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Original Article

Assisted reproductive techniques in Latin America: The Latin American Registry, 2013

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ABSTRACT

Multinational data on assisted reproduction techniques undertaken in 2013 were collected from 158 institutions in 15 Latin American countries. Individualized cycle-based data included 57,456 initiated cycles. Treatments included autologous IVF and intracytoplasmic sperm injection (ICSI), frozen embryo transfers, oocyte donations. In autologous reproduction, 29.22% of women were younger than 35 years, 40.1% were 35–39 years and 30.6% were 40 years or older. Overall delivery rate per oocyte retrieval was 20.6% for ICSI and 25.4% for IVF. Multiple births included 20.7% for twins and 1.1% for triplets and over. In oocyte donations, twins reached 30% and triplets 1.4%. In singletons, pre-term births were 7.5%: 36.58% in twins and 65.52% in triplets. The relative risk for prematurity was 4.9 (95% CI 4.5 to 5.3) in twins and 8.7 (95% CI 7.6 to 10.0) in triplets and above. Perinatal mortality was 29.4 per 1000 in singletons, 39.9 per 1000 in twins and 71.6 per 1000 in high order multiples. Elective single embryo transfer represented only 2% of cycles, with delivery rate of 39.1% in women aged 34 years or less. Given the effect of multiple births and prematurity, it is mandatory to reduce the number of embryos transferred in the region.

Keywords: Assisted reproductive technology, Epidemiology, IVF/ICSI, Latin America, Perinatal outcome, Registry.

INTRODUCTION

The Latin American Registry of Assisted Reproduction (RLA) established in 1990 was the first multinational and regional registry collecting data on Assisted Reproduction Technologies (ART). For the first twenty years, summary data was obtained electronically via web page from every participating institution, belonging to twelve countries in the region. Since 2010, new software has been developed and implemented, which allows for the collection of cycle-based data from every treatment cycle. Data collection is therefore recorded individually, starting with controlled ovarian stimulation (COS) until birth or miscarriage.

Today, individualised data is obtained from ART treatments done in 158 institutions in 15 countries, covering more than 80% of ART cycles performed in the region. This report corresponds to the 25th edition of RLA. Previous reports, from 1990 to 1998, are available as printed copies, and those from 1999 to 2009 as PDF files, which can be downloaded from the web page of the Latin American Network of Assisted Reproduction (REDLARA) at: www.redlara.com. Today, reports are published simultaneously in RBM Online, and in the JBRA Assisted Reproduction, the official journal of REDLARA.

The main RLA objectives have been to: a) disseminate information on ART procedures performed in Latin America, b) monitor outcomes, as well as trends in safety and efficacy among centres and countries, c) empower infertile couples in their capacity to evaluate risks and benefits when requesting ART treatments, and d) develop a robust database for epidemiological studies.

In this report we are communicating information on availability, effectiveness, and perinatal outcomes of ART treatment initiated between 1st January 2013 and 31st December 2013, and babies born up to September 2014. It is also our aim to describe regional trends on how ART is practiced in the region, including the number of embryos transferred, multiple births and its impact on pre-term births and perinatal mortality.

MATERIALS AND METHODS

ART data was collected from 158 centres in 15 countries (supplementary table I), covering in vitro fertilisation (IVF), intra-cytoplasmic sperm injection (ICSI), oocyte donation (OD) (both fresh and frozen), frozen embryo transfer (FET), and preimplantation genetic diagnosis and screening, registered together as PGD. In addition to ART, data on intrauterine insemination using husband (IUI-H) and donor (IUI-D) semen was also included. This report includes treatments started between 1st January 2013 and 31st December 2013, and babies born up to September 2014. As part of the accreditation programme, all participating institutions agreed to have their data registered and published by the Latin American Registry of ART. Given it is a multinational registry, no other consent form was requested.

As was the case in the two previous years, data was collected using an individualised cycle based software. The method of collecting and reporting data is also similar to that used in the two previous years, making all tables comparable (Zegers-Hochschild *et al*., 2015).

Each centre entered its data directly in an online RLA web-based system. Built-in algorithms for internal consistency; any error or discrepancy, not identified by the software, was discussed and clarified by RLA´s central office. Given that the RLA is a voluntary multinational registry, centres are not obliged to upload each case immediately as the cycle is initiated. Therefore, some cases are sent to the RLA upon recruitment while others are included retrospectively.

Since the new cycle based registry has only been available for two years, the calculation of cumulative delivery rates could not be performed directly. Therefore, we made estimates by adding deliveries derived from fresh and frozen transfers in every age group.

When appropriate, the chi-squared test was used to analyse independence of categorical variables. A *P*-value less than 0.05 was considered statistically significant. Relative risks are presented with the corresponding 95% confidence interval. All terminologies used in this

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registry correspond to the glossary published in 2009 by the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) and the World Health Organization (WHO) (Zegers-Hochschild *et al*., 2009). We registered cases of severe ovarian hyperstimulation syndrome, where hospitalization or medical interventions were required.

