

FEELING Study

*A multi-centre, multinational, cross-sectional, incident case control study on **F**actors associated with the development of **E**ndometrioma and **dEep infiLtrating** endometriosis*

Professor C. Chapron and the FEELING Study Group

Investigators

-  France: Prof. C Chapron (principal investigator)
-  China: Prof. J. Lang, Prof. Y. Zhou, Prof. X. Zhang and Prof. M. Xue
-  Russia: Prof. A. Popov and Prof. V. Romanov

Financial disclosure

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Study Objectives

Primary Objective

- Identify factors associated with endometrioma and/or deep infiltrating endometriosis.

Main secondary objective

- Identify factors associated with superficial endometriosis.

Other secondary objectives

- To identify factors associated with endometriosis (superficial endometriosis, endometrioma and deep infiltrating endometriosis).
- To identify factors associated with endometrioma and/or deep infiltrating endometriosis according to subject ethnicity.
- To describe subject's characteristics by endometriosis status.
- To describe profiles of subjects according to endometriosis status (superficial endometriosis, endometrioma and deep infiltrating endometriosis) by subject ethnicity

Main risk factors under exploration

- Personal (medical history, gynecological, surgical and family history etc.)
- Hormonal (past hormonal treatment for dysmenorrhea, current use for contraception etc.)
- Immunological (association with other diseases)
- Environmental / dietary / lifestyle
- Ethnicity

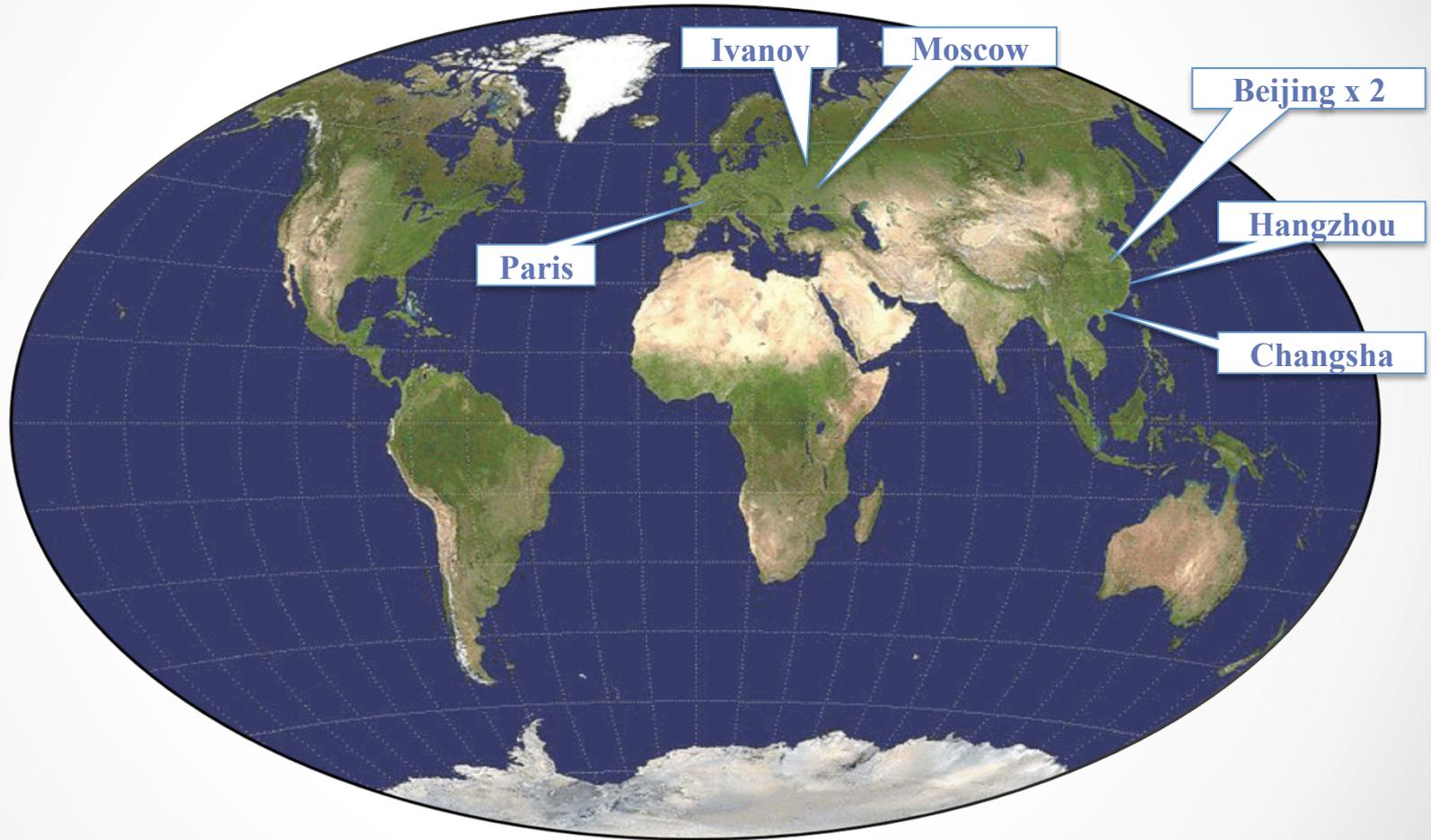
Patients groups

Inclusion criteria:

Having undergone a laparoscopy or laparotomy for a benign gynecological indication in the last 3 months (excluding pregnancy)

	China	Russia	France	Total
No endometriosis (No EM)	156	88	44	288
Superficial endometriosis (SUP)	156	88	44	288
Endometrioma (OMA)	156	88	44	288
Deep infiltrating endometriosis (DIE)	78	43	22	143
Total	546	307	154	1007

Investigational Sites (7 centers)



Endometriosis: Time from symptoms to diagnosis

Endometriosis	China 	Russia 	France 	Total
No. patients	331	180	63	574
Mean age first endometriosis symptoms (years [95% CI])	28.15 [27.37; 28.93] *	27.66 [26.92; 28.39] **	22.54 [20.65; 24.43] *,**	27.38
Mean time between first endometriosis symptoms and first medical attention (years [95% CI])	2.13 [1.62; 2.64] *,**	0.78 [0.43; 1.13] *,***	5.06 [3.66; 6.47] *,**,***	2.03
Mean time between first medical attention and diagnosis (years [95% CI])	1.81 [1.48; 2.14] *	1.93 [1.53; 2.33] **	3.67 [2.66; 4.67] *,**	2.04

