women with multiple risk factors for preterm birth or where ultrasound assessment suggests a high risk (cervix is 25 mm or less before 24 weeks of gestation).

5.4. Labour and delivery

Intrapartum electronic fetal heart rate monitoring should be recommended to all women who conceived after ART with the aim of early detection and prevention of potential hypoxia during labour. Due to the inherent precious nature of ART pregnancies, both obstetricians and parents often choose caesarean section as a safer approach where the timing and events can be controlled to ensure safe delivery of the baby. In terms of clinical outcomes, however, there is no advantage in doing a caesarean without a medical indication and the decision should be taken only after through discussion of risks and benefits with the patient, especially in relation to future pregnancies. The decision should be based on the woman's individual circumstance and her wishes should be respected as long as clinically reasonable.

5.5. Postnatal period

Breast feeding should be actively encouraged and supported. Careful attention should be paid to ongoing thromboprophylaxis. Many of the long-term outcomes of assisted reproduction are difficult to evaluate due to the variability in ART methods as well as data reporting and there is a need for a standardised methodology for follow-up of children born after ART. Every clinic should therefore strive to continue collecting data in the immediate postnatal period as well as the long-term outcomes of children born from ART pregnancies.

6. Summary

As the use of ART rises across the world, obstetricians will have to care for increasing numbers of women who have conceived after assisted conception. Present data suggest an increased risk of adverse maternal and perinatal outcomes for ART pregnancies but the absolute risks appear small. The current evidence regarding childhood outcomes is inadequate and prospective long-term studies are needed to eliminate the effect of confounders and draw definite conclusions about long-term outcomes after ART. Clinicians need to be aware of the increased complications in ART pregnancies and provide appropriate counselling and care for these women, starting from prior to conception until after delivery. All men with severe oligozoospermia or azoospermia should be offered genetic counselling and karyotyping for chromosomal abnormalities and cystic fibrosis before attempting IVF–ICSI. ART pregnancies are at a high risk of developing gestational diabetes and pre-eclampsia, and therefore screening should be undertaken for these conditions and aspirin treatment should be started from 12 weeks until the end of pregnancy. Due to the increased risk of structural and chromosomal fetal anomalies, both serum and ultrasound screening should be offered to these women. Close monitoring of fetal growth is necessary throughout pregnancy with serial biometry and, if required, Doppler ultrasound once fetal growth restriction is suspected. Couples conceiving through ART already have to deal with a considerable amount of stress arising out of the management of their subfertility. It is important therefore that obstetricians and primary care physicians provide them with accurate counselling and an effective plan of care throughout the pregnancy so as to ensure the best possible outcomes for the mother and the baby.

Conflict of interest

Neither of the authors has any conflicts of interest to declare.

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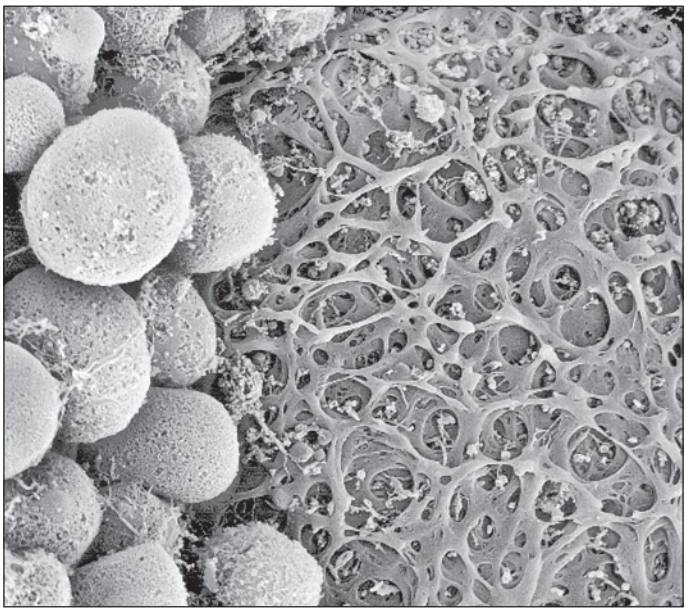


Rasterelektronenmikroskopische Aufnahme einer Eizelle mit Cumuluszellen vor der Reifung, Blick auf die Zona pellucida (Tiermodell, 2200-fache Vergrößerung).
[Quelle: Prof. Dr. med. vet. Sabine Kölle, München]

Sehr geehrte Damen und Herren, liebe Kolleginnen und Kollegen,
das Deutsche IVF-Register wird 30!

Keine vier Jahre nach der ersten Geburt nach einer IVF-Behandlung und in dem Jahr der Geburt des ersten „IVF-Babys“ in Deutschland haben sich 1982 die damals fünf aktiven Zentren zusammengeschlossen, um gemeinsam ihre Tätigkeit auf diesem Gebiet und die Ergebnisse dieser damals so neuen und für viele revolutionären Behandlung zu dokumentieren und der Öffentlichkeit zugänglich zu machen. Mit dem Register ist es uns aber nicht nur gelungen, die Ergebnisse unserer Arbeit der Wissenschaft und interessierten Öffentlichkeit darzustellen, sondern wir konnten und können zeigen, dass wir nicht im Hinterzimmer an faustischen Homunkuli experimentieren. Seit 1996 die Auswertungen in gebundener Form veröffentlicht werden, ist dieses jährlich erscheinende Jahrbuch zu einem wichtigen Nachschlagewerk für Patienten, die Ärzteschaft, Politiker und Journalisten geworden. Höchste deutsche Gerichte stützen sich in ihren Entscheidungen auf die Auswertungen. Mehr als 1,2 Millionen Zyklen wurden seit 1982 in unserem Register dokumentiert, seit 1997 wurden mehr als eine Million Zyklen elektronisch erfasst – weiterhin einzigartig in der Welt. Waren es 1982 **742** Behandlungszyklen, über die berichtet wurde, so sind es im vorliegenden Jahrbuch 2011 **80.943** Behandlungszyklen. Lassen Sie uns daran erinnern, dass es vor Einführung des GMG (Gesundheitsmodernisierungsgesetz) sogar 105.854 waren! Lag die durchschnittliche klinische Schwangerschaftsrate pro Transfer im Jahr 1982 bei 7 %, so beträgt sie 2010 nach durchgeführter IVF- oder ICSI-Behandlung 29,3 %. Die natürliche Fruchtbarkeitsrate beim Menschen liegt zwischen 27 und 30 % pro Zyklus – der Vergleich ist ein klares Indiz für die hervorragende Qualität der Reproduktionsmedizin in Deutschland, bedenkt man, dass ja bei den behandelten Paaren eine nachgewiesene Fortpflanzungsstörung vorliegt.

Bedingt durch eine Vielzahl gesellschaftlicher Veränderungen ist der Anteil der mit IVF oder ICSI behandelten Frauen in der Altersgruppe 35 und älter in den letzten 16 Jahren von 38,7 % auf 54,4 % gestiegen. Es ist aber festzuhalten, und die immens große Fallzahl des Deutschen IVF-Register erlaubt solche statischen Betrachtungen, dass, bei guter Eierstockreaktion, Frauen zwischen 40 und 42 Jahren in Deutschland Schwangerschaftschancen haben, die im Mittel zwischen 22 % und 23 % liegen. Ein ganz wesentliches und ebenfalls politisch relevantes Ergebnis ist der Nachweis, dass sich die Schwangerschaftschance einer Frau bis 35 Jahre im sechsten Behandlungszyklus nicht wesentlich von der in den drei ersten Behandlungszyklen unterscheidet. Die Annahmen aus dem Jahr 1990 und 2003 sind also nicht zutreffend und die Politik ist aufgerufen, zu handeln.

Noch immer warten die betroffenen Paare darauf, dass die vielen Ankündigungen der Politik, mehr für die Paare mit Störungen der Fortpflanzungsfähigkeit zu tun, endlich realisiert werden. In einem so reichen, aber kinderarmen Land werden die Betroffenen zwischen den verschiedenen politischen Ebenen zerrieben – beschämend. Lediglich die Länder der „Sachsenschiene“, Sachsen, Sachsen-Anhalt und ab 2013 auch Niedersachsen sehen sich in der Lage, dort wohnhafte Paare bei der Finanzierung der Kinderwunschbehandlung zu unterstützen, vorausgesetzt, sie lassen sich auch in diesem Bundesland behandeln. Der Wohnort entscheidet also über sozialpolitische Leistungen und wie hoch der durch das Paar aufzubringende Eigenanteil ist. Das darf nicht sein.

Einige gesetzliche Krankenkassen machen sich inzwischen die Möglichkeiten des GKV-Versorgungsstrukturgesetzes zunutze und bieten Paaren Satzungsleistungen an, die die enorme finanzielle Belastung der Paare durch den 50%igen Eigenanteil reduzieren und in manchen Fällen sogar die Vorgaben des §27a SGB V umgehen. Zusammen mit den Patientenpaaren begrüßen wir diese Erleichterungen.

Allen, die dazu beigetragen haben, dass das Deutsche IVF-Register in den letzten 30 Jahren seine vorzügliche Reputation in der ganzen Welt erworben hat, ist an dieser Stelle ausdrücklich zu danken. Der Dank gilt an erster Stelle allen Mitarbeiterinnen und Mitarbeitern in den reproduktionsmedizinischen Zentren. Nur durch ihr kontinuierliches und oft mühsames Zusammentragen aller relevanten Daten kann ein solches Register leben und kann die herausragende Qualität dieses Registers hochgehalten werden. Der Dank gilt auch den Mitarbeiterinnen und Mitarbeitern der Ärztekammer Schleswig-Holstein, wo in den letzten 17 Jahren die Datenauswertung erfolgte und bis zum letzten Jahr auch die Geschäftsführung. Ebenso gilt unser Dank MRU-Consulting, die jetzt die Geschäftsstelle führt und uns in der Erstellung der englischen Texte hervorragend unterstützt hat. Das Register zollt auch den bisherigen Vorsitzenden Herrn Prof. F. Lehmann, der das Register 1982 ins Leben gerufen hat, Herrn Prof. H. Rjosk und Herrn Prof. R. Felberbaum Dank. Anerkennung und Dank geht auch an alle bisherigen Mitglieder des Vorstands, des Beirats und des Kuratoriums, die alle in diesen 30 Jahren sehr viel Freizeit geopfert haben, um mit ihrem großen Engagement das Register zu dem zu machen, was es heute ist.

Ihr

Dr. med. K. Bühler
Vorstandsvorsitzender D·I·R e.V.

Reproduktionsmedizin 2011 in Deutschland: Sicher und erfolgreich

Auch im 30. Jahr nach seiner Gründung veröffentlicht das Deutsche IVF-Register (D·I·R) wieder umfassend die Daten, die mit den im Jahre 2011 in Deutschland erbrachten reproduktionsmedizinischen Leistungen in Zusammenhang stehen. Im Jahr 2011 wurden 49.696 Frauen mit extrakorporaler Fertilisation, also Befruchtung außerhalb des Körpers (Assisted Reproductive Technique [ART]) behandelt. Im Vergleich dazu waren es im Jahr 2010 47.159 Frauen. Als die (Muster-)Richtlinie Assistierte Reproduktion der Bundesärztekammer im Jahr 2000 bundesweit umgesetzt und damit die Teilnahme am Register für alle Zentren verpflichtend war, wurde für nur 38.442 Frauen eine Behandlung dokumentiert; 2003, im Jahr vor Einführung des Gesundheitssystem-Modernisierungsgesetzes (GMG), waren es sogar 63.111. Im Durchschnitt unterzog sich jede dieser Frauen 1,63 (idem) Behandlungszyklen.

Plausibilität und Prospektivität sind hoch

2011 wurden 80.943 Behandlungszyklen im D·I·R dokumentiert. 97,5 % dieser Datensätze wurden schon aufgrund der Kontrolle während der Dateneingabe als „plausibel" klassifiziert. Das bedeutet, alle im Fragenkatalog des D·I·R erhobenen Informationen wurden vollständig angegeben und erscheinen in sich „stimmig". Natürlich können mit der Plausibilitätskontrolle nicht alle Daten umfassend überprüft und alle Eingabefehler ausgeschlossen werden. Für einen Großteil kann aber dadurch die Logik, insbesondere zu anderen Items, überprüft werden. Ein weiteres, das Deutsche IVF-Register auszeichnende Merkmal, ist die „prospektive" Dateneingabe: Der jeweilige Behandlungszyklus wird innerhalb der ersten acht Tage nach Behandlungsbeginn im System angemeldet – zu einem Zeitpunkt also, wenn im Allgemeinen der Zyklusausgang noch nicht bekannt ist. Dieses Verfahren der kontinuierlichen und prospektiven Datenerfassung trägt erheblich zur Datenqualität bei und erlaubt durch die Auswertung der großen Fallzahlen, dass verlässliche Schlüsse gezogen und Behandlungsstrategien verglichen werden können. Waren in den Vorjahren wegen der damaligen Implementierung neuer Erfassungssoftware-Lösungen die Raten gesunken, so können wir für 2011 wieder ein Ansteigen der Plausibilitäts- und Prospektivitätsraten auf 97,5 % respektive 86,1 % feststellen. Zu diesem Anstieg tragen auch die neuen Softwarelösungen bei, da sie den Zentren die Einhaltung der Kriterien erleichtern.

Flächendeckende Versorgung ist gewährleistet

Die Zahl der in Deutschland die Befruchtung außerhalb des Körpers durchführenden Zentren ist 2011 auf 128 angestiegen. Auch wenn wir eine Konzentration der Zentren für diese hochspezialisierten Behandlungen in den Städten sehen, ist die flächendeckende Versorgung gewährleistet. Das Teilnehmerverzeichnis am Endes des Jahrbuchs zeigt die bundesweite, bedarfsgerechte Verteilung.

Behandlungszahlen steigen allmählich wieder

Die stetige Zunahme der Behandlungen nach dem dramatischen Abfall 2004 ist zum einen auf die deutliche Zunahme bei den Behandlungen mittels intracytoplasmatischer Spermieninjektion (ICSI) zurückzuführen. Im Beitrag über die Spermienparameter (S. 11) werden die Gründe hierfür aufgezeigt. Bei der Betrachtung der gesamteuropäischen Daten wird offensichtlich, dass es sich dabei nicht um eine auf Deutschland beschränkte Entwicklung handelt. Die Behandlungsmethode ICSI zeigt sich zunehmend als das Verfahren der Wahl. Die durchschnittliche Schwangerschaftsrate bei den sog. „Frisch-Zyklen" von 28,7 % (30,2 %/Transfer im IVF-Verfahren; 28,3 %/Transfer bei dem Einsatz von ICSI) entspricht der natürlichen monatlichen Fruchtbarkeitsrate. Wir stellen aber auch fest, dass das Verfahren der Gefrierkonservierung von Eizellen im Pronukleus-Stadium mit einem nachfolgenden Auftau- und Übertragungszyklus nominell und relativ in den letzten fünf Jahren deutlich zugenommen hat. 2006 wurden 9983 (≙ 19,9 % aller Behandlungszyklen) solcher Zyklen durchgeführt. 2011 waren es 16.958 (≙25 %).

Sinkende Mehrlingszahlen

Das Risiko einer Drillingsgeburt hat über all die Jahre deutlich abgenommen. Wurden 1997 noch durchschnittlich 2,49–2,56 Embryonen transferiert, so sanken diese Zahlen 2011 auf 1,99 bzw. 2,02. Diese Abnahme um etwa 20 % führt dazu, dass der Anteil der geborenen Drillingskinder an der Gesamtzahl der nach reproduktionsmedizinischen Maßnahmen geborenen Kinder um 80 % abgenommen hat. Der Vergleich der Zahl der Mehrlingsgeburten nach ART mit den Gesamtzahlen des Statistischen Bundesamtes zeigt, dass die in Deutschland durchgeführten reproduktionsmedizinischen Maßnahmen für 17,7 % der Mehrlingsgeburten verantwortlich sind (2101 von 11.838).

Rolle des Alters wird immer noch verkannt

Die Darstellung der altersabhängigen Schwangerschafts- und Fehlgeburtenraten ist seit Jahren ein wertvolles Instrument bei der individuellen Aufklärung der Paare. In unseren Gesprächen stellen wir fest, dass die Begrenztheit des reproduktiven Fensters – die kontinuierliche Abnahme der monatlichen Schwangerschaftschance ab dem 32./33. Lebensjahr der Frau – nach wie vor zu wenig bekannt ist. War 1996 nur jede dritte Frau bei der Behandlung 35 Jahre und älter, so waren es 2011 mehr als die Hälfte.

Embryoqualität ist entscheidend

Wie zu erwarten, kann auch dieses Jahr wieder eindrücklich dargestellt werden, dass die individuellen Schwangerschaftschancen neben dem Alter in hohem Maße von der zu beobachtenden Embryoqualität abhängen. Bei einer als „ideal" eingestuften Qualität birgt bis zum Alter von 40 Jahren der Transfer von mehr als zwei Embryonen keinerlei Vorteil. Er erhöht vielmehr das Risiko einer höhergradigen Mehrlingsschwangerschaft – und diese gilt es mit allen Mitteln zu vermeiden. Obwohl der elektive „Single-Embryo-Transfer" aufgrund der rechtlichen Rahmenbedingungen in

Deutschland nicht möglich ist, werden wir daran arbeiten, die Rate der Mehrlingsschwangerschaften noch weiter zu senken.

Extrakorporale Befruchtungen sind sicher

Das Geburtsgewicht der nach ART geborenen Kinder unterscheidet sich nicht signifikant von dem der Kinder, die ohne den Einsatz von ART empfangen wurden.

Im Jahr 2011 wurden in 0,27 % aller Behandlungen schwerwiegende Komplikationen bei der Eizellentnahme dokumentiert. Bei der extrakorporalen Befruchtung handelt es sich daher um eine sichere Methode.

Daten- und Ergebnisqualität nehmen stetig weiter zu

Wie eingangs schon dargestellt, überprüft das Deutsche IVF-Register kontinuierlich die Datenqualität der übermittelten Informationen. Dies geschieht hinsichtlich Prospektivität und Plausibilität bereits bei der Dateneingabe. Aber auch viele andere Parameter aus jedem Zentrum werden einer Prüfung unterzogen: die Anzahl der angemeldeten und später wieder gelöschten Zyklen, das Verhältnis der Kryo-Auftauzyklen zur Gesamtzahl der Frisch-Zyklen, das Anmeldedatum der Zyklen und ggf. eine auffällige Häufung an Tag 7 oder 8, die Normalverteilung der angegebenen Schwangerschaftsdauer, u. v. m.

Natürlich erfolgt auch eine Überprüfung der Ergebnisqualität der einzelnen Zentren. Jedem Zentrum wird auf der Basis von 47 Items ein sogenanntes „Zentrumsprofil“ erstellt und übermittelt. Anhand der grafischen Darstellung der Perzentilenkurven, in die die Ergebnisse aller Zentren eingehen, wird jedes Zentrum in die Lage versetzt, die eigene Position im Vergleich zu den anderen Zentren (diese sind pseudonymisiert) zu erkennen. Dieses Verfahren hat sich schon vor Jahrzehnten im Rahmen der Perinatalerhebung bewährt. Bei extremen Abweichungen kann das Zentrum seitens des D·I·R um eine Stellungnahme gebeten werden. Auch die IVF-Kommission der jeweiligen Landesärztekammer erhält diese Profile, so dass die Qualitätssicherung entsprechend der gesetzlichen Bestimmungen auch regional vorgenommen werden kann.

Unter dem Strich – das Jahr 2011

- Von 1997 bis 2011 sind im Register insgesamt 172.993 geborene Kinder dokumentiert
- Bei ungestörter Eierstockfunktion kam es im Jahr 2011 – gemittelt über alle Altersklassen – in 36,1 % aller Embryotransfers zu einer Schwangerschaft nach konventioneller IVF
- Bei einer Therapie mit ICSI betrug diese Wahrscheinlichkeit 33,6 %
- In Kryozyklen (Transfer nach zuvor eingefrorenen und wieder aufgetauten Eizellen im Vorkernstadium) lag die Wahrscheinlichkeit bei 19,7 %
- Bei ungestörter Eierstockfunktion zeigen die Daten für 2010, dass von 23,7 % aller Embryotransfers eine Geburt gemeldet wurde
- 2011 waren mehr als die Hälfte aller behandelten Frauen 35 Jahre und älter. 1996 – vor nur 15 Jahren – war lediglich jede dritte Frau älter als 35
- Mit zunehmendem Alter der Frau steigt die Wahrscheinlichkeit einer Fehlgeburt stark an, während sich die Eizellreserve und -qualität verringern.
- Die Gesamtschwangerschaftswahrscheinlichkeit steigt mit der Zahl der durchgeführten Behandlungen bzw. der transferierten Embryonen stetig an
- Die Mehrlingsrate hat sich gegenüber den vergangenen Jahren weiter verringert. Die in Deutschland durchgeführten reproduktionsmedizinischen Maßnahmen sind nur für 17,7 % der Mehrlingsgeburten verantwortlich (2101 [D·I·R] von 11.838 [Quelle: Statistisches Bundesamt]).
- Patientenpaare werden auch im Jahr 2011 in Deutschland im internationalen Vergleich hervorragend behandelt
- Wichtig für die Patientenpaare ist
  - die Folgen des Alters auf die Entwicklung der natürlichen Fruchtbarkeit zu kennen
  - die rechtzeitige Entscheidung zur angebrachten Therapie
  - nicht zu schnell aufzugeben

Mit all diesen Maßnahmen wird die hohe Ergebnisqualität der Reproduktionsmedizin in Deutschland und die sehr gute Datenqualität unseres Registers ständig verbessert.

♦ ♦ ♦

Überlegungen zur Indikation reproduktionsmedizinischer Therapien bei männlicher Subfertilität

Seit einigen Jahren nimmt der Anteil der sog. ICSI-Zyklen an den extrakorporalen Therapien kontinuierlich zu und hat mittlerweile die 75 % überschritten (S. 16). Dieser Trend ist nicht mit einer methodisch bedingten, grundsätzlich besseren Fertilisationsrate, höheren Transferrate oder höheren Schwangerschaftsrate in einem sog. ICSI-Zyklus im Vergleich zur richtig indizierten konventionellen IVF zu erklären.

Fertilisationsversagen ist der schlechteste Ausgang einer Behandlung

Bereits im Jahrbuch 2009 wurden Daten gezeigt, die belegen, dass ab einer Spermiendichte von < 25×10^6/ml im Nativejakulat und < 15×10^6/ml nach Spermaaufbereitung und/oder einer Spermienprogressivmotilität < 20 % nativ und < 10 % nach Aufbereitung und/oder einer Gesamtmotilität < 40 % nativ und < 65 % nach Aufbereitung ein Fertilisationsversagen bei einer klassischen IVF bei bis zu 40 % der Behandlungen droht. Ein Fertilisationsversagen ist der schlechteste Ausgang eines Behandlungszyklus, da das betroffene Paar keine Chance auf eine Schwangerschaft hatte und bei der begrenzten Anzahl von Versuchen zu Lasten der Kostenträger ein Versuch vergeben wurde. Deshalb gilt es, ein Fertilisationsversagen mit allen Mitteln zu vermeiden. Die Veröffentlichung der neuen unteren Referenzwerte im Laborhandbuch der Weltgesundheitsorganisation (WHO) 2010 hat hier zu großer Verunsi-

cherung geführt, da auf der 5. Perzentile liegende Parameter oft als „Normalwerte“ missverstanden werden.

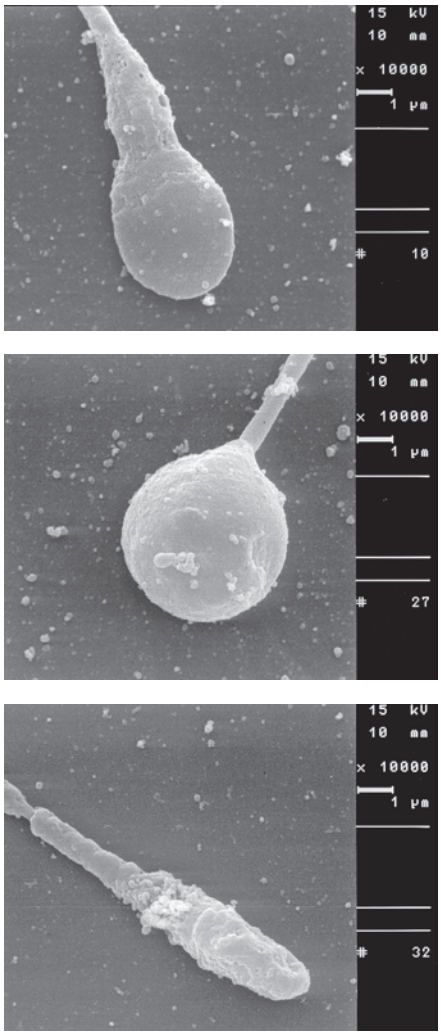
Neue WHO-Referenzwerte sagen nur bedingt etwas über die Fertilität aus

Die Referenzwerte in dieser aktuellen 5. Auflage des WHO-Handbuches zur Untersuchung und Aufbereitung des menschlichen Ejakulates (WHO 2010) eignen sich aber nicht zur Indikationsstellung einer reproduktionsmedizinischen Therapie oder Auswahl einer reproduktionsmedizinischen Methode, da es sich um Referenzwerte für fertile Männer handelt, deren Partnerinnen im Laufe eines Jahres spontan schwanger wurden.

Üblicherweise überstreicht bei Laborparametern der Referenzbereich 95 % aller Werte. Jenseits dieser Grenzen liegen die Werte einer signifikant unterschiedlichen Population. Für Spermiogrammparameter ist jedoch ein einseitiges Referenzintervall sinnvoller, da sehr hohe Werte die Fertilität nicht beeinträchtigen werden. Insofern wurde aus statistischen Gründen die 5-%-Perzentile als unterer Referenzwert definiert; das heißt: 95 % der Väter gewordenen Männer hatten Spermiogramme mit einem Samenvolumen von > 1,5 ml, einer Gesamtspermienzahl von > 39×10^6/ml, einer Spermienkonzentration > 15×10^6/ml, einer Progressivmotilität über 32 % bei einer Gesamtmotilität > 40 %. Die Normalformen lagen oberhalb von 4 %. Insofern hat diese Grenzziehung der WHO nur systematisch-methodische Gründe und sagt, wie die WHO selbst anmerkt, nur sehr bedingt etwas über die Fertilität aus. Zudem werden Ejakulatanalysen meistens nicht bei gerade Vater gewordenen Männern durchgeführt, sondern bei Männern aus Partnerschaften mit unerfülltem Kinderwunsch.

Normale Spermiogramme beweisen nicht die männliche Fertilität

Hier kann eine prospektive, niederländische Multicenter-Studie zur spontanen Konzeptionsaussicht von 3345 subfertilen Paaren ohne relevanten weiblichen Sterilitätsfaktor herangezogen werden, deren Datenbasis damit fast an die des WHO-Kollektivs heranreicht. Aus einer erweiterten Analyse dieser Studie wissen wir, dass selbst bei Spermiogramm-



Variabilität im Erscheinungsbild menschlicher Spermien (Normalform oben, auffällige Morphologien Mitte und unten. [Quelle: Prof. Dr. Dr. h.c. Hans Wilhelm Michelmann und Dr. Peter Schwartz, Göttingen.]

konzentrationen oberhalb von 40×10^6/ml und einer schnellen Progressivmotilität von idealen 50 %, die Aussicht innerhalb eines Jahres spontan zu konzipieren, bestenfalls 65 % beträgt. Trotz scheinbar „normaler Spermiogrammparameter“ ist im Vergleich zu nachweislich fertilen Männern die Fertilität nicht einmal halb so hoch. Mit den alten WHO-Mindestwerten von 1999 (Spermienkonzentration von 20×10^6/ml, Anteil schnell progressiver motiler Spermien von 25 %) ist die Fertilität auf < 1/4 reduziert. Bezogen auf die 5. Perzentile der Referenzwerte der WHO 2010 liegt die Wahrscheinlichkeit auf eine fortlaufende Schwangerschaft in einem Jahr nur bei 31,53 %, d. h. für 70 % der Männer mit Frauen ohne relevanten Sterilitätsfaktor wird es auch in einem weiteren Jahr nicht zu einer Schwangerschaft kommen. Pro Zyklus beträgt die Spontankonzeptionsrate lediglich 3,11 %. Die Fertilität bei den Männern ist damit auf weniger als 1/8 der normalen Fertilität reduziert.

Dauer des unerfüllten Kinderwunsches indiziert reproduktionsmedizinische Maßnahme

Aus Spermiogrammen lässt sich also der Grad der Fertilitätsminderung von Männern aus subfertilen Partnerschaften ohne relevanten weiblichen Sterilitätsfaktor ablesen. Da auch „ideale Werte“ in diesem Kollektiv eine männliche Subfertilität nicht ausschließen, besteht die Indikation zu reproduktionsmedizinischen Maßnahmen. Diese kann sich daher alleine aus der Zeitdauer des unerfüllten Kinderwunsches ergeben. Welche reproduktionsmedizinische Technik zum Einsatz kommt, richtet sich im Weiteren wesentlichen nach den Resultaten der Spermaaufbereitung und der Ausbeute an progressiv motilen Spermien. Nur so lässt sich das Risiko eines kompletten und inkompletten Fertilisationsversagens auf ein Minimum reduzieren. Das ist den deutschen IVF-Zentren in der Vergangenheit vorbildlich gelungen, wie die Zahlen des aktuellen Jahrbuches und auch vergangener Jahre zeigen.

Literatur: bei der Geschäftsstelle des D·I·R

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Zukunft im IVF-Labor

Gastbeitrag von Prof. Dr. rer. nat. Markus Montag, Heidelberg

Eine Betrachtung der Frage nach der Zukunft im IVF-Labor kann von verschiedenen Seiten erfolgen: Zukunft im Sinne von was kommt an Neuem auf uns zu, aber auch Zukunft in Hinblick auf wie geht es weiter.

Vor dem Blick in die Zukunft ein Blick zurück

Was hat die jüngste Vergangenheit im IVF-Labor gebracht: Neue Kulturmedien insbesondere für die Kultur bis zum Tag 5, optimierte Einfrierverfahren für Eizellen und Embryonen mittels der Vitrifikation, kleinere Inkubatoren und reduzierte Sauerstoffatmosphäre, Qualitätsmanagement wie Zertifizierung und Akkreditierung. Auch wenn das eine oder andere die Schwangerschaftsrate positiv verändert haben mag: Der große Durchbruch war noch nicht dabei.

Wenn man die Zukunft unter dem Aspekt einer Steigerung der Erfolgsraten sieht, dann liegt der größte Nutzen aus Sicht der Patienten zukünftig sicher darin, die Behandlungs- und Laborqualität in Zentren mit niedrigen Erfolgsraten zu verbessern. Dies vor dem Hintergrund von globalen Schwangerschaftsraten die bei 20–25 % pro Behandlungszyklus liegen und der Tatsache, dass laut D·I·R im Jahr 2010 unter den 100 größten IVF-Zentren immerhin 40 Zentren eine Schwangerschaftsrate pro Transfer von unter 25 % aufwiesen. Dies muss auch bei neuen Labormethoden und Vorgehensweisen berücksichtigt werden, setzen diese doch eine gewisse Grundqualität voraus, um mit neuen, technisch anspruchsvollen Verfahren den Erfolgszugewinn in der Routine zu bekommen, den man erwartet.

Morphokinetik gewinnt an Bedeutung

Ganz oben auf der Liste der zukünftigen Aspekte, die von Bedeutung sein werden, steht die nach wie vor größte Herausforderung im IVF-Labor: die Identifikation der Embryonen eines Behandlungszyklus, die eine hohe Implantationsrate besitzen. Hier wird in den nächsten Jahren die Morphokinetik, d. h. die morphologische Beurteilung von Embryonen über die Zeit, zunehmend eine dominierende Rolle spielen. Wird die Morphokinetik um einfache und physiologisch bedeutsame diagnostische Methoden ergänzt – hier wären neben der array-CGH vor allem verbesserte metabolische Konzepte zu nennen – dann kann sich in Verbindung mit der Vitrifikation zwangsläufig der elektive „Single-Embryo-Transfer“ durchsetzen und damit eine weitere Reduzierung der Mehrlingsrate.

Ökonomie hält Einzug ins IVF-Labor

Ein völlig anderer Aspekt, der die Zukunft im IVF-Labor bestimmt, ist die Ökonomie. International sind Laborverbünde verstärkt im Kommen und die Übernahme von IVF-Zentren durch Investoren ist nichts Neues. Dies wird unweigerlich zu neuen Konzepten führen, von zentralen IVF-Laboratorien bis hin zur Nutzung von elektronischen Kommunikationssystemen zur standardisierten Beurteilung von Embryonen und deren Auswahl für den Transfer.

Insofern birgt die Zukunft viele interessante Herausforderungen, aber sie setzt auch eine gewisse Offenheit voraus, sich mit Veränderungen auseinanderzusetzen und Altes und Gewohntes zu überdenken.

Behandlungsergebnisse 2011

Arbeitsgruppen für IVF-, ICSI-, GIFT- und Kryotransfer-Behandlungen

Registerteilnehmer	n = 128
Daten zum Stichtag (21.08.2012) exportiert	n = 128
dokumentierte Behandlungszyklen	n = 80.943 (100,00 %)
plausibel	n = 78.922 (97,50 %)
prospektiv (alle Behandlungen)	n = 67.935 (86,08 %)
prospektiv (IVF, ICSI, IVF/ICSI)	n = 45.078 (84,93 %)
Anzahl der behandelten Frauen*	n = 49.696
Behandlungszyklen/Frau (Mittelwert)	1,63

*) Basismenge: alle Frauen mit Altersangabe; unplausible Zyklen werden auch gezählt

Anzahl der Zentren 1982 - 2011

für IVF-, ICSI- und Kryotransfer-Behandlungen

	1982	1986	1990	1994	1996	1998	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IVF	5	28	53	66	66	86	100	107	112	114	118	117	120	118	117	119	121	124
ICSI	0	0	0	32	59	85	98	108	112	116	120	117	120	118	120	119	124	128
Kryo	0	0	0	19	35	63	77	95	97	101	112	109	109	112	112	117	120	125
Gesamt*					71	86	102	108	112	116	120	117	121	118	120	121	124	128

*) Für die Jahre vor 1996 (Einführung der elektronischen Datenverarbeitung im DIR) können hierzu keine Angaben gemacht werden.

Anzahl der Behandlungen 1982 - 2011 (plausible Zyklen)

IVF, ICSI, IVF/ICSI, Kryotransfer

	1982	1986	1990	1994	1998	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IVF	742	3.806	7.343	16.175	16.763	28.945	28.506	23.936	28.058	11.848	11.098	11.082	11.362	11.264	11.585	11.346	11.341
ICSI				5.856	23.578	15.752	24.897	37.692	51.389	25.339	25.532	28.015	31.452	34.333	36.712	38.463	40.641
IVF/ICSI					424	790	695	678	987	446	590	672	798	834	873	989	1.094
Kryo				499	4.616	9.457	12.195	14.923	14.265	16.883	14.471	14.926	16.566	17.646	17.866	17.969	19.228
Keine *					67	6.562	7.507	9.802	11.133	4.928	4.539	4.600	5.137	5.825	5.946	6.289	6.618
Gesamt**	742	4.201	8.653	23.684	45.459	61.531	73.819	87.044	105.854	59.448	56.232	59.295	65.316	69.902	72.984	76.072	78.922

Ab 1999 werden alle begonnene Behandlungen dokumentiert.
*) Keine Behandlung: abgebrochene Behandlungen vor durchgeführter Eizellbehandlung.
**) Der Wert "Gesamt" enthält auch GIFT-Fälle. Da diese seit 2005 nur noch in nicht mehr dokumentationswürdigem Ausmaß auftraten, wird auf eine einzelne Darstellung verzichtet.