RESULTS

Participating centres

One hundred and fifty-eight centres in fifteen countries reported ART procedures performed during 2013. They included: 36,494 initiated autologous fresh IVF/ICSI cycles; 10,912 FET; 8,434 oocytes donation (OD) (heterologous) cycles of which, 5,927 were fresh transfers and 2,507 FET; and 1,616 initiated cycles for fertility preservation (FP).

Access to ART procedures, defined as the sum of IVF/ICSI initiated cycles, FET and OD cycles, per million women aged 15-45 years, reached a mean of 425, bearing a large variation between countries (Table 1).

Size of participating institutions

Excluding fertility preservation, a total of 55,840 initiated cycles was reported. The number of initiated cycles by institution ranged from 23 to 2,765, where 21% of reporting centres performed ≤ 100 cycles; 35% between 100 and 250 cycles; 21% between 251 and 500 cycles; 17% between 500 and 1,000 cycles; and 6% ≥ 1,000 cycles.

ART procedure and access

As in previous years, the majority of initiated cycles were reported by Brazil, representing 44% of all cycles, followed by Argentina with 23% and Mexico 13% (Table 1). In addition the majority of reporting clinics are located in these countries (35%, 17% and 18%, respectively).

Out of 36,494 initiated autologous cycles, which represents a 14.56% increase with respect to 2012, 3.85% were cancelled before follicular aspiration. Therefore a total of 35,089 OPU were performed; and in 96.25% of them, at least one mature oocyte was recovered. The preferred technique for insemination was ICSI (84.7%). In 25,590 cases, at least one embryo was transferred.

The three main reasons to explain the 7,710 cases where in spite of having mature oocytes, no embryos were transferred, included: 5,168 cases of total embryo freezing; 1,326 cases of absence of embryos for transfer; and 1,216 cases of complete fertilization failure. Information on the 472 remaining cases includes a mixture of abnormal oocytes and absence of normal embryos for transfer.

One hundred and forty-five centres registered 10,912 FET cycles representing 8.32% increase over the previous year and 144 centres reported 5,927 fresh OD cycles representing 9.84% increase over 2012. In 63% of these cycles, oocytes were donated from exclusive donors, i.e., women that underwent controlled ovarian hyperstimulation (COS) and oocyte pick up with the only purpose of donating their oocytes.

Pregnancies and deliveries

Table 2 shows the clinical pregnancy rate (CPR) and delivery rate (DR) per oocyte pick-up (OPU) in fresh autologous cycles. Both CPR and DR per OPU were higher in IVF cycles than in ICSI cycles (31.45% and 25.75%, $P<0.001$; 25.39%, and 20.61%, $P<0.001$, respectively). In both instances, the differences reached statistical significance; however, the lack of random allocation of subjects in each treatment category must be considered carefully before reaching any conclusion.

In OD cycles, the CPR and DR per ET were 47.25% and 39.05%, respectively (Table 3). Similar trends were observed in the case of FET cycles: both CPR and DR were higher when embryos were obtained from donated oocytes (Table 3: 38.17% and 33.58%; 31.09% and 26.65%, respectively). However, no differences were found when DR of FET with donated oocytes was compared with autologous FET in a subgroup of women aged less than 35 years

Table 1. ART procedures and access in 2013.

Country	Number of clinics		Assisted reproductive techniques						Total (****)	Access (*****)
		IVF/ICSI (*)	IVF (**)	ICSI (**)	FET	OD	OD (FET)	FP (***)		
Argentina	27	7769	749	6,255	2,481	1,655	815	396	12,720	1,368
Bolivia	2	280	195	71	17	46	3	840	346	141
Brazil	56	17,042	1,060	14,974	5,833	1,159	579	0	24,613	512
Chile	8	1,646	130	1,405	543	170	84	61	2,443	634
Colombia	9	967	288	613	182	209	95	5	1,453	136
Ecuador	6	654	206	391	159	208	72	145	1,093	297
Guatemala	1	99	52	47	16	20	1	9	136	39
Mexico	28	4,476	1,494	2,648	929	1,421	378	31	7,204	251
Nicaragua	1	100	29	67	0	10	0	0	110	72
Panama	2	408	0	362	83	56	17	5	564	710
Paraguay	1	37	9	22	2	0	0	2	39	24
Peru	6	1,404	470	837	390	587	306	98	2,687	367
Dominican R.	1	49	18	30	6	36	2	0	93	40
Uruguay	2	340	35	239	52	56	19	5	467	652
Venezuela	8	1,223	438	638	219	294	136	19	1,872	274
Total	158	36,494	5,173	28,599	10,912	5,927	2,507	1,616	55,840	425

(*) Initiated cycles; (**) oocyte pick ups with ≥1 mature oocyte; (***) initiated fertility preservation cycles; (****) excludes FP; (*****) number of cycles/million of women 15-45 years

