

Review

Uterine peristalsis and fertility: current knowledge and future perspectives: a review and meta-analysis



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Dr Nienke Kuijsters obtained her medical degree in 2013 in the Netherlands. Since 2012 she has been involved in research on dynamics and measurement of contractions in non-pregnant uteri. In 2015 she started as a PhD candidate at the University of Technology in Eindhoven (the Netherlands), focusing on objective measurement of uterine peristalsis. The research is under supervision of professor Dr Schoot, who is a gynaecologist specialized in minimal invasive surgery and fertility. Since 2015 he is also a visiting professor at the Ghent University Hospital, Ghent, Belgium.

KEY MESSAGE

Uterine contractions play their part in fertility. However, to use them to improve pregnancy rates we need more research on their physiology and on the development of an objective, patient- and user-friendly measuring tool to identify and monitor patients with (ab)normal uterine activity, and the effect of potential therapies.

ABSTRACT

Although uterine contractions in the non-pregnant uterus have been studied extensively, the knowledge gained has not been used in general fertility treatment work-up. In this review paper, we provide an overview of the current knowledge on uterine peristalsis (UP), based on the available literature. This literature shows that UP influences pregnancy chances in both natural and artificial cycles. Although the physiological background of these contractions is not completely clear, we know that several factors can be of influence, like uterine pathologies and hormones. Several options to alter pregnancy outcome by interfering with uterine contractions have been studied. Our meta-analysis on therapeutic options shows positive results of progesterone at time of embryo transfer in IVF cycles or prostaglandins at time of intrauterine insemination, although the quality of evidence is low. These therapies are probably most beneficial in selected groups of patients with abnormal contraction patterns. The introduction of an objective and user-friendly UP measuring tool suitable for use in daily practice would make it possible to identify and monitor these patients. We suggest that future research should focus on the physiology of initiation of UP and on the development of an effective standard measuring tool.

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Introduction

Success of fertility treatment is moderate, and generally remains at about 30% per cycle. In a substantial number of these patients no underlying reason for failure can be found, and hence no causal treatment is available. In fertility treatment, the least controlled phase of the treatment is the period between embryo transfer and pregnancy testing. In this phase, uterine peristalsis (UP) plays its part in nidation (Fanchin and Ayoubi, 2009; Fanchin et al., 1998; Ijland et al., 1997a; Zhu et al., 2014). Knowledge of UP might provide an insight into a patient's fertility status and improve treatment.

Although this factor influencing fertility has been studied extensively since the 1990s, initially promising research results have not yet found their way into widespread clinical application. Although research on UP has lost its initial novelty, papers published on a regular basis demonstrate that this topic is still of interest. Over the years, researchers from various specialisms have compiled a significant amount of data. Still, a summary of the existing knowledge to date does not exist.

In this review, we provide a complete overview of research performed to date on contractions in the non-pregnant uterus. Topics include the embryological and physiological origin of uterine contractions (UC), different measuring methods, their clinical relevance, different mechanisms involved in UP control, and therapeutic approaches to enhance fertility. In conclusion, the potential direction of future research on this topic is discussed.

Methods

In a number of different phases, we searched PubMed for works published from 1900 to January 2016, looking for different subjects and using a variety of keyword combinations. We combined the terms 'uterine contractions', 'uterine peristalsis', 'endometrial waves' and 'junctional zone contractions' with terms including 'IVF', 'in-vitro fertilization', 'assisted reproductive techniques', 'pregnancy rate', 'implantation rate', 'embryology', 'histology', 'interstitial cells', 'pace-maker cells', 'hormones', 'oxytocin', 'prostaglandins', 'adenomyosis', 'endometriosis', 'leiomyoma', 'hydro salpinx', 'treatment', 'transvaginal ultrasound', 'intrauterine pressure measurement', 'hysterosalpingo scintigraphy' and 'magnetic resonance imaging'. In addition, we eliminated articles not written in English. This strategy yielded 724 hits on PubMed and 26 additional references, mainly acquired by cross-referencing. Of the 745 articles remaining after the duplicates were removed, 561 articles were assumed relevant based on their title and their abstracts were screened, retaining 331 articles for full-article assessment. Ultimately 152 articles were included in this review, of which 27 were also included in the meta-analysis (Figure 1).

We looked at nine different groups of therapies which might have an increasing or decreasing influence on UP and improve pregnancy chances. To create a clear overview of the effect of the different therapies on pregnancy rates, we performed a meta-analysis of the data available. To see whether the therapies have a significant effect

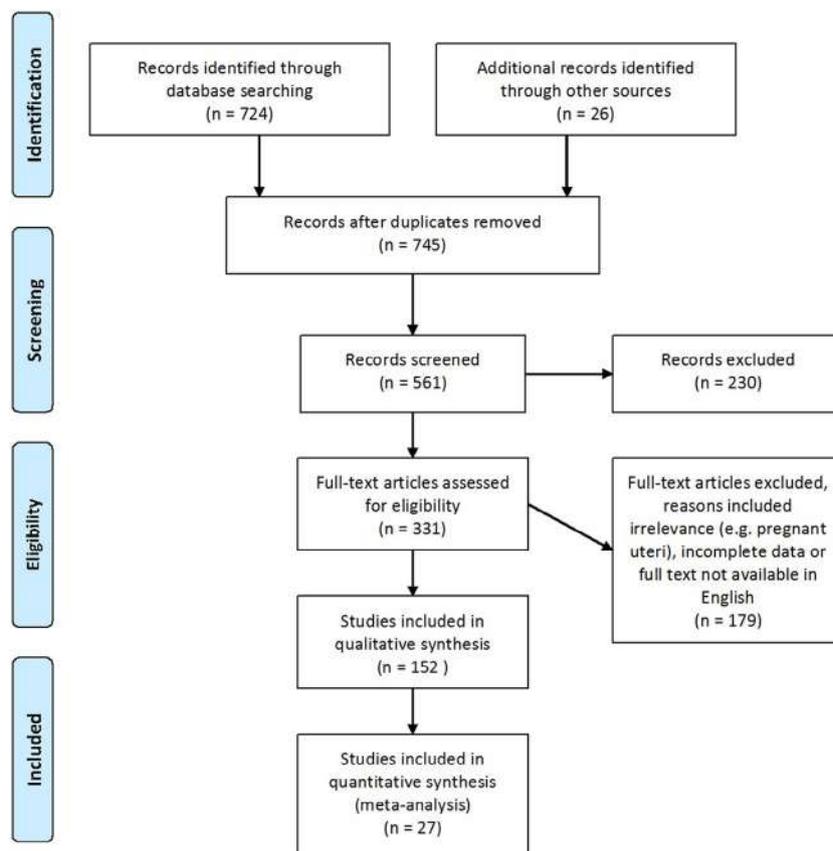


Figure 1 – Flow diagram for the selection of papers included in the meta-analysis.

Table 1 – Characteristics of UP. Frequency, amplitude and direction of UC in different phases of the menstrual cycle (van Gestel et al., 2001).

	Menstruation	Follicular phase		Luteal phase	
		Mid	Late	Early	Late
Frequency (contr./min)	0.33–3.0	1.5–3.3	3.0–6.0	2.0–4.0	0.8–1.8
Amplitude (mmHg)	13.6	5.2	2.9	Amplitude rises	
Direction	FC	FC/CF	CF	CF/opposing	Opposing/no contractions

CF = cervix to fundus; FC = fundus to cervix; opposing = contractions starting in the cervical as well as in the fundal region; UC = uterine contraction; UP = uterine peristalsis.

on pregnancy rate we calculated the relative risk (RR) using a fixed-effects model. Because some therapeutic groups showed significant heterogeneity between studies, we also performed a random-effects analysis. We included all studies in which the intervention was compared with a control group or placebo group and in which 'pregnancy rate' was an outcome (Table 2). Cohort studies, interventional studies without control group, in-vitro studies, studies with an outcome different from pregnancy rate and studies with insufficient data available were excluded from the meta-analysis, but are still mentioned (Table 3). We put studies which used control groups [no (additional) treatment] and studies with placebo groups together in one analysis, as we do not expect the placebo effect to have any influence on the outcome pregnancy rate. We assessed the quality of these studies following the GRADE recommendations (Guyatt et al., 2008).

Several terms are commonly used to refer to uterine movement of the non-pregnant uterus, including UC, UP, junctional zone contractions, endometrial waves and subendometrial contractions. In this review, we use the term 'uterine contractions' when discussing individual contractions and the term 'uterine peristalsis' when discussing the overarching rhythmic mechanism.

Origin of UP

Anatomy and embryology

The myometrium of the uterus has three separate layers of smooth muscle. The interior layer is called the stratum subvasculare, the middle layer is the stratum vasculare, and the exterior layer is the stratum supravasculare. The stratum vasculare is the thickest layer and contains numerous venous plexuses and lymphatic drainage (Ross and Pawlina, 2010). The uterus is equipped with a sympathetic and parasympathetic nervous system. The parasympathetic nerves originate from the sacral radix 2 to 4 and pass through the sacral plexus before entering the uterus at the cervical end. The sympathetic roots leave the spine at T10 to L2, and pass the superior hypogastric plexus, the hypogastric nerve, and the inferior hypogastric plexus to form a uterovaginal plexus, and enter the uterus fundus-laterally (Waschke and Paulsen, 2011).

The different layers of the uterine wall originate from two different embryological sites. The endometrial epithelium and the stratum subvasculare of the myometrium originate from the Müllerian ducts (or paramesonephric ducts). The stratum vasculare and supravasculare are of non-Müllerian origin (Noe et al., 1999). At approximately the 6th week of gestation, the Müllerian ducts are formed by invagination and subsequent fusion of the epithelial lining of the coelom. The Müllerian ducts progressively grow caudally to enter the pelvis, where they swing medially to fuse before the eighth week (Figure 2; see also Supplementary Video S1). Following this fusion, the endometrium and

a circular muscle layer develop, and form what will become the future uterus and Fallopian tubes before the 26th week (Moore et al., 2000; Noe et al., 1999). This circular myometrium is the stratum subvasculare surrounding the uterine cavity (Weiss et al., 2006). The non-Müllerian stratum vasculare and supravasculare develop later, starting at the 27th week of gestation and even continuing postnatally. The stratum vasculare develops as a mesh-like myometrial layer, while the stratum supravasculare develops as a longitudinally arranged outer layer (Figure 3) (Noe et al., 1999).

The endometrial-subendometrial unit

The different embryological origin of the outer part (vasculare and supravasculare) and inner part (endometrium and subvasculare) already suggests that they are two different units. Several researchers have shown both functional and architectural differences between these units.

Consider the fact that the subendometrial myometrium (stratum subvasculare) is the only layer that contracts when UP occurs. This is different from painful contractions that occur during labour or menstruation in which the outer layers are involved (de Ziegler et al., 2001). The inner part of the myometrium shows contractions that vary in frequency and direction throughout the menstrual cycle. In general, they provide active sperm transport, guide the embryo to its implantation site, and decrease after ovulation to support implantation (Bulleteri et al., 2000; Ijland et al., 1996b; Lyons et al., 1991).

On T2-weighted MRI, this subendometrial myometrium is easily distinguished from the other layers of the myometrium (Brosens et al., 1998). When using nuclear staining, the stratum subvasculare shows three times more nuclear area and less extracellular matrix compared with the outer layers. This reflects a higher smooth muscle density. This difference in smooth muscle density appears to be gonadal-hormone dependent, because differences are less noticeable in pre-menarche and post-menopause (Brosens et al., 1998).