Diagnosis of endometriosis

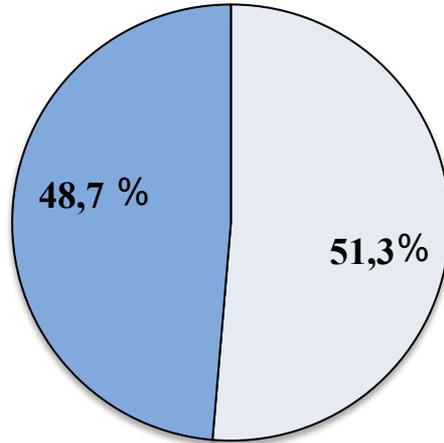
Overall

Surgery indications

n=1007

□ Suspected EM

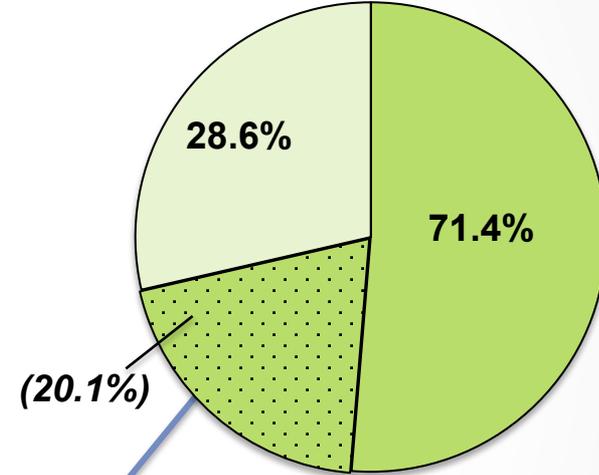
■ Other *



Surgery results

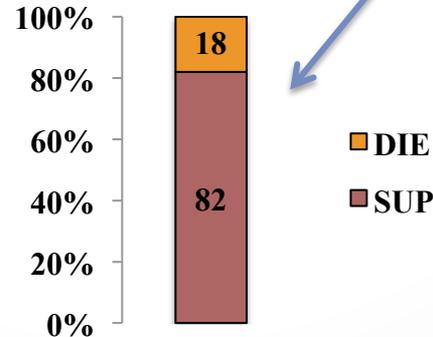
■ Confirmed

□ No EM



(20.1%)

*Benign ovarian cyst, uterine myoma, salpingitis, PCOs, tubal infertility treatment

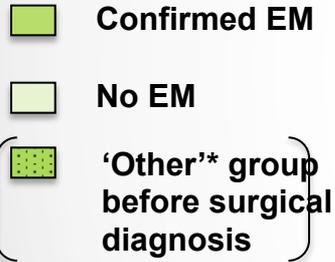


Superficial endometriosis is a real disease

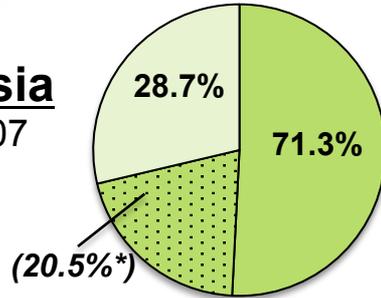
	Comparison between superficial endometriosis (n = 156) and control (n = 468)	
	OR (95% CI)	P value
Infertility	3.2 (1.7 - 6.2)	< 0.001
Severe dysmenorrhea	1.7 (0.9 - 3.2)	NS
Severe GI symptoms	3.4 (1.1 - 11)	0.038
OCs treatment	2.3 (1 - 5.4)	0.043
Family history of Osis	4.1 (1.2 - 14.3)	0.022
Absenteeism from school during menstruation	2 (1 - 3.7)	0.029

Diagnosis of endometriosis

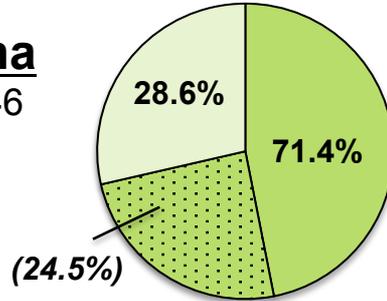
Surgery results



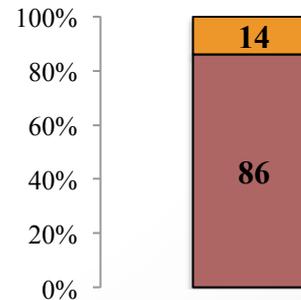
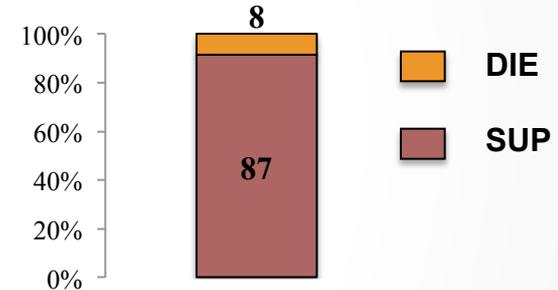
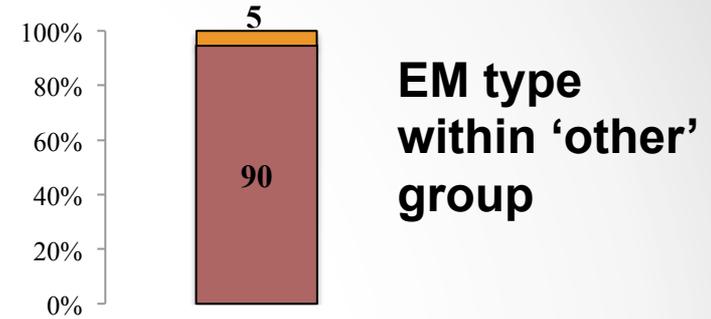
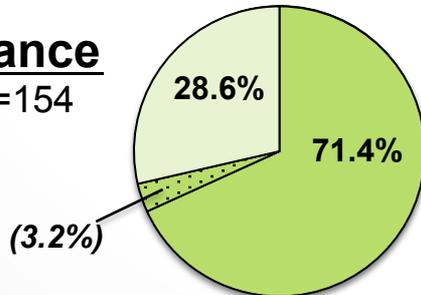
Russia
n=307