Table 2. Clinical pregnancy rate and delivery rate in fresh autologous IVF/ICSI cycles in 2013.			
ART procedure	Oocyte pick up (OPU)	Clinical pregnancy rate per OPU	Delivery rate per OPU
ICSI	28,599	25.75%	20.61%
IVF	5,173	31.45%	25.39%

OPU= oocyte pick up with at least one mature oocyte

Table 3. Clinical pregnancy rate and delivery rate in OD, FET, FET (OD) cycles in 2013.			
ART procedure	Embryo transfer (ET)	Clinical pregnancy rate per ET	Delivery rate per ET
OD	5,927	47.25%	39.05%
FET	10,912	33.58%	26.65%
OD (FET)	2,507	38.17%	31.09%

OD= oocyte donation
FET= frozen/thawed embryo transfer

(33.19% and 31.50% respectively; RR 1.05, CI95% 0.87-1.27). Delivery rate in 3,640 embryo donors was 41.31% compared with 35.55% in 2,287 embryo transfers among shared donors, i.e. women undergoing assisted reproduction and at the same time donated part of the oocytes recovered. The differences in DR in these two conditions were highly significant (*P*= 0.015) in favour of using exclusive donors, OR 1.28 (CI 95% 1.14.- 1.42). It is not possible from the data collected in the registry, to gather information on the different criteria used to decide which and how many oocytes were donated for third party reproduction.

Age of women undergoing ART procedures and delivery rate

The mean age of women undergoing autologous IVF/ICSI was 36.38 years (SD 4.55). The distribution of initiated IVF/ICSI cycles according to the woman's age is shown in Figure 1. The majority of cycles was performed in women aged 35-39 years (40.13%). Furthermore, 30.65% of women undergoing IVF/ICSI were ≥ 40 years. In the case of fresh OD cycles, the mean age of woman reached 41.49 years (SD=5.01); of which 50.76% were 43 years and older.

As expected, the delivery rate per embryo transfer in autologous ART was significantly influenced by the age of the female partner. The effect of age on the DR/ET in fresh cycles is shown in Figures 2 and 3. DR per ET decreased with age, from 38.37% in the younger population to 9.12% in the oldest group (*P*<0.001). In the case of OD, the age of oocyte recipients did not systematically affect DR per ET, as seen in figure 3. DR/ET reached 41.42% in women aged ≤34 years (n=478 ET); 42.26% in women aged 35 to 39 (n=1,053 ET); 40.17% in women aged 40 to 42 (n=1,419 ET); and 37.03% in women aged ≥43 years (n=3,027 ET) (*P*=0.009).

Number of embryos transferred and multiple births

Fresh autologous IVF/ICSI

Table 4 shows the outcome of 25,590 fresh autologous IVF/ICSI ET with a mean number of embryos transferred of 2.1 (SD= 0.71), 2.2 when cleaving-embryos were transferred, and 2.0 when blastocyst-stage embryos were transferred. In the majority of cases (57.2%), two embryos were transferred; while the transfer of 3 and ≥4 embryos represented 23.4% and 2.5% of ET respectively. The transfer of more than two embryos was not associated

Figure 1. Age distribution of women initiating autologous or heterologous IVF/ICSI cycles, 2013.

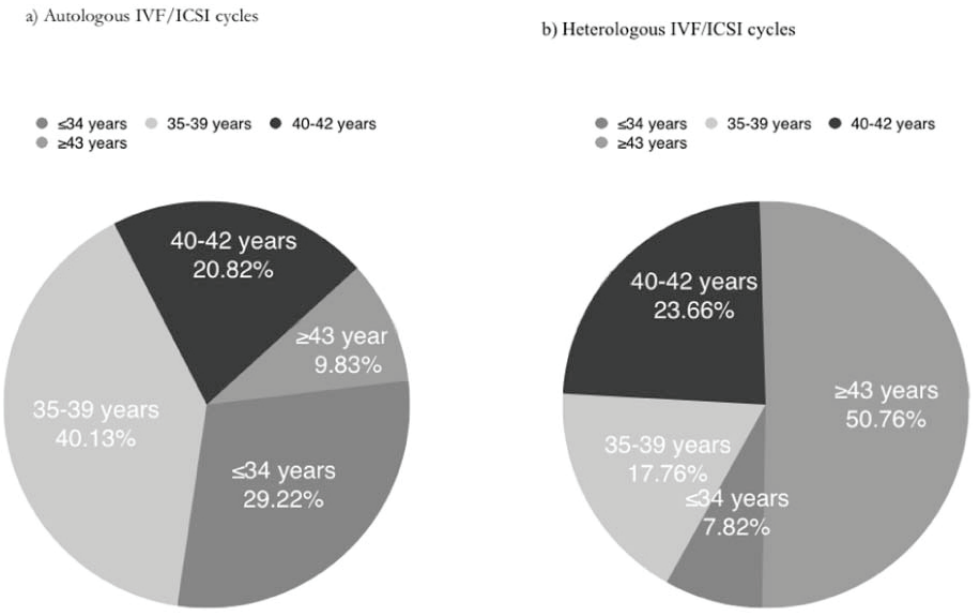


Table 4. Clinical pregnancy rate, delivery rate and gestational order according to the number of embryos transferred in fresh autologous IVF/ICSI cycles in 2013.