Another aspect that distinguishes the inner and outer functional units is the expression of oestrogen progesterone receptors. Noe et al. (1999) evaluated this expression with immunostaining in all layers of the uterus and in different phases of the menstrual cycle. They found that receptor expression follows a cyclic pattern in the epithelial and stromal parts of the endometrium and in the stratum subvasculare. Oestrogen and progesterone receptor expression in the stratum supravasculare and the outer two-thirds of the stratum vasculare are stable throughout the cycle. The inner one-third of the stratum vasculare acts as a transitional zone, showing a reduced cyclic pattern.

Initiation of contractions

In rats, the sympathetic and parasympathetic autonomic nervous systems affect uterine smooth muscle. Sympathetic nerves release

Table 2 – Therapeutic options included in meta-analysis.

Studies included from meta-analysis												
	Author (year)	Type of research	N	Population	Intervention	Results	Risk of bias ^a					Comments
							A	B	C	D	E	
Steroid hormones	van der Linden et al. (2015)	Systematic review	642 women (live birth) 841 women (clinical PR)	IVF patients	Progesterone	LB: OR 1.77 (1.09–2.86) Clin. PR: OR 1.89 (1.30–2.75) Sub-analysis treatment duration: Stop at preg. test: OR 1.42 (0.74–2.74) Up to 12 weeks: OR 2.17 (1.37–3.43)	?	?	?	?	+	This study also looked at the effect of HCG and progesterone combined with oestrogen or GnRH agonists to improve LB and PR. As we do not expect these drugs to have an effect on UP, we do not consider these comparisons in this paper. Risk of bias: in most of 7 included studies ^b risk is unclear.
Prostaglandins	Barroso et al. (2001)	Prospective randomized study	59 cycles 29 misoprostol	IUI patients	Misoprostol 200 µg vag.	PR: miso: 31%, control: 20% (sig. difference)	?	?	?	+	?	
	Brown et al. (2001)	Placebo-controlled RCT	274 women/ 494 cycles 253 misoprostol	IUI patients	Misoprostol 400 µg vag.	PR: miso: 17%, placebo: 9% (P = 0.004). No significant side-effects	+	+	+	+	-	
Anticholinergic agents	Moslemizadeh et al. (2009)	Double-blind RCT	66 women 33 misoprostol	IUI patients	Misoprostol 200 µg vag.	PR: miso: 15.15%, placebo: 18.2% (NS)	+	+	+	+	?	
	Sohrabvand et al. (2009)	RCT	66 women (I: 22 indomethacin II: 22 hyoscine III: 22 control)	First IVF cycle	Indomethacin 10 mg Hyoscine 100 mg 30 min before ET	I: PR 13.6% II: PR 45.5% III: PR 36.0% Hyoscine sig. higher PR compared with indomethacin or control Indomethacin no effect	?	?	?	?	-	Study also looked at abdominal cramps: both hyoscine and indomethacin showed significantly fewer cramps compared with control
	Zargar et al. (2013)	RCT	142 cycles (71 hyoscine bromide)	IVF or ICSI patients	Hyoscine bromide 25 mg 30 min before ET	Hyoscine: PR 29.6% Control: PR 12.7% Sig. difference (P = 0.014)	?	?	-	+	?	Stratification for oocyte/embryo number and age: only significant difference if ≤10 oocytes, ≤5 embryos and age ≤35
Beta-adrenergic receptor antagonists	Pinheiro et al. (2003)	Prospective non-blind randomized study	225 women (I: 87 terbutaline II: 60 ritodrine III: 45 control)	ICSI patients	I: terbutaline 10 mg once daily II: ritodrine 20 mg once daily III: nothing	PR: I: 29.88%, II: 33.33%, III: 28.88% IR: I: 13.25%, II: 17.5%, III: 15.07% Miscarriage: I: 26.92%, II: 10%, III: 15.38% NS	+	?	?	-	-	The evaluation was interrupted in three patients of Group I and in 30 patients of Group II due to a high incidence of side-effects (palpitations/tremor)
	Rabiee et al. (2011)	RCT	100 women (50 ritodrine)	IVF patients	Ritodrine 10 mg once daily for 10 days	PR: ritodrine: 14%, control: 16% (P > 0.5)	?	?	-	+	?	1 patient in ritodrine group reported headaches and vertigo
	Tsirigotis et al. (2000)	RCT	27 women (15 ritodrine)	IVF patients with repeated failure	Ritodrine 5 mg four times daily for 12 days	Ritodrine: IR 14.8%, PR 46.7% Control: IR 4.2%, PR 16.7% RR: 2.80, 95% CI: 0.71–11.08	?	?	?	+	-	
Oxytocin receptor antagonists	Moraloglu et al. (2010)	Placebo-controlled RCT	180 women (90 atosiban)	ICSI patients with top-embryos	Atosiban 37.5 mg	IR/transfer: atosiban 20.4%, placebo 12.6% PR/cycle: atosiban 46.7%, placebo 28.9% Miscarriages: atosiban 16.7%, placebo 24.4% (all significant) No side-effects reported	-	?	+	+	?	
	Ng et al. (2014)	RCT	800 women (400 atosiban)	IVF patients	Atosiban bolus 6.75 mg + 18 mg/h infusion for 1 h + 6 mg/h for 2 h	NS difference in LB rate (39.8 vs 38.0%, rate ratio 1.051, 95% CI: 0.884–1.251) NS difference in pos. preg. test, PR, ongoing preg., miscarriage, multiple preg., ectopic PR and IR	+	+	+	+	+	
Prostaglandin synthetase inhibitors	Bernabeu et al. (2006)	RCT	136 women (72 indomethacin)	Oocyte donation recipients	Indomethacin 3 × 100 mg	IR indom: 27.8%, control: 26.4% (NS) PR indom: 59.7%, control: 59.4% (NS) Perhaps better rates in ovarian failure subgroup (29.2 vs 21.0% NS)	+	-	-	-	?	
	Dal Prato and Borini (2009)	RCT	200 women (100 piroxicam)	IVF or ICSI patients	Piroxicam 10 mg oral (co-intervention: vaginal progesterone gel)	Chemical PR: piroxicam 37%, control 47% Clinical PR: piroxicam 34%, control 38% IR: piroxicam 19.2%, control 21.9% Miscarriage: piroxicam 11.8%, control 13.2% Conclusion: no additional effect of piroxicam when progesterone is used	+	+	-	+	?	

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Table 2 – (continued)

Studies included from meta-analysis												
Author (year)	Type of research	N	Population	Intervention	Results	Risk of bias ^a					Comments	
						A	B	C	D	E		
Firouzabadi et al. (2007)	Placebo-controlled RCT	180 (90 piroxicam)	IVF patients	Piroxicam 10 mg 1–2 h before ET	Piroxicam: IR 12.3%, chem. PR 26.7%, clin. PR 25.5% Placebo: IR 7.7%, chem. PR 15.6%, clin. PR 10% P-value: IR 0.04, chem. PR 0.09, clin. PR 0.015	+	+	+	+	?		
Moon et al. (2004)	Placebo-controlled RCT	188 fresh IVF cycles (94 piroxicam) 78 cryo. cycles (39 piroxicam)	IVF patients	Piroxicam 10 mg	Fresh IVF group: IR: piroxicam 18.7%, placebo 8.6% (P < 0.05) PR: piroxicam 46.8%, placebo 27.6% (P < 0.05) Also sign in every cause of infertility, besides unexplained infertility! Sign in age group <40, not above 40. Cryo group: IR: piroxicam 9.4%, placebo 2.3% (P < 0.05) PR: piroxicam 25.6%, placebo 7.7% (P < 0.05)	?	?	+	+	?		
Rubinstein et al. (1999)	Placebo-controlled RCT	298 women (149 aspirin)	IVF patients	Aspirin (acetylsalicylic acid) 100 mg once daily	PR: aspirin: 45%, placebo: 28% (P < 0.05) IR: aspirin: 17.8%, placebo: 9.2% (P < 0.05) Aspirin group: improved ovarian responsiveness and uterine and ovarian blood flow velocity	+	+	+	+	?		
Sohrabvand et al. (2009)	See Anticholinergic agents											
Weckstein et al. (1997)	Prospective randomized study	28 women (15 aspirin)	Oocyte donation recipients (with history of TET <8 mm)	Aspirin 81 mg once daily	IR: aspirin: 24%, control: 9% (P < 0.05) PR: aspirin: 60%, control: 31% (NS) Deliveries: aspirin: 47%, control: 31% (NS) No significantly bigger TET Women with TET <8 mm during ET: IR: aspirin (n = 6): 38%, control (n = 12): 8% (P < 0.01) PR: aspirin: 83%, control: 25% (P < 0.05) Deliveries: aspirin: 50%, control: 25% (NS)	+	-	-	-	?		
Nitric oxide donors	Farzi et al. (2005)	Placebo-controlled RCT	100 cycles (50 nitroglycerine)	Fresh ICSI ETs	Nitroglycerine 0.4 mg 15 min before ET	Nitroglycerine: PR 38% Placebo: PR 34% NS difference	?	?	+	+	?	
	Ohl et al. (2002)	Placebo-controlled RCT	138 women (70 nitroglycerine)	IVF patients with repeated failure	Nitroglycerine patches (5 mg) from ET until preg. test	Nitroglycerine: IR 10.6%, PR 28.6% Placebo: IR 11.6%, PR 27.9% NS difference	+	+	+	-	-	
	Shaker et al. (1993)	Placebo-controlled RCT	120 women (60 glyceryl trinitrate)	First IVF attempts	Glyceryl trinitrate (400 µg sublingual spray) 3 min before ET	Glyceryl trinitrate: PR 30.0% Placebo: PR 31.7% NS difference	?	?	+	+	?	Also no effect on facilitating easy passage for ET catheter

contr. = contraction; CF = direction from cervix to fundus; ET = embryo transfer; freq. = frequency; GnRH = gonadotrophin-releasing hormone; HRT = hormone replacement therapy; ICSI = intracytoplasmic sperm injection; IR = implantation rate; IU = international units; IUI = intrauterine insemination; IV = intravenous; LB = live birth; MRI = magnetic resonance imaging; NS = not significant; OC = oral contraceptives; POF = premature ovarian failure; PR = pregnancy rate; preg. = pregnant or pregnancy; RCT = randomized controlled trial; sig. = significant; TET = total endometrial thickness; TVUS = transvaginal ultrasound; UC = uterine contraction; UP = uterine peristalsis; vag. = vaginal.

^a Risk of bias: + = low risk of bias, - = high risk of bias, ? = unclear bias. A: randomization, B: allocation concealment, C: blinding of participants and researchers, D: completeness of data reporting, E: other bias (e.g. multiple cycles per woman included).

^b [Abate et al., 1999, 1999a](#); [Artini et al., 1995](#); [Belaisch-Allart et al., 1987](#); [Hurd et al., 1996](#); [Kupferminc et al., 1990](#); [Wong et al., 1990](#).

noradrenaline, which binds either to alpha-adrenergic receptors to promote contraction, or to beta-adrenergic receptors to promote relaxation ([Papka et al., 1996](#)). The effect of the parasympathetic nerves depends on the type of neurotransmitter released; for example, acetylcholine is responsible for contraction and nitric oxide for relaxation ([Papka et al., 1995, 1999](#)). Little is known regarding what influences these synapses to release each neu-

rotransmitter. While no corresponding studies have been performed in human uteri, the human autonomic nervous system is known to be comparable to that of rat uteri ([Morizaki et al., 1989](#)). The fact that women with spinal cord injuries can still become pregnant and deliver vaginally ([Sterling et al., 2013](#)) implies that, in addition to the autonomic nervous system, local mechanisms might be involved in controlling UP.