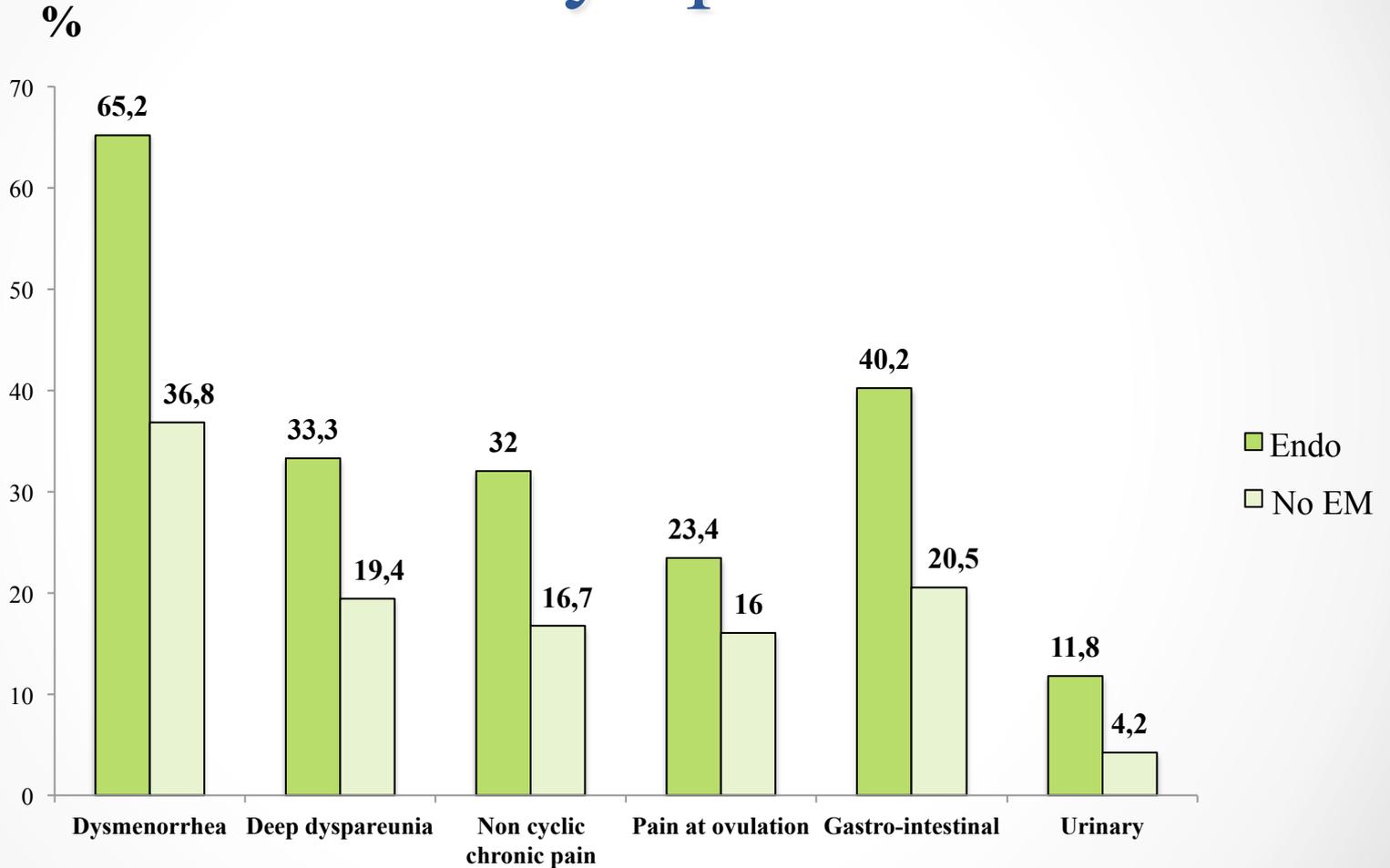
China
n=546



France
n=154

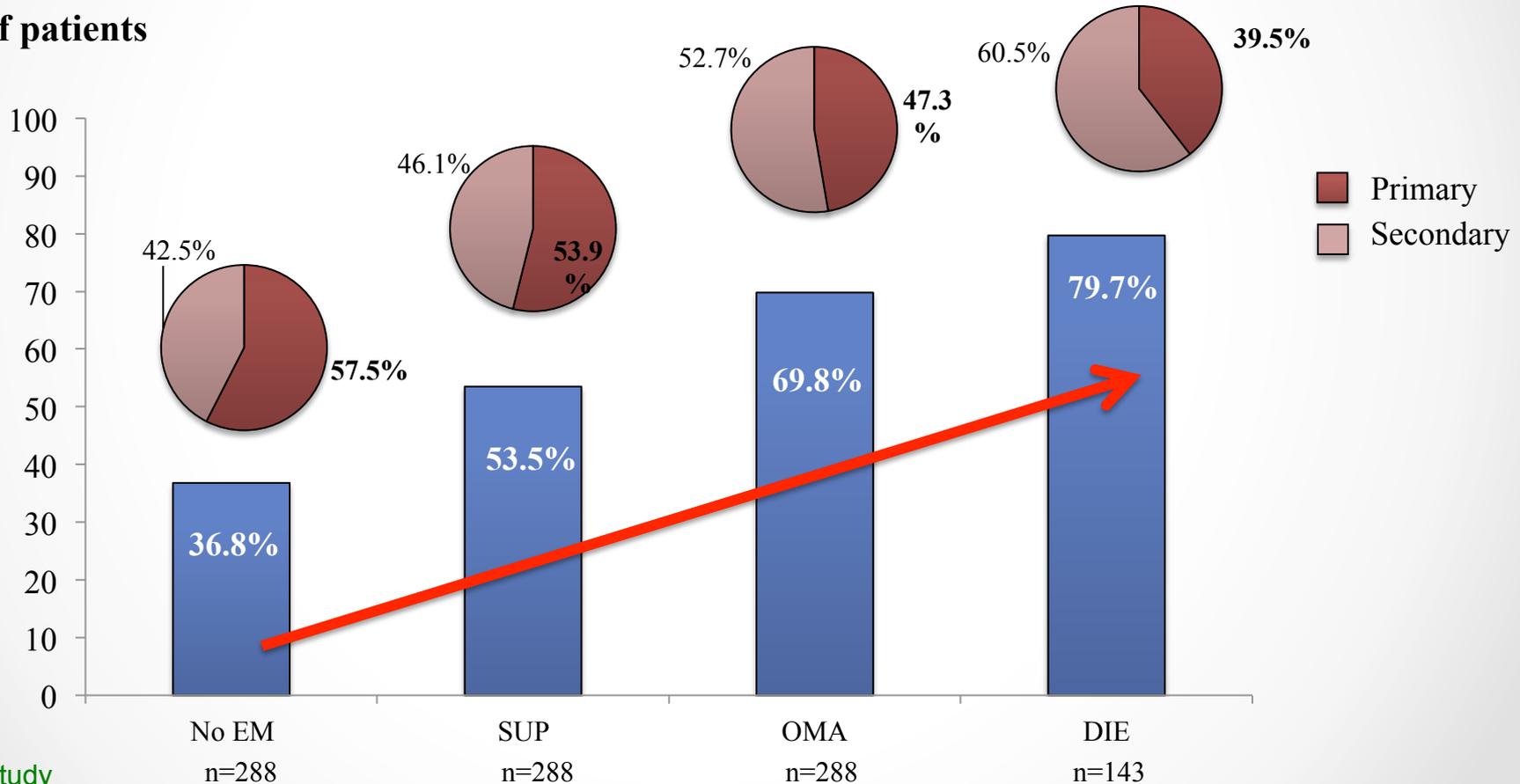


Main symptoms

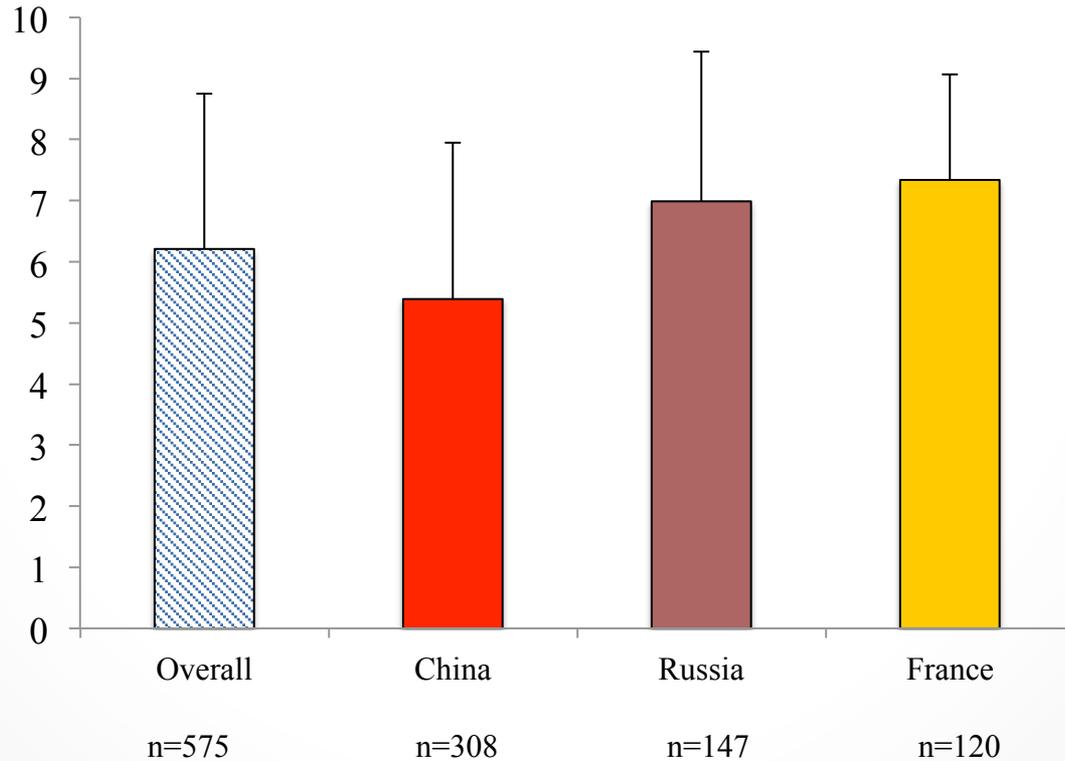


Dysmenorrhea: by endometriosis type

% of patients

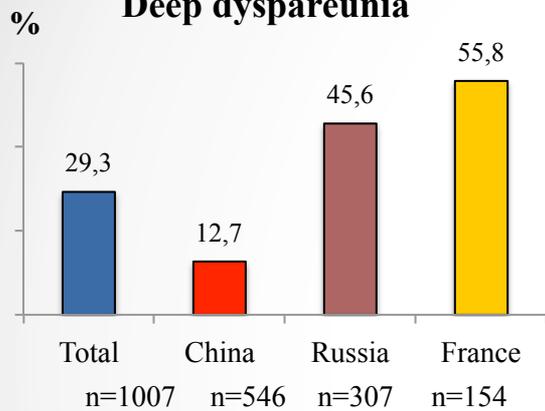


Dysmenorrhea INTENSITY on a scale of 1-10

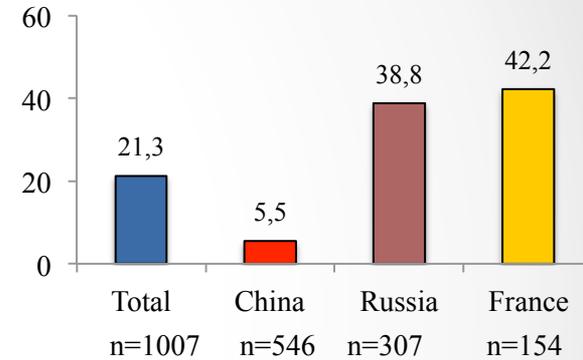