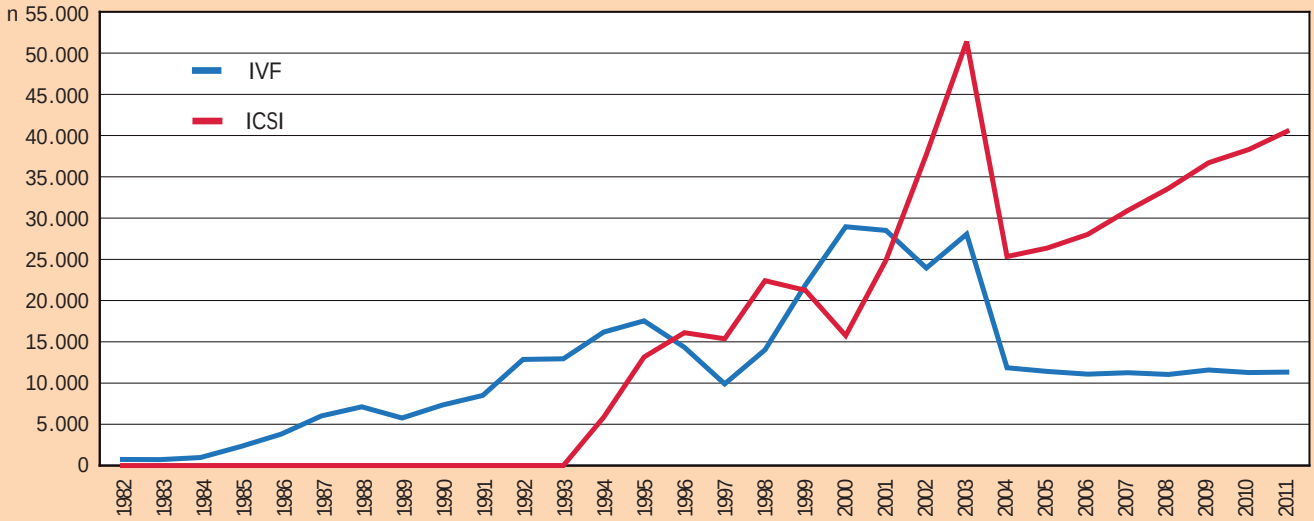
Anzahl aller Behandlungen 2011 (prospektive Zyklen)

IVF, ICSI, IVF/ICSI, Kryotransfer

	IVF	ICSI	IVF/ICSI	Kryo	Keine Beh.	Summe
Anzahl	9.524	34.637	917	16.958	5.899	67.935
in %	14,02	50,99	1,35	24,96	8,68	100,00

Anzahl der Follikelpunktionen 2011

IVF, ICSI*



	1982	1986	1990	1996	1998	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IVF	742	3.806	7.343	14.344	14.024	28.945	28.506	23.936	28.058	11.848	11.410	11.082	11.362	11.264	11.585	11.346	11.341
ICSI				16.108	22.420	15.752	24.897	37.692	51.389	25.339	26.370	28.015	31.452	34.333	36.712	38.463	40.641
Gesamt**	742	3.806	7.343	30.452	37.933	45.487	54.098	62.306	80.434	37.633	38.382	39.769	43.612	46.431	49.170	50.798	53.076

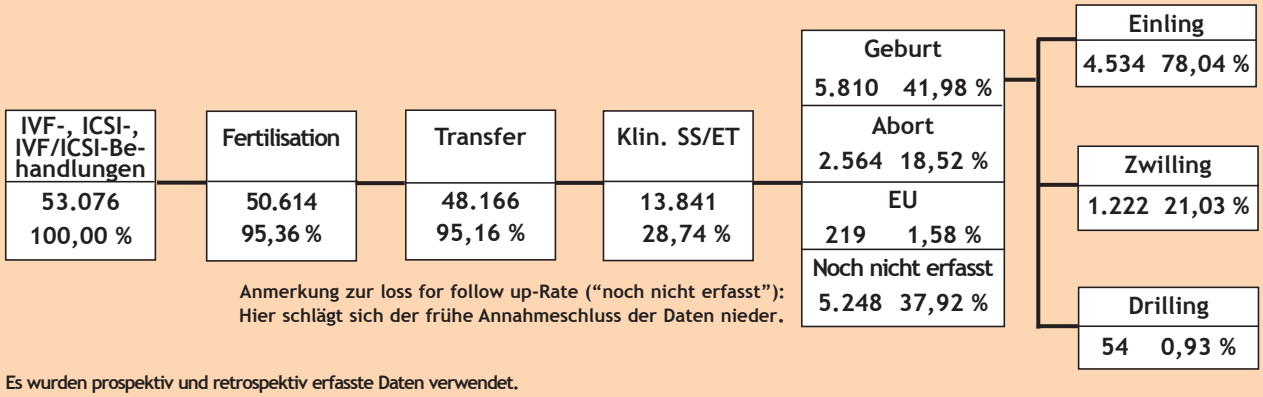
*) Follikelpunktionen, die zu einer Eizellbehandlung mit IVF und/oder ICSI geführt haben.

**) In der Gesamtsumme ist jeweils auch der Wert für IVF/ICSI enthalten, für 2011 waren dies z. B. 1.094 Punktionen.

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Zusammenfassung der Kurzstatistik 2011 für IVF, ICSI und IVF/ICSI

Deutsches IVF-Register Stand: 21.08.2012



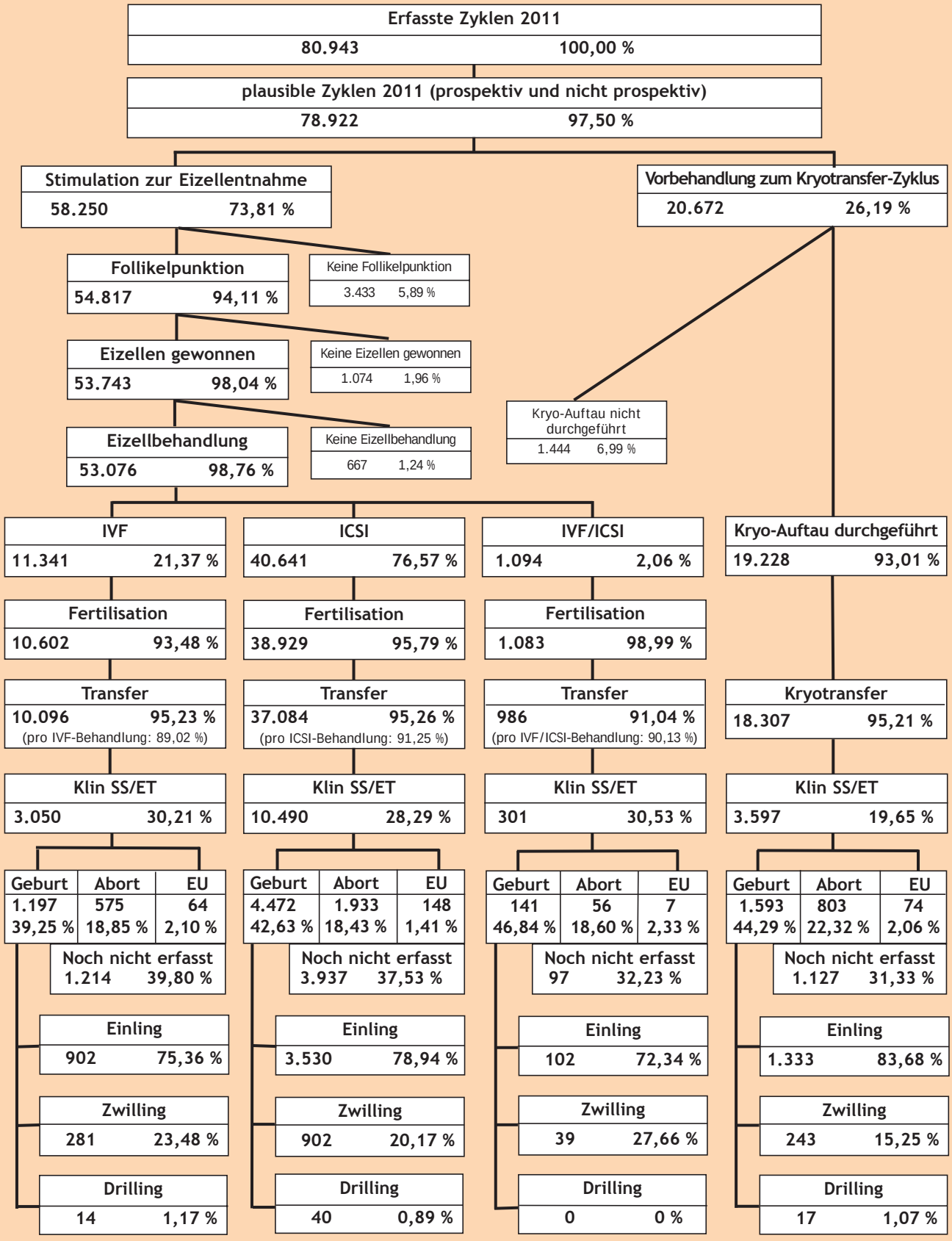
Anmerkung zur loss for follow up-Rate ("noch nicht erfasst"):
Hier schlägt sich der frühe Annahmeschluss der Daten nieder.

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

D.I.R.-Kurzstatistik 2011

Deutsches IVF-Register

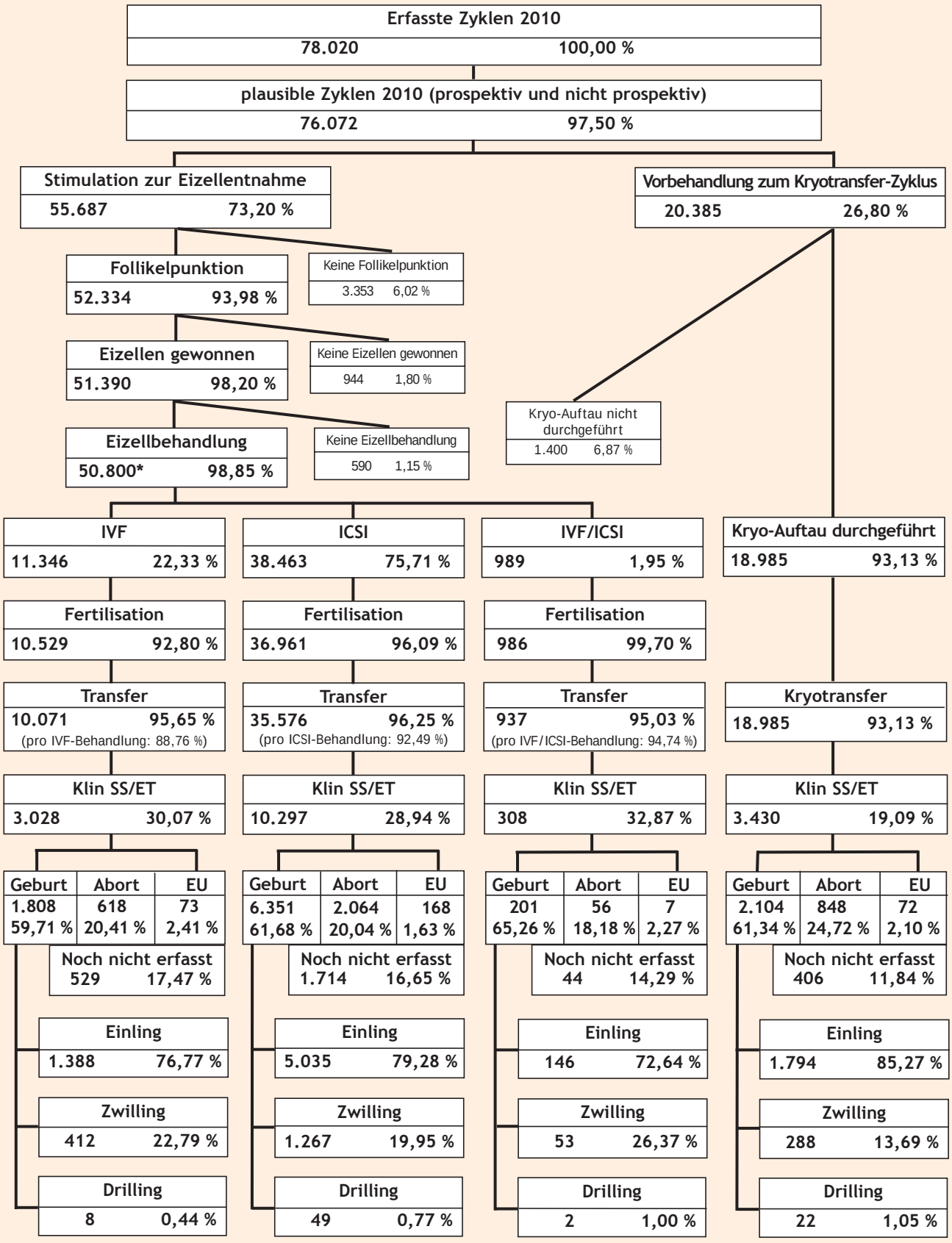
Stand: 21.08.2012



D.I.R.-Kurzstatistik 2010

Deutsches IVF-Register

Stand: 21.08.2012



*) Hierin sind auch 2 GIFT-Behandlungen eingeschlossen.

Klinische SS, Aborte, EUs und Totgeburten 2010

2010	IVF		ICSI		IVF/ICSI		Kryotransfer	
	n	%	n	%	n	%	n	%
Durchgeführte Behandl.	11.346		38.463		989		18.985	
Klin. SS	3.028	100,00	10.297	100,00	308	100,00	3.430	100,00
Keine Angaben	529	17,47	1.714	16,65	44	14,29	406	11,84
Geburten	1.808	59,71	6.351	61,68	201	65,26	2.104	61,34
Aborte	618	20,41	2.064	20,04	56	18,18	848	24,72
Induz. Aborte u. fetale Reduk.*	36 (39)	1,19	129 (161)	1,25	4 (5)	1,30	35 (40)	1,02
Extrauteringravidität	73	2,41	168	1,63	44	14,29	72	2,10
Kinder	2.328		7.908		268		2.520	
Tot geborene Kinder **	26	1,12	69	0,87	3	1,12	16	0,63
Fehlbildungen	15	0,64	73	0,92	3	1,12	18	0,71
Baby-take-home-rate ***		15,94		16,52		20,34		11,09
		16,72[1]		17,30[1]		21,27[1]		11,23[1]
		17,73[2]		19,19[2]		23,97[2]		12,61[2]

Es wurden sowohl prospektiv als auch retrospektiv erfasste Daten verwendet.

*) Anzahl der Zyklen, in denen ein induzierter Abort/fetale Reduktion dokumentiert wurde. Eine genauere Differenzierung ist zzt. nicht möglich. In Klammern steht die Anzahl der Embryonen.

**) Anzahl der tot geborenen Kinder bezogen auf die Anzahl der Kinder

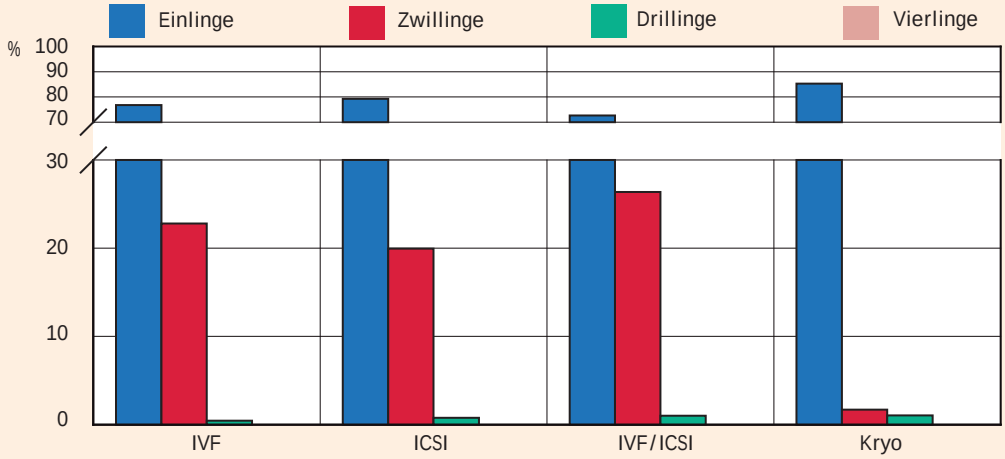
***) Anzahl der Geburten pro Anzahl der durchgeführten Behandlungen in Prozent

1) Zyklen mit unbekanntem Schwangerschaftsausgang wurden von der Basismenge subtrahiert.

2) Für Zyklen mit unbekanntem Schwangerschaftsausgang wurde die wahrscheinliche Geburtenrate (Geburt pro SS) ermittelt und zu den bekannten Geburten addiert.

Geburtenrate/Transfer bei Patientinnen mit 2 transf. Embryonen und mind. 2 PN im Überschuss: IVF 23,30 %, ICSI 23,81 %, IVF/ICSI 24,87 %

Mehrlingsgeburten 2010



Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

	IVF			ICSI			IVF/ICSI			Kryotransfer		
	n	%	%	n	%	%	n	%	%	n	%	%
Klin. SS/ET	3.028	100,00		10,297	100.00		308	100,00		3.430	100,00	
Geburten	1.808	59,71	100,00	6,351	61.68	100,00	201	65,26	100,00	2.104	61,34	100,00
Einlinge	1.388	45,84	76,77	5,035	48.90	79,28	146	47,40	72,64	1.784	52,01	85,27
Zwillinge	412	13,61	22,79	1,267	12.30	19,95	53	17,21	26,37	288	8,40	1,69
Drillinge	8	0,26	0,44	49	0.48	0,77	2	0,65	1,00	22	0,64	1,05
Vierlinge	-	-	-	-	-	-	-	-	-	-	-	-
Keine Angaben	529	17,47		1,714	16.64		44	14,29		406	11,84	
Aborte	618	20,41		2,064	20.04		56	18,18		848	24,72	
Extrauteringrav.	73	2,41		168	1.63		7	2,27		72	2,10	

Geburten in Abhängigkeit von der Anzahl übertragener Embryonen und Altersgruppen 2000 - 2010 - IVF, ICSI, IVF/ICSI, Kryotransfer

Alter der Frau		Einling		Zwilling		Drilling		Vierling		Gesamt
		n	%	n	%	n	%	n	%	n
bis 24 Jahre	1 Embryo	119	100,00	0	-	0	-	0	-	119
	2 Embryonen	1.517	77,20	440	22,39	8	0,41	0	-	1.965
	3 Embryonen	269	68,45	103	26,21	19	4,83	2	0,51	393
	Summe	1.905	76,91	543	21,92	27	1,09	2	0,08	2.477
25 - 29 Jahre	1 Embryo	1.041	98,30	18	1,70	0	-	0	-	1.059
	2 Embryonen	13.737	75,92	4.282	23,67	73	0,40	2	0,01	18.094
	3 Embryonen	2.543	69,03	934	25,35	204	5,54	3	0,08	3.684
	Summe	17.321	75,85	5.234	22,92	277	1,21	5	0,02	22.837
30 - 34 Jahre	1 Embryo	2.427	98,14	46	1,86	0	-	0	-	2.473
	2 Embryonen	27.481	77,87	7.667	21,73	141	0,40	1	0,00	35.290
	3 Embryonen	7.098	70,92	2.508	25,06	396	3,96	6	0,06	10.008
	Summe	37.006	77,47	10.221	21,40	537	1,12	7	0,01	47.771
35 - 39 Jahre	1 Embryo	2.574	98,24	46	1,76	0	-	0	-	2.620
	2 Embryonen	19.654	83,64	3.788	16,12	55	0,23	1	0,00	23.498
	3 Embryonen	9.443	76,83	2.577	20,97	268	2,18	2	-	12.290
	Summe	31.671	82,46	6.411	16,69	323	0,84	3	0,01	38.408
40 und älter	1 Embryo	442	98,44	7	1,56	0	-	0	-	449
	2 Embryonen	2.032	92,15	169	7,66	3	0,14	1	0,05	2.205
	3 Embryonen	2.148	87,21	305	12,38	10	0,41	0	-	2.463
	Summe	4.622	90,33	481	9,40	13	0,25	1	0,02	5.117

Gesamtzahl der Geburten 2000 - 2010: 116.610

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Geburten in Abhängigkeit von der Anzahl übertragener Embryonen 2000 - 2010 - IVF, ICSI, Kryotransfer

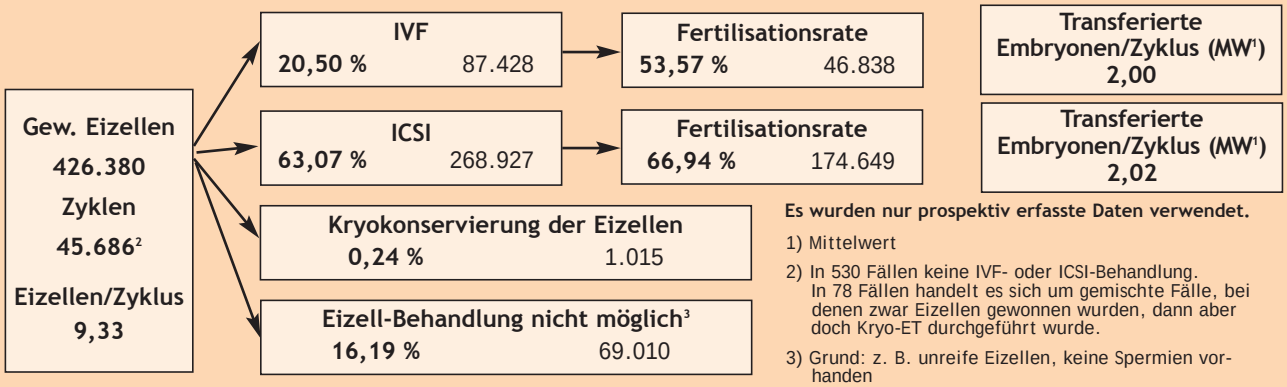
IVF	Einling		Zwilling		Drilling		Vierling		Gesamt
	n	%	n	%	n	%	n	%	n
1 Embryo	1.724	98,51	26	1,49	0	-	0	-	1.750
2 Embryonen	16.223	76,56	4.888	23,07	78	0,37	1	0,00	21.190
3 Embryonen	5.588	71,12	1.916	24,39	347	4,42	6	0,08	7.857
Summe	23.535	76,42	6.830	22,18	425	1,38	7	0,02	30.797

ICSI	Einling		Zwilling		Drilling		Vierling		Gesamt
	n	%	n	%	n	%	n	%	n
1 Embryo	3.206	98,56	47	1,44	0	-	0	-	3.253
2 Embryonen	37.034	79,21	9.558	20,44	157	0,34	3	0,01	46.752
3 Embryonen	11.174	74,59	3.354	22,39	446	2,98	6	0,04	14.980
Summe	51.414	79,12	12.959	19,94	603	0,93	9	0,01	64.985

Kryotransfer	Einling		Zwilling		Drilling		Vierling		Gesamt
	n	%	n	%	n	%	n	%	n
1 Embryo	1.609	97,52	41	2,48	0	-	0	-	1.650
2 Embryonen	10.136	86,19	1.584	13,47	40	0,34	0	-	11.760
3 Embryonen	4.491	79,26	1.077	19,01	97	1,71	1	0,02	5.666
Summe	16.236	85,11	2.702	14,16	137	0,72	1	0,01	19.076

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Fertilisationsrate IVF und ICSI 2011



Es wurden nur prospektiv erfasste Daten verwendet.

1) Mittelwert

2) In 530 Fällen keine IVF- oder ICSI-Behandlung. In 78 Fällen handelt es sich um gemischte Fälle, bei denen zwar Eizellen gewonnen wurden, dann aber doch Kryo-ET durchgeführt wurde.

3) Grund: z. B. unreife Eizellen, keine Spermien vorhanden

Transferierte Embryonen/Zyklus (MW*) und Kinder IVF, ICSI 1997 - 2011

(prospektiv und nicht prospektive Daten)

		1997	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
IVF	Transf. Embryo.	2,49	2,29	2,25	2,19	2,17	2,15	2,11	2,08	2,08	2,06	2,03	2,01	1,99
	Kinder/Transfer	0,21	0,23	0,24	0,22	0,23	0,23	0,24	0,25	0,25	0,24	0,24	0,22	0,15
	Kinder/Geburt	1,31	1,28	1,27	1,26	1,26	1,25	1,23	1,23	1,24	1,24	1,22	1,24	1,26
ICSI	Transf. Embryo.	2,56	2,39	2,30	2,21	2,17	2,15	2,11	2,09	2,08	2,08	2,06	2,05	2,02
	Kinder/Transfer	0,22	0,23	0,24	0,22	0,23	0,23	0,24	0,24	0,24	0,23	0,23	0,22	0,15
	Kinder/Geburt	1,29	1,26	1,23	1,23	1,23	1,22	1,22	1,20	1,21	1,22	1,21	1,21	1,22
Kryo -ET	Transf. Embryo.	2,34	2,25	2,20	2,14	2,12	2,14	2,10	2,10	2,07	2,07	2,05	2,04	2,02
	Kinder/Transfer	0,10	0,12	0,12	0,12	0,12	0,12	0,14	0,14	0,14	0,14	0,14	0,14	0,10
	Kinder/Geburt	1,14	1,16	1,16	1,16	1,16	1,17	1,16	1,16	1,16	1,15	1,16	1,16	1,18

Indikationsverteilung IVF und ICSI 2011

IVF

Frau Indikation \ Mann Indikation	Normal	%	Eingeschr. Spermiogr.	%	Sonstige**	%	Summe	%
Normal	978	10,27	708	7,43	568	5,96	2.254	23,67
Tubenpathologie	1.407	14,77	486	5,10	447	4,69	2.340	24,57
Endometriose	455	4,78	242	2,54	222	2,33	919	9,65
Hyperandrog./PCO	202	2,12	110	1,15	106	1,11	418	4,39
Pathologischer Zyklus	362	3,80	206	2,16	176	1,85	744	7,81
Psychogene Faktoren	8	0,08	1	0,01	1	0,01	10	0,10
Sonstige*	605	6,35	536	5,63	940	9,87	2.081	21,85
Keine Angaben	27	0,28	8	0,08	723	7,59	758	7,96
Summe	4.044	42,46	2.297	24,12	3.183	33,42	9.524	100,00

ICSI

Frau Indikation \ Mann Indikation	Normal	%	Eingeschr. Spermiogr.	%	Azoo-spermie	%	Sonstige**	%	Summe	%
Normal	627	1,81	10.082	29,11	869	2,51	2.713	7,83	14.291	41,26
Tubenpathologie	483	1,39	1.717	4,96	49	0,14	547	1,58	2.796	8,07
Endometriose	209	0,60	1.296	3,74	55	0,16	557	1,61	2.117	6,11
Hyperandrog./PCO	102	0,29	1.164	3,36	52	0,15	347	1,00	1.665	4,81
Pathologischer Zyklus	179	0,52	1.838	5,31	87	0,25	379	1,09	2.483	7,17
Psychogene Faktoren	1	0,00	21	0,06	2	0,01	15	0,04	39	0,11
Sonstige*	483	1,39	4.594	13,26	270	0,78	3.105	8,96	8.452	24,40
Keine Angaben	19	0,05	144	0,42	34	0,10	2.597	7,50	2.794	8,07
Summe	2.103	63,07	20.856	60,21	1.418	4,09	10.260	29,62	34.637	100,00

*) Hier sind auch die Indikationen "Spermien-Antikörper" und "Path. Zervixfaktor" eingeschlossen.

**) Hier ist auch die Indikation "Path. Funktionstest" eingeschlossen.

Es wurden nur prospektiv erfasste Daten verwendet.

Behandlungsergebnisse IVF, ICSI, Kryotransfer 2011

prospektive Zyklen

IVF 2011

	n	%	Fertilisier. %	Embryo. vorh. %	Transfer %	Klin. SS %
IVF	9.524	100,00				
Erfolgreiche Fertilisier. *	8.904	93,49	100,00			
Mind. 1 Embryo vorh.	8.472	88,95	95,15	100,00		
Transfer durchgeführt	8.470	88,93	95,13	99,98	100,00	
Klin. SS	2.582	27,11	29,00	30,48	**30,48**	100,00
Geburt	1.027					39,78
Abort	485					18,78
Extrauteringravidität	58					2,25
Keine Angaben	1.012					39,19

ICSI 2011

	n	%	Fertilisier. %	Embryo. vorh. %	Transfer %	Klin. SS %
ICSI	34.637	100,00				
Erfolgreiche Fertilisier. *	33.170	95,76	100,00			
Mind. 1 Embryo vorh.	31.560	91,12	95,15	100,00		
Transfer durchgeführt	31.551	91,09	95,12	99,97	100,00	
Klin. SS	8.937	25,87	26,94	28,32	**28,33**	100,00
Geburt	3.877					43,38
Abort	1.681					18,81
Extrauteringravidität	125					1,40
Keine Angaben	3.254					36,41

ICSI 2011 - Spermagewinnung TESE und Kryo-TESE

	n	%	Fertilisier. %	Embryo. vorh. %	Transfer %	Klin. SS %
ICSI	2.143	100,00				
Erfolgreiche Fertilisier. *	1.971	91,97	100,00			
Mind. 1 Embryo vorh.	1.866	87,07	94,67	100,00		
Transfer durchgeführt	1.866	87,07	94,67	100,00	100,00	
Klin. SS	449	20,95	22,78	24,06	**24,06**	100,00
Geburt	182					40,53
Abort	94					20,94
Extrauteringrav.	2					0,45
Keine Angaben	171					38,08

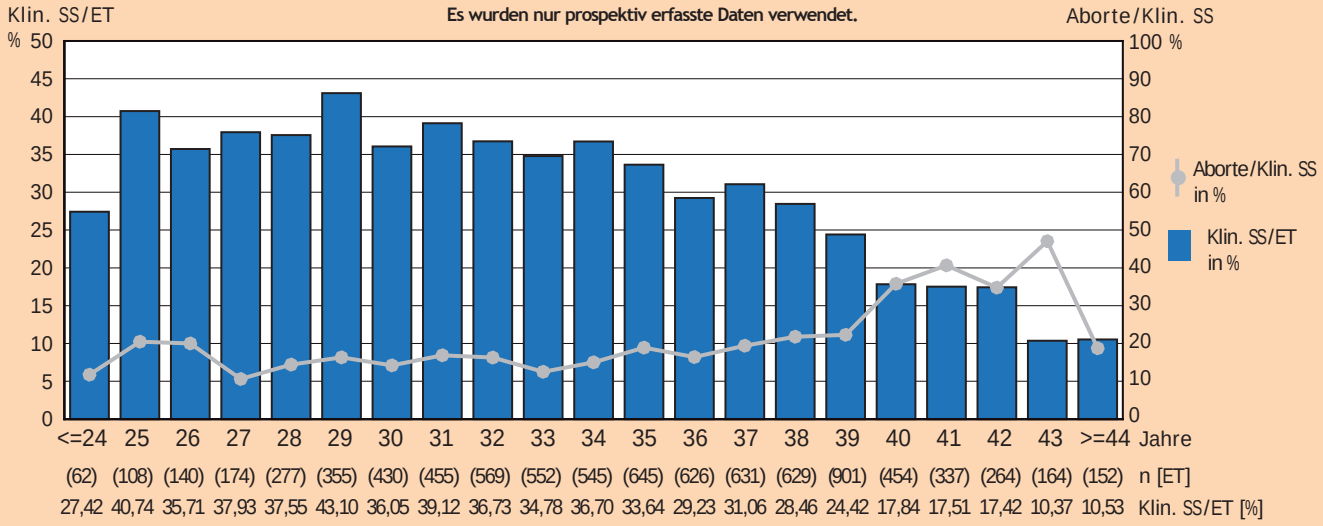
Kryotransfer 2011

	n	%	PN %	Transfer %	Klin. SS %
Kryotransferzyklen	16.958	100,00			
Aufgetaute PN vorh.	15.843	93,42	100,00		
Transfer durchgeführt	15.581	91,88	98,35	100,00	
Klin. SS	3.105	18,31	19,60	**19,93**	100,00
Geburt	1.385				44,61
Abort	702				22,61
Extrauteringravidität	65				2,09
Keine Angaben	953				30,69

*) Erfolgreiche Fertilisierung mindestens einer Eizelle pro Zyklus

Behandlungsergebnisse in Abhängigkeit vom Alter der Frau

IVF - 2011

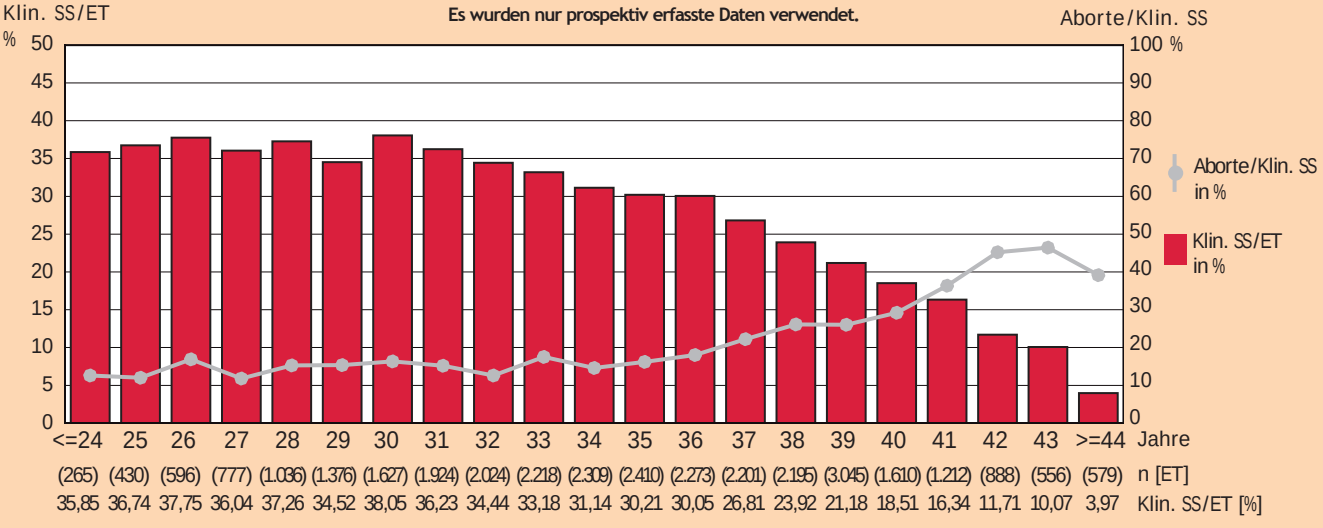


Alter in Jahren	Punktion	Gew. Eizellen (MW)	Insemin. (MW)	Transf.	Transf./Pkt. %	Transf. Emb. (MW)	Klin. SS	Klin. SS/ Pkt. %	Klin. SS/ET %	Klin.SS/ET bei 2 transf. Emb. u. mind. 2 PN im Überschuss
<= 29	1.255	11,21	11,01	1.116	88,92	1,95	434	34,58	**38,89**	42,64
30 - 34	2.813	10,14	9,93	2.551	90,69	1,97	934	33,20	**36,61**	40,35
35 - 39	3.841	8,16	7,98	3.432	89,35	2,01	995	25,90	**28,99**	33,73
>= 40	1.614	5,97	5,86	1.370	84,88	2,06	218	13,51	**15,91**	21,71
Gesamt*	9.524	8,78	8,59	8.470	88,93	2,00	2.582	27,11	**30,48**	36,14

*) In der Menge gesamt ist ein Fall mit unbekannter Altersangabe enthalten (4 gew. Eizellen, 4 insem., 1 Klin. SS).