Table 3 – Therapeutic options not included in meta-analysis.

Studies excluded from meta-analysis								
	Author (year)	Type of research	N	Population	Intervention	UP measurement	Results	Comments
Surgery	Kido et al. (2011)	Prospective cohort study	20 women in periovulatory phase	Symptomatic myoma	Uterine artery embolization	MRI	UP occurs in significantly more patients after embolization: Observer A: $P < 0.01$ Observer B: $P < 0.05$	
	Kishi et al. (2014)	Retrospective cohort study	102 women	Subfertile adenomyosis patients	Adenomyectomy	None	PR <40 years: 41.3% PR ≥40 years: 3.7% Factors associated with pregnancy: history of IVF treatment: OR 6.22 Posterior wall involved: OR 0.18 Age: OR 0.77	
	Mäkäräinen (1988)	Prospective cohort study	27 women (17 endometriosis, 10 controls)	Endometriosis patients	Endometriosis surgery or Danazol (600 mg/day)	Intrauterine pressure measurement	Higher basal pressure and lower contr. freq. during menstrual and luteal phase in endometriosis group compared with controls. NS change after treatment	
	Osada et al. (2011)	Prospective interventional study	104 women	Adenomyosis patients (26 subfertile)	Triple-flap method adenomyectomy	None	Sig. reduction of pain and blood loss: both $P < 0.01$ PR: 16/26 = 61.5% 4 spontaneous, 14 via IVF LB rate: 14/26 = 53.8% No uterine complications	
	Yoshino et al. (2012)	Prospective cohort study	15 women	Fertility patients with myoma	Myomectomy	MRI (implantation phase)	UC normalized after myomectomy in 14/15 patients. Both PR and LB rate 8 months after myomectomy were 40%	
Steroid hormones	Ayoubi et al. (2001)	Prospective double-blind parallel study	22 women (three treatment groups)	POF patients under hormonal substitution	Progesterone 4/8% vaginal gel from cycle day 15 I: 45 mg (n = 8) II: 90 mg (n = 7) III: 180 mg (n = 7)	TVUS: computerized	Decrease of contr. freq.: I: 35.2%, II: 37.5%, III: 32.5% (all sig. decreased $P < 0.05$) NS between dose groups. Total group: Sig. decrease in contr. freq. after 3 days ($P = 0.0172$)	
	Fanchin et al. (2001a, 2001b)	Prospective interventional study	84 women (two treatment groups)	IVF patients	Progesterone 8% vaginal gel A: start on day of oocyte retrieval (n = 43) B: start on evening of ET (2 days later) (n = 41)	TVUS: computerized At HCG administration and at ET	A: contr. freq. HCG: 4.6/min, contr. freq. ET: 2.8/min ($P < 0.001$) PR: 42%, ongoing PR: 35%, IR: 18% B: contr. freq. HCG: 4.5/min, contr. freq. ET: 4.1/min (NS) PR: 29%, ongoing PR: 22%, IR: 12%	
	Maslow and Lyons (2003)	Prospective cohort study	62 women (34 OCs, 28 controls)	Healthy women with proven fertility	OC (oestrogen + progesterone)	TVUS: visual assessment	Absence of UP mid-cycle: OC group: 50% Control group: 0% ($P < 0.01$) CF contractions: OC group: 38% Control group: 79% ($P < 0.01$) Contr. freq., amplitude and distance travelled by contr. sig. lower in the OC group ($P < 0.001$)	
Oxytocin	Kunz et al. (1998a, 1998b)	Prospective interventional study	19 women 4 early follicular, 9 mid-follicular, 6 late follicular	Healthy volunteers	Oxytocin 3 IU IV	TVUS: visual assessment	Before vs after oxytocin Sig. difference in contr. freq. in early and mid-follicular phase, not in late follicular phase. Placebo bolus had no effect.	The report also describes three other studies, not mentioned here
	Wildt et al. (1998)	Prospective interventional study	50 women	Infertility patients	Oxytocin 3 IU IV	Hysterosalpingoscintigraphy (HSSG)	After oxytocin administration: Sig. more radioactivity at ipsilateral side of dominant follicle ($P < 0.05$), not on contralateral side.	Wildt also shows sig. higher spontaneous PR in women with transport to the ipsilateral side (21.7%) compared with women with no shown transport to the tubes (2%)
Prostaglandins	Billiet et al. (2008)	Multicentre RCT	199 women/466 cycles 99: m-p-m, 100: p-m-p	IUI patients	Misoprostol (m) 400 µg vag./ placebo (p)	None	PR: NS difference in crossover, odd-number or first-cycle analysis Ongoing preg.: NS	Prematurely discontinued because of high rate of severe adverse effects (cramp + cervical bleeding)
Anticholinergic agents	Daido et al. (2013)	Prospective interventional study	25 women	Healthy, periovulatory phase	Buscopan (hyoscine butylbromide) 20 mg	MRI	I Pre-injection: 6.14 contr./3 min II 2–5 h post-injection: 4.73 contr./3 min III 5–8 h post-injection: 5.17 contr./3 min IV 8–10 h post-injection: 5.38 contr./3 min Sig. diff. I vs II and I vs III	Effect on bowel was significantly bigger compared with effect on myometrium

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Table 3 – (continued)

Studies excluded from meta-analysis								
	Author (year)	Type of research	N	Population	Intervention	UP measurement	Results	Comments
	Kido et al. (2009)	Case study	3 women (5 cycles)	Women with repeated IVF failure	Buscopan 20 mg	MRI	5 pregnancies, 3 ongoing, 1 miscarriage, 1 ectopic	Very small group, contraction frequency before transfer was: 2.3/2/0.7 per minute which is not really high. No control MRI was done to confirm if contraction frequency was less
	Nakai et al. (2008)	Prospective cohort study	21 women	14 healthy women (I) 7 fertility patients (II) All with regular cycles	Buscopan 20 mg	MRI	Total: before: 4.57 contr./2 min, after: 3.52 contr./2 min Diff: 23% (P = 0.003) I: before 4.14, after 0.93 less II: before 5.44, after 1.29 less Between I and II NS	No diff. in direction before and after Sporadic myometrial contr. and bowel movement decreased significantly
Beta-adrenergic receptor antagonists	Hanevik et al. (2012)	RCT	279 women (167 intervention)	IVF or ICSI patients	Acetylsalicylic acid (ASA) 75 mg daily after ET Terbutaline 5 mg 3 and 6 h after ET and the next morning	None	Intention to treat: Intervention: PR 30.5%, LB 28.7% Control: PR 42.0%, LB 33.9% NS Per protocol: Intervention: PR 36.6%, LB 34.4% Control: PR 45.3%, LB 37.9% NS	All patients got both ASA and terbutaline as intervention
Oxytocin receptor antagonists	Bloekel et al. (2009)	Placebo-controlled RCT	125 women (I: 41, II: 42, III: 42)	Oocyte donors	Day 2 after oocyte retrieval: I: barusiban (bolus 9 mg + 2.16 mg/h for 4 h) II: atosiban iv (bolus 6.75 mg + 18 mg/h for 4 h) III: saline placebo iv	TVUS: computerized	Uterine contr. freq. remained stable during the first 2 days after oocyte retrieval Significant decrease Day 2 vs 5 after oocyte retrieval irrespective of treatment group (P < 0.001). Barusiban vs placebo: P < 0.001 Atosiban vs placebo: P = 0.024	
	Lan et al. (2012)	Prospective cohort study	71 women (10 high contr. freq. = 4/min or more)	Cryo-cycles in women with repeated IVF failure	Atosiban 36.75 mg	TVUS: computerized (before and after atosiban)	IR/transfer: 13.9% PR/cycle: 43.7% Contraction frequency [contr./min]: Total: before 1.5/after 0.65 (P < 0.01) High frequency: 4.7/1.28 (P < 0.01) Low frequency: 0.98/0.55 (P < 0.01)	
Prostaglandin inhibitors	Pierzynski et al. (2004)	In-vitro study	15 preterm, 12 term pregnant women	Women undergoing CS	Atosiban and barusiban	In-vitro observation of myometrium strips	Potential to inhibit oxytocin induces myometrium contraction is equal between atosiban and barusiban	
	Asgarnia et al. (2007)	Placebo-controlled RCT	500 cycles (250 piroxicam)	IVF patients	Piroxicam 10 mg 1-2 h before ET	None	PR: NS diff. between piroxicam and placebo (P > 0.05)	
	Hanevik et al. (2012)	See Beta-adrenergic receptor antagonists						
	Maslow and Lyons (2004)	Prospective interventional study	20 women	Healthy women with known fertility	Ibuprofen 1200 mg (n = 13), 800 mg (n = 4)	TVUS: visual assessment (mid-cycle)	1200 g: Sig. contr. reduction after 60 min (P = 0.004), 90 min (P = 0.004), and 120 min (P = 0.01) 800 mg: No sign. Because of small group. Same reducing trend though	
	Wada et al. (1994)	Prospective cohort study	99 women (I: 37, with impaired perfusion) (II: 62, normal perfusion)	Cryo-ETs	1st attempt: I: aspirin 150 mg (n = 26) or 300 mg (n = 11) from day 13 of HRT. II: no aspirin 2nd attempt: I: allocated to start at day 13 or day 1 II: n = 10 allocated to start at day 1	None	I: NS diff. in cancellation and pregnancy rate between 150 and 300 mg. In 2nd attempt good perfusion in 82% of start aspirin at day 1 and 20% of start at day 13 (P < 0.02) PR: higher in patients starting at day 1. II: aspirin did not make a difference.	

contr. = contraction; CF = direction from cervix to fundus; ET = embryo transfer; freq. = frequency; HRT = hormone replacement therapy; ICSI = intracytoplasmic sperm injection; IR = implantation rate; IU = international units; IUI = intrauterine insemination; IV = intravenous; LB = live birth; MRI = magnetic resonance imaging; NS = not significant; OC = oral contraceptives; POF = premature ovarian failure; PR = pregnancy rate; preg. = pregnant or pregnancy; RCT = randomized controlled trial; sig. = significant; TET = total endometrial thickness; TVUS = transvaginal ultrasound; UC = uterine contraction; UP = uterine peristalsis; vag. = vaginal.