Number of transferred embryos	Total ET		CPR/ET	Deliveries				
	Number	%		Total (number)	DR/ET	Singleton (%)	Twin (%)	≥Triplets (%)
1	4,323	16.9	18.07%	583	13.49%	97.60	2.40	0.00
2	14,648	57.2	39.15%	4,652	31.76%	76.74	22.66	0.60
3	5,978	23.4	39.28%	1,891	31.63%	75.73	21.95	2.33
≥4	641	2.5	35.26%	164	25.59%	78.66	16.46	4.88
Total	25,590	100	35.50%	7,290	28.49%	78.19	20.71	1.09

ET= embryo transfers
CPR= clinical pregnancy rate
DR= delivery rate

Table 5. Clinical pregnancy rate, delivery rate and gestational order according to the number of embryos transferred in fresh heterologous IVF/ICSI cycles in 2013.

Number of transferred embryos	Total ET		CPR/ET	Deliveries				
	number	%		Total (number)	DR/ET	Singleton (%)	Twin (%)	≥Triplets (%)
1	416	7.02	40.87%	136	32.69%	97.06	2.94	0.00
2	3,901	65.82	47.73%	1,522	39.02%	68.73	30.75	0.53
3	1,511	25.49	48.71%	632	41.83%	62.34	34.18	3.48
≥4	99	1.67	36.36%	30	30.30%	60.00	30.00	10.00
Total	5,927	100	47.27%	2,320	39.14%	68.53	30.04	1.43

ET= embryo transfers
CPR= clinical pregnancy rate
DR= delivery rate

Table 6. Clinical pregnancy rate, delivery rate and gestational order according to the number of embryos transferred in autologous frozen/thawed embryo transfers in 2013.

Number of transferred embryos	Total ET		CPR/ET	Deliveries				
	number	%		Total (number)	DR/ET	Singleton (%)	Twin (%)	≥Triplets (%)
1	2,168	19.87	26.52%	443	20.43%	97.29	2.71	0.00
2	6,748	61.84	35.11%	1,883	27.90%	78.65	20.98	0.37
3	1,867	17.11	35.57%	542	29.03%	72.69	2.43	3.87
≥4	129	1.19	37.98%	35	27.13%	71.43	28.57	0.00
Total	10,912	100	33.51%	2,903	26.60%	80.30	18.74	0.96

ET= embryo transfers
CPR= clinical pregnancy rate
DR= delivery rate

Table 7. Clinical pregnancy rate, delivery rate and gestational order according to the number of embryos transferred in heterologous frozen/thawed embryo transfers in 2013.

Number of transferred embryos	Total ET		CPR/ET	Deliveries				
	Number	%		Total (number)	DR/ET	Singleton (%)	Twin (%)	≥Triplets (%)
1	388	15.48	31.20%	87	22.42%	96.55	3.45	0.00
2	1,544	61.59	37.69%	477	30.89%	75.45	24.53	0.00
3	541	21.58	44.01%	203	37.52%	70.44	26.50	2.96
≥4	34	1.36	47.06%	11	32.35%	72.73	27.27	0.00
Total	2,507	100	38.17%	778	31.03%	76.48	22.75	0.77

ET= embryo transfers
CPR= clinical pregnancy rate
DR= delivery rate

Table 8. Perinatal mortality according to gestational order in 2013.

ART procedure	Singleton			Twin			≥Triplets		
	LB	SB	ND	LB	SB	ND	LB	SB	ND
IVF/ICSI/other	5,541	158	33	2,863	112	55	217	10	14
FET	2,270	70	8	1,068	23	11	80	3	1
OD	1,577	16	9	1,371	11	14	100	4	0
FET(OD)	590	3	5	347	2	7	18	0	0
Total	9,978	247	55	5,649	148	87	415	17	15
Perinatal mortality (*)	29.38			39.94			71.59		

(*) proportion of still birth plus early neonatal death per 1,000 births
LB= live birth; SB= still birth; ND=early neonatal death

Table 9. Cumulative delivery rate in autologous IVF/ICSI cycles with at least one oocyte recovered in 2013.

	<35 years	35-39 years	40-42 years	≥43 years
Total OPU	10,390	14,152	7,186	3,313
Deliveries IVF/ICSI	3,035	3,164	909	182
Deliveries FET	1,252	1,156	355	140
Cumulative delivery rate	41.26%	30.53%	17.59%	9.72%

Figure 2. Effect of age category of female partner on the delivery rate per embryo transfer in fresh autologous IVF/ICSI, 2013.