Behandlungsergebnisse in Abhängigkeit vom Alter der Frau

ICSI - 2011



Alter in Jahren	Punktion	Gew. Eizellen (MW)	Injektion (MW)	Transf.	Transf./Pkt. %	Transf. Emb. (MW)	Klin. SS	Klin. SS/ Pkt. %	Klin. SS/ET %	Klin.SS/ET bei 2 transf. Emb. u. mind. 2 PN im Überschuss
<= 29	4.821	12,22	9,73	4.480	92,93	1,99	1.619	33,58	**36,14**	39,07
30 - 34	10.860	10,89	8,74	10.102	93,02	2,00	3.468	31,93	**34,33**	38,00
35 - 39	13.327	8,62	6,92	12.124	90,97	2,03	3.171	23,79	**26,15**	30,72
>= 40	5.628	6,35	5,11	4.844	86,07	2,05	678	12,05	**14,00**	19,48
Gesamt*	34.637	9,46	7,59	31.551	91,09	2,00	8.937	25,80	**28,33**	33,66

*) In der Menge gesamt ist ein Fall mit unbekannter Altersangabe enthalten (4 gew. Eizellen, 3 inj., 1 Klin. SS).

Klin. SS/ET in Abhängigkeit von der Anzahl übertragener Embryonen und Altersgruppen 2011

IVF	1 Embryo		2 Embryonen		3 Embryonen		Gesamt	
	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %
bis 24 Jahre	5	0,00	55	29,09	2	50,00	62	27,42
25 - 29 Jahre	108	22,22	890	41,69	56	39,29	1.054	39,56
30 - 34 Jahre	306	21,24	2.027	38,83	218	37,61	2.551	36,61
35 - 39 Jahre	560	17,68	2.286	31,06	586	31,74	3.432	28,99
40 - 44 Jahre	317	6,62	603	15,09	401	25,44	1.321	16,20
45 Jahre und älter	21	4,76	15	6,67	13	15,38	49	8,16
Gesamt	1.317	15,95	5.876	33,63	1.277	31,01	8.470*	30,48

ICSI	1 Embryo		2 Embryonen		3 Embryonen		Gesamt	
	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %
bis 24 Jahre	25	20,00	222	38,29	18	27,78	265	35,85
25 - 29 Jahre	368	21,20	3.520	37,67	327	36,70	4.215	36,16
30 - 34 Jahre	1.119	20,73	7.866	36,50	1.117	32,68	10.102	34,33
35 - 39 Jahre	2.010	14,03	7.689	28,66	2.425	28,25	12.124	26,15
40 - 44 Jahre	1.183	7,19	1.934	16,39	1.450	18,62	4.567	14,71
45 Jahre und älter	106	1,89	88	1,14	83	3,61	277	2,17
Gesamt	4.811	14,22	21.320	31,92	5.420	26,72	31.551*	28,32

Kryo-ET	1 Embryo		2 Embryonen		3 Embryonen		Gesamt	
	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %
bis 24 Jahre	21	9,52	100	12,00	20	35,00	141	14,89
25 - 29 Jahre	313	13,10	1.405	24,48	417	22,06	2.161	22,12
30 - 34 Jahre	921	13,14	3.500	23,00	1.094	25,32	5.558	21,72
35 - 39 Jahre	1.114	10,68	3.419	20,47	1.183	23,84	5.740	19,20
40 - 44 Jahre	417	9,35	1.006	16,90	493	16,63	1.922	15,19
45 Jahre und älter	11	0,00	27	14,81	21	4,76	59	8,47
Gesamt	2.797	11,51	9.457	21,52	3.228	22,96	15.680**	19,85

*) In jeweils 1 Fall ist das Alter unbekannt.
**) Transferierte Embryonen plus PN; in 99 Fällen nicht berechenbar.

Es wurden nur prospektiv erfasste Daten verwendet.

Klin. SS/ET in Abhängigkeit von der Embryonenqualität 2011

IVF, ICSI, IVF/ICSI

Qualität		<= 29 Jahre		30 - 34 Jahre		35 - 39 Jahre		>= 40 Jahre		Gesamt	
ideal	nicht ideal	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %	ET	Klin. SS/ET %
0	1	85	7,06	255	7,84	480	5,42	299	2,34	1.119	5,27
0	2	337	23,44	794	16,25	926	13,61	279	7,89	2.336	15,24
0	3	30	16,67	114	12,28	238	9,24	144	10,42	526	10,65
1	0	424	23,82	1.178	23,51	2.094	17,10	1.329	7,67	5.025	16,68
1	1	588	34,18	1.253	30,65	1.400	25,86	452	11,50	3.693	27,05
1	2	30	20,00	118	27,97	244	22,95	165	13,94	557	21,19
2	0	3.758	40,39	7.835	40,11	7.639	37,71	1.903	17,66	21.135	37,27
2	1	63	34,92	218	38,53	466	27,68	321	19,00	1.068	27,71
3	0	277	41,52	882	35,83	2.056	32,20	1.315	21,14	4.530	30,31
Summe		5.596	36,68	12.653	34,79	15.556	27,97	6.214	14,42	40.019*	29,24

*) In 30 Fällen ist die Qualität unbekannt.

Es wurden nur prospektiv erfasste Daten verwendet.

Klin. SS in Abhängigkeit der Embryonenqualität 2011

Kryotransfer

Qualität		nach IVF		nach ICSI	
ideal	nicht ideal	ET	Klin. SS/ET %	ET	Klin. SS/ET %
0	1	133	4,51	507	5,72
0	2	310	9,35	997	11,43
0	3	73	10,96	321	13,08
1	0	464	17,03	1.595	12,35
1	1	467	19,06	1.320	18,03
1	2	105	17,14	325	20,31
2	0	1.446	25,80	4.544	25,09
2	1	168	24,40	448	24,33
3	0	403	22,33	1.217	27,28
Summe*		3.569	20,54	11.274	20,11

*) In 24 Fällen war die vorher durchgeführte Behandlung IVF/ICSI, in 714 Fällen ist die vorausgegangene Behandlung unbekannt.

Es wurden nur prospektiv erfasste Daten verwendet.

Abortraten in Abhängigkeit vom Alter und der Anzahl übertragener Embryonen 2011

IVF, ICSI, IVF/ICSI

Alter in Jahren	1 Embryo		2 Embryonen		3 Embryonen		Gesamt	
	Klin. SS	Abort/Klin. SS %	Klin. SS	Abort/Klin. SS %	Klin. SS	Abort/Klin. SS %	Klin. SS	Abort/Klin. SS %
bis 24	5	0,00	102	12,75	6	16,67	113	12,39
25 - 29	104	15,38	1.728	14,29	142	21,83	1.974	14,89
30 - 34	299	20,07	3.743	14,59	459	16,99	4.501	15,20
35 - 39	389	26,48	2.998	19,68	881	22,93	4.268	20,97
40 - 44	106	37,74	420	36,43	377	33,95	903	35,55
45 und älter	3	66,67	2	50,00	5	20,00	10	40,00
Gesamt	906	24,39	8.994	17,23	1.871	23,57	11.771*	18,79

*) Bei zwei Fällen ist das Alter unbekannt.

Kryotransfer

Alter in Jahren	1 Embryo		2 Embryonen		3 Embryonen		Gesamt	
	Klin. SS	Abort/Klin. SS %	Klin. SS	Abort/Klin. SS %	Klin. SS	Abort/Klin. SS %	Klin. SS	Abort/Klin. SS %
bis 24	2	0,00	12	33,33	7	28,57	21	28,57
25 - 29	41	14,63	344	21,74	92	21,74	478	21,13
30 - 34	121	19,83	805	20,50	277	18,41	1.207	19,97
35 - 39	119	21,01	700	23,00	282	25,89	1.102	23,59
40 - 44	39	33,33	170	28,82	82	35,37	292	31,51
45 und älter	-	-	4	25,00	1	100,00	5	40,00
Gesamt	322	21,12	2.035	22,36	741	23,75	3.105*	22,61

*) Bei 7 Fällen ist die Anzahl der transferierten Embryonen unbekannt.

Es wurden nur prospektiv erfasste Daten verwendet.

Klin. SS-Raten in Abhängigkeit von der Stimulation

IVF, ICSI 2011

- IVF -

	u-FSH	rec-FSH	hMG	recLH u. recFSH	rec-FSH u. hMG	Sonstige*	Keine Angaben	Summe
GnRHa-kurz	4	283	453	17	143	10	4	914
Transferrate (%)	25,00	92,23	93,82	88,24	89,51	90,00	100,00	92,23
Klin. SS/Transfer (%)	0,00	28,35	29,18	20,00	20,31	22,22	25,00	27,28
GnRHa-lang	63	1.907	788	219	591	46	31	3.645
Transferrate (%)	87,30	89,88	88,07	81,28	91,37	89,13	93,55	89,19
Klin. SS/Transfer (%)	27,27	35,47	28,67	30,34	30,37	34,15	48,28	32,85
Ohne GnRH-Analoga	13	279	219	46	126	65	153	901
Transferrate (%)	92,31	88,53	93,61	89,13	91,27	80,00	77,12	88,90
Klin. SS/Transfer (%)	33,33	33,20	32,68	34,15	24,35	21,15	27,12	30,13
GnRH-Antagonisten	39	2.282	798	252	339	326	28	4.064
Transferrate (%)	89,74	90,32	87,59	79,37	85,84	84,97	82,14	88,24
Klin. SS/Transfer (%)	25,71	33,77	26,47	24,50	20,27	16,25	13,04	29,17
Summe	119	4.751	2.258	534	1.199	447	216	9.524

- ICSI -

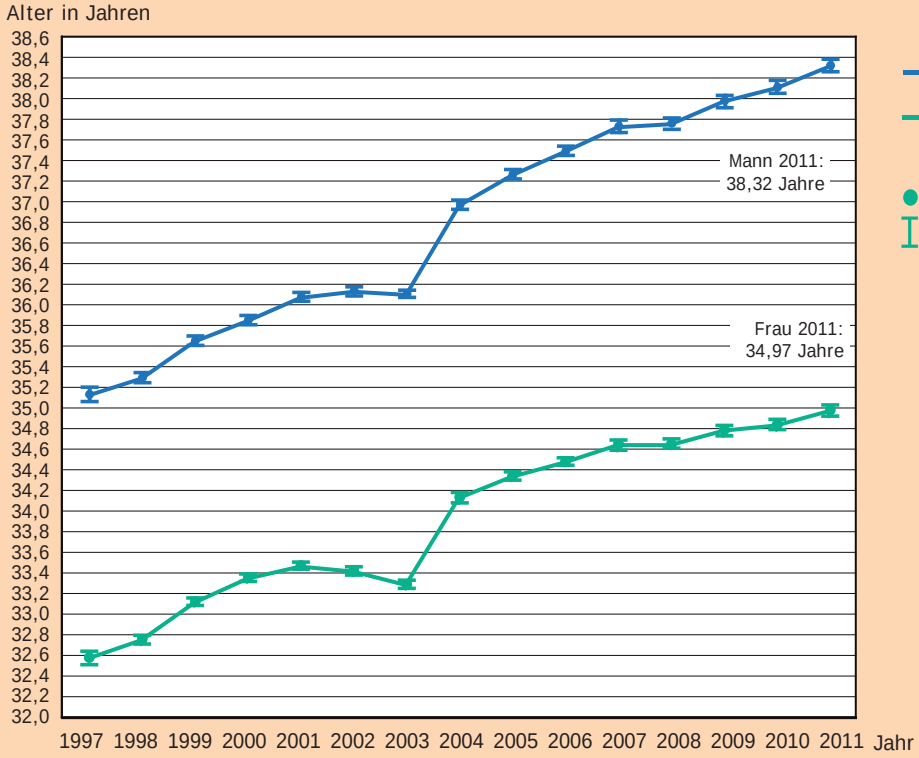
	u-FSH	rec-FSH	hMG	recLH u. recFSH	rec-FSH u. hMG	Sonstige*	Keine Angaben	Summe
GnRHa-kurz	66	984	1.061	82	386	118	9	2.706
Transferrate (%)	90,91	94,41	92,27	87,80	90,16	92,37	88,89	92,50
Klin. SS/Transfer (%)	13,33	22,93	20,53	18,06	15,23	10,09	25,00	20,00
GnRHa-lang	179	7.193	2.674	880	2.435	190	89	13.640
Transferrate (%)	96,09	93,67	92,93	88,98	94,37	92,63	95,51	93,39
Klin. SS/Transfer (%)	27,33	33,51	27,89	28,10	29,55	22,16	16,47	31,01
Ohne GnRH-Analoga	32	1.097	567	178	597	287	657	3.415
Transferrate (%)	93,75	91,70	89,95	85,96	90,62	83,28	74,73	87,37
Klin. SS/Transfer (%)	23,33	32,50	31,37	25,49	26,80	14,64	18,94	27,13
GnRH-Antagonisten	138	8.210	2.614	1.018	1.668	1.125	103	14.876
Transferrate (%)	90,58	91,08	87,95	85,66	90,77	85,42	87,38	89,62
Klin. SS/Transfer (%)	21,60	31,17	25,18	26,72	22,72	15,71	16,67	27,59
Summe	415	17.484	6.916	2.158	5.068	1.720	858	34.637

*) Z. B. u-FSH u. hMG, Clomifen/rec-FSH, Clomifen/hMG etc.

Es wurden nur prospektiv erfasste Daten verwendet.

Mittleres Alter der Frauen und Männer

1997 - 2011 - IVF, ICSI, IVF/ICSI



Mann

Frau

● : Mittelwert,

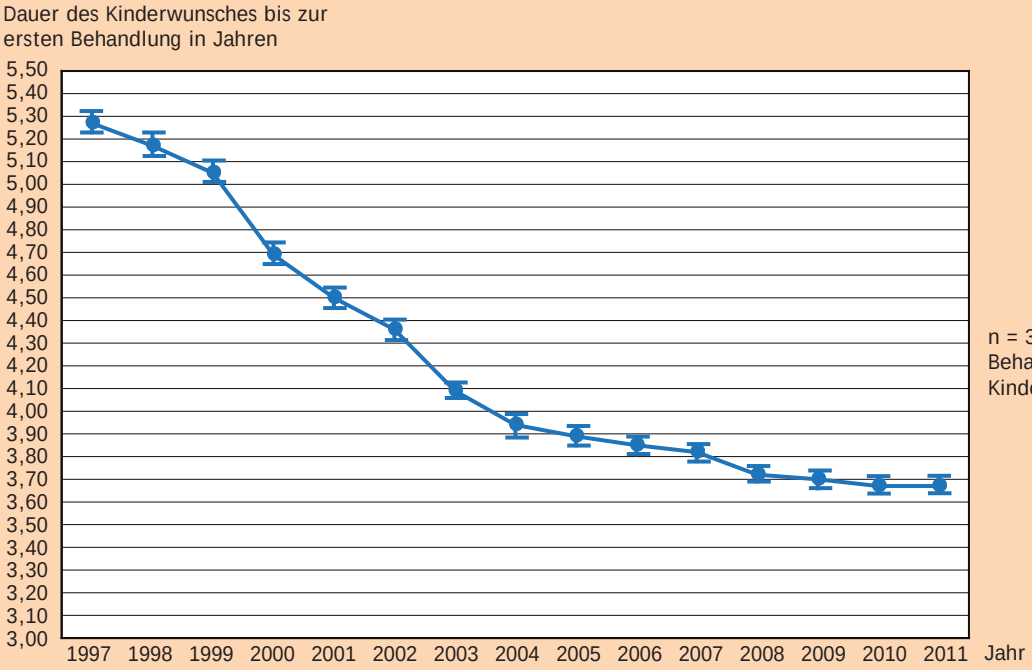
I : Konfidenzintervall 95 %. (Das Konfidenzintervall für die Frauen, 1997, sagt z. B. aus, dass das mittlere Alter der Frauen mit 95 %iger Wahrscheinlichkeit zwischen 32,51 und 32,65 Jahren liegt.

n = 663.076 Behandlungen mit plausiblen Altersangaben

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Dauer des Kinderwunsches bis zur ersten Behandlung

1997 - 2011 IVF, ICSI, IVF/ICSI

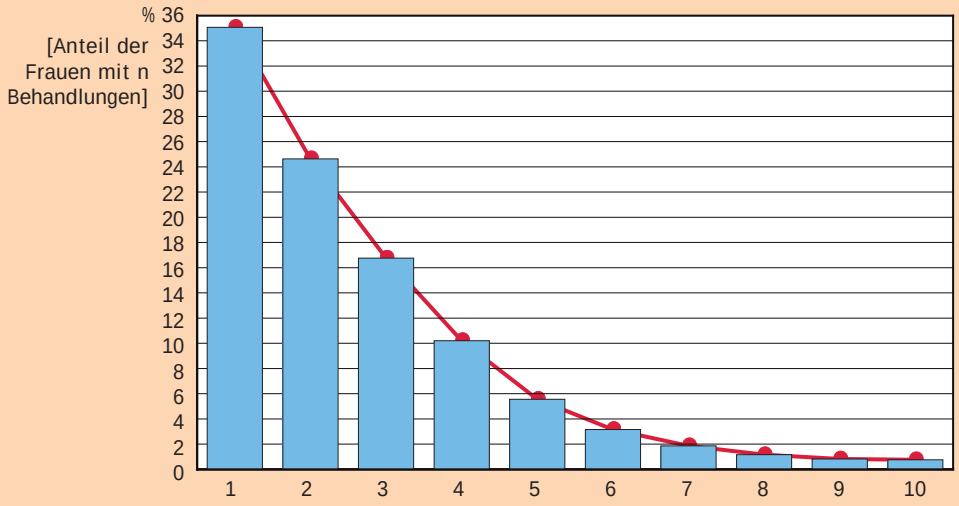


n = 321.588 erste Behandlungen mit bekannter Kinderwunschzeit

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Anzahl der Behandlungen pro Frau

1997 - 2011 IVF, ICSI, IVF/ICSI, Kryo-ET



n = 376.303 Frauen

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

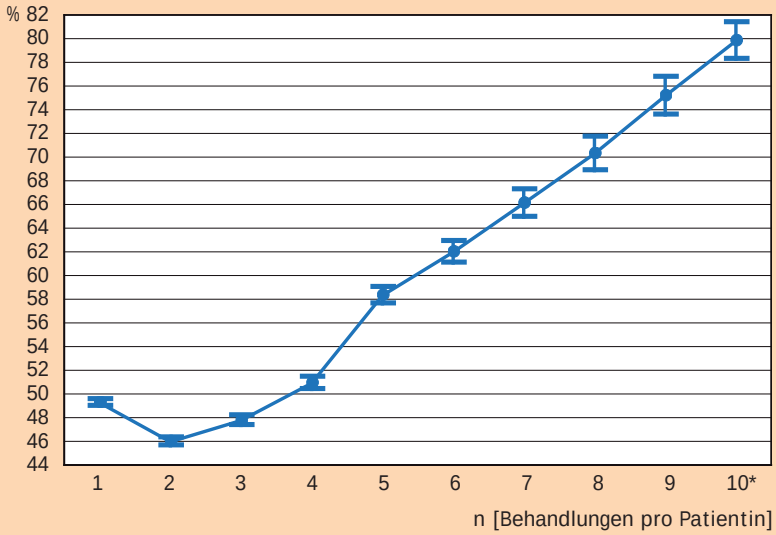
Gesamtschwangerschaftswahrscheinlichkeit pro Frau

1997 - 2011 IVF, ICSI, IVF/ICSI inklusive Kryo-ET

Gesamtschwangerschafts-wahrscheinlichkeit pro Frau in Abhängigkeit von der Anzahl der durchgeführten Behandlungen

n = 376.303 Frauen

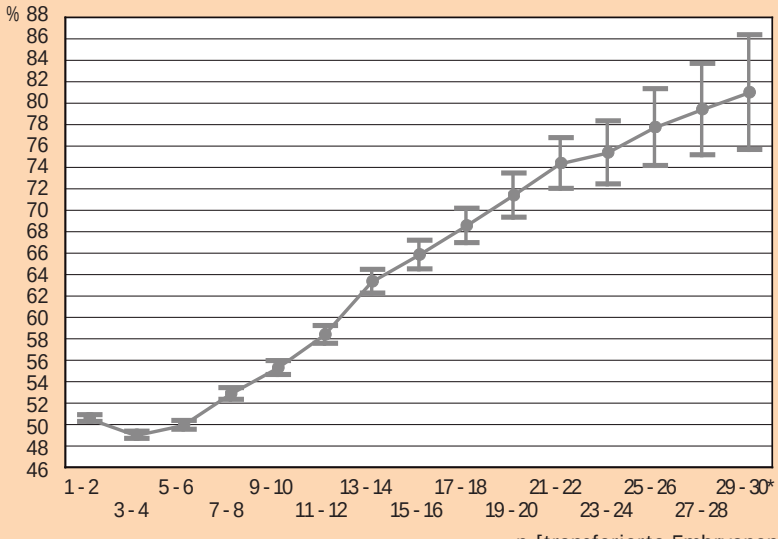
*) Eine Patientin, welche 10 Behandlungszyklen durchlaufen hat (n = 1.755), ist im Verlauf dieser Zyklen zu 80 % einmal schwanger geworden.



Gesamtschwangerschafts-wahrscheinlichkeit pro Frau in Abhängigkeit von der Summe der transferierten Embryonen

n = 376.303 Frauen

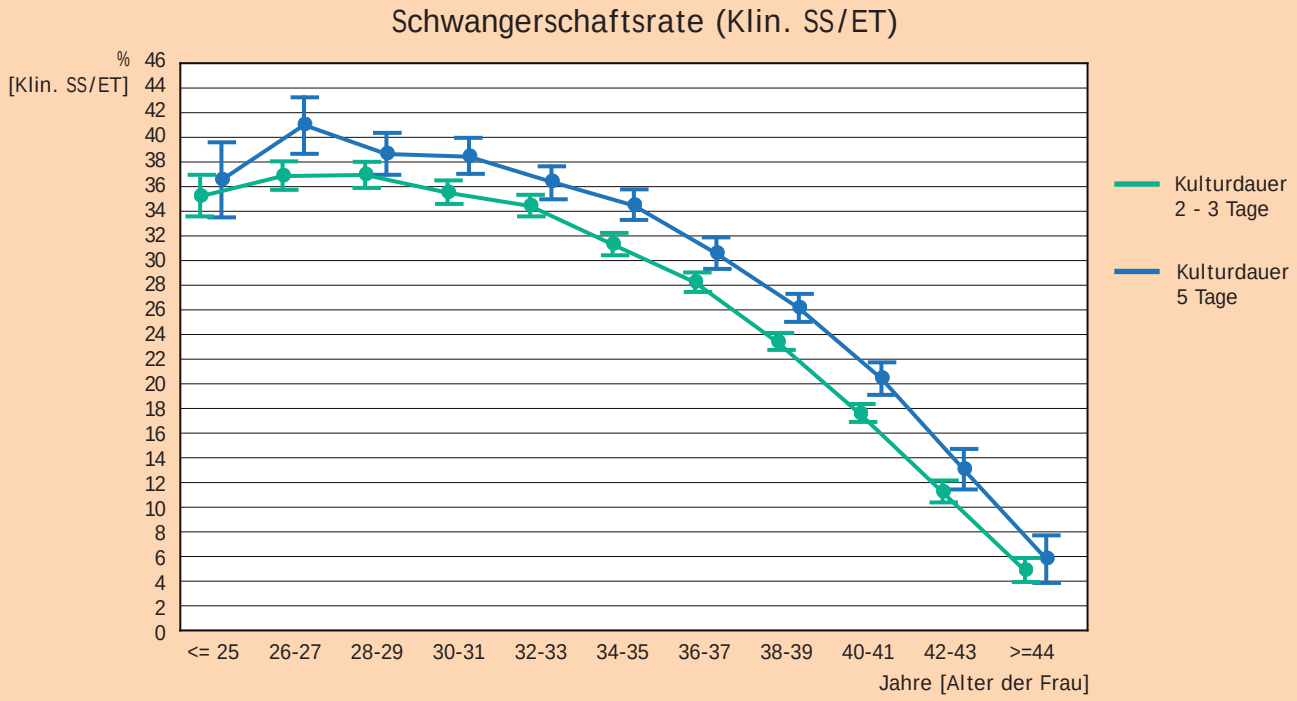
*) Eine Patientin, welche insgesamt 29-30 Embryonen (n = 213) transferiert bekam, ist im Verlauf dieser Behandlungszyklen zu 81 % mindestens einmal schwanger geworden.

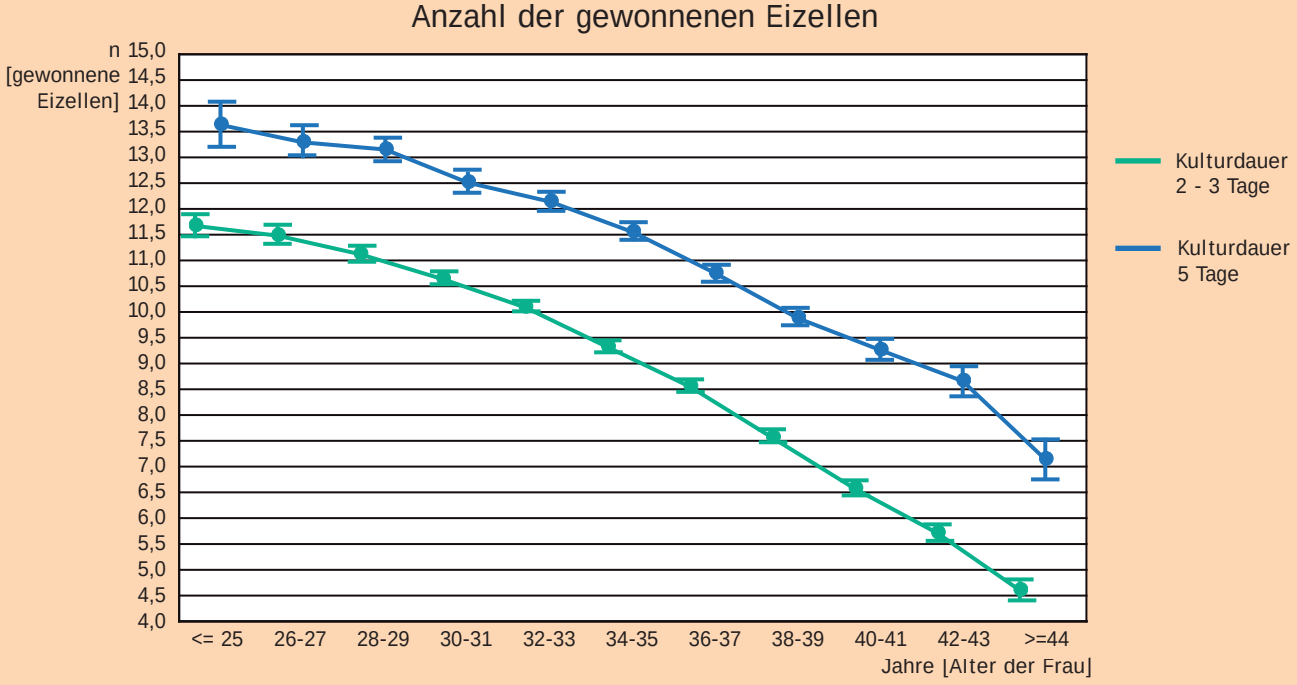


Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Schwangerschaftsrate in Abhängigkeit von der Anzahl der gewonnenen Eizellen und der Kulturdauer

2007 - 2011 IVF, ICSI, IVF/ICSI





n = 208.620 Behandlungen (Der Anteil der 5tägigen Kulturdauer ist im betrachteten Zeitraum von 15 % auf 21 % gestiegen.)

Fazit: Die höhere Schwangerschaftsrate bei 5 Tagen Kulturdauer lässt sich auch durch die besseren Voraussetzungen bei einer höheren Anzahl gewonnener Eizellen erklären.

Es wurden prospektiv und retrospektiv erfasste Daten verwendet.

Geborene Kinder 1997 - 2011

prospektive und retrospektive Daten

IVF, ICSI, IVF/ICSI

	Einlinge		Zwillinge		Drillinge		Vierlinge		Gesamt
	n	%	n	%	n	%	n	%	n
2001 *	6.798 (6.774)	60,89 (61,04)	3.956 (3.919)	35,43 (35,31)	411 (405)	3,68 (3,65)	0 (0)	- -	11.165 (11.098)
2002 *	7.746 (7.724)	62,59 (62,78)	4.256 (4.210)	34,39 (34,22)	366 (362)	2,96 (2,94)	8 (7)	0,06 (0,06)	12.376 (12.303)
2003 *	10.723 (10.688)	62,13 (62,78)	5.960 (5.866)	34,53 (34,22)	552 (533)	3,20 (2,94)	24 (24)	0,14 (0,14)	17.259 (17.111)
2004 *	5.368 (5.352)	63,69 (62,46)	2.826 (2.801)	33,53 (34,28)	234 (223)	2,78 (3,11)	0 (0)	- -	8.428 (8.376)
2005 *	5.527 (5.515)	63,84 (63,90)	2.936 (2.906)	33,91 (33,44)	183 (179)	2,11 (2,66)	12 (11)	0,14 (0,13)	8.658 (8.611)
2006 *	5.906 (5.894)	65,50 (64,05)	2.922 (2.890)	32,41 (33,75)	189 (174)	2,10 (2,08)	0 (0)	- -	9.017 (8.958)
2007 *	6.663 (6.628)	65,45 (64,69)	3.504 (3.471)	33,95 (33,88)	150 (143)	1,45 (1,40)	4 (4)	0,04 (0,04)	10.321 (10.246)
2008 *	6.696 (6.672)	64,09 (64,34)	3.528 (3.481)	33,77 (33,57)	216 (209)	2,07 (2,02)	8 (8)	0,08 (0,08)	10.448 (10.370)
2009 *	7.253 (7.217)	65,89 (66,02)	3.560 (3.523)	32,34 (32,23)	186 (183)	1,69 (1,67)	8 (8)	0,07 (0,07)	11.007 (10.931)
2010 *	6.767 (6.724)	64,42 (64,62)	3.554 (3.507)	33,83 (33,70)	183 (175)	1,74 (1,68)	0 (0)	- -	10.504 (10.406)
2011 *	4.671 (4.645)	63,64 (63,95)	2.498 (2.457)	34,03 (33,82)	171 (162)	2,33 (2,23)	0 (0)	- -	7.340 (7.264)

*) Die Werte in Klammern geben die Lebendgeburten an. Als Summen über alle Jahre (1997 - 2011) ergeben sich folgende Werte: Einlinge 92.314 (88.946), Zwillinge 50.242 (49.637), Drillinge 5.074 (4.818), Vierlinge 88 (85); gesamt: 147.618 (146.486)

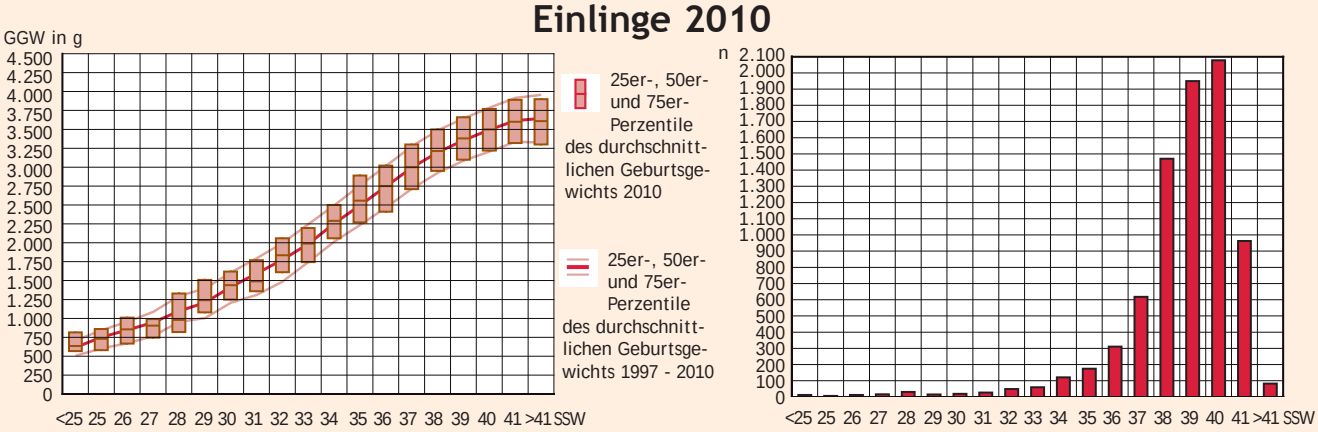
Gesamt (IVF, ICSI, IVF/ICSI, Kryotransfer)

	Einlinge		Zwillinge		Drillinge		Vierlinge		Gesamt
	n	%	n	%	n	%	n	%	n
2001 *	7.795 (7.764)	62,20 (62,33)	4.288 (4.248)	34,21 (34,10)	450 (444)	3,59 (3,56)	0 (0)	- -	12.533 (12.456)
2002 *	8.930 (8.902)	63,84 (64,02)	4.662 (4.615)	33,33 (33,19)	387 (382)	2,77 (2,75)	8 (7)	0,06 (0,05)	13.987 (13.906)
2003 *	11.922 (11.887)	63,16 (63,48)	6.334 (6.237)	33,55 (33,31)	597 (578)	3,16 (3,09)	24 (24)	0,13 (0,13)	18.877 (18.726)
2004 *	6.891 (6.869)	65,63 (65,81)	3.336 (3.306)	31,77 (31,68)	273 (262)	2,6 (2,51)	0 (0)	- -	10.500 (10.437)
2005 *	7.038 (7.020)	65,76 (65,93)	3.440 (3.408)	32,14 (32,01)	213 (209)	1,99 (1,96)	12 (11)	0,11 (0,10)	10.703 (10.648)
2006 *	7.419 (7.402)	66,87 (67,14)	3.450 (3.417)	31,10 (30,99)	222 (202)	2,00 (1,83)	4 (4)	0,04 (0,04)	11.095 (11.025)
2007 *	8.407 (8.364)	66,35 (66,45)	4.076 (4.043)	32,17 (32,12)	183 (176)	1,44 (1,40)	4 (4)	0,03 (0,03)	12.670 (12.587)
2008 *	8.444 (8.416)	65,79 (66,07)	4.142 (4.084)	32,27 (32,06)	240 (230)	1,87 (1,81)	8 (8)	0,06 (0,06)	12.834 (12.738)
2009 *	9.016 (8.969)	67,32 (67,42)	4.152 (4.114)	31,00 (30,92)	216 (213)	1,61 (1,60)	8 (8)	0,06 (0,06)	13.392 (13.304)
2010 *	8.619 (8.566)	66,18 (66,35)	4.156 (4.105)	31,91 (31,80)	249 (239)	1,91 (1,85)	0 (0)	- -	13.024 (12.910)
2011 *	6.054 (6.022)	65,34 (65,61)	2.990 (2.943)	32,27 (32,07)	222 (213)	2,40 (2,32)	0 (0)	- -	9.266 (9.178)

*) Die Werte in Klammern geben die Lebendgeburten an. Als Summen über alle Jahre (1997 - 2011) ergeben sich folgende Werte: Einlinge 110.920 (110.472), Zwillinge 56.506 (55.855), Drillinge 5.475 (5.306), Vierlinge 92 (89); gesamt: 172.993 (171.722)