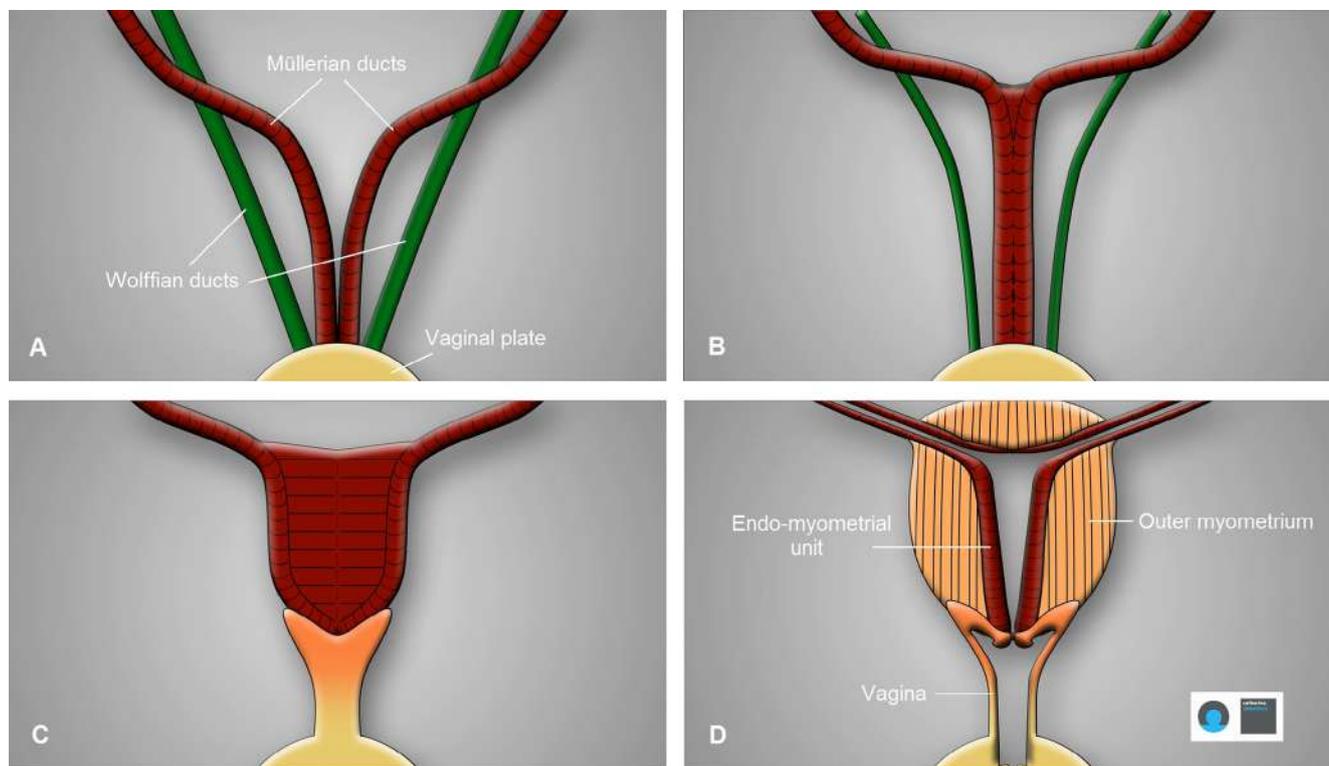


Figure 2 – Embryology of the uterus. A: Müllerian (red) and Wolffian (green) ducts. B: Müllerian ducts fuse, Wolffian ducts regress. C: fused Müllerian ducts form the subendometrial myometrium (stratum subvasculare) and endometrium, Wolffian ducts have disappeared. D: Stratum vasculare and stratum supravasculare are formed. [Noe et al., 1999] [See [Supplementary Video S1](#)].

The basis of this theory is the presence of cells with a possible pacemaker function in the uterine body. Interstitial pacemaker cells play a major role in other endodermal organs that are composed of smooth muscle, such as the gut, urinary tract or prostate [Al-Shboul, 2013; Exintaris et al., 2006; Feeney and Rosenblum, 2014; Nguyen et al., 2011; Niziaeva et al., 2014; Pasternak et al., 2013]. Of these, the best-known are the interstitial cells of Cajal (ICC) in the gut. They play a crucial role in the generation and coordination of peristalsis in the gastrointestinal (GI) tract, without any need for central innervation [Al-Shboul, 2013]. ICC are closely related to smooth muscle cells, and act as pacemaker cells by producing rhythmic oscillations in the resting membrane potential of the smooth muscle cells. These so-called ‘slow

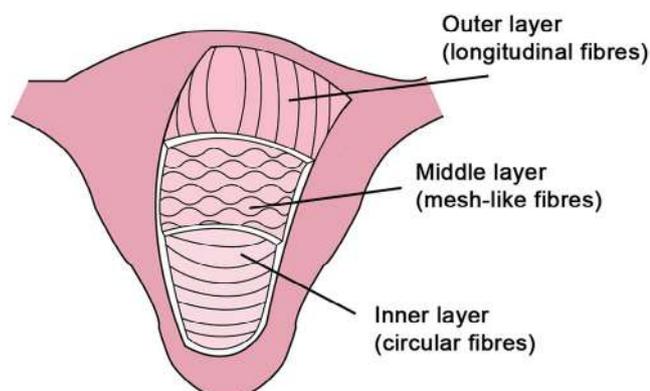


Figure 3 – Uterine layers. Inner circular layer, middle ‘mesh-like’ layer and outer longitudinal layer.

waves’ exhibit a characteristic frequency in each part of the GI tract. Alterations in membrane potential result in brief periods of high and low excitability. When excitability is high, a positive stimulus will lift the membrane potential above the threshold where an action potential is generated (see [Supplementary Videos S2 and S3](#)). Through a sudden rise in intracellular calcium, the contractile apparatus of the smooth muscle cells is activated and GI peristalsis is induced. The exact mechanism of electrical coupling is still unclear, but it appears to come about through various forms of cell-to-cell contact, for example gap junctions [Al-Shboul, 2013]. Cells with phenotypic markers that are comparable with ICC have been identified in human uteri, and are called interstitial Cajal-like cells (ICLC; Duquette et al., 2005). Cretoiu et al. [2006] found that these ICLC express oestrogen and progesterone receptors. The fact that ICLC are in close proximity to motor neurons and capillaries [Popescu et al., 2007] suggests that slow-wave frequencies might be mediated by multiple factors, including neurotransmitters, prostaglandins and hormones. However, conclusive functional evidence showing a pacemaker role for myometrial ICLC, similar to that of ICC in the human GI tract, has not yet been reported in the literature.

Measuring UP

Several different techniques have been used to monitor UP and its characteristics. Intrauterine pressure measurement (IUP) is theoretically the most accurate and objective for determining all effects and dimensions of UC. A single catheter, placed in the uterine cavity, can provide amplitude and frequency of UC, while multiple tip catheters can provide the direction of UC [Martinez-Gaudio et al., 1973].

A major drawback of IUPs is the invasive nature of the device, which causes discomfort for patients and makes routine use impractical. In addition, irritation induced by an intrauterine device may interfere with physiological contraction characteristics. When using an intrauterine method, the following question arises: are we measuring UP, produced by the inner part of the uterus, or are we measuring gross UC induced by mechanical stimuli via a reflex loop? In answer to this, [Bulletti et al. \(2000\)](#) compared frequency of UC detected by IUP and by non-invasive transvaginal ultrasound (TVUS) in the same subjects. Contraction frequencies were comparable, suggesting that the frequency changes recorded by IUP are most likely based on UP and not on a different mechanical reaction. Still, this method is not suitable to be used during embryo transfer (ET) because the catheter might injure the endometrium or the embryo itself.

TVUS assesses contraction frequency and allows visualization of the direction of contractions ([Ijland et al., 1996b, 1999](#)). Contractions are best visualized in the sagittal plane, where they can be seen as a wave of the endometrium. The method most frequently used to analyse TVUS recordings is to watch (and re-watch) video files at normal or accelerated speed. Due to their low frequency, identifying contractions is easier when watching recordings at four times real-time speed ([Ijland et al., 1996a](#)); contractions can be counted and the direction of the wave can be detected. However, TVUS cannot objectively measure contraction amplitude, and probe orientation and video quality are highly operator-dependent. Therefore, TVUS images are difficult to reproduce for follow-up and comparative studies; furthermore, TVUS is unsuitable for continuous recordings as it is semi-invasive ([Finberg, 2004; Solomon et al., 1994](#)).

The fact that assessment of videos is performed visually makes this way of measurement even more subjective. The subjectivity depends not only on the person performing the TVUS, but also the person performing the visual assessment. Our experience is that the quality of the recordings increases as the operator gains experience in performing TVUS for this purpose – as does the quality of the visual assessment. [van Gestel et al. \(2007\)](#) showed a high degree of inter-observer agreement for the visual assessment of contraction direction (Kappa value of 0.83); however, this study did not explore the agreement on contraction frequency or amplitude, which is considerably more difficult to define by eye. There are ways to use TVUS in a more objective way. One possibility is to use computerized image assessment, motion mode or M-mode ([Fanchin et al., 1998, 2000](#)). In M-mode, images of one selected vertical array line in the video are horizontally plotted in time, providing a representation of time-dependent changes in the endometrium–myometrium interface. This method is more objective, although it only provides information regarding one particular point in the uterus. Movements outside this region are not detected, which makes it impossible to determine whether movements could be due to probe movement. Furthermore, this method makes it impossible to detect direction of the movement in horizontal planes. The use of visual inspection of TVUS recordings for the measurement of UC has been shown to be useful in former research, but not in daily practice of a fertility clinic. Acquisition and analysis should be performed by experienced researchers and with a clear assessment protocol, as is usually the case when performed in a research setting.

Hysterosalpingo-radiionuclide scintigraphy (HSSG) provides the best measurement of direction of UC, and interpretation is relatively objective. This technique was originally designed to check patency of the Fallopian tubes. A suspension labelled with radioactive tracers is injected into the uterine cavity and migration of the suspension is

traced by a gamma camera ([Bulletti and de Ziegler, 2006; Kunz et al., 1996; Leyendecker et al., 1996](#)). The direction of UC can be assessed indirectly by measuring displacement of uterine content ([Bulletti and de Ziegler, 2006](#)). The main disadvantages of HSSG are the duration and cost of the procedure, as well as the inability to assess the amplitude and frequency of contractions. Furthermore, because of the risks associated with radiation exposure, this technique is not suitable for use in combination with ET.

MRI-based techniques provide detailed images of the different layers of the uterine wall, and can measure the frequency of UC ([Kido et al., 2005, 2007, 2008, 2009; Nakai et al., 2013; Watanabe et al., 2015](#)). However, measurement of amplitude is not possible with MRI. In addition, MRI-based techniques are both expensive and time-consuming.

In conclusion, we consider that the results shown in this review – based mainly on IUP and TVUS – are reliable, as long as the possible drawbacks are kept in mind. Potential future methods to monitor UP and its characteristics might include automated analysis of TVUS images or electrophysiological measurements. Electrohysterography (EHG) has already shown accurate, non-invasive characterization of UC during pregnancy and labour ([Rabotti et al., 2008, 2010; van't Hooff et al., 2013; Vinken et al., 2009](#)).

UP and its clinical relevance

Based on data derived from intrauterine pressure and ultrasound research, we know that UP characteristics change throughout the menstrual cycle ([Table 1](#)). Using ultrasound, UC can be visualized as wave-like movements, best visible at the junctional zone between myometrium and endometrium. Contractions from the fundus to cervix (FC) are observed primarily in the early to mid-follicular phase, and decrease as ovulation approaches. A switch in the direction of UC occurs in the late follicular phase, when waves from the cervix to fundus (CF) are observed ([Ijland et al., 1996a, 1996b, 1999](#)). These CF contractions are thought to assist rapid sperm transport and are mostly observed in the periovulatory period ([Ijland et al., 1996b](#)). In this phase, the frequency of UC is highest ([Bulletti et al., 2000](#)) and their direction is predominantly ipsilateral to the dominant follicle ([Kunz et al., 1996](#)). [Kunz et al. \(1998a\)](#) postulated that local hormones, produced at the site of the dominant follicle, stimulate asymmetrical UC. This utero-ovarian counter-current system ([Einer-Jensen and Hunter, 2005](#)) supplies oestradiol not only systematically, but also directly from the follicle to the fundus via blood supply, and plays a crucial role in directing the contractions ([Kunz et al., 1998a](#)). The fact that the uterus is mechanically able to direct its contractions to one side (assisting in rapid sperm transport), can be explained by its embryological development. As discussed under Origin of UP, Anatomy and embryology, both sides of the uterine corpus originate from a separate duct, which enables them to act semi-separately ([Noe et al., 1999](#)).