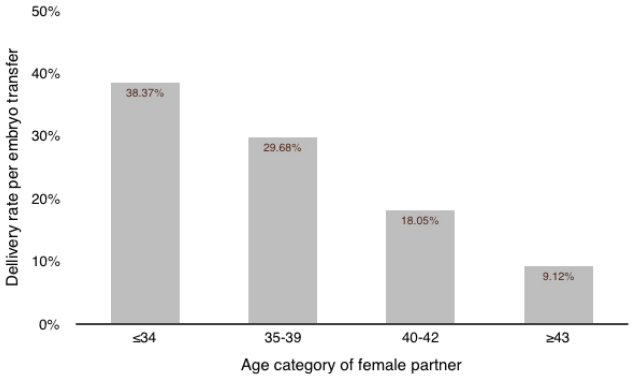


Figure 3. Effect of age of female partner on the delivery rate per embryo transfer in fresh autologous and heterologous IVF/ICSI, 2013.

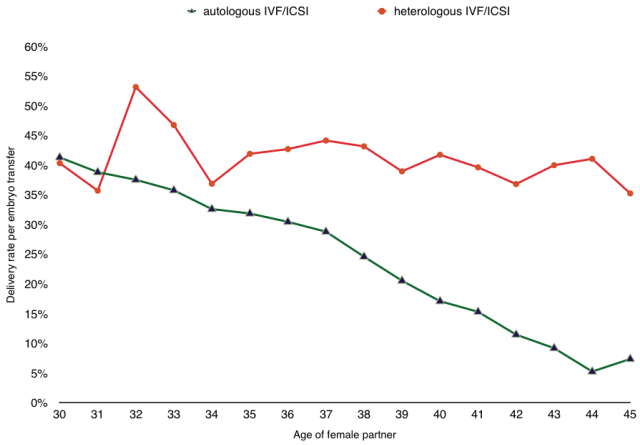


Figure 4. Effect of age of female partner on the miscarriage rate, 2013.

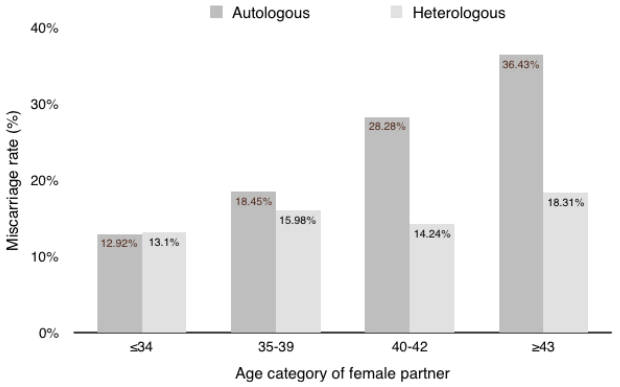
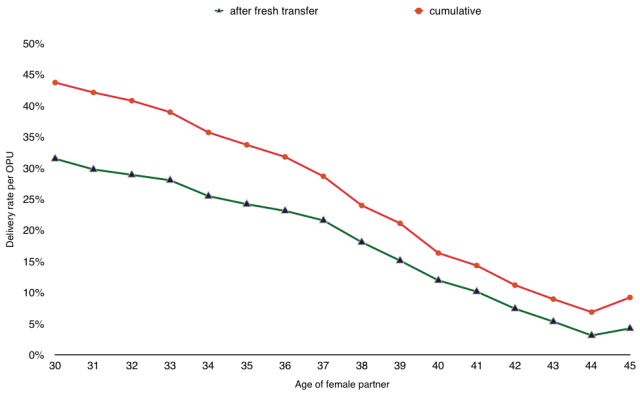


Figure 5. Cumulative delivery rate in autologous IVF/ICSI cycles with at least one oocyte recovered in 2013.



with a significant increase in CPR: 39.15% when two embryos were transferred, 39.28% when three embryos were transferred, and 35.26% when four or more embryos were transferred. However, the proportion of triplet deliveries increased with the transfer of more than two embryos. When two embryos were transferred, the proportion of triplet deliveries was 0.60%; increasing to 2.33% with the transfer of 3 embryos and 4.88% when >3 embryos were transferred.

Fresh heterologous IVF/ICSI

Table 5 shows the outcome of 5,927 transfer cycles with OD, with a mean number of embryos transferred of 2.2 (SD=0.61); 2.3 when cleaving-embryos were transferred, and 2.0 when blastocyst-stage embryos were transferred.

In 65.82% of cases, two embryos were transferred, and ≥ 3 embryos were transferred in 27.16%. As with autologous reproduction, the transfer of more than two embryos was not associated with a significant increase in CPR (47.73% with two embryos, 48.71% with three embryos and 36.36% with ≥4 embryos transferred). However, the delivery of triplets increased from 0.53% with the transfer of two embryos to 3.48% with three and 10.0% with the transfer of four or more embryos.