Overall symptoms by country

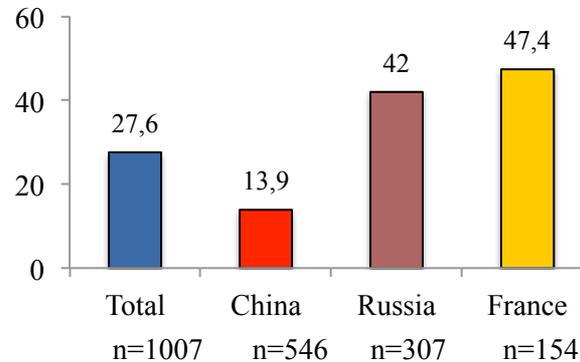
Deep dyspareunia



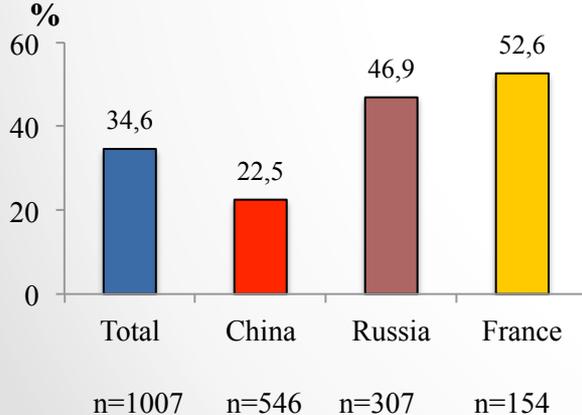
Pain at time of ovulation



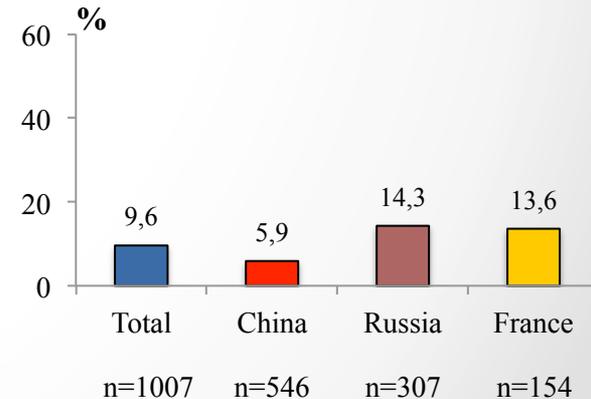
Non cyclic chronic pain



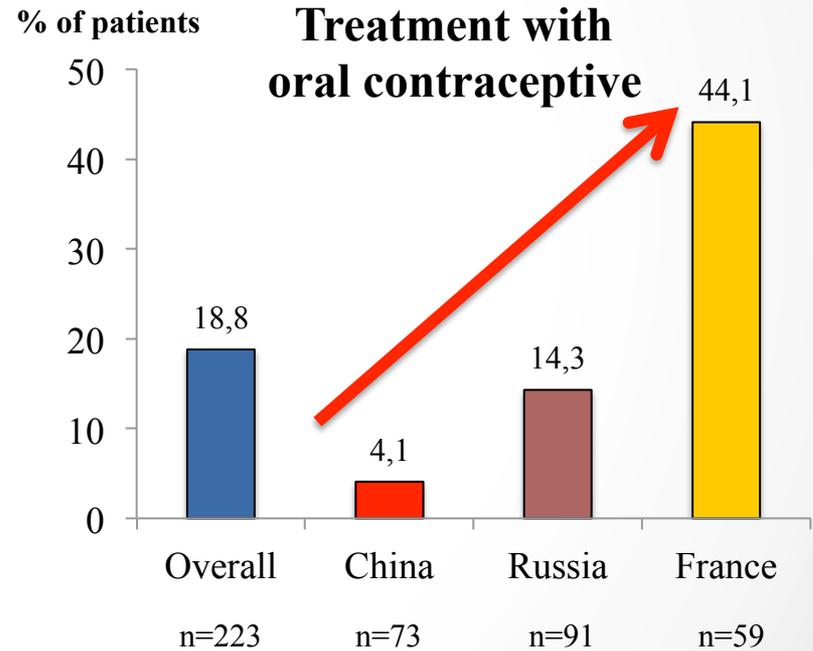
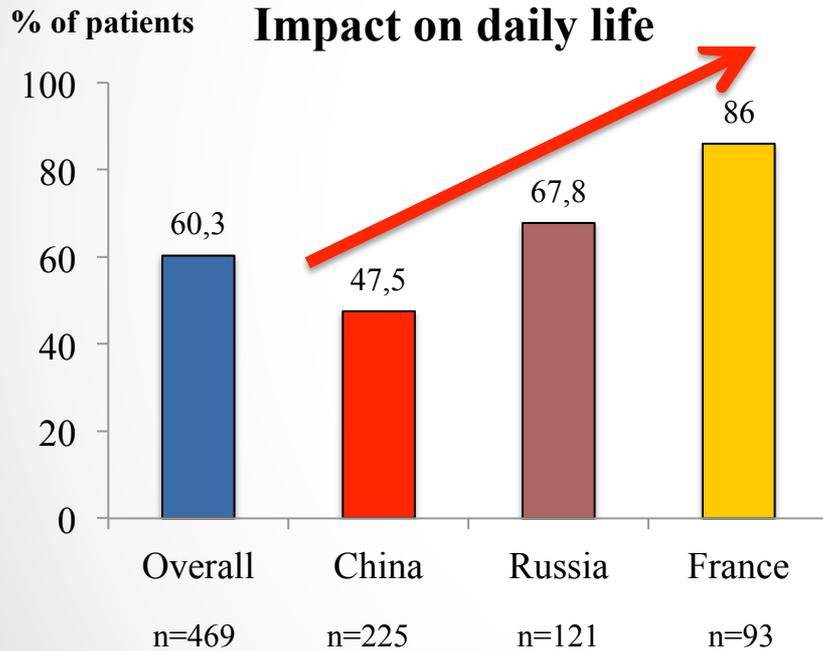
Gastro-intestinal



Urinary