After ovulation, opposing UC – defined as simultaneous contractions originating in the cervix and fundal area – appear. The function of these opposing UC is to prevent the embryo from being expelled from the cervix or from the tubes, providing nutrients, and positioning the embryo before implantation ([Bulletti et al., 2000; Ijland et al., 1996a](#)). In the luteal phase, the uterus is in a quiescent state, providing an optimal environment for implantation of the embryo ([Bulletti et al., 1997; Fanchin et al., 1998](#)).

As physiological UC seem to have particular functions in fertility ([Ijland et al., 1997b](#)), dysfunctional contractions can contribute to infertility. Impaired or dysfunctional CF contractions during the

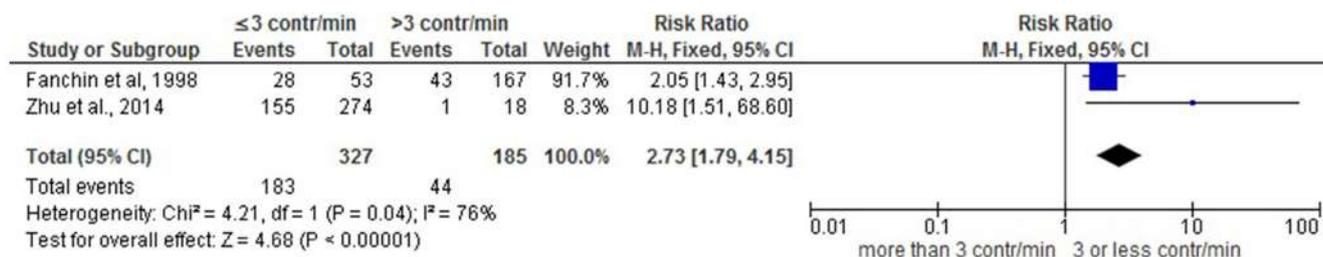


Figure 4 – High vs low contraction frequency. Outcome: pregnancy rate. [Results when using random-effects model: RR 3.83 [0.55–26.68].].

perioovulatory period result in impaired sperm transport, and therefore decrease fertility (Fanchin and Ayoubi, 2009).

One of the preconditions for successful implantation is a quiescent state of the uterus at the time an embryo reaches its implantation site. This is the case in natural cycles, but seems to play an even bigger role in IVF cycles. Both Fanchin et al. (1998) and Zhu et al. (2014) investigated whether the frequency of UP at the time of ET affects IVF success rates. They both found that increased contraction activity was negatively correlated to clinical pregnancies. A meta-analysis of their data shows a negative effect of increased contraction frequency (>3 contractions/minute) at the time of ET in IVF cycles: RR 2.73 [95% confidence interval (CI) 1.79–4.15] (very low quality of evidence) (Figure 4). Fanchin et al. (1998) extended their data to ongoing pregnancies, and implantation rates, and also found a significant difference between groups with high and low contraction frequency. In ovarian stimulation assisted reproductive technology cycles, uterine activity in the early luteal phase appears to be slightly higher compared with natural cycles: 4–6 contractions/minute versus 2–4 contractions/minute (Fanchin et al., 2000). In natural cycles, UP fades away rapidly after ovulation. Peristaltic activity following human chorionic gonadotrophin (HCG) administration in IVF cycles is prolonged (Fanchin et al., 2000; Zhu et al., 2012). Relaxation of the uterus is established 2 days later in IVF cycles compared with natural cycles (Ayoubi et al., 2003; Fanchin et al., 2001a). These findings show that dysfunctional UC, at the time of the ET, are more likely to occur in stimulated cycles than in natural cycles.

Based on the literature, the role of UC is considerable in fertility. Being able to accurately measure and influence UC could improve success rates in fertility treatment.

Factors influencing UP

Uterine disorders

Uterine pathology, such as endometriosis, adenomyosis and leiomyoma, affects peristalsis of the uterus. Several studies have suggested a relationship between uterine pathology and decreased fertility and spontaneous abortion. Women suffering from endometriosis show more UP and higher basal tone of the uterus compared with a control group (Bulletti et al., 1997). They also show more CF contractions in the early follicular phase (late menstrual phase), providing a rationale for retrograde menstruation (Leyendecker et al., 1996, 2004). This myometrial hypercontractility and dyskinesia, resulting in an aberrant wave direction, supports Sampson's theory on the aetiology of endometriosis (Sampson, 1927). Hypercontractility is also observed in women with recurrent abortions. This could explain why women with endometriosis, which is linked to hypercontractility, experience an increased incidence of spontaneous abortion (Bulletti et al., 1997).

Another theory suggests that endometriosis could be the cause of disrupted UP (de Ziegler et al., 2010). Ectopic endometrial cells are found to produce oestradiol when stimulated by prostaglandin E₂ (Attar et al., 2009). This rise in oestradiol possibly leads to hypercontractility of the subendometrial myometrium (Leyendecker et al., 2009). Adenomyosis is known to infiltrate and disrupt the subendometrial myometrium (Campo et al., 2012). This results in impairment of directed sperm transport in the perioovulatory period and causes infertility (Campo et al., 2012; Kissler et al., 2006; Leyendecker et al., 2004). Studying the influence of endometriosis and adenomyosis on fertility is complicated, as both entities exist alongside each other quite often – and sometimes one of the two conditions is not discovered until much later. This makes it problematic to determine which of the two, in fact, has the greatest influence on UC.

Women with intramural and submucosal leiomyomas have a decreased success rate in assisted reproductive techniques (Eldar-Geva et al., 1998; Healy, 2000). Leiomyomas are known to delay or disrupt normal UP (Nishino et al., 2005; Orisaka et al., 2007). In their pilot study, Orisaka et al. (2007) showed that abnormal UP during the mid-luteal phase might be one of the causes of infertility in women with leiomyomas.

Women with congenital uterine anomalies, such as septate uteri, demonstrate a high rate of pregnancy loss. This has been attributed to decreased blood supply in the septum (Taylor and Gornel, 2008). The extent to which abnormal UP plays a role in recurrent miscarriage in women with uterine anomalies remains questionable.

Hydrosalpinges do influence fertility, causing approximately 50% lower pregnancy rates, more miscarriages, and more ectopic pregnancies (Strandell, 2000). While the most common theory posed to explain this is the negative effect of the toxic tubal fluids on the embryo and receptivity of the endometrium, Eytan et al. (2001) suggested another explanation – the fluid mass in the Fallopian tubes increases the fundal intrauterine pressure. Such a pressure gradient from fundus to cervix would interfere with the UP from cervix to fundus that helps in positioning the embryo. Salpingectomy and closure of the Fallopian tubes by laparoscopic sterilization or hysteroscopically placed Essure® devices both seem to improve IVF outcomes in hydrosalpinx patients (Mijatovic et al., 2010, 2012; Strandell, 2007). The occlusion of the tubes might prevent the rise of intrauterine pressure.

Endocrine effects

Oestradiol concentrations demonstrate two peaks (one at the end of the follicular phase, and a lower peak during the mid-luteal phase), whereas progesterone starts to rise following an increase in luteinizing hormone concentrations in the luteal phase (Fauser, 2004). UP increases during the follicular phase of the menstrual cycle, as shown in Table 1 (Bulletti et al., 2000; Ijland et al., 1997a; Kunz et al., 1998b). Kunz et al. (1998b) suggested that this increase is controlled by oes-

tradiol secreted by the growing dominant follicle. They showed that elevated oestradiol concentrations in the early and mid-follicular phase lead to a significant increase in UP. However, administration of exogenous oestradiol did not significantly affect UP in the late follicular phase. They explained this discrepancy in results by suggesting that the frequency of UC reaches its intrinsic limits, which might be caused by the physiological boundaries of myocyte function because of a refractory period.

Another study showed that, in natural cycles, quiescence of the uterus is an effect of progesterone produced by the corpus luteum (Fanchin et al., 2000). As previously mentioned, UP decreases in the post-ovulatory phase, allowing embryo implantation to occur (Bulletti and de Ziegler, 2006; Fanchin et al., 1998; Ijland et al., 1997a; Kunz et al., 2006).

UP activity is negatively correlated with age (Arrowsmith et al., 2012; Kiguchi et al., 2017). Arrowsmith et al. (2012) showed that although UP is extremely low in post-menopausal women, it can still be present. They suggested that post-menopausal human myometrium remains responsive to its hormonal environment. This is supported by the fact that post-menopausal women start menstruating again after they start cyclic hormonal supplementation.

The pituitary hormone oxytocin is significantly elevated in the follicular phase of the normal cycle, compared with levels during the luteal phase, and peaks at the time of ovulation (Amico et al., 1981a; Dekker et al., 2004). Blaicher et al. (1999) found that oxytocin concentrations also peak during female sexual arousal, and postulated that oxytocin plays a possible role in sperm transport. Amico et al. (1981b) showed that women who chronically received oestradiol had significantly higher oxytocin levels than the control group.

Prostaglandins are important mediators of smooth muscle cell contractions in the uterus during labour (O'Brien, 1995). In the normal menstrual cycle, prostaglandin concentrations rise to a peak at mid-cycle, and then decline after ovulation (Vijayakumar and Walters, 1981). During the 1960s and 1970s, several authors suggested that prostaglandins increase UC at mid-cycle (Bygdeman et al., 1979; Eliasson and Posse, 1960; Martin et al., 1978), promoting rapid sperm transport to the Fallopian tubes. As seminal plasma contains prostaglandins (Robertson, 2005), it could provide its own transport via UC. While the majority of studies are performed using IUP measurement, which itself could induce UC, Maslow and Lyons (2004) proved the effect of prostaglandins using non-invasive TVUS. UC increased significantly after administration of vaginal prostaglandin gel at mid-cycle.

Mechanical effects

When discussing mechanical factors, we must take into account the fact that it is difficult to distinguish between gross uterine activity of the outer two-thirds of the myometrium and UP of the inner one-third of the myometrium. Gross uterine movement can be a result of a short loop reflex that occurs when manipulating the uterine wall (such as during the introduction of devices).

Intrauterine devices (IUDs) have proven to be an effective method of contraception (van Lunsen and Kremer, 2004). IUDs containing copper are believed to have two mechanisms of action, interfering with both the transport of sperm and the implantation of a fertilized ovum (Spinnato, 1997). For at least 45 years, researchers have known that IUDs affect electrical activity (Serr et al., 1970) and coordination of contractions in the uterus (Behrman et al., 1969). Maslow and Lyons (2003) found that women with copper-containing IUDs had different periovulatory UP than a control group of women who did not use IUDs. The percentage of women who had contractions from cervix

to fundus in the IUD group was significantly lower than in the non-IUD group (5% versus 79%). They also found that the percentage of women with uncoordinated contractions was higher in the IUD group compared with the control group (60% versus 7%). Additionally, the frequency and amplitude of UC were significantly lower in the IUD group than in the control group. Kido et al. (2008) confirmed these results by using MRI to analyse UP (see Measuring UP).

Mechanical stimuli can affect natural contractions during ET. The catheter used to insert the embryo into the uterine cavity may touch the uterine fundus, resulting in a traumatic insertion. Traumatic insertions generate strong, random contractions in the fundal area and FC contractions, while atraumatic insertions do not change UP (Lesny et al., 1998). UP does not significantly change after intrauterine insemination, in which the cervix is stimulated but not the uterine cavity itself (van Gestel et al., 2008). Use of a tenaculum to position the cervix during ET causes an increase in CF-directed UC (Lesny et al., 1999). Dorn et al. (1999) provided an explanation for this, by showing that the use of a tenaculum during ET can stimulate oxytocin release.

In conclusion, mechanical stimulation in the fundal part of the uterus appears to induce a local response and causes FC contractions, whereas stimulation of the cervix results in CF contractions. In addition to this locally initiated response, a central reaction occurs, which is mediated by oxytocin release from the pituitary gland.