Autologous frozen/thawed embryo transfers

Table 6 shows the outcome of 10,912 FET cycles, with a mean number of embryos transferred of 2.0 (SD=0.65). In the majority of cases (61.84%) two embryos were transferred. Compared with the transfer of two embryos, the transfer of three and ≥four embryos was not associated with a significant increase in CPR (35.11%, 35.57%, 37.98%, respectively). The proportion of triplet deliveries was higher when three embryos were transferred (3.87%) than when two embryos were transferred (0.37%).

Heterologous frozen/thawed embryo transfers

Table 7 shows the outcomes of 2,507 cases of FET with donated oocytes, with a mean number of embryos transferred of 2.08 (SD=0.65). Compared with the transfer of two embryos and in contrast with autologous FET cycles, the transfer of three and ≥four embryos was associated with a significant increase in CPR (37.69%, 44.01%; 47.06%, respectively; *P*<0.001). As was the case in autologous FET, the proportion of triplet deliveries was higher when three embryos were transferred (2.96%).

Elective singe and double embryo transfer (eSET & eDET)

Elective single embryo transfer (eSET) and elective double embryo transfer (eDET) accounted for 2% (n=512) and 23.24% (n=5,892) of autologous fresh embryo transfers, respectively. DR/ET reached 30.08% with eSET and 41.62% with eDET, which was significantly higher than non-elective transfers. DR in non-elective SET was only 11.26% in 3,811 transfers (*P*<0.0001), and non-elective DET was 25.13% in 8,756 ET (*P*<0.0001). In women aged ≤34 years DR after eSET and eDET reached 39.07% and 47.82%, respectively.

Perinatal outcome

A total of 16,042 live births were registered following treatment in 2013. Of these, 8,621 were born after autologous fresh transfers, 4003 after heterologous fresh and frozen transfers, and 3418 after autologous FET (Table 8).

The duration of gestation was reported in a total of 11,008 deliveries from both autologous and heterologous reproduction. Among 8,385 singletons, the mean gestational age at delivery was 37.55 weeks of amenorrhea. This mean dropped to 35.22 weeks a in 2,500 twin deliveries, 32.63 weeks in 120 triplet; and 29.67 weeks in three cases of quadruplets (*P*<0.001). The relative risk for prematurity was 4.9 (95% CI 4.5 to 5.3) in twins, and 8.7 (95% CI 7.6 to 10.0) in triplets and higher.

The percentage of preterm births was 7.51% in singletons, 36.58% in twins, 65.52% in triplets, and 100.00% in quadruplets (*P*<0.0001). The percentage of very preterm birth was 1.85% in singletons, 7.13% in twins, 21.38% in triplets and 66.67% in quadruplets (*P*<0.0001).

How preterm birth affects perinatal mortality can be inferred from Table 8. An increase in gestational order was significantly (*P*<0.0001) associated with pre term birth and consequently a rise in perinatal mortality. Singletons had a perinatal mortality of 29.38 per thousand, compared with 39.94 per thousand in twins and 71.59 per thousand in triplets and more (*P*<0.0001). Furthermore, perinatal mortality among singletons born after fresh OD was only 15.6 per thousand and 13.4 per thousand for frozen /thawed OD.

Spontaneous abortion rate

The spontaneous abortion rate in women undergoing fresh IVF–ICSI was 18.29%, which increased significantly with the age of the female partner, reaching 36.43% in women aged 42 years and older (*P*<0.0001). The miscarriage rate in women undergoing fresh OD was 16.48%, and there were no significant differences according to the age of recipients; the miscarriage rate reached 13.10%, 15.98%, 14.24%, and 18.31% in women aged ≤34 years, 35-39 years, 40-42 years and ≥43 years respectively (Figure 4).

The miscarriage rate in women undergoing FET was 19.52%. No subgroup analysis was performed in this case, since the RLA reports the age of the woman at the time of embryo transfer not at the time of embryo freezing.

Preimplantation Genetic Diagnosis (PGD)

The RLA registers PGD and PGS together. Eighty-six centres from twelve different countries reported 1,920 cycles of PGD. The majority was performed in blastocysts (55.79%). Overall, there were 708 embryo transfers. The mean age of women was 38 years (range 21 to 49 years). A mean of four embryos were analysed in each cycle, and a mean of one embryo was reported as normal. Two hundred and eight clinical pregnancies were registered and 172 deliveries (145 singletons and 27 twins), thus a total of 199 healthy babies were born

The use of PGD was not associated with any significant decrease in miscarriage rate, reaching 16.98%, 11.24%, 21.57% and 35.71% in women aged ≤34 years, 35-39 years, 40-42 years and ≥43 years, respectively.

Assisted hatching (AH)

Institutions in ten different countries reported 5,687 cycles with AH. The mean age of women undergoing assisted hatching was 37 years (range 19 to 49 years), and the mean number of embryos transferred was 2.2 (SD=0.80). Of the 4,767 embryo transfers reported, a clinical pregnancy was achieved in 1,775 cases, resulting in 1,400 deliveries (29.37%). Of these, 1,106 were singletons, 276 twins and 18 triplets.