Endometriosis: Impact on daily life and treatment

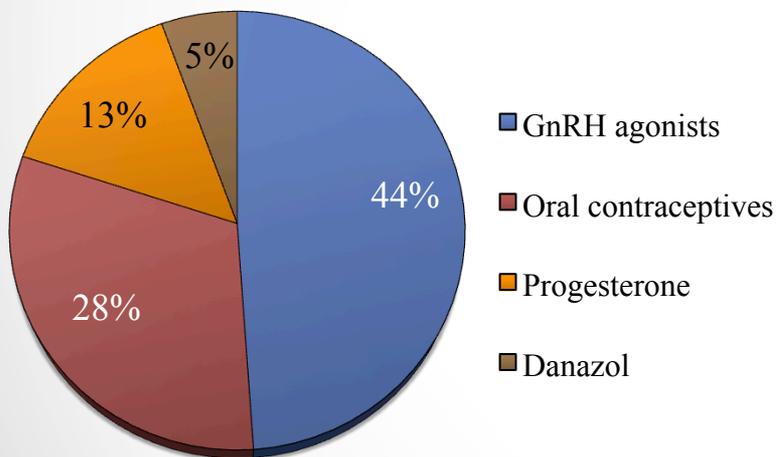


Previous Hormonal Treatment for endometriosis



N=49 missing

Distribution of hormonal treatments among patients (n=157)



	Total no. patients	China  (n=64)	Russia  (n=57)	France  (n=36)
Oral Contraceptive Pills	44	9%	56%	20%
GnRH Agonists	69	55%	12%	47%
Progesterone	20	8%	<1%	28%