Kinder in Abhängigkeit von der Schwangerschaftswoche (SSW) und vom Geburtsgewicht (GGW) 2010*

Einlinge 2010

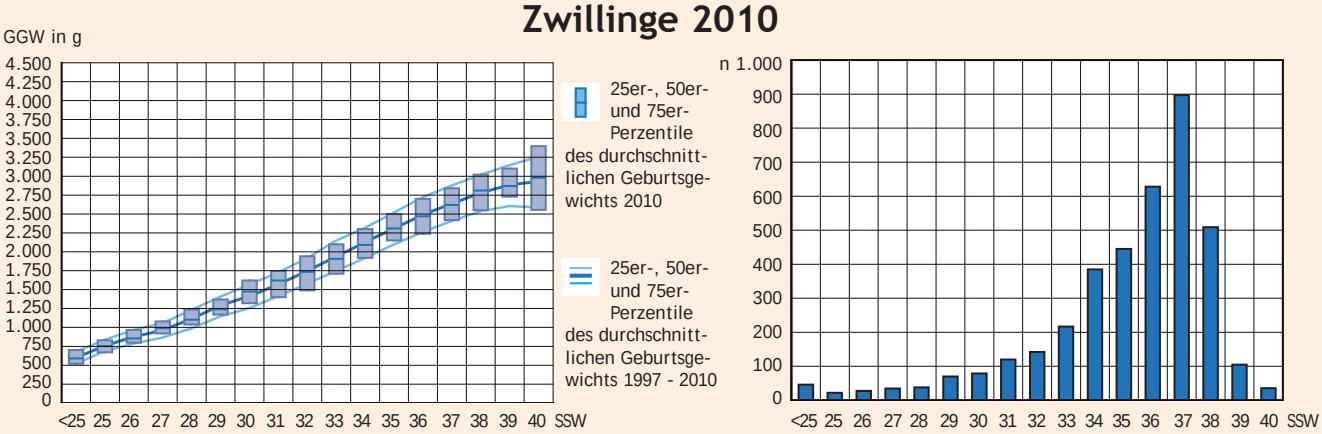


SSW	< 25	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	> 41	Gesamt
n	12	7	12	16	31	15	19	27	49	60	121	174	311	618	1.470	1.949	2.078	963	83	8.015
GGW Q 25	568	580	667	745	820	1.080	1.250	1.360	1.610	1.745	2.060	2.270	2.410	2.710	2.950	3.100	3.220	3.320	3.300	2.980
GW Median	635	730	855	905	980	1.240	1.440	1.490	1.835	1.990	2.290	2.557	2.750	3.000	3.212	3.380	3.500	3.600	3.610	3.320
GGW Q 75	815	860	1.010	990	1.330	1.510	1.620	1.770	2.060	2.195	2.500	2.890	3.020	3.300	3.500	3.650	3.660	3.770	3.890	3.650

Perzentilen 2010: p25 = 38. SSW, p50 = 39. SSW, p75 = 40. SSW; Perzentilen 1997 - 2010: p25 = 38. SSW, p50 = 39. SSW, p75 = 40. SSW

Anteil der vor der abgeschlossenen 37. SSW geborenen Kinder: 18,37 %

Zwillinge 2010



SSW	<25	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	Gesamt**
n	46	22	28	35	38	70	79	120	142	217	385	445	628	897	509	105	36	3.813
GGW Q 25	520	670	797	920	1.040	1.170	1.320	1.400	1.490	1.710	1.920	2.150	2.240	2.420	2.550	2.730	2.555	1.990
GGW Median	590	752	855	990	1.103	1.240	1.475	1.620	1.735	1.906	2.090	2.310	2.470	2.620	2.810	2.870	2.980	2.400
GGW Q 75	700	830	967	1.080	1.235	1.370	1.620	1.745	1.940	2.100	2.300	2.500	2.700	2.840	3.020	3.100	3.397	2.720

Perzentilen 2010: p25 = 34. SSW, p50 = 36. SSW, p75 = 37. SSW; Perzentilen 1997 - 2010: p25 = 34. SSW, p50 = 36. SSW, p75 = 37. SSW

Anteil der vor der abgeschlossenen 37. SSW geborenen Kinder: 82,66 %

**) In der Summe sind 11 Fälle enthalten, bei denen SSW > 40 ist

Drillinge 2010

SSW	24	25	26	27	28	29	30	31	32	33	34	35	Gesamt**
n	7	0	6	9	18	9	15	17	43	27	40	20	214
GGW Q 25	470	-	890	950	840	1.200	1.240	1.390	1.460	1.780	1.800	1.900	1.320
GGW Median	570	-	1.150	950	1.027	1.560	1.455	1.490	1.675	2.150	1.967	2.018	1.672
GGW Q 75	600	-	1.870	990	1.240	1.670	1.560	1.610	1.784	2.370	2.105	2.330	1.975

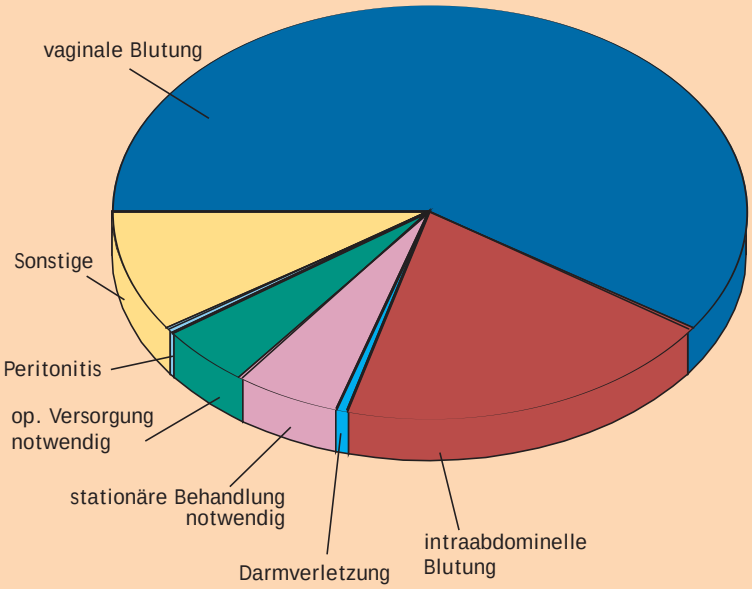
Perzentilen 2010: p25 = 30. SSW, p50 = 32. SSW, p75 = 34. SSW; Perzentilen 1997 - 2010: p25 = 30. SSW, p50 = 32. SSW, p75 = 33. SSW

Anteil der vor der abgeschlossenen 37. SSW geborenen Kinder: 98,60 %

**) In der Summe sind 3 Fälle enthalten, bei denen SSW > 35 ist

*) Kinder mit plausiblem Geburtsgewicht und SSW; prospektive und retrospektive Daten

Komplikationen bei der Eizellentnahme 2011



Eizellentnahmen gesamt	46.583	100,00 %
Keine Angaben	0	-
Keine Komplikationen	46.277	99,34
Komplikationen	306	0,66

Komplikation	n	%
vaginale Blutungen	183	59,80
intraabdom. Blutung	59	19,28
Darmverletzung	2	0,65
Peritonitis	1	0,33
stat. Behandl. notwendig	16	5,23
op. Versorgung notwendig	15	4,90
Sonstige	30	9,80
Gesamt	306	100,00

Es wurden nur prospektiv erfasste Daten verwendet.

Überstimulationssyndrom in Abhängigkeit von der Stimulation bei erfolgtem Transfer IVF, ICSI, IVF/ICSI 2011

	Stimulation	%	Zahl gew. Eizellen	OHSS III	OHSS III/Stim %
GnRHa-kurz	3.649	8,09	8,06	3	0,08
nur FSH	1.347		9,39	2	0,15
nur hMG	1.523		7,67	0	-
FSH und hMG	624		6,60	1	0,16
Sonstige	142		6,39	0	-
keine Angaben	13		5,54	0	-
GnRHa-lang	17.674	39,21	10,55	74	0,42
nur FSH	9.615		11,46	40	0,42
nur hMG	3.529		9,32	1	0,03
FSH und hMG	3.241		9,91	31	0,96
Sonstige	1.164		8,74	2	0,17
keine Angaben	125		9,22	0	-
Ohne GnRH-Analoga	4.354	9,66	8,19	6	0,14
nur FSH	1.438		10,07	4	0,28
nur hMG	793		8,81	1	0,13
FSH und hMG	771		9,09	1	0,13
Sonstige	538		6,44	0	-
keine Angaben	814		4,56	0	-
GnRH-Antagonisten	19.401	43,04	8,86	54	0,28
nur FSH	11.068		10,39	45	0,41
nur hMG	3.451		7,15	4	0,12
FSH und hMG	2.282		7,11	3	0,13
Sonstige	2.468		6,19	1	0,04
keine Angaben	132		5,98	1	0,76
Summe	45.078	100,00	9,40	137	0,30

Es wurden nur prospektiv erfasste Daten verwendet.

Therapieentscheidungen von Kinderwunschpaaren in Abhängigkeit vom Ausgang des vorherigen Zyklus

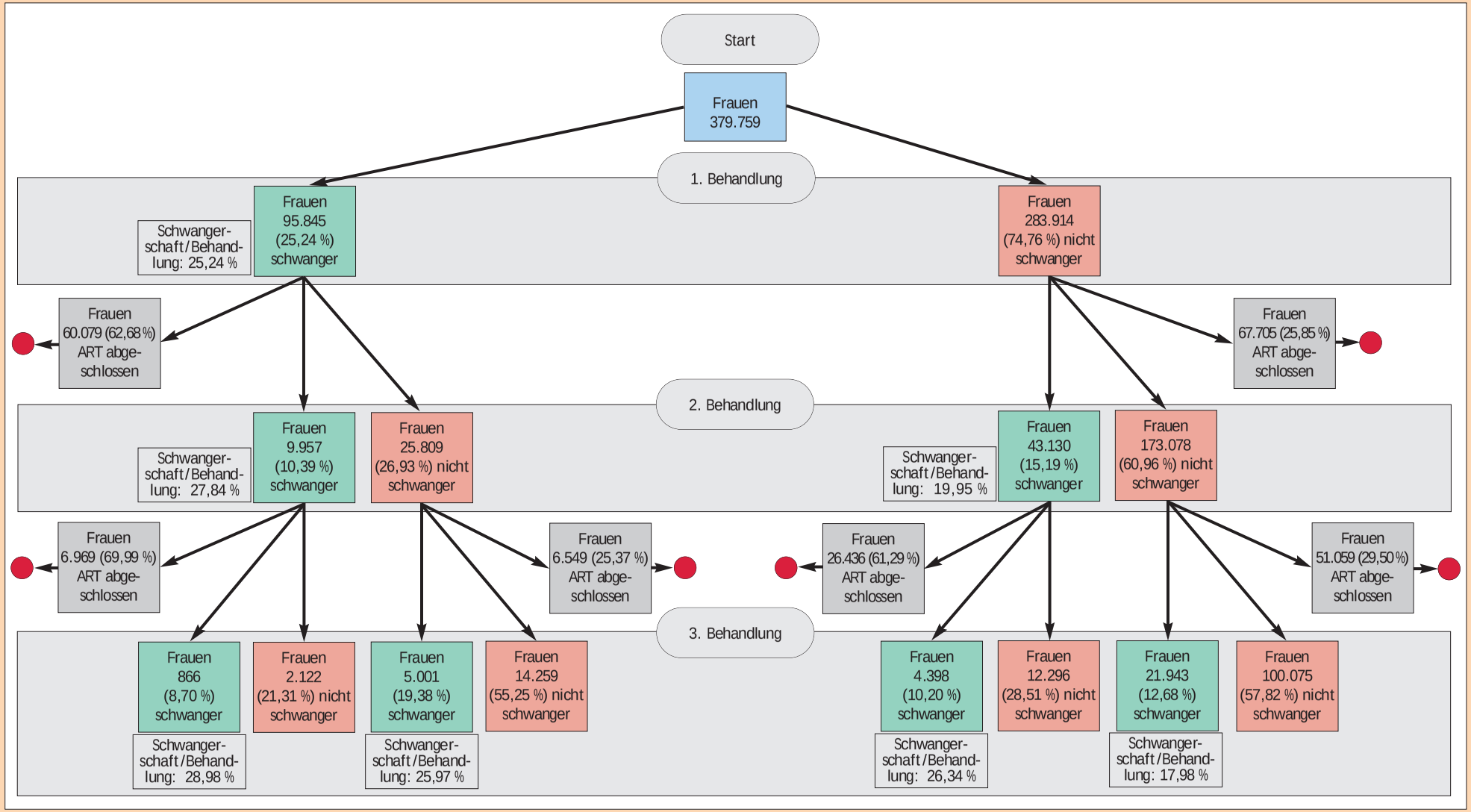
1997 - 2011, IVF, ICSI, IVF/ICSI, Kryo-ET

Frauen, die in der n. Behandlung schwanger geworden sind

Frauen, die in der n. Behandlung *nicht* schwanger geworden sind

Frauen, die keine weitere Behandlung gemacht haben (Endpunkt)

Fazit: Eine vorausgehende Schwangerschaft durch eine ART-Behandlung erhöht die Wahrscheinlichkeit erneut durch eine ART-Behandlung schwanger zu werden.



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human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Neonatal outcome and congenital malformations in children born after ICSI with testicular or epididymal sperm: a controlled national cohort study

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STUDY QUESTION: Does neonatal outcome including congenital malformations in children born after ICSI with epididymal and testicular sperm [testicular sperm extraction (TESE)/percutaneous epididymal sperm aspiration (PESA)/testicular sperm aspiration (TESA) (TPT)] differ from neonatal outcome in children born after ICSI with ejaculated sperm, IVF and natural conception (NC)?

SUMMARY ANSWER: Children born after TPT have similar neonatal outcome, including total malformation rates, as have children born after ICSI and IVF with ejaculated sperm. Testing for variance over the four groups may indicate smaller differences in specific malformation rates with TPT as the highest risk group.

WHAT IS KNOWN ALREADY: Regarding neonatal outcome as well as congenital malformations in children born after TPT, studies are few, with limited sample size, heterogeneous and often performed without relevant control groups.

STUDY DESIGN, SIZE, DURATION: Population-based cohort study including all Danish children born after TPT and fresh embryo transfer in Denmark from 1995 to 2009. Children born after transfer of frozen–thawed embryos were excluded. Control groups of children conceived by ICSI with ejaculated sperm, IVF and NC were identified by cross-linkage of the Danish IVF Register, Medical Birth Register (MBR) and National Hospital Discharge Register (HDR).

PARTICIPANTS/MATERIALS, SETTING: The study group consisted of 466 children born after TPT, while the control groups consisted of 8967 (ICSI with ejaculated sperm), 17 592 (IVF) and 63 854 (NC) children. Neonatal outcomes and congenital malformations were analysed for singletons and twins separately. Risk estimates for low birthweight (LBW, $<$2500 g) and preterm birth (PTB, $<$37 gestational weeks) were adjusted for maternal age, parity, child gender and year of childbirth. The study group was identified from the Danish national database on children born after TPT. Control groups were obtained from the IVF register and the MBR. All information included in the study was retrieved from the national registers.

MAIN RESULTS AND THE ROLE OF CHANCE: Considering singletons and twins as one group, the sex ratio (♂/♀) was significantly lower for children born after TPT (0.89) compared with conventional IVF (1.11; $P = 0.017$) but did not differ significantly when compared with ICSI with ejaculated sperm (0.94) and NC (1.05). The mean birthweight (BW) for singletons did not differ significantly between groups when including only first-born children. The mean gestational age (GA) in the TPT singletons (279 $\pm$ 12 days) was significantly higher compared with IVF (276 $\pm$ 18 days; $P = 0.02$), but similar to ICSI with ejaculated sperm and NC singletons when including only first-born children (277 $\pm$ 16 days and 279 $\pm$ 14 days, respectively). Rate of stillbirths, perinatal and neonatal mortality in the group of TPT singletons did not differ significantly from any of the control groups. Comparable results were found for the TPT twin group, except for perinatal mortality, which was significantly lower in the TPT group compared with naturally conceived twins. The adjusted risk of LBW was significantly higher for TPT versus NC singletons [adjusted odds ratio (AOR) = 0.67 (0.48–0.93)]; however AOR for PTB was similar in the two groups. Regarding twins, similar adjusted risks were observed for PTB and LBW between the TPT and all three control groups. Significantly more

Caesarean sections were performed after IVF (27.3% for singletons) and ICSI (25.1% for singletons) with ejaculated sperm compared with the TPT group (16.4% for singletons). The total rate of congenital malformations in the TPT group was 7.7% and did not differ significantly from any of the control groups. However, singleton TPT boys showed an increased rate of cardiac malformations (3.6%) compared with singleton boys after IVF (1.4%; $P = 0.04$) and NC (1.1%; $P = 0.02$). Considering the level of male infertility as a continuum over the four groups, tests for variance in the rate of cardiac malformations in singleton boys, and undescended testicles for singleton as well as twin boys were each significantly increased from NC to IVF to ICSI to TPT ($P < 0.001$). The rate of hypospadias showed the same pattern, but the TPT group did not differ significantly compared with the control groups.

LIMITATIONS, REASONS FOR CAUTION: One of the limitations is that the TPT group could not be classified according to testicular or epididymal sperm, as these data were not available in the IVF register. Another limitation is that registry-based studies are encumbered with the risk of reporting or coding errors or missing data due to insufficient coding. However, the quality of data on congenital malformations in HDR has, in other studies, been validated and found acceptable for epidemiological research, and furthermore, recordings on study and control groups are performed similarly.

WIDER IMPLICATIONS OF THE FINDINGS: Accumulating data show that TPT treatment is equally safe as conventional ICSI and IVF treatment and as NC with regard to neonatal outcome including congenital malformation.

STUDY FUNDING/POTENTIAL COMPETING INTERESTS: This study is supported by Laboratory of Reproductive Biology, Scientific Unit, Horsens Hospital. No competing interests declared.

Key words: neonatal outcome / congenital malformation / sex ratio / azoospermia / TESE/PESA/TESA

Introduction

Since the first children were born after ICSI using testicular sperm (Craft *et al.*, 1993; Schoysman *et al.*, 1993), the use of TESE (testicular sperm extraction), PESA (percutaneous epididymal sperm aspiration) and TESA (testicular sperm aspiration) has steadily increased. In 2010 a total of 234 TESE/PESA/TESA (TPT) treatments were performed in Denmark (The National Board of Health, Denmark).

Two meta-analyses and a large Swedish national cohort study have shown a statistically significant increased risk of birth defects of 30–40% after IVF/ICSI when compared with natural conception (NC, Hansen *et al.*, 2005; Källén *et al.*, 2005; Lie *et al.*, 2005). Although the risk of birth defects in IVF/ICSI singletons have declined over time, an increased risk of 10–20% in singletons conceived by assisted reproduction still remains (Källén *et al.*, 2010).

Following ICSI using ejaculated, epididymal or testicular sperm, the rate of malformations, particularly in the cardiovascular system and the urogenital tract, appears to be increased (Wennerholm *et al.*, 2000; Ludwig and Katalinic, 2002; Källén *et al.*, 2005; Fedder *et al.*, 2007).

In a previous Danish descriptive study based on a smaller cohort of the present material and also including children born of Norwegian couples treated in Denmark, a significantly decreased sex ratio (♂/♀) of 0.83 (~45.4% males) for children born after ICSI with sperm retrieved from testis or epididymis was observed when compared with a Danish national IVF cohort (1.13; ~53.1% males) (Fedder *et al.*, 2007).

Several studies have demonstrated that children born after ICSI with ejaculated sperm do not have poorer neonatal outcome than IVF children (Bonduelle *et al.*, 2002; Pinborg *et al.*, 2004). In a recent study neonatal outcome for children conceived by ICSI with epididymal sperm was found to be similar to that of children conceived by ICSI with ejaculated sperm (Woldringh *et al.*, 2011). However, a higher rate of hypospadias and cardiac malformations has been suggested after ICSI with epididymal or testicular sperm (Fedder *et al.*, 2007). However, according to neonatal outcome as well as congenital malformations in children born after ICSI with epididymal or testicular sperm, studies are few, with limited sample size, heterogeneous and often performed without relevant control groups (Woldringh *et al.*, 2010).

The aim of this study was to compare neonatal outcomes and rates of congenital malformations and imprinting disorders in a national cohort of children conceived after ICSI with epididymal or testicular sperm with appropriate control groups including children born after ICSI or IVF with ejaculated sperm or NC.

Materials and Methods

This population-based cohort study included all Danish children born after ICSI with epididymal or testicular sperm in Denmark from 1 January 1995 to 31 December 2009 (Group A). The TPT group (Group A) was identified from the Danish national TPT database, which was created along with a national questionnaire examination. All Danish fertility clinics contributed and a response rate of 97.5% was obtained with only 2.5% of TPT children missing (Fedder *et al.*, 2007). In Denmark, every human individual has a unique identification number in the Centralized Personal Registry (CPR number) that is widely used by healthcare and social service providers. No other information than CPR numbers for mother and child was taken from the original TPT database. All information for the study and the control groups were retrieved from the national registers including the Danish Medical Birth Register (MBR).

In total we identified 499 children born after ICSI with epididymal or testicular sperm. In the final study population we included only women with complete data on child sex, maternal age and gestational age in the MBR ($N = 466$; Group A). This group was sub-divided into 290 (62.2%) singletons and 176 (37.8%) twin children. The conventional IVF and ICSI groups were identified by a cross-linkage of the Danish IVF register and the MBR. In the MBR register date of childbirth was linked to a specific IVF/ICSI date of ovum pick-up in the IVF register by the unique maternal CPR number. If more dates of ovum pick-up matched the pre-defined criteria for date of child birth, we selected the date closest to the date of delivery.

The control groups consisted of 8967 children ($n = 5866$ singletons; $n = 3101$ twins) conceived by ICSI with ejaculated sperm (Group B) and 17 592 children ($n = 11\,060$ singletons; $n = 6532$ twins) conceived by conventional IVF (Group C). In order to compare with children born after NC we identified all twins born after NC during the same period via the MBR ($n = 30\,002$). A random sample of NC singletons, 2-fold the size of the IVF/ICSI singleton group and matched by date and year of birth, was selected from the MBR ($n = 33\,852$) Hence, the group of children conceived by NC consisted of 63 854 children (Group D). As the compulsory Danish IVF Register did not record treatment with ovulation induction/ovarian stimulation or intrauterine insemination until 2007, children born after such treatments may be included in the NC singleton and twin groups. However, the proportion of such children is only ~2% (http//:www.fertilitetsselskab.dk).

The following variables were retrieved from the registers: maternal age, parity, Caesarean section, birthweight (BW), gestational age, child gender, stillbirth, perinatal and neonatal mortality together with congenital malformations. In the MBR, the duration of gestation in IVF/ICSI pregnancies with fresh embryos is determined from 14 days before the date of oocyte pick-up.

The information on all discharge diagnoses regarding malformations, chromosome aberrations, imprinting related diseases and malignancies was obtained from the National Hospital Discharge Register (HDR) from date of birth until 31 December 2010. Thus, the follow-up period of the infants varied from 12 months to 15 years. All diagnoses were classified according to the International Classification of Diseases, 10th edition (ICD-10 codes) in HDR.

Children registered with one of the following diagnosis codes were recorded as having an 'imprinting-related disease': Angelman syndrome Q93.5C, Russel-Silver syndrome Q87.1G, Bechwith-Wiedeman Q87.3A, Prader Willi Q87.1E, retinoblastoma C69.2A, Wilms tumour C64, osteosarcoma C40–41, hepatoblastoma C22.2, histiocytosis maligna C96.1.

Definitions

Gestational age was defined as the period of 14 days prior to oocyte pick-up until delivery. To exclude outliers, only children with gestational age between 22 and 44 weeks and BW between 400 and 7000 g were included. Preterm birth (PTB) was defined as delivery before 37 completed weeks and very preterm birth (VPTB) was defined as delivery before 32 completed weeks of gestation. Low BW (LBW) was defined as <2500 g and very low BW (VLBW) as <1500 g. Stillbirth was defined as delivery of a dead child after gestational age of 22+0 weeks, and perinatal death was defined as intrauterine death (after gestational weeks of 22+0) or death during the first week of life (Days 0–6), while neonatal death was defined as death during the first 4 weeks of life (Days 0–27).

Malformations were defined as conditions registered in the International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10; Danish National Board of Health (1994) as a congenital malformation or chromosome abnormality (ICD-10: Q00-Q99). Complete data were obtained for >92% of the children according to sex, maternal age, parity, BW, gestational age, live births, stillbirth, peri-/neonatal mortality, Caesarean section and congenital malformations.

Statistics

Continuous data were analysed using linear regression, with an adjustment for dependence between twins using the robust variance estimation (Tables I and II). Dichotomous data were analysed using the binomial regression when there were >10 events in each group, with an adjustment for dependence between twins using the robust variance estimation.

Table I Demographic data on mothers and children born after ICSI with epididymal or testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D	*P* values[a]		
					A versus B	A versus C	A versus D
All children, *n*	466	8967	17 592	63 854			
Child sex ratio (♂/♀)	0.89	0.94	1.11	1.05	0.59	0.017	0.068
Singletons, *n*	290	5866	11 060	33 852			
Maternal age[b]	32.78 ± 4.27 (32.28–33.27)	33.16 ± 4.05 (33.06–33.26)	34.01 ± 4.04 (33.93–34.08)	30.23 ± 4.86 (30.18–30.28)	0.12	<0.001	<0.001
Children of primiparae (%)	77.4	70.6	70.9	43.1	0.01	0.02	<0.001
Child sex ratio (♂/♀)	0.91	0.93	1.12	1.07	0.86	0.08	0.17
Twin children, *n*	176	3101	6532	30 002			
Maternal age[b]	32.43 ± 3.38 (31.73–33.17)	32.41 ± 3.74 (32.41–32.59)	33.21 ± 3.80 (33.08–33.34)	31.18 ± 4.58 (31.09–31.23)	0.94	0.007	<0.001
Children of primiparae (%)	80.6	70.1	70.0	44.2	0.003	0.002	<0.001
Child sex ratio (♂/♀)	0.85	0.94	1.10	1.04	0.54	0.11	0.20

Treatments with frozen–thawed embryos were excluded.
[a]Linear regression/binomial regression with adjustment for dependence between twins using robust variance estimation.
[b]Maternal age shown as the mean ± SD (95% CI for mean).

Table II Birthweights (in grams) and gestational ages (in days) for singletons and twins born after ICSI with epididymal testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D	*P* values[a]		
					A versus B	A versus C	A versus D
Singletons							
Birthweight, all	3433 ± 545 (3370–3496)	3435 ± 621 (3419–3451)	3374 ± 661 (3362–3387)	3533 ± 579 (3526–3539)	0.96	0.13	0.004
Birthweight, first born	3395 ± 533 (3325–3466)	3395 ± 630 (3376–3414)	3338 ± 666 (3323–3353)	3446 ± 580 (3437–3456)	1.00	0.20	0.19
Gestational age, all	279 ± 11 (278–280)	277 ± 15 (276–277)	276 ± 17 (275–276)	279 ± 13 (279–279)	0.03	0.002	0.96
Gestational age, first born	279 ± 12 (277–280)	277 ± 16 (277–278)	276 ± 18 (276–276)	279 ± 14 (279–279)	0.12	0.02	0.64
Twin children							
Birthweight, all	2551 ± 591 (2439–2663)	2496 ± 601 (2468–2525)	2464 ± 625 (2444–2484)	2507 ± 609 (2498–2516)	0.34	0.13	0.43
Birthweight, first born	2487 ± 495 (2380–2594)	2429 ± 619 (2394–2464)	2410 ± 636 (2385–2435)	2375 ± 623 (2361–2390)	0.30	0.16	0.04
Gestational age, all	255 ± 14 (252–258)	254 ± 19 (253–255)	256 ± 22 (256–257)	258 ± 21 (257–258)	0.55	0.26	0.05
Gestational age, first born	254 ± 15 (251–258)	253 ± 21 (251–254)	256 ± 24 (255–257)	255 ± 23 (254–255)	0.28	0.35	0.84

The values are the mean ± SD (95% CI).
[a]Linear regression with adjustment for dependence between twins using robust variance estimation.

When there were <10 events in a group we used Fisher's exact test with an adjustment for dependence between twins using the Bonferroni adjustment (Tables I and III–VI).

Adjustments were performed for maternal age (<30, 30–34, 35–39, ≥40 years), parity (0 or ≥1 previous births), child gender and infant year of birth (1995–1997, 1998–2000, 2001–2003 and 2004–2006). Data were analysed in SPSS (PASW Statistics), version 18.01. Statistical significance was defined as a probability value of $P < 0.05$.

According to the Danish legislation, studies based solely on register data and with no personal involvement of the participants do not require approval from an ethical committee. The study was approved by the Danish Data Protection Agency (J. no. 2008-41-1891) and the National Board of Health. The authors have no conflicts of interest.

Results

Demographics/maternal background data

The mean maternal age in Groups A and B was similar (for singletons as well as twins), whereas the mean maternal age in the TPT group (A) was significantly lower than that in the group of conventional IVF (C) and significantly higher than that in the group of NC (D). The rate of primiparity in the TPT mothers was significantly higher when compared with the three control groups (Table I).

Evaluating singletons and twins as one group, the sex ratio (♂/♀) was significantly lower in Group A (0.89∼47.0% males) compared with that in Group C (1.11∼52.6% males; $P = 0.017$) but did not differ significantly compared with Group B (0.94∼48.4% males, $P = 0.59$) or Group D (1.05∼51.3% males; $P = 0.068$). We found no significant differences in the sex ratio in the analyses restricted to singletons and twins only (Table I).

Obstetric outcome

Singletons

The mean BW for singletons was significantly lower in the TPT (Group A) versus naturally conceived singletons (Group D), but similar compared with singletons born after ICSI with ejaculated sperm and IVF (Group B and C). The difference in the mean BW between Groups A and D disappeared when including only the first-born child in the analysis (Table II). The mean gestational age was similar for singletons in Groups A and D (279 days) but significantly longer than in Groups B (277 days; $P = 0.03$) and C (276 days; $P = 0.002$). When restricted to analyses on the first-born child, a significant difference in the mean gestational age remained only between Groups A and C (Table II).

The rate of LBW was significantly higher in Group A (5.9%) than that in Group D (3.5%) (Table III). A significantly lower rate of VLBW in Group A compared with children conceived by conventional IVF was observed (Table III). The rates of PTB and VPTB in Group A were significantly lower than that in Group C, and VPTB was also lower in Group A compared with Group B (Table III). The rate of Caesarean sections in Group A singletons was similar to the rate in Group D but significantly lower than the rates found in Groups B and C (Table III). The adjusted risk (AOR) of LBW was significantly higher in Group A compared with Group D, while no adjusted risk differences of PTB were demonstrated between the TPT group and any of the control groups (Table IV).

Table III Rates of LBW, VLBW, PTB, VPTB, stillbirths and Caesarean sections for children born after ICSI with epididymal or testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D	*P* values[a]		
					A versus B	A versus C	A versus D
Singletons							
LBW (<2500 g)	5.9 (3.5–9.2)	5.9 (5.3–6.5)	7.4 (6.9–7.9)	3.5 (3.3–3.7)	1.00	0.42	0.04
VLBW (<1500 g)	0.0 (0.0–1.3)	1.3 (1.0–1.6)	1.9 (1.7–2.2)	0.7 (0.7–0.8)	0.05	0.007	0.28
PTB (<37 weeks)	5.2 (2.9–8.4)	7.1 (6.4–7.8)	9.1 (8.6–9.6)	4.6 (4.4–4.9)	0.24	0.02	0.67
VPTB (<32 weeks)	0.0 (0.0–1.3)	1.6 (1.3–1.9)	2.1 (1.9–2.4)	0.8 (0.7–0.9)	0.02	0.005	0.18
Caesarean section	16.4 (11.7–22.0)	25.1 (23.7–26.4)	27.3 (26.3–28.4)	17.5 (17.0–18.0)	0.003	<0.001	0.72
Stillbirths	0.0 (0.0–1.3)	0.6 (0.4–0.8)	0.7 (0.6–0.9)	0.4 (0.3–0.5)	0.40	0.28	0.64
Perinatal death	0.0 (0.0–1.3)	0.8 (0.6–1.1)	1.3 (1.1–1.5)	0.6 (0.6–0.7)	0.17	0.06	0.27
Neonatal death	0.3 (0.0–1.9)	0.3 (0.2–0.5)	0.7 (0.5–0.8)	0.3 (0.2–0.3)	0.58	1.00	0.56
Twin children							
LBW (<2500 g)	43.5 (31.3–56.2)	43.7 (40.8–46.6)	45.1 (43.1–47.1)	42.6 (41.7–43.6)	1.00	1.00	1.00
VLBW (<1500 g)	1.2 (0.0–7.4)	6.9 (5.5–8.5)	8.2 (7.2–9.4)	7.1 (6.6–7.6)	0.08	0.02	0.06
PTB (<37 weeks)	48.9 (38.0–59.8)	44.7 (42.2–47.2)	40.2 (38.6–42.0)	37.8 (37.0–38.6)	0.44	0.10	0.03
VPTB (<32 weeks)	4.5 (1.0–10.6)	8.1 (6.8–9.6)	8.4 (7.5–9.4)	7.1 (6.7–7.6)	0.31	0.25	0.41
Caesarean section	49.6 (37.6–62.4)	59.0 (56.0–62.0)	58.3 (56.1–60.4)	53.1 (52.1–54.1)	0.16	0.21	0.72
Stillbirths	0.0 (0.0–4.9)	1.2 (0.7–1.9)	1.2 (0.9–1.7)	1.9 (1.6–2.1)	0.80	0.85	0.24
Perinatal death	0.0 (0.0–4.9)	2.4 (1.6–3.3)	2.8 (2.2–3.4)	3.3 (3.0–3.6)	0.22	0.15	0.04
Neonatal death	0.0 (0.0–4.9)	1.3 (0.8–2.2)	1.9 (1.4–2.5)	1.7 (1.5–2.0)	1.00	0.81	0.85

The values are % (95% CI). LBW, low birthweight; VLBW, very low birthweight; PTB, preterm birth; VPTB, very preterm birth.
[a]Singletons: Fisher's exact test. Twins: binomial regression with adjustment for dependence between twins using robust variance estimation when there were 10 or more events in each group, otherwise Fisher's exact test with Bonferoni's method adjustment for dependence between twins. The exact 95% CIs for rates were calculated using the F-distribution.

Twins

The mean BW and gestational age in Group A twins was similar to the other groups, while the mean BW of the first-born twins was higher in Group A compared with Group D (Table II). A very low frequency of VLBW was found in Group A (1.2%) compared with each of the other groups (6.9, 8.2, 7.1%), but Group A did not differ significantly from the other groups according to LBW (Table III). After adjusting for possible dependency between twins, a similar rate of Caesarean sections was found in Group A compared with any of the three control groups (Table III). No differences were found in the AOR of LBW and PTB (Table IV).

No statistically significant differences in rates of stillbirths or neonatal death associated with the mode of conception were observed. For twins in Group A the rate of perinatal deaths was found significantly lower than in Group D (Table III).

Congenital malformations

As shown in Table V no overall increased rate of congenital malformations was found in Group A compared with the other groups. However, the rate of neoplasms in bones or joint cartilages, including osteosarcomas, was found slightly increased for twin children born after ICSI with epididymal/testicular sperm (1.14%) compared with ICSI with ejaculated sperm (0.13%; $P = 0.03$) and NC (0.21%; $P = 0.04$), although not significantly increased when compared with conventional IVF (0.21%). No possible imprinting-related disorders except osteosarcomas were detected in any of the four groups.