Implantation rate (IR)

The IR in fresh IVF/ICSI cycles reached 20.98%. It was significantly associated with the age of the woman: 27,23% in women under 35 years, 20.09% in women aged 35 to 39 years, 12.88% in women aged 40 to 42 years, and 7.99% in women over 42 years (*P*<0.001). It was also significantly associated with the developmental stage at embryo transfer: 19.05% when cleaving-embryos were transferred, and 28.58% when blastocyst-stage embryos were transferred (*P*<0.001). The use of PGD was also associated to an increase in IR. Indeed, IR of chromosomal-

ly normal embryos reached 32.02% in women under 35 years, 30.67% in women aged 35 to 39 years, 22.22% in women aged 40 to 42 years, and 19.15% in women over 42 years.

Intrauterine insemination (IUI)

Ninety-four clinics in ten countries reported 6,250 cycles of IUI with semen of the male partner (IUI-H). The delivery rate per cycle was 14.91%, 10.04% of which were twin deliveries and 1.41% triplets-and-higher order. As with other fertility treatments, the age of the female partner, strongly influenced results. Delivery rate after IUI dropped from 18.4% per cycle in women under 35 years, to 13.4% in women 35 to 39 years. In women between 40 and 42, delivery rate was 7.1% dropping to 3.5% in women >42. Seventy-six clinics in ten countries reported 963 cycles of donor (IUI-D). The delivery rate per cycle (23.36%) was higher than for autologous IUI. The multiple delivery rate was 8.56%: 7.66% twins and 0.90% triplets and higher.

Cumulative/total delivery rate

Table 9 shows the cumulative delivery rate according to women's age. As expected, the most meaningful increment in delivery rate was seen in younger women (<35 years), where the delivery rate per oocyte pick up increased from 29.21% in all fresh cycles to 41.26%, while in women aged 43 and older, it only increased from 5.49% to 9.72%.

Figure 5 shows the cumulative delivery rate in autologous IVF/ICSI, according to the age of the female partner.

Fertility preservation

Sixty-six centres from twelve countries reported 1,616 initiated cycles for fertility preservation; 74% of these were performed in healthy women. Overall, the mean age of women undergoing this procedure was 37 years (SD=4.7). The mean number of oocytes preserved was 8 (range from nil to 39). In all cases, the technique for cryopreservation was vitrification. There were ten cases of OHSSS and one case of haemorrhage.

Complications

Clinics reported 218 cases of severe ovarian hyperstimulation syndrome (where hospitalization or medical interventions were required), corresponding to a rate of 1.97%. Other less frequent complications included fifty-nine cases of haemorrhage and twenty-one cases of infection. However, it is likely that complications were under-reported.

DISCUSSION

This is the 25th version of the RLA, which has been published continuously since 1990. The major change in data collection was introduced for cycles performed during 2011, when a cycle-based registry was implemented.

Between 2012 and 2013 there was an 18% increase in initiated cycles; from 47,326 cycles reported in 2012 to 55,840 reported in 2013. This increase is not explained only by an increase in the number of countries and centres registering their data, but also by an increase in the mean number of cycles registered by many institutions. In 2012 the mean number of cycles reported by clinics was 309, increasing to 355 in 2013 (Zegers-Hochschild *et al*., 2015). Nevertheless, with access to 425 cycles per million women aged 15-45 years, Latin America is far behind developed countries (Ishihara *et al*., 2015). It is worth mentioning that countries like Argentina, with a consistent policy towards recognizing the right to start a family as a human right, has the highest number of ART cycles per population. It is very likely that Argentina and now Uruguay, the only two countries in Latin America with laws providing universal access to ART, will increase the number of procedures per million of the population in these countries over the rest of the region. Countries where access to treatment depends on the individual capacity to pay will remain with low coverage.

Many centres have adopted the policy of delaying embryo transfer by freezing all embryos in order to transfer them in a subsequent cycle. In 2013, 5,168 cycles were reported, representing a major increase over the 3,393 cases reported in 2012.

We did not find any significant difference with the previous report regarding pregnancy and delivery rates, mean number of embryos transferred or the consistently low proportion of eSET or eDET (Zegers-Hochschild *et al*., 2015). Although this is partially influenced by the fact that ART in Latin America is mostly paid by the couples themselves, the reality is that in the absence of a forced policy restricting embryo transfer to a maximum or two embryos, many centres transfer 3 or 4 embryos even in cycles with donated oocytes. As a matter of fact, in 2013 more than 25% of fresh autologous and heterologous ART cycles had more than two embryos transferred; which was not associated with an increase in clinical pregnancy rates, but with a significant increase in the proportion of triplets and higher order births.

As expected, eSET and eDET were associated with higher CPR and DR than the single and double non-elective transfers. The data presented here should encourage professionals in Latin America to restrict the number of embryos to be transferred to a maximum of two. When comparing this information with other national registries, it is important to bear in mind that in Latin America, 30% of autologous assisted reproduction cycles initiated are in women who are 40 years and older and 70% are in women ≥ 35 years.