Treatment options

Earlier in this review, we discussed the fact that dysfunctional UP can negatively affect fertility, either by disrupted contraction patterns in the late follicular phase, or through mid-luteal hypercontractility (Bulletti and de Ziegler, 2006; Bulletti et al., 1997; de Vries et al., 1990; de Ziegler et al., 2001; Fanchin and Ayoubi, 2009; Fanchin et al., 1998; Kunz et al., 1996, 1997, 2006).

Several therapeutic approaches have been proposed to alter UP through surgical or pharmaceutical means (Tables 2 and 3). As mentioned in Methods, we performed a meta-analysis on the available data with the outcome pregnancy rate. The results are described in this review and in Figures 5 to 15.

Surgery: as discussed above, endometriosis is associated with both infertility and disrupted contraction patterns (Bulletti et al., 1997; Leyendecker et al., 1996, 2004). The treatment of endometriosis itself is either pharmaceutical or surgical, with pharmaceutical approaches being contraceptive and not allowing natural conception. In their article, de Ziegler et al. (2010) concluded that as long as age, ovarian reserve, tubal patency and sperm quality permit it, surgery should be considered in an early phase to enhance the chances of natural conception. While surgery improves pregnancy chances, that does not mean that it also normalizes UC, and there has been only scant research on this topic. Mäkäräinen (1988) found no difference in the hypercontractile pattern before and after surgery, although surgery did relieve pain symptoms.

With its infiltration of the junctional zone, adenomyosis is associated with disruption of UP (Campo et al., 2012; Kissler et al., 2006; Leyendecker et al., 2004). Although adenomyosis surgery is quite extensive and carries the risk of uterine rupture or placenta accreta/increta/percreta in subsequent pregnancies, it seems beneficial for a specific group of patients (Kishi et al., 2014; Osada et al., 2011). Especially in women under 40 years of age with histories of failed IVF treatment, pregnancy rates improve after surgery; however, there have been no studies on whether or not normalization of UP plays a role in these improvements.

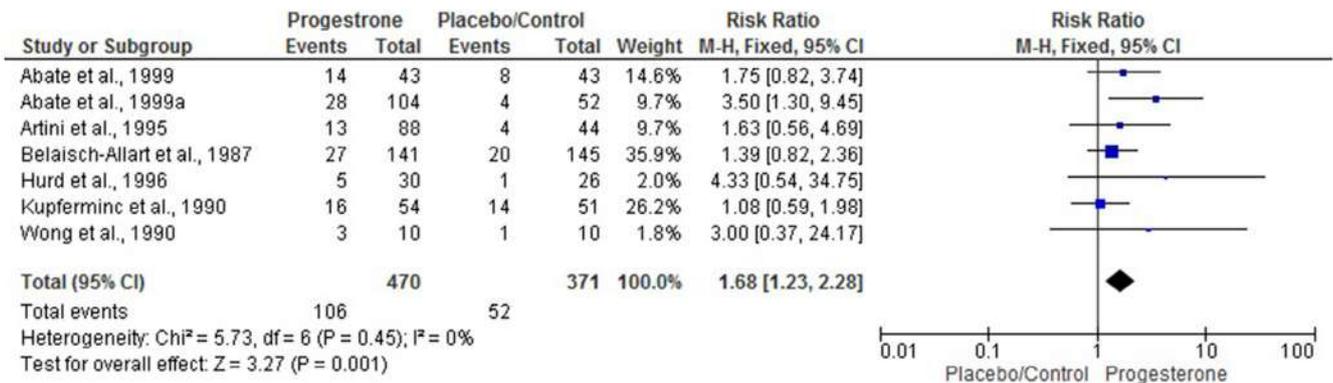


Figure 5 – Progesterone vs placebo/control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.56 (1.23–2.28).].

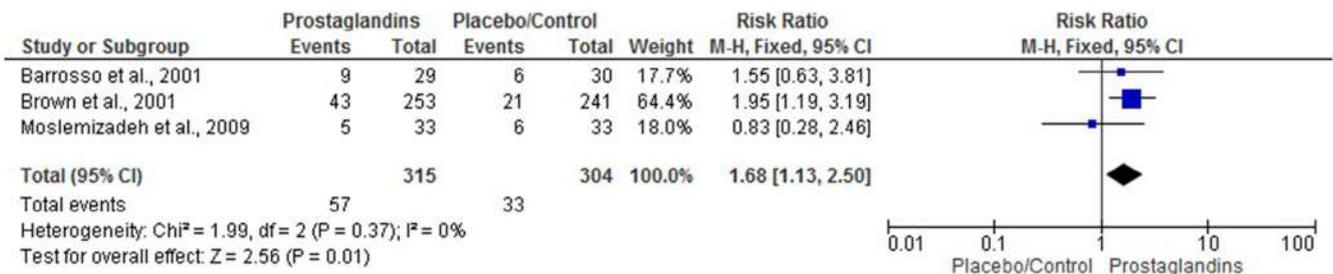


Figure 6 – Prostaglandins vs placebo/control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.66 (1.11–2.48).].



Figure 7 – Anticholinergic agents vs control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.71 (0.92–3.19).].

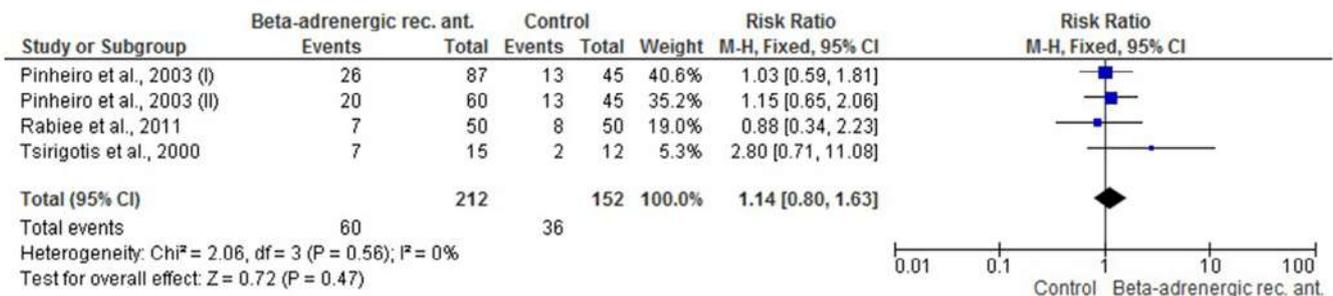


Figure 8 – Beta-adrenergic receptor antagonists vs control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.13 (0.79–1.61).] Pinheiro et al. (2003) compared both ritodrine (I) and terbutaline (II) with the control group, which is why there are two groups in the analysis.

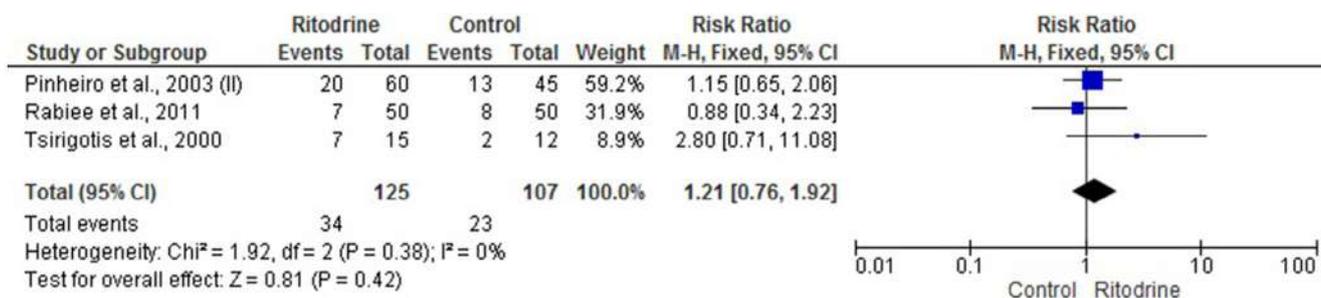


Figure 9 – Ritodrine vs control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.19 (0.75–1.90).].

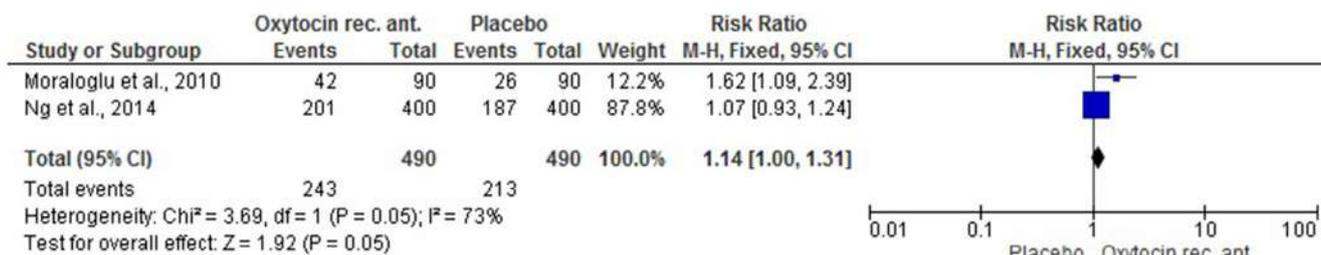


Figure 10 – Oxytocin receptor antagonists (atosiban) vs placebo. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.26 (0.85–1.78).].

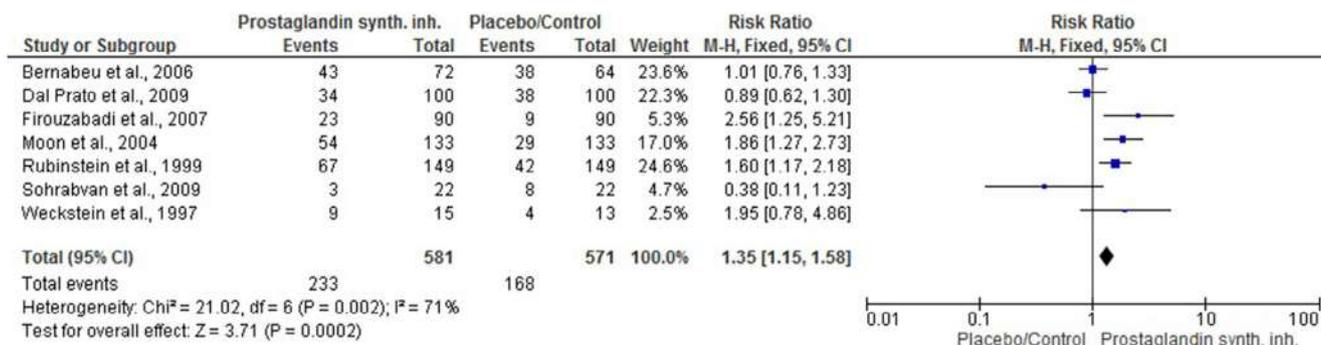


Figure 11 – Prostaglandin synthetase inhibitors vs placebo/control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.33 (0.96–1.85).] Moon et al. (2004) included 188 fresh IVF cycles and 78 cryopreservation cycles. In this analysis those groups were combined to find the overall effect of piroxicam.



Figure 12 – Piroxicam vs placebo/control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.55 (0.84–2.87).].



Figure 13 – Acetylsalicylic acid vs placebo/control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.63 (1.21–2.19).].