When focusing on specific organ systems, an increased rate of cardiac malformations, such as Fallots tetralogy and ventricular septal defects, was found for singleton boys conceived with epididymal or testicular sperm (3.6%) compared with singleton boys conceived by conventional IVF (1.4%, $P = 0.04$) or NC (1.1%; $P = 0.02$) (Table VI). Considering the groups as roughly representing a gradually increasing severity of male infertility from Group D to Group A, a significantly increased trend in cardiac malformations correlating with the severity of male infertility was found ($P < 0.001$).

No significant differences were found in the rates of hypospadias and non-descended testicles between Group A and the three control groups, neither for singletons nor twins. However, again considering Group D to A as a gradually increasing severity of male infertility, the rate of non-descended testicles gradually increased in boys (singletons as well as twins) ($P < 0.001$). The same trend existed for hypospadias both in singletons and twins, although this was not statistically significant (Table VI).

Discussion

This Danish nationwide cohort study shows that singletons as well as twins born after ICSI with epididymal or testicular sperm have similar perinatal/neonatal outcomes and similar total congenital malformation

Table IV Odds ratios of LBW and PTB for children born after ICSI with epididymal or testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D
Singletons				
LBW (<2500 g)	1.00 (ref.)	1.00 (0.61–1.65)	1.28 (0.68–2.40)	0.58 (0.44–0.77)
Crude				
Adjusted[a]	1.00 (ref.)	0.97 (0.60–1.58)	1.22 (0.66–2.23)	0.67 (0.48–0.93)
PTB (<37 weeks)	1.00 (ref.)	1.40 (0.67–2.93)	1.83 (0.70–4.79)	0.89 (0.56–1.42)
Crude				
Adjusted[a]	1.00 (ref.)	1.38 (0.66–2.85)	1.94 (0.70–5.38)	1.02 (0.60–1.74)
Twin children				
LBW (<2500 g)	1.00 (ref.)	1.01 (0.69–1.47)	1.06 (0.72–1.58)	0.96 (0.68–1.37)
Crude				
Adjusted[a]	1.00 (ref.)	1.06 (0.71–1.59)	1.16 (0.75–1.79)	1.20 (0.77–1.89)
PTB (<37 weeks)	1.00 (ref.)	0.85 (0.59–1.21)	0.70 (0.52–0.95)	0.64 (0.49–0.83)
Crude				
Adjusted[a]	1.00 (ref.)	0.86 (0.59–1.26)	0.87 (0.59–1.26)	0.84 (0.58–1.20)

The values are OR (95% CI). Binomial regression with adjustment for dependence between twins was done using the robust variance estimation. LBW, low birthweight; PTB, preterm birth.

[a]Adjusted for mothers' age (<30, 30–34, 35–39 and 40+ years), sex, birth year (1995–1997, 1998–2000,2001–2003, 2004–2009) and parity (1,2+).

rates compared with children born after IVF and ICSI with ejaculated sperm.

Comparing singletons born after ICSI with non-ejaculated sperm to natural conceived singletons we found a lower mean BW and a higher adjusted odds ratio of LBW. For TPT singleton boys we found a significantly higher rate of cardiac malformations but no increased rate in congenital malformations overall. In this registry-based study we were not able to relate outcome to the origin of sperm retrieved, e.g. testicular or epididymal, since this information was only available in the IVF register for the last period of the study. However, in our previous study a significantly higher rate of cardiac malformations were found in TPT children conceived with testicular as well as epididymal sperm, supporting the assumption that the origin of the sperm is not associated with the risk of developing specific malformations (Fedder *et al*., 2007).

The lowest sex ratio was found after ICSI with testicular or epididymal sperm (0.89) and conventional ICSI (0.94), while the highest ratio was found after IVF (1.11). The sex ratio of NC was as expected (1.05). An equal pattern was seen in our previous study, which also demonstrated an even lower sex ratio when testicular (compared with ejaculated) and particularly epididymal sperm were used for ICSI (Fedder *et al*., 2007). Other studies have also found significantly higher male/female ratios after conventional IVF (1.14 and 1.11) compared with ICSI (0.96 and 1.01) (Ericson and Källén, 2001; Bonduelle *et al*., 2002).

According to the well-known differences in perinatal outcomes between singletons and twins, separate analyses for singletons and twins were performed. In the twin analyses the unequal distribution of monozygotic (MZ) twins between the assisted reproductive technology (ART) groups (A, B and C) and the naturally conceived control group (Group D) may bias the comparisons between Groups A and D. The MZ twin rate in ART pregnancies is 1–2% compared with 20–30% in non-ART twin pregnancies. One way to overcome this problem is to make comparisons restricted to different-sex twin pairs, thereby excluding all the MZ twins. As twins were not the main focus of this study and due to the limited number of twin children ($n = 176$) in Group A, we decided not to make sub-analyses on different-sex twin pairs. Further, the MZ-twin rates may only influence the comparisons between Groups A and D.

The pattern of the mean BW was in accordance with previous studies: singletons were heavier than twins, boys heavier than girls and naturally conceived children heavier than children conceived by IVF or ICSI. Further, children conceived after ICSI with ejaculated as well as non-ejaculated sperm had a higher mean BW than IVF children (Bonduelle *et al*., 2002; Ludwig and Diedrich, 2002; Pinborg *et al*., 2004; Woldringh *et al*., 2011).

Obviously, severe male infertility is the most common reason for ICSI treatment and thus the female of an ICSI couple may in general be more 'reproductively healthy' than women treated with conventional IVF. For example, female diagnoses such as polycystic ovarian syndrome, fibroids or endometriosis may be less frequent in females in the ICSI population. This may explain the higher mean BW (although not significant) in the TPT/ICSI groups compared with the IVF group.

Despite an essential overlap between the TPT cohorts in this and our previous study, the rate of congenital malformations of 7.7% found in this study was significantly higher than the 3.4% found in our previous study (Fedder *et al*., 2007). There are two main reasons for this divergence, firstly malformation rates in our previous study were based on a self-reported questionnaire filled in by the parents and secondly, only major malformations were to be reported, while the present study is based on national register data including

Table V Total rates of congenital abnormalities and possible imprinting-related diseases after ICSI with epididymal or testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D	*P*-value[a]		
					A versus B	A versus C	A versus D
Total							
Congenital abnormalities	36, 7.73 (6.13–10.32)	850, 9.48 (8.83–10.13)	1468, 8.34 (7.90–8.79)	5140, 8.05 (7.81–8.29)	0.20	0.64	0.81
Neoplasms in bones and joint cartilage, including osteosarcoma	3, 0.64 (0.01–1.47)	11, 0.12 (0.05–0.20)	43, 0.24 (0.17–0.32)	122, 0.19 (0.16–0.23)	0.39	0.58	0.49
Singletons							
Congenital abnormalities	21, 7.24 (4.54–10.86)	467, 7.96 (7.28–8.68)	762, 6.89 (6.42–7.38)	1952, 5.77 (5.52–6.02)	0.74	0.81	0.31
Neoplasms in bones and joint cartilage, including osteosarcoma	1, 0.34 (0.01–1.91)	7, 0.12 (0.05–0.25)	29, 0.26 (0.18–0.38)	59, 0.17 (0.13–0.22)	0.32	0.54	0.40
Twins							
Congenital abnormalities	15, 8.52 (3.72–13.33)	383, 12.35 (11.00–13.70)	706, 10.81 (9.93–11.69)	3188, 10.63 (10.21–11.04)	0.13	0.36	0.39
Neoplasms in bones and joint cartilage, including osteosarcoma	2, 1.14 (0.09–6.85)	4, 0.13 (0.01–0.52)	14, 0.21 (0.10–0.33)	63, 0.21 (0.15–0.27)	0.03	0.08	0.04

The values are *n* % (95% CI).
[a]Singletons: Fisher's exact test. Twins: binomial regression with adjustment for dependence between twins using the robust variance estimation when there were 10 or more events in each group, otherwise Fisher's exact test with Bonferoni's method adjustment for dependence between twins. The exact 95% CIs for rates were calculated using the F-distribution.

minor malformations. Major congenital malformations have been defined as malformations causing functional impairment or requiring surgical correction, while remaining malformations are considered 'minor' (Fedder *et al.*, 2007). In a recent study, Belva *et al.* (2011) found the rate of major malformations in 724 children conceived by ICSI with epididymal or testicular sperm (4.8%) non-significantly increased compared with 2516 children conceived by ICSI with ejaculated sperm (3.4%). In a questionnaire study, Woldringh *et al.* (2011) found that 3.6% of 370 children conceived by ICSI with epididymal sperm had major malformations. This rate did not differ significantly from major malformation rates in children conceived by IVF or ICSI with ejaculated sperm. In a systematic review including five smaller studies, the 95% confidence interval (CI) of major malformations after ICSI with epididymal (2.0–4.3) and testicular sperm (0.0–9.2) was comparable to IVF (1.7–3.8) or ICSI with ejaculated sperm (1.9–8.4)(Woldringh *et al.*, 2010). These results all correspond to our findings.

Perhaps the 'definite health condition' was better described by the calculation of the rate of malformations per live year. However, this may over-correct the 'error' as most major malformations are expected to be detected in early life. As a diagnostic tool echocardiography is only performed if cardiovascular symptoms are present. Whenever echocardiography is performed systematically during follow-up of a cohort, e.g. a cohort of children conceived by ICSI, a higher incidence of cardiac malformations may be found, as also asymptomatic cases will be diagnosed (Lancaster *et al.*, 1995). An exception from this is undescended testicles, as the rate may increase during childhood due to re-ascending of the testicles (Fedder and Boesen, 1998).

In this study, the rate of undescended testicles seems directly related to the severity of the infertility in the father. The association between reduced semen quality, cryptorchidism and hypospadias is well documented, and the most likely explanation hereto is that fathers (with reduced semen quality) and their sons (with undescended testicles or hypospadias) share the same susceptibility genes for reproductive dysfunction (Skakkebæk *et al.*, 2001; Asklund *et al.*, 2007). However, in the present study the rate of hypospadias was not significantly associated with the severity of male infertility.

Data from the MBR and the HDR were recorded similarly for both study and control groups thereby allowing an identical methodology in order to compare neonatal outcomes and congenital malformation rates for a follow-up period of at least one year. One of the major limitations in the present study is that we were unable to classify the TPT group according to testicular or epididymal sperm as these data were not available in the IVF register. Previous studies have shown that the outcome may differ after use of immature testicular sperm and aged epididymal sperm (Fedder *et al.*, 2007; Woldringh *et al.*, 2010). The optimal evaluation of outcomes after ICSI using epididymal or testicular sperm should also take the aetiology of infertility into account. In non-obstructive azoospermia (NOA), the sperm is always retrieved from testicular tissue. However, it is not sufficient to distinguish between obstructive azoospermia (OA) and NOA (as done by, e.g. Belva *et al.*, 2011), since each of these conditions include a heterogeneous group of diagnoses. Further OA may develop into NOA (due to impaired sperm production), as sperm production decreases over time due to the obstruction, e.g. vasectomy (Thomas, 1987).

Table VI Congenital malformations in specific organ systems and chromosomal aberrations in children conceived by ICSI with epididymal or testicular sperm (Group A), ICSI with ejaculated sperm (Group B), conventional IVF (Group C) or NC (Group D).

	Group A	Group B	Group C	Group D	*P*-value[a]		
					A versus B	A versus C	A versus D
All children							
Malformations in total	36, 7.73 (5.13–10.32)	850, 9.48 (8.83–10.13)	1468, 8.34 (7.90–8.79)	5140, 8.05 (7.81–8.29)	0.20	0.64	0.81
Nervous (Q00–07)	0, 0.00 (0.00–0.97)	25, 0.28 (0.17–0.39)	42, 0.24 (0.16–0.32)	146, 0.23 (0.19–0.27)	1.00	1.00	1.00
Eye, ear, face (Q10–18)	0, 0.00 (0.00–0.97)	26, 0.29 (0.18–0.40)	51, 0.29 (0.21–0.37)	160, 0.25 (0.21–0.29)	0.62	0.63	0.63
Cardiac (Q20–28)	8, 1.72 (0.75–3.77)	186, 2.07 (1.76–2.39)	379, 2.15 (1.92–2.39)	1234, 1.93 (1.81–2.05)	1.00	1.00	0.68
Respiratory (Q30–34)	1, 0.21 (0.01–1.46)	29, 0.32 (0.21–0.44)	39, 0.22 (0.15–0.29)	152, 0.24 (0.20–0.28)	1.00	0.60	0.56
Orofacial clefts (Q35–37)	0, 0.00 (0.00–0.97)	22, 0.25 (0.14–0.35)	34, 0.19 (0.13–0.26)	143, 0.22 (0.19–0.26)	1.00	1.00	1.00
The tongue (Q38)	1, 0.21 (0.01–1.46)	21, 0.23 (0.13–0.34)	39, 0.22 (0.15–0.29)	115, 0.18 (0.14–0.22)	1.00	0.60	0.49
Gastrointestinal (Q39–45)	3, 0.64 (0.06–1.89)	39, 0.43 (0.30–0.57)	78, 0.44 (0.35–0.54)	243, 0.38 (0.33–0.43)	1.00	1.00	1.00
Female genitalia (Q50–52)	0, 0.00 (0.00–1.81)	4, 0.09 (0.02–0.23)	7, 0.08 (0.04–0.21)	22, 0.07 (0.04–0.10)	1.00	1.00	1.00
Non-descended testicles (Q53)	3, 1.37 (0.35–4.87)	40, 0.92 (0.64–1.21)	58, 0.63 (0.47–0.79)	144, 0.44 (0.37–0.51)	0.21	0.08	0.04
Hypospadias (Q54)	3, 1.37 (0.14–4.02)	28, 0.65 (0.41–0.88)	56, 0.61 (0.45–0.76)	182, 0.56 (0.47–0.64)	0.28	0.27	0.22
Other penis abnormalities (Q55)	0, 0.00 (0.00–2.06)	5, 0.12 (0.03–0.29)	7, 0.08 (0.03–0.17)	10, 0.03 (0.01–0.05)	1.00	1.00	1.00
Intersexuality (Q56)	0, 0.00 (0.00–0.97)	2, 0.02 (0.00–0.07)	2, 0.01 (0.00–0.05)	1, 0.00 (0.00–0.01)	1.00	1.00	1.00
Urinary (Q60–64)	2, 0.43 (0.06–1.89)	40, 0.45 (0.30–0.59)	56, 0.32 (0.23–0.40)	195, 0.31 (0.26–0.35)	0.69	0.34	0.30
Musculoskeletal (Q65–79)	15, 3.22 (1.42–5.02)	443, 4.94 (4.45–5.43)	701, 3.98 (3.66–4.31)	2651, 4.15 (3.97–4.33)	0.07	0.41	0.31
Other (Q80–89)	3, 0.64 (0.06–1.89)	32, 0.36 (0.23–0.48)	73, 0.41 (0.32–0.51)	257, 0.40 (0.35–0.45)	0.65	0.67	0.68
Chromosomal aberrations (Q90–99)	1, 0.21 (0.01–1.46)	22, 0.25 (0.14–0.36)	29, 0.16 (0.10–0.22)	101, 0.16 (0.13–0.19)	0.61	0.46	0.46
Boys, singletons							
Malformations in total	15, 10.87 (6.21–17.29)	254, 8.96 (7.94–10.07)	434, 7.44 (6.78–8.15)	1091, 6.24 (5.88–6.61)	0.45	0.14	0.03
Nervous (Q00–07)	0, 0.00 (0.00–2.64)	6, 0.21 (0.08–0.46)	9, 0.15 (0.07–0.29)	33, 0.19 (0.13–0.26)	1.00	1.00	1.00
Eye, ear, face (Q10–18)	0, 0.00 (0.00–2.64)	13, 0.46 (0.24–0.78)	17, 0.29 (0.17–0.47)	49, 0.28 (0.21–0.37)	1.00	1.00	1.00
Cardiac (Q20–28)	5, 3.62 (1.19–8.25)	49, 1.73 (1.28–2.28)	79, 1.36 (1.07–1.69)	184, 1.05 (0.91–1.21)	0.10	0.04	0.02
Respiratory (Q30–34)	1, 0.72 (0.02–3.97)	14, 0.49 (0.27–0.83)	18, 0.31 (0.18–0.49)	44, 0.25 (0.18–0.34)	0.51	0.36	0.30
Orofacial clefts (Q35–37)	0, 0.00 (0.00–2.64)	9, 0.32 (0.15–0.60)	13, 0.22 (0.12–0.38)	41, 0.23 (0.17–0.32)	1.00	1.00	1.00
The tongue (Q38)	0, 0.00 (0.00–2.64)	11, 0.39 (0.19–0.69)	22, 0.38 (0.24–0.57)	43, 0.25 (0.18–0.33)	1.00	1.00	1.00
Gastrointestinal (Q39–45)	1, 0.72 (0.02–3.97)	12, 0.42 (0.22–0.74)	28, 0.48 (0.32–0.69)	72, 0.41 (0.32–0.52)	0.46	0.49	0.44
Non-desended testicles (Q53)	2, 1.45 (0.18–5.14)	23, 0.81 (0.52–1.22)	29, 0.50 (0.33–0.71)	66, 0.38 (0.29–0.48)	0.32	0.16	0.10
Hypospadias (Q54)	1, 0.72 (0.02–3.97)	17, 0.60 (0.35–0.96)	30, 0.51 (0.35–0.73)	76, 0.43 (0.34–0.54)	0.58	0.52	0.45
Other penis abnormalities (Q55)	0, 0.00 (0.00–2.64)	4, 0.14 (0.04–0.36)	5, 0.09 (0.03–0.20)	5, 0.03 (0.01–0.07)	1.00	1.00	1.00
Intersexuality (Q56)	0, 0.00 (0.00–2.64)	1, 0.04 (0.00–0.20)	1, 0.02 (0.00–0.10)	0, 0.00 (0.00–0.02)	1.00	1.00	NA
Urinary (Q60–64)	1, 0.72 (0.02–3.97)	18, 0.64 (0.38–1.00)	26, 0.45 (0.29–0.65)	66, 0.38 (0.29–0.48)	0.60	0.47	0.41
Musculoskeletal (Q65–79)	5, 3.62 (1.19–8.25)	110, 3.88 (3.20–4.66)	190, 3.26 (2.82–3.75)	457, 2.61 (2.38–2.86)	1.00	0.81	0.42
Other (Q80–89)	0, 0.00 (0.00–2.64)	17, 0.60 (0.35–0.96)	23, 0.39 (0.25–0.59)	63, 0.36 (0.28–0.46)	1.00	1.00	1.00
Chromosomal aberrations (Q90–99)	1, 0.72 (0.02–3.97)	8, 0.28 (0.12–0.56)	6, 0.10 (0.04–0.22)	28, 0.16 (0.11–0.23)	0.35	0.15	0.20

Continued

TableVI *Continued*

	Group A	Group B	Group C	Group D	*P*-value[a]		
					A versus B	A versus C	A versus D
Boys, twins							
Malformations in total	9, 11.11 (3.12–26.17)	195, 12.96 (11.16–14.76)	390, 11.41 (10.26–12.57)	1734, 11.37 (10.80–11.94)	0.30	0.61	0.68
Nervous (Q00–07)	0, 0.00 (0.00–10.32)	4, 0.27 (0.06–1.01)	15, 0.44 (0.20–0.67)	54, 0.35 (0.25–0.45)	1.00	1.00	1.00
Eye, ear, face (Q10–18)	0, 0.00 (0.00–10.32)	7, 0.47 (0.10–1.37)	6, 0.18 (0.03–0.57)	42, 0.28 (0.18–0.37)	1.00	1.00	1.00
Cardiac (Q20–28)	0, 0.00 (0.00–10.32)	41, 2.72 (1.88–3.56)	104, 3.04 (2.42–3.67)	416, 2.73 (2.44–3.02)	1.00	1.00	1.00
Respiratory (Q30–34)	0, 0.00 (0.00–10.32)	6, 0.40 (0.07–1.30)	11, 0.32 (0.13–0.51)	54, 0.35 (0.26–0.45)	1.00	1.00	1.00
Orofacial clefts (Q35–37)	0, 0.00 (0.00–10.32)	5, 0.33 (0.04–1.18)	8, 0.23 (0.05–0.66)	53, 0.35 (0.25–0.45)	1.00	1.00	1.00
The tongue (Q38)	1, 1.23 (0.01–12.41)	5, 0.33 (0.11–0.77)	7, 0.20 (0.04–0.61)	42, 0.28 (0.18–0.37)	0.30	0.23	0.25
Gastrointestinal (Q39–45)	2, 2.47 (0.19–14.19)	4, 0.27 (0.02–1.08)	18, 0.53 (0.28–0.77)	79, 0.52 (0.40–0.64)	0.03	0.10	0.05
Non-desended testicles (Q53)	1, 1.23 (0.01–12.41)	17, 1.13 (0.60–1.66)	29, 0.85 (0.54–1.16)	78, 0.51 (0.40–0.63)	0.71	0.48	0.47
Hypospadias (Q54)	2, 2.47 (0.03–14.84)	11, 0.73 (0.30–1.16)	26, 0.76 (0.47–1.05)	106, 0.70 (0.55–0.84)	0.52	0.51	0.47
Other penis abnormalities (Q55)	0, 0.00 (0.00–10.32)	1, 0.07 (0.00–0.72)	2, 0.06 (0.00–0.36)	5, 0.03 (0.00–0.12)	1.00	1.00	1.00
Intersexuality (Q56)	0, 0.00 (0.00–10.32)	0, 0.00 (0.00–0.58)	0, 0.00 (0.00–0.26)	1, 0.01 (0.00–0.07)	NA	NA	1.00
Urinary (Q60–64)	0, 0.00 (0.00–10.32)	7, 0.47 (0.11–1.40)	15, 0.44 (0.20–0.67)	64, 0.42 (0.33–0.53)	1.00	1.00	1.00
Musculoskeletal (Q65–79)	3, 3.70 (0.21–16.63)	95, 6.31 (4.95–7.67)	181, 5.30 (4.44–6.15)	875, 5.74 (5.31–6.17)	0.70	1.00	1.00
Other (Q80–89)	0, 0.00 (0.00–10.32)	4, 0.27 (0.02–1.08)	12, 0.35 (0.15–0.55)	60, 0.39 (0.29–0.50)	1.00	1.00	1.00
Chromosomal aberrations (Q90–99)	0, 0.00 (0.00–10.32)	5, 0.33 (0.04–1.19)	6, 0.18 (0.03–0.57)	18, 0.12 (0.06–0.17)	1.00	1.00	1.00
Girls, singletons							
Malformations in total	6, 3.95 (1.46–8.39)	213, 7.03 (6.14–7.99)	328, 6.29 (5.64–6.98)	861, 5.27 (4.93–5.62)	0.19	0.31	0.58
Nervous (Q00–07)	0, 0.00 (0.00–2.40)	7, 0.23 (0.09–0.48)	5, 0.10 (0.03–0.22)	24, 0.15 (0.09–0.22)	1.00	1.00	1.00
Eye, ear, face (Q10–18)	0, 0.00 (0.00–2.40)	4, 0.13 (0.04–0.34)	20, 0.38 (0.23–0.59)	43, 0.26 (0.19–0.35)	1.00	1.00	1.00
Cardiac (Q20–28)	1, 0.66 (0.02–3.61)	41, 1.35 (0.97–1.83)	76, 1.46 (1.15–1.82)	172, 1.05 (0.90–1.22)	0.72	0.73	1.00
Respiratory (Q30–34)	0, 0.00 (0.00–2.40)	7, 0.23 (0.09–0.48)	8, 0.15 (0.07–0.30)	25, 0.15 (0.10–0.23)	1.00	1.00	1.00
Orofacial clefts (Q35–37)	0, 0.00 (0.00–2.40)	5, 0.16 (0.05–0.38)	7, 0.13 (0.05–0.28)	27, 0.17 (0.11–0.24)	1.00	1.00	1.00
The tongue (Q38)	0, 0.00 (0.00–2.40)	4, 0.13 (0.04–0.34)	8, 0.15 (0.07–0.30)	13, 0.08 (0.04–0.14)	1.00	1.00	1.00
Gastrointestinal (Q39–45)	0, 0.00 (0.00–2.40)	13, 0.43 (0.23–0.73)	22, 0.42 (0.26–0.64)	46, 0.28 (0.21–0.38)	1.00	1.00	1.00
Female genitalia (Q50–52)	0, 0.00 (0.00–2.40)	3, 0.10 (0.02–0.29)	6, 0.12 (0.04–0.25)	10, 0.06 (0.03–0.11)	1.00	1.00	1.00
Intersexuality (Q56)	0, 0.00 (0.00–2.40)	0, 0.00 (0.00–0.12)	1, 0.02 (0.00–0.11)	0, 0.00 (0.00–0.02)	NA	1.00	NA
Urinary (Q60–64)	1, 0.66 (0.02–3.61)	10, 0.33 (0.16–0.61)	10, 0.19 (0.09–0.35)	22, 0.13 (0.08–0.20)	0.42	0.27	0.19
Musculoskeletal (Q65–79)	4, 2.63 (0.72–6.60)	121, 3.99 (3.32–4.75)	176, 3.37 (2.90–3.90)	496, 3.03 (2.78–3.31)	0.52	0.82	1.00
Other (Q80–89)	2, 1.32 (0.16–4.67)	5, 0.16 (0.05–0.38)	17, 0.33 (0.19–0.52)	78, 0.48 (0.38–0.60)	0.04	0.10	0.17
Chromosomal aberrations (Q90–99)	0, 0.00 (0.00–2.40)	6, 0.20 (0.07–0.43)	11, 0.21 (0.11–0.38)	22, 0.13 (0.08–0.20)	1.00	1.00	1.00
Girls, twins							
Malformations in total	6, 6.32 (1.07–18.90)	188, 11.79 (10.04–13.54)	316, 10.19 (9.02–11.36)	1454, 9.89 (9.34–10.44)	0.44	0.62	0.87
Nervous (Q00–07)	0, 0.00 (0.00–8.86)	8, 0.50 (0.13–1.41)	13, 0.42 (0.19–0.65)	35, 0.24 (0.15–0.32)	1.00	1.00	1.00
Eye, ear, face (Q10–18)	0, 0.00 (0.00–8.86)	2, 0.13 (0.01–0.77)	8, 0.26 (0.06–0.72)	26, 0.18 (0.10–0.25)	1.00	1.00	1.00

Cardiac (Q20–28)	2, 2.11 (0.03–12.76)	55, 3.45 (2.47–4.43)	120, 3.87 (3.12–4.62)	462, 3.14 (2.82–3.46)	1.00	1.00	1.00
Respiratory (Q30–34)	0, 0.00 (0.00–8.86)	2, 0.13 (0.01–0.79)	2, 0.06 (0.01–0.40)	29, 0.20 (0.13–0.27)	1.00	1.00	1.00
Orofacial clefts (Q35–37)	0, 0.00 (0.00–8.86)	3, 0.19 (0.03–0.87)	6, 0.19 (0.03–0.63)	22, 0.15 (0.09–0.21)	1.00	1.00	1.00
The tongue (Q38)	0, 0.00 (0.00–8.86)	1, 0.06 (0.00–0.67)	2, 0.06 (0.01–0.41)	17, 0.12 (0.05–0.18)	1.00	1.00	1.00
Gastrointestinal (Q39–45)	0, 0.00 (0.00–8.86)	10, 0.63 (0.17–1.59)	10, 0.32 (0.11–0.82)	46, 0.31 (0.22–0.41)	1.00	1.00	1.00
Female genitalia (Q50–52)	0, 0.00 (0.00–8.86)	1, 0.06 (0.00–0.67)	1, 0.03 (0.00–0.28)	12, 0.08 (0.03–0.13)	1.00	1.00	1.00
Intersexuality (Q56)	0, 0.00 (0.00–8.86)	1, 0.06 (0.00–0.67)	0, 0.00 (0.00–0.28)	0, 0.00 (0.00–0.06)	1.00	1.00	1.00
Urinary (Q60–64)	0, 0.00 (0.00–8.86)	5, 0.31 (0.04–1.12)	5, 0.16 (0.02–0.57)	43, 0.29 (0.20–0.39)	1.00	1.00	1.00
Musculoskeletal (Q65–79)	3, 3.16 (0.18–14.32)	117, 7.34 (5.93–8.74)	154, 4.97 (4.12–5.81)	823, 5.60 (5.16–6.03)	0.72	1.00	1.00
Other (Q80–89)	1, 1.05 (0.01–10.68)	6, 0.38 (0.06–1.22)	21, 0.68 (0.39–0.97)	56, 0.38 (0.27–0.49)	0.33	0.68	0.36
Chromosomal aberrations (Q90–99)	0, 0.00 (0.00–8.86)	3, 0.19 (0.01–0.91)	6, 0.19 (0.03–0.63)	33, 0.22 (0.15–0.30)	1.00	1.00	1.00

Treatments with frozen–thawed embryos have been excluded. The values are *n* % (95% CI).
[a]Singletons: Fisher's exact test. Twins: binomial regression with adjustment for dependence between twins using the robust variance estimation when there were 10 or more events in each group, otherwise Fisher's exact test with Bonferoni's method adjustment for dependence between twins. The exact 95% CIs for rates were calculated using the F-distribution. NA, not applicable.

Ideally all pregnancies, also miscarriages and induced abortions due to congenital malformations or chromosomal abnormalities, should be included in the congenital malformation rate. Unfortunately this was not possible in the present study, as the majority of fertility clinics do not register all elective abortions and miscarriages. In a previous study <10% of the Danish TPT couples treated from 2002 and recorded with a delivery chose to have invasive prenatal diagnostics in the pregnancy (Fedder *et al.*, 2011). However, the majority had a nuchal translucency examination performed.

The quality of data on congenital malformations in the Danish National Patient Register has been validated and found acceptable for epidemiological research (Larsen *et al.*, 2003). However, registry-based studies are encumbered with the risk of reporting or coding errors or missing data due to insufficient coding. Methodological limitations in studies based on register data have been described by Toppari *et al.* (2001), who suggested that two-thirds of hypospadias in Denmark remained unreported. Thus, the rates of hypospadias and undescended testicles might be underestimated. This possible tendency of underestimation is the same as for both study and control groups as Q-diagnoses were recorded similarly in all four groups and may therefore not bias the results, although a Type II error may occur.

The low frequency of VLBW children in the TPT group may be due to selection bias as inclusion in the TPT database was based on self-reported questionnaires from the parents. Although the non-response rate was only 2.5%, selection bias cannot be excluded as couples with very preterm born children may be more reluctant to return the questionnaire.

In this cohort study including ~90 000 children we found no cases of Wilm's tumour in any of the groups. This also applied to the classical imprinting-related disorders such as Beckwith–Wiedemann syndrome (BWS) and Angelman syndrome (AS), which has been described to occur in 1:13 700 children and 1:16 000 children, respectively (Amor and Halliday, 2008). One explanation might be that registration of such seldom occurring disorders, which only in some cases are caused by imprinting (BWS ~65%, AS ~3% and Prader-Willi syndrome (PWS) <1%) are incomplete. Lidegaard *et al.* (2005) detected, in another population-based Danish register study, only three cases with PWS (suggested frequency 1:17 500 according to Amor and Halliday, 2008) out of 448 401 ART and control children. Another explanation is that PWS and AS cannot be diagnosed until a certain age of the child and that our follow-up period is too short to recognize the few cases with these rare syndromes. Meanwhile, we found a significantly increased rate of neoplasms in bones and joint cartilage in twin children, including an unknown number of osteoscarcomas in the TPT group. This finding may be random due to multiple comparisons. Osteosarcoma is the most common primary bone malignancy and arises most commonly in the metaphyseal region of long bones in adolescents and young adults during growth. It has a complicated molecular pathogenesis and it only involves imprinting in 5% of cases (Broadhead *et al.*, 2011).

In conclusion, this study shows that the sex ratio after ICSI with epididymal or testicular sperm was reduced compared with IVF but not compared with ICSI with ejaculated sperm and NC. For singletons the rate of LBW after TPT was increased compared with NC, but not compared with IVF or ICSI. The overall rate of congenital malformations was similar between the groups, but for TPT singleton boys

the rate of congenital cardiac malformations was increased compared with NC and conventional IVF, and for singleton as well as twin boys the rate of undescended testicles increased with the severity of male infertility. These data are reassuring, but larger TPT populations are still needed to confirm our results.

Authors' roles

J.F., A.L. and A.P. had the idea and designed this study. J.F. was the main author. All the authors contributed to the acquisition and analysis of the data and critically revised the manuscript.

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Conflict of interest

None declared.

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Outlook

Long-term effects of ovulation-stimulating drugs on cancer risk

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Abstract

Although nulliparity has been extensively related to the risk of ovarian, breast and endometrial cancers, with many studies showing the relationship largely attributable to infertility, treatment effects on cancer risk are poorly understood. Two early studies raised substantial concern when ovulation-stimulating drugs were linked with large increases in ovarian cancer, supporting the notion of an important aetiological role of incessant ovulation. Subsequent studies have been mainly reassuring, although some have suggested possible risk increases among nulligravid women, those with extensive follow-up, and those developing borderline tumours. Results regarding effects of fertility drugs on breast cancer risk are conflicting, with some showing no associations and others demonstrating possible risk increases, although for varying subgroups. In contrast, endometrial cancer results are more consistent, with two recent studies showing increased risks related to clomiphene usage. This is of interest given that clomiphene is structurally similar to tamoxifen, a drug extensively linked with this cancer. Given the recent marketing of fertility drugs and the fact that exposed women are only beginning to reach the cancer age range, further follow-up is necessary. This will also be important to fully resolve effects of exposures such as gonadotrophins, used more recently in conjunction with IVF.

Keywords: *cancer, epidemiology, fertility drugs, infertility, ovulation stimulation, risk*

Introduction

It is well established that nulliparity is a risk factor for ovarian, breast and endometrial cancers, with many studies suggesting that the association is largely attributable to infertility. Despite the extensive literature on the topic, causes of infertility and treatment effects on cancer risk are poorly understood.

Increasingly, women are delaying their first childbirth, resulting in many more women seeking advice for infertility. In fact, it is estimated that, by the year 2025, between 5.4–7.7 million women aged 15–44 will be diagnosed in the USA with some form of infertility (Stephen and Chandra, 1998). Consequentially, ovulation-stimulating drugs are among the fastest growing groups of drugs, with prescriptions in the USA nearly doubling between 1973 and 1991 (Wysowski, 1993).

The two most commonly used medications, clomiphene citrate and gonadotrophins, are effective at stimulating ovulation, a factor implicated in the aetiology of both breast and ovarian cancers (Fathalla, 1971; Henderson *et al.*, 1985). These drugs also raise both oestradiol and progesterone concentrations (Sovino *et al.*, 2002), hormones which are recognized as affecting the development and growth of breast and gynaecological cancers. Finally, as elaborated below, some clinical and epidemiological studies have linked usage of these drugs with an increased incidence of various cancers.

Ovarian cancer

Numerous clinical reports have raised concern about a potential link between use of ovulation-stimulating drugs and ovarian cancer risk (Fishel and Jackson, 1989; Dietl, 1991; Goldberg and Runowicz, 1992; Nijman *et al.*, 1992; Balasch *et al.*, 1993; Lopes and Mensier, 1993; Willemsen *et al.*, 1993; Adewole *et al.*,

1997; Unkila-Kallio *et al*., 1997). The association has biological credibility, given that 'incessant ovulation' and associated alterations in endogenous hormones during reproductive years are plausible explanations for several factors that alter ovarian cancer risk, including nulliparity and oral contraceptive use (Fathalla, 1971; Cramer and Welch, 1983; Whittemore *et al*., 1992a). Results from two epidemiological studies that found marked elevations in ovarian cancer risk associated with exposure to ovulation-stimulating drugs (Whittemore *et al*., 1992b; Rossing *et al*., 1994) provide additional support for this hypothesis.