This report shows that even twin deliveries are associated with an increased risk of preterm births, and perinatal mortality. We have no explanation for the increased perinatal mortality in singletons when compared with the previous year (29.3 and 25.2% per thousand respectively) and a simultaneous drop in perinatal mortality for twins and triplets (Zegers-Hochschild *et al.*, 2015). Overall, perinatal mortality after ART is higher than in spontaneous pregnancies as expressed in global statistics by country (Jackson *et al*., 2004). However, the mean age of women delivering in most countries in Latin America fluctuates between 20 and 30 years, while more than 70% of autologous assisted reproduction treatments in the region are performed in women ≥ 35 years, and 30% in women ≥ 40 years. Therefore, comparing perinatal mortality with the overall population needs to consider these variables.

When examining trends over the past 5 years, the mean number of embryos transferred in fresh autologous IVF/ICSI cycles dropped from 2.5 in 2008 to 2.1 in 2013. This results from a drop in the number of transfers with 3 and ≥4 embryos from 48.2% to 25.9%; and an increment in the number of SET from 11.9% to 18.1%. This was also accompanied by an increase in the number of FET from 4,225 to 10,912 in the last five years. Considering that the larger contributors to multiple births are young women, the mean number of ET in women under 35 decreased from 2.5 in 2008 to 2.3 in 2013. The question that needs to be answered is whether there has been an improvement in the performance of centers that justify the reduction of embryos to be transferred without severely jeopardizing pregnancy or delivery rates. A way to address this question is to look at implantation rates as an indirect marker of the quality of each embryo generated and transferred. In women under 35 years, the implantation rate was 23% in 2008 and 28% in 2013. Clinical pregnancy rates in 176 eSET performed in 2008 was 29.0% compared with 38.3% from 515 eSET in 2013. Also, the proportion of blastocyst-stage embryo transfers in fresh IVF/ICSI cycles

increased in these last 5 years, from 1,509 embryo transfers (8.2%) in 2008 to 5,564 transfers in 2013 (15.2%), resulting in an increase in implantation rate from 20.0% in day 3 compared with 28.6% in day 5 of embryo culture. This information suggests that although at a slow pace, centres are directing their efforts to strategies that help reduce the number of multiple births.

One of the main strengths of the RLA is the uniformity in terminology. All clinics reporting to RLA, use the glossary published in 2009 by the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) and the World Health Organization (WHO) (Zegers-Hochschild *et al*., 2009), translated into Spanish and Portuguese. The other strength is that the data-voluntarily reported by each centre is periodically checked by an external and independent accreditation team, composed of a clinician and an embryologist, responsible for visiting every center willing to provide its data to the RLA.

For the purpose of scientific comparisons among different therapeutic strategies, this registry does not allow for accurate comparisons; the main weakness is that registries report observational data, and not a summary of randomized controlled trials. Since this report examines observational data, the comparison of results cannot be considered as high-level evidence in favour or against certain procedures. This is the case with the significantly higher pregnancy and delivery rates achieved with IVF compared with ICSI cycles. It is quite possible that couples selected for IVF are expected to have better fertilization rates and can be more fertile couples altogether. Furthermore, the high proportion of ICSI over IVF does not seem to follow a biomedical reason (Ishihara *et al.,* 2015). As seen over time, in countries where ART is subsidized by public funds, the proportion of ICSI is relatively low, in the order of 60 to 70% in Australia and Northern Europe. In regions where ART is paid directly by consumer, the proportion of ICSI rises above 80%; and this is the case in Latin America, the Middle East and several countries in Europe (Ishira *et al.,* 2015; Zegers-Hochschild *et al.,* 2011). There is a general belief, that centres favour the use of ICSI in order to avoid unexpected failed fertilization or low fertilization rates with regular IVF.

Since the main drawback of ART procedures reported in Latin America is the high proportion of multiple-gestations, and the perinatal complications that follow; strategies to reduce the number of embryos transferred must be enforced. One such strategy is to transfer blastocyst-stage embryos instead of cleaving embryos. Especially so in women aged 34 years and less, in which the implantation rate of blastocysts is significantly higher than day 3 transfers (25.6% and 34.8%, respectively, $P<0.05$). Furthermore, delivery rates per embryo transfer of eSET in women <35, rises from 17.42% when day-three embryos are transferred, to 33.77% when blastocyst-stage embryos are transferred.

In summary, this is the fourth cycle-based registry published by the RLA. It is reassuring to patients and clinics that the results of ART procedures performed in the region are similar to other regions of the world (Ferraretti *et al*., 2013; Zegers-Hochschild *et al*., 2013). Although Latin America is on the right path to reducing the number of embryos transferred, we need a more drastic reduction in order to prevent multiple births, or at least, high order multiples and decrease the corresponding perinatal complications.

CONFLICT OF INTERESTS

No conflict of interest have been declared.

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Supplementary Data
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