In contrast to endometriosis and adenomyosis, surgical treatment of leiomyomas has a demonstrated effect on UC. Kido et al. (2011) studied the presence of UP in the periovulatory phase after uterine artery embolization of symptomatic fibroids using 3-T MRI. In a small group of patients with uterine leiomyomas, they found that periovulatory UP increases after uterine artery embolization. Other research has shown that myomectomies can normalize UP during the mid-luteal phase and increase pregnancy rates in patients being treated for infertility (Yoshino et al., 2012).

Steroid hormones: cyclic changes of UP patterns suggest that steroid hormones are influential (Bulletti et al., 2000; Fanchin et al., 2000; Ijland et al., 1997a; Kunz et al., 1998b). This is supported by the fact that artificially adjusted hormonal levels in fertile women change UP activity in the mid-cyclic and luteal phases. Maslow and Lyons (2003) studied UP in women using oral contraceptives, or OCs (with both oestrogen and progesterone), and found that they were 50% less likely to have mid-cycle UP compared with the natural cycle control group. The percentage of women who experienced CF contractions in the OC group (38%) was significantly lower than that in the control group (79%). The frequency and amplitude of mid-cycle UC were also significantly lower in the OC group than in the control group (Maslow and Lyons, 2003). The decreased oestradiol peak in women using OCs might lead to decreased peristaltic activity, although it is more likely that the progesterone component in OCs contributes to the inhibition of UP at mid-cycle.

Progesterone is a standard therapy used for luteal phase support in IVF cycles because of its role in endometrium proliferation. van der Linden et al. (2015) recently did a meta-analysis on the effect of progesterone as luteal support in assisted reproductive technology cycles. Using their data we found a RR of 1.68 [1.23–2.28] for clinical pregnancy when comparing the use of progesterone with a placebo or no treatment (Figure 5, I²: 0%). Based on the GRADE quality score we classified the quality of evidence as moderate (Table 4). Although van der Linden et al. (2015) do not specifically mention the effect of progesterone on contractions in the luteal phase, it most definitely plays a role in improving pregnancy rates. Ayoubi et al. (2001) showed a 35% decrease (P < 0.05) in contraction frequency within the first 5 days using vaginal progesterone administration, with maximal effect on the 4th day. Timing of progesterone administration is also quite important, according to Fanchin et al. (2001b). They showed a significant decrease of UP frequency between the day of HCG and day of ET when starting with progesterone administration on the day of oocyte retrieval (4.6 > 2.8 contr./min, P < 0.001), and no difference when starting on the evening of ET (4.5 > 4.1 contr./min). Therefore, the luteal support by progesterone might be based not only on endometrial proliferation, but also on decreasing UP.

Oxytocin: Kunz et al. (1998a) showed a significant increase in UP following oxytocin injections in the early and mid-follicular phases, but no change in the late follicular phase. A possible explanation for this is that the maximum contraction frequency was reached, comparable with administration of oestrogen (see Factors influencing UP, Endocrine effects). Further increase in UP frequency would simply not be possible because of the refractory period of myocytes. In addition to increasing the frequency of UC, Wildt et al. (1998) found that oxytocin administration also changes the direction of contractions from FC to CF and directs sperm transport to the ipsilateral side of the dominant follicle. This last feature might be of great importance, as women with a distribution of spermatozoa predominantly on the ipsilateral side show significantly higher pregnancy rates compared with women with no transport to the tubes (Wildt et al., 1998). We found no studies that observed pregnancy rates in women using oxytocin in, for instance, IUI cycles.

Prostaglandins: some studies found a significantly higher pregnancy rate in patients undergoing intrauterine insemination with vaginal administration of misoprostol, compared with a control group without misoprostol (Barroso et al., 2001; Brown et al., 2001). However, other studies did not find a significant difference in pregnancy rates (Billiet et al., 2008; Moslemizadeh et al., 2009). The multicentre randomized controlled trial (RCT) by Billiet et al. (2008) was discontinued prematurely because of a high rate of severe adverse events (cramps and cervical bleeding). Despite this, they reached a significant sample size of 466 cycles. Surprisingly, Brown et al. (2001), who did find significant effects on pregnancy rates, reported no difference in pain or spotting between the misoprostol group and control group while using the same vaginal application method. Combining the data of all studies mentioned in a meta-analysis, excluding the data of Billiet et al. (2008) was unavoidable because of selection bias in the study protocol (continued three-cycle treatment of women in crossover design placebo/misoprostol). The analysis (Figure 6) shows a RR of 1.68 (1.13–2.50) with no heterogeneity (I²: 0%) in favour of the misoprostol group (very low quality of evidence, Table 4). No articles were found in which the influence of prostaglandins on UP was studied.

Anticholinergic agents are known to suppress smooth muscle activity in the bowel (Dosda et al., 2003; Tytgat, 2007). In addition, the anticholinergic agent hyoscine butylbromide (buscopan) also has a relaxing effect in the smooth muscle of the uterus (Daido et al., 2013; Nakai et al., 2008). Using cine MRI, it was demonstrated that the frequency of UC significantly decreased (from 4.57 to 3.52 UC per 2 min) after administration of hyoscine butylbromide (Nakai et al., 2008). Daido et al. (2013) showed that this effect was weaker and shorter compared with the suppressing effects on bowel movement. Evidence that anticholinergic agents enhance fecundity is scarce; however, Kido et al.

Table 4 – GRADE quality assessment.

GRADE quality assessment Outcome: pregnancy rate								Relative effect	Absolute effect	
No. of interventions/total participants (studies)	Type of evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size	Overall quality	RR (95% CI)	Assumed risk without intervention ^h	Risk difference
Progesterone 470/841 (7 RCT)	4	0	0	0	-1	0	Moderate ⊕⊕⊕○	1.68 (1.23–2.28)	14.0%	9.5% more (3.2–19.7%)
Prostaglandins 314/609 (3 RCT)	4	-1	-1	0	-1	0	Very low ^a ⊕○○○	1.68 (1.13–2.50)	10.9%	7.4% more (1.4–16.4%)
Anticholinergic agents 93/186 (2 RCT)	4	-1	0	0	-1	0	Low ^b ⊕⊕○○	1.82 ^g (1.10–3.03)	18.3%	15.0% more (1.8–37.1%)
Beta-adrenergic receptor antagonists 212/364 (3 RCT)	4	-1	-1	0	-1	0	Very low ^c ⊕○○○	1.14 (0.80–1.63)	23.7%	No sig. diff.
Oxytocin receptor antagonists 490/980 (2 RCT)	4	0	-1	0	-1	0	Low ^d ⊕⊕○○	1.14 (1.00–1.31)	43.5%	No sig. diff.
Prostaglandin synthetase inhibitors 581/1152 (7 RCT)	4	-1	-1	0	-1	0	Very low ^e ⊕○○○	1.35 ^g (1.15–1.58)	29.4%	10.3% more (4.4–17.1%)
Nitric oxide donors 180/358 (3 RCT)	4	0	-1	0	-1	0	Low ^f ⊕⊕○○	1.03 (0.76–1.39)	30.9%	No sig. diff.

Type of evidence: if majority of included articles is randomized controlled trials (RCT) 4 points, if majority is observational 2 points.

Quality: if quality issues like sparse data, withdrawals, risk of bias by ways of blinding or allocation concealment and incomplete reporting of results, which would have had a significant effect on the outcome, a maximum of 3 points can be deducted.

Consistency: if all included studies do not show consistent results or there is substantial heterogeneity: -1 point, if there is a clear dose effect: +1 point.

Directness: issues that make the studied population not generalizable result in -1 or -2 points.

Imprecision: if studies are included of which confidence intervals cross the unity line: -1 point.

Effect size: if RR of all individual studies included are >2.00 and significant: +1 point, if >5.00 and significant: +2 points.

Overall quality: 4 or more points = good, 3 points = moderate, 2 points = bad, 1 or less points = very bad.

^a One study with inconsistent results, 1 study included multiple cycles per woman.

^b One study with incomplete reporting, not clear why only a part of the included patients was used for analysis, 1 study with no blinding.

^c One study with inconsistent results, 1 study with a big drop-out rate because of side-effects, 1 study with no blinding.

^d Heterogeneity of 73% (=substantial).

^e Two studies with inconsistent results, heterogeneity of 71% (=substantial), 1 study with 21% drop-out during study without known reason, 3 studies with no blinding.

^f One inconsistent study.

^g Findings not statistically significant when random-effects model was used.

^h Assumed risk is the mean of risk of the control group.



Figure 14 – Indomethacin vs control group. Outcome: pregnancy rate. [Results when using random-effects model: RR 0.72 (0.82–1.86).].

(2009) published three cases describing a possible positive therapeutic effect of hyoscine bromide in women with repeated IVF failure. A meta-analysis of two small placebo-controlled RCT [Sohrabvand et al., 2009; Zargar et al., 2013] also showed this positive effect on pregnancy rates: RR 1.82 (1.10–3.03), I^2 : 35% (Figure 7; low quality of evidence: Table 4).

Beta-adrenergic receptor antagonists such as ritodrine and terbutaline are well known for reducing UC in the pregnant uterus (de Heus et al., 2008). Few studies have investigated the therapeutic effect of beta-adrenergic receptor antagonists in assisted reproductive techniques, and the majority did not succeed in finding significant results (Hanevik et al., 2012; Pinheiro et al., 2003; Rabiee et al., 2011). Tsirigotis et al. (2000) did find a positive difference in clinical and ongoing pregnancies when using ritodrine compared with no intervention (46% versus 16.7% and 33.3% versus 0%, respectively). Although these data are based on a total of 27 patients, the RR of 2.80 to become pregnant with ritodrine has a broad confidence interval of 0.71–11.08. Combining all data, excluding Hanevik et al. (2012) (due to combined terbutaline and acetylsalicylic acid treatment), we observed a non-significant RR of 1.14 (0.80–1.63) (I^2 : 0%, Figure 8; very low quality of evidence: Table 4). A sub-analysis of ritodrine studies showed comparable results without statistical significance: RR 1.21 (0.76–1.92) (Figure 9). No articles were found in which the influence of beta-adrenergic receptor antagonists on UP was studied.

Oxytocin receptor antagonists: atosiban (a mixed vasopressin V_{1A} and oxytocin receptor antagonist) and barusiban (a specific oxytocin receptor antagonist) have proven to reduce UC and improve implantation and pregnancy rates (Lan et al., 2012; Moraloglu et al., 2010; Pierzynski et al., 2004). Blockeel et al. (2009) studied the effect of atosiban and barusiban on UC in a group of oocyte donors. Although to date only abstracts have been published, they did reportedly find a significant difference in UC frequency between days 2 and 5 following oocyte retrieval. In contrast to these results, Ng et al. (2014) did not show any clinical benefits of atosiban in a larger ($n = 800$) group of participants undergoing IVF (with or without a history of IVF failure). Combining the two available RCT [Moraloglu et al., 2010; Ng et al., 2014] no significant positive effect of atosiban was seen: RR 1.14 (1.00–1.31) (Figure 10; low quality of evidence: Table 4). A critical note is the substantial heterogeneity in this analysis (I^2 : 73%). Oxytocin receptor antagonists might be of greatest benefit to those patients for whom IVF failed in the past without a known cause. Careful selection of patients with luteal hypercontractility might positively influence results.