The earliest evidence of such a link derived from a meta-analysis of 12 case–control studies of ovarian cancer conducted by Whittemore and coworkers (Whittemore *et al*., 1992b). Only three of these studies, with 526 cases and 966 controls, provided information regarding the use of fertility drugs and there was scant information about the type of drug or the extent of its use. Self-reported prior usage of fertility medications was associated with an odds ratio (OR) of 2.8 (95% CI 1.3–6.1) as compared with women who had no history of infertility. The increased risk was limited to nulligravid women, who experienced a 27-fold increase in risk associated with drug usage (95% CI 2.3–315.6). However, this risk was based on only 12 exposed cases and one exposed control.

Results from a retrospective cohort study involving 3837 women evaluated for infertility in a single Seattle practice between 1974 and 1985 also raised concern (Rossing *et al*., 1994). More details on this and other completed cohort studies are shown in **Table 1**. Information on drug exposures and indications for usage was collected from medical records, and outcome information was obtained via linkage against a regional cancer registry. Effects of other risk factors were evaluated by abstracting information from medical records for all ovarian cancer cases and a subcohort sample of 135 women. Using appropriate case–cohort analytic techniques, they estimated that clomiphene use was associated with an adjusted 2.3-fold increased risk (95% CI 0.5–11.4), based on nine ovarian cancers.

Use of clomiphene for less than 1 year was not associated with an increased risk, but five of the nine women with cancer had taken the drug for 12 or more monthly cycles, resulting in a relative risk of 11.1 (95% CI 1.5–82.3). An enhanced risk associated with long-term treatment was observed in both those with and without ovulatory abnormalities. A large proportion of the observed tumours were borderline (five of the 11 in the cohort).

Although the results of these two initial studies were alarming, subsequent results from a number of case–control studies were largely reassuring (Franceschi *et al*., 1994; Mosgaard *et al*., 1997; Parazzini *et al*., 1997). A meta-analysis of eight studies involving data on 1060 cases and 1337 controls (Ness *et al*., 2002) also showed no risk associations with fertility drug use. In this study, after adjustment for types of infertility, the risk associated with drug usage was somewhat higher among nulligravid women (1.8) and among those who had more than 4 months of exposure (relative risk (RR) 1.5–1.7), but none of these risks was statistically significant.

The results of case control studies are limited by the fact that information on prior drug use is based on patient histories. Most have been further limited by small numbers of ovarian cancer cases reporting prior drug usage. For example, in the largest case–control study (Parazzini *et al*., 2001), based on 1031 cases and 2411 hospital controls, only 1.1–1.5% of the subjects reported prior usage of fertility drugs, resulting in only 15 cases and 26 controls with relevant exposures for analysis.

Although results have also been published from additional cohort studies (Ron *et al*., 1987; Shushan *et al*., 1996; Modan

Table 1. Major cohorts reporting associations between fertility drugs and cancer risk.

Location	*Reference*	*No. of subjects*	*Years evaluated*	*Average years of follow-up*	*Type of cancer*		
					Ovarian	*Breast*	*Endometrial*
Israel	Ron *et al*., 1987	2575	1964–1974	12.3	4	15	5
USA	Rossing *et al*., 1994, 1996	3837	1974–1985	12.3	11	–	–
Australia	Venn *et al*., 1995	10,358	1978–1992	6.5	6	34	5
Israel (Tel Hashomer)	Modan *et al*., 1998	2496	1964–1974	21.4	12	59	21
Israel (Beer-Sheba)	Potashnik *et al*., 1999	1197	1960–1984	17.9	2	20	2
Australia	Venn *et al*., 1999	29,666	Pre-1994	8.5	13	143	12
USA	Croughan-Minihane *et al*., 2001	51,371	1965–1998	5.6	50	–	–
The Netherlands	Klip *et al*., 2002	25,152	1980–1995	5.6	17	116	14
UK	Doyle *et al*., 2002	5556	1975–1989	7.9	6	55	4
Israel (Tel Aviv)	Dor *et al*., 2002	5026	1981–1992	3.6	1	11	2
Israel (Tel Aviv)	Lerner-Geva *et al*., 2003	1082	1984–1992	6.5	3	5	
USA	Althuis *et al*., 2005	12,193	1965–1988	18.8	45	292	39
	Brinton *et al*., 2004a,c						

et al., 1998; Potashnik *et al*., 1999; Dor *et al*., 2002; Doyle *et al*., 2002; Klip *et al*., 2002), most have involved small numbers of ovarian cancers, with the number of exposed cases ranging from two in the smallest study (Potashnik *et al*., 1999) to 12 in the largest study (Modan *et al*., 1998). These studies were also limited by lack of information on causes of infertility or on other factors that could independently influence ovarian cancer risk (including parity, oral contraceptive usage and socioeconomic status).

One of the most recently published studies was designed to overcome many of the limitations of previous studies (Brinton *et al*., 2004a). This retrospective cohort study followed 12,193 infertile women for a median of 18.8 years, and had detailed information on drug exposures and causes of infertility from medical records as well as questionnaire data on potential cancer risk factors for a substantial proportion of the patients. This study was unique in being able to identify subjects who underwent a bilateral oophorectomy and were thus no longer at risk for developing ovarian cancer. The number of ovarian cancers, 45, was larger than in other cohort studies, but this number was still too limited for analyses of small subgroups of women. The results were largely reassuring, showing no increase in risk associated with ever using either clomiphene or gonadotrophins. There were non-significant increases in risk (RR 1.5–2.5) associated with use of either clomiphene or gonadotrophins among the subjects followed for the longest periods of time (15 years or more).

While this study focused on women exposed to ovulation-stimulating agents prescribed during earlier times, a number of other studies have concentrated on exposures received during IVF. One other US study, published to date only in abstract form, found no evidence for an effect of ovulation-stimulating drugs on ovarian cancer risk. After 5.6 years of follow-up of 51,371 patients seen for conception or ovum donation in 15 California clinics, 50 ovarian cancers were diagnosed (Croughan-Minihane *et al*., 2001). The only significant associations with ovarian tumour risk observed in the study were with length of time in infertility treatment and nulligravidity. However, no associations of risk were found for ovulation-stimulating drugs and risk, even when dose, formulation and number of treatment cycles were considered.

Among 29,666 women referred to 10 Australian IVF clinics, 13 ovarian cancers were observed during a follow-up period averaging 7.8 years (Venn *et al*., 1999). The investigators had detailed information on indications for drug usage, but only limited information on patient characteristics. Comparing risks to the general population, the standardized incidence ratio (SIR) was 0.99, with no higher risk for the women who received at least one IVF treatment cycle (0.88) as compared with those who received no drug treatment (1.16). Women with unexplained infertility were at a significantly increased risk compared with the general population, but within this subgroup there was no difference in risk between treated and untreated women.

In a cohort of 25,152 women treated for subfertility in the Netherlands, 17 ovarian cancers developed during 5.6 years of follow-up (Klip *et al*., 2002). Strengths of this study included detailed information on causes of infertility and drug exposures from medical records, as well as on cancer risk predictors obtained through completed questionnaires from many of the study subjects. Thus, the study was able to assess risks associated with different parameters of drug exposures, while adjusting for other risk factors. Results showed no difference in risk between treated and untreated subjects, even when the number of cycles or ampoules received were considered.

While the results of the most recent studies are consistently reassuring when compared with the results of earlier studies, several observations indicate a need for further monitoring. These include the findings in the two most recent studies (Ness *et al*., 2002; Brinton *et al*., 2004a) of modest increases in risk estimates with either extended follow-up or increased exposure to ovulation-stimulating drugs. Given that these ovulation-stimulating drugs first became available beginning in the early 1960s, women who were exposed to them are just beginning to enter the ovarian cancer age range. Furthermore, less information is available on gonadotrophins than clomiphene, given that the latter was the drug of choice in earlier time periods. Thus, additional follow-up data are needed to fully evaluate effects of both exposures.

In addition, two recent investigations (Ness *et al*., 2002; Brinton *et al*., 2004a) and Whittemore's early meta-analysis (Whittemore *et al*., 1992b) found drug effects to be greatest among nulligravid women, suggesting the possibility of an enhanced effect of the medications among women with certain indications for usage.

That ovulation-stimulating drugs might preferentially affect the risk of borderline ovarian tumours is also suggested by several studies. Both cohort (Rossing *et al*., 1994; Shushan *et al*., 1996) and case–control (Parazzini *et al*., 1998; Ness *et al*., 2002) investigations have shown risk ratios in the range of 3–4 associated with fertility drug usage. In one study, the relationship was restricted to nulligravid women (Ness *et al*., 2002) and in another specifically to gonadotrophins (Shushan *et al*., 1996). These findings, in conjunction with case reports of ovarian neoplasms developing in women during or shortly after treatment with ovulation-stimulating agents (Dietl, 1991; Goldberg and Runowicz, 1992; Nijman *et al*., 1992; Willemsen *et al*., 1993; Hull *et al*., 1996; Adewole *et al*., 1997; Bayar *et al*., 2006), have led to speculations that ovarian stimulation may induce growth in existing highly differentiated indolent tumours. Alternatively, the findings simply could reflect more intensive medical surveillance among infertile women.

Breast cancer

The epidemiology of breast cancer has been extensively studied, with many investigations supporting the notion of an important aetiological role for endogenous as well as exogenous hormones (Bernstein, 2002). Specific concerns regarding the effects of fertility drugs have been raised by the recognized effects on breast cancer risk of ovulation and hormonal patterns (Henderson *et al*., 1985; Parazzini *et al*., 1993). Furthermore, there are a number of clinical reports of breast cancer occurring among users of such drugs (Arbour *et al*., 1994; Brzezinski *et al*., 1994; Jourdain *et al*., 1996; Unkila-Kallio *et al*., 1997).

Many cohort (Ron *et al*., 1987; Venn *et al*., 1995; Modan *et al*., 1998; Venn *et al*., 1999; Doyle *et al*., 2002; Klip *et al*.,

2002; Lerner-Geva *et al*., 2003) and case–control (Braga *et al*., 1996; Weiss *et al*., 1998; Ricci *et al*., 1999) studies have failed to find any remarkable associations between fertility drug use and breast cancer risk. Most, however, were limited by small numbers of cancers, imprecise information on patterns of, or indications for, drug usage, and incomplete ability to control for other related risk factors, including well-recognized reproductive risk factors.

Several studies have suggested links between fertility drugs and breast cancer risk, but the results are conflicting, with some suggesting potential increases in risk and others decreases. A recent case–control study involving over 4500 breast cancer cases was able to carefully control for potential confounding variables but had to rely on self-reports of infertility and had few women exposed to fertility drugs (Burkman *et al*., 2003). Although this study found no association of risk related to use of clomiphene, there was some indication of a risk elevation among women with long-term use of menopausal gonadotrophins. Use for at least 6 or more months or at least six cycles was associated with RR ranging from 2.7–3.8. The finding was somewhat unexpected given that neither of the constituents of human menopausal gonadotrophin – FSH and LH – are thought to have direct effects on breast tissue (Healy and Venn, 2003). Since gonadotrophin therapy increases both serum oestrogen and progesterone concentrations, the investigators suggested this as a possible explanation for their findings. Whether the increases in hormones that would be associated with six or more cycles of exposure would be sufficient to substantially affect the subsequent risk of breast cancer is questionable (Healy and Venn, 2003).

The opposite relationship, namely a non-significantly reduced risk of invasive and in-situ breast cancer associated with clomiphene (adjusted RR 0.5, 95% CI 0.2–1.2) was found in Rossing's retrospective cohort study (Rossing *et al*., 1996). This estimate was based on only 12 exposed cases and there was no indication of any further risk reduction with extended duration of use. A chemopreventive effect of clomiphene would be of interest given that it is a selective oestrogen receptor modulator (SERM), and thus could have properties similar to another SERM, tamoxifen (Fisher *et al*., 1998). Additional epidemiological support of a reduced risk of breast cancer associated with clomiphene use was provided from The Nurses Health Study II (Terry *et al*., 2006), which showed a RR of 0.40 (95% CI 0.2–0.7) associated with use of clomiphene among women treated for ovulatory infertility. Risk decreased significantly with duration of use of clomiphene, with users of 10 or more months having a RR of 0.25 (95% CI 0.09–0.75) compared with non-exposed women. The findings were based on self-reports of both drug usage as well as causes of infertility.

On the other hand, the recent multi-centre US cohort study, involving 292 breast cancer cases, failed to find any substantial alterations in risk related to ever using either clomiphene or gonadotrophins (Brinton *et al*., 2004b). However, there were small non-significant increases in risk after extended follow-up periods (>15 years), with the RR in the range of 1.4–2.5, similar to the long-term risks observed for ovarian cancer in this same cohort study. When analyses were restricted to invasive breast cancers, the RR after 20 years of follow-up became statistically significant (RR 1.6, 95% CI 1.0–2.5).

More recent results are now beginning to emerge regarding the effects on breast cancer risk among IVF exposed cohorts. In a study of 5788 women attending an Israeli clinic in whom 131 breast cancers developed, a significantly elevated risk was found related to clomiphene exposure (SIR 1.4, 95% CI 1.0–1.8) (Lerner-Geva *et al*., 2006). Even stronger results were found when internal analyses were conducted through a nested case–control study within the cohort (OR 2.7, 95% CI 1.3–5.7).

However, in a large cohort study in France, involving 92,555 women and 2571 invasive breast cancers, there was no evidence of any increases in risk, regardless of the exposure considered (Gauthier *et al*., 2004). This included overall treatment for infertility, IVF treatment, exposure to specific drugs (e.g., clomiphene), and specifics of exposures (duration of treatment, age at first use). The exposure information, however, was self-reported and no information was available on indications for drug usage, including causes of infertility. The only evidence of any increased risk associated with fertility treatment was among women with a family history of breast cancer (RR 2.32–2.77), with estimates based on fairly small numbers of affected women.

Two other epidemiological investigations of IVF-exposed women, one conducted in Australia (Venn *et al*., 1999) and the other in the Netherlands (Klip *et al*., 2002), did not find differences in risk between exposed and unexposed subjects. However, in the Australian study, an approximately two-fold increased risk of breast cancer was observed within 1 year of last treatment. This prompted the suggestion that ovulation-stimulating drugs might promote the rapid growth of pre-existing tumours, similar to the short-term transient increase in breast cancer following a recent pregnancy (Lambe *et al*., 1994). However, several other studies, which assessed detailed timing effects of last drug usage, found no support for a promotional effect by either clomiphene or gonadotrophins (Klip *et al*., 2002; Brinton *et al*., 2004b).

In the Australian study, Venn and coworkers also assessed causes of death among their cohort of infertile women, observing non-significant decreases in mortality for most causes as compared with the general population (Venn *et al*., 2001). Deaths due to breast cancer showed no appreciable differences between those who did and did not receive IVF. The data therefore provided little support for another report that demonstrated poor prognostic features among breast cancer patients with recent histories of exposure to fertility drugs (Siegelmann-Danieli *et al*., 2003).

Endometrial cancer

Endometrial cancers are well recognized as hormonally sensitive (Akhmedkhanov *et al*., 2001). There is a clinical report of three cases of adenomatous hyperplasia of the endometrium, a precursor condition, occurring among women exposed to ovulation-stimulating agents (Miannay *et al*., 1994). Few analytical studies, however, have assessed the relationship between endometrial cancer and use of fertility drugs.

One small case–control study that assessed the relationship found no association, but, with only seven exposed cases, the investigation had limited power to detect an effect (Benshushan

et al., 2001). Most cohort studies have not observed an association, but the majority had follow-up times of less than 10 years and few associated cases of endometrial cancer (between two and 14) (Venn *et al*., 1995, 1999; Potashnik *et al*., 1999; Klip *et al*., 2002).

The two largest cohort studies both raise some concern regarding effects of ovulation-stimulating agents on the endometrium. In an Israeli cohort, in which 21 uterine cancers were diagnosed during an average of more than 20 years of follow-up, a significant two-fold increase in risk was associated with fertility drug usage (Modan *et al*., 1998). Similarly, the multi-centre US cohort study, which detected 39 cases of endometrial cancer among cohort members, found clomiphene usage associated with a non-significant increase in risk (RR 1.8, 95% CI 0.9–3.3) (Althuis *et al*., 2005). Further, increases in risk were found among subjects with higher dosages of exposure or longer follow-up periods, with trends in risk for the latter variable being statistically significant. Drug effects were also more apparent among nulligravid and obese women (RR of 3.5 and 6.0, respectively).

Because tamoxifen, a SERM which bears structural similarities to clomiphene (Sovino *et al*., 2002), has been repeatedly linked with increases in endometrial cancer risk (Varras *et al*., 2003), these two studies raise concern despite the fact that they were based on fairly small numbers of cancers.

Future research needs

Given that clomiphene was first approved for clinical use in 1967 and gonadotrophins in 1969, the women who first used these drugs during their late twenties and early thirties have only recently reached the age when hormonally-related cancers are common. Most studies to date are reassuring in not showing a strong association between use of these medications and risks of most cancers. On the other hand, several studies have found increasing risks with greater exposures or extended follow-up, indicating that complacency is not warranted and that long-term effects should be further monitored, especially in view of changes in reproductive technology.

There has been little attention focused on the long-term effects of assisted reproductive technologies, which often involve much higher exposures to gonadotrophins than were received by women in previous eras. In addition, most IVF protocols include luteal phase support for several weeks with supplemental progestogens, which raises concern since these agents have been linked in several studies to increases in breast cancer risk (Key and Pike, 1988; Beral, 2003). Since in-vitro techniques have become common only in the last couple of decades, it may be some time before epidemiological studies can amass the follow-up times required to fully address long-term effects.

There is some consistency across studies of a modest enhancement of ovarian cancer risk associated with use of fertility drugs among women who remain nulligravid (Whittemore *et al*., 1992b; Ness *et al*., 2002; Brinton *et al*., 2004c). This may indicate an interactive effect of the drugs with the underlying causes of infertility, including those reflecting unique hormonal perturbations. On the other hand, it may be that women who continue to remain infertile may have received larger doses and longer durations of fertility or other medications than other women.

There are other issues of interest that have not been widely pursued. First is the question of whether women at particularly high risk of cancer, including those with a genetic predisposition, experience unusual risks from the use of fertility medications. Secondly, it is of interest whether fertility drugs have unusual effects among women who have used other hormones. This includes oral contraceptives, which have been shown to be associated with reduced risks of endometrial and ovarian cancers (Deligeoroglou *et al*., 2003) and somewhat increased risks of breast cancers (CGHFBC, 1996), and menopausal hormone replacement therapy, which has been linked with increases in the risk of all three cancer sites (Akhmedkhanov *et al*., 2001; Lacey *et al*., 2002; Beral, 2003).

Some (Rossing *et al*., 1994; Shushan *et al*., 1996; Parazzini *et al*., 1998; Ness *et al*., 2002, Brinton *et al*., 2004a), although not all (Brinton *et al*., 2004a), studies suggest an unusual occurrence of borderline ovarian cancers among women exposed to fertility medications. Whether this reflects a biological effect or is merely the result of more intensive surveillance of women treated with these drugs by ultrasound and clinical examination warrants further scrutiny. Biologically, it is of interest that oestrogen receptor expression is a common feature of borderline ovarian tumours. Thus, further study of the relationship of fertility medications to ovarian, as well as breast cancers, according to hormone receptor status would appear warranted. In addition, investigations of cancer associations by tumour histologies should also be undertaken, given clinical reports of several unusual types of ovarian cancer (e.g., clear cell, germ cell, granulosa cell tumours) occurring among fertility drug users (Willemsen *et al*., 1993; Tewari *et al*., 1998; Makrydimas *et al*., 2003).

Although most attention has focused on effects of fertility drugs on ovarian cancer risk, more recent investigations support the need for further attention on breast and endometrial cancers. This need is supported by the recognition that ovulation-stimulating drugs are effective at increasing both oestrogen and progestin concentrations, alterations that have been linked with both of these cancers. Further, a relationship with breast cancer would parallel findings of an increased risk of this tumour among mothers exposed to diethylstilbestrol during pregnancy (Titus-Ernstoff *et al*., 2001). The preliminary findings regarding an increased risk of endometrial cancer following exposure to clomiphene, a drug closely related to tamoxifen, especially warrants further follow-up in well-designed epidemiological investigations.

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Time to pregnancy: results of the German prospective study and impact on the management of infertility

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BACKGROUND: The likelihood of spontaneous conception in subsequent cycles is important for a balanced management of infertility. Previous studies on time to pregnancy are mostly retrospective and biased because of exclusion of truly infertile couples. The study aim was to present a non-parametric estimation of cumulative probabilities of conception (CPC) in natural family planning (NFP) users illustrating an ideal of human fertility potential. METHODS: A total of 346 women was observed who used NFP methods to conceive from their first cycle onwards. The couples practising NFP make optimal use of their fertility potential by timed intercourse. The CPC were estimated for the total group and for couples who finally conceived by calculating Kaplan-Meier survival rates. RESULTS: A total of 310 pregnancies occurred among the 346 women; the remaining 36 women (10.4%) did not conceive. Estimated CPC for the total group (*n* = 340 women) at one, three, six and 12 cycle(s) were 38, 68, 81 and 92% respectively. For those who finally conceived (truly fertile couples, *n* = 304 women), the respective pregnancy rates were 42, 75, 88 and 98% respectively. Although the numbers of couples in both groups were similar, the impact of age on time to conception, as judged by the Wilcoxon test, was less in the truly fertile than in the total group. CONCLUSIONS: Most couples conceive within six cycles with timed intercourse. Thereafter, every second couple is probably either subfertile or infertile. CPC decline with age because heterogeneity in fecundity increases. In the subgroup of truly fertile couples, an age-dependent decline in CPC is statistically less obvious because of high homogeneity, even with advancing age.

Keywords: cumulative probability of conception/management of infertility/natural family planning/survival rates/time to pregnancy

Introduction

The likelihood of conception in subsequent cycles is of major interest to clinicians and epidemiologists to measure human fertility and to balance the management of infertility, thereby avoiding over- and under-treatment. Recent literature contains very little prospective data on time to pregnancy (TTP) (Wilcox *et al*., 1988; Hilgers *et al*., 1992). One group examined fertility rates and pregnancy wastage prospectively in 200 presumably fertile couples trying for pregnancy over 12 menstrual cycles (Zinaman *et al*., 1996). These authors observed a maximal conception rate of ~30% per cycle and a cumulative pregnancy rate of 82% after 12 menstrual cycles. More recent studies (Juul *et al*., 1999; 2000; Jensen *et al*., 2001) only recorded TTP retrospectively among pregnant women using questionnaires to measure, for example, couple fertility by assessing exposures related to semen quality, age or environment. Although their observation of a 12-months pregnancy rate of ~80% was similar to that reported by others (e.g. Zinaman *et al*., 1996), their study design did not estimate real fecundity, due mainly to the fact that infertile couples were excluded (Jensen *et al*., 2000). Therefore, effects on the proportion of truly infertile couples, which is of major importance, cannot be assessed (Baird *et al*., 1986). Another disadvantage is the possible inaccuracy because at long-term recall, TTP may sometimes only be estimated roughly by couples completing the questionnaire. It is known from cited previous studies that most couples are likely to conceive early. Therefore, for validity of data, the precise shift from contraception to reproduction is very important. Although validation studies of TTP recall exist (Joffe *et al*., 1993), some doubts remain. Thus, prospective studies are urgently needed.

Reproductive behaviour in western society has changed dramatically during the past two decades. Twenty years of contraception may precede a first pregnancy; therefore, age effects on fertility are of extreme importance. An age-related decline in the fertility of couples was previously documented

for daily probabilities of conception (Dunson *et al*., 2002). Much more appropriate and informative are the age effects on couples' cumulative chances of conceiving.

In general, subfertility is defined as the inability to conceive within 12 months of unprotected intercourse. Cumulative pregnancy prospects over cycles with fertility-focused intercourse may be better than the usual dichotomous, simplified definition of fertile-subfertile with a failure to become pregnant during a 12-month period. The aim is to present a non-parametric estimation of cumulative probabilities of conception (CPC) in natural family planning (NFP) users, thereby illustrating an ideal of human fertility potential. These cumulative pregnancy prospects will probably help to decide whether sufficient exposure to the chance of conception has taken place, when to start a routine infertility investigation, and how to avoid a premature resort to assisted-reproduction techniques (ART) with their associated risks, especially in patients unsuccessfully practising a method of NFP to achieve a pregnancy.

For more than 15 years, a long-term prospective cohort study on the use of NFP has been conducted in Germany (Freundl *et al*., 1988; 1993; Frank-Herrmann *et al*., 1991; 1997). In Germany the use of symptothermal is recommended which has been proven to be the most efficient and reliable method of NFP (The European Natural Family Planning Study Groups, 1993; 1999). The double-check variation of the STM consists of recording the main symptoms of fertility: basal body temperature (BBT) and cervical mucus pattern and the application of calculation rules. The fertility awareness part of the STM focuses mainly on cervical mucus monitoring, which correlates very closely with rising estrogen levels and onset of the fertile period. The peak day (last day of highly fertile mucus) is a reliable indicator of very near-ovulation. The BBT rise indicates the beginning of the luteal phase and the end of the fertile period. This cycle monitoring by self-observation allows reliable ovulation detection (Freundl *et al*., 1984; Gnoth *et al*., 1996; Dunson *et al*., 1999) and location of the fertile window within the cycle for either avoiding or achieving pregnancy. Generally, recent fertility studies on users of NFP (e.g. Colombo and Masarotto, 2000; Dunson *et al*., 2001; 2002), are based on a fairly ideal sample of upper-class couples with high compliance and close follow-up by the study centre. The participants of this study practising NFP to achieve a pregnancy make optimal use of their fertility potential by accurate detection of the fertile window in their menstrual cycles and an above-average knowledge on reproductive basics such as optimal time and interval of intercourse.

The present study estimates CPC over time for a cohort of couples using NFP to conceive from their first cycle onwards. To the present authors' knowledge, this is the largest prospective study conducted to date on CPC and time to pregnancy in terms of participants and pregnancies.

Materials and methods

Data collection

The study was conducted in accordance with the principles of the Declaration of Helsinki. All participating women were instructed by experienced NFP teachers during the first 3–6 months of study participation until reliability in using the fertility awareness part of the STM was reached. The couples entered this study voluntarily after providing their informed consent. Several standardized questionnaires were completed in order to record all relevant data concerning parity, medical (especially obstetric) history, socioeconomic and demographic backgrounds and finally—when they ceased participation—the reasons for dropping out. By the end of March 2001, a total of 31,498 NFP cycle charts from 1357 women using the STM had been collected in the authors' database. This database (NFPDAT version 1.0) is based on Microsoft Access® (Gnoth *et al*., 1999), and guarantees maximum data quality by utilizing more than 200 validated error formulae and an automatic request for follow-up on participants, at least every 3 months. Among all participants, there were 346 couples who switched from contraception [NFP or oral contraceptives (~20%)] to reproduction using the STM for fertility-focused intercourse. For only a few of the former users of oral contraceptives (OC), the first cycles using the STM were also their first trying for pregnancy, as most had initially avoided pregnancy with the STM.

The 346 women were observed from their first cycle onwards in which they tried to conceive. Pregnancy was assessed by either ultrasound, positive pregnancy test or a luteal phase longer than 18 days. In both of the latter cases, only later-confirmed clinical pregnancies (live birth, ectopic implantation or clinical abortion) were included in the analyses.

Inclusion and exclusion criteria

The use of NFP is not bound to a regular cycle pattern (Frank-Herrmann *et al*., 1991), as it is often implicitly maintained. On the contrary, women trying to conceive use the advantages of NFP for fertility-focused intercourse (fertility awareness), especially in cases of irregular cycles or after discontinuation of oral contraceptives (Gnoth *et al*., 2002a).

During the early stages of the study, all women trying for pregnancy with the help of the fertility awareness part of the STM were included. Later before data were processed using the Statistical Analysis System (SAS) package to ensure unbiased analyses, some couples with previous fertility problems were also excluded in addition to those women taking hormonal medication or drugs that might affect fertility. One women requested fertility treatment during the course of this study and was excluded thereafter. After cessation of OC, only ovulatory cycles were included and any woman with more than three subsequent anovulatory cycles was excluded. Some women re-entered the study after breastfeeding or abortion. Hence, only women trying for a first pregnancy under the conditions of the study (which may not be necessarily the first pregnancy for the couple) were included in the analysis. Prior to every cycle, the family planning intention had to be indicated on the cycle sheet, and the women were asked to mark every episode of intercourse on the cycle sheet. Only cycles with at least one episode of unprotected intercourse in the fertile window were taken into account. Cycles with exclusively protected or no intercourse in the fertile phase were excluded. As all of the couples in this study had intercourse on the fertile days in most cycles, any major effect of coital pattern on estimation of cumulative probabilities of conception could be excluded. Only 3% of the cycles had to be excluded because of missing intercourse, or intercourse only outside the fertile window. In three couples, there was a longer pause with absolutely no intercourse up to 7 months, probably with an interim change in the family planning intention which was unreported.

Six women among those who finally conceived [truly fertile (TF) couples; see below] were completely excluded from the analysis of cumulative probabilities of conception because some cycles were completely missing and no information on episodes of intercourse

Table I. Cumulative probability of conception (CPC) for all couples and the truly fertile subgroup of women who finally conceived

Patient group	No. of cycle			
	1	3	6	12
All couples[a]	0.38 (0.026)	0.68 (0.026)	0.81 (0.022)	0.92 (0.017)
Truly fertile couples[b]	0.42 (0.028)	0.75 (0.025)	0.88 (0.018)	0.98 (0.009)

Values in parentheses are SEM.
[a]n = 340; six couples excluded due to inaccurate time to pregnancy.
[b]n = 304 couples; six couples excluded due to inaccurate time to pregnancy.

(exposure to pregnancy) was available, though a conception cycle was submitted later which led to inaccurate TTP.

Statistical methods and analysis

Statistical analyses were performed using the SAS package, version 8. On the basis of previous studies, the analysis was based on two *a priori* hypotheses that pregnancy rates decline with age in all couples and in TF couples. Hence, in addition to the usual exploratory analyses, *t*-tests, χ^2-tests for categorical data, Wilcoxon test and Log-rank test for conception probabilities based on Kaplan-Meier survival rates were also performed. The statistical method of Kaplan-Meier specifically allows for estimations of 'real CPC' without under- or overestimation, especially if some women were censored for reasons other than conception. Cumulative probability curves were computed from these estimates as '1 – survival rate', which provides distribution functions for the respective variables 'time to pregnancy' and 'time to drop-out', with a cut-off at 21 months observation because of the small numbers remaining. All analyses were carried out for the whole group, and separately for those who finally conceived (TF couples). Control was applied for the influence of confounding factors of major importance such as age, parity, educational level and socio-economic status.

Results

In total, 310 pregnancies (TF) occurred among 346 women during a maximum of 29 cycles of observation [mean 3.56 ± 4.03 (SD) for a total of 1208 cycles observed]. During this period, 36 women did not conceive [probably infertile (PI), 10.4%]. The mean number of cycles observed in the PI group until drop-out was 7.83 ± 5.43 (range 1–20) cycles. The mean age of all women (n = 343) was 29.0 ± 3.6 (range 20–44) years. There was no statistically significant difference in age between those women who finally succeeded or failed to conceive (TF 28.5 ± 3.5 years; n = 309; PI 28.9 ± 3.0 years; n = 34). The mean age of all men (n = 333) was 31.6 ± 5.5 years, and a significant difference (P = 0.027) was seen in the men's age in couples who either finally conceived (TF 31.4 ± 5.6 years; n = 297) or failed to conceive (PI 33.6 ± 5.3 years; n = 36) during the observation period.

Most of the couples were married, and ~60% of the women had a high-school or university degree. Approximately 50% of the women were housewives, and ~50% were working; 82% were Roman-Catholic.

Some 52% of the TF-group and 31% of the PI-group reported on a prior pregnancy before participating in the study ($P < 0.001$). As stated above, some women re-entered the study after live-birth or abortion. To avoid a possible bias in the statistical estimations, all couples were observed only for their first pregnancy under the conditions of the study. Hence, this 'first study-pregnancy' was not necessarily the first pregnancy of the couple.

Cumulative probabilities of conception

The estimated CPC for the whole group and for the TF group are shown in Table I and Figures 1 and 2. Only data from 340 of 346 women were included in this analysis. The TTP of six women from the TF group (now n = 304) was inaccurate because some cycles were completely missed (no information on exposure to pregnancy), although a conception cycle was submitted later, thereby leading to an inaccurate TTP.

A total of 8% of all participating women failed to conceive within 12 cycles of fertility-focused intercourse, and were deemed subfertile according to current clinical opinion (which expects an ~80% overall conception rate within 12 months). For ~30% of the women this was a secondary infertility.

By analysing CPC for the whole group (including subfertile and truly infertile couples), and then for the subgroup of those who finally conceived (TF couples) separately, very large subgroups (81 and 88% respectively) were identified of clearly highly fertile couples who conceived quite early within six cycles with timed intercourse. Approximately 20% of all couples, and only ~10% of finally conceiving couples (TF), did not conceive within six cycles. Consequently, among those women who did not become pregnant after six cycles with timed intercourse, almost every second couple may be regarded as subfertile or probably infertile (PI) according to current clinical definitions.

Fertility was not artificially overestimated due to the early drop-out of those women who did not become pregnant. The distribution function computed from the survival curve of cycles for those who did not conceive (PI) was significantly lower than for those who finally became pregnant (TF) (Figure 2). The mean participation time (observed cycles) was statistically longer for the PI group (7.83 ± 5.43 cycles) than the TF group (3.05 ± 3.52 cycles) ($P < 0.001$; Wilcoxon and Log-Rank tests). Among the PI group, 30 women stopped sending data to the research units and withdrew from the study; however, they continued with NFP to achieve pregnancy. Information obtained via the NFP investigators suggested that some women were disappointed because conception did not occur as early as expected. Five women were lost to follow-up, and one woman finally stopped attempting to conceive.

A statistically significant (P = 0.0371; Wilcoxon test for survival rates) age-related decrease in CPC was seen for all

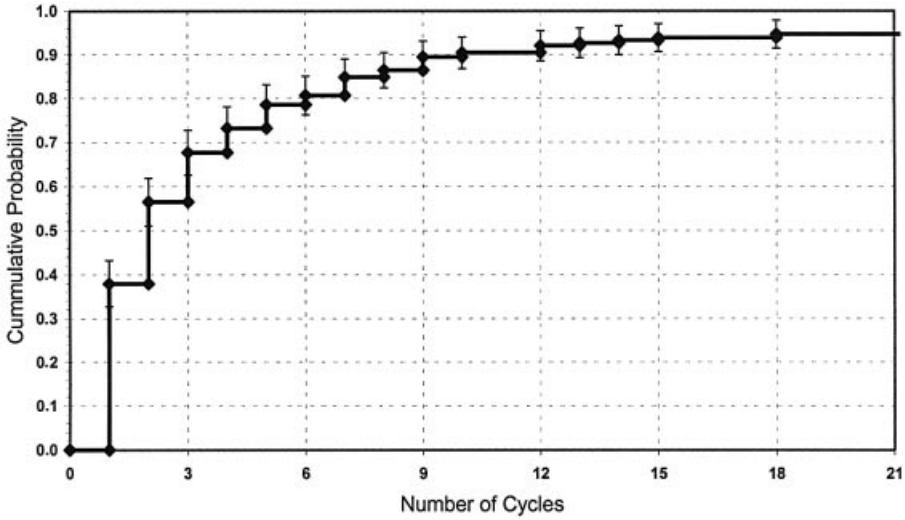

Figure 1. Cumulative probability distribution of conception over time [number of cycles with fertility-focused intercourse; time to pregnancy (TTP)] calculated from the Kaplan-Meier survival function (n = 340 couples, six excluded because of inaccurate TTP, censored for non-conception).