Patients may have received multiple treatments

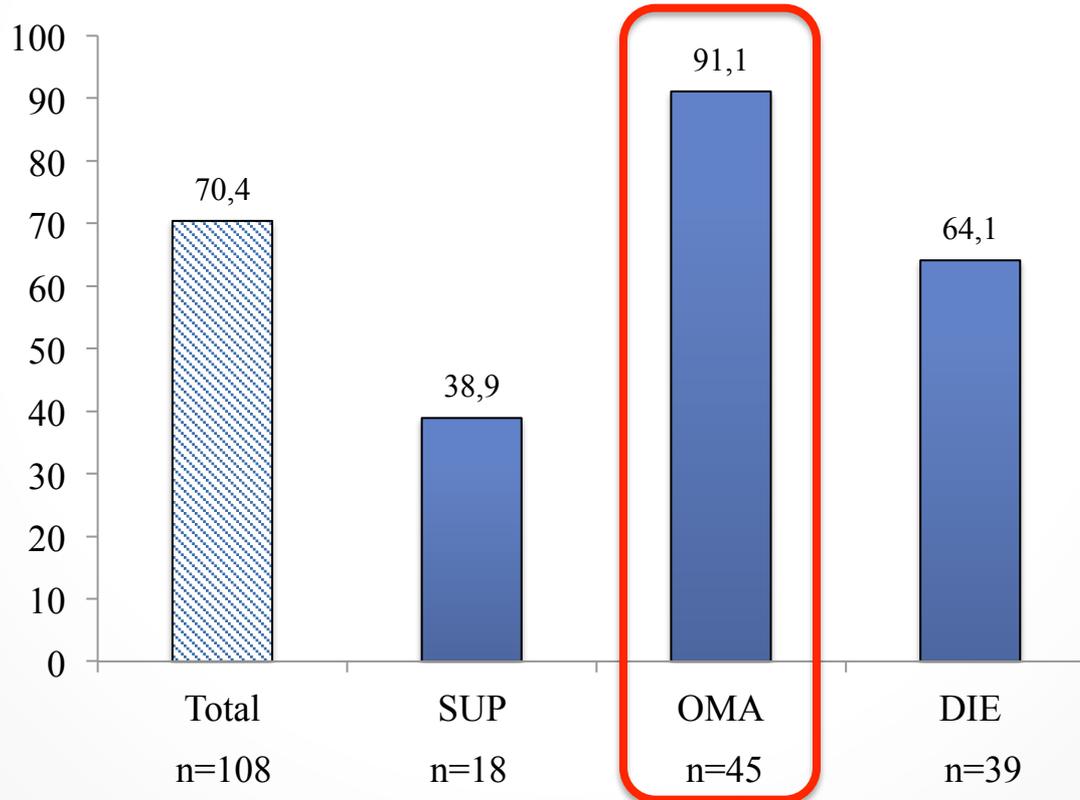


15 Chinese patients received traditional Chinese medication

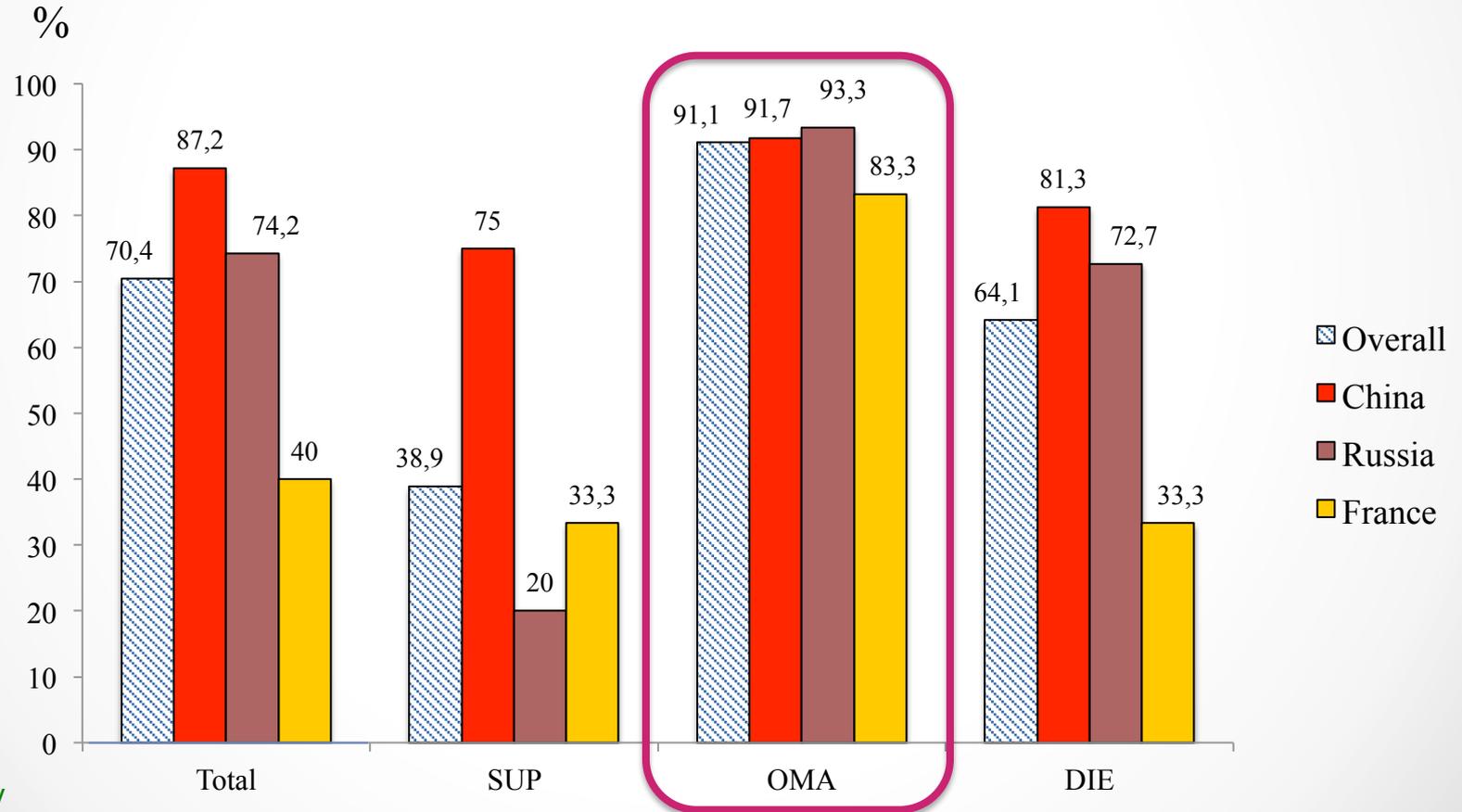
Global population: Previous surgery for OMA