Prostaglandin synthetase inhibitors: when using ibuprofen during mid-cycle, contraction frequency, amplitude and distance travelled decrease significantly (Maslow and Lyons, 2004); however, the clinical significance of this finding is limited, because one would preferably check this during the luteal phase. Moon et al. (2004) found that the

administration of the prostaglandin inhibitor piroxicam before ET increased both the implantation rate (18.7% versus 8.7%) and pregnancy rate (46.8% versus 27.6%), when compared with a placebo control group, as did Firouzabadi et al. (2007). By contrast, four other studies did not find a positive effect on success rates (for implantation or pregnancy) using either piroxicam or indomethacin (Asgharnia et al., 2007; Bernabeu et al., 2006; Dal Prato and Borini, 2009; Sohrabvand et al., 2009). Dal Prato and Borini (2009) suggested that these results differ due to the additional use of progesterone as luteal support. Both the Dal Prato and Borini (2009) and Bernabeu et al. (2006) studies used vaginal progesterone as luteal support for all participants, while Moon et al. (2004) and Firouzabadi et al. (2007) did not. Still, Asgharnia et al. (2007) and Sohrabvand et al. (2009) did not mention progesterone either and still did not show a significant difference with the control group. Studies of the prostaglandin synthetase inhibitor aspirin (acetylsalicylic acid) have shown slight improvement in implantation and pregnancy rates. It is suggested that this is due to an increase in uterine blood flow, and not specifically by interfering with UC (Rubinstein et al., 1999; Wada et al., 1994; Weckstein et al., 1997). The available data on the effect of prostaglandin synthetase inhibitors on pregnancy show a positive significant effect: RR 1.35 (1.15–1.58) (very low quality of evidence: Table 4), although with substantial heterogeneity (I^2 : 71%) (Figure 11). Sub-analysis of the studies using piroxicam or aspirin show significant effects with RR of respectively 1.46 (1.14–1.87) and 1.63 (1.21–2.19) (I^2 : 81% and 0%, respectively) (Figures 12 and 13). The analysis of the two studies using indomethacin shows no significant effect: RR 0.90 (0.68–1.19) (Figure 14).

Nitric oxide donors: nitric oxide is known for its ability to relax smooth muscle. Although several authors show that the use of nitric oxide donors, like nitroglycerine, does not improve pregnancy rate or live birth rate (Farzi et al., 2005; Ohl et al., 2002; Shaker et al., 1993), the meta-analysis resulted in a RR of 1.03 with no statistical significance (0.76–1.39) (Figure 15; low quality of evidence: Table 4). No heterogeneity was stated in this dataset (I^2 : 0%). No articles were found in which the influence of nitric oxide donors on UP was studied.

In conclusion, there are some possible agents that could interfere with UC and theoretically improve pregnancy rates. Of the data included in our meta-analysis, four therapy groups (progesterone, prostaglandins, anticholinergic agents and prostaglandin synthetase inhibitors) show a statistically significant difference in pregnancy rate compared with placebo or no treatment using a fixed-effects method, as do the subgroups piroxicam and acetylsalicylic acid (Figures 12 and 13). Of these statistically significant therapies, both the anticholinergic agents and the prostaglandin synthetase inhibitors show some to significant heterogeneity (35% and 71%, respectively), and therefore might not be representative. Taking this into account, we also performed a statistical analysis using a random-effects model. In this case both the anticholinergic agents [RR 1.71



Figure 15 – Nitric oxide donors vs placebo. Outcome: pregnancy rate. [Results when using random-effects model: RR 1.03 (0.76–1.40).].

[0.92–3.19]] and the prostaglandin synthetase inhibitors [RR 1.33 (0.96–1.85)] did not show a significant difference, while the progesterone and prostaglandin group did [RR 1.56 (1.15–2.13) and RR 1.66 (1.11–2.48), respectively].

Using the GRADE method [Guyatt et al., 2008] to assess the quality of the studies included in the meta-analysis, we concluded that the quality varied between very low and moderate (Table 4). The studies available on progesterone are of moderate quality and also show significant effect. The other therapies are of low or very low quality because of significant bias in the studies, inconclusive results within the therapy group or high heterogeneity. The fact that in all groups at least one study showed inconsistency [a confidence interval that crosses the unity line] indicates that most studies are based on a relatively small sample size.

All studies included in the meta-analysis focused solely on the effect of the therapies on pregnancy rate and not on contraction activity. Only progesterone, anticholinergic agents and oxytocin receptor antagonists have shown reduction of UP in observational studies. In addition, the role of oxytocin to increase contractility seems undeniable.

Regarding all of the therapies that have been suggested, the most critical step for success is to select the right patient groups, based on IVF indication (i.e. uterine abnormalities) and the status of their UC, for which the therapy can be expected to produce the greatest benefits. In our opinion, larger robust RCT are needed to investigate the effect of the most promising agents in this review. A suitable diagnostic tool to make an adequate patient selection and to monitor the effect on UP may be of great help for future clinical studies.

Discussion

During the past 20 years, a substantial number of studies have been presented concerning the physiology, diagnostics and clinical implications of UC. In this paper, a clear overview of available knowledge is provided. Literature shows that outside pregnancy, UP is mainly observed in the myometrial part of the endometrial–subendometrial unit, which forms a continuum with the Fallopian tubes. This unit differs significantly from the outer myometrium in embryological origin, architecture, cellular arrangement and function. The function of UP seems to be two-fold: providing strong enough contractions to guide spermatozoa to the ovum during ovulation; and creating an optimal, quiescent environment for implantation of an embryo during the luteal phase. Failure in one of these functions can interfere with fertility.

Besides the well-documented effect of progesterone on the endometrium, the positive influence on reducing uterine contractility

during assisted reproduction has also been investigated in depth. Drugs like anticholinergic agents and prostaglandin synthetase inhibitors seem to show promising results as well. However, until now, therapies that adjust UC have only been used in a research context. Researchers have not been able to provide solid and convincing proof that these drugs are beneficial (Figures 5 to 15; and Table 4). This might have something to do with the lack of knowledge about the physiology of UP and the fact that we are not yet able to determine what exact group of patients could benefit from these treatments.

Although there is no conclusive evidence to support that the uterus works as an autonomous organ, many facts support this idea. First of all, the uterus is an organ of endodermal origin like the gut, the urinary tract, prostate and gall bladder. All of these have a peristaltic contraction pattern and act autonomously through the initiation by interstitial pacemaker cells. In the gut, which is the best studied organ, the ICC produce a wave-like change in resting potential. However, these 'sub-threshold' potentials are not strong enough to induce a contraction independently. Exogenous stimuli – such as hormones, mechanical stimuli or signals from the central nervous system – can either enhance or reduce the level of muscular sensitivity to these potentials. If enough positive stimuli are present, the action potential will reach the threshold and a contraction will start, spreading like a wave. The fact that ICLC have already been uncovered in human uteri supports the idea that the uterus is able to work in a similar way, although the inability of researchers to prove their function makes this still just a theory.

In the light of uterine transplantations, first successfully performed by Brännström and his team in 2014 [Brännström, 2015], the idea of an autonomous uterus is interesting as well. In these cases, the uterus is not reconnected to the nervous system of the recipient. It would be very interesting to know whether these women had normal contraction activity after transplantation. The same applies to women with low spinal cord lesions, who still have contractions during labour which they don't feel, as there is no connection between the nervous system and the uterovaginal plexus. Would they show UP in their menstrual cycles?

We think these questions reveal great opportunities for future in-vivo and in-vitro research of the uterus, although to do so we need the most optimal way to measure contractions, and as discussed in this paper, all diagnostic tools used until now have their downsides. Both intrauterine pressure measurement and TVUS have been used frequently in research, and many of the existing conclusions are based on these tools. Intrauterine pressure measurements can be criticized because their invasive character possibly alters the characteristics of UC. Visual assessment of TVUS seems to be highly subjective, and too operator-dependent.

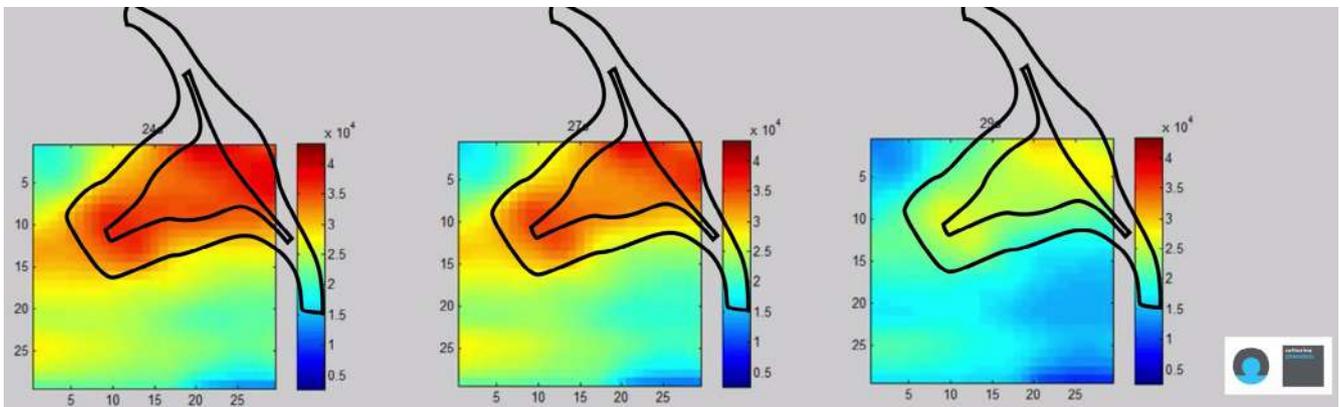


Figure 16 – Heat map showing uterine electrical activity measured by abdominal EHG. Left to right: showing a lot of electrical activity (red areas) and regressing. Notice that there are two specific areas that show maximum activity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

If the objective is to apply our knowledge of UP to daily practice in fertility clinics – for instance, to measure contraction frequency before ET or to select particular groups of patients for pharmaceutical interventions – we think that neither intrauterine pressure measurement nor TVUS are suitable. Both methods are too time-consuming and subjective, and are not easy to reproduce in daily practice – especially considering the fact that some patients are not visiting the same doctor for each of their appointments. Other, more objective options to measure contractions, like HSSG and MRI, are very costly, and cannot be performed on the spot; and in the case of HSSG, the procedure is not safe for the embryo. We think an accurate, objective and user-friendly measurement tool is needed before UC measurement can be incorporated into the standard work-up for fertility patients.

Future research should be focused on unravelling the initiation and distribution patterns of electricity in the uterus. Only when we know what happens in a ‘normal’ uterus can researchers study the effects of drugs. Histological and *in-vitro* tests with freshly harvested uteri would be necessary approaches, although EHG could answer some questions *in vivo* as well. EHG would make it possible to identify pacemaker regions and explore which regions are electrically most active in which phases of the cycle (Kuijsters et al., 2013; Rabotti et al., 2008). As an aid in this research direction, it is possible to show this activity in coloured heat maps to make it easier to identify these regions (Figure 16).

Of course, electrical activity might not mirror muscle activity one to one. To elaborate on the correlation between electrical activity and muscle contractions, comparisons with imaging of the uterine muscle are needed. MRI would be excellent for this purpose, but simultaneous EHG is not possible. Ultrasound results are easily compared with EHG measurements, but then again ultrasound is quite subjective. The use of strain imaging, a technique commonly used in cardiologic ultrasound (Hoit, 2011), might be able to make ultrasound more objective in the future (Kuijsters et al., 2014). Making use of the 3D features of ultrasound machines would also overcome the limitations of only assessing one plane.

In conclusion, we believe that UC remain a promising target to increase success rates in fertility treatment in the future. Based on the literature the main problems are the lack of knowledge on physiology and the inability to translate the current knowledge to the

doctor’s office. We think that future research should be based on these two things. We think new research should be focused on the origin and electrophysiology of UC, and secondly on development of an objective, patient- and user-friendly measuring tool to make this translation possible, and allow us to use UC to give more couples insight into their fertility problems and – more importantly – better treatment and better results.

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Appendix: Supplementary material

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