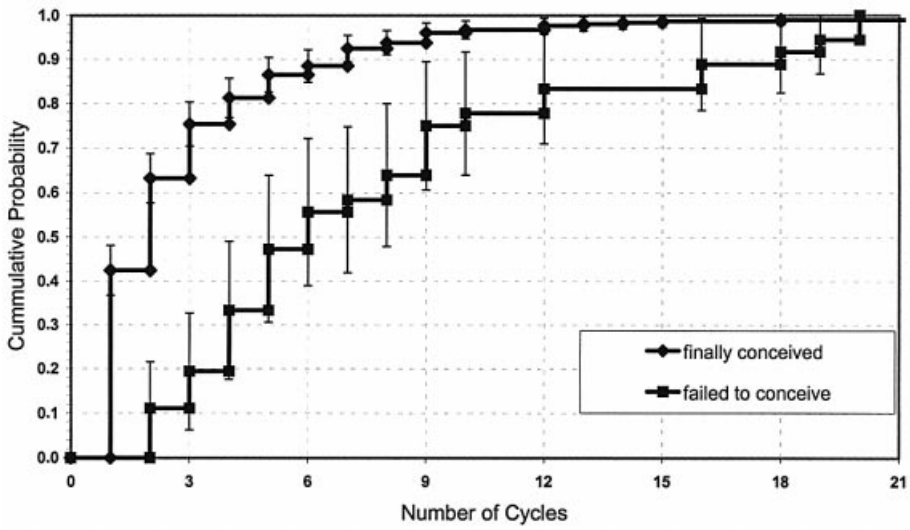

Figure 2. Cumulative exit rate from study calculated from the Kaplan-Meier survival function for couples who finally conceived [diamonds: truly fertile (TF); n = 304, TTP] and those who failed to conceive [square: probably infertile (PI); n = 36, time to drop-out] during the observation period. Wilcoxon and Log-rank test: $P < 0.001$.

couples (including subfertile and truly infertile couples) (Figure 3). The data for cycle 1 complied with data for daily probabilities of conception (Dunson *et al*., 2002). On examining the final cycle of observation, high prospects of conception were found (~90%, maximum of 29 cycles observed) in all age categories except for women aged >35 years (73%), mainly due to low numbers of participants. The estimated overall CPC was seen to decrease with age, but the final cumulative prospects were high and not significantly different [–2Log (Log-rank): $P = 0.0534$].

In women who finally became pregnant (TF), the results were less obvious (Figure 4), and although cycle fecundity seemed to decrease with age, the cumulative pregnancy rates were not statistically different. Neither the Log-rank-test ($P = 0.199$), Wilcoxon test ($P = 0.066$) nor –2Log (Log-rank) test ($P = 0.170$) revealed any difference for the different sections of the survival curve. After 12 cycles, all women reached an estimated plateau of 90–98% pregnancy rate. Thus, in this rather ideal sample of TF couples, age *per se* was not associated with any statistically significant reduction in CPC and decreased final pregnancy prospects.

Discussion

In this prospective study on CPC, a total of 310 pregnancies was observed among 346 women using NFP methods for timing of intercourse. Previous prospective studies on CPC have been much smaller in terms of participant and pregnancy numbers (Wilcox *et al*., 1988; Hilgers *et al*., 1992; Zinaman *et al*., 1996), and have also reported a longer average time to

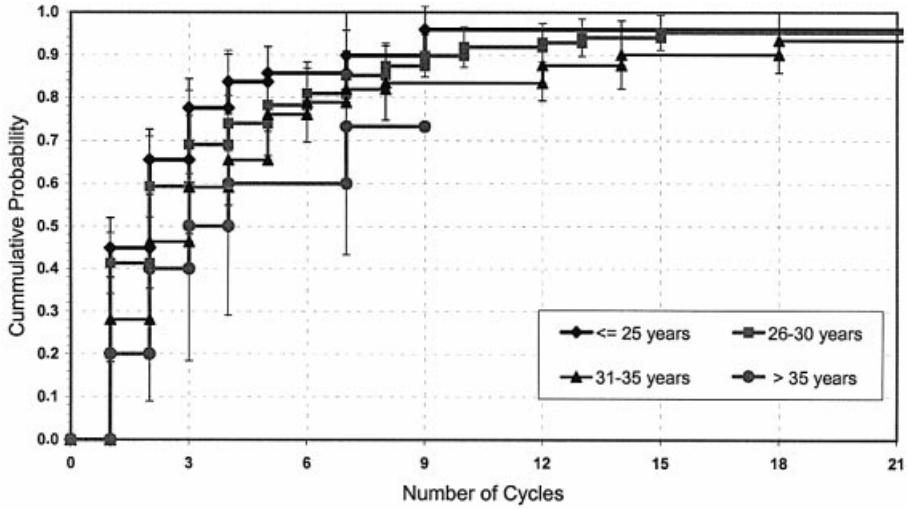

Figure 3. Cumulative probability distribution of conception for all couples in different age categories (<25 years, $n = 58$; 26–30 years, $n = 189$; 31–35 years, $n = 82$; ⩾35 years, $n = 10$) over time calculated from Kaplan-Meier survival functions [$n = 339$; seven couples excluded due to inaccurate TTP ($n = 6$) or woman's age not indicated ($n = 1$)].

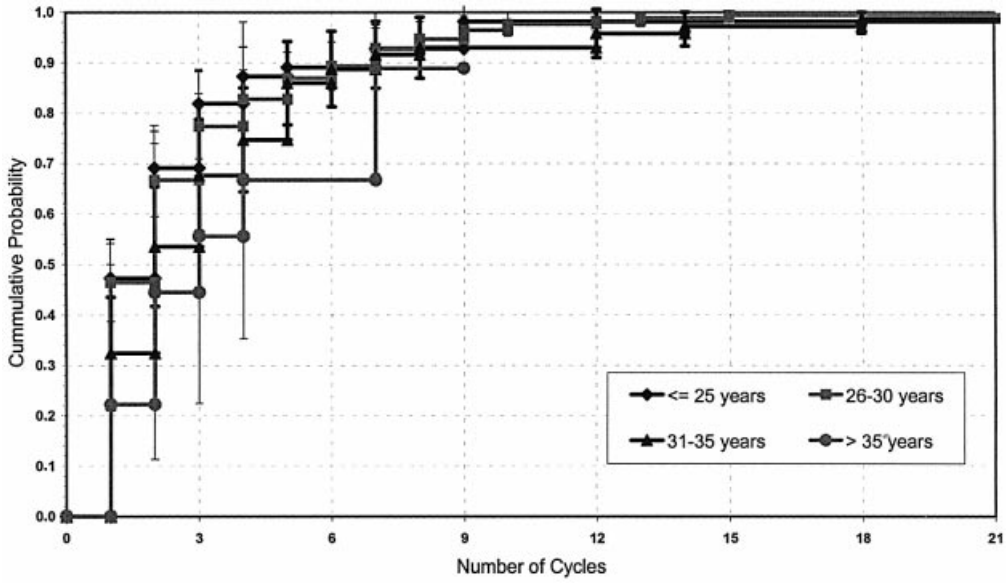

Figure 4. Cumulative probability distribution of conception for truly fertile couples in different age categories (<25 years, $n = 55$; 26–30 years, $n = 168$; 31–35 years, $n = 71$; ⩾35 years, $n = 9$) over time calculated from Kaplan-Meier survival functions [$n = 303$; seven couples excluded due to inaccurate TTP ($n = 6$) or woman's age not indicated ($n = 1$)].

pregnancy and a lower pregnancy rate at the 6- and 12-month periods. More recent studies have been mostly retrospective (Juul *et al*., 1999; 2000; Joffe, 2000; Jensen *et al*., 2001), but may be biased due to long-term recall of TTP and exclusion of truly infertile couples (Jensen *et al*., 2000). Nevertheless, the CPC of the present 'total' group (including subfertile and PI couples) at the 12-month period was comparable with that reported by others. The important advantage of this prospective study is the information it provides about the precise shift of contraception to reproduction, the long-term design (maximum 29 cycles of observation), and the power of the statistical method (Kaplan-Meier) used to minimize an artificial over-estimation of fertility due to early drop-out of women who did not conceive. In addition, the mean number of cycles of observation for those women who did not conceive was significantly greater then for those who finally became pregnant. In contrast to previous reports (Dunson and Weinberg, 2000; Dunson *et al*., 2002), a non-parametric model was preferred to assess fertility rates in the present study, mainly because presently there was no parametric model available which would describe with sufficient precision the entire process of fertility and its changes. This suggests that estimating CPC by monitoring survival functions and related probability distribution functions, as in the present study, is more accurate than using a parametric model.

Although the upper-class population of the present study may not be representative of the general population in Europe, the authors are unaware of any study linking social status to

variability of fertility. In Germany in 1999, the mean age of women at their first birth was 28.83 years, and this was comparable with the present study population. The influence of factors such as age (late first pregnancy), coital patterns or genital infections in different social classes on fertility is unknown, and indeed some of these effects might neutralize each other (e.g. higher age in upper-class groups and probable higher rate of genital infection in lower-class groups). It is known from previous studies (Frank *et al*., 1985; Frank-Herrmann *et al*., 1991) that the STM also provides effective contraception in so-called 'lower-class' couples; hence, it could be expected that the results obtained might be generalized to other populations in developed countries.

Users of NFP may represent a somewhat ideal sample, as they make optimal use of their fertility potential by accurate detection of the fertile window in their menstrual cycles and an above-average knowledge of reproductive basics such as optimal time and interval of intercourse. Nevertheless, it is known from the authors that Internet-based counselling of couples with infertility problems (www.meinkinderwunsch.de) that increasing numbers of women are practising natural methods before, and also in parallel with, infertility therapy. Hence, it is hoped that the results of the present study will aid those who counsel couples (e.g. prior to specialized infertility therapy, general practitioner, general gynaecologist) and direct them towards further steps of diagnosis and possible reference to a specialized centre. Moreover, these data may also help specialists to decide whether sufficient exposure to the chance of conception has occurred, as well as when to start further infertility investigation and resort to ART, especially in cases of unexplained infertility.

All participating women were trained and instructed by experienced NFP teachers in parallel with their study participation (1–6 months) until autonomy and reliability in using NFP was reached. About 20% of women switched from OC to the STM, and in only a few of the former OC users was their first cycle using STM also their first cycle in attempting pregnancy. This was due to the fact that in the past, most former OC users initially avoided pregnancy by using the STM. Hence, there was no difference in the correct location of the fertile window for experienced NFP users and absolute beginners, as has been shown previously (Frank-Herrmann *et al*., 1991; 1997) when NFP was used as an effective method of contraception.

In the present study, most couples attempting pregnancy had intercourse in the fertile window in almost every cycle, from the first cycle until conception or drop-out. The couples were obliged to record on the cycle sheet every episode of intercourse was recorded, and only 3% of cycles were excluded due to missed intercourse or intercourse only outside the fertile window. Three couples reported a longer pause, with no intercourse for up to 7 months, most likely with an interim change in their family planning intention. Therefore, before conducting the first analysis the decision was made to include only those cycles with prior documented family planning intention, and also those with unprotected intercourse at least once in the fertile window, the reason being that the aim was to propose NFP as a tool for diagnostic assessment of 'infertile' couples (see below).

About 80% of the couples conceived in the first six cycles when using the fertility awareness part of the STM with fertility-focused intercourse. These numbers partly confirm the data obtained from earlier and larger retrospective studies (Bonde *et al*., 1998; Juul *et al*., 1999; 2000; Joffe, 2000; Jensen *et al*., 2001), though a higher final cumulative probability of conception within 12 cycles was found. As expected, some 10.4% of women did not conceive within all observed cycles. For those who finally conceived, only 2% of the pregnancies occurred later than 12 cycles.

In another well-designed, prospective study (Bonde *et al*., 1998), cumulative pregnancy probabilities of almost 60% were obtained after six menstrual cycles. The higher CPC value compared with all cited studies accounts for the effects of information on the fertile period and of repeated timed intercourse. The effect of timed intercourse on pregnancy rates of women, with optimal use of their fertility potential, was also recently emphasized by others (Stanford *et al*., 2002).

These findings highlight the existence of a huge group of highly fertile couples who conceive quite early within six cycles with timed intercourse. About 20% of all couples, and only 10% of finally conceiving couples (TF), will not be successful within six cycles (see Table I). These TF couples represent an ideal homogeneous group without any infertility problems and, using a ~30% monthly chance of conception, they will achieve a pregnancy rate of almost 90% in six cycles, based on the formula:

Probability of conception within 6 months = $1 - (1 - \text{monthly probability of conception})^6$, which is precisely the relationship confirmed by the results of the present study.

Taking into account the results of the overall conception rates for all couples, among whom ~20% do not conceive in six cycles and ~10% do not conceive in 12 cycles, almost every second couple is probably subfertile or infertile after six unsuccessful cycles with timed intercourse. Thus, it is possible to suggest a new threshold such that, after six unsuccessful cycles with fertility-focused intercourse (the ideal exposure to pregnancy) prior to the first visit or during the following months, clinicians in primary care must assume subfertility or, in rare cases absolute infertility (such as tubal pathology or azoospermia), in almost every second case. In the present authors' opinion, this justifies an early and basic infertility work-up in these individual cases; in individual cases, the waiting time should not be extended to 12 cycles, before starting basic infertility work-up to avoid possible under-treatment of infertility later.

Couples with a good prognosis (unexplained infertility, no tubal affection, no oligoamenorrhoea, no oligoasthenozoospermia and no signs of reduced ovarian reserve; Navot *et al*., 1987; Seifer *et al*., 1997; Scheffer *et al*., 1999), and/or no suspicion of endometriosis, should be advised to wait as they have a reasonably good chance (>60%) of conceiving spontaneously during the next 36 months (Collins *et al*., 1995; Snick *et al*., 1997; Glazener *et al*., 2000; Glazener and Ford, 2002; Gnoth *et al*., 2002b). During this period, self-monitoring with NFP methods may be all that is necessary. However, it is

sometimes difficult to get patients with infertility problems to wait unless they are given detailed information about their prognosis, the proposed pattern (and difficulties) of investigation and treatment, as well as alternative ways of becoming parents (Schmidt, 1998).

An advanced infertility work-up which includes laparoscopy and hysteroscopy, endocrinological tests, in-vitro tests of sperm–cervical mucus interactions together with consultation with a reproductive gynaecologist and andrologist as well as ART, should be offered to couples with poor prognosis and more than 12 unsuccessful cycles with timed intercourse. They may benefit from an early resort to ART because in this case they are superior to expectant management (Evers *et al*., 1998). This balanced management avoids unreasonable early interventions such as IVF as first-line treatment (Karande *et al*., 1999), which may represent over-treatment and expose women to medical complications (e.g. multiple pregnancies and ovarian hyperstimulation syndrome) and unnecessary expense. It also avoids late interventions which may represent infertility under-treatment.

As expected, CPC was found to decrease with advancing female age in all couples. Indeed, previous reports on daily fecundability (Dunson *et al*., 2002) showed a decline for women in their late 20s as well as for men in their late 30s. In that study, 105 of the 782 participants were from a long-term study on NFP in Germany, and most had used the STM for contraception such that acts of unprotected intercourse were often located in border regions of the fertile window. Intercourse on days with the highest pregnancy prospect was somewhat under-represented. This mixture of pregnancy avoiders (predominantly) and achievers influenced coital pattern and may have affected the calculations of fertility. Another possible bias in the study was an overestimation of fertility due to the non-exclusion of participants who re-entered the study after breastfeeding or abortion.

Cumulative pregnancy rates in natural cycles are much more appropriate for assessing age-related effects than are daily pregnancy probabilities (te Velde *et al*., 2000). In the present study, all women had intercourse on the most fertile days of the cycle, thereby reducing any influence of coital pattern on fertility estimation. As expected, the CPC decreases significantly with age for all couples, and the final estimated pregnancy prospect is high (about 90%), except for women aged >35 years. However, the proportion of women falling into this age category is too small to prove (statistically) a significant decline in fertility. In the separately analysed, ideal subgroup of TF couples, the CPC did not differ significantly among the different age groups. Methodically, even when heavy censoring is employed (as in the present study), a Kaplan-Meier approach allows the analysis of non-censored subjects (i.e. TF couples) to calculate a distribution function of the numbers of cycles from the survival function, as those who failed to conceive (i.e. censored) were observed for a significantly longer period than the finally successful couples (i.e. non-censored) ($P < 0.001$; Wilcoxon and Log-rank test). Thus, for this ideal sample of TF couples, the effect of age on the decline in fertility was less obvious because of their high homogeneity with advancing age. Unfortunately, no information is available on the rate of ongoing pregnancies and live births in all cases. As the incidence of abortions is higher in older women, an outcome measure of live births would provide additional—and probably more solid—information in terms of an age-related birth rate. Consequently, it is difficult to draw final conclusions based on these findings.

With increasing age, there is an increasing proportion of couples with infertility problems, and this is related mainly to the woman. Although some fertility problems are associated with age (e.g. reduced ovarian reserve), they depend mainly on individual factors (te Velde and Pearson, 2002) that cause increasing heterogeneity in fecundity with age. In the present study, the inter-quartile range in cumulative probability of conception for women aged between 31 and 35 years extended from 28 to 76%, while for women aged >35 years it extended from 20 to 100%. It is this increased heterogeneity due to an increasing proportion of truly subfertile and infertile women which accounts for an age-related decrease in fertility, lowering the average for the whole group, and giving the illusion of a gradual age-related effect. The small differences in overall CPC between the age groups of <30 years account for a broad plateau of relatively high fertility in most couples, and a subsequent rapidly increasing infertility with a small plateau of highly fertile couples of greater age. The significant difference ($P = 0.0371$) between these groups is mainly due to the influence of women aged >35 years. In view of the effects of age on CPC for all and TF couples, the findings of the present study suggest that in this homogeneous setting a woman's fertility most likely does not decline gradually with advancing age. This stresses the importance of an early basic infertility investigation for probably subfertile or infertile couples in order to detect individual factors associated with a poor prognosis of achieving spontaneous conception, regardless of age. It is of interest to note that there was a significant association with men's age among TF couples; this confirms the data published by others (Dunson *et al*., 2002) and forms the basis for future investigations.

Last—but not least—NFP methods are widely used by women. Two European multicentre studies (The European Natural Family Planning Study Groups, 1993; 1999; Colombo and Masarotto, 2000) have shown that the NFP centres in Europe are now well structured to carry out prospective studies to measure a couple's fertility by assessing exposures related to semen quality, age or environment.

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ORIGINAL ARTICLE *Reproductive epidemiology*

Final ART success rates: a 10 years survey

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BACKGROUND: Cumulative pregnancy rates (CPRs) and live birth rates (CLBRs) are much better indicators of success in IVF programmes than cross-sectional figures per cycle or embryo transfer. They allow a better estimation of patient's chances of having a child and enable comparisons between centres and treatment strategies.

METHODS: A 10 year cohort study of patients undergoing their first assisted reproductive technique cycle was conducted. Patients were followed until live birth or discontinuation of treatment. All IVF and ICSI cycles and cryo-cycles with embryos derived from frozen pronuclear stage oocytes were included. The CPR and CLBR were estimated using the Kaplan–Meier method for both the number of treatment cycles and transferred embryos. The analysis assumed that couples who did not return for subsequent treatment cycles would have had the same chance of success as those who had continued treatment.

RESULTS: A total of 3011 women treated between 1998 and 2007 were included, and 2068 children were born; women already with a live birth re-entered the analysis as a 'new patient'. For 3394 'patients under observation' with 8048 cycles, the CLBR was 52% after 3 cycles (the median number of cycles per patient), 72% after 6 cycles and 85% after 12 cycles. A CLBR of ~50% was achieved for patients aged under 40 years, after the cumulative transfer of six embryos. The mean live birth rate from one fresh cycle and its subsequent cryo-cycle(s) was 33%. Our analysis also shows that ART can reach natural fertility rates but not exceed them.

CONCLUSIONS: Most couples with infertility problems can be treated successfully if they continue treatment. Thereby ART can reach natural fertility rates. Even with the restrictions in place as a result of the German Embryo Protection Law, CLBR reach internationally comparable levels.

Key words: cumulative pregnancy rate / cumulative live birth rate / natural fertility rate / German Embryo Protection Act

Introduction

All IVF patients want to know their chances of success. Generally, the success rates of assisted reproductive techniques (ARTs) are given as clinical pregnancy rates (PRs) per started cycle, oocyte retrieval or embryo transfer and often determined relative to maternal age. At first glance, these rates seem to be disappointingly low, but it is the final ART success rate that is most pertinent to a patient's decision on whether to undertake treatment (Hull, 1994). Furthermore, final ART success rates [cumulative pregnancy rate (CPR) and live birth rate (CLBR)] appear to be a much better indicator of quality and success in IVF programmes and probably allow better comparisons between different centres (Lintsen *et al.*, 2010). This is of particular importance for cross-comparison of IVF results between different countries, especially as an increasing number of patients are looking for cross-border treatment. CPR and CLBR should reflect possible advantages or disadvantages of national IVF policies (restrictions and liberations) and individual treatment strategies of different IVF clinics. Moreover, CPR and CLBR are the most important figures for basing economic and political considerations of ART efficacy and reimbursement costs.

The German national index and most of the international indexes have not published CLBR so far (www.deutsches-ivf-register.de). Several previous studies have calculated cumulative success rates but have some limitations because of inconsistent inclusion criteria, inconsistent treatment procedures or no reporting CLBR (Tan *et al.*, 1992; Hull, 1994; Bergh *et al.*, 1995; Dor *et al.*, 1996; Osmanagaoglu *et al.*, 1999; Kovacs *et al.*, 2001; Olivius *et al.*, 2002; Ubaldi *et al.*, 2004; Lundin and Bergh, 2007; Pelinck *et al.*, 2008; Sundstrom and Saldeen, 2009). More recent studies have published CPR comparing single versus double embryo transfer and discussed the impact on

treatment policy (Sundstrom and Saldeen, 2009; Gelbaya *et al.*, 2010), and one German study has reported on CPR with respect to national restrictions and dropout reasons (Schroder *et al.*, 2004). However, only one centre has published their CLBR, including cryo-cycles with transfers of previously frozen embryos, as well as their treatment policy in detail (Klipstein *et al.*, 2005; Malizia *et al.*, 2009; Moragianni and Penzias, 2010). Furthermore, in most previous studies on CLBR and CPR, the methodological management of women with live birth coming for another child remains completely unclear.

In Germany, the performance of an ART is bound by very strict regulations by law (German Embryo Protection Law of 13th December 1990 http://www.bmj.bund.de/files/-/1148/ESchG.pdf) and also influenced by general health insurances (Gemeinsamer Bundesausschuss der Ärzte und Krankenkassen, http://www.g-ba.de). Until 2004, up to four fresh IVF- and IVF/ICSI cycles were fully covered by insurance. Since then, half the cost of IVF- and IVF/ICSI cycles is covered by the couple with the remainder paid by insurance and only for a maximum of three cycles. Cryo-cycles are entirely privately funded. The change in the reimbursement regulation in 2004 caused a significant drop in the number of treatment cycles in Germany. All numbers and other statistical data are published yearly by the national IVF register and can be seen at www.deutsches-ivf-register.de.

According to the German Embryo Protection Law of 1990, the cell-culture of more than three pronuclears (PNs) is prohibited because only as many oocytes at the PN stage as are planned to be transferred in one cycle are allowed to be cultured. PNs that are not intended for implantation within one cycle have to be discarded or cryopreserved. As a consequence, prolonged embryo culture with the selection of the best embryos or blastocysts and embryo cryopreservation is prohibited. Embryo cryopreservation is allowed only in cases of emergency. There is an ongoing and viable discussion on the interpretation of the German Embryo Protection Law. Therefore, the question arises of whether the strategy of one IVF or ICSI-cycle and its subsequent cryo-cycle(s) yields a lower cumulative CPR and CLBR than one IVF or ICSI-cycle with prolonged embryo culture and embryo selection before transfer.

In this cohort study, we calculated CPR and CLBR by the Kaplan–Meier-method (Kaplan and Meier, 1958), which allows for the estimation of CPR and CLBR without under- or overestimation, which is of particular importance if patients are censored for reasons other than pregnancy or live birth. The Kaplan–Meier method assumes inherently that those who exit treatment for reasons other than pregnancy or live birth have the same probability of future success as those who continued.

We performed this 10-year survey from 1998 to 2007 in a single IVF centre in Germany in order to provide estimates of the final success that a couple would have if continuing treatment and to allow comparisons with international success figures. We included all IVF, IVF/ICSI and cryo-cycles involving the transfer of embryos derived from frozen PN stage oocytes.

Materials and Methods

Data collection and analysis

All ART cycles included IVF, IVF/ICSI and cryo-cycles with embryos from cryopreserved PN stage oocytes but no oocyte donations as it is prohibited in Germany. Cycles between January 1998 and December 2007 were observed in a cohort study, including all women undergoing their first fresh cycle in our centre. These women were followed as 'patients under observation' until either discontinuation of their treatment or live birth as the primary outcome. All patients without a live birth who returned for further treatment underwent a further attempt. Cycles without oocyte 6 retrieval were not included. Only cryo-cycles with embryo transfer were considered. For the Kaplan–Meier estimations, women already with a live birth re-entered the analysis as a 'new patient under observation' if they underwent further ART. Patients who did not return (perhaps because they changed the IVF centre or stopped treatment for any other reason) were censored after the last treatment.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Medical and laboratory data were recorded using the clinic management program MEDISTAR, the IVF laboratory managing program RECDATE and Microsoft EXCEL. Data collected included the length of time trying to conceive, information of previous treatments for infertility and, if available, the reason of discontinuation, relevant information about ovarian stimulation and procedures in the IVF laboratory and outcomes of the treatment cycles. All couples had to sign an informed consent about data storage and anonymous results reporting and transfer to the national register.

Data were analysed using the SAS package, version 9 (SAS Institute Inc., Cary/USA). Kaplan–Meier survival rates were estimated over all treatment cycles or number of transferred embryos. The usual survival rates with means and 2 standard errors approximating the 95% confidence interval (CI) were computed and the cumulative probability curves (non-parametric distribution functions) were derived for the CLBR or CPR. Since age is the major factor of importance for the success rates (Lass *et al.*, 1998; Bar-Hava *et al.*, 1999), Kaplan–Meier curves were additionally calculated separately for different age groups. Additionally, we also calculated non-estimated live birth rates (LBRs) and PRs for one treatment sequence, which is one fresh cycle followed by its subsequent cryo-cycle(s), to allow comparisons with cross-sectional statistics. Statistical significance was derived by the Log-rank-test for Kaplan–Meier survival rates and the *t*-test for other continuous data.

Fresh cycles

The fresh IVF- or IVF/ICSI-cycle treatment strategies have previously been described in detail (Gnoth *et al.*, 2008). The main indications for ART were male subfertility (65%), tubal pathology (12%), endometriosis (12%), idiopathic infertility (9%) and repeated polyfollicular development in gonadotrophin stimulation cycles for IUI (2%). The majority of patients began treatment with a monophasic oral contraceptive pill on Days 3–5 of the cycle. The long agonist protocol was used preferentially. In about 20% of all fresh cycles, stimulation was according to the antagonist protocol especially in cases of expected low ovarian response. Controlled ovarian hyperstimulation (COH) was performed with either recombinant follitropin α or β (rec FSH) or urinary HMG. The starting dosage was adjusted according to the patient's age, Anti-Müllerian hormone and antral follicle count. Most of our patients under 35 years of age were started with 150 mIU/ml. In patients with expected or proved low ovarian response ($\leq$4 oocytes in a previous cycle), we started with 300 mIU/ml. After 5 days of stimulation, the follicular development was assessed by ultrasound and hormonal measurements. If necessary, the dose of gonadotrophins was adjusted. Transvaginal oocyte retrieval was performed 35 h after ovulation induction. The luteal phase was supported with vaginal application of progesterone and in the case of low ovarian response, vaginal estradiol (E_2) was used additionally. In accordance with the regulations, two PN stage oocytes were cultured if a transfer of two embryos was planned

or three PN stage oocytes if three embryos should be transferred in one cycle. In all cases, a PN scoring was performed. All supernumerous PN stage oocytes were frozen. Approximately 30% of all fresh cycles were conducted as IVF and 70% were conducted as IVF/ICSI. The number of embryos transferred depended on maternal age, parity, number of previous attempts and the couple's wish, and was 2.06 per transfer on average. The ongoing clinical PR was considered to be the secondary outcome measure defined as a gestational sac and heart beat assessed by vaginal ultrasound 2–3 weeks after a positive pregnancy test.

Cryo-cycles

Cycles with the transfer of embryos derived from cryopreserved PN stage oocytes were performed after priming the endometrium with a vaginal application of 2–4 mg micronized E_2 per day. Luteal phase was initiated with additional vaginal application of progesterone after ultrasound assessment of the endometrium ideally showing a trilaminar pattern and a thickness of at least 7 mm. The PN stage oocytes were thawed on Day 3 of vaginal progesterone and transferred after 2 days of embryo culture (Day 5 of vaginal progesterone). Clinical pregnancy was confirmed as before.

Results

Overall 3011 individual women were eligible for inclusion. Women already with a live birth re-entered the analysis as a 'new patient'. Therefore, 3394 'patients under observation' contributed 8048 cycles, which are summarized in Table I. The mean duration of involuntary infertility was 3.4 years before ART indicating serious subfertility (Gnoth *et al.*, 2005). The overall mean number of treatment cycles was 2.7 (median: 3) per patient (range 1–22). This resulted in 2193 clinical pregnancies and 1718 deliveries, producing a total of 2068 children (1373 singletons, 680 twins and 15 triplets). The transfer of embryos in cryo-cycles accounted for 20% of live births. The miscarriage rate was 19.5%, and the ectopic PR was 2.2%. The clinical PR was 27.2% per oocyte retrieval. The transfer of three embryos in a cryo-cycle was as effective for PR per embryo transfer as the transfer of two embryos in a fresh cycle.

Cumulative live birth rates

Figure 1 shows the overall CLBR for all treatment cycles with oocyte retrieval and all age groups. The CLBR were 52% after 3 cycles (approximate 95% CI: 50–54%), 72% after 6 cycles (approximate 95% CI: 69–74%), 85% after 12 cycles (approximate 95% CI: 80–89%) and 94% after 18 treatment cycles (approximate 95% CI: 85–100%). The maximum number of treatment cycles that resulted in a successful pregnancy was 18 with the birth of healthy twins. Because of the re-entry of women after a live birth as 'new patients', we included 3394 'patients under observation' in the estimations of CLBRs and CPRs (Fig. 1). The proportion of re-entry in 'patients under observation' is 11.3%. The maximum of re-entry is three times with four children born to one woman after treatment for infertility in our centre. CLBR and CPR did not differ according to whether re-entry was allowed or not.

Figure 2 shows the CLBR, for all treatment cycles with oocyte retrieval, stratified for the different age groups. The Log-rank test revealed a significantly lower LBR for women over 40 years of age. Although the CLBR also seemed to be lower in age group over 35 up to 40 years of age, it failed to reach statistical significance when compared with the younger age groups.

Table I Basic characteristics of patients and treatment cycles.

Time	1998–2007
Total number of individual women	3011
Patients under observation	3394 (with 383 re-entries after live birth)
Total cycle number observed	8048
Patient's age (entire study, before and after the change of reimbursement policy in Germany in 2004)	33.7 ± 4.4 years; minimum 20 years, maximum 46 years of age (all patients. entire study) 34.33 ± 4.74 years (before 2004, not pregnant in study time)[a] 35.75 ± 4.4 years (2004 and beyond, not pregnant in study time)[a] 32.73 ± 8.8 years (before 2004, finally pregnant)[a] 33.71 ± 3.9 years (2004 and beyond, finally pregnant)[a]
Duration of infertility	3.4 years
Cycles/patient (entire study, before and after the change of reimbursement policy in Germany in 2004)	2.7 ± 1.3 (mean, entire study) 2.4 ± 1.7 (before 2004, not pregnant in study time)[a] 2.7 ± 1.9 (2004 and beyond, not pregnant in study time)[a] 1.9 ± 1.4 (2004 and beyond, finally pregnant) 1.9 ± 1.4 (2004 and beyond, finally pregnant)
Maximum cycles/patient	22
Oocytes/retrieval	10.35 (mean)
Embryos transferred/cycle	2.06 (mean)
IVF-cycles	30% of all fresh cycles
IVF/ICSI-cycles	70% of all fresh cycles
Cryo-cycles	34% of all cycles
Mean pregnancy rate	27.3%/cycle
Miscarriage rate	19.5%/cycle
Stillbirth rate	0.4%/birth
Ectopic pregnancy rate	2.2%/cycle

[a]Significant difference between the subgroups.

Figure 3 shows the CLBR according to the number of transferred embryos. Except for women over 40 years of age, an overall CLBR of ~50% was reached after the cumulative transfer of six embryos, in two or up to six cycles.

There was no statistical significant difference in the overall CLBR between the IVF and ICSI groups, when all ages were considered. However, when women over 35 and up to 40 were examined separately, ICSI was the more favourable option ($P = 0.002$ for CPR and $P = 0.0040$ for CLBR).

Cumulative pregnancy rates

The overall ongoing CPRs were 79% after 6 cycles (approximate 95% CI: 77–82%), 91% after 12 cycles (approximate 95% CI: 88–95%) and 100% after 18 treatment cycles.

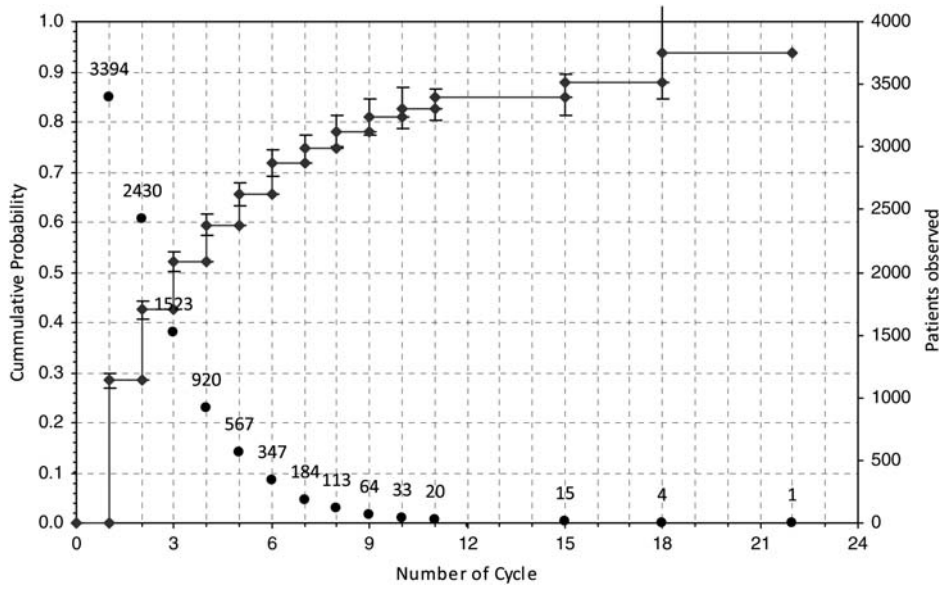

Figure 1 Overall CLBR (means ± 2 standard errors to give the 95% region) for all patients and age classes over the number of treatment cycles. For each cycle, the number of 'patients observed' up to this time is given.