11,5% of patients were previously diagnosed with endometriosis

Surgeries for endometrioma

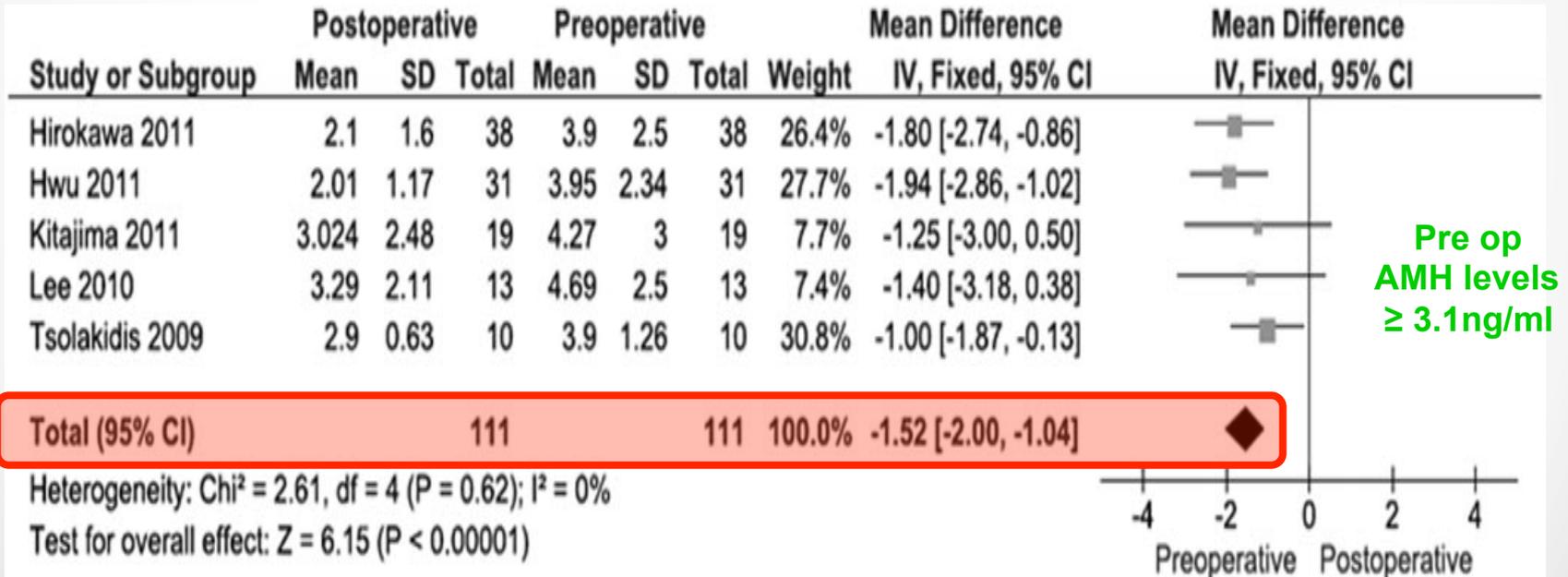


Previous surgery for OMA by endometriosis type



The Impact of Excision of Ovarian Endometrioma on Ovarian Reserve: A Systematic Review and Meta-Analysis

Raffi et al., JCEM (2012)



Endometriosis: Logistic regression analysis of factors predicting AMH levels < 1 ng/ml

Variable	Category	OR	95% CI	P-value
Age	≤29	—	—	—
	30–34	3.08	1.48–6.41	0.01
	35–39	6.99	3.47–14.11	0.001
	≥40	20.82	9.14–47.41	0.001
BMI	>25 versus ≤25	1.04	0.65–1.67	0.87
Infertility	None	—	—	—
	Primary	0.70	0.39–1.23	0.22
	Secondary	1.21	0.71–2.06	0.49
Smoking	Never	—	—	—
	Ex smoker	1.25	0.69–2.26	0.46
	Current smoker	0.51	0.30–0.88	0.02
Endometriosis	None (controls)	—	—	—
	SUP	0.61	0.20–1.90	0.40
	OMA, without prior surgery	0.66	0.30–1.47	0.31
	DIE, without prior surgery	1.29	0.74–2.27	0.38
	Prior OMA surgery (with/without current DIE or OMA)	3.00	1.40–6.41	0.01

OMA: Ovarian reserve and repetitive cystectomy

	First surgery for OMA	Recurrent surgery for Oma	P value
	(n = 17)	(n = 11)	
Cyst wall thicknes	1.1 ± 0.3	1.7 ± 0 .3	0.00003
Antral follicule count *	0.2	0.002	
Ovarian volume*	0.08	0.001	

*: *p value* (operated versus controlateral ovary)

Muzzi *et al.*, Fertil Steril (2015)

IVF outcome and diminished ovarian reserve: Post OMA cystectomy versus idiopathic

Characteristics	Subgroup A (Bologna criteria) (99 cycles)	Subgroup B (Bologna criteria) (189 cycles)	P-value
Implantation rate (%)	8/134 (6.0%)	37/290 (12.8%)	0.035
Clinical pregnancy rate per cycle (%)	9/99 (9.1%)	38/189 (20.1%)	0.016
Live birth rate (%)			
Per cycle	5/99 (5.1%)	29/189 (15.3%)	0.001
Per transfer	5/79 (6.3%)	29/173 (16.8%)	0.03
Spontaneous abortion rate (%) (before or after 12 weeks of gestation)	3/7 (42.9%)	8/37 (21.6%)	NS
Ectopic pregnancy rate (%)	1/9 (11.1%)	1/38 (2.6%)	NS
Multiple pregnancy rate (%)	2/7 (28.6%)	4/36 (11.1%)	NS

OMA: Spontaneous ovulation rate (n = 244)

Number of patients conceiving during the study protocol (n, %) 105 (43.0%)

Patients conceiving during the study protocol (n, %)*

without concomitant deep endometriosis 29 (47.5%; 35.0–60.0%)

with concomitant deep endometriosis 76 (41.5%; 34.4–48.6%)

Last cycle evaluated before conceiving (median, median, 25th–75th percentiles) 4 (3–5)

Side of ovulation when conceiving (n, %; 95% CI)**

Healthy ovary 56 (53.3%; 43.3–63.1%)

Affected ovary 49 (46.7%; 36.9–56.7%)

Operated bilateral OMAs: IVF-ICSI outcome

Characteristics	Operated bil Omas n = 68	No prior ovarian surgery n = 136	p
Cancelled cycle			<0.001
Hyper-response	1 (2%)	20 (15%)	
Poor response	17 (28%)	8 (6%)	
Dosage of rFSH/die	333 ± 133	212 ± 112	<0.001
Duration of stimulation (day) ^a	11.5 ± 2.3	11.8 ± 2.4	0.58
Number of follicles 11–15 mm ^a	3.2 ± 2.8	4.6 ± 3.3	0.009
Number of follicles > 15 mm ^a	5.2 ± 2.8	6.5 ± 2.7	0.006
Number of oocyte retrieved ^a	5.7 ± 4.0	7.2 ± 3.6	0.024
Number of oocyte used ^{a,b}	2.8 ± 2.3	3.8 ± 2.7	0.034
Number of embryos obtained ^{a,b}	2.0 ± 1.9	2.8 ± 2.0	0.024
Number of transfers not performed ^a	14 (28%)	16 (15%)	0.08
Number of embryos transferred ^c	2.0 ± 0.6	2.2 ± 0.7	0.20
Clinical pregnancy rate (PR)			
Number of pregnancies	5	26	
PR per starting cycle	7%	19%	0.037
PR per oocyte retrieval	10%	24%	0.051
PR per embryo transfer	14%	28%	0.11
Implantation rate	5 (7%)	33 (16%)	0.048
Delivery rate (DR)			
Number of deliveries	3	23	
DR per starting cycle	4%	17%	0.013
DR per oocyte retrieval	6%	21%	0.02
DR per embryo transfer	8%	25%	0.049