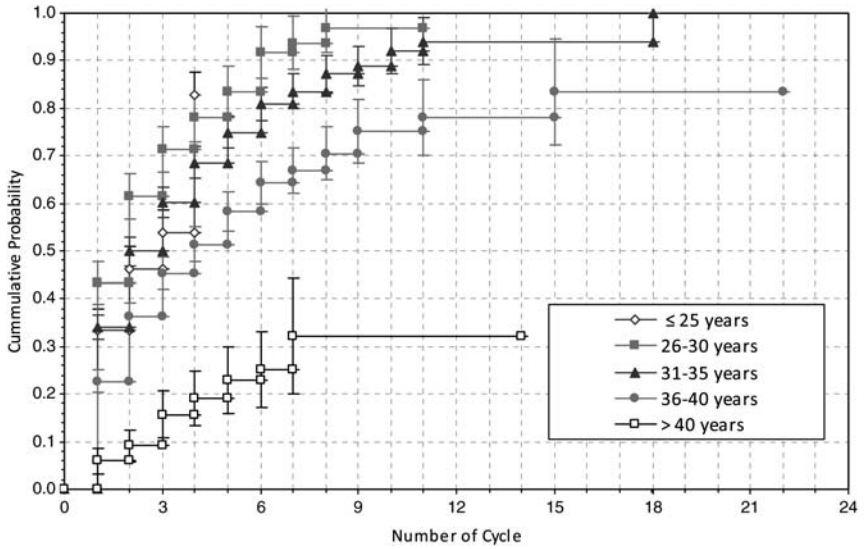

Figure 2 CLBRs (means ± 2 standard errors to give the 95% region) for all patients stratified for the different age groups.

Pregnancy and LBRs out of one fresh cycle and its cryo-cycles

The mean ongoing PR (not estimated) from one fresh cycle and its subsequent cryo-cycle(s) (therapy sequence) was 41%, 39% in the IVF group and 42% in the IVF/ICSI group. Women in their 30s were the biggest group seeking ART (74% of all women), and for this group the PR from one fresh cycles and its cryo-cycles was 43%. There was no difference in outcome between IVF and ICSI per therapy sequence.

The mean LBR (not estimated) out of one fresh cycle and its subsequent cryo-cycle(s) was 33%, 31% in the IVF group and 34% in the ICSI group. For women in their 30s, the mean LBR from one fresh cycle and its cryo-cycles was 34%. Again there was no statistically significant difference between IVF and ICSI per therapy sequence.

A maximum of four pregnancies and maximum of three live births occurred from one therapy sequence of one fresh cycle and its subsequent cryo-cycles.

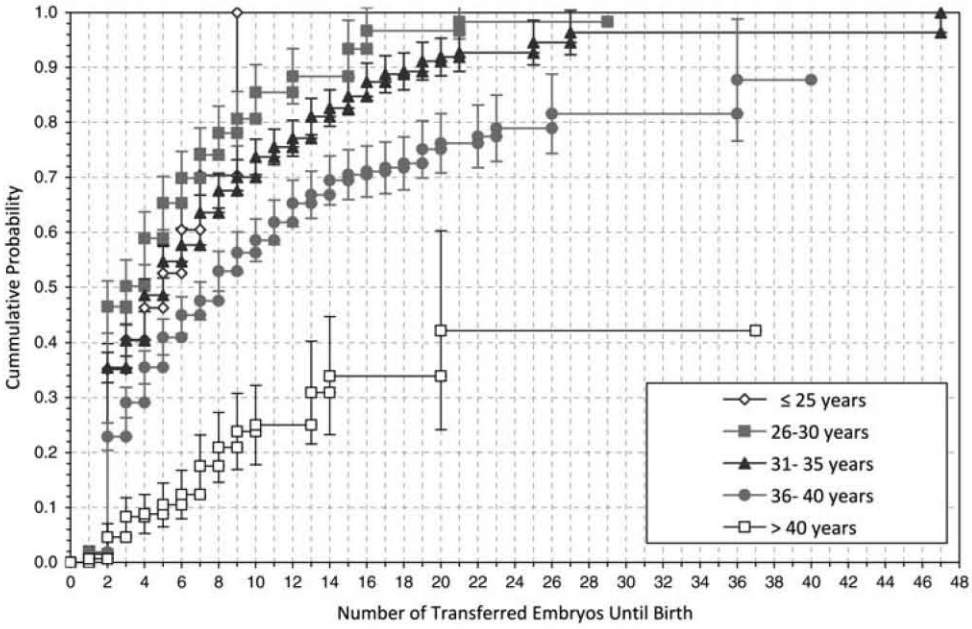

Figure 3 CLBRs (means ± 2 standard errors to give the 95% region) for all patients stratified for the different age groups over the number of transferred embryos.

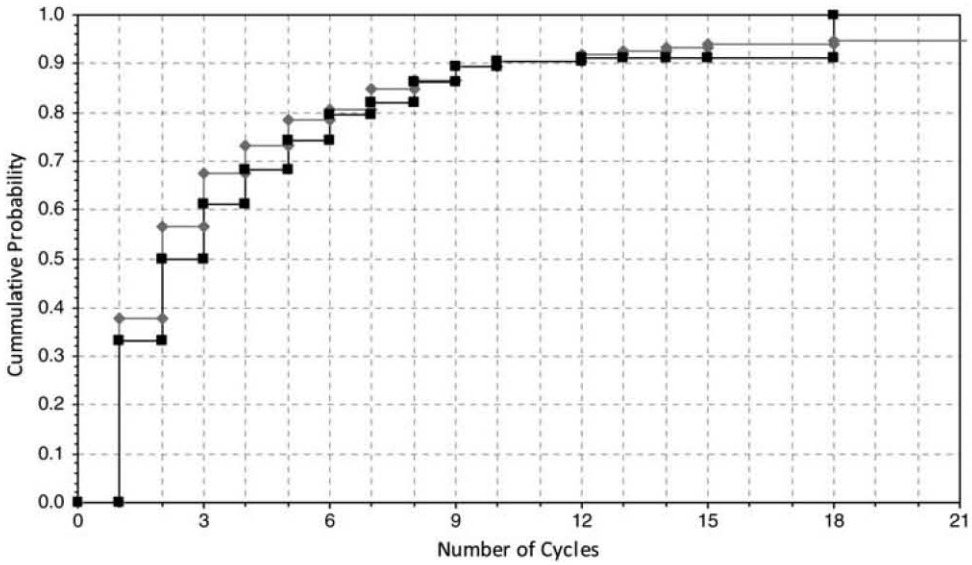

Figure 4 CPRs after ART (squares, 3394 patients) and CPRs in natural cycles [(Gnoth *et al.*, 2003), diamonds, 340 patients].

CPRs after ART and in natural cycles after spontaneous conception

When plotting our data of CPR after ART into the graph of CPR in natural cycles from our 'Time to pregnancy-study' (Gnoth *et al.*, 2003), the curve shapes were found to be nearly congruent (Fig. 4).

Discussion

A total of 3011 individual women who had treatment between 1998 and 2007 were included in our survey and 2068 children were born. Women already with a live birth re-entered the analysis as new 'patients under observation'. Our overall CLBR in 3394 'patients under observation' with 8048 cycles were 52% after 3 cycles

(median number of cycles per patient), 72% after 6 cycles, 85% after 12 and 94% after 18 treatment cycles. The mean, not estimated, LBR from one fresh cycle and its subsequent cryo-cycle(s) was 33%. Therefore, as previously noted (Damario *et al.*, 2000), cryopreservation of PN stage oocytes is an effective treatment strategy that optimizes the final results from one oocyte retrieval. Provided patients continue with treatment, the likelihood of success is high as shown by Kaplan–Meier figures. Obviously, during infertility treatment, many women re-evaluate their situation, and our figures are useful to aid their decisions on whether to continue with treatment, on the number of future cycles and on the number of embryos to be transferred the next time. This is important in cases in which only one embryo is intended or probably only available for the next transfer.

In this study, we did not classify patients or cycles according to the different causes of infertility because even recent studies have shown that CLBR do not vary substantially with the indication for ART (Dor *et al.*, 1996; Lintsen *et al.*, 2007, 2010).

With the use of the Kaplan–Meier method, which censors data for patients who did not return for further treatment for any reasons, we assume that those women would have had the same chance of a live birth by treatment as those who continued. This approach is a matter of contention as some authors have suggested it as possibly too optimistic (Stolwijk *et al.*, 1996, 2000; Sharma *et al.*, 2002) because of the possible early dropout of women with a poor prognosis and no realistic chance of a pregnancy or a live birth in subsequent treatment cycles (Hendriks *et al.*, 2008). So a rigorous pessimistic approach assumes that women, who did not return for further treatment, have a zero chance for achieving a pregnancy. On the other hand, patients with a poor prognosis might be more inclined to continue treatment if this seems to be the only chance of success (Roest *et al.*, 1998) resulting in an underestimation of real CPR and CLBR.

There are many factors that can result in such over- or underestimation of cumulative success rates if the reasons for dropout are not taken into account (Verberg *et al.*, 2008) although patients' true dropout reasons mostly remain unknown. The 'methodological' bias is mainly influenced by treatment strategy and counselling (Verberg *et al.*, 2008). So, the realistic CLBR lies in between the two extremes but may be closer to the optimistic assumption as natural conceptions do occur in women who have ceased ART. A study by Verhagen *et al.* (2008) found the PR in patients who were advised to stop treatment because of a medical indication (repeated fertilization failure after ICSI or very poor ovarian response), yet continued treatment, to be 14%. So, selective dropout of patients with poor treatment prognosis does not necessarily disadvantage our assumptions as it depends on the centre's treatment strategy and the population studied (Roest *et al.*, 1998; Schroder *et al.*, 2004). In case of a negative pregnancy test, patients with a good prognosis are generally encouraged to continue treatment. However, also in cases of doubtful prognosis, patients may be advised to go for further treatment cycles as the only reasonable way to achieve success (Croucher *et al.*, 1998; Klinkert *et al.*, 2004). Of course, this decision purely depends on the wishes of the couple. Another important aspect is the existence of alternatives for couples with a poor prognosis, e.g. oocyte donation, which is prohibited in Germany. As long as one, at least moderately developed embryo was present on the day of transfer, we encouraged patients to continue treatment in case of a negative test. So in this study, towards the higher number of treatment cycles, we may have an accumulation of patients with limited prognosis reducing the overestimation bias.

Our CPR and CLBR could also be biased because some couples, even with good prognosis, probably did not return for further treatment after unsuccessful cycles because of financial reasons. Before 2004, four cycles were fully reimbursed, but then legislation required couples to privately fund half the cost of ART, resulting in a massive drop in procedures conducted from 2003 to 2004 and beyond (yearbooks of the German IVF Index on www.deutsches-ivf-register.de). The mean maternal age and the mean number of cycles per 'patient under observation' who did not conceive increased significantly after 2003 in our study, reducing overestimation failures. However, the median number of treatment cycles remained unchanged with three cycles per 'patient under observation' before 2004 and beyond. The overall ART success rates were not affected by this policy change, which was proved by usual, continuous cross-sectional statistics and separate calculations of CLBR before and after 2004.

Women with a live birth re-entering the study for a next child were included as 'new patients under observation' in all estimations of CLBRs and CPRs. We are aware of this minimal lack of independence in censoring by re-entering individual women as new patients after a live birth. Re-entry of patients is not a problem in usual survival analysis (e.g. survival of cancer patients) but there is an inherited bias in cumulative ART success rates, which is not discussed in most success studies. In this study, the proportion of re-entries in 'patients under observation' is relatively low. However, this still might result in overestimation of cumulative ART success rates (Molloy *et al.*, 1995), though only with a significant effect on the first two cycles (Stolwijk *et al.*, 2000). Based on our experiences with the calculation of CPR in natural cycles, this bias of re-entry is very small because of the long child spacing in our population (Gnoth *et al.*, 2003). Therefore, CLBR and CPR did not differ whether re-entry was allowed or not. Allowing re-entry in the analysis best reflects the real situation in treatment and counselling of couples.

Some of our couples changed to another IVF centre, a practice also recorded in the national index where our patient's migration is around 7%. Therefore, for ~3–4% of our patients, their 'first cycle' in our centre may already be their cycle two or three, further reducing the overestimation bias just mentioned.

In exactly 4% of all fresh cycles with supernumerous PN stage oocytes, they were not cryopreserved, but discarded, mainly because of financial reasons of the couple. Therefore, the mean PR and LBR out of one fresh cycle are slightly underestimated as well.

An important strength of this survey is consistency in that the centre's treatment policy remained nearly unchanged throughout the entire survey with the same team of reproductive specialists and the same responsible embryologists. Treatment methods did not change substantially either in the entire survey except for a continuous increase in the proportion of ICSI cycles. Over time, antagonists were introduced, laser-assisted hatching was offered and recently polar body biopsy, spindle view and zona imaging has been added to the repertoire of methods. Quarterly, cross-sectional statistics showed a slight increase in clinical PRs per transfer over the years, which was not tested for significance and was not attributed to new methods or drugs yet.

For all the reasons above, we assume that the inherited methodological overestimation bias in our study is relatively small but it cannot

be assessed exactly. Possibly, the slightly optimistic success rates best reflect counselling situations: the couple's future chances of live birth is based on the rates of those who continued in the past.

Recently, single centre CLBRs were published by Malizia *et al.* from the Waltham-IVF centre, Boston/USA (Malizia *et al.*, 2009). Compared with their optimistic assumptions, our CLBR after six cycles is the same: 72%. This is very interesting, because of completely different treatment strategies in both IVF centres. According to the German Embryo Protection Law, it is not allowed to culture more PN stage oocytes than the embryos which are to be transferred later in that cycle. Therefore, embryo selection as performed by this and many other foreign centres probably with prolonged cell-culture is not possible here. We strictly cryopreserved all supernumerous PN stage oocytes for later cryo-cycles. Embryos were cryopreserved only in very rare cases for emergency reasons. Obviously, completely different treatment strategies may lead to the same results: a CLBR of 72% after six treatment cycles. Just for patients over 40 years of age, we achieved a lower CLBR presumably because of study cohort differences, as there was a high proportion of women over 40 entering the IVF programme but then turning to oocyte donation early in Waltham.

The congruent CPR after ART and CPR in natural cycles (Gnoth *et al.*, 2003) (Fig. 4) are in line with recently published simulation models (Stanford *et al.*, 2010) and provide reliable experimental evidence as support, because of the same methodological approaches in both of our studies. This strongly suggests that ART can reach natural fertility rates but cannot exceed them.

Most of the patients in this study did not undergo many treatment cycles (mean 2.7; median 3 with a CLBR of ~50%)—even those with reasonable good prognosis for final success—because they probably could not afford the emotional or financial cost independent of the reimbursement. However, from the medical point of view, there is no reason for generally restricting the number of cycles e.g. to three, as done in Germany.

It was our intention to calculate final success rates for live birth to facilitate counselling of couples with infertility problems and to highlight the potential of ART even under rigorous restrictions by law. In this respect, it is important to emphasize again that reproductive medicine can be successful for most couples if they continue treatment.

Authors' roles

C.G. played a role in study design, running of the cycles, statistical analysis and writing the manuscript. B.M. took part in raw data collection and quality checking. T.S. was involved in raw data preparation, statistical analysis and proofreading. K.F. and J.T. were involved in study design, running the cycles and proofreading. E.G. took part in statistical mentoring, performing the final statistical analysis and writing the manuscript.

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Long-term Economic Benefits Attributed to IVF-conceived Children: A Lifetime Tax Calculation

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Objective: To evaluate whether lifetime future net tax revenues from an in vitro fertilization (IVF)-conceived child are substantial enough to warrant public subsidy relative to the mean IVF treatment costs required to obtain 1 live birth.

Study Design: Mathematical generational accounting model.

Methods: The model estimates direct financial interactions between the IVF-conceived child and the government during the child's projected lifetime. In the model, we accrue IVF costs required to conceive the child to the government, and then we estimate future net tax revenue to the federal and state governments from this individual, offset by direct financial transfers from the government (eg, child allowances, education, Medicare, and Social Security). We discount lifetime costs and gross tax payments at Treasury Department rates to establish the present value of investing in IVF. We applied US Congressional Budget Office projected changes in tax rates over the course of the model.

Results: An IVF-conceived child, average in every respect (eg, future earnings, healthcare consumption, and life expectancy), represents a net positive return to the government. Based on an average employed individual born in 2005, the projected net lifetime tax contribution is US $606,200. Taking into consideration IVF costs and all direct financial interactions, the net present value is US $155,870.

Conclusions: Lifetime net taxes paid from a child relative to the child's initial IVF investment represent a 700% net return to the government in discounted US dollars from fully employed individuals. This suggests that removing barriers to IVF would have positive tax benefits for the government, notwithstanding its beneficial effect on overall economic growth.

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For author information and disclosures, see end of text.

The past decade has witnessed a dramatic increase in the demand for assisted reproductive technology (ART) such as in vitro fertilization (IVF).[1,2] Increasing demand for ART is related to increased infertility in modern populations, which may be attributed to couples' delaying efforts to get pregnant until they are older and less fertile, increasing obesity in the United States, sexually transmitted diseases, low sperm count, and the stress of modern daily life.[3-6] In countries where generous funding for fertility treatments is available, ART accounts for 4% to 6% of national births every year.[1,2] When the proportion of children born every year from ART is couched within the population aging debate faced by many countries and the economic consequences this creates, policy analysts have started to investigate the role that fertility treatments could play in solving severe demographic issues associated with an aging population and the resulting insolvency of Social Security.[7-10]

Despite increasing demand for ART treatments, financial constraints are causing many national health providers and private insurers to limit access, and most couples must pay out-of-pocket for these services.[11] For couples unable to afford ART, the options are limited; consequently, many withdraw from treatment or choose not to pursue treatment because of costs.[12-14] Furthermore, the established relationship between affordability and utilization of services would suggest that many couples are unable to receive treatment, with the likely consequence of fewer children being born every year.[15]

The economic and health consequences of financial barriers to medical treatment are frequent topics of interest for health economists and policy analysts.[16-18] With respect to ART services, treatment barriers create an additional issue, as successful use of this technology leads to the creation of human life that would not have been born were the technology not available. The immediate benefit of ART success is to fulfill a couple's desired family size, which leads to quality-of-life improvements. However, what is less well characterized is the economic effect that IVF-conceived children will make once they become economically active adults.

To assess the economic consequences of IVF-conceived children, we developed a mathematical model that explores the lifetime financial transactions between a single individual conceived by IVF and the government under a theoretical assumption that the government paid standard fees for that IVF treatment.

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To evaluate whether investing in IVF represents sound fiscal policy for the government, we theoretically assigned IVF costs to the US government in the model. The methods applied herein are based on generational accounting (GA) methods developed by Kotlikoff et al[19,20] and Sturrock[21] and used by treasury departments, including the US Congressional Budget Office, to assess whether current fiscal policies will adversely affect future generations (ie, shift costs to future generations). In this article, we describe a GA model to assess future net tax revenues derived from a hypothetical IVF-conceived child to establish whether policies that increase access to IVF treatment would generate long-term economic benefits. It is envisaged that this analysis can inform government and nongovernment agencies with a vested interest in future population age structures. Such an analysis is urgently needed in view of declining birthrates, increasing numbers of aging retired persons, and the predicted insolvency of Social Security.

METHODS

Based on the US GA model developed by Kotlikoff,[19] a basic mathematical model was developed taking the perspective of the US government to estimate the discounted lifetime net tax contribution derived from a single individual. The model describes the financial position between the child and the government during the child's projected lifetime. For comparison, the model estimates lifetime net tax contributions for a naturally conceived versus an IVF-conceived child, where the major cost difference is assumed to be IVF treatment costs and any extra costs related to the child's care. In this model, we assign IVF costs to the government to assess the merits of funding such a policy. All direct government expenditures and tax contributions were discounted using Treasury Department rates.

Conceptually, there are 3 broad stages in lifetime financial interactions, each with differing components of the financial exchange, as follows: (1) early life, when the government primarily contributes resources to individuals through child tax credits, healthcare, and educational expenses; (2) employment, when individuals begin returning resources to the government through federal, state, and local taxes; and (3) retirement, when the government expends additional resources on Social Security and old-age programs.

Two general models are estimated. The first model assumes that individuals graduate from high school and then follow the average higher education, employment, and unemployment trends (hereafter referred to as average employment). The second model assumes full-time education from ages 6 to 19 years, with full-time employment from age 20 years until retirement at age 65 years (hereafter referred to as full employment). The models assume that successful IVF treatment results in a single live birth (with a mean life expectancy of 79 years) and that the child is identical to a naturally conceived individual.[22,23] In all scenarios, the model includes hospital delivery costs, taking into consideration additional costs frequently accrued to IVF-conceived children attributed to low birth weight.[24,25]

Age-graded government expenses and tax contributions were assessed across a hypothetical individual's lifetime to derive discounted lifetime net tax contributions using net present value (NPV) calculations and undiscounted lifetime net tax contributions. Following similar GA calculations used to assess US immigration policy, we consider various costs generated and taxes paid.[26,27]

Expenditures

Two broad categories of federal and state government expenditures are considered, congestible goods and transfer programs.[28] Congestible goods have nonzero marginal costs and include expenditures such as roads, fire and police protection, airports, and sewers. Transfer programs include all government expenditures that can be assigned to specific individuals such as Social Security, Supplemental Security Income, Medicare, Medicaid, Aid to Families With Dependent Children, public assistance, food stamps, unemployment benefits, disability benefits, subsidized school lunch programs, and public education at all levels. There is also a child tax credit associated with individuals until age 17 years.

Revenues

Revenues collected by the government include federal and state income tax (the national mean rate in this model), corporate tax, excise tax, Federal Insurance Contributions Act tax, Supplemental Medical Insurance contributions, federal retirement tax, property tax, and sales tax. To calculate the accounting models, age profiles of each expenditure and revenue component were identified from existing data sources. Because the models describe financial interactions across an individual's lifetime, these age profiles are adjusted to account for depreciation of money over time through the application of a discount rate. The US Congressional Budget Office 2007 projections were used as the basis for estimates of inflation, individual earnings increases, tax rate increases, increases in Supplemental Medical Insurance revenue, and Medicare and Medicaid expenditures.[29] Increases in expenditures on schooling are based on historical rates of increase.[30] Beyond the period for which these long-term forecasts are available, we assume that particular components grow to keep pace with demographic and productivity growth. A discount rate of 4%

Table 1. Discounted Lifetime Net Tax Contributions and Breakeven Ages Based on Average Employment and on Full Employment[a]

Method of Conception and Age of Mother, y	Age-adjusted Cost per Live Birth Using IVF, US $[b]	Average Employment		Full Employment (ages 20-64 y)	
		Breakeven Age, y	Discounted Lifetime Net Tax Contribution, US $	Breakeven Age, y	Discounted Lifetime Net Tax Contribution, US $
Natural, all ages	Not applicable	37	190,515	34	292,285
IVF					
<35	27,373	40	160,540	36	266,310
35-37	32,041	40	155,870	37	257,640
38-40	43,509	41	144,405	38	246,175
41-42	158,225	44	116,240	40	218,007

IVF indicates in vitro fertilization.
[a]The average employment model assumes that individuals graduate from high school and then follow the average higher education, employment, and unemployment trends. The full employment model assumes full-time education from ages 6 to 19 years, with full-time employment from age 20 years until retirement at age 65 years. The breakeven point is the age at which the financial position between an individual and the state becomes positive in favor of the state.
[b]Derived from the mean IVF cost per cycle divided by the age-adjusted probability of live birth.

was applied to lifetime tax revenue and transfer payments. The discount rate was compounded continuously.

IVF Treatment Costs. The mean IVF treatment costs to produce a live birth are considered herein as a further expense unique to an individual conceived using IVF. The national mean cost per IVF treatment cycle in 2003 is US $12,400.[31] Cost per live birth is calculated as the mean cost per cycle divided by the age-adjusted probability of a live birth, where the treatment efficacy is known to vary primarily by the age of the mother (ie, lower success rates with older age) and by other factors.[31-34] The age-adjusted cost per live birth is given in Table 1.

Data Sources. Analyses are based primarily on 2 waves of the annual March Current Population Survey.[35] The Current Population Survey is a monthly survey of about 50,000 households conducted by the Bureau of the Census for the Bureau of Labor Statistics and is the primary source of information on the labor force characteristics of the US population. The sample is representative of the civilian noninstitutional population. Estimated sales tax revenue is obtained from the Consumer Expenditure Survey, also conducted by the Bureau of Labor Statistics. Government expenditures on congestible goods are obtained from the US Statistical Abstract, following prior work.[26] Educational expenditures are taken from the *Digest of Education Statistics*.[30]

Calculation of NPV. Given the baseline assumptions for the age profiles of expenditures and revenues, the net financial exchange of an individual at any age is derived in the accounting models simply as the discounted sum of all the economic components up to that age. Specifically, lifetime individual NPV is the discounted sum of all revenues to the government at all ages minus expenditures at all ages as follows:

$$\mathrm{NPV} = \sum_{t=0}^{T} \left(\frac{R_t - E_t}{(1+r)^t} \right) - K_o$$

where R_t indicates the sum of all revenues accruing from the individual at age t; E_t, the sum of all expenditures on the individual at age t; r, the rate of discount; T, the life expectancy at birth; and K_o, the initial direct costs of IVF in the base period. For individuals conceived by IVF, the direct cost of achieving a live birth is included in the expenditures as consisting of the cost of IVF treatment and the mean additional hospital costs associated with low birth weight attributed to IVF infants.[24,25]

RESULTS

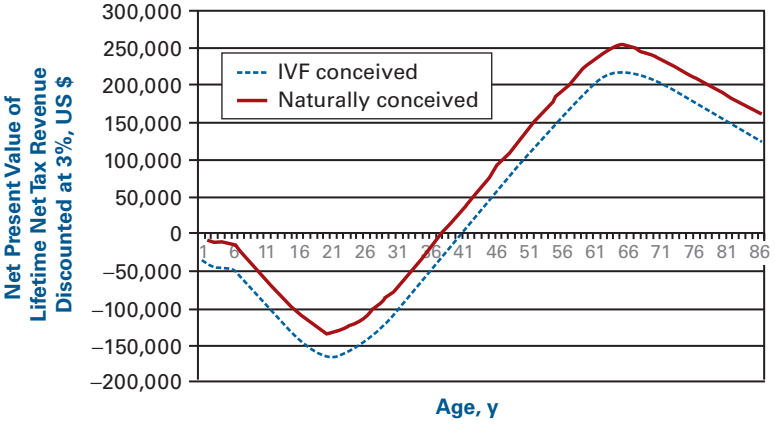
The projected lifetime net tax contribution trajectories for an average employment naturally conceived child and for an IVF-conceived child are shown in the Figure. There is a net increase in government revenue by age 37 years for naturally conceived children versus by age 40 years for an IVF-conceived child. The additional costs attributed to conceiving an IVF child are shown as an increased cost at birth. In all simulations, the financial position between the child and the government changes as the child enters the workforce and again at the point of leaving full-time employment, with a net profit to the taxing authority. In vitro fertilization coverage represents a minor component of the net cost for creation of new taxpayers.

The projected combined returns to the federal and state governments in lifetime net tax contributions from an IVF-

conceived child and from a naturally conceived child are given in Table 1. For a naturally conceived child, the mean discounted lifetime tax contribution amounts to US $292,285 for full employment; the projected net undiscounted lifetime tax contribution for a full employment individual born in 2005 is US $1,103,000 (Table 2). For IVF-conceived children, the net undiscounted lifetime tax contribution is similar to that for naturally conceived children even after IVF investment costs are factored into the analysis.

The age at which the financial position between a naturally conceived child and an IVF-conceived child changes with respect to the taxing authority is given in Table 1. We have labeled this as the breakeven age to highlight the age at which the government has recouped all direct financial transfers (discounted) in the early years to achieve working-age participation. Assuming full employment, the breakeven ages with net profit to the government are 34 years for naturally conceived children and 36 to 38 years for IVF children conceived to mothers younger than 41 years. The difference in the breakeven age for IVF-conceived children compared with naturally conceived children differs by 2 to 5 years depending on variations in increasing IVF investment costs attributed to older mothers.[12,32]

Figure. Lifetime Net Tax Contribution Trajectories Discounted at 3% Between the State and an Average Employment Naturally Conceived Individual vs In Vitro Fertilization (IVF)-conceived Individual



The average employment model assumes that individuals graduate from high school and then follow the average higher education, employment, and unemployment trends.

DISCUSSION

The approach used in this model assesses medical costs attributed to conceiving an IVF child as an investment required to achieve a live birth with consequent long-term economic returns. It is likely that the conceptual model described herein is of most relevance to countries with nationally funded health services where the taxing authority and the health service are 2 components of the overall government. Under these circumstances, the national health service pays for or provides IVF treatment, and the tax authority will collect tax revenue from the IVF-conceived child when he or she reaches working age.

There are obvious flaws in applying this methodological approach in the United States, where there is a clear separation between the payer (eg, infertile couples and private insurers) and the beneficiary of future tax payments from IVF children (ie, Internal Revenue Service). Despite these shortcomings, we have positioned IVF medical costs as accruing to the government to inform government health policy in this area and to stimulate debate.

The analysis described herein has taken the perspective of the taxing authority, where net tax contributions (ie, gross tax contributions minus direct government transfers and congestibles) are the sole economic variable considered. Because our approach has taken the perspective of the government, there are limitations to our model, which does not consider the broader economic benefits that individuals contribute to a country's economic growth. Consequently, the analysis presented herein is an underestimate of the true economic contributions that an individual has on the economy as a whole because we have not considered the gross domestic product contribution brought about by the increased demand for goods and services generated by this individual.

The methods applied in our work are based on GA, a method frequently used by government treasury departments as an alternative to the more commonly applied deficit accounting, which only considers current year accounts. Using GA helps bridge the gap between what has been promised in the future (eg, Medicare and Social Security payments) in relation to future revenue generated predominantly through taxation. From the government revenue–generating perspective, the number of taxpayers and the mean tax contribution per individual are relevant, as well as the importance of current birthrates, which will directly influence the number of taxpayers in the future and, depending on future spending promises, the tax rates paid by future generations.[19,20] Considering the effect that birthrates have on future fiscal imbalances between current and future generations, we believe that our approach is acceptable for evaluating IVF technology because of its established ability to significantly affect national birthrates.[1,2,9]

Several simplifying assumptions were made during the course of the work that can be challenged. In particular, cli-

Table 2. Undiscounted Lifetime Gross Tax Contributions for Average Employment and for Full Employment[a]

Method of Conception	Undiscounted Lifetime Gross Tax Contribution, US $	
	Average Employment	Full Employment (ages 20-64 y)
Natural	633,600	1,103,000
In vitro fertilization	606,200	1,076,000

[a]The average employment model assumes that individuals graduate from high school and then follow the average higher education, employment, and unemployment trends. The full employment model assumes full-time education from ages 6 to 19 years, with full-time employment from age 20 years until retirement at age 65 years.

nicians may criticize the assumption that IVF children are identical to naturally conceived children. Although we have adjusted initial costs to compensate for lower birth weight, we do not treat the subsequent education and employment trajectories of these individuals differently from those of naturally conceived individuals. Furthermore, additional medical costs frequently arise as a result of multiple pregnancies and premature birth. However, it is likely that much of this increased risk can be mitigated by a reduction in embryos transferred and multiple births when the burden of success is shared by a third-party payer.[36,37] For example, following the Belgian example, the government agreed to fund up to 6 IVF cycles for every infertile couple, while simultaneously regulating the number of embryos transferred in each cycle.[38] Support of IVF allows the funding authority to limit the number of embryos transferred and to obviate any of the extra risks associated with patient-funded IVF. The net result of this policy change for Belgium was a cost saving attributed to a reduction in multiple pregnancies.

In our model, we assumed that a child born from IVF would achieve average lifetime income earnings, which may be an oversimplification of future earnings based on current IVF utilization. What is known at present is that those seeking treatment for infertility and undergoing IVF are not representative of the US population because racial/ethnic and economic factors define treatment-seeking behavior.[39,40] In the current environment, which is dependent on out-of-pocket payments, those accessing and using IVF services are overrepresented by individuals with higher socioeconomic backgrounds and with the financial means to pay for IVF.[41,42] As a consequence of an increased proportion of higher socioeconomic families accessing infertility treatments, IVF children are more likely to achieve higher socioeconomic status in their lifetimes.[43] This is further supported by research suggesting that IVF-conceived children obtain higher academic scores compared with naturally conceived children.[44] This would suggest that in the present IVF access environment children conceived through IVF are likely to make future tax contributions above the mean figures described in our results.

The disparity in IVF utilization based on socioeconomic status raises questions regarding what could happen if barriers to IVF were lowered, allowing for a broader range of socioeconomic groups to access treatment. In our model, the calculations are based on the statistical mean for lifetime income, which is based on income from all socioeconomic groups, low and high. On this basis, if an increased proportion of families of lower socioeconomic status accessed IVF, this would not affect the conclusions of our work because the lower earning capacity has already been accounted for in the average lifetime financial calculations.

One of the underlying aims of this research is to highlight that economic barriers limit access to infertility treatments and that costs attributed to infertility are dependent on the perspective and the period during which costs and benefits are observed. Based on our analysis, we suggest that discounted future net tax contributions derived from IVF-conceived children could be used to justify government-funded IVF programs. Our work also highlights that there is a cost associated with not treating infertility in the form of lost tax revenue, which to the best of our knowledge has never been quantified. This study is not the first application of GA principles to address important policy questions. Previous explorations using GA models have evaluated the effect of US immigration policies on government fiscal imbalances.[45] Although it is tempting to compare our findings with those from immigration policy, we believe that this is not feasible because immigration and fertility policies are shaped by different

Take-away Points

- Financial and legislative barriers to fertility treatments prevent many couples from achieving their desired family size, resulting in fewer children being born.
- Taking the perspective of the government, fewer children born in current generations represents a loss in future tax revenue that would arise from these children after they enter the workforce.
- The costs attributed to in vitro fertilization (IVF) treatment are insignificant in light of the lifetime net tax contributions of IVF-conceived children.
- Minimizing barriers to fertility treatments is likely to have long-term economic benefits that need to be considered when making IVF funding decisions.

social and political issues, of which economics is only one of many components.

Based on projected tax revenue to the government, our analysis suggests that removal of financial barriers to IVF treatment, which may lead to increases in birthrates, could help to achieve broader demographic and economic policy goals. We acknowledge that this proposition may be provocative, but it is not without precedent. Within the United States, under the current system of sporadic IVF insurance coverage and various state mandates, a demographic effect has already been observed. In a recent study by Schmidt,[46] it was shown that in those states with legislated mandates there is an increased birthrate for women older than 35 years compared with states without mandates. Going a step further, in countries such as South Korea and Israel facing demographic crisis and regional instability, respectively, IVF funding policy is viewed as a pronatalist tool for influencing population growth.[47,48]

CONCLUSIONS

The principal aim of this research was to assess the net tax contributions of an IVF-conceived child, with the intention of informing future policy directives that may influence access to fertility treatments. In reality, there are many good reasons to justify improved IVF access, including medical need, equity, and respect for an individual's human right to a family, and reproductive rights. However, in many countries, including the United States, access to fertility care is limited, and many couples are unable to afford treatment. Based on the results shown herein, one could easily argue on the basis of economics that financial or legislative barriers to IVF treatments for infertile couples should be removed.

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