Unoperated Bilateral OMA: ART outcome

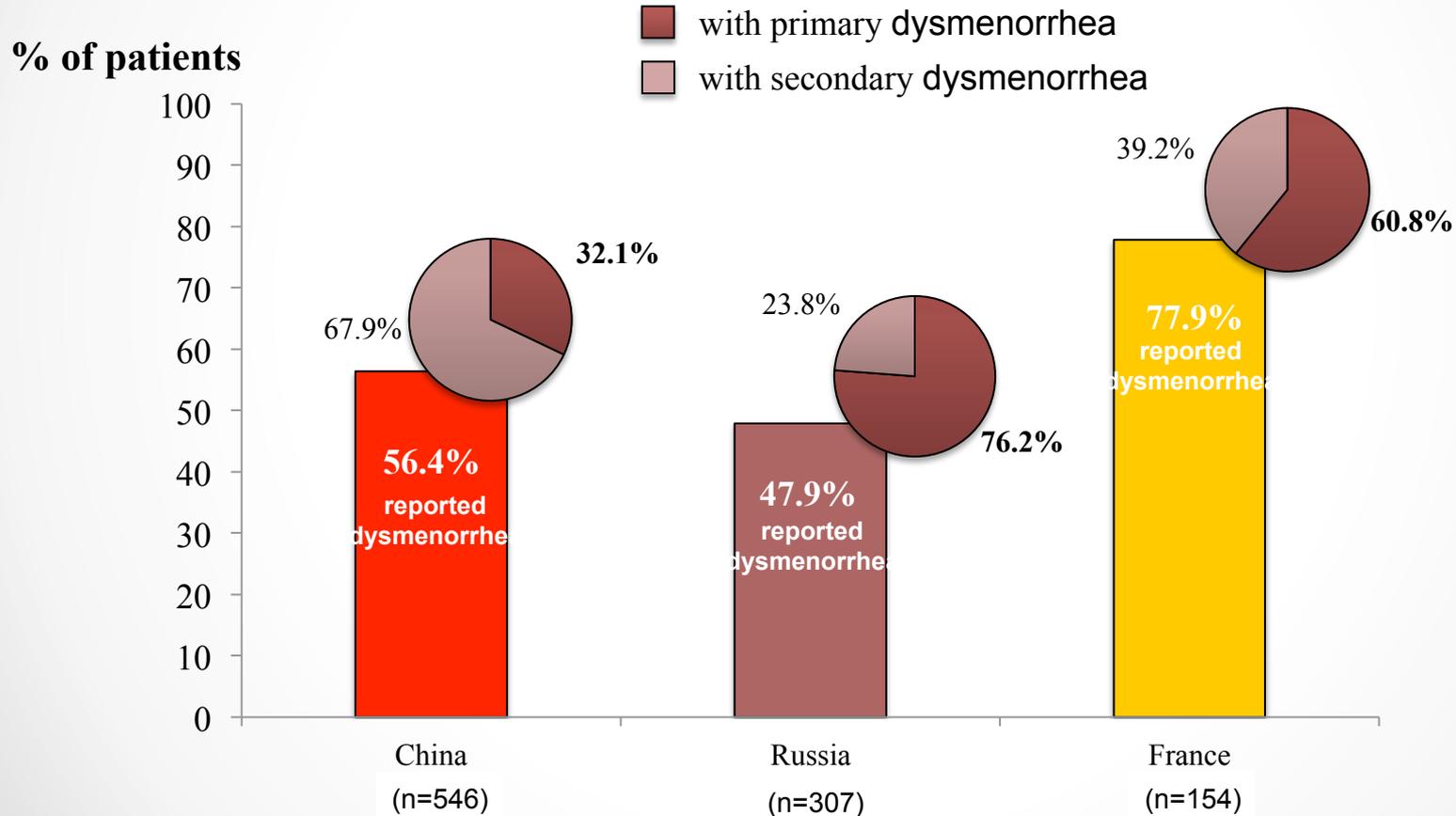
Characteristics	Case n = 39	Control n = 78	p
Protocol of ovarian stimulation			.81
Long protocol	15 (38%)	32 (41%)	
Protocol with GnRH antagonists	19 (49%)	39 (50%)	
Other	5 (13%)	7 (9%)	
Canceled cycle			.67
Hyperresponse	1 (3%)	1 (1%)	
Poor response	2 (5%)	2 (3%)	
Total amount of FSH used (IU) ^a	2,605 ± 885	2,365 ± 1,206	.24
Duration of stimulation (d) ^a	11.5 ± 2.9	11.0 ± 1.8	.32
Total no. of follicles >10 mm ^a	9.6 ± 3.3	14.1 ± 6.8	< .001
No. of follicles >15 mm ^a	6.2 ± 2.6	9.6 ± 4.8	< .001
No. of oocytes retrieved ^a	7.1 ± 3.2	9.8 ± 5.5	.001
No. of suitable oocytes ^{a,e}	5.1 ± 2.5	6.9 ± 4.2	.004
No. of subjects not retrieving suitable oocytes ^{a,e}	2 (6%)	3 (4%)	.66
No. of oocytes used ^{b,c}	4.8 ± 2.3	6.5 ± 3.9	.008
No. of embryos obtained ^c	2.6 ± 1.4	3.1 ± 1.5	.074
No. of high-quality embryos (types 1 and 2) ^c	1.9 ± 0.9	2.2 ± 1.5	.15
No. of embryo transfers not performed ^c	3 (9%)	2 (3%)	.32
Day of embryo transfer (since oocyte retrieval) ^d			.45
Day 2	9 (29%)	15 (21%)	
Day 3	22 (71%)	55 (79%)	
No. of embryos transferred ^d	2.1 ± 0.6	2.0 ± 0.5	.40
No. of clinical pregnancies	12	26	
PR per started cycle	31%	33%	.84
PR per oocyte retrieval ^a	33%	35%	1.00
PR per embryo transfer ^b	39%	37%	1.00
No. of embryos implanted	14	32	
Implantation rate ^c	22%	23%	1.00
No. of deliveries	9	23	
DR per started cycle	23%	29%	.52
DR per oocyte retrieval ^a	25%	31%	.66
DR per embryo transfer ^b	29%	33%	.82

Conclusions

- Major differences in perception of endometriosis between countries with different cultural, ethnic and socioeconomic backgrounds.
- Important variations in pain reporting and management as well as impact on daily activities across countries
- OMA: Surgeries done previously were mostly performed on ovarian endometrioma !!!
- Relationship between OMA and infertility needs to be investigated !!!

... further analyses on-going

Dysmenorrhea: by country



OMA: Fertility and Surgery

	Infertility	Surgeries	
	All	Previous surgeries	Surgeries for OMA
Overall patients (n=288)	27.1%	15.7%	91.1%
China (n=156)	22.4%	15.5%	91.7%
Russia (n=88)	36.4%	17.0%	93.3%
France (n=44)	25.0%	13.6%	83.3%

Endometriosis and IVF

Results according the endometriosis' phenotype ($n=359$)

	DIE	OMA	SUP	p value
Patients	212	98	49	
No. of cycles	425	200	95	
No. of ET	282/425 (66.4)	141/200 (70.5)	77/95 (81.1)	0.018
Clinical pregnancy rate per cycle	98/425 (23.1)	55/200 (27.5)	29/95 (30.5)	0.22
Clinical pregnancy rate per ET	98/282 (34.8)	55/141 (39)	29/77 (37.7)	0.67
Implantation rate	111/513 (21.6)	62/265 (23.4)	35/140 (25.0)	0.66
Abortion rate	30/98 (30.6)	22/55 (40.0)	16/29 (55.2)	0.049